Studies on the Degradation of Mevinolin and Compactin: A Formal Route to Semisynthetic Analogues

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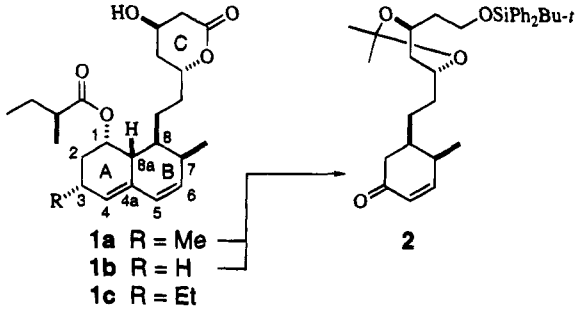
Received September 26, 1994[⊗]

Procedures are described for degrading mevinolin (**1a**) and compactin (**1b**) into the enone **2**, which is a substance that has been elaborated into **1a**, **1b**, and 3-ethylcompactin (**1c**). Consequently, **2** serves as an advanced intermediate for the construction of semisynthetic analogues of the mevinic acids. The degradation is based largely on a series of oxidations (epoxidation of allylic and homoallylic double bonds, α-hydroxylation of a ketone unit) and on S_N2' addition of phenyldimethylsilyl cuprates to a vinyl epoxide system). These reactions are applied in a way that leads to **33** and **50**, which are then cleaved with $Pb(OAc)_4$ or $NaIO_4$, respectively.

Introduction

We describe full details[1] of procedures for degrading the medically important fungal metabolites mevinolin (**1a**) and compactin (**1b**) into the enone **2**, a substance which we had previously made by total synthesis[2] and elaborated into both **1a** and **1b** and also[3] into the unnatural analogue, 3-ethylcompactin (**1c**).[4] On the basis of our synthetic work[2,3] it is clear that compound **2** can serve as an advanced intermediate for making semisynthetic analogues of **1a** and **1b**.[5] Such a possibility may have useful consequences in medicinal chemistry because of the potential importance of substances that retain (or improve upon) the cholestrol-lowering activity[6] of **1a** and **1b** but have better organ specificity and/or freedom from side effects.

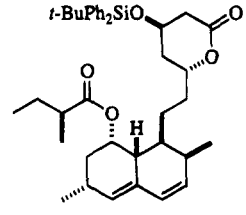


The level of biological activity of compounds such as **1a** and **1b** is sensitive to modifications in ring A,[3] and the synthesis developed in this laboratory[2,3] is general in the sense that it allows structural changes to be made to ring A, starting from the common enantiomerically pure intermediate **2**, which represents, in suitably protected form, the BC ring system. It is likely that our synthesis will also accommodate changes to ring B, such as replacement of the ring B methyl group by other alkyl units, but this has not been tried.

We have now supplemented the original synthetic work by degrading[7] **1a** and **1b** into enone **2** in a manner that makes the compound much more readily accessible: the original synthesis afforded **2** in 0.37% yield after a 25-step synthetic sequence from (*S*)-malic acid; we have now obtained **2** in 14 steps from **1a** in an overall yield of 7.6% and in 16.3% yield (13 steps) from compactin (**1b**).

Preliminary Studies

We began with a study of methods for cleaving the C(4)–C(4a) double bond. Treatment of mevinolin with *m*-chloroperbenzoic acid, according to a patent procedure,[8] gave the reported 4,4a-epoxide (*ca.* 80% pure by ^1H NMR), but the reaction was capricious in our hands and did not work the second and third time we tried it.



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Mevinolin was next silylated (**1a** → **3**), and treated under several different conditions with OsO_4, but we were unable to hydroxylate just one of the double bonds selectively, or even to hydroxylate them both,[9] in good yield.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1995.

(1) Preliminary communication: Clive, D. L. J.; Zhang, C. *J. Chem. Soc., Chem. Commun.* **1993**, 647.

(2) Clive, D. L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Siva Prasad, J.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018.

(3) Clive, D. L. J.; Keshava Murthy, K. S.; George, R.; Poznansky, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2099.

(4) Systematic numbering is used in the Experimental Section but not in the text.

(5) Review of mevinic acids: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(6) See literature cited in refs 2 and 3.

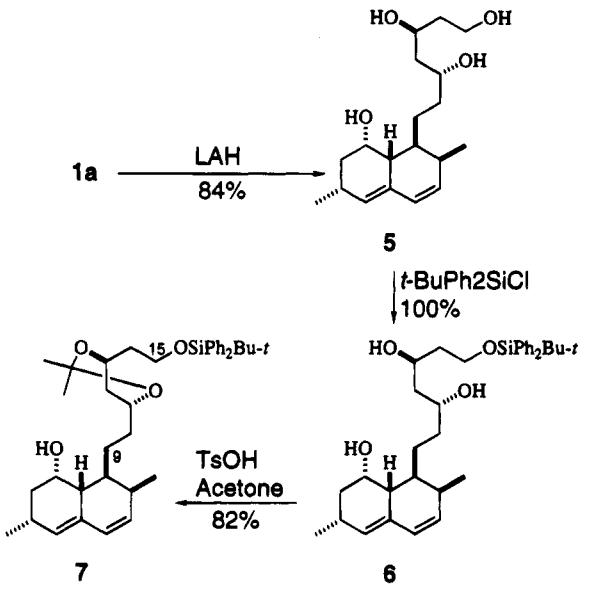
(7) For another degradation of ring A, see: Karanewsky, D. S. *Tetrahedron Lett.* **1991**, *32*, 3911.

(8) UK Patent Application GB 2 075 013, 11 Nov, 1981; *Chem. Abstr.* **1982**, *96*, 199426d. There appears to be a printing error on p 44 of the patent: the mass and analytical data given do not refer to the intended compound.

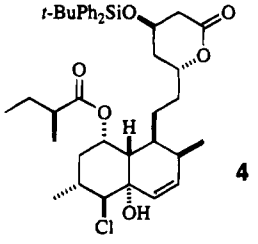
(9) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991.

0022-3263/95/1960-1413$09.00/0

Scheme 1



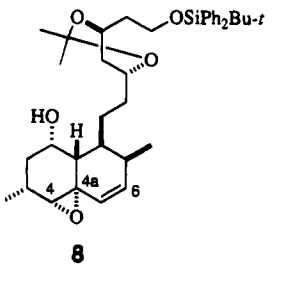
Guided by some reactions reported in the patent literature,[10] we then examined the response of compound **3** to PhSeCl and then to H_2O_2, hoping to obtain chlorohydrin **4**, but yields of product (which was not fully characterized) were low (20%). Exposure of **3** to PhSeCl/$AgOCOCF_3$ or to PhSeBr/AcOH/AcOK led in very poor yield to selenium-containing adducts.[11]

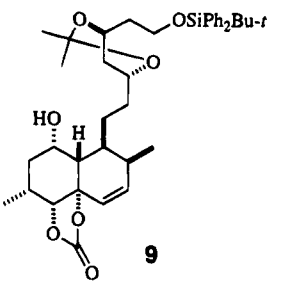


It was not clear why our preliminary experiments were so unpromising, and in the absence of a specific explanation, we arbitrarily decided to continue further work with compounds in which the lactone unit had been modified so as to make it less sensitive.

Degradation Studies Involving Prior Opening of the Lactone Unit. (a) Cleavage of the C(4)–C(4a) Double Bond. Natural mevinolin was converted into the protected alcohol **7**, in which the C(9)–C(15) subunit is the same as in the target enone **2**. Generation of **7** was easily accomplished by the straightforward reactions summarized in Scheme 1.[12]

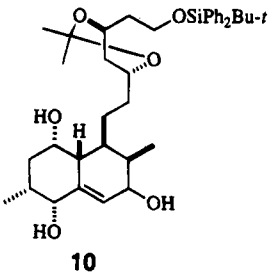
Treatment of alcohol **7** with *t*-BuOOH/VO(acac)$_2$ (benzene, $NaHCO_3$, 6 °C to room temperature) gave epoxide **8** in 77–82% yield. This epoxide is very sensitive to acid, and the presence of $NaHCO_3$ during the reaction is essential. Likewise, it is necessary to carry out chromatographic purification with a solvent that contains a little Et_3N.



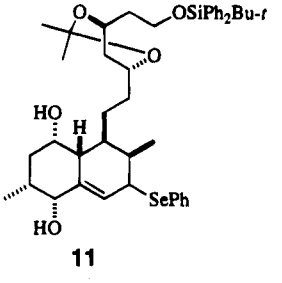


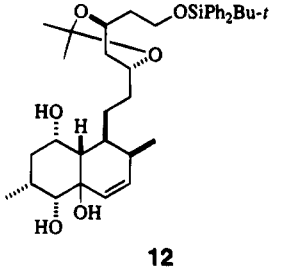
The hydroxyl group in **8** could not be acetylated, at least at room temperature (Ac_2O/DMAP/pyridine), and reaction with CO_2 in the presence of a palladium catalyst[13] did not lead to the expected product (**9**) (at room temperature or at 65 °C), even though close analogy exists[14] for the desired reaction.

Exposure of **8** to $NaIO_4$/THF/H_2O (room temperature) failed to result in cleavage of the C(4)–C(4a) bond[15] but gave instead what we believe to be triol **10**.[16]



Treatment of **8** with aryl selenide anions [$ArSe^-$, Ar = phenyl, 2,4,6-trimethylphenyl, or 2,4,6-tri(*tert*-butyl)-phenyl] was regiochemically unselective, with attack occurring equally at C(4) and C(6). Consequently, we did not pursue our plan to convert compounds of type **11** into diol **12**[17] by rearrangement of the derived selenoxide.





However, our next experiment with epoxide **8** finally did set the stage for cleaving the C(4)–C(4a) bond.

(10) E.g., Eur. Pat. Appl. 320052 A2, 14 June 1989; *Chem. Abstr.* **1990**, *111*, 233285x.

(11) *Cf.* Lee, T.-J.; Hoffman, W. F.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1992**, *57*, 1966.

(12) Acetylation of **5** then set the stage for attempts at hydroboration of the trisubstituted C(4)–C(4a) double bond. However, the acetate did not react with 9-BBN (1 equiv; THF, reflux) or with BH_3·SMe_2 (1 equiv; THF, reflux).

(13) The catalyst is made from $Pd(OAc)_2$ and $(i\text{-}PrO)_3P$. See ref 14.

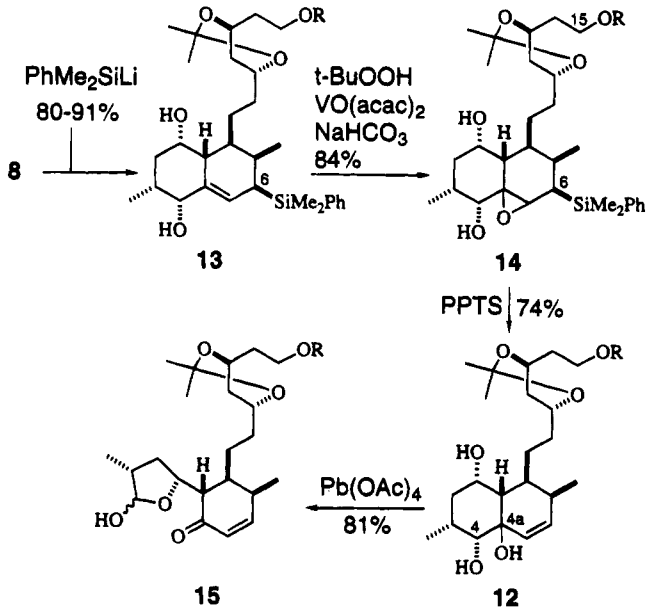
(14) Trost, B. M.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. Fujinami, T.; Suzuki, T.; Kamiya, M. *Chem. Lett.* **1985**, 199.

(15) Goldbach, M.; Jäkel, E.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1434. Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599. Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065.

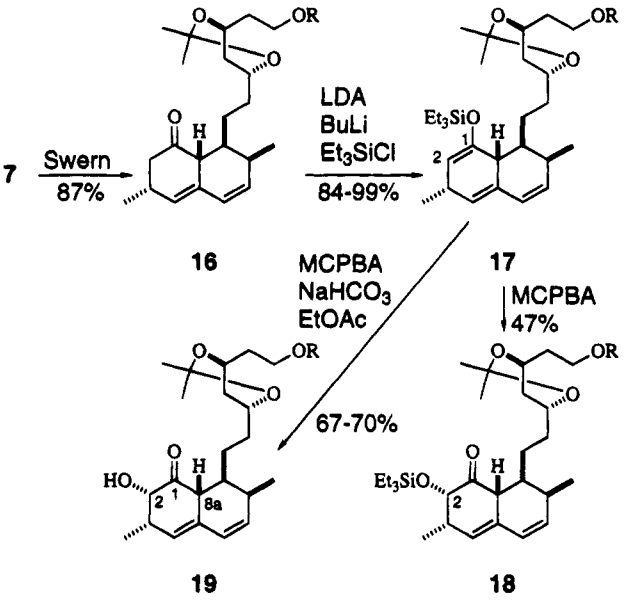
(16) Compound **10** had: IR ($CHCl_3$ cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (d, J = 7 Hz, 3 H), 0.8–2.1 [m, 40 H (should be 33 H)], 3.3–4.2 (m, 10 H), 5.93 (d, J = 5 Hz, 1 H), 7.32–7.48 (m, 6 H), 7.66–7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (tentative assignment: the abbreviations s′, d′, t′, and q′ refer to carbons attached to 0, 1, 2, or 3 hydrogens, respectively) δ 11.31 (q′), 16.28 (q′), 19.27 (s′), 19.93 (q′), 24.81 (t′), 26.92 (q′), 30.34 (q′), 31.17 (d′), 31.99 (d′), 33.61 (t′), 35.21 (d′), 36.71 (t′), 37.31 (t′), 39.43 (t′), 42.65 (d′), 59.75 (t′), 65.74 (d′), 67.08 (d′), 68.83 (d′), 69.65 (d′), 73.72 (d′), 98.56 (s′), 125.59 (d′), 127.65 (d′), 127.69 (d′), 129.62 (d′), 134.00 (s′), 134 04 (s′), 135.63 (d′), 141.91 (s′); exact mass m/z calcd for $C_{37}H_{53}O_6Si$ $(M - CH_3)^+$ 621.3611, found 621.3603.

(17) Stereochemistry at C(4a) not specified.

Scheme 2. R = $SiPh_2Bu$-*t*



Scheme 3. R = $SiPh_2Bu$-*t*



Treatment of **8** with $(PhMe_2Si)_2CuLi$[18] gave two products, one of which was identified as alcohol **13**, and this was the exclusive product (80–91%) when we used $PhMe_2SiLi$[19] instead of the cuprate (Scheme 2).

The allylic alcohol substructure of **13** undergoes smooth epoxidation (**13** → **14**, 85%) with *t*-BuOOH/$VO(acac)_2$ under mildly basic conditions ($NaHCO_3$). The use of a weakly basic medium is essential; in its absence the reaction is not very clean. At the time these experiments were first done we were unsure of the stereochemistry of **13** (and **14**) at C-6, but later, during the degradation of compactin, evidence was obtained to show that the silyl group is on the β face (as shown). This stereochemical assignment to **13** is based on a comparison with results (see later) for the compactin series in terms of TLC mobility, ^1H NMR patterns, and the effect on isomer ratios (C-6α versus C-6β) of changing the stoichiometry of the silyl cuprate, $PhMe_2SiLi/CuCN$.[20] The orientation of the epoxide oxygen in **14** is probably *syn* to the adjacent hydroxyl, on the basis of mechanistic considerations[21] and the ease of conversion of a derived diol into a ketal (see Scheme 5, **12** → **23**). However, we feel that this stereochemical assignment is less secure than that for the dimethylphenylsilyl group, and so the epoxide stereochemistry is not specified in the diagrams.

In order to open the epoxide and *still* preserve[22] the protecting group at C(15), compound **14** was treated with pyridinium *p*-toluenesulfonate to afford the desired triol **12**[23] in 74% yield. Compound **12** reacted with $Pb(OAc)_4$ to yield the expected cleavage product **15** in 81% yield (Scheme 2).

The above experiments establish a procedure for cleaving the C(4)–C(4a) double bond system, and we now turned our attention to the remaining problem of cleaving the C(1)–C(8a) single bond.

(b) Cleavage of the C(1)–C(8a) Bond before the C(4)–C(4a) Bond. Swern oxidation of **7** gave ketone **16** in 87% yield (Scheme 3), and this compound was converted (72%) into the silyl enol ether **17** by treatment with LDA and chlorotriethylsilane. We later found that the yield can be raised to 84–99% by adding 1.0 equiv of BuLi to the enolate (in THF at −78 °C) *before* introducing the chlorosilane.

Selective ozonolysis of the C(1)–C(2) double bond of **17** was unfruitful, but the compound does react with *m*-chloroperbenzoic acid in dichloromethane to produce **18** (47% yield) and another substance of undetermined structure (Scheme 3).[24]

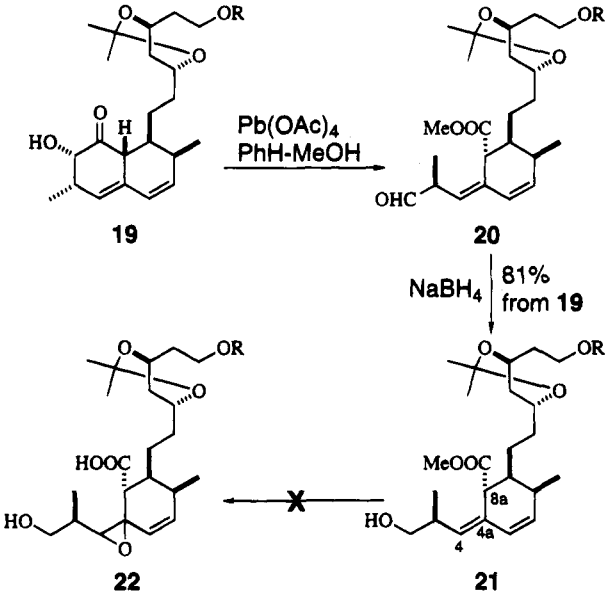
We also found that epoxidation of **17** with *m*-CPBA/$NaHCO_3$ gives products whose structure depends on the solvent: in ethyl acetate the α-hydroxy ketone **19** was obtained, but in dichloromethane the α-[(triethylsilyl)oxy] ketone **18** is isolated. An attempt at selective removal of the triethylsilyl group of **18** (Bu_4NF/THF) was unsuccessful, and the best route to the α-hydroxy ketone **19** is by use of *m*-CPBA/EtOAc/$NaHCO_3$ (67–70%). The stereochemistry of **19** at C(2) was established by decoupling and NOE ^1H NMR experiments. The decoupling helped to locate the C(2) and C(8a) hydrogens, and irradiation of the latter produced a 15% enhancement of the former. This effect clearly establishes that the C(2) hydroxyl is on the α face of the molecule.

We also tried to α-hydroxylate **16** directly to **19** by treatment of the derived potassium enolate (KHMDS) with 2-(benzenesulfonyl)-3-(*p*-nitrophenyl)oxaziridine (Davis' reagent);[25] however, a complex mixture was formed and the indirect method (**16** → **17** → **19**) is essential.

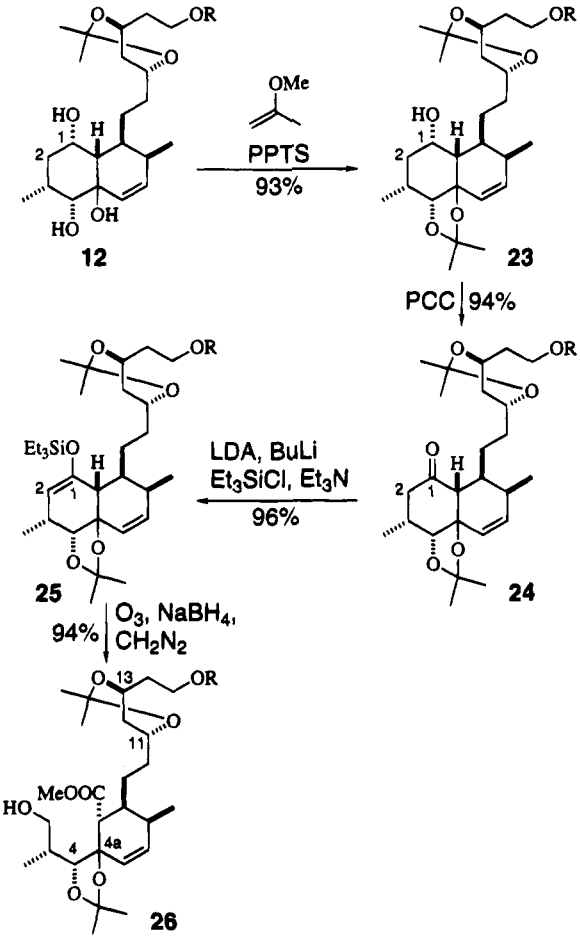
We next examined cleavage of the C(1)–C(2) bond of the hydroxy ketone **19** (Scheme 4). Use of $Pb(OAc)_4$/PhH/

(18) Fleming, I.; Marchi, D., Jr. *Synthesis* **1981**, 560.
(19) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) Sharma, S.; Oehlschlager, A. C. *Tetrahedron* **1989**, *45*, 557.
(20) A less marked dependence is shown by other allylic epoxides that we have studied: Clive, D. L. J.; Zhang, C.; Zhou, Y.; Tao, Y. *J. Organomet. Chem.*, in press.
(21) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. Kobayashi, M.; Kurozumi, S.; Toru, T.; Ishimoto, S. *Chem. Lett.* **1976**, 1341.
(22) Use of Bu_4NF/THF/room temperature leads to loss of the C(15) silyl group.
(23) Attempts to obtain crystals of **12** suitable for X-ray analysis were not successful. The C(4a) hydroxyl is probably *syn* to that at C(4).
(24) The assignment of stereochemistry at C(2) of **18** is based on the assignment for the derived alcohol **19**. The values of $J_{2,3}$ for both compounds are very similar.
(25) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3240.

Scheme 4. R = $SiPh_2Bu$-*t*



Scheme 5. R = $SiPh_2Bu$-*t*



MeOH (**19** → **20**),[26] followed by reduction ($NaBH_4$), gave **21** (tentative structural assignment) in 75% overall yield (Scheme 4). [In assigning a structure to **21** we assume that there is no change in the stereochemistry at C(8a) during the sequence.] However, our attempts to oxidize the C(4)–C(4a) double bond [*m*-CPBA/$NaHCO_3$/CH_2Cl_2; TBHP/$Mo(CO)_6$/Na_2HPO_4/4 Å sieves;[27] TBHP, $VO(acac)_2$[28]], so as to produce **22**, were unsuccessful.

At this point we sought to protect the vicinal diol unit of **12** so that the other ring A hydroxyl [at C(1)] could be manipulated selectively (Scheme 5).

As shown in Scheme 5, the required ketal **23** can be made in high yield. The remaining hydroxyl was then oxidized to a ketone (**24**) which, in turn, was converted into the silyl enol ether **25**. For the oxidation (**23** → **24**), Swern conditions did not work (the starting material was recovered) but PCC was very effective.

The C(1)–C(2) double bond of the silyl enol ether **25** was cleaved selectively (O_3/$NaBH_4$/CH_2N_2) to afford hydroxy ester **26**. Our plan at this stage was to unmask the protected C(4)–C(4a) vicinal diol and then cleave it with IO_4^- or $Pb(OAc)_4$. However, the C(4)–C(4a) ketal was too stable, and attempts at acidic hydrolysis (PPTS/MeOH) appeared (^1H NMR) to result in cleavage of the C(11)–C(13) ketal unit.

The above experiments had illustrated a method for cleaving the C(1)–C(2) single bond, although at the expense of generating problems in cleavage of the C(4)–C(4a) double bond. Extensive further work to find a better-behaved protecting group for the C(4)–C(4a) vicinal diol of **12** was unsuccessful, but eventually we made a small but decisive modification to our approach so that it then did lead to the required enone **2**. This successful route is summarized in Scheme 6.

(c) Cleavage of Both the C(1)–C(2) and C(4)–C(4a) Bonds. The starting point, epoxy silane **14**, is an intermediate used previously (see Scheme 2) in a sequence to cleave the C(4)–C(4a) double bond, and as already described, the compound is available by an efficient route.

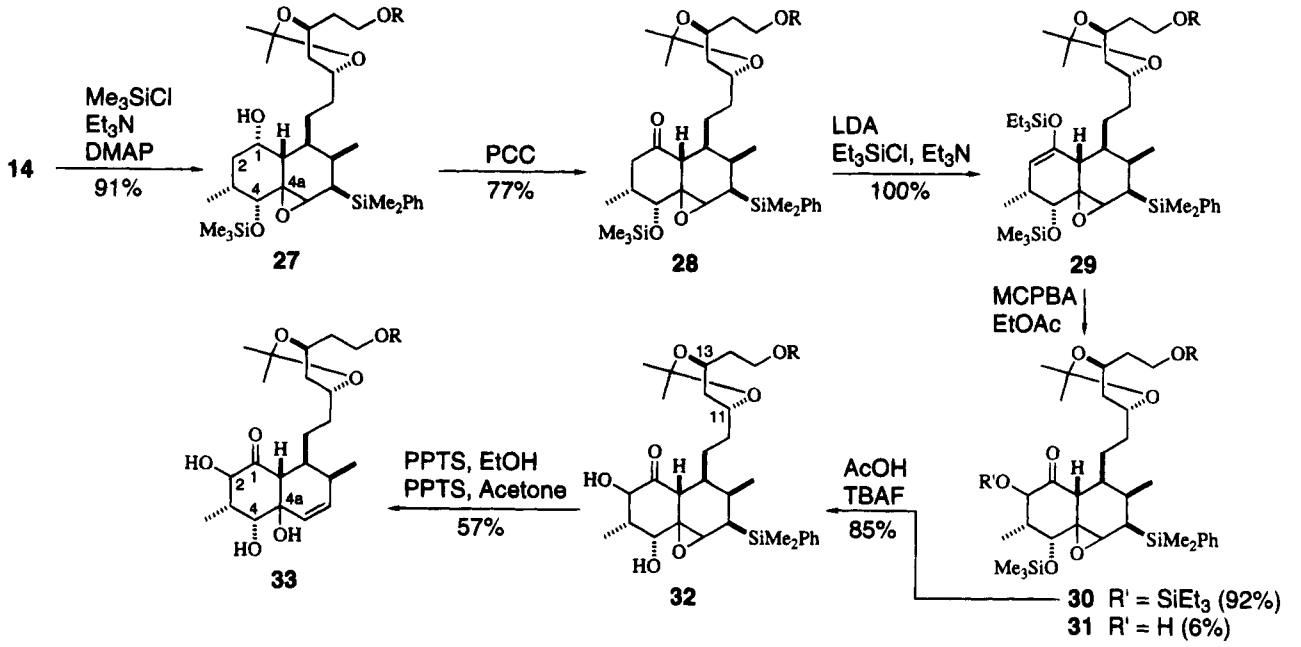
Selective silylation of the equatorial hydroxyl at C(4) (**14** → **27**; 91%) and oxidation (77%) took the route as far as ketone **28**. This was converted (100%) into the corresponding triethylsilyl enol ether **29**, from which a separable mixture of the α-oxygenated ketones **30** (92%) and **31** (6%) was readily obtained. [In the formation of **29** a second equivalent of BuLi was not needed after generation of the enolate—contrary to the situation (Scheme 3) with **17**.] Desilylation (**30** → **32**) was easily achieved, but generation of the allylic alcohol (**32** → **33**) was problematic. Numerous conditions were tried,[29] best results (57%) being obtained by sequential use of PPTS/EtOH and then (after evaporation of the solvent) PPTS/acetone, the last operation serving to restore the C(11)–C(13) ketal.

Finally, we exposed the trihydroxy ketone **33** to the action of $Pb(OAc)_4$ in 1:1 benzene–methanol. Our hope was that cleavage of both the C(4)–C(4a) diol and the C(1)–C(2) hydroxy ketone would occur so as to afford keto

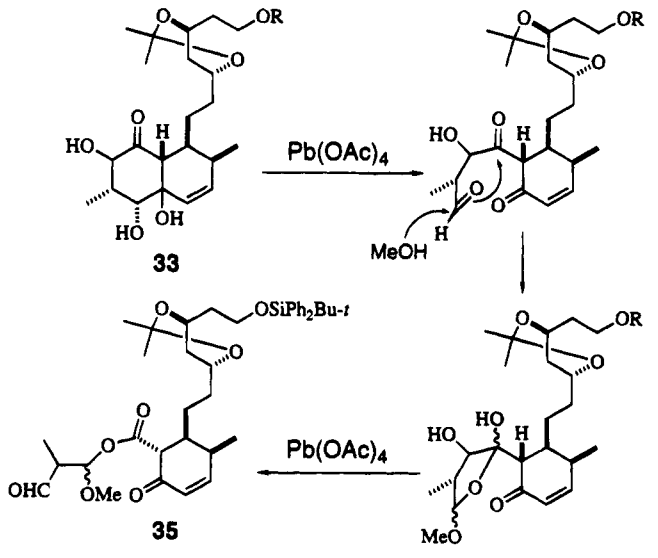
(26) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.
(27) DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**,*56*, 3564.
(28) The experiment with TBHP/$VO(acac)_2$ was tried twice.

(29) CH_3CN/HF (aq) (tried for **32** → **33**); AcOH/TBAF (tried for **30** → **33**); PPTS/THF (tried for **30** → **33**); PPTS/EtOH (tried for **30** → **33**); Et_3NHF/CH_2Cl_2 (tried for **30** → **33**); AcOH/MeOH (see ref 30) (tried for **32** → **33**); MgI_2/PhMe (see ref 31) (tried for **32** → **33**); $Ti(OPr\text{-}i)_4$ (see ref 32) (tried for **32** → **33**); $Al(OPr\text{-}i)_3$ (see ref 33) (tried for **32** → **33**); $BF_3{\cdot}Et_2O$ (tried for **32** → **33**).
(30) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981.
(31) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206.
(32) *Cf.* Morgans, D. J.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1981**, *103*, 462.
(33) Terao, S.; Kato, K. *Synthesis* **1979**, 467. Scheidl, F. *Synthesis* **1982**, 728.

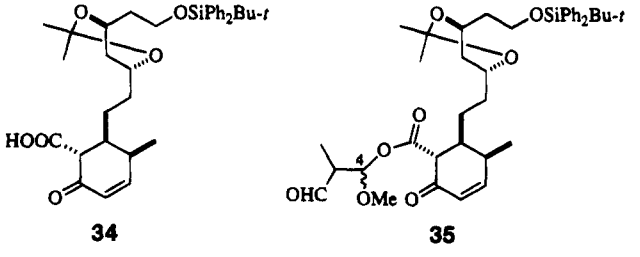
Scheme 6. R = $SiPh_2Bu$-*t*



Scheme 7. R = $SiPh_2Bu$-*t*



acid **34**. Decarboxylation would then give **2**—which is the desired target of the degradation.



In the event, the lead tetraacetate oxidation gave a material (*ca.* 67%) to which we tentatively assign structure **35** (Scheme 7). (H_4 and C_4 have chemical shifts close to those reported for simple models.[34]) Formation of **35** is understandable in the terms shown by Scheme 7.

(34) Pihlaja, K.; Lampi, A. *Acta Chem. Scand.* **1986**, *B 40*, 196.

We also tried other conditions for cleavage of **33**,[35] but our screening experiments[35] showed that the original process [$Pb(OAc)_4$/PhH–MeOH] is best, and so we examined conditions (see Table 1) for hydrolysis and decarboxylation[36] of **35**.

The best method (Table 1, entry g) involves refluxing a dioxane solution of **35** in the presence of a trace of acid.[37]

By means of the above experiments we had found a method for degrading mevinolin into the target enone **2**, but optimization of the last step (hydrolysis of **35**) would require some larger-scale tests. However, we did not want to do such experiments: we had just acquired a much larger supply of compactin than we had ever had of mevinolin, and it appeared that the most sensible course was to repeat the degradation on a larger scale, but using compactin.

Degradation of Compactin. We now began to apply the above experiments to compactin. At the start it was clear that some of the stages would work exactly as in the mevinolin series, but a few intermediates in that series are sufficiently sensitive that we anticipated having to modify our approach in response to the conformational differences between the two natural products.

As shown in Scheme 8, the first two steps—reduction with $LiAlH_4$ and selective silylation—proceeded without incident (**1b** → **36** → **37**) except for the fact that the reduction must be carried out at room temperature as opposed to the reflux temperature used with mevinolin. Failure to follow this procedure results in an unidentified byproduct. Ketalization, previously done with acetone in the presence of *p*-toluenesulfonic acid, gave the desired

(35) $Pb(OAc)_4$/AcOH, $Pb(OAc)_4$/PhH–MeOH/K_2CO_3, $Pb(OAc)_4$/PhH–Me_3SiOH, $NaIO_4$/THF–H_2O, $NaIO_4$/MeOH–H_2O, and Jones reagent/acetone each gave complex mixtures; there was no reaction with $Pb(OAc)_4$/THF–H_2O or $Pb(OAc)_4$/acetone–H_2O, and compound **35** formed with $Pb(OAc)_4$/AcOH–MeOH.

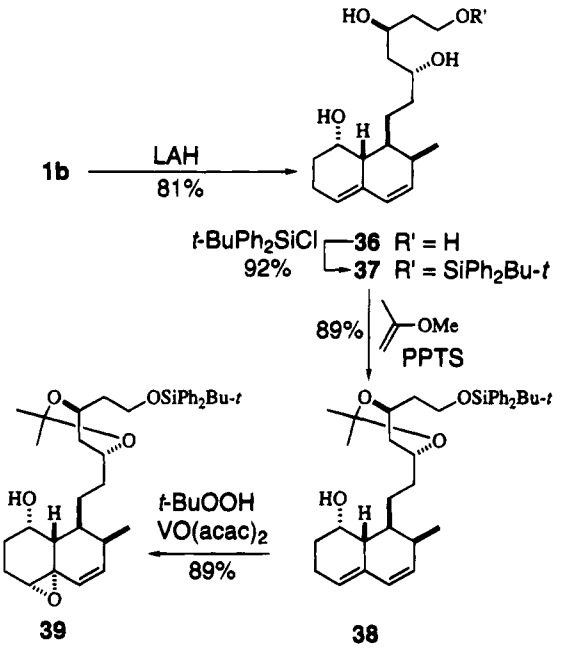
(36) *Cf.* Kayser, R. H.; Brault, M.; Pollack, R. M.; Bantia, S.; Sadoff, S. F. *J. Org. Chem.* **1983**, *48*, 4497. Hunter, D. H.; Patel, V.; Perry, R. A. *Can. J. Chem.* **1980**, *58*, 2271.

(37) The acid is provided by using a flask that has been washed in chromic acid, rinsed three to four times with tap water and three to four times with acetone, and dried in an oven (120 °C overnight).

Table 1. Hydrolysis Conditions for Compound 35

a AcOH–THF–H_2O	no reaction
b LiOH/MeOH–H_2O	starting material reacts, but derived keto acid or ketone not detected
c flash chromatography silica gel (48 h)	desired enone **2** formed
d TLC silica (from Merck plates Type Kieselgel 60 F_{254}) (4.5 h)	desired enone **2** formed
e Silicic acid (4 h)	no starting material remains. Polar product formed that does not react with CH_2N_2
f deposit with citric acid on flash chromatography silica (10 h)	more than half starting material remains
g dioxane, trace acid, reflux	desired enone **2** formed in 80% yield

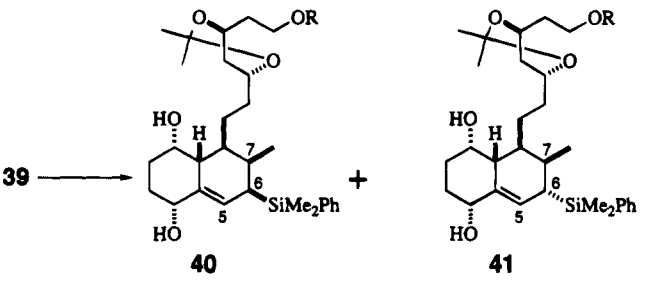
Scheme 8



ketal **38** in modest yield (67%), but use of 2-methoxypropene and pyridinium *p*-toluenesulfonate was much better (89%). Homoallylic epoxidation under our standard conditions took us to the olefinic epoxide **39**, whose stereochemistry is assigned on the basis of the oxidation mechanism.

Introduction of the dimethylphenylsilyl unit was the next step, and we expected some difficulties because of our experience in the mevinolin series. In that earlier work we had initially used a cuprate[18] made from copper(I) iodide and had found, besides **13**, a byproduct, which we believe (see below) to differ from **13** only in the stereochemistry at C(6). The ratio of the two products was highly variable from one experiment to the next. For these reasons we had tried the use of $PhMe_2SiLi$ itself and had found that only **13** was produced (80–91%). However, the problem had still not been solved because, when we tried to repeat the reaction several months later, the yield was poor (40–62%), although addition of lithium chloride usually, but not always, improved the result (50–85%). The outcome of these experiments was generally less satisfactory on a large (more than 100 mg) scale. When we came to use $PhMe_2SiLi$ in the compactin series, i.e., with epoxide **39**, a rather complex mixture was obtained, and we arbitrarily decided to examine the cuprate, but made this time from copper(I) cyanide.[19b] We were pleased to observe that cyanide-derived reagents give reproducible results and afford the isomeric silanes **40** and **41** in high overall yield (Scheme 9). The ratio of the isomers (established, without separation, by ^1H NMR

Scheme 9. R = $SiPh_2Bu$-*t*



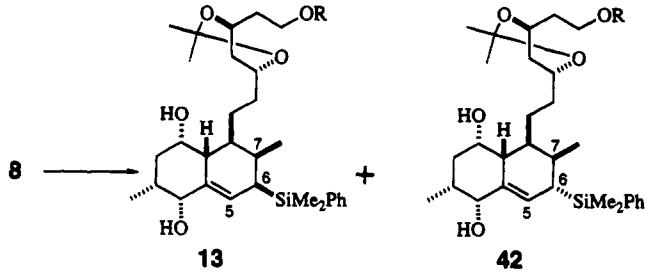
$PhMe_2SiLi$/CuCN	40 : 41	Total Yield
1:1	1 : 6	93%
2:1	11 : 1	95%
3:1	15 : 1	97%

measurements) depends on the composition of the cuprate, as shown in Scheme 9. Each of the three cuprates has been examined by NMR techniques[19b] but none has been used in preparative chemistry with olefinic epoxides, and the present results reveal some differences in behavior. Attempts to prepare crystals of **40** and **41** suitable for X-ray analysis were unsuccessful, but the stereochemistry was clear from the NMR data. The value for the coupling constant between the hydrogens on C(6) and C(7) indicates a *cis* relationship for those hydrogens in the case of **40** ($J_{6,7}$ = *ca.* 3.4 Hz) and a *trans* relationship for **41** ($J_{6,7}$ = *ca.* 0 Hz). The values of $J_{5,6}$ are 0 and 5.5 Hz for **40** and **41**, respectively. Examination of Dreiding models shows that the H-(6)–C(7)-H dihedral angle for **41** is likely to be close to 90°—a value entirely consistent with the small $J_{6,7}$.

It is unclear why the different reagents produce stereoisomeric products. Possibly, the reagents differ in aggregation and (hence) in steric bulk. Approach from the under face of the substrate would be less hindered unless the epoxide oxygen were complexed to the cuprate. In any event the results were very convenient for us, and we chose the 2:1 stoichiometry for the degradation, in part because we had formed the impression that isomer **40** is the more stable, and in part because that isomer seemed to correspond (TLC mobility and ^1H NMR pattern) to the material (**13**) we had obtained in the mevinolin series with $PhMe_2SiLi$. The 3:1 stoichiometry was not used because it is wasteful of the silicon component.

At this stage we thought we ought to try the new cuprate methods in the mevinolin series, and our results are shown in Scheme 10. Again, the experiments were easily reproducible and the stereochemistry of the products, assigned by analogy with the results from the compactin series (i.e., $J_{5,6}$ = 0 Hz for **13** and 4.5 Hz for

Scheme 10. R = $SiPh_2Bu$-*t*



13 42

$PhMe_2SiLi$/ CuCN	13 : 42	Total Yield
1:1	1 : 8	98%
2:1	7 : 1	97%
3:1	7 : 1	96%

42), could be controlled by a proper choice of reagent composition.

To return to the compactin series (see Scheme 11), we next followed our earlier procedure and carried out an allylic epoxidation (**40** → **43**). This proceeded smoothly, and the product was selectively silylated (**43** → **44**). Compound **44** is more sensitive to hydrolysis (loss of the trimethylsilyl group) than the corresponding mevinolin derivative (**27**, Scheme 6) and should be processed rapidly. Oxidation of the C(1) hydroxyl, previously done with pyridinium chlorochromate, initially proved troublesome, but we quickly found that use of *N*-methylmorpholine *N*-oxide and a catalytic amount of Pr_4NRuO_4[38] gave the required ketone **45** in almost quantitative yield.

From this point, our aim was to form the silyl enol ether **46** and to oxygenate it at C(2). The first of these two steps was tried by our original mevinolin procedure, which required warming the reaction mixture to room temperature in order to ensure complete reaction. However, in the present case this method led to decomposition of the desired compound (**46**) into an unidentified material. We found it best to keep the reaction mixture at −78 °C and to work it up after 25 min. Even at −78 °C some decomposition of **46** takes place, and it is necessary to monitor the progress of the reaction closely. A little starting material (**45**) always remains, but the yield is consistently *ca.* 80% on a 120-mg scale. We were not confident enough to try a large scale run, and fortunately, this problem could be bypassed, as described below. With some of the silyl enol ether **46** in hand, we examined its response to *m*-chloroperbenzoic acid and found that the two oxygenated products **47** and **48** are produced in a ratio that varies from run to run. In the mevinolin series the material corresponding to **48** was always by far the major product. The mixture of **47** and **48** could be selectively desilylated (**47** + **48** → **49**) in modest yield (73%).

Mainly because of the difficulties just described in making the silyl enol ether **46**, we sought an improved procedure and found it in treatment of the potassium enolate of ketone **45** with with 2-(benzenesulfonyl)-3-(*p*-nitrophenyl)oxaziridine (Davis' reagent) (Scheme 11).[25] The initial product of this α-oxygenation was not easily separable from the components derived from Davis' reagent, but brief treatment with Bu_4NF in the presence of AcOH served to give the diol **49**, which was easily separated and obtained in high yield.

(38) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

It would, of course, have been very convenient if **49** could be cleaved directly to keto acid **34**, but attempts to do this with $Pb(OAc)_4$, $NaIO_4$, HIO_4, or Jones reagent[39] were unsuccessful: we obtained complex mixtures or observed no reaction (for $NaIO_4$). Consequently, epoxide **49** was converted into the trihydroxy ketone **50** (see Scheme 12), but by a slightly different method from that employed in the mevinolin series (*cf.* Scheme 6). The use of acetic acid−methanol[30] had been unsuccessful with mevinolin, but here this mixture worked well.

Treatment of the trihydroxy ketone **50** with $Pb(OAc)_4$ in PhH−MeOH, followed by exposure to silicic acid, gave the desired enone **2** in poor yield, presumably by the same mechanism that operates in the mevinolin series. If a small sample of the crude product from the $Pb(OAc)_4$ experiment is left on a silica TLC plate (Merck silica gel 60 F-254) for 2 h and then recovered by extraction with dichloromethane, the enone **2** is again formed after the dichloromethane solution has stood for *ca.* 12 h. If the extract from the TLC plate is evaporated and refluxed for 2 h in dioxane the enone is also obtained, but the reaction is less clean. However, we found that trihydroxy ketone **50** can be degraded to enone **2** in one step by prolonged treatment (20−24 h) with $NaIO_4$ in aqueous methanol—conditions that did not work in the mevinolin series. The enone was isolated in 57% yield (after chromatographic purification) from an experiment run on 320 mg of the starting hydroxy ketone (see Scheme 12).

Conclusion

The procedure that had been developed for mevinolin can be applied with some modifications—that also raise the yield—to compactin, and the stage is now set to prepare semisynthetic analogues of the natural compounds. Our degradation of mevinolin involves 14 steps (7.6% overall yield); the corresponding sequence for compactin is almost the same length (13 steps) but gives a much better overall yield (16.3%). These results compare very favorably with the synthesis of enone **2** from (*S*)-malic acid, a process that required 25 steps and was accomplished in 0.37% yield.[2]

Experimental Section

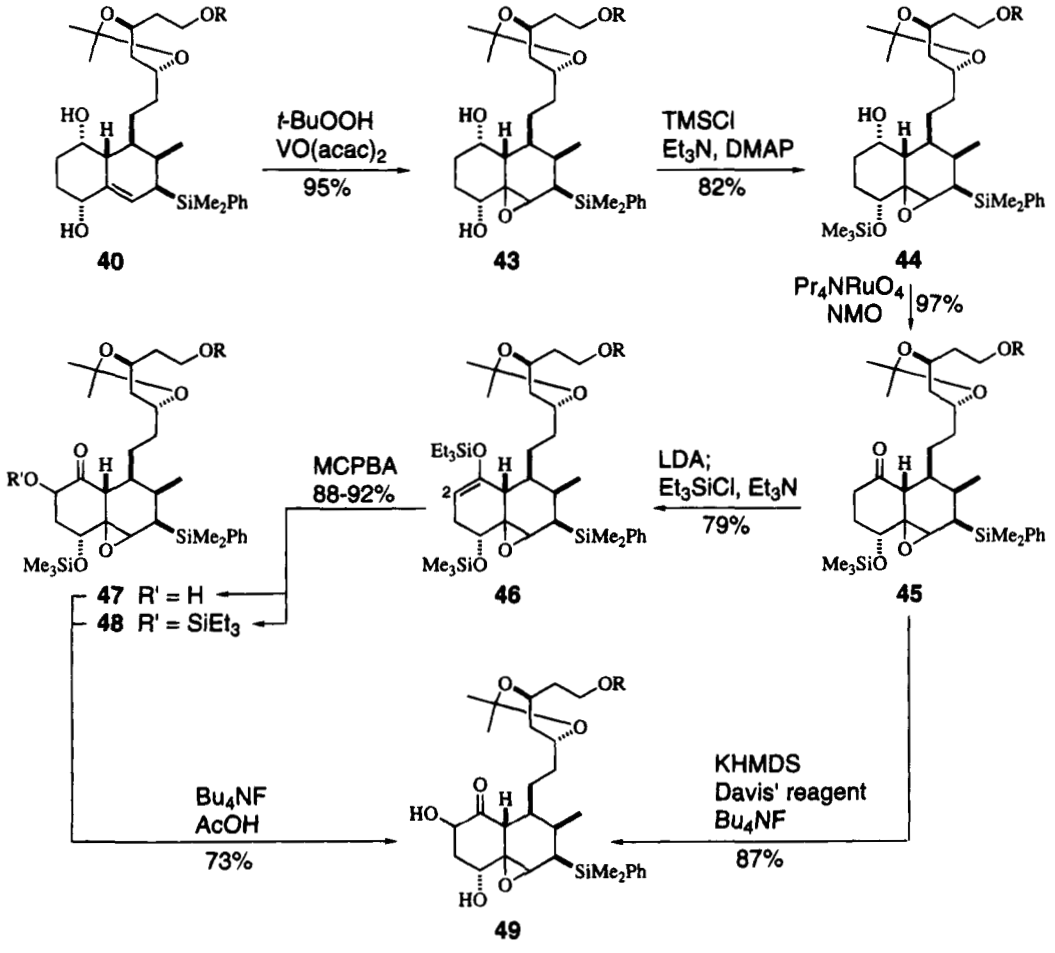
General. The same general procedures were followed as described previously,[40] and the following additional points apply: Microliter syringes were dried under oil-pump vacuum overnight. Small quantities of moisture-sensitive reagents were dispensed from stock solutions of such strength that the required aliquots could be measured conveniently with a microliter syringe (e.g., 10−20 μL amounts). Viscous starting materials were stored as stock solutions in benzene (which were kept frozen when not in use); aliquots were dispensed as required by syringe. Samples for combustion analysis, whether recrystallized or directly from flash chromatography (by simple evaporation of the solvent), were stored overnight under diffusion pump vacuum before being analyzed. *All evaporations of solvents were done at or below room temperature.*

Degradation of Mevinolin. [1*S*-[1α(3*R,5*S**),2α,6β,8β,-8aα]]-7-(1,2,6,7,8,8a-Hexahydro-8-hydroxy-2,6-dimethyl-1-naphthalenyl)-1,3,5-heptanetriol (5).** Mevinolin (1.0722 g, 2.65 mmol) in THF (10 mL) was added over 5 min to a

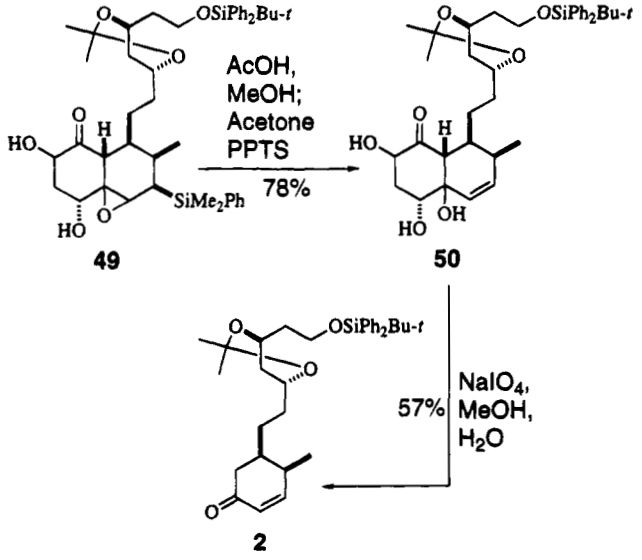
(39) Epifanio, R. de A.; Camargo, W.; Pinto, A. C. *Tetrahedron Lett.* **1988**, *29*, 6403.

(40) Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943.

Scheme 11. R = $SiPh_2Bu$-*t*



Scheme 12



stirred and cooled (−5 °C) suspension of $LiAlH_4$ (0.60 g, 15.8 mmol) in THF (50 mL). The mixture was stirred and allowed to attain room temperature (with the cold bath left in place) over 4–5 h. The mixture was then cooled to 0 °C, and water (1.8 mL) was added dropwise with stirring. Stirring was continued for 10 min, and aqueous NaOH (2 M, 1.8 mL) was then added. Stirring was continued for another 10 min, and then water (1.8 mL) was added as before. The cold bath was removed, and the mixture was stirred for an additional 20 min and filtered through a pad (2.5 × 3.5 cm) of Florisil. The pad was washed with acetone (120 mL). The combined filtrates were evaporated. The resulting white solid was dissolved in CH_2Cl_2 (150 mL), and the solution was washed with water (1 × 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using first 3:7 acetone–$CHCl_3$ and then 1:1 acetone–$CHCl_3$, gave **5** (722.2 mg, 84%) as a homogeneous (TLC, silica, 3:2 acetone–$CHCl_3$) white solid: IR ($CHCl_3$ cast) 3340 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 7.5 Hz, 3 H), 1.22–1.38 (m, 2 H), 1.40–1.76 (m, 8 H), 1.80–1.98 (m, 4 H), 2.12–2.20 (m, 1 H), 2.34–2.54 (m, 2 H), 2.62–2.74 (m, 1 H), 3.65–4.35 (m, 5 H), 5.52–5.58 (m, 1 H), 5.78 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.22, 20.07, 23.76, 27.45, 30.75, 33.93, 35.20, 35.61, 38.08, 38.84, 43.29, 61.67, 65.68, 71.46, 73.34, 128.58, 130.05, 131.63, 133.83; exact mass m/z calcd for $C_{19}H_{30}O_3$ $(M - H_2O)^+$ 306.2195, found 306.2183. For analysis a sample was recrystallized from acetone: mp 137.5–139.5 °C. Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.01; H, 9.98.

[1*S*-[1α(3*R,5*S**),2α,6β,8β,8aα]]-1-[[(1,1-Dimethylethyl)-diphenylsilyl]oxy]-7-(1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthalenyl)-3,5-heptanediol (6).** *tert*-Butyldiphenylsilyl chloride (0.64 mL, 2.45 mmol) was added to a stirred solution of tetraol **5** (722.2 mg, 2.23 mmol) and imidazole (378.9 mg, 5.57 mmol) in dry DMF (10 mL) at room temperature. Stirring was continued overnight, and the mixture was then diluted with EtOAc (100 mL), washed with water (1 × 30 mL), saturated aqueous NH_4Cl (1 × 30 mL), and brine (1 × 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using first 1:5 EtOAc–hexane and then 2:3 EtOAc–hexane, gave **6** (1.2656 g, 100%) as a homogeneous (TLC, silica, 2:3 EtOAc–hexane) white foam: IR ($CHCl_3$ cast) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.20 (d, J = 7.5 Hz, 3 H), 1.24–1.68 (m, 7 H), 1.70–1.82 (m, 1 H), 1.84–1.96 (m, 3 H), 1.98–2.18 (m, 1 H), 2.35–2.50 (m, 3 H), 3.78–3.88 (m, 2 H), 3.94–4.05 (m, 2 H), 4.10–4.24 (m, 2 H), 4.30–4.35 (m, 1 H), 5.52–5.58 (m, 1 H), 5.78 (dd, J = 9.5,

6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H), 7.35–7.50 (m, 6 H), 7.60–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.29, 19.07, 22.42, 23.54, 26.86, 27.69, 30.81, 33.67, 35.23, 35.44, 38.32, 38.92, 43.62, 63.23, 65.46, 71.00, 73.20, 127.88, 128.71, 129.94, 130.14, 131.78, 132.88, 133.64, 135.59; exact mass m/z calcd for $C_{35}H_{48}O_3Si$ (M − H_2O)$^+$ 544.3372, found 544.3382.

[1*S*-[1α,3α,7β,8β(4*S,6*R**),8aβ]]-8-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-1-naphthalenol (7).** p-Toluenesulfonic acid monohydrate (42 mg, 0.22 mmol) was added to a stirred solution of triol **6** (1.2656 g, 2.25 mmol) in dry acetone (20 mL). Stirring was continued overnight, and then solid $NaHCO_3$ (*ca.* 55 mg, 0.66 mmol) was added. The mixture was stirred for 10 min and then filtered. The solid was rinsed with dry acetone (*ca.* 5 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using first 1:19 EtOAc–hexane and then 1:9 EtOAc–hexane, gave alcohol **7** (1.1111 g, 82%) as a homogeneous (TLC, silica, 1:9 EtOAc–hexane) glass: IR ($CHCl_3$ cast) 3480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H), 1.12–1.50 [m, 14 H, including a doublet at δ 1.20 (J = 7.5 Hz, 3 H) and singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.54–1.85 (m, 5 H), 1.85–1.92 (m, 2 H), 2.08–2.18 (m, 1 H), 2.36–2.50 (m, 2 H), 3.64–3.74 (m, 1 H), 3.78–3.90 (m, 2 H), 4.08–4.18 (m, 1 H), 4.22–4.30 (m, 1 H), 5.52–5.57 (m, 1 H), 5.80 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H), 7.34–7.46 (m, 6 H), 7.64–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.07, 19.27, 19.90, 23.44, 23.70, 26.92, 27.62, 30.33, 30.87, 33.20, 35.67, 35.99, 37.59, 38.84, 39.42, 59.75, 65.38, 65.70, 68.71, 98.56, 127.64, 128.56, 129.60, 130.05, 131.61, 133.63, 134.00, 135.61; exact mass m/z calcd for $C_{37}H_{51}O_4Si$ (M − CH_3)$^+$ 587.3556, found 587.3538. Anal. Calcd for $C_{38}H_{54}O_4Si$: C, 75.70; H, 9.03. Found: C, 75.52; H, 8.98.

[1a*R*-[1aα,2β,4β,4aα,5α(4*R,6*S**),6α]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-1a,2,4,4a,5,6-hexahydro-2,6-dimethyl-3*H*-naphth[1,8a-*b*]oxiren-4-ol (8).** Homoallylic alcohol **7** (180 mg, 0.299 mmol) was added to a stirred mixture of vanadyl acetylacetonate (8 mg, 0.03 mmol) and $NaHCO_3$ (30 mg, 0.357 mmol) in dry benzene (8 mL). The mixture was stirred and cooled by a cold water bath (6 °C), and *tert*-butyl hydroperoxide (4.15 M in benzene, 86 μL, 0.359 mmol) was added dropwise (over *ca.* 1 min). The water bath was allowed to attain room temperature, and after 5 h, during which time the initial purple color faded to a pale yellow, the mixture was evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using first 1:19 EtOAc–hexane (the mixture containing 1% by volume of Et_3N) and then 1:9 EtOAc–hexane (the mixture containing 1% by volume Et_3N), gave epoxide **8** (152.3 mg, 82%) as a homogeneous (TLC, silica gel, 1:4 EtOAc–hexane) white foam: IR ($CHCl_3$ cast) 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.10–1.52 [m, 14 H, including a doublet at δ 1.25 (J = 7.5 Hz, 3 H) and singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.66–1.84 (m, 6 H), 2.05–2.14 (m, 1 H), 2.26–2.38 (m, 1 H), 2.48–2.55 (m, 1 H), 3.28 (dd, J = 3.5, 1.0 Hz, 1 H), 3.58 (d, J = 11.5 Hz, 1 H), 3.66–3.74 (m, 1 H), 3.78–3.90 (m, 2 H), 3.95–4.00 (m, 1 H), 4.10–4.18 (m, 1 H), 5.70 (d, J =9.5 Hz, 1 H), 6.16 (dd, J = 9.5, 5.5 Hz, 1 H), 7.35–7.46 (m, 6 H), 7.64–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.62, 19.22, 19.94, 20.33, 23.52, 25.83, 26.92, 30.36, 31.44, 33.72, 35.75, 36.15, 36.87, 37.54, 39.45, 59.77, 62.27, 65.69, 66.54, 67.17, 69.54, 98.47, 125.20, 127.67, 129.59, 134.05, 135.63, 142.78; exact mass m/z calcd for $C_{37}H_{51}O_5Si$ (M − CH_3)$^+$ 603.3506, found 603.3533; CIMS m/z calcd for $C_{38}H_{54}O_5Si$ 618, found 619 (M + 1)$^+$. Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.74; H, 8.79. Found: C, 73.27; H, 8.74.

Compound **8** is very sensitive to acids; failure to use $NaHCO_3$ and Et_3N, as described above, results in a low yield.

[1*R*-[1α,2α,4α,4aβ,5β(4*R,6*S**),6β,7β]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-7-(dimethylphenylsilyl)-1,2,3,4,4a,5,6,7-octahydro-2,6-dimethyl-1,4-naphthalenediol (13).** A stock solution of (dimethylphenylsilyl)lithium[19] was prepared by addition of lithium ribbon (111.3 mg, 16.0 mmol), cut into small pieces, to a solution of dimethylphenylsilyl chloride (0.76 mL, 4.58 mmol) in dry THF (15 mL) at 0 °C. The mixture was sonicated at 0 °C [Branson sonic bath, type B-12, 80W] for 30 min and then stirred at 0 °C overnight. An aliquot (1 mL) was added to water (10 mL), and the solution was titrated with 0.1 N hydrochloric acid using phenolphthalein as indicator. The average of several runs indicated that the solution of (dimethylphenylsilyl)lithium was 0.311 M. The organometallic was stored in a freezer (in an argon-filled vessel) and could be kept for at least 3 weeks.

(Dimethylphenylsilyl)lithium (0.311 M in THF, 2.35 mL, 0.729 mmol) was added dropwise (over *ca.* 5 min) to a stirred and cooled (−20 °C) solution of epoxide **8** (129.0 mg, 0.208 mmol) in THF (10 mL). Stirring was continued for 2 h (TLC control, silica, 1:3 EtOAc–hexane), and then water (0.2 mL) was added. The cold bath was removed, and the mixture was allowed to attain room temperature (*ca.* 30 min). The solution was filtered through a pad (2 × 3 cm) of a 2:1:1 mixture of Florisil, $NaHCO_3$ and $MgSO_4$. The pad was washed with THF (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using first 3:17 EtOAc–hexane (the mixture containing 1% by volume of Et_3N) and then 1:4 EtOAc–hexane (the mixture containing 1% by volume of Et_3N), gave **13** (144.5 mg, 89%) as a homogeneous (TLC, silica, 1:3 EtOAc–hexane) white foam: IR ($CHCl_3$ cast) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.34 (s, 6 H), 0.71 (d, J = 6.5 Hz, 3 H), 0.95–1.32 [m, 15 H, including a singlet at δ 1.05 (9 H)], 1.34–1.78 [m, 13 H, including singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.80–2.15 (m, 5 H), 2.28–2.36 (m, 1 H), 2.44–2.52 (m, 1 H), 3.64–3.80 (m, 3 H), 4.02–4.18 (m, 3 H), 5.86 (s, 1 H), 7.32–7.48 (m, 9 H), 7.50–7.58 (m, 2 H), 7.64–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −3.41, −3.31, 10.97, 19.21, 19.83, 25.36, 26.85, 29.70, 30.25, 31.43, 32.66, 34.07, 36.74, 37.35, 39.25, 39.36, 41.73, 59.71, 65.68, 66.14, 69.24, 74.19, 98.46, 125.89, 127.59, 127.82, 128.94, 129.55, 133.83, 133.94, 134.00, 135.55, 136.82, 138.69; CIMS m/z calcd for $C_{46}H_{66}O_5Si_2$ 754, found 755 (M + 1)$^+$. Anal. Calcd for $C_{46}H_{66}O_5Si_2$: C, 73.16; H, 8.81. Found: C, 73.36; H, 8.78.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,5β,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)octahydro-3,7-dimethyl-3*H*-naphth[1,8a-*b*]oxirene-5,8-diol (14).** Allylsilane **13** (129 mg, 0.186 mmol) was added to a stirred mixture of vanadyl acetylacetonate (5 mg, 0.0186 mmol) and $NaHCO_3$ (30 mg, 0.357 mmol) in dry benzene (6 mL). The mixture was stirred at room temperature and *tert*-butyl hydroperoxide (4.15 M in benzene, 86 μL, 0.359 mmol) was added dropwise (over *ca.* 1 min). Stirring was continued for 3 h, during which time the initial purple color faded to a pale yellow. The mixture was filtered through a pad (2 × 2 cm) of Florisil, and the pad was washed with EtOAc (10 mL). The combined filtrate was evaporated, and flash chromatography of the residue over silica gel (2 × 15 cm), using first 1:4 EtOAc–hexane and then 3:7 EtOAc–hexane, gave epoxide **14** (120.5 mg, 84%) as a homogeneous (TLC, silica gel, 1:3 EtOAc–hexane) white foam: IR ($CHCl_3$ cast) 3480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.38 (s, 3 H), 0.42 (s, 3 H), 0.74 (d, J = 6.5 Hz, 3 H), 1.06 (s, 9 H), 1.08–1.86 [m, 23 H, including a doublet at δ 1.18 (J = 6.5 Hz, 3 H), and singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 2.05–2.14 (m, 2 H), 2.26–2.38 (m, 1 H), 3.25 (s, 1 H), 3.66–3.82 (m, 4 H), 4.06–4.14 (m, 1 H), 4.16–4.22 (m, 1 H), 7.34–7.45 (m, 9 H), 7.52–7.58 (m, 2 H), 7.65–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ −3.18, −2.93, 12.41, 15.43, 19.19, 19.80, 24.38, 26.84, 28.35, 30.24, 31.32, 34.07, 34.27, 36.55, 37.34, 37.81, 39.34, 40.64, 49.74, 59.69, 62.73, 65.61, 67.49, 69.12, 69.44, 98.44, 127.57, 128.00, 129.21, 129.53, 133.75, 133.99, 135.54, 137.65; CIMS m/z calcd for $C_{46}H_{66}O_6Si_2$ 770, found 771 (M + 1)$^+$. Anal. Calcd for $C_{46}H_{66}O_6Si_2$: C, 71.64; H, 8.63. Found: C, 71.36; H, 8.74.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,5β,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)octahydro-3,7-dimethyl-8-[(trimethylsilyl)oxy]-3*H*-naphth[1,8a-*b*]oxiren-5-ol (27).** A 1:4 mixture of Et_3SiCl and Et_3N (0.20 mL, 0.370 mmol of Et_3SiCl) was added to a stirred and cooled (0 °C)

solution of epoxy silane **14** (158 mg, 0.205 mmol) and DMAP (10 mg, 0.0819 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 20 min (TLC control, silica, 1:4 EtOAc–hexane). Water (2.0 mL) was added at 0 °C, and stirring was continued for 10 min. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (2 × 5.0 mL). The combined aqueous layers were extracted with CH_2Cl_2 (1 × 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using first 1:9 EtOAc–hexane and then 15:85 EtOAc–hexane, gave alcohol **27** (156.8 mg, 91%) as a homogeneous (TLC, silica, 15:85 EtOAc–hexane) white foam: IR (CH_2Cl_2 cast) 3560 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 9 H), 0.39 (s, 3 H), 0.41 (s, 3 H), 0.71 (d, J = 7.0 Hz, 3 H), 1.07 (s, 9 H), 1.10–1.29 [m, 6 H, including a doublet at δ 1.24 (J = 7.8 Hz, 3 H)], 1.32–1.86 [m, 16 H, including singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 2.10–2.27 (m, 2 H), 2.50 (br doublet, J = 8.5 Hz, 1 H), 3.20 (s, 1 H), 3.63–3.88 (m, 3 H), 3.93 (d, J = 5.8 Hz, 1 H), 4.04–4.20 (m, 2 H), 7.32–7.47 (m, 9 H), 7.50–7.58 (m, 2 H), 7.63–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −2.91, −2.82, 0.13, 12.55, 16.09, 19.26, 19.89, 24.50, 26.91, 28.38, 30.32, 31.51, 34.47, 35.88, 36.57, 37.42, 38.19, 39.41, 41.61, 49.29, 59.75, 63.39, 65.67, 68.14, 69.34, 70.92, 98.51, 127.64, 127.66, 128.06, 129.25, 129.60, 133.91, 134.00, 134.05, 135.61, 137.70; CIMS m/z calcd for $C_{49}H_{74}O_6Si_3$ 842, found 860 (M + 18)$^+$.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-3,7-dimethyl-8-[(trimethylsilyl)oxy]-3H-naphth[1,8a-*b*]-oxiren-5(6*H*)-one (28).** Alcohol **27** (143.0 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL plus 2 × 2.0 mL as rinses) was added to a stirred mixture of pyridinium chlorochromate (73.1 mg, 0.339 mmol), NaOAc (56 mg, 0.678 mmol), and powdered 4 Å molecular sieves (75 mg) in CH_2Cl_2 (4.0 mL). The mixture was stirred for 22.5 h (TLC control, silica, 15:85 EtOAc–hexane), diluted with Et_2O (40.0 mL), and filtered through a pad (3 × 3 cm) of Florisil. The pad was washed with Et_2O (80 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 15:85 EtOAc–hexane, gave ketone **28** (109.5 mg, 77%) as a homogeneous (TLC, silica, 15:85 EtOAc–hexane) white foam: IR (CH_2Cl_2 cast) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 9 H), 0.37 (s, 3 H), 0.39 (s, 3 H), 0.72 (d, J = 6.5 Hz, 3 H), 0.98–1.12 [m, 13 H, including a doublet at δ 1.02 (J = 7.0 Hz, 3 H) and a singlet at δ 1.04 (9 H)], 1.17–1.47 [m, 12 H, including singlets at δ 1.33 (3 H) and δ 1.41 (3 H)], 1.62–1.85 (m, 4 H), 2.27–2.50 (m, 2 H), 2.58–2.78 (m, 2 H), 3.17 (s, 1 H), 3.62–3.76 (m, 2 H), 3.78–3.88 (m, 1 H), 4.03–4.13 (m, 1 H), 4.34 (d, J = 5.0 Hz, 1 H), 7.32–7.47 (m, 9 H), 7.49–7.55 (m, 2 H), 7.62–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −2.89, −2.86, 0.11, 12.69, 13.88, 19.26, 19.95, 25.47, 26.91, 27.75, 30.33, 31.37, 34.50, 35.69, 37.44, 38.44, 39.42, 47.53, 51.06, 51.14, 59.73, 65.48, 65.64, 69.53, 70.24, 98.45, 127.63, 127.67, 128.07, 129.28, 129.58, 133.92, 134.05, 135.61, 137.53, 206.88; FABMS m/z calcd for $C_{49}H_{72}O_6Si_3$ 840, found 841 (M + 1)$^+$ and 863 (M + 23)$^+$.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,7β,8β]]-[[4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)-1a,2,4,4a,7,8-hexahydro-3,7-dimethyl-5-[(triethylsilyl)oxy]-3*H*-naphth-[1,8a-*b*]oxiren-8-yl]oxy]trimethylsilane (29).** BuLi (1.6 M in hexane, 0.40 mL, 0.648 mmol) was added to a stirred and cooled (0 °C) solution of i-Pr_2NH (91.0 μL, 0.0648 mmol) in THF (6.0 mL). Stirring was continued for 10 min, and the solution was cooled to −78 °C. A solution of ketone **28** (109.1 mg, 0.130 mmol) in THF (4.0 mL plus 2 × 1.0 mL as rinses) was added dropwise (over *ca.* 5 min) with stirring, and after 30 min, 4:1 Et_3SiCl–Et_3N (81.0 μL, 0.389 mmol of Et_3SiCl) was added. Stirring was continued for 1 h, the cooling bath was removed, and the mixture was allowed to attain room temperature (*ca.* 40 min). Saturated aqueous $NaHCO_3$ (three drops) was added, and the mixture was stirred for 5 min. It was then filtered through a pad (2 × 2 cm) of a 2:1:1 mixture of Florisil, $NaHCO_3$, and $MgSO_4$. The pad was washed with EtOAc (20 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5:95 EtOAc–hexane, gave silyl enol ether **29** (125.0 mg, 100%) as a homogeneous (TLC, silica, 5:95 EtOAc–hexane) thick oil: IR (CH_2Cl_2 cast) 2955 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 9 H), 0.40 (s, 3 H), 0.41 (s, 3 H), 0.67–0.80 (m, 9 H), 0.88–1.24 [m, 25 H, including a singlet at δ 1.07 (9 H)], 1.32–1.65 [m, 10 H, including singlets at δ 1.37 (3 H) and δ 1.43 (3 H)], 1.66–1.76 (m, 1H), 1.78–1.89 (m, 1 H), 2.12–2.25 (m, 1 H), 2.48–2.62 (m, 2 H), 3.39 (s, 1 H), 3.65–3.77 (m, 2 H), 3.82–3.92 (m, 1), 4.07–4.18 [m, 2 H, including a doublet at δ 4.12 (J = 7.5 Hz, 1 H)], 4.72 (dd, J = 4.0, 1.5 Hz, 1 H), 7.32–7.47 (m, 9 H), 7.51–7.60 (m, 2 H), 7.65–7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ −2.79, −2.75, 0.08, 4.99, 6.82, 12.43, 16.64, 19.20, 19.76, 26.68, 26.81, 29.10, 30.26, 31.59, 34.82, 35.89, 37.53, 38.78, 39.40, 40.42, 52.89, 59.64, 64.40, 65.53, 68.87, 69.76, 98.35, 107.28, 127.59, 127.93, 129.05, 129.56, 133.90, 133.94, 135.54, 137.98, 151.10; FABMS m/z calcd for $C_{55}H_{86}O_6Si_4$ 954, found 955 (M + 1)$^+$.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-3,7-dimethyl-6-[(triethylsilyl)oxy]-8-[(trimethylsilyl)oxy]-3*H*-naphth[1,8a-*b*]oxiren-5(6*H*)-one (30) and [2*R*-[2α,3α,4α(4*R**,6*S**),4aα,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-6-hydroxy-3,7-dimethyl-8-[(trimethylsilyl)oxy]-3*H*-naphth[1,8a-*b*]oxiren-5(6*H*)-one (31).** A solution of silyl enol ether **29** (208.0 mg, 0.217 mmol) in EtOAc (3.0 mL plus 2 × 2.0 mL as rinses) was added quickly (over *ca.* 2 min) to a stirred and cooled (0 °C) mixture of *m*-chloroperbenzoic acid (80–85% w/w, 68.5 mg, *ca.* 0.326 mmol) and solid $NaHCO_3$ (55.0 mg, 0.652 mmol) in EtOAc (6.0 mL). Stirring was continued for 1.5 h at 0 °C (TLC control, silica, 1:9 EtOAc–hexane). Aqueous $NaHSO_3$ (10% w/v, 3.0 mL) was added at 0 °C, and stirring was continued for 5 min. The mixture was then diluted with EtOAc (10.0 mL), washed with water (3 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using successively 5:95 EtOAc–hexane, 1:9 EtOAc–hexane, and 1:4 EtOAc–hexane, gave ketone **30** (193.8 mg, 92%) and ketone **31** (10.8 mg, 6.0%), both as homogeneous (TLC, silica, 1:9 EtOAc–hexane) thick oils. Ketone **30** had: IR (CH_2Cl_2 cast) 1792 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 9 H), 0.37 (s, 3 H), 0.39 (s, 3 H), 0.60 (q, J = 8.0 Hz, 6 H), 0.72 (d, J = 7.0 Hz, 3 H), 0.89–0.99 [m, 12 H, including a doublet at δ 0.91 (J = 7.5 Hz, 3 H) and a triplet at δ 0.92 (J = 8.0 Hz, 9 H)], 1.00–1.13 [m, 10 H, including a singlet at δ 1.04 (9 H)], 1.17–1.50 [m, 11 H, including singlets at δ 1.31 (3 H) and δ 1.39 (3 H)], 1.55–1.75 (m, 3 H), 1.75–1.88 (m, 2 H), 2.23–2.36 (m, 1 H), 3.12 (s, 1 H), 3.42 (d, J = 11.0 Hz, 1 H), 3.62–3.75 (m, 2 H), 3.65–3.90 [m, 2 H, including a doublet at δ 3.87 (J = 3.0 Hz, 1 H)], 4.02–4.14 (m, 1 H), 4.63 (d, J = 5.0 Hz, 1 H), 7.31–7.47 (m, 9 H), 7.49–7.57 (m, 2 H), 7.63–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −2.90, −2.86, 0.05, 4.68, 6.73, 10.33, 12.59, 19.25, 19.85, 25.43, 26.89, 27.86, 30.29, 31.46, 34.21, 34.84, 37.41, 39.46, 45.34, 46.45, 51.18, 59.69, 65.61, 65.96, 66.77, 69.48, 80.90, 98.40, 127.62, 127.65, 128.05, 129.25, 129.57, 129.61, 133.91, 134.03, 135.60, 137.56, 207.82; FABMS m/z calcd for $C_{55}H_{86}O_7Si_4$ 970, found 971 (M + 1)$^+$ and 993 (M + 23)$^+$.

Ketone **31** had: ^1H NMR ($CDCl_3$, 300 MHz) (approximate integration) δ 0.12 (s, 9 H), 0.36 (s, 3 H), 0.38 (s, 3 H), 0.74 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.5 Hz, 3 H), 1.00–1.13 [m, 10 H, including a singlet at δ 1.03 (9 H)], 1.17–1.50 [m, 11 H, including singlets at δ 1.33 (3 H) and δ 1.40 (3 H)], 1.60–1.72 (m, 3 H), 1.75–1.85 (m, 2 H), 2.30–2.38 (m, 1 H), 2.45 (br s, 1 H), 3.15 (s, 1 H), 3.24 (d, J = 11.0 Hz, 1 H), 3.62–3.73 (m, 2 H), 3.77–3.85 (m, 1 H), 3.96–4.15 (m, 2 H,), 4.57 (d, J = 5.0 Hz, 1 H), 7.31–7.47 (m, 9 H), 7.49–7.57 (m, 2 H), 7.63–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −3.00, −2.88, 0.03, 10.99, 12.68, 19.19, 19.86, 25.29, 26.83, 28.11, 29.68, 29.97, 30.32, 31.39, 34.33, 35.48, 37.24, 39.32, 44.46, 45.61, 51.55,

59.64, 65.51, 65.58, 66.56, 69.38, 73.24, 79.72, 98.45, 127.58, 127.62, 128.03, 129.25, 129.56, 133.84, 133.99, 135.55, 137.40, 208.71.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,7β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-6,8-dihydroxy-3,7-dimethyl-3*H*-naphth[1,8a-*b*]oxiren-5(6*H*)-one (32).** Bu_4NF (1.0 M in THF, 0.73 mL, 0.728 mmol) was added to a stirred solution of ketone **30** (177.0 mg, 0.182 mmol) and AcOH (0.20 mL, 3.64 mmol) in THF (8.0 mL). Stirring was continued for 5 h (TLC control, silica, 4:6 EtOAc–hexane), and the solvents were evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using first 1:4 EtOAc–hexane and then 4:6 EtOAc–hexane, gave ketone **32** (122.2 mg, 85%) as a homogeneous (TLC, silica, 4:6 EtOAc–hexane) white foam: IR (CH_2Cl_2 cast) 3440, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 3 H), 0.41 (s, 3 H), 0.77 (d, J = 7.0 Hz. 3 H), 0.97–1.31 [m, 15 H, including a singlet at δ 1.04 (9 H) and a doublet at δ 1.07 (J = 7.0 Hz, 3 H)], 1.32–1.55 [m, 9 H, including singlets at δ 1.35 (3 H) and δ 1.42 (3 H)], 1.62–2.00 (m, 6 H), 2.27–2.39 (m, 1 H), 2.80–2.97 [m, 2 H, including a doublet at δ 2.92 (J = 10.5 Hz, 1 H)], 3.30 (s, 1 H), 3.66–3.89 (m, 3 H), 3.94 (d, J = 8.5 Hz, 1 H), 4.06–4.18 (m, 1 H), 4.29–4.38 (m, 1 H), 7.30–7.47 (m, 9 H), 7.48–7.57 (m, 2 H), 7.63–7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ −3.15, −2.95, 11.13, 12.48, 19.26, 19.91, 25.96, 26.90, 28.44, 30.32, 31.19, 34.43, 37.33, 37.37, 39.40, 40.51, 44.77, 54.05, 59.71, 62.67, 65.63, 66.14, 69.44, 76.47, 98.48, 127.63, 127.66, 128.14, 129.44, 129.59, 133.79, 133.98, 134.04, 135.60, 137.23, 210.19; FABMS m/z calcd for $C_{46}H_{64}O_7Si_2$ 784, found 785 $(M + 1)^+$.

[3*S*-[3α,4α,7β,8β(4*S,6*R**),8aβ]]-8-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-3,4,4a,7,8,8a-hexahydro-2,4,4a-trihydroxy-3,7-dimethyl-1(2*H*)-naphthalenone (33).** Pyridinium *p*-toluenesulfonate (15.0 mg, 0.0599 mmol) was added to a solution of ketone **32** (47.0 mg, 0.0599 mmol) in absolute EtOH (argon atmosphere). After *ca.* 12 h the EtOH was evaporated and the residue was dissolved in dry acetone (4.0 mL) and left for 5 h. The acetone was then evaporated, and flash chromatography of the residue over silica gel (1 × 15 cm), using first 1:4 EtOAc–hexane and then 1:1 EtOAc–hexane, gave ketone **33** (22.2 mg, 57%) as a homogeneous (TLC, silica, 1:1 EtOAc–hexane) white foam: IR (CH_2Cl_2 cast) 3440, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, J = 7.0 Hz, 3 H), 0.98–1.23 [m, 13 H, including a singlet at δ 1.04 (9 H) and a doublet at δ 1.15 (J = 7.0 Hz, 3 H)], 1.23–1.47 [m, 9 H, including singlets at δ 1.36 (3 H) and δ 1.43 (3 H)], 1.48–1.75 (m, 4 H), 2.10–2.60 (m, 5 H), 2.82 (d, J = 11.5 Hz, 1 H), 2.89–3.03 (m, 1 H), 3.63–4.03 [m, 5 H, including a doublet at δ 4.01 (J = 8.5 Hz, 1 H)], 4.05–4.20 (m, 1 H), 5.86 (dd, J = 10.0, 4.5 Hz, 1 H), 5.96 (dd, J = 10.0, 1.0 Hz, 1 H), 7.32–7.48 (m, 6 H), 7.62–7.73 (m 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 11.93, 13.34, 19.25, 19.93, 23.88, 26.90, 30.33, 31.15, 33.00, 34.11, 37.41, 39.41, 40.70, 47.14, 59.71, 65.64, 69.55, 71.47, 74.62, 76.64, 77.49, 98.47, 126.98, 127.63, 127.67, 129.58, 129.60, 133.98, 134.03, 135.60, 136.78, 211.51; exact mass m/z calcd for $C_{37}H_{51}O_7Si$ $(M - CH_3)^+$ 635.3404, found 635.3380; FABMS m/z calcd for $C_{38}H_{54}O_7Si$ 650, found 651 $(M + 1)^+$.

1-Methoxy-2-methyl-3-oxopropyl [1*R*-[1α,5β,6β-(4*R,6*S**)]]-6-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-2-oxo-3-cyclohexene-1-carboxylate (35).** $Pb(OAc)_4$ (50.0 mg, 0.113 mmol) was added to a stirred solution of hydroxy ketone **33** (35.0 mg, 0.0538 mmol) in 1:1 benzene–MeOH (6.0 mL) at room temperature. Stirring was continued for 1 h. The mixture was then diluted with CH_2Cl_2 (15 mL), washed with water (1 × 5 mL) and brine (1 × 10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:3 EtOAc–hexane, gave aldehyde **35** (24.0 mg, 66%) as a viscous oil: IR (CH_2Cl_2 cast) 1710, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.05–1.10 [3 H, two sets of doublets at δ 1.07 (J = 7.0 Hz) and δ 1.08 (J = 7.0 Hz)], 1.12–1.20 [3 H, two sets of doublets at δ 1.14 (J = 7.0 Hz) and δ 1.18 (J = 7.0 Hz)], 1.23–1.45 [m, 10 H, including two sets of two singlets (6 H, one set is at δ 1.33 and δ 1.40, and the other set is at δ 1.34 and δ 1.41], 1.47–1.75 (m, 4 H), 2.47–2.85 (m, 1 H), 2.63–2.73 (m, 1 H), 2.73–2.86 (m, 1 H), 3.30–3.40 (m, 1 H), 3.50 (s, 1.11 H), 3.56 (s, 1.89 H), 3.64–3.76 (m, 1 H), 3.72–3.87 (m, 2 H), 4.06–4.17 (m, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 6.05 (d, J = 5.0 Hz, 0.37 H), 6.13 (d, J = 4.0 Hz, 0.63 H), 7.04 (dd, J = 10.0, 6.0 Hz, 1 H), 7.34–7.47 (m, 6 H), 7.63–7.72 (m, 4 H), 9.75 (d, J = 1.2 Hz, 0.63 H), 9.79 (d, J = 1.5 Hz, 0.37 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 8.57, 9.19, 12.37, 19.26, 19.77, 25.68, 26.90, 29.76, 30.24, 30.95, 32.87, 37.20, 39.25, 39.33, 39.40, 50.39, 50.78, 56.90, 57.03, 57.60, 57.70, 59.66, 65.52, 68.64, 98.55, 99.23, 99.92, 127.04, 127.65, 129.62, 133.94, 134.01, 135.60, 156.26, 170.00, 170.25, 194.04, 200.96, 201.06; exact mass m/z calcd for $C_{34}H_{45}O_6Si$ $(M - C_5H_9O_2)^+$ 577.2992, found 577.2977; FABMS m/z calcd for $C_{39}H_{54}O_8Si$ 678, found 679 $(M + 1)^+$.

[4*R*-[4α,5α(4*R,6*S**)]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)-diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]-ethyl]-4-methyl-2-cyclohexen-1-one (2).** The flask used in this experiment must be washed with chromic acid and then rinsed with water (three to four times) and with acetone (three to four times) and finally oven dried (120°C) for 3–4 h or overnight.

A solution of aldehydes **35** (3.0 mg, 0.0042 mmol) in dry dioxane (2.0 mL) was refluxed for 10 h (TLC control, silica, 1:3 EtOAc–hexane). The solvent was evaporated, and flash chromatography of the residue over silica gel (4 × 0.5 cm, contained in a Pasteur pipet), using first 5:95 EtOAc–hexane and then 15:85 EtOAc–hexane, gave the desired enone **2** (2.0 mg, 84%) as a homogeneous (TLC, silica, 1:3 EtOAc–hexane) viscous oil: IR (CH_2Cl_2 cast) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.12 (q, J = 12.0 Hz, 1 H), 1.21–1.57 [m, 11 H, including singlets at δ 1.37 (3 H) and δ 1.43 (3 H)], 1.62–1.75 (m, 2 H), 2.06–2.20 (m, 1 H), 2.25–2.34 (m, 2 H), 2.47–2.61 (m, 1 H), 3.63–3.89 (m, 3 H), 4.06–4.17 (m, 1 H), 5.94 (d, J = 10.0 Hz, 1 H), 6.95 (dd, J = 10.0, 5.0 Hz, 1 H), 7.33–7.47 (m, 6 H), 7.62–7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.17, 19.27, 19.89, 26.91, 27.52, 30.32, 33.13, 33.64, 37.28, 37.46, 39.38, 39.93, 59.74, 65.72, 69.07, 98.52, 127.65, 128.18, 129.62, 134.01, 135.61, 155.99, 199.93; exact mass m/z calcd for $C_{32}H_{43}O_4Si$ $(M - CH_3)^+$ 519.2931, found 519.2938. Anal. Calcd for $C_{33}H_{46}O_4Si$: C, 74.11; H, 8.67. Found: C, 73.94; H, 8.79. The material was indistinguishable from an authentic sample made[2] by total synthesis.

Degradation of Compactin. [1S-[1α(3*R,5*S**),2α,8β,-8aα]]-7-(1,2,6,7,8,8a-Hexahydro-8-hydroxy-2-methyl-1-naphthalenyl)-1,3,5-heptanetriol (36).** Compactin (8.2825 g, 21.21 mmol) in THF (40 mL) was added over 10 min to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (3.22 g, 84.83 mmol) in THF (200 mL). Additional rinses of THF (3 × 10 mL) were used to dissolve and transfer the residual compactin. The cold bath was removed, and the mixture was stirred at room temperature for 9 h (TLC control, silica, 6:4 acetone–$CHCl_3$). The mixture was then cooled to 0 °C, and EtOAc (20 mL) was added. Stirring was continued for 30 min, and then water (3.5 mL) was added dropwise with stirring. After 15 min aqueous NaOH (15% w/v, 3.5 mL) was added. Stirring was continued for another 15 min, and then water (10.5 mL) was added as before. The cold bath was removed, the mixture was stirred for an additional 30 min, and then Celite (20 g) was added. Stirring was continued for 30 min, and the mixture was then filtered through a pad (9.5 × 6.5 cm) of Florisil. The pad was washed with MeOH (750 mL) until no more UV-active components were eluted (TLC). The combined filtrates were evaporated. The resulting white solid was dissolved in MeOH (150 mL), and flash silica gel (60 g) was added to the cloudy solution, which was then evaporated at room temperature. Flash chromatography of the residue over silica gel (5 × 15 cm), using first 3:7 acetone–$CHCl_3$ and then 7:3 acetone–$CHCl_3$, gave **36** (5.34 g, 81%) as a homogeneous (TLC, silica, 6:4 acetone–$CHCl_3$) white solid (mp 102–104 °C): IR ($CHCl_3$ cast) 3385 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, J = 6.0 Hz, 3 H), 1.20–2.08 (m, 11 H), 2.08–2.45 (m, 4 H), 2.83 [br s, 1 H (signal disappeared upon exchange with D_2O)], 3.41 [br s, 1 H (signal disappeared upon exchange with D_2O)], 3.70–3.90 (m, 2 H), 3.90–4.02 (m, 1 H), 4.03–4.17 (m,

1 H), 4.30 (s, 1 H), 4.38 [br s, 1 H (signal disappeared upon exchange with D_2O)], 4.60 (s, 1 H), 5.57 (s, 1 H), 5.72 (dd, J = 9.5, 6.0 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.12, 20.38, 21.95, 28.98, 30.76, 33.61, 35.30, 38.44, 38.64, 43.10, 60.86, 64.74, 71.08, 72.30, 123.69, 128.46, 133.19, 133.65; exact mass m/z calcd for $C_{18}H_{28}O_3$ $(M - H_2O)^+$ 292.2038, found 292.2041. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.70; H, 10.07.

[1*S*-[1α(3*R,5*S**),2α,8β,8aα]]-1-[[(1,1-Dimethylethyl)-diphenylsilyl]oxy]-7-(1,2,6,7,8,8a-hexahydro-8-hydroxy-2-methyl-1-naphthalenyl)-3,5-heptanediol (37).** *tert*-Butyldiphenylsilyl chloride (4.66 mL, 17.07 mmol) was added to a stirred and cooled (0 °C) solution of tetraol **36** (5.30 g, 17.07 mmol) and imidazole (2.91 g, 42.68 mmol) in dry DMF (30 mL). Stirring was continued for 1 h, and the mixture was then diluted with EtOAc (450 mL), washed with water (2 × 100 mL) and brine (1 × 100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 × 10 cm), using first 4:6 EtOAc–hexane and then 6:4 EtOAc–hexane, gave **37** (8.64 g, 92%) as a homogeneous (TLC, silica, 6:4 EtOAc–hexane) white foam: IR ($CHCl_3$ cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.23–2.23 (m, 13 H), 2.26–2.45 (m, 2 H), 2.71 (br s, 1 H), 3.77–3.91 (m, 2 H), 3.94–4.05 (m, 1 H), 4.05–4.20 (m, 2 H), 4.29 (s, 2 H), 5.57 (s, 1 H), 5.73 (dd, J = 9.5, 6.0 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H), 7.33–7.50 (m, 6 H), 7.60–7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.26, 19.07, 20.55, 22.20, 26.85, 28.97, 30.90, 33.65, 35.37, 38.51, 38.99, 43.55, 63.10, 64.57, 71.00, 72.99, 123.86, 127.85, 128.60, 129.91, 132.91, 132.99, 133.10, 133.81, 135.58; exact mass m/z calcd for $C_{34}H_{44}O_2Si$ $(M - 2\ H_2O)^+$ 512.3111, found 512.3111; FABMS m/z calcd for $C_{34}H_{48}O_4Si$ 548, found 549 $(M + 1)^+$. Anal. Calcd for $C_{34}H_{48}O_4Si$: C, 74.41; H, 8.82. Found: C, 74.32; H, 9.07.

[1*S*-[1α,7β,8β(4*S,6*R**),8aβ]]-8-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-1,2,3,7,8,8a-hexahydro-7-methyl-1-naphthalenol (38).** 2-Methoxypropene (2.75 mL, 28.64 mmol) was added dropwise (over *ca.* 2 min) to a stirred and cooled (0 °C) solution of triol **37** (7.86 g, 14.32 mmol) and pyridinium *p*-toluenesulfonate (360 mg, 1.43 mmol) in CH_2Cl_2 (200 mL). Stirring was continued for 10 min, and saturated aqueous $NaHCO_3$ (100 mL) was added. The mixture was diluted with CH_2Cl_2 (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and brine (1 × 150 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 × 10 cm), using 1:9 EtOAc–hexane, gave alcohol **38** (7.51 g, 89%) as a homogeneous (TLC, silica, 15:85 EtOAc–hexane) glass: IR ($CHCl_3$ cast) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 1.07 (s, 9 H), 1.09–1.52 [m, 10 H, including singlets at δ 1.38 (3 H) and δ 1.43 (3 H)], 1.52–1.88 (m, 7 H), 1.95–2.26 (m, 3 H), 2.26–2.48 (m, 2 H), 3.36–3.77 (m, 1 H), 3.78–3.91 (m, 2 H), 4.05–4.19 (m, 1 H), 4.25 (s, 1 H), 5.56 (s, 1 H), 5.74 (dd, J = 9.5, 7.0 Hz, 1 H), 5.95 (d, J = 9.5 Hz, 1 H), 7.30–7.47 (m, 6 H), 7.60–7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.01, 19.23, 19.89, 20.44, 23.22, 26.88, 29.04, 30.31, 30.90, 33.10, 36.05, 37.56, 38.92, 39.37, 59.70, 64.52, 65.66, 68.69, 98.52, 123.65, 127.61, 127.64, 128.43, 129.57, 133.28, 133.53, 133.94, 134.00, 135.50; exact mass m/z calcd for $C_{36}H_{49}O_4Si$ $(M - CH_3)^+$ 573.3400, found 573.3397. Anal. Calcd for $C_{37}H_{52}O_4Si$: C, 75.46; H, 8.90. Found: C, 75.19; H, 8.80.

[1a*R*-[1aα,4β,4aα,5α(4*R,6*S**),6α]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-1a,2,4,4a,5,6-hexahydro-6-methyl-3*H*-naphth[1,8a-*b*]oxiren-4-ol (39).** Homoallylic alcohol **38** (3.33 g, 5.65 mmol) was added to a stirred mixture of vanadyl acetylacetonate (150 mg, 0.565 mmol) and $NaHCO_3$ (666 mg) in dry benzene (70 mL). The mixture was stirred and cooled by a cold water bath (6 °C), and *tert*-butyl hydroperoxide (4.15 M in benzene, 1.90 mL, 7.92 mmol) was added dropwise (over *ca.* 5 min). The water bath was removed and the mixture allowed to attain room temperature. After 2 h, during which time the initial purple color faded to a pale yellow, the mixture was evaporated at *room temperature* (no higher!). Flash chromatography of the residue over silica gel (4 × 15 cm), using first 15:85 EtOAc–hexane (the mixture containing 1% by volume of Et_3N) and then 2:8 EtOAc–hexane (the mixture containing 1% by volume Et_3N), gave epoxide **39** (3.04 g, 89%) as a homogeneous (TLC, silica gel, 2:8 EtOAc–hexane) white foam, *which was stored frozen in benzene solution.* (In the flash chromatography the material should not be allowed to stay too long on the column. The column was packed dry and air bubbles were expelled using a portion of the first solvent system, which was then discarded. Our impression is that the compound is stable when pure and that the storage in frozen benzene may be unnecessary.): IR ($CHCl_3$ cast) 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, J = 7.5 Hz, 3 H), 1.06 (s, 9 H), 1.09–1.88 [m, 16 H, including singlets at δ 1.37 (3 H) and δ 1.41 (3 H)], 1.90–1.99 (m, 1 H), 2.01–2.25 (m, 3 H), 2.45–2.68 (m, 1 H), 3.30 (d, J = 4.0 Hz, 1 H), 3.53 (d, J = 11.5 Hz, 1 H), 3.64–3.73 (m, 1 H), 3.76–3.88 (m, 2 H), 3.94–4.02 (m, 1 H), 4.08–4.18 (m, 1 H), 5.17 (d, J = 9.5 Hz, 1 H), 6.13 (dd, J = 9.5, 5.0 Hz, 1 H), 7.33–7.45 (m, 6 H), 7.64–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.45, 19.18, 19.64, 19.85, 23.31, 26.83, 28.38, 29.65, 30.27, 31.45, 33.58, 35.81, 37.48, 39.34, 59.65, 61.94, 62.43, 65.60, 69.45, 98.38, 124.98, 127.55, 127.58, 129.50, 129.52, 133.92, 135.53, 142.79; exact mass m/z calcd for $C_{36}H_{49}O_5Si$ $(M - CH_3)^+$ 589.3349, found 589.3345. Anal. Calcd for $C_{37}H_{52}O_5Si$: C, 73.47; H, 8.66. Found: C, 73.76; H, 8.63.

[1*R*-[1α,4α,4aβ,5β(4*R,6*S**),6β,7β]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-7-(dimethylphenylsilyl)-1,2,3,4,4a,5,6,7-octahydro-6-methyl-1,4-naphthalenediol (40) and [1*R*-[1α,4α,4aβ,5β(4*R**,6*S**),6β,7α]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-7-(dimethylphenylsilyl)-1,2,3,4,4a,5,6,7-octahydro-6-methyl-1,4-naphthalenediol (41).** A stock solution of (dimethylphenylsilyl)lithium was prepared as described above (see preparation of **13**), except that the final stirring was done at −5 °C for 36 h. The solution of (dimethylphenylsilyl)lithium was 0.337 M.

In the reaction of epoxide **39** with the silyl cuprate the ratio of **40** to **41** depends on the ratio of (dimethylphenylsilyl)lithium to copper(I) cyanide. On the basis of ^1H NMR studies, the combined yields and the ratios of **40** to **41** for the different silyl cuprates are as follows:[19b] $PhMe_2SiCu(CN)Li$ (93%, 1:6), $(PhMe_2Si)_2Cu(CN)Li_2$ (95%, 11:1), $(PhMe_2Si)_3CuLi_2$ (97%, 15:1). It should be noted that if copper(I) iodide is used instead of copper(I) cyanide only a 1:1 mixture of diastereoisomers **40** and **41** is obtained. We decided to use compound **40** for the later operations, based on our impression that it is more stable than **41**. The preparations of the silyl cuprates were all carried out by the following procedure, varying *only* the ratio of (dimethylphenylsilyl)lithium to copper(I) cyanide.

(Dimethylphenylsilyl)lithium (0.337 M in THF, 9.97 mL, 3.36 mmol) was added dropwise (over *ca.* 6 min) to a stirred and cooled (−23 °C) solution of copper(I) cyanide (150.5 mg, 1.68 mmol) in THF (10 mL). Stirring was continued for 30 min, and the mixture was then cooled to −78 °C. After 10 min, epoxide **39** (406.5 mg, 0.672 mmol) in THF (3.0 mL plus 2 × 1.0 mL as rinses) was added dropwise (over *ca.* 3 min). Stirring was continued for 4 h, and then saturated aqueous NH_4Cl (2.0 mL) was added. The cold bath was removed, and the mixture was allowed to attain room temperature (*ca.* 30 min). The mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NH_4Cl (1 × 15 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using first 35:65 EtOAc–hexane (the mixture containing 1% by volume of Et_3N) and then 1:1 EtOAc–hexane (the mixture containing 1% by volume of Et_3N), gave **40** (460.1 mg, 92%) and **41** (21.9 mg, 4%), both as homogeneous (TLC, silica, 1:1 EtOAc–hexane) white foams. Compound **40** had: IR (CH_2Cl_2 cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 6 H), 0.68 (d, J = 8.0 Hz, 3 H), 0.98–1.85 [m, 29 H, including singlets at δ 1.07 (9 H), 1.34 (3 H) and δ 1.45 (3 H)], 1.85–2.00 (m, 3 H), 2.00–2.12 (m, 1 H), 3.66–3.90 (m, 3 H), 3.90–4.04 (m, 2 H), 4.07–4.19 (m, 1 H), 5.87 (s, 1 H), 7.30–7.48 (m, 9 H), 7.53–7.63 (m, 2 H), 7.63–7.76 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ −3.41, −3.32,

Table 2. 500 MHz NMR data for Stereoisomers 40 and 41

40	41
C(7)-Me δ 0.68 (d, J = 8.0 Hz)	C(7)-Me δ 0.80 (d, J = 7.0 Hz)
	C(8)-H δ 1.46–1.53 [m, 4 H (1 H is due to C(8)-H)]
	C(6)-H δ 1.62–1.74 [m, 4 H (1 H is due to C(6)-H)]
C(7)-H δ 2.00–2.12 (m)	C(7)-H δ 2.00–2.12 (m)
$J_{5,6}$ = 0 Hz	$J_{5,6}$ = 5.5 Hz

10.37, 19.45, 20.02, 26.09, 27.03, 29.23, 30.45, 30.65, 31.27, 31.69, 34.45, 37.74, 39.82, 40.34, 45.21, 60.19, 66.06, 66.96, 69.36, 71.65, 98.72, 118.35, 128.01, 128.14, 129.26, 129.96, 134.30, 134.36, 134.41, 135.92, 138.42, 139.26; exact mass *m/z* calcd for $C_{44}H_{61}O_5Si_2$ $(M - CH_3)^+$ 725.4058, found 725.4059, *m/z* calcd for $C_{45}H_{62}O_4Si_2$ $(M - H_2O)^+$ 722.4186, found 722.4168; FABMS *m/z* calcd for $C_{45}H_{64}O_5Si_2$ 740, found 741 $(M + 1)^+$. Anal. Calcd for $C_{45}H_{64}O_5Si_2$: C, 72.92; H, 8.70. Found: C, 73.02; H, 8.60.

Compound **41** had: IR (CH_2Cl_2 cast) 3440 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.34 (s, 3 H), 0.38 (s, 3 H), 0.80 (d, J = 7.0 Hz, 3 H), 1.00–1.25 [m, 12 H, including a singlet at δ 1.05 (9 H)], 1.26–1.60 [m, 13 H, including singlets at δ 1.31 (3 H) and δ 1.40 (3 H)], 1.62–1.90 (m, 7 H), 2.00–2.12 (m, 1 H), 3.64–3.77 (m, 2 H), 3.79–3.96 (m, 3 H), 4.05–4.18 (m, 1 H), 5.92 (d, J = 5.5 Hz, 1 H), 7.30–7.46 (m, 9 H), 7.49–7.56 (m, 2 H), 7.64–7.73 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ −3.25, −2.79, 15.34, 19.44, 20.11, 25.35, 27.02, 28.59, 30.44, 31.27, 34.24, 37.78, 39.83, 44.01, 60.02, 66.02, 69.21, 71.80, 98.70, 120.07, 127.99, 128.16, 129.43, 129.95, 134.38, 134.42, 134.50, 134.91, 135.93, 138.92; exact mass *m/z* calcd for $C_{44}H_{59}O_4Si_2$ $(M - CH_3 - 2\ H_2O)^+$ 707.3951, found 707.3941; FABMS *m/z* calcd for $C_{45}H_{64}O_5Si_2$ 740, found 741 $(M + 1)^+$. Anal. Calcd for $C_{45}H_{64}O_5Si_2$: C, 72.92; H, 8.70. Found: C, 72.78; H, 8.70.

The above experiment was done once on a comparatively large scale (using 5.7 g of starting material), and it gave **40** in 82% yield.[41]

The stereochemical assignment was made on the basis of ^1H NMR measurements run at 500 MHz. By decoupling measurements and a 2D ^1H–^1H correlation spectrum it was possible to identify a number of diagnostically significant signals in both isomers. The data are as shown in Table 2 (the numbering system is that used in the discussion, not the systematic numbering of the Experimental Section).

For **40**, $J_{5,6}$ = 0 Hz since the C(5)-H signal is a singlet. Irradiation at δ 0.68 [C(7)-Me] causes the multiplet due to the C(7)-H to collapse to a triplet (J = *ca.* 3.4 Hz); hence, $J_{6,7}$ = $J_{7,8}$ and, on this basis, we conclude that C(6)-H and C(8)-H adopt a similar angular position relative to C(7)-H. Consequently, the hydrogens on C(6), C(7), and C(8) are all *syn*. [The hydrogens on C(7) and C(8) are necessarily *syn* as that is their stereochemical relationship in compactin.]

For compound **41**, irradiation at δ 1.5 [C(8)-H] causes the signal due to C(7)-H to collapse to a quartet, and irradiation at δ 0.8 [C(7)-Me] changes the C(7)-H signal into a doublet. Hence, $J_{6,7}$ must be *ca.* zero.

[1*R*-[1α,2α,4α,4a*β*,5*β*(4*R,6*S**),6*β*,7*β*]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-7-(dimethylphenylsilyl)-1,2,3,4,4a,5,6,7-octahydro-2,6-dimethyl-1,4-naphthalenediol (13) and [1R-[1α,2α,4α,4a*β*,5*β*(4R*,6S*),6*β*,7α]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-7-(dimethylphenylsilyl)-1,2,3,4,4a,5,6,7-octahydro-2,6-dimethyl-1,4-naphthalenediol (42).** On the basis of ^1H-NMR studies, the combined yields and the ratios of **13** to **42** for the different silyl cuprates are as follows: $PhMe_2SiCu(CN)Li$ (98%, 1:8.0), $(PhMe_2Si)_2Cu(CN)Li_2$ (97%, 7:1), $(PhMe_2Si)_3CuLi_2$ (96%, 7.1:1). The preparations of the silyl cuprates were all carried out by the following procedure, varying *only* the ratio of (dimethylphenylsilyl)lithium to copper(I) cyanide.

(Dimethylphenylsilyl)lithium (0.337 M in THF, 0.74 mL, 0.249 mmol) was added dropwise (over *ca.* 70 s) to a stirred and cooled (−23 °C) solution of copper(I) cyanide (11.1 mg, 0.124 mmol) in THF (2.0 mL). Stirring was continued for 30 min, and the mixture was then cooled to −78 °C. After 10 min, epoxide **8** (30.0 mg, 0.0485 mmol) in THF (0.5 mL plus 0.5 mL as a rinse) was added dropwise (over *ca.* 1 min). Stirring was continued for 5 h, and then saturated aqueous NH_4Cl (0.5 mL) was added. The cold bath was removed, and the mixture was allowed to attain room temperature (*ca.* 30 min). The mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NH_4Cl (1 × 3 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using first 2:8 EtOAc–hexane (the mixture containing 1% by volume of Et_3N) and then 25:75 EtOAc–hexane (the mixture containing 1% by volume of Et_3N), gave a mixture of **13** and **42** (35.5 mg, 97%) as a pure (TLC, silica, 3:7 EtOAc–hexane), white foam. [The stereochemical assignments are made by analogy with the results for the compactin series.] ^1H-NMR analysis showed that the ratio of **13** to **42** is 7:1. Compound **13** (made by the present silyl cuprate method), was obtained pure by flash chromatography over silica gel, using 15:85 EtOAc–hexane and 2:8 EtOAc–hexane, and was identical (based on ^1H NMR, ^{13}C NMR and combustion analysis) with compound **13** as obtained previously by using just (dimethylphenylsilyl)lithium (i.e., not the cuprate). Compound **42** had: IR (CH_2Cl_2 cast) 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 3 H), 0.37 (s, 3 H), 0.81 (d, J = 6.5 Hz, 3 H), 1.00 [d, J = 6.5 Hz, 3 H), 1.03–1.17 (m, 12 H, including a singlet at δ 1.05 (9 H)], 1.32–1.46 [m, 9 H, including singlets at δ 1.37 (3 H) and δ 1.41 (3 H)], 1.47–1.98 [m, 9 H (1 H signal disappeared upon exchange with D_2O)], 2.03–2.15 (m, 1 H), 2.46 [br s or d depending on the concentration of the NMR sample, 1 H (signal disappeared upon exchange with D_2O)], 3.36–3.76 (m, 2 H), 3.80–3.90 (m, 1 H), 3.90–4.01 (m, 2 H), 4.07–4.18 (m, 1 H), 5.88 (d, J = 4.5 Hz, 1 H), 7.33–7.46 (m, 9 H), 7.48–7.55 (m, 2 H), 7.66–7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ −3.68, −3.49, 15.51, 16.88, 19.23, 19.93, 24.76, 26.87, 28.65, 30.30, 31.39, 33.75, 34.64, 36.12, 36.44, 37.39, 39.39, 41.03, 59.71, 62.58, 65.63, 66.02, 69.00, 74.37, 98.45, 127.62, 127.83, 129.19, 129.36, 129.58, 133.97, 134.19, 135.57, 138.27. A satisfactory mass spectrum could not be obtained. Anal. Calcd for $C_{46}H_{66}O_5Si_2$: C, 73.16; H, 8.81. Found: C, 73.24; H, 9.04.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,5*β*,8*β*]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)octahydro-3-methyl-3*H*-naphth[1,8a-*b*]oxirene-5,8-diol (43).** Allylsilane **40** (5.8213 g, 7.85 mmol) was added to a stirred mixture of vanadyl acetylacetonate (208 mg, 0.785 mmol) and $NaHCO_3$ (1.1640 g) in dry benzene (100 mL). The mixture was cooled by a cold water bath (8 °C), and *tert*-butyl hydroperoxide (4.15 M in benzene, 2.65 mL, 10.99 mmol) was added dropwise (over *ca.* 4 min). Stirring was continued for 6 h, during which time the initial purple color faded to a pale yellow. The mixture was evaporated, and flash chromatography of the residue over silica gel (5.5 × 15 cm), using first 3:7 EtOAc–hexane (the mixture containing 1% by volume Et_3N) and then 4:6 EtOAc–hexane (the mixture containing 1% by volume Et_3N) and finally 6:4 EtOAc–hexane (the mixture containing 1% by volume Et_3N), gave epoxide **43** (5.65 g, 95%) as a homogeneous (TLC, silica gel, 4:6 EtOAc–hexane) white foam. (In the flash chromatography the material should not be allowed to stay too long on the column. The column was packed dry, and air bubbles were expelled using a portion of the first solvent system, which was then discarded.): IR (CH_2Cl_2 cast) 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 3 H), 0.40 (s, 3 H), 0.72 (d, J = 7.0 Hz, 3 H), 0.77 (m, 1 H), 0.97–1.30 [m, 12 H, including a singlet at 1.04 (s, 9 H)], 1.30–1.60 [m, 12 H, including singlets at δ 1.35 (3 H) and δ 1.40 (3 H)], 1.60–1.89 (m, 5 H), 1.89–2.00 (m, 1 H), 2.00–2.11 (m, 1 H), 2.63 (d, J = 8.5 Hz, 1 H), 3.40 (s, 1 H), 3.62–3.89 (m, 4 H), 4.03–4.18 (m, 2 H), 7.30–7.45 (m, 9 H), 7.50–7.60 (m, 2 H), 7.62–7.73 (m, 4

(41) We thank Dr. Gil V. J. da Silva for this experiment.

H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ −3.17, −2.89, 12.42, 19.24, 19.86, 24.71, 26.88, 28.02, 28.24, 30.30, 31.40, 31.82, 34.49, 36.87, 37.36, 39.36, 40.73, 52.65, 59.68, 64.14, 65.63, 66.60, 68.28, 69.30, 98.48, 127.63, 127.65, 128.07, 129.30, 129.59, 133.78, 133.92, 133.99, 135.58, 137.62; exact mass m/z calcd for $C_{44}H_{61}O_6Si_2$ $(M - CH_3)^+$ 741.4006, found 741.4020, m/z calcd for $C_{45}H_{62}O_5Si_2$ $(M - H_2O)^+$ 738.4131, found 738.4139; FABMS m/z calcd for $C_{45}H_{64}O_6Si_2$ 756, found 779 $(M + 23)^+$. Anal. Calcd for $C_{45}H_{64}O_6Si_2$: C, 71.38; H, 8.52. Found: C, 71.16; H, 8.44.

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,5*β*,8*β*]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)octahydro-3-methyl-8-[(trimethylsilyl)oxy]-3*H*-naphth[1,8a-*b*]oxiren-5-ol (44).** A 1:4 mixture of Me_3SiCl–Et_3N (1.44 mL, 2.25 mmol of Me_3SiCl) was added to a stirred and cooled (0 °C) solution of epoxy silane **43** (1.135 g, 1.50 mmol) and DMAP (73.3 mg, 0.60 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 10 min (TLC control, silica, 2:8 EtOAc–hexane). Water (5.0 mL) was added at 0 °C, and stirring was continued for 10 min. The mixture was diluted with CH_2Cl_2 (30 mL), and the organic layer was washed with water (2 × 20.0 mL) and brine (1 x 30 mL), dried (Na_2SO_4), and evaporated. *Rapid* flash chromatography of the residue over silica gel [3 × 15 (or less) cm], using first 1:9 EtOAc–hexane (the mixture containing 1% by volume Et_3N) and then 15:85 EtOAc–hexane (the mixture containing 1% by volume Et_3N), gave alcohol **44** (1.013 g, 82%) as a homogeneous (TLC, silica, 15:85 EtOAc–hexane) white foam. (In the flash chromatography the material should not be allowed to stay too long on the column. The column was packed dry, and air bubbles were expelled using a portion of the first solvent system, which was then discarded.): IR (CH_2Cl_2 cast) 3540 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 9 H), 0.38 (s, 3 H), 0.39 (s, 3 H), 0.71 (d, J = 7.0 Hz, 3 H), 1.00–1.30 [m, 12 H, including a singlet at δ 1.04 (s, 9 H)], 1.32–1.58 [m, 12 H, including singlets at δ 1.35 (3 H) and δ 1.41 (3 H)], 1.63–2.10 (m, 7 H), 2.94 (d, J = 9.6 Hz, 1 H), 3.32 (s, 1 H), 3.63–3.87 (m, 4 H), 4.05–4.15 (m, 2 H), 7.30–7.44 (m, 9 H), 7.51–7.57 (m, 2 H), 7.62–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ −3.23, −2.94, 0.01, 12.38, 19.16, 19.80, 24.60, 26.81, 27.69, 28.11, 30.23, 31.56, 32.04, 34.48, 36.73, 37.32, 39.30, 41.03, 52.46, 59.62, 64.42, 65.56, 66.93, 69.26, 69.31, 98.39, 127.55, 127.57, 127.98, 129.19, 129.51, 133.75, 133.86, 133.92, 135.51, 137.48; FABMS m/z calcd for $C_{48}H_{72}O_6Si_3$ 828, found 851 $(M + 23)^+$. Anal. Calcd for $C_{48}H_{72}O_6Si_3$: C, 69.52; H, 8.75. Found: C, 69.60; H, 8.62.

The above experiment was done once on a comparatively large scale (using 7.9 g of starting material), and it gave **44** in 84% yield.[41]

[2*R*-[2α,3α,4α(4*R,6*S**),4aα,8*β*]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-3-methyl-8-[(trimethylsilyl)oxy]-3*H*-naphth[1,8a-*b*]oxiren-5(6*H*)-one (45).** Pr_4NRuO_4 (89 mg, 0.253 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of alcohol **44** (2.1000 g, 2.53 mmol), powdered 4 Å molecular sieves (1.2660 g, 500 mg/mmol), and 4-methylmorpholine *N*-oxide (593 mg, 5.06 mmol) in CH_2Cl_2 (100 mL). The cold bath was removed, and the mixture was stirred under argon for 6 h. The mixture (no evaporation of solvent) was then filtered through silica gel (4.5 × 10 cm), and the pad was washed with 3:7 EtOAc–hexanes (the mixture containing 1% by volume Et_3N). Evaporation of the solvents gave ketone **45** (2.04 g, 97%) as a homogeneous (TLC, silica, 2:8 EtOAc–hexane) white solid (mp 138–140 °C). (In the second silica gel chromatography the material should not be allowed to stay too long on the column. The column was packed dry, and air bubbles were expelled using a portion of the solvent system, which was then discarded.): IR (CH_2Cl_2 cast) 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 9 H), 0.38 (s, 3 H), 0.40 (s, 3 H), 0.73 (d, J = 6.9 Hz, 3 H), 0.98–1.10 [m, 10 H, including a singlet at δ 1.03 (9 H)], 1.20–1.47 [m, 12 H, including singlets at δ 1.28 (3 H) and δ 1.39 (3 H)], 1.63–1.72 (m, 3 H), 1.77–1.92 (m, 2 H), 2.03–2.10 (m, 1 H), 2.33–2.56 (m, 3 H), 3.30 (s, 1 H), 3.65–3.75 (m, 2 H), 3.78–3.85 (m, 1 H), 4.04–4.13 (m, 1 H), 4.24 (dd, J = 11.0, 5.0,Hz, 1 H), 7.33–7.46 (m, 9 H), 7.53–7.58 (m, 2 H), 7.64–7.70 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ −3.07, −2.79, -.0.01, 12.63, 19.44, 20.03, 26.10, 27.02, 28.23, 30.44, 32.12, 32.24, 34.72, 36.35, 37.71, 39.63, 40.15, 51.05, 60.17, 65.96, 66.45, 68.99, 69.62, 98.65, 127.99, 128.02, 128.36, 129.58, 129.94, 129.96, 134.25, 134.40, 134.43, 135.93, 138.09, 207.35; FABMS m/z calcd for $C_{48}H_{70}O_6Si_3$ 826, found 827 $(M + 1)^+$. Anal. Calcd for $C_{48}H_{70}O_6Si_3$: C, 69.68; H, 8.53. Found: C, 69.40; H, 8.66.

The above experiment was done once on a comparatively large scale (using 9.0 g of starting material), and it gave **45** in 98% yield.[41]

Conversion of 45 Directly into [2*R*-[2α,3α,4α(4*R,6*S**),4aα,8*β*]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-6,8-dihydroxy-3-methyl-3*H*-naphth[1,8a-*b*]oxiren-5(6*H*)-one (49).** Ketone **45** (2.3595 g, 2.85 mmol) in THF (10 mL plus 2 × 3.0 mL as rinses) was added dropwise (over *ca.* 5 min) to a stirred and cooled (−78 °C) solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 8.56 mL, 4.28 mmol) in THF (80 mL). Stirring was continued for 30 min, and then 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine[25] (1.1180 g, 4.28 mmol) in THF (14 mL) was added over *ca.* 5 min. Stirring was continued for 30 min, and then AcOH (3.26 mL, 57 mmol) was added. The cold bath was removed, and the mixture was allowed to attain room temperature (30–40 min). Bu_4NF (1.0 M in THF, 11.5 mL, 11.4 mmol) was added, and after 30 min (TLC control, silica, 3:7 EtOAc–hexane), the mixture was concentrated at room temperature to 5–10 mL. The residue was dissolved in EtOAc (150 mL), washed with saturated aqueous NH_4Cl (1 × 50 mL), water (2 × 50 mL), and brine (1 × 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 15 cm), using first 1:9 EtOAc–CH_2Cl_2, then 1:4 EtOAc–CH_2Cl_2, and finally 35:65 EtOAc–CH_2Cl_2, gave ketone **49** (1.9120 g, 87%) as a homogeneous (TLC, silica, 4:6 EtOAc–hexane) white foam. This material was identical with the compound obtained by a the earlier route.

The above experiment was done once on a comparatively large scale (using 8.6 g of starting material), and it gave **49** in 87% yield.[41]

[4*R*-[4α,7*β*,8*β*(4*R,6*S**),8aβ]]-8-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-3,4,4a,7,8,8a-hexahydro-2,4,4a-trihydroxy-7-methyl-1(2*H*)-naphthalenone (50).** AcOH (3.4 mL) was added to a stirred solution of epoxy silane **49** (849 mg, 1.101 mmol) in MeOH (20.6 mL). The resulting solution was stirred for 11 h. The solvents were evaporated, and as much as possible of the AcOH was removed at room temperature, using a Büchi rotovapor with a dry ice–acetone condenser. The residue (still smelling faintly of AcOH) was dissolved in dry acetone (20 mL). Pyridinium *p*-toluenesulfonate (83 mg, 0.33 mmol) was then added, and the mixture was stirred for 7.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 × 15 cm), using first 4:6 EtOAc–hexane, then 6:4 EtOAc–hexane, and finally 8:2 EtOAc–hexane, gave ketone **50** (549 mg, 78%) as a homogeneous (TLC, silica, 6:4 EtOAc–hexane) slightly yellow foam: IR (CH_2Cl_2 cast) 3410, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, J = 7.1 Hz, 3 H), 1.04 (s, 9 H), 1.08–1.61 [m, 11 H, including singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 1.65–1.76 (m, 2 H), 1.84 [s, 1 H (signal disappeared upon exchange with D_2O)], 1.90–2.18 [m, 4 H (1 H signal disappeared upon exchange with D_2O)], 2.26–2.34 (m, 1 H), 2.36–2.45 (m, 1 H), 2.53 [br s, 1 H (signal disappeared upon exchange with D_2O)], 2.76 (d, J = 12.0 Hz, 1 H), 3.69 (dt, J = 10.5, 5.0 Hz, 1 H), 3.74–3.88 (m, 2 H), 4.02–4.17 (m, 3 H), 5.92 (dd, J = 10.0, 5.0 Hz, 1 H), 5.99 (dd, J = 10.0, 1.0 Hz, 1 H), 7.35–7.48 (m, 6 H), 7.62–7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 13.73, 19.43, 20.09, 23.59, 27.02, 30.43, 30.93, 31.09, 34.04, 37.64, 39.04, 39.78, 46.65, 60.12, 65.96, 69.72, 70.30, 75.18, 76.35, 98.79, 126.25, 128.02, 129.96, 134.34, 134.39, 135.69, 135.92, 137.78, 210.24; exact mass m/z calcd for $C_{36}H_{49}O_7Si$ $(M - CH_3)^+$ 621.3247, found 621.3237. Anal. Calcd for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23. Found: C, 69.78; H, 8.34.

The above experiment was done once on a comparatively large scale (using 3.2 g of starting material) and it gave **50** in 73% yield.[41]

Conversion of 50 into 2 Using Sodium Periodate. $NaIO_4$ (543 mg, 2.542 mmol) was added to a stirred solution of triol **50** (323.8 mg, 0.508 mmol) in 3:1 MeOH–water. The resulting suspension was stirred at room temperature for 23 h. MeOH (40 mL) was added, and the mixture was filtered through a pad (2 × 2.5 cm) of Florisil. The pad was washed with MeOH (40 mL). The combined filtrates were evaporated, water being removed at room temperature using a Büchi rotovapor with a dry ice–acetone condenser. The residue was dissolved in acetone (40 mL), dried (Na_2SO_4), and evaporated. The resulting mixture was dissolved in dry acetone, pyridinium *p*-toluenesulfonate was added, and the mixture was stirred for 2.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.0 × 15 cm), using first 1:9 EtOAc–hexane and then 2:8 EtOAc–hexane, gave enone **2** (156.5 mg, 57%) as a homogeneous (TLC, silica, 3:7 EtOAc–hexane) viscous oil. The material was indistinguishable [^{1}H NMR, ^{13}C NMR, TLC (silica, 3:7 EtOAc–hexane)] from an authentic sample made[2] by total synthesis and with the sample made as described above by degradation of natural mevinolin. [We did not prove that the reketalization conditions were necessary, but our impression is that by applying that procedure the TLC spot corresponding to the desired product becomes stronger.]

The above experiment was done once on a comparatively large scale (using 2.0 g of starting material), and it gave **2** in 52% yield.[41]

Conversion of 50 into 2 Using Lead Tetraacetate. $Pb(OAc)_4$ (42.4 mg, 0.096 mmol) was added to a stirred solution of trihydroxy ketone **50** (29 mg, 0.045 mmol) in 1:1 benzene–MeOH (2.0 mL). After 5 min, aqueous $NaHSO_3$ (10% w/v, 2 drops) was added, and the mixture was diluted with CH_2Cl_2 (5 mL) and dried (Na_2SO_4). The solution was filtered through a short column (1 × 5 cm) of silica gel. The pad was washed with EtOAc (30 mL), and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (1.5 mL), and silicic acid (450 mg) was added. The resulting slurry was stirred under argon for 13 h, and direct chromatography (no evaporation of solvent) over silica gel (1 × 8 cm), using first 15:85 EtOAc–hexane and then 3:7 EtOAc–hexane, gave enone **2** (5.7 mg, 23%) as a homogeneous (TLC, silica, 3:7 EtOAc–hexane) viscous oil. The material was indistinguishable [^{1}H NMR, ^{13}C NMR, TLC (silica, 3:7 EtOAc–hexane)] from an authentic sample made[2] by total synthesis and with the sample made as described above by degradation of natural mevinolin.

Acknowledgment. We thank Sankyo Co. (Tokyo) and the Natural Sciences and Engineering Research Council of Canada for financial support. Our samples of mevinolin and compactin were kindly provided by Sankyo Co. We thank Dr. Gil V. J. da Silva for the large scale experiments indicated.

Supplementary Material Available: NMR spectra for compounds that were not analyzed and experimental procedures for **12**, **15–21**, **23–26**, and **46–49** (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941863B