A Concise Synthesis of (+)-Compactin Lactone by Asymmetric Dihydroxylation and Regioselective Cyclic Sulfite Opening Reactions

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A concise, enantioselective synthesis of compactin lactone **2** is described using the Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of cyclic sulfite as the key steps.

Introduction

Compactin **1a** and mevinolin **1b** (Figure 1) have attracted considerable global attention due to their unique structural features and biological activities as inhibitors of HMG-CoA reductase, which is the major rate-limiting enzyme responsible for the reduction of HMG-CoA to mevalonic acid.[1] Their ability to lower blood cholesterol levels, especially plasma low-density lipoprotein (LDL)[2] cholesterol in human beings, is important for the mitigation of arteriosclerosis. The key structural feature of these bioactive molecules is the chiral β-hydroxy-δ-lactone moiety **2**,[3] which in its open acid form closely mimics mevalonic acid, a crucial intermediate in the biosynthesis of cholesterol.

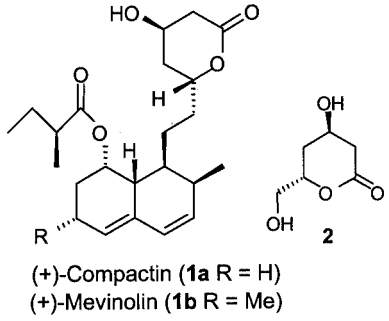
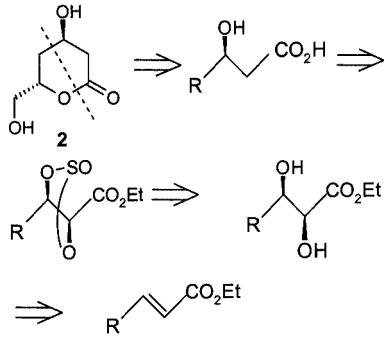


Figure 1. Structures of (+)-compactin (**1a**) and (+)-mevinolin (**1b**)

The unique structural features of this class of compounds, called "mevinic acids", and their potential applications as hypocholesterolemic agents have aroused great interest amongst synthetic organic chemists, resulting in an onslaught of activity directed at the stereocontrolled synthesis of the lactone moiety **2**.[4] Despite recent improvements in the synthetic methodology for the control of 1,3-asymmetry in the lactone **2**, most of them suffer either from low overall yields and/or a large number of steps involved. As part of our research interest in the asymmetric synthesis of bioactive molecules[5] mainly by stereoselective transformation of diols via cyclic sulfites/sulfates, we have developed an enantioselective synthesis of the δ-lactone unit of compactin. Herein we report a new and convenient synthesis of (4*R*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydropyran-2-one (**2**) in high enantiomeric excess utilizing the Sharpless asymmetric dihydroxylation (SAD) reaction and a regioselective opening of the cyclic sulfite as key steps.

Results and Discussion

Our synthetic approach for the synthesis of lactone **2** was envisioned through the retrosynthetic route shown in Scheme 1. The β-hydroxy acid was visualized as an ultimate precursor for the target molecule, which in turn could be obtained from the hydride opening of the corresponding cyclic sulfite and subsequent hydrolysis. The cyclic sulfite could be derived from an olefin through asymmetric dihy-



Scheme 1

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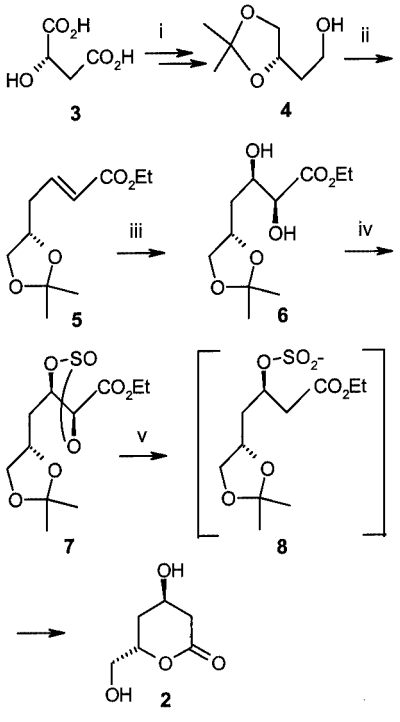
droxylation. The R group of the β-hydroxy acid represents the left half of the molecule **2**, which in turn could be derived from (*S*)-malic acid. Thus, the essential feature of our retro-analysis was the presumption that the nucleophilic opening of the cyclic sulfite would occur at the α-carbon. Another salient feature of the synthetic strategy was a one-pot reaction sequence of sulfite ester hydrolysis, acetonide deprotection and lactonization in order to furnish the desired lactone **2**. Thus, the C-6 chiral center of the lactone could be derived from (*S*)-malic acid while asymmetric dihydroxylation and the regioselective hydride opening of cyclic sulfite could establish the C-4 stereogenic center, which are the key steps in the synthesis.

The detailed synthetic route with reagents and reaction conditions is provided in Scheme 2. Our synthesis of target molecule **2** started from (*S*)-malic acid (**3**), which was converted into the known compound **4** following a literature procedure.[6] Swern oxidation of alcohol **4** followed by Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane furnished the *trans*-olefin **5**. The asymmetric dihydroxylation of olefin **5** with osmium tetroxide and potassium ferricyanide as cooxidant in the presence of 1,4-bis(dihydroquinidin-9-*O*-yl)phthalazine [$(DHQD)_2$-PHAL] as chiral ligand under the Sharpless asymmetric dihydroxylation reaction conditions,[7] gave the diol **6** in 84% yield with a good diastereoselectivity (94% *de*).[8]



Scheme 2. Reagents and conditions: (i) ref.[6]; (ii) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, (b) $Ph_3P{=}CHCO_2Et$, THF, room temp., 24 h, 83%; (iii) $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat), $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 24 h, 84%; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min, 90%; (v) $NaBH_4$, THF, 12 h, room temp., then 4 N H_2SO_4, MeOH, overnight, 63%

Further, in order to achieve the synthesis of the target compound **2** from **6**, we required C-2 deoxygenation through the regioselective hydride opening of a cyclic sulfite, deprotection of the acetonide and concomitant lactonization under acidic conditions. To this end, the diol **6** was reacted with thionyl chloride in the presence of Et_3N to afford the cyclic sulfite **7** in 90% yield.[9] The subsequent reactions involving one-pot conversion were carried out in the following manner: The treatment of cyclic sulfite **7** with one equivalent of $NaBH_4$ furnished the intermediate sulfite ester **8**, which, without any further isolation, was acidified with aqueous 4 N H_2SO_4 in MeOH to effect the one-pot sulfite ester hydrolysis, acetonide deprotection and lactonization, affording the lactone **2** in 63% yield.

Conclusion

In conclusion, a short, high yielding and efficient asymmetric synthesis of the lactone moiety of mevinic acids with the desired stereochemistry at C-4 and C-6 has been achieved. The presence of a hydroxylmethylene functionality at C-6 serves for easy coupling to the lower functionalized core of mevinic acids. The synthetic strategy can be extended to the synthesis of other isomers of the lactone moiety either by using the unnatural (*R*)-(+)-malic acid and/or employing the $(DHQ)_2$-PHAL ligand in asymmetric dihydroxylation. A short reaction sequence and high overall yield of the (+)-lactone renders our strategy a good alternative to the known methods.

Experimental Section

General Information: The solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60−80 °C was used. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded in $CDCl_3$ solution with residual $CHCl_3$ (δ = 7.27 ppm) as internal standard.

Compound 4: This compound was prepared following the literature method from (*S*)-malic acid.[6]

Compound 5: Dry DMSO (5.37 g, 4.9 mL, 68.70 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalyl chloride (4.36 g, 3 mL, 34.34 mmol) in CH_2Cl_2 (80 mL) at −78 °C. After 20 min, **4** (3.35 g, 22.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 30 min, giving a copious white precipitate. After stirring for 1 h at −60 °C, Et_3N (14.4 mL, 103.02 mmol) was added slowly and stirred for 1 h whilst allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into 2 N HCl (100 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde (3.1 g) as a pale yellow oil. This was used for the next step without further purification.

A solution of the aldehyde (3 g, 20.8 mmol) in THF (5 mL) at 0 °C was added to a solution of (ethoxycarbonylmethylene)triphenylphosphorane (9.75 g, 28 mmol) in dry THF (30 mL). The ice-bath

was removed and the reaction mixture was stirred for 24 h at room temperature and then concentrated. Column chromatography of the crude product on silica gel using petroleum ether/EtOAc (95:5) as eluent gave **5** (3.93 g, 83%) as a pale yellow oil: $[\alpha]_D^{20} = -17.9$ (c = 1, MeOH) {ref.[4o] $[\alpha]_D^{20} = -18$ (c = 2.48, MeOH)}. IR (neat): $\tilde{\nu}$ = 1713, 1650 cm^{-1}. ^1H NMR: δ = 1.25 (t, J = 8.0 Hz, 3 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 2.4−2.5 (dq, J = 2, 6 Hz, 2 H), 3.55 (dd, J = 2, 6 Hz, 1 H), 4.03−4.21 (m, 4 H), 5.85 (dt, J = 2, 16 Hz, 1 H), 6.90 (dt, J = 6, 16 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.04, 25.32, 26.65, 36.29, 59.82, 68.6, 74.11, 108.9, 123.61, 143.77, 165.53 ppm. EIMS: m/z (%) = 199 (59.5) [$M^+ - 15$], 169 (9.5), 139 (9.5), 111 (54.2), 101 (100), 83 (34), 67 (29.8), 55 (16.7). $C_{11}H_{18}O_4$ (214.25): calcd. C 61.66, H 8.46; found C 61.54, H 8.53.

Compound 6: OsO_4 (340 μL, 0.1 M soln in toluene, 0.8 mol %) and methanesulfonamide (0.4 g, 4.2 mmol) were added sequentially to a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2$-PHAL (33 mg, 42.4 mmol, 1 mol %) in tBuOH/H_2O (1:1, 50 mL) at 0 °C. After stirring for 5 min at 0 °C, the olefin **5** (0.9 g, 4.2 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave **6** (0.88 g, 84%) as a colorless syrupy liquid: $[\alpha]_D^{20} = +9.9$ (c = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3436, 1727 cm^{-1}. ^1H NMR: δ = 1.26 (t, J = 8.0 Hz, 3 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.8−1.9 (m, 2 H), 3.4 (s, 2 H), 3.6 (m, 1 H), 4.0−4.14 (m, 4 H), 4.28 (q, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 14.1, 23.6, 25.7, 36.8, 62, 68.1, 69.5, 70.25, 76.1, 108.8, 168.1 ppm. EIMS: m/z (%) = 233 (28) [$M^+ - 15$], 191 (8.7), 173 (8), 145 (10.8), 117 (24.7), 99 (69.3), 87 (100), 71 (66.9), 59 (77.7). $C_{11}H_{20}O_6$ (248.27): calcd. C 53.21, H 8.12; found C 52.98, H 8.31.

Compound 7: Et_3N (0.9 mL, 6.45 mmol) was added to a stirred ice-cooled solution of **6** (0.4 g, 1.61 mmol) in dry CH_2Cl_2 (5 mL) followed by a solution of $SOCl_2$ (0.18 mL, 2.45 mmol) in dry CH_2Cl_2 (2 mL) over 5 min. The reaction mixture was stirred for 30 min and then quenched by addition of H_2O (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and washed with brine (20 mL), dried (Na_2SO_4) and passed through a pad of neutral alumina. The filtrate was concentrated and column chromatography of the crude product on silica gel with petroleum ether/EtOAc (95:5) as eluent gave **7** (0.427 g, 90%) as a pale yellow oil: $[\alpha]_D^{20} = +87.9$ (c = 0.5, MeOH). IR (neat): $\tilde{\nu}$ = 1744, 1449, 1370, 1204 cm^{-1}. ^1H NMR: δ = 1.33 (t, J = 8.0 Hz, 3 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 2.2−2.35 (m, 2 H), 3.68 (dd, J = 2, 6 Hz, 1 H), 4.11 (dd, J = 2, 6 Hz, 2 H), 4.28 (q, J = 8.0 Hz, 2 H), 4.82 (m, 1 H), 5.28 (d, J = 8.0 Hz, 1 H) ppm. EIMS: m/z (%) = 295 (4.2) [$M^+ + 1$], 279 (100) [$M^+ - 15$], 169 (34.5), 155 (71.4), 127 (85.7), 99 (74.4), 81 (75.6), 69 (37.7), 59 (9). $C_{11}H_{18}O_7S$ (294.32): C 44.89, H 6.16, S 10.89; found C 45.07, H 6.39, S 10.66.

(+)-Compactin Lactone (2): $NaBH_4$ (22.5 mg, 0.594 mmol) was added under argon to a solution of cyclic sulfite **7** (175 mg, 0.594 mmol) in dry THF (8 mL). The reaction mixture was stirred under argon at room temperature for 12 h. The solvent was removed under reduced pressure and MeOH (5 mL) was added to the residue. The reaction mixture was acidified with 4 N H_2SO_4 (1 mL) and stirred at room temperature overnight. The solvent was stripped off under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:4) as eluent to give **2** (54 mg, 63%) as a colorless oil: $[\alpha]_D^{20} = +1.89$ (c = 0.5, MeOH). {ref.[4n] $[\alpha]_D^{29} = +1.81$ (c = 0.992, MeOH)}. IR (neat): $\tilde{\nu}$ = 3477, 2952, 1735 cm^{-1}. ^1H NMR: δ = 1.98 (m, 4 H), 2.71 (d, J = 4.0 Hz, 2 H), 4.0−4.07 (m, 2 H), 4.48 (quint, J = 4.0 Hz, 1 H), 4.7 (m, 1 H) ppm. EIMS: m/z (%) = 147 (4.2) [$M^+ + 1$], 115 (60), 73 (100).

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