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Synthesis of (+)-(3*R*,5*R*)-3-Hydroxy-5-decanolide and Massoialactone, and Formal Synthesis of Verbalactone

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Abstract: Total synthesis of (3*R*, 5*R*)-(+)-3-hydroxy-5-decanolide (**1**) and massoialactone (**2**), and formal synthesis of verbalactone (**3**), have been reported.

Keywords: Dimer, formal synthesis, δ-lactones, total synthesis

INTRODUCTION

Mevinic acids such as compactin and mevinolin that contain a β-hydroxy lactone system stimulated a great deal of interest. Despite its rather simple structure, the lactone moiety of the mevinic acids has proved to be essential for the biological activity of such compounds.[1] For these reasons, many efforts have been made to discover and synthesize numerous very potent and selective HMG-CoA reductase inhibitors in which the lactone moiety has been attached to simpler fragments, and in some cases, such analogs have proven to be more effective than the natural mevinic acids.[2] β-Hydroxy and α, β-unsaturated δ-lactone moieties are present in a number of bioactive natural products such as (–)-callystatin A[3] and (+)-discodermolide.[4] (+)-(3*R*, 5*R*)-3-Hydroxy-5-decanolide **1** is a potent inhibitor of the enzyme HMG-CoA reductase.[5]

Massoialactone **2** [6] is an alkyl lactone derived from the bark of the Massoia tree (*Cryptocaria massoia*), which is found throughout Malaysia, though the compound can also be found as a component of cane sugar

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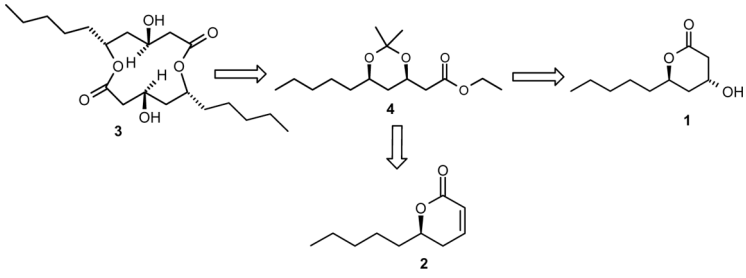
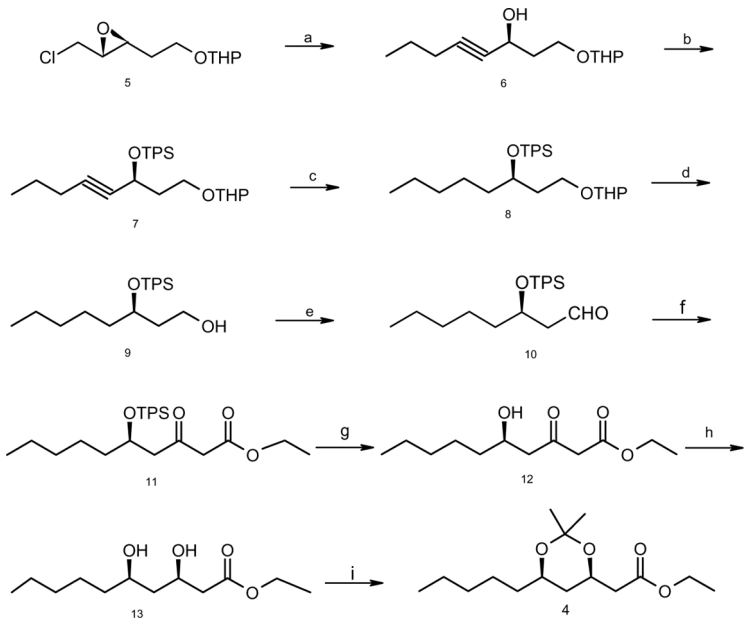
molasses, cured tobacco, and the essential oil of sweet osmanthus (*Osmanthus fragrans*). Once widely used as a natural coconut flavoring, natural massoialactone has been largely superseded by a synthetic alternative because the extraction process is expensive and the tree is killed during the process of removing the bark. Therefore, over the years, this molecule has received considerable interest, and many racemic[7–11] and enantioselective[12–21] syntheses have been reported. Verbalactone **3** [22] is a macrocyclic dimer lactone isolated from the roots of *verbascum undulatum* and exhibits antibacterial activity. This macrocyclic lactone is a symmetrical dimer of the lactone **1**. Only three synthetic procedures[23–25] for the construction of this dimer have been reported so far.

Still, the synthesis of these compounds in an optically pure form has turned out to be challenging, and it was always achieved in several steps either by means of asymmetric reactions or starting from optically active natural products. On account of such intriguing biological importance, we are particularly interested in the synthesis of naturally occurring β-hydroxy and α, β-unsaturated δ-lactones such as (3*R*, 5*R*)-(+)-3-hydroxy-5-decanolide **1**, massoialactone **2**, and verbalactone **3** (Scheme 1).

The synthesis of **1** started with the known 2, 3-epoxychloride **5** (Scheme 2). The 2, 3-epoxychloride **5** was directly converted into an alkylated chiral acetylenic carbinol **6** in 80% yield in one pot by subjecting it to a base-induced opening with Li metal in liquid NH_3 in tetrahydrofuran (THF), and the resulting alkynol without isolation was treated with 1-bromopropane at $-33^{\circ}C$ for 6 h. The spectral data of compound **6** was in good agreement with the assigned structure. The secondary hydroxyl of **6** was protected as silyl ether **7** in 90% yield using tertiarybutyldiphenylsilyl chloride (TBDPSCl) and imidazole in CH_2Cl_2 at room temperature. Next, hydrogenation of triple-bond compound **7** with 10% Pd/C in EtOAc at room temperature for 4 h yielded a saturated compound **8** in 90% yield followed by deprotection of the THP group using pyridinium

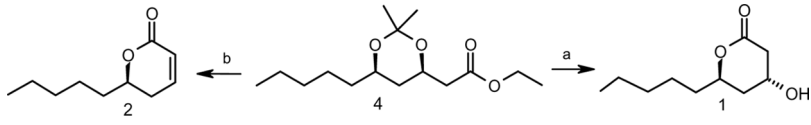


Scheme 1. Retrosynthetic plan for (3*R*,5*R*)-(+)-3-hydroxy-5-decanolide, massoialactone, and verabalactone.



Scheme 2. Reagents and conditions: (a) Li/liq NH_3, ferric nitrate (catalyst), dry THF, compound 5, −33 °C, 2 h, then propyl bromide, −33 °C, 6 h, 80%; (b) TBDPSCl, imidazole, DCM, 0 °C–rt, 1 h, 90%; (c) 10% Pd/C, EtOAc, H_2, rt, 4 h, 90%; (d) PPTS, methanol, rt, 2 h, 86%; (e) IBX, DMSO, DCM, 0 °C–rt, 3 h, 80%; (f) anhyd. $SnCl_2$, $N_2CHCOOEt$, DCM, 0 °C–rt, 6 h, 75%; (g) TBAF, THF, 1 h, 90%; (h) catecholborane, dry THF, −10 °C, 4 h, 92%; (i) 2, 2-DMP, PPTS, dry acetone, 85%.

paratoluenesulfonate in methanol and oxidation with iodoxbenzoic acid in DMSO afforded aldehyde **10**. Treatment of aldehyde **10** with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride in CH_2Cl_2 at room temperature led to the formation of β-keto ester **11** in 75% yield. Selective deprotection of TBDPS ether group was done using TBAF in THF at rt to produce δ–hydroxy-β-ketoester **12** in 90% yield. The stereoselective reduction of δ–hydroxy-β-ketoester **12** to the corresponding *syn*-1, 3-diol **13** was achieved using catecholborane (3.0 eq.) in THF at −10 °C in 92% yield with high diastereoselectivity (*syn*: *anti*, 99:1). To confirm the relative configuration of *syn*-1, 3-diol as well as to protect the diol function required for the following reaction, syn diol **13** was transformed into the corresponding acetonide derivative **4** using 2, 2-DMP and PPTS in dry acetone in 85% yield. The ^{13}C NMR chemical shifts of the two methyl groups in the acetonide part in **4** exhibited peaks at δ19.6 and 30.0 and the quaternary carbon at δ 99.0, indicating that the

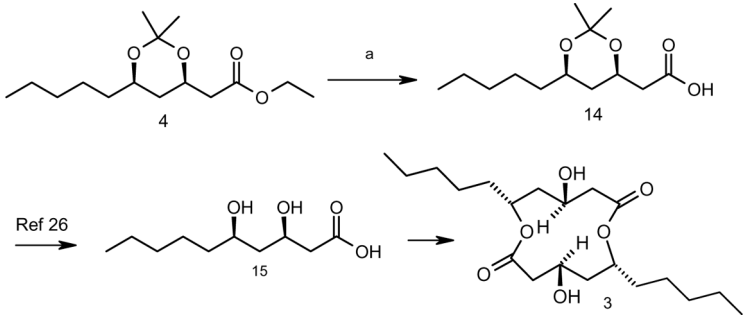


Scheme 3. Reagents and conditions: (a) 3 N NaOH, MeOH, rt, 1 h, pH 2.0, 80%; (b) benzene, *p*- TSA, 12 h, 64%.

two hydroxy groups are in a 1, 3-*syn* orientation.[26] In contrast, in the acetonide derivative prepared from a minor reduction product, signals were found at almost the same values, namely, δ 24.9 and 25.0, and the quaternary carbon at δ100.2, which were characteristic for the methyl groups in the acetonide part of 1, 3-*anti* diol moiety. The key intermediate **4** served as the divergent point for both natural products. With the protected ester readily in hand, the final drive was to synthesize two molecules **1** and **2**.

Thus, under hydrolysis conditions using 3 N NaOH in MeOH at rt maintining pH at 2.0 for 1 h, intermediate **4** yielded (3*R*,5*R*)-(+)-3-hydroxy-5-decanolide **1** in 80% yield. Accordingly, treatment of intermediate **4** with *p* TSA in benzene at rt for 12 h gave massoialactone **2** in 64% yield. The spectral data (^{1}H, ^{13}C NMR) and optical rotation values [$[\alpha]_D^{25}$: +22.0 (*c* 0.5, $CHCl_3$), $[\alpha]_D^{25}$: −113.0 (*c*1.0, $CHCl_3$)] lactones **1** and **2** are in good agreement with the reported compounds (Scheme 3).

Next, our goal was to synthesize verbalactone **3**. Thus, the intermediate **4** was converted into the required dihydroxycarboxylic acid **15** in two steps. Accordingly, hydrolysis of intermediate **4** using 4 N NaOH in EtOH at rt maintaining pH at 6.0 for 1 h furnished carboxylic acid **14** in 78% yield by keeping the protecting group intact (Scheme 4). The physical and spectroscopic data of **14** were identical to the reported values, [$\alpha]_D^{25}$: +3.6 (*c* 0.2, $CHCl_3$) and [lit.[25] [α $]_D^{25}$: + 3.4 (*c* 0.15, $CHCl_3$)]. Because the conversion of acid **14** to verbalactone **3** through



Scheme 4. Reagents and conditions: (a) 4 N NaOH, EtOH, rt, 1 h, pH 6.0, 78%.

15 has already been reported in the literature, the present sequence herein constitutes a formal synthesis of verbalactone **3** (Scheme 4).

EXPERIMENTAL

Reactions were conducted under a nitrogen atmosphere using anhydrous solvents such as dichloromethane (DCM), THF, CCl_4, benzene, and EtOAc. All reactions were monitored by thin-layer chromatography (TLC) using silica-coated plates and visualizing under UV light. Light petroleum of the distillation range 60–80 °C was used. Yields refer to chromatographically and spectroscopically (^1H, ^{13}C) homogeneous material. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator. ^1H NMR spectra were recorded on Varian FT 200-MHz (Gemini) and Bruker UXNMR FT 300-MHz (Avance) instruments in $CDCl_3$. Chemical shift values were reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70 eV on LC-MSD (Agilent Technologies). Column chromatography was performed on silica-gel (60–120 mesh) supplied by Acme Chemical Co., India. TLS was performed on Merck 60 F-254 silica-gel plates. Optical rotations were measured with a Jasco DIP-370 polarimeter at 20 °C.

(3*S*)-1-(Tetrahydro-2*H*-2-pyranyloxy)-4-octyn-3-ol (6)

To freshly distilled ammonia (200 mL) in a 500-mL, two-necked, round bottom flask fitted with a cold finger condenser, a catalytic amount of ferric nitrate (100 mg) was added, followed by lithium metal (2.87 g, 410.9 mmol) in fractions at –33 °C. The resulting gray suspension was stirred for 30 min. To this, epoxychloride **5** (15.0 g, 68.49 mmol) in dry tetrahydrofuran (30 mL) was added over a period of 10 min. The reaction mixture was then stirred for 2 h at –33 °C, and propyl bromide (12.6 g, 102.7 mmol) in dry tetrahydrofuran (50 mL) was added dropwise to the reaction mixture and stirred for another 6 h at the same temperature. The reaction mixture was quenched with solid NH_4Cl (12 g), and then excess ammonia was allowed to evaporate. The residue was dissolved in water, and the residue was filtered through a small pad of Celite®. The filtrate was extracted with ethyl acetate (4×100 ml). The organic layers were combined, washed once with water (1×100 ml) ml) and brine (80 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (pet. Ether–EtOAc 8:2) to afford the **6** as a

slightly yellow liquid (12.5 g, 80.5%). $[\alpha]_D^{25}$: −13.6 (*c*1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, $J = 7.5$ Hz, 3H), 1.37–2.10 (m, 10H), 2.18 (td, $J = 7.5$, 2.2 Hz, 2H), 3.44–3.59 (m, 1H), δ 3.63–3.74 (m, 1H), 3.76–3.95 (m, 1H), 4.07 (td, $J = 9.0$, 3.7 Hz, 1H), 4.48–4.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.7, 85.3, 80.7, 64.6, 62.0, 61.2, 37.2, 30.4, 25.2, 22.0, 20.6, 19.2, 13.7; IR (neat): 3422, 2933, 2870, 2250, 1277, 1202, 1120, 1067, 1029, 754 cm^{-1}; LCMS: *m*/*z* 249 ($M^+ + Na$). HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{22}O_3$ Na ($M^+ + Na$): 249.1461; found: 249.1464.

tert-Butyl(diphenyl)((1*S*)-1-[2-(tetrahydro-2*H*-2-pyranyloxy)-ethyl]-2-hexynyloxy)silane (7)

To a stirred solution of alcohol **6** (10.0 g, 44.2 mmol) and imidazole (6.0 g, 80.4 mmol) in dry DCM (70 mL), TBDPSCl (13.8 ml, 52.7 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then quenched with water (30 ml). The DCM layer was separated, and the aqueous layer was extracted with additional DCM (3 × 30 mL). Combined organic layers were washed with water (2 × 50 ml), brine (2 × 50 ml) and solution and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica-gel column chromatography (pet. ether–EtOAc 9:1) to afford **7** (18.5 g, 90% yield), as a colorless liquid. $[\alpha]_D^{25}$: −32.0 (*c*0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, $J = 7.5$ Hz, 3H), 1.06 (bs, 9H), 1.21–1.80 (m, 8H), 1.85–2.05 (m, 4H), 3.34–3.53 (m, 2H), 3.64–3.91 (m, 2H), 4.40 (t, $J = 3.7$ Hz, 1H), 4.47–4.56 (m, 1H), 7.27–7.47 (m, 6H), 7.67 (dd, $J = 7.5$, 1.5 Hz, 2H), 7.72 (dd, $J = 7.5$, 1.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 133.7, 129.5, 127.4, 98.6, 98.2, 85.6, 85.5, 81.2, 63.8, 38.9, 38.8, 30.5, 26.8, 25.4, 21.8, 20.6, 19.2, 13.4; IR (neat): 3070, 2933, 2860, 2250, 1589, 1466, 1427, 1385, 1357, 1262, 1200, 1111, 1033, 983, 819, 739, 703 cm^{-1}; ESIMS: *m*/*z* 487 ($M^+ + Na$); HRMS (ESI): *m*/*z* calcd. for $C_{29}H_{40}O_3Si$ Na ($M^+ + Na$): 487.2644; found: 487.2661.

tert-Butyl(diphenyl)((1*R*)-1-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]hexyloxy)silane (8)

To a solution of **7** (10.0 g, 21.5 mmol) in anhyd. ethyl acetate (50 mL), a catalytic amount of 10% Pd/C (1.5 g) was added, and the mixture was stirred at room temperature under an H_2 atmosphere for 4 h. Then, the catalyst was filtered off and washed with ethyl acetate (3 × 50 ml), and the filtrate was concentrated under reduced pressure and purified by

column chromatography (pet. ether–EtOAc 9:1) to afford **8** as a colorless liquid (9.0 g, 90%). $[\delta]_D^{25}$: −3.4 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, $J = 7.5$ Hz, 3H), 1.04 (bs, 9H), 1.08–1.63 (m, 10H), 1.73 (t, $J = 6.7$ Hz, 2H), 3.27–3.45 (m, 2H), 3.63–3.77 (m, 2H), 3.78–3.93 (m, 1H), 4.40 (m, 1H), 7.28–7.41 (m, 6H), 7.65 (dd, $J = 7.5$, 1.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7, 134.5, 129.4, 127.3, 98.6, 71.1, 64.2, 62.1, 36.7, 36.3, 31.8, 30.7, 27.0, 25.5, 24.4, 24.3, 22.5, 19.5, 13.9; IR (neat): 2933, 2859, 1589, 1466, 1427, 1381, 1200, 1111, 1073, 1032, 704 cm^{-1}; LCMS: *m/z* 491 ($M^+ + Na$); HRMS (ESI): *m/z* calcd. for $C_{29}H_{44}O_3$ Si Na ($M^+ + Na$): 491.2957; found: 491.2937.

(3*R*)-3-[1-(*tert*-Butyl)-1, 1-diphenylsilyl]oxyoctan-1-ol (9)

To a stirred solution of compound **8** (7.0 g, 14.9 mmol) in methanol (35 mL), a catalytic amount of pyridine *p*-toluenesulfonate (PPTS) (0.8 g) was added. The reaction mixture was stirred at room temperature for about 2 h, and methanol was removed under reduced pressure. The crude residue was purified by silica-gel column chromatography to afford **9** (4.9 g, 86%) as a viscous liquid. $[\alpha]_D^{25}$: −19.2 (*c*1.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): d 0.80 (t, $J = 7.5$ Hz, 3H), 0.98–1.20 (m, 16H), 1.25–1.68 (m, 3H), 1.73–1.86 (m, 2H), 3.55–3.67 (m, 2H), 3.68–3.80 (bs, 1H), 3.90 (q, $J = 6.7$ Hz, 1H), 7.30–7.44 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.8, 129.7, 127.5, 72.4, 59.8, 37.6, 36.2, 31.6, 27.0, 24.7, 22.4, 19.2, 13.9; IR (neat): 3381, 3069, 2930, 2857, 1587, 1466, 1427, 1382, 1108, 1051, 737, 702 cm^{-1}; LCMS: *m/z* 407 ($M^+ + Na$); HRMS (ESI): *m/z* calcd. for $C_{24}H_{36}O_2Si$ Na ($M^+ + Na$): 407.2382; found: 407.2362.

(8*R*)-8-[1-(*tert*-butyl)-1, 1-diphenylsilyl]oxytridecane-4, 6-dione (11)

To an ice-cooled solution of 2-iodoxybenzoic acid (5.1 g, 18.2 mmol) in DMSO (6 mL, mmol), a solution of alcohol **9** (3.5 g, 9.1 mmol) in anhyd. CH_2Cl_2 (20 mL) was added. The mixture was stirred at room temperature for 3 h and then filtered through a Celite® pad and washed with Et_2O (3×60 ml). The combined organic filtrates were washed with H_2O (2×20 ml) and brine (20 ml), dried (anhyd. Na_2SO_4), and concentrated under vacuum at temperatures colder than 45 °C. The crude product was purified by column chromatography to afford aldehyde **10** as an unstable viscous liquid (2.8 g, 80%), which was directly used for the next stage.

CH_2Cl_2 (10 mL) followed by ethyl diazoacetate (0.6 ml, 4.7 mmol) were added with stirring at room temperature to anhydrous tin(II) chloride (0.075 g, 0.39 mmol). A few drops of compound **10** (1.5g, 3.9 mmol) in

dry CH_2Cl_2 slowly were added to this suspension. When nitrogen evolution began, the remaining solution of compound was added dropwise over 10 min. After nitrogen evolution had stopped (6 h), the reaction was transferred to a separator funnel with saturated brine (NaCl, 20 mL) and extracted with diethyl ether (2×20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, and residue was purified by silica-gel column chromatography (pet. ether–EtOAc 9:1) to afford compound **11** (1.37 g, 75% yield) as a viscous liquid. $[\alpha]_D^{25}$: -10.8 (c1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.80 (t, $J = 7.5$ Hz, 3H), 1.02 (bs, 9H), 1.08–1.21 (m, 4H), 1.22–1.31 (m, 4H), 1.35–1.44 (m, 3H), 2.61 (d, $J = 5.8$ Hz, 2H), 3.24 (d, $J = 2.2$ Hz, 2H), 4.02–4.23 (m, 3H), 7.31–7.43 (m, 6H), 7.59–7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): d 203.0, 166.9, 135.8, 133.9, 129.6, 127.5, 91.1, 69.8, 61.1, 50.0, 42.7, 36.9, 31.5, 26.9, 24.4, 22.4, 14.0, 13.8; IR (neat): 2931, 2858, 1745, 1718, 1649, 1466, 1427, 1312, 1234, 1108, 1047, 738, 704 cm^{-1}; ESIMS: m/z 491 ($M^+ + Na$); HRMS (ESI): m/z calcd. for $C_{28}H_{40}O_4Si$ Na ($M^+ + Na$): 491.2593; found: 491.2572.

(8*R*)-8-Hydroxytridecane-4, 6-dione (12)

To compound **11** (1.1 g, 2.35 mmol) in dry tetrahydrofuran (10 ml), tetrabutyl ammonium fluoride (TBAF) (2.35 ml, 2.35 mmol, 1 M solution in tetrahydrofuran) was added dropwise at 0 °C, and the mixture was stirred for 60 min. Water (2 mL) was added, and the mixture was extracted with ethyl acetate (3×35 ml). The organic extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the product **12** (0.49 g, 90%), as a colorless liquid. $[\alpha]_D^{25}$: -27.5 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.21–1.5 (m, 11H), 2.54–2.74 (m, 2H), 3.41 (s, 2H), 3.96–4.09 (m, 1H), 4.19 (q, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 166.8, 67.5, 61.4, 49.9, 49.6, 36.4, 31.6, 25.1, 22.5, 14.0, 13.9; IR (neat): 3439, 2929, 2860, 1740, 1713, 1462, 1408, 1372, 1315, 1237, 1153, 1031 cm^{-1}; LCMS: m/z 253 ($M^+ + Na$); HRMS (ESI): m/z calcd. for $C_{12}H_{22}O_4Na$ ($M^+ + Na$): 253.1415; found: 253.1422.

Ethyl (3*R*, 5*R*)-3, 5-Dihydroxydecanoate (13)

A solution of compound **12** (0.4 g, 1.74 mmol), in dry tetrahydrofuran was chilled in an MeOH–ice bath (-10 °C) and charged with freshly distilled catecholborane (0.66 mL, 5.22 mmol). After 4 h, the reaction mixture was quenched by the addition of 1 mL of anhydrous MeOH and

2 mL of a saturated aqueous solution of sodium potassium tartarate. This mixture was allowed to stir at room temperature for 2 h. The layers were separated, and aqueous layer was extracted with ethyl acetate (3 × 30 ml). The organic extracts were washed with brine (30 ml) and dried over anhydrous Na_2SO_4, and the desired product was isolated by silica-gel column chromatography (pet. ether–EtOAc 6:4) to afford the diol **13** (0.33 g, 82%) as a liquid. $[\alpha]_D^{25}$: −9.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.22–1.48 (m, 11H), 1.50–1.56 (m, 2H), 2.42–2.46 (m, 2H), 3.77–3.89 (m, 1H), 4.11–4.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 72.2, 69.1, 60.7, 42.0, 37.7, 31.7, 29.6, 24.9, 22.5, 14.1, 13.9; IR (neat): 3419, 2925, 2855, 1727, 1461, 1376, 1252, 1165, 1065 cm^{-1}; LCMS: *m/z* 255 ($M^+ + Na$); HRMS (ESI): *m/z* calcd. for $C_{12}H_{24}O_4Na$ ($M^+ + Na$): 255.1566; found: 255.1573.

Ethyl 2-[(4*R*, 6*R*)-2, 2-Dimethyl-6-pentyl-1, 3-dioxan-4-yl]acetate (4)

To a solution of diol **13** (0.3 g, 1.3 mmol) in dry acetone (5 mL), 2, 2-dimethoxy propane (0.32 mL, 2.6 mmol) and a catalytic amount of PPTS (pyridine *p*-toluenesulfonate) (0.01 mg) were added. The mixture was stirred at ambient temperature for 3 h. Sodium bicarbonate (30 mg) was added to neutralize pyridine p-toluenesulfonate and filtered. Removal of solvent and purification by silica-gel column chromatography (pet. ether–EtOAc 8:2) afforded the acetonide **4** (0.3 g, 85%), as a light yellow liquid. $[\alpha]_D^{25}$: +8.0 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.89 (t, $J = 6.7$ Hz, 3H), 1.20–1.46 (m, 13H), 2.24–2.40 (ddd, $J = 5.4$, 6.08, 6.04 Hz, 1H), 2.42–2.53 (m, 1H), 3.66–3.84 (m, 1H), 4.12 (q, $J = 7.5$ Hz, 2H), 4.17–4.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 98.5, 68.7, 65.9, 60.3, 41.4, 36.4, 36.2, 31.7, 30.0, 24.5, 22.5, 19.6, 14.1, 13.9; IR (neat): 2987, 2932, 2862, 1739, 1461, 1377, 1261, 1223, 1197, 1168, 1130, 1023 cm^{-1}; LCMS: *m/z* 295 ($M^+ + Na$); HRMS (ESI): *m/z* calcd. for $C_{15}H_{28}O_4Na$ ($M^+ + Na$): 295.1885; found: 295.1897.

2-[(4*R*, 6*R*)-2, 2-Dimethyl-6-pentyl-1, 3-dioxan-4-yl]aceticacid (14)

Acetonide ester **4** (0.20 g, 0.74 mmol) was dissolved in MeOH (2 mL) and 4 N NaOH (1 mL) was added. The resulting mixture was left to stir at rt for 1 h. The solvents were then removed under reduced pressure and the crude product was redissolved with ethyl acetate. The PH of the aqueous layer was adjusted to 6.0 with aqueous HCL (1 N), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed once with water (15 ml) and brine (15 ml), dried over $MgSO_4$, and concentrated under reduced pressure.

Purification by silica-gel column chromatography (pet. ether–EtOAc 6:4) afforded the acid **14** (0.14 g, 78%), as a liquid. $[\alpha]_D^{25}$: + 3.6 (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, $J = 7.0$ Hz, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.18–1.64 (m, 10H), 2.43 (dd, $J = 5.4$, 15.7 Hz, 1H), 2.57 (dd, $J = 7.0$, 16.4 Hz, 1H), 3.63–3.93 (m, 1H), 4.15–4.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 99.1, 68.8, 65.9, 41.1, 36.2, 31.7, 30.0, 29.7, 24.5, 22.6, 19.7, 14.0; IR (neat): 3445, 2992, 2928, 2860, 1711, 1459, 1378, 1258, 1198, 1165, 1023 cm^{-1}; ESIMS: *m/z* 267 ($M^+ + Na$); HRMS (ESI): *m/z* calcd. for $C_{13}H_{24}O_4Na$ ($M^+ + Na$): 267.1572; found: 267.1569.

Massoialactone (2)

To a stirred solution of acetonide ester **4** (0.1g, 0.37 mmol) in benzene (5 mL), a pinch of *p*-tolunesulfonic acid (PTSA) was added. The reaction mixture was allowed to stir overnight at room temperature, and benzene was removed in vacuum. The crude product was purified by column chromatography (pet. ether–EtOAc 7:3) using silica-gel to give a lactone **2** (0.4 g, 64%) as a pale yellow liquid. $[\alpha]_D^{25}$: − 113.0 (*c*1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, $J = 6.0$ Hz, 3H), 1.22–1.46 (m, 6H), 1.47–1.70 (m, 1H), 1.71–1.87 (m, 1H), 2.27–2.35 (m, 2H), 4.33–4.44 (m, 1H), 5.99 (td, $J = 9.8$, 2.2 Hz, 1H), 6.80–6.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.5, 145.0, 121.4, 78.0, 34.8, 31.5, 29.4, 24.5, 22.5, 14.0; IR (neat): 2933, 1725, 1039 cm^{-1}; ESIMS: 169 ($M^+ + H$). HRMS (ESI): *m/z* calcd. for $C_{10}H_{17}O_2$ ($M^+ + H$): 169.1228; found: 169.1232.

(3*R*, 5*R*)-(+)-3-Hydroxy-5-decanolide (1)

A stirred solution of compound **4** (0.10 g, 0.37 mmol) was dissolved in MeOH (6 mL), then 3 N NaOH (0.6 mL) was added. The resulting mixture was left to stir at rt for 1 h, followed by thin-layer chromatography (TLC). The solvents were then removed under reduced pressure, and the crude product was redissolved in ethyl acetate (25 ml). The PH of the aqueous layer was adjusted to 2 with aqueous HCL (1 N), and the aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phase was washed once with water (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica-gel column chromatography (pet. ether–EtOAc 1:1) afforded the monomeric lactone **1** (0.055 g, 80%) as a colorless liquid. $[\alpha]_D^{25}$: + 22.0 (*c* 0.5, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 200 MHz): δ 0.90 (t, $J = 7.0$ Hz, 3H), 1.20–1.43 (m, 6H), 1.67–1.73(m, 1H), 1.47–1.77 (m, 2H), 1.95 (td, $J = 4.2$, 14.5 Hz, 1H), 2.55–2.67 (m, 2H),

4.27–4.38 (m, 1H), 4.60–4.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 76.0, 62.8, 38.8, 36.0, 35.3, 31.4, 24.2, 22.4, 14.0; IR (neat): 3482, 2928, 2861, 1716, 1460, 1386, 1255, 1065; ESIMS: m/z 187 ($M^+ + 1$). HRMS (ESI): m/z calcd. for $C_{10}H_{18}O_3Na$ ($M^+ + Na$): 209.1153; found: 209.1149.

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