= +464 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{12}H_{10}O_5Cr$: C, 50.36; H, 3.52. Found: C, 50.30, H, 3.47.

(+)-Ar(1*S*,2*R*)-Tricarbonyl[*o*-methoxyphenyl 2(*R*)-hydroxy-3(*E*)-pentenyl ketone]chromium (18). To a solution of $(^nBu)_2BOTf$ (330 mg, 2.4 mmol) and $(^iPr)_2NEt$ (307 mg, 2.4 mmol) in ether (10 mL) was added a solution of (1*S*)-(*o*-methoxyacetophenone)$Cr(CO)_3$ (340 mg, 1.2 mmol) in ether (10 mL) at -78 °C under argon. After the solution was stirred for 30 min, (*E*)-crotonaldehyde(170 mg, 2.4 mmol) in ether (0.5 mL) was added at the same temperature. The reaction mixture was stirred for 30 min at -78 °C and then quenched with buffer of phosphoric acid and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified with SiO_2 column chromatography to give Ar(1*S*,2*R*),(*R*)-(+)-18 (350 mg, 72%) as red oil and the corresponding stereoisomeric Ar(1*S*,2*R*),(*S*)-complex (15 mg, 8%). Ar(1*S*,2*R*),(*R*)-(+)-18: ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 2.96 (1 H, br s), 3.07 (1 H, dd, J = 8, 18), 3.15 (1 H, dd, J = 4, 18), 3.85 (3 H, s), 4.68 (1 H, m), 4.96 (1 H, t, J = 7), 5.04 (1 H, d, J = 7), 5.56 (1 H, m), 5.79 (1 H, dd, J = 6, 15), 5.82 (1 H, dt, J = 1, 7), 6.27 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}; MS m/e 356 (M^+), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ = +305 (c = 1.00, $CHCl_3$). **Stereoisomeric Ar(1*S*,2*R*),(*S*)-complex:** ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 3.04 (1 H, m), 3.12 (2 H, m), 3.85 (3 H, s), 4.59 (1 H, m), 4.95 (1 H, t, J = 7), 5.02 (1 H, d, J = 7), 5.59 (1 H, m), 5.77 (1 H, m), 5.81 (1 H, dt, J = 1, 7), 6.37 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}; MS m/e 356 (M^+), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ = +262 (c = 1.00, $CHCl_3$).

(-)-Ar(1*S*,2*R*)-Tricarbonyl[6-(*o*-methoxyphenyl)-4(*R*),6-(*R*)-diacetoxy-2(*E*)-hexene]chromium (19). To a suspended mixture of $LiAlH_4$ (24 mg, 0.63 mmol) in ether (5 mL) was added a solution of Ar(1*S*,2*R*),(*R*)-(+)-18 (105 mg, 0.29 mmol) in ether (5 mL) with stirring at -78 °C under nitrogen. After being stirred for 30 min at -78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was treated with Ac_2O (0.5 mL) and pyridine (2 mL) in the presence of a catalytic amount of *p*-(dimethylamino)pyridine. After being stirred for 2 h at room temperature, the reaction mixture was poured into cold 1 M aqueous HCl solution and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification with SiO_2 column chromatography gave Ar(1*S*,2*R*),(*R*)-(-)-19 (110 mg, 84%): mp 122 °C; ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 2.05 (3 H, s), 2.09 (3 H, s), 2.16 (2, H, m), 3.85 (3 H, s), 4.78 (1 H, t, J = 7), 4.99 (1 H, d, J = 7), 5.33 (1 H, m), 5.47 (1 H, dd, J = 7, 8), 5.58 (1 H, dt, J = 1, 7), 5.80 (2 H, m), 5.88 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1730, 1250 cm^{-1}; $[\alpha]^{25}_D$ = -45 (c = 0.10, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_8Cr$: C, 54.30; H, 5.01. Found: C, 54.39; H, 5.11.

(-)-Ar(1*S*,2*R*)-Tricarbonyl[dimethyl 5-(*o*-methoxyphenyl)-1(*S*)-methyl-5(*R*)-acetoxy-2(*E*)-pentenylmalonate]chromium (20). Bis(μ-chloro)bis(π-allyl)dipalladium (4.1 mg, 0.011 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe) (9.0 mg, 0.022 mmol) were placed in a 30-mL two-necked flask equipped with a serum cap and a three-way stopcock. The flask was filled with argon after evacuation, and to it were added through the serum cap with a syringe 5 mL of THF and 50 mg (0.11 mmol) of Ar(1*S*,2*R*),(*R*)-19 at 0 °C. The mixture was stirred at 0 °C for 5 min, and a solution of sodium dimethyl malonate was added at 0 °C, which was prepared in another flask by addition of 24 mg (0.18 mmol) of dimethyl malonate to a suspension of 5.4 mg (0.14 mmol) of 60% sodium hydride in mineral oil in THF (0.8 mL) at 0 °C. The reaction mixture was kept stirring at room temperature for 12 h, hydrolyzed with water, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography with ether/hexane gave 60 mg (99%) of Ar(1*S*,2*R*),(*S*)-(-)-20: ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7), 2.06 (3 H, s), 2.49 (1 H, m), 2.58 (1 H, m), 2.74 (1 H, m), 3.29 (2 H, d, J = 9), 3.71 (3 H, s), 3.74 (3 H, s), 3.79 (3 H, s), 4.79 (1 H, t, J = 7), 4.98 (1 H, d, J = 7), 4.53 (1 H, m), 4.58 (1 H, dt, J = 1, 7), 5.79 (1 H, dd, J = 1, 7), 5.83 (1 H, m); IR ($CHCl_3$) 1970, 1880, 1730, 1230 cm^{-1}; MS m/e 514 (M^+), 430 (M^+ - 3CO); $[\alpha^{25}_D]$ = -68 (c = 0.10, $CHCl_3$).

(-)-Ar(1*S*,2*R*)-Tricarbonyl[dimethyl 5-(*o*-methoxyphenyl)-1(*S*),5(*R*)-dimethyl-3(*E*)-pentenylmalonate]chromium (21). To a solution of (1*S*,*R*,*S*)-20 (50 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) was added trimethylaluminum in hexane (1.5 M, 0.32 mL, 0.48 mmol) at -78 °C under argon. The reaction mixture was warmed to 0 °C over 3 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel with ether/hexane to afford (-)-1,5-*syn*-21 (40 mg, 87%) which was identical with authentic racemate complex[18e] by ^1H NMR spectra: ^1H NMR ($CDCl_3$) δ 1.09 (3 H, d, J = 7), 1.11 (3 H, d, J = 7), 2.00-2.18 (1 H, m), 2.35-2.42 (1 H, m), 2.75-2.85 (1 H, m), 2.88-2.98 (1 H, m), 3.30 (1 H, d, J = 8), 3.69 (3 H, s), 3.71 (3 H, s), 3.72 (3 H, s), 4.86 (1 H, t, J = 7), 5.00 (1 H, d, J = 7), 5.44-5.60 (4 H, m); IR ($CHCl_3$) 1970, 1890, 1730, 1260 cm^{-1}; MS m/e 470 (M^+), 386 (M^+ - 3CO); $[\alpha]^{25}_D$ = -120, (c = 0.10, $CHCl_3$).

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Total Synthesis of Dihydromevinolin and a Series of Related 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors

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The natural product dihydromevinolin, **2**, and a series of structurally related 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, **3-6**, have been synthesized. The key features are an intramolecular Diels-Alder reaction to form a functionalized decalin skeleton with six asymmetric centers in a stereocontrolled manner, the selective manipulation of the functional groups, and an improved method for the introduction and elaboration of the δ-lactone portion. Analogue **6** was approximately 10-fold more potent than **2** as an inhibitor and was produced in multigram quantities.

Introduction

Coronary heart disease (CHD) and atherosclerosis are the major causes of mortality in the western world. Epidemiological studies have revealed that there is a strong correlation between the incidence of CHD and the level of cholesterol in the blood, particularly low-density lipo-

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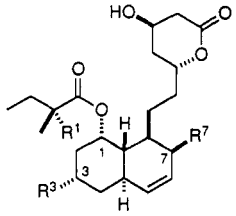
protein (LDL) cholesterol. Over the past 15 years a series of fungal metabolites and their derivatives, the mevinic acids, have been shown to be highly effective LDL cholesterol lowering agents, through their ability to inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the biosynthesis of cholesterol.[1] Although the mechanism of the hypolipidaemic effect is elaborate and involves the up-regulation of LDL receptors,[2] several clinical studies have suggested a relationship between the dose of HMG-CoA reductase inhibitor administered and the lowering of the serum cholesterol level.[3]

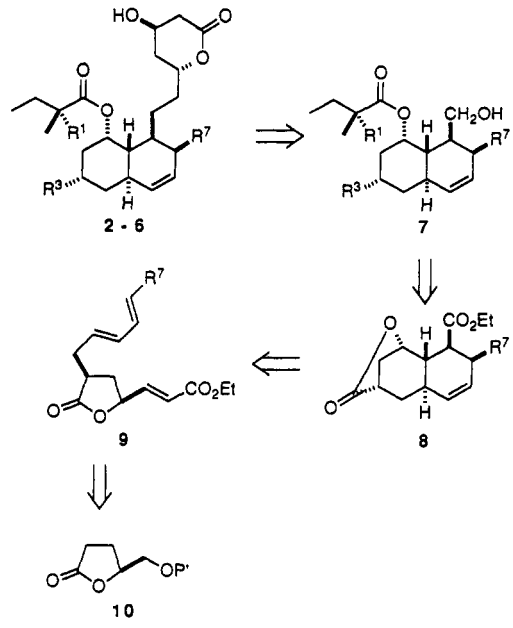
We have previously[4] described our strategy for developing more potent HMG-CoA reductase inhibitors based on the natural mevinic acids dihydrocompactin[5] (1) and dihydromevinolin[6] (2) and have shown that alterations of the C-3 and C-7 substituents[7] can lead to a 1000-fold variation in activity. In this publication we describe the total synthesis of dihydromevinolin (2) and show that the route can be readily adapted to produce the C-3 and C-7 substituted analogues 3–6.



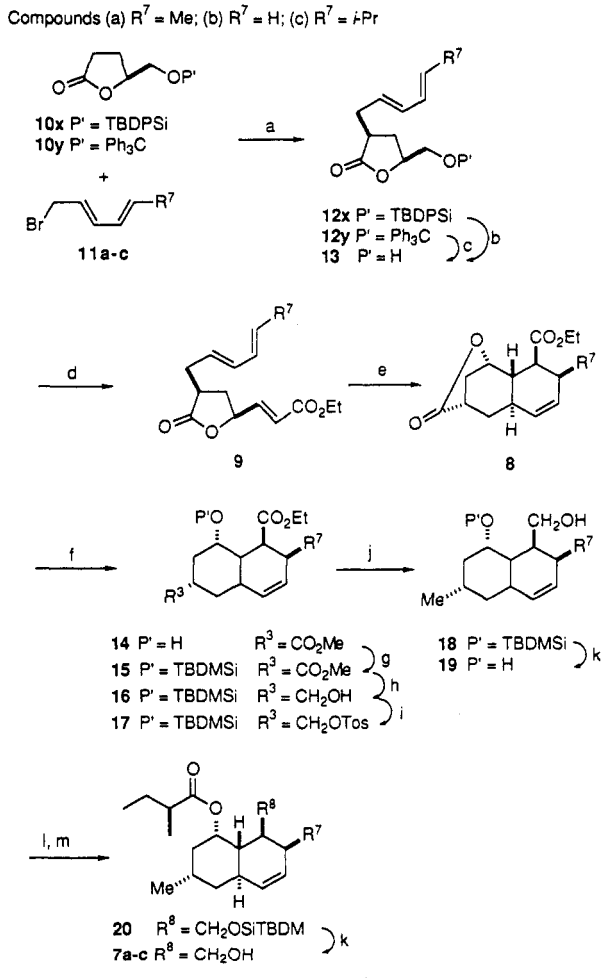
Dihydrocompactin 1 R^1 = H, R^3 = H, R^7 = Me
Dihydromevinolin 2 R^1 = H, R^3 = Me, R^7 = Me
3 R^1 = H, R^3 = Me, R^7 = H
4 R^1 = H, R^3 = Me, R^7 = *i*-Pr
5 R^1 = H, R^3 = *cis*-CH=CHMe, R^7 = Me
6 R^1 = Me, R^3 = *trans*-CH=CHMe, R^7 = Me

The major challenge in the synthesis of mevinic acids is the controlled construction of six chiral centers in the decalin portion of the molecule and two centers in the δ-lactone portion. It is known that for good inhibitory activity the absolute stereochemistry of both the decalin and lactone portions of the molecules must be the same as that found in the natural products.[8] An additional synthetic challenge is that for the compounds 5 and 6 two bulky groups have to be introduced in an unfavorable 1,3 diaxial relationship across the cyclohexane ring. Although there are many syntheses of mevinic acid fragments, few total syntheses of dihydrocompactin or dihydromevinolin have been published and none could be readily adapted to our requirements.[9-11] After considering various possible

Scheme I. Retrosynthetic Analysis



Scheme II[a]



[a] Reagents: (a) NaHMDS, 11; LiHMDS, *t*-BuBr; (b) TBAF; (c) HCl/MeOH; (d) DMSO/$(COCl)_2$; *i*-Pr_2NEt; Ph_3PCHCO_2Et; (e) 165 °C; (f) NaOMe; (g) TBDMSiOTf; (h) $LiEt_3BH$, 0 °C; (i) TosCl; (j) $LiEt_3BH$, 80 °C; (k) HF; (l) TBDMSiCl; (m) [(*S*)-EtCHMe-$CO]_2O$.

(1) Grundy, S. M. *N. Engl. J. Med.* **1988**, *319*, 24–33.
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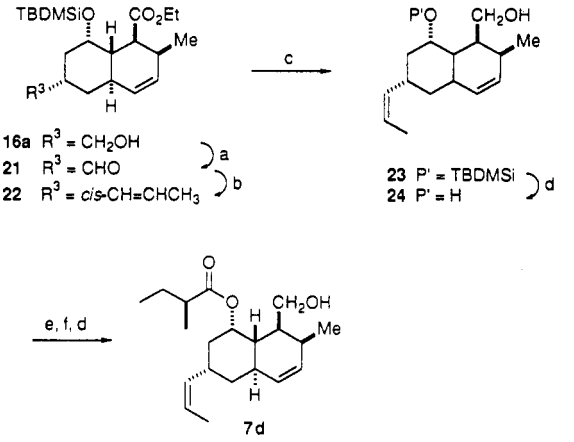
(7) The numbering of the mevinic acids is not standardized; we prefer to label the decalin ring so that the oxygen atom (highest priority) is at C-1. Systematic names are used in the Experimental Section.
(8) (a) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffmann, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170–181. (b) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858–1873.

retrosynthetic analyses, we decided to use the methodology[12] outlined in Scheme I to prepare the decalin fragment. This approach has the advantage that it would allow us to gain rapid access to a functionalized decalin by a route that (i) incorporated the six asymmetric centers in the correct configuration, (ii) introduced a functional group at the C-3 position that could be manipulated to give a series of analogues, and (iii) would readily allow the incorporation of different groups at the C-7 position. An additional positive aspect is that this strategy places an ester group at C-8, enabling us to explore different methodologies for the incorporation of the δ-lactone fragment. Although many methods of synthesizing possible δ-lactone intermediates have been reported,[13] few groups have addressed the difficulties of joining the lactone and decalin moieties.[9]

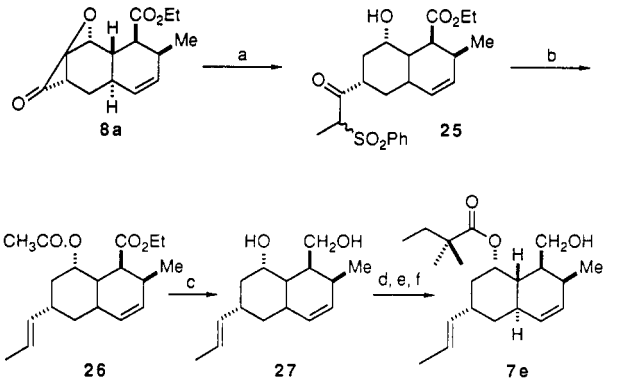
Synthesis of the Tricyclic Lactones 8. In order to confirm that the overall strategy was feasible, we initially decided to synthesize the natural product dihydromevinolin (**2**). The preparation of the required tricyclic lactone **8** (R^7 = Me) was straightforward and is outlined in Scheme II. The enolate of the protected, enantiomerically pure butyrolactone **10x** or **10y** was alkylated with the hexadienyl bromide **11a**[14] and then re-enolized and protonated from the less hindered face using the bulky *tert*-butyl bromide as the proton source. The TBDPSi-protected compound **10x** gave the two possible diastereoisomers in a syn:anti ratio of approximately 5:1 whereas the trityl-protected material **10y** gave a ratio closer to 15:1. The diastereoisomers were separated by chromatography, although clean separation was more difficult with the tritylated compounds. The major isomer **12x** or **12y** was deprotected to give the alcohol **13** which could be recrystallized to diastereomeric purity; again this process was less efficient with the trityl protecting group. Swern oxidation of the alcohol **13** and Wittig reaction with ethyl (triphenylphosphoranylidene)acetate in the same pot gave the *trans*-triene **9** (R^7 = Me) as the major isomer. This was thermally cyclized to yield the functionalized decalin **8a** which has the correct stereochemistry at the six chiral centers. The only byproduct (<5%) appeared to be another isomer, but 360-MHz proton NMR spectra did not allow the stereochemistry of this compound to be fully assigned. As has previously been discussed the high diastereoselectivity of this cyclization reflects the fact that the butyrolactone ring of **9** restrains the diene and dienophile such that they can only adopt one reactive conformation.[12a]

Scheme III[a]



[a] Reagents: (a) DMSO/$(CO\cdot Cl)_2$, Et_3N; (b) $EtPh_3P^+Br^-$/NaHMDS; (c) $LiEt_3BH$, 80 °C; (d) HF; (e) TBDMSiCl; (f) $[(S)\text{-}EtCHMeCO]_2O$.

Scheme IV[a]



[a] Reagents: (a) $EtSO_2Ph/n\text{-}BuLi$; (b) $NaBH_4$; Ac_2O; Na/Hg; (c) $LiAlH_4$; (d) TBDMSiCl; (e) $EtCMe_2CO\cdot Cl$; (f) HF.

Elaboration of the C-3 and C-1 Substituents. For the synthesis of dihydromevinolin (**2**) the carbonyl function at C-3 of **8a** has to be reduced to a methyl group. This transformation was efficiently (42% in five steps) achieved (Scheme II, R^7 = Me) by first opening the lactone ring with sodium methoxide, then protecting the C-1 hydroxyl group with *tert*-butyldimethylsilyl triflate, selectively reducing only the *axial* methyl ester with lithium triethylborohydride, tosylating the resulting primary alcohol, and finally, displacing the tosyl group with lithium triethylborohydride in refluxing THF. These more vigorous conditions also reduced the *equatorial* ethyl ester to a primary alcohol **18a**, as was desired for the next stage (see below).[15]

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(12) (a) Davidson, A. H.; Floyd, C. D.; Jones, A. J.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1985**, 1662–1664. (b) Davidson, A. H.; Jones, A. J.; Floyd, C. D.; Lewis, C. N.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, *1786*–1788.

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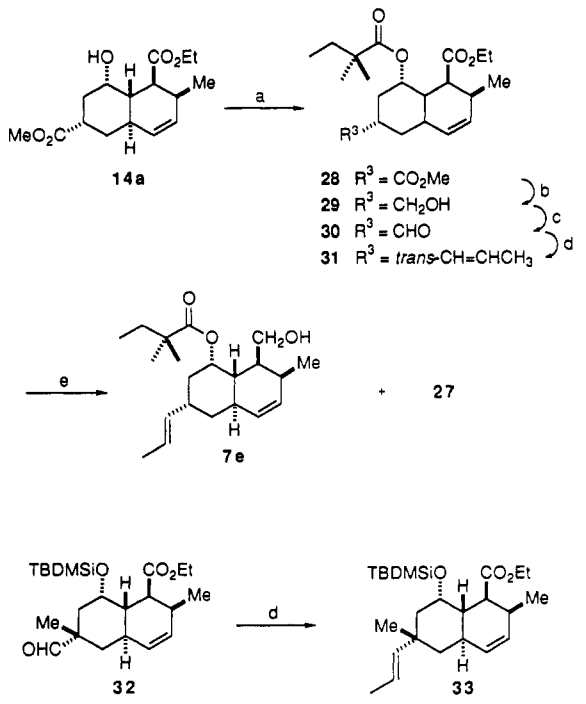
Scheme V[a]

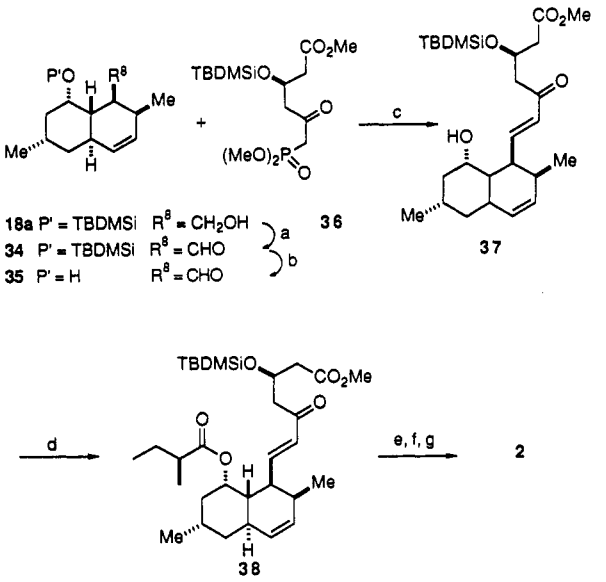


[a] Reagents: (a) $EtCMe_2CO\cdot Cl$; (b) $LiEt_3BH$, 0 °C; (c) PDC, 3-Å sieves, AcOH; (d) $MeCHI_2$, $CrCl_2$; (e) $LiEt_3BH$, 4 °C.

This route is ideally suited for the production of analogues at C-7. Substituting the diene **11a** used in the first alkylation step with the hydrogen **11b** or isopropyl **11c** analogues[16] led to **12b** or **12c**, which were taken through to the alcohols **18b** or **18c** with similar yields at each step. Interestingly there was little effect of the C-7 substituent on the rate or selectivity of the Diels–Alder reaction.[17] Following our initial work on dihydromevinolin (see below), we found that for the analogues it was more convenient to introduce the required C-1 ester at this point in the synthesis. Thus the silicon protecting groups were removed with hydrofluoric acid to give the diols **19**, and then protection of the primary alcohol, acylation of the secondary alcohol with (*S*)-2-methylbutyric anhydride,[18] and deprotection gave the primary alcohols **7b** and **7c** required for the coupling to the δ-lactone fragment.

The presence of the carbonyl functionality at C-3 makes the tricyclic lactones **8** ideally suited for the introduction of substituents other than methyl at this position. Thus the *cis*-alkene was prepared from the intermediate alcohol **16a** by Swern oxidation and Wittig reaction (Scheme III). Generation of the Wittig reagent from ethyltriphenylphosphonium bromide using lithium hexamethyldisilazide gave an inseparable mixture of cis and trans isomers, but use of sodium as the counterion gave solely the cis isomer **22**. No epimerization at the C-3 position was detected. Reduction of the ester followed by removal of the silyl protecting group gave the diol **24** (52% in four steps), which was acylated as described above to give **7d**.

Scheme VI[a]



[a] Reagents: (a) $DMSO/(CO\cdot Cl)_2$; Et_3N; (b) HF; (c) DBU/LiCl; (d) (*S*)-EtCHMeCO·Cl; (e) $Et_3SiH/(PPh_3)_3RhCl$; HF; (f) $Et_2BOMe/NaBH_4$; (g) TosOH.

The *trans*-alkene was initially prepared using sulfone chemistry (Scheme IV). Addition of the dianion of ethyl phenyl sulfone to the tricyclic lactone **8a** gave the keto sulfone **25**. Reduction with sodium borohydride, acetylation, and treatment with 6% sodium amalgam in buffered methanol–THF gave a moderate yield of the alkene **26** with a trans:cis ratio of 6:1. Reduction with lithium aluminum hydride then gave the diol **27**, which was treated as before to give **7e**.

For larger scale syntheses, and to improve the trans:cis ratio of the newly introduced group, an alternative route was developed (Scheme V). The tricyclic lactone **8a** was opened with sodium methoxide, and the secondary alcohol **14a** was immediately acylated with dimethylbutyryl chloride. Lithium triethylborohydride treatment at 0 °C showed complete selectivity between the three ester groups of the resulting **28** and reduced only the methyl ester to the alcohol **29**. Oxidation using PDC catalyzed by molecular sieves and acetic acid[19] gave the aldehyde **30**, which was immediately subjected to the Takai[20] olefination procedure (diiodoethane, chromium(II) chloride) in THF. This produced a greatly improved 15:1 trans:cis mixture in the crude product **31**. Careful reduction of the ethyl ester then gave the alcohol **7e** in much higher yield (42% over five steps) and purity to that prepared by the sulfone route, together with a moderate amount (36%) of the diol **27**, the product of overreduction. The diol **27** was converted to alcohol **7e** by protection, acylation, and deprotection as previously described (Scheme IV). The Takai olefination method appears to be particularly successful for hindered aldehydes since although in the synthesis of **31** a 15:1 trans:cis ratio was obtained, the more hindered C-3 disubstituted compound **32** gave exclusively the trans olefin **33**.[21]

(15) The alcohol **18a** (R^7 = Me) produced by this route has previously[12b] been desilylated and acylated with (*S*)-(+)-*O*-methylmandelic acid, and the resulting ester shown to have identical physical and spectral properties to those reported by Heathcock[10b] for material that was subsequently transformed into the natural product, dihydromevinolin (**2**).

(16) The dienyl bromides were prepared from the appropriate alcohols by bromination using the method of ref 14. Penta-2,4-dienol: Scheider, M. P.; Goldbach, M. *J. Am. Chem. Soc.* **1980**, *102*, 6114–6116. 6-Methylhepta-2,4-dienol: Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390–1403.

(17) For the most part none of the reaction rates and product ratios were significantly affected by the different C-7 substituents. The reduction of the ethyl ester of the unsubstituted compound **17b** was noticably faster than the displacement of the tosyl group, whereas in the substituted analogues **17a** and **17c** the reduction was the slower step. However, the elevated temperature was still necessary for any reduction of the ethyl ester to take place.

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(19) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699–1702.

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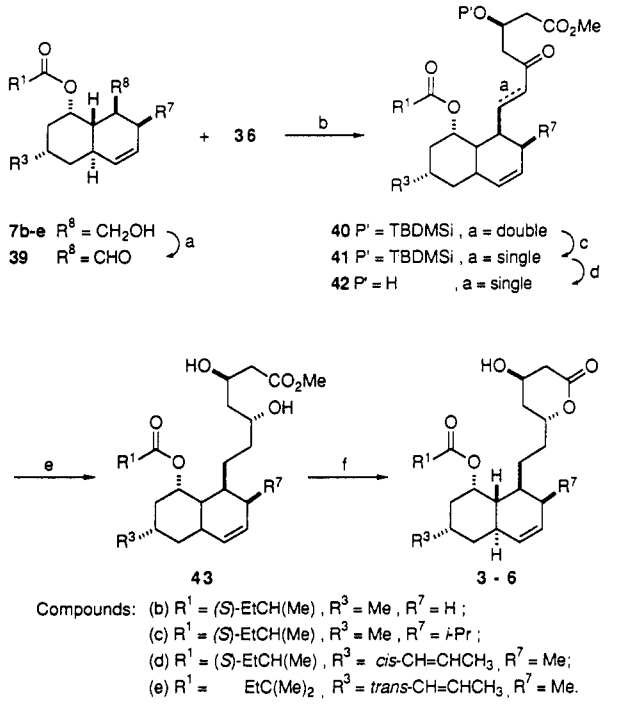
Scheme VII[a]



Compounds: (b) R^1 = (*S*)-EtCH(Me), R^3 = Me, R^7 = H;
(c) R^1 = (*S*)-EtCH(Me), R^3 = Me, R^7 = *i*-Pr;
(d) R^1 = (*S*)-EtCH(Me), R^3 = *cis*-CH=CHCH$_3$, R^7 = Me;
(e) R^1 = EtC(Me)$_2$, R^3 = *trans*-CH=CHCH$_3$, R^7 = Me.

[a] Reagents: (a) PDC, 3-Å sieves, AcOH; (b) see text; (c) NaHTe; (d) HF; (e) $Et_2BOMe/NaBH_4$; (f) H^+.

Introduction of the δ-Lactone Portion. To introduce the δ-lactone portion of the molecules we decided to use the methodology pioneered by Heathcock.[8b,10b] This is an attractive approach since the whole side chain is introduced as a single unit, which can be separately prepared in high enantiomeric excess.[13a,22,23] The two portions are coupled using a Wadsworth–Emmons reaction, and a series of mild reductions and a lactonization are all that is required to obtain the final product. The mildness of the transformations involved appeared to be very suitable for application to compounds that already had other ester and alkene functionalities present.

In order to convert the alcohol **18a** into dihydromevinolin (**2**), the route shown in Scheme VI was followed. Since the secondary alcohol was already protected, the primary alcohol was oxidized to the aldehyde **34** (60%) and the silicon protecting group removed (67–83%). Coupling with the keto phosphonate[13a] **36** using Roush–Masamune[24] conditions gave only a moderate yield (33%) of the enone **37**, possibly because the hydroxy aldehyde **35** was prone to decomposition and could not be obtained pure. Acylation of **37** with (*S*)-2-methylbutyryl chloride gave the intermediate **38** (30%) with spectral properties identical to those reported by Heathcock.[10b] The synthesis of the natural product was then completed in three further steps using the conditions described in the literature.

For the analogues **3–6** a modified approach was used. To avoid the unstable hydroxy aldehyde and the low-yielding acylation step of Scheme VI, the C-1 ester was introduced before the coupling step, as described earlier (Schemes II–V). In addition, alternative procedures for the later steps were developed, allowing us to complete the syntheses of the target molecules in good yield (Scheme VII). Thus the alcohols **7b–e** were oxidized to the aldehydes **39** required for the coupling reaction. On a small scale the Swern oxidation was effective, but for larger amounts the need for low temperatures and the noxious dimethyl sulfide produced prompted a search for alternative reagents. The catalyzed PDC method[19] was found to be particularly effective since it is rapid, can be carried out at room temperature, and is simply and rapidly worked up by filtration.

In the literature syntheses of compactin and dihydromevinolin the next step was the coupling reaction between the appropriate aldehyde and the keto phosphonate **36**, carried out using Roush–Masamune[24] conditions. However, it is reported[8b,10b] that under these conditions β-elimination of the silyloxy group in the enone product takes place and that to obtain the best yields the reaction has to be monitored carefully. We found that although the analogous elimination took place to some extent with our aldehydes **39**, the major problem was that the reaction was slow and low yielding. To speed up the reaction the use of 1 equiv of a strong base to form the keto phosphonate anion irreversibly was examined. An initial survey of bases showed that generation of the anion with lithium hexamethyldisilazide gave moderate but variable yields (20–50%) of coupled enone **40**, yet the reaction was still slow and some aldehyde was lost through epimerization. However, with continued experimentation, it was found that this key coupling reaction would proceed cleanly using lithium hydroxide (monohydrate) as the base and high yields (>80%) could be obtained.[23]

For the reduction of the double bond of the enone **38**, Heathcock had used triethylsilane and Wilkinsons catalyst, followed by treatment with hydrofluoric acid to deprotect both the resulting enol–silane and the C-3′ hydroxy group. Although we found this satisfactory for the synthesis of dihydromevinolin (**2**), it was not sufficiently selective in those compounds carrying alkenyl side chains at C-3, which suffered both reduction and isomerization. For the reduction of enones **40**, we therefore adopted the use of sodium hydrogen telluride in ethanol,[25] buffering the reaction with ammonium chloride. Without buffering, the reaction mixture rapidly becomes basic and β-elimination of the siloxy group takes place; however, with the ammonium chloride present and with careful deoxygenation of the solvent and apparatus almost quantitative yields of the reduced compounds **41** were obtained. Clean deprotection of the C-3′ hydroxyl group with hydrofluoric acid then gave the hydroxy ketones **42**.

The stereoselective reduction of the C-5′ carbonyl group was the remaining problem. Many of the previously reported syntheses of mevinic acids use a reducing agent that is only moderately selective, such as sodium or zinc borohydride, and separate the resulting diastereoisomers by column chromatography or HPLC.[8b,10a,b] It appeared to us that the most efficient method of obtaining the correct stereochemistry at C-5′ would be to relay the stereochem-

(21) Compound **32** was prepared in the same way as aldehyde **21**, except that the initial alkylation was carried out as two steps, the second using methyl iodide in place of *tert*-butyl bromide.

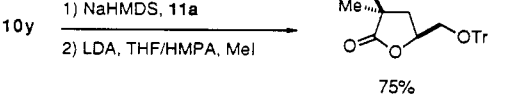


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Table I. Inhibitory Potency of Compounds 2–6 against Rat Liver HMG-CoA Reductase

compound[a]	R^1	R^3	R^7	IC_{50} (nM)[b]
mevinolin[c]	H	Me	Me	11
2	H	Me	Me	30
3	H	Me	H	1500
4	H	Me	*i*-Pr	1000
5	H	*cis*-CH=CHCH$_3$	Me	30
6	Me	*trans*-CH=CHCH$_3$	Me	3

[a] Tested as the sodium salt of the dihydroxy acid after hydrolysis of the lactone. [b] Mean of at least three determinations by the method of ref 27. [c] Has 4,4a double bond.

istry from the C-3′ position by using chelation control.[26] Therefore the hydroxy ketones **42** were treated with diethylmethoxyborane (generated in situ from methanol and triethylborane) to form the six-membered boron chelate. Reduction of the carbonyl group with sodium borohydride at low temperature followed by displacement and removal of the boron as trimethoxyborane left the crude 1,3-diols **43** in near quantitative yield with a syn:anti ratio of better than 95:5, as estimated from the ^{13}C NMR spectra. The diols were therefore lactonized using tosic acid in toluene or the more efficient aqueous hydrofluoric acid to give the target compounds **3–6**, which were purified by flash chromatography (Scheme VII).

Biological Activity. The compounds **2–6** were hydrolyzed to the sodium salts of the dihydroxy acids, and their ability to inhibit microsomal rat liver HMG-CoA reductase was evaluated,[27] using mevinolin as a standard.[3] The IC_{50} values are presented in Table I. The difference in activity between mevinolin and dihydromevinolin (**2**) is similar to that reported by other workers.[6] The much decreased ability of analogues **3** and **4** to inhibit the enzyme suggests the existence of a pocket that tightly binds to the C-7 methyl group; in contrast the C-3 position seems more tolerant to substitution (compounds **5** and **6**).[4] Based on its high inhibitory potency compound **6** was selected for further biological evaluation, the results of which will be published elsewhere.[4]

Conclusion. Whereas much of the chemistry of the mevinic acids previously described in the literature has been directed at syntheses of the natural products, the application of the synthetic methods described above gives an efficient enantioselective route not only to the natural product dihydromevinolin (**2**) but also to a series of structural analogues, **3–6**. The relaying of stereochemistry is efficient in that six chiral centers are set up in the decalin portion from a single chiral center in the γ-butyrolactone starting material. The improvements made for the coupling and elaboration of the δ-lactone portion of the molecules have led to the development of a synthetic route that can be and has been used to produce the multigram quantities of compounds required for full pharmacological evaluation.

Experimental Section

General. All nonaqueous reactions were carried out under an inert atmosphere using oven-dried glassware. THF refers to tetrahydrofuran, distilled from sodium/benzophenone. Ether refers to diethyl ether. Lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), and $LiEt_3BH$[28] were used as 1 M solutions in THF. Aqueous workup solutions were saturated, and the HCl solution was 2 M unless otherwise noted. Organic solutions were dried over anhydrous magnesium sulfate or sodium sulfate and evaporated under reduced pressure. Chromatography was carried out using 40–60-μm silica. Proton NMR spectra were recorded at 250 MHz and carbon spectra at 62.9 MHz in $CDCl_3$ unless noted otherwise and are given as ppm downfield from TMS. Coupling constants are in hertz. Infrared spectra were recorded as neat oils, as a solution in $CHCl_3$, or in the solid state.

(+)-(5*S*)-((*tert*-Butyldiphenylsiloxy)methyl)tetrahydrofuran-2-one (10x).[29] A solution of (+)-(5*S*)-(hydroxymethyl)-tetrahydrofuran-2-one[30] (25.1 g, 0.21 mol), *tert*-butyldiphenylsilyl chloride (58.3 g, 0.21 mol), and freshly distilled pyridine (70 mL) in dry CH_2Cl_2 (300 mL) was stirred for 20 h. The solution was washed with HCl(aq) (2 × 250 mL) and brine (100 mL), dried, and evaporated. The crude solid was recrystallized twice from petroleum ether–ether to give **10x** (47.6 g, 62%) as prisms; mp 75–77 °C; $[\alpha]^{23}_D$ +35.5 (*c* = 1.09, EtOH); IR ν_{max} (soln) 1770 and 1115 cm^{-1}; ^1H NMR (90 MHz) δ 7.8–7.3 (10 H, m), 4.57 (1 H, m), 3.88 (1 H, dd, *J* = 11 and 4), 3.71 (1 H, dd, *J* = 11 and 4), 2.8–2.0 (4 H, m), and 1.1 (9 H, s); ^{13}C NMR δ 176.9, 135.3, 132.7, 132.4, 129.7, 127.6, 79.6, 65.3, 28.3, 26.5, 23.3, and 18.9. Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.1; H, 7.4. Found: C, 71.4; H, 7.5.

(+)-(3*S*,5*S*)-3-[2′(*E*),4′(*E*)-Hexadienyl]-5-((*tert*-butyldiphenylsiloxy)methyl)tetrahydrofuran-2-one (12x) [by Combined Alkylation and Epimerization].[12b] The protected lactone **10x** (7.53 g, 21.3 mmol) in dry THF (100 mL) was cooled to −78 °C and then passed through a cannula into a cooled (−78 °C), stirred solution of NaHMDS (22.0 mmol) over 15 min. After the mixture was stirred for a further 10 min at −78 °C, freshly distilled 2(*E*),4(*E*)-hexadienyl bromide[14] (3.44 g, 21.4 mmol) in dry THF (20 mL) at −78 °C was rapidly added and stirring continued for 20 min. The cloudy mixture was then passed through the cannula into a cooled solution of LiHMDS (23.0 mmol) and stirred for 20 min at −78 °C. Freshly distilled 2-bromo-2-methylpropane (2.95 g, 21.5 mmol) in cold (−78 °C) THF (20 mL) was added, and the reaction mixture was stirred for 30 min at −78 °C and then quenched by addition of NH_4Cl(aq) (20 mL). The mixture was allowed to warm to rt, enough water was added to dissolve all the solid, and the resulting two phases were poured into ether (100 mL). The two layers were separated, and the organic phase was washed with NH_4Cl(aq) and brine (30 mL each). The combined aqueous solutions were extracted with ether (100 mL), and the organic layer was washed with brine (50 mL). The organic solutions were combined, dried, and evaporated to leave a crude orange oil (ca. 10 g). Flash chromatography eluting with 12:1 petroleum ether–EtOAc gave the dialkylated compound (0.6 g). Continued elution with 9:1 petroleum ether–EtOAc yielded the 3*R*,5*S* anti alkylated lactone (1.26 g, 14%) as an oil; IR ν_{max} (neat) 1775, 1430, and 1120 cm^{-1}; ^1H NMR (360 MHz) δ 7.7–7.6 (4 H, m), 7.5–7.4 (6 H, m), 6.08 (2 H, m), 5.66 (1 H, dq, *J* = 14 and 7), 5.50 (1 H, dt, *J* = 14 and 7), 4.54 (1 H, m), 3.86 (1 H, dd, *J* = 11 and 3), 3.66 (1 H, dd, *J* = 11 and 3), 2.90 (1 H, dq, *J* = 9 and 4), 2.60 (1 H, ddd, *J* = 14, 7, and 4), 2.34 (2 H, m), 2.05 (1 H, dt, *J* = 12 and 8), 1.76 (3 H, d, *J* = 7), and 1.05 (9 H, s). Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.6; H, 7.9. Found: C, 74.6; H, 7.9. Continued elution yielded some mixed fractions (0.35 g, 4%) and then the required syn-alkylated lactone **12x** (5.79 g, 63%): $[\alpha]^{23}_D$ +10.5 (*c* = 0.18, $CHCl_3$); IR ν_{max} (neat) 1775, 1595, 1430, and 1120 cm^{-1}; ^1H NMR (360 MHz) δ 7.7–7.6 (4 H, m), 7.5–7.4 (6 H, m), 6.06 (1 H, dd, *J* = 14 and 12), 5.98 (1 H, ddm, *J* = 14, 12, and 1), 5.62 (1 H, dq, *J* = 14 and 7), 5.46 (1 H, dt, *J* = 14 and 7), 4.46 (1 H, m), 3.86 (1 H, dd, *J* = 12 and 3), 3.72 (1 H, dd, *J* = 12 and 4), 2.73 (1 H, m), 2.65 (1 H, m), 2.3–2.2 (2 H, m), 1.94 (1 H, dt, *J* = 12 and 10), 1.72 (3 H, d, *J* = 7), and 1.06 (9 H, s); ^{13}C NMR δ 177.6, 135.3, 133.0, 132.8, 132.6, 131.0, 129.6, 127.9, 127.6, 126.5, 78.1, 64.3, 40.2, 33.0, 28.8, 26.6, 19.0, and 17.7. Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.6; H, 7.9. Found: C, 74.8; H, 8.0. The unwanted 3*R*,5*S* isomer can be converted to **12x** by treatment with LiHMDS and 2-bromo-2-methylpropane as above.

(+)-(3*S*,5*S*)-3-[2′(*E*),4′(*E*)-Hexadienyl]-5-(hydroxymethyl)tetrahydrofuran-2-one (13a).[12a] (a) From silylated

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(29) Although this product is mentioned in the literature, no analytical data is given: Hanessian, S.; Sahoo, S. P.; Murray, P. J. *Tetrahedron Lett.* **1985**, 5631.
(30) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.

material **12x**. Tetrabutylammonium fluoride (1 M in THF; 0.40 mol) was added to a solution of the alkylated lactone **12x** (156 g, 0.36 mol) in THF (1.4 L), and the mixture was stirred at rt until no starting material was detectable by TLC (ca. 1 h). Ether (0.5 L) was added and the murky solution washed with 3 M citric acid (3 × 500 mL). The aqueous layers were back extracted with more ether (2 × 250 mL) and the combined organic layers dried and evaporated. Chromatography eluting with methanol–dichloromethane (1:99 to 2:98) gave the alcohol (65.3 g, 91%) as a solid which could be used directly in the next step. A portion was recrystallized from petroleum ether–ether as microprisms: mp 62–63 °C (lit.[12a] mp 58–59 °C); $[\alpha]^{20}_D$ +43 (c = 0.043, MeOH); IR ν_{max} (soln) 3600 (br) and 1750 cm^{-1}; ^{1}H NMR (90 MHz) δ 6.2–5.3 (4 H, m), 4.5 (1 H, m), 3.8 (1 H, dd, J = 12 and 3), 3.6 (1 H, dd, J = 12 and 5), 3.4 (1 H, br s), 3.0–1.9 (5 H, m), and 1.75 (3 H, d, J = 6). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.4; H, 8.2.

(b) From tritylated material **12y**. Trifluoroacetic acid (60 mL) was added to a solution of the lactone **12y** (160 g, 0.36 mol) in chloroform (700 mL) and methanol (45 mL), and the mixture was stirred at rt until no starting material was detectable by TLC (ca. 3 h). The solution was washed with $NaHCO_3$(aq) (2 × 500 mL) and brine (500 mL), dried, and evaporated. Chromatography gave the alcohol as above (59 g, 82%).

(3*S*,5*S*)-3-[2′(*E*),4′(*E*)-Hexadienyl]-5-[2-(ethoxycarbonyl)-(*E*)-ethenyl]tetrahydrofuran-2-one (9a). A solution of DMSO (90 mL, 1.27 mol) in dry CH_2Cl_2 (250 mL) was cooled to −78 °C and added slowly to a cooled solution of oxalyl chloride (51 mL, 0.54 mol) in dry CH_2Cl_2 (200 mL). The mixture was stirred for 20 min at −78 °C, and then a precooled solution of the alcohol **13a** (75.7 g, 0.386 mol) in THF (1.2 L) was added through a cannula. After 30 min, distilled i-Pr_2NEt (270 mL, 1.55 mol) was injected, and the cloudy mixture was stirred for 5 min at −78 °C. The cooling bath was replaced by a large ice/water bath, and when the internal temperature reached ca. −10 °C the mixture was added to a solution of (carbethoxymethylene)triphenylphosphorane (271 g, 0.78 mol) in dry THF (1 L), and the reaction mixture was stirred for 20 h at rt in the dark. The mixture was evaporated to an oil, taken up in EtOAc (1 L) and washed with HCl(aq) (500 mL). The aqueous layer was back-extracted with EtOAc (2 × 500 mL), and the combined organic solutions were washed with brine (2 × 750 mL), dried, and evaporated to a crude oil. Flash chromatography eluting with 2:1 hexane–EtOAc gave a mixture of trienes separated from triphenylphosphine oxide and other impurities. A second column eluting with hexane–EtOAc (14:1 to 4:1) gave the required triene **9a** (53.4 g, 52%) as an oil and some mixed fractions; IR ν_{max} (neat) 1780, 1725, and 1670 cm^{-1}; ^{1}H NMR δ 6.90 (1 H, dd, J = 15 and 5), 6.2–6.0 (3 H, m), 5.68 (1 H, m), 5.46 (1 H, m), 4.97 (1 H, m), 4.23 (2 H, q, J = 7), 2.8–2.6 (4 H, m), 1.74 (3 H, d, J = 7), 1.64 (1 H, m), and 1.30 (3 H, t, J = 7); ^{13}C NMR δ 176.9, 165.4, 143.4, 133.5, 130.8, 128.6, 125.9, 122.1, 76.0, 60.6, 40.4, 34.0, 32.8, 17.8, and 14.1.

(+)-(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(Ethoxycarbonyl)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-6,8-naphthalenecarbolactone (8a). A 5-L flask was washed with hexamethyldisilazine, dried at 120 °C overnight, and allowed to cool under argon. A solution of the triene **9a** (35.85 g, 0.136 mol) and butylated hydroxytoluene (3.9 g, 0.018 mol) in dry mesitylene (3 L) was introduced and heated at reflux for 11 days. The vessel was cooled to ambient temperature and the solvent evaporated. The resulting oil was purified by chromatography eluting with 14:1 to 4:1 hexane–EtOAc to give the tricycle **8a** as a clear oil which crystallized on standing. Recrystallization from petroleum ether–ether gave white crystals (26 g, 73%): mp 60–62 °C; $[\alpha]^{22}_D$ +260 (c = 1.03, $CHCl_3$); IR ν_{max} (soln) 1775 and 1725 cm^{-1}; ^{1}H NMR (360 MHz) δ 5.5 (2 H, m), 5.06 (1 H, d, J = 6), 4.18 (2 H, q, J = 7), 2.87 (1 H, dd, J = 7 and 12), 2.8–2.7 (2 H, m), 2.50 (1 H, ddm, J = 12, 6, and 2), 2.36 (1 H, m), 2.06 (1 H, m), 1.90 (1 H, d, J = 11), 1.76 (1 H, t, J = 12), 1.43 (1 H, td, J = 13 and 2), 1.30 (3 H, t, J = 7), and 0.91 (3 H, d, J = 7); ^{13}C NMR δ 178.1, 172.4, 130.9, 127.8, 77.4, 59.9, 45.8, 38.9, 38.8, 38.3, 34.8, 32.3, 31.4, 16.9, and 13.9. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.2; H, 7.6. Found: C, 68.3; H, 7.6.

(+)-Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-6-(Carboxymethyl)-1,2,4a,5,6,7,8,8a-octahydro-8-hydroxy-2-methylnaphthalene-1-carboxylate (14a). NaHMDS (144.8 mmol) was added slowly to a stirred solution of the lactone **8a** (37.9 g, 143.4 mmol) in dry MeOH (1.6 L) at −20 °C. The cold solution was stirred for 2 h, and then NH_4Cl(aq) (400 mL) was added in several portions. The mixture was allowed to warm to 15 °C, the MeOH was evaporated, and the thick aqueous residue was extracted with ether (1 × 500 mL, 2 × 250 mL). The combined ether extracts were washed with HCl(aq) (200 mL), water (200 mL), and brine (200 mL), then dried, and evaporated. The residue was crystallized from hexane–ether to give the hydroxy diester **14a** (25.8 g, 61%) as plates: mp 115–118 °C; $[\alpha]^{22}_D$ +137 (c = 2.25, $CHCl_3$); IR ν_{max} (soln) 3400 (br), 1730, and 1720 cm^{-1}; ^{1}H NMR (360 MHz) δ 5.60 (1 H, ddd, J = 10, 4.5, and 2), 5.40 (1 H, d, J = 10), 4.29 (1 H, br s), 4.16 (2 H, m), 3.72 (3 H, s), 3.55 (1 H, br s), 2.90 (1 H, dd, J = 11.5 and 6), 2.85 (1 H, t, J = 6), 2.62 (1 H, m), 2.4–2.3 (2 H, m), 2.13 (1 H, d, J = 13), 1.83 (1 H, ddd, J = 15, 6, and 3.5), 1.51 (1 H, td, J = 11.5 and 2), 1.42 (1 H, td, J = 13 and 6), 1.27 (3 H, t, J = 7), and 0.91 (3 H, d, J = 7); ^{13}C NMR δ 177.7, 173.2, 131.1, 129.8, 65.1, 59.6, 51.9, 44.5, 39.8, 37.6, 33.6, 33.1, 32.0, 29.8, 17.3, and 14.0. Anal. Calcd for $C_{12}H_{24}O_5$; C, 64.8; H, 8.2. Found: C, 65.0; H, 8.3.

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-6-(Carboxymethyl)-1,2,4a,5,6,7,8,8a-octahydro-8-hydroxy-2-isopropylnaphthalene-1-carboxylate (14c). The synthesis was carried out as above but with 2(*E*),4(*E*)-6-methylheptadienyl bromide (**11c**) as starting material, and the product was obtained as plates: mp 137–138 °C; IR ν_{max} (KBr disk) 3470 (br), 1720, and 1710 cm^{-1}; ^{1}H NMR δ 5.7–5.58 (2 H, m), 4.29 (1 H, br s), 4.2–4.11 (2 H, q, J = 7), 3.72 (3 H, s), 3.5 (1 H, br m), 2.95 (1 H, dd, J = 13 and 7), 2.85 (1 H, m), 2.53 (1 H, m), 2.4–2.1 (3 H, m), 1.83 (1 H, ddd, J = 14.5, 6.5, and 3), 1.72–1.52 (2 H, m), 1.42 (1 H, td, J = 13 and 6), 1.28 (3 H, t, J = 7), 0.95 (3 H, d, J = 7), and 0.85 (3 H, d, J = 7); ^{13}C NMR δ 178.3, 173.6, 132.3, 125.2, 65.4, 59.8, 52.2, 45.4, 42.3, 41.7, 38.0, 34.0, 33.0, 29.8, 29.6, 22.8, 18.9, and 14.1. Anal. Calcd for $C_{18}H_{28}O_5 \cdot 0.25H_2O$: C, 65.7; H, 8.7. Found: C, 65.9; H, 8.5.

Ethyl (1*S*,4a*R*,6*S*,8*S*,8a*S*)-6-(Carboxymethyl)-1,2,4a,5,6,7,8,8a-octahydro-8-hydroxynaphthalene-1-carboxylate (14b). The synthesis was carried out as above but with 2(*E*),4(*E*)-pentadienyl bromide (**11b**) as starting material: ^{1}H NMR δ 5.62 (1 H, ddd, J = 10, 6.5, and 2), 5.47 (1 H, dd, J = 10 and 2), 4.16 (2 H, q, J = 7), 3.95 (1 H, br s), 3.72 (3 H, s), 2.85–2.64 (2 H, m), 2.55–2.12 (5 H, m), 1.78 (1 H, ddd, J = 13, 7, and 3.5), 1.64 (1 H, br m), 1.49 (1 H, td, J = 11.5 and 2), 1.36 (1 H, td, J = 13 and 6), and 1.27 (3 H, t, J = 7).

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-6-(carboxymethyl)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalene-1-carboxylate (15a). *tert*-Butyldimethylsilyl triflate[31] (1.0 mL, 5.7 mmol) was injected into a solution of the hydroxy diester **14a** (994 mg, 3.36 mmol) and freshly distilled 2,6-lutidine (1.0 mL; 8.4 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred until TLC indicated complete reaction (1 h) and then poured into HCl(aq) (30 mL). The organic layer was separated and washed with HCl(aq), NH_4Cl(aq), and brine (20 mL each), dried, and evaporated to an oil. Flash chromatography eluting with 9:1 petroleum ether–EtOAc gave the silylated diester **15a** (1.24 g, 90%) as a clear oil: IR ν_{max} (soln) 2940, 1730, and 1255 cm^{-1}; ^{1}H NMR (360 MHz) δ 5.54 (1 H, ddd, J = 2.5, 4.5, and 10), 5.46 (1 H, br d, J = 10), 4.31 (1 H, br s), 4.16 (1 H, dq, J = 10.5 and 7), 4.04 (1 H, dq, J = 10.5 and 7), 3.65 (3 H, s), 2.73 (1 H, dd, J = 6 and 11.5), 2.7–2.5 (3 H, m), 2.40 (1 H, d, J = 14), 2.25 (1 H, d, J = 13), 1.85 (1 H, ddd, J = 14, 7 and 2.5), 1.47 (1 H, br t, J = 11), 1.25 (3 H, t, J = 7), 0.83 (9 H, s), 0.02 (3 H, s), and −0.10 (3 H, s); ^{13}C NMR δ 176, 173.9, 131.3, 130.2, 67.1, 59.9, 51.5, 44.2, 40.6, 36.6, 35.1, 33.1, 32.4, 29.6, 26.1, 18.2, 17.9, 14.3, −3.7 and −5.8; MS m/z 410 (3, M$^+$), 353 (85, M − tBu), 145 (100).

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-6-(hydroxymethyl)-2-methylnaphthalene-1-carboxylate (16a). $LiEt_3BH$ (7.5 mmol) was added to a solution of the diester **15a** (1.24 g, 3.0 mmol) in THF (50 mL) at 0 °C and stirred until TLC indicated complete consumption of starting material (2 h). Water (1 mL) was carefully added to destroy excess reagent, followed by 3 M NaOH(aq) (2.5

(31) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1982**, 3455.

mL) and 30% H_2O_2 solution (2.6 mL) dropwise. The resulting cloudy mixture was stirred vigorously for 1 h at rt, reduced to about one-third in volume, and poured into brine (30 mL). The solution was extracted with ether (3 × 50 mL), and the combined organics were washed with brine, dried, and evaporated to an oil (1.2 g) which was used in the next step without further purification. Chromatography of a small portion eluting with 4:1 petroleum ether–EtOAc gave the pure alcohol **16a** as an oil: IR ν_{max} (soln) 3440 (br), 1725, and 1255 cm^{-1}; ^1H NMR (360 MHz) δ 5.56 (1 H, ddd, J = 10, 4.5, and 3), 5.42 (1 H, br d, J = 10), 4.38 (1 H, br d, J = 2.5), 4.16 (1 H, dq, J = 10.5 and 7), 4.06 (1 H, dq, J = 10.5 and 7), 3.85 (1 H, dd, J = 10 and 7), 3.68 (1 H, m), 2.76 (1 H, dd, J = 11.5 and 6), 2.60 (1 H, m), 2.48 (1 H, br t, J = 12), 2.1–1.8 (4 H, m), 1.6 (1 H, br s), 1.52 (1 H, t, J = 11), 1.28 (4 H, t and m), 0.90 (9 H, s), 0.86 (3 H, d, J = 7), 0.08 (3 H, s), and –0.05 (3 H, s).

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-6-[[(*p*-toluenesulfonyl)oxy]methyl]naphthalene-1-carboxylate (17a). Freshly recrystallized tosyl chloride (165 mg, 0.86 mmol) was added to a solution of the alcohol **16a** (301 mg, 0.79 mmol) and DMAP (20 mg) in dry CH_2Cl_2 (20 mL) and pyridine (1 mL). The mixture was protected from moisture and stirred for 90 h, then washed with HCl(aq) (2 × 10 mL), 3 M NaOH(aq), NH_4Cl(aq), and brine (10 mL each), dried, and evaporated to give the tosylate (403 mg, 95%) as an oil: IR ν_{max} (soln) 2980, 1725, and 1600 cm^{-1}; ^1H NMR (360 MHz) δ 7.78 (2 H, d, J = 8), 7.32 (2 H, d, J = 8), 5.53 (1 H, ddd, J = 9.5, 4.5, and 3), 5.21 (1 H, br d, J = 9.5), 4.38 (1 H, t, J = 10), 4.28 (1 H, br s), 4.14 (1 H, dq, J = 10.5 and 7), 4.04 (1 H, dq, J = 10.5 and 7), 3.95 (1 H, dd, J = 10 and 4), 2.65 (1 H, dd, J = 11 and 6), 2.56 (1 H, br q, J = 6), 2.42 (3 H, s), 2.17 (1 H, m), 2.10 (1 H, br t, J = 12), 1.8–1.6 (3 H, m), 1.44 (1 H, t, J = 11), 1.24 (3 H, t, J = 7), 1.17 (1 H, td, J = 13 and 4.5), 0.8 (12 H, s over d), –0.03 (3 H, s), and –0.10 (3 H, s). Anal. Calcd for $C_{28}H_{44}O_6SSi$: C, 62.6; H, 8.3. Found: C, 62.3; H, 8.1.

(+)-(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-1-(hydroxymethyl)-2,6-dimethylnaphthalene (18a). $LiEt_3BH$ (8.0 mmol) was added to a solution of the tosylate **17a** (1.6 g, 3.0 mmol) in THF (20 mL) and the mixture refluxed gently for 30 min by which time TLC indicated that most material had been converted to the intermediate ester. Refluxing was continued for 8 h with additon of more reagent at intervals (3 mL/h) until TLC indicated complete consumption of the intermediate. The mixture was cooled to 0 °C, and water (2 mL) was carefully added, followed by 3 M NaOH(aq) (11 mL). A 30% H_2O_2 solution (12 mL) was added dropwise to the vigorously stirred solution, and stirring was continued for 90 min at rt. The cloudy mixture was poured into brine (100 mL), the two layers separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were washed with NH_4Cl(aq) and brine, dried, and evaporated to an oil. Flash chromatography eluting first with petroleum ether and then 9:1 petroleum ether–EtOAc gave the alcohol **18a** (780 mg, 80%) as a waxy solid: mp 54–57 °C; $[\alpha]^{22}_D$ +138 (c = 1.69, $CHCl_3$); IR ν_{max} (soln) 3620, 2930, and 1460 cm^{-1}; ^1H NMR (360 MHz) δ 5.64 (1 H, ddd, J = 9.5, 4.5, and 2.5), 5.38 (1 H, d, J = 9.5), 3.98 (1 H, br q, J = 2), 3.90 (1 H, dd, J = 10.5 and 4), 3.48 (1 H, t, 10.5), 2.6–2.4 (2 H, m), 2.1–1.9 (2 H, m), 1.74 (1 H, br d, J = 14.5), 1.6–1.5 (2 H, m), 1.4–1.2 (2 H, m), 1.18 (3 H, d, J = 7), 1.08 (1 H, td, J = 10.5 and 2), 0.96 (3 H, d, J = 7), 0.92 (9 H, s), 0.14 (3 H, s), and 0.12 (3 H, s); ^{13}C NMR δ 132.2, 131.8, 68.3, 42.3, 39.8, 39.4, 38.7, 30.7, 29.4, 27.5, 26.0, 22.2, 18.3, 15.8, –2.1, and –5.5. Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.3; H, 11.2. Found: C, 70.5; H, 11.3.

(+)-(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-1-(hydroxymethyl)-2,6-dimethylnaphthalene (19a).[10b] A 19:1 CH_3CN/40% aqueous HF solution (10 mL) was added to the protected alcohol **18a** (31 mg, 0.09 mmol) and the solution stirred for 20 h. Solid $NaHCO_3$ was carefully added until the mixture was neutralized, and the organic solvent evaporated. The resulting oily solid was taken up in water (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic extracts were dried and evaporated. Chromatography eluting with 1:2 petroleum ether–ether, recrystallization from petroleum ether–ether, and drying over silica gel gave the diol **19a** (20 mg, 99%) as needles: mp 115–116 °C; $[\alpha]^{22}_D$ +152 (c = 0.98, $CHCl_3$); IR ν_{max} (soln) 3620, 3400 (br), 2910, and 1455 cm^{-1}; ^1H NMR (360 MHz) δ 5.56 (1 H, m), 5.40 (1 H, d, J = 10), 4.22 (1 H, br s), 3.75 (1 H, t, J = 10), 3.66 (1 H, d, J = 10), 2.9 (2 H, m), 2.51 (1 H, t, J = 11), 2.39 (1 H, m), 2.1–2.0 (2 H, m), 1.9–1.7 (2 H, m), 1.58 (1 H, br d, J = 12), 1.4–1.2 (2 H, m), 1.22 (3 H, d, J = 7), and 0.80 (3 H, d, J = 7). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.3; H, 10.55. Found: C, 74.3; H, 10.3.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-1-(hydroxymethyl)-2-isopropyl-6-methylnaphthalene (19c). Obtained as needles, mp 150–152 °C; $[\alpha]^{28}_D$ +208 (c = 0.82, MeOH); IR ν_{max} (soln) 3620, 3400 (br), 2910, and 1455 cm^{-1}; ^1H NMR δ 5.63–5.53 (2 H, m), 4.2 (1 H, br s), 3.87–3.75 (2 H, m), 2.44 (1 H, m), 2.27 (1 H, m), 2.07–1.96 (2 H, m), 1.84–1.55 (4 H, m), 1.4–1.25 (2 H, m), 1.18 (3 H, d, J = 7), 0.94 (3 H, d, J = 7), and 0.80 (3 H, d, J = 7). Anal. Calcd for $C_{13}H_{22}O_2 \cdot 0.25H_2O$: C, 74.2; H, 11.0. Found: C, 73.9; H, 10.7.

(1*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-1-(hydroxymethyl)-6-methylnaphthalene (19b): ^1H NMR δ 5.58 (1 H, m), 5.43 (1 H, d, J = 11), 4.25 (1 H, br s), 3.59 (2 H, m), 3.0 (2 H, br s), 2.48 (1 H, t, J = 11), 2.13–1.65 (5 H, m), 1.58 (1 H, dd, J = 13 and 2), 1.37–1.23 (2 H, m), 1.20 (3 H, d, J = 7), and 1.03 (1 H, dt, J = 12 and 2.5).

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*,2″*S*)-3′-(*tert*-Butyldimethylsiloxy)-7′-[1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethyl-8-[(2″-methylbutyryl)oxy]-1-naphthalenyl]-5′-oxohept-6′-enoate (38).[10b] A solution of DMSO (172 μL, 2.4 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a solution of oxalyl chloride (105 μL, 1.2 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C. The solution was stirred for 10 min, a solution of alcohol **18a** (156 mg, 0.48 mmol) in CH_2Cl_2 (0.5 mL) was slowly added, and stirring was continued for 40 min. Et_3N (0.60 mL, 4.3 mmol) was added, and the mixture was stirred for 5 min, allowed to warm to room temperature, and stirred for a further 40 min. Ether (20 mL) was added, and the mixture was washed with 1 M HCl(aq) (2 × 10 mL) and brine (10 mL). The organic layers were dried and evaporated to an oil (143 mg). Chromatography eluting with neat hexane, followed by ether, gave **34** as a colorless oil (93 mg, 60%): ^1H NMR δ 9.78 (1 H, d, J = 2), 5.61 (1 H, ddd, J = 10, 5, and 2), 5.42 (1 H, br d, J = 10), 4.34 (1 H, m), 2.87 (1 H, ddd, J = 12, 6, and 3), 2.8–1.2 (8 H, m), 1.19 (3 H, d, J = 7), 0.92 (3 H, d, J = 8), 0.89 (9 H, s), 0.07 (3 H, s), and –0.05 (3 H, s).

Aldehyde **34** (133 mg, 0.41 mmol) was dissolved in CH_3CN (14 mL), 40% aqueous HF solution (1.4 mL) was added, and the mixture was stirred at room temperature for 7 h. Water (1.5 mL) was added, the CH_3CN was removed at 20 °C, and the residue was partitioned between water (10 mL) and EtOAc (4 × 20 mL). The combined organic layers were dried and evaporated to leave the hydroxy aldehyde **35** (71 mg, 83%), contaminated with approximately 5% of unreacted material: ^1H NMR δ 9.83 (1 H, d, J = 2), 5.58 (1 H, ddd, J = 10, 5, and 2), 5.45 (1 H, br d, J = 10), 4.27 (1 H, m), 2.83 (1 H, ddd, J = 12, 6, and 3), 2.73 (1 H, m), 2.52 (1 H, br t, J = 12), 2.2–1.2 (6 H, m), 1.21 (3 H, d, J = 7), and 1.03 (3 H, d, J = 7).

LiCl (45 mg, 1.06 mmol) and DBU (96 μL, 0.66 mmol) were added to a solution of the hydroxy aldehyde **35** (98 mg, 0.47 mmol) and keto phosphonate[13a,22] **36** (263 mg, 0.69 mmol) in CH_3CN (0.6 mL), and the mixture was stirred for 5 h at room temperature. Ether (75 mL) and water (15 mL) were added, and the two layers separated. The ether layer was washed with 1 M H_3PO_4(aq) (15 mL), dried, and evaporated to a yellow oil (249 mg). Chromatography eluting with 4:1 hexane–ether gave the enone **37** (72 mg, 33%) as a colorless oil: ^1H NMR δ 6.90 (1 H, dd, J = 16 and 10), 6.23 (1 H, d, J = 16), 5.61 (1 H, ddd, J = 10, 5 and 2), 5.43 (1 H, br d, J = 10), 4.65 (1 H, m), 3.89 (1 H, m), 3.70 (3 H, s), 2.87 (1 H, dd, J = 16 and 6), 2.76 (1 H, dd, J = 16 and 6), 2.7–1.2 (12 H, m), 1.18 (3 H, d, J = 7), 0.98 (3 H, d, J = 7), 0.85 (9 H, s), 0.08 (3 H, s), and 0.05 (3 H, s).

Compound **37** (70 mg, 0.15 mmol) and DMAP (7 mg, 0.06 mmol) were stirred at 0 °C in pyridine (0.7 mL), and 2(*S*)-methylbutyryl chloride (78 mg, 0.64 mmol) was added dropwise. The mixture was stirred at room temperature for 18 h, and then ether (25 mL) and 0.2 M HCl(aq) (15 mL) were added. The organic layer was washed with $NaHCO_3$(aq) (5 mL) and brine (5 mL), dried, and evaporated to a brown oil (133 mg). Chromatography eluting with 4:1 hexane–EtOAc gave the product **38** as a colorless oil (25 mg, 30%) with spectral properties as previously

reported:[10b] ^{1}H NMR δ 6.75 (1 H, dd, J = 16 and 10), 5.97 (1 H, dd, J = 16 and 0.5), 5.61 (1 H, ddd, J = 10, 5, and 2), 5.42 (1 H, br d, J = 10), 4.89 (1 H, m), 4.59 (1 H, m), 3.64 (3 H, s), 2.9–1.2 (16 H, m), 1.08 (6 H, m), 0.95 (3 H, d, J = 7), 0.87 (3 H, t, J = 7), 0.82 (9 H, s), 0.05 (3 H, s), and 0.02 (3 H, s); ^{13}C NMR δ 175.3, 171.4, 148.5, 132.0, 131.9, 131.0, 70.6, 65.9, 51.4, 47.3, 42.8, 42.4, 41.4, 41.3, 40.5, 38.3, 35.7, 35.3, 29.9, 26.8, 26.4, 25.6, 21.0, 17.8, 16.4, 16.2, 11.8, 11.4, 4.8, and 5.1.

Dihydromevinolin (2). The enone **38** was converted to **2** by the method of Heathcock[10b] and had spectral and biological properties in accordance with those previously reported.[4] For purposes of comparison the proton NMR spectrum is given. ^{1}H NMR δ 5.63 (1 H, ddd, J = 10, 5, and 3), 5.37 (1 H, br d, J = 10), 5.19 (1 H, m), 4.62 (1 H, m), 4.35 (1 H, m), 2.73 (1 H, dd, J = 18 and 5), 2.58 (1 H, ddd, J = 18, 4, and 1.5), 2.46 (1 H, br t, J = 16), 2.32 (1 H, quintet, J = 7), 2.3 (1 H, m), 2.1–1.2 (15 H, m), 1.21 (1 H, dt, J = 10 and 2), 1.12 (3 H, d, J = 7), 1.08 (3 H, d, J = 7), 0.89 (3 H, t, J = 7), and 0.83 (3 H, d, J = 7).

C-7-Isopropyldihydromevinolin, (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-[2-(1,2,4a,5,6,7,8,8a-octahydro-8-[(2″-methylbutyryl)oxy]-2-isopropyl-6-methyl-1-naphthalenyl)ethyl]tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (4): obtained as an oil; IR ν_{max} (soln) 3450 (br) and 1725 cm^{-1}; ^{1}H NMR δ 5.68 (1 H, ddd, J = 10, 4, and 2.5), 5.6 (1 H, br d, J = 10), 5.2 (1 H, m), 4.62 (1 H, m), 4.36 (1 H, m), 2.75 (1 H, dd, J = 18 and 5), 2.60 (1 H, ddd, J = 18, 4, and 1.5), 2.4 (1 H, m), 2.35 (1 H, m, J = 7), 2.2–1.15 (17 H, m), 1.13 (3 H, d, J = 7), 1.10 (3 H, d, J = 7), 0.97 (3 H, d, J = 7), 0.90 (3 H, t, J = 7), and 0.80 (3 H, d, J = 7); MS *m/z* (CI) 435 (15, M + H$^+$), 417 (12), 333 (47), 315 (100).

C-7-Desmethyldihydromevinolin, (1*S*,4a*R*,6*S*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-[2-[1,2,4a,5,6,7,8,8a-octahydro-8-[(2″-methylbutyryl)oxy]-6-methyl-1-naphthalenyl]ethyl]tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (3): ^{1}H NMR δ 5.65 (1 H, m), 5.44 (1 H, br d, J = 10), 5.30 (1 H, m), 4.62 (1 H, m), 4.37 (1 H, m), 2.75 (1 H, dd, J = 17 and 5), 2.62 (1 H, ddd, J = 17, 4, and 1), 2.75–1.2 (20 H, m), 1.16–1.10 (6 H, m), and 0.91 (3 H, t, J = 7); ^{13}C NMR δ 176.2, 170.1, 132.4, 125.5, 76.0, 69.0, 65.8, 62.8, 47.2, 38.6, 38.5, 35.9, 35.6, 33.7, 32.4, 31.8, 29.7, 27.0, 26.6, 20.9, 16.4, 15.2, and 11.7.

(+)-Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(methoxycarbonyl)-2-methyl-8-[(2,2-dimethylbutyryl)oxy]naphthalene-1-carboxylate (28). A solution of the alcohol **14a** (37.5 g, 127 mmol), 2,2-dimethylbutyryl chloride (68.2 g, 453 mmol), and DMAP (2.1 g, 17 mmol) in pyridine (1 L) was stirred at 90 °C for 16 h. The dark reaction mixture was concentrated to 100 mL and partitioned between CH_2Cl_2 (2 × 500 mL) and HCl(aq) (500 mL). The combined organic layers were washed with water (2 × 400 mL) and Na_2CO_3(aq) (500 mL), dried, and evaporated under reduced pressure. Chromatography eluting with 9:1 hexane–EtOAc gave the ester **28** as a pale oil (46.0 g, 92%): $[\alpha]^{20}_D$ +166 (*c* = 1.4, $CHCl_3$); IR ν_{max} (neat) 2970, 1735, and 1725 cm^{-1}; ^{1}H NMR δ 5.55 (1 H, m), 5.47 (1 H, d, J = 10.3), 5.43 (1 H, m), 4.11 (2 H, q, J = 7.2), 3.67 (3 H, s), 2.73–2.46 (5 H, m), 2.32 (1 H, br d, J = 13.5), 1.91 (1 H, ddd, J = 15.2, 7.2, and 2.9), 1.65 (1 H, m), 1.49 (2 H, q, J = 7.5), 1.24 (3 H, t, J = 7.2), 1.25 (1 H, m), 1.09 (3 H, s), 1.07 (3 H, s), 0.89 (3 H, d, J = 6.7), and 0.81 (3 H, t, J = 7.5); ^{13}C NMR (100.6 MHz) δ 177.0, 174.9, 172.9, 130.9, 130.3, 69.0, 60.1, 51.7, 44.8, 42.8, 39.0, 36.6, 33.0, 32.6, 32.3, 31.7, 31.1, 24.5, 24.3, 17.6, 14.3, and 9.1. Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.78; H, 8.69.

(+)-Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(hydroxymethyl)-2-methyl-8-[(2,2-dimethylbutyryl)oxy]naphthalene-1-carboxylate (29). $LiEt_3BH$ (337 mmol) was added over 20 min to a stirred solution of the triester **28** (63.2 g, 160.5 mmol) in THF (800 mL) between −5 and 0 °C. After 1 h NH_4Cl(aq) (250 mL) was added cautiously, and the mixture was allowed to warm to rt. The THF was evaporated, and the residue was extracted with EtOAc (3 × 300 mL). The combined EtOAc extracts were washed with HCl(aq) (250 mL), Na_2CO_3(aq) (250 mL), and brine (100 mL), and the solvent was evaporated to give a gum. MeOH (250 mL) was added, and the solution was heated to approximately 50 °C for 10 min and evaporated. Chromatography eluting with 4:1 to 2:1 hexane–EtOAc and recrystallization from hexane gave the alcohol **29** as white needles (56.7 g, 96%): mp 91–93 °C; $[\alpha]^{23}_D$ +148 (*c* = 0.82, $CHCl_3$); IR ν_{max} (soln) 3620 (sharp), 2985, and 1725 cm^{-1}; ^{1}H NMR δ 5.64–5.58 (1 H, m), 5.44–5.40 (2 H, m), 4.18–4.05 (2 H, m), 3.82 (1 H, t, J = 10.0), 3.59 (1 H, dd, J = 10.5 and 5.8), 2.67–2.55 (2 H, m), 2.45–2.26 (1 H, m), 2.10–1.18 (12 H, complex m), 1.15 (3 H, s), 1.14 (3 H, s), 0.91 (3 H, d, J = 6.9), and 0.84 (3 H, t, J = 7.5); ^{13}C NMR (100.6 MHz) δ 176.9, 172.9, 131.2, 130.5, 69.8, 65.8, 60.1, 45.0, 42.9, 39.3, 33.2, 32.8, 32.5, 31.7, 29.8, 24.9, 24.6, 17.6, 14.3, and 9.3. Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.77; H, 9.37.

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2,2-dimethylbutyryl)oxy]-6-[(*E*)-prop-1-enyl]naphthalene-1-carboxylate (31). A solution of the alcohol **29** (56.7 g, 154.8 mmol) in dry CH_2Cl_2 (2 × 400 mL) was added to a stirred mixture of finely ground PDC (86.8 g, 230.8 mmol) and freshly activated, finely ground 3-Å molecular sieves (28.4 g). The mixture was cooled in a cold-water bath and dry AcOH (15.5 mL) added slowly. After 80 min, ether (3 L) was added and the mixture filtered through Kieselguhr to remove most of the insoluble chromium salts. The filtrate was passed down a silica column which was eluted with more ether. The solvent was evaporated and the residue azeotroped with toluene to leave the aldehyde **30** as a pale yellow oil (55.5 g, 98%), which solidified on standing, and was used immediately: ^{1}H NMR δ 9.65 (1 H, d, J = 1), 5.62–5.44 (3 H, m), 4.12 (2 H, q, J = 7.1), 2.59–2.24 (7 H, m), 2.04 (1 H, m), 1.66 (1 H, td, J = 10.9 and 1.6), 1.49 (2 H, qd, J = 7.7 and 2.3), 1.23 (3 H, t, J = 7.4), 1.09 (3 H, s), 1.07 (3 H, s), 0.89 (3 H, d, J = 6.8), and 0.80 (3 H, t, J = 7.4).

THF (1 L) was added to chromium(II) chloride (112.2 g, 0.91 mol) and stirred until a fine suspension resulted. A solution of the aldehyde **30** (41.6 g, 0.11 mol) and 1,1-diiodoethane (64.4 g, 0.23 mol) in THF (500 mL) was added, the reaction mixture was stirred for 15 h, water (750 mL) was added, and stirring continued for 5 min. The THF was removed under reduced pressure and the aqueous mixture extracted with ether (3 × 500 mL). The combined ethereal layers were washed with brine (500 mL), dried, and evaporated to leave a green oil. Chromatography eluting with 19:1 to 9:1 hexane–EtOAc gave the alkene **31** as a colorless oil (35.1 g, 82%): IR ν_{max} (neat) 2980, 1740, 1730, and 970 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.76 (1 H, ddq, J = 15.3, 8.0, and 1.6), 5.58 (1 H, ddd, J = 10.0, 4.6, and 2.7), 5.42–5.30 (3 H, m), 4.18–4.06 (2 H, m), 2.66 (1 H, dd, J = 11.5 and 6.0), 2.59 (1 H, m), 2.55–2.43 (2 H, m), 1.94 (1 H, dq, J = 15.0 and 2.0), 1.83 (1 H, ddd, J = 15.0, 6.0, and 3.4), 1.77 (1 H, dq, J = 13.2 and 2.2), 1.61 (3 H, ddd, J = 6.4, 1.5, and 1.0), 1.7–1.45 (3 H, m), 1.39 (1 H, td, J = 13.1 and 5), 1.22 (3 H, t, J = 7.0), 1.13 (3 H, s), 1.12 (3 H, s), 0.89 (3 H, d, J = 6.9), and 0.83 (3 H, t, J = 7.5); ^{13}C NMR (100.6 MHz) δ 177.6, 173.6, 136.8, 131.7, 131.5, 123.6, 70.7, 60.7, 45.7, 43.5, 39.7, 37.8, 36.5, 35.9, 33.9, 33.1, 30.9, 25.5, 25.4, 18.6, 18.3, 14.9, and 9.8. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.22; H, 9.68.

(1*S*,3*S*,4a*R*,7*S*,8*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-8-(hydroxymethyl)-7-methyl-3-[(*E*)-prop-1-enyl]-1-naphthalenyl 2,2-Dimethylbutyrate (7e). $LiEt_3BH$ (280 mmol) was added to a solution of the ester **31** (35.1 g, 93.3 mmol) in THF (350 mL) at −78 °C. The reaction mixture was allowed to warm to 4 °C and left for 14 h. NH_4Cl(aq) (500 mL) was cautiously added, the THF was removed, and the resulting aqueous mixture was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with HCl(aq) (500 mL), Na_2CO_3(aq) (250 mL), and brine (250 mL), dried, and evaporated. The residue was dissolved in MeOH (100 mL) and heated at 50 °C for 10 min, and the solvent was evaporated. This procedure was repeated once more. The residual pale yellow oil (29.6 g) was purified by chromatography eluting with hexane–EtOAc (85:15 to neat EtOAc) to give the alcohol **7e** as a white solid (18.1 g, 58%): IR ν_{max} (KBr disk) 3460 (br), 3010, 2960, 2930, 2910, 2890, and 1715 cm^{-1}; ^{1}H NMR δ 5.77 (1 H, ddq, J = 15.3, 8.1, and 1.6), 5.66 (1 H, ddd, J = 9.8, 4.8, and 2.5), 5.45–5.34 (2 H, m), 5.05 (1 H, q, J = 2.6), 3.65 (1 H, dt, J = 10.3 and 4.5), 3.50 (1 H, td, J = 10.3 and 5.0), 2.58–2.46 (3 H, m), 2.02–1.90 (2 H, m), 1.80–1.69 (2 H, m), 1.67–1.56 (3 H, m), 1.60 (2 H, q, J = 7.4), 1.41–1.13 (3 H, m), 1.18 (3 H, s), 1.17 (3 H, s), 0.95 (3 H, d, J = 7.0), and 0.87 (3 H, t, J = 7.4); ^{13}C NMR δ 176.2, 134.7, 131.2, 129.3, 121.6, 68.3, 60.5, 41.5, 38.6, 38.1, 35.9, 34.6, 33.9, 31.6, 29.9, 29.8, 23.2, 16.5, 14.2, and 7.7. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.36; H, 10.28. The diol **27** (8.0 g, 36%) was obtained on further elution.

(1*S*,3*S*,4a*R*,7*S*,8*S*,8a*S*)-8-Formyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-3-[(*E*)-prop-1-enyl]-1-naphthalenyl 2,2-Dimethylbutyrate (39e). The alcohol **7e** (16.3 g, 48.7 mmol), freshly recrystallized PDC (21.1 g, 56 mmol), and finely ground 3-Å molecular sieves (16 g) were stirred in CH_2Cl_2 (400 mL) at 0 °C. AcOH (5 mL) was added, and stirring was continued for 1 h at 0 °C before warming the mixture to rt. Ether (500 mL) was added and the mixture passed down a short silica column, eluting thoroughly with ether. The solvents were evaporated, toluene (100 mL) was added and evaporated to leave a semisolid material (16.4 g) which was purified by column chromatography eluting with 9:1 hexane–EtOAc to give the aldehyde **39e** (13.6 g, 84%): IR ν_{max} (KBr disk) 2956, 2920, and 1725 cm^{-1}; ^1H NMR (400 MHz) δ 9.71 (1 H, d, J = 2.6), 5.75 (1 H, ddq, J = 15.3, 7.9, and 1.7), 5.61 (1 H, ddd, J = 9.8, 4.4, and 2.7), 5.43–5.36 (2 H, m), 5.34 (1 H, q, J = 2.7), 2.71–2.62 (2 H, m), 2.54–2.46 (2 H, m), 1.98 (1 H, ddd, J = 15.0, 4.8, and 2.0), 1.87–1.66 (4 H, m), 1.63–1.61 (3 H, m), 1.60–1.50 (3 H, m), 1.42 (1 H, td, J = 13.1 and 5.0), 1.14 (3 H, s), 1.13 (3 H, s), 0.95 (3 H, d, J = 6.9), and 0.82 (3 H, t, J = 7.5); ^{13}C NMR δ 204.6, 177.8, 136.5, 131.9, 131.8, 123.9, 70.4, 51.7, 43.5, 38.8, 37.7, 36.4, 36.0, 33.9, 31.7, 30.9, 25.4, 25.3, 18.7, 18.0, and 10.0. Anal. Calcd for $C_{21}H_{32}O_3 \cdot 0.2H_2O$: C, 75.04; H, 9.72. Found: C, 75.04; H, 9.59.

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*)-3′-(*tert*-Butyldimethylsiloxy)-7′-{1,2,4a,5,6,7,8,8a-octahydro-2-methyl-8-[(2″,2″-dimethylbutyryl)oxy]-6-[(*E*)-prop-1-enyl]-1-naphthalenyl}-5′-oxohept-6′-enoate (40e). Ether (50 mL) was added to a mixture of the keto phosphonate **36**[13a,22] (11.0 g, 28.8 mmol) and $LiOH \cdot H_2O$ (1.21 g, 28.7 mmol), the mixture was stirred for 30 min, then a solution of the aldehyde **39e** (6.8 g, 20.5 mmol) in ether (50 mL) was added, and stirring was continued for 7 days. NH_4Cl(aq) (100 mL) was added and the mixture extracted with ether (3 × 100 mL). The combined ether extracts were washed with brine (100 mL), dried, and evaporated to leave a solid, which was purified by column chromatography eluting with 93:7 hexane–EtOAc to give recovered aldehyde **39e** (0.92 g, 13%) followed by the enone **40e** (9.18 g, 76%) which was recrystallized from ether–hexane: mp 93–94 °C; IR (KBr disk) 2970, 1740, 1720, 1698, and 1630 cm^{-1}; ^1H NMR δ 6.77 (1 H, dd, J = 17.5 and 10), 6.01 (1 H, d, J = 17.5), 5.75 (1 H, ddq, J = 15, 7.5, and 2.5), 5.65 (1 H, dq, J = 10.5 and 2.5), 5.5–5.3 (2 H, m), 4.95 (1 H, m), 4.62 (1 H, m), 3.68 (3 H, s), 2.83 (1 H, dd, J = 17.5 and 5), 2.74 (1 H, dd, J = 17.5 and 5), 2.65–2.2 (6 H, m), 2.05–1.2 (10 H, m), 1.14 (3 H, s), 1.12 (3 H, s), 0.95 (3 H, d, J = 7.5), 0.88–0.72 (12 H, m), 0.08 (3 H, s), and 0.03 (3 H, s); ^{13}C NMR δ 195.8, 175.1, 170.1, 147.1, 134.5, 130.7, 130.6, 129.5, 121.7, 68.8, 64.6, 50.0, 46.1, 41.3, 41.2, 41.1, 41.0, 40.0, 35.7, 34.5, 34.4, 34.0, 31.6, 29.3, 24.3, 23.2, 23.0, 16.5, 15.0, 7.8, –6.1, and –6.5. Anal. Calcd for $C_{34}H_{56}O_6Si$: C, 69.35; H, 9.58. Found: C, 69.34; H. 9.57.

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*)-7-{1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2″,2″-dimethylbutyryl)oxy]-6-[(*E*)-prop-1-enyl]-1-naphthalenyl}-3′-hydroxy-5′-oxoheptanoate (42e). A stirred suspension of tellurium powder (32.5 g, 255 mmol) and $NaBH_4$ (19.4 g, 510 mmol) in deoxygenated EtOH (800 mL) was heated to reflux for 45 min. The dark solution was cooled to rt, and then finely ground, deoxygenated solid NH_4Cl (68 g, 1.27 mol) was added, followed by a solution of the enone **40e** (24.9 g, 42.5 mmol) in deoxygenated EtOH (300 mL). Stirring was continued for 18 h, air was bubbled through the reaction mixture for 1 h, and the solids were removed by filtration through a short silica column, eluting with EtOAc. Evaporation of the solvents gave an oil which was taken up in CH_2Cl_2 (500 mL) and washed with brine (100 mL). The organic layer was dried and evaporated to leave the reduced product **41e** (23.5 g, 98%), which was used in the next step without further purification; ^1H NMR δ 5.74 (1 H, ddq, J = 15, 9, and 2), 5.63 (1 H, dq, J = 10.5 and 2.5), 5.38 (2 H, m), 5.18 (1 H, m), 4.57 (1 H, m), 3.65 (3 H, s), 2.68 (1 H, dd, J = 16 and 7), 2.58 (1 H, dd, J = 16 and 7), 2.47 (4 H, m), 2.25 (2 H, m), 2.03 (1 H, m), 1.90–1.48 (9 H, m), 1.43–1.05 (10 H, m), 0.85 (15 H, m), 0.06 (3 H, s), and 0.02 (3 H, s).

A solution of **41e** (47 g, 79.9 mmol) in 1:19 40% aqueous HF–CH_3CN (100 mL) was stirred for 3 h, EtOAc (500 mL) was added, and the mixture was adjusted to pH 8 with Na_2CO_3(aq). The aqueous layer was separated and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried, and evaporated to leave a gum, which was purified by column chromatography eluting with 3:2 hexane–EtOAc to give the keto alcohol **42e** (33.7 g, 89%): mp 67–68 °C; IR ν_{max} (soln) 3500, 2960, 1740, 1720, and 1110 cm^{-1}; ^1H NMR δ 5.72 (1 H, ddq, J = 15, 8, and 1.5), 5.62 (1 H, dq, J = 9.7 and 2.6), 5.35 (1 H, m), 5.15 (1 H, m), 4.42 (1 H, m), 3.69 (3 H, s), 2.68–2.35 (7 H, m), 2.23 (2 H, m), 2.02 (1 H, m), 1.8–1.43 (9 H, m), 1.42–1.05 (10 H, m), and 0.9–0.7 (6 H, m); ^{13}C NMR (100.6 MHz) δ 209.8, 177.2, 172.1, 136.1, 132.2, 131.0, 122.9, 69.4, 64.4, 51.7, 48.0, 42.9, 41.9, 40.9, 40.5, 37.3, 36.9, 35.9, 35.2, 33.0, 31.6, 31.2, 24.6, 24.5, 21.6, 17.8, 14.8, and 9.1. Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.56; H, 9.30. Found: C, 70.50; H, 9.27.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,4′*R*,6′*R*)-6′-[2-[1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2″,2″-dimethylbutyryl)oxy]-6-[(*E*)-prop-1-enyl]-1-naphthalenyl]ethyl]tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (6). Triethylborane (1.0 M in THF; 44.6 mL, 44.6 mmol) was added to a mixture of 4:1 THF–MeOH (446 mL). After 90 min the solution was cooled to –78 °C, and a solution of the keto alcohol **42e** (18.4 g, 38.7 mmol) in 4:1 THF–MeOH (446 mL) was added. The solution was stirred for 1 h at –78 °C, then $NaBH_4$ (1.6 g, 42.6 mmol) was added rapidly, and stirring continued for 3 h. NH_4Cl(aq) (250 mL) was added slowly, followed by sufficient water to just dissolve the solid, and the mixture was extracted with EtOAc (3 × 500 mL). The combined EtOAc extracts were washed with HCl(aq) (250 mL), $NaHCO_3$(aq) (330 mL), and brine (250 mL), dried, and evaporated. The residue was dissolved in MeOH (750 mL), heated to 50 °C for 1 h, and then evaporated to give the diol **43e** (17.9 g, 97%), which was used in the next step without further purification: ^1H NMR δ 5.76 (1 H, dd, J = 12 and 4), 5.65 (1 H, m), 5.4 (1 H, m), 5.38 (1 H, d, J = 9), 5.20 (1 H, m), 4.25 (1 H, m), 3.8 (1 H, m), 3.76 (1 H, br s), 3.73 (3 H, s), 3.33 (1 H, br s), 2.50 (2 H, d, J = 6), 2.5 (1 H, m), 2.31 (1 H, m), 2.0–1.0 (24 H, m), and 0.9–0.8 (6 H, m).

A solution of the crude diol **43e** (31.6 g, 66 mmol) in 1:19 40% aqueous HF–CH_3CN (1 L) was stirred for 4 h and then adjusted to pH 8 using $NaHCO_3$(aq). The mixture was extracted with EtOAc (3 × 500 mL), and the combined organic extracts were washed with brine (200 mL), dried, and evaporated to leave a solid. Purification by column chromatography eluting with 55:45 hexane–EtOAc gave the lactone **6** as an off-white solid (24.5 g, 80% from the keto alcohol **42e**). Recrystallization of another batch (38.8 g) from diisopropyl ether afforded **6** (25.6 g, 66%) as fine white needles: mp 129–133 °C; IR ν_{max} (soln) 3470, 2970, 1715, 920, and 760 cm^{-1}; ^1H NMR δ 5.85–5.55 (2 H, m), 5.45–5.3 (2 H, m), 5.18 (1 H, m), 4.60 (1 H, m), 4.36 (1 H, m), 2.74 (1 H, dd, J = 17 and 5), 2.62 (1 H, ddd, J = 17, 4, and 1), 2.50 (2 H, m), 2.31 (1 H, m), 2.2–1.85 (3 H, m), 1.8–1.5 (9 H, m), 1.45–1.2 (6 H, m), 1.18 (6 H, s), and 0.8 (6 H, m); ^{13}C NMR δ 179.5, 170.4, 136.0, 132.4, 130.8, 122.8, 76.1, 69.4, 62.6, 42.8, 41.8, 38.5, 37.3, 36.0, 35.2, 32.9, 31.5, 31.2, 29.6, 24.6, 23.1, 17.8, 14.8, and 9.2; HRMS found m/z 447.315 ($M + H^+$); $C_{27}H_{42}O_5$ + H requires 447.311. Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.3; H, 9.5.

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-6-formyl-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalene-1-carboxylate (21). A solution of DMSO (0.82 mL, 11.6 mmol) in CH_2Cl_2 (4 mL) was slowly added to a stirred solution of oxalyl chloride (0.47 mL, 5.4 mmol) in CH_2Cl_2 (5 mL) at –60 °C. After 5 min a solution of the alcohol **16a** (0.93 g, 2.4 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred a further 30 min. Et_3N (3.7 mL, 26.5 mmol) was added, the reaction was allowed to warm to rt, and stirring continued for 30 min. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with 0.2 M HCl(aq) (20 mL) and Na_2CO_3(aq) (20 mL). The organic solution was dried and evaporated leaving a pale yellow oil (1.00 g). This was purified by chromatography eluting with 1:1 hexane–ether to yield the aldehyde **21** (0.72 g, 77%) as a clear oil; ^1H NMR δ (C_6D_6) 9.61 (1 H, d, J = 1), 5.49 (2 H, m), 4.58 (1 H, m), 4.05 (2 H, m), 2.92 (1 H, dd, J = 12 and 6), 2.64 (2 H, m), 2.40 (1 H, ddt, J = 13, 3, and 2), 2.05 (1 H, ddt, J = 14, 3, and 2), 1.80 (1 H, tt, J = 7 and 2), 1.63 (1 H, td, J = 12 and 1), 1.52 (1 H, ddd, J = 14, 7, and 2), 1.07 (3 H, t, J = 7), 1.00 (13 H, m), 0.07 (3 H, s), and 0.05 (3 H, s).

Ethyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsiloxy)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-6-[(*Z*)-prop-1-enyl]naphthalene-1-carboxylate (22). A suspension of ethyltriphenylphosphonium bromide (5.00 g, 13.5 mmol) in THF

(17 mL) was stirred at 0 °C while NaHMDS (13.0 mmol) was added. The resulting solution was stirred for 15 min and then cooled to -78 °C. A solution of the aldehyde **21** (0.83 g, 2.2 mmol) in THF (8 mL) was added dropwise and stirring continued cold for 1 h and then at rt for 17 h. The mixture was diluted with ether (100 mL) and washed with NH_4Cl(aq) (40 mL) and brine (40 mL), and the organic layer was dried and evaporated to leave a semisolid (5.3 g). Chromatography eluting with 50:1 hexane–EtOAc gave the alkene **22** as a pale yellow oil (0.84 g, 99%): ^{1}H NMR δ 5.99 (1 H, m), 5.56 (1 H, ddd, J = 10, 5, and 3), 5.37 (1 H, br d, J = 10), 5.28 (1 H, dqd, J = 11, 7, and 1.1), 4.36 (1 H, m), 4.10 (2 H, m), 2.88 (2 H, m), 2.80 (2 H, dd, J = 12 and 6), 2.57 (2 H, m), 1.78 (1 H, m), 1.70 (1 H, ddd, J = 14, 5, and 3), 1.60 (1 H, m), 1.58 (3 H, dd, J = 7 and 1.8), 1.51 (1 H, td, J = 12 and 2), 1.36 (1 H, td, J = 13 and 5), 1.26 (3 H, t, J = 7), 0.87 (9 H, s), 0.86 (3 H, d, J = 7), 0.00 (3 H, s), and -0.09 (3 H, s).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(*tert*-Butyldimethylsiloxy)-1,2,3,4,4a,7,8,8a-octahydro-8-(hydroxymethyl)-7-methyl-3-[(*Z*)-prop-1-enyl]naphthalene (23). The ester **22** (0.19 g, 0.48 mmol) was stirred in THF (20 mL), and $LiEt_3BH$ (1.0 mmol) was added. The mixture was warmed to 80 °C and stirred for 6 h, while more $LiEt_3BH$ (1.0 mmol/h), was added. The temperature was lowered to 0 °C, and water (1 mL) was cautiously added, followed by 3 M NaOH(aq) (2 mL) and 30% H_2O_2 (2 mL). The resulting gel was stirred at rt for 2 h and then poured onto brine (15 mL) and extracted with ether (2 × 20 mL). The combined ethereal solutions were dried and evaporated. Chromatography eluting with 25:1 hexane–EtOAc gave the alcohol **23** as a colorless oil (0.12 g, 71%): ^{1}H NMR δ 5.99 (1 H, m), 5.64 (1 H, ddd, J = 10, 5, and 1.6), 5.36 (1 H, br d, J = 10), 5.30 (1 H, dqd, J = 10, 7, and 1), 4.01 (1 H, m), 3.90 (1 H, m), 3.49 (1 H, td, J = 11 and 6), 2.83 (1 H, m), 2.54 (2 H, m), 2.02 (1 H, tt, J = 11 and 5), 1.79 (1 H, ddd, J = 14, 5, and 1.9), 1.6 (2 H, m), 1.58 (3 H, dd, J = 7 and 1.9), 1.32 (1 H, td, J = 13 and 5), 1.13 (1 H, td, J = 11 and 2), 1.00 (1 H, s, removed by D_2O), 0.96 (3 H, d, J = 7), 0.91 (9 H, s), 0.08 (3 H, s), and 0.07 (3 H, s).

(1*S*,3*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-1-hydroxy-8-(hydroxymethyl)-7-methyl-3-[(*Z*)-prop-1-enyl]-naphthalene (24). The alcohol **23** (0.54 g, 1.54 mmol) was stirred at rt in 19:1 CH_3CN/40% aqueous HF (15 mL) for 15 h. Ether (150 mL) was added followed by Na_2CO_3(aq) (50 mL). The ethereal solution was separated and dried and the solvent removed to give the diol as an off-white solid (0.35 g, 97%). A small sample was recrystallized from hexane–CH_2Cl_2 for analysis: mp 131–133 °C; IR ν_{max} (CH_2Cl_2 soln) 3620 and 3495 cm^{-1}; ^{1}H NMR δ 6.00 (1 H, m), 5.56 (1 H, ddd, J = 10, 5, and 2.6), 5.43 (1 H, dqd, J = 11, 7, and 1.4), 5.37 (1 H, br d, J = 10), 4.24 (1 H, m), 3.76 (1 H, t, J = 10), 3.65 (1 H, dd, J = 10 and 1.4), 2.88 (1 H, m), 2.76 (1 H, br s, removed by D_2O), 2.53 (1 H, m), 2.41 (1 H, br s, removed by D_2O), 2.40 (1 H, m), 2.03 (1 H, m), 1.95 (1 H, m), 1.80 (1 H, ddd, J = 14, 6, and 3), 1.63 (3 H, dd, J = 7 and 1.8), 1.6 (1 H, m), 1.33 (1 H, td, J = 13 and 5), 1.30 (1 H, td, J = 11 and 2), and 0.82 (3 H, d, J = 7). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.93; H, 10.06.

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*,2″*S*)-3′-(*tert*-Butyldimethylsiloxy)-7′-[2-methyl-8-[(2″-methylbutyryl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-6-[(*Z*)-prop-1-enyl]-1-naphthalenyl]-5′-oxohept-6′-enoate (40d). The aldehyde **39d** was obtained from the diol **24** by protection of the primary alcohol, acylation of the secondary alcohol, deprotection of the primary alcohol, and oxidation to give the product as an oil: ^{1}H NMR δ 9.74 (1 H, d, J = 2), 5.79 (1 H, br t, J = 10), 5.62 (1 H, m), 5.42 (1 H, br d, J = 10), 5.36 (2 H, m), 2.91 (1 H, m), 2.70 (2 H, m), 2.52 (1 H, br t, J = 12), 2.30 (1 H, sextet, J = 7), 1.59 (3 H, dd, J = 7 and 1.5), 2.05–1.35 (7 H, m), 1.13 (3 H, d, J = 7), 0.97 (3 H, d, J = 7), and 0.88 (3 H, t, J = 7).

The aldehyde **39d** (91 mg, 0.29 mmol), the keto phosphonate[13a,22] **36** (160 mg, 0.42 mmol), and LiCl (18 mg, 0.42 mmol) were stirred at rt in CH_3CN (0.22 mL), and DBU (0.055 mL, 0.37 mmol) was added. The mixture was stirred at rt for 80 h, diluted with EtOAc (25 mL), and washed with 0.5 M H_3PO_4(aq) (10 mL) and brine (10 mL). The combined aqueous layers were extracted with EtOAc (25 mL), and the combined organic layers were dried and evaporated. Chromatography eluting with 19:1 hexane–EtOAc gave the enone **40d** as a colorless oil (32 mg, 20%); ^{1}H NMR δ 6.78 (1 H, dd, J = 16 and 10), 5.98 (1 H, d, J = 16), 5.74 (1 H, m), 5.61 (1 H, ddd, J = 10, 5, and 3), 5.42 (1 H, br d, J = 10), 5.30 (1 H, dq, J = 11 and 7), 4.88 (1 H, m), 4.58 (1 H, m), 3.63 (3 H, s), 2.89 (1 H, br s), 2.75 (2 H, m), 2.7–2.4 (4 H, m), 2.31 (1 H, m), 2.26 (1 H, sextet, J = 7), 1.55 (3 H, dd, J = 7 and 1.5), 2.1–1.3 (7 H, m), 1.11 (3 H, d, J = 7), 0.95 (3 H, d, J = 7), 0.85 (3 H, t, J = 7), 0.83 (9 H, s), 0.06 (3 H, s), and 0.02 (3 H, s).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-{2-[1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2″-methylbutyryl)oxy]-6-[(*Z*)-prop-1-enyl]-1-naphthalenyl]ethyl}-tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (5). Using methods similar to those described above the enone **40d** was converted to **5**, obtained as an oil: ^{1}H NMR δ 5.78 (1 H, m), 5.63 (1 H, m), 5.38 (1 H, br d), 5.33 (1 H, m), 5.20 (1 H, m), 4.60 (1 H, m), 4.38 (1 H, m), 2.87 (1 H, m), 2.74 (1 H, dd, J = 18 and 5), 2.60 (1 H, dd, J = 18 and 4), 2.51 (1 H, br t, J = 11), 1.57 (3 H, dd, J = 7 and 1.7), 2.4–1.2 (17 H, m), 1.11 (3 H, d, J = 7), 0.88 (3 H, t, J = 7), and 0.86 (3 H, d, J = 7).

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Supplementary Material Available: ^{1}H NMR spectra of the analogues **3**, **4**, and **5** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Preparation and Enzymatic Structure Determination of a Complete Set of 2^A,6^X-Bis-*O*-(sulfonyl)-β-cyclodextrins

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2^A,6^X-Bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (X = A–G) were prepared by the reaction of 2-*O*-(mesitylsulfonyl)-β-cyclodextrin with mesitylenesulfonyl chloride in pyridine. All regioisomers were isolated and their structures determined.

Bifunctionalization of cyclodextrins has attracted much attention with respect to the construction of artificial enzymes or receptors.[2] In this regard, it is usually necessary for the hydroxy groups of the cyclodextrins to be activated

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