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Access to an Optically Pure Key Intermediate of Dihydromevinolin

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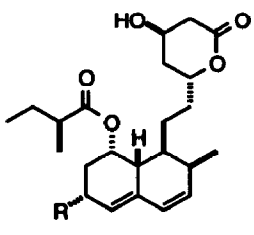
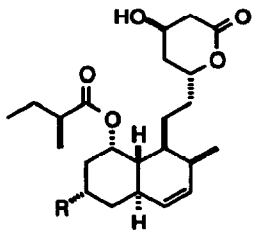
Abstract: An enantioselective route to the key intermediate of dihydromevinolin is described.

The mevinic acids compactin, mevinolin, and their dihydro-analogues have attracted considerable synthetic attention because of their biological activity as inhibitors of HMG CoA reductase, the rate-limiting enzyme in cholesterogenesis in man. Most plausible and intriguing strategy depends on the coupling of a decaline portion with a δ-lactone moiety.[1] Although several approaches have been attempted toward the construction of the decaline system present in mevinic acids, it is considered the intramolecular Diels-Alder (IMDA) reaction to be the most promising alternative. Interestingly, three different enantiomeric routes to the decaline portion have been reported in the literature recently,[2] all of which were achieved by IMDA reaction; Hanessian *et al.*[2a] and Lewis *et al.*[2b] have developed the enantioselective routes to the decaline systems using L-glutamic acid as the starting material, these routes were long and problematic. We report here a new efficient access to an optically pure key intermediate of dihydromevinolin, based on the allenyl ether IMDA strategy.[3]



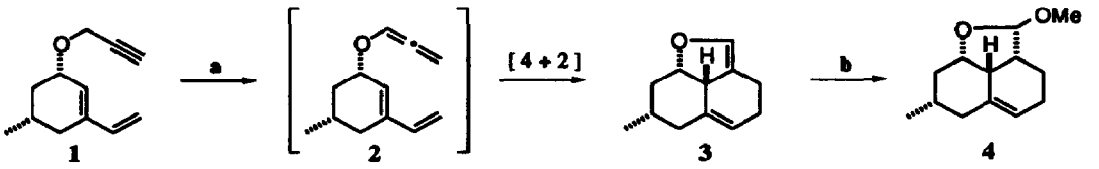
mevinolin (R=Me)
compactin (R=H)



dihyromevinolin (R=Me)
dihyrocompactin (R=H)

We prepared the desired substrate **1**, $[\alpha]_D^{23}$ +67.1° (*c* 1.3, $CHCl_3$)[4] from the readily available (*R*)-5-methyl-2-cyclohexenone[5] in four steps: (1) treatment of the enone, first with vinylmagnesium bromide in THF, then with aqueous H_2SO_4; (2) oxidation with MnO_2 in CH_2Cl_2; (3) reduction with $LiAlH_4$ in

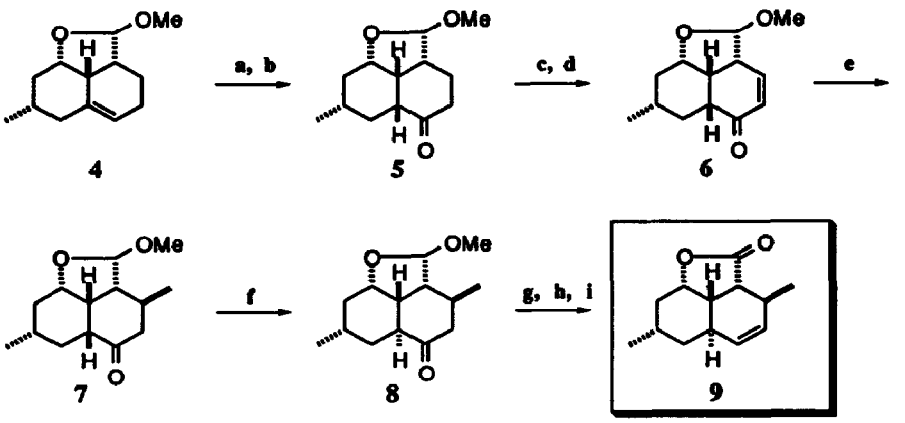
tetrahydrofuran; (4) etherfication with propargyl bromide [aq. NaOH-Et_2O, Bu_4NI(cat.); 41% overall yield]. When the ether **1** was heated in *t*-BuOH in the presence of *t*-BuOK (excess) for 1 h, the adduct **3** was obtained as the sole product *via* IMDA reaction of the allenyl ether intermediate **2** (Scheme 1). Without purification, the adduct **3** was treated with 5% solution of 10-camphorsulphonic acid (CSA) in methanol gave the methyl acetal **4**, $[\alpha]_D^{23}$ -52.0° (*c* 2.5, $CHCl_3$) in almost quantitative yield from the propargyl ether **1**.



Reagents and conditions ; (a) *t*-BuOK, *t*-BuOH, reflux., 1 h (b) 5% CSA in MeOH, 0 °C, 30 min., 99% yield from **1**.

Scheme 1

Hydroboration-oxidation of the alkene followed by oxidation (79% overall yield from **4**) furnished the *cis*-fused ketone **5**, $[\alpha]_D^{24}$ -129.1° (*c* 1.2, $CHCl_3$) (Scheme 2). The ketone was converted into the enone **6**, $[\alpha]_D^{25}$ -137.6° (*c* 1.2, $CHCl_3$) by Saegusa's method,[6] and stereoselective conjugate methylation was accomplished using lithium dimethyl cuprate to give the product **7**, $[\alpha]_D^{22}$ -40.1° (*c* 1.0, $CHCl_3$) as a



Reagents and conditions ; (a) BH_3•THF, THF, 0 °C, 20 h; 10% NaOH, 30% H_2O_2, 0 °C to room temperature, 2 h (b) PCC, Celite, CH_2Cl_2, 0 °C, 2 h, 79% yield from **4** (c) LDA, THF, -78 °C, 30 min.; TMSCl, -78 °C to room temperature, 2 h (d) $Pd(OAc)_2$, MeCN, 35 °C, 4 h, 89% yield from **5** (e) Me_2CuLi, Et_2O, 0°C, 2 h, 96% (f) K_2CO_3, MeOH, reflux., 2 h, 92% (g) *p*-$TsNHNH_2$, MeOH, reflux., 2 h (h) BuLi, THF, 0°C, 2 h (i) Jones reagent, acetone, 0°C, 2 h, 53% from **8**

Scheme 2

single diastereomer with the methyl group in axial position (96% yield). After epimerization of the methylated ketone **7** (92% yield), the resulting *trans*-fused ketone **8**, $[\alpha]_D^{26}$ +141.7° (*c* 1.0, $CHCl_3$) was converted into the less-substituted olefin by Bamford-Stevens reaction.[7] Finally, oxidation of the methyl acetal with Jones reagent afforded the desired fused tricyclic lactone **9**, $[\alpha]_D^{25}$ +121.6° (*c* 2.0, $CHCl_3$) in 53% overall yield from the ketone **8**, whose physical properties agreed with those reported by Hanessian.[2a] Since the lactone **9** has previously been converted into dihydromevinolin,[2a] our work reported herein constitutes its formal synthesis.

Thus, we have developed an efficient route to fused lactones *via* an IMDA reaction of allenyl ethers which permitted the preparation of the tricyclic intermediate for the convenient enantioselective synthesis of dihydromevinolin (11 steps in 32% total yield).

ACKNOWLEDGEMENT

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3. (a) We have already described the enantioselective route to forskolin intermediate by the analogous strategy, see: Nagashima, S.; Kanematsu, K. *Tetrahedron: Asymmetry*, **1990**, *1*, 743-749. (b) Similarly, an enantioselective approach to construction of the tetracyclic ring system leading to 3α-hydroxy-15-rippertene has recently been reported as the stage for the key IMDA reaction, see: Metz, P.; Bertels, S.; Fröhlich, R. *J. Am. Chem. Soc.*, **1993**, *115*, 12595-12596 and references cited therein.
4. All new compounds gave satisfactory analytical and/or spectral data. For example, **1** : ^{1}H-MNR ($CDCl_3$) δ 6.36 (dd, J=17.5, 10.6 Hz, 1H), 5.73 (bs, 1H), 5.18 (d, J=17.5 Hz, 1H), 5.03 (d, J=10.6 Hz, 1H), 4.40-4.25 (m, 1H), 4.27 (dd, J=15.7, 2.3 Hz, 1H), 4.20 (dd, J=15.7, 2.3 Hz, 1H), 2.42 (t, J=2.3 Hz, 1H), 2.30-2.25 (m, 1H), 2.22-2.05 (m, 1H), 1.82-1.59 (m, 2H), 1.17 (td, J=12.0, 10.0 Hz, 1H), 1.07 (d, J=6.3 Hz, 3H); MS m/z 176 (M^+, 12.3), 120 (45.9), 105 (100); HRMS m/z 176.1198 (calcd for $C_{12}H_{16}O$ 176.1200). **4** : ^{1}H-NMR ($CDCl_3$) δ 5.54 (m,

1H), 4.74 (d, J=3.6 Hz, 1H), 4.25 (q, J=5.2 Hz, 1H), 3.38 (s, 3H), 2.51 (m, 1H), 2.43-2.36 (m, 1H), 2.30-2.25 (m, 1H), 2.13-1.97 (m, 2H), 1.93-1.49 (m, 6H), 0.97 (d, J=6.9 Hz, 3H); MS m/z 208 (M^+, 4.9), 176 (85.6), 91 (100); HRMS m/z 208.1462 (calcd for $C_{13}H_{20}O_2$ 208.1464). **5** : ^{1}H-NMR ($CDCl_3$) δ 4.79 (s, 1H), 4.25 (dt, J=10.2, 7.3 Hz, 1H), 3.34 (s, 3H), 2.80 (dt, J=9.2, 7.8 Hz, 1H), 2.65-2.57 (m, 1H), 2.50 (td, J=7.7, 2.9 Hz, 1H), 2.38-2.31 (m, 2H), 2.10-1.77 (m, 3H), 1.64-1.43 (m, 2H), 1.03 (d, J=6.6 Hz, 3H), 1.01-0.87 (m, 1H); MS m/z 224 (M^+, 5.4), 192 (68.4), 164 (81.0), 122 (100); Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.75; H, 8.91. **6** : ^{1}H-NMR ($CDCl_3$) δ 6.72 (dd, J=10.1, 3.4 Hz, 1H), 6.06 (dd, J=10.1, 2.1 Hz, 1H), 4.88 (s, 1H), 4.21 (ddd, J=11.4, 9.0, 4.7 Hz, 1H), 3.36 (s, 3H), 3.14 (dt, J=8.1, 2.9 Hz, 1H), 3.00 (q, J=8.3 Hz, 1H), 2.56 (ddd, J=8.5, 5.2, 3.4 Hz, 1H), 2.19 (dt, J=12.8, 4.1 Hz, 1H), 1.82 (dt, J=13.4, 5.0 Hz, 1H), 1.72-1.58 (m, 2H), 1.06 (d, J=6.7 Hz, 3H), 0.91 (q, J=11.8 Hz, 1H); HRMS m/z 223.1325 (calcd for $C_{13}H_{19}O_3$ 223.1333); Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.29; H, 8.14. **7** : ^{1}H-NMR ($CDCl_3$) δ 4.84 (s, 1H), 4.20 (ddd, J=9.9, 8.7, 4.8 Hz, 1H), 3.37 (s, 3H), 2.93 (q, J=8.7 Hz, 1H), 2.57-2.49 (m, 1H), 2.44-2.37 (m, 1H), 2.12-1.56 (m, 7H), 1.08 (d, J=5.9 Hz, 3H), 1.06 (d, J=6.3 Hz, 3H), 1.09-0.95 (m, 1H); MS m/z 238 (M^+, 2.2), 206 (50.7), 178 (47.3), 136 (100); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.55; H, 9.34. **8** : ^{1}H-NMR ($CDCl_3$) δ 4.81 (s, 1H), 4.35 (q, J=5.9 Hz, 1H), 3.39 (s, 3H), 2.57-2.30 (m, 2H), 2.11-1.83 (m, 4H), 1.76-1.62 (m, 2H), 1.55-1.42 (m, 2H), 1.14-0.94 (m, 1H), 1.10 (d, J=5.3 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H); MS m/z 238 (M^+, 2.1), 206 (96.0), 178 (47.0), 136 (100); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.46; H, 9.27. **9** : ^{1}H-NMR ($CDCl_3$) δ 5.64 (dt, J=9.5, 2.3 Hz, 1H), 5.56 (dt, J=9.5, 2.4 Hz, 1H), 4.66 (td, J=6.9, 4.3 Hz, 1H), 2.56-2.52 (m, 1H), 2.45 (dd, J=7.3, 3.7 Hz, 1H), 2.01 (ddd, J=13.7, 7.2, 4.1 Hz, 1H), 1.96-1.78 (m, 3H), 1.69-1.48 (m, 3H), 1.24 (d, J=7.3 Hz, 3H), 1.03 (d, J=6.7 Hz, 3H).

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