Synthesis of Both the Enantiomers of (*Z*)-*cis*-9,10-Epoxy-6-heneicosene[†]

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Both the enantiomers of (*Z*)-*cis*-9,10-epoxy-6-heneicosene (**2**), a pheromone component of *Phragmatobia fuliginosa* L., were synthesized by employing the Sharpless asymmetric epoxidation as the key step.

Since Hill and Roelofs reported the isolation of (3*Z*,6*Z*)-*cis*-9,10-epoxy-3,6-heneicosadiene (**1**) as a component of the sex pheromone emitted by females of the salt marsh caterpillar moth *Estigmene acrea* Drury in 1981,¹⁾ many entomologists and chemists including us have been interested in investigating the sex pheromone of the Arctiidae family. Recently, Descoins *et al.* reported the isolation of a new pheromone (**2**) with an epoxy ring as the sex pheromone component produced by females of the ruby tiger moth, *Phragmatobia fuliginosa* (L.).²⁾ They found compounds **1** and **2** in an 85:15 ratio in female abdominal tip extracts. Only one synthesis of optically active **2** has been reported to date by Pougny *et al.*³⁾

They employed D-xylose as the starting material, and their synthetic routes were lengthy (11 steps) and hence inefficient. They used the Wittig reaction to generate the *Z*-double bond at C-6, and therefore, their synthetic **2** had at the most a 9:1 *Z/E* ratio. Even after their synthesis of (9*S*,10*R*)-**2**, the absolute configuration of the natural pheromone still remains unknown. So we decided to synthesize both the enantiomers of **2** more efficiently, and to clarify the stereochemistry-bioactivity relationship by submitting them to a bioassay.

As shown in Fig. 1, there are two possible ways [routes **a** and **b**] to construct **2**, using the same strategy as that for our previous synthesis of **1**.⁴⁾ That is to say, the Sharpless

Fig. 1. Target Molecule and Its Possible Synthetic Routes.

[†] Pheromone Synthesis, Part 112. For Part 111, see K. Mori and J. I. J. Ogoche, *Liebigs Ann. Chem.*, **1988**, 903.

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asymmetric epoxidation⁵⁾ and carbon-chain elongation by selective replacement of the TsO group in the presence of the epoxide with an organocopper reagent were the key reactions. Considering this, the epoxy alcohol **3a** would be an important intermediate in route **a**, and **4** in route **b**. These compounds (**3a** and **4**) were thought to be derived easily from propargyl alcohol (**5**) in 3 steps and 5 steps respectively. Therefore, route **a** has an advantage over route **b**. What is still better, the epoxy alcohol **3a** could be crystalline, because Sharpless *et al.* reported that *cis*-2,3-epoxy-1-tridecanol, which was one carbon shorter than **3a**, was crystalline, with an mp of 62.5~63.0°C.⁶⁾ Therefore, it would not be necessary to derive the corresponding crystalline 3,5-dinitrobenzoate of **3a** to improve the optical purity by repeated recrystallization, like our previous synthesis of **1**.⁴⁾ We thus selected the route **a** for synthesizing **2**.

As shown in Fig. 2, (*Z*)-tetradecen-1-ol **7**, the substrate required for the asymmetric epoxidation, was prepared by Ames' procedure.⁷⁾ 1-Bromoundecane was treated with $\text{LiC}\equiv\text{CCH}_2\text{OLi}$ to give **6** in an 88.5% yield. Hydrogenation of **6** over 5% Pd-BaSO₄ in the presence of quinoline in *n*-hexane gave a (*Z*)-allylic alcohol (**7**) in a 93.3% yield and 99% geometrical purity as checked by GLC. The olefinic alcohol **7** was submitted to the Sharpless asymmetric epoxidation by employing L-(+)-diisopropyl tartrate as the chiral

auxiliary to give (2*S*,3*R*)-**3a** in an 83.8% yield. Its optical purity was 92.0%, judging from the HPLC analysis of its (*R*)-MTPA ester (**3c**). Very fortunately, but as was expected, this was crystalline. Therefore, we tried to enhance the optical purity of **3a** by repeated recrystallization from *n*-hexane. Optically enriched (2*S*,3*R*)-**3a**, mp 62.5~63.5°C, $[\alpha]_D^{22} +8.3^\circ$ (EtOH), was obtained in a 61.7% yield from **7**. The HPLC analysis of its (*R*)-MTPA ester (**3c**) showed >99% optical purity. Finally, the corresponding tosylate (**3b**) derived from **3a** was treated with lithium di[(*Z*)-heptenyl] cuprate in THF, which was prepared from (*n*-C₅H₁₁)₂CuLi and HC≡CH by Normant's procedure,⁸⁾ to give (9*S*,10*R*)-**2**, $[\alpha]_D^{23} +9.4^\circ$ (CHCl₃), in a 41.7% yield. As racemization in the final step was thought to be unlikely to have taken place, the synthetic (9*S*,10*R*)-**2** must have had the same optical purity as that of **3a**. Normant *et al.* reported that (*Z*)-alkenes made by their procedure showed a greater than 99.9% geometrical purity. In our synthetic (9*S*,10*R*)-**2**, no isomer was detected by inspecting of ¹H NMR, ¹³C NMR and GLC results. The overall yield of (9*S*,10*R*)-**2** from undecyl bromide was 14.0% in 5 steps.

For the synthesis of (9*R*,10*S*)-**2**, an asymmetric epoxidation of **7** was carried out employing D-(-)-diisopropyl tartrate as the chiral auxiliary. The resulting (2*R*,3*S*)-**3a** was found to be of 88.7% *e.e.* as estimated by the HPLC analysis of its (*R*)-MTPA ester

Fig. 2. Synthesis of the Enantiomers of the Ene Epoxide **2**.

(3c). Optical enrichment of (2*R*, 3*S*)-**3a** was achieved as in the case of (2*S*, 3*R*)-**3a**, mp 62~63°C, $[\alpha]_D^{23} - 8.1^\circ$ (EtOH). The corresponding tosylate (2*R*,3*S*)-**3b** was treated with lithium di[(*Z*)-heptenyl]cuprate to give (9*R*,10*S*)-**2**, $[\alpha]_D^{23} - 9.1^\circ$ (CHCl₃). The overall yield of (9*R*,10*S*)-**2** from undecyl bromide was 14.1% in 5 steps.

In summary, a simple synthesis of both the enantiomers of (*Z*)-cis-9,10-epoxy-6-heneicosene (**2**) was achieved. Biological studies using our synthetic enantiomers of **2** will clarify the absolute configuration of the natural pheromone **2**.

Experimental

IR spectra were measured as films on a Jasco A-102 spectrometer. ¹H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer, or at 500 MHz on a Bruker AM-500 spectrometer. ¹³C NMR spectra were recorded with TMS as an internal standard at 25 MHz on a Jeol JNM-FX 100 spectrometer, and optical rotations were measured on a Jasco DIP-140 polarimeter.

cis-2,3-Epoxy-1-tetradecanol (**3a**).

(a) (2*S*,3*R*)-*Isomer*. Ti(OPr)₄ (8.04 g, 28.3 mmol) was added dropwise to stirred dry CH₂Cl₂ (230 ml) at -23°C under Ar. To this was added L-(+)-diisopropyl tartrate (7.18 g, 30.7 mmol). The mixture was stirred for 5 min at -23°C, before a solution of **7** (5 g, 23.6 mmol) in dry CH₂Cl₂ (8 ml) and *t*-BuOOH (4.50 M, 13.1 ml, 59 mmol) was added and the mixture stirred at -23°C. The mixture was left to stand for 36 hr at -23°C. The reaction was quenched by the addition of 10% tartaric acid aq. (60 ml) at -23°C with stirring. After stirring for 30 min at -23°C, the mixture was warmed to room temperature and stirred for 1 hr. The organic layer was separated, washed with water, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by SiO₂ chromatography (Merck Kieselgel 60, 200 g). Elution with *n*-hexane-ether (10:1~3:1) gave 4.51 g (83.8%) of **3a**, which was repeatedly recrystallized from *n*-hexane to give 3.32 g (61.7%) of pure **3a**, mp 62.5~63.5°C; $[\alpha]_D^{23} + 8.3^\circ$, (*c*=0.72, EtOH); IR $\nu_{\max}$ cm⁻¹ 3310 (m), 2920 (s), 2850 (s), 1460 (m), 1375 (w), 1030 (m), 890 (m), 845 (m), 715 (m); NMR δ (CDCl₃) 0.88 (3H, t, *J*=6 Hz), 1.05~2.10 (21 H, m), 2.70~3.25 (2H, m), 3.50~3.90 (2H, m); ¹³C-NMR δ (CDCl₃) 14.0, 22.6, 27.9, 29.3, 29.4, 29.5, 29.6, 31.9, 57.0, 57.3, 60.8; *Anal.* Found: C, 73.67; H, 12.40. Calcd. for C₁₄H₂₈O₂: C, 73.63; H, 12.36%. The optical purity of (2*S*,3*R*)-**3a** was determined by HPLC analyses of the corresponding (*R*)-MTPA ester **3c**: (column, Nucleosil 50-

5, 25 cm × 4.6 mm; *n*-hexane-1,2-dichloroethane (DCE)=4:1) *t_R* (min): (before purification; the flow rate, 1.1 ml/min), (2*S*,3*R*)-*isomer*: 34.5 (96.0%), (2*R*,3*S*)-*isomer*: 38.1 (4.0%); (after purification; flow rate, 1.0 ml/min) (2*S*,3*R*)-*isomer*: 43.1 (99.6%), (2*R*,3*S*)-*isomer*: 47.2 (0.4%). These proved the optical purity of crude (2*S*,3*R*)-**3a** to be 92%, and that of purified (2*S*,3*R*)-**3a** to be 99.2%.

(b) (2*R*,3*S*)-*Isomer*. In the same manner as that described above, **7** was epoxidized using D-(-)-diisopropyl tartrate as a chiral auxiliary to give 3.21 g (59.7%) of (2*R*,3*S*)-**3a** after repeated recrystallization. Mp 62~63°C; $[\alpha]_D^{23} - 8.1^\circ$ (*c*=0.91, EtOH). The IR and NMR spectra of (2*R*,3*S*)-**3a** were identical with those of (2*S*,3*R*)-**3a**. The optical purity of (2*R*,3*S*)-**3a** was determined by an HPLC analyses of corresponding (*R*)-MTPA ester **3c**: (column, Nucleosil 50-5, 25 cm × 4.6 mm): before purification; solvent; *n*-hexane-DCE=5:1, flow rate, 0.9 ml/min; *t_R* (min) (2*S*,3*R*)-*isomer*: 104 (6.1%), (2*R*,3*S*)-*isomer*: 107 (93.9%); after purification; solvent; *n*-hexane-DCE=4:1, flow rate, 1.0 ml/min) (2*S*,3*R*)-*isomer*: 43.9 (0.3%), (2*R*,3*S*)-*isomer*: 48.9 (99.7%). These proved the optical purity of crude (2*R*,3*S*)-**3a** to be 87.8% and that of purified (2*R*,3*S*)-**3a** to be 99.4%.

cis-2,3-Epoxytetradecyl tosylate **3b**.

(a) (2*S*,3*R*)-*Isomer*. TsCl (1.01 g, 5.26 mmol) was added to a solution of (2*S*,3*R*)-**3a** (1 g, 4.39 mmol) in dry C₅H₅N (15 ml) with stirring and ice-cooling. Stirring was continued overnight at 5°C. The mixture was poured into ice-cooled water and extracted with ether. The ether solution was washed with saturated cupric sulfate aq, water and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over SiO₂ (Merck Kieselgel 60, 20 g). Elution with *n*-hexane-ether (10:1~5:1) gave 1.12 g (66.7%) of (2*S*,3*R*)-**3b**. IR $\nu_{\max}$ cm⁻¹ 2925 (s), 2850 (s), 1595 (m), 1365 (s), 1185 (s), 1171 (s), 970 (s), 810 (s); NMR δ (CCl₄) 0.87 (3H, t, *J*=6 Hz), 1.0~1.6 (20H, m), 2.40 (3H, s), 2.65~3.10 (2H, m), 3.96 (2H, d, *J*=6 Hz), 7.25 (2H, d, *J*=8 Hz), 7.69 (2H, d, *J*=8 Hz). This was employed in the next step without further purification.

(b) (2*R*,3*S*)-*Isomer*. In the same manner as that described above, (2*R*,3*S*)-**3a** gave 1.20 g (71.4%) of (2*R*,3*S*)-**3b**, whose spectral data were identical with those of (2*S*,3*R*)-**3b**.

(6*Z*)-cis-9,10-Epoxyheneicosene **2**.

(a) (9*S*,10*R*)-*Isomer*. A solution of pentyllithium (0.30 N, 52.4 ml, 15.7 mmol) was added dropwise to a suspension of CuI (1.50 g, 7.85 mmol) in dry ether (30 ml) at -50°C under Ar. The mixture was stirred for 1 hr at -50°C. Acetylene (379 ml, 15.7 mmol) was bubbled into the reaction mixture with vigorous stirring. After stirring for 1 hr at -30°C, a solution of HMPA (6.6 ml) in dry THF (30 ml), a solution of (2*S*,3*R*)-**3b** (300 mg, 0.79 mmol) in dry THF (10 ml), and then (EtO)₃P (5.1 ml) were added to the reaction mixture. This was allowed to reach room

temperature slowly, and stirring was continued overnight at room temperature. The mixture was poured into saturated NH_4Cl aq. The organic layer was separated and the aq. layer was extracted with ether. The combined organic solution was washed with water and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 25 g). Elution with *n*-hexane-ether (200:1 ~ 100:1) gave a crude product. This was rechromatographed over SiO_2 (Kieselgel 60, 10 g). Elution with benzene gave 101 mg (41.7%) of pure (9*S*,10*R*)-**2**. $[\alpha]_D^{23} +9.4$ ($c=0.55$, CHCl_3); IR ν_{max} cm^{-1} 3030 (m), 2980 (s), 2945 (s), 2870 (s), 1460 (m), 1380 (w); NMR δ (500 MHz, CDCl_3) 0.89 (3H, t, $J=6.9$ Hz), 0.90 (3H, t, $J=7.0$ Hz), 1.20 ~ 1.60 (26H, m), 2.04 (2H, dt, $J=7.1$, 7.1 Hz), 2.19 (1H, ddd, $J=6.9$, 7.5, 14.0 Hz), 2.38 (1H, ddd, $J=6.2$, 6.9, 14.0 Hz), 2.90 ~ 2.96 (2H, m), 5.39 ~ 5.46 (1H, m), 5.50 ~ 5.56 (1H, m); ^{13}C -NMR δ (25 MHz, CDCl_3) 14.1, 22.6, 22.7, 26.3, 26.7, 27.4, 27.8, 29.4, 29.6, 31.5, 32.0, 56.6, 57.3, 123.9, 132.7; GLC (OV-101 column, 0.25 mm $\times$ 50 m, at 200°C; Carrier gas, nitrogen, 1.2 kg/cm²): t_R 13.2 min (single); MS (m/z) 368 (M^+ , 3.0%), 237 (5.2%), 197 (12.1%), 183 (11.2%), 149 (13.7%), 137 (21.3%), 110 (28.4%), 109 (21.1%), 97 (23.8%), 95 (44.7%), 83 (31.2%), 82 (32.3%), 81 (79.9%), 69 (100%, base peak); Found: MS (m/z) 308.3120 (M^+). Calcd. for $\text{C}_{21}\text{H}_{40}\text{O}$: 308.3079.

(b) (9*R*,10*S*)-Isomer. In the same manner as that just described above (2*R*,3*S*)-**3b** gave 97.5 mg (40.3%) of (9*R*,

10*S*)-**2**, $[\alpha]_D^{23} -9.10$ ($c=0.62$, CHCl_3). The IR, NMR and mass spectra of (9*R*,10*S*)-**2** were identical with those of (9*S*,10*R*)-**2**. Found: MS (m/z) 308.2996 (M^+). Calcd. for $\text{C}_{21}\text{H}_{40}\text{O}$: 308.3079.

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