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# Facile total synthesis of (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide from carbohydrate, a mosquito oviposition attractant pheromone

Saibal Das [a], Anand Kumar Mishra [a], Ashish Kumar [a], Ahamad Al Khazim Al Ghamdi [b], Jhillu Singh Yadav [a,*]

[a] *Division of Natural Product Chemistry, Indian Institute of Chemical Technology (CSIR), Hyderabad 500 607, AP, India*
[b] *Engineer Abdullah Baqshan for Bee Research, King Saudi University, Saudi Arabia*

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ABSTRACT

Total synthesis of (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide, a major component of mosquito oviposition attractant pheromones is reported. The key synthetic steps involve epoxide opening by lithiated salt of ethylpropionate and acid catalysed lactonization. The total synthesis was achieved in 11 linear steps staring from a readily available carbohydrate δ-gluconolactone in 18% overall yield making it simple, practical and elegant.



## 1. Introduction

In 1979, (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **1** was isolated by the group of Pickett and Laurence from apical droplets formed on the egg of the mosquito *Culex pipens fatigans*[1] and was established as a major component of mosquito oviposition attractant pheromones. The first synthesis of the two enantiomers of **1** was reported by Fuganti et al. in the year 1982.[2] Since then numerous synthesis of **1** have been reported[3–39] realizing its need and importance. In pursuit of our earlier efforts[40] and owing to the significance of **1** herein we disclosed a facile synthesis starting from an easily available carbohydrate δ-gluconolactone.

## 2. Results and discussion

The retrosynthetic plan for the target compound **1** is depicted in Scheme 1. The compound (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **1** was envisaged from the intramolecular cyclization of hydroxyl ester compound **2** wherein the terminal ester and secondary alcohol could lead to the preferred six member lactone. Compound **2** was planned to be obtained from an intermediate **3** by the epoxide opening with ethylpropiolate followed by saturation of the terminal alkyne chain. In continuation, epoxide **3** was visualized to be obtained from hydrazone compound **4** in simple steps including Grignard reaction and epoxide formation to incorporate the appropriate side chain followed by terminal epoxide respectively. Subsequently, compound **4** could be obtained from readily available δ-gluconolactone **6** as reported earlier by our group[41] via intermediate **5**.

We began our synthesis from a known diol **5** (Scheme 2) obtained in two steps from commercially available δ-gluconolactone as developed earlier in our group.[41] The oxidative cleavage of diol **5** with $NaIO_4$ provided the corresponding terminal aldehyde as expected, which upon treatment with tosylhydrazine in MeOH led to the formation of aldehyde hydrazone **4** in 78% yield (for two subsequent steps).

The conversion of hydrazone **4** to its allyl alcohol was accomplished by its treatment with 3 equiv of *n*-octylmagnesiumbromide and desired compound **7** was achieved in 76% yield.[42] Significantly, exclusive formation of *E*-olefin was observed and confirmed by its $^1$H NMR at $\delta = 5.35$ (dd, $J = 15.4$, 6.2 Hz) ppm. The secondary hydroxyl group of compound **7** was then protected as its benzyl ether **8** in 98% yield as planned followed by the deprotection of primary acetonide group by the treatment with catalytic *p*-TSA in MeOH to obtain the anticipated diol **9** in 80% yield. Then the conversion of diol **9** to its corresponding epoxide **3** was obtained in 75% yield (for two steps) via usual selective tosylation of primary alcohol, followed by its treatment with NaH in anhydrous THF.[43] Now the opening of the epoxide was executed using lithium salt of ethyl propiolate to provide the homopropargylic alcohol **10** in 80% yield (Scheme 3).[44]

Towards the construction of desired six-membered saturated lactone, a two step sequence was performed, which consisted in hydrogenation of intermediate **10** using Pd/C in presence of $H_2$ to

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
*E-mail address:* yadavpub@iict.res.in (J.S. Yadav).

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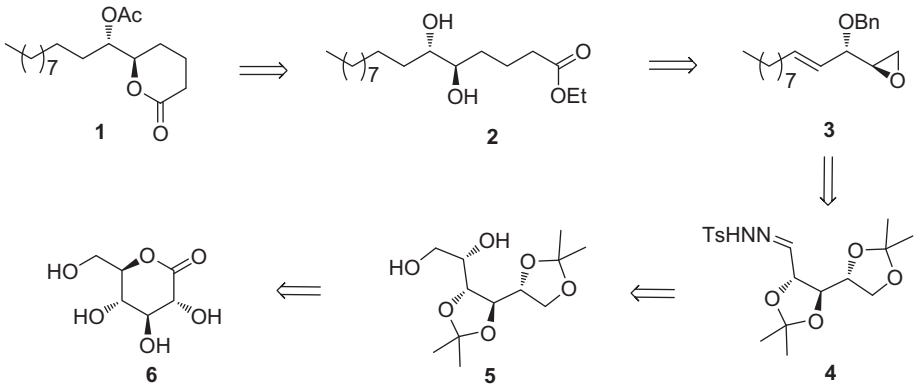
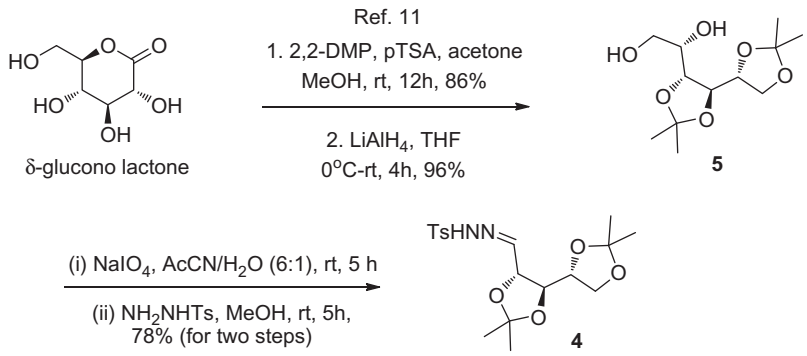
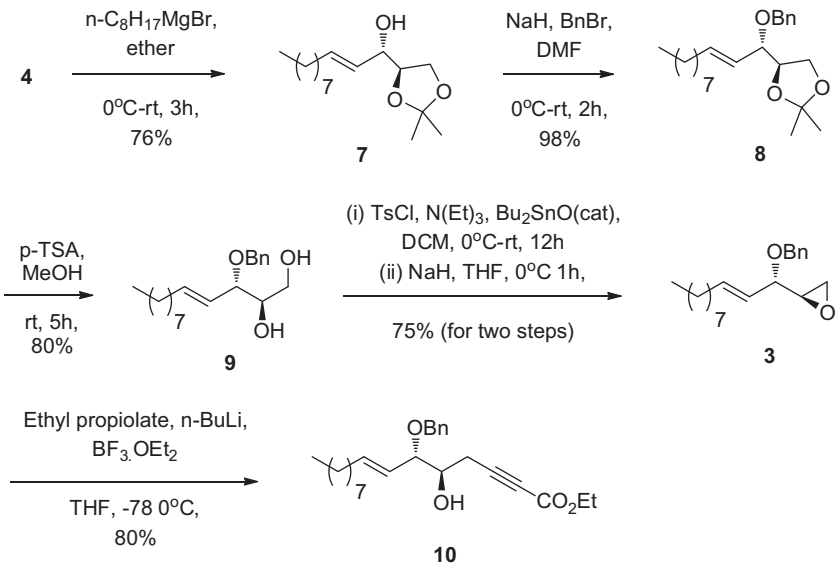


**Scheme 1.** Retrosynthetic strategy for **1**.



**Scheme 2.** Synthesis of hydrazone intermediate **4**.



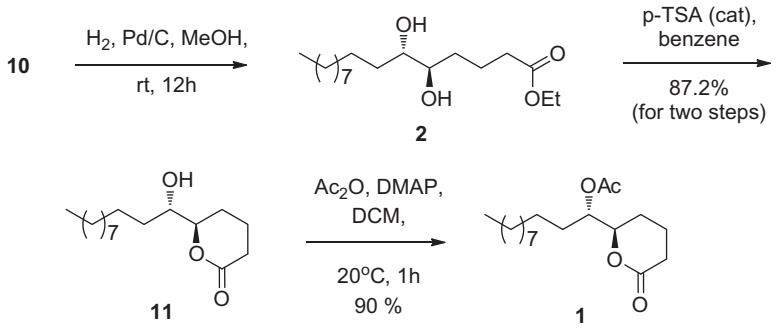
**Scheme 3.** Synthesis of homo propargylic alcohol intermediate **10**.

attain saturated compound **2** followed by lactonization via catalytic *p*-TSA to obtain the desired six-membered lactone **11** (Scheme 4) as a sole product in 87% yield (for two steps).[44,45]

Finally, the total synthesis of (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **1** was achieved by acetylation of the alcohol **12** using $Ac_2O$, DMAP, in 90% yield.[15] The synthetic material showed IR, $^1H$, $^{13}C$ NMR spectral data and optical rotation {$[\alpha]_D^{32}$ −33 (*c* 0.4, $CHCl_3$)} in good agreement with the literature reports.[2,4,15]

## 3. Conclusion

In conclusion we have accomplished a facile total synthesis of (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **1**, of mosquito oviposition attractant pheromones in 11 linear steps with 18% overall yield from δ-gluconolactone. The synthesis involves simple and convenient reactions like epoxide opening by lithiated salt of ethylpropiolate, acid catalysed lactonization to form six-mem-




**Scheme 4.** Synthesis of homo propargylic alcohol intermediate **10**.

bered lactone making it practical and elegant for further development.

## 4. Experimental section

### 4.1. General methods

Reactions were conducted under $N_2$ in anhydrous solvents such as $CH_2Cl_2$, THF, and AcOEt as mentioned. Yields refer to chromatographically and spectroscopically ($^1H$ and $^{13}C$ NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Column chromatography (CC): silica gel (60–120 mesh. Acme Chemical Co., India). TLC: Merck 60 F-254 silica gel plates and light petroleum ether (bp 60–808) for reaction monitoring; detection by UV light. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1H$ NMR and $^{13}C$ spectra were recorded on Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. HR-ESI-MS: QSTAR-XL hybrid ms/ms system (Applied Biosystems/MDS Sciex, Foster City, USA), equipped with an ESI source (IICT, Hyderabad); in *m*/*z*. The optical rotations were measured on a Jasco Dip 360 Digital polarimeter.

### 4.2. 4-Methyl-*N*′-[{(4*S*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl}methylene] benzenesulfono hydrazide (4)

A solution of diol **5** (12 g, 45.7 mmol) in AcCN and water (6:4, 200 mL) was treated with $NaIO_4$ (14.7 g, 68.6 mmol) portion wise at 0 °C and stirred at room temperature for 5 h, then filtered and acetonitrile was evaporated under reduced pressure, washed with DCM (250 mL) and the solvent was evaporated to afford the desired aldehyde (10 g, 95%) as a yellowish oil, which was immediately used for the next reaction without additional purification. A mixture of aldehyde (10 g, 43.42 mmol) and *p*-toluene sulfonyl hydrazine (8.08 g, 43.42 mmol) in 100 ml of methanol was stirred for 5 h at room temperature under $N_2$. Methanol was evaporated under reduced pressure, petroleum ether (75 mL) was added and the precipitated white solid was filtered and dried under vacuum to yield tosylhydrazone **4** (14.188 g, 82%). Mp 153–155 °C. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta_H$ (ppm) 7.10–7.80 (m, 5H), 6.52 (br s, 1H), 3.50–4.25 (m, 5H), 2.41 (s, 3H), 1.42 (s, 6H), 1.38 (s, 6H). (ESI): *m*/*z* = 399 $[M+H]^+$. HRMS: calcd for $C_{18}H_{27}N_2O_6S$ $[M+H]^+$ 399.1589; found: 399.1600.

### 4.3. (*S*,*E*)-1-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]undec-2-en-1-ol (7)

To a solution of Grignard reagent [prepared in situ from Mg (1.86 g, 75.2 mmol) and *n*-octylbromide (14.5 g, 75.2 mmol) in ether (300 mL)] at 0 °C was added a solution of the aldehyde hydrazone **4** (10 g, 25 mmol) in ether (100 mL). The mixture was allowed to reach room temperature slowly and was stirred for 3 h, quenched with aqueous saturated $NH_4Cl$, extracted with $Et_2O$ (3 × 200 mL), brine wash, dried over anhydrous $Na_2SO_4$ and removal of the solvent followed by purification gave product **7** (5.15 g, 76%) as a viscous liquid. $[\alpha]_D^{30}$ +15.4 (*c* 2.37, $CHCl_3$); IR (KBr): *ν* ($cm^{-1}$) 3454, 2925, 2855, 1460, 1067, 917. $^1H$ NMR (300 MHz, $CDCl_3$): *δ* (ppm) 5.68–5.81 (m, 1H), 5.35 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.15–4.23 (m, 1H), 3.98–4.06 (m, 1H), 3.81–3.93 (m, 2H), 1.97–2.09 (m, 2H), 1.41 (s, 3H), 1.18–1.38 (m, 15H), 0.89 (t, 3H, *J* = 6.7 Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): *δ* (ppm) 134.3, 127.1, 109.1, 78.4, 71.5, 64.6, 32.2, 31.7, 29.3, 29.1, 29.0, 28.9, 26.3, 25.0, 22.5, 13.9. (LC–MS): *m*/*z* = 293 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 293.2087; found: 293.2101.

### 4.4. (*R*)-4-[(*S*,*E*)-1-(Benzyloxy)undec-2-enyl]-2,2-dimethyl-1,3-dioxolane (8)

To a stirred solution of **7** (1 g, 3.69 mmol) in dry DMF (12 mL), NaH (142 mg, 5.91 mmol) and benzyl bromide (759 mg, 4.4 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Excess NaH and benzyl bromide were removed by addition of methanol and $Et_3N$. The reaction mixture was evaporated, diluted with dichloromethane, washed with water (3 × 100 mL), dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography gave product **8** (1.306 g, 98%) as a colorless oil. $[\alpha]_D^{30}$ +42.9 (*c* 1, $CHCl_3$); IR (KBr): *ν* ($cm^{-1}$) 2926, 2855, 1457, 1374, 1073, 737, 698. $^1H$ NMR ($CDCl_3$, 300 MHz): *δ* (ppm) 7.20–7.37 (m, 5H), 5.64–5.76 (m, 1H), 5.33–5.45 (m, 1H), 4.64 (d, 1H, *J* = 12 Hz), 4.36 (d, 1H, *J* = 11.3 Hz), 3.99–4.13 (m, 2H), 3.80–3.86 (m, 1H), 3.65–3.72 (m, 1H), 2.11 (q, 2H, *J* = 6.79 Hz), 1.19–1.46 (m, 18H), 0.88 (t, 3H, *J* = 6.79 Hz), $^{13}C$ NMR ($CDCl_3$, 75 MHz): *δ* (ppm) 138.3, 137.2, 128.9, 127.8, 127.4, 126.3, 109.3, 80.4, 77.8, 69.9, 66.7, 32.4, 31.8, 29.4, 29.2, 29.1, 26.5, 25.4, 22.6, 14.0. (LC–MS): *m*/*z* = 383$[M+Na]^+$. HRMS: calcd For $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 383.2562; found: 383.2567.

### 4.5. (2*R*,3*S*,*E*)-3-(Benzyloxy)tridec-4-ene-1,2-diol (9)

To a stirred solution of **8** (1 g, 2.77 mmol) in MeOH (12 mL) at 0 °C was added PTSA (cat.) and stirred for 8 h at room temperature. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ and evaporated under reduced pressure, then extracted with ethyl acetate (3 × 30 ml), washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. The crude residue was chromatographed to give diol **9** (711 mg, 80%) as a viscous liquid. $[\alpha]_D^{30}$ +27.7 (*c* 1, $CHCl_3$); IR (KBr): *ν* ($cm^{-1}$) 3408, 2924, 2854, 1458, 1092, 1061, 753, 697. $^1H$ NMR ($CDCl_3$, 300 MHz): *δ* (ppm) 7.26–7.38 (m, 5H), 5.70–5.82 (m, 1H), 5.41 (dd, 1H, *J* = 15.1, 8.3 Hz), 4.61 (d, 1H, *J* = 11.3 Hz), 4.34 (d, 1H, *J* = 11.3 Hz), 3.86 (dd, 1H, *J* = 8.3, 4.5 Hz), 3.63–3.76 (m, 3H), 2.64 (br s, 1H), 2.47

(br s, 1H), 2.11 (q, 2H, $J$ = 6.7 Hz), 1.19–1.47 (m, 12H), 0.88 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 137.9, 128.3, 127.7, 126.1, 81.1, 73.3, 70.1, 63.2, 32.3, 31.7, 29.3, 29.2, 29.1, 29.0, 22.6, 14.2. (LC–MS): $m/z$ = 343 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 343.2249; found: 343.2261.

### 4.6. (*R*)-2-[(*S*,*E*)-1-(Benzyloxy)undec-2-enyl]oxirane (3)

To diol **9** (500 mg, 1.56 mmol) in dry $CH_2Cl_2$ were added triethylamine (173 mg, 1.72 mmol), *p*-toluenesulfonyl chloride (327 mg, 1.72 mmol) and dibutyltin oxide (cat.). The resulting solution was stirred for 12 h at room temperature. After complete conversion as confirmed by TLC, the mixture was quenched with satd $NH_4Cl$ solution and extracted with $CH_2Cl_2$ (3 × 20 mL). Removal of solvent followed by purification on silica gel column chromatography gave the pure tosyl derivative. To a stirred suspension of freshly activated sodium hydride (67 mg, 2.79 mmol) in dry THF (10 mL) at 0 °C, tosyl derivative in dry THF (8 mL) was added dropwise. After completion of the reaction (2 h), the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure, purification by silica-gel column chromatography afforded **3** (350 mg, 75% for two steps) as a viscous liquid. $[\alpha]_D^{30}$ +19.5 (*c* 1, $CHCl_3$); IR (KBr): $\nu$ ($cm^{-1}$) 2925, 2854, 14.59, 1067, 973. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ (ppm) 7.18–7.34 (m, 5H), 5.61–5.76 (m, 1H), 5.39 (dd, 1H, $J$ = 15.8, 7.5 Hz), 4.58 (d, 1H, $J$ = 12.0 Hz), 4.4 (d, 1H, $J$ = 12.0 Hz), 3.70 (dd, 1H, $J$ = 7.5, 3.7 Hz), 2.94–3.01 (m, 1 H), 2.70 (t, $J$ = 4.5 Hz, 1 H), 2.58–2.68 (m, 1 H), 2.09 (q, $J$ = 6.7 Hz, 2 H), 1.19–1.46 (m, 12 H), 0.89 (t, 3H, $J$ = 6.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 137.2, 128.2, 127.6, 127.5, 125.7, 79.0, 70.4, 53.5, 44.8, 32.3, 31.8, 29.6, 29.3, 29.3, 29.1, 28.9, 22.6, 14.0. (LC–MS): $m/z$ = 325 $[M+Na]^+$. HRMS: calcd for $C_{20}H_{30}NaO_2$ $[M+Na]^+$ 325.2138; found: 325.2153.

### 4.7. (5*R*,6*S*,*E*)-Ethyl-6-(benzyloxy)-5-hydroxyhexadec-7-en-2-ynoate (10)

To a solution of lithium salt of ethyl propiolate [prepared in situ from ethyl propiolate (130 m g, 1.32 mmol) and *n*-butyl lithium (85 mg, 1.32 mmol) in THF (5 mL) at −78 °C, 0.5 h] at −78 °C was added $BF_3{\cdot}OEt_2$ (85 mg, 1.32 mmol). The resulting mixture was stirred for 5 minutes. Then the solution of epoxide **3** (200 mg, 0.66 mmol), in dry THF was added to reaction mixture and the mixture was stirred for 3 h at same temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure, purification by silica-gel column chromatography afforded **10** (212 mg, 80%) as a viscous liquid. $[\alpha]_D^{30}$ +14.3 (*c* 0.75, $CHCl_3$); IR (KBr): $\nu$ ($cm^{-1}$) 3453, 2924, 2853, 2237, 1711, 1460, 1368, 1251, 1072. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ (ppm) 7.21–7.35 (m, 5H), 5.73–5.84 (m, 1H), 5.40 (dd, 1H, $J$ = 15.8, 8.3 Hz), 4.59 (d, 1H, $J$ = 12.0 Hz), 4.34 (d, 1H, $J$ = 11.3 Hz), 4.18 (q, 2H, $J$ = 6.7 Hz), 3.75–3.91 (m, 2H), 2.54 (dd, 2H, $J$ = 6.0, 2.2 Hz), 2.22 (br d, 1H, $J$ = 3.7 Hz), 2.07–2.17 (m, 2H), 1.18–1.47 (m, 15H), 0.88 (t, 3H, $J$ = 6.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 153.5, 138.9, 138.0, 128.3, 127.7, 127.6, 125.2, 85.7, 81.8, 74.5, 71.2, 70.1, 61.8, 32.4, 31.8, 29.3, 29.2, 29.1, 29.0, 22.8, 22.6, 14.1, 14.0. (LC–MS): $m/z$ = 423 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 423.2511; found: 423.2521.

### 4.8. (5*R*,6*S*)-Ethyl-5,6-dihydroxyhexadecanoate (2)

Mixture of **10** (100 mg, 0.249 mmol) and Pd/C (10% Pd, 18 mg, 0.169 mmol) in MeOH was stirred for 12 h at rt under hydrogen atmosphere. Reaction mixture was filtered over celite, the filtrate was concentrated under reduced pressure, purification by silica-gel column chromatography afforded **2** (71 mg, 90%) as a white solid. Mp 90–92 °C, (lit.[15] 91–93 °C); $[\alpha]_D^{30}$ +1.0 (*c* 0.8, $CH_2Cl_2$); [lit.[15] $[\alpha]_D^{32}$ +0.9 (*c* 0.7, $CH_2Cl_2$)]; IR (KBr): $\nu$ ($cm^{-1}$) 3283, 2922, 2854, 1730, 1466, 1381, 1071. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.12 (q, $J$ = 7.1 Hz, 2H), 3.49–3.58 (m, 2H), 2.30–2.37 (m, 2H), 1.61–1.90 (m, 4H), 1.21–1.53 (m, 21H), 0.88 (t, 3H, $J$ = 6.7 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 173.8, 74.6, 74.0, 60.3, 34.0, 31.9, 31.4, 30.4, 29.6, 29.5, 29.3, 25.9, 22.6, 21.1, 14.2, 14.0. (LC–MS): $m/z$ = 339 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 339.2511; found: 339.2523.

### 4.9. (*R*)-6-[(*S*)-1-Hydroxyundecyl]tetrahydro-2*H*-pyran-2-one (11)

To a stirred solution of **2** (50 mg) in benzene PTSA (cat.) was added. Reaction mixture was allowed to be stirred for 12 h at rt, was quenched by saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure, purification by silica-gel column chromatography afforded **11** (41 mg, 96.7%) as a white solid. Mp 67–68 °C, (lit.[15] 67–68 °C); $[\alpha]_D^{30}$ −11.0 (*c* 0.8, $CH_2Cl_2$); [lit.[15] $[\alpha]_D^{32}$ −12.6 (*c* 1.05, $CH_2Cl_2$)]; IR (KBr): $\nu$ ($cm^{-1}$) 3279, 2921, 2853, 1715, 1458, 1283, 1071. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ (ppm) 4.15–4.25 (m, 2H), 3.74–3.81 (m, 1H), 2.41–2.61 (m, 2H), 1.74–2.03 (m, 4H), 1.18–1.57 (m, 18H), 0.88 (t, 3H, $J$ = 6.98 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 171.7, 83.4, 72.3, 31.8, 31.6, 29.7, 29.5, 29.2, 25.8, 22.6, 21.0, 18.2, 14.0 ppm. (LC–MS): $m/z$ = 293 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{30}NaO_3$ $[M+Na]^+$ 293.2087; found: 293.2102.

### 4.10. (5*R*,6*S*)-6-Acetoxy-5-hexadecanolide (1)

To **11** (20 mg, 0.073 mmol) in $CH_2C1_2$ (5 mL), at 25 °C, was added 4,4-dimethylamino pyridine (54 mg, 0.44 mmol) and acetic anhydride (45 mg, 0.44 mmol). After 1 h at 20 °C, the reaction was quenched with brine. Extraction with $CH_2C1_2$ (3 × 10 mL), drying with $Na_2SO_4$, filtration, concentration under reduced pressure and flash chromatography afforded **1** (21 mg, 90%) as a colorless oil. $[\alpha]_D^{32}$ −33 (*c* 0.4, $CHCl_3$); [lit.[4] $[\alpha]_D^{20}$ −35.4 (*c* 0.85, $CHCl_3$)]; IR (KBr): $\nu$ ($cm^{-1}$) 2924, 2853, 1737, 1373, 1240, 1073. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ (ppm) 4.93–5.03 (m, 1H), 4.35 (ddd, $J$ = 3.0, 7.5, 10.5 Hz, 1H), 2.55–2.66 (m, 1H), 2.40–2.51 (m, 1H), 2.08 (s, 3H), 1.75–2.06 (m, 2H), 1.52–1.74 (m, 4H), 1.13–1.40 (m, 16H), 0.88 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ (ppm) 170.8, 170.4, 80.5, 74.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.2, 23.5, 22.7, 21.0, 18.2, 14.1. (LC–MS): $m/z$ = 335 $[M+Na]^+$. HRMS: calcd for $C_{18}H_{32}NaO_4$ [M+Na] 335.2198; found: 335.2195.

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