Synthesis of (+)-Dihydromevinolin by Selective Reduction of Mevinolin

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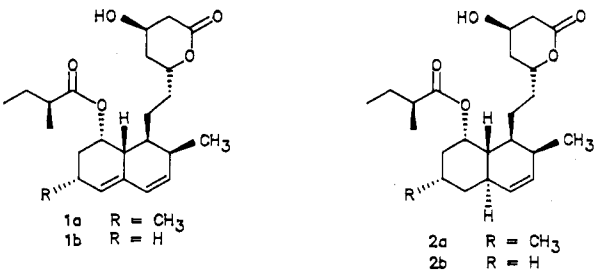
The fungal metabolites mevinolin (Mevacor) (**1a**)[1] and compactin (**1b**)[2] have attracted considerable attention due to their hypocholesterolemic activity. They function as extremely potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis.

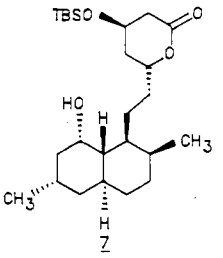
Recently we became interested in selective reductive transformations of the mevinolin diene system. Of particular interest was dihydromevinolin (**2a**)[3] which is a natural product formed in small quantities in the mevinolin fermentation process (Scheme I). It exhibits similarly potent biological activity. Unfortunately, this congener has also been the most difficult monoolefin isomer to prepare synthetically from mevinolin. Previous efforts by Wendler produced the natural trans isomer in low yield by a lengthy nonselective route.[4] Total syntheses of this molecule and the corresponding compactin analogue **2b** have been reported.[5] We sought a practical route to **2a** from the readily available natural product mevinolin **1a**.

We report a method for the direct conversion of the diene **4** to the desired trans-fused monoene with very high regio-, chemo-, and stereoselectivity. This transformation hinges on selective reduction of the more hindered double bond from the more sterically congested α-face. The use of this reduction was demonstrated by the synthesis of the natural product dihydromevinolin **2a** from mevinolin **1a**. The overall route to **2a** is depicted in Scheme II. Mevinolin (Mevacor) (**1a**) was saponified (LiOH/MeOH, reflux) and lactonized to give diol intermediate **3**, which was selectively protected (TBSCl/DMF/imidazole) to give monosilylated diol **4** (63% yield from **1a**).[6] The crucial reduction of **4** to **5** was carried out by using the Crabtree catalyst $[Ir(cod)(py)(PCy_3)]PF_6$.[7] Our initial interests were in exploiting the directing effect of the C-1 hydroxyl group to establish the trans ring junction. This catalyst is reported to be extremely selective in the reduction of alcohol

Scheme I



containing monoolefins.[8] This is due to the formation of a covalent iridium–oxygen bond, which then allows delivery of hydrogen from the hydroxyl bearing face of the molecule. Since the selective monoreduction of conjugated dienes with this catalyst has not been reported, we were uncertain as to whether monoreduction would be possible. Our initial results (using 2.5 mol % catalyst, CH_2Cl_2, room temperature, 1 atm of H_2) demonstrated that the hydroxyl directing effect was excellent. No cis-fused derivatives could be detected. However, significant quantities of the over-reduced *trans*-tetrahydro product **7**[9] were produced along with monoolefin **5** even though some diene still remained. Compound **7** was produced exclusively upon prolonged reduction.



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We sought to attenuate the reactivity of this normally highly active catalyst so that the slower, second reduction might be prevented. This was accomplished by adding alcohols to compete with the substrate for the iridium catalyst. Initial results with methanol (1–3 equiv relative to **4**) did indeed favor more selective formation of **5**. Unfortunately, methanol competed too effectively with the substrate for the catalyst, thus leading to catalyst deactivation. However, the use of a more hindered alcohol, 2-propanol (3 equiv), allowed the reaction to proceed to 95% conversion (85% the desired monoolefin **5**, 9.5% of tetrahydro product **7**).[10]

The resulting mixture of **5** and **7** was acylated[5c] with (*S*)-2-methylbutyric acid anhydride[11] to give **6**. Desilylation using tetra-*n*-butylammonium fluoride (THF, AcOH)[12] followed by recrystallization (Et_2O/hexanes) gave dihydromevinolin in 52% yield from **5** (40% overall yield from **4**). It is interesting to note that the reduction of mevinolin (**1a**) or hydroxy-protected mevinolin **8** with the iridium catalyst leads exclusively to formation of the 1,4-

(1) (a) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957. (b) Endo, A. *J. Antibiot.* **1979**, *32*, 852; **1980**, *33*, 334.

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(3) Albers-Schonberg, G.; Joshua, H.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507.

(4) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991; U.S. Patent No. 4,490,546.

(5) (a) Falck, J. R.; Yang, Y.-L. *Tetrahedron Lett.* **1984**, 3563. Heathcock, C. H.; Haley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858. Heathcock, C. H.; Hecker, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 4586. Heathcock, C. H.; Rosen, T. *Tetrahedron* **1986**, *42*, 4909. Davidson, A. H.; Jones, A. J.; Floyd, C. D.; Lewis, C.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1786. Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Tetrahedron Lett.* **1984**, 1655. (b) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1982**, 4305. Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811 (dihydrocompactin). (c) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, 1811 (mevinolin).

(6) Willard, A. K.; Smith, R. L. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 337.

(7) (a) Crabtree, R. H. *Acct. Chem. Res.* **1979**, *12*, 331. (b) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205.

(8) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (c) Evans, D. A.; Morrisey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637; *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(9) Hoffman, W. F.; Smith, R. L.; Willard, A. K. U.S. Patent No. 4,444,784.

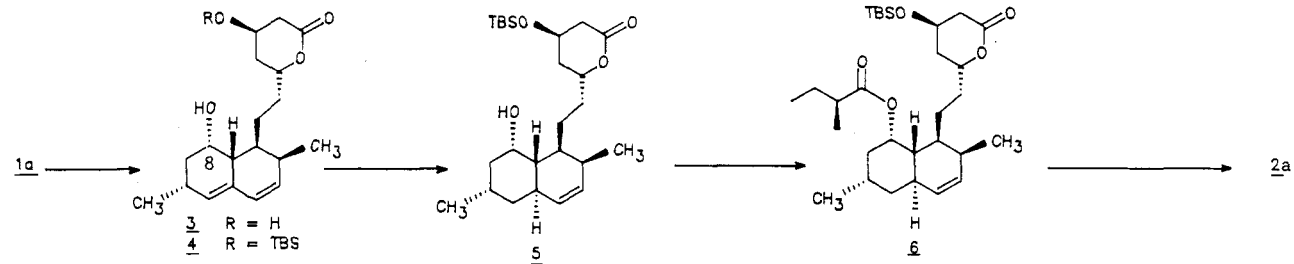
(10) The ratio of products was determined by ^1H NMR spectroscopy. The starting material **4** was separated from reduced products by filtration of an ether solution through Florisil. Preparatively, undesired tetrahydro impurity **7** was carried through the subsequent steps and removed during crystallization of the final product **2a**.

(11) Wang, N.-Y.; Hsu, C.-T.; Sih, C. J. *J. Am. Chem.* Soc. **1981**, *103*, 6538.

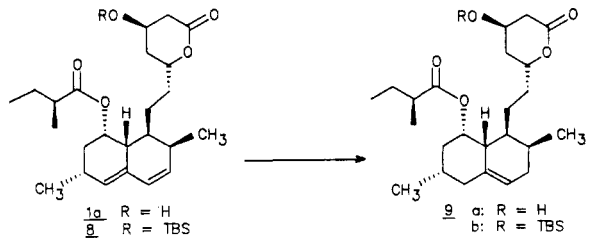
(12) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849.

0022-3263/89/1954-3207$01.50/0

Scheme II



Scheme III



reduction product **9**[4] (Scheme III). This result was somewhat unexpected since Crabtree reports that the ester functionality can also be used for directed hydrogenation.[8a] Apparently in the case of this very hindered ester, 1,4-reduction of the diene supersedes 1,2-reduction.

Experimental Section

General Procedure. Melting points were determined in capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300-MHz instrument. Flash chromatography refers to the procedure of Still[13] and was done on E. Merck silica gel of particle size 40–63 μm.

6(*R*)-[2-[8(*S*)-Hydroxy-2(*S*),6(*S*)-dimethyl-1,2,4a-(*R*),5,6,7,8,8a(*S*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5). A solution of diene **4**[6] (1.36 g, 3.12 mmol) in anhydrous dichloromethane (4.2 mL) and 2-propanol (0.72 mL, 9.4 mmol) was briefly purged with argon gas. [Ir(cod)(py)(PCy_3)]PF_6[8b] (0.063 g, 2.5 mol %) was added, and the mixture was reduced at atmospheric hydrogen pressure at ambient temperature for 21 h. The progress of the reaction could be monitored by ^1H NMR analysis of reaction aliquots. The volatiles were removed in vacuo, and the resulting solid was taken up in boiling Et_2O (150 mL) and vacuum filtered through a 1-in. pad of Florisil. The filtrate was evaporated in vacuo to a white crystalline solid (mp 146–147 °C), which was determined by ^1H NMR to be a 9:1 mixture of the title compound **5** and the *trans*-tetrahydro derivative **7** (76% yield of **5**). Recrystallization (EtOAc/hexanes) provided analytically pure **5**: mp 147.5–148 °C; ^1H NMR ($CDCl_3$) δ 5.62 (ddd, J = 2.5, 4.9, 9.5 Hz, 1 H), 5.38 (d, J = 9.5 Hz, 1 H), 4.67 (m, 1 H), 4.29 (m, 1 H), 4.17 (m, 1 H), 1.0–2.1 (m, 11 H), 0.85 (m, 12 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.6, 132.4, 131.5, 76.4, 67.1, 63.6, 42.8, 39.3, 39.1, 37.2, 36.9, 33.0, 31.5, 29.7, 27.0, 25.7, 23.1, 21.7, 18.0, 15.0, −4.8; IR ($CHCl_3$) 3680, 3020, 2970, 1720, 1260, 1210, 730 cm^{-1}. Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.16. Found: C, 68.41; H, 10.00.

6(*R*)-[2-[8(*S*)-Hydroxy-2(*S*),6(*S*)-dimethyl-1,2,3,4,4a-(*R*),5,6,7,8,8a(*S*)-decahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (7). A solution of diene **5** (1.34 g, 3.1 mmol) in dichloromethane (15 mL) was reduced (40 psi of hydrogen pressure, ambient temperature, 24 h) in the presence of [Ir(cod)(py)(PCy_3)]PF_6 (63 mg, 2.5 mol %). The title compound **7**[9] was isolated as described above in 98% yield (1.32 g, mp 140–141 °C, lit.[9] mp 136–138 °C): ^1H NMR ($CDCl_3$) δ 4.66 (m, 1 H), 4.28 (m, 1 H), 4.08 (m, 1 H), 2.47–2.68 (m, 2 H), 0.92–2.14 (m, 21 H), 0.87 (s, 9 H), 0.82 (d, J = 7.2 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); HRMS (EI) calcd for $C_{25}H_{46}O_4Si$ 438.3165, found 438.3157.

(13) Still, W. G.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

6(*R*)-[2-[8(*S*)-[(2-Methylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9a). A solution of Mevacor (0.63 g, 1.6 mmol) in dichloromethane (15 mL) was reduced (1 atm of hydrogen pressure, ambient temperature, 1.5 h) in the presence of [Ir(cod)(py)(PCy_3)]PF_6 (0.031 g, 2.5 mol %). The title compound (**9a**)[4,9] was isolated as described above as a colorless oil in 90% yield (0.586 g), whose physical properties were identical with those reported:[9] ^1H NMR ($CDCl_3$) δ 5.48 (br s, 1 H), 5.28 (m, 1 H), 4.63 (m, 1 H), 4.35 (m, 1 H), 2.74 (dd, J = 16.0, 7.0 Hz, 1 H), 2.61 (dd, J = 16.0, 4.0 Hz, 1 H), 1.22–2.45 (m, 20 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.0 (d, J = 7.0 Hz, 3 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H); HRMS (EI) calcd for $C_{24}H_{38}O_5$ 406.2719, found 406.2721.

6(*R*)-[2-[8(*S*)-[(2-Methylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-1,2,4a(*R*),5,6,7,8,8a(*S*)-octahydronaphth-1(*S*)-yl]-ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6). A solution of alcohol **5** (0.50 g, equivalent to 1.03 mmol, 90% pure, containing 10% of **7**) in anhydrous pyridine (7 mL) under an N_2 atmosphere was treated with (*S*)-2-methylbutyric acid anhydride[11] (0.86 g, 4.6 mmol). 4-(Dimethylamino)pyridine (0.040, 0.32 mmol) was added, and the mixture was stirred at ambient temperature for 26 h. The mixture was diluted with Et_2O (40 mL) and washed with H_2O (2 × 20 mL), 0.1 M HCl solution (20 mL), saturated $NaHCO_3$ solution (20 mL), and saturated NaCl solution (20 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oil (1.7 g), which was purified by flash chromatography (20% EtOAc in hexanes). The title compound **6** was obtained as a white crystalline solid contaminated with approximately 10% of the corresponding acylated tetrahydro derivative. The mixture was used as is in the next reaction: ^1H NMR ($CDCl_3$) δ 5.62 (m, 1 H), 5.36 (d, J = 9.3 Hz, 1 H), 5.14 (m, 1 H), 4.36 (m, 1 H), 4.25 (m, 1 H), 2.13–2.65 (m, 5 H), 0.73–2.10 (m, 36 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

6(*R*)-[2-[8(*S*)-[(2-Methylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-1,2,4a(*R*),5,6,7,8,8a(*S*)-octahydronaphth-1(*S*)-yl]-ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2a, Dihydromevinolin). A solution of silyl ether **6** (0.562 g, equivalent to 0.97 mmol) in THF (10 mL) was cooled to 12 °C and treated sequentially with acetic acid (0.37 mL, 6.4 mmol) and tetra-*n*-butylammonium fluoride/THF solution (1 M, 5.2 mL, 5.2 mmol). The mixture was stirred at ambient temperature for 8 h, diluted with EtOAc (35 mL), and washed with 1 N HCl solution (4 × 15 mL), saturated $NaHCO_3$ solution (15 mL), and saturated NaCl solution (15 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo to a yellow oil, which was purified by flash chromatography (30% EtOAc in hexanes). The resulting white solid was recrystallized from Et_2O/hexanes to give the title compound **2a** as white needles, mp 131–131.5 °C (0.208 g, 52% yield, lit.[3] mp 131–132 °C), from **5**. The physical properties of the synthetic sample matched those of the natural product in every respect. A (250-MHz) ^1H NMR sample of the natural product in $CDCl_3$ spiked with the synthetic **2a** showed the two to be identical.

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Registry No. **1a**, 75330-75-5; **2a**, 77517-29-4; **4**, 79902-31-1; **5**, 120417-22-3; **6**, 85648-17-5; **6** dihydro deriv., 120417-23-4; **7**, 79902-65-1; **9a**, 79691-09-1; (*S*)-2-methylbutyric acid anhydride, 84131-91-9.