Synthesis of (–)-(5*R*,6*S*)-6-Acetoxyhexadecanolide, a Mosquito Oviposition Attractant Pheromone of *Culex pipiens fatigans*[1]

Gowravaram Sabitha,* R. Swapna, E. Venkata Reddy, J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: sabitha@iictnet.org

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Abstract: Asymmetric total synthesis of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide has been achieved via a key intermediate which was prepared by a Grignard reaction from an alcohol. The alcohol was easily accessed via two different routes.

Key words: lactone, total synthesis, natural product, (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide, pheromone

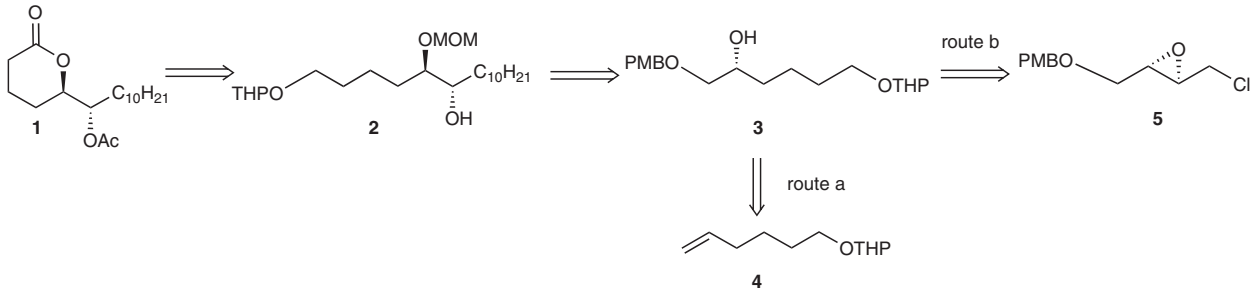
Functionalized δ-lactones have attracted substantial attention in recent years due to their synthetic importance as building blocks in natural products synthesis[2] and as well as their frequent presence in structural moieties of insect pheromones. One such example is (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**1**), isolated by Laurence and Pickett in 1982 from the apical droplet of mosquito (*Culex pipiens fatigans*) eggs.[3] The substance attracts other gravid females of the same and some related mosquito species inducing them to oviposit in the same spot where the original eggs are found. These behaviors can be used to lure the mosquito away from populated areas to a place where they can be readily trapped. It has the ability to transmit the West Nile Virus.[4] In the last few years many syntheses of **1** have appeared in the literature.[5] Owing to their physiological activities, much effort has been expanded on the synthesis of 6-substituted δ-lactones. In continuation of our efforts on δ-lactones,[6] we herein report the synthesis of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide.

The retrosynthetic strategy for (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**1**) is outlined in Scheme 1. The key intermediate **2** was prepared from the compound **3** by a Grignard reaction. This intermediate was synthesized by two different routes from THP protected hex-5-en-1-ol **4** and epoxy chloride **5**.

In route a, the THP ether **4** was epoxidized using dry MCPBA and sodium bicarbonate in anhydrous dichloromethane, followed by quenching with saturated sodium sulfite to afford epoxide **6** in 96% yield. The epoxide **6** was subjected to hydrolytic kinetic resolution (HKR)[7] using 0.005 equivalent of chiral Jacobsen's (*S*,*S*)-salen Co(III) acetate catalyst [(*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co(III) acetate, freshly prepared from (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co(III) chloride and acetic acid] to afford enantio-enriched (>96% ee) epoxide **7** and the terminal diol **8** in 47% yield. The primary hydroxyl group of the diol **8** was protected as its *p*-methoxybenzyl ether using 1 equivalent of PMBBr and 1.5 equivalents of NaH in anhydrous THF at 0 °C to afford the compound **3** in 80% yield (Scheme 2).

In route b, the known epoxy chloride **5**[7] was chosen as the starting material. The conversion of epoxy chloride **5** to the substituted chiral acetylenic alcohol **9**[8] in 70% yield was accomplished by treating compound **5** with 6 equivalents of Li metal in liquid ammonia at –78 °C followed by 2 equivalents of THP protected bromoethanol. In the next step, the reduction of the triple bond in compound **9** over 10% Pd/C and Na_2CO_3 in EtOAc furnished the corresponding saturated compound **3** in 90% yield (Scheme 3).

Thus, the intermediate **3** was prepared by two different routes as shown in Schemes 2 and 3. This was further utilized for the synthesis of the target molecule **1**. Accord-



Scheme 1 Retrosynthetic route for (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**1**)

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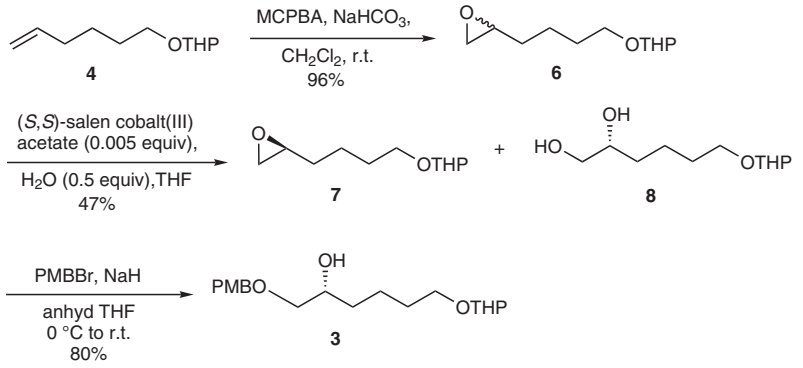
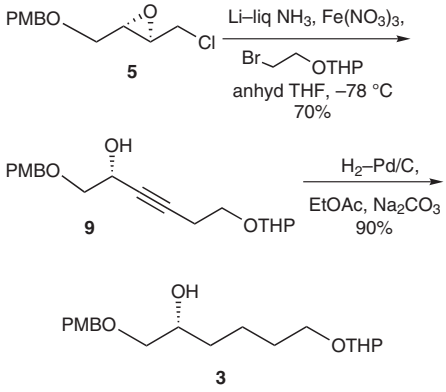


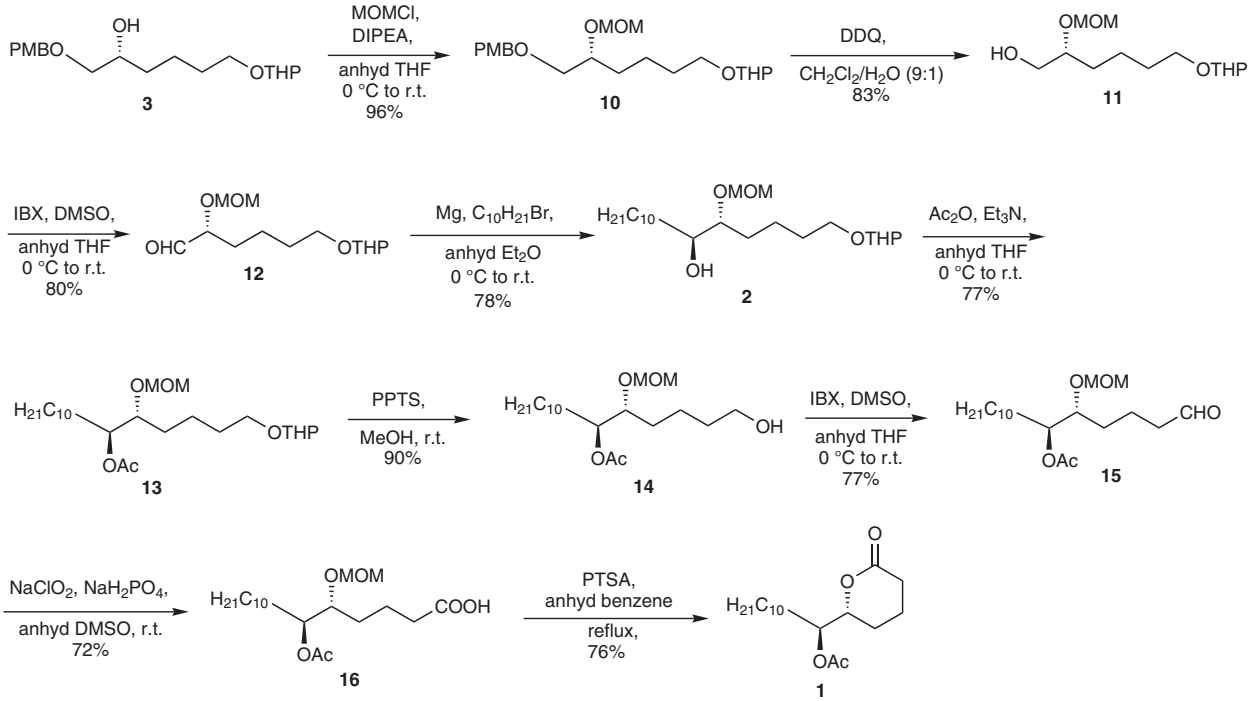
Scheme 2

ingly, the secondary hydroxyl group of compound **3** was protected as its methoxymethyl ether using 3 equivalents of Hunig's base (*i*-Pr_2EtN) and 2 equivalents of MOMCl in anhydrous CH_2Cl_2 at room temperature affording **10** in 96% yield.[9] Deprotection of PMB group of compound **10** was done by treatment with 1.5 equivalents of DDQ in CH_2Cl_2/H_2O (9:1) to afford compound **11** in 83% yield. Oxidation of compound **11** with IBX (*o*-iodoxybenzoic acid) in DMSO–CH_2Cl_2 at 25 °C afforded aldehyde **12** in 80% yield (Scheme 4).

The aldehyde **12** was treated with the Grignard reagent prepared from decylmagnesium bromide (freshly prepared from 1-bromodecane and Mg in anhyd diethyl ether) affording the key intermediate **2** as a major product with *anti*-selectivity (80% ee) in 78% yield.[10] The secondary hydroxyl group of compound **2** was protected by using acetic anhydride and triethylamine in anhydrous CH_2Cl_2 to afford acetate **13**. Deprotection of the THP group in **13** using PTSA in MeOH[11] resulted in alcohol **14** in 90% yield. The alcohol **14** was oxidized to aldehyde **15** using IBX in 77% yield. The aldehyde **15** was further oxidized with $NaClO_2$ and NaH_2PO_4 in DMSO and water to afford the corresponding acid **16** in 72% yield.[12] Finally the syn-



Scheme 3



Scheme 4

thesis of target molecule **1** was achieved in 76% yield by in situ deprotection of MOM group and subsequent cyclization by using catalytic amount of PTSA in anhydrous benzene under reflux (Scheme 4).[13] The synthetic material showed IR, ^{1}H, ^{13}C NMR spectral data and optical rotation {$[\alpha]_D^{25}$ –35.0 (c = 1.5, $CHCl_3$)} in good agreement with the natural lactone.

Reactions were conducted under N_2 using anhyd solvents such as CH_2Cl_2, THF, CCl_4, benzene and EtOAc. All reactions were monitored by 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 (^{1}H, ^{13}C) homogeneous material. Air sensitive reagents were transferred by syringe or cannula. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator. ^{1}H NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) 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. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 polarimeter at 20 °C.

2-(5-Hexenyloxy)tetrahydro-2*H*-pyran (4)

In a 100 mL round-bottomed flask fitted with a N_2 adaptor, the hex-5-en-1-ol (10 g, 100.0 mmol) in anhyd CH_2Cl_2 (80 mL) was taken and a catalytic amount of PTSA was added. Then the mixture was cooled to 0 °C. To this 3,4-dihydro-2*H*-pyran (6.5 mL, 110.0 mmol) was added dropwise. After completion of addition, the mixture was allowed to stir for 3 h. The mixture was diluted with CH_2Cl_2, and the organic layer was washed with H_2O, aq $NaHCO_3$, and dried (Na_2SO_4). Concentration under reduced pressure and purification over silica gel column chromatography afforded pure tetrahydropyranyl ether **4** (18.2 g, 95%) as a viscous liquid.

^{1}H NMR ($CDCl_3$, 300MHz): δ = 5.84–5.71 (m, 1 H), 5.02–4.90 (m, 2 H), 4.55 (t, J = 3.2 Hz, 1 H), 3.50–3.30 (m, 2 H), 2.15–2.03 (m, 2 H), 1.88–1.4 (m, 12 H).

2-[4-(2-Oxiranyl)butoxy]tetrahydro-2*H*-pyran (6)

To a suspension of $NaHCO_3$ (5.8 g, 70.0 mmol) in CH_2Cl_2 (60 mL) was added the compound **4** (13 g, 70.0 mmol) in CH_2Cl_2 (30 mL) under N_2. Then, dry MCPBA (14.3 g, 80.0 mmol) was added in small portions to the mixture at 0 °C. It was stirred at r.t. for 10 h until completion of the reaction (TLC monitoring). The mixture was diluted with CH_2Cl_2 and the CH_2Cl_2 layer was washed with a solution of Na_2SO_3 followed by aq 5% $NaHCO_3$ solution and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography to afford the pure epoxide **6** (14.1 g, 96%) as a viscous liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.55 (t, J = 3.2 Hz, 1 H), 3.87–3.67 (m, 2 H), 3.52–3.32 (m, 2 H), 2.86 (m, 1 H), 2.70 (m, 1 H), 2.42 (m, 1 H), 1.88–1.42 (m, 12 H).

(2*R*)-6-(Tetrahydro-2*H*-2-pyranyloxy)hexane-1,2-diol (8)

A mixture of (*S*,*S*)-Jacobsen catalyst [(*S*,*S*)-*N*-*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co(III) acetate] (195 mg, 0.32 mmol, 0.005 equiv) in CH_2Cl_2 and AcOH (39 mg, 0.65 mmol, 0.01 equiv) was stirred while open to the air for 1 h at r.t. The solvent was removed by rotary evaporation, and the brown residue was dried under vacuum. Epoxide **6** (13 g, 65 mmol, 1 equiv) was added in one portion, and the stirred mixture was cooled in an ice-water bath. H_2O (65 mg, 35 mmol, 0.55 equiv) was slowly added until the temperature of the mixture began to rise. The temperature rose to ~25 °C before dropping to 15 °C, at which point H_2O addition was continued at a rate that maintained the reaction temperature near 20 °C. After 1 h, the addition was complete, the ice bath was removed, and the reaction was stirred at r.t. for 24 h and then quenched with aq sat. $NaHCO_3$ solution. The filtrate was washed with H_2O, brine and dried (Na_2SO_4). The organic layer was concentrated to give the crude material, which after column chromatography provided the pure product **8** (6.1 g, 47%, 96% ee) as a liquid; $[\alpha]_D^{25}$ –18.02 (c = 1.5, $CHCl_3$).

IR (neat): 3403, 2940, 2867, 1121, 1073, 1028 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.54 (t, J = 3.7 Hz, 1 H), 3.90–3.32 (m, 7 H), 1.90–1.40 (m, 12 H).

ESIMS: m/z = 241 (M^+ + Na).

(2*R*)-1-(4-Methoxyphenoxy)-6-(tetrahydro-2*H*-2-pyranyloxy)hexan-2-ol (3)

To a stirred suspension of freshly activated NaH (0.660 g, 27.0 mmol) in anhyd THF (30 mL) at 0 °C, was added dropwise alcohol **8** (4 g, 18.3 mmol) in anhyd THF (10 mL). After stirring for 30 min, PMBBr (3.1 g, 18.3 mmol) in anhyd THF (10 mL) was added. After completion of the reaction (3 h), the mixture was quenched with aq sat. NH_4Cl solution and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by silica gel column chromatography afforded **3** (5.4 g, 80%) as a viscous liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20 (d, J = 9.0 Hz, 2 H), 6.83 (d, J = 8.3Hz, 2 H), 4.54 (t, J = 3.0 Hz, 1 H), 4.45 (s, 2 H), 3.85–3.66 (m, 6 H), 3.51–3.20 (m, 4 H), 1.85–1.30 (m, 12 H).

(2*R*)-1-(4-methoxyphenoxy)-6-(tetrahydro-2*H*-2-pyranyloxy)hex-3-yn-2-ol (9)

To a freshly distilled liquid ammonia (50 mL) in 100 mL two-neck round-bottomed flask fitted with a cold finger condenser was added a catalytic amount of $Fe(NO_3)_3$, followed by the piecewise addition of Li metal (1.9 g, 272.7 mmol) at –78 °C, and the resulting gray colored suspension was stirred for 30 min. To this was added epoxy chloride **5** (11 g, 45.4 mmol) in anhyd THF (10 mL) over a period of 15 min. The mixture was then stirred for 2 h at the same temperature. After 2 h, THP protected bromoethanol (20.5 g, 90.8 mmol) was added dropwise to the mixture. The reaction was stirred at the same temperature for 6 h, and quenched by the addition of solid NH_4Cl, and then the ammonia was allowed to evaporate. The mixture was partitioned between H_2O and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were washed once with H_2O, and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum–EtOAc (6:4) to afford the pure **9** as a clear colorless liquid (10.6 g, 70%); $[\alpha]_D^{25}$ –1.2 (c = 1.5, $CHCl_3$).

IR (neat): 3425, 2941, 2867, 1513, 1248, 1032 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.2 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.60 (t, J = 3.2 Hz, 1 H), 4.50 (d, J = 3.5 Hz, 2 H), 3.85–3.66 (m, 6 H), 3.51–3.40 (m, 4 H), 2.48 (td, J = 5.2, 1.8 Hz, 2 H), 1.68–1.30 (m, 6 H).

ESIMS: m/z = 357 (M^+ + Na).

(2*R*)-1-(4-Methoxyphenoxy)-6-(tetrahydro-2*H*-2-pyranyloxy)hexan-2-ol (3)

To a solution of compound **9** (10 g, 29.9 mmol), and Na_2CO_3 (6.2 g, 59.8 mmol) in anhyd EtOAc (5 mL) was added a catalytic amount of Pd/C (10%) and the mixture was stirred at r.t. under H_2 atmosphere for 6 h. Then the catalyst was filtered off, washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography elut-

ing with petroleum ether–EtOAc (6:4) to afford compound **3** as a colorless liquid (9.0 g, 90%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 4.54 (t, *J* = 3.0 Hz, 1 H), 4.45 (s, 2 H), 3.85–3.66 (m, 6 H), 3.51–3.20 (m, 4 H), 1.85–1.30 (m, 12 H).

2-{[(5*R*)-5-(Methoxymethoxy)-6-(4-methoxyphenoxy)hexyl]oxy}tetrahydro-2*H*-pyran (10)

To solution of compound **3** (4.3 g, 12.72 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C under N_2, was added *i*-Pr_2NEt (6.6 mL, 38.16 mmol) dropwise and after 5 min MOM-Cl (3.6 mL, 38.16 mmol) was added dropwise. After stirring for 2 h at r.t., the mixture was diluted with H_2O. Aq sat. NH_4Cl solution was added, the layers were separated and the organic layer was dried (Na_2SO_4). The residue was purified on silica gel column and eluted with hexane–EtOAc (9:1) to afford the pure compound **10** as a clear colorless liquid (4.6 g, 96%); $[\alpha]_D^{25}$ –3.28 (*c* = 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.2 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 8.3 Hz, 2 H), 4.65 (ABq, *J* = 6.7 Hz, 2 H), 4.54 (t, *J* = 3.0 Hz, 1 H), 4.43 (s, 2 H), 3.85–3.64 (m, 6 H), 3.50–3.28 (m, 7 H), 1.85–1.30 (m, 12 H).

(2*R*)-2-(Methoxymethoxy)-6-(tetrahydro-2*H*-2-pyranyloxy)hexan-1-ol (11)

To a stirred solution of compound **10** (4.0g, 10.4 mmol) in CH_2Cl_2 (4.5 mL) and H_2O (0.5 mL) was added DDQ (2.3 g, 10.4 mmol) at r.t. The mixture was stirred for 2.5 h at r.t. before being quenched by the addition of aq sat. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the compound **11** (2.3 g, 83%) as a pure yellow oil; $[\alpha]_D^{25}$ –17.41 (*c* = 1.5, $CHCl_3$).

IR (neat): 3455, 2941, 1120, 1033 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.79–4.53 (m, 3 H), 3.95–3.29 (m, 10 H), 1.85–1.30 (m, 12 H).

ESIMS: *m*/*z* = 285 (M^+ + Na).

(2*R*)-2-(Methoxymethoxy)-6-(tetrahydro-2*H*-2-pyranyloxy)hexanal (12)

To an ice-cooled solution of iodoxybenzoic acid (4.3 g, 15.2 mmol) in DMSO (4 mL) was added a solution of alcohol **11** (2.0 g, 7.6 mmol) in anhyd CH_2Cl_2 (10 mL). After stirring for 2 h at r.t., the mixture was filtered through a Celite pad and washed with Et_2O. The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with petroleum ether–EtOAc (8:2) to afford the aldehyde **12** as a viscous liquid (1.58 g, 80%)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.58 (s, 1 H), 4.69 (ABq, *J* = 6.7 Hz, 2 H), 4.54 (t, *J* = 3.0 Hz, 1 H), 3.86–3.65 (m, 2 H), 3.51–3.27 (m, 6 H), 1.85–1.30 (m, 12 H).

(5*R*,6*S*)-5-(Methoxymethoxy)-1-(tetrahydro-2*H*-2-pyranyloxy)hexadecan-6-ol (2)

To a suspension of Mg (1.37 g, 28.5 mmol) in anhyd Et_2O (50 mL), was added dropwise 1-bromodecane (11.8 mL, 28.5 mmol) under N_2 at 0 °C. The mixture was allowed to stir for 0.5 h at r.t. To this Grignard reagent, was added aldehyde **12** (3.0 g, 5.7 mmol) in anhyd Et_2O (10 mL) at 10 °C. The mixture was stirred for 5–6 h and then quenched with aq sat. NH_4Cl solution and filtered over Celite. The filtrate was washed with H_2O, brine and dried (Na_2SO_4). The organic layer was concentrated to give the crude material, which after column chromatography provided the pure product **2** (3.6 g, 78%) as a liquid; $[\alpha]_D^{25}$ –8.04 (*c* = 1.5, $CHCl_3$).

IR (neat): 3469, 2926, 2854, 1460, 1141, 1034 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.63 (ABq, *J* = 6.5 Hz, 2 H), 4.53 (t, *J* = 3.1 Hz, 1 H), 3.86–3.65 (m, 2 H), 3.51–3.27 (m, 7 H), 1.70–1.22 (m, 30 H), 0.90 (t, *J* = 6.5 Hz, 3 H).

ESIMS: *m*/*z* = 425 (M^+ + Na).

(1*S*)-1-[(1*R*)-1-(Methoxymethoxy)-5-(tetrahydro-2*H*-pyranyloxy)pentyl]undecyl Acetate (13)

To a stirred solution of compound **2** (1.6g, 4.9 mmol) in anhyd CH_2Cl_2 (3 mL) was added Et_3N (1.1 mL, 7.9 mmol) followed by Ac_2O (0.56 mL, 5.9 mmol) and a catalytic amount DMAP at 0 °C. The mixture was stirred for 1 h and then diluted with CH_2Cl_2. The organic layer was washed successively with H_2O, aq 5% $NaHCO_3$ solution, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure followed by column chromatography using silica gel (60–120 mesh) afforded the acetate **13** (1.6 g, 92%) as a colorless liquid; $[\alpha]^{25}_D$ –1.94 (*c* = 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.92 (m, 1 H), 4.63 (ABq, *J* = 6.5 Hz, 2 H), 4.54 (t, *J* = 3.1 Hz, 1 H), 3.84–3.66 (m, 2 H), 3.54–3.30 (m, 6 H), 2.05 (s, 3 H), 1.70–1.22 (m, 30 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.7, 98.8, 96.5, 78.0, 74.5, 67.3, 62.3, 55.8, 31.8, 30.7, 30.3, 29.9, 29.8, 29.9, 29.8, 29.5, 29.5, 29.5, 29.3, 25.5, 25.4, 22.6, 21.1, 19.5, 14.1.

ESIMS: *m*/*z* = 467 (M^+ + Na).

(1*S*)-1-[(1*R*)-5-Hydroxy-1-(methoxymethoxy)pentyl]undecyl Acetate (14)

To a stirred solution of compound **13** (1.6 g, 3.6 mmol) in MeOH (30 mL) was added a catalytic amount of PPTS. The mixture was stirred at r.t. for about 2 h and then MeOH was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to afford **14** (1.16 g, 90%) as a viscous liquid; $[\alpha]_D^{25}$ –0.73 (*c* = 1.5, $CHCl_3$).

IR (neat): 3448, 2926, 2854, 1737, 1239, 1035 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.96 (m, 1 H), 4.65 (ABq, *J* = 6.5 Hz, 2 H), 3.70–3.36 (m, 6 H), 2.08 (s, 3 H), 1.80–1.23 (m, 22 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

ESIMS: *m*/*z* = 383 (M^+ + Na).

(1*S*)-1-[(1*R*)-1(Methoxymethoxy)-5-oxypentyl]undecyl Acetate (15)

To an ice-cooled solution of iodoxybenzoic acid (1.16 g, 4.1 mmol) in DMSO (4 mL) was added a solution of alcohol **14** (1.0 g, 2.7 mmol) in anhyd CH_2Cl_2 (10 mL). After stirring for 2 h at r.t., the mixture was filtered through a Celite pad and washed with Et_2O. The combined organic layers were washed with H_2O, brine, and dried (Na_2SO_4), then concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with petroleum ether–EtOAc (8:2) to afford to the aldehyde **15** as a viscous liquid (0.800 g, 77%); $[\alpha]_D^{25}$ –12.7 (*c* = 1.5, $CHCl_3$).

IR (neat): 3450, 2926, 2854, 1738, 1461, 1372, 1239, 1031 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.77 (s, 1 H), 4.95 (m, 1 H), 4.64 (ABq, *J* = 7.0 Hz, 2 H), 3.62–3.32 (m, 4 H), 2.46 (td, *J* = 5.4, 1.5 Hz, 2 H), 2.08 (s, 3 H), 1.80–1.23 (m, 22 H), 0.90 (t, *J* = 6.7 Hz, 3 H),

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 201.9, 170.5, 96.6, 77.9, 74.3, 55.9, 43.6, 31.8, 29.8, 29.6, 29.4, 29.6, 29.2, 25.7, 25.5, 22.6, 21.0, 18.3, 18.0, 14.0.

ESIMS: *m*/*z* = 381 (M^+ + Na).

(5*R*,6*S*)-6-(Acetyloxy)-5-(methoxymethoxy)hexadecanoic Acid (16)

To a stirred solution of compound **15** (0.7 g, 1.95 mmol) in DMSO (5 mL) was added an aq solution of NaH_2PO_4 (0.305 g, 1.95 mmol) dropwise at 0 °C. To this well-stirred mixture at 0 °C was added aq $NaClO_2$ (0.175 g, 1.95 mmol) solution and the mixture was allowed to stir for 1 h at r.t. To the mixture was added aq 5% $NaHCO_3$ solution. The organic phase extracted into CH_2Cl_2 and the aqueous phase was acidified with conc. HCl. The organic layer was filtered through the small pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with petroleum ether–EtOAc (5:5) to afford **16** as a colorless oil (0.520 g, 72%); $[\alpha]_D^{25}$ –16.1 (c = 1.5, $CHCl_3$).

IR (neat): 3447, 2925, 2854, 1738, 1460, 1372, 1238, 1030 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.94 (m, 1 H), 4.64 (ABq, J = 6.2 Hz, 2 H), 3.53 (m, 1 H), 3.37 (s, 3 H), 2.36 (t, J = 6.7 Hz, 2 H), 2.08 (s, 3 H), 1.80–1.23 (m, 22 H), 0.88 (t, J = 6.7 Hz, 3 H).

ESIMS: m/z = 397 (M^+ + Na).

(–)-(5*R*,6*S*)-6-Acetoxyhexadecanolide (1)

To a stirred solution of compound **16** (0.4 g, 1.06 mmol) in anhyd benzene (10 mL) was added a catalytic amount of PTSA under N_2. The mixture was refluxed for 2 h and the solvent was removed under vacuum, and then quenched with aq $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 ×), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the lactone **1** (0.25 g, 76%); $[\alpha]_D^{25}$ –35 (c = 1.5, $CHCl_3$).

IR (neat): 2925, 2854, 1737, 1461, 1372, 1238, 1027 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.94 (m, 1 H), 4.30 (m, 1 H), 2.66–2.18 (m, 2 H), 2.07 (s, 3 H), 1.98–1.22 (m, 22 H), 0.89 (t, J = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.9, 170.6, 80.4, 74.3, 31.8, 29.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.3, 23.4, 22.6, 20.9, 18.3, 14.0.

ESIMS: m/z = 313 (M^+ + 1).

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