Total Synthesis and Biological Evaluation of Structural Analogues of Compactin and Dihydromevinolin

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The full experimental details for the total synthesis of (+)-compactin and 19 structural analogues are reported. We have evaluated three classes of analogues as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase: (1) functional and stereoisomeric analogues that possess the full carbon skeleton of compactin or dihydromevinolin, (2) functional analogues in which one carbon of the skeleton has been replaced by oxygen, and (3) analogues in which all of the 3,5-dihydroxyvaleric acid moiety has been omitted. Our most potent inhibitors belong to the first class of analogues. Compounds **42** (5-ketocompactin) and **69** (5-ketodihydromevinolin) are as active as the natural products compactin and dihydromevinolin, respectively (I_{50} = 1–20 nM). The corresponding enones **37** and **68** are less active, having I_{50} values 20–30 times larger. Inverting the stereochemistry at C-3 or C-5 or about the hexahydronaphthalene ring of compactin results in the elevation of the I_{50} to values in the micromolar range, comparable to the K_M of the natural substrate 3-hydroxy-3-methylglutaryl coenzyme A. Class 2 analogues are active in this concentration range also. The synthetic sequence developed for compactin and its analogues includes a new method that permits the selective preparation of either the *R* or the *S* epimer at C-3 of the 3,5-dihydroxyvaleric acid moiety. This entails the reaction of anhydride **9** with either (*R*)- or (*S*)-1-phenylethanol in the presence of 4-(*N*,*N*-dimethylamino)pyridine and triethylamine. The prochiral recognition is surprisingly high; under optimum conditions, the reaction of **9** with (*R*)-1-phenylethanol leads to a 15:1 ratio of diesters **17** and **18**.

Approximately one-half of the deaths that occur in the United States each year are attributed to atherosclerosis.[1] Epidemiological, clinical, and laboratory research has confirmed that the probability of contracting atherosclerosis is related to high levels of plasma lipids, particularly cholesterol in the form of its conjugate with apolipoprotein B (low-density lipoprotein, LDL).[2] Several hypocholesterolemic agents have been devised for use in lowering LDL levels. One of these agents, cholestyramine, has been utilized in a major study with 2000 patients having primary hypercholesterolemia over a 7-year period; LDL levels were lowered by 11% and nonfatal myocardial infarctions and coronary deaths were lowered by 19% in this group.[3] However, this drug must be used in large amounts and is not convenient for the patient.[4]

It has been clear for some time that a more attractive therapy might involve the regulation of de novo cholesterol synthesis. In humans, more than one-half of total body cholesterol is derived from this process.[5] An important step in the biosynthesis of cholesterol and other isoprenoids is the reduction of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid, catalyzed by the enzyme HMG CoA reductase (HMGR). This enzyme is the site of primary regulation for sterol biosynthesis. There has been a large amount of interest in the possibility of controlling it pharmacologically as a way to cope with hypercholesterolemia, and a few medicinal agents have been introduced that may have the effect of diminishing HMGR activity.[6]

In 1976, Endo and co-workers at the Sankyo Co. in Japan examined the metabolites of *Penicillin citrinum* and isolated a material that turns out to be an exceedingly potent competitive inhibitor of HMGR.[7] The same compound was subsequently isolated from *Penicillin brevicompactum* by Brown and co-workers of Beecham Pharmaceuticals in England and named compactin (**1**).[8] Compactin is a very effective competitive inhibitor of HMGR, having K_i = 1.4 nM.[9] For comparison, K_m for HMG CoA is about 10^4 nM; thus, the affinity of HMGR for compactin is almost 10 000 times its affinity for its natural substrate. A second, more active fungal metabolite was isolated by Endo from *Monascus ruber*[10] and by a Merck group from *Aspergillus terreus*.[11] The new substance, called monacolin K by Endo and mevinolin by the Merck group, was shown to have stereo structure **2**. The active forms of compactin and mevinolin are the open-chain dihydroxy acids **3** and **4**, respectively.[11]

Compactin and mevinolin have both been shown to be effective in lowering plasma cholesterol levels in clinical trials,[12–15] and it is clear that these compounds have a

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(3) (a) Lipid Research Clinics Program: The Lipid Research Clinics Coronary Prevention Trial Results: I. Reduction in Incidence of Coronary Heart Disease, *JAMA, J. Am. Med. Assoc.* **1984**, *251*, 351. (b) Lipid Research Clinics Program: The Lipid Research Clinics Coronary Prevention Trial Results: II. The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering, *JAMA, J. Am. Med. Assoc.* **1984**, *251*, 365.
(4) Brown, M. S.; Goldstein, J. L. *The Pharmacological Basis of Therapeutics*; Gilman, A. G., Goodman, L. S., Rall, T. W.; et al., Eds.; Macmillan: New York, 1985; pp 827–845.
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(7) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31. (d) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.
(8) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(9) (a) Tanzawa, K.; Endo, A. *Eur. J. Biochem.* **1979**, *98*, 195. (b) Fears, R.; Richards, D.; Ferres, H. H. *Atherosclerosis* **1980**, *35*, 439. (c) Endo, A. *Atherosclerosis (Berlin)* **1980**, *5*, 152.
(10) (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852. (b) Endo, A. *J. Antibiot.* **1980**, *33*, 334.
(11) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, G.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirschfield, J.; Hoogstein, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

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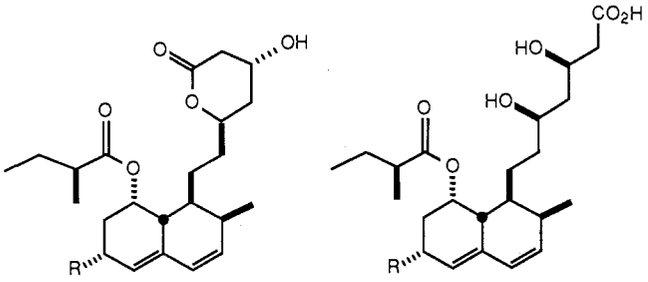


1 : R=H
2 : R=Me

3 : R=H
4 : R=Me

potential pharmacological use as hypocholesterolemic agents. It is important to understand more fully how compactin and mevinolin inhibit HMGR; from such an understanding, even more effective inhibitors may be developed. In fact, a large amount of effort has been devoted to the synthesis of mevinic acids.[16] In a recent paper,[17] we reported our approach to elaborating aldehydes such as **5** into mevinic acids and we have since reported the application of the strategy to a total synthesis of (+)-dihydromevinolin.[18] In the present paper, we report the full experimental details for the total synthesis of (+)-compactin (**1**) and the synthesis and biological evaluation of a number of structural analogues of compactin and dihydromevinolin.

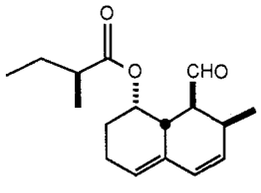
In the course of our investigations, the Merck group have published several papers and patents[19] on simple compactin analogues. One patent[20] dealing with the preparation of a naphthalene analogue has been assigned to the Sandoz Co. and a paper from G. D. Searle & Co.[21] has appeared. No biological activity data has been reported for analogues that have the full compactin or mevinolin skeleton.

Table I. Reaction of Anhydride **9** with (*R*)-2-Phenylethanol

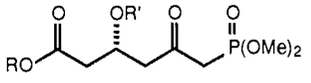
entry	temp, °C	base	(equiv)	yield, %	ratio, 17:18
1	−30	Et_3N	(1.0),		
		DMAP	(0.25)	65	8:1
2	25[a]	Et_3N	(1.0)	70	1:1.2
3	−30	DBU	(1.0)	80	1:3
4	−30	Et_3N	(1.0),		
		DMAP	(0.5)	68	10:1
5	−30	DMAP	(1.0)	70	12:1
6	−40	Et_3N	(1.0),		
		DMAP	(0.25)	70	10:1
7	−40	DMAP	(1.0)	75	15:1

[a] Seven kilobars of pressure.

Synthesis of Enantiomerically Homogeneous 3-Hydroxyglutarate Reagents. The basic strategy of our approach was to condense a protected β-hydroxy keto phosphonate with the optically active hexalin aldehyde **5**. As a starting material for the preparation of **6**, hydroxy acid **7** was attractive, since the compound is available in optically active form by chymotrypsin-mediated hydrolysis of dimethyl 3-hydroxypentanedioate.[22] Although enantiomerically enriched **7** is available by this method, decreases in the optical yield of the enzymatic reaction result if the pH of the reaction mixture is not properly controlled. Even with the utmost care, it is impossible to secure **7** in an enantiomeric purity of more than 80% ee.[23] Furthermore, since **7** is not crystalline, it is not possible to enhance its enantiomeric purity by recrystallization. Thus, we explored alternative ways to obtain compound **7** or some synthetic equivalent in enantiomerically homogeneous form.



5



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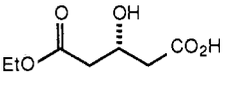

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As shown in Scheme I, treatment of commercially available diethyl 3-hydroxypentanedioate with *tert*-butylchlorodimethylsilane and imidazole affords silyl ether **8** in 95% yield. Compound **8** is converted to the corresponding dicarboxylate, which is cyclized to obtain crystalline **9** in 70% yield for the two-step sequence.[24] Treatment of diethyl 3-hydroxypentanedioate with *N*-

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(15) "Therapeutic Response to Lovastatin (Mevinolin) in Nonfamilial Hypercholesterolemia", *JAMA, J. Am. Med. Assoc.* **1986**, *256*, 2829.

(16) For a review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

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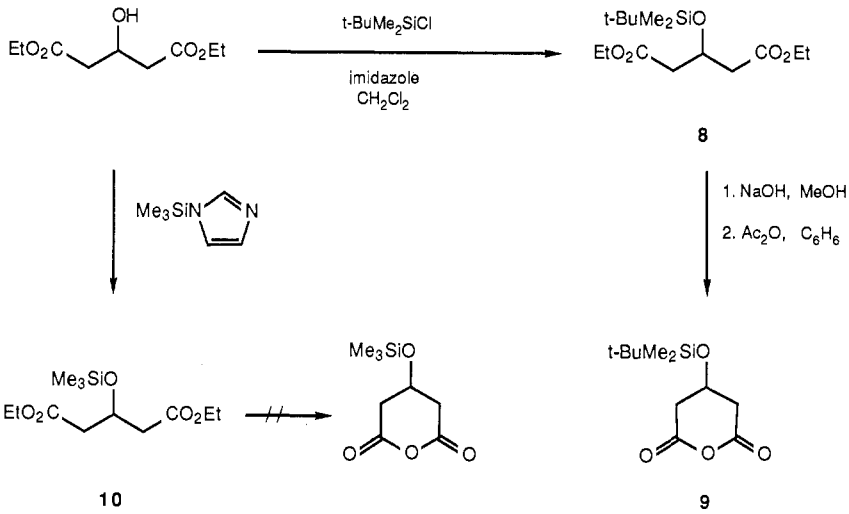
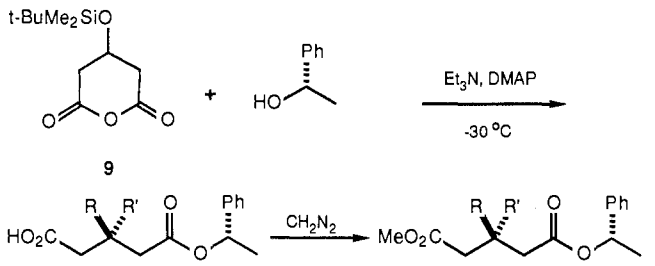
(24) On a relatively small scale (less than 5 mmol), the corresponding dipotassium salt is converted into **9** in greater than 80% yield. However, the disodium salt is more convenient for larger scale preparations, because it is pulverized more readily and is more soluble in benzene than its potassium counterpart. Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657.

Scheme I

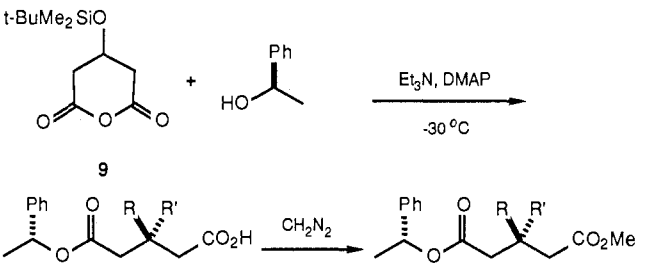


Scheme II



11 : R=H, R'=t-BuMe$_2$SiO
12 : R=t-BuMe$_2$SiO, R'=H
13 : R=H, R'=t-BuMe$_2$SiO
14 : R=t-BuMe$_2$SiO, R'=H

Scheme III

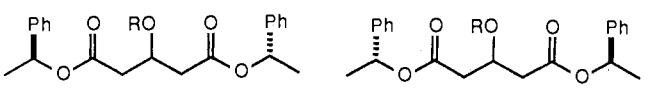


15 : R=H, R'=t-BuMe$_2$SiO
16 : R=t-BuMe$_2$SiO, R'=H
17 : R=H, R'=t-BuMe$_2$SiO
18 : R=t-BuMe$_2$SiO, R'=H

(trimethylsilyl)imidazole[25] furnishes analytically pure trimethylsilyl ether **10** in quantitative yield. However, this material decomposes upon attempted conversion to the corresponding anhydride.

Reaction of anhydride **9** with (*S*)-phenethyl alcohol in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at −30 °C, followed by treatment of the resulting acids (**11** and **12**) with diazomethane furnishes diesters **13** and **14**. A surprisingly high degree of prochiral recognition is observed in the anhydride opening; when the reaction is carried out at −30 °C, **13** and **14** are isolated in a ratio of 6:1 (70% yield) (Scheme II). The enantiomeric diesters (**17** and **18**) are obtained by employing (*R*)-phenethyl alcohol in the anhydride opening (Scheme III).

The chemical yield for the two-step transformation (**9** → **13** + **14** or **9** → **17** + **18**) is 70–75%. Minor side products are the respective bis(phenylethyl) glutarate esters **19** and **20**, presumably formed by attack of the intermediate carboxylate on anhydride **9**, followed by acylation of a second molecule of alcohol by the resulting mixed anhydride. Similar observations of asymmetric induction in the opening of substituted glutaric anhydrides by chiral amines have appeared recently in the literature.[26]



19 : R=t-BuMe$_2$Si
21 : R=H
20 : R=t-BuMe$_2$Si
22 : R=H

The prochiral recognition in these acylation reactions may be discussed with the aid of Scheme IV, which sets forth a suggested mechanism for the reaction of **9** with (*R*)-2-phenylethanol. In the absence of DMAP the reaction is very slow. Thus, we assume that the first step is reaction of anhydride **9** with DMAP to give the *R* and *S* intermediates shown in Scheme IV. Since anhydride **9** and DMAP are both achiral, the rates of formation of these two enantiomeric intermediates must be equal. Prochiral recognition presumably occurs in the competitive reactions of the intermediates with chiral alcohol, giving **15** and **16**. In the reaction of the enantiomeric *N*-acylpyridinium intermediates with (*R*)-2-phenylethanol, acid **15** (and ultimately, diester **17**) predominates; therefore, for this alcohol, $k_S > k_R$.

The results of a number of experiments that were carried out in order to optimize the degree of prochiral recognition in the reaction of anhydride **9** with (*R*)-2-phenylethanol are summarized in Table I. In the absence of DMAP, the reaction proceeds at a pressure of 7 kbar, but with essentially no prochiral recognition (entry 2). The reaction occurs at ambient pressure in the absence of DMAP if 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is used as the base instead of triethylamine; in this case, however, the major product is **18**, rather than **17**. This observation shows that reaction of alcohol (or alkoxide ion) with the cyclic anhydride itself shows a sense of prochiral recognition opposite to that seen in the reaction of the alcohol with the two *N*-acylpyridinium salt intermediates. It follows that, to the extent that any anhydride opening occurs by this mechanism in the DMAP-mediated reaction,

(25) Birkofer, L.; Ritter, A. *Angew, Chem., Int. Ed. Engl.* **1965**, *4*, 417.

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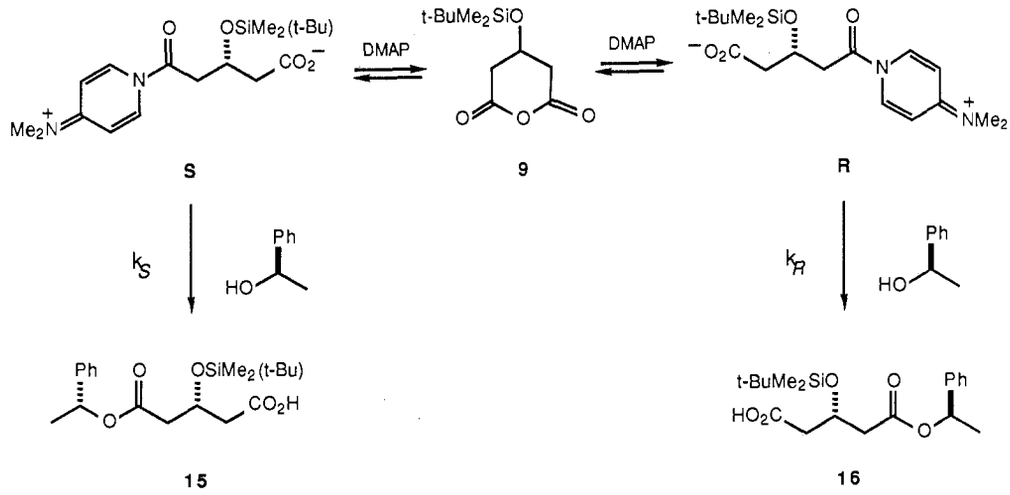
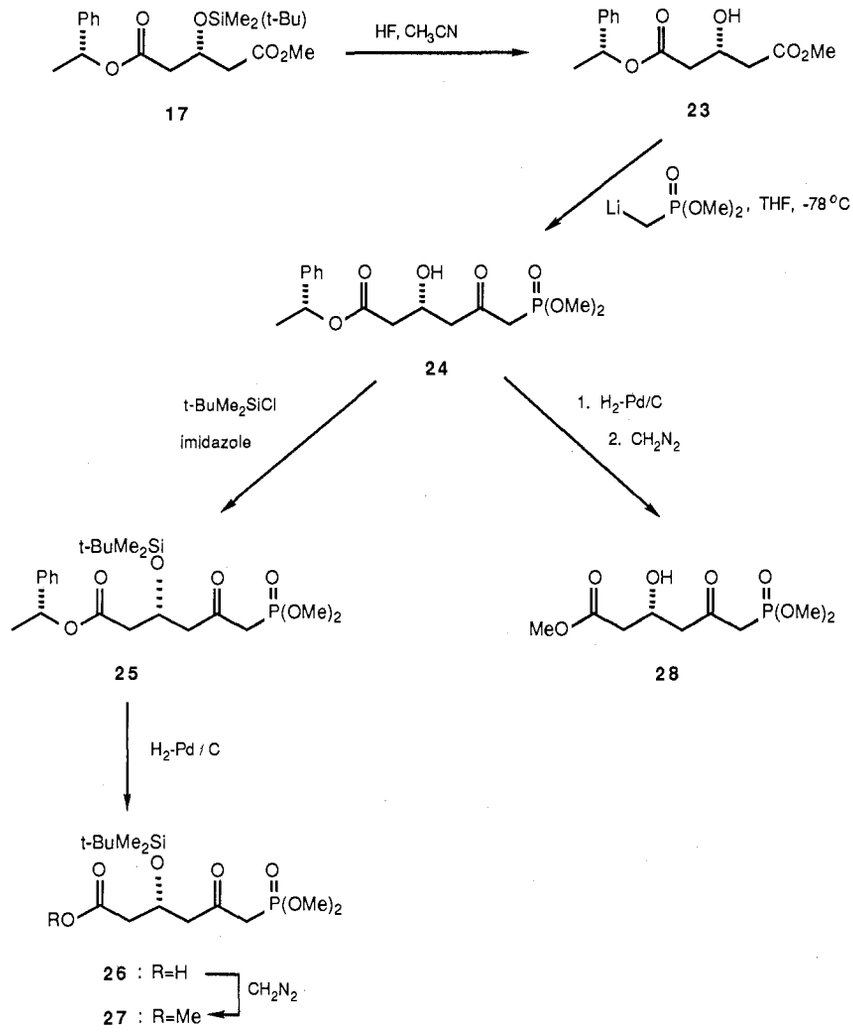
Scheme IV

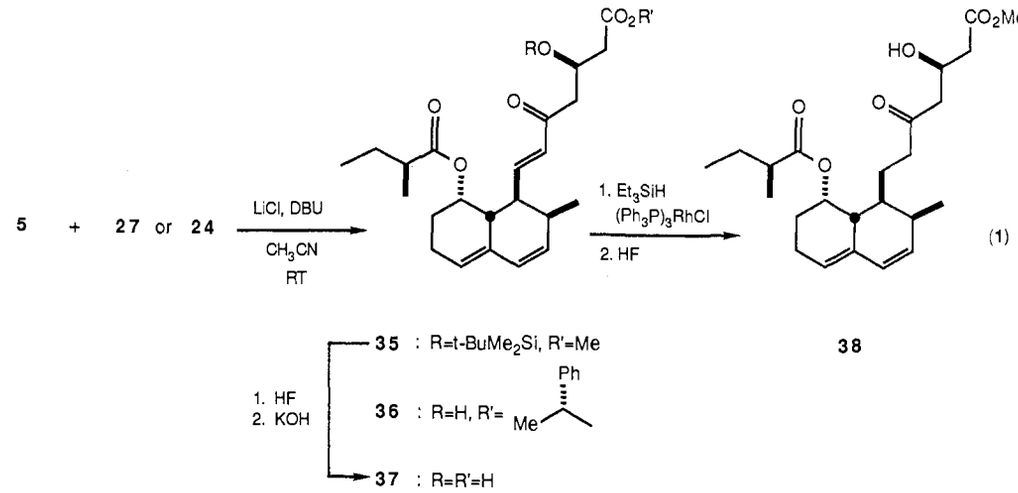


Scheme V

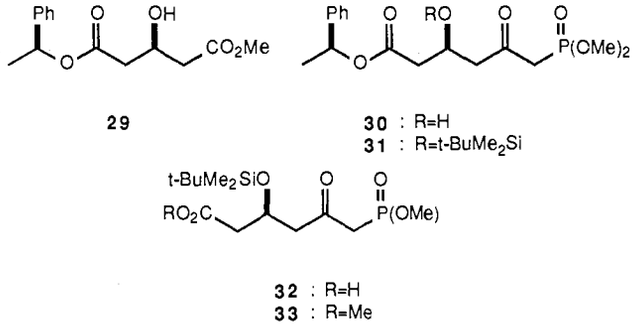


net prochiral recognition will be diminished. A way to enhance stereoselectivity would be to increase the amount of DMAP. Entries 4 and 5 in Table I show that this hypothesis was confirmed. Finally, as expected, enhanced stereoselectivity is observed at lower temperatures (entries 6 and 7). The optimum conditions, leading to a 15:1 ratio of **17** and **18**, employ 1.0 equiv of DMAP at −40 °C; larger amounts of the base led to no further improvement and lower temperatures resulted in a reaction rate too slow for convenient application.

The diastereomeric mixtures **13**/**14** and **17**/**18** are separable by preparative high-performance liquid chromatography (HPLC). Although some of the transformations to be described in the sequel were developed with the mixtures (8:1), each compound described was eventually prepared in greater than 99% enantiomeric purity. The transformation of **17** to several keto phosphonate synthons is summarized in Scheme V. Desilylation of **17** provides hydroxy ester **23** (100%), which is condensed with dimethyl lithiomethylphosphonate to obtain keto phospho-



nate **24** (43% yield), attack occurring exclusively at the methyl ester.[27] Silylation of **24** followed by hydrogenolysis of the phenylethyl ester and esterification of the resulting acid provides keto phosphonate **27** in 79% yield for the three-step sequence. The progress of the silylation reaction must be monitored carefully to minimize the formation of a bis-silylated material formed by further reaction of the β-keto phosphonate with the silyl chloride. Hydrogenolysis of **24** followed by diazomethane esterification of the resulting carboxylic acid provides ester **28**. The enantiomeric series of phosphonate reagents (**30–33**) is obtained from diester **13** by an identical sequence of reactions.



Synthesis of Compactin and Functional Analogues. Reaction of aldehyde **5**[28] with phosphonate **27** in the presence of lithium chloride and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)[29] produces enone **35**. The reaction is quite clean; the only materials isolated are coupled product (35–60%), recovered aldehyde (35–50%), and recovered phosphonate.[30] It should be noted that the coupling procedure is sufficiently mild that the (*S*)-2-methylbutyryl moiety may be present, thus obviating the need to employ a protecting group for the C-8 hydroxyl. Condensation of **5** and hydroxy keto phosphonate **24** also occurs under these mild conditions to provide β-hydroxy ketone **36** in 42% yield. The fully deprotected derivative **37** is produced from **35** by sequential desilylation and saponification. Selective 1,4-reduction of the enone functionality is accomplished smoothly with triethylsilane and tris(triphenylphosphine)rhodium(I) chloride;[31] concentration of the reaction mixture and treatment of the residue with aqueous HF in acetonitrile furnishes hydroxy ketone **38** in 87% yield (eq 1).

Conversion of **38** to compactin and several derivatives is summarized in Scheme VI. Sodium borohydride reduction of **38** gives diastereomers **39** and **40** in a ratio of about 2:1. The diols are separated easily by HPLC, and the major product is lactonized to obtain (+)-compactin (**1**) (70% yield). The minor diol **40** is lactonized to provide 5-*epi*-compactin (**41**). Saponification of **38** affords derivative **42**. The spectra of **1** and **41** are quite different; in trans lactone **1**, J_{ab} and J_{ac} are 5.0 and 3.8 Hz, respectively, consistent with H_a being equatorial. In the spectrum of the cis lactone **41**, J_{ab} and J_{ac} are 5.8 and 8.0 Hz, respectively, consistent with H_a being axial.

In connection with the total synthesis of compactin itself, it was important to establish that one can differentiate spectroscopically between compactin and 3,5-bis-*epi*-compactin (**48**), which has the same relative stereochemistry on the lactone ring as **1**. We were also interested in preparing stereoisomers **48** and **49** for biological evaluation. The synthesis of these isomers is shown in Scheme VII. Coupling of aldehyde **5** with keto phosphonate reagent **43** provides enone **44** in 50% yield. Conjugate reduction of the enone furnishes **45**, which is treated with sodium borohydride to obtain a mixture of diols **46** (major) and **47**. After separation, the diols are lactonized to obtain **48** and **49**. The 250-MHz ^1H NMR spectra of lactones **1** and **48** are virtually identical in the region corresponding to the methylene protons adjacent to the lactone carbonyl. However, the two compounds may be distinguished easily from the upfield regions of their spectra. In the spectrum of compactin, the ring-methyl doublet and the methyl triplet of the methylbutyrate side chain overlap such that one observes a three-line pattern. In the spectrum of **48** all lines for the doublet and triplet are seen.

By the same method, starting with aldehyde **50**,[29] diastereomers **51** ("tetra-*epi*-compactin") and **52** ("penta-*epi*-compactin") were prepared.

Preparation of Glutarate Analogues. As shown in Scheme VIII, glutarates **55** and **56** were prepared by acy-

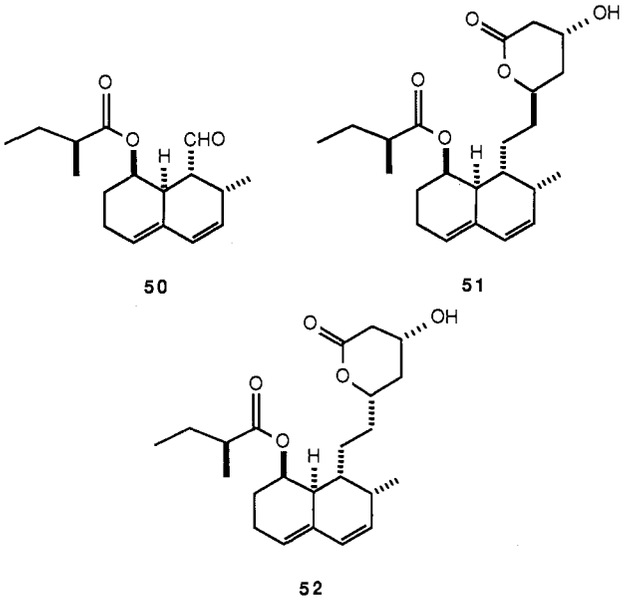
(27) Silyl ether **17** must be deprotected prior to the phosphonate reaction; if **17** is treated with dimethyl (lithiomethyl)-phosphonate, a substantial amount (ca. 30%) of β elimination occurs. In addition, preference for attack of the phosphonate reagent at the methyl ester is only modest (3:1).

(28) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.

(29) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakay, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(30) Attempts to obtain a greater conversion by longer reaction time or higher temperature resulted in lower yields, due to subsequent β elimination of the product. With less hindered aldehydes, the Horner–Emmons reaction is faster and excellent yields of enone may be obtained at conversions approaching 100%.

(31) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5035.



50 51 52

lation of the corresponding alcohols[29] with glutaric anhydride; chemical yields for these transformations were on the order of 55–60%.

To prepare glutarate analogues having the C-3 hydroxy group, acids **57** and **58** were prepared by hydrogenolysis of phenylethyl esters **13** or **14**, respectively, according to Scheme IX. Conversion of these compounds to their *tert*-butyldimethylsilyl esters and subsequent treatment with oxalyl chloride in the presence of catalytic *N,N*-dimethylformamide (DMF)[32] furnishes the corresponding acid chlorides. Reaction of the acid chlorides with alcohol **53** affords esters **61** or **62**.[33] The method of Bartlett and Johnson[34] is employed to selectively cleave the methyl ester, providing glutarate analogues **63** and **64** (this step proceeds to give the carboxylic acid in 20–42% yield for the four cases that were examined). The ^{1}H NMR spectrum of the crude product mixture indicates the presence of a substantial quantity of alcohol **53**. Thus, attack of mercaptide at the carbonyl of the primary acyl linkage in **61** is presumably the factor responsible for the low yield of **63**. Alternative methods for hydrolysis of the methyl ester were not investigated, since sufficient quantities of material for biological evaluation were obtained. A similar sequence of reactions, using alcohol **54** yields analogues **65** and **66**.

Evaluation of HMGR Inhibitory Activity of Mevinic Acid Analogues. Biological activities have been evaluated with rat liver microsomes. The effect of the potential inhibitor on the initial velocity of mevalonate production was determined in a radioactive assay system modeled after that described by Edwards et al.[35] and used extensively for the evaluation of HMGR inhibitors.[36]

Table II. Inhibition of Rat Liver HMG CoA Reductase by Analogues of Compactin and Dihydromevinolin

inhibitor	I_{50},[a,b] nM
1 ((+)-compactin)	13
42 (5-ketocompactin)	32
37 (compactin enone)	630
41 (5-*epi*-compactin)	2000
49 (3-*epi*-compactin)	4000
48 (3,5-bis-*epi*-compactin)	2000
51 (tetra-*epi*-compactin)	10000
52 (penta-*epi*-compactin)	79000
67 (dihydromevinolin)	1.6
69 (5-ketodihydromevinolin)	1.0
68 (dihydromevinolin enone)	320
55 (glutarate)	7100
56 (tetra-*epi*-glutarate)	110000
63 (3-hydroxyglutarate)	630
64 (3-*epi*-3-hydroxyglutarate)	5000
65 (tetra-*epi*-3-hydroxyglutarate)	>25000
66 (penta-*epi*-3-hydroxyglutarate)	25000

[a] Concentration required to inhibit mevalonate production by 50% relative to uninhibited control. [b] Four concentrations of inhibitor ranging over four appropriate orders of magnitude were assayed in duplicate along with uninhibited controls. Inhibited rates were compared to control rates to provide percent inhibition values at each inhibitor concentration. Duplicates differed by <7% inhibition. Duplicate percent inhibition values were averaged and average percent inhibitions were plotted against log inhibitor concentrations. I_{50} values were derived by extrapolation.

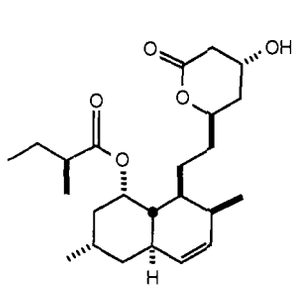
We have evaluated three classes of analogues: (1) functional and stereoisomeric analogues that possess the full carbon skeleton of compactin or dihydromevinolin; (2) functional analogues in which one carbon of the skeleton has been replaced by oxygen; and (3) analogues in which all of the 3,5-dihydroxyvaleric acid moiety has been omitted. The results will be briefly discussed under these categories.

(1) Functional and Stereoisomeric Analogues That Possess the Full Carbon Skeleton of Compactin or Dihydromevinolin. We have standardized on assaying lactones in their open-chain forms so comparisons with 5-keto analogues will be more valid. It has been shown that the open-chain forms are 5–10 times more active than the lactone forms.[11] I_{50} values for compactin and seven compounds that have the full carbon skeleton are listed in Table II. Enone **68** and saturated ketone **69** were obtained in connection with our recent total synthesis of dihydromevinolin (**67**).[18] Data for these three compounds are also shown.

The data in Table II show several interesting things. First, in agreement with the previous literature,[37] our dihydromevinolin was found to be slightly more potent as an inhibitor than our compactin. It is significant that ketones **42** and **69** show the same activity as compactin and dihydromevinolin, respectively. It is possible that these analogues bind to the enzyme and are reduced, giving the active inhibitors. The Merck group has recently filed for patent coverage on the 5-keto analogue of mevinolin, which was prepared from a natural substance;[38] however, no information on biological activity of this material has been disclosed.

Although saturated ketones **42** and **69** have the same activity as the corresponding natural products, the analogous enones **37** and **68** are less active by a factor of about 50. This significant difference in activity may contain information pertaining to the preferred conformations of **42** and **69** (and, by inference, of the natural substrate)

(32) Wissner, A.; Grudzinkas, C. V. *J. Org. Chem.* **1978**, *43*, 3972.
(33) With relatively unhindered alcohols, we normally generate solutions of acid chlorides **57** and **58**, which are used as such. However, for the acylation of **53** and **54**, it is necessary to concentrate the crude acid chloride and subject it to high vacuum. One molar equivalent of *tert*-butylchlorodimethylsilane is formed in the preparation of **57** and **58**. If the silyl chloride is not removed, silylation of the alcohol is competitive with acylation.
(34) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1972**, 4457.
(35) Edwards, P. A.; Lemongello, D.; Fogelman, A. N. *J. Lipid. Res.* **1979**, *20*, 40.
(36) See, inter alia: Baran, J. S.; Laos, I.; Langford, D. D.; Miller, J. E.; Jett, C.; Taite, B.; Rohrbacher, E. *J. Med. Chem.* **1985**, *28*, 597.
(37) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.
(38) Hoffman, W. F.; Lee, T. J.; Stokker, G. E., Merck & Co., Inc., Eur. Patent Appl. 142,146 A2, May 22, 1985.



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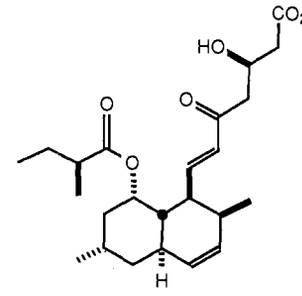

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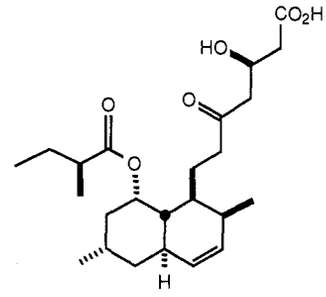

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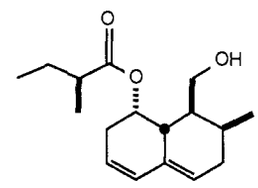
when they bind to the active site.

The 5-epi isomer **41**, the 3-epi isomer **49**, and the 3,5-bis-epi compound **48** are all less active than compactin by factors of about 200.[39] This information suggests that the stereochemistry of the first hydride delivery is to the *si* face of the thio ester carbonyl group of the natural substrate. The low activity of the 3-epi compound shows that the C-3 hydroxy group probably plays an important role as a point of attachment of the inhibitors to the active site—most likely by hydrogen bonding.

Compound **51** has the "correct" stereochemistry at C-3 and C-5 for optimal binding of the inhibitor to the active site. Nevertheless, its activity is reduced by a factor of about 800, relative to **1**. The penta-epi isomer **52**, which also has the incorrect stereochemistry at C-5, is even less active—less than $^1/_{500}$ as active as **1**. These results show that the shape of the hexalin unit is rather important in achieving effective inhibition of the enzyme. In fact, the apparent activity observed with **51** may be exaggerated. This isomer was prepared from aldehyde **50** by a synthesis that included a chromatographic separation of the (*R*)-*O*-methylmandelate esters of alcohols **5** and **50**. Even if the chromatographic separation used to separate these diastereomers gives alcohol **50** of 99.9% de, the residual 0.05% **5** would lead eventually to **51** containing enough **1** to account for all of the observed activity.

(2) Functional Analogues in Which One Carbon of the Skeleton Has Been Replaced By Oxygen. Biological data for glutarate esters **55**, **56** and **63–66** are summarized in Table II. All of the glutarate esters were significantly less active than compactin acid. The most active analogue, **63**, does have about 3% residual activity. However, none of the other compounds are within a factor of 300 of the natural inhibitor. Nevertheless, the activity seen is well above the noise level and shows that these simple analogues do bind to the enzyme active site. For example, the I_{50} for glutarate **63** is on the order of 15 times less than the K_m for HMG coenzyme A itself, while those for **64–66** are approximately equal to the K_m of the natural substrate. It is possible that some or all of these glutarate esters undergo reduction under the conditions of the assay. If this were to be the case, in contrast to the situation with ketones **42** and **69**, a product would be formed (alcohol **53**, vide infra) that is not an active inhibitor.

(3) Analogues in Which All of the 3,5-Dihydroxyvaleric Acid Moiety Has Been Omitted. Alcohol **53** is an intermediate on the way to compactin, and compounds **70** and **71** resulted from an unexpected elimination reaction encountered in that project.[29] These hexalin units show no inhibitory activity.



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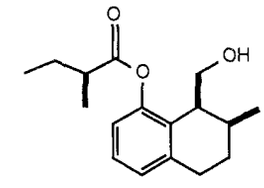

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Experimental Section

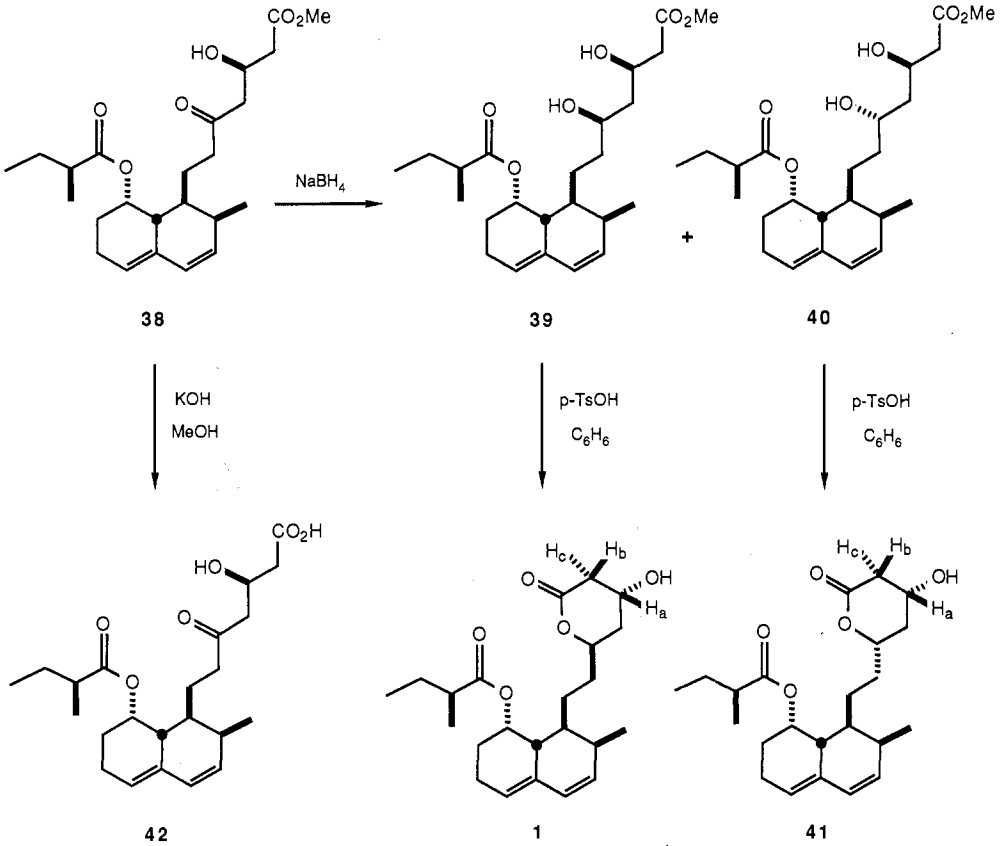
General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran were distilled from sodium/benzophenone immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored over 4-Å molecular sieves. Dichloromethane was distilled from phosphorus pentoxide. Boiling points and melting points are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 or Model 1420 infrared recording spectrophotometer. ^{1}H NMR spectra were determined with FT spectrometers operating at 200 or 250 MHz. ^{13}C NMR spectra were measured at 62.89 MHz. All NMR spectra were determined with $CDCl_3$ as the solvent. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were obtained with Atlas MS-12, Consolidated 12-110B, or Kratos MS-50 mass spectrometers. Ultraviolet (UV) spectra were recorded with a Varian 219 UV spectrometer. Gravity column chromatography was done with Merck silica gel 60 (70–230 mesh ASTM), and flash chromatography[40] was done with MN silica gel 60 (230–400 mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm) and compound visualization was effected with a 5% solution of 12-molybdophosphoric acid in ethanol or a solution of 10% vanillin and 5% sulfuric acid in 95% ethanol. High-pressure liquid chromatography (HPLC) was done with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters Prep LC/system 500 (preparative). μ-Porasil columns were used unless otherwise indicated. Capillary GLPC analysis was done with a Hewlett-Packard 5790A series gas chromatograph (12 m, cross-linked methylsilicone, programmed, 45 °C, 3 °C/min). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

Diethyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (8). Under a nitrogen atmosphere, into a 500-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 36.8 g (180 mmol) of diethyl 3-hydroxyglutarate and 100 mL of CH_2Cl_2. To this stirring solution were added 20.4 g (300 mmol) of imidazole and 30.1 g (200 mmol) of *tert*-butylchlorodimethylsilane. The resulting white suspension was stirred at room temperature for 4 h, 40 min, 2.04 g (30.0 mmol) of imidazole and 3.01 g (20.0 mmol) of *tert*-butylchlorodimethylsilane were added, and the mixture was stirred for 80 min. The reaction mixture was diluted with 200 mL of ether and washed with two 50-mL portions of H_2O and 50 mL of brine. The combined aqueous washings were extracted with 50 mL of ether, the combined organic fractions were dried over $MgSO_4$, and the solvent

(39) Stokker, G. E.; Rooney, C. S.; Wiggins, J. M.; Hirshfield, J. *J. Org. Chem.* **1986**, *51*, 4931. The authors report similar inhibitory potency for the corresponding C-5 diasteromer of mevinolin.

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

Scheme VI



was removed with a rotary evaporator to afford 60 g of yellow liquid. The crude product was distilled through a vacuum-jacketed column to obtain 48.6 g (85% yield) of silyl ether **8** as a colorless liquid, bp 112–114 °C (0.05 mm). IR (film): 2940, 2865, 1745 cm^{-1}. ^1H NMR: δ 0.07 (s, 6), 0.84 (s, 9), 1.26 (t, 6, J = 7.1), 2.54 (d, 4, J = 6.2), 4.12 (q, 2, J = 7.1), 4.13 (q, 2, J = 7.2), 4.55 (quintet, 1, J = 6.2). Anal. ($C_{15}H_{30}O_5Si$) C, H.

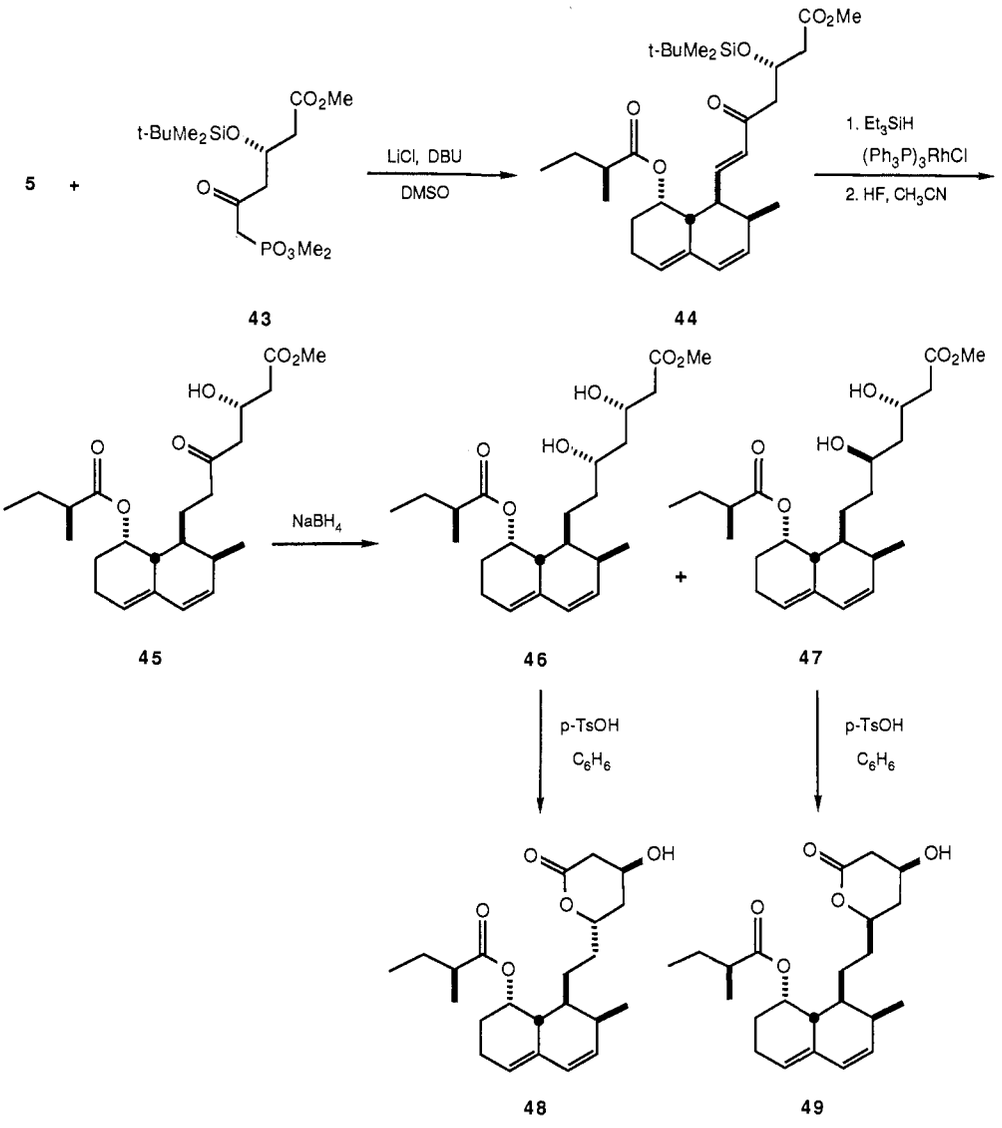
3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Anhydride (9). Under a nitrogen atmosphere, into a flame-dried 500-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed 45.0 g (142 mmol) of diester **8**. To the stirring liquid, at 0 °C, were added 11.4 g (284 mmol) of NaOH pellets and 190 mL of CH_3OH. The cold bath was removed, and the resulting suspension was stirred at room temperature for 11 h, 20 min. The solvent was removed with a rotary evaporator, and residual CH_3OH was removed under high vacuum (10 h, 0.02 mm) to obtain 43.2 g of off-white solid. The crude dicarboxylate, 300 mL of benzene, and 204 mL of acetic anhydride were placed in a 1-L round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar under a nitrogen atmosphere. The mixture was heated at reflux for 80 min, diluted with 1 L of $CHCl_3$, and washed with several portions of saturated aqueous $NaHCO_3$ and brine. The organic solution was dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The resulting brown liquid was heated under high vacuum (2 h, 50–60 °C, 0.04 mm). Upon cooling to room temperature, the product (ca. 25 g) crystallized. The brown solid was recrystallized from hexanes and rinsed well with hexanes to obtain 14.7 g of an orange crystalline solid. The mother liquor was condensed to give an additional 1.2 g of product. The overall yield of useful anhydride (**9**) was 15.9 g (46% yield). IR ($CHCl_3$): 2925, 2860, 1820, 1765, 1255 cm^{-1}. ^1H NMR: δ 0.10 (s, 6), 0.86 (s, 9), 2.72 (dd, 2, J = 2.7, 16), 2.92 (dd, 2, J = 3.8, 16), 4.38 (m, 1).

Diethyl 3-[(Trimethylsilyl)oxy]pentanedioate (10). Under a nitrogen atmosphere, into a 25-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 2.00 g (9.80 mmol) of diethyl 3-hydroxyglutarate and 5 mL of CH_2Cl_2. To the stirring solution, at 0 °C, was added 1.73 mL (1.65 g, 11.8 mmol) of *N*-(trimethylsilyl)imidazole, and the mixture was stirred at room temperature. After 12.5 h, an additional 0.17 mL (165 mg, 1.18 mmol) of *N*-(trimethylsilyl)-imidazole was added, and the mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with 30 mL of ether and washed with two 15-mL portions of brine. The combined aqueous washings were extracted with 20 mL of ether, the combined organic fractions were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator to obtain 2.69 g (quantitative yield) of analytically pure **10** as a light yellow liquid. IR (film): 2975, 1730, 1370, 1250 cm^{-1}. ^1H NMR: δ 0.01 (s, 9), 1.16 (t, 6, J = 7.2), 2.42 (d, 4, J = 6.3), 4.02 (dd, 2, J = 5.4, 7.2), 4.08 (dd, 2, J = 5.4, 7.2), 4.46 (m, 1). Anal. ($C_{12}H_{24}O_5Si$) C, H.

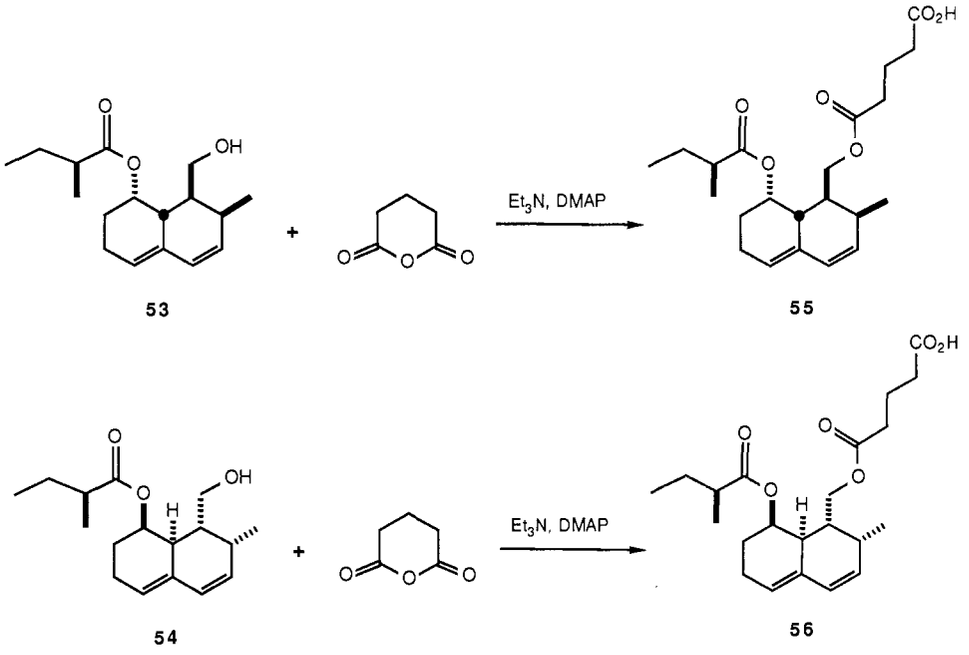
(3*S*,1′*S*)-Methyl 1′-Phenylethyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (13). Under an argon atmosphere, into a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 0.57 mL (414 mg, 4.10 mmol) of triethylamine, 124 mg (1.02 mmol) of (*N*,*N*-dimethylamino)-pyridine (DMAP), 0.74 mL (751 mg, 6.15 mmol) of (*S*)-phenylethanol, and 4 mL of CH_2Cl_2. The system was cooled in an ice/acetone bath, 1.00 g (4.10 mmol) of anhydride **9** was added, and the brown solution was stirred for 7 h, 35 min at −10 to −15 °C and 1 h, 45 min at 0 °C. The reaction mixture was diluted with 85 mL of ether and washed with 15 mL of 1 M aqueous H_3PO_4, 10 mL of saturated aqueous $NaHCO_3$, and 10 mL of brine. The ether solution was dried over $MgSO_4$ and the solvent was removed with a rotary evaporator to obtain 1.57 g of crude acid **11** as a yellow oil, which was used without further purification.

In a 500-mL round-bottomed flask (smooth glass joint) immersed in an ice bath was generated a solution of approximately 1 g (25 mmol) of diazomethane in ether. To this solution was added the foregoing acid **11** in a small amount of ether. The cold bath was removed, the reaction mixture was allowed to stand at room temperature for 40 min, and N_2 was bubbled through the solution for 1 h, 50 min (fire-polished pipet). The solution was dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain a yellow oil. The crude product was purified by column chromatography (60 g of silica gel), gradually increasing the polarity of the eluant (1:7 ether/hexanes → 1:6 ether/hexanes → 1:4 ether/hexanes) to obtain 790 mg (51%) of diastereomeric diesters **13** and **14** (6:1). IR ($CHCl_3$): 2970, 2870, 1750 cm^{-1}. Anal. (mixture) ($C_{20}H_{32}O_5Si$) C, H. Compound **13**: $[\alpha]^{25}_D$ −22.4° ($CHCl_3$, *c* 2.04). Also isolated was 490 mg of a 4:1 mixture of **13** and **14** (24%) and diester **20** (6%), and 55.0 mg (3%) of pure compound

Scheme VII



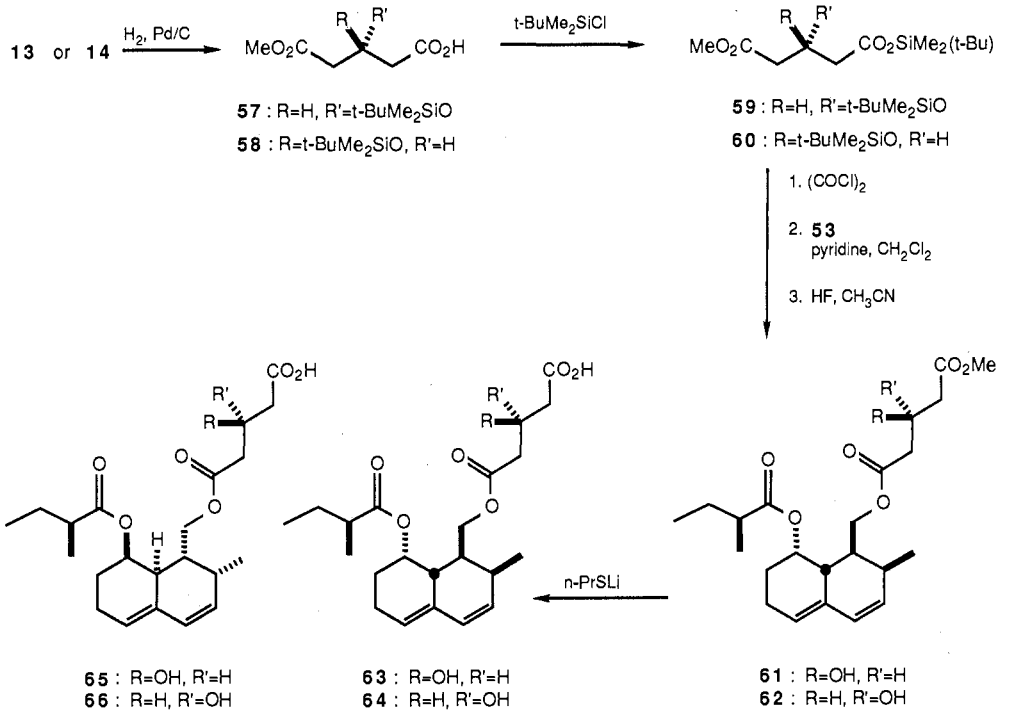
Scheme VIII



20. Compound **20**: Anal. ($C_{27}H_{38}O_5Si$) C, H. All fractions were colorless oils. The ^1H NMR spectra of **13**, **14**, and **20** were identical with those of their enantiomers (vide infra).

(3*R*,1′*R*)-Methyl 1′-Phenylethyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (17). Under an argon atmosphere, into an oven-dried 100-mL round-bottomed flask equipped with a

Scheme IX



magnetic stirring bar and a rubber septum were placed 6.63 g (54.3 mmol) of (*R*)-phenylethanol, 889 mg (7.29 mmol) of DMAP, 4.06 mL (2.94 g, 29.2 mmol) of Et_3N, and 15 mL of CH_2Cl_2. The system was cooled to −60 °C, and 7.12 g (29.2 mmol) of anhydride **9** was added. The resulting brown solution was warmed to −40 °C over a period of 45 min. The solution was stirred at −30 to −40 °C for 3.5 h, −25 to −35 °C for 4 h, and −15 to −20 °C for 1.75 h. The reaction mixture was diluted with 150 mL of ether and washed with 50 mL of 1 M aqueous H_3PO_4 and 20 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were acidified with 1 M aqueous H_3PO_4 and extracted with 50 mL of Et_2O. The combined organic fractions were dried ($MgSO_4$) and concentrated with a rotary evaporator to obtain 15.0 g of **15** as a dark orange liquid, which was used without further purification.

In a 500-mL round-bottomed flask (smooth glass joint) immersed in an ice bath was generated approximately 3.8 g (90 mmol, 0.3 M in ether) of diazomethane from Diazald. To this ice-cold solution was added the acid prepared above in a minimal amount of ether. The resulting solution was allowed to stand at room temperature for 1 h. Nitrogen was bubbled through the solution for 35 min (fire-polished pipet), and this solution was allowed to stand over $MgSO_4$ overnight. Filtration followed by concentration with a rotary evaporator afforded 14.0 g of orange liquid. The crude material was subjected to high vacuum for several hours, and the resulting liquid (13.0 g) was subjected to flash column chromatography (400 g of silica gel) eluting first with 1:6 ether/hexanes and then 1:5 ether/hexanes to obtain 7.13 g (69% yield) of an 8:1 mixture of diesters **17** and **18** as a colorless liquid. Diastereomers **17** and **18** are separable by HPLC. IR ($CHCl_3$): 2970, 2870, 1750 cm^{-1}. Compound **17**: $[\alpha]^{25}_D$ +21.9° (*c* 2.03, $CHCl_3$). ^1H NMR: δ 0.00 (s, 3), 0.04 (s, 3), 0.80 (s, 9), 1.54 (d, 3, *J* = 6.6), 2.57 (m, 4), 3.66 (s, 3), 4.54 (m, 1), 5.88 (q, 1, *J* = 6.6), 7.38 (m, 5). Compound **18**: ^1H NMR: δ 0.05 (s, 6), 0.83 (s, 9), 1.54 (d, 3, *J* = 6.6), 2.55 (m, 4), 3.65 (s, 3), 4.54 (m, 1), 5.88 (q, 1, *J* = 6.6), 7.38 (m, 5). Anal. (mixture) ($C_{20}H_{32}O_5Si$) C, H.

Also isolated was 840 mg of a mixture of the diesters (**17** and **18**) and **19** (1:1.2). Compound **19**: IR (film): 2940, 2860, 1735 cm^{-1}. ^1H NMR: δ 0.00 (s, 3), 0.03 (s, 3), 0.80 (s, 9), 1.53 (d, 3, *J* = 6.6), 1.54 (d, 3, *J* = 6.6), 2.58 (m, 4), 4.55 (m, 1), 5.87 (q, 1, *J* = 6.6), 5.88 (q, 1, *J* = 6.6), 7.38 (m, 10). Anal. ($C_{27}H_{38}O_5Si$) C, H.

Experiments were carried out to optimize the degree of prochiral recognition in the foregoing reaction. The following procedure gave the highest diastereomeric ratio. To a mixture of 0.100 g (0.82 mmol) of (*R*)-(+)-phenylethanol and 0.055 g (0.45 mmol) of DMAP in 0.50 mL of CH_2Cl_2, cooled to −60 °C, was added 0.110 g (0.45 mmol) of anhydride **9**. The resulting brown solution was warmed to −40 °C over a period of 45 min and stirred at this temperature for 24 h. The reaction mixture was diluted with 25 mL of ether and washed successively with 10 mL of 1 M H_3PO_4 and 5 mL of saturated $NaHCO_3$. The combined aqueous washings were made acidic with 1 M H_3PO_4 and extracted with 10 mL of ether. The combined organic fractions were dried ($MgSO_4$) and concentrated with a rotary evaporator to obtain 200 mg of an orange oil. This material was dissolved in a minimum amount of ether and added to 3 mL of a 0.28 M solution of CH_2N_2 in ether (0.84 mmol, prepared from Diazald). After stirring overnight, the ether solution was concentrated with a rotary evaporator to obtain 180 mg of a pale yellow oil. This material was purified by radial preparative layer chromatography (1 mm plate of silica gel, 5:1 hexane/EtOAc as eluant) to obtain 138 mg (80%) of a 15:1 mixture of diastereomeric esters **17** and **18**, identified by their ^1H NMR spectra (vide supra).

(3*R*,1′*R*)-Methyl 1′-Phenylethyl 3-Hydroxypentanedioate (23). In an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was placed 1.00 g (2.63 mmol) of silyl ether **17**. To the system was added 25 mL of a 1:19 solution of aqueous HF (Mallinckrodt, 40%) in CH_3CN. The reaction mixture was stirred at room temperature for 75 min, diluted with 80 mL of ether, and washed carefully with two 15-mL portions of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether, the combined organic fractions were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to afford 726 mg of pale yellow liquid. The crude product was purified by column chromatography (7 g of silica gel) with 2:1 ether/hexanes as the eluant to obtain 694 mg (99% yield) of alcohol **23** as a colorless liquid. ^1H NMR: δ 1.55 (d, 3, *J* = 6.6), 2.56 (m, 4), 3.36 (d, 1, *J* = 4.0), 3.71 (s, 3), 4.47 (m, 1), 5.92 (q, 1, *J* = 6.6), 7.38 (m, 5). Anal. ($C_{14}H_{18}O_5$) C, H.

The enantiomeric alcohol **29** prepared by desilylation of **13** exhibits an identical ^1H NMR spectrum. IR ($CHCl_3$): 3550, 2960, 1730 cm^{-1}. Anal. ($C_{14}H_{18}O_5$) C, H. If silyl ether **17** is contaminated with **19**, the corresponding alcohol **21** is also isolated as a white solid, mp 48–50 °C. IR ($CHCl_3$): 3560, 3000, 2840, 1730 cm^{-1}. ^1H NMR: δ 1.54 (d, 3, *J* = 6.6), 1.55 (d, 3, *J* = 6.6), 2.54 (m, 4), 3.34 (d, 1, *J* = 4.1), 4.43 (m, 1), 5.908 (q, 1, *J* = 6.6), 5.914 (q, 1, *J* = 6.6), 7.38 (m, 10). Anal. ($C_{21}H_{24}O_5$) C, H. The enantiomeric alcohol **22** exhibits an identical ^1H NMR spectrum. Anal. ($C_{21}H_{24}O_5$) C, H.

(*R*)-Dimethyl [[4-[[(*R*)-Phenylethoxy]carbonyl]-3-hydroxybutyryl]methyl]phosphonate (24). In an oven-dried 50-mL round-bottomed flask equipped with a magnetic stirring

bar and a rubber septum was placed 11.9 mL (17.7 mmol) of 1.49 M *n*-BuLi in hexanes. The system was immersed in a room-temperature water bath, and a stream of argon was passed over the solution to evaporate the hexanes. The system was immersed in a −78 °C cooling bath and charged with 3.4 mL of THF. The cooling bath was removed until all of the *n*-BuLi was in solution. To this vigorously stirring solution, at −78 °C, was added 2.20 mL (2.52 g, 20.3 mmol) of dimethyl methylphosphonate over a period of 1 h, during which time 1 mL of THF was added. The resulting suspension was stirred at −78 °C for 15 min. To the system was added dropwise a solution of 726 mg (2.73 mmol) of ester **23** in 0.35 mL of THF. The syringe that delivered the ester was rinsed with 0.3 mL of THF. The reaction mixture was stirred at −78 °C for 10 min, and an ice-cold mixture of 13 mL of 1 M aqueous H_3PO_4 and ether was poured into the flask. After warming to room temperature, the mixture was partitioned between 1 M aqueous H_3PO_4 and EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to afford 1.11 g of light yellow liquid. The crude material was purified by flash column chromatography (8.5 g of silica gel), eluting first with ether and then with EtOAc to obtain 421 mg (43% yield) of phosphonate **24** as a pale yellow oil. IR ($CHCl_3$): 3570, 3010, 2870, 1720 cm^{-1}. ^1H NMR: δ 1.55 (d, 3, J = 6.6), 2.56 (m, 2), 2.81 (m, 2), 3.12, 3.13 (2 d, 2, J = 23), 3.40 (d, 1, J = 4.0), 3.78 (d, 6, J = 11), 4.50 (m, 1), 5.91 (q, 1, J = 6.6), 7.38 (m, 5). Anal. ($C_{16}H_{23}O_7P$) C, H.

(*R*)-Dimethyl [[3-[(*tert*-Butyldimethylsilyl)oxy]-4-[[(*R*)-phenylethoxy]carbonyl]butyryl]methyl]phosphonate (25). Under a nitrogen atmosphere, in a 10-mL round-bottomed flask were placed 226 mg (0.631 mmol) of alcohol **24** and 0.6 mL of CH_2Cl_2. To this stirring solution were added 72.2 mg (1.06 mmol) of imidazole and 105 mg (0.70 mmol) of *tert*-butylchlorodimethylsilane. After the mixture was stirred at room temperature for 3 h, 50 min, 24.0 mg (0.35 mmol) of imidazole and 35.0 mg (0.23 mmol) of *tert*-butylchlorodimethylsilane were added to the system. After a further period of 2 h, 15 min, additional imidazole (8.0 mg, 0.12 mmol) and *tert*-butylchlorodimethylsilane (12.0 mg, 0.080 mmol) were added. The reaction mixture was stirred for an additional period of 2 h, 5 min, diluted with EtOAc, and washed with water. The organic phase was dried ($MgSO_4$) and concentrated with a rotary evaporator to afford 363 mg of a light yellow oil. The crude material was purified by flash column chromatography (5 g of silica gel) with 2:1 EtOAc/hexanes as the eluant to obtain 251 mg (84% yield) of **25** as a colorless oil. IR ($CHCl_3$): 3015, 2970, 2870, 1730 cm^{-1}. ^1H NMR: δ 0.02 (s, 3), 0.04 (s, 3), 0.81 (s, 9), 1.53 (d, 3, J = 6.6), 2.48 (dd, 1, J = 5.6, 15), 2.58 (dd, 1, J = 6.0, 15), 2.87 (m, 2), 3.08 (d, 2, J = 23), 3.77 (d, 6, J = 14), 4.54 (m, 1), 5.87 (q, 1, J = 6.6), 7.37 (m, 5). Anal. ($C_{22}H_{37}O_7SiP$) C, H.

The crude material is usually contaminated with small amounts of a byproduct, the enol silane resulting from further silylation of **25**. However, this impurity is easily removed during the chromatographic purification. ^1H NMR: δ −0.06 (s, 3), 0.04 (s, 3), 0.23 (s, 3), 0.24 (s, 3), 0.77 (s, 9), 0.95 (s, 9), 1.51 (d, 3, J = 6.6), 2.50 (m, 2), 2.78 (m, 2), 3.688, 3.694 (2 d, 6, J = 11), 4.53 (m, 1), 4.57 (d, 1, J = 8.2), 5.86 (q, 1, J = 6.6), 7.37 (m, 5). Anal. ($C_{28}H_{51}O_7PSi_2$) C, H.

(*R*)-Dimethyl [[3-[(*tert*-Butyldimethylsilyl)oxy]-4-carbomethoxybutyryl]methyl]phosphonate (27). In a 100-mL round-bottomed flask were placed 251 mg (0.53 mmol) of ester **25** and 13 mL of ether. To this solution was added 51.0 mg of 10% Pd/C, and the flask was attached to an atmospheric hydrogenation apparatus. The system was placed under an atmosphere of H_2. The reaction mixture was stirred at room temperature for 1 h, 55 min, diluted with EtOAc, and filtered through a Celite pad. The Celite was rinsed well with EtOAc, and the filtrate was concentrated with a rotary evaporator to obtain 199 mg of a colorless oil, which was used without further purification.

In a 100-mL round-bottomed flask were placed the crude acid **26** prepared above and 1 mL of ether. To this solution was cautiously added 7 mL (2.1 mmol) of 0.3 M CH_2N_2/ether (prepared from Diazald), and the resulting solution was allowed to stand at room temperature for 10–15 min. Nitrogen was bubbled through the solution (fire-polished pipet) until it was colorless. The reaction mixture was concentrated with a rotary evaporator, and the crude material (212 mg) was purified by flash column chromatography (3 g of silica gel) with 7:2 EtOAc/hexanes as the eluant to obtain 186 mg (92% yield) of **27** as a colorless oil. IR ($CHCl_3$): 2970, 2870, 1740 cm^{-1}. ^1H NMR: δ 0.06 (s, 3), 0.07 (s, 3), 0.84 (s, 9), 2.46 (dd, 1, J = 6.4, 15), 2.56 (dd, 1, J = 5.8, 15), 2.88 (d, 2, J = 6.0), 3.11 (d, 2, J = 23), 3.66 (s, 3), 3.790, 3.786 (2 d, 6, J = 11), 4.58 (m, 1). Anal. ($C_{15}H_{31}O_7PSi$) C, H.

(*R*)-Dimethyl (4-Carbomethoxy-3-hydroxybutyryl)-methylphosphonate (28). Into a 50-mL round-bottomed flask equipped with a magnetic stirring bar were placed 126 mg (0.35 mmol) of **24**, 7 mL of ether, and 3 mL of EtOAc. To the system was added 83.3 mg of 10% Pd/C, and the flask was attached to an atmospheric hydrogenation apparatus. The system was placed under an atmosphere of H_2. The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated with a rotary evaporator to obtain 80.1 mg of colorless oil.

In a 25-mL Erlenmeyer flask was placed 10 mL (2.4 mmol) of 0.24 M CH_2N_2/ether. To this solution, at 0 °C, was added the acid prepared above in a minimal amount of EtOAc. The cold bath was removed, and the solution was allowed to stand at room temperature for 15 min. Nitrogen was bubbled (fire-polished pipet) through the solution for 25 min. Concentration (rotary evaporator) afforded 91.0 mg of yellow oil which was purified by flash column chromatography (1 g of silica gel) with EtOAc as the eluant to obtain 63.0 mg (67% yield) of **28** as a colorless oil, which was analytically pure. IR ($CHCl_3$): 2990, 1730 cm^{-1}. ^1H NMR: δ 2.54 (d, 2, J = 6.3), 2.85 (m, 2), 3.15 (d, 1, J = 23), 3.16 (d, 1, J = 23), 3.43 (d, 1, J = 4.1), 3.71 (s, 3), 3.80 (d, 6, J = 11), 4.52 (m, 1). Anal. ($C_9H_{17}O_7P$) C, H.

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-3′-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthalenehept-1′-enoate (35). Under an argon atmosphere, into an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 22.1 mg (0.080 mmol) of aldehyde **5**, 46.3 mg (0.121 mmol) of phosphonate **27**, and 80 μL of DMSO. To the solution was added approximately 20 granules of LiCl. To this stirring suspension was added 12.0 μL (12.2 mg, 0.080 mmol) of DBU. The reaction mixture became dark orange, and all of the solids gradually dissolved. The reaction mixture was stirred at room temperature for 30 h and partitioned between ether and 4 mL of ice-cold 1 M aqueous H_3PO_4. The layers were separated, and the organic phase was washed twice with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to afford 61.2 mg of yellow oil. The crude product mixture was purified by column chromatography (6 g of silica gel; 1:5 ether/hexanes → 2:5 ether/hexanes → EtOAc) to obtain 23.6 mg (55% yield) of pure **35** as a colorless oil. Also isolated were 9.4 mg (42%) of recovered **5** and 17.4 mg of recovered **27**. Compound **35**: IR 2940, 2865, 1760 cm^{-1}. ^1H NMR: δ 0.03 (s, 3), 0.05 (s, 3), 0.82 (s, 9), 0.86 (t, 3, J = 7.4), 1.00 (d, 3, J = 7.0), 1.10 (d, 3, J = 7.0), 1.34–2.62 (complex, 12), 2.76 (m, 2), 3.65 (s, 3), 4.61 (m, 1), 4.99 (br s, 1), 5.60 (br s, 1), 5.71 (dd, 1, J = 5.7, 9.7), 6.00 (d, 1, J = 9.7), 6.03 (d, 1, J = 16), 6.81 (m, 1). Anal. ($C_{30}H_{48}O_6Si$) C, H.

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-(*R*)-1-Phenylethyl 1,2,6,7,8,8a-Hexahydro-5′-hydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)-oxy]-3′-oxo-1-naphthalenehept-1′-enoate (36). Under an argon atmosphere, in an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 17.9 mg (0.065 mmol) of aldehyde **5**, 33.4 mg of keto phosphonate **24**, and 50 μL of CH_3CN. To this stirring suspension was added 20–30 granules of LiCl followed by 12.1 μL (12.3 mg, 0.081 mmol) of DBU. The mixture gradually became brown and homogeneous. The reaction mixture was partitioned between 6 mL of ether and 2 mL of H_2O. An additional 25 mL of ether was added, the layers were separated, and an ice-cold mixture of 8 mL of ether and 2 mL of 0.5 M aqueous H_3PO_4 was added to the organic phase. The layers were separated, and the organic phase was washed with brine. The ether solution was dried ($MgSO_4$) and concentrated (rotary evaporator) to afford 29.0 mg of pale yellow oil. The crude material was purified by column chromatography (2 g of silica gel) with 1:1 ether/hexanes as the eluant to obtain 14.0 mg (42% yield) of enone **36**. IR ($CHCl_3$): 3420, 1730, 1670 cm^{-1}. ^1H NMR: δ 0.87 (t, 3, J = 7.4), 0.99 (d, 3, J = 7.0), 1.11 (d, 3, J = 7.0), 1.29–2.89 (complex, 14), 1.55 (d, 3, J =

6.6), 3.53 (d, 1, J = 3.9), 4.49 (m, 1), 5.04 (br s, 1), 5.62 (br s, 1), 5.72 (dd, 1, J = 5.7, 9.8), 5.92 (q, 1, J = 6.6), 6.02 (d, 1, J = 9.4), 6.03 (d, 1, J = 16), 6.83 (m, 1), 7.37 (m, 5). Anal. ($C_{32}H_{40}O_6$) C, H.

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-1,2,6,7,8,8a-Hexahydro-5′-hydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthaleneheptenoic Acid (37). In an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 9.6 mg (0.018 mmol) of silyl ether **35**. To the system was added 0.18 mL of a 1:19 solution of HF in CH_3CN. The resulting solution was stirred at room temperature for approximately 1 h, diluted with ether, and washed carefully with two portions of saturated aqueous $NaHCO_3$. The ether solution was dried ($MgSO_4$) and concentrated with a rotary evaporator to afford 9.0 mg of colorless oil. The crude material was purified by column chromatography (1 g of silica gel) using 2:3 EtOAc/hexanes as the eluant to obtain 7.0 mg (93% yield) of pure hydroxy ester as a colorless oil. IR ($CHCl_3$): 3540, 2940, 1730, 1670 cm^{-1}. ^{1}H NMR: δ 0.90 (t, 3, J = 7.4), 1.03 (d, 3, J = 7.0), 1.14 (d, 3, J = 7.0), 1.40 (m, 1), 1.62 (m, 2), 2.15 (m, 3), 2.32 (m, 2), 2.58 (m, 4), 2.74 (dd, 1, J = 4.3, 17), 2.85 (dd, 1, J = 7.8, 16), 3.59 (d, 1, J = 4.0), 3.74 (s, 3), 4.50 (m, 1), 5.07 (br s, 1), 5.65 (br s, 1), 5.74 (dd, 1, J = 5.6, 9.7), 6.04 (d, 1, J = 9.7), 6.12 (d, 1, J = 16), 6.88 (m, 1). High-resolution MS: m/z 418.2340 (calcd for $C_{24}H_{34}O_6$, 418.2355).

Under a nitrogen atmosphere, into a round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed the foregoing methyl ester. To the system was added 0.43 mL (0.043 mmol) of 0.1 M KOH in MeOH/H_2O (2:1). The resulting yellow solution was stirred at room temperature for 85 min. To the system was added 5 mL of ether and 4 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the ether solution was extracted with additional saturated aqueous $NaHCO_3$. Ethyl acetate was added to the combined bicarbonate extracts, and the mixture was acidified with 1 M aqueous H_3PO_4. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to obtain 7.2 mg of hydroxy acid **37** as a colorless oil. IR ($CHCl_3$): 3550–2450, 1730, 1670, 1630 cm^{-1}. ^{1}H NMR: δ 0.88 (t, 3, J = 7.4), 1.01 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.41 (m, 2), 1.67 (m, 2), 2.10 (m, 3), 2.37 (m, 2), 2.60 (m, 4), 2.73 (dd, 1, J = 3.9, 17), 2.86 (dd, 1, J = 8.0, 16), 4.52 (m, 1), 5.06 (br s, 1), 5.63 (br s, 1), 5.72 (dd, 1, J = 5.8, 9.7), 6.02 (d, 1, J = 9.7), 6.05 (d, 1, J = 16), 6.87 (dd, 1, J = 9.6, 16). High-resolution MS: m/z 404.2184 (calcd for $C_{23}H_{32}O_6$, 404.2199).

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-5′-hydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthaleneheptanoate (38). Under an argon atmosphere, in a 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 43.7 mg (0.082 mmol) of **35**. To the system was added 0.8 mL of a solution of 5.0 mg of $(Ph_3P)_3ClRh$ in 2.7 mL of benzene followed by 0.44 mL of triethylsilane. This stirring solution was heated at approximately 70 °C for 35 min. The reaction mixture was concentrated with a rotary evaporator and subjected to high vacuum for 5–10 min. To the flask containing the resulting orange oil was added 6 mL of a 1:19 solution of aqueous HF (Mallinckrodt, 40%) in CH_3CN. The reaction mixture was stirred at room temperature for 50 min, diluted with ether, and washed carefully with saturated aqueous $NaHCO_3$. The ether solution was dried ($MgSO_4$) and concentrated (rotary evaporator) to afford 43.6 mg of light yellow oil. The crude product was purified by column chromatography (2.5 g of silica gel) using 2:3 EtOAc/hexanes as the eluant to obtain 29.9 mg (87% yield) of **38** as a colorless oil which became a waxy white solid upon standing in a refrigerator, mp 46–49 °C. IR: 3540, 3480, 1760 cm^{-1}. ^{1}H NMR: δ 0.87 (t, 3, J = 7.4), 0.87 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.33–2.67 (complex, 18), 3.39 (d, 1, J = 3.7), 3.70 (s, 3), 4.45 (m, 1), 5.32 (br s, 1), 5.56 (br s, 1), 5.72 (dd, 1, J = 6.0, 9.4), 5.97 (d, 1, J = 9.7). High-resolution MS: m/z 420.2524 (calcd for $C_{24}H_{36}O_6$, 420.2511).

(1*S*,2*S*,8*S*,8a*R*,3′*R*,5′*R*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-3′,5′-dihydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-1-naphthaleneheptanoate (39) and (1*S*,2*S*,8*S*,8a*R*,3′*S*,5′*R*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-3′,5′-dihydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-1-naphthaleneheptanoate (40). Under an argon atmosphere, into an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 16.8 mg (0.040 mmol) of ketone **38** and 0.8 mL of CH_3OH. To this stirring solution, at −14 °C, was added 4.9 mg (0.13 mmol) of sodium borohydride. The reaction mixture was stirred at −13 to −15 °C for 27 min. To the system was added a mixture of 6 mL of ether and 3 mL of saturated aqueous $NaHCO_3$, the cold bath was removed, and the mixture was stirred at room temperature for 45 min. Additional ether was added, and the organic phase was separated from the aqueous phase and solids. The ether solution was washed with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to afford 19.0 mg of colorless oil. The crude product mixture was purified by HPLC (μ-Porasil semipreparative column, 2:3 EtOAc/hexanes, 4 mL min^{-1}) to obtain 9.6 mg of **39** and 4.6 mg of **40**, each as a colorless oil. Compound **39**: ^{1}H NMR δ 0.88 (t, 3, J = 7.4), 0.88 (d, 3, J = 7.0), 1.11 (d, 3, J = 7.0), 1.20–2.43 (complex, 16), 2.48 (d, 2, J = 6.2), 3.41 (m, 1), 3.71 (s, 3), 3.81 (m, 2), 4.24 (m, 1), 5.35 (br s, 1), 5.54 (br s, 1), 5.73 (dd, 1, J = 6.0, 9.6), 5.97 (d, 1, J = 9.7). Compound **40**: IR: 3520, 1760 cm^{-1}. ^{1}H NMR: δ 0.89 (overlapping d and t, 6), 1.12 (d, 3, J = 7.0), 1.22–2.58 (complex, 19), 3.44 (m, 1), 3.72 (s, 3), 3.88 (m, 1), 4.38 (m, 1), 5.34 (br s, 1), 5.54 (br s, 1), 5.74 (dd, 1, J = 6.1, 9.7), 5.97 (d, 1, J = 9.7). High resolution MS: m/z 422.2653 (calcd for $C_{24}H_{38}O_6$, 422.2668).

(+)-Compactin (1). Under an argon atmosphere, into an oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 9.6 mg (0.023 mmol) of **39** and 2.2 mL of benzene. To the system was added 2.2 mg (0.012 mmol) of p-TsOH·H_2O. The reaction mixture was stirred at room temperature for 40 min and concentrated (rotary evaporator), and 2.2 mL of fresh benzene was added. The mixture was stirred for 25 min and concentrated, and 2.2 mL of fresh benzene was added. The mixture was stirred for 10 min, and a small amount of solid $NaHCO_3$ was added. This mixture was stirred for 2 min, diluted with EtOAc, and washed with H_2O and brine. The EtOAc solution was dried ($MgSO_4$) and concentrated with a rotary evaporator to afford 11.0 mg of crude product. This material was purified by column chromatography (1 g of silica gel) using 1:1 EtOAc/hexanes as the eluant to obtain 6.2 mg (70% yield) of **1**. The ^{1}H NMR spectrum of the material thus obtained was identical with that of a sample of the natural product. ^{1}H NMR: δ 0.89 (overlapping d and t, 6), 1.12 (d, 3, J = 7.0), 1.23–2.20 (complex, 14), 2.35 (m, 3), 2.61 (ddd, 1, J = 1.3, 3.8, 18), 2.74 (dd, 1, J = 5.0, 18), 4.37 (br s, 1), 4.62 (m, 1), 5.34 (br s, 1), 5.56 (m, 1), 5.74 (dd, 1, J = 6.0, 9.6), 5.98 (d, 1, J = 9.7). High-resolution MS: m/z 390.2399 (calcd for $C_{23}H_{34}O_5$, 390.2406).

(2*S*,1′*S*,7′*S*,8′*S*,8a′*R*,2″*S*,4″*R*)-2-Methylbutanoic Acid, 1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl Ester or 5-*epi*-Compactin (41). Under an argon atmosphere, in a 25-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 4.6 mg (0.011 mmol) of diol **40** and 1.1 mL of benzene. To the system was added 1.1 mg (0.0057 mmol) of p-TsOH·H_2O. The mixture was stirred at room temperature for 15 min and approximately 1 mg of p-TsOH·H_2O was added to the system. After 20 min, the reaction mixture was concentrated with a rotary evaporator. To the system was added 1.1 mL of benzene. The reaction mixture was stirred at room temperature for 20 min and concentrated (rotary evaporator), and 1.1 mL of fresh benzene was added to the system. The mixture was stirred at room temperature for 20 min and a small amount of solid $NaHCO_3$ was added to the system. After 2 min, this mixture was diluted with EtOAc and washed with water and brine. The organic solution was dried ($MgSO_4$) and concentrated with a rotary evaporator to afford 4.1 mg of oil. The crude product was purified by HPLC using 1:1 EtOAc/hexanes as the eluant (4 mL min^{-1}) to obtain 3.3 mg of pure 5-*epi*-compactin (**41**). ^{1}H NMR: δ 0.89 (t, 3, J = 7.4), 0.89 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.2–2.4 (complex, 17), 2.46 (dd, 1, J = 8.0, 17), 2.90 (ddd, 1, J = 1.3, 5.8, 17), 4.22 (m, 2), 5.31 (m, 1), 5.56 (m, 1), 5.73 (dd, 1, J = 5.8, 9.6), 5.98 (d, 1, J = 9.7). High-resolution MS: m/z 390.2401 (calcd for $C_{23}H_{34}O_5$, 390.2406).

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-1,2,6,7,8,8a-Hexahydro-5′-hydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthaleneheptanoic Acid (42). Under a nitrogen atmosphere,

in a 10-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar was placed keto ester **38**. To the system was added 0.18 mL (0.018 mmol) of 0.1 M KOH in $MeOH/H_2O$ (2:1). The resulting light yellow solution was stirred at room temperature for 95 min. The reaction mixture was partitioned between 5 mL of ether and 4 mL of saturated aqueous $NaHCO_3$. Additional ether was added, and the layers were separated. The ether solution was extracted with several portions of saturated aqueous $NaHCO_3$. To the combined bicarbonate extracts was added 10 mL of ether. The mixture was acidified with 1 M aqueous H_3PO_4, the layers were separated, and the aqueous phase was extracted with ether and EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to obtain 2.7 mg of hydroxy acid **42** as a colorless oil which was judged to be pure from its ^1H NMR spectrum. ^1H NMR: δ 0.88 (t, 3, J = 7.4), 0.88 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1.2–2.5 (complex, 15), 2.56 (d, 2, J = 6.2), 2.65 (m, 2), 4.46 (m, 1), 5.34 (br s, 1), 5.56 (br s, 1), 5.72 (dd, 1, J = 6.0, 9.7), 5.98 (d, 1, J = 9.7). MS (70 eV): m/z 406 (parent), 57 (base).

(1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-5′-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthalenehept-1′-enoate (44). Under an argon atmosphere, in an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 89.2 mg (0.234 mmol) of keto phosphonate **43**, 37.9 mg (0.137 mmol) of aldehyde **5**, and 0.125 mL of DMSO. To the system was added approximately 40 granules of LiCl. To this stirring suspension was added 20.5 μL (20.9 mg, 0.137 mmol) of DBU. The solids dissolved, and the resulting yellow solution gradually became brown. The solution was stirred at room temperature for 42 h and partitioned between ether and 6 mL of ice-cold 1 M aqueous H_3PO_4. The layers were separated, and the organic phase was washed with two portions of brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to afford 119 mg of yellow oil. The crude material was purified by column chromatography (9 g of silica gel) eluting sequentially with 1:5 EtOAc/hexanes and 2:5 EtOAc/hexanes to obtain 36.7 mg (50% yield) of pure enone **44** as a colorless oil. IR (film): 3030, 2970, 1740, 1700, 1675 cm^{-1}. ^1H NMR: δ 0.02 (s, 3), 0.05 (s, 3), 0.81 (s, 9), 0.86 (t, 3, J = 7.4), 1.00 (d, 3, J = 7.0), 1.10 (d, 3, J = 7.0), 1.38 (m, 1), 1.65 (m, 3), 2.17 (m, 3), 2.22–2.63 (complex, 5), 2.71 (dd, 1, J = 6.1, 16), 2.85 (dd, 1, J = 6.3, 16), 3.66 (s, 3), 4.63 (m, 1), 5.00 (br s, 1), 5.61 (br s, 1), 5.72 (dd, 1, J = 5.7, 9.6), 6.03 (m, 2), 6.84 (m, 1). High-resolution MS: m/z 532.3228 (calcd for $C_{30}H_{48}O_6Si$, 532.3220).

(1*S*,2*S*,8*S*,8a*R*,5′*S*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-5′-hydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-3′-oxo-1-naphthaleneheptanoate (45). Under an argon atmosphere, into an oven-dried 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 34.8 mg (0.065 mmol) of enone 44 and 0.66 mL of a solution of 5.0 mg of $(Ph_3P)_3ClRh$ in 2.7 mL of benzene. To this stirring solution was added 0.36 mL of triethylsilane, and the reaction mixture was heated at 65–70 °C for 40 min. The mixture was concentrated with a rotary evaporator and subjected to high vacuum for approximately 10 min. To the flask containing the resulting oil was added 5.5 mL of a 1:19 solution of HF (Mallinckrodt, 40% aqueous HF) in CH_3CN. This solution was stirred at room temperature for 55 min, diluted with ether, and washed carefully with two portions of saturated aqueous $NaHCO_3$. The ether solution was dried ($MgSO_4$) and concentrated with a rotary evaporator to afford 33.3 mg of yellow oil. The crude material was purified by column chromatography (2 g of silica gel) using 2:3 EtOAc/hexanes as the eluant to obtain 19.3 mg of pure ketone **45** as a colorless oil. IR (film): 3500, 3020, 1720 cm^{-1}. ^1H NMR: δ 0.86 (t, 3, J = 7.3), 0.86 (d, 3, J = 7.0), 1.11 (d, 3, J = 7.0), 1.23–2.58 (complex, 16), 2.61 (d, 2, J = 6.1), 3.41 (d, 1, J = 3.7), 3.70 (s, 3), 4.42 (m, 1), 5.31 (br s, 1), 5.55 (br s, 1), 5.71 (dd, 1, J = 6.0, 9.5), 5.97 (d, 1, J = 9.6). High-resolution MS: m/z 420.2521 (calcd for $C_{24}H_{36}O_6$, 420.2512).

(1*S*,2*S*,8*S*,8a*R*,3′*S*,5′*S*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-3′,5′-dihydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-1-naphthaleneheptanoate (46) and (1*S*,2*S*,8*S*,8a*R*,3′*R*,5′*S*,2″*S*)-Methyl 1,2,6,7,8,8a-Hexahydro-3′,5′-dihydroxy-2-methyl-8-[(2-methyl-1-oxobutyl)oxy]-1-naphthaleneheptanoate (47). Under an argon atmosphere, in an oven-dried 10-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 18.6 mg (0.044 mmol) of ketone **45** and 0.9 mL of CH_3OH. To this stirring solution, at −11 °C, was added 5.6 mg (0.15 mmol) of $NaBH_4$. The reaction mixture was stirred for 40 min. During this period, the temperature of the cold bath rose to −7 °C. To the system was added a mixture of 6 mL of ether and 3 mL of saturated aqueous $NaHCO_3$, the cold bath was removed, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ether, and the layers were separated. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated (rotary evaporator) to afford 22.6 mg of colorless oil. The crude diols (2–3:1 **46**/**47**) were separated by HPLC and had the following properties. IR (mixture, $CHCl_3$): 3500, 2950, 1730 cm^{-1}. **Compound 46**: ^1H NMR δ 0.89 (overlapping d and t, 6, J = 7.6), 1.12 (d, 3, J = 7.0), 1.1–2.5 (complex, 18), 3.34 (m, 1), 3.72 (s, 3), 3.83 (m, 2), 4.26 (m, 1), 5.33 (m, 1), 5.54 (m, 1), 5.74 (dd, 1, J = 6.0, 9.5), 5.97 (d, 1, J = 9.7). High-resolution MS: m/z 422.2685 (calcd for $C_{24}H_{38}O_6$, 422.2669). Compound **47**: ^1H NMR δ 0.88 (overlapping d and t, 6), 1.11 (d, 3, J = 6.9), 1.2–2.6 (complex, 19), 3.40 (m, 1), 3.72 (s, 3), 3.85 (m, 1), 4.36 (m, 1), 5.38 (m, 1), 5.57 (m, 1), 5.74 (dd, 1, J = 5.9, 9.5), 5.97 (d, 1, J = 9.5).

(2*S*,1′*S*,7′*S*,8′*S*,8a′*S*,2″*S*,4″*S*)-2-Methylbutanoic Acid, 1,2,3,7,8,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl Ester or 3,5-Bis-*epi*-compactin (48). Under an argon atmosphere, in a 25-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 8.3 mg (0.020 mmol) of hydroxy ester **46** and 1.9 mL of benzene. To this stirring solution was added 1.9 mg (0.010 mmol) of p-TsOH·H_2O. The mixture was stirred at room temperature for 20 min, and the solvent was removed with a rotary evaporator. To the system was added 1.9 mL of benzene, the reaction mixture was stirred at room temperature for 20 min, and a small amount of solid $NaHCO_3$ was added to the system. The mixture was stirred for 2 min, diluted with EtOAc, and washed with water and brine. The organic solution was dried ($MgSO_4$), and the solvent was removed with a rotary evaporator to afford 9.4 mg of a pale yellow oil. The crude material was purified by column chromatography (1 g of silica gel) using 1:1 EtOAc/hexanes as the eluant to obtain 7.3 mg (95% yield) of **48** as a colorless oil. IR ($CHCl_3$): 3450, 2950, 1735 cm^{-1}. ^1H NMR: δ 0.89 (t, 3, J = 7.4), 0.89 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.2–2.0 (complex, 14), 2.36 (m, 3), 2.61 (ddd, 1, J = 1.4, 3.6, 18), 2.72 (dd, 1, J = 4.8, 18), 4.40 (m, 1), 4.67 (m, 1), 5.35 (m, 1), 5.57 (m, 1), 5.74 (dd, 1, J = 5.9, 9.5), 5.98 (d, 1, J = 9.7). High-resolution MS: m/z 390.2401 (calcd for $C_{23}H_{34}O_5$, 390.2406).

(2*S*,1′*S*,7′*S*,8′*S*,8a′*R*,2″*R*,4″*S*)-2-Methylbutanoic Acid, 1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl Ester or 3-*epi*-Compactin (49). Under an argon atmosphere, in an oven-dried 25-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2.4 mg (0.0056 mmol) of hydroxy ester **47** and 0.5 mL of benzene. To this stirring solution was added 0.5 mg (0.003 mmol) of p-TsOH·H_2O. The reaction mixture was stirred at room temperature for 30 min and concentrated with a rotary evaporator. To the system was added 0.5 mL of benzene and 0.5 mg (0.003 mmol) of p-TsOH·H_2O. The reaction mixture was stirred for 20 min and concentrated with a rotary evaporator. To the system was added 0.5 mL of benzene and the reaction mixture was stirred for 25 min. To the system was added a small amount of solid $NaHCO_3$. The mixture was stirred for 2 min, diluted with EtOAc, and washed with water and brine. The EtOAc solution was dried ($MgSO_4$) and concentrated with a rotary evaporator. The crude material was purified by column chromatography (1 g of silica gel) using 1:1 EtOAc/hexanes as the eluant to obtain 2.6 mg of lactone **49** as a colorless oil. The ^1H NMR spectrum of the product indicated that it was a 6.5:1 mixture of **49** and **48**. ^1H NMR: δ 0.88 (t, 3 J = 7.4), 0.89 (d, 3 J = 7.1), 1.12 (d, 3 J = 7.0), 1.25–2.40 (complex, 17), 2.46 (dd, 1, J = 7.7, 17), 2.90 (ddd, 1 J = 1.2, 5.9, 17), 4.14 (m, 1), 4.24 (m, 1), 5.38 (m, 1), 5.57 (m, 1), 5.74 (dd, 1, J = 6.0, 9.6), 5.98 (d, 1, J = 9.7).

(2*S*,1′*R*,7′*R*,8′*R*,8a′*R*,2″*R*,4″*R*)-2-Methylbutanoic Acid, 1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-(tetrahydro-4-

hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl Ester or Tetra-*epi*-compactin (51) and (2*S*,1′*R*,7′*R*,8′*R*,8a′*R*, 2″*S*,4″*R*)-2-Methylbutanoic Acid, 1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl Ester or Penta-*epi*-compactin (52). With 25.9 mg (0.094 mmol) of aldehyde **50** and 59.4 mg (0.155 mmol) of keto phosphonate **27** as starting material, the foregoing procedure for the preparation of compactin and 5-*epi*-compactin was carried out. The initial Wadsworth–Emmons coupling gave 30.7 mg (62% yield) of enone as a colorless oil. IR ($CHCl_3$): 2980, 1735, 1675 cm^{-1}. ^1H NMR: δ 0.02 (s, 3), 0.05 (s, 3), 0.82 (s, 9), 0.86 (t, 3 J = 7.5), 1.00 (d, 3, J = 7.1), 1.07 (d, 3, J = 7.0), 1.42 (m, 2), 1.68 (m, 3), 2.09–2.62 (complex, 6), 2.72 (dd, 1, J = 6.2, 16), 2.86 (dd, 1, J = 6.3, 16), 3.66 (s, 3), 4.62 (m, 1), 5.02 (m, 1), 5.44 (m, 1), 5.61 (br s, 1), 5.72 (dd, 1, J = 5.6, 9.7), 6.03 (overlapping d and d, 2), 6.82 (m, 1). High-resolution MS: m/z 532.3217 (calcd for $C_{30}H_{48}O_6Si$, 532.3220).

A portion of this material (11.3 mg, 0.021 mmol) was reduced with triethylsilane, as described above, to provide 6.9 mg (78% yield) of keto ester as a colorless oil. IR ($CHCl_3$): 3540, 2980, 1725 cm^{-1}. ^1H NMR: δ 0.88 (overlapping d and t, 6), 1.12 (d, 3, J = 7.0), 1.24–2.58 (complex, 16), 2.62 (d, 2, J = 6.1), 3.41 (d, 1, J = 3.6), 3.70 (s, 3), 4.44 (m, 1), 5.33 (br s, 1), 5.56 (br s, 1), 5.72 (dd, 1, J = 6.0, 9.2), 5.97 (d, 1, J = 9.6). High-resolution MS: m/z 420.2518 (calcd for $C_{24}H_{36}O_6$, 420.2512).

Reduction of this compound (10.1 mg, 0.024 mmol) with $NaBH_4$ gave 11.7 mg of a mixture of two diastereomeric alcohols as a colorless oil. The two were separated by HPLC using 2:3 EtOAc/hexanes as the eluant.

High-R_f compound (major): ^1H NMR δ 0.89 (overlapping d and t, 6), 1.11 (d, 3, J = 7.0), 1.60 (m, 11), 2.17 (m, 2), 2.38 (m, 3), 2.49 (d, 2, J = 5.9), 3.28 (m, 1), 3.72 (s, 3), 3.81 (m, 2), 4.23 (m, 1), 5.34 (br s, 1), 5.55 (br s, 1), 5.74 (dd, 1, J = 6.0, 9.5), 5.97 (d, 1, J = 9.6).

Low-R_f compound (minor): ^1H NMR δ 0.89 (t, 3, J = 7.3), 0.89 (d, 3, J = 7.0), 1.10 (d, 3, J = 7.0), 1.3–2.6 (complex, 18), 3.45 (m, 2), 3.72 (s, 3), 3.85 (m, 1), 4.38 (m, 1), 5.39 (m, 1), 5.57 (m, 1), 5.74 (dd, 1, J = 5.9, 9.4), 5.97 (d, 1, J = 9.6).

A sample of the mixture of hydroxy esters was lactonized (p-TsOH·H_2O/benzene) to obtain a mixture of lactones **51** and **52**. IR ($CHCl_3$): 3560, 3470, 2980, 1730 cm^{-1}. ^1H NMR: δ 0.89 (m, 6), 1.12 (d, 3), 1.17–2.95 (complex, 17), 4.12 (m, 1), 4.24 (m, 1), 4.39 (m, 1), 4.67 (m, 1), 5.34 (m, 1), 5.56 (m, 1), 5.74 (dd, 1, J = 6.0, 9.4), 5.98 (d, 1, J = 9.7). High-resolution MS: m/z 390.2409 (calcd for $C_{23}H_{34}O_5$, 390.2406).

"Tetra-*epi*-compactin" (51). The major hydroxy ester (high-R_f compound) was lactonized by treatment with p-TsOH in benzene, resulting in lactone **51**. ^1H NMR ($CDCl_3$) δ 0.89 (overlapping d and t, 6), 1.12 (d, 3, J = 7.0), 1.20–2.50 (complex, 17), 2.61 (ddd, 1), 2.73 (dd, J = 17.7, 4.8), 4.40 (m, 1), 4.70 (m, 1), 5.32 (br s, 1), 5.55 (br s, 1), 5.74 (dd, 1, J = 7.0, 9.4), 5.98 (d, 1, J = 9.7).

"Penta-*epi*-compactin" (52). The minor hydroxy ester (low-R_f compound) was similarly lactonized to obtain **52**. ^1H NMR ($CDCl_3$) δ 0.89 (overlapping d and t, 6), 1.12 (d, 3, J = 7.0), 1.20–2.50 (complex, 18), 2.90 (ddd, 1, J = 17.1, 5.9, 1.1), 4.14 (m, 1), 4.26 (m, 1), 5.32 (br s, 1), 5.55 (br s, 1), 5.74 (dd, 1, J = 6.0, 9.4), 5.98 (d, 1, J = 9.7).

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[(Glutaryloxy)methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (55 and 56). Under a nitrogen atmosphere, into a 25 mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 28.4 mg (0.102 mmol) of alcohols **53** and **54** and 0.8 mL of CH_2Cl_2. To this stirring solution were added 0.050 mL (40.4 mg, 0.40 mmol) of triethylamine, 24.4 mg (0.20 mmol) of DMAP, and 45.6 mg (0.40 mmol) of glutaric anhydride. After 3 h, TLC showed no alcohol remaining. The reaction mixture was diluted with 10 mL of ether and washed with 10% aqueous HCl. The ethereal solution was diluted with ca. 10 mL of hexanes and extracted with four 10-mL portions of saturated aqueous $NaHCO_3$. The combined bicarbonate washings were acidified with 10% aqueous HCl and extracted with ether and $CHCl_3$. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator to obtain 23.2 mg (58% yield) of **55** and **56** as an off-white solid/oil mixture. IR (thin film): 3400–2400, 1700 (br), 1400, 900 cm^{-1}. High-resolution MS: m/z 392.2205 (calcd for $C_{22}H_{32}O_6$, 392.2200).

Glutarates **55** and **56** were prepared separately from the corresponding enantiomerically homogeneous alcohols by an analogous procedure. Compound **55**: ^1H NMR δ 0.89 (t, 3, J = 7.3), 0.92 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1.39–2.58 (complex, 16), 3.98 (dd, 1, J = 8.9, 11), 4.22 (dd, 1, J = 4.8, 11), 5.18 (br s, 1), 5.59 (br s, 1), 5.71 (dd, 1, J = 4.8, 9.6), 5.99 (d, 1, J = 9.7). Compound **56**: ^1H NMR δ 0.90 (overlapping d and t, 6), 1.13 (d, 3, J = 7.0), 1.38–2.57 (complex, 16), 3.96 (dd, 1, J = 8.9, 11), 4.24 (dd, 1, J = 4.8, 11), 5.18 (br s, 1), 5.59 (br s, 1), 5.71 (dd, 1, J = 6.1, 9.4), 5.99 (d, 1, J = 9.7).

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-carbomethoxybutanoic Acid (57). In an oven-dried 100-mL round-bottomed flask was placed 74.2 mg (0.2 mmol) of diester **13** and 4 mL of ether. To this solution was added 17.4 mg of 10% Pd/C (purchased from Englehard Industries). The flask was attached to an apparatus for maintaining an atmosphere of hydrogen. The mixture was stirred with a magnetic stirrer for 20 min and then filtered through a pad of diatomaceous earth. Removal of solvent was accomplished with a rotary evaporator; 50.3 mg (93%) of acid **57** was obtained as a colorless oil. IR (neat): 3500–2500 (br), 2960, 2935, 1742, 1716 cm^{-1}. ^1H NMR: δ 0.07 (s, 3), 0.85 (s, 9), 2.60 (m, 4), 3.73 (s, 3), 4.55 (quintet, 1, J = 6.3).

Methyl *tert*-Butyldimethylsilyl (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (59). In an oven-dried 10-mL round-bottomed flask was placed 53.9 mg (0.2 mmol) of the acid **57**, 0.25 mL of CH_2Cl_2, 27.2 mg (0.4 mmol) of imidazole, and 30.1 mg (0.2 mmol) of *tert*-butyldimethylsilyl chloride (purchased from Petrarch Chemical Co.). The reaction mixture was stirred for 2 h at room temperature, diluted with 20 mL of ether, and then washed with 10 mL of water, 5 mL of saturated aqueous $NaHCO_3$, and 5 mL of brine. The combined aqueous washings were extracted with 10 mL of ether, which was added to the original organic solution. The combined organic solutions were dried over $MgSO_4$. After removal of the $MgSO_4$ by filtration, the solvents were removed with a rotary evaporator to obtain 67.4 mg of **59** as a colorless oil. The material may be purified by chromatography on silica gel to obtain a white crystalline solid, mp 44–46 °C. IR ($CHCl_3$): 2950, 2860, 1735, 1720 cm^{-1}. ^1H NMR: δ 0.06 (s, 3), 0.08 (s, 3), 0.26 (s, 6), 0.84 (s, 9), 0.93 (s, 9), 2.56 (m, 4), 3.67 (s, 3), 4.52 (quintet, 1, J = 6.1). Anal. ($C_{18}H_{38}O_5Si_2$) C, H.

(1*S*,2*S*,8*S*,8a*R*)-1-[[(*S*)-(3-Hydroxy-4-carbomethoxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (61). In a 10-mL round-bottomed flask was placed 65.3 mg (0.167 mmol) of **59** and 0.3 mL of a solution prepared from 2 drops of DMF in 3 mL of CH_2Cl_2. To this solution, at 0 °C, was added 24.4 mg (0.192 mmol) of oxalyl chloride, dropwise with a syringe. The resulting mixture was stirred for 1.5 h at 0 °C and for 40 min at room temperature. The volatile materials were removed with a rotary evaporator. The resulting acyl chloride is normally used directly, without further purification.

Under an argon atmosphere, in a 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 0.47 mmol of acid chloride from **59** and 0.5 mL of CH_2Cl_2. To this stirring solution, at 0 °C, was added a solution of 0.039 mL (38.0 mg, 0.48 mmol) of pyridine in 0.2 mL of CH_2Cl_2. To the system was added 26.0 mg (0.094 mmol) of alcohol **53**. The reaction mixture was stirred for 8 h, during which time the ice bath gradually expired. The mixture was diluted with 30 mL of ether and washed with 1 M aqueous H_3PO_4, saturated aqueous $NaHCO_3$, and brine (5–10-mL portions). The combined aqueous washings were extracted with 20 mL of ether, the combined organic fractions were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator to obtain 162 mg of yellow oil. The crude material was purified by column chromatography (8 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 53.3 mg of the *tert*-butyldimethylsilyl ether of compound **61** as a colorless oil. IR (film): 2920, 2850, 1740 cm^{-1}. ^1H NMR: δ 0.05 (s, 6), 0.83 (s, 9), 0.88 (complex, 6), 1.13 (d, 3, J = 7.0), 1.45 (m, 1), 1.66 (m, 2), 2.15 (m, 4), 2.50 (complex, 7), 3.66 (s, 3), 3.96 (dd, 1, J = 9.3, 11), 4.22 (dd, 1, J = 4.9, 11), 4.52 (m, 1), 5.15 (br s, 1), 5.58 (br s, 1), 5.72 (dd, 1, J = 6.1, 9.5), 5.98 (d, 1, J = 9.7).

Under a nitrogen atmosphere, in a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum

was placed the foregoing silyl ether. To the system was added 4.0 mL of a 1:19 solution of 40% aqueous HF in CH_3CN. The resulting solution was stirred at room temperature for 1 h, 40 min, diluted with $CHCl_3$, and washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous washings were extracted with $CHCl_3$, the combined organic fractions were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 50.9 mg of light yellow oil. The crude material was purified by column chromatography (1.5 g of silica gel) with 3:2 ether/hexanes as the eluant to obtain 35.7 mg (85% yield from **53**) of alcohol **61** as a colorless oil. IR (film): 3520, 2970, 1735 cm^{-1}. ^1H NMR: δ 0.89 (t, 3, J = 7.4), 0.93 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1.42 (m, 1), 1.67 (m, 2), 2.18 (m, 4), 2.46 (complex, 7), 4.30 (d, 1, J = 3.9), 3.71 (s, 3), 4.02 (dd, 1, J = 8.6, 11), 4.25 (dd, 1, J = 5.3, 11), 4.44 (m, 1), 5.18 (m, 1), 5.59 (br s, 1), 5.71 (dd, 1, J = 6, 9.6), 5.99 (d, 1, J = 9.7). High-resolution MS: m/z 422.2306 (calcd for $C_{23}H_{34}O_7$, 422.2305).

(1*S*,2*S*,8*S*,8a*R*)-1-[[(*S*)-(3-Hydroxy-4-carboxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8a-hexahydronaphthalene (63). To a solution of 31.1 mg (0.074 mmol) of methyl ester **61** in 0.08 mL of oxygen-free HMPA, at 0 °C, was added 0.14 mL (0.077 mmol) of 0.56 M lithium propylmercaptide in oxygen-free HMPA. The mixture was stirred under a nitrogen atmosphere for 5 h, 40 min, during which time the ice bath expired. The brown solution was diluted with ether and washed with 1 M aqueous H_3PO_4 and four portions (5–10 mL) of water. The ether solution was extracted with four portions of saturated aqueous $NaHCO_3$ (40 mL). The bicarbonate extracts were acidified with 1 M aqueous H_3PO_4 and extracted with four portions of $CHCl_3$ (50 mL). The $CHCl_3$ extracts were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 6.2 mg (20% yield) of acid **63** as a yellow oil. ^1H NMR: δ 0.89 (t, 3, J = 7.4), 0.93 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1,2–2.65 (complex, 15), 4.03 (dd, 1, J = 8.4, 11), 4.26 (dd, 1, J = 5.4, 11), 4.45 (m, 1), 5.19 (br s, 1), 5.60 (br s, 1), 5.71 (dd, 1, J = 5.9, 9.6), 5.99 (d, 1, J = 9.7).

(1*S*,2*S*,8*S*,8a*R*)-1-[[(*R*)-(3-Hydroxy-4-carbomethoxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (62). Under an argon atmosphere, in a 10-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 0.36 mmol of the acid chloride derived from **60** and 0.48 mL of CH_2Cl_2. To this stirring solution, at 0 °C, was added a solution of 30 μL (29.3 mg, 0.37 mmol) of pyridine in 0.16 mL of CH_2Cl_2. To the system was added 25.0 mg (0.090 mmol) of alcohol **53**. The reaction mixture was stirred for 9 h, during which time the ice bath gradually expired. The mixture was diluted with 30 mL of ether and washed with 1 M aqueous H_3PO_4, saturated aqueous $NaHCO_3$, and brine (five 10-mL portions). The combined aqueous washings were extracted with 20 mL of ether, the combined organic fractions were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 102 mg of brown oil. The crude material was purified by column chromatography (8 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 45.6 mg of the *tert*-butyldimethylsilyl ether of alcohol **62** as a colorless oil. IR (film): 3030, 2920, 2860, 1740 cm^{-1}. ^1H NMR: δ 0.05 (s, 6), 0.83 (s, 9), 0.89 (complex, 6), 1.15 (d, 3, J = 7), 1.45 (m, 1), 1.67 (m, 2), 2.17 (m, 4), 2.50 (complex, 7), 3.66 (s, 3), 3.95 (dd, 1, J = 9.7, 11), 4.24 (dd, 1, J = 4.7, 11), 4.51 (m, 1), 5.16 (br s, 1), 5.58 (br s, 1), 5.71 (dd, 1, J = 5.9, 9.6), 5.98 (d, 1, J = 9.7).

Under a nitrogen atmosphere, in a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed the foregoing silyl ether. To the system was added 3.4 mL of a 1:19 solution of 40% aqueous HF in CH_3CN. The resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was diluted with 30 mL of $CHCl_3$ and washed with saturated aqueous $NaHCO_3$ and brine (5–10 mL portions). The combined aqueous washings were extracted with 30 mL of $CHCl_3$, the combined organic fractions were dried, and the solvent was removed with a rotary evaporator to obtain 52.1 mg of yellow oil. The crude material was purified by column chromatography (2.5 g of silica gel) with 3:2 ether/hexanes as the eluant to obtain 33.9 mg (81% yield from **53**) of alcohol **62**. IR (film): 3500, 3020, 2970, 2880, 1735 cm^{-1}. ^1H NMR: δ 0.89 (complex, 6), 1.12 (d, 3, J = 7.0), 1.44 (m, 1), 1.66 (m, 2), 2.16 (m, 4), 2.45 (m, 7), 3.46 (m, 1), 3.70 (s, 3), 4.00 (dd, 1, J = 8.7, 11), 4.26 (dd, 1, J = 5.2, 11), 4.42 (m, 1), 5.18 (br s, 1), 5.58 (br s, 1), 5.70 (dd, 1, J = 5.9, 9.6), 5.98 (d, 1, J = 9.7). High-resolution MS: m/z 422.2316 (calcd for $C_{23}H_{34}O_7$, 422.2305).

(1*S*,2*S*,8*S*,8a*R*)-1-[[(*R*)-(3-Hydroxy-4-carboxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8a-hexahydronaphthalene (64). To a solution of 32.0 mg (0.076 mmol) of methyl ester **62** in 0.08 mL of oxygen-free HMPA, at 0 °C, was added 145 μL (0.081 mmol) of 0.56 M lithium propylmercaptide in oxygen-free HMPA. The mixture was stirred under an argon atmosphere for 1 h, 50 min at 0 °C and 4 h at room temperature. The brown solution was diluted with 10 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and four 10-mL portions of water. The ether solution was extracted with four portions of saturated aqueous $NaHCO_3$ (50 mL). The bicarbonate extracts were acidified with 1 M aqueous H_3PO_4 and extracted with five 15-mL portions of $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to obtain 8.1 mg (26% yield) of acid **64** as a pale yellow oil. ^1H NMR: δ 0.89 (overlapping d and t, 6), 1.14 (d, 3, J = 7), 1.35–2.62 (complex, 15), 4.01 (dd, 1, J = 8.7, 11), 4.25 (dd, 1, J = 5, 11), 4.45 (m, 1), 5.21 (br s, 1), 5.59 (br s, 1), 5.71 (dd, 1, J = 6, 10), 5.99 (d, 1, J = 10).

(1*R*,2*R*,8*R*,8a*S*)-1-[[(*S*)-(3-Hydroxy-4-carboxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (65). In a similar manner, 20.0 mg (0.072 mmol) of alcohol **54** was converted into 7.4 mg of acid **65** as a pale yellow oil. ^1H NMR: δ 0.90 (overlapping d and t, 6), 1.13 (d, 3, J = 7.0), 1.38–2.62 (complex, 15), 4.00 (dd, 1, J = 8.3, 11), 4.30 (dd, 1, J = 5.5, 11), 4.44 (m, 1), 5.20 (br s, 1), 5.60 (br s, 1), 5.71 (dd, 1, J = 5.9, 9.8), 5.99 (d, 1, J = 9.8).

(1*R*,2*R*,8*R*,8a*S*)-1-[[(*R*)-(3-Hydroxy-4-carboxybutyryl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (66). In a similar manner, 21.8 mg (0.078 mmol) of alcohol **54** was converted into 7.5 mg of acid **66** as a waxy white solid. ^1H NMR: δ 0.90 (overlapping d and t, 6), 1.13 (d, 3, J = 7.0), 1.38–2.64 (complex, 15), 4.02 (dd, 1, J = 8.2, 11), 4.27 (dd, 1, J = 5.4, 11), 4.45 (m, 1), 5.59 (br s, 1), 5.71 (dd, 1, J = 6.0, 9.6), 5.99 (d, 1, J = 9.7).

Enzymatic Assay. The potency of compactin and each analogue as an inhibitor of HMG CoA reductase catalysis was measured with rat liver microsomes. The liver preparations were made in the laboratories of Professor George Popjàk, Department of Biological Chemistry, UCLA and Professor Kenneth Feingold, Department of Medicine, University of California at San Francisco according to Edwards protocol and were stored at −78 °C.[35] The effect on the initial velocity of mevalonate production was determined in a radioactive assay system modeled after that of Edwards et al.[35] Each 500-μL assay mixture contained 150 mM phosphate buffer, pH 6.8, 180 mM KCl, 16 mM Na_2EDTA, 9 mM dithiothreitol, 10.0 mM D-glucose 6-phosphate, 2.1 mM NADP, 20 μM (*R*,*S*)-(3-^{14}C)-3-hydroxy-3-methylglutaryl coenzyme A, 2 units of D-glucose-6-phosphate dehydrogenase, and 1.3 mg of microsomes (0.068 mg of protein). Lactone inhibitors were preincubated with all but substrate, protein, and dehydrogenase for 30 min at 37 °C to permit ring opening. Dehydrogenase and microsomes were added and after an additional 10 min preincubation, the assay was initiated by addition of substrate. In the case of non-lactone inhibitors, all but substrate and inhibitor were preincubated for 10 min and then the assay was initiated by addition of inhibitor and substrate. Inhibitors were administered in 10 μL of DMSO (control samples received DMSO only). Catalysis was terminated with 33% aqueous KOH (50 μL). After 30 min, 25 μL of aqueous 0.05% bromophenol, 70000 dpm of (5-^{3}H)mevalonolactone in 25 μL of H_2O (recovery standard), and 90 μL of 5 N aqueous HCl were added. Samples sat for at least 1 h and then were each passed through a column of Bio-Rad AG 1 × 8 exchange resin (200–400 mesh, formate form) and eluted with water. The sample volume plus 1.1 mL was allowed to elute before a 5-mL sample was collected for scintillation counting. Quantities of collected (^{14}C)mevalonate were corrected for (^{3}H)mevalonate recovery before conversion to catalytic rates. Conversion of (*S*)-HMG coenzyme A to product was limited to less than 20% to insure the measurement of initial velocities.

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Registry No. **1**, 73573-88-3; **5**, 96575-19-8; **8**, 91424-39-4; **9**, 91424-40-7; **10**, 91424-41-8; 11, 109720-91-4; **12**, 109720-92-5; **13**, 96555-56-5; 14, 109720-93-6; **15**, 109720-94-7; **16**, 109720-95-8; **17**, 96555-51-0; **18**, 96555-52-1; **19**, 109720-96-9; **20**, 109720-97-0; **21**, 109720-98-1; **22**, 109720-99-2; **23**, 96575-20-1; **24**, 96555-53-2; **25**, 96555-54-3; **26**, 96555-55-4; **27**, 96555-58-7; **28**, 109721-00-8; **29**, 109721-01-9; (1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-**35** (R = *t*-BuMe$_2$Si, R^1 = Me), 109785-23-1; (1*R*,2*R*,8*R*,8a*S*,5′*R*,2″*S*)-**35** (R = *t*-BuMe$_2$Si, R^1 = Me), 109785-24-2; (1*S*,2*S*,8*S*,8a*R*.5′*R*,2″*S*)-**35** (R = H, R^1 = Me), 109721-02-0; **36**, 109721-03-1; **37**, 109744-47-0; (1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-**38**, 96555-61-2; (1*R*,2*R*,8*R*,8a*R*,5′*R*,2″*S*)-**38**, 109721-04-2; (1*S*,2*S*,8*S*,8a*R*,5′*R*,2″*S*)-**39**, 79814-60-1; (1*R*,2*R*,8*R*,8a*S*,5′*R*,2″*S*)-**39**, 109785-25-3; (1*S*,2*S*,8*S*,8a*R*,5′*R*,2′′′*S*)-**40**, 79896-20-1; (1*R*,2*R*,8*R*,8a*S*,5′*R*,2″*S*)-40, 109785-26-4; **41**, 84173-31-9; **42**, 109744-48-1; **43**, 109721-05-3; **44**, 109785-27-5; **45**, 109721-06-4; **46**, 79896-21-2; **47**, 79896-19-8; **48**, 84173-29-5; **49**, 84173-30-8; **50**, 109721-07-5; **51**, 109785-28-6; **52**, 109785-29-7; **53**, 85540-02-9; **54**, 85540-13-2; **55**, 85540-03-0; **56**, 85540-14-3; **57**, 109744-49-2; **58**, 109721-08-6; **59**, 91424-35-0; **59** acid chloride, 109721-09-7; **60**, 91424-36-1; **60** acid chloride, 109721-10-0; **61**, 109721-11-1; **61** *t*-BuMe$_2$Si ether, 109721-12-2; **62**, 109721-13-3; **62** *t*-BuMe$_2$Si ether, 109721-14-4; **63**, 96555-62-3; **64**, 96555-63-4; **65**, 109721-15-5; **66**, 109721-16-6; HMGR, 9028-35-7; *t*-BuMe$_2$SiOCH(CH$_2$CO$_2$Na)$_2$, 109721-17-7; (*R*)-(MeO)$_2$P(O)-CH$_2$C(O)CH$_2$CH(OH)CH$_2$CO$_2$H, 109721-18-8; diethyl 3-hydroxyglutarate, 32328-03-3; (*S*)-1-phenylethanol, 1445-91-6; (*R*)-1-phenylethanol, 1517-69-7; glutaric anhydride, 108-55-4.

Quantitative Structure–Activity Relationships of the Bitter Thresholds of Amino Acids, Peptides, and Their Derivatives

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Bitter thresholds of a total of 93 amino acids, peptides, and their derivatives were analyzed quantitatively by use of hydrophobicity parameters reported for amino acid side chains and those for the whole molecules estimated from partition coefficients obtained experimentally. We also explored the steric parameters that best explained the variation in the intensity of bitterness attributable to the molecular shape. The results showed that the total length along the zigzag peptide backbone chain of the molecule is an important factor. The bitterness of nonzwitterionic *N*-acyl and ester derivatives and that of neutral *N*-acyl ester derivatives were expressed by a single, common equation together with those of zwitterionic amino acids and peptides. Thus the interaction via the charge with the receptor site was probably not an indispensable factor for triggering of the bitter sensation. This study, together with earlier ones, may serve as a prototype of approaches toward unraveling structure–activity relationships of complex molecules like amino acids, peptides, and their derivatives that are of medicinal or agricultural importance.

Amino acids and peptides have long been studied by chemists because of their importance as flavoring constituents of foods as well as their significance in biological processes. The tastes of amino acids are various. Among them, bitter and sweet tastes have been extensively examined by a number of researchers. The results have been puzzling. The D enantiomers of some bitter L-amino acids such as leucine, phenylalanine, tryptophan, and tyrosine are sweet, but both enantiomers of some other amino acids, including alanine, serine, threonine, and ornithine, are sweet.[1] Many dipeptides and tripeptides are bitter. There is no simple correspondence for the tastes of component amino acids; for example, peptides D-Leu-Gly and D-Leu-D-Leu, which contain sweet amino acids, are bitter.[2] These complex features have made it difficult to obtain an overall view of their structure–activity relationships.

The state of structure–activity relationship studies of bitter compounds has been summarized by Belitz et al.[3] On the basis of data already reported, what we can say about the structural characteristics of bitter compounds is that there is always a polar function and a hydrophobic group within the molecule, the former probably affecting taste quality and the latter affecting taste intensity. Since the hydrophobic moieties are sterically various, the participation of steric factors has been suggested also. To obtain more information, a quantitative approach may be of use. For derivatives of amino acids and peptides, Gardner has investigated the relationship between the bitter thresholds and molecular connectivity, finding a significant correlation with the first-order-valence corrected index $^1\chi^v$.[4] This correlates with the partition coefficients of a wide range of compounds, so he suggested that the result is a reflection of the influence of hydrophobicity on bitterness. Despite the likelihood that the bitter intensity is also related to steric factors, the dimensional features on a whole-molecular basis of amino acids and peptides have not been parameterized and incorporated into quantitative regression analysis. In this study, we analyzed quantitatively the structure–bitterness relationships of these classes of compounds, by using the hydrophobic parameters derived from partition coefficients found experimentally[5,6] and exploring steric parameters that can explain the variation of the intensity of bitterness. This approach could be extended to derivatives of amino acids and peptides that have medicinal and agricultural importance, as well as to other classes of bitter compounds.

Bitter Thresholds. The threshold data of compounds **1–10**, **72–74**, **76**, **78**, **79**, **81–88**, and **90** were taken from literature reported by Wieser and Belitz in 1975,[1] and those of compounds **11–21**, **23–31**, **33–48**, **50**, **54–71**, and **91–99** were from literature reported by the same workers in 1976.[2] The values of 24 compounds (**1–5**, **7**, **12**, **14**, **16**, **18**, **19**, **27–29**, **34**, **50**, **55–58**, **60**, **61**, **73**, **76**, and **81**) in Table I were

(1) Wieser, H.; Belitz, H.-D. *Lebensm. Unters.-Forsch.* **1975**, *159*, 65.
(2) Wieser, H.; Belitz, H.-D. *Lebensm. Unters.-Forsch.* **1976**, *160*, 383.
(3) Belitz, H.-D.; Chen, W.; Jugel, H.; Stempfl, H.; Treleano, R.; Wieser, H. *Chem. Ind. (London)* **1983**, 23.
(4) Gardner, R. J. *J. Sci. Food Agric.* **1980**, *31*, 23.
(5) Fauchere, J.-L.; Pliska, V. *Eur. J. Med. Chem.—Chim. Ther.* **1983**, *18*, 369.
(6) Akamatsu, M.; Asao, M.; Iwamura, H.; Fujita, T., Kyoto University, Faculty of Agriculture, Kyoto, unpublished data.

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