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RESEARCH ARTICLE

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Synthesis of the enantiomers of 13-methylheptacosane, the sex pheromone of pear psylla, *Cacopsylla pyricola*

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Abstract

An efficient and gram-scale enantioselective synthesis of (*R*)- and (*S*)-13-methylheptacosane, the sex pheromone of pear psylla, has been developed. The key steps of the approach included Evans' chiral auxiliaries and Wittig coupling of chiral phosphonium salt with aldehyde.

KEYWORDS

13-methylheptacosane, chiral auxiliaries, enantioselective synthesis, pear psylla, sex pheromone

1 | INTRODUCTION

Pear psylla (*Cacopsylla pyricola*) is a serious pest of pears, which has caused significant economic damage in North America and Europe.[1,2] Current control of this pest relies mainly on insecticides.[3] However, the increasing resistance to many insecticides, such as pyrethroid[4,5] and orgno-phosphorous,[6,7] has made the control more difficult. Therefore, it is essential to search more efficient and environment-friendly alternative control methods to insecticides.

The pest management based on sex pheromones is a safe, effective and promising technique.[8,9] In 2009, the sex pheromone produced by the female pear psylla was identified as 13-methylheptacosane (*rac*-**1**) by Guédot, meanwhile their bioassays indicated that males were attracted to synthetic racemic **1**.[10] Although this result opened a new strategy to monitor and trap pear psylla, the absolute configuration of the sex pheromone remains unknown.[11] Previous literatures reported that the bioactivity of sex pheromones was often closely relayed to chirality.[12–14] The stereochemistry on this sex pheromone still needs to be assigned by further biological studies of (*R*)-**1** and (*S*)-**1** (Figure 1), which promotes the synthesis of the enantiomers of 13-methylheptacosane. Mori has prepared (*R*)-**1** and (*S*)-**1** from two kinds of chiral sources, the enantiomers of citronellal[11] and citronellol.[15] Herein, we reported an efficient and gram-scale synthesis of both enantiomers of the sex pheromone of pear psylla via Evans' chiral auxiliaries. The key steps of our strategy involve diastereoselective methylation of oxazolidinone amide and Wittig reaction of chiral phosphonium salt with aldehyde. Compared with Mori's processes,[15] our synthesis was easier to scale up and afforded the sex pheromones of pear psylla with higher enantiomeric purity.

2 | MATERIALS AND METHODS

2.1 | Instruments and materials

All reactions were conducted under an argon atmosphere with Schlenk techniques. The solvents were purified referring to the standard strategy and distilled before use. Other commercial reagents were used directly. Melting points were measured on a Beijing Tech X-4 melting point apparatus without correction. Differential scanning calorimetry (DSC) thermograms were recorded on EXSTAR6000. Optical rotations were determined by a Perkin–Elmer PE-341 polarimeter. ^{1}H, ^{13}C nuclear magnetic resonance (NMR),

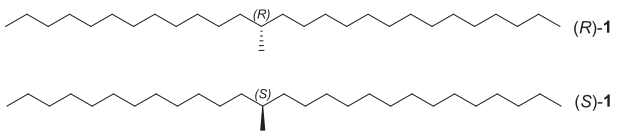


FIGURE 1 The structures of (*R*)-and (*S*)-13-methylheptacosane

and ^{19}F NMR spectra were obtained from a Bruker DP-X300 MHz or ASCEND™500 spectrometer with internal tetramethylsilane for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. High-resolution mass spectrometry (HRMS) data were recorded on Thermo Scientific Exactive Plus (EMR) with a quadrupole mass analyzer. Mass spectrometry (MS) data were collected from Exactive GC–MS (EI).

2.2 | Synthesis of (*R*)-4-benzyl-3-tetradecanoyl-oxazolidin-2-one ((*R*)-3) (new compound)

Tetradecanoic acid **2** (2.28 g, 10 mmol) was dissolved in dichloromethane (DCM) (20 ml) at 0°C; the catalytic amount of DMF was then added. After oxalyl chloride (1.90 g, 15 mmol) was added slowly via syringe, the reaction mixture was stirred for 1 h at the same temperature. The solvent was removed under reduced pressure to give the crude tetradecanoyl chloride as a slight yellow solid.

(*R*)-4-benzyloxazolidin-2-one (1.45 g, 8.25 mmol, >99% ee) was dissolved in tetrahydrofuran (THF) (20 ml), NaH (0.50 g, 60% in mineral oil, 12.3 mmol) was then added slowly at 0°C. The resulting mixture was warmed to 25°C and stirred for 2 h. The crude tetradecanoyl chloride was added. After the reaction mixture was stirred for another 3 h at 25°C, it was quenched with saturated aqueous NH_4Cl solution (10 ml). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 ml). The combined organic layers were washed with brine (50 ml) and dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1:10) to provide oxazolidinone amide (*R*)-**3** as a white solid (2.99 g, 94% yield). mp 58–59°C; $[\alpha]_D^{20} = -28.2$ ($c = 2.14$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.38–7.18 (m, 5H), 4.68 (ddt, $J = 13.1$, 7.0, 3.4 Hz, 1H), 4.32–4.04 (m, 2H), 3.31 (dd, $J = 13.3$, 3.3 Hz, 1H), 3.03–2.71 (m, 3H), 1.80–1.53 (m, 2H), 1.35–1.27 (m, 20H), 0.89 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.59, 153.60, 135.48, 129.56, 129.08, 127.47, 66.28, 55.29, 38.08, 35.68, 32.06, 29.82, 29.80, 29.78, 29.76, 29.63, 29.54, 29.49, 29.28, 24.42, 22.83, 14.25; HRMS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{38}O_3N$, 388.2846; found, 388.2829.

2.3 | Synthesis of (*R*)-4-benzyl-3-((*R*)-2-methyltetradecanoyl)oxazolidin-2-one ((*R*)-4) (new compound)

Under an argon atmosphere, the oxazolidinone amide (*R*)-**3** (3.87 g, 10 mmol) was dissolved in dry THF (80 ml), and the solution was cooled to −78°C. Sodium hexamethyldisilazide (NaHMDS, 7.12 ml, 2.0 M in THF, 14.25 mmol) was then added over 15 min via syringe pump. The resulting mixture was stirred for 1 h at the same temperature, and MeI (7.34 g, 3.22 ml, 52 mmol) was added. After the reaction solution was stirred for additional 2 h at −78°C, it was quenched with saturated aqueous NH_4Cl solution (75 ml). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 75 ml). The combined organic layers were washed with brine (300 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1:10) to give oxazolidinone amide (*R*)-**4** (3.41 g, 85% yield, >99% ee, dr > 99:1) as a white solid. (*R*)-**4** was recrystallized from dry ether and DSC thermograms showed that it was diastereomerically pure and different from *rac*-**4**. Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) with a Daicel Chiralcel OD-H column (5% 2-propanol in *n*-hexane, 1.0 ml/min, 210 nm); major (*R*)-enantiomer $t_r = 9.73$ min. mp 33–34°C; $[\alpha]_D^{20} = -40.4$ ($c = 0.91$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.42–7.13 (m, 5H), 4.68 (ddt, $J = 10.0$, 6.7, 3.3 Hz, 1H), 4.29–4.07 (m, 2H), 3.72–3.68 (m, 1H), 3.28 (dd, $J = 13.3$, 3.3 Hz, 1H), 2.77 (dd, $J = 13.3$, 9.6 Hz, 1H), 1.84–1.65 (m, 1H), 1.53–1.24 (m, 21H), 1.23 (d, $J = 6.8$ Hz, 3H), 0.89 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 177.51, 153.19, 135.52, 129.58, 129.06, 127.46, 66.14, 55.50, 38.09, 37.86, 33.60, 32.05, 29.80, 29.78, 29.73, 29.65, 29.48, 27.40, 22.81, 17.49, 14.23; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{39}O_3NNa$, 424.2822; found, 424.2811.

2.4 | Synthesis of (*R*)-2-methyltetradecan-1-ol ((*R*)-5) (CAS 108349-45-7)

Oxazolidinone amide (*R*)-**4** (8.90 g, 22.16 mmol) was dissolved in THF (80 ml), and the solution of $NaBH_4$ (3.35 g, 88.65 mmol) in water (10 ml) was then added dropwise over 30 min at 0°C. The reaction mixture was warmed to 25°C and stirred for 3 h, followed by the slow addition of 2-M aqueous HCl solution until pH was 6. The resulting mixture was extracted with Et_2O (3 × 30 ml), and the combined ether extracts were

washed with saturated aqueous $NaHCO_3$ solution (20 ml) and brine (2 × 20 ml) sequentially. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1:5) to afford alcohol (*R*)-**5** (4.30 g, 85% yield, >99% ee, determined by ^{19}F NMR analysis of its Mosher ester) as a colorless oil. $[\alpha]_D^{20} = +4.5$ ($c = 1.68$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 3.51 (dd, $J = 10.5$, 5.8 Hz, 1H), 3.41 (dd, $J = 10.5$, 6.5 Hz, 1H), 1.69–1.47 (m, 2H), 1.42–1.17 (m, 22H), 0.91 (d, $J = 6.0$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 68.56, 35.92, 33.31, 32.07, 30.10, 29.82, 29.80, 29.50, 27.14, 22.83, 16.72, 14.24; HRMS (ESI, *m*/*z*):$[M + Na]^+$ calcd for $C_{15}H_{32}ONa$, 251.2345; found, 251.2345.

2.5 | Synthesis of (*R*)-1-bromo-2-methyltetradecane ((*R*)-6) (new compound)

Under an argon atmosphere, alcohol (*R*)-**5** (3.12 g, 13.64 mmol) and triphenylphosphine (5.37 g, 20.46 mmol) were dissolved in CH_2Cl_2 (40 ml); carbon tetrabromide (6.78 g, 20.46 mmol) was then added in portions over 30 min at 0°C. After the reaction mixture was stirred for 20 min at 0°C, it was warmed to room temperature and stirred for additional 12 h. The solvent was removed under reduced pressure, followed by the addition of *n*-hexane (100 ml). The resulting mixture was filtered through a pad of Celite and washed with *n*-hexane (100 ml). The combined filtrates were concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether) to obtain hydrocarbon bromide (*R*)-**6** (3.89 g, 98% yield) as a colorless oil. $[\alpha]_D^{20} = +0.35$ ($c = 2.3$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 2.65 (dd, $J = 9.8$, 4.9 Hz, 1H), 2.57 (dd, $J = 9.8$, 6.2 Hz, 1H), 1.14–0.98 (m, 1H), 0.72–0.51 (m, 22H), 0.28 (d, $J = 6.6$ Hz, 3H), 0.16 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 41.67, 35.39, 35.06, 32.09, 29.87, 29.81, 29.79, 29.74, 29.51, 27.04, 22.85, 18.95, 14.25; HRMS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{32}Br$, 291.1682; found, 291.1726.

2.6 | Synthesis of (*R*)-2-methyl tetradecyltriphenylphosphonium bromide ((*R*)-7) (new compound)

Under an argon atmosphere, hydrocarbon bromide (*R*)-**6** (2.00 g, 6.87 mmol) and triphenylphosphine (2.70 g, 10.30 mmol) were added to CH_3CN (40 ml) at room temperature. The reaction solution was then heated to 85°C and stirred for 24 h. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol 10:1) to provide phosphonium salt (*R*)-**7** (1.90 g, 50% yield) as a colorless oil. $[\alpha]_D^{20} = -0.68$ ($c = 1.17$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.20–6.87 (m, 15H), 3.84–3.75 (m, 1H), 3.50–3.26 (m, 1H), 2.06–2.04 (m, 1H), 1.79–1.01 (m, 22H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.80 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.07, 135.05, 133.72, 133.64, 130.60, 130.50, 119.24, 118.56, 38.20, 38.13, 31.92, 29.66, 29.64, 29.62, 29.57, 29.50, 29.35, 29.30, 26.78, 22.69, 21.13, 21.07, 14.14; HRMS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{47}BrP$, 553.2593; found, 553.2607.

2.7 | Synthesis of (*R*)-13-methylheptacosane ((*R*)-1) (CAS 340006-05-5)

Under an argon atmosphere, phosphonium salt (*R*)-**7** (2.72 g, 4.91 mmol) was dissolved in dry 1,2-dimethoxyethane (30 ml), and the solution of *n*-BuLi (3.93 ml, 2.5 M in *n*-hexane, 9.83 mmol) was then added dropwise via syringe at room temperature. The resulting mixture was stirred for 2 h at 25°C to obtain phosphorus ylide solution. The resulting phosphorus ylid solution was then cooled to −40°C, followed by the addition of solution of *n*-tridecanal (1.46 g, 7.37 mmol) in dry 1,2-dimethoxyethane (15 ml) via syringe at the same temperature. The reaction mixture was warmed gradually to 25°C and stirred for 5 h. After the reaction was quenched with saturated aqueous NH_4Cl solution (10 ml), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 ml). The combined organic phases were washed with brine (20 ml) sequentially, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column silica gel chromatography (petroleum) to give (*R*)-15-methylheptacos-13-ene (1.31 g) as a colorless viscous liquid.

In a three-neck 100-ml flask, 10% platinum on carbon (0.50 g) was placed and charged with hydrogen. The solution of (*R*)-15-methylheptacos-13-ene (1.31 g, 3.33 mmol) in ethanol (20 ml) and catalytic amount of acetic acid was then added slowly at room temperature. After the reaction mixture was stirred for 12 h at the same temperature under hydrogen, it was filtered and the filter was washed with *n*-hexane (50 ml). The combined filtrate and washing were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane) to obtain target pheromone (*R*)-**1** (1.29 g,

67% yield two steps) as a white solid. mp 29–30°C; $[\alpha]_D^{20} = -0.35$ ($c = 2.27$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 1.45–1.02 (m, 49H), 0.96–0.87 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 37.34, 32.99, 32.16, 30.28, 29.94, 29.90, 29.60, 27.32, 22.91, 19.91, 14.28; EIMS (*m*/*z* [%]): 71 (60), 85 (58), 207 (100), 225 (33), 281 (38).

2.8 | Synthesis of (*S*)-4-benzyl-3-tetradecanoyloxazolidin-2-one ((*S*)-3) (CAS 145816-90-6)

According to the similar procedure for oxazolidinone amide (*R*)-**3**, tetradecanoic acid (6.85 g, 30 mmol), oxalyl chloride (5.71 g, 45 mmol) and (*S*)-4-benzyloxazolidin-2-one (3.54 g, 20 mmol, >99% ee) afforded oxazolidinone amide (*S*)-**3** as a white solid (7.51 g, 97% yield). mp 58–59°C; $[\alpha]_D^{20} = +28.2$ ($c = 1.29$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 7.44–7.10 (m, 5H), 4.68 (ddt, $J = 10.3$, 6.8, 3.4 Hz, 1H), 4.30–4.10 (m, 2H), 3.31 (dd, $J = 13.3$, 3.2 Hz, 1H), 3.09–2.64 (m, 3H), 1.72–1.65 (m, 2H), 1.35–1.27 (m, 20H), 0.89 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.59, 153.58, 135.49, 129.55, 129.07, 127.45, 66.27, 55.28, 38.09, 35.67, 32.05, 29.78, 29.75, 29.62, 29.53, 29.48, 29.28, 24.43, 22.81, 14.23; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_{24}H_{37}O_3NNa$, 410.2666; found, 410.2670.

2.9 | Synthesis of (*S*)-4-benzyl-3-((*S*)-2-methyltetradecanoyl)oxazolidin-2-one ((*S*)-4) (new compound)

According to the similar procedure for oxazolidinone amide (*R*)-**4**, oxazolidinone amide (*R*)-**3** (3.87 g, 10 mmol), MeI (7.10 g, 50 mmol) and sodium hexamethyldisilazide (NaHMDS, 2.0 M in THF, 10 ml, 20 mmol) afforded oxazolidinone amide (*S*)-**4** (3.49 g, 87% yield) as a white solid. (*S*)-**4** was recrystallized from dry ether and DSC thermograms showed that it was diastereomerically pure and different from *rac*-**4**. Enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (5% 2-propanol in *n*-hexane, 1.0 ml/min, 210 nm); major (*S*)-enantiomer $t_r = 11.03$ min. mp 33–34°C; $[\alpha]_D^{20} = +40.73$ ($c = 5.5$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 7.40–7.16 (m, 5H), 4.68 (ddt, $J = 9.9$, 6.7, 3.5 Hz, 1H), 4.26–4.07 (m, 2H), 3.72–3.68 (m, 1H), 3.27 (dd, $J = 13.3$, 3.2 Hz, 1H), 2.77 (dd, $J = 13.3$, 9.5 Hz, 1H), 1.83–1.59 (m, 2H), 1.28–1.24 (m, 20H), 1.22 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 177.53, 153.21, 135.53, 129.60, 129.07, 127.47, 66.16, 55.52, 38.10, 37.87, 33.61, 32.07, 29.81, 29.79, 29.75, 29.66, 29.50, 27.42, 22.83, 17.50, 14.25; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{39}O_3NNa$, 424.2822; found, 424.2830.

2.10 | Synthesis of (*S*)-2-methyltetradecan-1-ol ((*S*)-5) (CAS 156394-18-2)

According to the similar procedure for alcohol (*R*)-**5**, oxazolidinone amide (*S*)-**4** (6.37 g, 15.86 mmol) and $NaBH_4$ (2.4 g, 63.44 mmol) afforded alcohol (*S*)-**5** (3.19 g, 88% yield, >99% ee, determined by ^{19}F NMR analysis of its Mosher ester) as a colorless oil. $[\alpha]_D^{20} = -11.36$ ($c = 0.88$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 3.51 (dd, $J = 10.5$, 5.8 Hz, 1H), 3.41 (dd, $J = 10.5$, 6.5 Hz, 1H), 1.83–1.55 (m, 2H), 1.38–1.18 (m, 22H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 68.53, 35.90, 33.32, 32.07, 30.10, 29.83, 29.80, 29.50, 27.14, 22.83, 16.72, 14.23; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{32}ONa$, 251.2345; found, 251.2351.

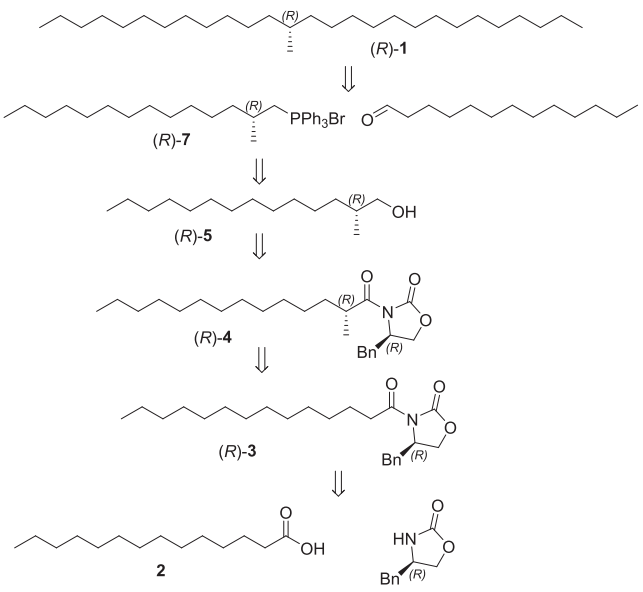
2.11 | Synthesis of (*S*)-1-bromo-2-methyltetradecane ((*S*)-6) (CAS 2410601-40-8)

According to the similar procedure for hydrocarbon bromide (*R*)-**6**, alcohol (*S*)-**5** (8.76 g, 38.35 mmol), carbon tetrabromide (19.08 g, 57.52 mmol), and triphenylphosphine (15.09 g, 57.52 mmol) afforded hydrocarbon bromide (*S*)-**6** (10.94 g, 98% yield) as a colorless oil. $[\alpha]_D^{20} = -0.31$ ($c = 5.23$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ): 3.41 (dd, $J = 9.8$, 5.0 Hz, 1H), 3.33 (dd, $J = 9.8$, 6.2 Hz, 1H), 1.86–1.74 (m, 1H), 1.50–1.27 (m, 21H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 41.69, 35.39, 35.06, 32.09, 29.87, 29.82, 29.79, 29.74, 29.51, 27.04, 22.85, 18.96, 14.26; HRMS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{32}Br$, 291.1682; found, 291.1740.

2.12 | Synthesis of (*S*)-2-methyl tetradecyltriphenylphosphonium bromide ((*S*)-7) (new compound)

According to the similar procedure for phosphonium salt (*R*)-**7**, hydrocarbon bromide (*S*)-**6** (6.00 g, 20.60 mmol) and triphenylphosphine (21.09 g, 80.40 mmol) afforded phosphonium salt (*S*)-**7** (5.93 g, 52% yield) as a colorless oil. $[\alpha]_D^{20} = +3.32$ ($c = 4.33$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.02–7.08 (m, 15H), 3.76 (tt, $J = 68.2$, 34.2 Hz, 1H), 3.48–3.23 (m, 1H), 2.01

(d, J = 32.0 Hz, 1H), 1.73 (t, J = 33.3 Hz, 1H), 1.32–1.01 (m, 21H), 0.96 (d, J = 6.5 Hz, 3H), 0.80 (t, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.07, 135.05, 133.72, 133.64, 130.60, 130.50, 119.23, 118.56, 38.20, 38.13, 31.92, 29.66, 29.64, 29.62, 29.57, 29.49, 29.35, 29.30, 26.78, 22.69, 21.13, 21.07, 14.14; HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{33}H_{47}BrP$, 553.2593; found, 553.2675.



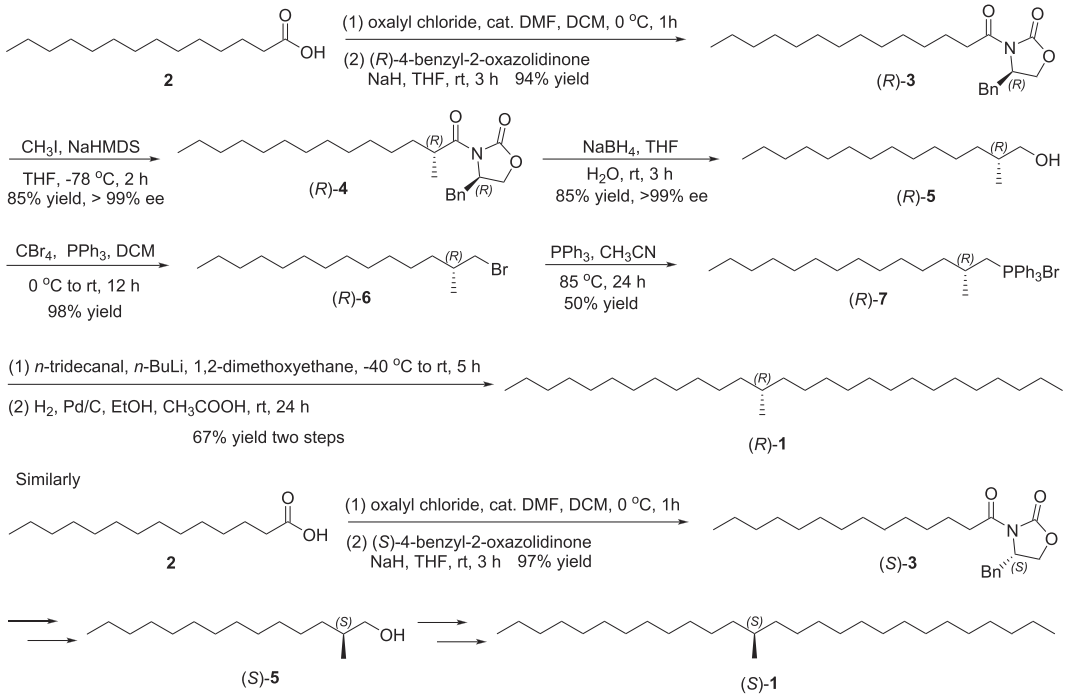
SCHEME 1 Retrosynthetic analysis of (*R*)-13-methylheptacosane

2.13 | Synthesis of (*S*)-13-methylheptacosane ((*S*)-1) (CAS 340006-23-7)

According to the similar procedure for sex pheromone (*R*)-**1**, (*S*)-**7** (2.86 g, 5.17 mmol), *n*-tridecanal (1.54 g, 7.75 mmol) and 10% platinum on carbon (0.50 g) afforded sex pheromone (*S*)-**1** (1.37 g, 68% yield two steps) as a white solid. mp 29–30°C. $[\alpha]_D^{20}$ = +0.13 (c = 3.02 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.45–1.10 (m, 49H), 0.94–0.85 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 37.27, 32.92, 32.10, 30.21, 29.91, 29.88, 29.84, 29.54, 27.26, 22.86, 19.89, 19.87, 14.28; EIMS (m/z[%]): 71 (60), 85 (58), 207 (100), 225 (33), 281 (39).

3 | RESULTS AND DISCUSSION

The retrosynthetic analysis of (*R*)-13-methylheptacosane is outlined in Scheme 1. The target sex pheromone (*R*)-**1** could be prepared via the Wittig coupling of phosphonium salt (*R*)-**7** with *n*-tridecanal and hydrogenation reduction. The bromination of chiral alcohol (*R*)-**5** and reacting with triphenylphosphine were envisaged to afford the key chiral intermediate (*R*)-**7**. Most importantly, the chiral methyl of (*R*)-**5** could be introduced by Evans' chiral auxiliaries including acylation of myristic acid **2**, asymmetric methylation of (*R*)-4-benzyl-3-tetradecanoyloxazolidin-2-one oxazolidinone



SCHEME 2 Synthesis of (*R*)- and (*S*)-13-methylheptacosane

amide ((*R*)-**3**) and the reduction of oxazolidinone amide (*R*)-**4**. (*S*)-13-methylheptacosane ((*S*)-**1**) could be obtained following the similar approach using (*S*)-4-benzyloxazolidin-2-one.

As outlined in Scheme 2, our synthetic sequence began with the reaction of myristic acid **2** with oxalyl chloride to provide tetradecanoyl chloride.[16] The subsequent acylation with (*R*)-4-benzyloxazolidin-2-one (>99% ee) afforded (*R*)-4-benzyl-3-tetradecanoyloxazolidin-2-one ((*R*)-**3**) in 94% yield.[17] Deprotonation of chiral oxazolidinone amide (*R*)-**3** with hexamethyldisilazide (NaHMDS) in THF, followed by diastereoselective methylation with iodomethane gave oxazolidinone amide (*R*)-**4** in 85% yield and with >99% ee.[18,19] DSC thermograms and NMR spectra showed that (*R*)-**4** was diastereomerically pure. The governing precedents of Evans' chiral auxiliaries favored the absolute configuration of new stereocenter at the C2 position of (*R*)-**4** as (*R*).[20] The chiral auxiliary was then removed with simultaneous reduction using $NaBH_4$ provided (*R*)-2-methyltetradecan-1-ol ((*R*)-**5**) in 85% yield (>%99 ee, determined by ^{19}F NMR analysis of its Mosher ester).[21,22] Alcohol (*R*)-**5** was converted to primary bromide (*R*)-**6** almost quantitatively by treating with PPh_3 and CBr_4.[23] Finally, the Wittig reaction[24] of phosphonium salt (*R*)-**7** derived from hydrocarbon bromide (*R*)-**6**[25] with *n*-tridecanal and followed hydrogenation reduction gave the target sex pheromone (*R*)-**1**.[26] The specific rotation and NMR spectrum of (*R*)-**1** were consistent with the literature data.[11]

Similarly, the acylation of (*S*)-4-benzyl-2-oxazolidinone (>99% ee) with tetradecanoyl chloride derived from myristic acid **2** provided oxazolidinone amide (*S*)-**3** in 97% yield. The following asymmetric methylation and reduced cleavage of the chiral auxiliary resulted in the formation of chiral alcohol (*S*)-**5** (>99% ee, determined by ^{19}F NMR analysis of its Mosher ester). The final bromination, Wittig coupling, and hydrogenation afforded (*S*)-13-methylheptacosane ((*S*)-**1**). Its specific rotation $\{[\alpha]_D^{20} = +0.13$ ($c = 3.02$ in $CHCl_3$)$\}$ was identical to the literature value $\{[\alpha]_D^{24} = +0.121$ ($c = 5.16$ in $CHCl_3$)$\}$, while its NMR spectrum matched the data of (*S*)-**1** synthesized by Mori.[11]

Because there was no step to cause racemization at C-13, the synthetic enantiomers of 13-methylheptacosane were considered to be >99% ee, which were consistent with compounds **4** and **5** and the chiral auxiliaries.

4 | CONCLUSION

In summary, we have completed an efficient and gram-scale synthesis of (*R*)- and (*S*)-13-methylheptacosane, the sex pheromone of pear psylla. Central to our approach were Evans' chiral auxiliaries and Wittig coupling of chiral phosphonium salt with aldehyde. The sex pheromones synthesized herein were valuable for the pest management of pear psylla.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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