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(+)-(3*S*,4*S*)-3-BUTYL-4-VINYLCYCLOPENTENE IN BROWN ALGAE OF THE GENUS *DICTYOPTERIS*

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Abstract—(−)-(3*R*,4*R*)-3-Butyl-4-vinylcyclopentene [(−)-**1**] was synthesized *via* (+)-(1*S*,5*R*)-3-oxabicyclo [3,3,0] oct-6-en-2-one. Synthetic (−)-**1** coincided with the peak with later retention time of racemic (±)-**1** in a chiral GC (CP-Cyclodex 236M), while the natural **1** in essential oils from the marine brown algae, *Dictyopteris prolifera* and *D.* sp. was identical with the earlier retention time peak. Thus, the absolute configuration of the natural product in *Dictyopteris* oils was determined as (+)-(3*S*,4*S*) with *ca* 100% enantiomeric excess.

INTRODUCTION

Multifidene [(+)-(3*S*,4*S*)-3-(1*Z*-but-1-enyl)-4-vinylcyclopentene] and viridiene [(+)-(3*R*,4*S*)-3-(1*Z*-buta-1,3-dienyl)-4-vinylcyclopentene] are known as male gamete-attracting and releasing substances in the marine brown algae, *Cutleria multifida* and *Desmarestia viridis*, respectively [1]. As an interesting compound structurally related to the pheromones, *cis*-3-butyl-4-vinylcyclopentene (**1**) was identified by GC-mass spectrometric analyses [2] in essential oils of the brown algae, *Dictyopteris membranacea*, from the Mediterranean [3] and *D. prolifera* from the Sea of Japan [4]. However, the chiral properties, including absolute configuration and the biological activities of **1** have not been investigated so far. Here, we intended to synthesize optically active *cis*-3-butyl-4-vinylcyclopentene [(−)-**1**] *via* biologically asymmetric oxidation of racemic *cis*-3-cyclopentene-1,2-dimethanol as a substrate for horse liver alcohol dehydrogenase (HLADH) [5–9] and to determine the absolute configuration of the natural product (**1**) from *D. prolifera* and *D.* sp using the synthetic specimen.

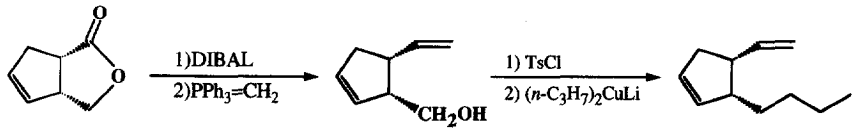
RESULTS AND DISCUSSION

Synthesis of (−)-(3R,4R)-3-*butyl*-4-*vinylcyclopenten*[(−)-**1**]

For preparation of the chiral key synthon, *cis*-3-cyclopentene-1,2-dimethanol was oxidized by incubation with immobilized HLADH on Sepharose 4B resin to give a 1:1 mixture of (+)-(1*S*,5*R*)-3-oxabicyclo [3,3,0] oct-6-en-2-one [(+)-**2**] and (+)-(1*S*,5*R*)-3-oxabicyclo [3,3,0] oct-7-en-2-one [(+)-**3** [8–12]. Separation of the lactone isomers [(+)-**2** and (+)-**3**] was achieved by low pressure column chromatography on silica gel. The lactone [(+)-**2**] eluted later was isolated in 34.5% yield and 99.2% isomerical purity (GC); $[\alpha]_D^{22}$ +58.9° (*c* 4.83, CH_2Cl_2) [1]. The pure lactone [(+)-**2**] was converted by reduction with diisobutylaluminum hydride (DIBAL), followed by Wittig reaction with methylidenetriphenylphosphorane, to (−)-(1*R*,5*R*)-*cis*-5-vinyl-2-cyclopenten-1-methanol [(−)-**4**] in 62% yield [8, 13, 14] (Fig. 1). This alcohol [(−)-**4**] was treated with *p*-toluenesulfonyl chloride to give (−)-(1*R*,5*R*)-*cis*-(5-vinyl-2-cyclopentene-1-yl)-methyl *p*-toluenesulfonate [(−)-**5**], quantitatively [2]. At the final step, the tosylate [(−)-(1*R*,5*R*)-**5**] was elongated by coupling with lithium dipropylcuprate [15, 16], affording (−)-(3*R*,4*R*)-*cis*-3-butyl-4-vinylcyclopentene [(−)-**1**] in 53% yield; $[\alpha]_D^{20}$ −17° (*c* 0.909, pentane) (over 99% e.e.). The overall yield of (−)-**1** was 7.6% based on (±)-**2** (6 steps).

Absolute configuration of cis-3-*butyl*-4-*vinylcyclopentene in essential oils from brown algae*

Previously, it has been reported that the ocean smell of an essential oil from the brown alga, *D. prolifera*, consists of mainly C_{11}-hydrocarbons, i.e. dictyopterenes A, B, C′ and D′ and *cis*-3-butyl-4-vinylcyclopentene (**1**), and some unknown compounds [4]. Here, the occurrence and composition of the cyclopentene [1] was explored in essential oils of some *Dictyopteris*, such as *D. prolifera*, *D. sp.*, *D. undulata* and *D. divaricata* (Table 1). In *D.* sp. [17], the cyclo-



(+)-2 (-)-4 (-)-1

Fig. 1. Synthetic route of (−)-(3*R*,4*R*)-3-butyl-4-vinylcyclopentene [(−)-**1**].

Table 1. C_{11}-Hydrocarbons identified in essential oils of the genus *Dictyopteris*

Hydrocarbons	Composition (%)*			
	DP	DU	DD	DS
(3*S*,4*S*)-3-Butyl-4-vinylcyclopentene	2.5	—	—	58.1
Dictyopterene A	63.3	20.9	—	10.9
4-(1*Z*)-Hexenylcyclopentene	t	—	—	—
Dictyopterene D′				
(ectocarpene)	15.9	40.7	t	20.5
(*E*-isomer)	—	—	—	t
Dictyopterene C′	18.2	38.5	t	10.5

* Total C_{11}-hydrocarbons: 100%, t: trace, DP: *D. prolifera*, DU: *D. undulata*, DD: *D. divaricata*, DS: *D.* sp.

pentene derivative (**1**) was the major constituent of the C_{11}-hydrocarbons. Synthetic (−)-(3*R*,4*R*)-**1** coincided with the peak which appeared late on in the chiral GC (CP-Cyclodex 236 M, 40 m) of the racemic mixture [(±)-**1**], while the natural product (**1**) from the essential oils of *D. prolifera* and *D.* sp. coincided with the front peak and, furthermore, synthetic (−)-**1** and natural **1** were separated from each other (Fig. 2). Conclusively, natural **1** was not identical with synthetic (−)-(3*R*,4*R*)-**1**, that is, natural **1** and synthetic (−)-**1** were enantiometers of each other; thus, the absolute configuration of natural **1** is (+)-(3*S*,4*S*)-3-butyl-4-vinylcyclopentene [(+)-**1**] with *ca* 100% enantiomeric excess. This absolute configuration is the same as that of the analogous algal pheromones, multifidene and viridiene. Structural and stereochemical relationships between (+)-(3*S*,4*S*)-**1** and the pheromones are also seen between those of dictyotene, ectocarpene and desmarestene. Thus, it is expected that (+)-(3*S*,4*S*)-3-butyl-4-vinylcyclopentene could be identified as a new 12th algal pheromone from some brown algae, while *D. prolifera* and *D.* sp. are vegetative plants.

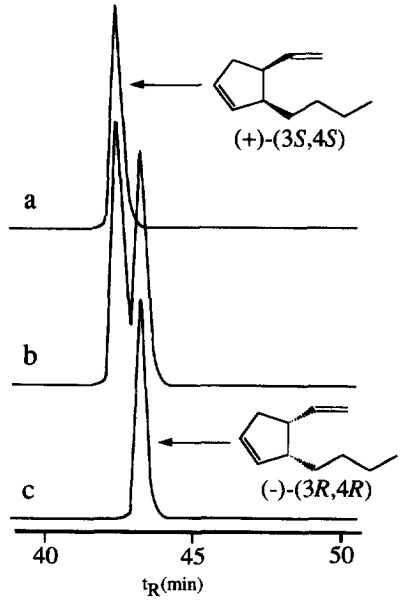


Fig. 2. Enantiomer separation of *cis*-3-butyl-4-vinylcyclopentene [(−)-**1**] by chiral GC. (a) *cis*-3-Butyl-4-vinylcyclopentene from *D. prolifera*; (b) racemic *cis*-3-butyl-4-vinylcyclopentene; (c) synthetic (−)-(3*R*,4*R*)-3-butyl-4-vinylcyclopentene.

EXPERIMENTAL

cis-3-*Cyclopentene*-1,2-*dimethanol.* A soln of (±)-**2** (8.0 g, 55.7 mmol) [18] in dry THF (40 ml) was added slowly at room temp to a suspension of $LiAlH_4$ (1.7 g, 44.8 mmol) in THF (100 ml). After stirring for 30 min under reflux, excess hydride was quenched with 5 N NaOH (5 ml) and the granular pp. filtered off. The filtrate was extracted with EtOAc and dried over Na_2SO_4. The extract was concd *in vacuo* and the residue distilled to give 5.3 g (66.9%) of *cis*-3-cyclopentene-1,2-dimethanol as a colourless oil, bp 99–100°/0.5 mmHg. IR(film) cm^{-1}: 3300 (OH), 3060 (=C–H). ^1H NMR (250 MHz, $CDCl_3$): δ 2.03–2.11 (*m*, 1H), 2.34–2.41 (*m*, 1H), 2.64–2.70 (*m*, 1H), 3.03 (*s*, 1H), 3.58–3.68 (*m*, 3H), 3.74–3.84 (*m*, 2H), 5.53–5.83 (*m*, 2H).

(+)-(1S,5R)-3-*Oxabicyclo*[3,3,0]*oct*-6-*en*-2-*one* [(+)-**2**]. *cis*-3-Cyclopentene-1,2-dimethanol (3 g, 22 mmol), NAD^+ (1.2 g, 1.8 mmol) and FMN (16.5 g, 34.5 mmol) were dissolved with stirring in 0.075 M glycine–$Na_4P_2O_7$ buffer (pH 9, 500 ml) [8]. To the mixt. was added Sepharose-bound horse liver alcohol dehydrogenase (Sigma) (130 mg) and stirred for 22 hr. The immobilized enzyme was filtered off and washed with 0.05 M K-Pi buffer (pH 7, 100 ml). The combined filtrate was acidified to pH 3 with conc. HCl, extracted

with $CHCl_3$ and dried over Na_2SO_4. The extract was concd *in vacuo* and the residue filtered through silica gel to remove FMN and other by-products. The products [(+)-**2** and (+)-**3**] were sepd by low pressure CC over silica gel (isooctane–Et_2O), monitoring the eluent refractometrically. The lactone isomer (+)-**2** eluted second and was obtained in 34.5% yield (476.4 mg, 3.8 mmol) as a colourless oil. IR (film) cm^{-1}: 3060 (=C–H), 1750 (C=O), 1610 (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.70–2.80 (*m*, 2H), 3.12–3.16 (*m*, 1H), 3.57–3.62 (*m*, 1H), 4.23–4.45 (*m*, 2H), 5.65–5.89 (*m*, 2H). $[\alpha]_D^{22}$ +58.9° (*c* 4.83, CH_2Cl_2). And (+)−**3** as a colourless oil in 39.1% yield (537.1 mg, 4.3 mmol). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.31–2.36 (*m*, 1H), 2.70–2.78 (*m*, 1H), 3.22–3.30 (*m*, 1H), 3.64–3.68 (*m*, 1H), 3.86–3.90 (*m*, 1H), 4.55–4.60 (*t*, 1H), 5.75–5.91 (*m*, 2H). $[\alpha]_D^{22}$ +320.0° (*c* 2.32, CH_2Cl_2).

(−)-(1R,5R)-5-*Vinyl*-2-*cyclopenten*-1-*methanol* [(−)-**4**]. Diisobutylaluminum hydride (DIBAL: 1.5 M in toluene; 0.7 ml, 1.1 mmol) was added carefully to a stirred soln of (+)-**2** (140 mg, 0.9 mmol) at −78° under N_2 [8]. After stirring for 2 hr at −78°, the hydride was quenched with dry MeOH (20 ml) and the mixt. added to a soln of methylidene triphenylphosphorane [methyltriphenylphosphonium bromide (0.6 g, 1.6 mmol), *n*-BuLi (1.6 M in hexane; 1.5 ml, 2.4 mmol) in dry THF (10 ml)]. The reaction mixt. was stirred for 1 hr and then H_2O (50 ml) was added. The soln was poured into brine and extracted with Et_2O. The Et_2O extract was concd *in vacuo* to give a residue, which was purified by CC over silica gel (hexane–ether, 7:3) to give 70.6 mg (62%) of (−)-**4** as a colourless oil. IR(film) cm^{-1}: 3360 (OH), 3070 (=C–H), 1640 (C=C), 1620 (C=C), 920, 820 (=CH_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.53 (*s*, 1H), 2.21–2.53 (*m*, 2H), 2.86–3.28 (*m*, 2H), 3.58–3.60 (*d*, 2H), 5.04–5.17 (*m*, 2H), 5.62–5.67 (*m*, 1H), 5.87–6.10 (*m*, 2H).

(−)-(1R,5R)-(5-*Vinyl*-2-*cyclopenten*-1-*yl*) *methyl p-toluenesulfonate* [(−)-**5**]. A mixt. of (−)-**4** (50 mg, 0.36 mmol) and *p*-toluenesulfonyl chloride (110 mg, 0.56 mmol) in dry pyridine (3 ml) was stirred for 14 hr at 0° under N_2. The mixt. was poured into ice-H_2O and extracted with Et_2O, washed with satd $CuSO_4$, satd $NaHCO_3$ soln and brine, and dried with Na_2SO_4. The extract was concd *in vacuo* to give 100.6 mg (quant.) of (−)-**5** as a yellow oil. IR (film) cm^{-1}: 3070 (=C–H), 2950, 2930, 2860, 1640 (C=C), 1600 (C=C), 1500, 1460, 1360, 1310, 1290, 1210, 1190, 1170 (O=S=O), 1100, 960, 880, 840, 820, 660 (S–O–C). ^{1}H-NMR (60 MHz, $CDCl_3$): δ 0.70–1.00 (*m*, 2H), 2.48 (*s*, 3H), 3.00–3.12 (*m*, 2H), 3.93–4.07 (*m*, 2H), 4.88–5.21 (*m*, 2H), 5.64–5.83 (*m*, 3H), 7.30–7.89 (*m*, 4H).

(−)-(3R,4R)-3-*Butyl*-4-*vinylcyclopentene* [(−)-**1**]. *n*-C_3H_7Li (1.25 M in Et_2O, 3 ml, 3.8 mmol) which was prepd from Li (128 mg, 18.2 mmol) and *n*-C_3H_7Br (0.32 ml, 5.3 mmol) in dry Et_2O (3.2 ml) was added to a soln of CuI (350 mg, 1.8 mmol) in dry Et_2O (3 ml) at −40° under N_2. After the mixt. was stirred for 1 hr at −78°, (−)-**5** (100 mg, 0.36 mmol) was added. The mixt. was stirred for 6 hr at −40°, then the reaction mixt. was poured into ice-satd NH_4Cl soln, extracted with Et_2O, washed with satd NH_4Cl soln, satd $NaHCO_3$ soln and brine, and dried with Na_2SO_4. The extract was concd *in vacuo* and the residue chromatographed over silica gel (pentane) to give 32.3 mg (53.0%) of **1** as a colourless oil. IR (film) cm^{-1}: 3050 (=C–H), 2930, 2860, 1640 (C=C), 1620 (C=C), 1470, 1380, 1000, 910, 800, 720. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78–0.83 (*t*, 3H), 1.14–1.31 (*m*, 6H), 2.01–2.38 (*m*, 2H), 2.52–2.58 (*m*, 1H), 2.75–2.88 (*quint.*, 1H), 4.82–4.98 (*m*, 2H), 5.61–5.88 (*m*, 3H); ^{13}C-NMR (62.5 MHz, $CDCl_3$): 14.09, 23.03, 29.74, 30.41, 37.71, 46.40, 48.44, 114.10, 129.17, 135.21, 140.27; MS (eV): 150 (9.3), 121 (11.6), 107 (14.0), 93 (81.4), 79 (100), 55 (9.3), 41 (12.8). $[\alpha]_D^{20}$ −17° (*c* 0.909, pentane).

Absolute configuration of cis-3-*butyl*-4-*vinylcyclopentene in* Dictyopteris *oils*. Fresh fronds were homogenized in distilled H_2O and the homogenate steam-distilled. The distillate was extracted with pentane, dried over Na_2SO_4 and cond *in vacuo* to give an essential oil. The essential oil was analyzed by GC-MS. GC analysis was carried out on a fused silica glass capillary column (0.25 mm × 50 m, DB-1). The column temp was programmed from 75° (10 min hold) to 240° at 3° min^{-1}. The ionization energy was 20 eV. The peak at 20.6 min was identical with racemic **1** and synthetic (−)-**1**; *m/z* (rel. int.) 41 (20), 55 (9.0), 66 (28), 67 (28), 76 (33), 77 (16), 79 (100), 91 (29), 93 (75), 107 (9), 121 (7), 150 (5, $[M]^+$). Racemic **1** was sepd into two peaks (1:1) by chiral GC (0.25 mm × 40 m, CP-Cyclodex 236M; column temp. 40° (hold 4 min) −215° (1° min^{-1}). The oils from *D. prolifera* and *D.* sp. were chromatographed on 25% silver nitrate–silica gel (pentane–Et_2O) to give a small amount of **1** containing traces of contaminants. The longer R_t peak (43.4 min) coincided with synthetic (−)-(3*R*,4-*R*)-**1** and the shorter R_t one (43.0 min) with natural **1** in the essential oils (Fig. 2).

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