**Synthesis of Japonilure, the Pheromone of Japanese Beetle**

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Japonilure ([4R,5Z]-5-tetradecen-4-olide) 1 is the pheromone produced by the female of the Japanese beetle, *Popillia japonica*. This beetle is a notorious pest of a variety of trees, crops, and lawns all over the world. Tuminson *et al.* reported the pheromone activity of Japonilure 1 against male Japanese beetle was strongly inhibited by its enantiomer. That is, optical purity is most important in synthesis of this pheromone. There have been several reports about the synthesis of 1 to date.† ‡ The drawback in most of those syntheses was that the optical yield was not satisfactory. We decided to develop an alternative synthetic route to optically pure 1.

We report here a novel synthesis of 1 starting from o-rubose. This was subjected to preferential acetal formation by Stiller’s procedure to give 2.† This was reacted with heptylidenetriphenylphosphorane to give a syrupy 3a as a geometrical mixture (E:Z = 7:3) in an 85% yield. The corresponding tosylate 3b was treated with sodium hydride to give an epoxide 4 in an 88% yield. Treatment of 4 with the dibutyl salt of phenylthioacetic acid, followed by lactonization,†‡ gave the corresponding 2-phenylthio lactone 5 in a 62% overall yield. Reductive desulfurization and hydrogenation of the C=C double bond were done at the same time by treatment of 5 with Raney nickel under a hydrogen atmosphere to give 6 in a 73% yield. Conversion from 6 to 1 proceeded in a same manner reported by NISHIDA *et al.*.** Comparison of the reported of the specific rotation of 1†‡† with that of ours suggested our synthetic pheromone to be 100% optically pure.

In summary, Japonilure 1 was synthesized from o-rubose in an optically pure state.

**Experimental**

All nmr's were uncorrected. IR spectra were measured on a Jasco FT/IR 5000 spectrometer. 1H-NMR (300 MHz) and 13C-NMR (75 MHz) spectra were recorded with TMS as an internal standard on a Brucker AC-300P spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter.

**Chemical Reactions**

1. **(2R,3R,4S)-5-tetradecen-1-olide 3a.**

   - Reaction of 3a with diethylamine under basic conditions to give 4.

2. **(2S,3R,4S)-2-Hydroxy-3,4-(isopropylidenedioxy)-5-dodecenyloxy tosylate 3b.**

   - Treatment of 3b with sodium hydride to give an epoxide 4 in an 88% yield.

3. **(2R,3R,4S)-2-Epoxy-3,4-(isopropylidenedioxy)-5-dodecene 4.**

   - Reaction of 4 with sodium hydride under basic conditions to give 6.

   - Conversion from 6 to 1 proceeded in a same manner reported by NISHIDA *et al.*

4. **(2R,3R,4S)-2-Epoxy-3,4-(isopropylidenedioxy)-5-dodecene 4.**

   - Reaction of 4 with sodium hydride under basic conditions to give 6.

   - Conversion from 6 to 1 proceeded in a same manner reported by NISHIDA *et al.*

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2930 (s), 2860 (m), 1245 (m), 1218 (s), 1054 (s). 1H-NMR (CDCl₃) δ: 0.88–0.93 (3H, m), 1.23–1.55 (14H, m), 2.04–2.19 (2H, m), 2.66–2.71 (1H, m), 2.79–2.84 (1H, m), 2.95–3.01 (1H, m), 3.75 (1H, t, J = 6.7 Hz), 4.70 (0.7H, t, J = 7.2 Hz), 5.06 (0.3H, ddd, J = 0.9, 6.4 and 8.8 Hz), 5.53–5.66 (1H, m), 5.73–5.82 (0.3H, m), 5.91 (0.7H, dt, 6.8 and 15.3 Hz). Anal. Found: C, 70.55; H, 10.25%. Calcd. for C₇₃H₆₆O₂: C, 70.83; H, 10.30%.

(2R,4R,5R,6S)-5,6-(Isopropylidenedioxy)-2-phenylthio-7-tetradecen-4-olide 5. To a stirred solution of phenylthioacetic acid (2.8 g, 17 mmol) in dry THF (40 mL) was added a solution of lithium hexamethyldisilazide (34 mL, 1M in THF, 34 mmol) at 0 °C under argon atmosphere. The mixture was allowed to attain room temperature over 1 hr. A solution of epoxide 4 (2.1 g, 8.4 mmol) in dry THF (40 mL) was added to this mixture. After stirring overnight at room temperature, the reaction mixture was poured into 1 N hydrochloric acid (15 mL) and extracted with ether. The ethereal layer was washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in dry CH₂Cl₂ (40 mL) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.1 g, 11 mmol) and 4-(dimethylamino)pyridine (40 mg) for 1 hr at room temperature. The mixture was then poured into saturated NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed over SiO₂ (Merck Kieselgel 60, 30 g). Elution with n-hexane-ethyl acetate (8:1) gave 2.1 g (62%) of 5, 8(2) 1.5283, [α]D⁻²⁻ = +22.9° (c = 1.05, CHCl₃); IR νmax 2928 (s), 2858 (m), 1781 (s), 1439 (m), 1164 (w). 1H-NMR (CDCl₃) δ: 0.85–0.95 (3H, m), 1.20–1.48 (14H, m), 1.98–2.15 (2H, m), 2.22–2.33 (1H, m), 2.59–2.75 (1H, m), 3.88–4.39 (3H, m), 4.63–4.70 (0.8H, m), 4.97–5.08 (0.2H, m), 5.25–5.47 (1H, m), 5.64–5.75 (0.2H, m), 5.77–5.88 (0.8H, m), 7.21–7.44 (3H, m), 7.53–7.62 (2H, m). Anal. Found: C, 67.96; H, 7.75%. Calcd. for C₇₃H₆₆O₂S: C, 68.28; H, 7.97%.

(4R,5S,5S)-5,6-(Isopropylidenedioxy)-tetradecan-4-olide 6. 5 (300 mg, 1.2 mmol) was stirred and heated with Raney nickel (W-2, 200 mg) in ethanol (15 mL) under hydrogen atmosphere with reflux overnight. Then the suspension was filtered through a celite pad. The filtrate was concentrated in vacuo. The residue was chromatographed over SiO₂ (Merck Kieselgel 60, 10 g). Elution with n-hexane-ethyl acetate (4:1) gave 270 mg (73%) of 6, 8(2) 1.4597, [α]D⁻²⁻ = +0.5° (c = 1.0, MeOH); [α]D⁻²⁻ = −2.87° (c = 1.05, CHCl₃); IR νmax 2928 (s), 2860 (s), 1787 (s), 1462 (m), 1373 (m), 1176 (w), 1H-NMR (CDCl₃) δ: 0.88 (3H, t, J = 6.7 Hz), 1.22–1.70 (20H, m), 2.14–2.67 (4H, m), 4.02 (1H, dd, J = 6.0 and 7.5 Hz), 4.11–4.26 (1H, m), 4.48 (1H, q, J = 7.1 Hz). Anal. Found: C, 68.02; H, 10.27%. Calcd. for C₇₃H₆₆O₂: C, 68.42; H, 10.13%.

Japonilure 1. This was prepared from 6 in the same manner as already described by Nishida et al. [α]D⁻²⁻ = −70.2° (c = 0.5, CHCl₃); IR νmax 2930 (s), 2858 (m), 1781 (s), 1462 (m), 1180 (s), 1013 (m), 980 (m), 909 (m), 1H-NMR (CDCl₃) δ: 0.88 (3H, t, J = 6.7 Hz), 1.23–1.47 (12H, m), 1.95 (1H, dddd, J = 8.2, 9.0, 9.1, and 12.6 Hz), 2.03–2.17 (2H, m), 2.38 (1H, dddd, J = 6.5, 6.5, 12.1, and 12.6 Hz), 2.52–2.61 (2H, m), 5.25 (1H, dddd, J = 0.9, 6.5, 8.3, and 9.0 Hz), 5.46 (1H, dt, J = 8.3, 10.8, and 1.5 Hz), 5.67 (1H, dt, J = 0.9, 10.8, and 7.6 Hz). 13C-NMR (CDCl₃) δ: 14.1, 22.6, 27.8, 29.0, 29.2, 29.3, 29.4, 29.4, 31.8, 76.4, 127.2, 135.1, 177.0. Found: MS (m/z) 224.1740 (M⁺). Calcd. for C₇₃H₆₆O₂: 224.1702.

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References