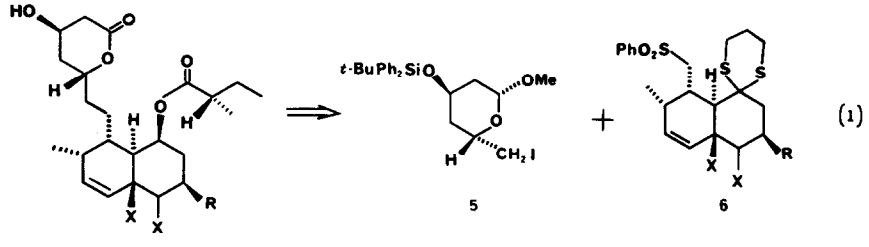
Tetrahedron Letters,Vol.25,No.33,pp 3563-3566,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (+)-DIHYDROMEVINOLIN

J. R. Falck* and Yuh-Lin Yang
Department of Molecular Genetics
University of Texas Health Science Center At Dallas
Dallas, Texas 75235 U.S.A.

Summary: The potent hypocholesterolemic agent (+)-dihydromevinolin was synthesized from chiral pyranoside 5 and octahydronaphthalene 6 which was obtained from maleic anhydride Diels-Alder adduct 7 by intramolecular sulfoxide acylation and methyl cuprate addition.

The fungal metabolites compactin (1) and mevinolin (2) have gained prominence[1] as hypocholesterolemic agents because of their low toxicity and extremely potent competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase[2], the rate limiting enzyme in cholesterogenesis. In contrast, their equally potent congeners dihydrocompactin[3] (3) and dihydromevinolin[4] (4) have been less well studied, due in part to limited availability from natural sources. Recently, we disclosed a convergent approach to the mevinic acids involving union of chiral pyranoside 5 with an appropriate hydronaphthalene 6 (eq. 1) and its application to (+)-dihydrocompactin[5]. The versatility of this approach is demonstrated herein by the first total synthesis of (+)-dihydromevinolin[6].

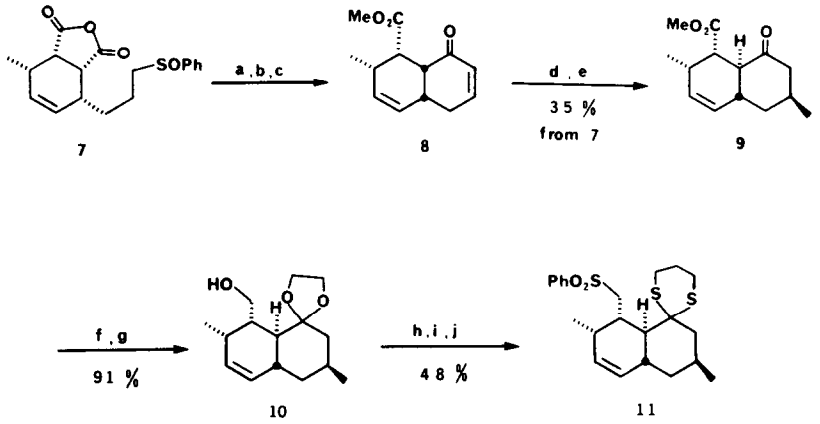


5 6 (1)

1 Compactin: R = H , X = $\Delta^{4a,5}$
2 Mevinolin: R = Me, X = $\Delta^{4a,5}$
3 Dihydrocompactin: R = X = H
4 Dihydromevinolin: R = Me, X = H

Entry into the mevinolin series (Scheme I) was achieved by intramolecular acylation of sulfoxide[5] 7 (mp 155-156°C), esterification, and subsequent thermal dehydrosulfenylation affording mainly cis-fused dienone 8. Smooth conjugate addition of methyl cuprate[1d] and NaOMe catalyzed equilibration yielded 9[7,8] (mp 57-58°C, 35% from 7). Sequential ketalization of 9 and $LiAlH_4$ reduction evolved 10 (mp 81-83°C, 91%) which was converted to sulfone 11 (mp 203-204°C, 48%) by simultaneous ketal cleavage and alcohol-iodide interchange using in situ generated trimethylsilyl iodide[9], sulfonylation with benzenesulfinate anion supported on Amberlyst A-26[10], and $BF_3 \cdot Et_2O$ catalyzed thioketalization.

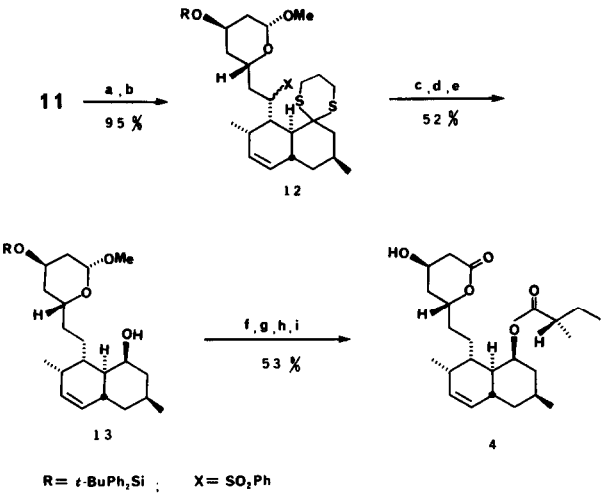
Scheme I



(a) 2 equiv $LiN(SiMe_3)_2$, THF, -78°C, 5 days; then -40°C, 8h; (b) CH_2N_2; (c) $P(OMe)_3$, CCl_4, 55°C, 5h; (d) Me_2CuLi, Et_2O, 0°C, 0.5h; (e) NaOMe, MeOH, 40°C, 24h; (f) $(HOCH_2)_2$, TsOH, PhH, 80°C, 72h; (g) $LiAlH_4$, THF, 2h; (h) Me_3SiCl, NaI, CH_3CN, 0.5h; (i) $PhSO_2$-Amberlyst A-26, PhH, 80°C, 5h; (j) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 15h.

Alkylation of the dianion[11] of racemic 11 with 5[12] secured 12 (95% based on recovered 11) as a diastereomeric mixture (Scheme II). Dithiane hydrolysis with $HgCl_2$, sodium amalgam excision of the phenylsulfone[13] and stereospecific ketone reduction resulted in 13 (mp 145-146°C, 52%) and an equal amount of diastereomer which were separated chromatographically (SiO_2, 1:1 Et_2O/hexane, $R_f \sim 0.46$ and 0.39, respectively). Elaboration of 13 required N,N'-dicyclohexylcarbodiimide (DCC) esterification with (S)-(+)-2-methylbutyric acid (Aldrich), acidic lactol hydrolysis, pyridinium chlorochromate (PCC) oxidation[14] to the corresponding lactone, and HF desilylation affording 4 (53%) identical in all respects with an authentic sample[15], mmp 131°C (lit.[4] mp 131-132°C).

Scheme II



(a) 2 equiv BuLi, 20% HMPA/THF, 0°C, 30 min; (b) 5, THF, -78°C, warm to rt, 4h; (c) $HgCl_2$, $CaCO_3$, CH_3CN/H_2O 4:1, 80°C, 8h; (d) 6% Na(Hg), MeOH, 1h; (e) $Li(s\text{-}Bu)_3BH$, THF, 0°C, 0.5h; (f) S-(+)-$CH_3CH_2CH(CH_3)CO_2H$, DCC, DMAP, CH_2Cl_2, 72h; (g) 10% HCl/THF 3:5, 50°C, 4h; (h) PCC-Al_2O_3, CH_2Cl_2, 8h; (i) 48% HF/CH_3CN 1:10, 50°C, 6h.

Acknowledgment: The authors are grateful to Dr. Sukumar Manna for the preparation of numerous intermediates and to Dr. Robert L. Smith (Merck Sharp and Dohme) for a generous sample of natural (+)-dihydromevinolin. This work was supported by a grant-in-aid from the American Heart Association with funds contributed in part by the Texas Affiliate.

References and Notes

1. Total syntheses: (a) Wang, N.-Y.; Hsu, C.-T.; Sih, C.J. J. Amer. Chem. Soc. 1981, 103, 6538-6539; (b) Hirama, M.; Uei, M. ibid. 1982, 104, 4251-4253; (c) Grieco, P.A.; Zelle, R.E.; Lis, R.; Finn, J. ibid. 1983, 105, 1403-1404; (d) Hirama, M.; Iwashita, M. Tetrahedron Letters 1983, 24, 1811-1812; (e) Girotra, N.N.; Wendler, N.L. ibid., 1982, 23, 5501-5504.
2. Brown, M.S.; Faust, J.R.; Goldstein, J.L.; Kaneko, I.; Endo, A. J. Biol. Chem. 1978, 253, 1121-1128. Endo, A. Trends Biochem. Sci. 1981, 6, 10-13. Endo, A. Methods Enzymology 1981, 72, 684-689. Monger, D.J.; Lim, W.A.; Kézdy, F.J.; Law, J.H. Biochem. Biophys. Res. Comm. 1982, 105, 1374-1380. Bach, T.J.; Lichtenthaler, H.K. Naturwissenschaften 1982, 69, 242-243.

3. Lam, Y.K.T.; Gullo, V.P.; Goegelman, R.T.; Jorn, D.; Huang, L.; DeRiso, C.; Monaghan, R.L.; Putter, I. J. Antibiotics 1981, 34, 614-616.
4. Albers-Schönberg, G.; Joshua, H.; Lopez, M.B.; Hensens, O.D.; Springer, J.P.; Chen, J.; Ostrove, S.; Hoffman, C.H.; Alberts, A.W.; Patchett, A.A. J. Antibiotics 1981, 34, 507-512.
5. Yang, Y.-L.; Manna, S.; Falck, J.R. J. Amer. Chem. Soc., in press.
6. Chemical transformation from mevinolin: Kuo, C.H.; Patchett, A.A.; Wendler, N.L. J. Org. Chem. 1983, 48, 1991-1998.
7. For all new compounds, satisfactory ir, nmr and mass spectral data were obtained on chromatographically homogeneous samples.
8. Physical data for 7: NMR ($CDCl_3$) δ 1.44 (3H,d,J~7Hz), 1.60-2.60 (6H,m), 2.70-3.00 (2H,m), 3.10-3.50 (2H,m), 5.60-5.90 (2H,m), 7.30-7.70 (5H,m); TLC, SiO_2, 5% MeOH/CH_2Cl_2, R_f ~ 0.36. 9: NMR ($CDCl_3$) δ 0.87 (3H,d,J~7Hz), 0.97 (3H,d,J~7Hz), 1.50-3.00 (9H,m), 3.65 (3H,s), 5.39 (1H,brd,J~10Hz), 5.62 (1H,ddd,J ~2.5,4.5,10Hz); TLC, SiO_2, Et_2O/hexane 1:1, R_f ~ 0.35. 10: NMR ($CDCl_3$) δ 1.06 (3H,d,J ~ 7Hz), 1.08 (3H,d,J ~ 7Hz), 1.16-2.64 (9H,m), 3.00-3.28 (1H,m), 3.28-3.80 (2H,m), 3.80-4.16 (4H,m), 5.28 (1H,brd,J ~ 10Hz), 5.56 (1H,ddd,J ~2.5,4.5,10Hz); TLC, SiO_2, Et_2O/hexane 2:1, R_f ~ 0.23. 11: NMR ($CDCl_3$) δ:0.96 (3H,d,J ~7Hz), 0.99 (3H,d,J ~ 7Hz), 1.16-3.48 (16H,m), 5.07 (1H,dd,J ~ 2.5,14Hz), 5.26 (1H,brd,J ~ 10Hz), 5.58 (1H,ddd,J ~2.5,4.5,10Hz), 7.28-7.68 (3H,m), 7.72-8.04 (2H,m); TLC, SiO_2, Et_2O/hexane 1:1, R_f ~0.40.
9. Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. J. Org. Chem. 1979, 44, 1247-1251.
10. Manescalchi, F.; Orena, M.; Savoia, D. Synthesis 1979, 445-446.
11. Mussatto, M.C.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. J. Org. Chem. 1980, 45, 4002-4005.
12. Prepared from the corresponding alcohol by tosylation and displacement with NaI in acetone: Yang, Y.-L.; Falck, J.R. Tetrahedron Letters 1982, 23, 4305-4308; $[\alpha]_D^{23}$-35.3° (c 2.7, $CHCl_3$).
13. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. Tetrahedron Letters, 1976, 3477-3478.
14. Cheng, Y.S.; Liu, W.L.; Chen, S.H. Synthesis 1980, 223.
15. Physical data for 13: $[\alpha]_D^{23}$ + 25.8° (c 1.65, $CHCl_3$); NMR ($CDCl_3$) δ0.92 (3H,d,J ~7Hz), 1.15 (9H,s), 1.27 (3H,d,J ~ 7Hz), 1.30-2.70 (17H,m), 3.55 (3H,s), 3.72-4.08 (1H,m), 4.08-4.20 (1H,m), 4.20-4.36 (1H,m), 4.84 (1H,dd,J ~3,10Hz), 5.38 (1H,brd,J ~ 10Hz) 5.64 (1H,ddd,J ~2.5,4.5,10Hz), 7.24-7.48 (6H,m), 7.48-7.76 (4H,m); TLC, SiO_2, Et_2O/hexane 1:1, R_f ~ 0.46.

(Received in USA 30 May 1984)