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SYNTHESIS OF ENANTIOMERIC PURE INTERMEDIATE FOR THE LACTONE PORTION OF COMPACTIN AND MEVINOLIN.

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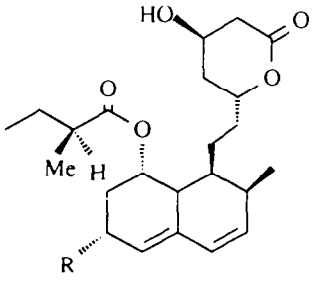
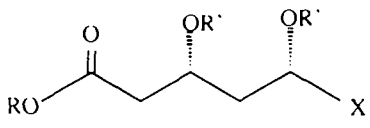
Abstract. A diastereo and enantioselective synthesis of compound ***11****, a potential useful intermediate for the lactone portion of mevinolin and compactin, was developed. Our strategy is based on the high stereoselective Michael addition of alkoxide to chiral norephedrine-derived oxazolidine* ***4****.*

Compactin **1**, mevinolin **2** and related compounds are potent inhibitors of 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis.[1] These compounds have been shown to lower serum cholesterol levels in animal models and man and thus may provide important tools in the prevention and treatment of coronary artery disease.[1] In recent years, these compounds have been the targets of an increasing number of synthetic efforts,[2] directed toward the development of structurally simplified HMG-CoA reductase inhibitors. The structural modifications regard mainly the lipophilic part of the molecule, the lactone portion being essential for biological activity. Introduction of the required 4R,6R lactone-ring stereochemistry has proved to be the most problematic.[3] For this reason it could be helpful to have a diastereoisomeric and enantiomeric pure lactone intermediate, like **3** (Figure 1), possesing a versatile functionality X (e.g. X=CHO, Figure 1) which provides a useful handle for manipulation to more complex structures.

Figure 1



R= H **1**
R= Me **2**



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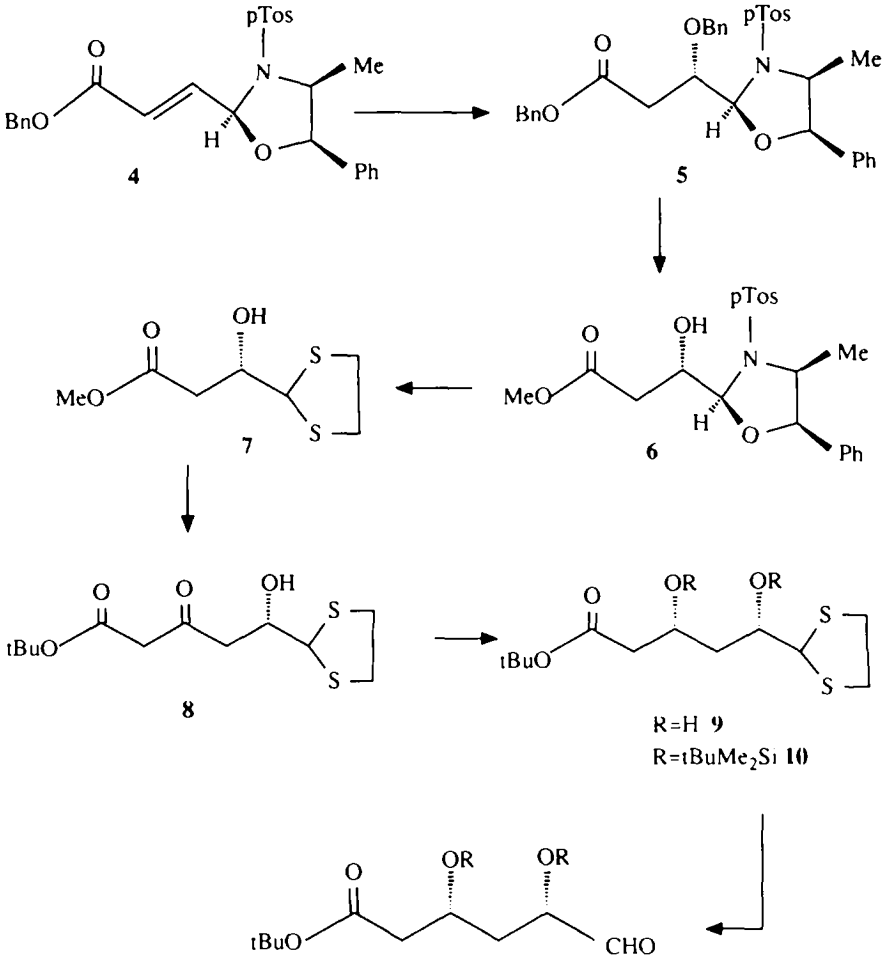
Here, we wish to report a diastereo- and enantioselective approach to lactone-intermediate **11** (Scheme 1) based on the use of chiral norephedrine-derived oxazolidines.[4] These substrates have proved to be excellent Michael acceptors that add nucleophiles selectively on the *si* face.[4]

Scheme 1

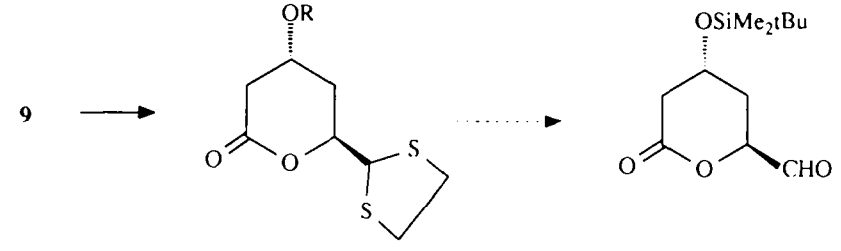


Our method starts with α,β-unsaturated benzyl ester **4** which can easily be prepared on a large scale from the commercially available (1R,2S)-norephedrine. Benzyl ester **4** was subjected to sodium benzylate addition (4 eq $PhCH_2ONa$, $PhCH_2OH$:THF 2:1, -30°C, 60h) affording compound **5** in 93:7 diastereoisomeric ratio (^{13}C NMR) and 96% isolated chemical yield (Scheme 1).[4g,5] **5** was then hydrogenated (H_2, Pd/C, MeOH/THF/H_2O) to remove the benzyl groups. The resulting crude β-hydroxy acid was transformed into the corresponding methyl ester **6** by treating its cesium salt with methyl iodide in DMF at room temperature. After flash chromatography, the methyl ester **6** was isolated in 82% overall yield as a single isomer (>98:2 by ^1H and ^{13}C NMR spectroscopy). The chiral oxazolidine was then removed by treating **6** with ethanedithiol and boron trifluoride etherate in methylene chloride to give dithiolane **7** (85% yield) and optically pure (1R,2S)-N-Tosyl norephedrine

(90% recovery). Treatment of ester **7** with 5 equivalents of t-butylacetate lithium enolate in tetrahydrofuran at -78°C for 30 min and at 0°C for 30 min resulted in the formation of β-keto-δ-hydroxy ester **8** in 95% yield. The β-keto functionality was then reduced with complete stereocontrol by treating **8** with methoxydiethylborane-sodium borohydride in tetrahydrofuran-methanol (4:1)[6] affording the *syn*-diol **9** as the only detectable isomer (^1H and ^{13}C NMR) in 95% yield. The *syn* configuration and the diastereoisomeric purity were determined by ^{13}C NMR spectroscopy. To this end, a mixture of *syn* and *anti* diol **9** (1.2:1), obtained by reduction of **8** with $NaBH_4$ in THF/MeOH (5:1), was analyzed *via* ^{13}C NMR. The relevant diagnostic resonances are those due to the two carbinol carbons that in 1,3-*syn* diols always resonate more downfield than those in 1,3-*anti* diols (Solvent $CDCl_3$: *syn*-diol **9**: Cβ 68.1, Cδ 75.3; *anti*-diol **9**: Cβ 65.4, Cδ 72.1).[6,7] The *syn*-diol **9** was then protected as bis(t-butyldimethylsilyl)ether ($tBuMe_2SiOTf$, imidazole, DMF 82% yield) and the dithiolane **10**[8] was hydrolized (MeI, $CaCO_3$, acetone/H_2O) to aldehyde **11** (70% yield).

We also investigated the possibility of obtaining the analogous intermediate in the cyclic form. In order to achieve this goal, the diol ester **9** was saponified with sodium hydroxide in aqueous methanol, acidified to pH 4, and the resulting acid was lactonized by heating in toluene at 90°C for 3 days to afford lactone **12** in 82% yield (Scheme 2). The β-hydroxy lactone **12** was then transformed into t-butyldimethylsilyl ether **13** (85% yield). Although a number of different reaction conditions were tried, every attempt to hydrolize the dithiolane to aldehyde **14** was unsuccesseful. Most of the conditions developed, afforded only extensive decomposition of the starting material. These negative results can be ascribed to the instability of the β-substituted δ-lactone ring. The inability to obtain the cyclic form **14** is not a very serious problem since most of the reported syntheses of mevinic derivatives postpone the lactone-cyclization to a later stage of the synthetic scheme.[2] Moreover such cyclization step may well be unnecessary for the biological activity since it is well known that the active forms of mevinolin and compactin are the respective open-chain dihydroxy acids.[9]

Scheme 2



R=H **12**

R=tBuMe$_2$Si **13**

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In summary, we have reported a new and interesting application of chiral norephedrine-derived oxazolidines to the diastereo- and enantioselective synthesis of compound **11**. This intermediate can be useful for manipulation to more complex structures allowing a potential access into a range of optically active mevinic derivatives.

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EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in a 1 dm cell of 1 ml capacity by using a Perkin-Elmer 457 spectrophotometer. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography. "Dry" solvents were distilled under N_2 just before use: tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone; dimethyl formamide (DMF) and methylene chloride from CaH_2. All reactions employing dry solvents were run under nitrogen (from liquid N_2) atmosphere.

α,β-Unsaturated benzyl ester **4**. This compound was synthesized from the corresponding α,β-unsaturated aldehyde which was obtained as reported in ref.4c. A solution of the α,β-unsaturated aldehyde (7.0 g, 18.87 mmol) in tBuOH (75.6 ml) and 2-methyl-2-butene (16.98 ml) was treated with a solution of $NaClO_2$ (6.0 g, 56.6 mmol) and NaH_2PO_4 H_2O (7.8 g, 56.6 mmol) in 61 ml of water. The reaction mixture was stirred at room temperature overnight. The volatile components were removed under vacuum, the residue was tacken up with 100 ml of 10% HCl and extracted with methylene chloride. The combined organic extracts were washed with water, dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude α,β-unsaturated acid was dissolved in methanol (37.7 ml) and treated with a methanolic solution of KOH (0.4 M, 47.2 ml). After stirring at room temperature for 5 min, the solvent was evaporated. The potassium carboxylate was suspended in CH_3CN (188 ml); benzyl bromide (11.2 ml, 94.35 mmol) and tetrabutylammonium hydrogensulfate (320 mg, 0.94 mmol) were added and the reaction mixture was stirred for 6 h. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (n-hexane/AcOEt 8/2) to give benzyl ester **4** in 88% yield. ^1H NMR ($CDCl_3$, 200MHz) δ: 0.83 (3H, d, J=7.25Hz), 2.50 (3H, s), 4.08-4.21 (1H, m), 4.44 (1H, d, J=5.01Hz), 5.24 (2H, s), 5.65 (1H, d, J=4.40Hz), 6.39 (1H, d, J=16.00Hz), 7.06 (1H, dd, J=16.00, 4.40Hz), 7.30-7.90 (15H, m). ^{13}C NMR ($CDCl_3$, 50.3MHz) (selected data) δ: 17.1, 21.6, 58.4, 66.6, 81.6, 87.8, 165.5. IR ($CHCl_3$) ν: 1721, 1595, 1350, 1160 cm^{-1}. $[\alpha]_D^{25}$= -40.0° (c 0.89, $CHCl_3$).

β-Benzyloxy benzyl ester **5**. A suspension of 60% NaH in mineral oil (334 mg, 8.36 mmol) was treated with 3.6 ml of benzyl alcohol and stirred under nitrogen at 40°C. After 1 h, the reaction mixture was diluted with 1.82 ml of THF and cooled at -30°C. At this temperature, a solution of **4** (1 g, 2.09 mmol) in benzyl alcohol/THF (3.6 ml/1.82 ml) was added and the reaction mixture was stirred for 60 h. The reaction was then quenched with 1.7 M AcOH in THF (5.4 ml), water was added and the mixture extracted with ethyl ether. The organic extracts were dried over sodium sulfate, the solvent evaporated and benzyl alcohol was removed by Kugelrohr distillation in vacuo. The crude product was purified by flash chromatography (n-hexane/AcOEt 8/2) to give **5** (93:7 diastereoisomeric ratio, 96% yield). ^1H NMR ($CDCl_3$, 200MHz) δ: 0.82 (3H, d, J=6.69Hz), 2.49 (3H, s), 2.93 (2H, d, J=6.30Hz), 3.96 (1H, dq, J=6.69, 6.45Hz), 4.21 (1H, d, J=6.45Hz), 4.59 (1H, td, J=6.30, 2.70Hz), 4.79 (2H, s), 5.05 (1H, d, J=2.70Hz), 5.14 (1H, d, J=12.9Hz), 5.23 (1H, d, J=12.9Hz), 7.10-7.68 (20H, m). ^{13}C NMR ($CDCl_3$, 50.3MHz) (selected data) δ: 17.5, 21.6, 34.7, 58.5, 66.5, 73.9, 77.9, 81.0, 90.4, 171.4. IR ($CHCl_3$) ν: 1735, 1450, 1350, 1160, 1085 cm^{-1}. $[\alpha]_D^{25}$=-39.1° (c 0.76, $CHCl_3$). mp 86°C.

Minor diastereoisomer: ^1H NMR ($CDCl_3$, 200MHz) δ: 0.90 (3H, d, J=6.08Hz), 2.89 (2H, d, J=6.09Hz), 4.17 (1H, d, J=7.00Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: 60.6, 65.1, 75.1, 77.3.

Methyl ester **6**. Benzyl ester **5** (4.25 g, 7.26 mmol) in 100 ml of THF/MeOH/H_2O (2.5/1.2/1.0) was hydrogenated in the presence of a catalytic amount of 10% Pd/C. After 48 h, the reaction mixture was filtered and the solvent evaporated under reduced pressure to give the crude β-hydroxy acid. ^1H NMR (CD_3OD, 200MHz) δ: 0.81 (3H, d, J=6.54Hz), 2.47 (3H, s), 2.60-2.83 (2H, m), 4.03-4.16 (1H, m), 4.17 (1H, d, J=5.10Hz), 4.45-4.52 (1H, m), 5.09 (1H, d, J=3.22Hz), 7.12-7.95 (9H, m). ^{13}C NMR (CD_3OD, 50.3MHz) (selected data) δ: 18.0, 21.7, 37.2, 60.1, 71.5, 82.4, 93.7, 176.2. Minor diastereoisomer: ^{13}C NMR (CD_3OD, 50.2MHz) δ: 17.5, 70.6, 82.5, 93.4.

A solution of the crude β-hydroxy acid in THF (270 ml) and H_2O (26 ml) was neutralized to pH 7 with 20% Cs_2CO_3 and evaporated to dryness under reduced pressure. The cesium salt was then stirred for 3 h with methyl iodide (0.54 ml, 8.7 mmol) in dry DMF (114 ml). The solvent was concentered under reduced pressure, the crude mixture was diluted with water and extracted with AcOEt. The organic extracts were dried over

sodium sulfate and the solvent evaporated. The crude product was purified (and separated from the minor diastereoisomer) by flash chromatography (n-hexane/AcOEt 7/3) to give methyl ester **6** in 82% yield. ^{1}H NMR ($CDCl_3/D_2O$, 200MHz) δ: 0.92 (3H, d, J=6.54Hz), 2.50 (3H, s), 2.74 (1H, dd, J=14.92, 7.96Hz), 2.90 (1H, dd, J=14.92, 4.48Hz), 3.80 (3H, s), 4.01-4.15 (1H, m), 4.25 (1H, d, J=5.80Hz), 4.37-4.46 (1H, m), 5.05 (1H, d, J=4.97Hz), 7.05-7.90 (9H, m). IR ($CHCl_3$) ν: 3500, 1735, 1600, 1430, 1350, 1160 cm^{-1}. $[\alpha]_D^{25}$=+14.4° (c 0.77, $CHCl_3$).

Minor diastereoisomer: ^{1}H NMR ($CDCl_3$, 200MHz) δ: 0.89 (3H, d, J=6.45Hz), 2.50 (3H, s), 2.81 (2H, d, J=6.94Hz), 3.11 (1H, d, J=6.17Hz), 3.78 (3H, s), 4.00-4.13 (1H, m), 4.31 (1H, d, J=6.17Hz), 4.41-4.52 (1H, m), 5.10 (1H, d, J=3.09Hz), 7.12-7.90 (9H, m).

Dithiolane **7**. A solution 0.1M of methyl ester **6** (1.14 g, 2.7 mmol) in dry methylene chloride was treated with 1,2-ethanedithiol (2.7 ml) and boron trifluoride etherate (490 μl, 4.05 mmol) under nitrogen and stirred for 2 h at room temperature. The reaction mixture was quenched with 5% $NaHCO_3$ aqueous solution and extracted with methylene chloride. The organic extracts were dried over sodium sulfate, the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (benzene/Et_2O 7/3) to give dithiolane **7** (85% yield). ^{1}H NMR ($CDCl_3/D_2O$) δ: 2.59 (1H, dd, J=8.55, 15.92Hz), 2.80 (1H, dd, J=3.29, 15.92Hz), 3.20-3.32 (4H, m), 3.74 (3H, s), 3.95-4.04 (1H, m), 4.53 (1H, d, J=7.23Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: 38.0, 38.7, 39.1, 51.8, 58.1, 72.1, 172.0. IR ($CHCl_3$) ν: 3520, 1730, 1430, 1160 cm^{-1}. $[\alpha]_D^{25}$=-23.1° (c 0.76, $CHCl_3$).

β-Keto-δ-hydroxy ester **8**. A solution of diisopropylamine (620 μl, 4.4 mmol) in dry THF (4 ml) at 0°C under nitrogen was treated with a solution of nBuLi (2.8 ml, 1.5M in n-hexane). After stirring for 15 min, the reaction mixture was cooled at -78°C and t-butylacetate (478 μl, 4.4 mmol) was added dropwise. After 45 min, a solution of ester **7** (182 mg, 0.86 mmol) in THF (4.0 ml) was added and the reaction mixture stirred at -78°C for 30 min and at 0°C for 30 min. The reaction mixture was quenched with AcOH (850 μl). A saturated solution of K_2CO_3 was then added to the resulting mixture which was extracted with AcOEt. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The product **8** was isolated by flash chromatography (n-hexane/AcOEt 7/3) in 95% yield. ^{1}H NMR ($CDCl_3/D_2O$, 200MHz) δ: 1.52 (9H, s), 2.82 1H, dd, J=17.14, 8.78Hz), 2.98 (1H, dd, J=17.14, 3.43Hz), 3.20-3.32 (4H, m), 3.43 (2H, s), 3.97-4.10 (1H, m), 4.51 (1H, d, J=6.58Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: 27.6, 38.0, 38.6, 47.1, 51.1, 58.1, 71.4, 81.8, 166.0, 202.1. IR ($CHCl_3$) ν: 3540, 2980, 1730, 1710, 1365, 1140 cm^{-1}. $[\alpha]_D^{25}$=-16.5° (c 0.73, $CHCl_3$).

β,δ-*Syn*-diol **9**. A solution of β-keto ester **8** (296 mg, 1.01 mmol) in dry THF/MeOH (8.03 ml/1.98 ml) at -78°C under nitrogen was treated with a 1M THF solution of Et_2BOMe (1.1 ml). After 15 min, 95% $NaBH_4$ (44.4 mg, 1.11 mmol) was added. After 90 min at -78°C the reaction mixture was quenched with AcOH (1 ml), diluted with AcOEt and washed with a $NaHCO_3$ aqueous solution. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The residue thus obtained was azeotroped a few times with methanol until the hydrolysis of the boronate was complete, then purified by flash chromatography (n-hexane/AcOEt 6/4) to give *syn*-diol **9** in 95% yield. ^{1}H NMR ($CDCl_3/D_2O$, 200MHz) δ: 1.49 (9H, s), 1.58-1.80 (1H, m), 1.89 (1H, ddd, J=14.38, 3.17, 2.11Hz), 2.43 (2H, dd, J=6.30, 1.58Hz), 3.17-3.29 (4H, m), 3.76 (1H, ddd, J=7.40, 2.11, 9.52Hz), 4.25 (1H, ddt, J=3.17, 9.51, 6.30Hz), 4.47 (1H, d, J=7.40Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: 27.9, 37.9, 38.6, 40.0, 42.6, 58.9, 68.0, 75.2, 81.1, 171.5. IR ($CHCl_3$) ν: 3490, 2990, 1710, 1360, 1145 cm^{-1}. $[\alpha]_D^{25}$=-14.5° (c 0.8, $CHCl_3$).

A mixture of *syn* and *anti* diol (1.2:1) was obtained by reduction of **8** with $NaBH_4$ in THF/MeOH 5/1 at 0°C. *Anti* diol: ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: 27.9, 37.8, 40.6, 42.3, 59.4, 65.4, 72.1, 81.2, 172.1.

Bis(t-butyldimethylsilyl) ether **10**. A solution of *syn* diol **7** (260 mg, 0.8 mmol) in dry DMF (2.6 ml) was treated, at 0°C under nitrogen, with imidazole (260 mg, 3.86 mmol) and $tBuMe_2SiOTf$ (440 μl, 1.92 mmol). After 30 min, the reaction mixture was warmed at room temperature and, after 3 h, treated with water and diluted with AcOEt. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane/AcOEt 96/4) to give compound **10** in 82% yield. ^{1}H NMR ($CDCl_3$, 200MHz) δ: 0.10 (3H, s), 0.11 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.89 (9H, s), 0.92 (9H, s), 1.46 (9H, s), 1.86-1.98 (2H, m), 2.34 (1H, dd, J=14.95, 6.27Hz), 2.45 (1H, dd, J=14.95, 5.68Hz), 3.13-3.25 (4H, m), 3.83 (1H, ddd, J=5.68, 5.68, 5.68Hz), 4.20-4.35 (1H, m), 4.17 (1H, d, J=5.68Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: -4.3, 17.9, 18.0, 25.7, 25.8, 28.1, 38.3, 38.7, 41.6, 44.1, 58.3, 66.6, 73.5, 80.2, 170.5. IR ($CHCl_3$) ν: 2920, 1720, 1250, 1090, 830 cm^{-1}. $[\alpha]_D^{25}$=-19.7° (c 0.71, $CHCl_3$).

Aldehyde **11**. A solution of compound **10** (500 mg, 0.94 mmol) in 4:1 acetone/H_2O (18.8 ml) was treated with $CaCO_3$ (280 mg, 2.8 mmol) and MeI (580 μl, 9.4 mmol) and refluxed for 2 days. The reaction mixture was then filtered on a celite pad washing the salts with AcOEt. The filtrate was washed with a 5M $AcONH_4$ solution then with water, dried and the solvent evaporated under reduced pressure. After flash chromatography

(n-hexane/AcOEt 96/4), aldehyde **11** was isolated in 70% yield. ^{1}H NMR ($CDCl_3$, 200MHz) δ: 0.10 (12H, s), 0.85 (9H, s), 0.91 (9H, s), 1.44 (9H, s), 1.93 (2H, dd, J=5.71, 5.71Hz), 2.38 (1H, dd, J=14.18, 7.09Hz), 2.49 (1H, dd, J=14.18, 5.26Hz), 4.11 (1H, dt, J=1.11, 5.71Hz), 4.31 (1H, ddt, J=7.09, 5.26, 5.71Hz), 9.62 (1H, d, J=1.11Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: -4.4, -4.1, 17.8, 18.1, 25.6, 25.7, 27.9, 40.4, 43.7, 65.3, 74.6, 80.4, 201.2. IR ($CHCl_3$) ν: 2975, 1735, 1370, 1250, 1030, 830 cm^{-1}. $[\alpha]_D^{25}$=-1.4° (c 0.70, $CHCl_3$).

β-Hydroxy lactone **12**. A solution of t-butyl ester **9** (479 mg, 1.64 mmol) in methanol (15 ml) was treated with 1N NaOH (8.2 ml) and stirred for 90 min at room temperature. After adding 5% aqueous HCl until pH 4, the reaction mixture was concentrated and then extracted with AcOEt. The organic extracts were dried over sodium sulfate filtered and the solvent evaporated under reduced pressure. The resulting crude acid was dissolved in toluene (40 ml) and heated at 90°C for 3 days. Evaporation of the solvent until 1/3 of the initial volume allowed the precipitation of the lactone **12** which was filtered and used without further purification. (82% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.89 (1H, ddd, J=13.30, 10.30, 2.51Hz), 2.18-2.29 (1H, m), 2.43 (1H, bs), 2.65-2.75 (2H, m), 3.20-3.40 (4H, m), 4.45 (1H, m), 4.68 (1H, d, J=5.28Hz), 4.80 (1H, ddd, J=10.30, 5.28, 3.30Hz). ^{13}C NMR ($CDCl_3$, 50.3MHGz) δ: 33.0, 38.3, 38.6, 38.8, 55.9, 62.3, 79.5, 170.1.

Lactone **13**. A solution of hydroxylactone **12** (187 mg, 0.85 mmol) in dry DMF (840 µl) was treated at room temperature with imidazole (127 mg, 18.7 mmol) and $tBuMe_2SiOTf$ (215 µl, 0.93 mmol). After 3 h, water was added and the resulting mixture was extracted with AcOEt. The organic extracts were dried, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane/AcOEt 8/2) to give the lactone **13** in 82% yield. ^{1}H NMR ($CDCl_3$, 200MHz) δ: 0.09 (6H, s), 0.88 (9H, s), 1.82 (1H, ddd, J=13.72, 10.57, 2.3Hz), 2.13 (1H, ddd, J=13.72, 3.34, 3.00Hz), 2.60 (2H, d, J=3.80Hz), 3.20-3.30 (4H, m), 4.10-4.45 (1H, m), 4.69 (1H, d, J=5.56Hz), 4.78 (1H, ddd, J=10.57, 5.56, 3.34Hz). ^{13}C NMR ($CDCl_3$, 50.3MHz) δ: -4.2, 17.8, 25.6, 33.4, 38.6, 38.7, 39.1, 56.0, 63.3, 79.4, 169.2. IR ($CHCl_3$) ν: 2920, 1735, 1240, 1080 cm^{-1}. $[\alpha]_D^{25}$=-7.2° (c 0.25, $CHCl_3$). mp 68°C.

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