A Convenient Preparation of Optically Active Diepoxyhenicosene (Leucomalure), Lymantrid Sex Pheromone, by Chiral HPLC

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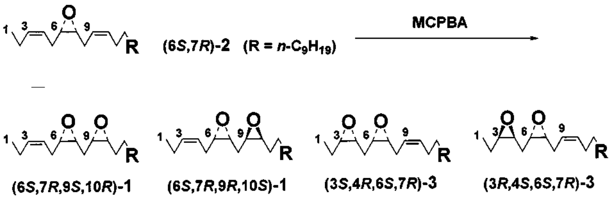
From optically active (3Z,9Z)-*cis*-6,7-epoxy-3,9-henicosadiene (**2**), all stereoisomers of (3Z)-*cis*-6,7-*cis*-9,10-diepoxy-3-henicosene [leucomalure (**1**)], a sex pheromone component of the Satin moth, were prepared in addition to the *cis*-3,4-*cis*-6,7-diepoxy analog (**3**). Specifically, MCPBA oxidation of each enantiomer of this epoxydiene yielded a mixture of four compounds, namely two diastereomeric sets of leucomalure and the positional isomer, which were easily separable by chiral HPLC equipped with either a Chiralpak AD column or a Chiralcel OJ-R column. Their chemical structures were determined by 2D-NMR analyses, and it was further confirmed that the chiral HPLC columns also had a high capability of resolving the enantiomers of these diepoxides.

Introduction

(*Z*,*Z*,*Z*)-3,6,9-Trienes with a C_{17} to C_{23} straight chain and their monoepoxy derivatives have been identified as sex pheromone components of female moths mainly in the families of Geometridae, Noctuidae, and Arctiidae.[1] Recently, Gries et al. have reported that the Satin moth in the family of Lymantriidae secreted a diepoxy derivative, (3*Z*)-*cis*-6,7-*cis*-9,10-diepoxy-3-henicosene (**1**), which was named leucomalure[2]. This is the first discovery of a lepidopterous pheromone including such a homoconjugated diepoxy function, and the stereochemistry is still unknown. To understand which configuration of the chiral pheromone is accepted by the male moth, authentic samples of every possible stereoisomer are necessary. While the monoepoxy derivatives have been successfully synthesized using either Sharpless asymmetric epoxidation of an allylic alcohol[3−9] or pig pancreatic lipase catalyzed asymmetric hydrolysis of a *meso*-diacetoxyepoxybutane[10], stereoselective construction of both epoxy rings of leucomalure by these reactions seems to be quite difficult. In this paper we describe a convenient preparation of the optically active leucomalure and its positional isomers utilizing HPLC with a chiral column, which could be applied to analyzing the absolute configuration of the natural pheromone produced by the females.

Results and Discussion

The (6*S*,7*R*) isomer of (3*Z*,9*Z*)-*cis*-6,7-epoxy-3,9-henicosadiene (**2**), which was prepared by chiral HPLC resolution of the racemic mixture,[11][12] was treated with *m*-chloroperbenzoic acid (MCPBA) to yield a mixture of the following four compounds: (6*S*,7*R*,9*S*,10*R*) and (6*S*,7*R*,9*R*,10*S*) isomers of leucomalure (**1**) and (3*S*,4*R*,6*S*,7*R*) and (3*R*,4*S*,6*S*,7*R*) isomers of (9*Z*)-*cis*-3,4-*cis*-6,7-diepoxy-9-henicosene (**3**) (Scheme 1). On chiral HPLC, equipped with a Chiralpak AD column, this mixture exhibited four separated peaks (compounds I−IV) in a ratio of 3:2:3:2 as shown in Figure 1A, and the chemical structure of each component was analyzed by NMR. Compounds I and IV showed the methyl proton signal at 1-position at a higher field than those of compounds II and III, and their ^{1}H-^{1}H COSY spectra confirmed that the former two were 6,7;9,10-diepoxide (**1**) and the latter two were 3,4;6,7-diepoxide (**3**). Two protons at 8-position of compound I resonated at the same field indicating a symmetrical (6*S*,7*R*,9*R*,10*S*) configuration, whereas those of compound IV possessing (6*S*,7*R*,9*S*,10*R*) configuration were located in different magnetic environments. Since two epoxy rings of (6*S*,7*R*,9*S*,10*R*)-**1** are oriented to the same face and cause a rather large steric strain, the chemical shift values of ^{13}C signals from 6- to 10-position of this isomer are slightly smaller than those of (6*S*,7*R*,9*R*,10*S*)-**1**. For the same reason, we propose the (3*S*,4*R*,6*S*,7*R*) configuration for compound II and the (3*R*,4*S*,6*S*,7*R*) configuration for compound III. These assignments indicate that MCPBA has attacked a double bond from the opposite face of the homoconjugated epoxy ring in a stereoselective manner.



Scheme 1. Chemical structures of the diepoxy compounds produced by MCPBA oxidation of (3*Z*,6*S*,7*R*,9*Z*)-*cis*-6,7-epoxy-3,9-henicosadiene [(6*S*,7*R*)-**2**]

MCPBA oxidation of (6*R*,7*S*)-**2** produced another mixture of compounds V−VIII in a 3:2:2:3 ratio, which were

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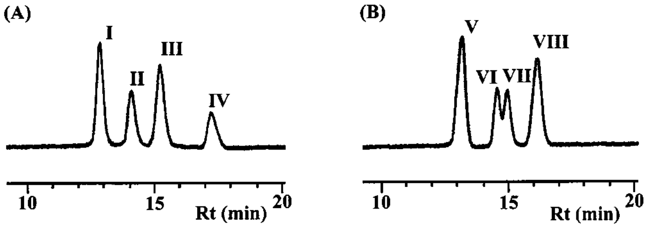

Figure 1. Chromatograms of MCPBA oxidation products, compounds I−IV derived from (3*Z*,6*S*,7*R*,9*Z*)-*cis*-6,7-epoxy-3,9-henicosadiene [(6*S*,7*R*)-**2**] (A) and compounds V−VIII from the enantiomer [(6*S*,7*R*)-**2**] (B)

Table 1. Enantiomeric separation of (3*Z*)-*cis*-6,7-*cis*-9,10-diepoxy-3-henicosene (leucomalure, **1**) and (9*Z*)-*cis*-3,4-*cis*-6,7-diepoxy-9-henicosene (**3**) by chiral HPLC

Compound	R_t [min] (*S*,*R*,*R*,*S*)[a]	R_t [min] (*R*,*S*,*S*,*R*)	Separation factor (α)	R_t [min] (*S*,*R*,*S*,*R*)	R_t [min] (*R*,*S*,*R*,*S*)	Separation factor (α)
(A) Chiralpak AD column						
1	12.86[b]	16.14	1.54	17.21	14.68[b]	1.33
3	13.18[b]	15.18	1.34	14.01[b]	14.94	1.14
(B) Chiralcel OJ-R column						
1	13.82[b]	15.53	1.17	15.30	13.99[b]	1.12
3	14.09[b]	14.09	1.00	14.63[b]	16.82	1.20

[a] (*S*,*R*,*R*,*S*) means (6*S*,7*R*,9*R*,10*S*) isomer of **1** and (3*S*,4*R*,6*R*,7*S*) isomer of **3**. − [b] R_t values of the isomers with a partial structure of (1*S*,2*R*,7*Z*)-1,2-epoxy-7-monoene.

also separable on chiral HPLC as shown in Figure 1B. NMR data of compounds V, VI, VII, and VIII coincided with those of compounds III, IV, II, and I, respectively, indicating the corresponding enantiomers. Their retention time (R_t) and separation factor (α) values in Table 1A revealed that enantiomeric separation of these diepoxy compounds was sufficiently accomplished by the Chiralpak AD column. In addition to this normal phase column, the Chiralcel OJ-R column operating under reversed phase conditions was also useful in their optical resolution except for (3*S*,4*R*,6*R*,7*S*)-**3** and the enantiomer (Table 1B). The elution order of the resolved enantiomers was the same on these two chiral columns.

These chiral columns have exhibited good resolution of monoepoxy derivatives of (3*Z*,6*Z*,9*Z*)-3,6,9-trienes and have led to the proposal of synthetic chiral pheromones for field tests.[11][12] Furthermore, the configurations of natural pheromone components biosynthesized by geometrid moths have been determined by chiral HPLC analyses.[12][13] This time we found that they possess a high ability to separate the positional isomers, diastereomers, and intended enantiomers of the diepoxy derivatives. Interestingly enough, Table 1 suggests that the shorter-R_t enantiomers have a common partial structure, (1*S*,2*R*,7*Z*)-1,2-epoxy-7-monoene. This result coincides with an elution profile of monoepoxy derivatives of (3*Z*,6*Z*,9*Z*)-3,6,9-trienes; i.e., isomers with a (1*S*,2*R*,4*Z*,7*Z*)-1,2-epoxy-4,7-diene system elute faster than the corresponding enantiomers (Figure 2).

Figure 2. Common chemical structure of *cis*-epoxy compounds which elute faster from chiral HPLC columns than the enantiomers

Because of the success in enantiomeric separation of monoepoxides derived from (6*Z*,9*Z*)-6,9-dienes on the chiral HPLC column,[14] three stereoisomers of diepoxides lacking a double bond at the 3-position were prepared by a further MCPBA oxidation of (6*S*,7*R*,9*Z*)-6,7-epoxy-9-henicosene and (6*Z*,9*R*,10*S*)-9,10-epoxy-6-henicosene. They could also be isolated using the Chiralpak AD column, and the (6*S*,7*R*,9*R*,10*S*) isomer was distinguished as a common component among the oxidation products of the two monoepoxides. By catalytic hydrogenation, compound I was converted into this stereoisomer of *cis*-6,7-*cis*-9,10-diepoxyhenicosane, indicating its original (6*S*,7*R*,9*R*,10*S*) configuration.

Diastereomers and positional isomers of the diepoxide eluted from a standard achiral MPLC column with moderately different R_t values. Thus, all stereoisomers of **1** were also isolated from MCPBA-oxidized products of racemic **2** by subsequent separation on the achiral MPLC and chiral HPLC. MCPBA oxidation of (3*Z*,6*Z*)-*cis*-9,10-epoxy-3,6-henicosadiene specifically proceeded at the double bond in 3-position, therefore **1** was not produced from this monoepoxide.

Experimental Section

Chromatography: Chiral HPLC involved a JASCO PU-980 Liquid Chromatograph equipped with an integrator (System Instrument Chromatocorder 21J), RI detector (Labo System RI-98SCOPE), and one of following columns: Chiralpak AD (0.46 cm ID × 25 cm, Daicel Chemical Industry Co., Ltd., Tokyo, Japan) or Chiralcel OJ-R (0.46 cm ID × 15 cm, Daicel Chemical Industry Co., Ltd.). For the former normal phase column, 1.0% 2-propanol in *n*-hexane was used as solvent at a flow rate of 0.45 mL/min. For the latter reversed phase column, 10% water in methanol was used at a flow rate of 0.50 mL/min. The MPLC system was constructed with a solvent pump (Yanaco L-4000 W liquid chromatograph), double Lobar columns (Merck Lichroprep Si 60, 10 mm ID × 240 mm, 40−63 μm) and an RI detector. As solvent, 8% THF in *n*-hexane was used at a flow rate of 2.5 mL/min. GC analysis was achieved using an HP GC System 6890 series with a flame ionization detector and a DB-23 capillary column (0.25 mm ID × 30 m, J & W Scientific). The temperature program was 50 °C for 2 min, 10 °C/min to 180 °C, and finally 2 °C/min to 220 °C.

Spectroscopy: ^{1}H and ^{13}C NMR: JEOL Alpha500 Fourier transform spectrometer at 500.2 and 125.7 MHz for $CDCl_3$ solutions containing TMS as an internal standard. ^{1}H-^{1}H-COSY and HMQC spectra were also measured with the same spectrometer using the usual pulse sequences and parameters. − Electron impact GC MS: JEOL JMS-AM II 20 mass spectrometer equipped with the same DB-23 capillary column for GC, and the column temperature program was 80 °C for 2 min, 10 °C/min to 160 °C, and finally 4 °C/min to 220 °C. The ionization voltage was 70 eV, and the ion source temperature was 240 °C. − The specific rotation of each $CHCl_3$ solution was measured with a JASCO DIP-4 polarimeter.

Synthesis of all Stereoisomers of 1 and 3 from Chiral 2: Optical pure (6*S*,7*R*) and (6*R*,7*S*) isomers of **2** (5.0 mg, 16 μmol) were obtained by chiral HPLC resolution of the racemic mixture.[11] These enantiomers, separately dissolved in dry CH_2Cl_2 (20 mL), were added to MCPBA (70% pure, 4.0 mg, 23 μmol) and stirred at 0 °C for 1 h. After further stirring at room temperature for 2 h, the reaction mixtures were washed with 3 N NaOH solutions and dried with Na_2SO_4. Preparative TLC gave a mixed product of compounds I−IV (2.6 mg, 50% yield) derived from (6*S*,7*R*)-**2** and that of compounds V−VIII (2.8 mg, 54% yield) derived from (6*R*,7*S*)-**2**. Each compound was isolated by chiral HPLC with the Chiralpak AD column.

Compounds I {(6*S*,7*R*,9*R*,10*S*)-1: $[\alpha]_D = +17.6$ (*c* = 1.0)} and VIII {(6*R*,7*S*,9*S*,10*R*)-1: $[\alpha]_D = -19.2$ (*c* = 1.0)}: ^{1}H NMR: δ = 0.98 (1-H, t, *J* = 7 Hz), 2.07 (2-H, dq, *J* = 7.5, 7 Hz), 5.54 (3-H, dtt, *J* = 10.5, 7.5, 1.5 Hz), 5.41 (4-H, dddt, *J* = 10.5, 7, 7, 1.5 Hz), 2.22 (5-H, ddd, *J* = 15, 7, 6.5 Hz), 2.38 (5-H, ddd, *J* = 15, 7, 6.5 Hz), 3.01 (6-H, ddd, *J* = 6.5, 6.5, 4.5 Hz), 3.14 (7-H or 9, ddd, *J* = 6.5, 6.5, 4.5 Hz), 1.77 (8-H, dd, *J* = 6.5, 6.5 Hz), 3.13 (9-H or 7, ddd, *J* = 6.5, 6.5, 4.5 Hz), 2.99 (10-H, td, *J* = 6, 4.5 Hz), 1.52 (11-H, m), ca. 1.28 (12-H to 20-H), 0.88 (21-H, t, *J* = 7 Hz). − ^{13}C NMR: δ = 14.2 (C-1), 20.8 (C-2), 134.6 (C-3), 122.9 (C-4), 26.2 (C-5), 54.3 (C-6), 54.4 (C-7), 27.2 (C-8), 56.4 (C-9), 57.1 (C-10), 27.9 (C-11), 26.5 (C-12), 29.2−29.5 (C-13 to C-18), 31.8 (C-19), 22.7 (C-20), 14.1 (C-21). − GC MS (relative intensity): R_t = 29.77 min: *m*/*z* = 304 (0.2) $[M - H_2O]^+$, 235 (1), 128 (1), 111 (15), 109 (27), 95 (41), 81 (61), 67 (85), 55 (100).

Compounds IV {(6*S*,7*R*,9*S*,10*R*)-1: $[\alpha]_D = +3.1$ (*c* = 0.8)} and VI {(6*R*,7*S*,9*R*,10*S*)-1: $[\alpha]_D = -3.2$ (*c* = 0.7)}: ^{1}H NMR: δ = 0.99 (1-H, t, *J* = 7 Hz), 2.07 (2-H, dq, *J* = 7.5, 7 Hz), 5.55 (3-H, dtt, *J* = 10.5, 7.5, 1.5 Hz), 5.40 (4-H, dddt, *J* = 10.5, 7, 7, 1.5 Hz), 2.23 (5-H, ddd, *J* = 15, 7, 7 Hz), 2.42 (5-H, ddd, *J* = 15, 7, 7 Hz), 3.03 (6-H, ddd, *J* = 7, 7, 4.5 Hz), 3.10 (7-H or 9, ddd, *J* = 7, 6, 4.5 Hz), 1.77 (8-H, ddd, *J* = 14.5, 6, 6 Hz), 1.83 (8-H, ddd, *J* = 14.5, 7, 7 Hz), 3.09 (9-H or 7, ddd, *J* = 7, 6, 4.5 Hz), 2.97 (10-H, ddd, *J* = 6.5, 6, 4.5 Hz), 1.55 (11-H, m), ca. 1.28 (12-H to 20-H), 0.88 (21-H, t, *J* = 7 Hz). − ^{13}C NMR: δ = 14.1 (C-1), 20.8 (C-2), 134.6 (C-3), 122.8 (C-4), 26.2 (C-5), 54.2 (C-6), 54.2 (C-7), 26.9 (C-8), 56.1 (C-9), 56.7 (C-10), 27.9 (C-11), 26.6 (C-12), 29.2−29.5 (C-13 to C-18), 31.9 (C-19), 22.7 (C-20), 14.1 (C-21). − GC MS (relative intensity): R_t = 31.53 min; *m*/*z* = 304 (0.4) $[M - H_2O]^+$, 235 (3), 128 (1), 111 (21), 109 (29), 95 (45), 81 (58), 67 (83), 55 (100).

Compounds II {(3*S*,4*R*,6*S*,7*R*)-3: $[\alpha]_D = +1.5$ (*c* = 0.5)} and VII {(3*R*,4*S*,6*R*,7*S*)-3: $[\alpha]_D = -2.3$ (*c* = 0.6)}: ^{1}H NMR: δ = 1.07 (1-H, t, *J* = 7 Hz), ca. 1.55 (2-H, m), 2.94 (3-H, ddd, *J* = 6.5, 6.5, 4.5 Hz), 3.10 (4-H, ddd, *J* = 7, 6, 4.5 Hz), 1.77 (5-H, ddd, *J* = 14.5, 6, 6 Hz), 1.83 (5-H, ddd, *J* = 14.5, 7, 7 Hz), 3.10 (6-H, ddd, *J* = 7, 6, 4.5 Hz), 3.00 (7-H, ddd, *J* = 6.5, 6.5, 4.5 Hz), 2.22 (8-H, ddd, *J* = 14, 7, 6.5 Hz), 2.42 (8-H, ddd, *J* = 14, 7, 6.5 Hz), 5.42 (9-H, dddt, *J* = 10.5, 7, 7, 1.5 Hz), 5.55 (10-H, dtt, *J* = 10.5, 7.5, 1.5 Hz), 2.04 (11-H, dt, *J* = 7.5, 7.5 Hz), ca. 1.28 (12-H to 20-H), 0.88 (21-H, t, *J* = 7 Hz). − ^{13}C NMR: δ = 10.6 (C-1), 21.1 (C-2), 57.9 (C-3), 56.1 (C-4), 26.8 (C-5), 54.2 (C-6), 54.3 (C-7), 26.2 (C-8), 123.3 (C-9), 133.1 (C-10), 27.5 (C-11), 29.2−29.5 (C-12 to C-18), 31.9 (C-19), 22.7 (C-20), 14.1 (C-21). − GC MS (relative intensity): R_t = 31.26 min; *m*/*z* = 304 (0.7) $[M - H_2O]^+$, 235 (2), 128 (7), 111 (10), 109 (38), 95 (45), 81 (82), 67 (89), 55 (100).

Compounds III {(3*R*,4*S*,6*S*,7*R*)-3: $[\alpha]_D = -17.5$ (*c* = 0.8)} and V {(3*S*,4*R*,6*R*,7*S*)-3: $[\alpha]_D = +16.9$ (*c* = 0.8)}: ^{1}H NMR: δ = 1.07 (1-H, t, *J* = 7 Hz), ca. 1.55 (2-H, m), 2.96 (3-H, ddd, *J* = 6.5, 6.5, 4.5 Hz), 3.14 (4-H, ddd, *J* = 7, 5, 4.5 Hz), 1.75 (5-H, ddd, *J* = 14.5, 7, 5 Hz), 1.80 (5-H, ddd, *J* = 14.5, 7, 5 Hz), 3.14 (6-H, ddd, *J* = 7, 5, 4.5 Hz), 3.01 (7-H, ddd, *J* = 6.5, 6.5, 4.5 Hz), 2.21 (8-H, ddd, *J* = 14, 7, 6.5 Hz), 2.38 (8-H, ddd, *J* = 14, 7, 6.5 Hz), 5.43 (9-H, dddt, *J* = 10.5, 7, 7, 1.5 Hz), 5.54 (10-H, dtt, *J* = 10.5, 7.5, 1.5 Hz), 2.04 (11-H, dt, *J* = 7.5, 7.5 Hz), ca. 1.28 (12-H to 20-H), 0.88 (21-H, t, *J* = 7 Hz). − ^{13}C NMR: δ = 10.5 (C-1), 21.2 (C-2), 58.2 (C-3), 56.3 (C-4), 27.1 (C-5), 54.3 (C-6), 54.5 (C-7), 26.3 (C-8), 123.4 (C-9), 133.1 (C-10), 27.5 (C-11), 29.2−29.5 (C-12 to C-18), 31.9 (C-19), 22.7 (C-20), 14.1 (C-21). − GC MS (relative intensity): R_t = 29.77 min; *m*/*z* = 304 (0.2) $[M - H_2O]^+$, 235 (1), 128 (5), 111 (10), 109 (31), 95 (50), 81 (85), 67 (93), 55 (100).

Hydrogenation of Compound I and the Stereochemistry Assignment: Compound I (200 μg) was dissolved in *n*-hexane (0.5 mL), including 5% Pd/$BaSO_4$ (100 μg), and vigorously stirred under H_2 for 10 min. After filtration of the catalyst, the hydrogenated product (*cis*-6,7-*cis*-9,10-diepoxyhenicosane) was analyzed by chiral HPLC with the Chiralpak AD column. For this diepoxide (R_t = 12.49 min), the (6*S*,7*R*,9*R*,10*S*) configuration was assigned, in comparison with the following R_t values of the authentic compounds prepared by the oxidation of epoxyhenicosene: (6*S*,7*R*,9*R*,10*S*) isomer: 12.49 min; (6*S*,7*R*,9*S*,10*R*) isomer: 14.30 min; (6*R*,7*S*,9*R*,10*S*) isomer: 14.67 min.

MPLC Separation of Diepoxides Derived from Racemic 2: A racemic mixture of **2** (100 mg, 370 μmol) was oxidized with MCPBA in the same manner and a mixture of all stereoisomers of **1** and **3** (69 mg, 58% yield) was prepared. Separation of the positional isomers as well as diastereomers with the following R_t values was accomplished by MPLC: (6*S*,7*R*,9*R*,10*S*)- and (6*R*,7*S*,9*S*,10*R*)-**1**: 39.4 min; (6*S*,7*R*,9*S*,10*R*)- and (6*R*,7*S*,9*R*,10*S*)-**1**: 33.7 min; (3*S*,4*R*,6*S*,7*R*)- and (3*R*,4*S*,6*R*,7*S*)-**3**: 37.2 min; (3*R*,4*S*,6*S*,7*R*)- and (3*S*,4*R*,6*R*,7*S*)-**3**: 41.9 min.

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