Total Synthesis of Insect Pheromones (R)-4-Dodecanolide and (S)-5-Hexadecanolide

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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 and comprise of structural moieties that are frequently present in, for example, insect pheromones, cardenolides, lignans, and flavor components. 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. It was also produced during the bioconversion of soy bean fatty acids by Pencillium Roqueforti spores in the presence of an exogenous lipase and has been used as a flavoring agent; it has been isolated from various fruits and butterfat. The δ-lactone (S)-5-hexadecanolide (2) (Figure 1) was isolated from the mandibular glands of the oriental hornet Vespa orientalis; 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 and (S)-5-hexadecanolide 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 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.

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

![Scheme 1](image-url)
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, (3R)-undec-1-yn-3-ol (4) was first protected as its methoxymethyl ether using Hünig’s base (i-Pr₂EtN, 2 equiv) and methoxymethyl chloride (3 equiv) in dry dichloromethane at room temperature to afford 8 in 90% yield (Scheme 2). The acetylenic compound 8 was then subjected to methoxycarbonylation18 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 13C NMR spectral data in good agreement with the natural lactone ([α]D<sup>25</sup> +36.4 (c 1, MeOH), [Lit.12d [α]D<sup>25</sup> +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

\[ \text{Scheme 2 Reagents and conditions: (a) MOMCl, i-Pr₂NEt, anhyd CH₂Cl₂, 0 °C to r.t., 2 h, 90%; (b) 1.6 M BuLi in hexane, CICO₂Me, anhyd THF, –78 °C, 30 min, 90%; (c) Pd/C, H₂, EtOAc, 4 h, 90%; (d) PTSA, MeOH, r.t, 12 h, 80%.} \]

\[ \text{Scheme 3 Reagents and conditions: (a) Ph₃P, NaHCO₃, CCl₄, reflux, 4 h, 80%; (b) Li/liq NH₃, Fe(NO₃)₃ (cat.), anhyd THF, C₂H₄Br, 8 h, 60%; (c) MOMCl, i-Pr₂NEt, 0 °C to r.t., 2 h, 98%; (d) 10% Pd/C, H₂, EtOH, r.t., 6 h, 80%; (e) IBX, anhyd DMSO, anhyd CH₂Cl₂, r.t., 2 h, 77%; (f) NaClO₂, NaH₂PO₄, aq DMSO, r.t., 1 h, 71%; (g) PTSA, MeOH, r.t., 12 h, 80%.} \]
aldehyde 13 in 77% yield with 2-idoxybenzoic acid (IBX) in anhydrous dimethyl sulfoxide and anhydrous dichloromethane and then 13 was further oxidized with sodium chloride and sodium dihydrogen phosphate in aqueous dimethyl sulfoxide to afford the corresponding acid 5 in 71% yield. 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 N2 atmosphere and monitored by TLC on silica gel (60–120 mesh, 230–400 mesh, Merck). NMR spectra were recorded on Bruker (300 MHz 1H, 75 MHz 13C) spectrometers using CDCl3 as solvent. ESI-MS were recorded with a Thermo Nicolet Nexus 670 spectrophotometer.

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

To a solution of 4 (1.5 g, 8.9 mmol) in anhyd CH2Cl2 (10 mL) at 0 °C under N2 atmosphere, was added i-Pr2NEt (3.10 mL, 17.8 mmol) dropwise and, after 5 min, MOMCl (2.71 mL, 33.6 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h and then diluted with H2O and washed with sat. aq NH4Cl and brine. The organic phase was dried (anhyd Na2SO4) 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%).

$\Delta_1^\text{D} \rightarrow -13.5 \,(c\,1\,\text{CHCl}_3)$.

IR (neat): 2929, 2858, 2235, 1252, 1031 cm–1.

1H NMR (200 MHz, CDCl3); 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 (t, J = 2.2, 11.4 Hz), 1.76–1.61 (m, 2 H), 1.50–1.23 (m, 12 H), 0.89 (t, J = 6.6 Hz, 3 H).

13C NMR (75 MHz, CDCl3); 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 (4R)-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 N2 atmosphere. The soln was then cooled to ~78 °C and 1.6 M BuLi in hexane (5.89 g, 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 NH4Cl and brine. The organic phase was dried (anhyd Na2SO4) 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%).

$\alpha_\text{D}^\text{25} +5.6 \,(c\,1\,\text{CHCl}_3)$.

IR (neat): 2929, 2858, 2235, 1722, 1252, 1032 cm–1.

1H NMR (300 MHz, CDCl3); δ = 4.48 (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).

13C NMR (75 MHz, CDCl3); δ = 153.52, 94.48, 86.4, 76.6, 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+ 1).

Methyl (4R)-4-(Methoxymethoxy)dodecane-1-ol (7)

To a stirred soln of 3 (0.5 g, 1.8 mmol) in MeOH was added a catalytic amount of PTSA under a N2 atmosphere. The mixture was stirred at r.t. for 12 h and then quenched by addition of solid NaHCO3, 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 7 as a colorless liquid; yield: 0.285 g (80%).

$\alpha_\text{D}^\text{25} +36.4 \,(c\,1\,\text{MeOH})$.

IR (neat): 2928, 2856, 1777, 1216, 1038 cm–1.

1H NMR (200 MHz, CDCl3); 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).

13C NMR (75 MHz, CDCl3); 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).

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

Anhyd CH2Cl2 (20 mL) was added to powdered activated 4Å molecular sieves and the suspension was cooled to ~24 °C. Ti(Oi-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 a further 30 min. 3.3 g tert-Butyl hydroperoxide in toluene (8.49 mL, 28 mmol) was then added and the resulting mixture was stirred at ~24 °C for ~4 h for 3 h. It was then warmed to 0 °C, quenched by addition of H2O (6 mL) and stirred at r.t. for 1 h. 30% aq NaOH soln saturat-
ed 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 CH2Cl2. The organic phase was separated and the aqueous phase was extracted with CH2Cl2. The combined organic layers were washed with brine and dried (anhyd Na2SO4). 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%).

$\alpha_\text{D}^\text{25} +13.3 \,(c\,1\,\text{CHCl}_3)$.

IR (neat): 3438, 2960, 2856, 1049 cm–1.

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1H NMR (200 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): 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.

IR (neat): 2940, 2866, 1029 cm–1.

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

[4-Dodecanolide and (S)-5-(Methoxymethoxy)hexadecanal (12)]

To an ice-cooled solution of 2-iodoxybenzoic acid (2.3 g, 8.2 mmol) in DMSO (5 mL) was added a solution of alcohol (1.0 g, 3.3 mmol) in anhyd EtOH (5 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad and washed with EtOAc. The combined organic filtrates were washed with H2O and brine, dried (anhy Na2SO4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 8:2) to afford aldehyde (13) as a colorless liquid; yield: 0.764 g (77%); 93% ee.

1H NMR (300 MHz, CDCl3): 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 (dd, J = 1.5, 7.5 Hz, 2 H), 1.62–1.26 (m, 26 H), 0.88 (t, J = 6.7 Hz, 3 H).

13C NMR (75 MHz, CDCl3): 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).

(5R)-5-(Methoxymethoxy)hexadecan-1-ol (11)

To a stirred solution of 6 (1.8 g, 5.3 mmol) in anhyd CH2Cl2 (10 mL) at 0 °C under N2 atmosphere, was added i-Pr2NEt (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 H2O, washed with sat. aq NH4Cl and brine. The organic phase was dried (anhy Na2SO4) 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.

1H NMR (300 MHz, CDCl3): δ = 4.90 (d, J = 6.7 Hz, 1 H), 4.56 (t, J = 3.3 Hz, 1 H), 4.05 (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), 1.73–1.3 (m, 26 H), 0.89 (t, J = 6.7 Hz, 3 H).

13C NMR (75 MHz, CDCl3): 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 = 338 (M+ + 1).

(5S)-5-(Methoxymethoxy)hexadecanal (5)

Compound 13 (0.6 g, 2 mmol) was dissolved in DMSO (5 mL) and to this was added dropwise NaH2PO4·2H2O (0.363 g, 2.3 mmol) in H2O (5 mL) at 0 °C. To this well-stirred mixture at 0 °C was added NaHCO3 (0.209 g, 2.3 mmol) in H2O (5 mL) and it was stirred at r.t. for 1 h. To the mixture was added 5% NaHCO3. The aqueous phase was acidified with conc HCl and the organic phase was extracted into CH2Cl2. 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%).

IR (neat): 3432, 3252, 2854, 1726, 1460, 1040 cm–1.

MS (ESI): m/z = 325 (M+ + Na).
\( \text{1}^1 \text{H NMR (200 MHz, CDCl}_3\): } \delta = 4.58 (s, 2 H), 3.51 (m, 1 H), 3.35 (s, 3 H), 2.36 (t, J = 6.7 Hz, 2 H), 1.74–1.26 (m, 24 H), 0.88 (t, J = 6.7 Hz, 3 H).

\( \text{1}^3 \text{C NMR (75 MHz, CDCl}_3\): } \delta = 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 PTSA (0.009 g, 0.047 mmol) under an N\(_2\) atmosphere. The mixture was stirred at r.t. under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to afford I as yellow liquid; yield: 0.192 g (80%); 93% ee.

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References

(1) ICT Communication No. 050818.


(15) (3R)-Undec-1-yn-3-ol (4): clear colorless liquid; IR (neat): 3358, 2929, 2858, 2115, 1034 cm\(^{-1}\); \( \text{1}^1 \text{H NMR (200 MHz, CDCl}_3\): } \delta = 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); \( \text{1}^3 \text{C NMR (75 MHz, CDCl}_3\): } \delta = 85.1, 72.7, 72.73, 62.2, 37.6, 31.8, 29.4, 29.2, 24.9, 22.6, 24.9, 14.0.

