# Total Synthesis of Insect Pheromones (*R*)-4-Dodecanolide and (*S*)-5-Hexadecanolide[1]

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**Abstract:** The asymmetric total synthesis of naturally occurring insect pheromones, (*R*)-4-dodecanolide and (*S*)-5-hexadecanolide has been achieved in a simple and efficient way with high yields.

**Keywords:** pheromone, natural product, dodecanolide, hexadecanolide, chiral lactones

Optically active 5- and 6-alkyl-substituted γ- and δ-lactones are attractive building blocks in the synthesis of natural products[2] and comprise of structural moieties that are frequently present in, for example, insect pheromones,[3] cardenolides,[4] lignans, and flavor components.[5] In addition to these important properties, they are key synthons for several biologically important molecules. The γ-lactone (*R*)-4-dodecanolide (**1**) (Figure 1) is a defensive secretion isolated from the pygidial glands of rove beetles, *Bledius mandibularis* and *Bledius spectabilis*.[6] It was also produced during the bioconversion[7] of soy bean fatty acids by *Pencillium Roqueforti* spores in the presence of an exogenous lipase and has been used as a flavoring agent;[8] it has been isolated from various fruits[9] and butterfat.[10] The δ-lactone (*S*)-5-hexadecanolide (**2**) (Figure 1) was isolated from the mandibular glands of the oriental hornet *Vespa orientalis*;[11] it is a pheromone that stimulates the workers to construct queen cells. This lactone is also found in some fruits, such as apricots and peaches. Both **1** and **2** have a chiral lactone unit in their structure. Owing to their remarkable physiological activities, several approaches leading to (*R*)-4-dodecanolide[12] and (*S*)-5-hexadecanolide[12e,13] have been reported. Although a great number of synthetic routes to the title compounds have been published, there is still a need to explore short and efficient routes to these compounds. A continuation of our interest in the synthesis of lactones[14] prompted us to take up the total synthesis of (*R*)-4-dodecanolide and (*S*)-5-hexadecanolide due to their simple structure coupled with biological activities; the results are presented herein.

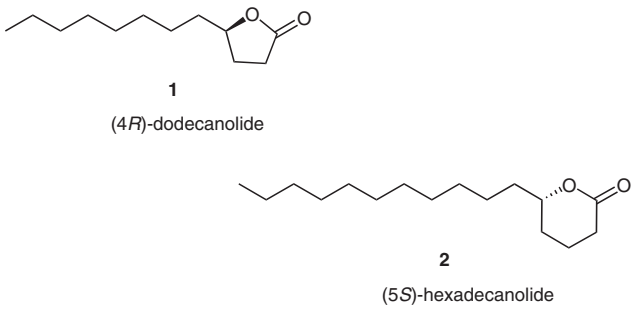
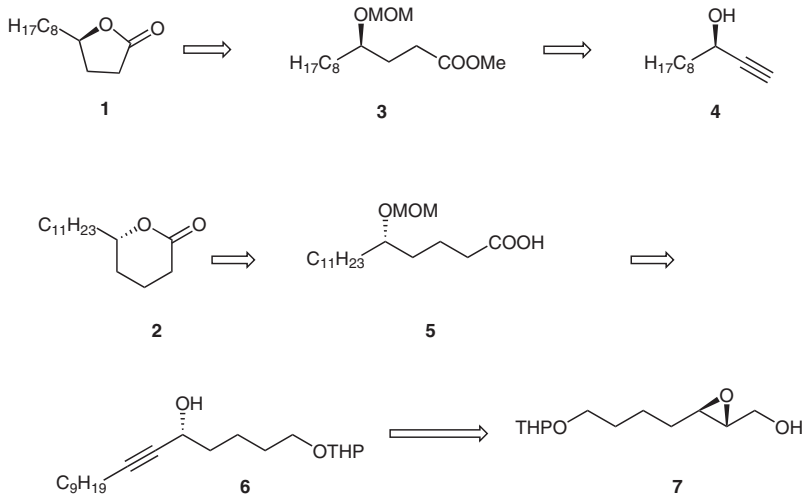



**Figure 1**

The retrosynthetic analysis for the two lactones **1** and **2** is outlined in Scheme 1.




**Scheme 1**

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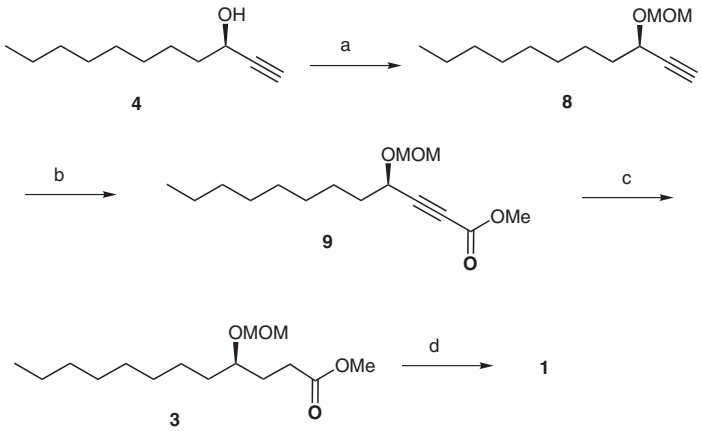


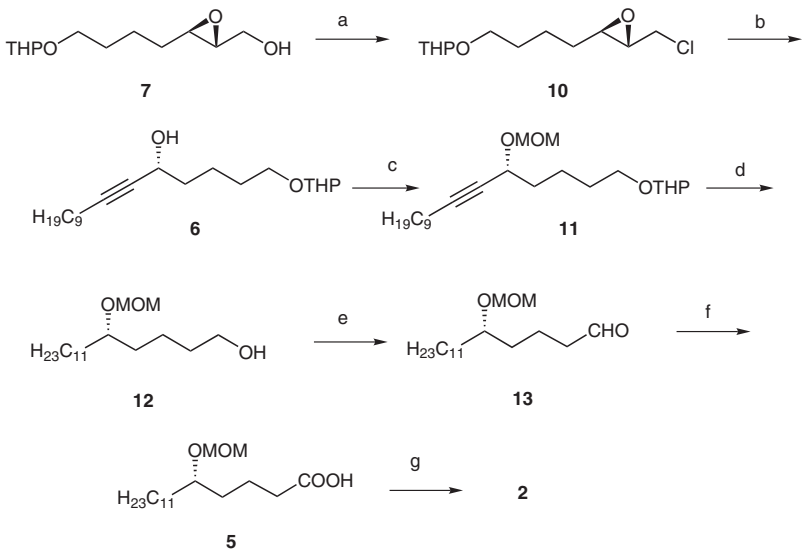

**Scheme 2** Reagents and conditions: (a) MOMCl, *i*-$Pr_2NEt$, anhyd $CH_2Cl_2$, 0 °C to r.t., 2 h, 90%; (b) 1.6 M BuLi in hexane, $ClCO_2Me$, anhyd THF, –78 °C, 30 min, 90%; (c) Pd/C, $H_2$, EtOAc, 4 h, 90%; (d) PTSA, MeOH, r.t, 12 h, 80%.

The synthesis of (*R*)-4-dodecanolide (**1**) began with the key precursor, chiral propargyl alcohol **4**,[15] which was prepared by a known procedure.[16] The free hydroxy of the chiral alcohol, (3*R*)-undec-1-yn-3-ol (**4**) was first protected as its methoxymethyl ether using Hünig's base (*i*-$Pr_2EtN$, 2 equiv) and methoxymethyl chloride (3 equiv) in dry dichloromethane at room temperature to afford **8**[17] in 90% yield (Scheme 2). The acetylenic compound **8** was then subjected to methoxycarbonylation[18] with methyl chloroformate (1 equiv) in the presence of 1.6 M butyllithium in hexane (1 equiv) at –78 °C to give the acetylenic ester **9** in 90% yield.

Catalytic hydrogenation of the ester **9** using palladium on carbon and hydrogen in ethyl acetate afforded the saturated ester **3** in 90% yield. Finally, the cyclization of compound **3** with 4-toluenesulfonic acid in methanol afforded the target lactone (*R*)-4-dodecanolide (**1**) by in situ deprotection of the methoxymethyl group followed by cyclization (Scheme 2). The synthetic material showed IR and $^1H$ and $^{13}C$ NMR spectral data in good agreement with the natural lactone {$[\alpha]_D^{25}$ +36.4 (*c* 1, MeOH), [Lit.[12d] $[\alpha]_D^{25}$ +37.5 (*c* 1, MeOH)]}.

The synthesis of (*S*)-5-hexadecanolide (**2**) began with the 2,3-epoxy alcohol **7** (Scheme 3). The alcohol was converted into the corresponding epoxy chloride **10** on reaction with triphenylphosphine in refluxing carbon tetrachloride in the presence of sodium hydrogen carbonate. The epoxy chloride **10** was subjected to base-induced opening with lithium amide in liquid ammonia at –33 °C and further treated with nonyl bromide leading to the chiral acetylenic alcohol **6** directly in a one-pot procedure (Scheme 3).

The secondary hydroxy group of compound **6** was protected as its methoxymethyl ether by treatment with Hünig's base and methoxymethyl chloride in anhydrous dichloromethane at room temperature to afford compound **11** in 98% yield. In the next step, the reduction of the triple bond and subsequent deprotection of the tetrahydropyranyl group of compound **11** over 10% palladium on carbon gave **12** in 80% yield. The alcohol **12** was oxidized to the




**Scheme 3** *Reagents and conditions:* (a) $Ph_3P$, $NaHCO_3$, $CCl_4$, reflux, 4 h, 80%; (b) Li/liq $NH_3$, $Fe(NO_3)_3$ (cat.), anhyd THF, $C_9H_{19}Br$, 8 h, 60%; (c) MOMCl, *i*-$Pr_2NEt$, 0 °C to r.t., 2 h, 98%; (d) 10% Pd/C, $H_2$, EtOH, r.t., 6 h, 80%; (e) IBX, anhyd DMSO, anhyd $CH_2Cl_2$, r.t., 2 h, 77%; (f) $NaClO_2$, $NaH_2PO_4$, aq DMSO, r.t., 1 h, 71%; (g) PTSA, MeOH, r.t., 12 h, 80%.

aldehyde **13** in 77% yield with 2-iodoxybenzoic acid (IBX) in anhydrous dimethyl sulfoxide and anhydrous dichloromethane and then **13** was further oxidized with sodium chlorite and sodium dihydrogen phosphate in aqueous dimethyl sulfoxide to afford the corresponding acid **5** in 71% yield.[19] Finally the synthesis of target molecule **2** was achieved in 80% yield by in situ deprotection of the methoxymethyl group and subsequent cyclization (Scheme 3).

In conclusion, we have achieved simple, short and efficient total syntheses of (*R*)-4-dodecanolide and (*S*)-5-hexadecanolide in good yields by utilizing chiral acetylenic alcohols as key intermediates.

All solvents were distilled before use. Dry solvents were prepared according to standard procedures. All reactions were carried out under a $N_2$ atmosphere and monitored by TLC on silica gel (60–120 mesh, Merck). NMR spectra were recorded on Bruker (300 MHz $^1$H, 75 MHz $^{13}$C) and Varian (200 MHz $^1$H, 50 MHz $^{13}$C) NMR spectrometers using $CDCl_3$ as solvent. ESI-MS were recorded with LC-MSD-Trap-SL (Agilent technologies). IR spectra were recorded with FTIR (Thermo Nicolet Nexus 670 spectrophotometer).

**(3*R*)-3-(Methoxymethoxy)undec-1-yne (8)**

To a soln of **4** (1.5 g, 8.9 mmol) in anhyd $CH_2Cl_2$ (10 mL) at 0 °C under $N_2$ atmosphere, was added *i*-$Pr_2NEt$ (3.10 mL, 17.8 mmol) dropwise and, after 5 min, MOMCl (2.71 mL, 33.8 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h and then diluted with $H_2O$ and washed with sat. aq $NH_4Cl$ and brine. The organic phase was dried (anhyd $Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 9:1) to afford pure **8** as a clear colorless liquid; yield: 1.7 g (90%).

$[\alpha]_D^{25}$ –13.5 (*c* 1, $CHCl_3$).

IR (neat): 2929, 2858, 2235, 1252, 1031 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.90 (d, *J* = 6.6 Hz, 1 H), 4.53 (d, *J* = 6.6 Hz, 1 H), 4.27 (td, *J* = 2.2, 6.6 Hz, 1 H), 3.35 (s, 3 H), 2.32 (d, *J* = 2.2 Hz, 1 H), 1.78–1.61 (m, 2 H), 1.50–1.23 (m, 12 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 94.0, 82.6, 73.3, 65.4, 55.6, 53.6, 31.8, 29.4, 29.2, 29.1, 25.2, 22.6, 14.1.

MS (ESI): *m*/*z* = 213 ($M^+$ + 1).

**Methyl (4*R*)-4-(Methoxymethoxy)dodec-2-ynoate (9)**

Acetylenic compound **8** (1.0 g, 4.71 mmol) was dissolved in freshly distilled anhyd THF (5 mL) in an oven-dried round-bottomed flask under $N_2$ atmosphere. The soln was then cooled to –78 °C and 1.6 M BuLi in hexane (5.89 mL, 9.43 mmol) was added. The mixture was stirred at –78 °C for 2 h and then methyl chloroformate (0.54 mL, 7.07 mmol) in anhyd THF (5 mL) was added slowly and the mixture was stirred at –78 °C for 2 h. The mixture was diluted with EtOAc and washed with sat. aq $NH_4Cl$, and brine. The organic phase was dried (anhyd $Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (PE–EtOAc, 8:2) to afford **9** as a viscous liquid; yield: 1.14 g (90%).

$[\alpha]_D^{25}$ +5.6 (*c* 1, $CHCl_3$).

IR (neat): 2929, 2858, 2235, 1722, 1252, 1032 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.88 (d, *J* = 6.7 Hz, 1 H), 4.56 (d, *J* = 6.7 Hz, 1 H), 4.41 (t, *J* = 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.38 (s, 3 H), 1.82–1.74 (m, 2 H), 1.51–1.30 (m, 12 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 153.52, 94.48, 86.4, 76.62, 65.17, 55.59, 52.51, 38.85, 34.83, 31.71, 29.27, 29.06, 25.57, 22.62, 14.05.

MS (ESI): *m*/*z* = 270 ($M^+$).

**Methyl (4*R*)-4-(Methoxymethoxy)dodecanoate (3)**

To a soln of **9** (1.0 g, 3.7 mmol) in anhyd EtOAc (5 mL) was added a catalytic amount of 10% Pd/C and the mixture was stirred at r.t. under a $H_2$ atmosphere for 4 h. Then the catalyst was filtered off, washed with EtOAc, and the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, PE–EtOAc, 9:1) to afford **3** as a colorless liquid; yield: 0.91 g (90%).

$[\alpha]_D^{25}$ +1.5 (*c* 1, $CHCl_3$).

IR (neat): 2928, 2856, 1742, 1216, 1038 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.57 (s, 2 H), 3.65 (s, 3 H), 3.56–3.48 (m, 1 H), 3.34 (s, 3 H), 2.36 (t, *J* = 7.5 Hz, 2 H), 1.92–1.66 (m, 2 H), 1.47–1.27 (m, 14 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 174.1, 95.4, 76.6, 55.5, 51.4, 34.1, 31.8, 29.8, 29.72, 29.5, 29.2, 25.2, 22.6, 14.1.

MS (ESI): *m*/*z* = 297 ($M^+$ + Na).

**(*R*)-4-Dodecanolide (1)**

To a stirred soln of **3** (0.5 g, 1.8 mmol) in MeOH was added a catalytic amount of PTSA under a $N_2$ atmosphere. The mixture was stirred at r.t. for 12 h and then quenched by addition of solid $NaHCO_3$, which was then filtered off and the solvent was removed from the filtrate under reduced pressure to give a residue that was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to afford **1** as yellow liquid; yield: 0.285 g (80%).

$[\alpha]_D^{25}$ +36.4 (*c* 1, MeOH).

IR (neat): 2928, 2856, 1777, 1216, 1038 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.47–4.34 (m, 1 H), 2.51–2.20 (m, 4 H), 1.91–1.26 (m, 14 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 177.3, 81.0, 35.6, 31.8, 29.4, 29.3, 29.1, 28.8, 27.9, 25.2, 22.6, 14.1.

MS (ESI): *m*/*z* = 199 ($M^+$ + 1).

**(2*S*,3*S*)-2,3-Epoxy-7-(tetrahydro-2*H*-pyran-2-yloxy)heptan-1-ol (7)**

Anhyd $CH_2Cl_2$ (20 mL) was added to powdered activated 4Å molecular sieves and the suspension was cooled to –24 °C. Ti(O*i*-Pr)$_4$ (1.061 g, 3.73 mmol) and D-(–)-DET (0.770 g, 3.73 mmol) were subsequently added with stirring and the resulting mixture was stirred at –24 °C for 30 min, (*E*)-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-en-1-ol (4 g, 18.69 mmol) in anhyd $CH_2Cl_2$ (20 mL) was added and the resulting mixture was stirred at –24 °C for a further 30 min. 3.3 M *tert*-Butyl hydroperoxide in toluene (8.49 mL, 28 mmol) was then added and the resulting mixture was stirred at –24 °C for 3 h. It was then warmed to 0 °C, quenched by addition of $H_2O$ (6 mL) and stirred at r.t. for 1 h. 30% aq NaOH soln saturated with NaCl (6 mL) was then added and the mixture stirred vigorously at r.t. for a further 30 min. The resulting mixture was washed well with $CH_2Cl_2$. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine and dried (anhyd $Na_2SO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, PE–EtOAc, 5:5) to afford **7** as a viscous liquid; yield: 3.4 g (80%).

$[\alpha]_D^{25}$ +13.3 (*c* 1, $CHCl_3$).

IR (neat): 3438, 2960, 2856, 1049 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.55 (t, *J* = 3.02 Hz, 1 H), 3.87–3.56 (m, 4 H), 3.51–3.33 (m, 2 H), 2.92 (m, 1 H), 2.87 (m, 1 H), 1.91–1.44 (m, 12 H), 2.22 (br s, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 98.7, 67.5, 62.5, 61.9, 58.6, 55.8, 31.3, 30.6, 29.3, 25.3, 22.7, 19.5.

MS (ESI): *m*/*z* = 303 ($M^+$ + 1).

**(2*R*,3*S*)-1-Chloro-2,3-epoxy-7-(tetrahydro-2*H*-pyran-2-yloxy)heptane (10)**

To a stirred soln of **7** (3.0 g, 13.04 mmol) in anhyd $CCl_4$ (20 mL) was added $Ph_3P$ (5.22 g, 19.56 mmol) and $NaHCO_3$ (1.095 g, 13.04 mmol). The resulting mixture was vigorously refluxed for 4 h. The solids were removed by filtered and washed with $Et_2O$. The solvent was removed from the filtrate under reduced pressure and the residue was purified by column chromatography (silica gel, PE–EtOAc, 9:1) to afford **10** as a viscous liquid; yield: 2.5 g (80%).

$[\alpha]_D^{25}$ +8.02 (*c* 1, $CHCl_3$).

IR (neat): 2940, 2866, 1029 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.54 (t, *J* = 3.2 Hz, 1 H), 3.84–3.67 (m, 2 H), 3.61 (m, 2 H), 3.33 (m, 2 H), 2.29 (m, 1 H), 2.82 (m, 1 H), 1.92 –1.42 (m, 12 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 98.7, 67.2, 61.8, 59.3, 56.8, 48.2, 31.7, 30.6, 29.3, 25.4, 22.7, 19.5.

MS (ESI): *m*/*z* = 249 ($M^+$ + 1).

**(5*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)hexadec-6-yn-5-ol (6)**

To freshly distilled $NH_3$ (50 mL) in a 100-mL two-necked, round-bottomed flask fitted with a cold finger condenser was added a catalytic amount of $Fe(NO_3)_3$, followed by the addition of Li metal pieces (0.508 g, 72.5 mmol) at –33 °C and the resulting grey-colored suspension was stirred for 30 min. To this soln was added **10** (2.4 g, 9.6 mmol) in anhyd THF (10 mL) over a period of 15 min. The mixture was then stirred at this temperature for 2 h. Then, nonyl bromide (5.8 mL, 30.2 mmol) was added dropwise to the mixture and it was stirred at this temperature for 6 h. The reaction was quenched by the addition of solid $NH_4Cl$ and then $NH_3$ was allowed to evaporate. The mixture was extracted with $H_2O$ and EtOAc. The combined organic layers were washed with $H_2O$ (1 ×), and brine, and dried (anhyd $Na_2SO_4$); the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to afford pure **6** as a clear colorless liquid; yield: 1.92 g (60%); 94% ee.

$[\alpha]_D^{25}$ +24.4 (*c* 1, $CHCl_3$).

IR (neat): 3432, 2925, 2854, 2230, 1465, 1050 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.54 (t, *J* = 3.3 Hz, 1 H), 4.26 (t, *J* = 5.9 Hz, 1 H), 3.86–3.66 (m, 2 H), 3.51–3.37 (m, 2 H), 2.20 (td, *J* = 1.6, 6.7 Hz, 2 H), 1.72–1.13 (m, 26 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 93.7, 82.1, 78.5, 67.1, 63.5, 62.2, 35.8, 32.8, 31.6, 29.5, 29.3, 29.2, 29.1, 28.8, 28.6, 25.3, 22.7, 22.6, 19.5, 18.6, 14.1.

MS (ESI): *m*/*z* = 339 ($M^+$ + 1).

**(5*R*)–5-(Methoxymethoxy)-1-(tetrahydro-2*H*-pyran-2-yloxy)hexadec-6-yne (11)**

To soln of **6** (1.8 g, 5.3 mmol) in anhyd $CH_2Cl_2$ (10 mL) at 0 °C under $N_2$ atmosphere, was added *i*-$Pr_2NEt$ (4.3 mL, 26 mmol) dropwise and, after 5 min, MOMCl (1.03 mL, 13 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h and then diluted with $H_2O$, washed with sat. aq $NH_4Cl$ and brine. The organic phase was dried (anhyd $Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure **11** as a clear colorless liquid; yield: 1.9 g (98%); 94% ee.

$[\alpha]_D^{25}$ +8.31 (*c* 1, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.90 (d, *J* = 6.7 Hz, 1 H), 4.56 (t, *J* = 3.3 Hz, 1 H), 4.50 (d, *J* = 6.7 Hz, 1 H), 4.26 (t, *J* = 5.9 Hz, 1 H), 3.88–3.66 (m, 2 H), 3.51–3.37 (m, 2 H), 3.34 (s, 3 H), 2.19 (td, *J* = 1.7, 6.7 Hz, 2 H), 1.73 –13 (m, 26 H), 0.89 (t, *J* = 6.7 Hz, 3 H,).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 98.8, 93.8, 78.4, 67.3, 65.7, 62.2, 55.5, 35.8, 31.8, 30.7, 29.6, 29.4, 29.2, 29.1, 28.8, 28.6, 25.5, 22.6, 22.1, 19.5, 18.6, 14.1.

MS (ESI): *m*/*z* = 383 ($M^+$ + 1).

**(5*S*)-5-(Methoxymethoxy)hexadecan-1-ol (12)**

To a soln of **11** (1.8 g, 4.7 mmol) in anhyd EtOH (5 mL) was added a catalytic amount of 10% Pd/C and the mixture was stirred at r.t. under a $H_2$ atmosphere for 6 h. Then the catalyst was filtered off and washed with EtOAc and the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, PE–EtOAc, 6:4) to afford **12** as a colorless liquid; yield: 1.14 g (80%).

$[\alpha]_D^{25}$ +5.51 (*c* 1, $CHCl_3$).

IR (neat): 3432, 2925, 2854, 1461, 1040 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.60 (s, 2 H), 3.62 (t, *J* = 6.1 Hz, 2 H), 3.49 (m, 1 H), 3.35 (s, 3 H), 1.59–1.34 (m, 26 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 95.3, 77.5, 62.5, 55.4, 34.2, 33.9, 33.2, 31.8, 29.8, 29.5, 29.3, 29.2, 22.5, 21.4, 14.1.

MS (ESI): *m*/*z* = 325 ($M^+$ + Na).

**(5*S*)-5-(Methoxymethoxy)hexadecanal (13)**

To an ice-cooled soln of 2-iodoxybenzoic acid (2.3 g, 8.2 mmol) in DMSO (5 mL) was added a soln of alcohol **12** (1.0 g, 3.3 mmol) in anhyd $CH_2Cl_2$ (10 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad and washed with $Et_2O$. The combined organic filtrates were washed with $H_2O$ and brine, dried (anhyd $Na_2SO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 8:2) to afford aldehyde **13** as a viscous liquid; yield: 0.764 g (77%); 93% ee.

$[\alpha]_D^{25}$ +9.82 (*c* 1, $CHCl_3$).

IR (neat): 2927, 2855, 1726, 1460, 1035 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 2.2 Hz, 1 H), 4.59 (AB q, *J* = 6.8 Hz, 2 H) 3.51 (m, 1 H), 3.34 (s, 1 H), 2.43 (td, *J* = 1.5, 7.5 Hz, 2 H), 1.62–1.26 (m, 26 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 202.3, 95.4, 77.1, 55.4, 43.8, 34.2, 33.6, 31.9, 29.7, 29.6, 29.3, 25.2, 22.6, 17.9, 14.1.

MS (ESI): *m*/*z* = 323 ($M^+$ + Na).

**(5*S*)-5-(Methoxymethoxy)hexadecanoic Acid (5)**

Compound **13** (0.6 g, 2 mmol) was dissolved in DMSO (5 mL) and to this was added dropwise $NaH_2PO_4{\cdot}2H_2O$ (0.363 g, 2.3 mmol) in $H_2O$ (5 mL) at 0 °C. To this well-stirred mixture at 0 °C was added $NaClO_2$ (0.209 g, 2.3 mmol) in $H_2O$ (5 mL) and it was stirred at r.t. for 1 h. To the mixture was added 5% $NaHCO_3$. The aqueous phase was acidified with concd HCl and the organic phase was extracted into $CH_2Cl_2$. The combined organic extracts were then filtered through a small pad of Celite and filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 5:5) to afford **5** as colorless oil; yield: 0.505 g (80%).

$[\alpha]_D^{25}$ +5.49 (*c* 1, $CHCl_3$).

IR (neat): 2926, 2854, 1710, 1461, 1038 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.58 (s, 2 H), 3.51 (m, 1 H), 3.35 (s, 3 H), 2.36 (t, *J* = 6.71 Hz, 2 H), 1.74–1.26 (m, 24 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 179.4, 95.2, 55.4, 34.1, 33.9, 31.9, 29.7, 29.6, 29.3, 25.2, 22.6, 20.4, 14.1.

MS (ESI): *m*/*z* = 339 ($M^+$ + Na).

**(*S*)-5-Hexadecanolide (2)**

To a stirred soln of **5** (0.3 g, 0.94 mmol) in MeOH was added a catalytic amount of PTSA (0.009 g, 0.047 mmol) under an $N_2$ atmosphere. The mixture was stirred at r.t. for 12 h and then the reaction was quenched by addition of solid $NaHCO_3$ (0.039 g, 0.47 mmol), the mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to afford **1** as yellow liquid; yield: 0.192 g (80%); 93% ee.

$[\alpha]_D^{25}$ –27.10 (*c* 1, $CHCl_3$).

IR (neat): 2921, 2852, 1727, 1465, 1251, 1044 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.27–4.19 (m, 1 H), 2.60–2.35 (m, 2 H), 1.95–1.26 (m, 24 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.9, 80.5, 35.8, 31.8, 29.6, 29.5, 29.5, 29.4, 29.42, 29.41, 29.3, 27.7, 24.9, 22.6, 18.4, 14.1.

MS (ESI): *m*/*z* = 255 ($M^+$ + 1).

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(15) (3*R*)-Undec-1-yn-3-ol (**4**): clear colorless liquid; IR (neat): 3358, 2929, 2858, 2115, 1034 cm; $^1$H NMR (200 MHz, $CDCl_3$): δ = 4.32 (br s, 1 H), 2.39 (d, *J* = 2.2 Hz, 1 H), 1.86 (br d, *J* = 4.4 Hz, 1 H), 1.74–1.61 (m, 2 H), 1.49–1.27 (m, 12 H), 0.89 (t, *J* = 6.6 Hz, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 85.1, 72.7, 72.73, 62.2, 37.6, 31.8, 29.4, 29.2, 24.9, 22.6, 14.0.
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