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Diterpenes from the Far-eastern brown alga *Dictyota dichotoma*

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Abstract

Two diterpenes, ent-erogorgiaene and (+)-1,5-cyclo-5,8,9,10-tetrahydroerogorgiaene, were isolated from the Russian Far-eastern population of the brown alga *Dictyota dichotoma* along with three previously known from this alga terpenoids. In addition, pentadecane was the first time isolated as natural product from this species. The structures of all compounds and their stereochemistry were determined using 1D and 2D NMR (^{1}H–^{1}H COSY, DEPT, HSQC, HMBC and NOESY), mass spectrometry, and optical rotation data.

Keywords: *Dictyota dichotoma*; Dictyotaceae; Diterpenes; Sesquiterpenes; Ent-erogorgiaene; (+)-1,5-Cyclo-5,8,9,10-tetrahydroerogorgiaene; NMR; Tumor cells; Cytotoxic activity

1. Introduction

Brown algae belonging to the family Dictyotaceae have given rise to a great number of secondary metabolites (Faulkner, 2002) possessing antibiotic, antifungal, antiviral, cytotoxic and antitumor activities (Amico et al., 1980; Sun et al., 1983; Ishitsuka et al., 1988; Siamopoulou et al., 2004). So far new studies on these algae frequently lead to the isolation of new natural products in spite of the fact that Dictyotaceae is one of the most studied algal families in respect of secondary metabolites (Duran et al., 1997; Siamopoulou et al., 2004). It is well known that diterpenoids, which are generally grouped in several types, such as dolabellanes, hydroazulenoids, xenicanes and so-called extended sesquiterpenoids, proved to be main secondary metabolites of these algae depending upon time and locality of collection. However, there were no reports on natural products from the Russian populations of the species belonging to Dictyotaceae. In continuation of our studies on natural products from the Far-eastern algae (Lyakhova et al., 2004), we have made an investigation of a sample of the brown alga *Dictyota dichotoma*, collected in Troitsa Bay of the Peter the Great Gulf southward Vladivostok. Herein we report the isolation, structures and stereochemistry of two new diterpenoids unprecedented in brown algae. In addition, four previously known compounds were isolated.

2. Results and discussion

Four diterpenoid metabolites, one sesquiterpenoid and one hydrocarbon, including two new ones (**1** and **2**) have been isolated from ethanolic extract of *D. dichotoma* by column chromatography on silica gel followed by HPLC. The diterpenoids isopachydictyol A (Duran et al., 1997) and pachydictyol A (Hirschfeld et al., 1973) as well as sesquiterpenoid axenol (De Rosa et al., 1994) have been identified by comparison of their NMR, EIMS spectral data and physical constants with literature data. Hydrocarbon was identified as pentadecane using NMR and EIMS spectra by comparison with those of standard sample. The pentadecane is reported for the first time as *D. dichotoma* metabolite.

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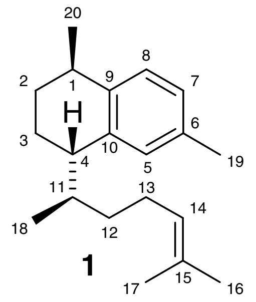

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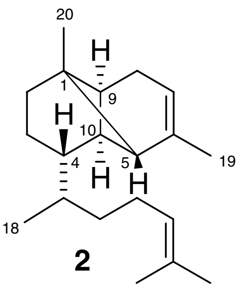

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The structural determination of diterpenes (**1**) and (**2**) was based on spectroscopic methods and comparison with literature data. Compound **1** was isolated as colourless oil and analysed for the molecular formula $C_{20}H_{30}$ on the basis of HREIMS. The ^{13}C spectrum exhibited 20 signals (five CH_3, four CH_2, seven CH and four C). The ^1H and ^{13}C NMR spectra (Table 1) indicated the presence of a 1,2,4-trisubstituted benzene ring, a trisubstituted double bond, an aromatic, two olefinic, and two other methyl groups. All these data suggested that the compound is a bicyclic benzene-containing diterpene. The COSY-45-HSQC experiments revealed the $(CH_3)CH{-}(CH_2)_2{-}CH{-}CH(CH_3){-}(CH_2)_2{-}CH{=}C(CH_3)_2$ fragment. The HMBC correlations, given in Table 1, allowed us to bind this fragment to trisubstituted benzene cycle and determine the position of benzylic methyl. As result, it was suggested that compound **1** has a serrulatane skeleton system identical to that of erogorgiaene, an antimycobacterial diterpene recently isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* (Rodriguez and Ramirez, 2001).

The relative stereochemistry for the stereocentres of **1** was established by NOESY (Table 1) and ^1H NMR decoupling experiments. There were NOESY correlations H-1/H_α-3 and H-4/H_β-2. The irradiation of H-1 (δ 2.66, *m*) collapsed a triplet of doublets of doublets of H_β-2 (δ 1.27, $J = 11.7$, 9.7, 3.1 Hz) to a triplet of doublets ($J = 11.8$, 3.1 Hz). Large coupling between H-1 and H_β-2 showed these protons to be pseudoaxial and, therefore, H-4 and H_α-3 are also pseudoaxial, but substituents at C-1 and C-4 are pseudoequatorial. The very intense NOE correlation of CH_3-18/H_α-3 suggested that the predominating conformation of **1** is that having *gauche* interaction of CH_3-18 and C-3. This was confirmed by the very intense NOE correlation between H-5/H-11. Thus, the spatial proximity of H_β-2 and H-4 on the one face of the molecule and H-1, H_α-3 and CH_3-18 on the opposite face were established. It corresponded to 1*S*, 4*R*, 11*S* or 1*R*, 4*S*, 11*R* configurations in **1**. The 1*S*, 4*R*, 11*S* absolute configuration of erogorgiaene was confirmed by enantioselective total

Table 1
^{13}C NMR (125.7 MHz) and ^1H NMR (500 MHz), HMBC and NOESY spectroscopic data for compounds **1**[a] and **2**[b]

C[c]	**1**				**2**			
	δ_C	δ_H (*J* Hz)	HMBC	NOESY	δ_C	δ_H (*J* Hz)	HMBC	NOESY
1	33.2 *d*	2.66 *m*	9	3α	39.3 *s*			
2	32.2 *t*	H_α1.80 *m* H_β			36.2 *t*	1.60 *m*		
		1.27 *td d* (11.7, 9.7, 3.1)	9			1.72 *td* (10.0,3.5)	1, 4, 9, 20	20
3	22.0 *t*	1.47 (H_α) *m*	10		20.3 *t*	1.52 *m*	4	18
		1.74 (H_β) *m*	10	1, 18		1.52 *m*		
4	41.9 *d*	2.90 *m*	9, 10	2β, 5[d],13[d]	42.9 *d*	1.71 *m*	9, 18	
5	128.5 *d*	7.10 *s*	4, 9, 19	4[d], 11, 18[d], 19	54.8 *d*	1.51 *m*	1, 4, 9, 10, 19	
6	134.9 *s*				143.9 *s*			
7	126.6 *d*	6.95 *br d* (7.9)	5, 9, 19	19	116.0 *d*	5.19 *bs*	5, 19	
8	126.9 *d*	7.16 *d* (7.9)		20	30.0 *t*	2.17 *dq* (17.1, 2.7)	9	20
						2.20 *dq* (17.1, 2.3)	7, 6	
9	140.6 *s*				37.0 *d*	2.11 *dt* (6.5, 3.0)	5, 7	18
10	140.0 *s*				45.2 *d*	1.62 *s*	1, 5, 6, 8, 11	18
11	37.5 *d*	2.20*m*		5	37.3 *d*	1.41 *m*	12	
12	35.6 *t*	1.48 *m*		14	34.2 *t*	1.39 *m*	4, 11, 13, 14	18
		1.36 *m*		14, 18		1.06 *m*	18	
13	26.8 *t*	2.10 *m*		4[d], 18	25.9 *t*	1.90 *m*	18	
		2.10 *m*				1.98 *m*	15	17
14	125.5 *d*	5.28 *br t* (7.2)	12, 13, 16, 17	12, 16	125.1 *d*	5.09 *brt* (7.0)	12, 16, 17	
15	131.0 *s*				131.0 *s*			
16	18.0 *q*	1.72 *br s*	14, 15, 17	14	17.6 *q*	1.60 *brs*	14, 15, 17	
17	25.9 *q*	1.60 *br s*	14, 15, 17		25.7 *q*	1.68 *brs*	14, 15, 16	13
18	14.7 *q*	0.72 *d* (6.6)	4, 11, 12	3α, 5[d], 12, 13	15.5 *q*	0.81 *d* (7.0)	4, 11, 12	3, 9 10, 12
19	21.3 *q*	2.20 *s*	5, 6, 7	5, 7	23.1 *q*	1.66 *q* (2.0)	5, 6, 7	
20	22.1 *q*	1.22 *d* (6.9)	1, 2, 9	8	19.2 *q*	0.78 *s*	1, 2, 5, 9	2, 8

[a] Measured in C_6D_6.
[b] Measured in $CDCl_3$.
[c] Assignments were made with the aid of the ^1H–^1H COSY and HSQC spectra.
[d] Cross peaks of low intensity.

syntheses (Cesati et al., 2004; Davies and Walji, 2005). However, diterpene (**1**) demonstrated the negative optical rotation with value similar to that of erogorgiaene ($[\alpha]_D^{20} - 28.0°$ against $[\alpha]_D^{25} + 24.4°$ for erogorgiaene) and, therefore, has the 1*R*, 4*S*, 11*R* absolute configuration. It was proved to be the previously unknown *ent*-erogorgiaene or (−)erogorgiaene.

Diterpene (**2**) was isolated as colourless oil and analysed for the molecular formula $C_{20}H_{32}$ on the basis of HRE-IMS. The ^{13}C spectrum exhibited 20 signals (five CH_3, five CH_2, seven CH and three C). The ^1H and ^{13}C NMR spectra (Table 1) indicated the presence of two trisubstituted double bonds [δ_H 5.09 (1H, *br t*, $J = 7.0$), δ_C 125.1 (*d*), 131.0 (*s*); δ_H 5.19 (1H, *br s*), δ_C 116.0 (*d*), 143.9 (*s*)], three olefinic [δ_H 1.68 (3H, *s*), δ_C 25.7 (*q*); δ_H 1,66 (3H, *q*, $J = 2.0$), δ_C 23.1 (*q*); δ_H 1.60 (3H, *br s*), δ_C 17.6 (*q*)], one secondary and one tertiary methyl groups [δ_H 0.81 (3H, *d*, $J = 7.0$), δ_C 15.5 (*q*); δ_H 0.78 (3H, *s*), δ_C 19.2 (*q*)]. All the above mentioned data suggested that the compound is a tricyclic diterpene.

The COSY-45-HSQC experiments, supported by internal HMBC correlations, revealed the $CH{-}CH(CH_3){-}(CH_2)_2{-}CH{=}C(CH_3)_2$ substructure similar to that in **1** along with $CH{-}C(CH_3){=}CH{-}CH_2$ fragment. The total structure and relative stereochemistry of 1,5-cyclo-5,8,9,10-tetrahydroerogorgiaene (**2**) was finally solved via HMBC experiments (see Fig. 1) and NOESY (Table 1), respectively. The proton H-10 showed HMBC correlations with signals of quaternary carbons C-6 and C-1, methylene carbon C-8 and two methine carbons C-11 and C-5. Along with other HMBC correlations, such as H_3-20/C-1, C-2, C-5, H-9/C-5, C-7 and H-5/C-9, it deduced the cyclobutane system in **2**.

It is of special interest that practically no coupling was observed between H-10 and adjacent protons H-4, H-5 and H-9 suggesting a dihedral angle of approximately 90° between these protons. The same absence of coupling was indicated in the ^1H NMR spectrum of lemnalol, a sesquiterpene also containing a similar bridged cyclobutane system (Kikuchi et al., 1982). Moreover, some other features of the ^1H NMR spectrum of **2** looked like those of well known natural sesquiterpenes, containing a bridged cyclobutane system. For example, a signal of olefinic methyl CH_3-19 was indicated as quartet because of five-bond coupling with methylene protons $H_{\alpha,\beta}$-8. A four-bond coupling with constant about 6 Hz was observed between bridgehead protons H-9 and H-5. This was in accordance with some peculiarities of the ^1H NMR spectrum of α-pinene (Bates and Thalacker, 1968). The core part of **2** was identical to that of α-copaene, a constituent of a number of plant oils. The stereochemistry of (−)-α-copaene was established in 1965 by its conversion into (−)-cadinene and other chemical transformations (De Mayo et al., 1965; Kapadia et al., 1965).

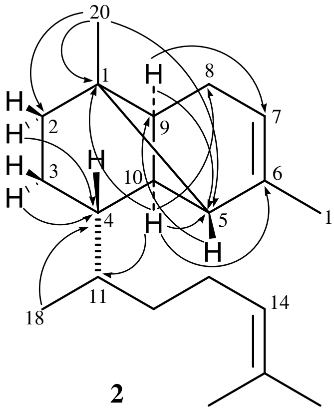

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Fig. 1. The key HMBC correlations for compound **2**.

The cross peaks H-2/H-20, H-8/H_3-20, H-9/H_3-18, H-10/H_3-18 in the NOESY spectrum of **2** indicated that H-9, H-10 and C-11 are allocated on the one face of the molecule. All these data along with results of HMBC experiments indicated the 1*R**, 4*S**, 5*S**, 9*S**, 10*S**, 11ξ relative stereochemistry of **2**.

The diterpene (**1**) proved to be closely related to some metabolites of gorgonian corals belonging to the so-called pseudopterane series, which are well known as anti-inflammatory and analgesic metabolites (Look et al., 1986). Earlier, some cases of biochemical parallelism in terpenoid biosynthesis between brown algae and cnidarians were described (Faulkner, 2002; Braekman et al., 1978). This biochemical parallelism may probably be explained by the participation of microalgal symbionts of *Pseudopterogorgia* spp. in biosynthesis of diterpenes (Boehnlein et al., 2005). Enantioisomeric metabolites have rarely been found in differing from each other marine organisms (Faulkner, 2002), although some cases were described when marine invertebrates belonging to the same genus or even species produced antipodial secondary metabolites (Makarieva et al., 1981; Duque et al., 2004).

To the best of our knowledge, diterpene (**2**) possesses a new skeleton system. It is a new representative of a series of so-called extended sesquiterpenoids isolated from brown algae.

The cytotoxicity of pachidictyol A and axenol for several human tumor and mouse JB6 Cl 41 epithelial cell lines was tested using the MTS method (Barltrop et al., 1991). Both compounds showed moderate activity against human tumor cell lines and were significantly less cytotoxic against normal mouse epithelial cells. Furthermore, pachidictyol A was two times more cytotoxic (IC_{50}= 98 μM, 74 μM, 99 μM, 110 μM against HeLa, THP-1, SNU C-4 and JB6 Cl 41 cells, respectively) than axenol (IC_{50} = 182 μM, 155 μM, 185 μM, 237 μM against HeLa, THP-1, SNU C-4 and JB6 Cl 41 cells, respectively).

3. Experimental

3.1. General

^1H NMR (500 MHz) and ^{13}C NMR (125.7 MHz), DRX – 500 “Bruker”, measured in C_6D_6 and $CDCl_3$, TMS as int.

standard (coupling constant, *J* in Hz); GLC–MS: HP-5MS capillary column at 70 → 270 °C, helium, 70 eV; HREIMS: HRMS AMD-604 connected with GH HP 5890, DB-5 capillary column at 70 → 250 °C, 70 eV. Optical rotation measurements were performed on a Polarimeter 343, Perkin–Elmer. CC: silica gel (KSK, Russia, 0.50–1.60 mm). HPLC: ULTRASPHERA™ Si (5 μm, 250 × 4.6 mm). TLC: silica gel plate (Sorbfil, Russia, 5–17 μm). All known metabolites were identified by comparison of their spectral data with those of the authentic specimens. Yields are based on the weight of dry alga.

3.2. Collection

A sample of *D. dichotoma* was collected in Troitsa Bay of the Peter the Great Bay, Sea of Japan, Russia, at a depth of 1–1.5 m, in August 2004. The voucher specimen is deposited in the Herbarium of the Pacific Institute of Bioorganic Chemistry (90415a).

3.3. Extraction and isolation

Fresh alga (dry weight 53 g) was exhaustively extracted with EtOH at room temperature. The EtOH extract was evaporated to a dark brawn gum (22.8 g) that was purified by column flash-chromatography on silica gel using EtOAc as eluent. The EtOAc solution was dried to dark brown oil (7.4 g) that was divided into four fractions by silica gel CC using step-wise gradient (hexane–EtOAc).

Further silica gel CC (hexane) separations of fraction 1 eluted with hexane yielded two fractions. First of them was chromatographed on a silica gel column impregnated with 20 wt% $AgNO_3$ using step-wise gradient (hexane–benzene) to obtain pentadecan (19.6 mg; 0.04%). The next fraction was subjected to normal phase HPLC (hexane) to yield ent-erogorgiaene (**1**) (1.2 mg; 0.002%).

Fraction 2 was rechromatographed by CC over silica gel in step-wise gradient (hexane–EtOAc) to give four fractions. First of them was submitted to HPLC on silica gel (hexane) to yield 1,5-cyclo-5,8,9,10-tetrahydroerogorgiaene (**2**) (0.7 mg; 0.001%). The second fraction was further subjected to normal phase HPLC (hexane–EtOAc, 40:1) to yield pure isopachydictyol A (31.7 mg; 0.06%), pachydictyol A (54.3 mg; 0.1%) and axenol (8.3 mg; 0.02%).

3.4. *Ent*-erogorgiaene (*1*)

Colourless oil; $[\alpha]_{\mathrm{D}}^{20} - 28.0°$ ($CHCl_3$; *c* 0.05); ^{1}H and ^{13}C NMR, see Table 1; GLC–MS *m*/*z* (%) 270 [M^{+}] (19), 199 (9), 186 (36), 159 (100), 157 (15), 143 (11), 129 (14), 115 (5), 105 (6), 91 (4), 69 (5). HR-MS *m*/*z*: 270.2341. Calc. for $C_{20}H_{30}$, 270.2347 [M^{+}].

3.5. 1,5-Cyclo-5,8,9,10-tetrahydroerogorgiaene (*2*)

Colourless oil; $[\alpha]_{\mathrm{D}}^{20} + 4.0°$ ($CHCl_3$; *c* 0.05); ^{1}H and ^{13}C NMR, see Table 1; GLC–MS *m*/*z* (%) 272 [M^{+}] (9), 187 (11), 159 (100), 145 (16), 132 (21), 119 (94), 105 (72), 91 (36), 81 (27), 69 (30), 55 (23). HR-MS *m*/*z*: 272.2505. Calc. for $C_{20}H_{32}$, 272.2504 [M^{+}].

3.6. Cell viability assay

Human tumor HeLa (cancer of the cervix), THP-1 (leukemia), SNU C-4 (colon cancer) and mouse epithelial JB6 Cl 41 cell lines were used for the assay. Cells were cultured overnight in 96-well plates (6000 cells/well) using 10% FBS-MEM. Then the medium was replaced with 10% FBS-MEM containing the substances at different concentrations in a volume of 0.1 ml and the cells were incubated for 22 h. Then 20 μl of the MTS reagent was added into each well. After 2 h the MTS reduction was measured spectrophotometrically at 492 nm and at 690 nm as a background using the μQuant microplate reader (Bio-Tek Instruments Inc., USA). For each compound, two independent experiments with three samples for each concentration were performed.

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