Three Dolabellanes and a Macrolide from the Sponge *Dysidea* sp. from Palau

Qing Lu and D. John Faulkner*

Scripps Institution of Oceanography, University of California at San Diego, La Jolla, California 92093-0212

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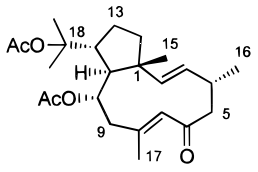
A specimen of *Dysidea* sp. from Palau contained three new dolabellane diterpenes **1**−**3** and an unstable 14-membered macrolide, arenolide (**4**), which showed modest cytotoxicity. From a chemotaxonomic viewpoint, these metabolites are so unusual that we discuss their possible origin.

As part of a program to discover new cytotoxic agents, we submitted a number of extracts derived from samples that had not previously shown any activity in other bioassays for screening in a high throughput cytotoxicity assay. While this exercise generally resulted in the identification of known cytotoxins, we found promising activity in the methanolic extract of a specimen of *Dysidea* sp. that had been collected in Palau in 1981 and stored in methanol. *Dysidea* species usually produce sesquiterpenes,[1−3] merosesquiterpenes,[2,4] and other terpenoids,[2,5] while those *Dysidea* species that contain symbiotic cyanobacteria are the source of brominated biphenyl ethers[2,6] or chlorinated amino acid derivatives[2,7] produced by the cyanobacteria.[8] In this paper, we report the isolation of three diterpenes of the dolabellane class and a 14-membered macrolide and comment on this apparent chemotaxonomic irregularity.



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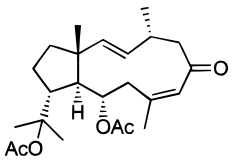

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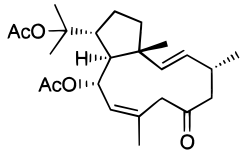

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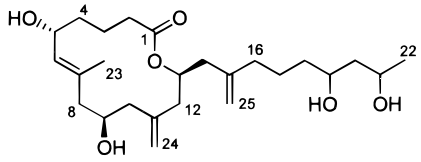

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Results and Discussion

The hexane-soluble material from a methanolic extract of the sponge was chromatographed on silica gel to obtain (1*R**,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**1**, 0.01% dry wt), (1*R**,2*E*,4*R**,7*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**2**, 0.003% dry wt), and (1*R**,2*E*,4*R**,8*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,8-dien-6-one (**3**, 0.005% dry wt). The material that was soluble in ethyl acetate was purified by reversed-phase chromatography and reversed-phase HPLC to separate arenolide[9] (**4**, 0.007% dry wt) from a polymeric material that appeared to arise from polymerization of arenolide.

(1*R**,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,7-dien-6-one (**1**) was obtained as a colorless viscous oil. The molecular formula, $C_{24}H_{36}O_5$, which was derived from HRMS and ^{13}C NMR data, requires seven degrees of unsaturation. The IR spectrum contained a strong ester band at 1730 cm^{-1} and a band at 1680 cm^{-1} that was assigned to an unsaturated ketone. The latter assignment was supported by an absorption in the UV spectrum at 244 nm (ϵ 3200). Analysis of the NMR data (Table 1) revealed the presence of two acetate groups [δ 1.91 (s, 3 H) and 2.06 (s, 3 H)], a β,β-disubstituted α,β-unsaturated ketone [δ_H 6.05 (br s, 1 H); δ_C 201.5 (s), 146.3 (s) and 131.3 (d)], and a disubstituted double bond [δ_H 4.99 (dd, 1 H, J = 16, 1 Hz) and 5.53 (dd, 1 H, J = 16, 6 Hz); δ_C 138.2 (d) and 132.1 (d)]. Interpretation of the COSY, HMQC, and HMBC data allowed the remaining two degrees of unsaturation to be assigned to a dolabellane carbon skeleton. The Me-15 signal at δ 0.85 (s, 3H) showed HMBC correlations to C-1, C-2, C-11, and C-14, which placed the disubstituted double bond next to the ring junction. The Me-16 signal at 1.01 (d, 3 H, J = 7 Hz) correlated with the C-3, C-4, and C-5 signals, allowing it to be placed on a methine carbon adjacent to the other terminus of the disubstituted double bond. Correlations from both H_2-5 signals and H-7 to the carbonyl signal at δ 201.5 required the carbonyl group to be positioned at C-6 and correlations from Me-17 to C-7, C-8, and C-9 placed the methyl group at C-8. The H-10 methine signal at δ 4.80 (ddd, 1 H, J = 10, 4, 1.5 Hz) showed correlations to C-1, C-8, C-9, C-11, and to the acetate signal at δ 170.2: these data confirmed the presence of an 11-membered ring and allowed the two sets of acetate signals to be differentiated. The correlations from both methyl signals at δ 1.38 (s, 3 H) and 1.60 (s, 3 H) to C-12, the C-18 signal at δ 84.7, and to their partner's carbon signal required the presence of an 18-acetoxy isopropyl group, the position of which was defined by the correlations from H-12 to C-10, C-11, C-13, C-18, and C-20.

* To whom correspondence should be addressed. Tel: (619) 534-4259. Fax: (619) 534-2997. E-mail: jfaulkner@ucsd.edu.

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Table 1. ^{13}C (100 MHz, $CDCl_3$) and ^1H (400 MHz, $CDCl_3$) NMR Data for (1*R**,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,7-dien-6-one (1)

C no.	δ_C	δ_H	mult, *J* (Hz)	COSY	HMBC
1	47.8				
2	138.2	4.99	dd, 16, 1	H-3	C-1, C-4, C-14, C-15
3	132.1	5.53	dd, 16, 6	H-2, H-4	C-1, C-4, C-16
4	34.1	2.54	m	H-3, H-5, H-5′, H-16	C-5
5	51.2	2.30	m	H-5′, H-4	C-3, C-4, C-6, C-7, C-16
		2.69	dd, 11, 3.5	H-5, H-4	
6	201.5				
7	131.3	6.05	br s	H-17	C-6, C-8, C-9, C-17
8	146.3				
9	43.9	2.30	m, 2 H	H-10	C-7, C-8, C-10, C-11, C-17
10	72.0	4.80	ddd, 10, 4, 1.5	H-9, H-11, H-12	C-1, C-8, C-9, C-11, OAc
11	53.9	1.61	m	H-10, H-12	C-1, C-2, C-9, C-12, C15, C-18
12	44.9	3.13	m	H-9, H-10, H-11, H-13′	C-10, C-11, C-13, C-18, C-20
13	26.2	1.47	m	H-12, H-13′	C-1, C-11, C-14
		1.93	m	H-12, H-13	
14	39.1	1.42	m	H-13′	C-1, C-13, C-15
		1.49	m	H-13′	
15	17.5	0.85	s, 3 H	C-1, C-2, C-11, C-14	
16	18.4	1.01	d, 7, 3H	H-3, H-4	C-3, C-4, C-5
17	21.5	2.01	br s, 3 H	H-7	C-7, C-8, C-9
18	84.7				
19	26.7	1.60	s, 3 H	C-12, C-18, C-20	
20	23.3	1.38	s, 3 H	C-12, C-18, C-19	
OAc	21.1	2.06	s, 3 H		
	170.2				
OAc′	23.0	1.91	s, 3 H		
	170.0				

The stereochemistry shown was assigned by interpretation of ^1H NMR coupling constants and a NOESY spectrum. The *E*-geometry of the 2,3-olefin was assigned on the basis of a 16 Hz coupling constant, while the *E*-geometry of the 7,8-olefin resulted in an NOE correlation between H-7 and both H-10 (δ 4.80) and H-9 [δ 2.30 (m, 2 H)]. There were NOE correlations between Me-15 and H-10 and H-12, which required a trans ring junction and indicated that both H-10 and H-12 were on the same (upper) face of the compound as Me-15. The stereochemistry at C-4 could be deduced from NOE correlations between H-2 and Me-16, H-11, and H-14a, all of which are on the lower face of the molecule, thereby defining the structure as (1*R**,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**1**).

The two minor dolabellanes, (1*R**,2*E*,4*R**,7*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**2**) and (1*R**,2*E*,4*R**,8*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,8-dien-6-one (**3**), are both isomers of ketone **1** that differ only in the geometry or location of one of the double bonds. The *Z*-geometry of the 7,8-olefin in ketone **2** was clearly defined by a NOE correlation between the H-7 signal at δ 6.02 (br s, 1 H) and the Me-17 signal at 1.91 (br s, 3 H). Further analysis of the NOESY spectrum revealed that the relative stereochemistry at C-1, C-4, C-10, C-11, and C-12 was the same in both **1** and **2**. It is interesting to note that changing the geometry of the 7,8-olefinic bond has a profound effect on the chemical shifts of the H-2 and H-3 signals, which, in ketone **2**, overlap at δ 5.37 (vs 4.99 and 5.53 in **1**). To rule out a possible change of geometry of the 2,3-olefin, the ^1H NMR spectrum was recorded in C_6D_6 solution, which resulted in the H-2 and H-3 signals being clearly separated at δ 5.45 (d, 1 H, J = 16 Hz) and 5.33 (dd, 1 H, J = 16, 8 Hz). In addition, we observed that the 7*Z*-ketone **2** gradually isomerized to the 7*E*-ketone **1** when stored in $CDCl_3$ solution.

Table 2. ^{13}C (100 MHz, $CDCl_3$) and ^1H (400 MHz, $CDCl_3$) NMR Data for (1*R**,2*E*,4*R**,8*Z*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,8-dien-6-one (**3**)

C no.	δ_C	δ_H	mult, *J* (Hz)	COSY
1	48.6			
2	139.5	5.20	dd, 16, 1.5	H-3
3	130.1	5.76	dd, 16, 6	H-2, H-4, H-7′
4	32.6	2.68	m	H-3, H-5, H-5′, H-16
5	48.0	2.18	dd, 12, 4.5	H-4, H-5′, H-7′
		2.92	dd, 12, 5.5	H-4, H-5, H-16
6	209.0			
7	48.0	2.62	d, 18	H-7′, H-9, H-17
		4.16	d, 18	H-5, H-7′, H-9, H-17
8	133.1			
9	126.1	5.55	br d, 10	H-7, H-7′, H-10, H-17
10	68.0	5.32	br d, 10	H-9, H-11
11	53.4	1.45	m	H-10, H-12
12	43.6	3.11	m	H-11, H-13, H-13′
13	26.3	1.37	m	H-12, H-13′
		1.90	m	H-12, H-13
14	38.3	1.44	m	H-13
		1.47	m	H-13
15	16.4	0.81	s, 3 H	
16	17.7	1.17	d, 7, 3H	H-4
17	25.6	1.79	br s, 3 H	H-7, H-7′, H-9
18	84.7			
19	26.6	1.57	s, 3 H	
20	23.4	1.33	s, 3 H	
OAc	21.0	1.99	s, 3 H	
	170.2			
OAc′	23.2	1.93	s, 3 H	
	170.0			

Ketone **3** contained a β,γ-unsaturated ketone in place of the conjugated ketone in **1**. In the ^1H NMR spectrum (Table 2), the H-10 signal at δ 5.32 (br d, 1 H, J = 10 Hz) was coupled to the H-9 olefinic signal at 5.55 (br d, 1 H, J = 10 Hz) that in turn showed long-range coupling to the Me-17 signal at δ 1.79 (br s, 3 H) and to the H_2-7 methylene signals at δ 2.62 (d, 1 H, J = 18 Hz) and δ 4.16 (d, 1 H, J = 18 Hz). The (8*Z*)-geometry of the olefinic bond was assigned on the basis of NOE correlations between H-9 and Me-17 and between H-10 and the H-7 signal at δ 4.16. Further analysis of the NOESY spectrum revealed that the relative stereochemistry at all remaining chiral centers was the same as in ketone **1**.

The macrolide, arenolide (**4**), was isolated as a colorless viscous oil. The high-resolution mass measurement established the molecular formula as $C_{25}H_{42}O_6$. The IR spectrum contained a strong hydroxyl band at 3375 cm^{-1} and bands at 1730 (sh) and 1715 cm^{-1}, both of which must be due to the lactone carbonyl. The ^{13}C NMR spectrum contained the expected 25 signals with 38 attached protons, which required that there be four hydroxyl groups in the compound. The ^{13}C NMR spectrum contained signals due to a lactone carbonyl at δ 172.5, a trisubstituted olefin (δ 135.7, 129.4), and two olefinic methylene groups (δ 142.5, 145.1, 117.9, 112.6). Since the molecular formula requires five unsaturation equivalents, arenolide (**4**) must be monocyclic. The ^1H NMR spectrum (Table 3) contained sequentially coupled signals at δ 1.22 (d, 3 H, J = 6.5 Hz), 4.13 (sextet, 1 H, J = 6.5 Hz), 1.58 (m, 2 H), 3.94 (pentet,

Table 3. ^{13}C (100 MHz, $CDCl_3$) and ^1H (400 MHz, $CDCl_3$) NMR Data for Arenolide (**4**)

C no.	δ_C	δ_H	mult, *J* (Hz)	COSY	HMBC
1	172.5				
2	34.3	2.12	m	H-2′, H-3	C-1, C-3, C-4
		2.33	m	H-2, H-3	
3	21.5	1.59	m, 2 H	H-2, H-2′, H-4, H-4′	C-1, C-2, C-5
4	36.5	1.44	m	H-3, H-4′, H-5	C-1, C-3, C-5, C-6
		1.80	m	H-3, H-4, H-5	
5	68.1	4.36	m, 11.5, 8, 3.5	H-4, H-4′, H-6	C-7
6	129.4	5.10	d, 11.5		
7	135.7				
8	44.6	1.88	dd, 14.5, 10	H-8′, H-9	C-6, C-7, C-10, C-23
		2.64	dd, 14.5, 4	H-6, H-8, H-9	
9	68.7	3.84	tdd, 10, 4, 1.5	H-8, H-8′, H-10, H-10′	
10	43.6	1.93	dd, 14, 10.5	H-9, H-10′, H-24′	C-9, C-11, C-12, C-24
		2.67	d, 14	H-9, H-10, H-24′	
11	142.5				
12	38.4	2.22	m	H-12′, H-13	C-10, C-11,C-13, C-14, C-24
		2.42	dd, 16, 3.5	H-12, H-13	
13	71.4	5.21	tt, 7, 3.5	H-12, H-12′, H-14	C-11
14	39.5	2.15	m	H-13, H-14′	C-13, C-15, C-16, C-25
		2.30	m	H-14	
15	145.1				
16	35.6	2.05	t, 7, 2 H	H-17, H-25′	C-15, C-17, C-18
17	23.7	1.48	m, 2 H	H-16, H-18	
18	36.9	1.46	m, 2 H	H-17, H-19	C-17
19	69.1	3.94	pent, 6	H-18, H-20	
20	44.2	1.58	m, 2 H	H-19, H-21	C-18, C-19, C-21, C-22
21	65.5	4.13	sext, 6.5	H-20, H-22	C-19
22	23.6	1.22	d, 6.5, 3 H	H-21	C-20, C-21
23	20.1	1.77	s, 3 H	H-6	C-6, C-7, C-8
24	117.9	4.95	s	H-12, H-12′, H-24′	C-10, C-12
		5.08	s	H-10, H-10′, H-24	
25	112.6	4.72	s	H-14, H-14′, H-25′	C-14, C-16
		4.78	s	H-16, H-25	

1 H, $J = 6$ Hz), and 1.46 (m, 2 H), which were assigned to a $CH_3CH(OH)CH_2CH(OH)CH_2-$ terminus. Further analysis of the COSY spectrum allowed us to trace the $^1H-^1H$ couplings of a second moiety from H_2-2 to the H_2-16 allylic methylene group, and the HMQC and HMBC data confirmed these assignments. The link between the two chains, a single methylene group, was established from HMBC data that showed a correlation between the H_2-16 and C-18 signals and from both the H_2-16 and H_2-18 signals to the C-17 signal. The location of the ester carbonyl (C-1) was determined from the HMBC correlations between the carbonyl signal at δ 172.5 and the H_2-2 and H_2-3 signals. No correlation was observed between H-13 and C-1, and therefore, the downfield chemical shift of the H-13 signal at δ 5.21 (tt, 1 H, $J = 7$, 3 Hz) was used to differentiate the methine bearing the ester group from those bearing hydroxyl groups (δ 4.36, 4.13, 3.94, and 3.84).

The relative stereochemistry about the 14-membered ring was determined by interpretation of the NOESY data. The H-13 signal showed a correlation to the H-25 signal at δ 4.72, which in turn showed a NOE to the H-24 signal at 4.95. If we arbitrarily assume that H-13 is in a pseudoaxial conformation below the plane of the 14-membered ring, we can deduce that both the 15(25)- and 11(24)-olefins are nearly perpendicular to and below the plane of the ring. The NOESY experiment did not differentiate between the second H-24 signal at δ 5.08 and the H-6 signal at δ 5.10, but a NOEDS experiment showed NOEs from the H-9 signal at δ 3.84 to both H-24 and H-6, implying that both are below the plane of the ring. Since the trisubstituted olefin is essentially perpendicular to the ring, the methyl group (Me-23) at C-7 must be above the plane of the ring. The correlation between the Me-23 and H-5 signals indicates that H-5 is also on the upper face of the ring, resulting in the geometry proposed. There is a slight possibility that the 14-membered ring adopts an unusual conformation in which C-9 points into the ring, in which case the observed NOEs would require the opposite configuration at C-9, but this seems unlikely on the basis of molecular modeling. When allowed to stand in $CDCl_3$ solution, arenolide (**4**) polymerized to give a product that had an ^1H NMR spectrum that was very similar if not identical to the major component of the crude ethyl acetate extract.

The dolabellanes **1** and **3** and arenolide (**4**) were evaluated for *in vitro* cytotoxicity against HCT human colon carcinoma cells and A2780 human ovarian carcinoma cells using the MTS assay.[10] The compounds showed relatively low cytotoxicity in the two human tumor cell lines after 72 h exposure (HCT116 IC_{50}'s: **1**, 80 mM; **3**, 105 mM; **4**, 21 mM: A2780 IC_{50}'s: **1**, 42 mM; **3**, 25 mM; **4**, 9.8 mM), but it is probable that much of the arenolide (**4**) had polymerized prior to the assay being run.

Diterpenes of the dolabellane class have previously been isolated from sea hares of the genus *Dolabella*,[11] which obtain them from brown algae of the genus *Dictyota*[12] and from gorgonian corals of the genus *Eunicea*.[13] Macrolides such as arenolide (**4**) are normally associated with bacteria or with certain symbiotic dinoflagellates.[14] Neither dolabellanes nor macrolides have been previously reported from *Dysidea* species. After finding no trace of merosesquiterpenes in the extracts, we reexamined the specimen and found that every piece of sponge was of a homogeneous *Dysidea* sp., that the sample contained less than 1% of foreign

material (sand), and that, in particular, brown algae and gorgonians were absent. While there is always the possibility of contamination during an extended period in storage, the lack of contamination of other samples of this vintage coupled with the fact that none of the compounds have been encountered in other samples suggests that this is unlikely. At the suggestion of a reviewer, we have examined our collecting notes for 24 March 1981, but we cannot find any reasonable alternative source for these compounds and must reluctantly conclude that the sponge contained these chemotaxonomically unusual metabolites when collected. We therefore propose that the sponge may have absorbed the compounds released by organisms in the vicinity, a scenario that may also be employed to explain the presence of red algal metabolites in sponges.[15]

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were obtained using a Varian Gemini 400 spectrometer at 400 and 100 MHz, respectively. The DEPT, COSY, NOESY, HMQC, and HMBC experiments were performed on a Varian Unity Inova spectrometer at 300 MHz. IR and UV spectra were obtained using Perkin-Elmer 1600 and Perkin-Elmer Lambda 3B spectrophotometers, respectively. Optical rotations were measured on an Autopol-III automatic polarimeter using a 1 dm cell. Low-resolution mass spectra were recorded on a 5988A Hewlett-Packard mass spectrometer. High-resolution mass spectra were obtained from the Regional Mass Spectrometry Facility at the University of California, Riverside.

Animal Material. The sponge *Dysidea* sp. (collection no. 81-132) was collected by hand at "Short Drop-off" (−20 m) in Palau on March 24, 1981, and was stored in methanol. The sponge is characterized by a very high loading of sand within the fibers, so that the sponge is unexpectedly rough to the touch. Comparison with other tropical Pacific *Dysidea* specimens allowed elimination of *D. avara*, *D. arenaria*, *D. fragilis*, and *D. herbacea* as possible species. A voucher specimen has been deposited in the SIO Benthic Invertebrate Collection (registration no. P 1172).

Extraction and Isolation. The sponge (203 g dry weight after extraction), which had been stored in MeOH for 15 years, was cut into small pieces and extracted with MeOH (2 × 1 L). The combined MeOH extracts were concentrated and partitioned between CH_2Cl_2 (800 mL) and 15% MeOH in water (800 mL). The concentrated CH_2Cl_2 fraction was partitioned between hexane (800 mL) and 10% aqueous MeOH (800 mL). The aqueous phase was partitioned between CH_2Cl_2 (600 mL) and 60% MeOH in water (600 mL). The aqueous fraction was then partitioned between EtOAc (200 mL) and water (200 mL). The concentrated hexane fraction (390 mg) was chromatographed on silica gel using 20% EtOAc in hexane as eluant to afford (1*R**,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**1**, 20.8 mg, 0.01% dry wt, fractions 35−39) and (1*R**,2*E*,4*R**,8*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,8-dien-6-one (**3**, 9.8 mg, 0.005% dry wt, fractions 21−22). Fractions 29−32 were combined and purified by HPLC (Microsorb, Si 80-199-C5) using 30% EtOAc in hexane as eluant to obtain (1*R**,2*E*,4*R**,7*Z*,10*S**,11*S**,12*R**)-10,18-diacetoxydolabella-2,7-dien-6-one (**2**, 5.4 mg, 0.003% dry wt). The concentrated EtOAc fraction (140 mg) was subjected to flash chromatography on a reversed-phase C-18 Sep-Pak column using 30% water in MeOH as eluant. The first five fractions were combined and purified by reversed-phase HPLC (Dynamax, C_{18} 83-211-C) using 35% water in MeOH as eluant to give arenolide (**4**, 13.4 mg, 0.007% dry wt).

(1*R,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,7-dien-6-one (1):** colorless viscous oil; $[\alpha]_D$ −23.6° (*c* 0.97, $CHCl_3$); IR (film) 2950, 2870, 1730, 1680, 1620, 1460, 1370, 1250 cm^{-1}; UV ($CHCl_3$) 244 nm (ϵ 3200); ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m*/*z* (rel int) 404 (M^+, 1), 344 (M^+ − AcOH, 4), 284 (M^+ − 2AcOH, 19), 241 (10), 173 (100); HRCIMS *m*/*z* 427.2485 $[M + Na]^+$ (calcd for $C_{24}H_{36}O_5Na$, 427.2460).

(1*R,2*E*,4*R**,7*Z*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,7-dien-6-one (2):** colorless viscous oil; $[\alpha]_D$ −19.4° (*c* 0.36, $CHCl_3$); IR (film) 2940, 2870, 1730, 1460, 1370, 1250 cm^{-1}; UV ($CHCl_3$) 245 nm (ϵ 1700); ^{1}H NMR ($CDCl_3$, 400 MHz), δ 6.02 (br s, 1 H, H-7), 5.37 (m, 2 H, H-2,H-3), 4.96 (td, 1 H, J = 6, 2.5 Hz, H-10), 3.06 (m, 1 H, H-12), 2.66 (m, 1 H, H-4), 2.53 (dd, 1 H, J = 12.5, 6 Hz, H-5), 2.48 (m, 1 H), 2.41 (m, 1 H), 2.24 (dd, 1 H, J = 12.5, 10 Hz, H-5), 2.06 (s, 3 H, OAc), 1.96 (s, 3 H, OAc), 1.91 (br s, 3 H, H-17), 1.84 (t, 1 H, J = 8 Hz), 1.50 (s, 3 H, H-19), 1.49 (s, 3 H, H-20), 1.10 (d, 3 H, J = 7 Hz, H-16), 0.93 (s, 3 H, H-15); ^{1}H NMR (C_6D_6, 400 MHz), d 5.69 (br s, 1 H, H-7), 5.45 (d, 1 H, J = 16 Hz, H-2), 5.33 (dd, 1 H, J = 16, 8 Hz, H-3), 5.13 (td, 1 H, J = 6, 2.5 Hz, H-10), 3.65 (m, 1 H), 2.76 (t, 1 H, J = 8 Hz), 2.42 (m, 1 H, H-4), 2.26 (m, 1 H), 2.22 (dd, 1 H, J = 12.5, 5.5 Hz), 1.96 (m, 1 H), 1.94 (m, 1 H), 1.85 (d, 3 H, J = 1.5 Hz, H-17), 1.82 (s, 3 H, OAc), 1.74 (s, 3 H, OAc), 1.59 (s, 3 H, H-19), 1.57 (s, 3 H, H-20), 0.96 (d, 3 H, J = 7 Hz, H-16), 0.93 (s, 3 H, H-15); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 203.8 (C-6), 170.3 (Ac), 170.0 (Ac), 148.1 (C-8), 139.9 (C-2), 130.2, 130.0, 85.6 (C-18), 71.6 (C-10), 59.0, 49.6, 47.2, 46.8, 40.2, 38.4, 34.7, 26.5, 25.8, 25.2, 24.7, 22.9, 21.5, 20.7, 20.3; EIMS *m*/*z* (rel int) 404 (M^+, 1), 344 (M^+ − AcOH, 5), 284 (M^+ − 2AcOH, 32), 241 (13), 173 (100); HRCIMS *m*/*z* 427.2448 $[M + Na]^+$ (calcd for $C_{24}H_{36}O_5Na$, 427.2460).

(1*R,2*E*,4*R**,8*Z*,10*S**,11*S**,12*R**)-10,18-Diacetoxydolabella-2,8-dien-6-one (3):** colorless viscous oil; $[\alpha]_D$ −13.8° (*c* 0.65, $CHCl_3$); IR (film) 2940, 2870, 1730, 1460, 1370, 1250 cm^{-1}; UV ($CHCl_3$) 242 nm (ϵ 1030); ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 2; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 2; EIMS *m*/*z* (rel int) 404 (M^+, 2), 344 (M^+ − AcOH, 3), 284 (M^+ − 2AcOH, 89), 241 (52), 107 (100); HRCIMS *m*/*z* 422.2915 $[M + NH_4]^+$ (calcd for $C_{24}H_{40}NO_5$, 422.2906).

Arenolide (4): colorless viscous oil; $[\alpha]_D$ +13.0° (*c* 0.64, $CHCl_3$); IR (film) 3375, 2930, 2870, 1730, 1715, 1640, 1430, 1370, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 3; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 3; EIMS *m*/*z* (rel int) 420 ($M^+ - H_2O$, 2), 402 ($M^+ - 2H_2O$, 4), 384 ($M^+ - 3H_2O$, 1), 181 (67), 119 (73), 105 (100); HRCIMS *m*/*z* 461.2858 $[M + Na]^+$ (calcd for $C_{25}H_{42}O_6Na$, 461.2879).

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