Total Synthesis of Both (+)-Compactin and (+)-Mevinolin. A General Strategy Based on the Use of a Special Titanium Reagent for Dicarbonyl Coupling

Derrick L. J. Clive,*[,1] K. S. Keshava Murthy, Andrew G. H. Wee, J. Siva Prasad, Gil V. J. da Silva, Marek Majewski, Paul C. Anderson, Claire F. Evans,[2] Richard D. Haugen,[2] Louis D. Heerze, and James R. Barrie[2]

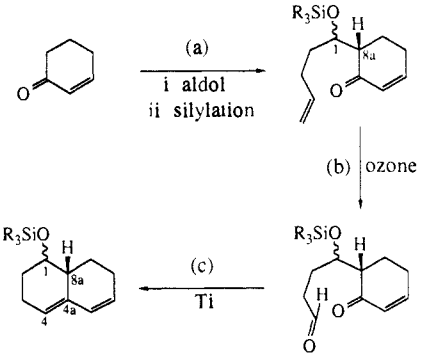
Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received June 26, 1989*

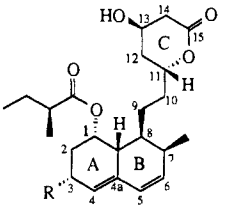
Abstract: A strategy is described for stereocontrolled synthesis of hypocholesterolemic compounds, (+)-compactin and (+)-mevinolin, by an approach (Scheme II) based on **6**, **7**, 4-pentenal (**9a**), and (*R*)-3-methyl-4-pentenal (**9b**). The Evans asymmetric Diels–Alder technique was used (Scheme III) to prepare **13**, which was converted into the cis ester **17**. Chain extension, iodolactonization, and elimination of HI then gave optically pure **6**. The homochiral epoxide **24**, made (Scheme IV) from (*S*)-malic acid, was converted into **25** and then, by iodocarbonation, hydrolysis, and ketalization, into the iodo ketal **7**. Evans asymmetric alkylation was used (Scheme V) to prepare **9b**. Ozonolysis, ketalization, and reduction ($LiAlH_4$) of **28** gave **31**, which was transformed by Swern oxidation, Wittig methylenation, and acid hydrolysis into **9b**. An optically pure intermediate (**8**), common to both syntheses, was assembled (Scheme VI) by alkylation of **6** with **7**, reduction to a mixture of lactols, allylic oxidation, and decarbonylation. Aldol condensation (Scheme VII) of **8** with 4-pentenal, triethylsilylation, and ozonolysis gave the enone aldehydes **39**, epimeric at C-1. A modified McMurry reaction requiring an excess of a reagent prepared from C_8K and $TiCl_3$ (2:1 molar ratio) in DME, produced the ethers **40**, which were converted into (+)-compactin by appropriate modification of the oxygen functionality. The strategy is general and was applied with minor modifications (Scheme VIII) to the synthesis of (+)-mevinolin.

Introduction[3]

The fungal metabolites (+)-compactin (**1a**)[4,5] and (+)-mevinolin (**1b**)[6] are the best-known of a small group[5b,7] of natural products that have attracted much attention on account of their usefulness as metabolic probes for studying cholesterol homeostasis[8] and their potential value in the treatment of hypercholesterolemic individuals. The primary characteristic of the two compounds is their ability[9] to lower blood levels of cholesterol, specifically plasma low density lipoprotein (LDL)[10] cholesterol, in man. This is a significant property because high blood levels of LDL cholesterol are associated[11] with coronary atherosclerosis,[12] a major[13] cause

Scheme I





(1) Dedication: To the memory of my father.

(2) Summer Undergraduate Research Student.

(3) Preliminary communication: 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.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914.

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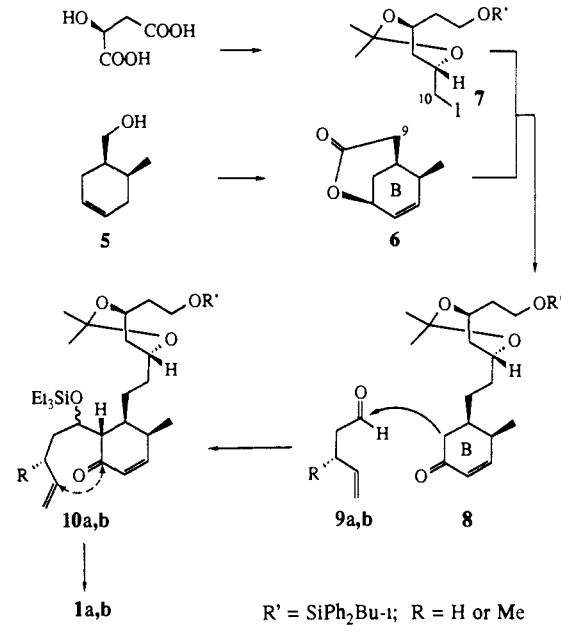
of death in Western industrialized societies.

The development of drugs[14] to treat hypercholesterolemia is, of course, regarded as a very important problem. Compactin and mevinolin represent lead compounds for one approach that is being investigated intensively. The compounds are reversible, competitive inhibitors[6a,15] of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), the enzyme involved[16] in the committing step of cholesterol biosynthesis. A significant portion of total body cholesterol is generated by endogenous synthesis,[8b] mainly in the liver, and the ability to perturb the biosynthetic process has turned out to be helpful in lowering blood cholesterol, although the mechanism is indirect. The biologically active forms of compactin and mevinolin are the corresponding hydroxy acids[6a,15a] resulting from hydrolysis of the lactone substructure. A cell responds[8a,16d,17] in a variety of ways to inhibition of HMG CoA reductase. More of the enzyme is synthesized, so that steroid production continues but, in addition, an increased number of LDL receptors is formed on the cell surface, and it is these additional receptors that are directly responsible for mediating the observed reduction in plasma LDL levels of the steroid. The supply of cholesterol to a cell is not seriously impaired; the essential difference is that it now occurs at a lower plasma LDL level.[8a,9a,18]

Our selection of compactin and the stereochemically more intricate mevinolin as targets for total synthesis was based in part on the fact that synthetic contributions might prove to be of value in the design of new inhibitors for HMG CoA reductase. We were aware that mevinolin **1b** is several times as powerful[6a] in its biochemical action as compactin **1a**, and, since the only difference between the two substances is the presence in one of a methyl group to replace a hydrogen, it was clear that the biological activity can be improved by modifications to ring A. There was little else in the way of structure-activity correlations available to us at the time,[19] and so we wanted to devise a synthesis that was sufficiently general to afford a variety of analogues without extensive modification of the approach for each compound. Our primary aim was to make analogues differing in the substitution pattern of ring A because we knew that such alterations could be useful.

Development of the Synthetic Plan. No total synthesis had been published in this area when we began, and none was to appear until we were already committed to an approach which, from our point of view, appeared sufficiently promising to warrant completion. Accordingly, our plan was not influenced by any need to avoid similarity with other routes, and the method we used turned out to be quite different from those developed elsewhere.[20-22]

Scheme II



We considered first the means by which ring A could be built onto the ring B portion. The presence of the C-1[4] oxygen function and the oxidation level of C-4a was very suggestive to us of an aldol condensation, and that thought led to the question of how to generate the 4,4a double bond. Posed in this way, the problem immediately brought to mind the idea of using an intramolecular McMurry reaction, and so we decided to attach the left-hand portion of ring A by the aldol and McMurry processes outlined in Scheme I. This was the only plan we considered seriously, because our commitment to it was reinforced by model studies which quickly suggested it would work. However, the preliminary experiments failed to indicate the difficulties we would encounter when the titanium-induced coupling (Scheme I, step c) was applied to sensitive and highly oxygenated materials. In retrospect, this situation was fortunate because it prompted us to develop a modification of the classical McMurry reagent, with the result that the annulation process used here (see Scheme I) represents a general method of ring construction.[23]

Our preliminary experiments[24] involved testing the above plan and dealt also with the synthesis[25] of the lactone portion (ring C)

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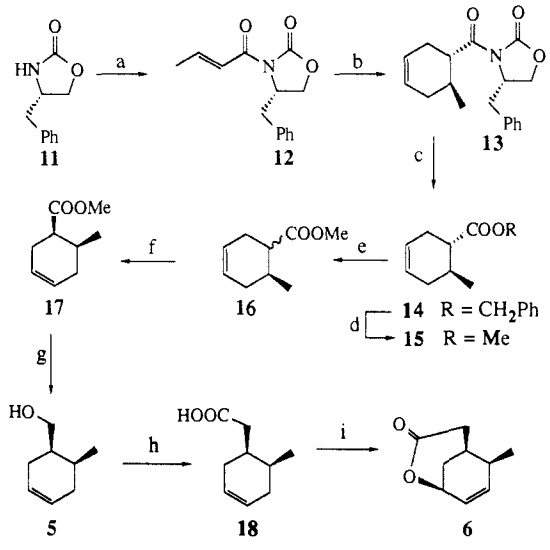
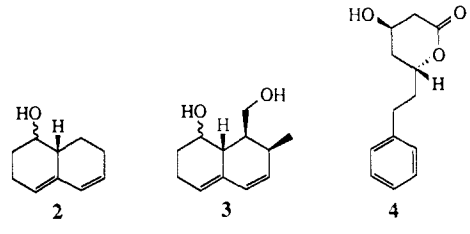
Scheme III[a]



[a](a) BuLi, THF, −78 °C; crotonyl chloride, −78 °C, 30 min; 79%; (b) butadiene, Et_2AlCl (3.15 mol per mol **12**), −10 °C, 16 h; 56%; (c) BnOLi, THF, 0 °C, 5 h; 87%; (d) MeOLi, MeOH–CH_2Cl_2, reflux, 46 h; 87%; (e) LDA, THF, −78 °C; add **15**, −78 °C, 45 min; AcOH, −78 °C; 90%; (f) spinning band distillation; (g) $LiAlH_4$, THF, reflux, 15 h; 99%; (h) (1) TsCl, CH_2Cl_2, pyridine, DMAP (catalyst), room temperature, 24 h; 90%; (2) NaCN, DMSO, 75 °C, 10 h; 92%; (3) aqueous NaOH, reflux, 24 h; 92%; (i) (1) NaI, 18-crown-6, CH_2Cl_2, MCPBA, ca. 0 °C, 1.25 h; 91%; (2) DBU, PhMe, reflux, 2 h; 79%.

and the problem of joining it to the other segments. This work which is described in the Supplementary Material, led to racemic **2** and **3** and to the optically pure lactone **4**.



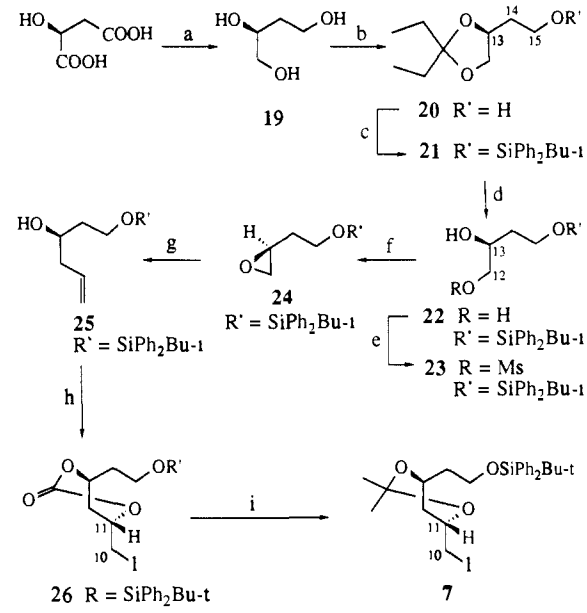
These experiments were carefully designed to explore a stereocontrolled and flexible approach to compactin and mevinolin with the serious intention of subsequently making both compounds. Our experience in preparing the model compounds served to define a plan in the form shown by Scheme II, and this is the manner in which the natural products were actually assembled.

The approach is built around the homochiral bicyclic lactone **6**, to which were attached the atoms destined to become the lactone subunit. This was achieved by alkylating **6** at C-9 with iodide **7**. Several more operations then gave the enone **8**—a key intermediate since it represents, in suitably protected form, the BC ring system of both natural products. The aldehydes **9a,b** provided the left-hand portion of ring A, and this unit was attached to enone **8** by aldol condensation (Scheme II, Robinson curved arrow). Then, at a slightly later stage (see **10a,b**), ozonolysis of the pendant olefin and intramolecular dicarbonyl coupling (Scheme II, dotted arrow), using a special titanium reagent, served to complete the diene chromophore.

Construction of the Homochiral Subunits. Preparation of the Ring B Precursor 6. The bicyclic lactone **6** was made from the homochiral cyclohexenemethanol **5** (Scheme II), which was constructed by two independent routes. The first involved elaboration of D-glucal triacetate and has already been described[26] in detail; however, for large scale work we used the Evans asymmetric Diels–Alder technique[27] (Scheme III). The chiral auxiliary **11**,[28] easily prepared in optically pure[29] form, was converted into **12** by acylation with the acid chloride of (*E*)-crotonic acid.[27] Diels–Alder reaction with butadiene then yielded the adduct **13**[30] from which the auxiliary was displaced (**13** → **14**) by the action of lithium benzyloxide. As we needed the methyl ester, we did try to displace the heterocyclic unit directly with lithium methoxide, but the reaction does not work. In contrast, ester exchange (**14** → **15**) with lithium methoxide proceeds smoothly, and, from this point, deprotonation and reprotonation generated a mixture of epimeric methyl esters **16** (cis:trans, 65:35). The desired cis isomer **17** was isolated by spinning band distillation.[31] Reduction gave alcohol **5**, and this was transformed into the bicylic lactone **6** by the reactions summarized in Scheme III. The process involved converting the hydroxyl function of **5** into a leaving group by tosylation followed by displacement with cyanide ion. Hydrolysis of the resulting homologated nitrile then took the sequence as far as acid **18**. Finally, iodolactonization[32] and elimination of hydrogen halide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) completed our synthesis of the bicyclic lactone **6**.

It should be explained that in the Diels–Alder reaction, use of a (*Z*)-crotonyl unit in the dienophile (cf. **12**) would be expected to produce a cis disubstituted cyclohexene directly and so remove

Scheme IV[a]



[a](a) BH_3–Me_2S, $(MeO)_3B$, THF, −5 °C, 51 h; ca. 100%; (b) 3,3-dimethoxypentane, CH_2Cl_2, $TsOH·H_2O$, room temperature, overnight; 71%; (c) *t*-$BuPh_2SiCl$, CH_2Cl_2, Et_3N, DMAP (catalyst), room temperature, 18 h; 96%; (d) 80% v/v aqueous AcOH, 50 °C, 4 h; 84%; (e) MsCl, CH_2Cl_2, pyridine, −30 °C, 3 h; room temperature, 40 h; 68%; (f) $BnMe_3N^+OH^-$, MeOH–ether, room temperature, 30 min; 91%; (g) CH_2=CHLi, CuCN, THF, −60 °C; add **24**, −10 °C, 4 h; 96%; (h) BuLi, THF, 0 °C; pass in CO_2 at 0 °C, 1 h; I_2, 0 °C, 15 min, room temperature 2 h; 74%; (i) (1) dry acetone, $TsOH·H_2O$ (0.61 mol per mol **26**), room temperature, 91 h; (2) *t*-$BuPh_2SiCl$, CH_2Cl_2, Et_3N, DMAP, room temperature, 2 h; 67% overall.

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(29) *rac*-**11** was prepared from *dl*-phenylalanine. The Mosher imides formed from *rac*-**11** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride were examined by ^1H NMR (200 MHz). The two diastereoisomers were readily distinguished, and examination of the Mosher imide from optically active **11** showed it to be optically pure.

(30) Formation of **13** proceeds with de >95%. Pure **13** is easily isolated.

(31) In principle, the trans isomer and the mixed fractions, which together amount to ca. 36% of the initial still pot charge, can be recycled. The desired cis isomer amounts to ca. 50% of the initial still pot charge.

(32) Srebnik, M.; Mechoulam, R. *J. Chem. Soc., Chem. Commun.* **1984**, 1070.

the need for epimerization[33] (cf. **16** → **17**). This approach was not tried because we suspected from other experiments that the *Z* geometry would not be preserved during cycloaddition, and, indeed, the unsuitability of (*Z*)-crotonyl systems was subsequently reported.[27b]

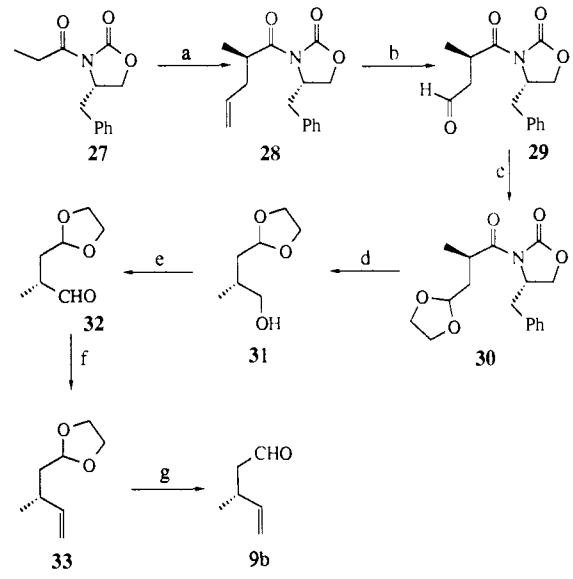
Attempts to gain access to optically pure ester **17** by chemical resolution starting from appropriate racemic precursors, such as the racemic acid[34] corresponding to **15** (see Scheme III), were not successful, and, in any case, only an unusually efficient resolution would have been acceptable.[35]

Preparation of the Ring C Precursor 7. The iodide **7**, which would provide the constituent atoms of the ring C lactone of both natural products, was prepared by reactions summarized in Scheme IV. The method is very similar to that used earlier in our model study,[25,36] but a number of significant improvements were introduced and a more felicitous choice of protecting group was made for the primary hydroxyl function. In this series of compounds we also verified the optical purity for the key intermediate, **24**; in the model work[25,36] optical purity was taken for granted, based on the mode of synthesis.[37]

Reduction[37b] of (*S*)-malic acid to (*S*)-1,2,4-butanetriol (**19**) was accomplished with borane–methyl sulfide complex. This method is far more convenient, at least in our experience, than other procedures that have been reported,[38] and it provides the triol in almost quantitative yield. Ketalization by a literature procedure[39] then gave alcohol **20**. The use of diethyl ketone here, instead of acetone, which is the obvious choice, is based on the fact that with the former ketone the product is not contaminated by the isomeric ketal involving the oxygens on C-13 and C-15.[40] The primary hydroxyl of **20** was protected (**20** → **21**) by silylation, and the ketal was then hydrolyzed (**21** → **22**) under conditions that do not disturb the silicon substituent. Selective mesylation afforded the primary mesylate **23**, and this led to optically pure epoxide **24** when treated with base. We were careful to ensure that our mesylate was free of isomeric material carrying the methanesulfonyloxy group on C-13 and the hydroxyl at C-12, as such a compound would generate the enantiomer of epoxide **24**. Fortunately, the secondary mesylate, which was formed to some extent, could be removed by chromatography, but, as a precaution, we proved that our epoxide was optically pure by the simple method described in the Supplementary Material. The remaining carbons for the ring C subunit were introduced with dilithium (cyano)divinylcuprate (**24** → **25**). At this stage, iodocarbonation[41] (**25** → **26**), followed by acid-catalyzed hydrolysis in acetone and ketalization in the same mixture (**26** → **7**), completed our preparation of the subunit destined to become the lactone ring. The product of iodocarbonation contained (^{1}H NMR) 11% of the C-11 epimer, but the iodo ketal **7** was pure. The conditions needed for hydrolysis and ketalization of **26** caused some loss of the silicon-protecting group; however, this problem was easily corrected by resilylating the crude product. The desired material was obtained in 67% overall yield from the carbonate.

Preparation of the Ring A Precursors, Aldehydes 9a and 9b. Aldehyde **9a** is a known[42] compound, but the methyl-substituted analogue **9b** is new and was made (Scheme V) by Evans asymmetric alkylation.[43] The chiral auxiliary **11**, recovered in 84% yield from the third stage of the Diels–Alder process, was acylated[44] with propionyl chloride (Scheme V) and then allylated[43,45] in the standard way (**27** → **28**). Ozonolysis of the terminal double bond gave aldehyde **29**, and this compound was ketalized (**29** → **30**) and reduced to the alcohol **31**. For control purposes it was now necessary to convert a racemic specimen of alcohol **31** into its Mosher ester by treatment with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The ^{1}H NMR spectrum of the derivative showed the convenient feature of cleanly separated signals from the individual diastereoisomers. Consequently, it was easy to prove that our optically active alcohol **31** was optically pure. Swern oxidation of that alcohol furnished the optically pure aldehyde **32**. Again, as a control measure, we reduced the aldehyde back to the alcohol, but there had been no loss of optical integrity. Wittig reaction (**32** → **33**) followed by mild acid hydrolysis completed the route to the ring A aldehyde **9b**.

Scheme V[a]



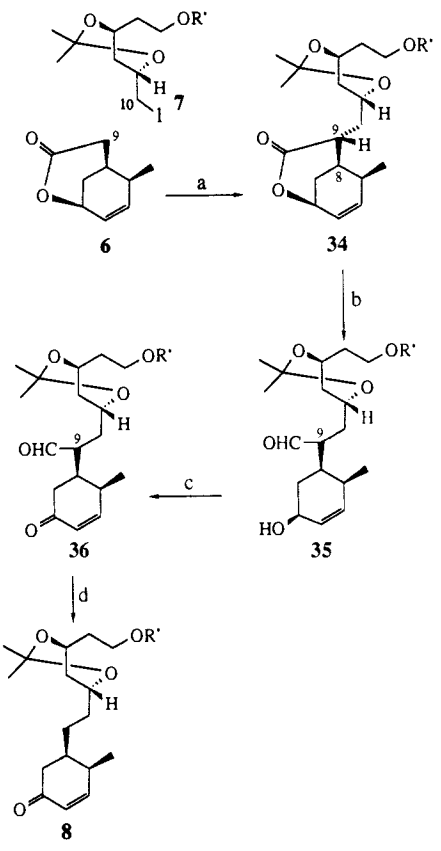
[a] (a) LDA, THF, −78 °C; add allyl bromide, −78 °C to room temperature over 2.5 h; 74%; (b) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, 30 min; room temperature 2 h; 96%; (c) $HOCH_2CH_2OH$, $TsOH·H_2O$, PhH, reflux, 4 Å molecular sieves in Soxhlet, 4.5 h; 87%; (d) $LiAlH_4$, THF, room temperature, 30 min; 96%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add **31**, −78 °C, 20 min; Et_3N, −78 °C, 20 min; warm to room temperature over 10 min; 90%; (f) $Ph_3P{=}CH_2$, THF, 0 °C, 35 min; 72%; (g) Et_2O–10% aqueous HCl, room temperature, 23 h; 69%.

The Wittig reaction in the above synthesis is a step where epimerization could occur, and so we degraded olefin **33**, by ozonolysis and reduction, back to alcohol **31**. The alcohol now contained 6% of its epimer, but we have reason to believe[46] that the impurity was introduced in the degradation sequence during silica gel chromatography of aldehyde **32**, and we recommend that such aldehydes be chromatographed only over Florisil.

Compounds **6**, **7**, **9a**, and **9b** represent all the required subunits; they were assembled into (+)-compactin and (+)-mevinolin as summarized in Schemes VI, VII, and VIII.

(33) The enantiomer of **12** would, of course, have to be used.
(34) Green, N.; Beroza, M. *J. Org. Chem.* **1959**, *24*, 761.
(35) Cf.: Sonnet, P. E.; McGovern, T. P.; Cunningham, R. T. *J. Org. Chem.* **1984**, *49*, 4639. The route (Scheme III) to optically pure **17** also constitutes a synthesis of the active isomer of trimedlure, a synthetic attractant for the Mediterranean fruit fly.
(36) See Supplementary Material.
(37) Reduction of (*S*)-malic acid is known to give optically pure triol. Cf.: (a) Tandon, V. K.; van Leusen, A. M.; Wynberg, H. *J. Org. Chem.* **1983**, *48*, 2767. (b) Hanessian, S.; Ugolini, A.; Dubé, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.
(38) For a list of methods, see literature cited in refs 37a and 37b.
(39) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2834.
(40) (a) Cf.: Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883. (b) Presumably, increased nonbonded interactions further destabilize the six-membered ketal with respect to the five-membered isomer when *diethyl* ketone is used.
(41) (a) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626. (b) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013.
(42) E.g.: Price, C. C.; Balsley, R. B. *J. Org. Chem.* **1966**, *31*, 3406.
(43) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(44) (a) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.
(45) Formation of **28** proceeds with de = 92%. Pure **28** is easily isolated by flash chromatography.
(46) (a) As described below, aldol reaction of **8** with **9b** gave a *single* alcohol which, after protection and ozonolytic cleavage of the pendant olefin, contained 6.3% of an isomer corresponding to epimerization at C-3. This type of problem was met in an acute form during synthesis of a mevinolin analogue. There, the epimerization occurred during chromatography over silica gel and could be avoided by using Florisil instead. (b) We presume that in making **32** from **31** we had done the silica gel flash chromatography more rapidly than when we isolated **32** from ozonolysis of **33**.

Scheme VI[a,b]



[a] (a) LDA (2 mol per mol 6), THF, −78 °C, 1.25 h; add 7 in THF–HMPA (2:1), −78 °C; room temperature 12 h; 77% after correction for recovered 6 (54%); (b) DIBAL, CH_2Cl_2, −78° C, 1.5 h; 90%; (c) MnO_2, AcONa, $CHCl_3$, room temperature, 69 h; 78%; (d) $(Ph_3P)_3RhCl$, PhMe–MeCN (8:1), reflux, 2.5 h; 50%. [b] R′ = $SiPh_2Bu$-*t*.

Preparation of the Protected BC Ring System of (+)-Compactin and (+)-Mevinolin. Preparation of the BC ring unit by the chemical operations shown in Scheme VI was based closely on our model studies.[36] Treatment of the bicyclic lactone **6** with 2 equiv of lithium diisopropylamide followed by addition of iodide **7** and hexamethylphosphoric triamide gave the coupled product **34** in 77% yield (after correction for recovered **6**). The product was a single isomer with the stereochemistry at C-9 tentatively assigned as shown, on the basis of the proton coupling constant $J_{8,9}$ (ca. 3 Hz). The recovered lactone was, of course, used in subsequent runs. Exposure of the coupled material to diisobutylaluminum hydride at a low temperature produced a lactol–hydroxy aldehyde equilibrium mixture for which only the open hydroxy aldehyde form (**35**) is shown in Scheme VI. The equilibrium between the two isomers is a mobile one, and allylic oxidation of the mixture afforded the keto aldehyde **36** in almost 80% yield as a single substance, whose stereochemistry at C-9 was not determined. The last step was the decarbonylation of **36**. The traditional reagent for this purpose is Wilkinson's catalyst,[47] and this was the only one we examined. The reaction is best done in a refluxing mixture of toluene and benzonitrile with an optimum reaction time of 2.5 h. Under these conditions the required enone **8** was isolable in 50% yield. This is a key intermediate in our synthesis because it represents, in suitably protected form, the complete BC ring system of both natural products, (+)-compactin and (+)-mevinolin.

Synthesis of (+)-Compactin. For the synthesis of compactin (see Scheme VII), the ketone **8** was deprotonated kinetically and condensed with 4-pentenal to produce **37**, as a mixture of isomers, epimeric at C-1, with the required threo[48] material constituting about 75% of the total. Analysis of the ^1H NMR spectrum of **37** indicated that the stereochemistry at C-8a was as shown, the aldehyde having approached from the less hindered face of the enolate generated from **8**. The fact that two epimers are obtained does not matter as the stereochemistry at C-1 is easily adjusted at a later stage. Triethylsilylation (**37** → **38**) followed by ozonolysis in dichloromethane and reductive workup with triphenylphosphine yielded the keto aldehydes **39**. The ozonolysis should be stopped about 10% short of completion for best results. This endpoint can be difficult to judge, especially on a small scale, and in some experiments we stopped the reaction too early. We generally prefer to use the special apparatus described by M. B. Rubin,[49] as it allows a known volume of solvent to be saturated with ozone at −78 °C and then transferred adiabatically into a cold solution of the substrate. Once the apparatus has been calibrated, overexposure of the substrate to ozone is easily avoided and recovered starting material can be used in a subsequent run.

The keto aldehydes **39** were then treated with low-valent titanium but with the alarming result that none of the desired products, **40** or **41**,[50] could be isolated. The present conditions were exactly those that had worked satisfactorily in our model studies[36] leading to **2** and **3** and had been chosen because they were the conditions reported[51a] to be best for intramolecular dicarbonyl coupling; nonetheless, the method was not successful here. There are several ways of making McMurry reagents;[51] the one we had used involves reduction of titanium trichloride with zinc–copper couple, but another common reagent[51,52] is made by reducing titanium trichloride with lithium aluminum hydride.[52] We arbitrarily decided to try this reagent but in the presence of triethylamine,[53] the purpose of the base being to quench Lewis acid sites and render the reagent less destructive of highly oxygenated substrates. There was indeed an improvement, for it was now possible to isolate the desired cyclization product **40** in 30–39% yield. We did not carry out a systematic study: the amine was simply used in large excess—4–10 mol per mol of titanium trichloride—and attempts to raise the yield further by changes in reaction temperature or time were not successful. Therefore, we accepted the present result for the time being as it provided enough material to complete the synthesis of compactin, but, later on, during the work on mevinolin that is described below, we discovered a titanium reagent which converts the aldehyde enones **39** into **40** in 85% yield.

The cyclized products **40** were desilylated with dilute aqueous hydrofluoric acid and subjected to ketalization conditions in order to compensate for partial loss of the ketal group (**40** → **41**). Although two steps are involved in converting **40** into **41**, the overall yield was still high (85%). The epimeric alcohols **41** were oxidized by the Swern method, and the resulting ketone **42**, which had the C-8 and C-8a hydrogens in a trans relationship on the basis of a *J* value of 12.0 Hz, was treated with L-Selectride to form a single alcohol **43**. The stereochemistry of the alcohol was assigned as shown because the ^1H NMR splitting pattern of the C-1 hydrogen had no large couplings, and the ^{13}C NMR chemical shift was upfield[54] of the corresponding signal for the C-1 epimer. This spectroscopic evidence is exactly parallel to that which had

(47) See: Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083. Domazetis, G.; Tarpey, B.; Dolphin, D.; James, B. R. *J. Chem. Soc., Chem. Commun.* **1980**, 939.

(48) This is the stereochemistry that corresponds to the natural products.

(49) Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

(50) In model studies leading to **2** and **3** (see Supplementary Material) we had found that filtration of the reaction mixture through Florisil is critical for retention of a trimethylsilyl group; when the mixture is filtered through Celite the corresponding alcohols **2** and **3** are isolated.

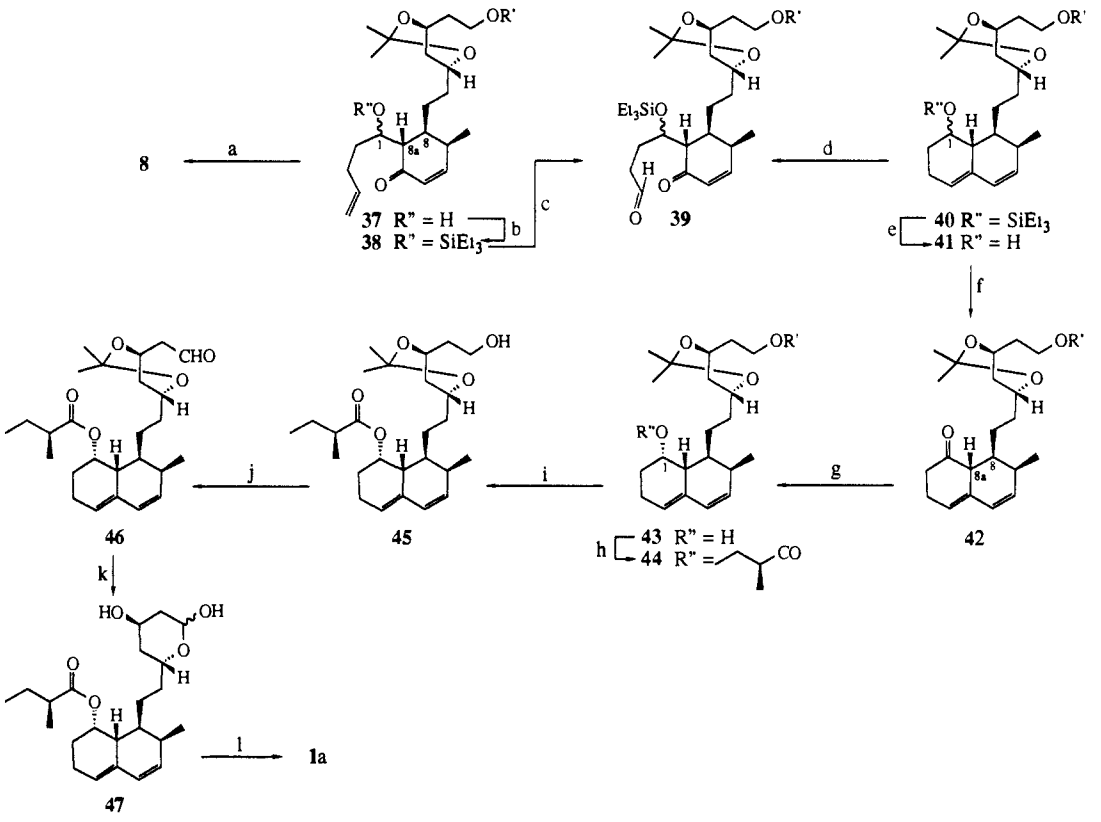
(51) (a) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255. (b) Review of titanium-induced dicarbonyl coupling: McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. (c) Mechanism of titanium-induced dicarbonyl coupling: Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. Y. *J. Org. Chem.* **1982**, *47*, 248.

(52) E.g.: Seebach, D.; Wiedmann, B.; Widler, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Salle and Sauerländer: Aarau, 1983; Vol. 3, p 217. McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896.

(53) McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660.

(54) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 167.

Scheme VII[a,b]



[a](a) LDA, Et_2O, −78 °C; add **8**, −78 °C, 1 h; add 4-pentenal, −78 °C, 10 min; 75%; (b) Et_3SiCl, *i*-Pr_2NH, DMAP (catalyst), Et_2O, room temperature, 36 h; 96%; (c) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, 20 min; room temperature, 8 h; 79% after correction for recovered **38** (12.5%); (d) C_8K, $TiCl_3$, DME; addition of **39** over 9 h; room temperature 5 h, reflux, 3 h; 85%; (e) 48% w/v aqueous HF diluted 50-fold with MeCN, room temperature, 1.75 h; 2-methoxypropene, pyridinium *p*-toluenesulfonate (catalyst), CH_2Cl_2, 0 °C, 40 min; 85% overall; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add **41**, −78 °C, 15 min; Et_3N, −78 °C, 5 min; warm to room temperature over 20 min; 93% after correction for recovered **41** (18%); (g) L-Selectride, THF, −78 °C, 1 h; −43 °C, 12 h; 80%; (h) (*S*)-2-methylbutyric anhydride, Et_3N, DMAP (catalyst), CH_2Cl_2, room temperature, 68 h; 99%; (i) $Bu_4N^+F^-$, THF, room temperature, 1.75 h; 92%; (j) $(COCl)_2$, DMSO, CH_2Cl_2; −78 °C; add **45**, −78 °C, 20 min; Et_3N, −78 °C, 10 min; warm to room temperature over 30 min; 91%; (k) aqueous 10% v/v HCl, THF, room temperature, 2 h; 88%; (l) Ag_2CO_3/Celite, PhMe, 95 °C, 2 h; 61%. [b]R′ = $SiPh_2Bu$-*t*.

been used[36] for the model compounds **2** and **3**.

Acylation (**43** → **44**) with (*S*)-α-methylbutyric anhydride[21a] proceeded slowly but in almost quantitative yield, and all that was then required to complete the synthesis was elaboration of the lactone. To prepare for this, the ester **44** was desilylated with tetrabutylammonium fluoride, and the resulting primary alcohol **45** was oxidized, again using the Swern process, to aldehyde **46**. Treatment with dilute hydrochloric acid produced the lactols **47**. Finally, oxidation with Fétizon's reagent[55] generated synthetic (+)-compactin in 61% yield. The substance was indistinguishable [^{1}H NMR (400 MHz), ^{13}C NMR (50.32 MHz)], from natural material and had mp 148–151 °C [lit.[5a] 152 °C] and $[\alpha]^{30}_D$ +218.6° (*c* 0.38749, CH_2Cl_2). The natural compound had $[\alpha]^{29}_D$ +221.2° (*c* 0.32873, CH_2Cl_2).

Synthesis of (+)-Mevinolin and Development of the Special Titanium Reagent. The synthesis of mevinolin (Scheme VIII) was carried out in an entirely comparable fashion but using the ring A aldehyde **9b**. Certain improvements were made to a number of the steps; and it was during this phase of the project that we discovered a titanium reagent with which the intramolecular dicarbonyl coupling could be carried out in very high yield.

Kinetic deprotonation of the BC ring unit **8** and treatment with the methyl-substituted aldehyde **9b** gave the aldol product **48** in 78% yield. Unlike the situation in the compactin series, only a single aldol was isolated, and it had the desired stereochemistry not only at C-8a but also at C-1. This was clear from a spectral comparison with the corresponding compound **37** from the compactin work. Silylation (**48** → **49**) and ozonolysis produced the keto aldehyde **50**. The ^{1}H NMR spectrum of this material showed the presence of 6.3% of the C-3 epimer. We suspect[46] that epimerization occurred during silica gel chromatography, but, in any event, the impurity was removed after attachment of the methylbutyroyl side chain.

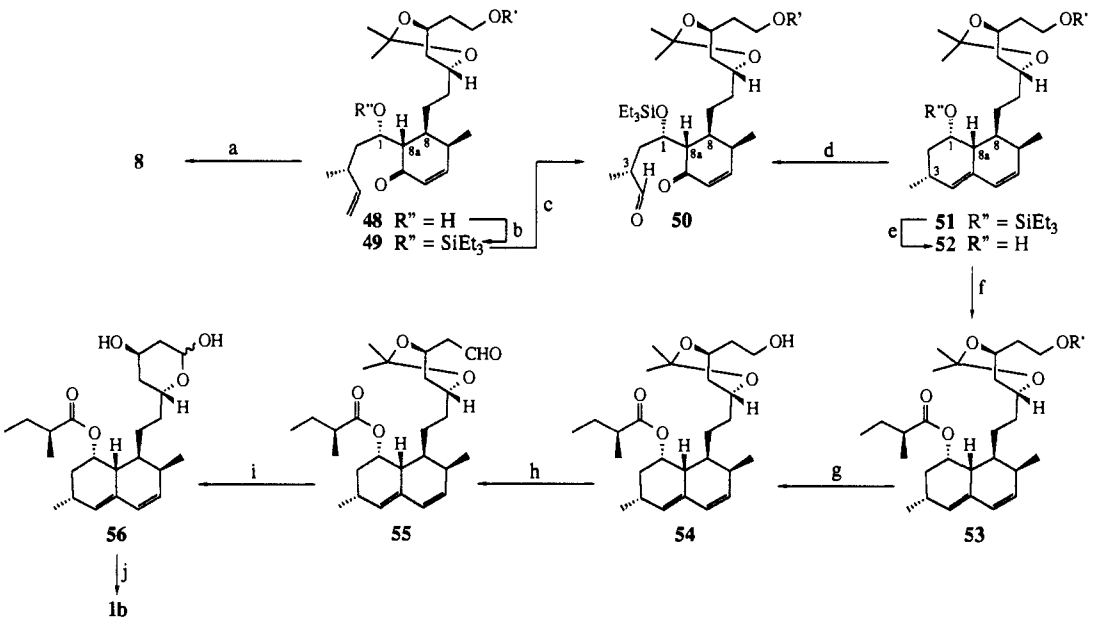
Having made the keto aldehyde, we were ready to close ring A by intramolecular McMurry coupling. However, we anticipated from our experience with compactin, that the yield would be poor, and so we decided to modify our preparation of the reagent. At about this time, the use of C_8K to generate active metals[56] caught our attention, and we prepared what we thought was zero-valent titanium by reducing the titanium trichloride with C_8K.[57] Using the compactin keto aldehyde **39** as a model, the coupling was carried out in 71% yield; however, attempts to repeat this result were not successful, and the subsequent yields were close to zero. A detailed consideration of the precise circumstances surrounding the one really successful experiment made us suspect that, through unintentional contact with air, there had been an error in the actual weight used of one or both of the sensitive reagents, C_8K and titanium trichloride. The merit of this thought was quickly established as we found that the yield in the dicarbonyl coupling of keto aldehyde **50** is very sensitive to the potassium graphite–titanium trichloride ratio and to the relative amount of the reagent and substrate. We carry out the reaction in 1,2-dimethoxyethane (DME) and, for optimum results, use the following *relative* molar quantities: keto aldehyde (1)C_8K (34)$TiCl_3$ (17). Under these

(55) Balogh, V.; Fétizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339.

(56) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775.

(57) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1983**, *48*, 4108.

Scheme VIII[a,b]



[a](a) LDA, Et_2O, −78 °C; add **8**; −78 °C, 45 min; add **9b**, −78 °C, 10 min; 78%; (b) Et_3SiCl, *i*-Pr_2NH, DMAP, Et_2O, 0 °C; room temperature, reaction arbitrarily stopped after 24 h; 85% after correction for recovered **48** (19.5%); (c) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, then remove cold bath, 3 h; 85% after correction for recovered **49** (30%); (d) C_8K, $TiCl_3$, DME; addition of **50** over 9 h; room temperature 5 h, reflux, 4 h; 86%; (e) $Bu_4N^+F^-$, THF, room temperature, 22 h; *t*-$BuPh_2SiCl$, CH_2Cl_2, Et_3N, DMAP (catalyst), room temperature, 24 h; 95% overall; (f) (*S*)-2-methylbutyric anhydride, Et_3N, DMAP, CH_2Cl_2, room temperature, arbitrarily stopped after 72 h; 91% after correction for recovered **52** (12%); (g) $Bu_4N^+F^-$, THF, room temperature, 3 h; 95%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add **54**, −78 °C, 20 min; Et_3N, −78 °C, 10 min; warm to room temperature over 20 min; 97%; (i) aqueous 10% v/v HCl, THF, room temperature, 4 h; 97%; (j) Ag_2CO_3/Celite, PhMe, 85–95 °C, 1 h; 77%. [b] R′ = $SiPh_2Bu$-*t*.

conditions the yield of the cyclized compound **51** is 86%. As stated earlier, the corresponding yield in the compactin series is 85%.

Although potassium graphite has been used before[58] to generate low-valent titanium, it was used in a stoichiometric amount designed to produce Ti(0), conditions which give only a 31% yield in our case. Potassium metal has also been investigated[51c] in this context, and it was found that with a potassium–titanium trichloride ratio corresponding to our value, the yield in the *intermolecular* coupling of cyclohexanone is only 50%.[51c,59]

As the keto aldehyde **50** had contained 6.3% of its C-3 epimer, it was reassuring to find that in the cyclized material **51** the amount of this impurity was unchanged, suggesting that the stereochemistry at C-3 had been preserved. From this stage a slightly different sequence from that used in the compactin series was applied as it proved to be more efficient. In the present case, both silyl-protecting groups of **51** were removed by exposure to tetrabutylammonium fluoride, a reagent which left the ketal unit intact. Then the *tert*-butyldiphenylsilyl group was replaced by selective reaction at the primary hydroxyl. Although two steps are involved, the overall yield is still 95%. The alcohol produced (**52**) was acylated with (*S*)-α-methylbutyric anhydride, again in a very slow but efficient process, bringing the sequence to **53**, which was free of the small amount of impurity that had been carried over from the ozonolysis. Now, only elaboration of the lactone remained. This was accomplished in exactly the same way as in the compactin series: desilylation with tetrabutylammonium fluoride (**53** → **54**), Swern oxidation (**54** → **55**), and exposure to dilute hydrochloric acid gave the lactols **56**. Lastly, Fētizon oxidation produced (+)-mevinolin in 77% yield. The synthetic compound was indistinguishable [^{1}H NMR (300 MHz), ^{13}C NMR (75.47 MHz)] from natural material and had mp 155.5–158.5 °C [lit.[6] 157–159 °C] and $[\alpha]^{27.5}_D$ +334.7° (*c* 0.254275, CH_3CN). The natural material had $[\alpha]^{27.5}_D$ +331.6° (*c* 0.10675, CH_3CN).

(58) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1985**, *280*, 307.

(59) In that work (ref 51c) the ratio of reagent to substrate was different from ours.

Conclusions

The above syntheses of two dominant members of the mevinic acid class are highly stereocontrolled and represent a general route that can accommodate changes to ring A and probably elsewhere.[60] The approach illustrates an annulation method based on an experimental modification of the classical McMurry process, and this modification works very well even in circumstances where (in our hands) the traditional methods[51b] proceed poorly or not at all. Our experiments also show that an asymmetric center adjacent to a carbonyl group is not epimerized during this titanium-induced coupling.

Experimental Section

General Procedures. Experimental procedures are given in the Supplementary Material. *Tentative* assignments to ^{13}C NMR employ the abbreviations s′, d′, t′, and q′, which refer respectively to zero, one, two, and three attached protons.

(A) Synthesis of the Lactone Subunit 7. Compounds 19–26. These compounds were prepared by the methods summarized in Scheme IV. Full experimental details are given in the Supplementary Material.

(4*S*-*cis*)-(1,1-Dimethylethyl)[2-[6-(iodomethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethoxy]diphenylsilane (7). Iodo carbonate **26** (14.25 g, 27.17 mmol) was dissolved in dry acetone (250 mL) containing *p*-toluenesulfonic acid monohydrate (3.20 g, 16.82 mmol). The solution was protected from atmospheric moisture by a drying tube packed with Drierite and stirred for 91 h at room temperature (TLC control). Anhydrous triethylamine (3.5 mL, 25.1 mmol) was then added, and stirring was continued for 10 min. The acetone was evaporated, and the residual oil was dissolved in ethyl acetate (200 mL), washed successively with water (100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and brine (1 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent

(60) We have used the method to prepare 3-ethylcompactin (**1**, R= Et).

(61) Osborn, A.; Wilkinson, G. *Inorg. Synth.* **1967**, *10*, 67.

(62) The starting material was dissolved in DME (4 mL), and the solution was drawn up into the syringe. A further portion of DME (1 mL) was injected into the flask. This rinse was also drawn into the syringe followed by a bubble of argon (to expel all of the solution by the end of the addition). The addition was done by using a syringe pump.

(63) Made by the literature method but on 1/6th the reported scale: dried at 45 °C (protection from light) and then at room temperature (oil-pump, 15 h, protection from light).

and flash chromatography of the residue over silica gel (6.5 × 17 cm) with 1:4 ether–petroleum ether gave **7** (5.73 g, 39%). Further elution with 1:2 ethyl acetate–petroleum ether gave an unidentified product (1.22 g) and (4*S*-*cis*)-[6-(iodomethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethanol (2.72 g), resulting from loss of the silicon-protecting group. This material was resilylated as follows: *tert*-butyldiphenylsilyl chloride (2.78 mL, 10.69 mmol) was injected over about 5 min to a stirred and cooled (0 °C) solution of the alcohol (2.67 g, 8.896 mmol), triethylamine (1.6 mL, 11.5 mmol), and 4-(dimethylamino)pyridine (1.08 g, 8.84 mmol) in dichloromethane (10 mL). Stirring was continued for 2 h, during which time the mixture had attained room temperature. The mixture was diluted with dichloromethane (50 mL), washed with water (2 × 50 mL) and brine (1 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 × 17 cm) with 1:4 ether–petroleum ether gave **7** (4.09 g, 85%). The total yield of **7** amounted to 9.82 g (67%). The iodo ketal had mp 41–44 °C; $[\alpha]^{28}_D$ +0.468° (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9 H), 0.95–1.18 (m, 1 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.65–1.80 (m, 3 H), 3.00–3.20 (m, 2 H), 3.65–3.80 (m, 1 H), 3.80–3.95 (m, 2 H), 4.05–4.25 (m, 1 H), 7.35–7.50 (m, 6 H), 7.65–7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 9.58 (t′), 19.21 (s′), 19.85 (q′), 26.86 (q′), 29.97 (q′), 36.93 (t′), 39.06 (t′), 59.53 (t′), 65.59 (d′), 69.34 (d′), 99.33 (s′), 127.62 (d′), 127.66 (d′), 129.60 (d′), 133.83 (s′), 133.88 (s′), 135.55 (d′); exact mass, *m/z* 523.1166 [calcd for $C_{24}H_{32}IO_3Si$ (M − CH_3)$^+$, *m/z* 523.1165]. Anal. Calcd for $C_{25}H_{35}IO_3Si$: C, 55.76; H, 6.55; Si, 5.22. Found: C, 55.60; H, 6.76; Si, 5.00. The hydroxy ketal, (4*S*-*cis*)-[6-(iodomethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethanol, had ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (q, *J* = 6.5 Hz, 1 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.65–1.80 (m, 3 H), 2.40 (br s, 1 H), 3.50–3.21 (m, 2 H), 3.70–3.84 (m, 2 H), 3.82–3.96 (m, 1 H), 4.05–4.16 (m, 1 H).

(B) Synthesis of the Ring B Subunit 6. [1*S*-[1α(*R),6β]]-3-[(6-Methyl-3-cyclohexen-1-yl)carbonyl]-4-(phenylmethyl)-2-oxazolidinone (13).** This experiment was done in a fume hood. A dry 3-L, three-necked flask, which had been marked at the 1.6-L level and containing a magnetic stirring bar, was capped with two septa, one of which carried inlet and exit needles for argon. The central neck was fitted with a special condenser that consisted of a glass tube wound in a spiral and contained in a cup packed with dry ice–acetone. Butadiene, dried by passage through Drierite (1.8 × 16.0 cm), was led into the spiral tube, where it condensed and eventually collected in the flask, which was also cooled to −78 °C. When 1.6 L of liquid butadiene had been collected, the special condenser was replaced by a pressure equalizing dropping funnel which had been marked at the 600-mL level. A solution of oxazolidinone **12**[27] (84.0 g, 0.342 mol) in dry dichloromethane (500 mL) was added by cannula to the stirred olefin. Then diethylaluminum chloride (1.8 M in toluene, 600 mL, 1.08 mol) was transferred rapidly, also by cannula, to the dropping funnel and was added over about 10 min to the stirred reaction mixture. The inlet and exit needles for argon were removed, and one of the septa was replaced by a drying tube packed with Drierite. The reaction mixture was stirred for about 16 h at −7 °C to −10 °C, this temperature being maintained by an alcohol bath with an immersion cooler. A few drops of the reaction mixture were quenched with dilute hydrochloric acid and extracted with ethyl acetate. The organic solution was examined by TLC (silica, 1:4 ethyl acetate–petroleum ether). No starting material remained. Hydrochloric acid (1 N) was added slowly by dropper with magnetic stirring and cooling (bath temperature −40 °C to −70 °C) until the lower aqueous layer was acidic. The solution changes from yellow to colorless at this stage, but more hydrochloric acid was added until the aqueous phase was at pH 2. The reaction mixture was then poured into a 5-L beaker and stirred for 2 h. The resulting white emulsion was filtered by suction through a Whatman No. 2 paper. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 300 mL). The combined organic solutions were washed with water (2 × 200 mL) and brine (1 × 250 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the resulting yellow oil over silica gel (10 × 20 cm) with 1:4 ethyl acetate–petroleum ether and crystallization from hot 95% ethanol gave pure (^1H NMR, 200 MHz) **13** (57.80 g, 56%): mp 81–83 °C; $[\alpha]^{20}_D$ +149.416° (*c* 1.57, $CDCl_3$); FT-IR ($CHCl_3$ cast) 1772, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.65–2.50 (m, 5 H), 2.78 (dd, *J* = 13.5, 9.5 Hz, 1 H), 3.27 (dd, *J* = 13.5, 3.5 Hz, 1 H), 3.70 (dt, *J* = 5.5, 10.0 Hz, 1 H), 4.10–4.22 (m, 2 H), 4.62–4.80 (m, 1 H), 5.60–5.78 (m, 2 H), 7.26–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.52 (q′), 29.02 (t′), 30.32 (d′), 32.97 (t′), 37.86 (t′), 44.17 (d′), 55.24 (d′), 65.96 (t′), 124.66 (d′), 126.34 (d′), 127.30 (d′), 128.87 (d′), 129.42 (d′), 135.25 (s′), 153.06 (s′), 176.39 (s′); exact mass, *m/z* 299.1521 (calcd for $C_{18}H_{21}NO_3$, *m/z* 299.1521). Anal. Calcd for $C_{18}H_{21}NO_3$, C, 72.22; H, 7.07; N, 4.68. Found: C, 72.16; H, 6.98; N, 4.52.

Compounds 14–17, 5, and 18. These compounds were prepared by the methods summarized in Scheme III. Full experimental details are given in the Supplementary Material. A sample of the ester **14** was hydrolyzed (aqueous methanolic sodium hydroxide; room temperature; 4 h) without (^1H NMR, 200 MHz) significant (<1.7%) epimerization, and the trans acid was shown by the literature method[35] to be >99.5% optically pure.

(1*S*-*endo*)-6-Methyl-2-oxabicyclo[3.3.1]non-7-en-3-one (6). (a) (1*S*,6-*endo*,8-*exo*)-8-Iodo-6-methyl-2-oxabicyclo[3.3.1]nonan-3-one. Sodium iodide, dried at 100 °C for 12 h (15.0 g, 100.1 mmol), and 18-crown-6 (0.540 g, 2.04 mmol) were added to a mechanically stirred solution of acid **18** (3.00 g, 19.45 mmol) in dry dichloromethane. After 15 min the reaction mixture was cooled in an ice–salt bath, and *m*-chloroperbenzoic acid (89%, 5.47 g, 28.21 mmol) in dichloromethane (100 mL) was added at a fast dropwise rate over about 15 min. The mixture became thick and dark brown in color. Vigorous stirring was maintained throughout the addition and for 1 h more. The mixture was then diluted with dichloromethane (100 mL), washed successively with 10% w/v aqueous sodium thiosulfate (3 × 60 mL), saturated aqueous sodium bicarbonate (3 × 50 mL), and water (2 × 50 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (6.5 × 17 cm) with 3:7 ethyl acetate–hexane gave material that was dissolved in the minimum volume of hot ethyl acetate. The solution was diluted with hexane until just tubid and allowed to cool to room temperature. It was then kept overnight in a refrigerator to afford the pure (TLC, silica, 1:3 ethyl acetate–hexane) iodo lactone (5.00 g, 91%) as white needles: mp 70–71 °C, $[\alpha]^{25}_D$ +27.65° (*c* 5.6, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.99 (d, *J* = 6.8 Hz, 3 H), 1.59 (ddd, *J* = 16.0, 12.5, 4.5 Hz, 1 H), 1.80–2.35 (m, 4 H), 2.50–2.78 (m, 3 H), 4.60 (br s, 1 H), 4.76 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 18.70 (q′), 26.75 (t′), 27.63 (d′), 30.03 (d′), 30.61 (t′), 31.57 (d′), 33.88 (t′), 77.75 (d′), 170.32 (s′); exact mass, *m/z* 279.9954 (calcd for $C_9H_{13}O_2I$, *m/z* 279.9960).

(b) (1*S*-*endo*)-6-Methyl-2-oxabicyclo[3.3.1]non-7-en-3-one (6). The above iodo lactone (3.50 g, 12.50 mmol) was dissolved in toluene (25 mL), and 1.8-diazabicyclo[5.4.0]undec-7-ene (4.76 g, 31.27 mmol) was added. The mixture was refluxed for 2 h under argon. It was then cooled and diluted with ethyl acetate (250 mL). The solution was washed successively with water (25 mL), 10% v/v aqueous hydrochloric acid (3 × 50 mL), water (50 mL), 10% w/v aqueous sodium thiosulfate (2 × 50 mL), and water (3 × 50 mL), and dried (Na_2SO_4). Evaporation of the solvent below 45 °C gave material which was dissolved in the minimum volume of hot ethyl acetate. The solution was diluted with hexane till just turbid and then cooled, first to room temperature and then in a refrigerator. This procedure afforded **6** as shining plates. Several reactions on about the same scale were carried out until 23.00 g of starting iodide had been processed to afford **6** (9.90 g, 79%): mp 76–77 °C; $[\alpha]^{24}_D$ −246.35° (*c* 1.275, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz)) δ 1.08 (d, *J* = 7.6 Hz, 3 H), 1.86–2.05 (m, 1 H), 2.15–2.40 (m, 2 H), 2.44–2.70 (m, 3 H), 4.68–4.82 (m, 1 H), 5.70 (dt, *J* = 9.5, 1.6 Hz, 1 H), 5.90–6.05 (m, 1 H); ^{13}C ($CDCl_3$, 75.469 MHz) δ 17.77 (q′), 29.80 (t′), 29.99 (d′), 30.19 (t′), 35.34 (d′), 69.87 (d′), 125.32 (d′), 136.13 (d′), 171.94 (s′); exact mass, *m/z* 152.0842 (calcd for $C_9H_{12}O_2$, *m/z* 152.0837). A sample of **6** made by using **5** that had been derived from D-glucal, had $[\alpha]^{25}_D$ −247.40° (*c* 3.164, $CHCl_3$).

(C) Synthesis of the BC Ring System 8. [1*S*-[1α,4α-(4*S,6*R**),5α,6β]]-4-[[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-6-methyl-2-oxabicyclo-[3.3.1]non-7-en-3-one (34).** Lithium diisopropylamide was prepared by dropwise addition of *n*-butyllithium (1.55 M in hexanes, 12.80 mL, 19.84 mmol) over 10 min to a stirred and cooled (ice bath) solution of diisopropylamine (2.87 mL, 20.48 mmol) in THF (25.5 mL). The solution was cooled to −78 °C, and the lactone **6** (1.520 g, 9.99 mmol) in THF (8.5 mL plus 8.5 mL as a rinse) was added dropwise over about 10 min. The mixture was stirred at −78 °C for 1.25 h, and then iodide **7** (5.380 g, 9.99 mmol) in a mixture of THF (16 mL) and HMPA (13.5 mL) was added by cannula over about 15 min, more THF (8 mL) being used as a rinse. Stirring was continued overnight, the cold bath being left in place and allowed to attain room temperature. The mixture was then cooled to −78 °C, and saturated aqueous ammonium chloride (11 mL) was added. The mixture was diluted with ethyl acetate (80 mL), washed with water (40 mL) and brine (40 mL), and dried (Na_2SO_4). Evaporation of the solvent below 30 °C and flash chromatography of the residue over silica gel (3.5 × 17 cm) with 1:4 ethyl acetate–petroleum ether gave **34** (1.980 g, 35%) as well as lactone **6** (0.83 g). Coupled product **34** (77% yield, after correction for recovered **6**) had $[\alpha]^{28}_D$ −47.9° (*c* 1.00, $CHCl_3$); IR (film) 1722, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.12 (d, *J* = 7.5 Hz, 3 H), 1.08–1.15 (m, 1 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 1.45 (dt, *J* = 13.0, 2.5 Hz, 1 H), 1.56 (ddd, *J* = 14.5, 10.0, 4.8 Hz, 1 H), 1.60–1.75 (m, 2 H), 1.85 (dt, *J* = 13.5, 2.0 Hz, 1 H), 1.95 (ddd, *J* = 10.5, 7.5, 3.0 Hz, 1 H), 2.10 (br s, 1 H), 2.19–2.26 (m, 1 H), 2.48–2.58 (m, 1 H), 2.70 (br t, *J* = 6.0 Hz, 1 H), 3.68 (dt, *J* = 10.0, 5.0 Hz, 1 H), 3.80–3.90 (m, 1 H), 4.10–4.22 (m, 2 H), 4.69–4.76 (m, 1 H),

5.72 (dt, J = 9.5, 1.5, 1 H), 5.94–6.0 (m, 1 H), 7.35–7.45 (m, 6 H), 7.65–7.70 (m, 4 H). [Decoupling experiments showed that $J_{8,9}$ (numbering of diagram **34**) is ca. 3 Hz.] ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 17.34 (q'), 19.15 (s'), 19.90 (q'), 26.82 (q'), 29.59 (t'), 30.14 (q'), 36.53 (d'), 36.70 (d'), 37.28 (d'), 37.55 (t'), 39.30 (t'), 42.06 (t'), 59.56 (t'), 65.50 (d'), 68.27 (d'), 70.20 (d'), 98.50 (s'), 125.21 (d'), 127.56 (d'), 129.51 (d'), 133.89 (s'), 135.51 (d'), 136.87 (d'), 175.74 (s'); exact mass, m/z 547.2870 [calcd for $C_{33}H_{43}O_5Si$ $(M - CH_3)^+$, m/z 547.2879]. Anal. Calcd for $C_{34}H_{46}O_5Si$: C, 72.56; H, 8.24; Si, 4.99. Found: C, 72.36; H, 8.48; Si, 4.84.

[1*S*-[1α,3α,4α(4*S,6*R**)5α,6β]]- and [1*S*-[1α,3β,4α(4*S**,6*R**)-5α,6β]]-4-[[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-6-methyl-2-oxabicyclo[3.3.1]non-7-en-3-ol (35).** Diisobutylaluminum hydride (1 M in dichloromethane, 2.0 mL, 2.00 mmol) was injected over about 5 min into a stirred and cooled (−78 °C) solution of lactone **34** (797.5 mg, 1.42 mmol) in dichloromethane (8 mL). Stirring at −78 °C was continued for 1.5 h, saturated aqueous ammonium chloride (3 mL) was added, the cold bath was removed, and the reaction mixture was left for 1 h to warm to room temperature. The mixture was diluted with dichloromethane (100 mL) and filtered through a pad of Celite (4.0 × 4.0 cm). The filtrate was washed with brine and dried ($MgSO_4$). Evaporation of the solvent below 30 °C and flash chromatography of the residue over silica gel (3 × 12 cm) with 1:3 ethyl acetate–petroleum ether gave **35** (720 mg, 90%): IR (film) 3550–3250, 1720, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.08 (d, J = 7.5 Hz, 3 H), 1.05–1.20 (m, 1 H), 1.35 (s, 3 H), 1.30–1.47 (m, 2 H), 1.41 (s, 3 H), 1.62–1.85 (m, 5 H), 1.94–2.08 (m, 1 H), 2.09–2.29 (m, 2 H), 2.45–2.60 (m, 1 H), 3.65–3.75 (m, 1 H), 3.80–3.90 (m, 2 H), 4.05–4.65 (m, 2 H), 5.72–5.85 (m, 2 H), 7.35–7.50 (m, 6 H), 7.65–7.75 (m, 4 H); exact mass, m/z 531.2915 [calcd for $C_{33}H_{43}O_4Si$ $(M - H_2O - CH_3)^+$], m/z 531.2931. Satisfactory combustion analysis could not be obtained for this compound.

[4*R*-[4α[*R(1*R**,2*S**)]6α]]-6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]ethyl]-2,2-dimethyl-α-(2-methyl-5-oxo-3-cyclohexen-1-yl)-1,3-dioxane-4-propanal (36).** Manganese dioxide [manganese(IV) oxide, activated, Aldrich, no. 21 764-6, 2.874 g, 33.06 mmol] and anhydrous sodium acetate (203.3 mg, 2.48 mmol) were added to a stirred solution of lactol **35** (934.0 mg, 1.65 mmol) in dry chloroform (16 mL). Stirring at room temperature and under argon was continued for 74.5 h, further reagents and solvent being added as follows: manganese dioxide (2.882 g), sodium acetate (208 mg), and chloroform (2 mL) after 25 h; manganese dioxide (2.878 g) and sodium acetate (215 mg) after 50 h; manganese dioxide (2.882 g), sodium acetate (209 mg), and chloroform (2 mL) after 69 h. At the end of the specified period the mixture was filtered through a pad of Celite, and the solids were washed well with dichloromethane. The combined solvents were evaporated (water-pump), and flash chromatography of the residue over silica gel (3.5 × 17 cm) with 1:49 methanol–dichloromethane gave **36** (730.7 mg, 78%) as a thick oil: IR (film) 1720, 1678, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.19 (q, J = 11.6 Hz, 1 H), 1.38 (s, 3 H), 1.38–1.41 (m, 1 H), 1.42 (s, 3 H), 1.60–1.80 (m, 4 H), 2.26–2.52 (m, 3 H), 2.60–2.75 (m, 2 H), 3.65–3.90 (m, 3 H), 4.05–4.15 (m, 1 H), 6.0 (d, J = 10.0 Hz, 1 H), 7.02 (dd, J = 10.0, 6.0 Hz, 1 H), 7.32–7.45 (m, 6 H), 7.65–7.72 (m, 4 H), 9.60 (d, J = 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 11.72 (q'), 19.21 (s'), 19.70 (q'), 26.86 (q'), 30.05 (q'), 30.90 (d'), 33.46 (t'), 36.64 (d'), 37.32 (t'), 37.63 (t'), 39.23 (t'), 49.52 (d'), 59.53 (t'), 65.43 (d'), 65.86 (d'), 98.76 (s'), 127.62 (d'), 127.65 (d'), 128.09 (d'), 129.61 (d'), 133.84 (s'), 133.91 (s'), 135.56 (d'), 155.19 (d'), 198.09 (s'), 203.66 (d'); exact mass, m/z 547.2875 [calcd for $C_{33}H_{43}O_5Si$ $(M - CH_3^+$, m/z 547.2880]. Anal. Calcd for $C_{34}H_{46}O_5Si$: C, 72.56; H, 8.24. Found: C, 72.55; H, 8.20.

The experiment was repeated on a larger scale using manganese dioxide (17.80 g, 204.7 mmol), anhydrous sodium acetate (1.25 g, 15.2 mmol), lactol **35** (5.75 g, 10.18 mmol), and dry chloroform (80 mL). The following additional quantities of reagents were added: manganese dioxide (17.8 g), sodium acetate (1.25 g); manganese dioxide (1.78 g), sodium acetate (1.25 g); manganese dioxide (1.78 g), sodium acetate (1.25 g). Additional chloroform was not added in this large scale run. The product was isolated in 71% yield after chromatography over silica gel (4 × 17 cm).

[4*R*-[4α(4*R,5*R**),6α]]-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 (8).** Enone aldehyde **36** (871 mg, 1.548 mmol) was dissolved in a mixture of dry toluene (16 mL) and dry benzonitrile (2 mL). Freshly prepared[61] Wilkinson's catalyst (1.430 g, 1.546 mmol) was added, and the mixture was refluxed under argon, the progress of the reaction being closely followed by TLC (1:4 ethyl acetate–petroleum ether). When the starting material had disappeared (2.5 h), the mixture was cooled to room temperature and then to −10 °C (ice–methanol bath). The precipitated rhodium complex was filtered off through a pad of Florisil (4 × 4 cm) and washed with ethyl acetate. The combined filtrates were concentrated. Flash chromatography of the residue over silica gel (3 × 17 cm) using first 1:4 ether–petroleum ether to remove triphenylphosphine and benzonitrile and then 1:4 ethyl acetate–petroleum ether gave an oil (731.1 mg). Two other portions (300 mg and 505 mg) of **36** were processed in the same way to afford the crude oily product (708.9 mg). The combined crude material (1.440 g) from all three experiments was purified by using a Waters PrepLC System 500A instrument with two PrepPak-500/Silica cartridges and 2.5% v/v acetone–dichloromethane as eluent. A refractive index detector and flow rate of 100 mL min^{-1} were used. The mixture (1.440 g) was dissolved in 50 mL of dichloromethane, and 20-mL injections were made. This procedure gave the desired enone **8** (800 mg, 50%): $[\alpha]^{27}_D$ +51.96° (c 1.40, $CHCl_3$); IR (film) 1675, 1620, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (d, J = 7.0 Hz, 3 H), 1.03 (s, 9 H), 1.10 (q, J = 12.0 Hz, 1 H), 1.22–1.31 (m, 1 H), 1.35 (s, 3 H), 1.42 (s, 3 H), 1.32–1.55 (m, 4 H), 1.65–1.72 (m, 2 H), 2.05–2.38 (m, 3 H), 2.45–2.60 (m, 1 H), 3.65–3.85 (m, 3 H), 4.07–4.15 (m, 1 H), 5.94 (d, J = 10.0 Hz, 1 H), 6.95 (dd, J = 10.0, 5.5 Hz, 1 H), 7.32–7.45 (m, 6 H), 7.62–7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.11 (q'), 19.20 (s'), 19.83 (q'), 26.85 (q'), 27.44 (t'), 30.26 (q'), 33.05 (d'), 33.57 (t'), 37.21 (t'), 37.37 (d'), 39.31 (t'), 39.86 (t'), 59.65 (t'), 65.63 (d'), 68.99 (d'), 98.44 (s'), 127.59 (d'), 127.61 (d'), 128.10 (d'), 129.57 (d'), 133.86 (s'), 133.91 (s'), 135.53 (d'), 155.92 (d'), 199.82 (s'); exact mass, m/z 534.31186 (calcd for $C_{36}H_{46}O_4Si$, m/z 534.31652); exact mass, m/z 519.2944 [calcd for $C_{32}H_{43}O_4Si$ $(M - CH_3)^+$, m/z 519.2930]. Anal. Calcd for $C_{33}H_{46}O_4Si$, m/z 534.31652); exact mass, m/z 519.2944 [calcd for $C_{32}H_{43}O_4Si$ $(M - CH_3)^+$, m/z 519.2930]. Anal. Calcd for $C_{33}H_{46}O_4Si$: C, 74.11; H, 8.67. Found: C, 74.18; H, 8.72.

(D) Synthesis of Compactin. The experimental procedures used to assemble compactin (Scheme VII) are very similar to those used for Mevinolin and are given in the Supplementary Material.

(E) Synthesis of the Ring A Aldehyde (9b) for Mevinolin. Compounds 28–33. These were prepared by the standard methods summarized in Scheme V. Full experimental details are given in the Supplementary material. Compound **31** was shown to be optically pure.

(*R*)-3-Methyl-4-pentenal (9b). A solution of **33** (360 mg, 2.532 mmol) in ether (50 mL) was stirred vigorously for 23 h with 10% v/v aqueous hydrochloric acid (30 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (1 × 30 mL), water (1 × 30 mL), and brine (1 × 30 mL), and were then dried (Na_2SO_4). The solvent was evaporated at 1 atmosphere with use of a Vigreaux column, and Kugelrohr distillation of the residue at 1 atm gave **9b** (173.4 mg, 69%), contaminated (^{1}H NMR) by 10 mol % of ether. Compound **9b** had FT-IR ($CDCl_3$ cast) 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (d, J = 7.0 Hz, 3 H), 2.38 (ddd, J = 17.0, 7.5, 2.5 Hz, 1 H), 2.47 (ddd, J = 16.5, 7.0, 2.5 Hz, 1 H), 2.78 (septet of t, J = 7.0, 1.4 Hz, 1 H), 5.00 (dt, J = 10.2, 1.0 Hz, 1 H), 5.04 (dt, J = 17.5, 1.5 Hz, 1 H), 5.79 (ddd, J = 17.5, 10.5, 7.0 Hz, 1 H), 9.74 (t, J = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.84 (q'), 32.20 (d'), 49.85 (t'), 113.57 (t'), 142.22 (d'), 202.04 (d'); exact mass, m/z 98.0718 (calcd for $C_6H_{10}O$, m/z 98.0732).

(F) Synthesis of Mevinolin. [4*S*-[4α,5α(4*S,4*S**),6β(1*R**,3*S**)]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-6-(1-hydroxy-3-methyl-4-pentenyl)-4-methyl-2-cyclohexen-1-one (48).** *n*-Butyllithium (1.6 M in hexanes, 0.19 mL, 0.304 mmol) was added dropwise to a stirred and cooled (ice bath) solution of diisopropylamine (0.042 mL, 0.300 mmol) in ether (3.0 mL). Stirring at 0 °C was continued for 10 min, and the solution was then cooled to −78 °C. Enone **8** (124.0 mg, 0.2319 mmol) in ether (2.0 mL plus 1.0 mL as a rinse) was added by syringe over about 15 min. Stirring at −78 °C was continued for 45 min, and then aldehyde **9b** (113.8 mg, 1.159 mmol) in ether (2 mL plus 0.25 mL as a rinse) was added, also by syringe, over about 5 min. After a further 10 min, glacial acetic acid (0.066 mL, 1.153 mmol) was injected, the cold bath was removed, and, after 10 min, ether (20 mL) and water (15 mL) were added with stirring. The phases were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (1 × 20 mL) and brine (1 × 20 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm) using 1:4, 3:7, and 2:3 ether–petroleum ether gave aldol **48** (115.7 mg, 78%) as a homogeneous (TLC, silica, 2:3 ether–petroleum ether) oil: FT-IR (CH_2Cl_2 cast) 3420, 1713, 1674, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.11 (d, J = 7.6 Hz, 3 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 1.20–1.80 (series of multiplets, 10 H), 2.09 (d, J = 6.0 Hz, 1 H), 2.11–2.21 (m, 1 H), 2.33 (t, J = 6.0 Hz, 1 H), 2.39–2.60 (m, 1 H), 2.60–2.81 (m, 1 H), 3.62–3.78 (m, 2 H), 3.78–3.97 (m, 2 H), 4.04–4.19 (m, 1 H), 4.98 (dd, J = 10.0, 2.0 Hz, 1 H), 5.05 (ddd, J = 17.5, 2.0, 1.0 Hz, 1 H), 5.64

(ddd, J = 17.0, 10.0, 8.5 Hz, 1 H), 5.92 (dd, J = 10.0, 2.4 Hz, 1 H), 6.69 (ddd, J = 10.0, 3.5, 0.5 Hz, 1 H), 7.32–7.46 (m, 6 H), 7.60–7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 15.70, 19.21, 19.83, 21.43, 23.18, 26.85, 30.28, 31.53, 33.97, 34.73, 37.30, 39.30, 40.73, 43.57, 55.60, 59.62, 65.57, 68.22, 69.32, 98.44, 114.03, 127.63, 128.14, 129.58, 133.94, 135.55, 143.6, 154.14, 201.53; exact mass, m/z 519.2962 [calcd for $C_{32}H_{43}O_4Si$, $(M - CH_3 - C_6H_{10}O)^+$ m/z 519.2930].

[4*S*-[4α,5α(4*S,6*R**),6β(1*R**,3*S**)]]-5-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-4-methyl-6-[3-methyl-1-[(triethylsilyl)oxy]-4-pentenyl]-2-cyclohexen-1-one (49).** Dry diisopropylamine (0.071 mL, 0.507 mmol), 4-(dimethylamino)pyridine (20.0 mg, 0.1637 mmol), and chlorotriethylsilane (0.085 mL, 0.506 mmol) were added to a stirred and cooled (ice bath) solution of alcohol **48** (107.4 mg, 0.1697 mmol) in dry ether (3 mL). After 30 min the ice bath was removed, and stirring was continued for 24 h at room temperature (TLC control, silica, 1:4 ether–petroleum ether). Water (5 mL) and ether (25 mL) were then added. The aqueous layer was separated, and the ether layer was washed with water (1 × 15 mL). The combined aqueous phases were extracted with ether (3 × 20 mL), and the combined ether extracts were washed with saturated aqueous sodium bicarbonate (1 × 15 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm) using first 1:4 ether–petroleum ether and then 1:1 ether–petroleum ether gave **49** [87 mg, 85% after correction for recovered starting material (21 mg)] as a homogeneous (TLC, silica, 1:4 ether–petroleum ether), thick oil: FT-IR (CH_2Cl_2 cast) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.59 (q, J = 8.0 Hz, 6 H), 0.96 (t, J = 8.0 Hz, 9 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.06 (d, $J \sim$ 7 Hz, 3 H), 0.95–1.18 (m, 1 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 1.24–1.59 (m, 6 H), 1.59–1.85 (m, 3 H), 2.06–2.19 (m, 1 H), 2.20–2.38 (m, 1 H), 2.43 (dd, J = 9.0, 4.0 Hz, 1 H), 2.62–2.78 (m, 1 H), 3.61–3.90 (m, 3 H), 4.03–4.18 (m, 1 H), 4.48 (dt, J = 8.0, 4.0 Hz, 1 H), 4.94–5.07 (m, 2 H), 5.72 (ddd, J = 17.5, 10.5, 7.5 Hz, 1 H), 5.88 (dd, J = 10.0, 1.5 Hz, 1 H), 6.79 (dd, J = 10.0, 4.5 Hz, 1 H), 7.31–7.47 (m, 6 H), 7.60–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.36, 7.06, 14.13, 19.25, 19.84, 21.60, 24.42, 26.89, 30.31, 31.28, 33.81, 34.34, 37.43, 39.24, 39.44, 41.73, 54.22, 59.67, 65.56, 69.19, 70.76, 98.46, 113.22, 127.62, 127.65, 128.55, 129.59, 134.01, 135.59, 144.19, 154.15, 199.68; exact mass, m/z 746.4767 (calcd for $C_{45}H_{70}O_5Si_2$, m/z 746.4762). Anal. Calcd for $C_{45}H_{70}O_5Si_2$: C, 72.33; H, 9.44. Found: C, 72.45; H, 9.51.

[1*S*-[1α(α*S,γ*R**),5β,6β(4*S**,6*R**)]]-6-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-α,5-dimethyl-2-oxo-γ-[(triethylsilyl)oxy]-3-cyclohexene-1-butanal (50).** This experiment was done by using the apparatus described by Rubin[49] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a dry ice–acetone bath, was bubbled for 4 min into dry dichloromethane (5 mL) at −78 °C. The resulting solution was transferred into the other bulb of the apparatus, which contained a cold (−78 °C) solution of **49** (59.5 mg, 0.0796 mmol) in dichloromethane (3 mL). The resulting mixture was stirred for 5 min, and triphenylphosphine (65.0 mg, 0.248 mmol) was then tipped in. The cold bath was removed, and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 18 cm) using successively 1:9, 2:8, and 3:7 ether–petroleum ether gave **50** [35.2 mg, 85% after correction for recovered **49** (18.1 mg)] as an apparently homogenous (TLC, silica, 4:6 ether–petroleum ether) oil: FT-IR (CH_2Cl_2 cast) 1726, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.57 (q, J = 8.0 Hz, 6 H), 0.94 (t, J = 8.0 Hz, 9 H), 1.04 (s, 9 H), 1.08 (d, J = 7.5 Hz, 3 H), 1.13 (d, J = 7.0 Hz, 3 H), 1.05–1.16 (m, 1 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 1.31–1.48 (m, 3 H), 1.48–1.80 (m, 5 H), 1.92 (ddd, J = 12.0, 8.0, 4.0 Hz, 1 H), 2.08–2.20 (m, 1 H), 2.43–2.56 (m, 1 H), 2.47 (dd, J = 8.0, 5.0 Hz, 1 H), 2.67–2.81 (m, 1 H), 3.62–3.90 (m, 3 H), 4.06–4.17 (m, 1 H), 4.54 (dt, J = 8.0, 4.0 Hz, 1 H), 5.89 (dd, J = 10.0, 1.8 Hz, 1 H), 6.81 (dd, J = 10.0, 5.0 Hz, 1 H), 7.31–7.50 (m, 6 H), 7.60–7.74 (m, 4 H), 9.66 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.15, 6.96, 14.10, 14.31, 19.23, 19.82, 24.14, 26.87, 30.29, 31.25, 33.67, 35.73, 37.41, 39.41, 43.08, 53.71, 59.66, 65.54, 69.05, 70.09, 98.45, 127.60, 127.63, 128.32, 129.57, 134.00, 135.57, 154.15, 199.45, 204.46; exact mass, m/z 748.4548 (calcd for $C_{44}H_{68}O_6Si_2$, m/z 748.45542); exact mass, m/z 733.43119 [calcd for $C_{43}H_{65}O_6Si_2$ $(M - CH_3)^+$, m/z 733.43194].

[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-naphthalenyl]oxy]triethylsilane (51).** Graphite powder (3.1022 g, 258.3 mmol) was heated with magnetic stirring at 130–140 °C for 1 h in a Schlenk tube purged by a slow stream of argon. [The Schlenk tube had a 24/40 neck (carrying a bent adaptor with tap), and a side arm (also carrying a tap) was located near the mouth of the tube.] Freshly cut pieces of potassium metal (1.114 g, 28.49 mmol) were added, and the hot mixture was stirred vigorously under the argon stream for 30 min, by which time a bronze-colored powder had formed. The potassium graphite (C_8K) was cooled to room temperature and used as described below.

Freshly prepared potassium graphite (C_8K) (364 mg, 2.693 mmol) and titanium trichloride (192.6 mg, 1.249 mmol) were weighed under argon in a glove bag and transferred successively to a 50-mL, three-necked flask containing dry DME (15 mL). The mixture was stirred and refluxed for 2 h under argon and then cooled to room temperature. Enone aldehyde **50** (55.2 mg, 0.0737 mmol) in dry DME (5 mL)[62] was added by syringe pump over 9 h to the stirred slurry of titanium reagent. Stirring was continued for an additional 5 h. The mixture was then refluxed for 4 h, cooled to room temperature, and filtered under a blanket of argon through a pad of Florisil (3.5 × 6 cm) contained in a sintered funnel equipped with an argon inlet near the top. The column was washed with ether (3 × 50 mL). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (1 × 15 cm) with 1:9 ether–petroleum ether gave **51** (45.6 mg, 86%) as an apparently homogeneous (TLC, silica, 1:9 ether–petroleum ether) oil: IR (CH_2Cl_2) 1428, 1378, 1112, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (dq, J = 8.0, 2.5 Hz, 6 H), 0.86 (d, J = 7.0 Hz, 3 H), 0.95 (t, J = 8.0 Hz, 9 H), 1.07 (s, 9 H), 1.15 (d, J = 7.5 Hz, 3 H), 1.09–1.28 (m, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.46–1.92 (m, 8 H), 2.04 (dq, J = 12.5, 2.5 Hz, 1 H), 2.29–2.46 (m, 2 H), 3.69 (dt, J = 10.0, 5.0 Hz, 1 H), 3.76–3.92 (m, 2 H), 4.08–4.20 (m, 1 H), 4.24–4.31 (m, 1 H), 5.40–5.48 (m, 1 H), 5.75 (dd, J = 9.5, 6.2 Hz, 1 H), 5.97 (d, J = 9.5, Hz, 1 H), 7.30–7.47 (m, 6 H), 7.60–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.50, 7.23, 14.22, 19.23, 19.78, 23.66, 24.15, 26.85, 28.01, 30.31, 30.43, 33.47, 35.90, 36.75, 37.35, 39.44, 39.75, 59.68, 65.58, 65.84, 69.76, 98.40, 127.61, 128.89, 129.57, 131.69, 132.83, 133.91, 133.98, 135.56; exact mass, m/z 716.4672 (calcd for $C_{44}H_{68}O_4Si_2$, m/z 716.4656).

[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 (52).** Tetrabutylammonium fluoride (1.1 M in THF, 0.60 mL, 0.66 mmol) was added to a solution of **51** (25.0 mg, 0.03486 mmol) in THF (1.5 mL), and the mixture was stirred for 22 h at room temperature (TLC control, silica, 3:2 ether–petroleum ether). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 10 cm) using first 1:1 ether–petroleum ether and then ether gave the C(1)–C(15)[4] diol [^{1}H NMR (200 MHz)] (12.7 mg, 99%) as a homogeneous (TLC, silica, ether) oil, which was used directly in the next step.

tert-Butyldiphenylsilyl chloride (0.01 mL, 0.038 mmol), triethylamine (0.006 mL, 0.043 mmol), and 4-(dimethylamino)pyridine (5.0 mg, 0.041 mmol) were added successively to a stirred and cooled (ice bath) solution of the above diol (12.7 mg, 0.0349 mmol) in dry dichloromethane (2 mL). The cold bath was removed, and the mixture was stirred for 24 h and was then evaporated. Flash chromatography of the residue over silica gel (1 × 16 cm) with 1:4 ether–petroleum ether gave **52** (20.0 mg, 95%) as a homogenous (TLC, silica, 1:4 ether–petroleum ether), colorless oil: FT-IR (CH_2Cl_2 cast) 3496, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.19 (d, J = 7.3 Hz, 3 H), 1.10–1.85 (series of multiplets, 10 H), 1.37 (s, 3 H), 1.43 (s, 3 H), 1.88 (dd, J = 4.5, 3.5 Hz, 2 H), 2.14 (dq, J = 12.5, 2.5 Hz, 1 H), 2.32–2.51 (m, 2 H), 3.69 (dt, J = 10.0, 5.0 Hz, 1 H), 3.77–3.90 (m, 2 H), 4.06–4.18 (m, 1 H), 4.18–4.30 (m, 1 H), 5.54 (t, J = 3.3 Hz, 1 H), 5.80 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5, Hz, 1 H), 7.30–7.48 (m, 6 H), 7.60–7.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.03, 19.23, 19.86, 23.38, 23.66, 26.86, 27.57, 30.28, 30.81, 33.13, 35.60, 35.93, 37.53, 38.76, 39.36, 59.68, 65.34, 65.64, 68.67, 98.52, 127.60, 127.63, 127.78, 128.51, 129.56, 130.01, 131.55, 133.80, 133.92, 134.00, 135.57; exact mass, m/z 602.3790 (calcd for $C_{38}H_{54}O_4Si$, m/z 602.3791).

[1*S*-[1α(*R),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-naphthalenyl 2-Methylbutanoate (53).** 4-(Dimethylamino)pyridine (28.0 mg, 0.2292 mmol), dry triethylamine (0.082 mL, 0.588 mmol), and (*S*)-2-methylbutyric anhydride (0.098 mg, 0.524 mmol) were added in that order to a stirred solution of **52** (18.0 mg, 0.02985 mmol) in dry dichloromethane (4 mL). The mixture was stirred for 72 h and was then evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm) with 2:23 ether–petroleum ether gave ester **53** [16.5 mg, 91% after correction for recovered **52** (2.2 mg)] as a homogeneous (TLC, silica, 1:9 ether–petroleum ether) oil: $[\alpha]^{27}_D$ +147.10° (c 0.1414, $CHCl_3$); IR (CH_2Cl_2) 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 1.04 (s, 9 H), 1.07 (d, J = 7.5 Hz, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.00–1.15 (m, 1 H), 1.15–1.75 (series of multiplets, 10 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 1.90 (ddd, J = 15.0, 7.6, 2.0 Hz, 1 H), 2.06 (dd, J = 15.0, 3.5 Hz, 1 H), 2.26 (dq, J = 12.2, 2.8 Hz, 1 H), 2.34 (q, J = 7.0 Hz, 1 H), 2.36–2.50 (m, 2 H), 3.62–3.78 (m, 2 H), 3.84 (dt, J = 10.0, 6.7 Hz, 1 H), 4.05–4.17 (m, 1 H), 5.36 (q, J = 2.5 Hz, 1 H), 5.52 (br

s, 1 H), 5.79 (dd, J = 9.5, 6.0 Hz, 1 H), 5.99 (d, J = 9.5, Hz, 1 H), 7.30–7.45 (m, 6 H), 7.60–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 11.77, 13.86, 16.24, 19.24, 19.93, 22.84, 23.97, 26.88, 27.55, 30.30, 30.73, 32.60, 33.90, 36.82, 37.38, 37.46, 39.41, 41.46, 59.66, 65.44, 67.94, 69.61, 98.42, 127.61, 127.64, 128.22, 129.42, 129.56, 132.00, 133.61, 134.03, 135.59, 176.62; exact mass, m/z 686.4374 (calcd for $C_{43}H_{62}O_5Si$, m/z 686.4366). Anal. Calcd for $C_{43}H_{62}O_5Si$: C, 75.17; H, 9.10. Found: C, 75.09; H, 9.22.

[1*S*-[1α(*R),3α,7β,8β(4*S**,6*R**),8aβ]]-1,2,3,7,8,8a-Hexahydro-8-[2-[6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-3,7-dimethyl-1-naphthalenyl 2-Methylbutanoate (54).** Tetrabutylammonium fluoride (1.1 M in THF, 0.060 mL, 0.066 mmol) was added to a solution of **53** (16.0 mg, 0.02329 mmol) in dry THF (1 mL), and the mixture was stirred at room temperature for 3 h (TLC control). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 16 cm) using first 2:3 ether–petroleum ether and then 3:2 ether–petroleum ether gave **54** (10.0 mg, 95%) as a homogeneous (TLC, silica, 7:3 ether–petroleum ether) oil: FT-IR (CH_2Cl_2 cast) 3460, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, J = 7.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 1.12–1.28 (m, 2 H), 1.37 (s, 3 H), 1.44 (s, 3 H), 1.35–1.51 (m, 3 H), 1.57–1.75 (m, 6 H), 1.89 (ddd, J = 15.0, 7.0, 2.5 Hz, 1 H), 1.99 (dd, J = 15.0, 3.0 Hz, 1 H), 2.24 (dq, J = 12.0, 2.0 Hz, 1 H), 2.28–2.49 (m, 3 H), 2.49–2.67 (br s, 1 H), 3.69–3.84 (m, 3 H), 4.04–4.13 (m, 1 H), 5.36 (q, J = 2.5 Hz, 1 H), 5.52 (br s, 1 H), 5.79 (dd, J = 10.0, 6.0 Hz, 1 H), 5.98 (d, J = 10.0, Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 11.73, 13.78, 16.19, 19.89, 22.78, 23.82, 26.83, 27.47, 30.20, 30.64, 32.56, 33.76, 36.78, 37.26, 38.03, 41.41, 61.02, 67.84, 69.44, 69.50, 98.55, 128.17, 129.40, 131.84, 133.46, 176.65; exact mass, m/z 448.3189 (calcd for $C_{27}H_{44}O_5$, m/z 448.3189).

[1*S*-[1α(*R),3α,7β,8β(4*S**,6*R**),8aβ]]-8-[2-[2,2-Dimethyl-6-(2-oxoethyl)-1,3-dioxan-4-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-1-naphthalenyl 2-Methylbutanoate (55).** Dry DMSO (0.010 mL, 0.1409 mmol) was added to a stirred solution of oxalyl chloride (0.008 mL, 0.0917 mmol) in dry dichloromethane (1 mL) at −78 °C (argon atmosphere). After 10 min alcohol **54** (9.4 mg, 0.0210 mmol) in dry dichloromethane (1 mL plus 0.5 mL as a rinse) was added by syringe. After 20 min, dry triethylamine (0.050 mL, 0.3587 mmol) was added, and, after a further 10 min, the cold bath was removed, and the solution was stirred for 20 min more. A few drops of water were then added, and the mixture was concentrated at room temperature. Flash chromatography of the residue over silica gel (1 × 16 cm) with 2:3 ether–petroleum ether gave aldehyde **55** (9.1 mg, 97%) as a homogeneous (TLC, silica, 2:3 ether–petroleum ether) oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 1.07 (d, J = 7.5 Hz, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.13–1.76 (m, 8 H), 1.36 (s, 3 H), 1.45 (s, 3 H), 1.89 (ddd, J = 15.0, 7.6, 2.5 Hz, 1 H), 2.00 (dd, J = 15.0, 3.5 Hz, 1 H), 2.24 (dq, J = 12.0, 2.5 Hz, 1 H), 2.29–2.65 (series of multiplets, 6 H), 3.71–3.83 (m, 1 H), 4.32–4.45 (m, 1 H), 5.36 (q, J = 3.0 Hz, 1 H), 5.52 (br s, 1 H), 5.78 (dd, J = 9.5, 6.0 Hz, 1 H), 5.99 (d, J = 9.5, Hz, 1 H), 9.78 (t, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 11.78, 13.86, 16.27, 19.83, 22.86, 23.90, 26.89, 27.55, 29.75, 30.09, 32.65, 33.77, 36.83, 37.37, 41.48, 49.88, 64.71, 67.91, 69.36, 98.81, 128.28, 129.51, 131.91, 133.49, 176.66, 201.05; exact mass, m/z 446.3041 (calcd for $C_{27}H_{42}O_5$, m/z 446.3032).

[1*S*-[1α(*R),3α,7β,8β(2*S**,4*S**,6*R**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4,6-dihydroxy-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-Methylbutanoate and [1*S*-[1α(*R**),3α,7β,8β-(2*S**,4*S**,6*S**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4,6-dihydroxy-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-Methylbutanoate (56).** Aqueous hydrochloric acid (10% v/v, 0.350 mL) was added to a solution of aldehyde **55** (8.8 mg, 0.0197 mmol) in THF (1 mL), and the mixture was swirled and left at room temperature for 4 h under argon. By this stage all of the starting material had been hydrolyzed (TLC, silica, ether). Solid sodium bicarbonate (200 mg) was added cautiously with stirring, followed by dichloromethane (10 mL) and water (2 mL). The organic phase was separated and washed with water (1 × 2 mL), and the combined aqueous phases were extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford, after drying for 12 h under oil pump vacuum, a mixture of anomeric lactols **56** (7.8 mg, 97%). These were oxidized immediately without characterization.

[1*S*-[1α(*R),3α,7β,8β(2*S**,4*S**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-Methylbutanoate [(+)-Mevinolin] (1b).** Silver carbonate on Celite[55,63] (262 mg, ca. 0.45 mmol) was added to a stirred solution of the dry lactols **56** (7.8 mg, 0.01918 mmol) in dry toluene (2 mL), and the mixture was stirred at 85–95 °C (oil bath temperature) for 1 h under argon. At this stage, TLC (silica, 9:1 ether–ethyl acetate) showed that all the starting material had reacted. The mixture was cooled to room temperature and filtered through a column of Celite (1 × 4 cm), the solids being washed with ethyl acetate (5 × 10 mL). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (1 × 16 cm) using first ether and then 9:1 ether–ethyl acetate gave synthetic mevinolin **1b** (6.0 mg, 77%) as a homogeneous [TLC, silica, 9:1 ether–ethyl acetate; ^{1}H NMR (300 MHz)], colorless, crystalline solid. For ease of handling, the material was recrystallized from dichloromethane–petroleum ether, without change in its ^{1}H NMR (300 MHz) spectrum, to afford long colorless needles: mp 155.5–158.5 °C (lit.[6b] 157–159 °C); $[\alpha]^{27.5}_D$ +334.67° (c 0.254275, CH_3CN). An authentic sample had $[\alpha]^{27.5}_D$ +331.60° (c 0.10675, CH_3CN). The synthetic compound was indistinguishable [^{1}H NMR (300 MHz), ^{13}C (75.469 MHz), HRMS] from natural material.

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Supplementary Material Available: Discussion, experimental details, and appropriate spectroscopic data for all the model studies; experimental details and appropriate spectroscopic data for the synthesis of compactin (i.e., reactions of Scheme VII); **9a**; **11**, **14–17**, **5**, and **18** (i.e., reactions of Scheme III); **19–26** (i.e., reactions of Scheme IV); **28–33** (i.e., reactions of Scheme V); 3,3-dimethoxypentane; (*S*)-phenylalaninol; and *rac*-**31**; and procedures for the determination of the optical purity of **24** and **31** (115 pages). Ordering information is given on any current masthead page.