Note

Synthesis of Both Enantiomers of 15-Hexadecanolide, a Sex Pheromone Component of the Stink Bug, Piezodus kybneri

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Both enantiomers of 15-hexadecanolide, a sex pheromone component of the stink bug (Piezodus kybneri), were synthesized by using the Yamaguchi or Mitsunobu macrolactonization reaction of (R)-15-hydroxyhexadecanoic acid prepared from ethyl (R)-β-hydroxybutyrate in 5 steps.

Key words: 15-hexadecanolide; sex pheromone; stink bug; Piezodus kybneri; macrolactonization

Leal et al. have recently reported the isolation and structural elucidation of the male-released sex pheromone of the stink bug, Piezodus kybneri, a notorious pest of legumes such as soybeans and kidney beans. They revealed, by investigating the airborne volatiles of the male bugs, the pheromone to be a mixture of three components: β-sesquiphellandrene, (R)-15-hexadecanolide, and methyl (Z)-8-hexadecenoate in a ratio of 10:4:1. The (R)-absolute configuration of the second pheromone component, 15-hexadecanolide, was established by comparing its biological activity and GLC retention time in a chiral capillary column with those of synthetic (R)- and (S)-15-hexadecanolides, (R)- and (S)-1 (Scheme). Both of the synthetic samples supplied by us were prepared from a common seco-acid (4) by using three types of macrolactonization procedure involving the retention or inversion of the configuration at the 15-hydroxy position of 4. In this note, we describe in detail our syntheses of (R)- and (S)-1.

In order to obtain the common precursor (4) leading to (R)-1 or (S)-1, ethyl (R)-β-hydroxybutyrate was chosen as the starting material. After its protection (TBSCI, imidazole, DMF, 95% yield) and reduction (DIBAL, toluene, 70% yield), the resulting aldehyde (2) was subjected to a Wittig reaction with the potassium salt of (11-carboxyundecylidene)triphenylphosphorane to give 3a, the TBS group of which was then deprotected by treating with aqueous hydrofluoric acid in acetonitrile to afford 3b as a crystalline solid on a 70% yield from 2. The double bond of 3b was saturated by catalytic hydrogenation to give common intermediate 4 as colorless crystals. Macrolactonization of 4 under Yamaguchi’s conditions afforded (R)-1 in an 84% yield, [α]D −18.2° (c 1.20, hexane). On the other hand, submission of 4 to Mitsunobu's macrolactonization, which is known to proceed with an inversion of configuration of the hydroxy-bearing stereogenic center, gave (S)-1 in a 31% yield, [α]D +18.7° (c 1.00, hexane). The 1H-NMR spectral data for the synthetic samples were virtually identical with those of an authentic sample of (R)-hexadecanolide which had previously been isolated as a constituent of galbanum resin and synthesized by Bestmann and Kellermann in a different manner.

Chiral capillary GLC analyses of the synthetic samples showed both of them to be optically pure.

Scheme Syntheses of (R)- and (S)-Hexadecanolides.

Experimental

IR spectra were measured as films for oils or as KBr discs for solids with a JASCO FT/IR-5000 spectrometer. 1H-NMR spectra were recorded with TMS as an internal standard in CDCl3 by a JEOL JNM-A500 spectrometer. High-resolution mass spectra (70 eV) were

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Abbreviations: TBSCI, t-butyldimethylsilyl chloride; DMF, N,N-dimethylformamide; DIBAL, diisobutylaluminum hydride.
measured with a Shimadzu GCMS 9020-DF spectrometer, and optical rotation values were measured with a JASCO DIP-370 polarimeter. Tetrahydrofuran was purified by distilling from benzophenone ketyl. Merck Kieselgel 60 Art 7734 was used for silica gel column chromatography.

(11-Carboxyundecyl)triphenylophosphonium bromide. This phosphonium salt was prepared according to the procedure employed by Dawson and Vasser for the preparation of (7-carboxyheptyl)triphenylophosphonium bromide. A solution of commercially available 12-bromododecanolic acid (0.300 g, 1.07 mmol) and triphenylphosphine (0.280 g, 1.07 mmol) in acetonitrile (3 ml) was stirred at reflux for 64 h and then concentrated in vacuo to give the crude phosphonium salt as a sticky oil. This was mixed with ether and stirred for a few minutes. The supernatant as an etherereal solution was removed, and the residual oil was dried in vacuo and employed for the next step without further purification.

(R, Z)-15-Hydroxy-12-hexadecenoic acid (3b). To a solution of the phosphonium salt (0.52 g, 0.96 mmol) just prepared in tetrahydrofuran-hexamethylphosphoramide triamide (4:1, 5 ml) was added dropwise a solution of potassium bis(trimethylsilyl)amide in toluene (0.5 m solution, 3.70 ml, 1.83 mmol) over 30 min while cooling with a water bath. After 40 min, aldehyde 2 (1.5 g, 22.5 g, 3.13, hexane) was added dropwise, and the resulting mixture was stirred for 50 min at room temperature. The reaction mixture was acidified with a solution of oxalic acid (0.160 g, 1.78 mmol) in water and extracted with ether. The ether solution was successively washed with water and brine, dried (MgSO₄) and concentrated in vacuo to give 0.79 g of crude 3a, which was then dissolved in acetonitrile (2 ml). To this solution was added 46% hydrofluoric acid (0.110 ml, 3.45 mmol), and the mixture was stirred for 30 min at room temperature. The reaction mixture was adjusted to pH 10–11 with 2 m NaOHaq. and water, and extracted with ether. The aqueous layer was acidified with oxalic acid and extracted with ether. The ether solution was dried (MgSO₄) and concentrated in vacuo. The residue was purified by silica gel chromatography (0 g, hexane-ethyl acetate, 3:2) and recrystallization (hexane-ether, 25:1) to give 0.52 g (70%) of 3b as a colorless microcrystalline solid, mp 49–50°C, [α]Dº+ 4.59° (c 1.13, 95% ethanol). IR νmax cm⁻¹: 3410 (m), 3030 (w), 2920 (s), 2860 (s), 2670 (w), 1700 (s). 1H-NMR δ: 1.21 (3H, d, J=6.3 Hz, 16-H), 1.25–1.37 (14H, m, 4-10-H), 1.63 (2H, q, J=7.3 Hz, 3-H₂), 2.05 (2H, br q, J=7.1 Hz, 11-H₂), 2.15–2.21 (1H, m, 14-H), 2.23–2.29 (1H, m, 14-H), 2.34 (2H, t, J=7.3 Hz, 2-H), 3.84 (1H, ddq, J=7.2, 5.3, 6.3 Hz, 15-H), 5.36–5.42 (1H, m, CH=CH), 5.56 (1H, dt, J=11.0, 7.4, 1.5 Hz, CH=C). HRMS m/z (M+H+O): calcd. for C₁₆H₃₅O₂, 252.2088; found, 252.2069.

(S)-15-hexadecanolide [(S)-1]. To a solution of 4 (0.100 g, 0.368 mmol) and triethylamine (62.0 µl, 0.442 mmol) in tetrahydrofuran (1.4 ml) was added dropwise 2,4,6-trichlorobenzoyl chloride (60.0 µl, 0.386 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was diluted with toluene (170 ml), and the supernatant solution was transferred to a dropping funnel. The solution was added dropwise over 14 h to a solution of 4-(N,N-dimethylinamino)pyridine (0.290 g, 2.36 mmol) in toluene (60 ml) at 100°C. After being stirred for an additional 3 h, the reaction mixture was successively washed with 0.5 m HCl aq. (50 ml), sat. NaHCO₃ and brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane-ether, 50:1) to give 0.078 g (84%) of (R)-1, [α]Dº−18.2° (c 1.20, hexane), IR νmax cm⁻¹: 2930 (s), 2860 (s), 1735 (s), 1460 (w), 1375 (w), 1340 (w), 1260 (m), 1205 (m), 1180 (m), 1130 (m), 1110 (m), 790 (w). 1H-NMR δ: 1.22 (3H, d, J=6.3 Hz, 16-H), 1.25–1.42 (20H, m, 4-13-H₂), 1.47–1.63 (3H, m, 3-H, 14-H₂), 1.67–1.76 (1H, m, 3-H), 2.28 (1H, ddd, J=6.1, 6.8, 14.5 Hz, 2-H), 2.32 (1H, ddd, J=6.3, 8.3, 14.5 Hz, 2-H), 4.93–4.99 (1H, m, 15-H). HRMS m/z (M⁺): calcd. for C₁₆H₃₆O₂, 254.2244; found, 254.2237.

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