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Note

Simple Synthesis of the Major Sex Pheromone Components of *Drosophila ananassae* and *D. pallidosa*

Akira MORITA,[1] Shigeru MATSUYAMA,[2] Yuzuru OGUMA,[3] and Shigefumi KUWAHARA[1,†]

[1]*Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan*
[2]*Institute of Applied Biochemistry, University of Tsukuba, Tsukuba, Ibaraki 305-8572, Japan*
[3]*Division of Structural Biosciences, Graduate School of Life and Environmental Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8572, Japan*

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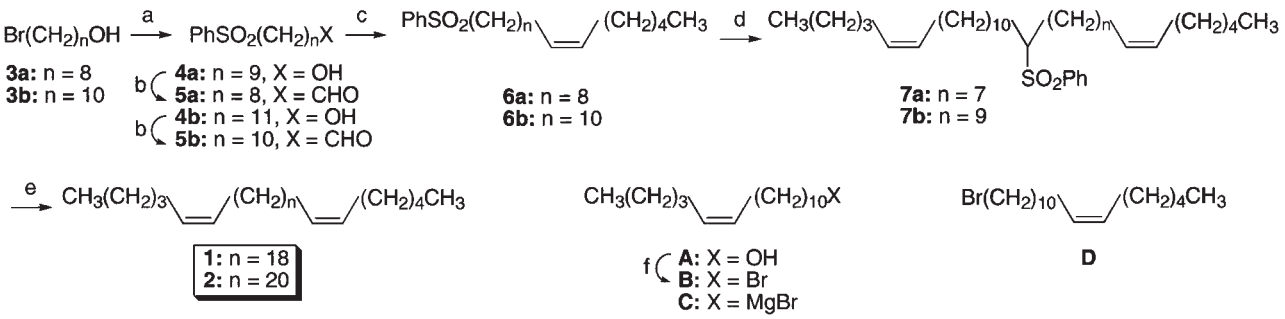
The major sex pheromone components of *Drosophila ananassae* and *D. pallidosa*, (*Z*,*Z*)-5,25-hentriacontadiene and (*Z*,*Z*)-5,27-tritriacontadiene, respectively, were synthesized by using the Wittig olefination and sulfone coupling reactions as the C–C bond-forming steps.

Key words: pheromone; *Drosophila ananassae*; *Drosophila pallodosa*; fruit fly

Two closely related fruit flies, *Drosophila ananassae* and *D. pallidosa*, are known to be sympatric but to show no postmating isolation.[1,2)] The difference in the courtship song between the two species has recently been revealed to play a crucial role in premating sexual isolation between them,[3)] and the genetic background of the difference in the courtship song has gradually been elucidated.[4)] On the other hand, two long-chain alkadienes, (5*Z*,25*Z*)-5,25-hentriacontadiene (**1**) and (5*Z*,27*Z*)-5,27-tritriacontadiene (**2**) (Scheme 1), are known as the major sex pheromone components in female cuticular extracts of *D. ananassae* and *D. pallidosa*, respectively, and the difference in the contents of the two components is also considered to be a key factor in premating isolation between the two species.[1,2)] It is now expected that the identification of genes controlling the pheromone production and recognition could provide a genetic basis for sexual isolation, leading eventually to understanding the mechanism of speciation.[5)] To promote such studies by using a model system composed of the two sympatric sibling species, the supply of sufficient amounts of the pheromone samples (**1** and **2**) is badly needed, which prompted us to develop a simple synthetic route to **1** and **2**.

The synthesis of **1** and **2** has previously been reported in brief without any experimental details by Nemoto *et al.*[1,2)] They employed the Grignard coupling reaction of **C** and **D** as the final step in the synthesis of **2**, which brought about undesirable homo-coupled hydrocarbon byproducts, making them use labor-intensive preparative GLC to purify the final product.[1)] With this in mind, we planned our synthesis of **1** and **2** as shown in Scheme 1. In order to obtain **1**, bromoalcohol **3a**[6)] was converted, without protecting its hydroxyl group, into sulfone **4a** by treating with the anion derived from methyl phenyl sulfone.[7)] The Swern oxidation of **4a** to



Scheme 1. Reagents: a) $PhSO_2Me$, *n*-BuLi, THF–HMPA (97% for **4a**, 88% for **4b**); b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (quant. for **5a**, 99% for **5b**); c) $Ph_3P(CH_2)_5Me{\cdot}Br$, KHMDS, THF–HMPA (92% for **6a**, 91% for **6b**); d) *n*-BuLi, **B**, THF–HMPA (70% for **7a** and 62% for **7b**); e) SmI_2, THF–HMPA (74% for **1**, 76% for **2**); f) Br_2, Ph_3P, Py, CH_2Cl_2 (96%).

† To whom correspondence should be addressed. Tel/Fax: +81-22-717-8783; E-mail: skuwahar@biochem.tohoku.ac.jp

aldehyde **5a** was followed by exposure to *Z*-selective Wittig olefination conditions[8] to afford olefin **6a**, whose geometrical homogeneity was checked by its ^{13}C-NMR spectrum, in which no peak other than those assignable to **6a** was observed. The coupling of sulfone **6a** and bromide **B**,[9] which had been prepared by $LiAlH_4$-reduction of commercially available (*Z*)-11-hexadecenal (Aldrich, >95% purity) and subsequent bromination of the resulting alcohol (**A**), gave **7a** possessing all the carbon atoms and appropriately arranged double bonds for **1**. Reductive removal of the sulfonyl moiety was first attempted by treating **7a** with an excess amount of lithium in ethylamine at −15 °C for 1 hour.[7] This reduction method, however, brought about partial over-reduction, giving substantial amounts of two corresponding monoene products. Eventually, the reductive elimination reaction was effected cleanly with samarium(II) iodide in THF–HMPA[10] to furnish **1** in a 74% yield after SiO_2–$AgNO_3$ chromatographic purification. By following the same five-step sequence of reactions, **2** was obtained from **3b** *via* **4b**, **5b**, **6b** and **7b**. The overall yields of **1** and **2** were 46% and 37%, respectively.

Experimental

IR spectra were measured as films by a Jasco IR Report-100 spectrometer. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer (300 MHz) or a Varian UNITYplus-500 spectrometer (500 MHz). GLC analyses were performed on a Hewlett-Packard 6890 gas chromatograph. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography.

*9-Benzenesulfonyl-1-nonanol (**4a**).* To a stirred solution of methyl phenyl sulfone (2.25 g, 14.4 mmol) in THF–HMPA (10:1, 66 ml) was added dropwise a solution of butyllithium in hexane (1.6 M, 9.0 ml, 14.4 mmol) at −78 °C. After 30 min, a solution of **3a** (0.995 g, 4.76 mmol) in THF (10 ml) was added, and the resulting mixture was warmed gradually to room temperature over 8 h. The mixture was poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (40 g; hexane–ethyl acetate, 10:1) to give 1.31 g (97%) of **4a** as a white solid, recrystallization of which from hexane-ethanol afforded colorless flakes, mp 44.5–45.5 °C; IR ν_{max} cm^{-1}: 3325 (s), 1580 (m), 1300 (s), 1140 (s); ^{1}H-NMR (300 MHz) δ: 1.20–1.40 (10H, m), 1.55 (2H, qui, J = 7.1 Hz), 1.66–1.76 (2H, m), 3.05–3.15 (2H, m), 3.64 (2H, t, J = 6.3 Hz), 7.55–7.94 (2H, m), 7.64–7.70 (1H, m), 7.90–7.94 (2H, m); HR-FABMS m/z ([M + H]$^+$): calcd. for $C_{15}H_{25}O_3S$, 285.1525; found, 285.1529.

*9-(Benzenesulfonyl)nonanal (**5a**).* To a stirred solution of oxalyl chloride (0.482 g, 3.80 mmol) in dichloromethane (30 ml) was added dropwise a solution of DMSO (0.605 g, 7.75 mmol) in dichloromethane (6 ml) at −78 °C. After 10 min, a solution of **4a** (0.804 g, 2.83 mmol) in dichloromethane (8 ml) was added, and the mixture was stirred for 30 min. To this mixture was then added Et_3N (2.0 ml, 14.4 mmol), and the resulting mixture was gradually warmed to room temperature, poured into water and extracted with ether. The ethereal solution was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (20 g; hexane–ethyl acetate, 3:1) to give 0.797 g (quant.) of **5a**; IR ν_{max} cm^{-1}: 3050 (w), 3000 (m), 2715 (m), 1712 (s), 1300 (s), 1140 (s); ^{1}H-NMR (300 MHz) δ: 1.22–1.42 (8H, m), 1.60 (2H, qui, J = 7.3 Hz), 1.65–1.77 (2H, m), 2.41 (2H, dt, J = 1.8, 7.4 Hz), 3.04–3.11 (2H, m), 7.55–7.61 (2H, m), 7.64–7.70 (1H, m), 7.90–7.93 (2H, m), 9.76 (1H, t, J = 1.8 Hz); HR-FABMS m/z ([M + H]$^+$): calcd. for $C_{15}H_{23}O_3S$, 283.1368; found, 283.1372.

*(Z)-15-Benzenesulfonyl-6-pentadecene (**6a**).* To a stirred suspension of hexyltriphenylphosphonium bromide (0.456 g, 1.07 mmol) in THF–HMPA (3:1, 8 ml) was added dropwise a solution of potassium hexamethyldisilazide (KHMDS) in toluene (0.7 M, 1.50 ml, 1.05 mmol) at 0 °C. After 30 min, a solution of **5a** (0.221 g, 0.713 mmol) in THF (4 ml) was added at −78 °C, and the mixture was stirred for 30 min. The reaction mixture was gradually warmed to room temperature, poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (5 g; hexane–ethyl acetate, 5:1) to give 0.252 g (94%) of **6a**; IR ν_{max} cm^{-1}: 3050 (w), 2990 (m), 1580 (w), 1300 (s), 1140 (s); ^{1}H-NMR (300 MHz) δ: 0.88 (3H, t, J = 6.9 Hz), 1.20–1.40 (16H, m), 1.65–1.76 (2H, m), 1.95–2.04 (4H, m), 3.05–3.11 (2H, m), 5.28–5.40 (2H, m), 7.54–7.61 (2H, m), 7.64–7.70 (1H, m), 7.90–7.94 (2H, m); ^{13}C-NMR (125 MHz) δ: 14.07, 22.56, 22.60, 27.11, 27.15, 28.24, 28.96, 29.06, 29.11, 29.41, 29.61, 31.50, 56.29, 128.04, 129.23, 129.67, 130.02, 133.58, 139.19; HR-EIMS m/z (M$^+$): calcd. for $C_{21}H_{34}O_2S$, 350.2279; found, 350.2279.

*(Z)-16-Bromo-5-hexadecene (**B**).* To a stirred solution of triphenylphosphine (0.349 g, 1.33 mmol) in dichloromethane (4 ml) was added dropwise bromine (0.156 g, 0.976 mmol) at −30 °C. After 30 min, a solution of **A** (0.201 g, 0.836 mmol) and pyridine (0.10 ml, 1.24 mmol) in dichloromethane (5 ml) was added dropwise, and the reaction mixture was gradually warmed to room temperature. The mixture was concentrated *in vacuo*, diluted with pentane and filtered. The filtrate was concentrated *in vacuo*, and the residue was chromatographed over silica gel (5 g, hexane) to give 0.243 g (96%) of **B**; IR ν_{max} cm^{-1}: 3000 (m), 1650 (w), 720 (m), 661 (m), 641 (m); ^{1}H-NMR (300 MHz) δ: 0.90 (3H, t, J = 7.2 Hz), 1.25–1.46 (18H, m), 1.86 (2H, qui, J = 7.0 Hz), 1.97–2.06 (4H, m), 3.41 (2H, t, J = 7.0 Hz), 5.30–5.41 (2H, m); ^{13}C-NMR (125 MHz) δ: 13.99, 22.34, 26.90, 27.17, 28.16, 28.76, 29.26, 29.42, 29.47, 29.49, 29.74, 31.95, 32.82, 34.06, 129.84, 129.86; HR-EIMS m/z (M$^+$):

calcd. for $C_{16}H_{31}{}^{79}Br$, 302.1809; found, 302.1615.

*(5Z,25Z)-17-Benzenesulfonyl-5,25-hentriacontadiene (**7a**).* To a stirred solution of **6a** (0.214 g, 0.610 mmol) in THF–HMPA (30:1, 6.3 ml) was added dropwise a solution of butyllithium in hexane (1.6 M, 0.385 ml, 0.616 mmol) at −78 °C. One minute after the addition, a solution of **B** (0.145 g, 0.478 mmol) in THF (3 ml) was added, and the resulting mixture was gradually warmed to room temperature, poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (5 g; hexane–ethyl acetate, 200:1) to give 0.193 g (70%) of **7a** together with 40 mg of **6a** and 34 mg of **B**; IR ν_{max} cm^{-1}: 3050 (w), 3000 (w), 1300 (m), 1140 (m); ^{1}H-NMR (300 MHz) δ: 0.89 (3H, t, $J = 7.1$ Hz), 0.90 (3H, t, $J = 7.1$ Hz), 1.18–1.36 (36H, m), 1.49–1.62 (2H, m), 1.76–1.88 (2H, m), 1.93–2.07 (2H, m), 2.89 (1H, tt, $J = 7.0$, 4.9 Hz), 5.28–5.41 (4H, m), 7.53–7.59 (2H, m), 7.62–7.68 (1H, m), 7.86–7.90 (2H, m); HR-EIMS m/z (M^+): calcd. for $C_{37}H_{64}O_2S$, 572.4627; found, 572.4629.

*(5Z,25Z)-5,25-Hentriacontadiene (**1**).* To neat sulfone **7a** (67.2 mg, 0.117 mmol) was successively added a solution of samarium(II) iodide in THF (0.1 M, 12.0 ml, 1.20 mmol) and HMPA (1.2 ml) at 30 °C, and the mixture was stirred for 1 h at the same temperature, poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel impregnated with 1.5 wt. % of silver nitrate (2 g, hexane) to give 37.6 mg (74%) of **1**; IR ν_{max} cm^{-1}: 3000 (w), 2920 (s), 2850 (s), 1655 (w), 1465 (m), 1380 (w), 1120 (m), 720 (m), 670 (m); ^{1}H-NMR (500 MHz) δ: 0.89 (3H, t, $J = 6.8$ Hz), 0.90 (3H, t, $J = 6.8$ Hz), 1.23–1.37 (42H, m), 1.99–2.05 (8H, m), 5.32–5.39 (4H, m); ^{13}C-NMR (125 MHz) δ: 14.00, 14.08, 22.35, 22.58, 26.90, 27.17, 27.19, 29.31, 29.45, 29.55, 29.65, 29.69, 29.77, 31.53, 31.97, 129.83, 129.89, 129.90 (two overlapping peaks) (only 18 of 31 peaks required for **1** were observed due to peak-overlapping in the methylene region); GLC (Quadrex FFAP capillary column, 0.25 mm ID × 25 m, 0.25 μm film thickness; temperature, 50 °C (1 min) + 8 °C/min to 230 °C (20 min); He carrier gas at 1 ml/min): t_R 26.47 min (97.2% purity); HR-EIMS m/z (M^+): calcd. for $C_{31}H_{60}$, 432.4695; found, 432.4704.

*Compounds **4b**, **5b**, **6b**, **7b** and **2**.* These compounds were prepared in a similar manner to that described for the preparation of **4a**, **5a**, **6a**, **7a** and **1**, respectively, except that **3b**, instead of **3a**, was used as the starting material. The IR spectra were virtually identical with those of the corresponding lower homologs. The ^{1}H- and ^{13}C-NMR spectra were almost the same as those of the corresponding lower homologs, except that the peak areas of the methylene regions were larger than those of the corresponding lower homologs by four proton units. Other selected physical properties of these compounds are as follows: **4b** (88% yield); mp 59.5–60 °C (colorless flakes); HR-FABMS m/z ($[M + H]^+$): calcd. for $C_{17}H_{29}O_3S$, 313.1837; found, 313.1843. **5b** (99% yield); mp 46.5–47.5 °C (recrystallization from hexane); HR-FABMS m/z ($[M + H]^+$): calcd. for $C_{17}H_{27}O_3S$, 311.1681; found, 311.1681. **6b** (91% yield); ^{13}C-NMR (125 MHz) δ: 14.08, 22.56, 22.60, 27.15, 28.25, 28.98, 29.20, 29.22, 29.41, 29.42, 29.71, 31.50, 56.30, 128.04, 129.23, 129.80, 129.94, 133.59, 139.17 (only 19 of 21 peaks required for **6b** were observed due to peak-overlapping in the methylene carbon region); HR-EIMS m/z (M^+): calcd. for $C_{23}H_{38}O_2S$, 378.2592; found, 378.2596. **7b** (62% yield); HR-EIMS m/z (M^+): calcd. for $C_{39}H_{68}O_2S$, 600.4940; found, 600.4940. **2** (76% yield); ^{13}C-NMR (125 MHz) δ: 14.01, 14.08, 22.34, 22.58, 26.90, 27.12, 29.31, 29.45, 29.55, 29.65, 29.69, 29.70, 29.76, 31.52, 31.96, 129.83, 129.89, 129.91 (two overlapping peaks) (only 18 of 33 peaks required for **2** were observed due to peak-overlapping in the methylene region); GLC (under the same conditions as those employed for **1**): t_R 29.91 min (98.2% purity); HR-EIMS m/z (M^+): calcd. for $C_{33}H_{64}$, 460.5008; found, 460.5009.

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