Expedient, Stereocontrolled Synthesis of (+)-Compactin Lactone via Intramolecular Reformatsky Reaction

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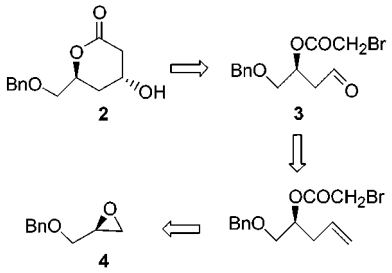
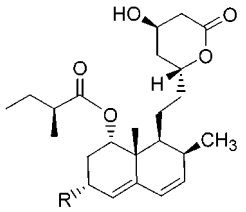
Abstract: A concise, stereodefined synthesis of compactin lactone is described. Samarium(II) iodide mediated intramolecular Reformatsky reaction is the key step in the synthesis.

Compactin (**1a**) and Mevinolin (**1b**) are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme involved in cholesterol biosynthesis.[1] These fungal metabolites have attracted much attention on account of their usefulness as metabolic probes for studying cholesterol homeostasis.[2] Their ability to lower blood cholesterol levels, especially plasma low-density lipoprotein (LDL)[3] cholesterol in human beings, provided tools for the mitigation of arteriosclerosis. The pivotal structural feature of these bioactive molecules is the chiral β-hydroxy-δ-lactone moiety[4] **2**, which in its open form, closely mimics mevalonic acid, a crucial intermediate in the biosynthetic pathway leading to cholesterol. The potential utility of this class of compounds as hypocholesterolemic agents and their interesting structural features have prompted extensive synthetic investigations[5] of this lactone, yet its synthesis remains a formidable challenge. Despite recent improvements in synthetic methodology for controlling 1,3-asymmetry in the lactone **2**, most of the syntheses suffer from low overall yields and, in some cases, a large number of steps. Now we have developed an efficient, stereocontrolled, high-yielding and reliable protocol to the (+)-compactin lactone **2**.

Scheme 1





(+)-Compactin (**1a** R = H)

(+)-Mevinolin (**1b** R = CH_3)

Intramolecular Reformatsky reactions of bromoacetates derived from β-hydroxy carbonyl substrates served as a potential route to 1,3-asymmetric induction by a carbon−carbon bond-forming process. Inspired by Molander's methodology,[6] samarium(II) mediated intramolecular Reformatsky reaction of the β-bromoacetoxy aldehyde **3** was envisaged as the key step in our synthesis of **2** (Scheme 1). The synthesis of the requisite **3** was planned starting from readily accessible (*R*)-*O*-benzylglycidol **4**. Earlier, Takano[5m] and co-workers reported a seven-step synthesis of **2** starting from epoxide **4**. Formation of carboxylic acid derivatives and cyclization to α,β-unsaturated lactone followed by catalytic hydrogenation were some of the salient features of their synthetic method. In our independent approach, sequential oxirane ring opening with vinylmagnesium bromide to give homoallyl alcohol, bromoacetylation, and ozonolysis provided a shorter route to lactone precursor **3**.

Thus, glycidyl ether **4** was reacted with vinylmagnesium bromide at −10 °C in the presence of a catalytic amount of copper(I) cyanide to furnish (4*S*)-5-benzyloxy-4-hydroxy-1-pentene (**5**) in excellent yield (Scheme 2). Bromoacetylation of the alkenol **5** with bromoacetyl bromide at 0 °C using 2,6-lutidine as the base afforded (4*S*)-5-benzyloxy-4-bromoacetoxy-1-pentene (**6**) in 89% yield. When pyridine was employed as the base in this reaction, a substantial amount of the pyridine-substituted product was formed as a byproduct. Ozonolysis of **6** followed by stirring with DMS at 0 °C for 10 h smoothly provided (3*S*)-4-benzyloxy-3-bromoacetoxybutanal (**3**). However, this β-bromoacetoxy aldehyde was prone to undergo elimination when passed through a silica column during the process of its purification. Hence, crude aldehyde was as such used for the next step. Treatment of **3** with *freshly prepared* samarium(II) iodide in THF at 0 °C for 2 h yielded (+)-lactone **2** in excellent yield (91% from **6**). Initial formation of Sm^{3+} ester enolate, cyclization through a rigid cyclic transition structure

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(6) (a) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. (b) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

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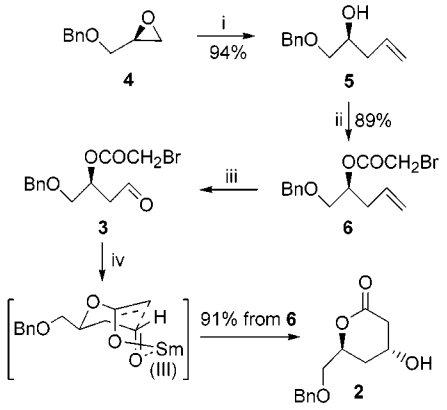
Scheme 2 [a]



[a] Reagents and conditions: (i) CH_2=CH−MgBr, CuCN, −10 °C; (ii) $BrCOCH_2Br$, 2,6-lutidine, 0 °C; (iii) O_3, CH_2Cl_2−MeOH; DMS; (iv) SmI_2, THF, 0 °C, 2 h.

enforced by chelation, was proposed[6] as the rationale for the stereoselectivity observed in samarium(II) iodide mediated intramolecular Reformatsky reactions. In the present case, exclusive formation of the (+)-lactone **2** (>95:5; vide ^{1}H and ^{13}C NMR) presumably proceeded via a low-energy transition structure (Scheme 2) assuming a chair-like conformation with the benzyloxymethyl group in the favorable equatorial position.

In conclusion, we have provided a new, concise, and stereocontrolled approach to the (+)-compactin lactone **2**. A shorter reaction sequence and high overall yield of the optically pure lactone rendered our protocol an alternative to the known methods.

Experimental Section

All experiments were carried out under argon in flame- or oven-dried glassware using syringe−septum cap techniques. THF was freshly distilled from sodium benzophenone ketyl under argon prior to use. Dichloromethane was distilled from calcium hydride. Flash column chromatography was performed using Merck silicagel 60 (Art. No. 7734). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ solution, and chemical shifts (δ) were given in parts per million relative to TMS. Carbon multiplicities were assigned by DEPT experiments.

(4*S*)-5-Benzyloxy-4-hydroxy-1-pentene (5). A round-bottom flask was charged with copper(I) cyanide (0.030 g, 0.55 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and THF (5 mL) was added. This suspension was cooled to −10 °C and vigorously stirred, and vinylmagnesium bromide (1 M in THF, 2.6 mL, 2.6 mmol) was injected into it. A solution of glycidyl ether **4** (0.41 g, 2.5 mmol) in THF (5 mL) was added slowly to the above reagent, and the mixture was stirred at −10 °C for 16 h. The reaction mixture was neutralized to pH 7 using 0.5 N HCl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes, 1:6) to furnish alcohol **5** (0.451 g, 94%) as a colorless oil: $[\alpha]_D^{23}$ +2.21 (*c* 2.8, $CHCl_3$); ^{1}H NMR 7.28−7.37 (m, 5H), 5.75−5.88 (m, 1H), 5.07−5.13 (m, 2H), 4.55 (s, 2H), 3.84−3.90 (m, 1H), 3.51 (dd, 1H, *J* = 9.6, 3.2 Hz), 3.37 (dd, 1H, *J* = 9.6, 7.2 Hz), 2.46 (s, 1H), 2.24−2.46 (m, 2H); ^{13}C NMR 137.90 (C), 134.18 (CH), 128.38 (CH), 127.71 (CH), 127.67 (CH), 117.58 (CH_2), 73.84 (CH_2), 73.31 (CH_2), 69.66 (CH), 37.85 (CH_2); IR (neat) 3416, 3070, 3030, 2893, 1641, 1450, 1273, 1094 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 193 (M + 1, 41), 192 (M^+, 92), 174 (M − 18, 98), 132 (M − 60, 100); HRMS (EI, 70 eV) $C_{12}H_{16}O_2$ calcd 192.1138, found 192.1147.

(4*S*)-5-Benzyloxy-4-bromoacetoxy-1-pentene (6). To a solution of homoallyl alcohol **5** (0.383 g, 1.99 mmol) in dry dichloromethane (10 mL) at 0 °C was added 2,6-lutidine (0.5 mL, 4.1 mmol) followed by bromoacetyl bromide (0.3 mL, 3.2 mmol), and the reaction mixture was stirred at 0 °C for 2 h. After the consumption of **5** (monitored by TLC), the reaction mixture was neutralized to pH 7 using 0.5 N HCl and the organic layer was separated. The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes, 1:10). Bromoacetoxypentene **6** (0.554 g, 89%) was obtained as a colorless oil: $[\alpha]_D^{24}$−1.25 (*c* 10.0, toluene); ^{1}H NMR 7.24−7.35 (m, 5H), 5.67−5.55 (m, 1H), 5.05−5.16 (m, 3H), 4.54 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 3.79 (s, 2H), 3.55 (s, 1H), 3.53 (s, 1H), 2.23−2.48 (m, 2H); ^{13}C NMR 166.5 (C), 137.7 (C), 132.5 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 118.3 (CH_2), 73.7 (CH), 73.0 (CH_2), 70.0 (CH_2), 35.0 (CH_2), 25.9 (CH_2); IR (neat) 3030, 2896, 1741, 1642, 1495, 1433, 1363, 1277 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 314 (M + 2, 63), 312 (M^+, 62), 260 (19), 258 (34), 233 (61), 206 (39); HRMS (EI, 70 eV) $C_{14}H_{17}O_3Br$ calcd 312.0361 and 314.0341, found 312.0370 and 314.0357.

(4*R*,6*S*)-6-Benzyloxymethyl-4-hydroxy-tetrahydro-2-pyrone (2). A solution of dichloromethane (10 mL) containing bromoacetoxypentene **6** (0.308 g, 0.99 mmol) and methanol (0.5 mL) was bubbled with ozone gas at −78 °C until a blue color persisted (about 3−4 min), and then DMS (1 mL) was added. The reaction mixture was warmed to 0 °C and stirred for an additional 10 h and then concentrated under reduced pressure. The residue was dissolved in ether (20 mL). The ethereal solution was washed with distilled water (5 mL) followed by brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting (3*S*)-4-benzyloxy-3-bromoacetoxybutanal[7] (**3**) was used in the next step without further purification.

A round-bottom flask was charged with samarium (40 mesh, 0.500 g, 3.33 mmol), connected to a vacuum system, heated on a flame (2−3 min), and cooled under a slow flow of argon. A solution of 1,2-diiodoethane (0.562 g, 2 mmol) in THF (12 mL) was added to the samarium under argon, and the mixture was stirred at room temperature until the solution turned deep blue in color (2 h). The reagent was cooled to 0 °C, and a solution of aldehyde **3** in THF (0.5 mL) was added to it; the mixture was stirred at 0 °C for 2 h. The reaction mixture was added to a saturated aqueous solution of NH_4Cl (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes, 4:1) to give (+)-compactin lactone **2** (0.212 g, 91% from **6**): $[\alpha]^{30}_D$ +6.82 (*c* 0.85, $CHCl_3$) (lit.[5e] $[\alpha]^{29}_D$ +6.59 (*c* 1.03, $CHCl_3$)); ^{1}H NMR 7.26−7.37 (m, 5H), 4.83−4.88 (m, 1H), 4.58 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.36−4.40 (m, 1H), 3.68 (dd, 1H, *J* = 10.4, 3.6 Hz), 3.60 (dd, 1H, *J* = 10.4, 4.4 Hz), 2.67 (dd, 1H, *J* = 18.0, 4.8 Hz), 2.59 (dd, 1H, *J* = 18.0, 1.2 Hz), 1.92−1.99 (m, 2H); ^{13}C NMR 170.5 (C), 137.6 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 75.0 (CH), 73.5 (CH_2), 71.5 (CH_2), 62.4 (CH), 38.5 (CH_2), 32.0 (CH_2); IR (neat) 3416, 3031, 2906, 1720, 1249, 1087, 744 cm^{-1}; MS (FAB) *m*/*z* (%) 237 (M + 1, 8), 238 (M + 2, 2), 91 (100).

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(7) To characterize (3*S*)-4-benzyloxy-3-bromoacetoxybutanal (**3**), it was prepared from **6** (0.10 g) following the procedure described in Experimental Section and purified by HPLC (E. Merck Catal. 51469 LiChrosorb CN-7μm column) eluting with EtOAc/hexanes (1:4). Pure aldehyde **3** was obtained as a colorless oil: $[\alpha]_D^{24}$ −12.8 (*c* 1.02, $CHCl_3$); ^{1}H NMR 9.71 (dd, 1H, *J* = 1.6, 1.2 Hz), 7.24−7.36 (m, 5H), 5.45−5.50 (m, 1H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.51 (d, 1H, *J* = 12.0 Hz), 3.80 (s, 2H), 3.63 (dd, 1H, *J* = 10.8, 3.2 Hz), 3.6 (dd, 1H, *J* = 10.8, 4.4 Hz), 2.81 (d, 1H, *J* = 1.6 Hz), 2.80 (d, 1H, *J* = 1.2 Hz); ^{13}C NMR 198.3 (CH), 166.4 (C), 137.3 (C), 128.3 (CH), 127.8 (CH), 127.6 (CH), 73.2 (CH_2), 69.8 (CH_2), 69.7 (CH), 44.4 (CH_2), 25.5 (CH_2); IR (neat) 3030, 2896, 1741, 1720, 1433, 1363 cm^{-1}; MS (FAB) *m*/*z* (%) 313 (M + 1, 100), 251 (M − 61, 39) 249 (M − 59, 39) 225 (M − 87, 39).