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A Facile Synthesis of Both Enantiomers of 6-Acetoxy-5-hexadecanolide, a Major Component of Mosquito Oviposition Attractant Pheromones

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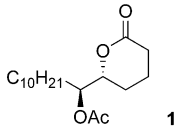
The stereoselective synthesis of (–)-(5*R*,6*S*)-*erythro*-6-acetoxy-5-hexadecanolide, the major component of a mosquito oviposition attractant pheromone, and its enantiomer are reported. The synthesis was completed over seven steps in 28 % overall yield by using Sharpless asymmetric epoxidation and $ZrCl_4$-catalyzed cyclic acetal formation as the key steps.

Introduction

The mosquito oviposition attractant pheromones were isolated by Laurence and Pickett from apical droplets formed on the egg of the mosquito *Culex pipens fatigans* (= *quinquefasciatus*).[1] The absolute configuration of the natural pheromone was identified as (–)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**1**), which acts as an oviposition attractant pheromone by attracting other gravid females of the same and some related species and induces them to oviposit in the same spot where the original eggs are found.[2] This behaviour can be used to tempt the mosquito away from populated areas to a place where they can be readily trapped.



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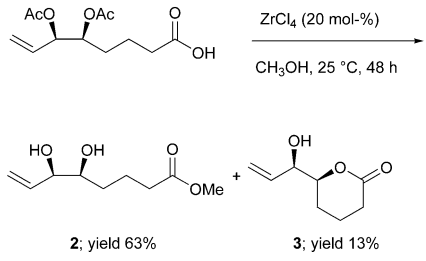
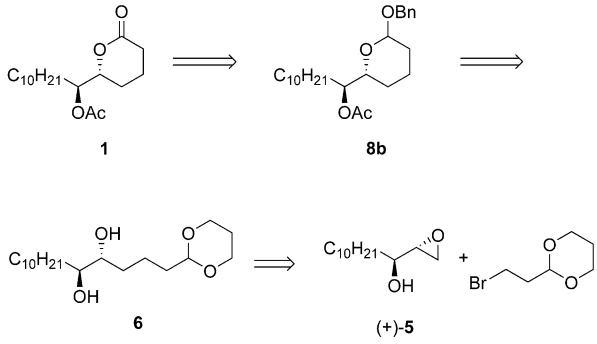
The first synthesis of the two enantiomers of the *erythro* isomer of **1** was reported by Fuganti in 1982.[3] Since then numerous enantioselective syntheses of *erythro*-6-acetoxy-5-hexadecanolide have been reported[4–33] but the development of a short synthetic route with good overall yield was lacking and therefore of interest. As part of our work on the development of compounds with potential for the resolution of inflammation, we recently reported the synthesis and biological evaluation of Lipoxin A_4 analogues.[34] We have also improved the synthetic methodology for the preparation of **2**, a key intermediate of Lipoxin A_4, and we have found the δ-lactone **3** as a by-product which contains the key-structural unit in the mosquito attractant pheromone **1**, Scheme 1.[35] The exploitation of this chemistry suggested an alternative asymmetric retrosynthetic route of **1** to us, Scheme 2, and now we wish to report the results of our investigations.



2; yield 63% **3**; yield 13%

Scheme 1. $ZrCl_4$-catalyzed one-pot esterification and diacetate deprotection.



1 **8b** **6** (+)-**5**

Scheme 2. Retrosynthetic route for (–)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**1**).

Thus, (±)-tridec-1-en-3-ol (**4**) was synthesized in 78% yield by the reaction of undecanal with vinylmagnesium bromide, Scheme 3. The (+)-(*S*)-1-[(*R*)-oxiran-2-yl]undecan-1-ol (**5**) was synthesized in 40% yield and in 97% *ee* using $Ti(OiPr)_4$, L-(+)-diisopropyl tartrate and cumene hydroperoxide as the oxidant. Unreacted (*R*)-tridec-1-en-3-

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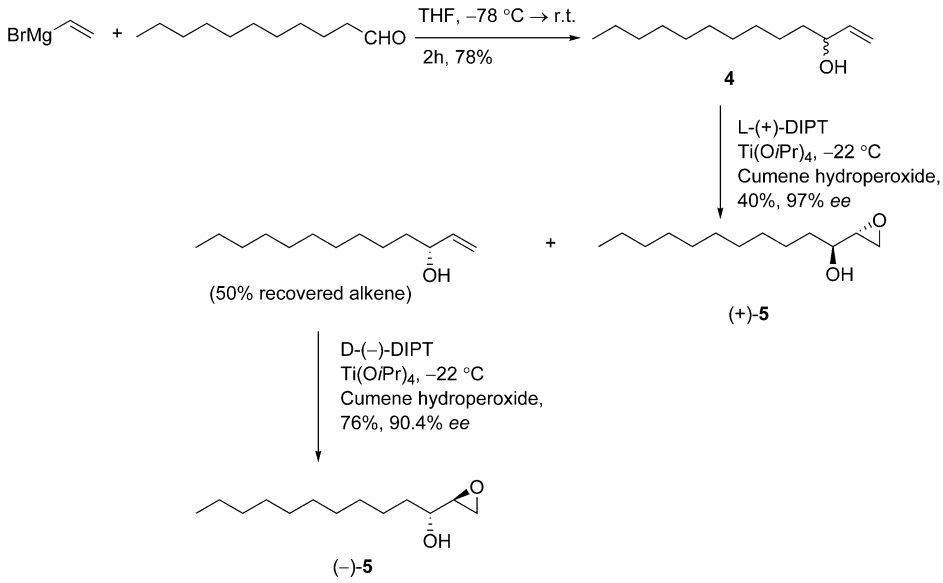
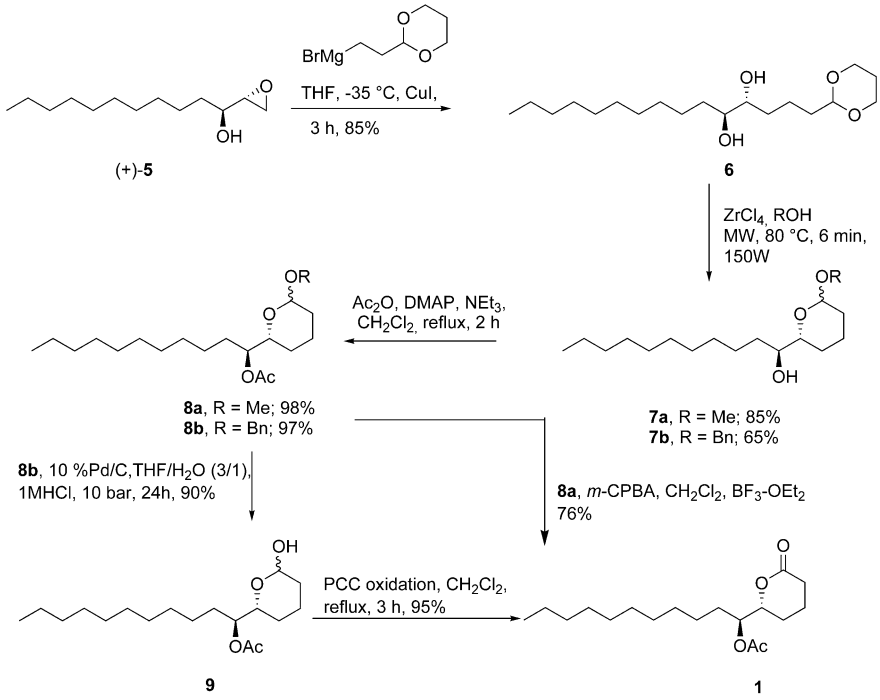


Scheme 3. Enantioselective synthesis of epoxides (+)- and (–)-**5**.

ol was recovered in 50% yield, which when subjected to the same epoxidation protocol, albeit with (–)-diisopropyl tartrate, was converted into (–)-(*R*)-1-[(*S*)-oxiran-2-yl]undecan-1-ol (**5**) in 76% isolated yield and 90.4% *ee*.

The epoxide (+)-**5** was treated with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane at –35 °C in THF using 20 mol-% of CuI, Scheme 4.[34,35] The 4*R*,5*S* diol **6** was converted into the methoxy-substituted tetrahydropyrane **7a** using $ZrCl_4$ (10 mol-%) as the Lewis acid for the deprotection of the 1,3-dioxane and its subsequent cyclisation under microwave irradiation at 80 °C. Compound **7a**, thus formed in 85% yield with an epimeric ratio of 7:3, was protected as the acetate **8a** in the presence of acetic anhydride and a catalytic amount of DMAP (20 mol-%) in dichloromethane and triethylamine. We have investigated various methods, e.g. (BBr_3 in dichloromethane, 3 N HCl, BF_3–diethyl ether, Me_3SiCl and NaI, trytilium hexafluoride phosphate) for the deprotection of the methoxy group but we obtained very poor yields of lactol **9** (up to 35%).



Scheme 4. Synthesis of (5*R*,6*S*)-(–)-*erythro*-6-acetoxy-5-hexadecanolide (**1**).

Therefore, we prepared the benzyl ether **7b** in 65% yield from diol **6** using the same $ZrCl_4$-catalyzed protocol under microwave irradiation. The acetal **7b** was then converted into the acetate **8b** in 97% yield and the benzyl ether deprotected using 10% Pd/C in THF/H_2O (3:1) with an additional trace amount of 1 M HCl under 20 bar pressure of H_2 at room temp. to provide the corresponding lactol **9** in 90% isolated yield.[36] Lactol **9** was then oxidized using PCC in dichloromethane at 50 °C to afford (5*R*,6*S*)-(–)-*erythro*-6-acetoxy-5-hexadecanolide (**1**) in 95% yield. We also investigated the one-pot acetal deprotection and oxidation[37,38] of compound **8a** in the presence of BF_3–diethyl ether and *m*-chloroperbenzoic acid which afforded (5*R*,6*S*)-(–)-*erythro*-6-acetoxy-5-hexadecanolide (**1**) in 76% yield. The spectroscopic and physical data of compound (5*R*,6*S*)-**1** were identical with the literature reports and the enantiomeric excess (>99.9%) was determined by HPLC using a chiralpak OD column. The opposite enantiomer was also synthesised, starting with (*R*)-1-[(*S*)-oxiran-2-yl]undecan-1-ol and employing the same synthetic strategy to afford (5*S*,6*R*)-(+)-*erythro*-6-acetoxy-5-hexadecanolide (**1**) in a 95.5% *ee* as determined by HPLC. The optical rotation of both enantiomers is in concurrence with literature reports.[3,5,10,11,33]

Conclusion

In summary we have synthesised both enantiomers of *erythro*-6-acetoxy-5-hexadecanolide (**1**) with >99% *ee* in a 28% overall yield of both enantiomer by using Sharpless asymmetric epoxidation as one of the key steps. We have also used our recently developed $ZrCl_4$-catalyzed deprotection of 1,3-dioxane and ring closure to prepare a benzyloxy-substituted tetrahydropyrane as the key intermediate for the mosquito pheromone synthesis. We are currently investigating the application of this methodology in the total synthesis of other natural products and the results of these studies will be reported in due course.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz (operating frequencies: ^{1}H, 399.8 MHz; ^{13}C, 100.61 MHz, respectively) and 500 MHz (operating frequencies: ^{1}H, 499.77 MHz; ^{13}C, 125.67 MHz, respectively) FT spectrometers at ambient temperature. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. The reactions under microwave irradiations were carried out using a CEM Discover microwave reactor. HRMS were obtained using a Micromass/Waters LCT instrument. Infrared spectra were recorded with a Perkin–Elmer Infrared FT spectrometer. Optical rotation values were measured with a Perkin–Elmer 343 polarimeter. All optical rotations were obtained at room temp. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254 (Merck) and either visualized in a UV light or vanillin/CH_3COOH and H_2SO_4. Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.063 mm). HPLC analysis was performed with a LC2010A machine equipped with a UV/Vis detector employing a Chiracel OD column from Daicel Chemical Industries. The compound **6** was synthesized according to literature report.[34,35] All reagents were purchased from Sigma–Aldrich and used as received. Solvents were dried immediately before use by using solvent drying system pure solv 300-M-3.

Microwave Irradiation Experiments: All microwave experiments were performed using the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL) using the high-absorbance level. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

Tridec-1-en-3-ol (4): Vinylmagnesium bromide was prepared by addition of vinyl bromide (3.88 mL, 50 mmol) to preactivated magnesium turnings (1.21 g, 50 mmol) in THF (50 mL) using a dry ice condenser and stirring at room temp. for 45 min. The vinylmagnesium bromide solution was slowly transferred to pre-cooled undecylaldehyde (9.3 mL, 45 mmol) in 20 mL of diethyl ether at –78 °C and the resulting mixture stirred for an hour, warmed to room temp., stirred for a further hour and then quenched with 2 N HCl (50 mL). The reaction mixture was extracted with diethyl ether (50 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). After concentration of the combined extracts, the resulting residue was purified by kugelrohr distillation (140 °C/1 mbar) to afford the title compound as a colourless oil (7.00 g, 78%). IR (neat): $\tilde{\nu}$ = 3352, 2925, 2854, 1466, 1067, 990, 920 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddd, *J* = 17.1, 10.4, 6.2 Hz, 1 H), 5.20 (tt, *J* = 17.2, 1.4 Hz, 1 H), 5.08 (tt, *J* = 10.4, 1.4 Hz, 1 H), 4.11–4.04 (m, 1 H), 1.56–1.42 (m, 2 H), 1.30–1.20 (m, 16 H), 0.87 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 114.5, 73.2, 37.0, 31.9, 29.6 (4 C), 29.3, 25.3, 22.7, 14.1 ppm. GCMS (ESI): calcd. for $C_{13}H_{26}O$ $[M]^+$ 198.1984; found 198.1992.

(*S*)-1-[(*R*)-Oxiran-2-yl]undecan-1-ol (5): 4-Å molecular sieves (1.0 g) and CH_2Cl_2 (30 mL) were placed in a two-necked 100-mL round-bottomed flask, followed by addition of Ti(O*i*Pr)$_4$ (955 µL, 3.23 mmol) and (+)-diisopropyltartrate (883.4 µL, 4.2 mmol) at –35 °C under nitrogen and the resulting mixture was stirred for 30 min. The tridec-1-en-3-ol (6.4 g, 32.3 mmol) was added and stirred for 30 min, than cumene hydroperoxide (4.6 mL, 0.75 equiv.) was added during 20 min at the same temperature and then it was increased to –22 °C. The reaction progress was checked by TLC to monitor the consumption of cumene hydroperoxide. The reaction was completed in 30 h, then quenched with saturated sodium sulfate solution (3 mL). Diethyl ether (30 mL) was added and the resulting mixture stirred for 3 h at room temp. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum. The epoxide was purified by column chromatography using pentane/EtOAc (9.5:0.5→8.5:1.5) to give 2.4 g of unreacted tridec-1-en-3-ol and 2.8 g (40%) of epoxide **5** as a solid; m.p. 25–27 °C, ref.[5] 25–26 °C. $[\alpha]_D^{20}$ = +16.1 [*c* = 1, in $CHCl_3$], ref.[5] $[\alpha]_D^{20}$ = +16.2 (*c* = 1.01, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3433, 2926, 2855, 1256, 1436, 1092, 906 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85–3.80 (m, 1 H), 3.01 (tt, *J* = 3.9, 3.0 Hz, 1 H), 2.81 (dd, *J* = 5.0, 2.8 Hz, 1 H), 2.73 (dd, *J* = 5.0, 4.0 Hz, 1 H), 1.84 (d, *J* = 2.5 Hz, 1 H), 1.60–1.28 (m, 18 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.4, 54.5, 43.4, 33.4, 31.9, 29.7, 29.6 (2C), 29.5, 29.3, 25.3, 22.7, 14.1 ppm. GCMS (ESI): calcd. for $C_{13}H_{26}O_2$ $[M]^+$ 214.1933; found 214.1927.

(*R*)-1-[(*S*)-Oxiran-2-yl]undecan-1-ol (5): The synthesis of (–)-**5** was carried out according to the procedure above and the recovered allylic alcohol was used as substrate and isolated in a 76% yield; m.p. 25–27 °C, ref.[5] 25–26 °C. $[\alpha]_D^{20}$ = –14.6 (*c* = 1.0, in $CHCl_3$, ref.[5] $[\alpha]_D^{20}$ = –16.6 (*c* = 1.12, in $CHCl_3$).

Determination of *ee* Values of Epoxide 5: The epoxides (+) and (–)-**5** were converted into the corresponding (*S*)-1-[(*R*)-oxiran-2-yl]-undecyl 2-phenoxyacetates.[39] Epoxide (+)-**5** (21.4 mg, 0.1 mmol), triethylamine (28 μL, 0.2 mmol), and DMAP (25 mol-%) were dissolved in THF (1 mL), followed by addition of benzoyl chloride (12 μL, 0.1 mmol) and 2-phenoxyacetic acid (15.2 mg, 0.1 mmol) and the resulting reaction mixture was stirred for 24 h. 5% HCl (1 mL) was added, the mixture was extracted with ethyl acetate (2 × 5 mL) and the organic layer was washed with water (1 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by column chromatography using 9:1 (pentane/EtOAc). The enantiomeric excess of the phenoxy acetate derivative was determined by HPLC using chiralpak OD column; 1 mL/min flow rate, 90:10 hexane/isopropyl alcohol as mobile phase and 220 nm λ_{max}.

Spectroscopic Data for (*S*)-1-[(*R*)-Oxiran-2-yl]undecyl-2-phenoxy Acetate: Isolated as a colourless oil in 95% yield with 97% *ee* and r_t 8.2 min (minor) and r_t 11.1 min (major). $[\alpha]_D^{20}$ = –8.7 (*c* = 0.5, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 2 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 6.92 (dd, *J* = 0.9, 8.7 Hz, 2 H), 4.87 (dd, *J* = 5.5, 12.6 Hz, 1 H), 4.65 (s, 2 H), 3.01–2.94 (m, 1 H), 2.72 (dd, *J* = 4.0, 5.1 Hz, 1 H), 2.68 (dd, *J* = 2.6, 5.1 Hz, 1 H), 1.70 (dd, *J* = 6.8, 14.4 Hz, 2 H), 1.26 (s, 16 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.5, 157.8, 129.5, 121.8, 114.6, 73.9, 65.2, 52.0, 45.2, 31.9, 31.6, 31.3, 29.6 (2 C), 29.5, 29.4, 29.3 (2 C), 24.9, 22.7, 14.1 ppm. The *ee* of (*R*)-1-[(*S*)-oxiran-2-yl]undecyl 2-phenoxyacetate was found to be 90.4% and r_t 8.2 min (major) and r_t 11.1 min (minor). $[\alpha]_D^{20}$ = +7.9 (*c* = 1.4, in $CHCl_3$).

(4*S*,5*R*)-1-(1,3-Dioxan-2-yl)hexadecane-4,5-diol (6): Isolated as yellow solid in 85% yield; m.p. 85 °C. $[\alpha]_D^{20}$ = –3.2 (*c* = 1.0, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3306, 2915, 2848, 1408, 1355, 1297, 1149, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (t, *J* = 4.7 Hz, 1 H), 4.11–4.03 (m, 2 H), 3.92–3.84 (m, 1 H), 3.78–3.73 (m, 3 H), 2.12–2.02 (m, 2 H), 1.84–1.26 (m, 24 H), 0.88 (t, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.2, 74.6, 74.3, 66.8 (2 C), 34.9, 31.9, 31.3, 30.1, 29.7, 29.6 (3 C), 29.3, 26.0, 25.8, 22.6, 20.3, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{39}O_4$ $[M + H]^+$ 331.2848; found 331.2848.

(4*R*,5*S*)-1-(1,3-Dioxan-2-yl)hexadecane-4,5-diol (6): $[\alpha]_D^{20}$ = +3.8 (*c* = 1.0, in $CHCl_3$).

(*R*)-1-[(*S*)-6-Methoxy-tetrahydro-2*H*-pyran-2-yl]undecan-1-ol (7a): $ZrCl_4$ (6.8 mg, 5 mol-%) and diol **6** (200 mg, 0.606 mmol) were dissolved in methanol (400 μL) and irradiated under MW (150 W) at 60 °C for 6 min. The title compound was purified by flash column chromatography using pentane/EtOAc (8.5:1.5) as eluent to afford it as a liquid (85%) with epimeric ratio (7:3). $[\alpha]_D^{20}$ = –52.5 (*c* = 1.0, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3465, 2925, 2854, 1440, 1355, 1121, 1020 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (br. s, 0.7 H), 4.34 (dd, *J* = 9.5, 2.1 Hz, 0.3 H), 3.69 (br. s, 0.3 H), 3.68–3.62 (m, 0.7 H), 3.60 (br. s, 0.7 H), 3.48 (s, 0.9 H), 3.38–3.36 (m, 0.3 H), 3.35 (s, 2.1 H), 2.04 (br. s, 0.3 H), 1.95 (br. s, 0.7 H), 1.86–1.39 (m, 8 H), 1.38–1.18 (m, 16 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 98.8, 73.6, 71.3, 54.5, 32.0, 31.9, 29.7 (2 C), 29.6 (3 C), 29.3, 26.0, 23.9, 22.7, 17.5, 14.1 ppm (major diastereomer) and 103.5, 78.8, 73.4, 55.9, 32.3, 31.9, 31.1, 29.7 (2 C), 29.6 (3 C), 25.9, 22.7, 21.7, 17.5, 14.1 ppm (minor diastereomer). HRMS (ESI): calcd. for $C_{17}H_{34}NaO_3$ $[M + Na]^+$ 309.2406, found 309.2402.

(*R*)-1-[(*S*)-6-Benzyloxy-tetrahydro-2*H*-pyran-2-yl]undecan-1-ol (7b): $ZrCl_4$ (44.6 mg, 10 mol-%) and diol **6** (662 mg, 2 mmol) were dissolved in benzyl alcohol (621 μL, 6 mmol) and irradiated under MW (150 W) at 80 °C for 6 min. The title compound **7b** was purified by flash column chromatography using pentane/EtOAc (8.5:1.5) as eluent to afford **7b** as a liquid (65%) with epimeric ratio (0.72:0.28). $[\alpha]_D^{20}$ = –42.9 (*c* = 1.0, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3465, 2925, 2854, 1455, 1351, 1121, 1020 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 5 H), 4.87 (d, *J* = 2.3 Hz, 0.72 H), 4.79 (d, *J* = 12.1 Hz, 0.28 H), 4.62 (d, *J* = 12.1 Hz, 0.72 H), 4.53 (d, *J* = 12.1 Hz, 0.28 H), 4.44 (d, *J* = 2.0 Hz, 0.28 H), 4.41 (d, *J* = 12.1 Hz, 0.72 H), 3.66–3.60 (m, 1 H), 3.53–3.47 (m, 0.72 H), 3.29–3.24 (m, 0.28 H), 1.90–1.30 (m, 10 H), 1.29–1.10 (m, 14 H), 0.80 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.3, 128.3 (2 C), 127.7 (2 C), 127.5, 96.9, 73.6, 71.6, 68.6, 32.0, 31.9, 29.8, 29.7, 29.6 (2 C), 29.3, 26.0, 23.9, 22.7, 17.6, 14.1 ppm (major diastereomer) and 138.0, 128.3 (2C), 127.9 (2C), 127.6, 101.4, 78.9, 73.4, 70.0, 32.3, 31.3, 29.7, 29.6 (3 C), 29.3, 25.9, 21.7, 17.6, 14.1 ppm (minor diastereomer). HRMS (ESI): calcd. for $C_{23}H_{38}NaO_3$ $[M + Na]^+$ 385.2719, found 385.2715.

(*S*)-1-[(*R*)-6-Benzyloxy-tetrahydro-2*H*-pyran-2-yl]undecan-1-ol (7b): $[\alpha]_D^{20}$ = +34.1 (*c* = 1.0, in $CHCl_3$)

General Procedure for Acetyl Protection of Alcohols: Alcohol **7a**–**b** (1 mmol) was dried under vacuum and dissolved in CH_2Cl_2 (3 mL) and triethylamine (1 mL), DMAP (24.4 mg, 0.2 mmol), and acetic anhydride (189 μL, 2 mmol) was added. The reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography using pentane/EtOAc (9:1) as eluent.

(*S*)-1-Acetoxy-[(*R*)-6-methoxy-tetrahydro-2*H*-pyran-2-yl]undecane (8a): Compound **8a** was isolated in 98% yield as a colourless liquid. $[\alpha]_D^{20}$ = –52.3 (*c* = 2.5, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2855, 1731, 1461, 1247, 1033 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91 (ddd, *J* = 9.7, 6.4, 3.6 Hz, 0.3 H), 4.87–4.81 (m, 0.7 H), 4.72 (br. s, 0.7 H), 4.28 (dd, *J* = 9.5, 2.0 Hz, 0.3 H), 3.74 (ddd, *J* = 11.6, 5.2, 2.0 Hz, 0.7 H), 3.47 (s, 0.9 H), 3.43–3.36 (m, 0.3 H), 3.34 (s, 2.1 H), 2.06 (s, 2.1 H), 2.04 (s, 0.9 H), 1.85–1.50 (m, 7 H), 1.49–1.20 (m, 17 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 98.5, 75.8, 69.5, 54.4, 31.9, 29.9, 29.6 (3 C), 29.5 (2 C), 29.3, 26.5, 25.5, 22.7, 21.1, 17.7, 14.1 ppm (major diastereomer) and 170.5, 103.5, 76.7, 75.6, 55.8, 30.9, 30.4, 29.9, 29.6 (3 C), 29.5 (2 C), 29.3, 26.6, 25.1, 21.7, 17.7, 14.1 ppm (minor diastereomer). HRMS (ESI): calcd. for $C_{19}H_{36}NaO_4$ $[M + Na]^+$ 351.2511, found 351.2527.

(*S*)-1-Acetoxy-[(*R*)-6-benzyloxy-tetrahydro-2*H*-pyran-2-yl]undecane (8b): Compound **8b** was isolated in 97% yield as a colourless liquid. $[\alpha]_D^{20}$ = –38.1 (*c* = 1.0, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2855, 1743, 1458, 1239, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.97–4.93 (m, 1 H), 4.90–4.84 (m, 1 H), 4.72 (d, *J* = 11.9 Hz, 0.75 H), 4.61 (d, *J* = 12.0 Hz, 0.25 H), 4.47 (d, *J* = 11.0 Hz, 0.75 H), 4.43 (dd, *J* = 11.0, 2.1 Hz, 0.25 H), 3.85 (ddd, *J* = 11.6, 5.2, 1.8 Hz, 0.75 H), 3.39 (ddd, *J* = 11.2, 6.2, 1.9 Hz, 0.25 H), 2.08 (s, 0.75 H), 2.06 (s, 2.25 H), 1.90–1.60 (m, 6 H), 1.50–1.20 (m, 18 H), 0.89 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 138.2, 128.3 (2 C), 127.7 (2 C), 127.5, 96.6, 75.8, 69.9, 68.4, 31.9, 30.0, 29.6 (3 C), 29.5 (2 C), 29.3, 26.5, 25.5, 22.7, 21.1, 17.8, 14.1 ppm (major diastereomer); 170.5, 137.9, 128.3 (2 C), 128.0 (2 C), 127.6, 101.1, 76.8, 75.6, 69.7, 31.0, 30.4, 29.6 (3 C), 29.5 (2 C), 29.3, 26.6, 25.2, 21.8, 21.1, 17.8, 14.1 ppm (minor

diastereomer). HRMS (ESI): calcd. for $C_{25}H_{40}NaO_4$ $[M + Na]^+$ 427.2824, found 427.2823.

(*R*)-1-Acetoxy-[(*S*)-6-benzyloxy-tetrahydro-2*H*-pyran-2-yl]undecane (8b): $[\alpha]_D^{20}$ = +44.2 (*c* = 1.0, in $CHCl_3$).

(*S*)-1-Acetoxy-[(*R*)-6-hydroxy-tetrahydro-2*H*-pyran-2-yl]undecane (9): Compound **8b** (202.1 mg, 0.5 mmol) was dissolved in THF/H_2O (4 mL, 3:1) and 10% Pd/C (20 mg) was added under a blanket of nitrogen. The reaction mixture was pressurized with 20 bar H_2 in an autoclave. The reaction was monitored by TLC using pentane/EtOAc (8:2) as eluent and after 24 h the reaction mixture was filtered through a pad of Celite and washed with EtOAc (100 mL). The solvent was removed under vacuum and the crude material was purified by flash column chromatography using pentane/EtOAc (8.5:1.5) as eluent to give compound **9** in 90% yield as a colourless liquid. $[\alpha]_D^{20}$ = –40.1 (*c* = 1.5, in $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2926, 2856, 1728, 1372, 1248, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.32 (br. s, 0.5 H), 4.95–4.84 (m, 1 H), 4.70 (ddd, *J* = 9.1, 6.1, 2.0 Hz, 0.5 H), 4.00 (ddd, *J* = 11.7, 4.4, 2.1 Hz, 0.5 H), 3.49 (ddd, *J* = 7.1, 5.0, 1.7 Hz, 0.5 H), 2.77 (d, *J* = 6.1 Hz, 0.5 H), 2.38–2.30 (m, 0.5 H), 2.07 (2s, 3 H), 1.91–1.83 (m, 1 H), 1.72–1.58 (m, 5 H), 1.41–1.25 (m, 18 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8, 170.7, 96.7, 92.0, 77.3, 75.7, 75.5, 69.9, 32.7, 31.9, 29.9, 29.6 (3 C), 29.5 (2 C), 29.3, 26.2, 26.0, 25.5 (2 C), 22.7, 21.7, 21.2, 17.1, 14.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{34}NaO_4$ $[M + Na]^+$ 337.2355, found 337.2351.

(*R*)-1-Acetoxy-[(*S*)-6-hydroxy-tetrahydro-2*H*-pyran-2-yl]undecane: $[\alpha]_D^{20}$ = +43.9 (*c* = 1.5, in $CHCl_3$).

(–)-(5*R*,6*S*)-6-Acetoxyhexadecanolide 1: Compound **9** (100 mg, 0.32 mmol) was oxidized using PCC (207 mg, 3 equiv.), Celite (30 mg) and sodium acetate (79 mg, 3 equiv.) in 5 mL of CH_2Cl_2 at 50 °C for 2 h. The reaction progress was monitored by TLC using pentane/EtOAc (7:3) as an eluent. The reaction mixture was passed through a pad of Celite and concentrated under reduced pressure. The reaction mixture was purified by flash column chromatography using pentane/EtOAc (8:2) as an eluent to afford compound **1** as an oil in 95% yield. The enantiomeric excess was determined using chiralpak OD column, flow rate 1 mL/min and 96:4 hexane/isopropyl alcohol as mobile phase at 220 nm λ_{max}. The retention time is 13.23 min (5*S*,6*R*) and 14.78 min (5*R*,6*S*). $[\alpha]_D^{20}$ = –35.4 (*c* = 0.85, in $CHCl_3$, *ee*, >99.9%). IR (neat): $\tilde{\nu}$ = 2925, 2854, 1744, 1371, 1230, 1052 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.98 (dt, *J* = 5.0, 7.8 Hz, 1 H), 4.35 (ddd, *J* = 3.3, 4.6, 11.0 Hz, 2 H), 2.66–2.55 (m, 1 H), 2.50–2.40 (m, 1 H), 2.08 (s, 3 H), 2.02–1.76 (m, 2 H), 1.74–1.52 (m, 4 H), 1.40–1.16 (m, 16 H), 0.88 (t, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8, 170.5, 80.5, 74.3, 31.9, 29.6 (2 C), 29.5 2 C, (), 29.4 (2 C), 29.3, 25.3, 23.5, 22.6, 21.0, 18.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{31}NaO_4$ $[M - H]^-$ 311.2222, found 311.2230.

Other Method: To a solution of acetal **8a** (35.1 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added *m*-chloroperbenzoic acid (25.8 mg, 0.15 mmol) and $BF_3{\cdot}OEt_2$ (16.5 μL, 0.13 mmol) sequentially. After stirred at room temperature for 30 min, the mixture was cooled to 0 °C and Et_3N (69.6 μL, 0.5 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min, then concentrated, and the resulting residue was purified by column chromatography using pentane/EtOAC (8:2) to give the (5*R*,6*S*)-6-acetoxyhexadecanolide **1** (27 mg, 76%) as a liquid.

(+)-(5*R*,6*S*)-6-Acetoxyhexadecanolide 1: $[\alpha]_D^{20}$ = +38.5 (*c* = 1.0, in $CHCl_3$, *ee*, 95.5%).

Supporting Information (see also the footnote on the first page of this article): Relevant ^1H, ^{13}C NMR spectra and HPLC traces are included.

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