Remote Diastereoselection in the Asymmetric Total Synthesis of Mevinolin

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Abstract: The asymmetric total synthesis of mevinolin (1a) is described. The key diastereoselective processes used to parlay the lone stereogenic center of asymmetrically produced (S)-pulegone (2a) to mevinolin include orthoester-Claisen rearrangement of 2d to 3a, stereoselective iodolactonization of 3e to 4, Eschenmoser-Claisen rearrangement of 6 to 7a, stereoselective intramolecular ene reaction of 7b to 8, and a highly diastereoselective cyclocondensation of aldehyde 10 with Danishefsky's diene. The cyclocondensation reaction was found to be quite sensitive to the reaction conditions in which the use of TiCl₄ produced a 90:10 mixture of 11/12 while MgBr₂ gave a 22:78 mixture.

Previous approaches to the synthesis of the HMG-CoA reductase inhibitors mevinolin (1a) and compactin (1b) have treated the problem of forming the stereogenic centers in the lactone and hexahydronaphthalene portions as two separate issues.¹⁻⁴ In keeping with our general strategy to construct new stereogenic centers under the influence of preexisting ones, we reasoned that is should be feasible to generate the lactone chirality in the asymmetric environment of a preformed hexahydronaphthalene unit. In this report we describe the total synthesis of mevinolin in which all of the stereogenic centers of the mevinolin skeleton have been elaborated from the lone center of (S)-pulegone (2a).

(S)-Pulegone (2a), prepared by asymmetric synthesis, 5.6 was converted to the allylic alcohol 2d via a three-step protocol (1. NaBH₄/CeCl₃,MeOH;⁷ 2. O₃, MeOH/CH₂Cl₂, -78 °C, then Me₂S; 3. Ph₃P=CH₂, THF) in 75% overall yield (Scheme I). To introduce the next stereogenic center, an orthoester-Claisen rearrangement⁸ was carried out on 2d [CH₃CH₂C(OEt)₃, toluene, 90 °C] to give an 89:11 mixture of ester 3a and its β -methyl diastereomer (not shown), respectively, in 85% yield. The homologated acid 3e (via 3b-d), on iodolactonization (I2, NaHCO3), provided 4 as a nicely crystalline material (63% yield), which was

(2) Semisynthetic modifications of mevinolin: (a) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. J. Org. Chem. 1983, 48, 1991. (b) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. J. Med. Chem. 1986, 29, 849.

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 Metabolism: Serizawa, N.; Serizawa, S.; Nakagawa, K.; Furuya, K.; Okazaki, T.; Terahara, A. J. Antibiot. 1983, 36, 887. Serizawa, N.; Naka-gawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. J. Antibiot. 1983, 36, 604. Yamashita, H.; Tsubokawa, S.; Endo, A. J. Antibiot. 1985, 38, 605. Haruyama, H.; Kuwano, H.; Kinoshita, T.; Terahara, A.; Nishigaki, T.; Tamura, C. Chem. Pharm. Bull. 1986, 34, 1459.

1.; Tamura, C. Chem. Pharm. Bull. 1986, 34, 1439.
(4) For a review on synthetic approaches to mevinic acids, see: Rosen, T.; Heathcock, C. Tetrahedron 1986, 42, 4909. See also: Danishefsky, S. J.; Simoneau, B. J. Am. Chem. Soc., following paper in this issue.
(5) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. J. Am. Chem. Soc. 1984, 106, 5208, and references therein. Corey, E. J.; Ensley, H. E.; Suggs, I. W. J. Org. Chem. 1976, 41, 380. J. W. J. Org. Chem. 1976, 41, 380.

(6) We thank our kilo laboratory for carrying out the preparation of (S)-pulegone.

(7) Luche, J. L.; Hann, L. R.; Crabbe, P. J. Chem. Soc., Chem. Commun. 1978, 601.

(8) See, for example: Daub, G. W.; Shanklin, P. L.; Tata, C. J. Org. Chem. 1986, 51, 3402. Koreeda, M.; Brown, J. J. Org. Chem. 1983, 48, 2122. readily separable from the iodolactone derived from the β -methyl diastereomer (not shown).⁹ On heating with DBU (105 °C), iodolactone 4 underwent smooth elimination to give lactone 5 in 80% yield. Eschenmoser's variation of the Claisen rearrangement was enlisted for the stereospecific introduction of the side chain.^{10,11} For this, lactone 5 was reduced to allylic alcohol 6 (LiAlH₄, 96%) and then heated with the dimethyl acetal of N,N-dimethylacetamide to give amide 7a in 88% yield. After an uneventful Swern oxidation¹² of 7a to aldehyde 7b (90%), we were ready to examine an intramolecular ene reaction for the construction of the hexahydronaphthalene unit.

While the feasibility of forming bicyclic structures such as required here via an intramolecular ene reaction is implicit in the tandem ene reactions described by Snider,13 the level and sense of stereoselectivity was uncertain. On exposure to an excess of dimethylaluminum chloride (CH₂Cl₂, -20 °C, 20 min), aldehyde 7b underwent a smooth intramolecular ene reaction to a single isomer 8 in 88% yield. That the hydroxyl and methyl groups in 8 are cis 1,3 diaxially oriented illustrates the powerful directing effect of the two substituents on the cyclohexenyl ring and provides an interesting contrast to a fully acyclic example reported recently¹⁴ where the preferred product relationship is trans (1,3 axialequatorial). The side chain was straightforwardly homologated by one carbon to acetoxyaldehyde 10 via 9a¹⁵ in ca. 70% overall yield (Scheme II).

Our strategy for the diastereoselective construction of the lactone moiety was to involve the decalin ring oxygen as a con-

(11) Alternate means to introduce the side chain have been explored. For example, on treatment with allyltrimethylsilane/SnCl4, lactone 5 is converted into a ca 4:1 mixture of i and ii, respectively. This reaction and subsequent transformations will be reported in due course.



(12) Mancuso, A. J.; Swern, D. Synthesis 1981, 165.

(12) Milder, B. B.; Deutsch, E. A. J. Org. chem. 1983, 48, 1822. Snider,
 B. B.; Goldman, B. E. Tetrahedron 1986, 42, 2951.

(14) Johnston, M. I.; Kwass, J. A.; Beal, R. B.; Snider, B. B. J. Org. Chem. 1987, 52, 5419

(15) $\mathbf{8} \rightarrow \mathbf{9a}$, TMS-imidazole; $\mathbf{9a} \rightarrow \mathbf{9b}$, LiEt₃BH, THF; $\mathbf{9b} \rightarrow \mathbf{9c}$, Swern¹² oxidation, $\mathbf{9c} \rightarrow \mathbf{9d}$, Ph₃P=CHOMe, THF; then Bu₄N⁺F⁻; $\mathbf{9d} \rightarrow \mathbf{9e}$, Ac₂O, pyr; $\mathbf{9e} \rightarrow \mathbf{10}$, H₂O, HOAc, THF.

^{(1) (}a) Isolation: Endo, A.; Kuroda, M.; Tsujita, Y. J. Antibiot. 1976, 29, 1346. Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. J. Chem. Soc., Perkin Trans. 1 1976, 1165. 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. Endo, A. J. Med. Chem. 1985, 28, 401. (b) In vivo activity, see for example: Illingworth, D. R.; Bacon, S. Am. J. Cardiol. 1987, 60, 33G. Goel, V.; Dujovne, C. A.; Clin. Res. 1987, 35, 876A. Lee, T. J. Trends Pharmacol. Sci. 1987, 8, 442

⁽⁹⁾ The relative stereochemistry of 4 was confirmed by X-ray analysis on racemic 4. The iodolactone from the epimer of 3e was also a spirolactone. Only traces, if any, of other lactones were produced.

⁽¹⁰⁾ Wick, A.; Felix, D.; Stern, K.; Eschenmoser, A. Helv. Chim. Acta 1964, 47, 2425.

Scheme I



venient linking point in the first stage. However, rather than attempting the covalent attachment of a latent lactone functionality to the decalin ring oxygen, which could then be delivered intramolecularly to the side chain, we elected first to explore an approach based on coordinative effects. It was reasoned that the side chain had sufficient flexibility and length to accommodate a conformation that would allow the acetate and aldehyde oxygens to coordinate Lewis acids. It was further speculated that such a macrocyclic array might lock the aldehyde carbonyl such that one face would be preferentially exposed to incoming nucleophiles.¹⁶ A convenient four-carbon reagent would be 1-methoxy-3-[(trimethylsilyl)oxy]butadiene which, on cyclocondensation with the aldehyde, would provide the necessary functionality to construct the lactone.¹⁷ Under the best conditions to date, reaction of aldehyde 10 with 1-methoxy-3-[(trimethylsilyl)oxy]butadiene in the presence of $TiCl_4(CH_2Cl_2, -40 \ ^{\circ}C)$ produces a 90:10 mixture of pyranones 11 and 12 in ca. 65% yield (Scheme II).¹⁸

While this result is indeed gratifying from the standpoint of synthesis, results from additional experiments suggest the need for caution in the mechanistic interpretation. We were quite surprised to discover that when $MgBr_2(CHCl_3, -20 \text{ to } 5 \,^{\circ}\text{C})$ is used as the Lewis acid the diastereoselection is reversed i.e., a 22:78 mixture of 11 and 12 (81% yield) is produced. This extraordinary reversal of *facial* selectivity merely on switching the Lewis acid from Ti⁴⁺ to Mg²⁺ possibly reflects the difference of coordination geometries and/or a change in mechanism. More information regarding the nature of these interactions will be required to unravel this striking effect.

The inseparable mixture of pyranones 11 and 12 was treated with methanol/triethylamine to produce an 85:15 mixture of axial/equatorial adducts in 75% yield (as well 14% starting material) from which methanol adduct 13a was isolated (Scheme III). Stereospecific reduction of 13a with Li(s-Bu)₃BH (THF, -78 °C) gave alcohol 13b (95%), which on deacetylation (DiBAL, THF) produced diol 13c. Hydrolysis to 14a (HOAc, H₂O) followed directly by oxidation (Ag₂CO₃-Celite¹⁹) gave lactone 14b (75%) which was identical with authentic material prepared from mevinolin.²⁰

(18) The crude product is treated with TFA/THF to effect complete conversion of products to 11 and 12.

(19) Fetizon, M.; Golfier, M. Compt. Rend. 1968, 267, 900.

The conversion of 14b to mevinolin started with monosilylation to silyl ether 14c followed by stereospecific epoxidation (VO-(acac)₂, t-BuOOH) to epoxide $15a^{21}$ (81%). On exposure to trimethylsilyl triflate²² (toluene, 2,6-lutidine, -55 to -30 °C) the epoxide ester 15b (from alcohol $15a^{23}$) was transformed to silyl ether 16a which, on brief treatment with buffered tetrabutylammonium fluoride in THF, gave 16b (84%). Elimination to the diene 17 was carried out with Burgess' reagent²⁴ in 62% yield and

(20) The conversion of mevinolin to **14b** was carried out according to the general procedures described in ref 2a,b and U.S. patents 4,444,784; 4,450,171; and 4,293,496. The two materials were identical chromatographically and by mixed ¹H and ¹³C NMR. **14b** from mevinolin: mp 136-137 °C; $[\alpha]_{25}^{25} = +88.2^{\circ}$ (c = 0.76, EtOH). **14b** from pulegone: mp 135-136 °C, $[\alpha]_{25}^{25} = +88.8^{\circ}$ (c = 0.99, EtOH); Anal. for $C_{19}H_{30}O_4$, C, H. The conversion of **14b** to mevinolin was carried out with material derived from mevinolin. **14b**: ¹H NMR δ 5.48 (br s, 1 H), 4.66 (br m, 1 H), 4.30 (ddd, J = 3.5, 3.8, 3.8 Hz, 1 H), 4.29 (br, OH, 1 H), 4.05 (br s, 1 H), 2.67 (dd, J = 4.9, 17.9 Hz, 1 H), 2.56 (dd, J = 3.7, 17.9 Hz, 1 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.78 (d, J = 6.7 Hz, 3 H); ¹³C NMR δ (C) 171.3, 132.5, (CH) 123.0, 76.2, 69.8, 62.3, 44.8, 37.5, 27.8, 27.5, (CH₂) 40.8, 39.1, 38.5, 35.9, 33.1, 32.2, 24.5, (CH₃) 21.4, 13.6.

(21) Epoxidation with m-chloroperbenzoic acid was less selective, i.e., a 95:5 α : β mixture of epoxides was obtained (the α -epoxide is 15a). Not surprisingly, when the free hydroxyl of 14c was esterified first with the α methylbutyrate side chain, the epoxidation with m-chloroperbenzoic acid was much less selective, i.e., a 33:67 α ; β mixture of epoxides was obtained (the α -epoxide is **15b**). **15a**: $[\alpha]_D = +30.5^{\circ}$ (c = 0.97, CHCl₃); IR (CHCl₃) 1722 ; ¹H NMR δ 4.57 (br m, 1 H), 4.21 (m 2 H), 2.75 (d, J = 5.3 Hz, 1 H), 2.58 (dd, J = 4.1, 17.6 Hz, 1 H), 2.48 (dd, J = 3.6, 17.6 Hz, 1 H), 1.22 (d, J = 7.3 Hz, 3 H), 0.83 (s, 9 H), 0.76 (d, J = 6.9 Hz, 3 H), 0.03 (s, 6 H); ¹³C NMR δ (C) 170.4, 60.7, 17.9, (CH) 76.5, 68.4, 63.5, 53.4, 40.3, 33.2, 27.3, 26.4, (CH₂) 39.2, 39.1, 39.0, 36.8, 33.8, 31.9, 24.7, (CH₃) 25.6 (3), 22.8, 14.0, -5.0 (2); Anal. for $C_{25}H_{44}O_3Si$, C, H. **15b**: $[\alpha]_D = +44.6^\circ$ (c = 1.09, CHCl₃); IR (CHCl₃) 1720 cm⁻¹; ¹H NMR δ 5.53 (ddd, J = 3 Hz, 1 H), 4.51 (m, 1 H), 4.23 (nm, 1 H), 2.69 (d, J = 5.2 Hz, 1 H), 2.53 (center AB, 2 H), 2.38 (q, J = 6.9, 7.3 Hz, 1 H), 1.18 (d, J = 7.0 Hz, 3 H), 1.11 (d, J = 7.3 Hz, 3 H), 0.84 (s, 9 H), 0.84 (t, J = 7.4 Hz, 3 H), 0.76 (d, J = 7.1 Hz, 3 H), 0.06 (s, 6 H); ¹³C NMR δ (C) 176.3, 170.3, 58.6, 17.9, (CH) 76.4, 69.0, 63.5, 53.0, 15.5, 55. 6.9, 6.9 Hz, 1 H), 1.11 (d, J = 6.9 Hz, 3 H), 0.85 (s, 9 H), 0.04 (s, 6 H); ¹³C NMR δ (C) 175.8, 170.3, 59.4, 18.0, (CH) 76.4, 71.1, 63.6, 59.5, 41.7, 39.3, 37.8, 26.9, 24.3, (CH₂) 39.8, 39.4, 37.0, 36.8, 33.7, 31.1, 26.7, 25.1, (CH₃) 25.7 (3), 22.6, 16.9, 15.8, 11.8, -5.0 (2). Taken together, the above results indicate the need for assignment corrections in the epoxidation step reported by Kuo et al.^{2a} It is noteworthy that the stereoselectivity in the epoxidation of the α -methylbutyrate ester of 14c can be improved to an 89:11 α : β epoxide mixture with the use of CF₃CO₃H (CH₂Cl₂, KH₂PO₄, -78 to -45 °C, 63% vield).

⁽¹⁶⁾ For stereocontrolled reactions in macrocyclic rings, see: Still, W. C.; Galynker, I. Tetrahedron 1981, 37, 3981.

⁽¹⁷⁾ The utility of this diene, especially in regard to the formation of tetrahydro-4-hydroxy-2*H*-pyran-2-ones has been amply demonstrated by Danishefsky and co-workers, see for example: Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. J. Am. Chem. Soc. **1982**, 104, 358.

⁽²²⁾ Murata, S.; Suzuki, M.; Noyori, R. J. Am. Chem. Soc. 1979, 101, 2738.

⁽²³⁾ Esterification was carried out with the corresponding anhydride, cf: Hsu, C.-T.; Wang, N.-Y.; Latimer, L. H.; Sih, C. J. J. Am. Chem. Soc. 1983, 105, 593.

Scheme II

Scheme III



desilylation (Bu₄N⁺F⁻, THF, HOAc) provided mevinolin (1a).

In conclusion, this asymmetric total synthesis of mevinolin features several diastereoselective processes to produce the stereogenic centers of the mevinolin skeleton starting from the one asymmetrically derived center of (S)-pulegone, eliminating the need for chiral auxilliaries or resolutions.

Experimental Section

General Procedure. Unless otherwise noted all reactions were run under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium-benzophenone, dichloromethane was dried over 4-Å molecular sieves. Chromatography was done on 230-400 mesh silica gel. Final reaction mixtures were dried over anhydrous sodium sulfate and filtered, and solvent was removed under reduced pressure. Rotations were carried out at 25 °C. ¹H and ¹³C NMR spectra were obtained in CDCl₃ on a Varian XL-200 spectrometer (200 MHz for proton), significant chemical shifts are reported in ppm (δ units) downfield from TMS, and J values are given in Hertz.

Claisen Rearrangement of 2d to 3a. The Claisen rearrangement of 2d was carried out by heating 2d with triethyl orthopropionate as solvent (0.6 ml/mmol) and 10 mol % propionic acid with distillation of ethanol. At

90 °C the reaction ran for 8 h to produce an 89:11 mixture of **3a** and its epimer. At 115 °C the reaction ran for 40-60 min to produce an 85:15 mixture: ¹H NMR δ 5.36 (s, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 2.30 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 5.8 Hz, 3 H); ¹³C NMR major isomer **3a** δ (C) 176.7, 134.6, (CH) 123.0, 31.2 (CH₂) 60.1, 42.1, 38.0, 33.9, 28.4, 28.0 (CH₃) 21.7, 16.7, 14.3; minor isomer δ (C) 134.7, (CH₂) 38.1, (CH₃) 16.8.

Iodolactonization of 3e to 4. To a stirred solution of 5.0 g (25.4 mmol) of acid 3e in 80 mL of CH₃CN was added 20 mL of H₂O, 10.82 g (130 mmol) of solid NaHCO₃ and 16.5 g (65 mmol) of I₂. The dark mixture was stirred at room temperature for 2.5 h, poured into 500 mL of ether, and washed successively with saturated Na₂S₂O₃, H₂O, and brine; 8.0 g of crude lactone 4 containing the iodolactone from the epimer of 3e was obtained. Recrystallization from ether/hexane gave 4.88 g of pure 4 (additional 4 was obtained by chromatography of the mother liquors): mp 99.5–100.8 °C; $[\alpha]_D = -141.2^\circ$ (c = 1.04, CHCl₃); Anal. for C₁₂-H₁₉IO₂,C, H;IR (CHCl₃) 1720 cm⁻¹; ¹H NMR δ 4.40 (s, 1 H), 2.63 (dd, J = 2.3, 14.5 Hz, 1 H), 2.26 (dd, J = 2.8, 14.5 Hz, 1 H), 1.30 (t, 12.6 Hz, 1 H), 1.03 (d, J = 6.3 Hz, 3 H), 0.98 (d, J = 6.3 Hz, 3 H); ¹³C NMR δ (C) 171.2, 82.9, (CH) 43.7, 40.6, 40.3, (CH₂) 37.8, 31.4, 28.9, 28.2, 23.9, (CH₃) 21.3, 20.7. ¹H NMR for the iodolactone from the epimer of 3e δ 4.42 (s, 1 H), 2.66 (br d, J = 14.3 Hz, 1 H), 2.44 (br d, J = 14.3 Hz, 1 H), 1.00 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 5.8 Hz, 3 H).

Claisen Rearrangement of 6 to 7a. A mixture of 0.393 g (1.98 mmol) of 6, 1.5 mL of dry xylenes, and 1.5 mL of N,N-dimethylacetamide/ dimethyl acetal (distilled) was heated at 130 °C for 18 h during which time ca. 0.3 mL of liquid was distilled out. Volatiles were removed under reduced pressure, and the residue was stirred with 20 mL of CH₃OH and

⁽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. A strong solvent dependence was observed for this reaction. With 2,6-lutidine as solvent, diene 17 was accompanied by 14% of an isomeric diene. Compare for example: Kozikowski, A. P.; Li, C.-S. J. Org. Chem. 1987, 52, 3541.

0.2 g of K₂CO₃ for 2.5 h. The mixture was filtered, evaporated, taken up in CH₂Cl₂, and washed successively with H₂O and brine. Chromatography (EtOAc/*i*-PrOH 98.5:1.5) gave 0.022 g of starting material **6** and 0.468 g of alcohol **7a**. The analytical sample was distilled bulb-tobulb [oven at 145 °C (0.025 mmHg)]: Anal. for C₁₆H₂₉NO₂: C, H; [α]_D = -113.1° (c = 0.55, CHCl₃); ¹H NMR δ 5.28 (br s, 1 H), 3.64 (m, 2 H), 3.00 (s, 3 H), 2.95 (s, 3 H), 2.68 (m, 1 H), 2.35 (dd, J = 5.9, 14.4 Hz, 1 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.0 Hz, 3 H); ¹³C NMR δ (C) 172.8, 136.3, (CH) 125.6, 35.8, 30.4, 27.5, (CH₂) 60.8, 45.8, 39.5, 35.0, 27.8, 26.6, (CH₃) 37.5, 35.5, 19.8, 16.1.

Ene Reaction of 7b to 8. To a solution of 0.412 g (1.55 mmol) of 7b in 18 mL of CH₂Cl₂ at -20 °C was added 3.89 mL of Me₂AlCl solution (1.0 M in hexanes) over 1.5 min. The mixture was stirred for 20 min and then quenched by addition of H₂O. The mixture was taken up in CH₂Cl₂ and washed with brine. Chromatography (EtOAc/*i*-PrOH 98.51.5) gave 0.3622 g of 8. The analytical sample was recrystallized from ether: mp 152-153 °C; $[\alpha]_D = -29.6^\circ$ (c = 0.50, CHCl₃); Anal. for C₁₆H₂₇NO₂, C, H, N; ¹H NMR δ 5.44 (br s, 1 H), 3.81 (br s, 1 H), 3.65 (br s, 1 H, OH), 3.01 (s, 3 H), 2.95 (s, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.87 (d, J = 7.2 Hz, 3 H); ¹³C NMR δ (C) 173.4, 133.6, (CH) 121.7, 68.5, 45.8, 34.0, 32.0, 28.0, (CH₂) 40.8, 38.5, 36.9, 32.6, (CH₃) 37.2, 35.8, 21.0, 14.5.

Cyclocondensation of 10 with 1-Methoxy-3-[(trimethylsily])oxy]-1,3butadiene. To a solution of 0.9051 g (3.25 mmol) of aldehyde 10 in 26 mL of CH_2Cl_2 at -78 °C was added 3.58 mL of 1.0 M TiCl₄ in CH_2Cl_2 (Aldrich) over 4.5 min. After 2 min flask was set in a bath at -40 °C and stirring continued for 5 min; then 1.1219 g of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (ca. 95% purity by NMR) in 7.8 mL of CH_2Cl_2 was added dropwise over 16 min. The mixture was stirred for 40 min and then quenched by the addition of saturated NaHCO₃. The mixture was taken up in EtOAc and washed successively with saturated NaHCO₃ and brine. The residue was stirred with 24 mL of THF and 2.8 mL of trifluoroacetic acid for 1 h. After aqueous workup, the residue was chromatographed (hexanes/EtOAc 1:1) to give 0.7451 g of pyraAcknowledgment. We express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for determination of spectral and analytical data, and to A. Williams for technical assistance.

Registry No. 1a, 75330-75-5; **2a**, 3391-90-0; **2b**, 118760-35-3; **2c**, 118759-44-7; **2d**, 118682-25-0; **3a**, 118682-26-1; **3a** (epimer), 118682-27-2; **3b**, 118682-28-3; **3c**, 118682-29-4; **3d**, 118682-30-7; **3e**, 118713-57-8; **4**, 118682-31-8; **5**, 118682-32-9; **6**, 118682-33-0; **7a**, 118682-34-1; **7b**, 118682-35-2; **8**, 118682-36-3; **9a**, 118713-58-9; **9b**, 118682-37-4; **9c**, 118682-38-5; (*E*)-9d, 118713-60-3; **10**, 118682-39-6; **11**, 118682-40-9; **12**, 118682-41-0; **13a**, 118682-42-1; **13a** (H = α), 118759-45-8; **13b**, 118682-43-2; **13c**, 118682-44-3; **14a**, 118682-45-4; **14b**, 118682-46-5; **14c**, 118682-47-6; **14c** ((*S*)- α -methylbutyrate), 85613-99-6; **15a**, 118682-48-7; **15b**, 85614-07-9; **15b** (β -epoxide), 85648-19-7; **16a**, 118682-48-7; **15b**, 118682-50-1; **17**, 79691-11-5; i, 118682-53-3; ii, 118682-53-4; **Ph**₃P=CH₂, 3487-44-3; CH₃C(OMe)₂NMe₂, 18871-66-4; Ph₃P=CHOMe, 20763-19-3; [(*S*)-*C*₂H₃CH(CH₃)CO]₂O, 84131-91-9; TMSCH₂CH=CH₂, 762-72-1; Danishefsky's diene, 54125-02-9.

Supplementary Material Available: Spectral data (including ¹³C NMR) for 2b,c, 3b-e, 5, 6, 9a-e, 10, 13a-c, 14a,c, 16a,b, and 17 (3 pages). Ordering information is given on any current masthead page.

Total Syntheses of ML-236A and Compactin by Combining the Lactonic (Silyl) Enolate Rearrangement and Aldehyde-Diene Cyclocondensation Technologies

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Abstract: The sequence of a lactonic Claisen rearrangement and a Lewis acid catalyzed cyclocondensation of an aldehyde with an appropriate diene affords a new route to the title series.

The lowering of human blood serum cholesterol levels by mevinoids,¹ through suppression of HMG-CoA reductase (HMGR), already finds growing application in cardiovascular medicine.² Since the HMGR-mediated reductive conversion of 3-hydroxy-3-methylglutarate to mevalonate is a rate-limiting step in de novo cholesterol biosynthesis in humans, its inhibition is a prime target for medical intervention. Not surprisingly, the challenge of providing new routes to the compactin-mevinolin family has stimulated many approaches and successes.^{3a,b} We have been developing some new ideas with a view to this objective.^{4a-c} Total syntheses of ML-236A and of enantiomerically pure compactin are described below.

Our stereochemical strategy centers on four key processes. The first takes advantage of the remarkable syn selectivity exhibited

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(b) The work described herein was described at the 7th IUPAC Conference on Organic Synthesis (Nancy, France) July 7, 1988. For a discussion of the background and synthetic logic, see: Danishefsky, S. J.; Simoneau, B. Pure Appl. Chem. 1988, 60, 1555.
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