# 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 $TiCl_4$ produced a 90:10 mixture of **11**/**12** while $MgBr_2$ 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. $NaBH_4/CeCl_3$,MeOH;[7] 2. $O_3$, $MeOH/CH_2Cl_2$, −78 °C, then $Me_2S$; 3. $Ph_3P{=}CH_2$, THF) in 75% overall yield (Scheme I). To introduce the next stereogenic center, an orthoester–Claisen rearrangement[8] was carried out on **2d** [$CH_3CH_2C(OEt)_3$, 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 ($I_2$, $NaHCO_3$), provided **4** as a nicely crystalline material (63% yield), which was 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** ($LiAlH_4$, 96%) and then heated with the dimethyl acetal of *N*,*N*-dimethylacetamide to give amide **7a** in 88% yield. After an uneventful Swern oxidation[12] 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 ($CH_2Cl_2$, −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 recently[14] where the preferred product relationship is *trans* (1,3 axial–equatorial). The side chain was straightforwardly homologated by one carbon to acetoxyaldehyde **10** via **9a**[15] 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-

(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.

(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.

(3) Metabolism: Serizawa, N.; Serizawa, S.; Nakagawa, K.; Furuya, K.; Okazaki, T.; Terahara, A. *J. Antibiot.* **1983**, *36*, 887. Serizawa, N.; Nakagawa, 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.

(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, J. W. *J. Org. Chem.* **1976**, *41*, 380.

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

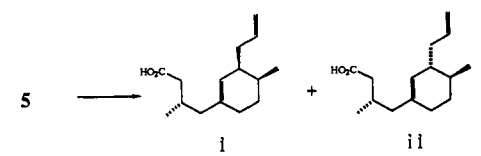
(7) Luche, J. L.; Hann, L. R.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

(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.

(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.

(11) Alternate means to introduce the side chain have been explored. For example, on treatment with allyltrimethylsilane/$SnCl_4$, 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.




i ii

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

(13) Snider, 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) **8** → **9a**, TMS-imidazole; **9a** → **9b**, $LiEt_3BH$, THF; **9b** → **9c**, Swern[12] oxidation, **9c** → **9d**, $Ph_3P{=}CHOMe$, THF; then $Bu_4N^+F^-$; **9d** → **9e**, $Ac_2O$, pyr; **9e** → **10**, $H_2O$, HOAc, THF.

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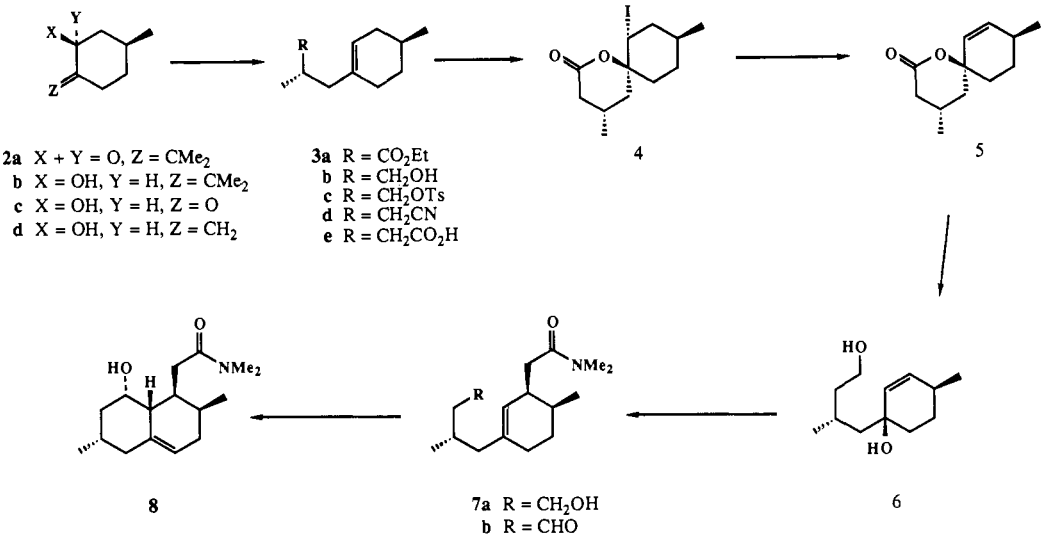
**Scheme I**




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 °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 to 5 °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 $Ti^{4+}$ to $Mg^{2+}$ 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 $Li(s\text{-}Bu)_3BH$ (THF, −78 °C) gave alcohol **13b** (95%), which on deacetylation (DiBAL, THF) produced diol **13c**. Hydrolysis to **14a** (HOAc, $H_2O$) followed directly by oxidation ($Ag_2CO_3$–Celite[19]) gave lactone **14b** (75%) which was identical with authentic material prepared from mevinolin.[20]

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 triflate[22] (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' reagent[24] in 62% yield and

(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.

(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.

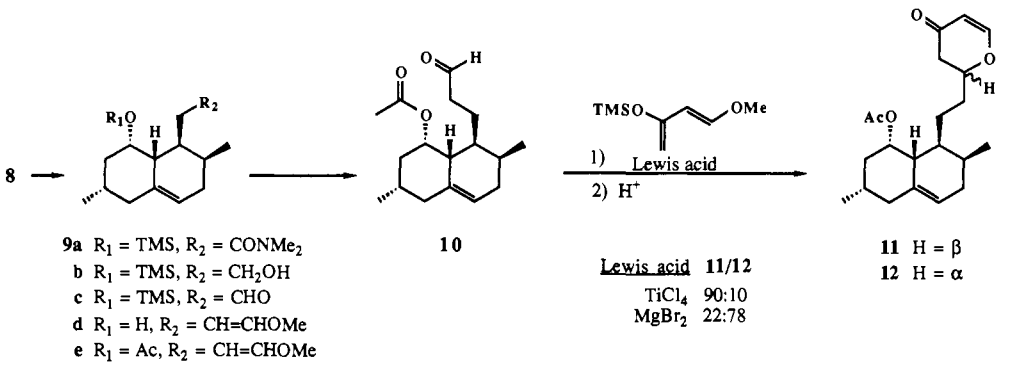
(20) The conversion of mevinolin to **14b** was carried out according to the general procedures described in ref 2a,b and U.S. patents 4,444,784; 4,450,171; and 4,293,496. The two materials were identical chromatographically and by mixed $^1H$ and $^{13}C$ NMR. **14b** from mevinolin: mp 136–137 °C; $[\alpha]^{25}_D = +88.2°$ (*c* = 0.76, EtOH). **14b** from pulegone: mp 135–136 °C, $[\alpha]^{25}_D = +84.8°$ (*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); $^{13}C$ NMR δ (C) 171.3, 132.5, (CH) 123.0, 76.2, 69.8, 62.3, 44.8, 37.5, 27.8, 27.5, ($CH_2$) 40.8, 39.1, 38.5, 35.9, 33.1, 32.2, 24.5, ($CH_3$) 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**: $[\alpha]_D = +30.5°$ (*c* = 0.97, $CHCl_3$); IR ($CHCl_3$) 1722 $cm^{-1}$; $^1H$ 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); $^{13}C$ 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, ($CH_2$) 39.2, 39.1, 39.0, 36.8, 33.8, 31.9, 24.7, ($CH_3$) 25.6 (3), 22.8, 14.0, −5.0 (2); Anal. for $C_{25}H_{44}O_5Si$, C, H. **15b**: $[\alpha]_D = +44.6°$ (*c* = 1.09, $CHCl_3$); IR ($CHCl_3$) 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 (tq, 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); $^{13}C$ NMR δ (C) 176.3, 170.3, 58.6, 17.9, (CH) 76.4, 69.0, 63.5, 53.0, 41.5, 39.4, 33.4, 27.3, 26.2, 24.1, ($CH_2$) 39.3, 39.0, 36.8, 35.6, 33.9, 31.9, 26.5, ($CH_3$) 25.7 (3), 21.6, 16.6, 14.2, 11.7, −5.0 (2); Anal. for $C_{30}H_{52}O_6Si$, C, H. β-Epoxide epimer of **15b** (structure not shown): $^1H$ NMR δ 5.29 (br s, 1 H), 4.55 (m, 1 H), 4.24 (ddd, *J* = 3.4, 3.6, 3.6 Hz, 1 H), 2.99 (br s, 1 H) 2.59 (dd, *J* = 4.0, 18.0 Hz, 1 H), 2.48 (dd, *J* = 3.8, 18.0 Hz, 1 H), 2.32 (tq, *J* = 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); $^{13}C$ 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, ($CH_2$) 39.8, 39.4, 37.0, 36.8, 33.7, 31.1, 26.7, 25.1, ($CH_3$) 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 $CF_3CO_3H$ ($CH_2Cl_2$, $KH_2PO_4$, −78 to −45 °C, 63% yield).

(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**



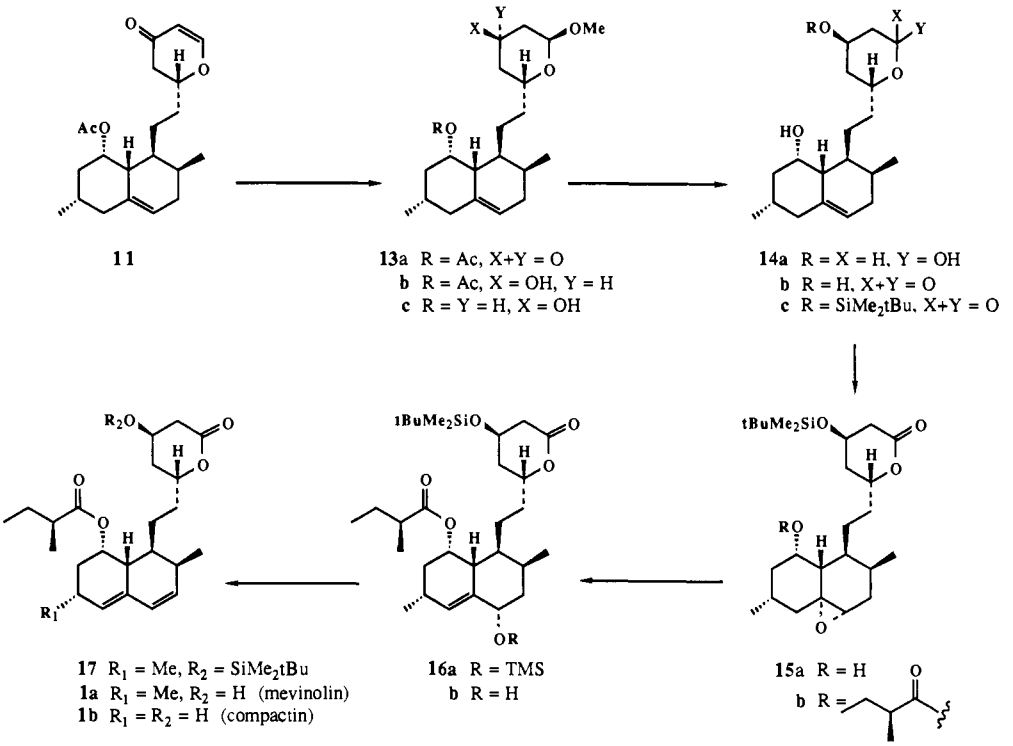

**9a** $R_1$ = TMS, $R_2$ = $CONMe_2$
**b** $R_1$ = TMS, $R_2$ = $CH_2OH$
**c** $R_1$ = TMS, $R_2$ = CHO
**d** $R_1$ = H, $R_2$ = CH=CHOMe
**e** $R_1$ = Ac, $R_2$ = CH=CHOMe

**10**

Lewis acid **11/12**
$TiCl_4$ 90:10
$MgBr_2$ 22:78

**11** H = β
**12** H = α

**Scheme III**




**11**

**13a** R = Ac, X+Y = O
**b** R = Ac, X = OH, Y = H
**c** R = Y = H, X = OH

**14a** R = X = H, Y = OH
**b** R = H, X+Y = O
**c** R = $SiMe_2tBu$, X+Y = O

**15a** R = H
**b** R =

**16a** R = TMS
**b** R = H

**17** $R_1$ = Me, $R_2$ = $SiMe_2tBu$
**1a** $R_1$ = Me, $R_2$ = H (mevinolin)
**1b** $R_1$ = $R_2$ = H (compactin)

desilylation ($Bu_4N^+F^-$, 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 $^{13}C$ NMR spectra were obtained in $CDCl_3$ 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); $^{13}C$ NMR major isomer **3a** δ (C) 176.7, 134.6, (CH) 123.0, 31.2 ($CH_2$) 60.1, 42.1, 38.0, 33.9, 28.4, 28.0 ($CH_3$) 21.7, 16.7, 14.3; minor isomer δ (C) 134.7, ($CH_2$) 38.1, ($CH_3$) 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 $CH_3CN$ was added 20 mL of $H_2O$, 10.82 g (130 mmol) of solid $NaHCO_3$ and 16.5 g (65 mmol) of $I_2$. The dark mixture was stirred at room temperature for 2.5 h, poured into 500 mL of ether, and washed successively with saturated $Na_2S_2O_3$, $H_2O$, 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° (*c* = 1.04, $CHCl_3$); Anal. for $C_{12}H_{19}IO_2$,C, H;IR ($CHCl_3$) 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); $^{13}C$ NMR δ (C) 171.2, 82.9, (CH) 43.7, 40.6, 40.3, ($CH_2$) 37.8, 31.4, 28.9, 28.2, 23.9, ($CH_3$) 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 $CH_3OH$ 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 $K_2CO_3$ for 2.5 h. The mixture was filtered, evaporated, taken up in $CH_2Cl_2$, and washed successively with $H_2O$ 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-to-bulb [oven at 145 °C (0.025 mmHg)]: Anal. for $C_{16}H_{29}NO_2$: C, H; $[\alpha]_D$ = -113.1° (*c* = 0.55, $CHCl_3$); $^1H$ NMR $\delta$ 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), 2.11 (dd, *J* = 8.7, 14.4 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.0 Hz, 3 H); $^{13}C$ NMR $\delta$ (C) 172.8, 136.3, (CH) 125.6, 35.8, 30.4, 27.5, ($CH_2$) 60.8, 45.8, 39.5, 35.0, 27.8, 26.6, ($CH_3$) 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 $CH_2Cl_2$ at -20 °C was added 3.89 mL of $Me_2AlCl$ solution (1.0 M in hexanes) over 1.5 min. The mixture was stirred for 20 min and then quenched by addition of $H_2O$. The mixture was taken up in $CH_2Cl_2$ and washed with brine. Chromatography (EtOAc/*i*-PrOH 98.5:1.5) gave 0.3622 g of **8**. The analytical sample was recrystallized from ether: mp 152-153 °C; $[\alpha]_D$ = -29.6° (*c* = 0.50, $CHCl_3$); Anal. for $C_{16}H_{27}NO_2$, C, H, N; $^1H$ NMR $\delta$ 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); $^{13}C$ NMR $\delta$ (C) 173.4, 133.6, (CH) 121.7, 68.5, 45.8, 34.0, 32.0, 28.0, ($CH_2$) 40.8, 38.5, 36.9, 32.6, ($CH_3$) 37.2, 35.8, 21.0, 14.5.

**Cyclocondensation of 10 with 1-Methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene.** 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 $TiCl_4$ 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 $NaHCO_3$. The mixture was taken up in EtOAc and washed successively with saturated $NaHCO_3$ 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 pyranones **11** and **12** as an inseparable 90:10 mixture as judged from $^{13}C$ NMR. **11**: $^1H$ NMR $\delta$ 7.31 (d, *J* = 6.0 Hz, 1 H), 5.44 (br s, 1 H), 5.35 (d, *J* = 6.0 Hz, 1 H), 5.18 (ddd, *J* ~ 3.2 Hz, 1 H), 4.32 (m, 1 H), 2.49 (dd, *J* = 12.3, 17.1 Hz, 1 H), 2.37 (dd, J = 4.8, 17.1 Hz, 1 H), 1.96 (s, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H); $^{13}C$ NMR for **11** with the distinguishing resonances for **12** in parentheses $\delta$ (C) 192.7, 170.7, 132.1, (CH) 163.3, 122.2, 106.9, 79.4(79.7), 72.3(72.6), 43.2, 38.1(38.7), 27.8, 27.6, ($CH_2$) 41.9(41.7), 40.7, 35.8, 32.1, 31.8, 24.0, $CH_3$: 21.4, 20.2, 14.0.

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**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**, 118713-59-0; (*Z*)-**9d**, 118682-51-2; (*E*)-**9e**, 118722-37-5; (*Z*)-**9e**, 118713-60-3; **10**, 118682-39-6; **11**, 118682-40-9; **12**, 118682-41-0; **13a**, 118682-42-1; **13a** (H = $\alpha$), 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*)-$\alpha$-methylbutyrate), 85613-99-6; **15a**, 118682-48-7; **15b**, 85614-07-9; **15b** ($\beta$-epoxide), 85648-19-7; **16a**, 118682-49-8; **16b**, 118682-50-1; **17**, 79691-11-5; i, 118682-52-3; ii, 118682-53-4; $Ph_3P{=}CH_2$, 3487-44-3; $CH_3C(OMe)_2NMe_2$, 18871-66-4; $Ph_3P{=}CHOMe$, 20763-19-3; $[(S)\text{-}C_2H_5CH(CH_3)CO]_2O$, 84131-91-9; $TMSCH_2CH{=}CH_2$, 762-72-1; Danishefsky's diene, 54125-02-9.

**Supplementary Material Available:** Spectral data (including $^{13}C$ 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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