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

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Abstract: Asymmetric total synthesis of (–)-(5R,6S)-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, (–)-(5R,6S)-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 and as well as their frequent presence in structural moieties of insect pheromones. One such example is (–)-(5R,6S)-6-acetoxyhexadecanolide (I), isolated by Laurence and Pickett in 1982 from the apical droplet of mosquito (Culex pipiens fatigans) eggs. 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. In the last few years many syntheses of I have appeared in the literature. 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, we herein report the synthesis of (–)-(5R,6S)-6-acetoxyhexadecanolide.

The retrosynthetic strategy for (–)-(5R,6S)-6-acetoxyhexadecanolide (I) 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) 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 was chosen as the starting material. The conversion of epoxy chloride 5 to the substituted chiral acetylenic alcohol 9 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 Na2CO3 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-

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**Scheme 1** Retrosynthetic route for (–)-(5R,6S)-6-acetoxyhexadecanolide (I)
The secondary hydroxyl group of compound 3 was protected as its methoxymethyl ether using 3 equivalents of Hunig’s base (i-Pr₂EtN) and 2 equivalents of MOMCl in anhydrous CH₂Cl₂ at room temperature affording 10 in 96% yield. Deprotection of PMB group of compound 10 was done by treatment with 1.5 equivalents of DDQ in CH₂Cl₂/H₂O (9:1) to afford compound 11 in 83% yield. Oxidation of compound 11 with IBX (o-iodoxybenzoic acid) in DMSO–CH₂Cl₂ 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. The secondary hydroxyl group of compound 2 was protected by using acetic anhydride and triethylamine in anhydrous CH₂Cl₂ to afford acetate 13. Deprotection of the THP group in 13 using PTSA in MeOH 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 NaClO₂ and NaH₂PO₄ in DMSO and water to afford the corresponding acid 16 in 72% yield. Finally the syn-

Scheme 2

Scheme 3

Scheme 4
thesis of target molecule 1 was achieved in 76% yield by
in situ deprotection of MOM group and subsequent cy-
cyclization by using catalytic amount of PTSA in anhydrous
benzene under reflux (Scheme 4). The synthetic materi-
alm showed IR, 1H, 13C NMR spectral data and optical rota-
tion [(d)J25 = -35.0 (c = 1.5, CHCl3)] in good agreement
with the natural lactone.

Reactions were conducted under N2 using anhyd solvents such as
CH2Cl2, THF, CCl4, benzene and EtOAc. All reactions were moni-
tored 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 spectrscopically (1H, 13C)
homogeneous material. Air sensitive reagents were transferred by
syringe or cannula. Evaporation of solvents was performed at re-
duced pressure, using a Büchi rotary evaporator. 1H NMR spectra
were recorded on Varian FT-200 MHz (Gemini) and Bruker
UXNMR FT-300 MHz (Avance) in CDCl3. 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). Col-
umn 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-Hexyloxy)tetrahydro-2H-pyran (4)
In a 100 mL round-bottomed flask fitted with a N2 adaptor, the hex-
5-en-1-ol (10 g, 100.0 mmol) in anhyd CH2Cl2 (80 mL) was taken
and a catalytic amount of PTSA was added. Then the mixture was
cooled to 0 °C. To this, a 3,4-dihydro-2H-pyran (6.5 mL, 110.0 mmol)
was added dropwise. After completion of the mixture, the mixture
was allowed to stir for 3 h. The mixture was diluted with CH2Cl2,
and the organic layer was washed with H2O, aq NaHCO3, and dried
(Na2SO4). Concentration under reduced pressure and purification
over silica gel column chromatography afforded pure tetrahydropyr-
anyl ether 4 (18.2 g, 95%) as a viscous liquid.

1H NMR (CDCl3, 300 MHz): 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), 1.85–1.30 (m, 12 H).

2-[4-(2-Oxiranylbutoxy)tetrahydro-2H-pyran (6)
To a suspension of NaN3 (5.8 g, 70.0 mmol) in CH2Cl2 (60 mL) was added the compound 4 (13 g, 70.0 mmol) in CH2Cl2 (30 mL) under
N2. 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 CH2Cl2, and the CH2Cl2 layer was washed with a solu-
tion of Na2SO4, followed by aq 5% NaHCO3 solution and H2O. The organic layer was dried (Na2SO4) and concentrated 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.

1H NMR (CDCl3, 300 MHz): δ = 4.55 (t, J = 3.2 Hz, 1 H), 3.87–3.67 (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).

(2R)-6-(Tetrahydro-2H-2-pyranolyloxy)hexane-1,2-diol (8)
A mixture of [(S,S)-Jacobsen catalyst [(S,S)-N,N′-bis(3,5-di-tet-tu-
bylsalicylidene)-1,2-cyclohexanediamino-Cori(III) acetate] (195 mg,
0.32 mmol, 0.005 equiv) in CH2Cl2 and AcOH (39 mg, 0.65 mmol,
0.01 equiv) was stirred while open to the air for 1 h at r.t. The sol-
vent 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. H2O (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 H2O 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 re-
moved, and the mixture was stirred at r.t. for 24 h and then
quenched with aq sat. NaHCO3 solution. The filtrate was washed with
H2O, brine and dried (Na2SO4). The organic layer was concen-
trated to give the crude material, which after column chromatogra-
phy provided the pure product 8 (6.1 g, 47%, 96% ee) as a liquid;
[α]D25 = -18.02 (c = 1.5, CHCl3).

IR (neat): 3425, 2940, 2867, 1121, 1073, 1028 cm–1.

1H NMR (CDCl3, 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).

(2R)-1-(4-Methoxyphenyl)-6-(tetrahydro-2H-2-pyranoly-
oxo)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,
PMBr3 (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
NaH2CO3 solution and extracted with EtOAc. The organic layer was
washed with H2O, brine, dried (Na2SO4) and concentrated in vacuo.
Purification of the residue by silica gel column chromatog-
raphy afforded 3 (5.4 g, 80%) as a viscous liquid.

1H NMR (CDCl3, 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).

(2R)-1-(4-Methoxyphenyl)-6-(tetrahydro-2H-2-pyranoly-
oxo)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(NO3)3, followed by the piecewise addition
of Li metal (1.9 g, 27.27 mmol) at —78 °C, and the resulting gray
colored suspension was stirred for 30 min. To this was added epoxi
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 temper-
ature. After 2 h, THF protected bromoethanol (20.5 g, 90.8 mmol)
was added to the mixture. The reaction was stirred at the same temperature for 6 h, and quenched by the addition of solid
NH4Cl, and then the ammonia was allowed to evaporate. The mix-
ture was partitioned between H2O and EtOAc, and the aqueous layer
was extracted with EtOAc. The combined organic layers were
washed once with H2O and brine, and dried (Na2SO4). 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%);
[α]D25 = -1.2 (c = 1.5, CHCl3).

IR (neat): 3425, 2941, 2867, 1513, 1248, 1032 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 4.66 (t, J = 5.5 Hz, 1 H), 3.52–3.17
(m, 2 H), 2.86 (m, 1 H), 1.72–1.32 (m, 12 H), 1.18–1.30 (m, 12 H).

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

(2R)-1-(4-Methoxyphenyl)-6-(tetrahydro-2H-2-pyranoly-
oxo)hexan-2-ol (3)
To a solution of compound 9 (10 g, 29.9 mmol), and Na2CO3 (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 H2 at
mixture was stirred at r.t. under H2 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-

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

1H NMR (CDCl3, 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).

To a stirred solution of compound (4.5 mL) and H2O (0.5 mL) was added DDQ (2.3 g, 10.4 mmol) at 0 °C. The mixture was stirred for 2.5 h at r.t. before being quenched with Na2SO4 solution and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford the pure compound 10 as a colorless liquid (4.6 g, 96%); [α]25D = −3.28 (c = 1.5, CHCl3).

IR (neat): 3455, 2941, 1120, 1033 cm–1.

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

(1S)-1-[(1R)-1-(Methoxymethoxy)-5-(tetrahydro-2H-pyran-2-yl)oxy]undecyl Acetate (13)

To a stirred solution of compound 2 (1.6 g, 4.9 mmol) in anhyd CH2Cl2 (3 mL) was added Et3N (1.1 mL, 7.9 mmol) followed by Ac2O (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 CH2Cl2. The organic layer was washed successively with H2O, aq 5% NaHCO3 solution, brine and dried (Na2SO4). 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; [α]25D = −1.94 (c = 1.5, CHCl3).

IR (neat): 3489, 2926, 2854, 1737, 1239, 1035 cm–1.

1H NMR (CDCl3, 300 MHz): δ = −1.94 (m, 1 H), 4.63 (ABq, J = 6.5 Hz, 2 H), 3.48–3.66 (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).

13C NMR (CDCl3, 75 MHz): δ = 170.9, 98.5, 97.1, 77.9, 74.3, 55.9, 46.7.

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

(1S)-1-[(1R)-1-(Methoxymethoxy)-5-(tetrahydro-2H-pyran-2-yl)oxy]pentylundecyl 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 MeOH was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to afford 14 (1.6 g, 90%) as a viscous liquid; [α]25D = −0.73 (c = 1.5, CHCl3).

IR (neat): 3489, 2926, 2854, 1737, 1239, 1035 cm–1.

1H NMR (CDCl3, 300 MHz): δ = −1.94 (m, 1 H), 4.63 (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).

(1S)-1-[(1R)-1-(Methoxymethoxy)-5-(tetrahydro-2H-pyran-2-yl)oxy]undecyl Acetate (15)

To an ice-cooled solution of isobenzozic acid (1.6 g, 4.1 mmol) in DMSO (4 mL) was added a solution of alcohol 14 (1.0 g, 2.7 mmol) in anhyd CH2Cl2 (10 mL). After stirring for 2 h at r.t., the mixture was filtered through a Celite pad and washed with Et2O. The combined organic layers were washed with H2O, brine, dried (Na2SO4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford the aldehyde 15 as a viscous liquid (1.5 g, 80%).

1H NMR (CDCl3, 300 MHz): δ = 170.9, 98.5, 97.1, 77.9, 74.3, 55.9, 46.7.

IR (neat): 3489, 2926, 2854, 1737, 1372, 1239, 1035 cm–1.

1H NMR (CDCl3, 300 MHz): δ = −0.73 (c = 1.5, CHCl3).

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

Synthesis of (−)-(5R,6S)-6-Acetoxyhexadecanolate (2424)

To a suspension of Mg (1.37 g, 28.5 mmol) in anhyd Et2O (50 mL), was added H2O (28.5 mmol), then washed with Na2SO4 solution and filtered over Celite. The filtrate was washed with H2O, brine and dried (Na2SO4). 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; [α]25D = −8.04 (c = 1.5, CHCl3).

IR (neat): 3469, 2926, 2854, 1460, 1114, 1034 cm–1.

1H NMR (CDCl3, 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).

(1S)-1-[(1R)-1-(Methoxymethoxy)-5-(tetrahydro-2H-pyran-2-yl)oxy]pentylundecyl Acetate (13)

To a stirred solution of compound 2 (1.6 g, 4.9 mmol) in anhyd CH2Cl2 (3 mL) was added Et3N (1.1 mL, 7.9 mmol) followed by Ac2O (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 CH2Cl2. The organic layer was washed successively with H2O, aq 5% NaHCO3 solution, brine and dried (Na2SO4). 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; [α]25D = −1.94 (c = 1.5, CHCl3).

1H NMR (CDCl3, 400 MHz): δ = 0.92 (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).

IR (neat): 3489, 2926, 2854, 1737, 1239, 1035 cm–1.

13C NMR (CDCl3, 75 MHz): δ = 170.9, 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, 29.5, 29.5, 29.3, 25.5, 25.4, 22.6, 21.1, 19.5, 14.1.

ESIMS: m/z = 381 (M+ + Na).
To a stirred solution of compound 15 (0.7 g, 1.95 mmol) in DMSO (5 mL) was added an aq solution of NaH$_2$PO$_4$ (0.305 g, 1.95 mmol) dropwise at 0 °C. To this well-stirred mixture at 0 °C was added aq 5% NaHCO$_3$ solution. The mixture was allowed to stir for 1 h at r.t. To the mixture was added aq NaHCO$_3$ solution. 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 (5:1) to afford 16 as a colorless oil (0.520 g, 72%); $[\alpha]_{D}^{25} = -313$ (M$^+$ + 1).

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

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