1.24–1.56 (4, m), 1.86–1.95 (1, m), 2.09–2.17 (1, m), 2.33 (1, septet, J = 6.9, H.5), 3.13 (1, s, H.3), 4.12–4.24 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 241 (M^+ – $CH(CH_3)_2$, 36), 227 (24), 129 (57), 85 (66), 83 (100), 57 (44), 43 (68). A mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.53; H, 9.93. Found: C, 67.59; H, 9.90.

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Supplementary Material Available: 2D NOESY ^1H NMR spectra of **18** and *cis*-**19** and low-temperature ^1H and ^{13}C spectra of **4a** and **4a** + $TiBr_4$ (6 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.

Remote Diastereoselection in the Asymmetric Synthesis of Pravastatin

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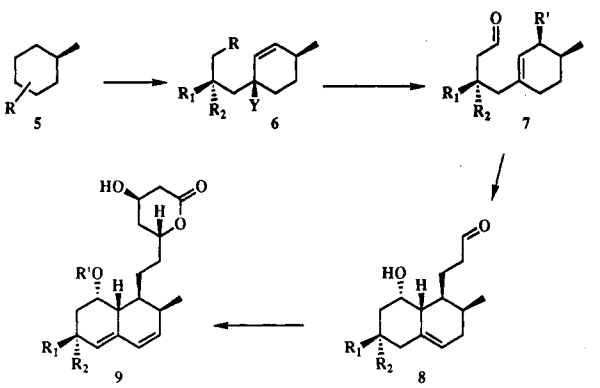
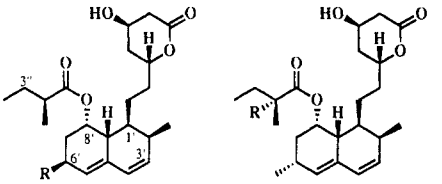
The first total synthesis of pravastatin (**3**) is described. The desymmetrization of 1-methyl-4-methylenecyclohexane (**10**) by an asymmetric ene reaction to form **11a** provided the initial asymmetric framework. The remaining stereogenic centers were introduced sequentially by a series of diastereoselective processes which include the iodolactonization of **11a** to **13**, the Eschenmoser–Claisen rearrangement of **17** to **18**, the stereoselective intramolecular ene reaction of **20** to **21**, and the diastereoselective condensation of aldehyde **27** with diene **28**.

An important new therapeutic strategy in the management of atherosclerosis has emerged from investigations on the mevinic acid family of compounds.[1] Treatment in vivo with these substances, which are competitive inhibitors of HMG-CoA reductase, results in the beneficial alteration of serum lipid levels.[2] The first member of this group, isolated from microbial sources, was mevastatin (**1**),[3-5] which was joined a few years later by the isolation of an even more active inhibitor, lovastatin (**2**). In the course of the clinical development for mevastatin, a more active metabolite, pravastatin (**3**), was isolated as a minor component in the urine of dogs.[6] This 6′-β-hydroxylation of mevastatin is now carried out by a more efficient microbial process.[7] Both lovastatin and pravastatin are currently prescribed for the reduction of serum cholesterol levels.

Scheme I





1 R = H Mevastatin
3 R = OH Pravastatin

2 R = H Lovastatin
4 R = Me Simvastatin

A noteworthy aspect of these inhibitors, in addition to their much higher affinity for the enzyme than the natural

(1) The names for these substances have varied during the course of time and among research groups. We will use the current names for **1**, mevastatin (also referred to as compactin, ML-236B, CS-500), **2**, lovastatin (also referred to as mevinolin, MB-530B, MK-803, Mevacor), **3**, pravastatin (also referred to as eptastatin, CS-514, SQ-3100), and **4**, simvastatin, a semisynthetic derivative of lovastatin (also referred to as synvinolin, MK-733, Zocor).

(2) Lovastatin, pravastatin, and simvastatin all reduce total serum cholesterol and triglyceride levels, improve LDL to HDL cholesterol ratios, and in preliminary tests appear to halt or reverse the progression of atherosclerotic lesions. Grundy, S. M. *N. Engl. J. Med.* **1988**, *319*, 24. Grundy, S. M. *N. Engl. J. Med.* **1988**, *319*, 1222. Chao, Y.; Chen, J. S.; Hunt, V. M.; Kuron, G. W.; Karkas, J. D.; Liou, R.; Alberts, A. W. *Eur. J. Clin. Pharmacol.* **1991**, *40* (S1), S11. Illingworth, D. R.; Bacon, S. *Am. J. Cardiol.* **1987**, *60*, 33G. MacDonald, J. S.; Gerson, R. J.; Kornbrust, D. J.; Kloss, M. W.; Prahlada, S.; Berry, P. H.; Alberts, A. W.; Bokelman, D. L. *Am. J. Cardiol.* **1988**, *62*, 16J. Tobert, J. A. *Am. J. Cardiol.* **1988**, *62*, 28J. Miettien, T. A. *Eur. J. Clin. Pharmacol.* **1991**, 40 (S1), S19. Duggan, D. E.; Chen, I.; Bayne, W. F.; Halpin, R. A.; Duncan, C. A.; Schwartz, M. S.; Stubbs, R. J.; Vickers, S. *Drug Metab. Disp.* **1989**, *17*, 166. Mabuchi, H.; Fujita, H.; Michishita, I.; Takeda, M.; Kajinami, K.; Koizumo, J.; Takeda, R.; Takegoshi, T.; Wakasugi, T.; Ueda, K.; Miyamoto, S.; Watanabe, A.; Oota, M. *Atherosclerosis* **1988**, *72*, 183. Sato, Y.; Goto, Y.; Nakaya, N.; Hata, Y.; Homma, Y.; Naito, C.; Hayashi, H.; Ito, H.; Yamamoto, M.; Takeuchi, I.; Mori, K.; Hara, T.; Yoshida, S.; Shira, K.; Sasaki, N.; Shinomiya, M.; Murano, S.; Morisaki, N.; Nishiide, T.; Kanzaki, T.; Wantanabe, N.; Ishikawa, T. *Atherscerlosis* **1988**, *72*, 205. Serizawa, N.; Matsuoka, T. *Biochim. Biophys. Acta* **1991**, *1084*, 35. McTavish, D.; Sorkin, E. M. *Drugs* **1991**, *42*, 65. Pan, H. Y. *Eur. J. Clin. Pharmacol.* **1991**, *40* (S1), S15. Tsujita, Y.; Watanabe, Y. *Cardiovasc. Drug Res.* **1989**, *7*, 110. Malini, P. L.; Ambrosioni, E.; DeDivitiis, O.; DiSomma, S.; Rosiello, G.; Trimarco, B. *Clin. Ther.* **1991**, *13*, 500.

(3) Isolation from *Penicillium brevicompactum* and X-ray structure: Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans.* **1976**, 1165.

(4) Isolation from *Penicillium citrinum*, Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.

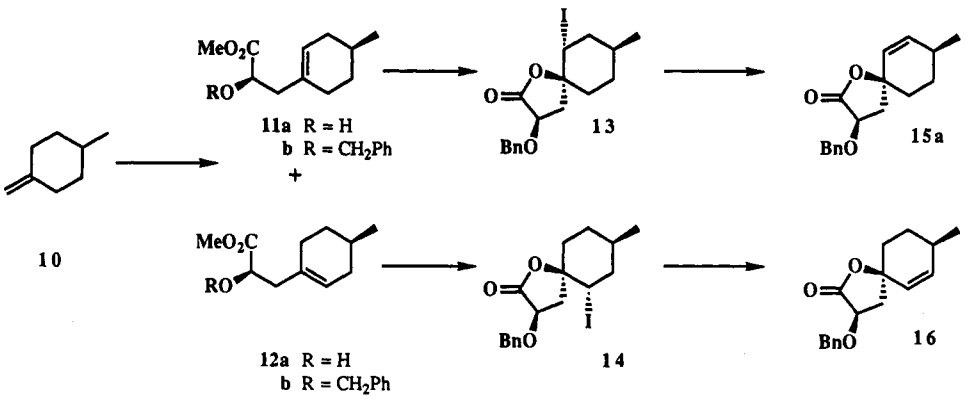
(5) Inhibition of cholesterol biosynthesis in rats. Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31.

(6) Serizawa, N.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 604. Haruyama, H.; Kuwano, H.; Kinoshita, T.; Terahara, A.; Nishigaki, T.; Tamura, C. *Chem. Pharm. Bull.* **1986**, *34*, 1459. Haruyama, H.; Kondo, M. *Chem. Pharm. Bull.* **1987**, *35*, 170. Sato, S.; Furukawa, Y. *J. Antibiot.* **1988**, *41*, 1265.

(7) Serizawa, N.; Nakagaw, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 604. Serizawa, N.; Nakagawa, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 608. Serizawa, N.; Serizawa, S.; Nakagawa, K.; Furuya, K.; Ozaki, T.; Terahara, A. *J. Antibiot.* **1983**, *36*, 887. Ditschuneit, H. H.; Kuhn, K.; Ditschuneit, H. *Eur. J. Clin. Pharmacol.* **1991**, *40* (S1), S27.

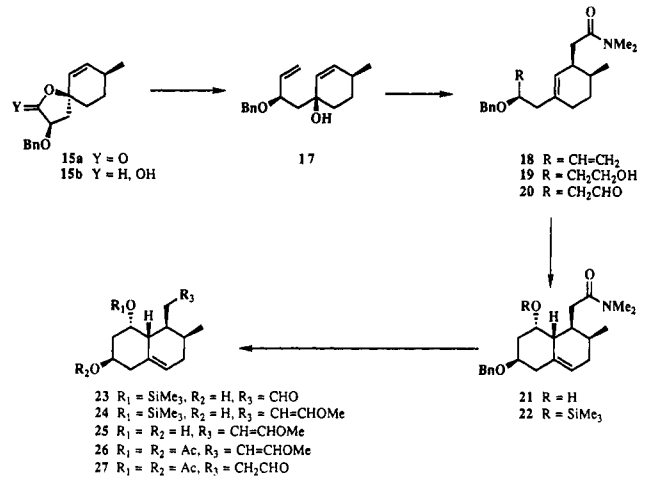
0022-3263/92/1957-7133$03.00/0

Scheme II



substrate, HMG-CoA,[8] is that the on rate of 1 (and presumably for the others) is nearly diffusion controlled and ca. 100-fold faster than that of HMG-CoA, a property which has implications for an important binding role of the hexahydronaphthalene portion of the molecule.[9] Modification of that part of the molecule can produce significant changes in its biological properties. Relative to 1, the 6′-β-hydroxyl group of pravastatin not only increases the activity but enhances the water solubility by ca. 100-fold and significantly reduces the lipophilicity relative to 1, 2 or 4.[10] This latter property has been attributed, at least in part, to some of the dramatic differences observed between pravastatin and the more lipophilic substances 1, 2, and 4 when examined in cultured cell systems. For example, while the uptake of 1–4 occurs similarly in rat liver cell preparations, in other cell lines which still show little difference among 1, 2, and 4, the degree of cellular uptake of pravastatin is significantly reduced.[11] It has been suggested that the liver uptake of these substances occurs by a specific carrier-mediated transport mechanism in distinction to a non-carrier-mediated transport mechanism used in the other cells.[12] Since the liver is a major site for serum cholesterol production and metabolism, an efficient organ-specific delivery of these inhibitors would be desirable. However, transport processes and metabolism in living systems obfuscate the direct extrapolation of in vitro data to the in vivo situation, a complication which continues to fuel the debate over the relative efficacies of 2, 3, and 4.[13] Nonetheless, in the mevinic acid series, with the exception of the formation of pravastatin, further metabolism produces substances which have reduced activity and ultimately enhanced excretion properties.[14] Thus, in the synthesis planning stages, preferential consideration should be given to those synthetic pathways which provide op-

Scheme III



(8) The K_i values for the acid forms of 1–4 are as follows: 1, 1.4 nM, 2, 2.3 nM, 3, 0.64 nM, 4, 1.2 nM, compared with a K_m of 4.0 μM for HMG-CoA. Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothtock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957. Alberts, A. W. *Atherosclerosis Rev.* **1988**, *18*, 123. (MR07) Tsujita, Y.; Kuroda M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, M.; Tanaka, M.; Masuda, H.; Tarimi, C.; Wantanabe, Y.; Fujii, S. *Biochim. Biophys. Acta* **1986**, *877*, 50.

(9) An analysis of the nature of the binding of 1 to HMG-CoA reductase has been discussed in detail. Nakamura, C. E.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1364. Abeles, R. H. *Drug Dev. Res.* **1987**, *10*, 221.

(10) A relative ranking of lipophilicity has been reported for both the lactones (pravastatin = 1, mevastatin = 25, lovastatin = 67, simvastatin = 173) and for the acid forms (pravastatin = 1, mevastatin = 25, lovastatin = 85, simvastatin = 195). The saturation solubilities in water of the lactone forms were measured: pravastatin = 0.18 mg/mL, mevastatin = 0.0014 mg/mL, lovastatin = 0.0013 mg/mL, simvastatin = 0.0015 mg/mL. Serajuddin, A. T. M.; Ranadive, S. A.; Mahoney, E. M. *J. Pharm. Sci.* **1991**, *80*, 830.

(11) These types of differences have been reported in rat hepatocytes, rat spleen cells, rat whole lens, mouse L cells, rabbit aortic fibroblasts, human skin fibroblasts, human HepG2 cells and human N1 fibroblasts. The case of rat lens, where large differences were observed between pravastatin and lovastatin with whole lens preparations but not with lens homogenates, supports a transport model. Tsujita, Y.; Kuroda, M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, M.; Tanaka, M.; Masuda, H.; Tarimi, C.; Wantanabe, Y.; Fujii, S. *Biochem. Biophys. Acta* **1986**, *877*, 50. Koga, T.; Shimada, Y.; Kuroda, M.; Tsujita, Y.; Hasegawa, K.; Yamazaki, M. *Biochim. Biophys. Acta* **1990**, *1045*, 115. Shaw, M. K.; Newton, R. S.; Sliskovic, D. R.; Roth, B. D.; Ferguson, E.; Krause, B. R. *Biochim. Biophys. Res. Commun.* **1990**, *170*, 726.

(12) Mahoney, E. M., Child, M. J.; Smith-Monroy, C. A. *Circulation* **1990**, *82*, III-6.

(13) Tsujita, Y.; Kuroda, M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, M.; Tanaka, M.; Masuda, H.; Tarimi, C.; Wantanabe, Y.; Fujii, S. *Biochim. Biophys. Acta* **1986**, 877, 50. Koga, T.; Shimada, Y.; Kuroda, M.; Tsujita, Y.; Hasegawa, K.; Yamazaki, M. *Biochim. Biophys. Acta* **1990**, *1045*, 115. Germerhausen, J. I.; Hunt, V. M.; Bostedor, R. G.; Bailey, P. J.; Karkas, J. D.; Alberts, A. W. *Biochem. Biophys. Res. Commun.* **1989**, *158*, 667. Mosley, S. T.; Kalinowski, S. S.; Schafer, B. L.; Tanaka, R. D. *J. Lipid Res.* **1989**, *30*, 1411. Chen, I.; Vickers, S.; Duncan, C. A.; Ellsworth, R. L.; Duggan, D. E. *FASEB J.* **1988**, *2*, A1061.

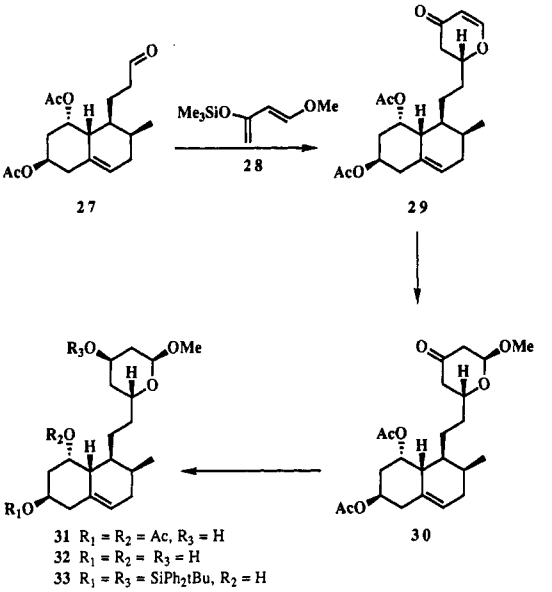
(14) Compounds 2, 3, and 4 undergo considerable metabolism (further hydroxylation, glucuronidation, conjugation, and dehydration) to substances with significantly diminished activity. 2: Vyas, K. P.; Kari, P. H.; Pitzenberger, S. M.; Halpin, R. A.; Ramjit, H. G.; Arison, B.; Murphy, J. S.; Hoffman, W. F.; Schwartz, M. S.; Ulm, E. H.; Duggan, D. E. *Drug Metab. Disp.* **1990**, *18*, 203. Vyas, K. P.; Kari, P. H.; Prakash, S. R.; Duggan, D. E. *Drug Metab. Disp.* **1990**, *18*, 218. Greenspan, M. D.; Yudkovitz, J. B.; Alberts, A. W.; Argenbright, L. S.; Arison, B. H.; Smith, J. L. *Drug Metab. Disp.* **1988**, *16*, 678. 3: Everett, D. W.; Chando, T. J.; Didonato, G. C.; Singhvi, S. M.; Pan, H. Y.; Weinstein, S. H. *Drug Metab. Disp.* **1991**, *19*, 740. Nakamura, T.; Yoda, K.; Kuwano, H.; Miyaguchi, K.; Muramatsu, H.; Tanakhagi, H.; Kinoshita, T. *Xenobiotica* **1991**, *21*, 277. Everett, D.; Singhvi, S. M.; Frantz, B. M.; Willard, D. A. *Clin. Res.* **1989**, *37*, 341A. 4: Vickers, S. Duncan, C. A.; Vyas, K. P.; Hari, P. H.; Arison, B.; Prakash, S. R.; Ramjit, H. G.; Pitzenberger, S. M.; Stokker, G.; Duggan, D. E. *Drug Metab. Disp.* **1990**, *18*, 476. Vyas, K. P.; Kari, P. H.; Vickers, S.; Duncan, C.; Pitzenberger, S.; Arison, B.; Ramjit, H. G.; Duggan, D. E. *FASEB J.* **1988**, *2*, A1060.

portunities to incorporate structure modifications designed to enhance the metabolic characteristics of the parent. In 1989 we reported a generalized route to the mevinic acids as illustrated by the total synthesis of lovastatin.[15] Further refinement and adaptation has ultimately led to the first total synthesis of pravastatin (3), which we now describe herein.

The original strategy, as outlined in Scheme I, was to employ an initial stereogenic center to guide the formation of the remaining rings and stereogenic centers without the further intervention of asymmetric reagents or catalysts.[16] The key stages involve (a) the generation of asymmetry in the acyclic portion of the monocyclic unit **6** from the chiral precursor **5**, (b) the stereoselective introduction of the next ring substituent to form **7**, (c) the stereoselective ring closure of **7** to **8**, and (d) the formation of the lactone ring by the diastereoselective addition of a nucleophile to the aldehyde moiety of **8**.

A more effective variation of this strategy could be realized, however, if the stereogenic centers at both the acyclic and cyclic portions of **6** were formed simultaneously. One tactic to accomplish this operation was embodied in the desymmetrization of the axially symmetric 1-methyl-4-methylenecyclohexane using an enantioselective process. Recently, the asymmetric ene reaction of methyl glyoxylate with methylenecyclohexane was reported to proceed with a high degree of enantioselectivity.[17] Applying those conditions to our case, 1-methyl-4-methylenecyclohexane (**10**) reacted with methyl glyoxylate to form an inseparable mixture of the two diastereomers **11a** and **12a** in a 68:32 ratio, respectively, in 72% yield (Scheme II). The enantioselectivity at the α-hydroxy position was high[18] despite the modest diastereoselection at the more challenging remote center.[19] Without separation, the mixture was carried through benzylation of the hydroxyl group (80%), hydrolysis, and iodolactonization to **13**, **14** (82% yield) followed by dehydroiodination with DABCO in DMSO (99%) to give **15a** and **16** as a chromatographically separable mixture.[20] To set the stage for the stereospecific side chain introduction, the lactone **15a** was reduced to lactol **15b** followed by Wittig methylenation to give **17** (75% yield for two steps, Scheme III). Heating **17** with the dimethyl acetal of dimethylacetamide produced, via the stereospecific [3,3] rearrangement, amide **18** in 92% yield. Hydroboration and oxidation then provided aldehyde **20**. While the intramolecular ene reaction of **20** with dimethylaluminum chloride produced the desired ene product **21** regioselectively and stereospecifically, it was accompanied by substantial amounts of simple methyl addition to the aldehyde. This is to be contrasted with our previous experience in a related system where the β-oxy substituent was protected as its *tert*-butyldimethylsilyl ether.[16] In that case methyl addition to the aldehyde was not observed. This difference may stem from the greater tendency of a benzyloxy group to participate in chelation processes than that of the corresponding silyloxy group, thereby rendering the carbonyl more susceptible to nucleophilic attack.[21] Although changing protecting groups would have eliminated this byproduct formation, an alternate solution presented itself in the observation that old bottles of dimethylaluminum chloride seemed to produce better results than new bottles. Indeed, attenuation of the chelating properties of the Lewis acid by addition of methanol (1:1) allows the ene reaction of **20** to proceed smoothly and reproducibly, generating **21** as a single isomer in 73% yield without formation of the methyl addition byproduct.

Scheme IV



The next series of operations were directed toward modifying the side chain in preparation for the lactone assembly phase of the synthesis. Silylation of **21** to **22** followed by the simultaneous benzyl group cleavage and amide reduction with lithium in liquid ammonia produced hydroxy aldehyde **23** (64% overall). The one-carbon extension was accomplished by methoxymethylenation of the aldehyde **23**, and the subsequent conversion under standard conditions (see the Experimental Section, **24** → **25** → **26** → **27**) gave the required acetoxy aldehyde **27** in good overall yield.

In our previous work, the chelative participation of the 8′-acetoxy group was found to be essential for good diastereoselectivity in the aldehyde addition step.[22] The

(15) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskoković, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596.

(16) For early developments of this strategy, see: Barrish, J. C.; Wovkulich, P. M.; Tang, P. C.; Batcho, A. D.; Uskoković, M. R. *Tetrahedron Lett.* **1990**, *31*, 2235.

(17) Mikami, K.; Terada, T.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

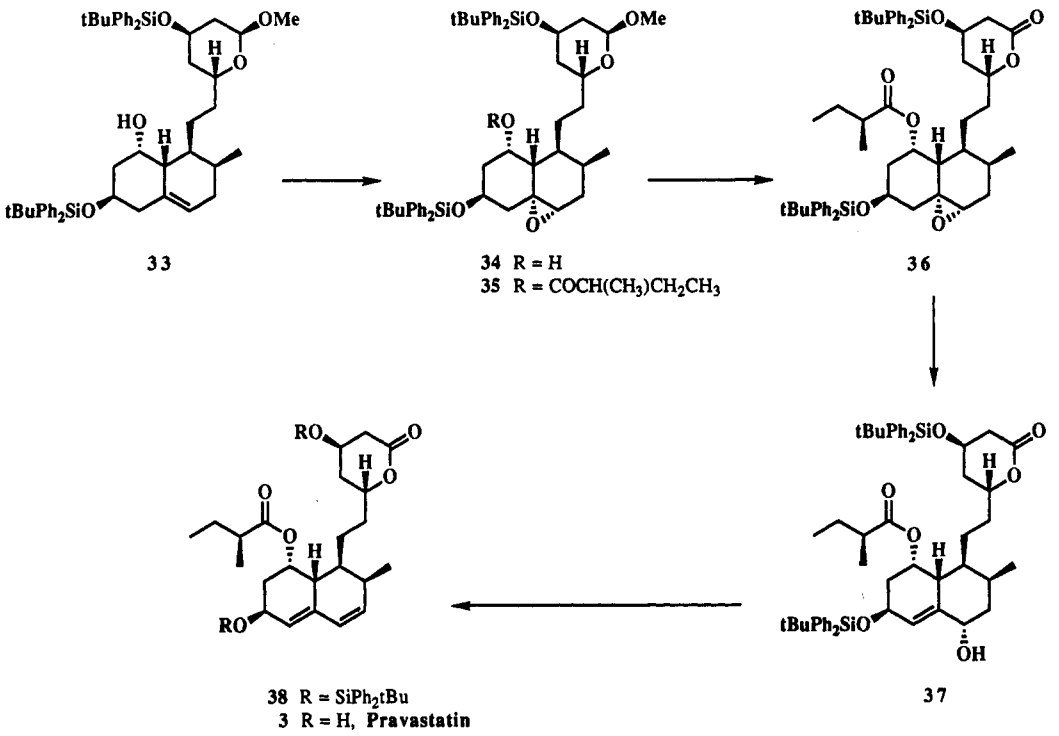
(18) The enantiomeric excess was assessed by nmr of **11a**, **12a** in the presence of Eu(hfc)$_3$, which, in the racemic material, shows two sets of methyl doublets (CHCH_3). The ee was conservatively estimated to be 97% ee.

(19) The axial symmetry of the system presents a particular challenge for desymmetrization operations, as evidenced by the generally low selection observed for the reaction of other 4-substituted cyclohexanone derivatives. Whether the present result reflects a low facial selectivity of the incoming eneophile or a low selectivity for proton abstraction is unknown at this point. The ene reaction of 8-phenylmenthyl glyoxylate with 1-*tert*-butyl-4-methylenecyclohexane also showed similar diastereoselectivity at the remote center. Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, J. C.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993.

(20) The relative configuration of the major isomer **15b** was confirmed by X-ray crystallographic analysis. In a separate experiment, bromolactonization provided the corresponding bromo lactones, from which the major isomer was isolated and the relative and absolute configuration determined by X-ray crystallographic analysis.

(21) The difference in chelation for benzyl vs silyl ethers has been observed spectroscopically. Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 182. Internal chelation by the benzyl ether would involve the metal complexed anti to the aldehyde proton, presumably a more reactive species than the with metal complexed syn to the aldehyde proton. For a recent discussion of chelation effects and carbonyl reactivity, see: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. An internally bis chelated ion complex with Et_2AlCl (in the form of $Et_2Al^+Et_2AlCl_2^-$) has been proposed as the reactive species in an intramolecular Diels–Alder reaction. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. Clearly, additional studies will be needed to fully delineate the interplay between the nucleophilic and chelative properties of the organoaluminum species in this reaction.

Scheme V



present case is similar with the potentially important difference of having an additional coordination site in **27** (i.e. the 6′-acetoxy group). Nevertheless, the reaction of **27** with diene **28** catalyzed with $TiCl_4$ performed admirably to produce, after acidic workup, the desired enone **29** accompanied by its diastereomer (not shown) in a 92:8 ratio (62% yield) (Scheme IV).[23] Without separation, this mixture was allowed to undergo the 1,4 addition of methanol in the presence of triethylamine and gave, after purification, acetal **30** in 66% yield. Stereoselective reduction with lithium tri-*sec*-butylborohydride gave alcohol **31** (86% yield), which after removal of the acetate groups and regioselective disilylation provided alcohol **33**.

Full elaboration of the lactone portion and the introduction of the diene system were the final matters to address. The stereospecific hydroxyl-assisted epoxidation of alcohol **33** provided, as required for the diene formation, epoxide **34**, which was esterified directly with (*S*)-2-methylbutyric anhydride to give **35** in excellent overall yield (Scheme V). Hydrolysis and concomitant oxidation of the acetal of **35**, accomplished in one operation with chromium trioxide in methylene chloride/aqueous acetic acid, afforded lactone **36**. The epoxide to diene transformation was effected smoothly by the two-stage protocol involving elimination of the epoxide to the allylic alcohol **37** with trimethylsilyl triflate followed by dehydration with Burgess' reagent to give the silylated pravastatin derivative **38**.[24] Final desilylation of this acid sensitive diene ether with buffered tetrabutylammonium fluoride produced pravastatin **3**, identical in all respects to authentic material.

In conclusion, this first total synthesis of pravastatin illustrates the utility of a linear asymmetric strategy for the preparation of members of the mevinic acid family and establishes a secure framework for future ventures.

Experimental Section

General Procedure. Unless otherwise noted all reactions were run under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone; dichloromethane was stored over 4-Å molecular sieves. Chromatography was performed on 230–400-mesh silica gel. The TLC silica gel used in some filtrations refers to EM silica gel 60 GF_{254}. Final reaction mixtures were dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure. Rotations were carried out at 25 °C. NMR spectra were obtained in $CDCl_3$ at 400 MHz for ^1H and 50 MHz for ^{13}C; significant chemical shifts are reported in ppm (δ units) downfield from TMS, and J values are given in hertz.

(*R*)-α-Hydroxy-4-methyl-1-cyclohexene-1-propanoic Acid, Methyl Ester (11a). To a solution of 5.00 g (0.01746 mol) of (*S*)-(+)-1,1-bi-2-naphthol in 500 mL of CH_2Cl_2 was added 85 g of 4-Å molecular sieves, followed by 5.62 g (0.01725 mol) of $(i\text{-PrO})_2TiBr_2$ in 25 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1.5 h and then cooled to −70 °C, and 38.46 g (0.3496 mol) of 1-methyl-4-methylenecyclohexane followed by 15.40 g (0.175 mol) of freshly distilled methyl glyoxylate was added. This mixture was kept in a freezer (−23 °C) for 48 h and then filtered, rinsing with hexane/ethyl acetate (EtOAc) (4:1). The filtrate was passed through silica gel, eluting with hexane/EtOAc (4:1), concentrated under reduced pressure, and distilled (bp 77 °C, 0.05 mmHg) to give 25.0 g (72%) of the 68:32 **11a**, **12a** mixture: $[\alpha]^{25}_D = -41.2°$ (c = 2.0, EtOH); ^1H NMR δ 0.96 (d, J = 6.3 Hz, 3 H), 3.77 (s, 3 H), 4.26–4.33 (m, 1 H), 5.50 (s, 1 H); IR 3540, 1735 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.31; H, 9.21. An estimate of the diastereomeric ratio (68:32) could be made by irradiation of the multiplet at 4.3 ppm and observation of one of the allylic protons. The major diastereomer **11a** appeared at 2.31 (d, J = 14.2 Hz), minor at 2.29 (d, J = 14.2 Hz).

(*R*)-α-(Phenylmethoxy)-4-methyl-1-cyclohexene-1-propanoic Acid, Methyl Ester (11b). To a mixture of 45.0 g (0.227 mol) of **11a**, **12a**, 75.0 g (0.297 mol) of benzyl 2,2,2-tri-

(22) See ref 15. In unpublished results from that work, participation of the acetoxy group in the diastereoselective addition to the aldehyde was demonstrated by the near complete loss of diastereoselection when ether solvents replaced methylene chloride (with either $TiCl_4$ or $MgBr_2$), when a Lewis acid incapable of the bidentate chelation (BF_3·Et_2O) was used or when the acetate was replaced with the corresponding *tert*-butyldimethylsilyl ether.

(23) One noticeable difference between this case and the previous work is the appearance of a precipitate when the aldehyde **25** is added to $TiCl_4$, and which disappears after the diene **26** addition.

(24) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, 38,26. Burgess, E. M.; Penton, H. R.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1977**, *56*, 40. Unlike the lovastatin case (see ref 15) where formation of the isomeric diene necessitated the use of 2,6-lutidine as solvent, very little of the isomeric diene was formed from **37**.

chloroacetimidate, and 400 mL of cyclohexane at 0 °C was added a solution of 0.3 mL of CF_3SO_3H in 10 mL of CH_2Cl_2. The mixture was left overnight at room temperature and then filtered, washing with pentane to remove the precipitate (CCl_3CONH_2). The filtrate was then passed through TLC silica gel (5 cm), eluting with hexane/EtOAc (10:1). Distillation (bp 133 °C at 0.05 mmHg) gave 52.0 g (79%) of the **11b, 12b** mixture. An analytical sample was obtained by chromatography, eluting with hexane/EtOAc (95:5). **11b, 12b**: $[\alpha]^{25}_D$ = +25.86° (*c* = 1.1, EtOH); ^{1}H NMR δ 0.93 (d, *J* = 6.2 Hz, 3 H), 3.72 (s, 3 H), 4.03–4.08 (m, 1 H), 4.41 (d, *J* = 11.9 Hz, 1 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 5.46 (s, 1 H), 7.3–7.35 (m, 5 H); IR 1742 cm^{-1}.

(*R*)-6-Iodo-8-methyl-3-(phenylmethoxy)-1-oxaspiro[4.5]-decan-2-one (13, 14). To a solution of 53.0 g (0.184 mol) of the **11b, 12b** mixture in 300 mL of methanol at room temperature was added a solution of 11.0 g (0.196 mol) of KOH in 30 mL of H_2O. After all of the ester was transformed into the salt, most of the methanol was removed under reduced pressure, and the mixture was diluted with 300 mL of H_2O and then extracted with hexane/EtOAc (1:1). The aqueous phase was transferred to a three-neck flask where, with vigorous stirring, a mixture of 45.6 g (0.1796 mol) of I_2 dissolved in aqueous KI (35.0g, 0.211 mol) was added. After addition of half of the iodine solution, 100 mL of hexane/EtOAc (2:1) was added, and the iodine addition continued. The mixture was stirred for an additional hour at room temperature, treated with aqueous $NaHSO_3$, and extracted with hexane/EtOAc (2:1). The extract was filtered through TLC silica gel (5 cm) to give 60 g (82%) of crude crystalline iodo lactones. An analytical sample was obtained by chromatography eluting with hexane/EtOAc (90:10). Iodo lacetones **13, 14**: mp 85–87 °C (hexane); ^{1}H NMR **13** 0.98 (d, *J* = 6.2 Hz, 3 H), 4.33–4.40 (m, 1 H), 4.69, (d, *J* = 11.8 Hz, 1 H), 4.92 (d, *J* = 11.8 Hz, 1 H), 7.28–7.43 (m, 5 H); **14** 0.96 (d, *J* = 6.1 Hz, 3 H), 4.45–4.51 (m, 1 H), 4.75 (d, *J* = 11.8 Hz, 1 H), 4.95 (d, *J* = 11.8 Hz, 1 H), 7.28–7.43 (m, 5 H); IR 1772 cm^{-1}. Anal. Calcd for $C_{17}H_{21}IO_3$; C, 51.01; H, 5.29; I, 31.70. Found: C, 51.09; H, 5.21; I, 32.00.

[3*R*-[3α,5α(*S)]]-8-Methyl-3-(phenylmethoxy)-1-oxaspiro[4.5]dec-6-en-2-one (15a).** A mixture of 50.0 g (0.1249 mol) of iodo lactones **13, 14**, 50.0 g (0.446 mol) of 1,4-diazabicyclo-[2.2.2]octane, and 200 mL of dimethyl sulfoxide (DMSO) was stirred at 132–140 °C for 15 min. The cooled mixture was poured into 500 mL of H_2O and extracted with hexane/EtOAc (2:1). After removal of solvent under reduced pressure, the residue ws dissolved in 200 mL of hexane/EtOAc (10:1) and filtered through TLC silica gel (5 cm), washing with hexane/EtOAc (4:1). Removal of solvent under reduced pressure gave 33.9 g (99%) of the crystalline mixture of lactones **15a** and **16**. Chromatographic separation, eluting with hexane/EtOAc (93:7), gave 23.0 g (67%) of **15a** [mp 67–68 °C (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = +84.38° (*c* = 0.98, EtOH); ^{1}H NMR δ 1.03 (d, *J* = 7.1 Hz, 3 H), 2.08–2.28 (m, 2 H), 2.39 (dd, *J* = 8.1, 13.3 Hz, 1 H), 4.32 (t, *J* = 8.1 Hz, 1 H), 4.73 (d, *J* = 11.8 Hz, 1 H), 4.99 (d, *J* = 11.8 Hz, 1 H), 5.48 (dm, *J* = 9.8 Hz, 1 H), 5.81 (dm, *J* = 9.8 Hz, 1 H), 7.28–7.40 (m, 5 H); ^{13}C NMR (C) 174.5, 137.2, 80.6; (CH) 139.7, 128.5 (2), 128.2 (2), 126.4, 73.7, 30.3; (CH_2) 72.3, 41.4, 35.6, 27.5; (CH_3) 20.7; IR 1775, 1645 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40; Found: C, 74.88; H, 7.29] and 10.9 g (32%) of **16**: mp 86–87.5 °C (hexane/EtOAc, 98:2); $[\alpha]^{25}_D$ = +26.51° (*c* = 1.14, EtOH); ^{1}H NMR δ 1.03 (d, *J* = 7.1 Hz, 3 H), 2.17 (dd, *J* = 7.4, 13.4 Hz, 1 H), 2.34 (dd, *J* = 8.0, 13.4 Hz, 1 H), 4.29 (t, *J* = 7.8 Hz, 1 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 4.98 (d, *J* = 11.7 Hz, 1 H), 5.65 (dm, *J* = 9.9 Hz, 1 H), 5.83 (dd, *J* = 2.4, 9.9 Hz, 1 H), 7.28–7.40 (m, 5 H); ^{13}C NMR (C) 174.4, 137.2, 80.8; (CH) 139.6, 128.5 (2), 128.1 (3), 127.8, 74.0, 30.0; (CH_2) 72.4, 41.6, 43.3, 27.4; (CH_3) 20.6; IR 1770, 1648 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.50.

Conversion of Lactone 15a to Olefin 17. To a solution of 28.62 g (0.105 mol) of lactone **15a** in 450 mL of CH_2Cl_2 at −40 °C was added 130 mL of diisobutylaluminum hydride solution (1 M in CH_2Cl_2). The mixture was allowed to warm to 0 °C and stirred at that temperature until the reduction to the lactol **15b** was complete. The mixture was cooled to −20 °C and quenched by the addition of 30 mL of H_2O. After the mixture was stirred at room temperature for 2 h, the solid was removed by filtration, washing with EtOAc. Concentration under reduced pressure afforded 28.8 g of lactol **15b**, which was used directly in the next step. To a slurry of 56.0 g (0.158 mol) of methyltriphenylphosphonium bromide and 400 mL of tetrahydrofuran (THF) at 10 °C was added a solution of 17.0 g (0.1515 mol) of potassium *tert*-butoxide in 60 mL of THF. After being stirred for 1 h at room temperature, the mixture was recooled to 10 °C, and 28.0 g (0.1022 mol) of the lactol **15b** from above in 60 mL of THF was added. The mixture was stirred at room temperature for 1 h, the excess ylide quenched by the addition of isobutanal, and the mixture concentrated to ca. 30% of its volume under reduced pressure. The residue was treated with 500 mL of hexane and filtered, washing with hexane and concentrated under reduced pressure. Chromatography of the residue, eluting with hexane/EtOAc (10:1), gave 21.0 g of olefin **17** (75%). **17**: $[\alpha]^{25}_D$ = +28.62° (*c* = 0.89, EtOH); ^{1}H NMR δ 1.00 (d, *J* = 7.1 Hz, 3 H), 2.01 (dd, *J* = 8.7 Hz, 1 H), 2.03 (m, 1 H), 4.19–4.25 (m, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 4.62 (d, *J* = 11.4 Hz, 1 H), 5.25 (d, *J* = 10.2 Hz, 1 H), 5.26 (d, *J* = 17.6 Hz, 1 H) 5.51 (dt, *J* = 10.1, 1.9 Hz, 1 H), 5.58 (dm, *J* = 10.1 Hz, 1 H), 5.77 (ddd, *J* = 7.8, 10.2, 17.6 Hz, 1 H) 7.2–7.38 (m, 5 H); IR 3475 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.36; H, 8.88. Found: C, 79.23; H, 8.83.

[1*S*-[1α,3(*S),6α]]-3-[2-(Phenylmethoxy)-3-butenyl]-*N*,-*N*,6-trimethyl-2-cyclohexene-1-acetamide (18).** A mixture of 20.0 g (0.0735 mol) of **17** and 40.95 g (0.307 mol) of freshly distilled *N*,*N*-dimethylacetamide dimethyl acetal was heated (130 °C oil bath) for 48 h, during which time the generated methanol was allowed to distill out. The cooled mixture was diluted with 250 mL of hexane/EtOAc (2:1) and was washed with brine. Chromatographic purification, eluting with hexane/EtOAc (1:1), gave 23.0 g of amide **18** (92%) accompanied by 1.0 g (5%) of starting material **17**. **18**: $[\alpha]^{25}_D$ = −68.55° (*c* = 1.02, EtOH); ^{1}H NMR δ 0.85 (d, *J* = 7.0 Hz, 3 H), 2.94 (s, 3 H), 2.96 (s, 3 H), 3.87 (q, *J* = 6.1 Hz, 1 H), 4.34 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 5.19 (d, *J* = 16.7 Hz, 1 H) 5.20 (d, *J* = 10.8 Hz, 1 H), 5.33 (s, 1 H), 5.72 (m, 1 H), 7.23–7.36 (m, 5 H); IR 1730, 1631 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.1. Found: C, 77.11; H, 9.09; N, 3.91.

[1*S*-[1α,3(*S),6α]]-3-[4-Hydroxy-2-(phenylmethoxy)butyl]-*N*,*N*,6-trimethyl-2-cyclohexene-1-acetamide (19).** A solution of disiamylborane (freshly prepared from 27.0 g (0.385 mol) of 2-methyl-2-butene), 300 mL of THF, and 92 mL (0.184 mol) of BH_3·SMe_2 (2M in THF) was added over a period of 1 h to a room temperature solution of 23.0 g (0.06735 mol) of **18** in 100 mL of THF. After 30 min, 25 mL of H_2O was added, and volatiles were removed under reduced pressure. The residue was diluted with 250 mL of methanol (MeOH) and cooled with a cold water bath; 30 mL of 30% H_2O_2 was added slowly, after which the MeOH was removed under reduced pressure. The residue was taken up in 200 mL of hexane/EtOAc (1:1) and washed with 1 N NaOH. Chromatography, eluting with hexane/EtOAc/MeOH (10:10:1), gave 18.0 g (74%) of alcohol **19**: $[\alpha]^{25}_D$ = −98.29° (*c* = 0.93, EtOH); ^{1}H NMR δ 0.86 (d, *J* = 7.0 Hz, 3 H), 2.95 (s, 3 H), 2.98 (s, 3 H), 3.67–3.82 (m, 3 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.64 (d, *J* = 11.4 Hz, 1 H), 5.39 (s, 1 H), 7.27–7.40 (m, 5 H); IR 3620, 1632 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.89. Found: C, 73.43; H, 9.43; N, 3.86.

[1*S*-[1α,2α,6α,8β,8aα]]-1,2,3,5,6,7,8,8a-Octahydro-8-hydroxy-*N*,*N*,2-trimethyl-6-(phenylmethoxy)-1-naphthaleneacetamide (21). To a solution of 20 mL (0.229 mol) of oxalyl chloride in 400 mL of CH_2Cl_2 at −60 °C was added slowly 43 mL (0.606 mol) of DMSO in 100 mL of CH_2cl_2. After 15 min 17.5 g (0.0487 mol) of alcohol **19** in 50 mL of CH_2Cl_2 was added. The mixture was allowed to warm to −30 °C. After 3 min the mixture was recooled to −60 °C and 140 mL of triethylamine (Et_3N) was added. The mixture allowed to warm to 0 °C, 200 mL of H_2O was added, the CH_2Cl_2 layer was separated and concentrated under reduced pressure, and the residue was dissolved in 200 mL of hexane/EtOAc (1:1) and washed with brine. Chromatography, eluting with hexane/EtOAc/acetone (20:40:1), gave 14.7 g (84%) of aldehyde **20**: ^{1}H NMR δ 0.84 (d, *J* = 7.0 Hz, 3 H), 2.94 (s, 3 H), 2.97 (s, 3 H), 4.07 (m, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 5.38 (s, 1 H), 7.27–7.40 (m, 5 H), 9.76 (t, *J* = 2.0 Hz, 1 H).

Methanol (3.2 g, 0.1 mol) in 100 mL of CH_2Cl_2 was added slowly to a solution of 100 mL of dimethylaluminum chloride solution (1 M in hexane) at −20 °C. The mixture was stirred at room temperature for 1 h, cooled to −40 °C, and added to a solution

of 14.0 g (0.0392 mol) of aldehyde **20** in 200 mL of methylene chloride (200 mL) at −40 °C. The mixture was allowed to warm to room temperature. After 0.5 h the mixture was quenched by addition of saturated $KHCO_3$, stirred at room temperature for 1 h, and then filtered. Crystallization of the crude product from acetone gave 10.2 g (73%) of ene product **21**. An additional 1.3 g (9%) was obtained by chromatography of the mother liquor: mp 116–117 °C; $[\alpha]^{25}_D$ = +27.72° (*c* = 1.0, EtOH); ^{1}H NMR δ 0.87 (d, *J* = 7.0 Hz, 3 H), 2.98 (s, 3 H), 3.03 (s, 3 H), 3.76–3.87 (m, 2 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 11.7 Hz, 1 H), 5.53 (bs, 1 H), 7.23–7.37 (m, 5 H); IR 3385, 1625 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.81; H, 8.77; N, 3.80.

[1*S*-[1α,2α,6α,8β,8aα]]-1,2,3,5,6,7,8,8a-Octahydro-*N*,*N*,2-trimethyl-6-(phenylmethoxy)-8-[(trimethylsilyl)oxy]-1-naphthaleneacetamide (22). A mixture of 9.0 g (0.0252 mol) of ene product **21** and 9.0 mL (0.0613 mol) of (trimethylsilyl)-imidazole in 100 mL of THF was stirred at room temperature for 2 h and then quenched by the addition of 50 mL of H_2O. The mixture was extracted with hexane/EtOAc (1:1), and the residue was filtered through TLC silica gel (4 cm), washing with hexaneEtOAc (2:1), to give 10.75 g (99.4%) of silyl ether **22**: $[\alpha]^{25}_D$ = +54.27° (*c* = 1.01, EtOH); ^{1}H NMR δ 0.09 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 2.69 (dm, *J* = 12.4 Hz, 1 H), 2.95 (s, 3 H), 2.99 (s, 3 H), 3.68 (m, 1 H), 4.25 (nm, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 5.60 (bs, 1 H), 7.22–7.38 (m, 5 H); IR 1629 cm^{-1}; MS *m*/*e* 430 [M$^+$ + 1].

[1*S*-[1α,2α,6α,8β,8aα]]-1,2,3,5,6,7,8,8a-Octahydro-2-methyl-6-hydroxy-8-[(trimethylsilyl)oxy]-1-naphthaleneacetamide (23). To a refluxing solution of 2.0 g (0.004 65 mol) silyl ether **22** in 100 mL of THF and 100 mL of liquid NH_3 was added 0.15 g (0.0216 mol) of lithium. After 1 h the dark blue mixture was quenched by the addition of saturated aqueous NH_4Cl, the mixture was concentrated, and the residue was chromatographed, eluting with hexane/EtOAc (2:1) to give 0.890 g (64%) of aldehyde **23**: ^{1}H NMR δ 0.11 (s, 9 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 3.80–4.05 (m, 1 H), 4.13 (bs, 1 H), 5.56 (bs, 1 H), 9.79 (s, 1 H); IR 3605, 1720 cm^{-1}; MS *m*/*e* 222 [M$^+$ − $SiMe_3$ − H], 206 [M$^+$ − $HOSiMe_3$].

[1*S*-[1α,2α,6α,8β,8aα]]-1,2,3,5,6,7,8,8a-Octahydro-2-methyl-6-hydroxy-8-[(trimethylsilyl)oxy]-1-naphthalenepropionaldehyde (27). To a slurry of 17.6 g (0.051 34 mol) of (methoxymethyl)triphenylphosphonium chloride and 250 mL of THF at room temperature was added a solution of 4.8 g (0.4277 mol) of potassium *tert*-butoxide in 100 mL of THF. The mixture was stirred for 1 h, and then 4.2g (0.014 19 mol) of aldehyde **23** in 25 mL of THF was added. After 15 min the mixture was quenched by the addition of 10 mL of H_2O, concentrated under reduced pressure, and chromatographed (hexane/EtOAc, 4:1) to give 4.12 g (86%) of olefin **24** as a 55:45 *E*/*Z* mixture: ^{1}H NMR major 0.09 (s, 9 H), 0.79 (d, *J* = 6.6 Hz, 1 H), 2.53 (dm, *J* = 12.9 Hz, 1 H), 3.51 (s, 3 H), 3.83–4.07 (m, 1 H), 4.07–4.18 (m, 1 H), 4.65 (dt, *J* = 12.9, 7.8 Hz, 1 H), 5.51 (bs, 1 H), 6.25 (d, *J* = 12.9 Hz, 1 H); minor 0.10 (s, 9 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 2.53 (dm, *J* = 12.9 Hz, 1 H), 3.56 (s, 3 H), 3.83–4.07 (m, 1 H), 4.07–4.18 (m, 1 H), 4.29 (dt, *J* = 5.2, 6.5 Hz, 1 H), 5.51 (bs, 1 H), 5.91 (d, *J* = 5.2 Hz, 1 H). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.61; H, 9.94. Found: C, 66.50; H, 10.09.

A solution of 4.0 g (0.0123 mol) of **24** in 50 mL of THF and 15 mL of a tetrabutylammonium fluoride (1 M in THF) was stirred at room temperature for 3 h, after which time the mixture was concentrated under reduced pressure, taken up in 100 mL of hexane/EtOAc (1:1), and washed with brine. The crude diol **25** was dissolved in 50 mL of pyridine and treated with 10 mL of acetic anhydride and 0.05 g of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). The mixture was stirred overnight at room temperature, quenched by the addition of 5 mL of H_2O, and concentrated under reduced pressure. The residue was taken up in hexane/EtOAc (1:1) and washed with aqueous $KHCO_3$. A 4.1-g (99%) yield of the crude diacetate **26** was obtained: ^{1}H NMR major olefin: 0.79 (d, *J* = 6.9 Hz, 3 H), 2.01 (s, 3 H), 2.02 (s, 3 H), 2.64 (dm, *J* = 11.4 Hz, 1 H), 3.49 (s, 3 H), 4.59 (dt, *J* = 11.8, 7.6 Hz, 1 H), 4.80–4.98 (m, 1 H), 5.33 (nm, 1 H), 5.56 (bs, 1 H), 6.25 (d, *J* = 11.8 Hz, 1 H), and minor olefin 0.81 (d, *J* = 6.9 Hz, 3 H), 2.01 (s, 3 H), 2.03 (s, 3 H), 2.64 (dm, *J* = 11.4 Hz, 1 H), 3.55 (s, 3 H), 4.24 (dt, *J* = 6.9, 7.5 Hz, 1 H), 4.80–4.98 (m, 1 H), 5.33 (nm, 1 H), 5.56 (bs, 1 H), 5.89 (d, *J* = 6.9 Hz, 1 H).

A solution of 2.7 g (8.036 mmol) of enol ether **26** in 50 mL of acetone was heated at 56 °C for 2 h with 0.250 g of *p*-toluenesulfonic acid in 4 mL of H_2O. The cooled mixture was neutralized with aqueous $KHCO_3$, concentrated under reduced pressure, and chromatographed, eluting with hexane/EtOAc (2:1), to give 2.26 g (87%) of aldehyde **27**: $[\alpha]^{25}_D$ = +73.6° (*c* = 1.82, EtOH); ^{1}H NMR δ 0.80 (d, *J* = 6.9 Hz, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.67 (dm, *J* = 12.8 Hz, 1 H), 4.92 (m, 1 H), 5.39 (bs, 1 H), 5.57 (bs, 1 H), 9.74 (t, *J* = 1.6 Hz, 1 H); IR 2725, 1725 cm^{-1}; HRMS calcd 323.1859, found 323.1869.

Diastereoselective Condensation of Aldehyde 27 with Diene 28 To Form Enone 29. To a solution of 2.2672 g (0.0071 mol) of **27** in 61 mL of dry CH_2Cl_2 at −78 °C was added 8.10 mL of $TiCl_4$ solution (1 M in CH_2Cl_2) over 6 min. After 3 min the reaction vessel was set in a bath at −40 °C (a precipitate formed) and stirred for 6 min, after which 2.3049 g (0.013 38 mol) of diene **28** in 24 mL of dry CH_2Cl_2 was added over 26 min. After being stirred an additional 30 min, the mixture was taken up in EtOAc and washed successively three times with saturated $NaHCO_3$ and once with brine and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was stirred for 1 h with 40 mL of a 1.4 M solution of trifluoroacetic acid solution in THF. The mixture was neutralized by addition of solid $NaHCO_3$, taken up in EtOAc and washed successively with 2 X saturated $NaHCO_3$ and 1 X brine and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was chromatographed on silica gel to give 1.6984 g (62%) of enone **29** as a 92:8 mixture of diastereomers by ^{13}C NMR: ^{1}H NMR δ 0.76 (d, *J* = 6.0 Hz, 3 H), 1.98 (s, 3 H), 1.99 (s, 3 H), 2.60 (ddd, *J* = 2.9, 4.5, 12.6 Hz, 1 H), 4.32 (m, 1 H), 4.87 (dddd, *J* = 4.9, 4.9, 11.7, 11.7 Hz, 1 H), 5.34 (d, *J* = 6.0 Hz, 1 H), 5.34 (m, 1 H), 5.53 (m, 1 H), 7.30 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (resonances for the minor isomer are in parentheses) (C) 192.4, 170.4, 170.3, 130.8; (CH) 163.1, 123.9, 106.9, (79.6), 79.2, 70.4, 69.1, 42.6, 37.4, 27.1; (CH_2) 41.9 (41.7), 40.1, 36.1, 32.0, 31.9, 24.4; (CH_3) 21.2, 21.1, 13.2.

Methanol Adduct 30. A solution of 2.7633 g (0.007 08 mol) of enone **29** and 1.6 mL of Et_3N in 35 mL of MeOH was stirred at room temperature for 20 h, 50 mL of toluene was added, and volatiles were removed under reduced pressure. The residue was filtered through TLC silica gel (3 cm) washing with hexane/EtOAc (2:1). Chromatography, eluting with hexane/EtOAc (3:2), gave 1.8 g (66%) of ketone **30** accompanied by 0.35 g (13%) of starting material **29**. **30**: $[\alpha]^{23}_D$ = +92.5° (*c* = 1.2, $CHCl_3$); ^{1}H NMR δ 0.83 (d, *J* = 6.9 Hz, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 3.35 (s, 3 H), 3.92–4.2 (m, 1 H), 4.93 (dddd, *J* = 4.7, 4.7, 11.5, 11.5 Hz, 1 H), 5.10 (d, *J* = 4.3 Hz, 1 H), 5.37 (s, 1 H), 5.59 (s, 1 H); ^{13}C NMR (C) 204.7, 170.5, 170.3, 131.0; (CH) 124.1, 99.4, 70.8, 69.2, 68.9, 42.9, 38.4, 27.5; (CH_2) 47.5, 46.4, 40.3, 36.2, 33.9, 32.0, 25.2; (CH_3) 54.8, 21.3, 21.2, 13.7; IR 1730 cm^{-1}; HRMS [M$^+$ + 1] calcd 423.2383, found 423.2350.

Alcohol 31. Ketone **30** (1.85 g, 0.004 38 mol) in 10 mL of THF was added slowly to a solution of 5.68 mL of lithium tri-*sec*-butylborohydride (1 M in THF) and 50 mL of THF at −78 °C. After the mixture was stirred for 30 min, the reaction was quenched by the addition of 40 mL of H_2O, followed by the addition of 5 mL of 30% of H_2O_2. The mixture was allowed to warm to room temperature, at which time 100 mL of EtOAc was added and the mixture was washed with brine. Chromatography of the product, eluting with hexane/EtOAc (1:1), gave 1.6 g (86%) of alcohol **31**: $[\alpha]^{25}_D$ = +95.7° (*c* = 1.28, $CHCl_3$); ^{1}H NMR δ 0.82 (d, *J* = 6.8 Hz, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.27 (dm, *J* = 13.5 Hz, 1 H), 2.66 (dm, *J* = 12.6 Hz, 1 H), 3.37 (s, 3 H), 3.88–3.97 (m, 1 H), 4.04 (bs, 1 H), 4.84 (d, *J* = 3.3 Hz, 1 H), 4.92 (dddd, *J* = 4.7, 4.7, 11.5, 11.5 Hz, 1 H), 5.36 (bs, 1 H), 5.58 (bs, 1 H); IR 1732 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_7$: C, 65.07; H, 8.55. Found: C, 64.89; H, 8.45.

Disilyl Ether 33. A mixture of 0.4 g (0.94 mmol) of **31** and 0.030 g (0.005 36 mol) of KOH in in 10 mL of methanol was heated (60 °C) for 2 h, cooled, treated with dry ice, and concentrated. The residue was taken up in EtOAc and filtered through TLC silica gel. After filtration and concentration under reduced pressure the crude triol **32** was dissolved in 4.0 mL of dimethylformamide (DMF) and reacted with 0.5 g (0.007 35 mol) of imidazole and 1.25 g (0.004 55 mol) of *tert*-butylchlorodiphenylsilane. After being heated at 80 °C for 3 h the cooled

mixture was stirred with 0.5 mL of H_2O for 15 min. After extractive workup the crude product was chromatographed, eluting with hexane/EtOAc (10:1), to give 0.76 g (99%) of silyl ether **33**: $[\alpha]^{25}_D$ = +32.6° (*c* = 1.15, $CHCl_3$); ^1H NMR δ 0.75 (d, *J* = 6.8 Hz, 3 H), 1.05 (s, 18 H), 3.34 (s, 3 H), 3.92–4.03 (m, 2 H), 4.03–4.17 (m, 2 H), 4.63 (bs, 1 H), 5.38 (bs, 1 H), 7.30–7.45 (m, 12 H), 7.60–7.73 (m, 8 H). Anal. Calcd for $C_{51}H_{68}O_5Si_2$: C, 74.95; H, 8.39. Found: C, 74.87; H, 8.47.

Epoxide 34. To a solution of 1.30 g (0.001 59 mol) of **33** and 0.087 g (0.328 mmol) of $VO(acac)_2$ in 40 mL of CH_2Cl_2 at −10 °C was added 1.3 mL of 3 M *tert*-butyl hydroperoxide solution. The mixture was stirred at 0 °C for 3 h and then left overnight in a freezer at −20 °C. The mixture was filtered through TLC silica gel, washing with hexane/EtOAc (4:1), and concentrated under reduced pressure to give 1.30 g of the crude epoxide **34**, which was used directly in the next step. An analytical sample of **34** was obtained by chromatography, eluting with hexane/EtOAc (4:1): $[\alpha]^{25}_D$ = +34.08° (*c* = 1.015, $CHCl_3$); ^1H NMR δ 0.76 (d, *J* = 6.9 Hz, 3 H), 1.05 (s, 18 H), 2.71 (d, *J* = 5.2 Hz, 1 H), 4.02–4.20 (m, 3 H), 4.30–4.40 (m, 1 H), 4.63 (bs, 1 H), 7.3–7.5 (m, 12), 7.6–7.8 (m, 8 H); IR 3560 cm^{-1}; MS *m/e* 833 [M^+ + 1].

Epoxy Ester 35. A mixture of 1.30 g (0.001 56 mol) of the crude epoxide **34** from above, 5 mL of pyridine, 0.08 g of DMAP, and 1.3 mL of (*S*)-(+)-2-methylbutyric anhydride[25] was stirred at room temperature for 2 days and then quenched by the addition of 1 mL of H_2O. After being stirred for 15 min the mixture was diluted with 25 mL of hexane/EtOAc (4:1) and washed with saturated $KHCO_3$. Chromatography of the crude product, eluting with hexane/EtOAc (5:1), gave 1.30 g (89%) of the butyrate ester **35** along with 0.074 g (5.7%) of the starting alcohol **34**. **35**: $[\alpha]^{25}_D$ = +55.3° (*c* = 1.13, $CHCl_3$); ^1H NMR δ 0.73 (t, *J* = 7.5 Hz, 3 H), 0.76 (d, *J* = 6.1 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 1.02 (s, 9 H), 1.04 (s, 9 H), 2.69 (d, *J* = 5.1 Hz, 1 H), 3.32 (s, 3 H), 4.0–4.07 (m, 2 H), 4.13–4.23 (m, 1 H), 4.60 (bs, 1 H), 5.26 (bs, 1 H), 7.30–7.43 (m, 12 H), 7.58–7.65 (m, 6 H), 7.65–7.72 (m, 2 H); IR 1720 cm^{-1}. Anal. Calcd for $C_{56}H_{76}O_7Si_2$: C, 73.32; H, 8.35. Found: C, 73.29; H, 8.41.

Oxidation of Epoxy Ester 35 to Lactone 36. To a stirred solution of 0.100 g (0.109 mmol) of acetal **35** in 4.0 mL of CH_2Cl_2 was added a solution of 0.9 mL of acetic acid, 0.088 g (0.88 mmol) of CrO_3, and 0.15 mL of H_2O. After 2 h the mixture was filtered through TLC silica gel, washing with hexane/EtOAc (4:1). Chromatography of the product, eluting with hexane/EtOAc (4:1), gave 0.066 g (67%) of the lactone **36**: $[\alpha]^{25}_D$ = +31.8° (*c* = 0.9, $CHCl_3$); ^1H NMR δ 0.74 (t, *J* = 7.4 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 1.03 (s, 9 H), 1.05 (s, 9 H), 2.41 (dd, *J* = 4.6, 17.6 Hz, 1 H), 2.56 (dm, *J* = 17.6 Hz, 1 H), 2.69 (d, *J* = 5.1 Hz, 1 H), 4.17–4.27 (m, 2 H), 4.60–4.70 (m, 1), 5.30 (bs, 1 H), 7.31–7.50 (m, 12 H), 7.58–7.70 (m, 8 H); IR 1722 cm^{-1}. Anal. Calcd for $C_{55}H_{72}O_7Si_2$: C, 73.29; H, 8.05. Found: C, 73.10; H, 7.97.

Lactone 36 to Allylic Alcohol 37. To a solution of 1.5 mL of 2,6-lutidine, 0.60 mL of trimethylsilyl trifluoromethanesulfonate, and 10 mL of CH_2Cl_2 at −60 °C was added 0.260 g (0.288 mmol) of epoxide **36** in CH_2Cl_2. The mixture was allowed to warm to 10 °C over 2 h, after which time it was filtered through TLC silica gel, washing with hexane/EtOAc (4:1). The crude product was dissolved in 5 mL of THF and reacted with a solution of 2.0 mL of acetic acid and 0.30 mL of 1 M tetrabutylammonium fluoride in THF. After 30 min the mixture was diluted with 50 mL of hexane/EtOAc (2:1) and washed with 3 × 15 mL of H_2O. The product was chromatographed, eluting with hexane/EtOAc (2:1), to give 0.181 g (72%) of alcohol **37**: $[\alpha]^{25}_D$ = +25.2° (*c* = 1.49, $CHCl_3$); ^1H NMR δ 0.70 (t, *J* = 7.5 Hz, 3 H), 0.84 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 7.2 Hz, 3 H), 1.04 (s, 9 H), 1.06 (s, 9 H), 2.39 (dd, *J* = 4.7, 17.6 Hz, 1 H), 2.55 (dm, *J* = 17.6 Hz, 1 H), 4.14–4.26 (m, 2 H), 4.34–4.41 (m, 1 H), 4.60–4.68 (m, 1 H), 7.32–7.47 (m, 12 H), 7.56–7.74 (m, 8 H); IR 1722, 3600 cm^{-1}; MS *m/e* 901 [M^+ + 1]. Anal. Calcd for $C_{55}H_{75}O_7Si_2$: C, 73.29; H, 8.05. Found: C, 72.74; H, 7.90.

Allylic Alcohol 37 to Pravastatin Silyl Ether 38. To a heated solution (oil bath, 80 °C) of 0.149 g (0.165 mmol) of alcohol **37** in 10 mL of dry benzene was added 0.082 g (0.344 mmol) of *N,N*-diethyl-*N*-[[(methoxycarbonyl)amino]sulfonyl]ethanaminium hydroxide, inner salt (Burgess' reagent). After 15 min the mixture was cooled and filtered through TLC silica gel, and the crude product was chromatographed, eluting with hexane/EtOAc (4:1) to give 0.125 g (86%) of diene **38**: $[\alpha]^{25}_D$ = +75.6° (*c* = 1.3, $CHCl_3$); ^1H NMR δ 0.68 (t, *J* = 7.4 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.2 Hz, 3 H), 1.05 (s, 9 H), 1.06 (s, 9 H), 2.40 (dd, *J* = 4.7, 17.5 Hz, 1 H), 2.56 (dm, *J* = 17.5 Hz, 1 H), 4.23 (bs, 1 H), 4.34–4.42 (m, 1 H), 4.62–4.71 (m, 1 H), 5.25 (bs, 1 H), 5.51 (bs, 1 H), 5.82 (dd, *J* = 6.0, 9.8 Hz, 1 H), 5.94 (d, *J* = 9.8 Hz, 1 H), 7.31–7.48 (m, 12 H), 7.57–7.72 (m, 8 H); IR 1722 cm^{-1}. Anal. Calcd for $C_{55}H_{70}O_6Si_2$: C, 74.78; H, 7.99. Found: C, 74.48; H, 7.94.

Pravastatin 3. A mixture of 1.98 mL of 1.0 M tetrabutylammonium fluoride in THF solution, 0.113 mL (1.98 mmol) of acetic acid, and 0.0356 g (1.98 mmol) of H_2O was added to 0.1456 g (0.165 mmol) of the disilyl derivative **38** in a polyethylene vial. The mixture was stirred for 29 h, taken up in EtOAc, and washed successively with saturated $NaHCO_3$, H_2O, and brine. Chromatography, eluting with EtOAc, provided 0.0567 g (85%) of pravastatin. Pravastatin (**3**): mp 140–142 °C (from hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ = +190° (*c* = 0.50, CH_3OH) [authentic sample $[\alpha]^{25}_D$ = +188.8° (*c* = 0.63, CH_3OH), lit.[6] +194° (*c* = 0.51, CH_3OH)]; ^1H NMR and UV were identical to the authentic sample.

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