Enantioselective Total Synthesis of (+)-6-*epi*-Mevinolin and Its Analogs. Efficient Construction of the Hexahydronaphthalene Moiety by High Pressure-Promoted Intramolecular Diels−Alder Reaction of (*R*,2*Z*,8*E*,10*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2,8,10-dodecatrien-4-one

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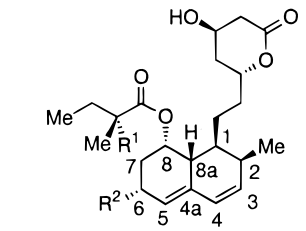
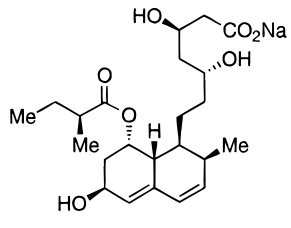
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, (+)-6-*epi*-mevinolin (**2a**) and (+)-6-*epi*-4a,5-dihydromevinolin (**2b**), were prepared by combining two nonracemic units, phosphonate **3** and decalin **4**, which were prepared from enantiopure 3-substituted pentanedioic acid monoesters **5a** and **5b**, respectively. Each acid was synthesized from cyclic anhydrides **7a** and **7b** by diastereoselective ring opening by means of (*S*)-benzyl mandelate as a common chiral auxiliary. The construction of decalin moiety **4** was accomplished by asymmetric intramolecular Diels−Alder (IMDA) reaction of nonracemic trienone **6** bearing a methyl group as a chiral controller. The IMDA diastereoselectivity of trienone **6** is discussed in terms of the configuration of (*E*)- and (*Z*)-dienophiles which are activated by an endogenous carbonyl group. The IMDA reaction of (*R*)-(*Z*)-**6** under high pressure is highly selective and gives *cis*-decalins exclusively with preferential formation of **4** over **16**. The inhibitory activity of (+)-6-*epi*-mevinolin (**2a**) and several analogs against HMG-CoA reductase was compared with mevinolin (**1b**). (+)-6-*epi*-Mevinolin (**2a)** was shown to be half as potent as mevinolin (**1b**) while (+)-6-*epi*-4a,5-dihydromevinolin (**2b)** was as potent as mevinolin.

Compactin (**1a**),[1] isolated from the culture broth of the fungus *Penicillium citrinum* and *Penicillinus brevicompactum*, was found to be a potent inhibitor against HMG-CoA reductase (HMGR), a rate-limiting enzyme in the biosynthesis of endogenous cholesterol.[2] Structurally related compounds, mevinolin (**1b**)[3] and the 4a,5-dihydro derivatives of **1a** and **1b**,[4,5] were isolated thereafter, and numerous structural modifications have been done to improve their potency and pharmacological properties as a potential therapeutic for treating hypercholesterolemia. Consequently, a number of novel HMGR inhibitors have been discovered[6−8] and three inhibitors of natural origin,[6,7] mevinolin (**1b**), pravastatin (**1d**),[9] and simvastatin (**1c**),[10] have been marketed.

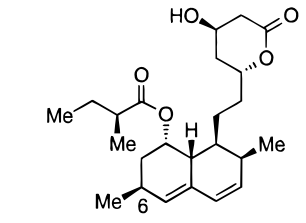
The (3*R*)-hydroxy lactone moiety is essential for HMGR inhibition; however, the structural requirement for the remaining decalin moiety is not strict. There have been some reports on the substituent effects at the 6-position on the decalin moiety,[7] and most involving α-alkyl substituents.[7a,b] We were particularly interested in introducing the 6*β*-methyl group into compactin because simple replacement of the C-6 hydrogen with the α-methyl group (mevinolin (**1b**)) or the *β*-hydroxy group (pravastatin (**1d**)) had led to successful drugs. Here, we report on the enantioselective total synthesis and HMGR



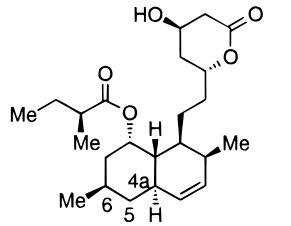
1a R^1 = H , R^2 = H compactin
1b R^1 = H , R^2 = Me mevinolin
1c R^1 = Me, R^2 = Me simvastatin



1d pravastatin sodium



2a (+)-6-*epi*-mevinolin



2b (+)-6-*epi*-4a,5-dihydromevinolin

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) Isolation of (+)-compactin: (a) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165. (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.

(2) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.

(3) Isolation of (+)-mevinolin: (a) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schönberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957. (b) Endo, A. *J. Antibiot.* **1980**, *33*, 334.

(4) Isolation of (+)-4a,5-dihydrocompactin: Lam, Y. K. T.; Gullo, V. P.; Goegelman, R. T.; Jorn, D.; Huang, L.; DeRiso, C.; Monaghan, R. L.; Putter, I. *J. Antibiot.* **1981**, *34*, 614.

(5) Isolation of (+)-4a,5-dihydromevinolin: Albers-Schönberg, G.; Joshua, H.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507.

(6) (a) Review: Endo, A.; Hasumi, K. *Nat. Prod. Rep.* **1993**, *10*, 541. (b) For a review on synthetic work, see: Chapleur, Y. The Chemistry and Total Synthesis of Mevinic Acids in *Recent Progress in the Chemistry of Antibiotics*; Lukacs, G., Ueno, S., Eds.; Springer: New York, 1993; Vol. 2, pp 829−937. Recent synthetic work on natural products: (c) Total synthesis of (+)-compactin: Hagiwara, H.; Nakano, T.; Kon-no, M.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 777. (d) Total synthesis of (+)-mevinolin: Clive, D. L. J.; Murthy, K. S. K.; Wee, A, G, H.; Prasad, J. S.; da Silva, G. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (e) Total synthesis of (+)-4a,5-dihydrocompactin: Hagiwara, H.; Kon-no, M.; Nakano, T.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2417. (f) Total synthesis of (+)-4a,5-dihydromevinolin: Hanessian, S.; Roy, P. J.; Petrini, M.; Hotges, P. J.; Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766 and earlier references cited therein.

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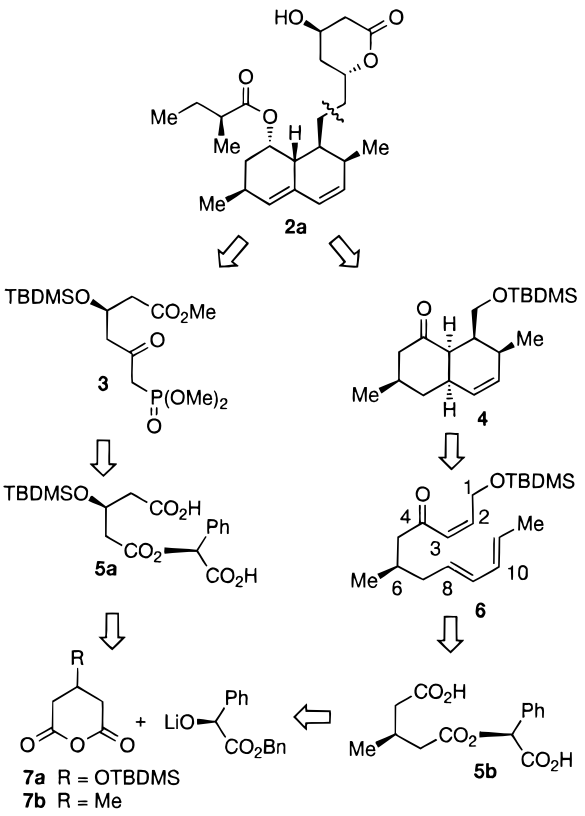
Scheme 1. Retrosynthetic Analysis



inhibitory activity of (+)-6-*epi*-mevinolin (6β-methylcompactin) (**2a**), (+)-6-*epi*-4a,5-dihydromevinolin (**2b**), and their analogs.[11]

Results and Discussion

We planned to prepare **2a** by combining two enantiopure units, lactone precursor **3** and decalin moiety **4** (Scheme 1). Heathcock[12a] and Karanewsky[12c] had demonstrated that enantiopure phosphonate **3** is a useful synthon for HMGR inhibitors. We later found a more practical synthesis of **3** which utilized desymmetrization of 3-(silyloxy)pentanedioic anhydride **7a** by means of (*S*)-benzyl mandelate to give diastereomerically pure dicarboxylic acid **5a**.[13]

The synthesis of enantioenriched diacid **5b** was also reported in our report[13] starting from 3-methylpentanedioic anhydride **7b** and (*S*)-benzyl mandelate, and **5b** was further transformed to (*R*)-3-methylvalerolactone **18** (Scheme 3). We assumed that the enantioenriched dodecatrienone **6** could be derived from **5b**, and subsequent IMDA reaction of **6** would lead to decalin unit **4**. In our scheme, all of the stereocenters were envisaged to be derived from a single source, (*S*)-benzyl mandelate.

Synthesis of Racemic Trienones and Their IMDA Reaction. We tried to construct the decalin framework of mevinolins by IMDA cyclization of 6-methyl-2,8,10-dodecatrien-4-one **6**. We thought that the endogenous carbonyl group at C-4 would facilitate the IMDA reaction by activating the dienophile, and it could be reduced to the hydroxy group in a later step. The C-6 methyl group was expected to work as a chiral controller to regulate the introduction of the remaining stereocenters.

The IMDA reaction has been explored as a useful protocol for assembling several stereogenic centers in a single step.[14,15] There have been reports on the IMDA reaction of 1,7,9-decatrien-3-ones,[16,17] and the influence of a substituent at the 5-position of decatrienones (corresponding to the 6-position of 2,8,10-dodecatrien-4-one) has been demonstrated. However, the influence of the configuration of the dienophile has not been investigated, probably because of the configurational lability of both dienophiles and the IMDA adducts.

For preliminary investigation of the IMDA reaction of trienone **6**, we prepared racemic **6** with both the (*E*)- and (*Z*)-configurations (Scheme 2). (2*E*,4*E*)-1-Bromo-2,4-hexadiene (**8**)[18] was converted into aldehyde **9** (six steps, 23% yield). The isomeric purity of the (*E*,*E*)-diene part of **9** was estimated to be about 80% by ^{13}C NMR analysis. Treatment of **9** with the (*E*)-vinyllithium reagent, prepared from (*E*)-vinyltin **10**,[19] and subsequent Swern oxidation gave (*E*)-**6** (40% yield). Trienone (*Z*)-**6** was prepared in 37% yield from **9** in a similar way. Aldehyde **9** was treated with the (*Z*)-vinyllithium reagent, prepared from (*Z*)-vinyl iodide **11**,[20] and oxidized to give (*Z*)-**6**. As neat (*E*)-**6** and (*Z*)-**6** oligomerize at room temperature, they were stored at −20 °C in a dichloromethane solution.

The IMDA reactions of (*E*)-**6** were slow in solution at room temperature, and we tried to increase the rate by using higher pressure, by adding Lewis acids, and by heating (Table 1). Only the (*E*,*E*)-diene isomer underwent IMDA cyclization. The other isomers were recovered. All four possible diastereomeric adducts were obtained regardless of the reaction conditions, and *cis*-

(7) Recent synthetic work on decalin derivatives: (a) Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 5596. (b) Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413. (c) Stokker, G. E. *J. Org. Chem.* **1994**, *59*, 5983. (d) Turabi, N.; DiPietro, R. A.; Mantha, S.; Ciosek, C.; Rich, L.; Tu, J.-I. *Bioorg. Med. Chem.* **1995**, *3*, 1479.

(8) Recent work on novel synthetic HMG-CoA reductase inhibitors: (a) Chan, C.; Bailey, E. J.; Hartley, C. D.; Hayman, D. F.; Hutson, J. L.; Inglis, G. G. A.; Jones, P. S.; Keeling, S. E.; Kirk, B, E.; Lamont, R. B.; Lester, M. G.; Pritchard, J. M.; Ross, B. C.; Scicinski, J. J.; Spooner, S. J.; Smith, G.; Steeples, I. P.; Watson, N. S. *J. Med. Chem.* **1993**, *36*, 3646. (b) Connolly, P. J.; Westin, C. D.; Loughney, D. A.; Minor, L. K. *J. Med. Chem.* **1993**, *36*, 3674. (c) Masamichi, W.; Haruo, K.; Teruyuki, I.; Tetsuo, O.; Shujiro, S.; Kentaro, H. *Bioorg. Med. Chem.* **1997**, *5*, 437.

(9) Serizawa, N.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 604.

(10) Simvastatin displays two or three times more activity than mevinolin. Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849.

(11) Konoike, T.; Araki, Y. Jpn. Kokai Tokkyo Koho JP 06,157,393 [94,157,393], 1994. The preliminary results were reported: Araki, Y.; Konoike, T. *Abstracts of Papers*, 37th Symposium on the Chemistry of Natural Products, Tokushima, Japan, 1995, p 631.

(12) (a) Rosen T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. (b) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374. (c) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744.

(13) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849.

(14) Reviews on the intramolecular Diels−Alder reaction, see: (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (d) Ahlbrecht, H. In *Methods Org. Chem. (Houben−Weyl)*, Vol. E21c of 4th ed.; Helmchen, G., Ed.; Thieme: Stuttgart, 1995.

(15) The intramolecular Diels−Alder reaction approach for construction of the decalin framework of mevinic acids, see: (a) Schnaubelt, J.; Reissig, H.-U. *Synlett* **1995**, 452. (b) Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613 and references cited therein.

(16) (a) Gras, J.-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, *20*, 4549. (b) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002.

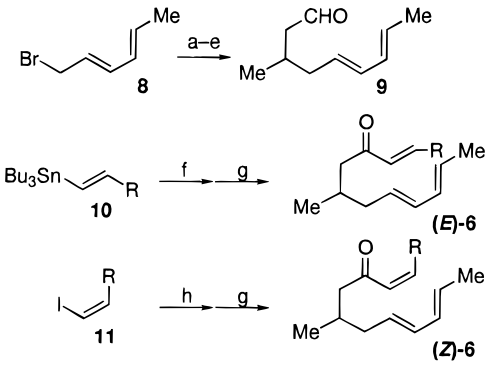
(17) (a) Zschiesche, R.; Grimm, E. L.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1086. (b) Frey, B.; Hunig, S.; Koch, M.; Reissig, H.-U. *Synlett* **1991**, 854. (c) Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663.

(18) Jacobsen, M. *J. Am. Chem. Soc.* **1955**, *77*, 2461.

(19) (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Bansal, R.; Cooper, G. F.; Corey, E. J. *J. Org. Chem.* **1991**, *56*, 1329.

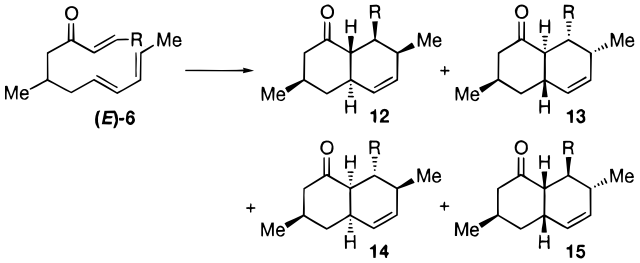
(20) (a) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 6729. (b) Jones, K.; Storey, M. D. *Tetrahedron* **1993**, *49*, 4901.

Scheme 2. Preparation of Racemic (*E*)- and (*Z*)-Trienones 6 (R = $CH_2OTBDMS$)



Reagents and conditions: (a) *i*-Pr_2NH, BuLi, $EtCO_2Bu^t$, THF, –78 °C then **8**, –78 °C; (b) $LiAlH_4$, Et_2O, 0 °C; (c) MsCl, pyridine, rt; (d) KCN, KI, DMF–H_2O (3:1), reflux; (e) DIBALH, CH_2Cl_2, 0 °C; (f) BuLi, THF, –78 °C then **9**, –78 °C; (g) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C then NEt_3, –78 °C; (h) BuLi, Et_2O, –78 °C then **9**, –90 °C.

Table 1. The IMDA Cyclization of (*E*)-6[a] (R = $CH_2OTBDMS$)



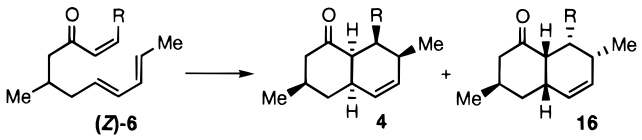
		yield (%)			
entry	conditions	**12**	**13**	**14**	**15**
1	10 kbar, rt	7	2	47	22
2	Et_2AlCl, 0 °C	13	trace	27	11
3	PhCl, reflux	17	3	29	22

[a] (*E*,*Z*)- and (*Z*,*E*)-diene isomers were recovered.

decalins (**14** and **15**) were obtained in preference to *trans*-decalins (**12** and **13**) in all the reactions. These findings are in accord with previous observations of the major adducts being *cis*-decalins generated via the endo transition state.[21] The configurations of the cycloadducts were determined by analyses of the $^1H-^1H$ coupling constants in the ^1H NMR spectra and the chemical shifts in the ^{13}C NMR spectra.[22] *trans*-Decalins **12** and **13** have the same configurations as those of (+)-6-*epi*-mevinolin and mevinolin, respectively. However, we did not exploit **12** and **13** for the synthesis of (+)-6-*epi*-mevinolin or mevinolin because these *trans*-decalins were minor products in the IMDA reaction and could not be purified by simple silica gel chromatography.

The IMDA reactions of (*Z*)-**6**, which were also slow at room temperature, were conducted under conditions similar to those of the IMDA reaction of (*E*)-**6.** These reactions of (*Z*)-**6** were more selective than those of (*E*)-**6** and gave only *cis*-decalins with a preference for **4** over **16** (Table 2). The high pressure-promoted IMDA reaction[23] gave the most satisfactory result in terms of the yield and stereoselectivity (**4** (53% yield) and **16** (8% yield)). Under Lewis acid-catalyzed condition, (*Z*)-**6** partially isomerized to (*E*)-**6**, and the IMDA adducts from (*E*)-**6** were present as contaminants of *cis*-decalins **4** and **16**. In contrast, double bond isomerization of (*Z*)-**6** to silyl enol ether **17** was observed on heating, and *cis*-decalins were obtained in low yield.

Table 2. The IMDA Cyclization of (*Z*)-6[a] (R = $CH_2OTBDMS$)



		yield (%)	
entry	conditions	**4**	**16**
1	10 kbar, rt	53	8
2	$EtAlCl_2$, 0 °C[b]	42	16
3	PhCl, reflux[c]	20	5

[a] (*E*,*Z*)- and (*Z*,*E*)-diene isomers were recovered. [b] (*Z*)-**6** isomerized partially to (*E*)-**6** under the condition, and hence the IMDA adducts from (*E*)-**6** contaminated **4** and **16**. [c] Thermal isomerization of (*Z*)-**6** competed with the IMDA reaction, and silyl enol ether **17** was obtained in 22% yield.

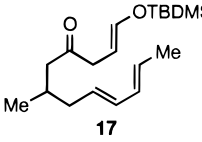
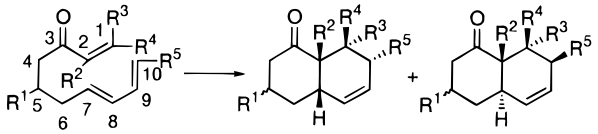


Table 3. Thermal IMDA Reaction of 1,7,9-Decatrien-3-one and Analogs[16,17]



						ratio	
entry	R^1	R^2	R^3	R^4	R^5	*cis*-decalins	*trans*-decalins
1	CO_2Me	H	H	H	H	100	1
2	CO_2Me	Me	H	H	H	61	39
3	CO_2Me	H	Me	Me	H	45	55
4	H	Me	H	H	H	62	38
5	H	Me	H	H	Me	57	43

cis-Decalins **4** and **16** were epimerized by treatment with NaOMe in MeOH into *trans*-decalins **12** and **13**, respectively, in high yields. These findings suggested that the IMDA cyclization of nonracemic (*Z*)-**6** and subsequent epimerization of the major adduct would be a promising protocol for the synthesis of *trans*-decalin **12** and of (+)-6-*epi*-mevinolin.

There are a few reports on the IMDA reactions of 1,7,9-decatrien-3-one and analogs, and the predominance of *cis*-decalins from the endo transition state was established for the parent substrate.[16] Table 3 shows some examples of IMDA reactions of substituted decatrienones under thermal conditions.[17] The methoxycarbonyl group at the 5-position did not affect the selectivity, and *cis*-decalins were obtained exclusively (entry 1). The exist-

(21) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.
(22) (a) Beierbeck, H.; Saunders, J. K. *Can. J. Chem.* **1976**, *54*, 2985. (b) Beierbeck, H.; Saunders, J. K.; ApSimon, J. W. *Can. J. Chem.* **1977**, *55*, 2813. (c) Irikawa, H.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2086.
(23) Review on organic synthesis under high pressure, see: Isaacs, N. S. *Tetrahedron* **1991**, *47*, 8463. High pressure-mediated IMDA reactions, see: (a) Buback, M.; Abeln, J.; Hubsch, T.; Ott, C.; Tietze, L. F. *Liebigs Ann.* **1995**, 9. (b) Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355 and references cited therein.

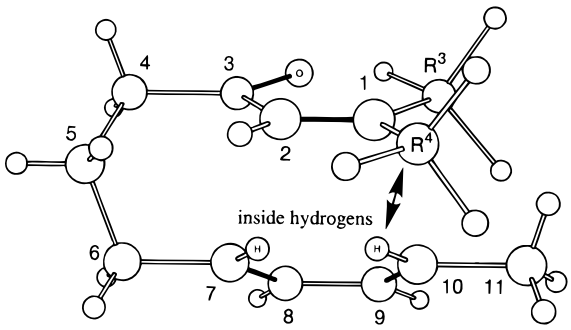


Figure 1. Endo-boat transition state for the IMDA reaction of 1,1-disubstituted undeca-1,7,9-trien-3-one, leading to *cis*-decalins.

ence of a methyl group at the 2-position of 5-(methoxycarbonyl)-1,7,9-decatrien-3-one (entry 2) diminished the *cis* preference and resulted in mixtures of *cis*- and *trans*-decalins (61:39). When two methyl groups were introduced at the terminal 1-position (entry 3), *trans*-decalins became the major products (45:55). A similar decrease in the *cis* adduct was observed for 2-methyl substituents when no methoxycarbonyl group was present at the 5-position (entries 4, 5).

The stereoselectivity of the IMDA reaction has generally been explained by considering the steric and electronic interactions in the transition states. The results obtained for methylated decatrienones can be discussed in relation to steric repulsion between a diene and a dienophile portion. Houk's theoretical study of the Diels–Alder transition state[24] suggests a nonparallel alignment of the two planes, one occupied by a dienophile and the other by a diene (Figure 1). In this transition state, the methyl group on the opposite side of the carbonyl group (R^2 and R^4 in Table 3) experiences a steric repulsion with the inside hydrogen of the diene, while the methyl group on the same side of the carbonyl (R^3) does not. This steric repulsion explains the decreased preference formation of *cis*-decalins for trienones methylated at positions R^2 and R^4 (Table 3, entries 2, 3, 5).

The ratios of the *cis*- and *trans*-decalins in our IMDA reactions of (*E*)- and (*Z*)-trienone **6** are explained in the context of the steric repulsion between the $TBDMSOCH_2$ group and the inside hydrogen of the diene. Comparison of the transition states of the IMDA reaction of (*E*)-**6** and (*Z*)-**6** leads to the conclusion that the exclusive formation of *cis*-decalins from (*Z*)-**6** should be expected. In the endo transition state of (*E*)-**6** that conceivably leads to *cis*-decalin, the C-1 $TBDMSOCH_2$ group displays an unfavorable nonbonded interaction with the C-10 inside hydrogen. This steric repulsion is avoided in the exo transition state leading to *trans*-decalin, and hence all possible diastereomers were obtained for the IMDA cyclization of (*E*)-**6**. In contrast to (*E*)-**6**, the endo transition state in the IMDA reaction of (*Z*)-**6** is free from such repulsion, and *cis*-decalins **4** and **16** were obtained exclusively.

The product ratio of the two *cis*-decalins, **4** and **16**, can be explained by considering the energy difference between the two transition states, boat **A** and chair **B,** which lead to *cis*-decalin **4** and **16**, respectively (Figure 2). The stabilities of these transition states have been compared in terms of the energy difference of the conformation of the tether connecting the diene and the dienophile. In the energetics of conformations around the $sp^3–sp^2$ bond of alkenes or carbonyl groups, it is generally believed that a skew butene conformation is more stable than a gauche butene, and likewise, an eclipsed ethanone conformation is more stable than a gauche ethanone.[25] In this regard, transition state **A** (Figure 2) has two stable $sp^3–sp^2$ conformations which are an eclipsed ethanone conformation around the C-4–C-5 unit and a skew butene conformation around the C-7–C-8 unit. Chair transition state **B** (Figure 2) has a gauche ethanone conformation and a gauche butene conformation around the $sp^3–sp^2$ single bonds, which are less stable than transition state **A**. The preference of **4** over **16** results from these steric factors in transition states **A** and **B**.

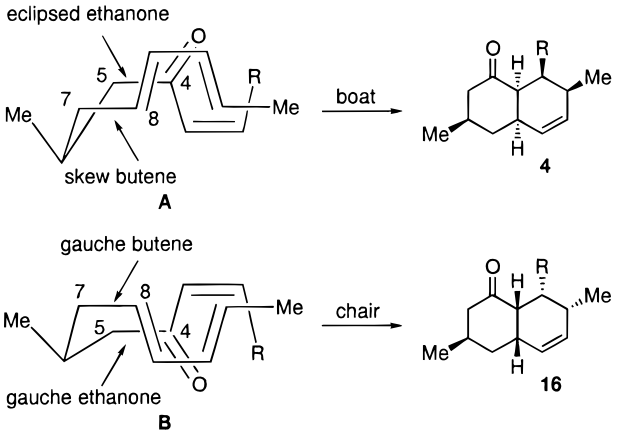
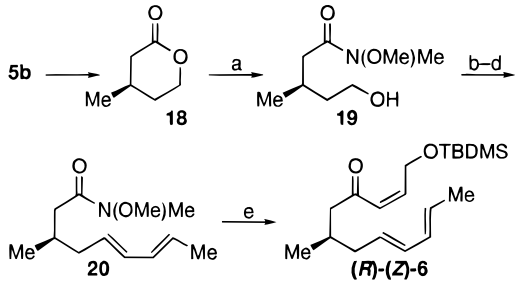


Figure 2. Steric interactions in the transition states leading to *cis*-decalins (R = $CH_2OTBDMS$).

Scheme 3. Preparation of (*R*)-(*Z*)-6



Reagents and conditions: (a) MeHNOMe, CH_3CN, 9 kbar, rt; (b) PDC, CH_2Cl_2, rt; (c) (*E*)-1-phenylsulfonyl-2-butene, BuLi, THF, –78 °C, then BzCl, –78 °C to 0 °C; (d) 5% Na(Hg), MeOH–EtOAc (2:1), –20 °C, (e) **11**, BuLi, Et_2O, –100 °C to –78 °C.

Synthesis of Enantioenriched Trienone (*R*)-(*Z*)-6. Scheme 3 shows the synthesis of trienone (*R*)-(*Z*)-**6** which is a precursor of octalin (*R*)-**4**. The stereocenter at the 6-position of (*R*)-(*Z*)-**6** was derived from (*R*)-4-methyltetrahydropyran-2-one (**18**).[26] As reported in our previous paper,[13] **18** was synthesized with high optical purity (93% ee) from diacid **5b**, prepared by desymmetrization of 3-methylpentanedioic anhydride (**7b**)[27]

(24) Transition state modeling study for IMDA reaction was reported by using a combination of molecular mechanics and *ab initio* methods: (a) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796. (b) Brown, F. K.; Singh, U. C.; Kollman, P. A.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**, *57*, 4862.

(25) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 10.

(26) (a) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556. (b) Lam. L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. (c) Terunuma, D.; Motegi, M.; Tsuda, M.; Sawada, T.; Nozawa, H.; Nohira, H. *J. Org. Chem.* **1987**, *52*, 1630.

(27) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.

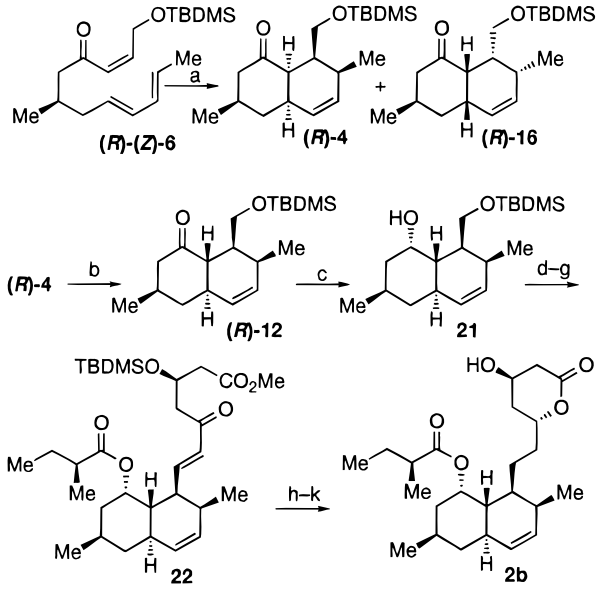
with (*S*)-benzyl mandelate. The (*R*)-lactone **18** was first converted to the Weinreb amide **19**.[28] As lactone **18** was prone to polymerization, we surveyed the reaction conditions for preparing **19**. Weinreb's original aluminum reagent,[29] prepared from Me_3Al and MeHNOMe·HCl, gave amide **19** in moderate yield (70%), but this method required a laborious filtration to remove the aluminum salts, followed by silica gel chromatography. A thermal reaction of **18** and MeHNOMe in CH_3CN (110 °C) gave only polymeric products. High pressure aminolysis[30] proved to be most satisfactory, giving amide **19** (90% yield) by pressurizing a mixture of lactone **18**, MeHNOMe, and CH_3CN under 9 kbar at room temperature. Amide **19**, obtained by simple evaporation of volatile materials, was pure enough for practical use. This procedure offered the advantage of eliminating an aqueous workup which would have been difficult for water-soluble **19**. These results showed that high pressure aminolysis is beneficial for Weinreb amide formation in several respects, including simple operation, mild neutral reaction condition, easy workup, and high efficiency.

PDC oxidation of amide alcohol **19** afforded the aldehyde, which was converted to diene **20** by the Julia olefin synthesis.[31] The aldehyde was treated with lithiated (*E*)-1-benzenesulfonyl-2-butene,[32] and the resulting lithium alkoxide was benzoylated. Reductive elimination of the benzoyloxy sulfone by sodium amalgam gave an isomeric mixture of (*E*,*E*)-diene **20** and other dienes. The purity of the (*E*,*E*)-diene part was 75% (^{13}C NMR). Treatment of **20** with the (*Z*)-vinyllithium reagent, prepared from (*Z*)-vinyl iodide **11**, gave trienone (*R*)-(*Z*)-**6** (72% yield).

Synthesis of (+)-6-*epi*-4a,5-Dihydromevinolin (2b). High pressure-promoted IMDA cyclization of (*R*)-(*Z*)-**6** gave a mixture of *cis*-decalins (*R*)-**4** and (*R*)-**16** at room temperature under 10 kbar (Scheme 4). *cis*-Decalin (*R*)-**4** was isolated by silica gel chromatography, and its 8a-position was epimerized to give the *trans*-isomer (*R*)-**12** (92% yield). L-Selectride reduction of (*R*)-**12** gave the (8*S*)-alcohol **21**, which served as a common intermediate for (+)-6-*epi*-mevinolin (**2a**) and (+)-6-*epi*-4a,5-dihydromevinolin (**2b**).

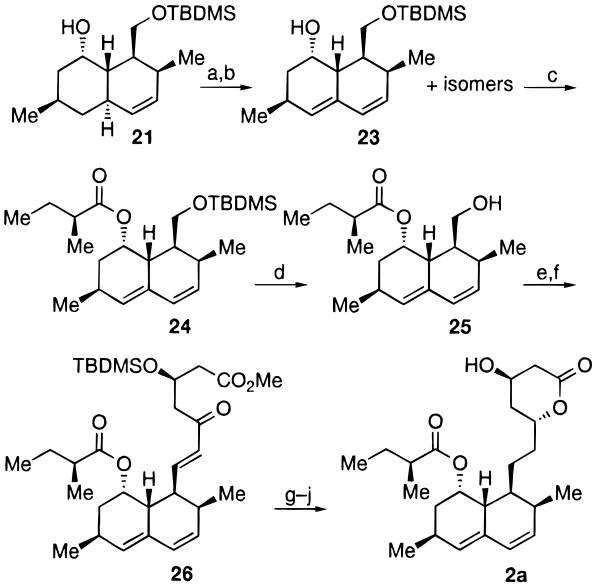
(+)-6-*epi*-4a,5-Dihydromevinolin (**2b**) was prepared from **21** by a sequence of reactions similar to Heathcock's method.[12a] Alcohol **21** was acylated with commercially available (*S*)-2-methylbutyric anhydride, and the silyl protecting group was removed. Swern oxidation, followed by Horner−Wadsworth−Emmons olefination of the resulting aldehyde with phosphonate **3** (Cs_2CO_3 in 2-propanol),[33] gave the (*E*)-enone **22**. $(Ph_3P)_3RhCl$-catalyzed hydrosilylation of **22** with Et_3SiH gave a mixture of (*E*)- and (*Z*)-silyl enol ethers. Subsequent desilylation afforded the saturated ketone, which was reduced to the syn-diol ($NaBH_4$ and Et_2BOMe in THF−MeOH at −78 °C).[34] The anti-diol was not observed by ^{13}C NMR. Final lactonization by HF/pyridine[35] gave (+)-6-*epi*-4a,5-dihydromevinolin (**2b**).

Scheme 4. Synthesis of (+)-6-*epi*-4a,5-Dihydromevinolin (2b)



Reagents and conditions: (a) CH_2Cl_2, 10 kbar, rt; (b) MeONa/MeOH, rt; (c) L-Selectride, THF, 0 °C; (d) (*S*)-2-methylbutyric anhydride, DMAP, pyridine, 50 °C; (e) aq HF/CH_3CN (1:19), rt; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (g) **3**, Cs_2CO_3, 2-propanol, rt; (h) $(Ph_3P)_3RhCl$, Et_3SiH, benzene, 65 °C; (i) aq HF/CH_3CN (1:19), rt; (j) Et_2BOMe, $NaBH_4$, THF–MeOH (4:1), −78 °C; (k) HF/pyridine, CH_3CN, rt.

Scheme 5. Synthesis of (+)-6-*epi*-Mevinolin (2a)



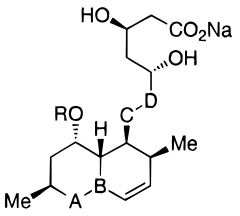
Reagents and conditions: (a) Br_2, NEt_3, $CHCl_3$, 0 °C; (b) DBU, benzene, reflux; (c) (*S*)-2-methylbutyric anhydride, DMAP, pyridine, 50 °C; (d) TBAF, AcOH, THF, reflux; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (f) **3**, Cs_2CO_3, 2-propanol, rt; (g) $(Ph_3P)_3RhCl$, Et_3SiH, benzene, 65 °C; (h) aq HF/CH_3CN (1:19), rt; (i) Et_2BOMe, $NaBH_4$, THF–MeOH (4:1), −78 °C; (j) HF/pyridine, CH_3CN, rt.

Synthesis of (+)-6-*epi*-Mevinolin (2a). The 4a,5-double bond was introduced to **21** for the synthesis of (+)-6-*epi*-mevinolin **2a** (Scheme 5). The double bond in **21** was brominated with Br_2 and NEt_3, and subsequent dehydrobromination by DBU gave diene **23** in 32% yield along with two double-bond isomers (13% and 10% yield).[36] Conversion of **23** into (+)-6-*epi*-mevinolin **2a** was accomplished by the same procedure as that of **2b** except

(28) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
(29) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(30) Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3138.
(31) (a) Julia, M.; Paris, J.-M.; *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607.
(32) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.
(33) Yamanoi, T.; Akiyama, T.; Ishida, E.; Abe, H.; Amemiya, M.; Inazu, T. *Chem. Lett.* **1989**, 335.
(34) Chen, K.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(35) Johnson, W. S.; Kelson, A. B.; Elliot, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757.
(36) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180.

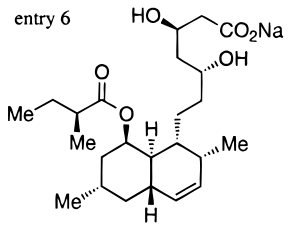
Table 4. HMG-CoA Reductase Inhibitory Activities

(+)-mevinolin IC_{50} = 32.3 nM (relative potency = 1)
(+)-4a,5-dihydromevinolin IC_{50} = 27.9 nM (1.2)



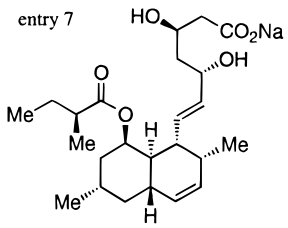
entry	A-B	C-D	RO	IC_{50} (relative potency)
1	CH=C	CH_2CH_2	(*S*)-2-methylbutyroxy	61.4 nM (0.5)
2	CH_2-CH	CH_2CH_2	(*S*)-2-methylbutyroxy	27.2 nM (1.2)
3	CH_2-CH	CH_2CH_2	butyroxy	61.9 nM (0.5)
4	CH_2-CH	CH_2CH_2	2,2-dimethylbutyroxy	>200 nM
5	CH_2-CH	(*E*)-CH=CH	(*S*)-2-methylbutyroxy	>200 nM

entry 6



IC_{50} >200 nM

entry 7



IC_{50} = 91.3 nM (0.4)

for the desilylation of **24** which was achieved with TBAF and AcOH to give **25** (98% yield). The desilylation of **24** by TBAF without AcOH gave a significant amount of the acyl migration product. Alcohol **25** was converted into (+)-6-*epi*-mevinolin **2a** by a procedure similar to that employed for the preparation of **2b**.

HMGR Inhibition Activity. We prepared several mevinolin analogs including **2a** and **2b**, and they were converted into the corresponding sodium salts of the carboxylic acids, a biologically active form of HMGR inhibitors. Their *in vitro* inhibitory activities for rat liver microsomal HMGR[37] were compared with that of mevinolin (Table 4).

The relative potency of (+)-6-*epi*-mevinolin (**2a**) (entry 1) is about half that of mevinolin, which is in contrast to the enhanced activity of pravastatin (**1d**)[9] and several 6α-alkyl substituted compactins.[7a,b] (+)-6-*epi*-4a,5-Dihydromevinolin (**2b**) (entry 2) is twice as potent as (+)-6-*epi*-mevinolin (**2a**) and as potent as mevinolin (**1b**). In the natural series, mevinolin and its 4a,5-dihydro derivative were reported to have equal potency for HMGR inhibitors.[5]

We modified the acyloxy side chain at the 8-position of (+)-6-*epi*-4a,5-dihydromevinolin (**2b**). Replacement of the (*S*)-2-methylbutyroxy group with the butyroxy group (entry 3) lowered the activity by one-half. (+)-6-*epi*-4a,5-Dihydrosimvastatin (entry 4), which has a 2,2-dimethylbutyroxy group, showed diminished activity although simvastatin (**1c**) is twice as potent as mevinolin **1b**.[10]

We introduced the double bond into the (+)-6-*epi*-4a,5-dihydromevinolin (**2b**) between its lactone and decalin unit (entry 5) because more recent and potent synthetic HMGR inhibitors often have a double bond at this position;[8] however, the resulting compound was not active. Although the analog whose decalin unit is enantiomeric to that of (+)-6-*epi*-4a,5-dihydromevinolin was inactive (entry 6), the introduction of the double bond led to recovery of the potency to one-third of that of (+)-6-*epi*-4a,5-dihydromevinolin (entry 7).

(37) Kuroda, M.; Endo, A. *Biochim. Biophys. Acta* **1977**, *486*, 70.

Conclusion

We have achieved an enantioselective total synthesis of (+)-6-*epi*-mevinolins **2a** and **2b**, which is the first synthesis of 6β-alkyl substituted compactins. All stereocenters of (+)-6-*epi*-mevinolins, except for the butyroxy group at the 8-position, were generated from a single chiral auxiliary, (*S*)-benzyl mandelate. We used the IMDA reaction of the (6*R*)-trienone **6** to construct the decalin unit. The diastereoselectivity of this addition is dependent on the configurations of the dienophile moiety. We evaluated the HMGR inhibitory potency of several 6-*epi*-mevinolin analogs and found (+)-6-*epi*-4a,5-dihydromevinolin (**2b**) to have the highest potency, being as potent as mevinolin. The high pressure procedure proved quite effective for the IMDA reaction and Weinreb amide formation.

Experimental Section

General. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sieves type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished under aspirator pressure using a rotary evaporator. TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}, and compound visualization was effected with 10% H_2SO_4 containing 5% of ammonium molybdate and 0.2% of ceric sulfate. Gravity chromatography was done with Merck silica gel 60 (70−230 mesh). ^{1}H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ solutions at 200 and 50.3 MHz, unless specified otherwise. *J* values are given in hertz. The high pressure apparatus was purchased from Hikari High Press Inc. High-resolution mass spectra (HR-LSIMS) were recorded on a Hitachi M-90 instrument.

(5*E*,7*E*)-3-Methyl-5,7-nonadienal (9). Diisopropylamine (64.20 g, 634.4 mmol) was dissolved in THF (300 mL), and BuLi (400 mL of 1.6 M hexane solution, 640 mmol) was added dropwise over 20 min at −78 °C. After 30 min, *tert*-butyl propionate (82.60 g, 634.4 mmol) was added dropwise over 30 min, and the mixture was stirred for 30 min. (2*E*,4*E*)-1-Bromo-2,4-hexadiene (**8**)[18] (102.16 g, 634.4 mmol) in THF (100 mL) was added over 20 min, and the whole mixture was stirred for an additional 3 h at −78 °C. The reaction mixture was quenched with water and extracted with ethyl acetate (EtOAc) three times. The organic extracts were washed with saturated $NaHCO_3$, combined, dried, and concentrated. Residual oil was distilled (bp 75−103 °C at 6 torr) to give *tert*-butyl (4*E*,6*E*)-2-methyl-4,6-octadienoate (112.79 g, 85% yield). IR (film) 2972, 1726, 1365 cm^{-1}; ^{1}H NMR δ 1.09 (d, 3, *J* = 6.8), 1.43 (s, 9), 1.73 (d, 3, *J* = 6.0), 2.0−2.5 (m, 3), 5.3−5.8 (m, 2), 5.9−6.1 (m, 2); TLC (EtOAc/hexane = 1/9) R_f 0.56.

The ester (112.79 g, 536.3 mmol) in Et_2O (200 mL) was added to $LiAlH_4$ (20.4 g, 536.3 mmol) in Et_2O (400 mL) dropwise over 1 h at 0 °C. The mixture was stirred at room temperature for 67 h. After cooling down to 0 °C, saturated Na_2SO_4 (20 mL) was added carefully with vigorous stirring and $MgSO_4$ was added. The mixture was diluted with Et_2O, and solids were filtered off through a pad of Hyflo Super-cel. Solids were washed with Et_2O and then with EtOAc. The filtrates were combined and concentrated. Residual oil was distilled (bp 89−92 °C at 4 torr) to give (4*E*,6*E*)-2-methyl-4,6-octadien-1-ol (62.50 g, 83% yield). IR (film) 3334, 2912, 1451 cm^{-1}; ^{1}H NMR δ 0.92 (d, 3, *J* = 6.8), 1.73 (d, 3, *J* = 6.4), 1.8−2.2 (m, 3), 3.46 (dd, 1, *J* = 6.0, 10.6), 3.51 (dd, 1, *J* = 6.0, 10.6), 5.4−5.7 (m, 2), 5.9−6.1 (m, 2); ^{13}C NMR δ 16.5, 18.0, 36.1, 36.5, 67.7, 127.1, 129.7, 131.7, 132.0; TLC (EtOAc/hexane = 1/6) R_f 0.21.

MsCl (27.66 mL, 357 mmol) was added to a solution of (4*E*,6*E*)-2-methyl-4,6-octadien-1-ol (38.54 g, 275 mmol) in

pyridine (200 mL) over 1 min. The reaction mixture was stirred at room temperature for 40 min. Next, Et_2O and H_2O were added to the mixture, and the organic phase was separated. The aqueous phase was extracted twice with Et_2O, and the organic extracts were combined, dried, and concentrated to give the crude mesylate. IR (film) 2956, 1456 cm^{-1}; ^1H NMR δ 0.99 (d, 3, J = 6.6), 1.74 (d, 3, J = 6.4), 1.9−2.3 (m, 3), 3.00 (s, 3), 3.9−4.2 (m, 2), 5.4−5.7 (m, 2), 5.9−6.1 (m, 2); TLC (EtOAc/toluene = 1/10) R_f 0.42.

The crude mesylate was dissolved in DMF (250 mL) and warmed to 70 °C. A mixture of KCN (23.25 g, 357 mmol) and KI (22.74 g, 137 mmol) in H_2O (80 mL) was gradually poured in, and the resulting mixture was refluxed for 30 h. After being cooled to room temperature, the mixture was poured into ice−cold H_2O and extracted twice with Et_2O. Each organic extract was washed successively with H_2O, 1 N HCl, saturated $NaHCO_3$, and brine. The organic layers were combined and then dried, concentrated, and distilled (bp 99−104 °C at 5 torr) to obtain (5*E*,7*E*)-3-methyl-5,7-nonadienenitrile (33.66 g, 82% yield). IR (film) 2958, 2242, 1454 cm^{-1}; ^1H NMR δ 1.08 (d, 3, J = 6.6), 1.74 (d, 3, J = 6.6), 1.8−2.0 (m, 1), 2.0−2.4 (m, 4), 5.3−5.8 (m, 2), 5.9−6.1 (m, 2); TLC (EtOAc/hexane = 1/9) R_f 0.42.

DIBALH (270 mL of 1.0 M toluene solution, 270 mmol) was added dropwise to a solution of the nitrile (33.66 g, 226 mmol) in CH_2Cl_2 (340 mL) over 30 min at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After cooling to 0 °C, MeOH (32 mL) was added cautiously until the gas evolution ceased. The mixture was stirred at room temperature for 30 min and then poured into a mixture of ice and 1 N HCl. The mixture was extracted twice with Et_2O, and each organic extract was washed successively with H_2O, saturated $NaHCO_3$, and brine. The combined organic extract was dried, concentrated, and distilled (bp 86−87 °C at 6 torr) to give aldehyde **9**. Further purification by silica gel chromatography (EtOAc/hexane = 1/9 to 1/6) and distillation (bp 84.5 °C at 5.5 torr) gave aldehyde **9** (21.01 g, 61% yield). IR ($CHCl_3$) 3019, 1721 cm^{-1}; ^1H NMR δ 0.97 (d, 3, J = 6.0), 1.74 (d, 3, J = 6.1), 2.0−2.3 (m, 4), 2.3−2.5 (m, 1), 5.3−5.7 (m, 2), 5.9−6.1(m, 2), 9.75 (t, 1, J = 2.1); ^{13}C NMR δ 18.1, 20.0, 28.6, 40.0, 50.4, 127.4, 129.0, 131.8, 132.9, 201.8; TLC (EtOAc/hexane = 1/9) R_f 0.40. Anal. Calcd For $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.75; H, 10.59. The ratio of the diene part was estimated to be 10:1:1 for (*E*,*E*):(*E*,*Z*):(*Z*,*E*)-isomers by ^{13}C NMR analysis.

***tert*-Butyldimethyl-[[(3*E*)-(tributylstannanyl)allyl]-oxy]silane (10).**[19] To a solution of propargyl alcohol (28.0 g, 0.5 mol) in CH_2Cl_2 (200 mL) was added *tert*-butylchlorodimethylsilane (75.4 g, 0.5 mol) followed by imidazole (68.1 g, 1.0 mol) at room temperature. The reaction mixture was refluxed for 1 h and then quenched with ice and H_2O. The mixture was extracted three times with CH_2Cl_2, and the organic extracts were combined, dried, and concentrated. Residual oil was distilled (bp 48−50 °C at 11 torr) [lit.[38] bp 45 °C at 10 torr] to give 3-[(*tert*-butyldimethylsilyl)oxy]propyne (68.7 g, 81% yield). ^1H NMR δ 0.13 (s, 6), 0.91 (s, 9), 2.39 (t, 1, J = 2.4), 4.31 (d, 2, J = 2.4); TLC (hexane) R_f 0.14.

The silyl ether (30.6 g, 180 mmol) was dissolved in benzene, and tributyltin hydride (49.9 mL, 180 mmol) and AIBN (0.30 g, 1.8 mmol) were added at room temperature. The reaction mixture was refluxed for 20 min and concentrated, and then the residual oil was purified by silica gel chromatography (EtOAc/hexane = 1/100 to 1/10) to give **10** (70.2 g, 85% yield). ^1H NMR δ 0.07 (s, 6), 0.91 (s, 9), 0.8−1.0 (m, 15), 1.2−1.6 (m, 12), 4.21 (dd, 2, J = 1.0, 3.6), 6.0−6.3 (m, 2); TLC (hexane) R_f 0.35.

(2*E*,8*E*,10*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2,8,10-dodecatrien-4-one (*E*)-6. To a solution of tin reagent **10** (34.0 g, 73.7 mmol) in THF (170 mL) was added BuLi (36.9 mL of 1.6 M hexane solution, 59.0 mmol) dropwise over 10 min at −78 °C. After stirring for 10 min, aldehyde **9** (7.48 g, 49.1 mmol) in THF (75 mL) was added dropwise over 15 min. The mixture was stirred at −78 °C for 50 min and then quenched with saturated $NaHCO_3$ and extracted twice with EtOAc. The organic extracts were washed with H_2O, combined, dried, and concentrated. Residual oil was purified by silica gel chromatography (EtOAc/hexane =1/15, 1/6, 1/1) to give the allylic alcohol (15.8 g, 99% yield). ^1H NMR δ 0.07 (s, 6), 0.91 (s, 9), 0.92 (d, 3, J = 6.6), 1.3−2.2 (m, 5), 1.73 (d, 3, J = 6.8), 4.1−4.3 (m, 3), 5.4−5.8 (m, 4), 5.9−6.1 (m, 2); TLC (EtOAc/hexane = 1/9) R_f 0.20.

To a solution of oxalyl chloride (7.92 g, 62.4 mmol) in CH_2Cl_2 (100 mL) were added DMSO (9.75 g, 125 mmol) in CH_2Cl_2 (20 mL) and the alcohol (13.5 g, 41.6 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After stirring for 20 min at −78 °C, NEt_3 (40.6 mL, 291 mmol) was added dropwise over 20 min, and stirring was continued for 20 min at −78 °C. Next, the reaction mixture was diluted with CH_2Cl_2 and acidified with 1 N HCl. The organic phase was separated, and the aqueous phase was extracted twice with CH_2Cl_2. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/19 to 1/9) gave trienone (*E*)-**6** (9.00 g, 67% yield). ^1H NMR δ 0.08 (s, 6), 0.91 (d, 3, J = 6.3), 0.93 (s, 9), 1.73 (d, 3, J = 6.3), 1.9−2.2 (m, 3), 2.52 (dd, 1, J = 7.7, 15.5), 2.57 (dd, 1, J = 5.4, 15.5), 4.36 (dd, 2, J = 2.2, 3.5), 5.4−5.7 (m, 2), 5.9−6.1 (m, 2), 6.36 (dt, 1, J = 2.2, 15.8), 6.84 (dt, 1, J = 3.5, 15.8); TLC (EtOAc/hexane = 1/19) R_f 0.31; HR-LSIMS m/z 322.2317 M^+ (calcd for $C_{19}H_{34}O_2Si$, 322.2325).

***tert*-Butyl-[[(3*Z*)-Iodoallyl]oxy]dimethylsilane11.**[20b] (*Z*)-3-Hydroxy-1-iodopropene was prepared according to Moss's procedure.[20a] To a solution of (*Z*)-3-hydroxy-1-iodopropene (56.4 g, 306 mmol) in CH_2Cl_2 (280 mL) were added *tert*-butyldimethylchlorosilane (57.2 g, 368 mmol) and imidazole (41.7 g, 613 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and poured into ice and H_2O, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and each organic extract was washed with brine, dried, and concentrated. Residual oil was distilled (bp 79−88 °C at 5 torr) to give iodide **11** (87.6 g, 96% yield). IR (film) 2952, 1468, 1254 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.91 (s, 9), 4.25 (dd, 2, J = 1.8, 5.2), 6.23 (dt, 1, J = 1.8, 7.8), 6.42 (dt, 1, J = 5.2, 7.8); TLC (hexane) R_f 0.19. Anal. Calcd For $C_9H_{19}OISi$: C, 36.25; H, 6.42; I, 42.55. Found: C, 36.14; H, 6.32; I, 42.34.

(2*Z*,8*E*,10*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2,8,10-dodecatrien-4-one (*Z*)-6. To a solution of iodide **11** (11.93 g, 40 mmol) in Et_2O (150 mL) was added BuLi (25 mL of 1.6 M hexane solution, 40 mmol) over 15 min at −78 °C. The mixture was stirred at −78 °C for 2 h and then cooled to −95 °C. Aldehyde **9** (2.44 g, 16 mmol) in Et_2O (25 mL) was added over 15 min, and the mixture was stirred at −90 °C for 1 h. The reaction mixture was quenched with 1 N HCl and extracted twice with Et_2O. The organic extracts were washed with H_2O, combined, dried, and concentrated. Residual oil was purified by silica gel chromatography (EtOAc/hexane = 1/6) to give the allylic alcohol (3.52 g, 68% yield). IR ($CHCl_3$) 3420, 2926, 1460 cm^{-1}; ^1H NMR δ 0.09 (s, 6), 0.91 (s, 9), 0.9−1.0 (m, 3), 1.1−2.2 (m, 5), 1.73 (d, 3, J = 6.8), 4.1−4.4 (m, 2), 4.50 (q, 1, J = 7.0), 5.4−5.7 (m, 4), 5.9−6.1 (m, 2); TLC (EtOAc/hexane = 1/6) R_f 0.27.

To a solution of oxalyl chloride (1.97 g, 15.48 mmol) in CH_2Cl_2 (20 mL) was added DMSO (2.2 mL, 30.96 mmol) followed by the alcohol (3.53 g, 10.88 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After stirring for 30 min at −78 °C, NEt_3 (10.1 mL, 72.24 mmol) was added dropwise over 5 min, and stirring was continued for 1.5 h at −78 °C. Next, the reaction mixture was diluted with Et_2O and acidified with 1 N HCl. The organic phase was separated, and the aqueous phase was extracted twice with Et_2O. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/30) gave trienone (*Z*)-**6** (2.51 g, 72% yield). IR ($CHCl_3$) 2950, 1680, 1406 cm^{-1}; ^1H NMR δ 0.07 (s, 3), 0.08 (s, 3), 0.90 (s, 9), 0.90 (d, 2, J = 5.8), 1.73 (d, 3, J = 6.6), 1.9−2.6 (m, 5), 4.71 (dd, 2, J = 2.2, 4.2), 5.3−5.8 (m, 2), 5.9−6.4 (m, 2), 6.10 (dt, 1, J = 2.2, 11.6), 6.24 (dt, 1, J = 4.2, 11.6); TLC (toluene) R_f 0.63.

IMDA Cyclization under High Pressure. A stock solution of trienone (9.2 mL of 50 mg/mL CH_2Cl_2 solution, 1.43 mmol) was placed in a Teflon capsule, which was then put in a high pressure apparatus. The reaction was carried out at 10 kbar for 8 h at room temperature. The pressure was released, and the solvent was evaporated. Residual oil was

(38) Yerino, L. V.; Osborn, M. E.; Mariano, P. S. *Tetrahedron* **1982**, *38*, 1579.

subjected to silica gel chromatography (EtOAc/hexane = 1/30, 1/19, 1/9), and the reaction products were separated. For the reaction of (*E*)-**6**: **12** (7% yield), **13** (2% yield), **14** (47% yield), **15** (22% yield). For the reaction of (*Z*)-**6**: **4** (53% yield), **16** (8% yield).

IMDA Cyclization under Lewis Acid Catalyst. To a solution of trienone in CH_2Cl_2 was added 1 equiv of Lewis acid (Et_2AlCl or $EtAlCl_2$, each 1 M hexane solution) at 0 °C. After 1 h, the mixture was quenched with 1 N HCl and extracted twice with CH_2Cl_2. The organic extracts were washed with brine, dried, and concentrated. Residual oil was subjected to silica gel chromatography (EtOAc/hexane = 1/30, 1/19, 1/9), and the reaction products were separated. For the reaction of (*E*)-**6**: **12** (13% yield), **13** (trace), **14** (27% yield), **15** (11% yield). For the reaction of (*Z*)-**6**: **4** (42% yield), **16** (16% yield).

IMDA Cyclization under Thermal Conditions. A solution of trienone in chlorobenzene was refluxed for 15 h and then concentrated. Residual oil was subjected to silica gel chromatography (EtOAc/hexane = 1/30, 1/19, 1/9), and the reaction products were separated. For the reaction of (*E*)-**6**: **12** (17% yield), **13** (3% yield), **14** (29% yield), **15** (22% yield). For the reaction of (*Z*)-**6**: **4** (20% yield), **16** (5% yield), **17** (22% yield).

(1*R,2*R**,4a*S**,6*S**,8a*R**)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (12).** IR ($CHCl_3$) 2950, 1705, 1089, 834 cm^{-1}; ^1H NMR δ 0.01 (s, 3), 0.04 (s, 3), 0.87 (s, 9), 0.95 (d, 3, J = 7.0), 1.05 (d, 3, J = 6.0), 1.1−1.4 (m, 1), 1.8−2.6 (m, 8), 3.60 (dd, 1, J = 8.6, 9.7), 4.07 (dd, 1, J = 3.1, 9.7), 5.41 (ddd, 1, J = 1.6, 1.6, 10.0), 5.67 (ddd, 1, J = 2.2, 2.8, 10.0); ^{13}C NMR δ −5.7, −5.5, 16.4, 18.2, 22.4, 25.9, 31.4, 35.9, 37.9, 41.7, 44.1, 48.8, 51.5, 61.3, 128.4, 134.3, 212.7; TLC (EtOAc/hexane = 1/19) R_f 0.44.

(1*R,2*R**,4a*S**,6*R**,8a*R**)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (13).** ^1H NMR δ 0.04 (s, 6), 0.88 (s, 9), 0.96 (d, 3, J = 6.9), 0.99 (d, 3, J = 6.7), 1.6−2.8 (m, 9), 3.63 (dd, 1, J = 8.7, 9.8), 4.05 (dd, 1, J = 3.2, 9.8), 5.37 (d, 1, J = 9.8), 5.69 (ddd, 1, J = 1.8, 4.5, 9.8); TLC (EtOAc/hexane = 1/19) R_f 0.44.

(1*R,2*S**,4a*R**,6*R**,8a*R**)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (14).** ^1H NMR δ 0.09 (s, 6), 0.93 (s, 9), 1.01 (d, 3, J = 6.4), 1.07 (d, 3, J = 6.8), 1.1−1.4 (m, 1), 1.6−2.0 (m, 4), 2.1−2.5 (m, 4), 3.49 (dd, 1, J = 7.0, 10.0), 3.66 (dd, 1, J = 2.5, 10.0), 5.45 (d, 1, J = 10.0), 5.67 (ddd, 1, J = 2.2, 4.6, 10.0); ^{13}C NMR δ −5.8, −5.7, 18.4, 20.4, 22.5, 26.0, 32.5, 34.3, 38.1, 39.1, 42.5, 48.1, 54.4, 64.5, 129.1, 132.9, 214.7; TLC (EtOAc/hexane = 1/19) R_f 0.30.

(1*R,2*S**,4a*R**,6*S**,8a*R**)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (15).** ^1H NMR δ 0.02 (s, 3), 0.03 (s, 3), 0.89 (s, 9), 0.97 (d, 3, J = 6.8), 1.07 (d, 3, J = 7.2), 1.5−2.3 (m, 6), 2.48 (t, 1, J = 7.0), 2.65 (dd, 2, J = 5.0, 13.4), 3.42 (dd, 1, J = 8.2, 10.0), 3.59 (dd, 1, J = 4.2, 10.0), 5.51 (s, 2); ^{13}C NMR δ −5.6, 18.4, 20.3, 21.0, 26.0, 30.1, 31.4, 33.6, 36.7, 41.1, 47.7, 51.8, 64.7, 129.0, 134.1, 213.5; TLC (EtOAc/hexane = 1/19) R_f 0.36.

(1*R,2*R**,4a*S**,6*S**,8a*S**)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (4).** IR ($CHCl_3$) 2950, 1686, 1458 cm^{-1}; ^1H NMR δ 0.01 (s, 6), 0.86 (s, 9), 1.01 (d, 3, J = 6.4), 1.01 (d, 3, J = 7.6), 1.1−1.4 (m, 1), 1.7−2.0 (m, 2), 2.2−2.7 (m, 6), 3.70 (d, 2, J = 7.4), 5.39 (br d, 1, J = 10.0), 5.59 (ddd, 1, J = 2.6, 2.6, 10.0); ^{13}C NMR δ −5.6, −5.5, 18.4, 18.5, 22.3, 26.0, 30.8, 33.7, 36.1, 37.8, 44.3, 48.9, 49.8, 60.9, 129.9, 130.9, 215.6; TLC (EtOAc/hexane = 1/19) R_f 0.35.

(1*R,2*R**,4a*S**,6*R**,8a*S**)-1-{[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one (16).** ^1H NMR δ 0.03 (s, 6), 0.05 (s, 3), 0.88 (s, 9), 0.97 (d, 3, J = 6.0), 0.99 (d, 3, J = 7.5), 1.5−2.7 (m, 8), 2.82 (br s, 1), 4.02 (dd, 1, J = 3.4, 7.5) 5.33 (dt, 1, J = 1.8, 10.0), 5.66 (dt, 1, J = 3.3, 10.0); ^{13}C NMR δ −5.6, −5.5, 16.5, 18.3, 22.1, 26.0, 28.5, 30.5, 38.7, 39.3, 43.2, 46.3, 50.7, 63.9, 128.6, 136.0, 211.9; TLC (EtOAc/hexane = 1/19) R_f 0.54.

(1*E*,8*E*,10*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-1,8,10-dodecatrien-4-one (17). IR ($CHCl_3$) 2950, 1708, 1660 cm^{-1}; ^1H NMR δ 0.14 (s, 6), 0.89 (d, 3, J = 6.4), 0.92 (s, 9), 1.73 (d, 3, J = 6.6), 1.9−2.6 (m, 5), 2.92 (dd, 2, J = 1.2, 7.6), 5.04 (dt, 1, J = 7.6, 12.2), 5.4−5.7 (m, 2), 5.9−6.1 (m, 2), 6.28 (dt, 1, J = 1.2, 12.2); ^{13}C NMR δ −5.3, −5.3, 18.0, 18.2, 19.9, 25.6, 29.3, 39.9, 42.2, 48.2, 103.4, 127.2, 129.3, 131.5, 132.3, 143.3, 209.2; TLC (EtOAc/hexane = 1/19) R_f 0.29.

(*R*)-5-Hydroxy-3-methylpentanoic Acid, *N*-Methoxy-*N*-methylamide (19). In a Teflon capsule were placed lactone **18** (2.90 g, 25.4 mmol) and *N*,*O*-dimethylhydroxylamine (2.33 g, 38.1 mmol), and the tube was filled with CH_3CN. The capsule was then placed in a high pressure apparatus, and the reaction was carried out at 9 kbar for 7 h at room temperature. The pressure was released, and the solvent and excess amine were evaporated. Residual oil was purified by silica gel chromatography (EtOAc/acetone = 3/1 to 1/1) to give **19** (3.98 g, 90% yield). IR ($CHCl_3$) 3418, 3000, 1634, 1455 cm^{-1}; ^1H NMR δ 1.01 (d, 3, J = 6.6), 1.4−1.7 (m, 2), 2.1−2.5 (m, 3), 3.20 (s, 3), 3.64 (t, 2, J = 5.9), 3.69 (s, 3); ^{13}C NMR δ 21.0, 26.3, 32.4, 39.0, 40.2, 60.6, 61.5, 174.9; $[\alpha]^{24}_D$ +0.8 (*c* 1.01, $CHCl_3$); TLC (EtOAc) R_f 0.26; HR-LSIMS *m*/*z* 176.1294 [M + H]$^+$ (calcd for $C_8H_{18}NO_3$, 176.1285).

(3*R*,5*E*,7*E*)-3-Methyl-5,7-nonadienoic Acid, *N*-Methoxy-*N*-methylamide (20). To a solution of **19** (13.41 g, 76.53 mmol) in CH_2Cl_2 was added PDC (58.76 g, 153 mmol) at room temperature. Stirring was continued for 4.5 h, and the mixture was diluted with Et_2O (400 mL). The orange suspension was filtered through a pad of Hyflo Super-cel, and the filtrate was concentrated. Residual oil was purified by silica gel chromatography (EtOAc/hexane = 2/1) to give the aldehyde (7.57 g, 57% yield). IR ($CHCl_3$) 3002, 1717, 1646, 1457 cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 6.6), 2.2−2.8 (m, 5), 3.18 (s, 3), 3.68 (s, 3), 9.76 (t, 1, J = 2.0); $[\alpha]^{23}_D$ −6.17 (*c* 1.49, $CHCl_3$); TLC (EtOAc) R_f 0.59; HR-LSIMS *m*/*z* 173.1052 M$^+$ (calcd for $C_8H_{15}NO_3$, 173.1051).

(*E*)-1-Benzenesulfonyl-2-butene[32] (8.41 g, 42.8 mmol) was dissolved in THF (130 mL), and BuLi (26.8 mL of 1.6 M hexane solution, 42.9 mmol) was added dropwise over 15 min at −78 °C. After 30 min, the aldehyde (7.42 g, 42.8 mmol) was added, and the mixture was stirred for 30 min. Next, benzoyl chloride (9.95 mL, 85.7 mmol) was added, and the stirring was continued at −78 °C for 40 min and at 0 °C for 1 h. The reaction mixture was poured into ice-cold saturated NH_4Cl (200 mL) and extracted with EtOAc (2 × 200 mL). The organic extracts were washed with brine (2 × 200 mL), combined, dried, and concentrated. Residual oil was dissolved in MeOH (180 mL) and EtOAc (90 mL), and 5% Na(Hg) (52.0 g, 113.1 mmol Na) was added at −20 °C. The mixture was stirred for 2 h at −20 °C and decanted. The precipitate was washed with EtOAc (50 mL) by decantation. The organic layer was washed with brine (200 mL), and the aqueous phase was extracted with EtOAc (200 mL). The combined organic extract was dried and concentrated. Residual oil was purified by silica gel chromatography (EtOAc/hexane = 1/3 to 1/2) to give diene **20** (4.86 g, 54% yield). IR ($CHCl_3$) 3002, 1642, 1456 cm^{-1}; ^1H NMR δ 0.94 (d, 3, J = 6.0), 1.73 (d, 3, J = 6.2), 1.9−2.5 (m, 5), 3.17 (s, 3), 3.66 (s, 3), 5.3−5.8 (m, 2), 5.9−6.5 (m, 2); ^{13}C NMR δ 18.0, 19.9, 30.1, 32.2, 38.4, 40.0, 61.2, 127.1, 129.7, 131.6, 132.1, 174.0; $[\alpha]^{23}_D$ −4.84 (*c* 1.26, $CHCl_3$); TLC (EtOAc/hexane = 1/3) R_f 0.31; HR-LSIMS *m*/*z* 211.1582 M$^+$ (calcd for $C_{12}H_{21}NO_2$, 211.1571). The ratio of isomeric dienes was determined to be 7:1:2 for (*E*,*E*):(*E*,*Z*):(*Z*,*E*) or (*E*,*E*):(*Z*,*E*):(*E*,*Z*)-isomers by ^{13}C NMR analysis.

(*R*,2*Z*,8*E*,10*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2,8,10-dodecatrien-4-one [(*R*)-(*Z*)-6]. A solution of **11** (10.34 g, 34.65 mmol) in Et_2O (100 mL) was cooled to −78 °C, and BuLi (21.6 mL of 1.6 M hexane solution, 34.7 mmol) was added dropwise. The reaction mixture was stirred for 1 h and then cooled to −100 °C. Amide **20** (2.44 g, 11.6 mmol) in Et_2O (25 mL) was added dropwise over 20 min so that the inner temperature was kept below −90 °C. The reaction mixture was stirred at −78 °C for 1 h and poured into ice-cold saturated NH_4Cl. The mixture was extracted twice with EtOAc, and the organic extract was washed with saturated $NaHCO_3$ and brine. The combined organic extract was dried and concentrated. Purification by silica gel chromatography (toluene) gave trienone (*R*)-(*Z*)-**6** (2.68 g, 72% yield) as a colorless oil. $[\alpha]^{24}_D$ −49.6 (*c* 1.38, $CHCl_3$). IR, ^1H NMR data, and TLC R_f value were identical to those of (*Z*)-**6**.

(1*S*,2*S*,4a*R*,6*R*,8a*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one [(*R*)-4]. (*R*)-(*Z*)-**6** (9.2 mL of 50 mg/mL CH_2Cl_2 solution, 1.43 mmol) was placed in a Teflon capsule, which was then put in a high pressure apparatus. The reaction was carried out at 10 kbar for 8 h at room temperature. The pressure was released, and the solvent was evaporated. Residual oil was purified by silica gel chromatography (EtOAc/hexane = 1/30, 1/19, 1/9) to obtain (*R*)-**4** (212 mg, 46% yield). $[\alpha]^{24}_D$ +50.0 (*c* 1.59, $CHCl_3$); HR-LSIMS *m*/*z* 322.2309 M^+ (calcd for $C_{19}H_{34}O_2Si$, 322.2326). IR, ^1H NMR, ^{13}C NMR data and TLC R_f value were identical to those reported for **4**. Another diastereomer (*R*)-**16** was also obtained. ^1H and ^{13}C NMR data and TLC R_f value were identical to those of **16**.

(1*S*,2*S*,4a*R*,6*R*,8a*S*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2,6-dimethyl-1,2,4a,5,6,7-hexahydro-8*H*-naphthalen-8-one [(*R*)-12]. To a solution of (*R*)-**4** (2.35 g, 7.28 mmol) in MeOH (12 mL) was added NaOMe (7.0 mL of 28% MeOH solution, 36.4 mmol) dropwise at room temperature. After 1 h, the reaction mixture was poured into ice-cold 1 N HCl (50 mL) and extracted with EtOAc (2 × 100 mL). The organic extracts were washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Residual material was purified by silica gel chromatography (EtOAc/hexane = 1/30) to give (*R*)-**12** (2.17 g, 92% yield). $[\alpha]^{24}_D$ +168.4 (*c* 1.24, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62. Found: C, 70.61; H, 10.71; HR-LSIMS *m*/*z* 321.2253 $[M - H]^+$ (calcd for $C_{19}H_{33}O_2Si$, 321.2248). IR and ^1H NMR data and TLC R_f value were identical to those of **12**.

(1*S*,2*S*,4a*R*,6*R*,8*S*,8a*S*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2,6-dimethyl-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene (21). To a solution of (*R*)-**12** (2.05 g, 6.35 mmol) in THF (40 mL) was added L-Selectride (12.7 mL of 1 M THF solution, 12.7 mmol) dropwise at −78 °C. After stirring for 30 min at 0 °C, H_2O (3.2 mL), EtOH (8.0 mL), 6 N NaOH (8.0 mL), and 30% H_2O_2 (12.0 mL) were added successively, and the mixture was stirred for 15 min at 0 °C. The reaction mixture was poured into a mixture of H_2O (50 mL) and EtOAc (80 mL) and partitioned. The aqueous phase was extracted with EtOAc (80 mL), and the combined organic extract was dried and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/19) to give alcohol **21** (2.06 g, 100% yield). IR ($CHCl_3$) 3470, 2950, 1454 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.6−0.8 (m, 1), 0.79 (d, 3, *J* = 7.0), 0.89 (d, 3, *J* = 6.8), 0.91 (s, 3), 1.0−1.3 (m, 2), 1.6−1.8 (m, 1), 1.8−2.0 (m, 3), 2.2−2.5 (m, 2), 3.49 (q, 1, *J* = 1.6), 3.59 (dd, 1, *J* = 2.7, 9.7), 3.69 (dd, 1, *J* = 9.6, 9.7), 4.12 (m, 1), 5.40 (br d, 1, *J* = 10.0), 5.49 (ddd, 1, *J* = 2.0, 2.2, 10.0); $[\alpha]^{24}_D$ +42.9 (*c* 1.26, $CHCl_3$); TLC (EtOAc/hexane = 1/19) R_f 0.40. Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18. Found: C, 70.10; H, 11.05; HR-LSIMS *m*/*z* 325.2555 $[M + H]^+$ (calcd for $C_{19}H_{37}O_2Si$, 325.2560).

Methyl (1*S*,2*S*,4a*R*,6*R*,8*S*,8a*S*,3′*R*,2″*S*)-7′-{2,6-Dimethyl-8-[(2″-methylbutyryl)oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-3′-[(*tert*-butyldimethylsilyl)oxy]-5′-oxo-6′-heptenoate (22). To a solution of **21** (98 mg, 0.30 mmol) in pyridine (2 mL) was added (*S*)-(+)-2-methylbutyric anhydride (90 μL, 0.45 mmol) and DMAP (7.3 mg, 0.06 mmol) at room temperature. After being stirred at room temperature for 2 days, the reaction mixture was diluted with Et_2O and poured into ice-cold 1 N HCl. The organic phase was separated, and the aqueous phase was extracted with Et_2O. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/30) gave the ester (123 mg, 100% yield). IR ($CHCl_3$) 2950, 1715, 1458 cm^{-1}; ^1H NMR δ 0.00 (s, 3), 0.03 (s, 3), 0.87 (s, 9), 0.88 (d, 3, *J* = 6.0), 0.91 (d, 3, *J* = 6.6), 0.92 (t, 3, *J* = 7.4), 0.6−0.9 (m, 1), 1.0−1.3 (m, 2), 1.15 (d, 3, *J* = 7.0), 1.3−2.1 (m, 6), 2.2−2.6 (m, 3), 3.45 (dd, 1, *J* = 10.0, 10.4), 3.62 (dd, 1, *J* = 4.3, 10.4), 5.03 (br d, 1, *J* = 2.2), 5.39 (br d, 1, *J* = 10.0), 5.61 (ddd, 1, *J* = 2.5, 4.5, 10.0); $[\alpha]^{22}_D$ +87.8 (*c* 1.12, $CHCl_3$); TLC (EtOAc/hexane = 1/30) R_f 0.46.

The silyl protecting group was removed by treatment with a 1:19 mixture of 46% aqueous HF solution and CH_3CN (1.5 mL) at room temperature for 1 h. The reaction mixture was diluted with EtOAc and poured into ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/3) to give the alcohol (85 mg, 96% yield). IR ($CHCl_3$) 3486, 2956, 1715, 1457 cm^{-1}; ^1H NMR δ 0.6−0.9 (m, 1), 0.89 (d, 3, *J* = 6.4), 0.92 (t, 3, *J* = 7.3), 0.93 (d, 3, *J* = 7.0), 1.0−1.3 (m, 2), 1.16 (d, 3, *J* = 7.0), 1.4−1.9 (m, 6), 1.9−2.1 (m, 1), 2.2−2.6 (m, 2), 3.54 (dd, 1, *J* = 9.0, 10.5), 3.71 (dd, 1, *J* = 5.4, 10.5), 5.06 (m, 1), 5.41 (br d, 1, *J* = 10.0), 5.61 (ddd, 1, *J* = 2.6, 2.6, 10.0); $[\alpha]^{24}_D$ +115 (*c* 1.22, $CHCl_3$); TLC (EtOAc/hexane = 1/6) R_f 0.10.

To a solution of oxalyl chloride (168 mg, 1.33 mmol) in CH_2Cl_2 (2 mL) were added DMSO (188 μL, 2.65 mmol) and the alcohol (260 mg, 0.883 mmol) in CH_2Cl_2 (4 mL) at −78 °C. After stirring for 30 min at −78 °C, NEt_3 (862 μL, 6.18 mmol) was added dropwise, and stirring was continued for 30 min at −78 °C. The reaction mixture was then diluted with Et_2O and acidified with 1 N HCl. The organic phase was separated, and the aqueous phase was extracted with Et_2O. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/6) gave the aldehyde (238 mg, 92% yield). ^1H NMR δ 0.7−1.0 (m, 1), 0.89 (t, 3, *J* = 7.5), 0.91 (d, 3, *J* = 7.2), 0.96 (d, 3, *J* = 7.0), 1.13 (d, 3, *J* = 7.0), 1.2−1.9 (m, 6), 1.9−2.1 (m, 1), 2.2−2.4 (m, 2), 2.6−2.8 (m, 2), 5.34 (m, 1), 5.46 (br d, 1, *J* = 10.0), 5.58 (ddd, *J* = 2.6, 2.7, 10.0), 9.75 (d, 1, *J* = 2.5); TLC (EtOAc/hexane = 1/6) R_f 0.36.

The mixture of the aldehyde (238 mg, 0.814 mmol), Cs_2CO_3 (531 mg, 1.63 mmol), and phosphonate **3** (624 mg, 1.63 mmol) in 2-propanol (1 mL) was stirred at room temperature for 4 h and then diluted with EtOAc. After being cooled to 0 °C, 5% citric acid solution was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and each organic extract was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/9) to give enone **22** (407 mg, 91% yield). ^1H NMR δ 0.04 (s, 3), 0.07 (s, 3), 0.7−1.0 (m, 1), 0.84 (s, 9), 0.89 (t, 3, *J* = 7.4), 0.89 (d, 3, *J* = 6.4), 0.96 (d, 3, *J* = 7.0), 1.13 (d, 3, *J* = 7.0), 1.0−1.9 (m, 6), 1.9−2.1 (m, 1), 2.2−2.6 (m, 4), 2.46 (dd, 1, *J* = 6.6, 14.7), 2.55 (dd, 1, *J* = 5.3, 14.7), 2.74 (dd, 1, *J* = 6.3, 15.9), 2.80 (dd, 1, *J* = 6.3, 15.9), 3.67 (s, 3), 4.62 (quintet, 1, *J* = 6.5), 4.89 (br s, 1), 5.46 (br d, 1, *J* = 10.0), 5.59 (ddd, 1, *J* = 2.2, 2.5, 10.0), 6.00 (d, 1, *J* = 15.8), 6.79 (dd, 1, *J* = 10.4, 15.8); TLC (EtOAc/hexane = 1/9) R_f 0.17; HR-LSIMS *m*/*z* 548.3512 M^+ (calcd for $C_{31}H_{52}O_6Si$, 548.3529).

(1*S*,2*S*,4a*R*,6*R*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-[2-{1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-8-[(2″-methylbutyryl)oxy]-1-naphthalenyl}ethyl]tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (6-*epi*-4a,5-dihydromevinolin) (2b). A solution of $(Ph_3P)_3RhCl$ (15 mg, 0.016 mmol), **22** (298 mg, 0.543 mmol), and Et_3SiH (2.60 mL, 16.3 mmol) in benzene (7.5 mL) was heated to 70 °C with stirring for 1.5 h. The volatile materials were removed by evaporation, and to the resulting oil was added 6 mL of a solution of 46% aqueous HF and CH_3CN (1:19) at room temperature. After stirring for 1 h, Et_2O and saturated $NaHCO_3$ were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and each organic extract was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/3 to 1/2) to give the saturated ketone (150 mg, 64% yield). ^1H NMR δ 0.6−1.0 (m, 1), 0.84 (t, 3, *J* = 6.8), 0.88 (d, 3, *J* = 7.2), 0.92 (d, 3, *J* = 7.4), 1.15 (d, 3, *J* = 7.0), 1.0−1.8 (m, 10), 1.9−2.1 (m, 1), 2.1−2.5 (m, 4), 2.51 (d, 1, *J* = 6.2), 2.62 (d, 1, *J* = 5.6), 3.71 (s, 3), 4.45 (quintet, 1, *J* = 6.0), 5.18 (br s, 1), 5.41 (br d, 1, *J* = 10.0), 5.59 (ddd, 1, *J* = 2.6, 2.6, 10.0); TLC (EtOAc/hexane = 1/2) R_f 0.28.

To a solution of the ketone (122 mg, 0.281 mmol) in THF (3 mL) was added Et_2BOMe (0.31 mL of 1.0 M THF solution, 0.31 mmol) at −78 °C. After stirring for 35 min, $NaBH_4$ (12 mg, 0.31 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. EtOAc and 1 N HCl were added to the mixture, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and each organic extract was washed with brine, dried, and concentrated. Residual material was dissolved in MeOH and concentrated under reduced pressure. This operation was repeated three times. Purification by silica gel chromatography (EtOAc/hexane = 2/3) gave the syn-diol (91 mg, 74% yield). ^1H NMR δ 0.6−1.0 (m, 1),

0.85 (t, 3, J = 7.0), 0.88 (d, 3, J = 6.4), 0.92 (d, 3, J = 7.4), 1.0−1.3 (m, 3), 1.13 (d, 3, J = 7.2), 1.3−1.8 (m, 10), 1.9−2.1 (m, 1), 2.2−2.4 (m, 3), 2.49 (d, 2, J = 6.2), 3.72 (s, 3), 3.80 (m, 1), 4.26 (m, 1), 5.20 (br s, 1), 5.40 (br d, 1, J = 9.8), 5.60 (ddd, 1, J = 2.4, 2.8, 9.8); TLC (EtOAc/hexane = 1/1) R_f 0.41.

To a solution of the diol (20.2 mg, 0.046 mmol) in CH_3CN (0.2 mL) was added HF/pyridine (60 μL) dropwise at room temperature. After being stirred for 2 h, the reaction mixture was diluted with EtOAc and poured into ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic layer was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 2/1) to give 6-*epi*-4a,5-dihydromevinolin (**2b**) (9.1 mg, 49% yield). IR ($CHCl_3$) 3454, 2952, 1715, 1456 cm^{-1}; ^{1}H NMR δ 0.6−1.0 (m, 1), 0.86 (d, 3, J = 6.9), 0.89 (d, 3, J = 7.2), 0.90 (t, 3, J = 7.5), 1.0−2.1 (m, 13), 1.14 (d, 3, J = 7.0), 2.2−2.5 (m, 3), 2.61 (ddd, 1, J = 1.5, 3.9, 17.7), 2.73 (dd, 1, J = 4.8, 17.7), 4.37 (br s, 1), 4.62 (m, 1), 5.19 (br s, 1), 5.41 (br d, 1, J = 9.9), 5.60 (ddd, 1, J = 2.7, 4.8, 9.9); ^{13}C NMR δ 11.7, 14.9, 16.9, 22.1, 23.4, 26.8, 27.4, 31.6, 33.1, 36.1, 36.7, 37.6, 38.6, 39.3, 41.5, 41.5, 41.9, 62.7, 69.5, 76.2, 130.8, 132.2, 170.3, 176.3; $[\alpha]^{25}_D$ +102 (*c* 0.46, $CHCl_3$); TLC (EtOAc/hexane = 2/3) R_f 0.17; HR-LSIMS m/z 407.2790 $[M + H]^+$ (calcd for $C_{24}H_{39}O_5$, 407.2795).

(1*S*,2*S*,4a*R*,6*R*,8*S*,8a*S*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2,6-dimethyl-8-hydroxy-1,2,6,7,8,8a-hexahydronaphthalene (23). To a solution of **21** (487 mg, 1.5 mmol) in $CHCl_3$ (5 mL) were added NEt_3 (0.836 mL, 6.0 mmol) and bromine (3.0 mL of 2 M $CHCl_3$ solution, 6.0 mmol) dropwise at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into ice-cold $NaHSO_3$ and extracted twice with CH_2Cl_2. The organic extract was dried and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/19) to give the dibromide (722 mg, 99% yield). IR ($CHCl_3$) 3466, 2944, 1454 cm^{-1}; ^{1}H NMR δ 0.10 (s, 6), 0.92 (s, 9), 1.0−1.4 (m, 2), 1.23 (d, 3, J = 7.0), 1.24 (d, 3, J = 7.8), 1.4−1.7 (m, 2), 1.8−2.1 (m, 2), 2.3−2.6 (m, 3), 3.37 (m, 1), 3.48 (dd, 1, J = 2.0, 10.0), 3.71 (dd, 1, J = 8.0, 10.0), 4.14 (quintet, 1, J = 2.9), 4.58 (br s, 1), 4.84 (br s, 1); ^{13}C NMR δ −5.6, −5.5, 18.1, 18.3, 22.3, 25.0, 25.8, 34.9, 38.5, 38.6, 41.0, 59.0, 60.4, 66.3, 66.8; $[\alpha]^{24}_D$ −5.4 (*c* 1.19, $CHCl_3$); TLC (EtOAc/hexane = 1/19) R_f 0.24; HR-LSIMS m/z 483.0917 $[M + H]^+$ (calcd for $C_{19}H_{37}O_2SiBr_2$, 483.0928).

To a solution of the dibromide (666 mg, 1.37 mmol) in benzene (7 mL) was added DBU (2.06 mL, 13.7 mmol) dropwise at room temperature. The reaction mixture was refluxed for 5 h, cooled to room temperature, and diluted with EtOAc. The mixture was poured into ice-cold 1 N HCl, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and each organic extract was washed with saturated $NaHCO_3$, dried, and concentrated. Purification by silica gel chromatography (toluene) gave diene **23** (196 mg, 44% yield) along with isomers. IR ($CHCl_3$) 3450, 2952, 1452 cm^{-1}; ^{1}H NMR δ 0.11 (s, 3), 0.12 (s, 3), 0.86 (d, 3, J = 7.0), 0.92 (s, 9), 1.04 (d, 3, J = 7.0), 1.2−1.4 (m, 1), 1.9−2.2 (m, 2), 2.2−2.3 (m, 1), 2.3−2.5 (m, 1), 2.5−2.7 (m, 1), 3.67 (dd, 1, J = 3.0, 10.2), 3.72 (br s, 1), 3.74 (dd, 1, J = 8.2, 10.2), 4.22 (br s, 1), 5.47 (br s, 1), 5.65 (dd, 1, J = 5.8, 9.4), 5.96 (d, 1, J = 9.4); ^{13}C NMR δ −5.6, −5.6, 14.8, 18.2, 21.5, 25.9, 26.0, 33.7, 37.6, 39.1, 40.8, 65.5, 66.7, 128.9, 130.7, 132.4, 133.0; $[\alpha]^{23}_D$ +113.6 (*c* 1.09, $CHCl_3$); TLC (toluene) R_f 0.30.

(1*S*,2*S*,6*R*,8*S*,8a*S*,2′*S*)-1-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2,6-dimethyl-8-[(2′-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (24). To a solution of **23** (183 mg, 0.567 mmol) in pyridine (2 mL) were added (*S*)-(+)-2-methylbutyric anhydride (175 μL, 0.851 mmol) and DMAP (14 mg, 0.113 mmol) at room temperature. After stirring at 50 °C for 6 h, the reaction mixture was cooled to 0 °C, diluted with Et_2O, and poured into ice-cold 1 N HCl. The organic phase was separated, and the aqueous phase was extracted with Et_2O. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (CH_2Cl_2/hexane = 1/4) gave ester **24** (188 mg, 82% yield). IR ($CHCl_3$) 2954, 1713, 1456 cm^{-1}; ^{1}H NMR δ 0.01 (s, 3), 0.04 (s, 3), 0.87 (s, 9), 0.90 (t, 3, J = 7.6), 0.96 (d, 3, J = 7.0), 1.01 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1.2−1.6 (m, 3), 1.6−1.8 (m, 1), 1.8−2.1 (m, 1), 2.1−2.5 (m, 3), 2.5−2.7 (m, 1), 3.49 (dd, 1, J = 9.6, 9.8), 3.68 (dd, 1, J = 4.0, 9.8), 5.16 (br s, 1), 5.41 (br s, 1), 5.77 (dd, 1, J = 5.8, 9.8), 5.96 (d, 1, J = 9.8); $[\alpha]^{23}_D$ +168 (*c* 1.21, $CHCl_3$); TLC (toluene) R_f 0.72.

(1*S*,2*S*,6*R*,8*S*,8a*S*,2′*S*)-1-(Hydroxymethyl)-2,6-dimethyl-8-[(2′-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (25). To a solution of ester **24** (170 mg, 0.418 mmol) in THF (1.7 mL) were added AcOH (0.215 mL, 3.76 mmol) and TBAF (2.1 mL of 1.0 M THF solution, 2.1 mmol) at room temperature. After being heated under reflux for 1.5 h and then cooled, the mixture was diluted with EtOAc and poured into ice-cold $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/3) gave alcohol **25** (120 mg, 98% yield). IR ($CHCl_3$) 3474, 2954, 1711, 1453 cm^{-1}; ^{1}H NMR δ 0.90 (t, 3, J = 7.4), 0.99 (d, 3, J = 6.6), 1.02 (d, 3, J = 6.6), 1.13 (d, 3, J = 7.2), 1.1−1.8 (m, 3), 1.9−2.1 (m, 1), 2.1−2.5 (m, 4), 2.5−2.7 (m, 1), 3.58 (ddd, 1, J = 5.2, 9.2, 10.2), 3.77 (ddd, 1, J = 4.9, 4.9, 10.2), 5.19 (br s, 1), 5.43 (br s, 1), 5.78 (dd, 1, J = 5.8, 9.8), 5.99 (d, 1, J = 9.8); $[\alpha]^{25}_D$ +205 (*c* 1.07, $CHCl_3$); TLC (EtOAc/hexane = 1/4) R_f 0.18; HR-LSIMS m/z 292.2044 M^+ (calcd for $C_{18}H_{28}O_3$, 292.2037).

Methyl (1*S*,2*S*,6*R*,8*S*,8a*S*,3′*R*,2″*S*)-7′-{2,6-Dimethyl-8-[(2″-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl}-3′-[(*tert*-butyldimethylsilyl)oxy]-5′-oxo-6′-heptenoate 26. To a solution of oxalyl chloride (77 mg, 0.605 mmol) in CH_2Cl_2 (1 mL) were added DMSO (86 μL, 1.21 mmol) and a solution of alcohol **25** (118 mg, 0.403 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After stirring for 30 min at −78 °C, NEt_3 (394 μL, 2.83 mmol) was added dropwise, and stirring was continued for 30 min at −78 °C. The reaction mixture was then diluted with Et_2O and poured into ice-cold NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with Et_2O. Each organic extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/9) gave the aldehyde (103 mg, 88% yield). IR ($CHCl_3$) 2956, 1717, 1453 cm^{-1}; ^{1}H NMR δ 0.86 (t, 3, J = 7.4), 0.97 (d, 3, J = 6.8), 1.04 (d, 3, J = 6.8), 1.10 (d, 3, J = 7.0), 1.2−1.5 (m, 2), 1.5−1.8 (m, 1), 2.1−2.5 (m, 3), 2.6−3.0 (m, 3), 5.44 (br s, 1), 5.52 (br s, 1), 5.73 (dd, 1, J = 5.4, 9.8), 6.01 (d, 1, J = 9.8), 9.75 (d, 1, J = 1.8); $[\alpha]^{22}_D$ +222 (*c* 1.28, $CHCl_3$); TLC (EtOAc/hexane = 1/9) R_f 0.32; HR-LSIMS m/z 290.1875 M^+ (calcd for $C_{18}H_{26}O_3$, 290.1880).

A mixture of the aldehyde (91 mg, 0.313 mmol), Cs_2CO_3 (306 mg, 0.940 mmol), and phosphonate **3** (360 mg, 0.940 mmol) in 2-propanol (0.3 mL) was stirred at room temperature for 7.5 h. The mixture was diluted with EtOAc and poured into ice-cold NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/9) gave enone **26** (101 mg, 59% yield). IR ($CHCl_3$) 2968, 1721, 1456 cm^{-1}; ^{1}H NMR δ 0.07 (s, 6), 0.84 (s, 9), 0.87 (t, 3, J = 7.2), 1.01 (d, 3, J = 7.0), 1.02 (d, 3, J = 6.8), 1.11 (d, 3, J = 7.0), 1.2−1.5 (m, 2), 1.5−1.8 (m, 1), 2.1−2.4 (m, 4), 2.4−2.7 (m, 4), 2.75 (dd, 1, J = 6.3, 16.1), 2.80 (dd, 1, J = 6.0, 16.1), 3.67 (s, 3), 4.62 (quintet, 1, J = 5.9), 5.00 (br s, 1), 5.48 (br s, 1), 5.75 (dd, 1, J = 5.6, 9.8), 6.02 (d, 1, J = 9.8), 6.04 (d, 1, J = 16.0), 6.82 (dd, 1, J = 9.8, 16.0); $[\alpha]^{23}_D$ +85.6 (*c* 1.02, $CHCl_3$); TLC (EtOAc/hexane = 1/6) R_f 0.33; HR-LSIMS m/z 546.3379 M^+ (calcd for $C_{31}H_{50}O_6Si$, 546.3374).

(1*S*,2*S*,6*R*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-[2-{1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-[(2″-methylbutyryl)oxy]-1-naphthalenyl}ethyl]tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (6-*epi*-mevinolin) (2a). The mixture of **26** (80 mg, 0.146 mmol), $(Ph_3P)_3RhCl$ (2.7 mL of 5 mg/mL benzene solution, 0.0146 mmol), and Et_3SiH (1.17 mL, 7.30 mmol) was stirred at 65 °C for 2 h. The volatile materials were evaporated, and the residue was treated with a 1:19 mixture of 46% aqueous HF solution and CH_3CN (1.5 mL) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with Et_2O, and poured into ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried,

and concentrated. The residue was purified by silica gel chromatography (EtOAc/toluene = 1/3) to give the saturated ketone (46 mg, 72% yield). IR ($CHCl_3$) 3508, 2960, 1715, 1437 cm^{-1}; ^1H NMR δ 0.87 (t, 3, J = 7.4), 0.87 (d, 3, J = 7.0), 1.01 (d, 3, J = 6.8), 1.12 (d, 3, J = 7.0), 1.1−1.9 (m, 6), 2.1−2.5 (m, 7), 2.51 (d, 2, J = 6.4), 2.62 (m, 2), 3.39 (br s, 1), 3.71 (s, 3), 4.43 (m, 1), 5.31 (br s, 1), 5.42 (br s, 1), 5.74 (dd, 1, J = 6.0, 9.8), 5.98 (d, 1, J = 9.8); $[\alpha]^{24}_D$ +154 (*c* 1.24, $CHCl_3$); TLC (EtOAc/toluene = 1/9) R_f 0.19; HR-LSIMS *m/z* 434.2678 M^+ (calcd for $C_{25}H_{38}O_6$, 434.2666).

To a solution of the ketone (39 mg, 0.09 mmol) in THF (0.8 mL) and MeOH (0.2 mL) was added Et_2BOMe (0.10 mL of 1.0 M THF solution, 0.10 mmol) at −78 °C. The mixture was stirred at −78 °C for 50 min, and then $NaBH_4$ (3.8 mg, 0.10 mmol) was added. The reaction mixture was stirred at −78 °C for 2 h, diluted with EtOAc, and poured into ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried, and concentrated. Residual oil was dissolved in MeOH and concentrated under reduced pressure. This operation was repeated three times. Purification by silica gel chromatography (EtOAc/hexane = 1/1) gave syn-diol (19 mg, 48% yield). IR ($CHCl_3$) 3498, 2952, 1714, 1453 cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7.4), 0.89 (d, 3, J = 7.0), 1.02 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.1−1.8 (m, 9), 2.1−2.5 (m, 5), 2.49 (d, 2, J = 6.2), 3.42 (m, 1), 3.72 (s, 3), 3.80 (m, 1), 4.26 (quintet, 1, J = 6.4), 5.34 (br s, 1), 5.41 (br s, 1), 5.76 (dd, 1, J = 5.8, 9.4), 5.97 (d, 1, J = 9.4); $[\alpha]^{25}_D$ +108 (*c* 1.52, $CHCl_3$); TLC (EtOAc/hexane = 1/1) R_f 0.34; HR-LSIMS *m/z* 436.2813 M^+ (calcd for $C_{25}H_{40}O_6$, 436.2822).

To a solution of the diol (7.9 mg, 0.018 mmol) in CH_3CN (0.1 mL) was added HF/pyridine (24 μL) dropwise at room temperature. After being stirred for 1 h, the reaction mixture was diluted with EtOAc and poured into ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic extract was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 2/1) to give 6-*epi*-mevinolin **2a** (3.5 mg, 48% yield). IR ($CHCl_3$) 3416, 2952, 1717, 1258 cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7.0), 0.90 (d, 3, J = 6.6), 1.02 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.0), 1.2−2.1 (m, 9), 2.1−2.5 (m, 5), 2.62 (ddd, 1, J = 1.1, 4.0, 17.6), 2.74 (dd, 1, J = 5.0, 17.6), 4.38 (m, 1), 4.62 (m, 1), 5.33 (br s, 1), 5.41 (br s, 1), 5.76 (dd, 1, J = 6.0, 9.6), 5.98 (d, 1, J = 9.6); ^{13}C NMR δ 11.8, 13.8, 16.9, 21.3, 24.1, 26.6, 26.7, 31.0, 33.0, 35.5, 36.3, 36.8, 37.6, 38.7, 41.7, 62.8, 68.4, 76.1, 128.2, 130.1, 132.8, 133.2, 170.0, 176.7; $[\alpha]^{25}_D$ +115.4 ± 4.4 (*c* 0.35, $CHCl_3$); TLC (EtOAc/hexane = 2/1) R_f 0.36; HR-LSIMS *m/z* 404.2563 M^+ (calcd for $C_{24}H_{36}O_5$, 404.2561).

Compounds Listed in Table 4. Entry 1. The compound was prepared by hydrolysis of **2a**. ^1H NMR (CD_3OD) δ 0.76 (t, 3, J = 7.2), 0.77 (d, 3, J = 6.8), 0.88 (d, 3, J = 6.8), 0.98 (d, 3, J = 7.0), 0.7−1.6 (m, 12), 2.0−2.3 (m, 4), 3.5−3.7 (m, 1), 3.8−4.0 (m, 1), 5.15 (br s, 1), 5.23 (br s, 1), 5.62 (dd, 1, J = 5.8, 9.6), 5.81 (d, 1, J = 9.6); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.62.

Entry 2. The compound was prepared by hydrolysis of **2b**. ^1H NMR (CD_3OD) δ 0.8−1.0 (m, 9), 1.13 (d, 3, J = 7.0), 1.0−2.5 (m, 19), 3.6−3.7 (m, 1), 4.0−4.1 (m, 1), 5.15 (br s, 1), 5.38 (br d, 1, J = 9.4), 5.5−5.7 (m, 1); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.72.

Entry 3. This compound was prepared by acylation of **21** with butyric anhydride, followed by a sequence of transformations of the acylated compound in a similar manner to that used to prepare **2b**. ^1H NMR (CD_3OD) δ 0.6−2.0 (m, 19), 0.61 (d, 3, J = 6.6), 0.84 (d, 3, J = 6.6), 0.88 (t, 3, J = 7.2), 2.24 (t, 3, J = 7.2), 3.63 (br s, 1), 4.01 (br s, 1), 4.5−5.6 (m, 2); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.70.

Entry 4. This compound was prepared by acylation of **21** with 2,2-dimethylbutyryl chloride, followed by a sequence of transformations of the acylated compound in a similar manner to that used to prepare **2b**. ^1H NMR (CD_3OD) δ 0.8−2.4 (m, 35), 3.71 (br s, 1), 4.10 (br s, 1), 5.0−5.7 (m, 2); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.74.

Entry 5. The compound was prepared by a procedure similar to that for the preparation of **2b** except that the hydrosilylation step was eliminated. ^1H NMR (CD_3OD) δ 0.7−0.9 (m, 9), 1.06 (d, 3, J = 7.0), 1.1−2.4 (m, 19), 3.9−4.1 (m, 1), 4.1−4.2 (m, 1), 5.2−5.6 (m, 4); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.77.

Entries 6 and 7. This compound was prepared by a slight modification of Heathcock's procedure[39] which utilized chiral α-methoxyphenylacetic acid for the optical resolution of the intermediary racemic diol for dihydromevinolin synthesis. We applied his method for the optical resolution of the racemic diol derived from racemic **21**, and prepared compounds, which have a decalin moiety enantiomeric to (+)-6-*epi*-4a,5-dihydromevinolin, as described above. **Entry 6**: ^1H NMR (CD_3OD) δ 0.7−1.0 (m, 9), 1.16 (d, 3, J = 7.0), 1.0−2.5 (m, 19), 3.6−3.8 (m, 1), 4.0−4.2 (m, 1), 5.17 (br s, 1), 5.41 (br d, 1, J = 9.8), 5.5−5.7 (m, 1); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.71. **Entry 7**: ^1H NMR (CD_3OD) δ 0.8−1.0 (m, 9), 1.14 (d, 3, J = 7.0), 1.0−2.5 (m, 17), 3.9−4.1 (m, 1), 4.2−4.4 (m, 1), 4.6−5.1 (m, 2), 5.3−5.5 (m, 1), 5.5−5.7 (m, 1); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.70.

HMG-CoA Reductase Inhibition Assay. Preparation of Rat Liver Microsomes. Sprague-Dawley rats, which were allowed free access to ordinary diets containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsomes. The microsomes obtained were then purified as described by Kuroda.[37] The microsomal fraction obtained by centrifugation at 105000*g* was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in 100 mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The homogenate obtained was cooled and kept at −80 °C.

Measurement of HMG-CoA Reductase Inhibitory Activities. The rat liver microsome sample (8 mg/mL, 100 mL), which was preserved at −80 °C, was fused at 0 °C and diluted with 0.7 mL of a cold potassium phosphate buffer (100 mM, pH 7.4). This was mixed with 0.8 mL of 100 mM EDTA (buffered with the potassium phosphate buffer) and 0.4 mL of 100 mM dithiothreitol solution (buffered with the potassium phosphate buffer), and the mixture was kept at 0 °C. The microsome solution (1.675 mL) was mixed with 670 mL of 25 mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to the solution of 0.5 mM [3-^{14}C]HMG-CoA (3 mCi/mmol). A solution (5 mL) of sodium salt of a test compound dissolved in potassium phosphate buffer was added to 45 mL of the above mixture. The resulting mixture was incubated at 37 °C for 30 min and cooled. After termination of the reaction by addition of 10 mL of 2 N HCl, the mixture was applied to preparative TLC on silica gel of 0.5 mm in thickness (Merck AG, Art 5744). The chromatograms were developed in toluene/acetone (1/1) to nearly the top and bands of R_f value between 0.45 to 0.60 obtained by scraping. The products obtained were put into a vial containing 10 mL of scintillator to measure specific radioactivity with a scintillation counter. The activities of the test compounds are shown in Table 4, and compared with that of mevinolin (sodium salt).

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Supporting Information Available: Experimental procedures for the synthesis of the compounds in Table 4 and ^1H NMR spectra of compounds not analyzed (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(39) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586.