Synthesis of the Racemate of (Z)-exo-α-Bergamotenal, a Pheromone Component of the White-spotted Spined Bug, Eysarcoris parvus Uhler

Babak Heidary Alizadeh, Shigefumi Kuwahara, Walter Soares Leal, and Hong-Chao Men

Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, I-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan
1Honorary Maeda-Duffey Laboratory, Department of Entomology, University of California Davis, I Shields Ave., Davis, CA 95616-8585, USA
2Laboratory of Chemical Prospecting, National Institute of Sericultural and Entomological Science, 1-2 Ohwashi, Tsukuba 305-8634, Japan

Received January 7, 2002; Accepted February 4, 2002

The racemate of (Z)-exo-α-bergamotenal, a sex pheromone component of the white-spotted spined bug, was synthesized from racemic exo-α-bergamotene by a five-step sequence involving regioselective epoxidation and (Z)-selective Wittig olefination reactions. The 1H- and 13C-NMR spectra of the synthetic sample were identical with those of the natural material.

Key words: bergamotenal; sesquiterpene; pheromone; white-spotted spined bug; Eysarcoris parvus

The white-spotted spined bug (Eysarcoris parvus Uhler) is a notorious pest to many agricultural crops, especially for rice production in Japan. A few years ago, we reported the presence of the male-specific sex pheromone of the stink bug consisting of three components,1,2 and quite recently, the structure of one of these components was proposed to be (Z)-exo-α-bergamotene (I) from analyses of its IR, MS, and NMR data (Leal, W. S., Men, H.-C., Kuwahara, S., Hasegawa, M., manuscript in preparation). Although this aldehyde (I) had been prepared for use in perfumery from (Z)-exo-α-bergamotanol (8) contained in sandalwood essential oil,3,4 our literature survey revealed I to be a new naturally occurring compound. From the standpoint of chemical ecology, it is worth mentioning that structurally related endo-bergamotane-type sesquiterpenes (9 and 10) have been isolated from wild tomato leaves (Lycopersicon hirsutum) as components of the oviposition stimulant of the corn earworm (Heliothis zea).5,7 To the best of our knowledge, however, the isolation of I from the stink bug is the first example of obtaining bergamotane-type natural products from non-plant sources, except for the case of which α-trans-bergamotol acetate was obtained as a volatile metabolite from Caribbean coral of the genus Gorgonia, although the geometry of the double bond was not specified.8 This unique finding prompted us to embark on the synthesis of I to confirm the proposed structure and to supply a sufficient amount of the sample for biological studies. To begin with, we report in this note the synthesis of the racemate of I.

Known bicyclic ketone 3a,9,10 which had been prepared from farnesic acid chloride (2) via [2+2] cycloaddition of an intermediary vinlyketene, was first treated with hydrazine in acetic acid to give the corresponding hydrazone (3b).9 According to Corey’s method,9 this hydrazone (3b) was exposed to basic conditions (tert-BuOK, DMSO) to obtain Δ2,15-olefinic hydrocarbon 4a (exo-β-bergamotene), which is known to be convertible into the corresponding Δ2,1,olefin (4b, exo-α-bergamotene) by treating with hydriodic acid in benzene.11 To our surprise, however, this Wolff-Kishner reduction directly gave the thermodynamically more stable Δ2,15-product (4b) almost exclusively (4a:4b = ca. 1:27) instead of 4a which had previously been obtained by Corey and Desai.5 The double bond migration from the Δ2,15- to the Δ2,3-position is considered to be ascribable to the reaction time and temperature applied, since 3b was treated with potassium tert-butoxide in DMSO for 12 h at room temperature in the preceding experiment,9 while in our case, the hydrazone (3b) was exposed to basic conditions for a longer period (30 h) at a higher temperature (65°C). In order to confirm this presumption, the reduction was repeated by using exactly the same conditions as those reported in the literature.9 Under these condi-

---

1 To whom correspondence should be addressed. Phone & Fax: +81-22-717-8783; E-mail: skuwahar@biochem.tohoku.ac.jp
4 Present address: Experiment & Research Center, Japan Applied Microbiology Research Institute Co. LTD, Yamanashi Business Park D-3, Nitaanda 326-9, Otooguro, Tamaho-cho, Nakagoma, Yamanashi 409-3812, Japan
proceeded regioselectively to give a mixture of chloroperbenzoic acid. Fortunately, this oxidation around the selectivity was probably due to steric hindrance bis-epoxidation product 5. DMSO at 60°C for 28 h, it was gradually trans-,

.5.18–5.23 (1H, m, 3-H); HREIMS \( \text{m/z} \): calcd. for C15H24, 204.1878; found, 204.1881. The \( \text{H}-\text{NMR} \) spectral data of 4a were identical with those reported in the literature.11)

The epoxide ring \( \text{D} \) into the 2,3-double bond of \( \text{D} \), which was then exposed to \( \text{D} \)-selective Wittig olefination conditions2) to give 7 in an 83% yield after chromatographic purification. This ester (7) was reduced with diisobutylaluminum hydride to afford allylic alcohol 8. Finally, oxidation of 8 with manganese dioxide completed the synthesis of (±)-1. The \( \text{H}-\text{and} \) \( \text{C}-\text{NMR} \) spectra of the synthetic sample were identical to those of the natural pheromone component. The synthesis of 1 in an optically active form is now underway to determine the absolute configuration of 1.

**Experimental**

IR spectra were measured with a Jasco IR Report-100 spectrometer. \( \text{H}-\text{NMR} \) spectra were recorded with a Varian Gemini 2000 (300 MHz) spectrometer in CDCl3 with tetramethydsilane as an internal standard, unless otherwise stated. Mass spectra were recorded with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

\( \text{(1R\text{*},5R\text{*},6S\text{*})-2,6-Dimethyl-6-(4-methyl-3-pentenyl)bicyclo[3.1.1]hept-2-ene (4b).} \) To a stirred solution of 3a (1.41 g, 6.47 mmol) and acetic acid (0.55 ml, 9.61 mmol) in absolute ethanol (97 ml) was added anhydrous hydrazine (1.24 g, 38.7 mmol), and the mixture was stirred at 30°C for 48 h. The mixture was then diluted with ether (300 ml), and the resulting ethereal solution was successively washed with 1 M NaOH aq. and brine, dried (MgSO4) and concentrated in vacuo to give 1.70 g of crude 3b as a yellow oil; IR \( \nu_{\text{max}} \text{cm}^{-1} : 3350 (m), 3070 (w), 1690 (m), 1640 (m). \) As described in the text, compound 3b was converted into a 1:27 mixture of 4a and 4b in a 42% yield by treating with potassium tert-butoxide in DMSO for 30 h at 65. However, by raising the reaction temperature to 85°C, the reaction time could be shortened to 15 h, and the chemical yield of 4b was improved to 52%, while the ratio of 4a and 4b (1:27) was maintained, as shown in the following description. Crude hydrazone 3b (1.70 g) was dissolved in DMSO (64 ml), and potassium tert-butoxide (7.89 g, 70.3 mmol) was added to the solution. The mixture was stirred at 85°C for 15 h, and then diluted with pentane (400 ml). The pentane solution was successively washed with 1 M HCl aq. and brine, dried (MgSO4) and concentrated in vacuo to give 0.680 g (52%) of 4b and 0.025 g (2%) of 4a. 4b: \( \text{Rf} = 0.78 \) [Merck silica gel 60 F254 (No. 5715), developed with hexane]; IR \( \nu_{\text{max}} \text{cm}^{-1} : 3020 (w), 2920 (s), 1465 (m), 1375 (m), 1215 (w), 1120 (w), 1085 (w), 1015 (w), 890 (w), 790 (m); \( \text{H}-\text{NMR} \) \( \delta : 0.83 (3H, s, 6-\text{CH}_3) \), 1.17 (1H, d, \( J = 8.5 \text{ Hz} \), 7-H), 1.58–1.74 (2H, m, 1’-H), 1.63 (3H, br s, 4’-CH3), 1.66 (3H, q, \( J = 1.7 \text{ Hz} \), 2-CH3), 1.70 (3H, br s, 4’-CH3), 1.91–2.06 (3H, m), 2.08–2.19 (2H, m), 2.20–2.30 (1H, m, 4-H), 2.32 (1H, dt, \( J = 8.5, 5.8 \text{ Hz} \), 7-H), 5.17 (1H, tm, \( J = 7.1 \text{ Hz} \), 3’-H), 5.18–5.23 (1H, m, 3-H); HREIMS \( m/z \) (M+): calcd. for C15H24 204.1878; found, 204.1881. The \( \text{H}-\text{NMR} \) spectral data of 4b were identical with those reported in the literature.13)](4a): \( \text{Rf} = 0.69 \) [Merck silica gel 60 F254 (No. 5715), developed with hexane]; IR \( \nu_{\text{max}} \text{cm}^{-1} : 3070 (w), 2950 (s), 2925 (s), 2850 (s), 1640 (w),
Synthesis of (±)-(Z)-exo-α-Bergamotenal

1460 (m), 1380 (m), 880 (w); 1H-NMR δ: 0.71 (3H, s, 6-CH3), 1.42 (1H, d, J=9.9 Hz, 7-H), 1.54–1.68 (2H, m), 1.62 (3H, 4'-CH3), 1.70 (3H, s, 4''-CH3), 1.78–1.86 (2H, m), 1.89–2.09 (3H, m), 2.20–2.35 (2H, m), 2.46–2.63 (2H, m), 4.56 (1H, br s, 2-methylene), 4.62–4.64 (1H, m, 2-methylene), 5.16 (1H, tm, J=7.4 Hz, 3'-H). The 1H-NMR spectral data of 4a were identical with those reported in the literature.9)

Isomerization of 4a into 4b. A mixture of 4a (16.0 mg, 0.0784 mmol) and potassium tert-butoxide (48.0 mg, 0.428 mmol) in DMSO (1 ml) was stirred at 60°C for 28 h. The mixture was diluted with hexane and successively washed with 1 M HCl aq. and brine. The organic layer was dried (MgSO4) and concentrated in vacuo to give an oil (10 mg), whose 1H-NMR analysis revealed that the crude product was a 27:1 mixture of 4b and 4a.

(1R*,5R*,6S*)-2,6-Dimethyl-6-(4-methyl-3,4-epoxypropyl)bicyclo[3.1.1]hept-2-ene (5). To a stirred mixture of 4b (550 mg, 2.70 mmol), 0.5 m NaHCO3 aq. and dichloromethane (24 ml) was added a solution of chloroperbenzoic acid (65 mg, 0.29 mmol) in THF (24 ml) was added a solution of periodic acid (730 mg, 3.20 mmol) in THF (3 ml) was added dropwise a 1 M solution of NaH (60% in mineral oil, 77.3 mg, 1.93 mmol, washed 3 times with hexane under argon) in THF (5 ml) was added a solution of 2-((di-o-tolylphosphonopheno)propionate (500 mg, 1.44 mmol) in THF (5 ml) at 0°C, and the mixture was stirred at 15°C for 15 min. To this mixture was added dropwise a solution of 6 (220 mg, 1.23 mmol) in THF (7 ml) at –78°C. The mixture was stirred at the same temperature for 30 min, and then allowed to warm gradually to 0°C over 2 h. The mixture was poured into sat. NH4Cl aq. and extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried (MgSO4) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane-ethyl acetate, 8:1) to give 340 mg (81%) of 7. IR νmax cm⁻¹: 2975 (s), 2950 (s), 2875 (m), 1715 (vs), 1450 (m), 1370 (m), 1320 (vs), 1245 (m), 1215 (m), 1160 (m), 1105 (m), 1080 (w), 1030 (w); 1H-NMR δ: 0.84 (3H, s, 6-CH3), 1.19 (1H, d, J=1.9 Hz, 7-H), 1.29 (3H, s, 4''-CH3), 1.32 (3H, s, 4'-CH3), 1.62–1.74 (2H, m, 1'-H), 1.65 (3H, q, J=1.9 Hz, 2-CH3), 1.88–2.06 (3H, m), 2.08–2.18 (2H, m), 2.20–2.32 (1H, m, 4-H), 2.32 (1H, dt, J=8.5, 5.8 Hz, 7-H), 2.74 (1H, t, J=6.2 Hz, 3'-H), 5.21 (1H, br s, 3-H); HREIMS m/z (M⁺): calcd. for C17H26O2, 262.1933; found, 262.1935.

Ethyl (Z)-5-[(1R*,5R*,6S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-2-methyl-2-pentenoate (8). To a stirred suspension of NaH (60% in mineral oil, 77.3 mg, 1.93 mmol, washed 3 times with hexane under argon) in THF (5 ml) was added a solution of 7 (220 mg, 1.23 mmol) in THF (5 ml) at 0°C, and the mixture was stirred at 15°C for 15 min. To this mixture was added dropwise a solution of 6 (220 mg, 1.23 mmol) in THF (7 ml) at –78°C. The mixture was stirred at the same temperature for 30 min, and then allowed to warm gradually to 0°C over 2 h. The mixture was poured into sat. NH4Cl aq. and extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried (MgSO4) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane-ethyl acetate, 10:1) to give 270 mg (83%) of 7. IR νmax cm⁻¹: 2975 (s), 2950 (s), 2920 (vs), 2875 (s), 1715 (vs), 1450 (m), 1370 (m), 1220 (s), 1180 (s), 1160 (m), 1105 (m), 1080 (w), 1030 (w); 1H-NMR δ: 0.84 (3H, s, 6-CH3), 1.19 (1H, d, J=8.5 Hz, 7'-H), 1.30 (3H, t, J=7.1 Hz, O-C-CH3), 1.65 (3H, q, J=1.6 Hz, 2'-H), 1.65–1.75 (2H, m, 5'-H), 1.90 (3H, d, J=1.1 Hz, 2'-CH3), 2.01 (1H, br t, J=5.6 Hz, 1'-CH), 2.08–2.18 (2H, m), 2.20–2.32 (1H, m), 2.32 (1H, dt, J=8.5, 5.6 Hz, 7'-H), 2.40–2.52 (2H, m), 4.21 (2H, q, J=7.1 Hz, O-H), 5.18–5.23 (1H, m, 3'-H), 5.98 (1H, t, J=7.4, 1.1 Hz, 3'-H); HREIMS m/z (M⁺): calcd. for C17H26O2, 262.1933; found, 262.1935.

(±)-(1R*,5R*,6S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-ylpropional (6). To a stirred solution of 5 (520 mg, 2.36 mmol) in THF (3 ml) was added dropwise a solution of periodic acid (730 mg, 3.20 mmol) in water (1.9 ml) at 0°C. After 2 h, the reaction mixture was quenched with water (1.3 ml) and filtered through a Celite pad. The filtrate was dried over MgSO4 and concentrated in vacuo. The residue (66.3 mg) was chromatographed over silica gel (30 g, hexane-ethyl acetate, 10:1) to give 52.0 mg (99.7%) of 8. IR νmax cm⁻¹: 3310 (m), 3010 (w), 2950 (s), 2910
(Z)-5-(1R*,5R*,6S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl-2-methyl-2-pentenal (I). A mixture of 8 (38.0 mg, 0.173 mmol) and manganese dioxide (38.0 mg, 0.173 mmol) and manganese dioxide (chemically treated, purchased from Wako Pure Chemical Industries, 0.31 g, 3.6 mmol) in dry hexane (7 ml) was stirred at 0°C for 24 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue (49 mg) was chromatographed over silica gel (18 g, hexane-ethyl acetate, 10:1) to give 37.4 mg (99% yield) of *Z*-cis-6-oxo-6,7-dihydro-2-(2-methylpentyl)chromone (9).

The 1H-NMR spectrum of 9 was identical with that reported in the literature. 3

Acknowledgments

This work was supported, in part, by grant-aid for scientific research (C) from the Ministry of Education, Science, Sports and Culture, Japan (No. 13660103). We are grateful to Ms. T. Yamada (Tohoku University) for measuring the mass spectra.

References


