Enzymatic Acylation and Ring-Closing Olefin Metathesis: A Convenient Strategy for the Lactone Moiety of Compactin and Mevinolin

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Compactin (**1**) and mevinolin (**2**) are potent inhibitors of HMG-CoA reductase, the rate-limiting enzyme involved in cholesterol biosynthesis.[1] Both of these compounds have been shown to reduce serum cholesterol levels in animals as well as in humans.[2] The therapeutic efficacy of mevinolin has been well documented.[3] One of the key structural features of these fungal metabolites is the presence of a (4*R*,6*R*)-tetrahydro-2-pyrone unit that is essential for their biological properties.[4] As a consequence, a great deal of synthetic studies have been devoted to the optically active synthesis of the *β*-hydroxy-*δ*-lactone, as well as on the replacement of the complex hexahydronaphthalene moieties of compactin or mevinolin.[5] This effort has resulted in the discovery of numerous very potent and selective HMG-CoA reductase inhibitors in which the *δ*-lactone moiety has been attached to simpler aromatic fragments.[6] As part of our interest in the enzymatic methodologies for 1,3-diol synthons, we have developed an enantioselective synthesis of the *δ*-lactone unit of mevinolin (Figure 1). Herein, we report a convenient synthesis of (4*R*,6*S*)-tetrahydro-2-pyrone derivative **3** in high enantiomeric excess, utilizing an immobilized lipase catalyzed selective acylation of (±)-1-(benzyloxy)-4-penten-2-ol and a ring-closing olefin metathesis with Grubbs' catalyst as the key steps.

The key starting material, racemic homoallylic alcohol **5**, was prepared in multigram quantities by treatment of commercial benzyloxyacetaldehyde with allyltrimethylsilane in the presence of $TiCl_4$ in CH_2Cl_2 at −78 °C for 30 min. Enzymatic acylation of the racemic alcohol **5** with immobilized lipase PS-30 (25 wt % with respect to lipase PS-30) in the presence of isopropenyl acetate in dimethoxyethane at 37 °C for 36 h afforded the optically active alcohol ent-**5** (44% yield) and the acylated alcohol **6** (50% yield), which were separated by silica gel chromatography (Scheme 1).[7] The optical purity of ent-**5** (95% ee, $[\alpha]^{23}_D$ +2.1 (*c* 1.25, $CHCl_3$) was determined by formation of the Mosher ester and ^{19}F NMR analysis.[8] The control experiment without the enzyme proved that the nonenzymatic

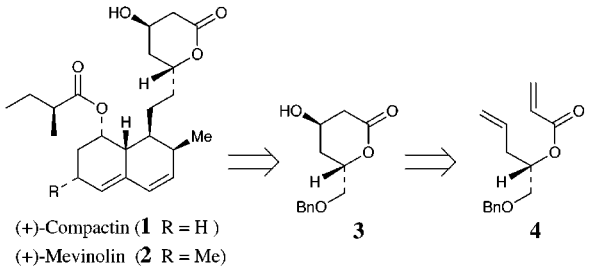
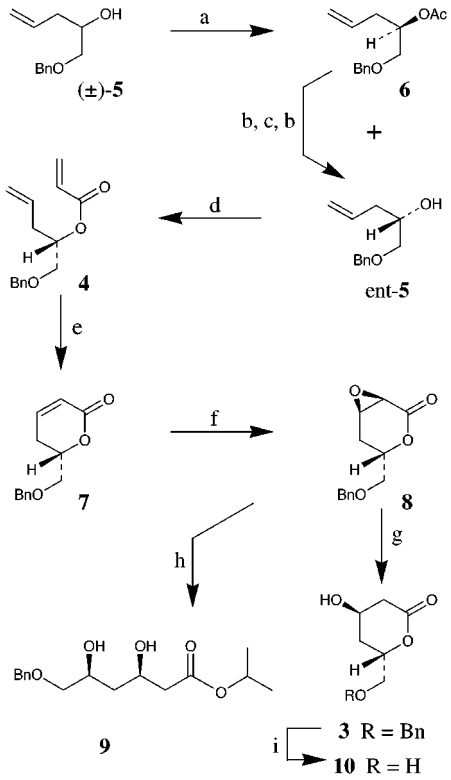


Figure 1.

Scheme 1[a]



[a] (a) immobilized lipase PS-30, CH_2=C(Me)OAc, DME, 37 °C, 36 h; (b) LiOH, THF−H_2O (1:4), 23 °C, 12 h; (c) *p*-NO_2PhCO_2H, Ph_3P, EtO_2C−N=N−CO_2Et, 23 °C, 12 h (91%); (d) CH_2=CHCOCl, Et_3N, DMAP (cat.), −15 °C, 30 min (75%); (e) $(PCy_3)_2Cl_2Ru$=CHPh (10 mol %), $Ti(OiPr)_4$ (0.3 equiv), CH_2Cl_2, 40 °C, 15 h (91%); (f) aq. NaOH, H_2O_2, MeOH, 23 °C (81%); (g) PhSeSePh, $NaBH_4$, *i*PrOH, AcOH, 0 °C (93%); (h) PhSeSePh, $NaBH_4$, *i*PrOH, 23 °C (90%); (i) H_2, Pearlman's catalyst, EtOAc, 5 h, 23 °C (70%).

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reaction was extremely slow (only a trace amount of acylated product after 48 h at 37 °C). The acetate **6** can be readily converted to 2-(*S*)-1-benzyloxy-4-penten-2-ol ent-**5** in a three-step sequence involving (1) saponification of **6** with aqueous lithium hydroxide at 23 °C for 12 h; (2) Mitsunobu inversion[9] of the resulting 2-(*R*)-alcohol with Ph_3P, *p*-NO_2-benzoic acid in the presence of diethylazodicarboxylate at 23 °C for 12 h; and (3) aqueous lithium hydroxide promoted saponification of the resulting benzoate derivative. The (*S*)-alcohol ent-**5** thus obtained (79% overall in three steps) has shown high optical purity (>96% ee) after formation of the Mosher ester and ^{19}F NMR analysis. The represented absolute configurations of the resolved alcohols were assigned on the basis of comparison of optical rotation with the literature data.[10]

Optically active homoallylic alcohol ent-**5** was converted to acrylate ester **4** by reaction with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 at −15 °C for 30 min. The acrylate ester **4** was isolated in 75% yield after silica gel chromatography. Olefin metathesis of **4** with commercially available Grubbs' catalyst (10 mol %) in the presence of $Ti(OiPr)_4$ (0.3 equiv) in refluxing CH_2Cl_2 for 15 h furnished the α,β-unsaturated δ-lactone **7** in 91% yield.[11] The ring-closing metathesis of acrylates utilizing Grubbs' catalyst thus provides a convenient access to various α,β-unsaturated γ- and δ-lactones.[12] Epoxidation of the unsaturated δ-lactone **7** with alkaline hydrogen peroxide in methanol at 23 °C for 30 min furnished the epoxide **8** as a single isomer in 81% yield after silica gel chromatography.[13] Treatment of **8** with diphenyldiselenide and sodium borohydride in 2-propanol at 23 °C in the absence of acetic acid furnished the isopropyl ester **9** exclusively in 90% yield after silica gel chromatography. Compound **9** consists of an important *syn*-1,3-diol subunit that is inherent to numerous biologically active natural products.[14] Exposure of the epoxide **8** to diphenyldiselenide and sodium borohydride in 2-propanol at 0 °C in the presence of acetic acid, however, afforded the β-hydroxylactone **3** in 93% yield after silica gel chromatography.[15] The removal of the benzyl protecting group was effected by catalytic hydrogenation of **3** over Pearlman's catalyst in ethyl acetate to furnish the compactin lactone **10** ($[\alpha]^{23}_D$ +1.8, *c* 0.18, MeOH; lit.[15a] $[\alpha]^{23}_D$ +1.81, *c* 0.992, MeOH).

In conclusion, lipase PS-catalyzed acylation and ring-closing olefin metathesis strategy provides convenient access to the lactone moiety of compactin in optically active form. Chemoselective reduction of the epoxylactone to the 1,3-diol subunit and the hydroxylactone unit is also noteworthy. Further application of this methodology in synthesis is currently underway.

Experimental Section

Melting points were recorded and are uncorrected. Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran and diethyl ether, distillation from sodium/benzophenone; methylene chloride, distillation from CaH_2; triethylamine, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

1-(Benzyloxy)-4-penten-2-ol [(±)-5]. To a stirred solution of benzyloxyacetaldehyde (2.5 g, 16.6 mmol) in dichloromethane (200 mL) was added titanium tetrachloride (1.8 mL, 16.6 mmol) at −78 °C. The resulting mixture was stirred for 10 min, allyltrimethylsilane (3.2 mL, 20 mmol, precooled to −78 °C) was added, and the mixture was stirred at −78 °C for 30 min. The reaction was then quenched with H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ solution and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure provided a residue that was purified by column chromatography on silica gel (10% EtOAc in hexanes as the eluent) to afford the title alcohol (±)-**5** (2.7 g, 84%) as an oil: IR (film) 3433, 2905, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25−2.28 (m, 2H), 3.40 (dd, 1H, *J* = 9.7, 3.3 Hz), 3.52 (dd, 1H, *J* = 9.7, 7.5 Hz), 3.91 (m, 1H), 4.56 (s, 2H), 5.05−5.15 (m, 2H), 5.88 (m, 1H), 7.29−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9, 69.7, 73.3, 73.9, 117.6, 127.7, 128.4, 134.2, 137.9; MS (CI) *m*/*z* 193 ($M^+ + H$).

(*R*)-1-(Benzyloxy)-4-penten-2-oyl acetate [6] and (*S*)-1-(Benzyloxy)-4-penten-2-ol [(+)-5]. To a stirred solution of alcohol (±)-**5** (2.35 g, 12.2 mmol) in a mixture of isopropenyl acetate (60 mL) and 1,2-dimethoxyethane (60 mL) was added immobilized lipase PS-30 (2.3 g). The resulting mixture was stirred at 37 °C for 36 h. The mixture was cooled to 23 °C and filtered. After removal of the solvent under reduced pressure, silica gel chromatography (5% EtOAc in hexanes) afforded the ester **6** (1.45 g, 50%): $[\alpha]^{23}_D$ −5.43 (*c* 3.13, $CHCl_3$); IR (film) 2920, 2861, 1739, 1372, 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.37−2.41 (m, 2H), 3.52 (d, 2H, *J* = 4.8 Hz), 4.54 (ABq, 2H, $\Delta\nu_{AB}$= 28.9, *J* = 12.1 Hz), 5.07−5.11 (m, 3H), 5.69 (m, 1H), 7.29−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 35.4, 70.5, 71.9, 73.1, 118.0, 127.6, 127.7, 128.4, 133.2, 138.0, 170.6. Optically pure alcohol (+)-**5** (1.03 g, 44%): $[\alpha]^{23}_D$ +2.08 (*c* 1.25, $CHCl_3$); lit.[10] $[\alpha]_D^{23}$ +1.96 (*c* 2.3, $CHCl_3$); MS (CI) *m*/*z* 193 ($M^+ + H$).

(*R*)-1-(Benzyloxy)-4-penten-2-ol [(−)-5]. To a stirred solution of ester **6** (1.25 g, 5.4 mmol) in THF (5 mL) and H_2O (20 mL) was added $LiOH\cdot H_2O$ (0.45 g, 18.8 mmol). The solution was stirred at room temperature for 12 h and was quenched by saturated NH_4Cl (30 mL). The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc (2 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give the pure alcohol (918 mg, 90%): $[\alpha]^{23}_D$ −2.20 (*c* 2.64, $CHCl_3$).

(*S*)-1-(Benzyloxy)-4-penten-2-oyl *p*-Nitrobenzoate. To a stirred solution of the alcohol (−)-**5** (482 mg, 2.51 mmol), triphenylphosphine (3.29 g, 12.6 mmol), and *p*-nitrobenzoic acid (1.84 g, 11.0 mmol) in dry benzene (80 mL) at 23 °C was added dropwise diethylazodicarboxylate (1.94 mL, 12.6 mmol). After 12 h, the mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography (2.5% EtOAc in hexanes) to give the ester (786 mg, 91%): $[\alpha]^{23}_D$ +3.51 (*c* 2.51, $CHCl_3$); IR (film) 1724, 1526, 1348, 1273, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52−2.57 (m, 2H), 3.68 (d, 2H, *J* = 4.4 Hz), 4.57 (ABq, 2H, $\Delta\nu_{AB}$ = 28.9, *J* = 12.2 Hz), 5.08 (dd, 1H, *J* = 10.1, 0.8 Hz), 5.14 (dd, 1H, *J* = 17.1, 1.6 Hz), 5.39 (m, 1H), 5.79 (m, 1H), 7.29−7.32 (m, 5H), 8.24 (ABq, 4H, $\Delta\nu_{AB}$= 35.0, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 70.4, 73.2, 73.6, 118.6, 123.5, 127.6, 127.8, 128.4, 130.8, 132.7, 135.8, 137.8, 150.5, 164.2.

Conversion of *p*-Nitrobenzoate to (*S*)-1-(Benzyloxy)-4-penten-2-ol [(+)-5]. To a stirred solution of the above ester (761

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mg, 2.22 mmol) in THF (20 mL) and H_2O (80 mL) was added $LiOH·H_2O$ (326 mg, 7.8 mmol). The solution was stirred at room temperature for 4 h and was quenched by saturated NH_4Cl (30 mL). The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give pure alcohol (+)-**5** (412 mg, 97%): $[\alpha]^{23}_D$ +2.16 (*c* 2.59, $CHCl_3$).

(*S*)-1-(Benzyloxy)-4-penten-2-ol Acryloyl Ester [4]. To a stirred solution of alcohol (+)-**5** (886 mg, 4.61 mmol) and 4-(dimethylamino)pyridine (56 mg, 0.46 mmol) in dichloromethane (60 mL) was added triethylamine (1.93 mL, 13.8 mmol). The mixture was cooled to −15 °C, and acryloyl chloride (0.56 mL, 6.9 mmol) was added slowly. After stirring for 30 min, the reaction was quenched with aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Silica gel chromatography (5% EtOAc in hexanes) gave the ester **4** as an oil (850 mg, 75%): $[\alpha]^{23}_D$ +1.58 (*c* 1.27, $CHCl_3$); IR (film) 3068, 3031, 2906, 2863, 1724, 1630, 1405, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39−2.49 (m, 2H), 3.58 (d, 2H, J = 4.9 Hz), 4.55 (ABq, 2H, $\Delta\nu_{AB}$ = 28.4, J = 12.4 Hz), 5.06 (dd, 1H, J = 10.5, 1.4 Hz), 5.10 (dd, 1H, J = 17.5, 1.4 Hz), 5.17 (m, 1H), 5.74 (m, 1H), 5.83 (dd, 1H, J = 10.5, 1.6 Hz), 6.14 (dd, 1H, J = 17.5, 10.5 Hz), 6.42 (dd, 1H, J = 17.5, 1.6 Hz), 7.28−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 70.4, 72.0, 73.1, 118.0, 127.5, 127.6, 128.3, 128.5, 130.7, 133.1, 137.9, 165.6; MS (CI) *m*/*z* 247 (M^+ + H); HRMS (EI) *m*/*z* calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1251.

(*S*)-6-Benzyloxymethyl-5,6-dihydro-2-pyrone [7]. To a stirred solution of ester **4** (694 mg, 2.82 mmol) in dichloromethane (180 mL) was added titanium isopropoxide (0.25 mL, 0.85 mmol). The resulting mixture was heated at 40 °C for 1 h, and then Grubbs' catalyst (230 mg, 0.28 mmol) dissolved in dichloromethane (10 mL) was added dropwise to the mixture. The mixture was heated at 40 °C for 15 h. After this period, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc in hexanes) to give the lactone **7** (562 mg, 91%) as an oil: $[\alpha]^{23}_D$ −116 (*c* 1.3, $CHCl_3$); IR (film) 3061, 3031, 2913, 2867, 1724, 1386, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37−2.60 (m, 2H), 3.70 (d, 2H, J = 4.8 Hz), 4.58−4.63 (m, 3H), 6.02 (ddd, 1H, J = 9.8, 2.9, 1.0 Hz), 6.89 (ddd, 1H, J = 9.8, 5.9, 2.5 Hz), 7.29−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 70.7, 73.6, 76.5, 121.1, 127.6, 127.8, 128.4, 137.6, 144.8, 163.6; HRMS (EI) *m*/*z* calcd for $C_{13}H_{14}O_3$ (M^+) 219.1021, found 219.1004.

(3*R*,4*R*,6*S*)-6-(Benzyloxy)methyl-3,4-epoxy-tetrahydro-2-pyrone [8]. To a stirred solution of the α,β-unsaturated lactone **7** (368 mg, 1.69 mmol) in MeOH (15 mL) was added 30% aqueous H_2O_2 (0.65 mL, 5.69 mmol) and 6 N aqueous NaOH (0.17 mL, 1 mmol) at 23 °C. After stirring for 1 h, the mixture was diluted with Et_2O (50 mL) and H_2O (20 mL), and the solution was acidified to pH 3−4 by addition of concentrated HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure, and the residual oil in benzene (15 mL) was heated at reflux with azeotropic removal of water. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (30% EtOAc in hexanes as the eluent) to give pure **8** (342 mg, 81%) as colorless oil: $[\alpha]_D^{23}$ +46.7 (*c* 1.3, $CHCl_3$); IR (film): 2924, 2866, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (m, 1H), 2.35 (m, 1H), 3.54−3.64 (m, 3H), 3.68 (m, 1H), 4.59 (ABq, 2H, $\Delta\nu_{AB}$ = 17.9, J = 12.0 Hz), 4.65 (m, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 49.0, 52.0, 70.4, 73.0, 73.4, 127.6, 127.8, 128.4, 137.5, 167.2; MS (CI) *m*/*z* 235 (M^+ + H); HRMS (EI) *m*/*z* calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0883.

(3*R*,5*S*)-6-Benzyloxy-3,5-dihydroxyhexanoic Acid Isopropyl Ester [9]. To a stirred suspension of diphenyl diselenide (1.58 g, 5.06 mmol) in *i*PrOH (30 mL) was added $NaBH_4$ (383 mg, 10.1 mmol) at 23 °C. The resulting mixture was stirred for 1 h, and a solution of epoxy lactone **8** (790 mg, 3.37 mmol) in *i*PrOH (10 mL) was added dropwise. After stirring for an additional 1 h, the mixture was diluted with EtOAc (30 mL), and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure provided a residue that was purified by silica gel chromatography (50% EtOAc in hexanes as the eluent) to give the pure ester **9** (891 mg, 90%) as a white solid (mp 56−57 °C): $[\alpha]^{23}_D$ −12.8 (*c* 1.92, $CHCl_3$); IR (film) 3411, 2982, 2910, 1709, 1453, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 6H, J = 6.4 Hz), 1.60−1.66 (m, 2H), 2.42−2.47 (m, 2H), 3.42−3.45 (m, 2H), 4.07 (m, 1H), 4.27 (m, 1H), 4.56 (s, 2H), 5.05 (m, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 38.9, 41.8, 68.2, 68.3, 70.5, 73.4, 74.1, 127.8, 127.8, 128.5, 137.9, 172.0; HRMS (EI) *m*/*z* calcd for $C_{16}H_{24}O_5$ (M^+) 296.1624, found 296.1639.

(4*R*,6*S*)-6-(Benzyloxy)methyl-4-hydroxy-tetrahydro-2-pyrone [3]. To a stirred suspension of diphenyl diselenide (150 mg, 0.48 mmol) in 2-propanol (5 mL) was added $NaBH_4$ (36 mg, 0.96 mmol) at 23 °C. The resulting mixture was stirred for 2 min, and AcOH (0.13 mL, 2.24 mmol) was added. After stirring for an additional 5 min, the mixture was cooled to 0 °C, and a solution of the epoxy lactone **8** (74.4 mg, 0.32 mmol) in *i*PrOH (4 mL) was added dropwise to the mixture. The resulting mixture was stirred for 30 min at 0 °C and then diluted with EtOAc (30 mL). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue that was purified by silica gel chromatography (70% EtOAc in hexanes as the eluent) to furnish **3** (70 mg, 93%) as a colorless oil: $[\alpha]^{23}_D$ +6.8 (*c* 0.4, $CHCl_3$); IR (film) 3423, 2920, 2867, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90−1.96 (m, 2H), 2.55−2.66 (m, 2H), 3.59 (dd, 1H, J = 10.7, 4.4 Hz), 3.68 (dd, 1H, J = 10.7, 3.7 Hz), 4.34 (m, 1H), 4.55 (s, 2H), 4.84 (m, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 38.4, 62.1, 71.6, 73.4, 75.2, 127.6, 127.7, 128.4, 137.6, 170.9; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{17}O_4$ (M^+ + H) 237.1127, found 237.1123.

(4*R*,6*S*)-4-Hydroxy-6-hydroxymethyltetrahydro-2-pyrone [10]. To a stirred solution of the benzyl ether **3** (40.8 mg, 0.17 mL) in EtOAc (3 mL) containing 5 drops of $CHCl_3$ was added $Pd(OH)_2$ (6.9 mg); the resulting solution was placed under a H_2 balloon and stirred at 23 °C for 5 h. The mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual oil was purified by silica gel chromatography (EtOAc) to give pure **10** (17.2 mg, 70%) as a colorless oil: $[\alpha]^{23}_D$ +1.8 (*c* 0.18, MeOH); lit.[15a] $[\alpha]^{23}_D$ +1.81 (*c* 0.992, MeOH); IR (film) 3377, 2930, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90−2.04 (m, 4H), 2.68−2.76 (m, 2H), 3.68 (dd, 1H, J = 12.4, 4.6 Hz), 3.93 (dd, 1H, J = 12.4, 2.8 Hz), 4.48 (m, 1H), 4.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 38.5, 62.7, 64.5, 76.2, 169.6; MS (CI) *m*/*z* 147 (M^+ + H); HRMS (EI) *m*/*z* calcd for $C_6H_9O_3$ (M^+ − OH) 129.0552, found 129.0545.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **3**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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