Synthesis of (±)-mevalonic acid lactone via a *meso*-dialdehyde: a model for desymmetrization

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Dedicated to Professor A. Padwa on the occasion of his 65th birthday

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Abstract

Two procedures are described for the preparation of the racemic mevalonic lactone (±)-**2**, via a *meso*-dialdehyde **8**. The preparation of compound **8** in seven steps from cyclopentadiene is also described. This procedure intends to be model for a desymmetrization study of dialdehyde **8**, leading to optically active (–) (*R*)- and (+) (*S*)- mevalonolactone, **2**.

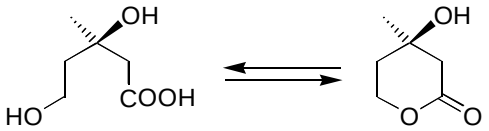
Keywords: Desymmetrization, model, mevalonic acid lactone

Introduction

Mevalonic acid, which exists in an equilibrium between its open (–)-(*R*)-**1** and cyclic form (mevalonolactone, (–)-(*R*)-**2**), is a key intermediate in cellular biochemistry.[1] It is a precursor for a number of biologically important lipids, including cholesterol, steroid hormones, bile acids, ubiquinone and dolichols. In addition, mevalonate-derived isoprenoids are intermediates in the biosynthesis of isoprenylated tRNAs, prenylated proteins involved in cell signaling and growth, and heme **a**, a prosthetic group of cytochrome oxidase. It is also the biogenetic precursor of most terpenoids, steroids, carotenoids and isoprenoids [2] and has therefore been a synthetic target of considerable interest.

Mevalonolactone (–)-(*R*)-**2** was first discovered and synthesized via resolution by Folkers and co-workers.[3] Since then a number of asymmetric syntheses of this molecule have been published, the most popular of which involves the Sharpless epoxidation of a suitable allylic alcohol.[4] The chiral pool materials such as linalool,[5] quinic acid,[6] 2-methyl-2-hydroxy-γ-butyrolactone,[7] a chiral equivalent of cyclohexa-2,5-dienone,[8] and the chiral template 1,2:5,6-di-O-isopropylidene-α-D-glucofuran-3-ulose[9] were reported as sources for the preparation of mevalonolactone. Other interesting synthetic methodologies involve the use of chiral

sulfoxides,[10] 1,3-oxathianes,[11] and axially dissymmetric binaphthyldiamines.[12] In addition, several enzymatic syntheses starting from achiral precursors have been described in the literature.[13] However, many of these methods suffer either from poor enantiomeric purity or low chemical yield,[10,12] and therefore there is room for new approaches.



(-) (*R*)-**1** (-) (*R*)- **2**

Scheme 1

Desymmetrization is proving to be a powerful synthetic tool,[14] and dialdehydes have been the focus of a number of studies.[15] With this methodology, instead of incorporating the chirality from the very beginning of the synthesis, a certain level of elaboration can be incorporated into the *meso*- molecule prior to the enantioselective desymmetrization step. We present here a model study of the synthesis of racemic mevalonic acid lactone (±)-**2**, which can be applied to a enantioselective synthesis of (–)-(*R*)- and (+)-(*S*)- mevalonolactone, **2**, as we have shown recently in the synthesis of (+)-(*S*)- and (–)-(*R*)- nor-methyl mevaldate derivatives.[16]

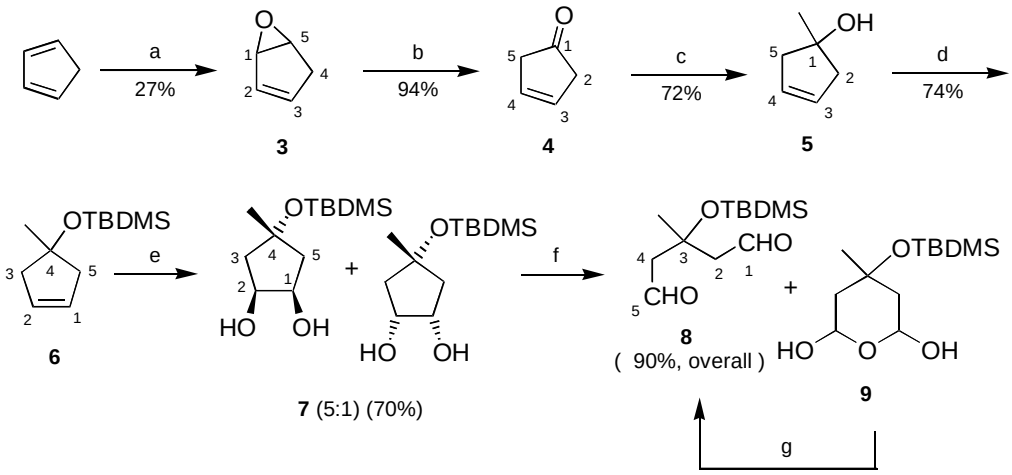
Results and Discussion

Although several approaches to analogues of the dialdehyde **8** have been reported,[17] we found it to be conveniently prepared through a seven-step sequence from cyclopentadiene. The alcohol **5** was obtained from cyclopentadiene *via* epoxide **3**, following the procedure of Crandall.[18] Rearrangement of **3** to cyclopent-3-enone, **4**, catalyzed by $Pd(Ph_3)_4$,[19] and treatment with MeMgCl led to the alcohol **5** in 18% overall yield. The alcohol **5** was protected as its *t*–butyldimethylsilyl ether **6** in 95% yield (TBDMSOTf–DIPEA, CH_2Cl_2, -78°C), identified by the disappearance of the hydroxyl absorption in the infrared spectrum and the replacement of the apparent singlet in the ^{1}H-NMR, corresponding to the methylene groups of the unprotected alcohol **5** at δ 2.44 ppm, with two 2H doublets (δ 2.43 and δ 2.25, J 15 Hz) in **6**. The protected alcohol **6** was transformed into a 5:1 mixture of diastereoisomeric diols **7** by the method of Matteson, employing catalytic osmium tetroxide in t-butanol at reflux with trimethylamine-*N*-oxide as the reoxidant.[20] Cleavage of **7** with sodium periodate in 8:2 dioxane–water, followed by exhaustive extraction with ethyl acetate furnished diol **8**, which forms the cyclic hydrate **9** on standing. It is possible to transform the hydrate back to the dialdehyde by treating with powdered 4Å molecular sieves in refluxing THF for 2 hours.

Once the *meso*-dialdehyde **8** was obtained, we aimed at a preparation of mevalonic lactone (±)-**2** which would be used for enantioselective differentiation of the aldehyde groups in

compound **8**. In order to do this, two different approaches to the mevalonic lactone were examined. In the first, a direct reduction of either of the prochiral aldehyde groups, followed by attack on the remaining carbonyl would lead to a ring closure. A final oxidation of the resulting alcohol, and deprotection of the silyl group would complete the synthesis of the racemic lactone (±)-**2**.

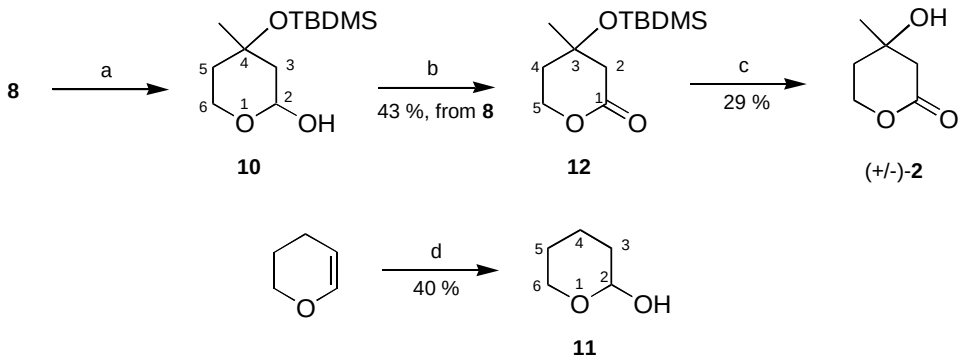
Treatment of the dialdehyde **8** with 1.5 equivalents of $NaBH_4$ in dry methanol at –30°C afforded the lactol **10**. As a model, 2-hydroxytetrahydropyran, **11,** was prepared as reported by Schniepp *et al.* in 40% yield (Scheme 3).[21] The ^{1}H-NMR spectra of lactols **10** and **11** were then compared, to support the production of the lactol **10**. In the ^{1}H-NMR spectrum of 2-hydroxytetrahydropyran, **11,** a broad singlet at δ 4.90 ppm corresponding to the anomeric proton was matched by a broad singlet at δ 4.98 ppm in the spectrum of lactol **10**. The protons of the methylene group adjacent to the lactol oxygen are diastereotopic, appearing as two separate multiplets at δ 4.03–4.00 and δ 3.55–3.47 in the hydroxytetrahydropyran **11** spectrum and at δ3.72–3.65 and δ3.55–3.42 in the lactol **10** spectrum.



Scheme 2. (a) CH_3CO_3H, CH_3CO_2Na, Na_2CO_3, CH_2Cl_2, T<10°C; (b) $Pd(Ph_3)_4$, CH_2Cl_2, r.t.; (c) MeMgBr; (d) TBDMSOTf, DIPEA, THF, -78°C; OsO_4, $(CH_3)_3NO$, pyr, t-BuOH, H_2O, reflux; $NaIO_4$, dioxane/H_2O, (8:2), r.t.; (g) 4Å mol. sieves, THF, reflux.

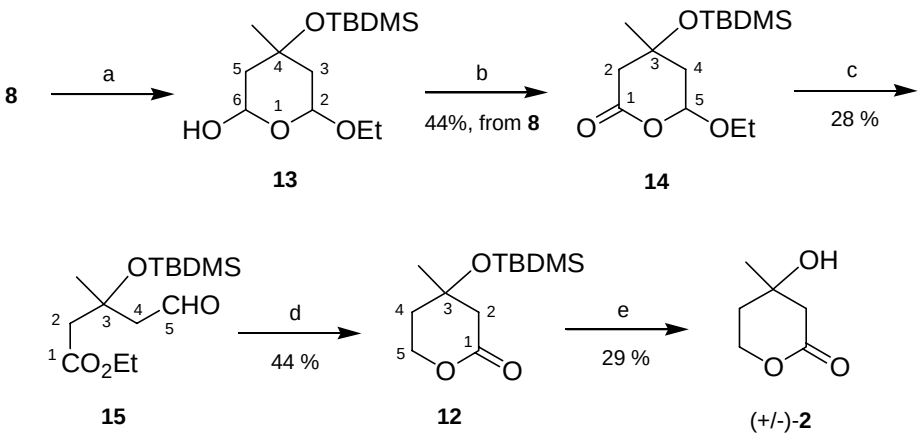
The remaining methylene groups were observed in the δ1.00–2.00 region. The presence of lactol **10** was further indicated by the observation of a molecular ion of m/z 229 corresponding to the loss of water in the mass spectrum. The crude lactol **10** was subsequently oxidized with a suspension of PCC and 4Å molecular sieves at room temperature over 24 hours to furnish the lactone **12,** in 43% yield over 2 steps, after chromatographic purification (Scheme 3). The lactone was characterized by two distinctive multiplets at δ4.51–4.41 and δ4.26–4.18, corresponding to the diastereotopic protons of the methylene group adjacent to the lactone oxygen, in the ^{1}H-NMR spectrum, and the strong lactone carbonyl absorption at 1743 cm^{-1} in the

infrared spectrum. Finally, treatment of the protected lactone **12** with HCl (10%, aqueous) in THF for 48 h afforded racemic mevalonic lactone (±)-**2** in 29% yield.



Scheme 3. (a) $NaBH_4$, MeOH, -30°C; (b) PCC, 4Å mol. sieves, CH_2Cl_2, r.t. (c) HCl (10%, aqueous), THF, r.t.; (d) HCl (2*M*), Δ.

The second alternative approach would aim to differentiate between the two prochiral aldehyde groups, by using an appropriate alcohol which would act as a chiral auxiliary in the stereo-differentiating process. Treatment of the adduct with an alkoxide would open the lactone, with the recovery of the chiral auxiliary. Reduction of the aldehyde, re-lactonization, and deprotection of the silyl group would yield the mevalonic acid lactone (±)-**2**. This approach has been put in practice in the synthesis, recently described by our group, of (+)-(*S*)- and (–)-(*R*)-nor-methyl mevaldate derivatives.[16] To this end, the dialdehyde **8** was treated with 1 equiv. of EtOH in THF and heated at reflux for 24 h. The crude reaction material obtained from this reaction was immediately oxidized with a suspension of PCC and 4Å molecular sieves at room temperature over 24 h, to furnish **14** in 44% yield over 2 steps, after chromatographic purification. Treatment of the compound **14** with sodium ethoxide in Et_2O at 0°C yielded **15**, which possesses a resonance in its ^{1}H-NMR spectrum at δ 9.75 (t, 1H, J 2.6 Hz), characteristic of an aldehyde adjacent to a methylene group. The next stage involved ring closure to provide the protected lactone **12**. Even though a two-step procedure was expected to be required, treatment of **15** with 2 equivalents of $NaBH_4$ in EtOH at –30°C, afforded directly the protected racemic lactone **12** in 44% yield. Finally, racemic mevalonolactone (±)-**2** was obtained from **12** by the procedure described previously.



Scheme 4. (a) Ethanol, THF, reflux, 24 h; (b) PCC, 4Å mol. sieves, CH_2Cl_2, r.t.; (c) EtONa, Et_2O, 0°C; (d) $NaBH_4$, MeOH, -30°C; (e) HCl (2M), $\tilde{\Delta}$

In conclusion, two procedures have been described for the preparation of the racemic mevalonic lactone (±)-**2**, vía a *meso*-dialdehyde **8**. The preparation of compound **8**, in seven steps, from cyclopentadiene is also described. This procedure is intended to be model for a desymmetrization study of dialdehyde **8**, leading to optically active (–)-(*R*) and (+)-(*S*) mevalonolactone, **2**.

Experimental Section

General Procedures. Spectroscopic data were recorded with the following instruments: Perkin Elmer Paragon FT-IR or Perkin Elmer 1720-X spectrophotometers (IR); Bruker WM 250, Bruker DPX250 (NMR: ^{1}H at 250 MHz, ^{13}C at 62.5 MHz) and Jeol EX 400 (NMR: ^{1}H at 400 MHz, ^{13}C at 100 MHz). The assignment of ^{1}H and ^{13}C NMR signals is based on two-dimensional NMR techniques. Signal positions are recorded in δ, with the abbreviations s, d, t, q, dd, ddd, dt, dq, br, and m, representing singlet, doublet, triplet, quartet, double doublet, double double doublet, double triplet, double quartet, broad and multiplet, respectively. Mass spectra (*m/z*) and accurate mass data (HRMS) were recorded on a Fisons VG Autospec mass spectrometer. Spectra were obtained using chemical ionization or electron impact methods as stated. Microanalyses were carried out by Medac Ltd. at Brunel University (UK). Melting points (m.p.) were determined with a Kofler hot stage microscope (Reichert) and are uncorrected. Flash column chromatography was performed according to the method by Still *et al.* with Silica gel 60 (Merck *9385)* using a head pressure by means of head bellows.[22] T.L.C. analyses were carried out using 0.25 mm silica gel precoated aluminum- or glass- backed plates with fluorescent indicator, UV_{254}. Spots were visualized by quenching of UV fluorescence, by staining with a potassium permanganate solution, by staining with a vanillin solution, or by staining with a molybdate solution. Reagents and solvents obtained from Aldrich, Avocado, BDH, Fisher, Fluka, and

Lancaster chemical suppliers were used directly as supplied or following purification according to procedures described by Perrin and Armarego.[23] Diethyl ether and tetrahydrofuran were distilled over sodium–benzophenone ketyl radical, and dichloromethane was distilled by refluxing over calcium hydride. Methanol and ethanol were distilled from calcium chloride and stored over 4Å molecular sieves. Diisopropylethylamine was distilled and stored over potassium hydroxide pellets. Light petroleum refers to the fraction in the boiling point range of 30–40^{o}C, which was fractionally distilled through a Vigreux column prior to use.

6-Oxa[3.1.0]bicyclohex-2-ene (3).[18] Freshly distilled cyclopentadiene (160.42 g, 2.43 mol) was added to mechanically stirred Na_2CO_3 (308.70 g, 2.91 mol) in CH_2Cl_2 (1.15 L) at 0^{o}C. Peracetic acid (335 mL, 1.94 mol) pre-treated with sodium acetate (5.97 g, 0.073 mol) was slowly added to the reaction mixture. The temperature of the reaction was kept below 20^{o}C throughout the addition. After 2 h the inorganic solids were removed by filtration and washed thoroughly with CH_2Cl_2 (1.5 L). The CH_2Cl_2 was removed by distillation at 760 mmHg to give the crude epoxide. Purification was achieved via distillation to give pure epoxide **3** as a pale yellow oil (52.93 g, 27 %), b.p. 36–38^{o}C/45 mm Hg; lit.[18] 39–41^{o}C/146 mm Hg); IR (film) ν_{max}, 3049, 2910, 1674 and 1283 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 6.17–6.13 (m, 1H, H-2), 6.01–5.96 (m, 1H, H-3), 3.94–3.90 (m, 1H, H-5), 3.84–3.81 (m, 1H, H-1), 2.69–2.59 (m, 1H, H-4α), and 2.44–2.34 (114, m, H-4β); ^{13}C-NMR (250 MHz, $CDCl_3$) δ_C 138.2, 131.6, 59.5, 57.2, and 36.0; EIMS m/z (%): 82 (100%, M^+); C_5H_6O requires 82.0419, found 82.0425.

Cyclopent-3-enone (4).[19] A catalytic amount of tetrakis(triphenylphosphine)palladium was added to a solution of epoxide **3** (11.21 g, 0.14 mol) in CH_2Cl_2 (75 mL) at 0^{o}C. The reaction was stirred for 21 h at room temperature. Most of the solvent was removed *in vacuo* and the residue then filtered through a pad of Celite®, washed through with diethyl ether (200 mL). Most of the ether was removed *in vacuo* and the remainder was removed under a stream of nitrogen to give pure ketone **4** as a yellow oil (10.56 g, 94 %); IR (film) ν_{max} : 2972, 2901, 1748 and 1611 cm^{-1}; ^{1}H-NMR (400 MHz, CDC1$_3$): δ_H 6.09 (br. s, 2H, H-3 and H-4), and 2.88 (4H, br. s, H-2 and H-5); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 217.6, 129.0, and 43.0; EIMS m/z (%): 82 (41%, M^+); C_5H_6O requires 82.0419, found 82.0426.

1-Methylcyclopent-3-enol (5).[23] Methyl magnesium chloride (27.2 mL of 3M solution), 81.72 mmol) was added to a solution of ketone **4** (6.70 g, 81.72 mmol) in diethyl ether (100 mL) at 0 ^{o}C. The reaction was stirred at 0^{o}C for 30 min. then quenched with saturated NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), water (1 x 30 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give pure alcohol **5** as a colorless oil (5.756 g, 72 %); IR (film) ν_{max}: 3370, 2967, 2927, and 1616 cm^{-1}; ^{1}H-NMR (400 MHz, CDC1$_3$): δ_H 5.67 (br s, 2H, H-3 and H-4), 2.44 (br s, 4H, H-2 and H-5), and 1.43 (s, 3H, CH_3); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 129.1, 79.4, 48.9, and 28.4; EIMS m/z (%): 98 (23%, M^+); $C_6H_{10}O$ requires 98.0731, found 98.0739.

4-Methyl-4-*tert*-butyldimethylsilyloxycyclopentene (6). *N*,*N*-Diisopropylethylamine (7.32 mL, 41.85 mmol) was added to alcohol **5** (3.42 g, 34.88 mmol) in CH_2Cl_2 (30 mL) at –78°C, followed by tert-butyldimethylsilyl trifluoromethanesulfonate (8.78 mL, 38.37 mmol). The reaction was stirred at –78°C for 2.5 h, and then warmed to room temperature. CH_2Cl_2 (50 mL) was added, and the mixture was washed with water (3x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the pure silyl ether **6** as a colorless oil (5.54 g, 74 %) IR (film) ν_{max} : 2957, 2930, and 1473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDC1_3$): δ_H 5.59 (s, 2H, H-l and H-2), 2.43 (d, 2H, H-3α and H-5α, *J* 15.3 Hz), 2.25 (d, 2H, H-3b and H-5β, *J* 15.3 Hz), 1.35 (s, 3H, CH_3), 0.84 (s, 9H, $(CH_3)_3C$), and 0.05 (s, 6H, $(CH_3)_2Si$); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 128.9, 81.3, 49.0, 30.1, 25.8, 18.2, –2.6, and –2.9.

4-Methyl-4-[*tert*-butyldimethylsilyloxy]cyclopentane-1,2-diol (7). *tert*-Butanol (2.0 mL), trimethylamine-*N*-oxide (0.15 g 1.361 mmol), pyridine (80 μL, 0.99 mmol) and water (1.6 mL) were added to silyl ether **6** (1 mmol) at room temperature. Osmium tetroxide (40 μL, 2.5 wt. % solution in t-BuOH, 0.003 mmol) was then added and the reaction heated to reflux for 20 h. The reaction was then cooled to room temperature, sodium bisulfite (20 mL, 20% w/v) was added and the reaction mixture was stirred for a further 1 h. Most of the butanol and water was removed *in vacuo*, and the residue was then extracted into diethyl ether (3 x 30 mL). The combined organic layers were washed wíth brine (1 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the pure diol **7**. Colorless solid (4.58 g, 70 %), as a mixture of two isomers in a ratio of 5:1, m.p. 58–60°C; (Found C, 58.5, H, 10.85%; $C_{12}H_{26}O_3Si$ requires C, 58.5, H, 10.65%); IR (film) ν_{max} : 3341, 3234, 2956, and 2934 cm^{-1} ; ^{1}H-NMR (400 MHz, $CDC1_3$): δ_H 4.23–4.19 (major isomer, m, 2H, H-1 and H-2), 4.11–4.00 (minor isomer), 2.21 (br. s, 2H, OH), 2.11–2.02 (m, 2H, H-3α and H-5α), 1.65 (dd, 2H, H-3β and H-5β, *J* 6.0 Hz, *J'* 13.8 Hz), 1.33 (s, 3H, H-4), 0.77 (s, 9H, $(CH_3)_3C$), and 0.00 (s, 6H, $(CH_3)_2Si$); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 74.1, 72.6, 48.6, 29.6, 25.6, 17.8, and –2.5; EIMS(CI) m/z (%): 247 (16%, MH^+); $C_{12}H_{27}O_3Si$ requires 247.1729, found 247.1718.

3-Methyl-3-[*tert*-butyldimethylsilyloxy]pentane-1,5-dialdehyde (8). Sodium periodate (4.77 g, 22.28 mmol) was added to a solution of diol **7** (5.48 g, 22.28 mmol) in dioxane and water (1.08 L, 8:2 v/v) at room temperature. The reaction was stirred for 7h, and the inorganic solids were then removed by filtration. The filtrate was extracted with ethyl acetate (3 x 400 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. A mixture of dialdehyde **8** and hydrate **9** was obtained. This mixture was dissolved in dry THF and treated with ground 4Å molecular sieves (21.5 g). The resulting slurry was kept under N_2 and heated with stirring to reflux for 2 hours. Then the reaction mixture was allowed to reach room temperature, filtered through a pad of Celite® and washed with Et_2O. Solvent was removed *in vacuo* to yield the pure dialdehyde **8** (5.13 g, 90%), m.p. 80–82°C; IR (film) ν_{max} : 2957, 2930, 1474, and 1463 cm^{-1}; ^{1}H-NMR (400 MHz, $CDC1_3$): δ_H 9.70 (t, 2H, H-1 and H-5, *J* 2.6 Hz), 2.55 (d, 4H, H-2α, H-4α, H-2β and H-4β, *J* 2.6 Hz), 1.16 (s, 3H, H-3), 0.71 (s, 9H, $(CH_3)_3C$), and 0.02 (s, 6H, $(CH_3)_2Si$); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 201.2, 67.1, 55.5,

30.5, 25.7, 18.0, –2.2, and –3.6; EIMS(CI) m/z (%): 245 (50%, MH^+), and 113 (100%, M^+-OTBS); $C_{12}H_{25}O_3Si$ requires 245.1573, found 245.1562.

2-Hydroxy-4-methyl-4-[*tert*-butyldimethylsilyloxy]tetrahydropyran (10). Sodium borohydride (0.06 g, 1.50 mmol) was added in two portions over 0.5 h to a solution of the dialdehyde **8** (1 mmol) in dry methanol at –30°C. The reaction was stirred at –30°C for 4 h, and then warmed to room temperature. The reaction mixture was acidified with a 1 M solution of HCl to pH 7.0 and most of the MeOH and water was removed *in vacuo*. The residue was extracted with diethyl ether (3 x 50 mL), washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude lactol. Purification was attempted using column chromatography on silica gel, eluting with diethyl ether–light petroleum, 2 : 3. However, a pure sample of the lactol **10** was never obtained, and therefore the reaction mixtures were used crude for later steps. Colorless oil; IR (film) ν_{max} : 3409, 2956, and 2930 cm^{-1}; ^{1}H-NMR (400 MHz, $CDC1_3$): δ_H 4.98 (br. s, l H, anomeric H, H-2), 3.72–3.65 (m, 1H, H-6α), 3.55–3.42 (m, l H, H-6β), 1.92–1.22 (m, 4H, H-3α H-5α, H-3β and H-5β), 1.12 (s, 3H, H-4), 0.78–0.61 (m, 9H, $(CH_3)_3C$), and 0.03–(-0.01) (m, 6H, $(CH_3)_2Si$); EIMS(CI) m/z (%): 229 (70%, M^+-OH); $C_{12}H_{25}O_2Si$ requires 229.1624, found 229.1618.

2-Ethoxy-6-hydroxy-4-methyl-4-[*tert*-butyldimethylsilyoxy]tetrahydropyran (13). Ethanol (1 mmol) was added to a solution of the dialdehyde **8** (1 mmol) in dry THF (5 mL). The mixture was refluxed for 24 h. The THF was then removed *in vacuo* to give crude lactol **13**. Pale yellow oil; IR (film) ν_{max} : 3421, 2956, and 2930 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 5.23 (br. s, l H, anomeric H-6), 5.10–5.03 (m, 1H, H-2), 3.94–3.87 (m, 1H, $OC\underline{H}HCH_3$), 3.56–3.46 (m, 1H, $OCH\underline{H}CH_3$), 1.92–1.36 (m, 4H, H-3α, H-5α, H-3β and H-5β), 1.29 (s, 3H, H-4), 1.17 (t, 3H, $OCH_2C\underline{H_3}$), 0.84–0.78 (m, 9H, $(CH_3)_3C$), and 0.03-(-0.02) (m, 6H, $(CH_3)_2Si$); EIMS(CI) m/z (%): 273 (20%, M^+–OH), 245 (25%, M^+–OEt), and 159 (9%, M^+–OTBS); $C_{14}H_{29}O_3Si$ requires 273.1886, found 273.1891.

General procedure for oxidation of lactols to lactones

5-Hydroxy-3-methyl-3-[*tert*-butyldimethylsilyloxy]pentanoic acid lactone 12, 5-Ethoxy-5-hydroxy-3-methyl-3-[*tert*-butyldimethylsilyloxy]pentanoic acid lactone (14). A solution of the lactol (1 mmol) in CH_2Cl_2 (20 mL) was added to a suspension of pyridinium chlorochromate (0.32 g, 1.5 mmol) and ground 4Å molecular sieves (400 mg) in CH_2Cl_2 (40 mL) at room temperature. The reaction mixture was stirred vigorously at room temperature for 24 h, diethyl ether (50 mL) was then added and the mixture was stirred for a further 1 h. The suspension was filtered over a pad of silica gel, and washed through with further ether. The ether was removed *in vacuo* to give crude lactone. Compound **12**: colorless oil (43 %, over 2 steps); IR (film) ν_{max} : 2960, 2929, and 1743 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 4.51–4.41 (m, 1H, H-5α), 4.26–4.18 (m, 1H, H-5β), 2.55 (dt, 1H, H-2α, *J* 1.6 Hz, *J'* 17.3 Hz), 2.30 (d, 1H, H-2β, *J* 17.3 Hz), 1.75–1.70 (m, 2H, H-4α and H-4β), 1.30 (s, 3H, H-3), 0.73 (s, 9H, $(CH_3)_3C$), and –0.02 (d, 6H, $(CH_3)_2Si$, *J* 5.8 Hz); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 172.5, 73.0, 68.6, 47.8, 39.3, 31.5, 28.0, 20.3, 0.04, and 0.0; EIMS(CI) m/z (%): 262 (23%, $M+NH_4^+$), 245 (100%, $M+H^+$), and 113 (47%, M–OTBS); $C_{12}H_{25}O_3Si$ requires 245.1573, found 245.1574. Compound **14**: Colorless oil

(0.14 g, 44 % over two steps), (Found C, 58.2, H, 9.70%; $C_{14}H_{28}O_4Si$ requires C, 58.3, H, 9.8%); IR (film) ν_{max} : 2932, 2858, and 1758 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 5.40 (dd, 1H, H-5, *J* 4.2 Hz, *J'* 8.1 Hz), 4.03-3.90 (dq, 1H, OC<u>H</u>HCH$_3$, *J* 2.5 Hz, *J'* 7.1 Hz), 3.62–3.50 (dq, 1H, OCH<u>H</u>CH$_3$, *J* 2.5 Hz, *J'* 7.1 Hz), 2.59 (dd, 1H, H-2α, *J* 2.7 Hz, *J'* 17.0 Hz), 2.35 (d, 1H, H-2β, *J* 17.0 Hz), 2.17–2.08 (m, 1H, H-4α), 1.64 (dd, 1H, H-4β, *J* 8.1 Hz, *J'* 13.9 Hz), 1.26 (s, 3H, H-3), 1.13 (t, 3H, OCH$_2$C<u>H$_3$</u>, *J* 7.1 Hz), 0.74 (s, 9H, $(CH_3)_3C$), and 0.00 (s, 6H $(CH_3)_2Si$); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 171.6, 104.1, 73.3, 67.7, 47.2, 45.3, 31.5, 28.0, 20.3, 17.3, 3.4, and 0.1; EIMS(CI) m/z (%): 289(5%, MH^+); $C_{14}H_{29}O_4Si$ requires 289.1835, found 289.1842.

Ethyl 3-methyl-5-oxo-3-[*tert*-butyldimethylsilyloxy]pentanoate (15). Sodium ethoxide (1.4 mL, 0.1 M solution, 0.14 mmol) was added dropwise to a solution of lactone **14** (0.14 g, 0.47 mmol) in diethyl ether (7 mL) at 0^{o}C. The reaction was stirred for 3 h at 0^{o}C, quenched with saturated NH_4Cl (5 mL), and then warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude mono-ester. Purification by column chromatography on silica gel, eluting with diethyl ether–light petroleum 1:2 gave pure mono-aldehyde **15** as a colorless oil (0.04 g, 28 %) ; IR (film) ν_{max} : 2932, 2858, 1730, and 1728 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 9.75 (t, 1H, H-5, *J* 2.6 Hz), 4.00 (q, 2H, OC<u>H$_2$</u>CH$_3$, *J* 7.2 Hz), 2.63–2.62 (m, 2H, H-4α and H-4β), 2.53 (d, 2H, H-2α and H-2β, *J* 3.0 Hz), 1.36 (s, 3H, H-3), 1.14 (t, 3H, OCH$_2$C<u>H$_3$</u>, *J* 7.2 Hz), 0.72 (s, 9H, $(CH_3)_3C$), and 0.00 (d, 6H, $(CH_3)_2Si$, *J* 3.3 Hz); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 204.1, 172.4, 75.3, 63.0, 56.8, 49.5, 30.9, 27.7, 20.1, 16.2, 0.00, and -0.01; EIMS(CI) m/z (%): 289 (4%, MH^+), and 157 (100%, M^+-OTBS); $C_{14}H_{29}O_4Si$ requires 289.1835, found 289.1824.

Racemic mevalonic acid lactone, (±-2). HCl (3.5 mL, 10%) was added dropwise to a solution of protected lactone **12** (0.03 g, 0.12 mmol) in THF (1.5 mL) at room temperature and was stirred at room temperature for 46 h. The mixture was saturated with NaCl, and extracted with hot ethyl acetate (4 x 10 mL). The combined organic layers were washed with brine (1 x 2 mL) and dried over $MgSO_4$. Purification by column chromatography on silica gel, eluting with ethyl acetate gave pure racemic mevalonic acid lactone (±)-**2** as a colorless oil (0.004 g, 29%), IR (film) ν_{max} : 3417, 2967, 2927, and 1753 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 4.60–4.49 (m, 1H, H-5α), 4.32–4.25 (m, 1H, H-5β), 2.60 (dt, 1H, H-2α, *J* 0.9 Hz, *J'* 17.4 Hz), 2.46 (d, 1H, H-2β, *J* 17.4 Hz), 1.88–1.83 (m, 2H, H4α and H4β), and 1.34 (s, 3H, H-3); ^{13}C-NMR (250 MHz, $CDCl_3$): δ_C 169.9, 67.2, 65.0, and 43.7, 34.8, 28.8; EIMS(CI) m/z (%): 148 (9%, $M+NH_4^+$), 131 (100%, MH^+), and 113 (17%, M^+–OH); $C_6H_{11}O_3$ requires 131.0708, found 131.0701.

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