Biomimetic Conversion of (3S)-(−)-Neodictyoprolenol to Optically Pure (1*S*,2*R*)-(−)-Dictyopterene B, Marine Algal Sex Pheromone

Tadahiko Kajiwara*, Yuuko Yamamoto[a], Yoshihiko Akakabe[a], Kenji Matsui[a], Hiroshi Shimizu[a], and Tesuo Kawai[b]

[a] Department of Biological Chemistry, Faculty of Agriculture, Yamaguchi University, Yamaguchi 753-8515, Japan. Fax: +81-839-33-5849. E-mail: kajiwara@agr.yamaguchi-u.ac.jp
[b] Lab. of Flavor Substances, Shiono Koryo Kaisha, Ltd. Nütaka 5-17-75, Yodogawa-ku, Osaka 532-0033, Japan

* Author for correspondence and reprint requests

Z. Naturforsch. **58c**, 109–112 (2003); received September 17, 2002

Both enantiomers of (3*S*)-(−)- and (3*R*)-(+)-Neodictyoprolenol [(3*S*,5*Z*,8*Z*)-(−)-1,5,8-undecatrien-3-ol] were successfully converted to the algal sex pheromone, (1*S*,2*R*)-(−)-dictyopterene B and (1*R*,2*S*)-(+)-dictyopterene B in high enantiomeric purities (*e.e.* > 99%), respectively, by the biomimetic reaction involving phosphorylation and elimination under a mild condition.

Key words: Biomimetic Conversion, Pheromones, Marine Algae

Introduction

Recent years, the study of volatile compounds in wet and fresh marine algae has developed rapidly (Moore, 1977; Suzuki *et al.*, 1981; Yamada *et al.*, 1986; Boland and Müller, 1987; Kajiwara *et al.*, 1993). The odoriferous compounds in thalli and gametes of Japanese marine algae have been explored for elucidation of their physiological significance in marine ecological systems. Characteristic volatiles such as dictyopterenes and the related C_{11}-compounds and sesquiterpenes have been identified as constituents of ocean smell and male gamete-attracting substance, and flavors reminiscent of algae (Kajiwara *et al.*, 1993). (3*S*)-(−)-Neodictyoprolenol [(3*S*,5*Z*,8*Z*)-(−)-1,5,8-undecatrien-3-ol; (3*S*)-(−)-**1**] had been proposed as a possible biosynthetic intermediate (Moore, 1977) of the sex pheromones of marine brown algae such as (1*S*,2*R*)-(−)-dictyopterene B [(1*S*,2*R*,1′*E*,3′*Z*)-(−)-1-(1′, 3′-hexadienyl)-2-vinylcyclopropane; (1*S*,2*R*)-(−)-**2**] (Müller *et al.*, 1985) and (6*S*)-(+)-dictyopterene D′ [(6*S*,1′*Z*)-(+)-(1′-butenyl)-1,4-cycloheptadiene; (6*S*)-(+)-**3**] (Müller *et al.*, 1971). However, the neodictyoprolenol has never been converted to the optically active dictyopterenes.

Very recently, the biomimetic pathway of (3*S*)-(−)-**1** to (1*S*,2*R*)-(−)-**2** was supported by a (3*S*)-**1** selective biogenetic conversion to (1*S*,2*R*)-**2** during the incubation of (±)-**1** with enzyme preparation from marine brown alga, *Dictyopteris prolifera* (Yamamoto *et al.*, 2001)

Materials and Methods

General experimental procedures

All air and moisture sensitive reactions were run under N_2 atmosphere. All solvents were distilled before use. IR spectra were measured with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were measured in $CDCl_3$ with TMS as the internal reference at 250 MHz with a Hitachi R-250 spectrometer and at 400 MHz with a JEOL JMN-LA400. ^{13}C-NMR spectra were measured in $CDCl_3$ at 62.5 MHz with the Hitachi R-250 spectrometer and at 100 MHz with a JEOL JMN-LA400. Optical rotations were recorded by JASCO DIP-370 Digital Polarimeter with chloroform as the solvent. GC analyses were performed with Shimadzu GLC-6A on a capillary column of DB-WAX® [GC condition 1: column, 0.25 mm × 60 m; He press., 165 kpa (33.5 cm/sec); make up press., 50 kpa; column temp, 80 to 220 °C at the rate of 2 °C/min], on a capillary column of CP-Cyclodex 236M® [GC condition 2: column, 0.25 mm × 50 m; He press., 150 kpa (33.2 cm/sec); make up press., 50 kpa; column temp, 110 °C hold], on a capillary column of Lipodex® [GC condition 3: column, 0.25 mm × 50 m; He press., 165 kpa (33.5 cm/sec); make up press., 50 kpa; column temp, 110 °C hold] and on a capillary column of DB-1® [GC condition 4: column, 0.25 mm × 60 m; He press., 165 kpa (33.0 cm/sec); make up press., 40 kpa; column temp, 70 to 220 °C at the rate of 5 °C/min]. Col-

0939–5075/2003/0100–0109 $ 06.00

umn chromatography was performed on Merck Kieselgel 60, Art No. 7734. HPLC were performed with Hitachi 655A-11 on a Chiralcel-OB® (HPLC condition 1: column, 4.6 mm × 250 mm; eluent, MeOH-H_2O (9:1); flow rate, 0.5 ml/min; detection at 247 nm) and on a Chiralcel-ODH® (HPLC condition 2: column, 4.6 mm × 250 mm; eluent, *n*-hexane; flow rate, 0.5 ml/min; detection at 210 nm).

Conversion of neodictyoprolenol to dictyopterene B

Preparation of (3S)-(–)-1

To a suspension of acetate of (±)-**1** (0.5 g, 2.4 mmol) in aq. phosphate buffer (pH 7.2, 15 ml) and acetone (10 ml) was added Chirazyme 435® (0.5 g). After being stirred for 5 h at room temp, the mixture was filtered and extracted with ether. The ethereal solution was washed with brine, and dried over Na_2SO_4 (anhydrous). The extract was concentrated *in vacuo*, and purified by silica gel column chromatography. Elution with *n*-hexane/AcOEt (5:1) first furnished acetate of (3*R*)-(+)-1 (0.3 g, 1.5 mmol) in 61% yield. Subsequently, (3*S*)-(–)-1 [0.1 g, 0.7 mmol] in 31% yield, $[\alpha]_D^{25} = -1.2°$ (*c* 5.02, $CHCl_3$)], was eluted. Its enantiomeric purity was estimated (as an acetate derivative) by chiral GC as *e.e.* > 99% (Yamamoto *et al.*, 1999).

Preparation of (3S)-(+)-1

To a solution of (±)-**1** (0.5 g, 2.9 mmol) in vinyl acetate (15 ml) was added Chirazyme 435® (0.5 g). After being stirred for 5 h at room temp, the mixture was filtered and extracted with ether. The ethereal solution was washed with brine, and dried over Na_2SO_4 (anhydrous). The extract was concentrated *in vacuo*, and purified by silica gel column chromatography. Elution with *n*-hexane/AcOEt (5:1) first afforded acetate (3*S*)-**1** (0.4 g, 1.7 mmol) in 60% yield. Subsequently, (3*R*)-(+)-**1** [0.2 g, 0.9 mmol; 32% yield; $[\alpha]_D^{25} = +1.2°$ (*c* 5.00, $CHCl_3$)], was eluted. Its enantiomeric purity was estimated as *e.e.* > 99% by chiral GC (Yamamoto *et al.*, 1999).

Preparation of (3S)-(+)-1p

To a rapidly stirring solution of (3*S*)-(–)-**1** (166 mg, 1.0 mmol, *e.e.* > 99%) in 10 ml of *n*-hexane was added lithium diisopropylamide (1.5 mmol) at – 75 °C. After stirring the solution for 1 h, tetraethyl pyrophosphate (378 mg, 1.6 mmol) was added by a syringe at – 76 °C, the white solution was warmed to 0 °C. The reaction mixture was quenched with saturated $NaHCO_3$ and warmed to room temp. The mixture was extracted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and with brine. The washed layer was dried over Na_2SO_4, and concentrated *in vacuo* to afford (3S)-(+)-1p [216 mg, 0.74 mmol, 74% yield; $[\alpha]_D^{25} = +30.5°$ (*c* 5.00, $CHCl_3$)]. The IR and ^{1}H-NMR spectra of (3*S*)-(+)-**1p** were identical with those of the racemates (Abraham *et al.*, 1991). IR (neat, NaCl, film) cm^{-1}; 3500, 3260, 3020, 3000, 2950, 2900, 1650, 1450, 1440, 1400, 1370, 1270, 1190, 1100, 1040, 830, 760. ^{1}H-NMR (250 MHz, $CDCl_3$) ppm; δ 5.85 (ddd, J_1 = 17.1 Hz, J_2 = 10.4 Hz, J_3 = 6.7 Hz, ^{1}H), 5.53–5.21 (m, 6H), 4.79 (m, ^{1}H), 4.10 (m, 4H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.50 (m, 2H), 2.06 (m, 2H), 1.31 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H).

Preparation of (3R)-(–)-1p

(3*R*)-(–)-**1p** was prepared similarly as (3*S*)-(+)-**1p** by using a mixture of (3*R*)-(+)-**1** (166 mg, 1.0 mmol, *e.e.* > 99%), lithium diisopropylamide (1.5 mmol) and tetraethyl pyrophosphate (378 mg, 1.6 mmol). The crude product was purified by column chromatography on a silica gel (elution with 50% ethyl acetate in hexane) to give (3*R*)-(–)-**1p** [209 mg, 0.71 mmol, 71% yield; $[\alpha]_D^{25} = -30.3°$ (*c* 5.01, $CHCl_3$)]. The IR and ^{1}H-NMR spectra of (3*R*)-(–)-**1p** were identical with those of (3S)-(+)-**1p.**

Conversion of (3S)-(+)-1p to (1S,2R)-(–)-2

To a rapidly stirring solution of (3*S*)-(+)-**1p** (100 mg, 0.35 mmol) in 30 ml of hexane was added potassium bis-(trimethylsilyl)amide (0.7 mmol, 0.5 M in THF 12.5 ml) at – 76 °C for 30 min, the dark orange colored solution was warmed to 0 °C and then the solution turned black orange color. The reaction was quenched with water and extracted with pentane. The organic layer was washed once with saturated $NaHCO_3$ and once with brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo.* Column chromatography (elution with pentane) of the concentrate afford (1*S*,2*R*)-(–)-**2** [43 mg, 84% yield; $[\alpha]_D^{25} = -50.3°$ (*c* 5.11, $CHCl_3$); *e.e.* > 99% as estimated by GC condition 3, the retention time =

24.6 min]. The IR, ^{1}H-NMR and ^{13}C-NMR spectra of (1*S*,2*R*)-(−)-**2** were identical with those of natural dictyopterene B[$[\alpha]_D^{25} = -43°$ (*c* 10.1, $CHCl_3$)] (Moore *et al.*, 1974). IR (neat, NaCl, film) cm^{-1}; 3090, 3025, 2980, 2950, 2890, 1650, 1640, 1465, 985, 945, 900, 855. ^{1}H-NMR (400 MHz, $CDCl_3$) ppm; δ 6.39 (dd, J_1 = 14.9 Hz, J_2 = 11.0 Hz, ^{1}H), 5.90 (dd, J_1 = 11.4 Hz, J_2 = 11.0 Hz, ^{1}H), 5.41 (ddd, J_1 = 17.1 Hz, J_2 = 8.8 Hz, J_3 = 8.3 Hz, ^{1}H), 5.29 (m, ^{1}H), 5.23 (m, ^{1}H), 5.03 (dd, J_1 = 17.1 Hz, J_2 = 2.0 Hz), 4.88 (dd, J_1 = 10.2 Hz, J_2 = 1.5 Hz, ^{1}H), 2.18 (d of quintets, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 2H), 1.48 (m, 2H), 0.98, (t, *J* = 5.1 Hz, 3H), 0.92–0.86 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) ppm; δ 140.26, 135.87, 131.57, 127.55, 124.04, 112.35, 25.15, 24.30, 21.04, 15.53, 14.32. GC-MS *m/z* (rel. intensity); 148 (M^+, 5), 133 (6), 119 (31), 105 (35), 91 (94), 79 (100), 66 (49), 41 (65), 39 (49), 27 (27).

Conversion of (3R)-(−)-1p to (1R,2S)-(+)-2

(3*R*)-(−)-**1p** (100 mg, 0.35 mmol) was cyclized to the desired cyclopropane using potassium bis-(trimethylsilyl) amide (0.7 mmol) in THF (30 ml) according to the similar procedure for (3*S*)-(−)-**1p**. The crude product was purified by column chromatography on a silica gel (elution with pentane) to afford (1*R*,2*S*)-(+)-**2** [42 mg, 0.3 mmol, 82% yield; $[\alpha]_D^{25} = +50.4°$ (*c* 5.11, $CHCl_3$; *e.e.* > 99% as estimated by GC condition 3, the retention time = 26.0 min)]. The IR, ^{1}H-NMR and ^{13}C-NMR spectra of (1*R*,2*S*)-(+)-**2** were identical with those of (1*S*,2*R*)-(−)-2.

Results and Discussion

Conversion of (3S)-(−)-neodictyoprolenol [(3S)-(−)-1] to (1S,2R)-(−)-dictyopterene B [(1S,2R)-(−)-2]

Recently, Abraham and Cohen (Abraham *et al.*, 1991) have reported a biomimetic synthesis of (±)-**2** *via* phosphorylation of racemic neodictyoprolenol [(±)-**1**] and subsequent elimination. However the phosphorylation of (3*S*)-(−)-**1** and (3*R*)-(+)-**1**, which were prepared by a chemo-enzymatic method through optical resolution of (±)-**1**, with tetraethylpyrophosphate (TEPP) in THF at − 76 °C according to the Cohen's method (Abraham *et al.*, 1991) caused racemization to some extent (20 ~ 50%). That was proven by examination with a chiral GC after the enantiospecific conversion of (3*S*)-**1p** to (1*S*,2*R*)-dictyopterene B, whereas the enantiomeric purities of the phosphorylation products (**1p**) could not be directly estimated on chiral phases examined. After several trials, using nonpolar solvents such as pentane, hexane, heptane, and toluene, the phosphorylation of (3*S*)-(−)-**1** {$[\alpha]_D^{25} = -1.2°$ (*c* 5.02, $CHCl_3$); *e.e.* > 99%} in hexane gave (3*S*)-(+)-**1p** {$[\alpha]_D^{25} = +30.5°$ (*c* 5.00, $CHCl_3$); 60% isolated yield} without appreciable racemization. The IR, ^{1}H-NMR and ^{13}C-NMR spectra of (3*S*)-(+)-**1p** were identical with those of the racemate (±)-**1p** (Abraham *et al.*, 1991). Then, the phosphate [(3*S*)-(+)-**1p**] was successfully converted *via* elimination-cyclization process by treatment with potassium bis (trimethylsilyl) amide from − 76 °C to 0 °C into the desired (1*S*,2*R*)-(−)-dictyopterene B [(1*S*,2*R*)-(−)-**2**] with $[\alpha]_D^{25} = -50.3°$ (*c* 5.11, $CHCl_3$); *e.e.* > 99% (24.6 min; estimated by chiral GC on Lipodex® under GC-condition 3) in the 83% yield (Fig. 1). The structure of (1*S*,2*R*)-(−)-**2** was confirmed by IR, ^{1}H- and ^{13}C-NMR spectra and coincided with that of natural(1*S*,2*R*)-(−)-**2** {$[\alpha]_D^{25} = -43°$ (*c* 10.1, $CHCl_3$)} (Moore *et al.* , 1974) from marine brown algae, the genus of *Dictyopteris*. On the other hand, (3*R*)-(+)-**1** [*e.e.* > 99%; $[\alpha]_D^{25} = +1.2°$ (*c* 5.00, $CHCl_3$)] was led to (1*R*,2*S*)-(+)-dictyoppterene B {(1*R*,2*S*)-(+)-2; 58% isolated yield; $[\alpha]_D^{25} = +50.4°$ (*c* 5.11, $CHCl_3$); *e.e.* > 99% (26.0 min; estimated by the GC analysis under GC-condition 3)} by the phosphorylation followed by the base-induced elimination and cyclization of (3*R*)-(−)-**1p** {$[\alpha]_D^{25} = -30.3°$ (*c* 5.01, $CHCl_3$)}. In the elimination products, the *cis*-disubstituted cyclopropane corresponding to dictyopterene B (**2**), which easily rearrange to dictyopterene D′ at room temperature (Schneider and Goldbach, 1980), was not detected. These results indicated that natural (1*S*,2*R*)- and unnatural (1*R*,2*S*)-isomers of **2** resulted *via* an intramolecular SN2 reaction mechanism from natural (3*S*)-and unnatural (3*R*)-forms of **1** (Yamamoto *et al.*, 1999), respectively as seen in Fig. 1.

Although some syntheses of optically active dictyopterene B (**2**) have been reported (Schottem *et al.*, 1985; Kajiwara *et al.*, 1980), they involve separation steps of formed geometrical mixture. Thus, this biomimetic synthesis of optically pure both enantiomers of **2** enable us to secure samples sufficient for further biological study.

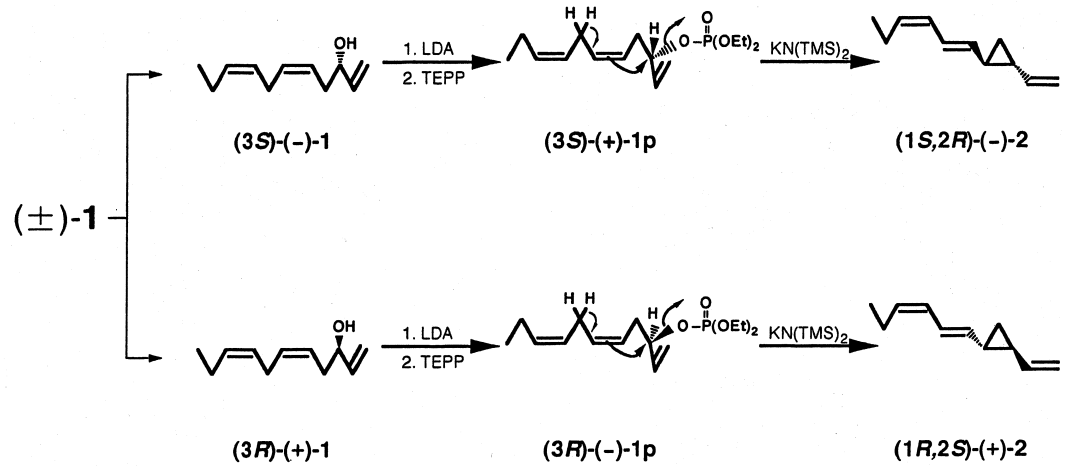

Fig. 1. The biomimetic conversion of (3*S*)-(–)- and (3*R*)-(+)-neodictyoprolenol (**1**) to (1*S*,2*R*)-(–)- and (1*R*,2*S*)-(+)-dictyopterene B (**2**).

Acknowledgments

This work was supported in part by a Grant-in Aid (No. 09556047, 07660140) (for T. K.) from the Ministry of Education, Science and Culture, Japan and the Naito Foundation (97-173) (for T. K.), and performed under JSPS-NRCT Core University Program.

Abraham W. D., and Cohen T. (1991), Biogenetically inspired stereospecific synthesis of the dienylvinylcyclopropane gamete attractant dictyopterene B. J. Am. Chem. Soc. **113**, 2313–2314.

Boland W., and Müller D. G. (1987), On the odor of the mediterranean seaweed *Dictyopteris membranacea*; new C_{11}-hydrocarbons from marine brown algae-III. Tetrahedron **28**, 307–310.

Kajiwara T., Nakatomi T., Sasaki Y., and Hatanaka A. (1980), Stereoselective synthesis of optically active dictyopterenes A and B and their geometrical isomers. Agric. Biol. Chem., **44**, 2099–2104.

Kajiwara T., Kodama K., Hatanaka A., and Matsui K. (1993), Volatile compounds from Japanese marine brown algae. In Bioactive volatile attractant from plants. Am. Chem. Soc. Symp. Ser. **525**, 103–120.

Moore R. E., Pettus J. A., Jr., and Mistysyn J. (1974), Odoriferous C_{11} hydrocarbons from Hawaiian *Dictyopteris*. J. Org. Chem. **39**, 2201–2207.

Moore R. E. (1977), Volatile compounds from Marine Algae. Acc. Chem. Res. **10**, 40–47.

Müller D. G., Jaenicke L., Donike M., and Akintobi T. (1971), Sex attractant in a brown alga: chemical structure. Science, **171**, 815–817.

Müller D. G., Clayton M. N., Grassman G., Boland W., Marner F.-J., Schotten T., and Jaenicke L. (1985), Cystophorene and hormosirene, sperm attractants in Australian brown algae. Naturwissenschaften **72**, 97–99.

Schneider M. P., and Goldbach M. (1980), Facile synthesis of fucoserratene and the (±)-dictyopterenes B, D, and D′ (= ectocarpene): constituents of marine brown algae. J. Am. Chem. Soc. **102**, 6114–6116.

Schotten T., Boland W., and Jaenicke L. (1985), Synthesis of enantiomerically pure pheromones of south-pacific brown algae: hormosirene and dictyopterene A. Helv. Chim. Acta **68**, 1186–1192

Suzuki M., Kowata N., and Kurosawa E. (1981), Epicubenol and related sesquiterpenoids from the brown alga *Dictyopteris divaricata*. Bull. Chem. Soc. Jpn. **54**, 2366–2368.

Yamada K., Tan H., Tatematsu H., and Ojika M. (1986), Dictyoprolene and neodictyoprolene, two new odoriferous compounds from the brown alga *Dictyopteris prolifera*: structures and synthesis. Tetrahedron **42**, 3775–3780.

Yamamoto Y., Akakabe Y., Matsui K., Shimidzu H., and Kajiwara T. (1999), Chemo-enzymatic syntheses of both enantiomers of neodictyoprolenol and neodictyoprolene; possible biosynthetic intermediates of sex pheromones in brown algae. Z. Naturforsch. **54c**, 1027–1032.

Yamamoto Y., Akakabe Y., Matsui K., Shimidzu H. and Kajiwara T. (2000), Neodictyoprolenol and dictyoprolenol, the possible biosynthetic intermediates of dictyopterenes, in the Japanese brown algae *Dictyopteris*. Z. Naturforsch. **56c**, 6–12.