Cadinane Sesquiterpenes from the Brown Alga *Dictyopteris divaricata*

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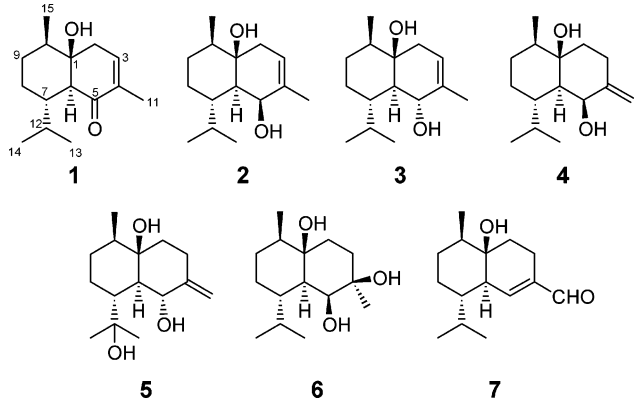
Seven new cadinane sesquiterpenes, (−)-(1*R*,6*S*,7*S*,10*R*)-1-hydroxycadinan-3-en-5-one (**1**), (+)-(1*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-3-ene-1,5-diol (**2**), (+)-(1*R*,5*R*,6*R*,7*S*,10*R*)-cadinan-3-ene-1,5-diol (**3**), (+)-(1*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-4(11)-ene-1,5-diol (**4**), (+)-(1*R*,5*R*,6*R*,7*R*,10*R*)-cadinan-4(11)-ene-1,5,12-triol (**5**), (−)-(1*R*,4*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-1,4,5-triol (**6**), and (−)-(1*R*,6*R*,7*S*,10*R*)-11-oxocadinan-4-en-1-ol (**7**), together with nine known compounds were isolated from the brown alga *Dictyopteris divaricata*. The structures of the new natural products, as well as their absolute configuration, were established by means of spectroscopic data including IR, HRMS, 1D and 2D NMR, single-crystal X-ray diffraction, and CD. All compounds were inactive against several human cancer cell lines including lung adenocarcinoma (A549), stomach cancer (BGC-823), breast cancer (MCF-7), hepatoma (Bel7402), and colon cancer (HCT-8) cell lines.

It is common that the same taxonomic species distributed in different regions contain different chemical constituents. As part of a recently initiated program to assess systematically the chemical and biological diversity of seaweeds distributed in the gulf of the Yellow Sea, China,[1,2] we collected the brown alga *Dictyopteris divaricata* Okam. belonging to Dictyotaceae. Although sesquiterpene-substituted phenols,[3−6] sesquiterpenes,[7−12] and C_{11} hydrocarbons[13−15] have been isolated from *Dictyopteris* species, only a few compounds have been reported from *D. divaricata*.[8−11] Subsequent chemical investigation of the ethyl acetate-soluble fraction of the ethanolic extract of *D. divaricata* has led to the isolation and structural elucidation of seven new cadinane sesquiterpenes (**1**−**7**) and a new sesquiterpene-substituted phenol named dictyvaric acid, together with nine known compounds, 3-farnesyl-*p*-hydroxybenzioc acid,[16] chromazonarol,[5,17] fucosterol,[18] (−)-torreyol,[19] 4*β*,5α-dihydroxycubenol,[12] dehydrovomifoliol,[20] 3*β*-hydroxy-5α,6α-epoxymegastigmen-9-one,[21] loliolide,[22] and isololiolide.[23] In previous papers,[24,25] we reported the structural elucidation of dictyvaric acid and the previously known compounds. This paper deals with the isolation and structure elucidation of compounds **1**−**7**. These compounds were evaluated against several human cancer cell lines, but found inactive (IC_{50} > 10 *μ*g/mL).



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Results and Discussion

The ethanolic extract of the alga was partitioned between water and ethyl acetate. The ethyl acetate phase was concentrated under vacuum and then subjected repeatedly to column chromatography over silica gel, Sephadex LH-20, and reversed-phase high-performance liquid chromatography (HPLC) to yield compounds **1**−**7**.

Compound **1** was obtained as colorless prisms from acetone with $[\alpha]_D^{20}$ −47 (*c* 0.18, MeOH) and showed absorption bands for hydroxyl (3512 cm^{-1}) and conjugated carbonyl (1664 cm^{-1}) groups in the IR spectrum. The EIMS of **1** gave a molecular ion peak at *m*/*z* 236 $[M]^+$, and the molecular formula was established as $C_{15}H_{24}O_2$ on the basis of the HREIMS at *m*/*z* 236.1761. The ^1H NMR spectrum in acetone-d_6 showed three methyl doublets at *δ* 0.64 (H-13), 0.91 (H-14), and 0.89 (H-15), one methyl multiplet with small long-range couplings at *δ* 1.67 (H-11), an exchangeable hydroxyl singlet at *δ* 3.15 (OH-1), and an olefinic proton multiplet at *δ* 6.34 (H-3), as well as signals with complex coupling patterns attributed to methylene and methine protons (Table 1). The ^{13}C NMR and DEPT spectra (Table 2) showed 15 carbon signals for four methyls, three methylenes, five methines (one olefinic), and three quaternary carbons (one oxygen bearing, one olefinic, and one carbonyl). With an unsaturation degree of four, **1** apparently contained two rings besides the carbonyl and the double-bond groups. The protonated carbons and attached protons were unambiguously assigned by HMQC. The $^1H-^1H$ COSY spectrum enabled extensive chains of coupling to be delineated. Vicinal and long-range coupling correlations from the olefinic proton (H-3) to the methylene (*δ* 2.55, H-2*β*; *δ* 2.42, H-2α) and the methyl (H-11) protons indicated that the methylene and the methyl groups were attached to the two ends of the double bond, respectively, while correlations between the methine proton (H-12, *δ* 2.40) and the protons of two methyl (H-13 and H-14) and the methine (H-7, *δ* 1.92) indicated the presence of an isopropyl group at C-7 (*δ* 37.2). In addition, H-7 correlated with protons of another methine (H-6, *δ* 2.47) and a methylene (*δ* 1.63, H-8*β*; *δ* 1.08, H-8α), with the coupling chain continuing from H_2-8 through H-9*β* (*δ* 1.45) and H-9α (*δ* 1.35) to H-10 (*δ* 1.53), and then to the methyl protons (H-15). On the basis of the HMBC experiment of **1** (Figure 1), the cadinane skeleton and locations of the functional groups were established for **1**. The two- and three-bond

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Table 1. ^{1}H NMR Data for Compounds **1**−**7**[a]

no.	1	2	3	4	5	6	7
2α	2.42 ddd (19.0, 3.0, 2.5)	1.92 br dd (17.0, 2.0)	1.90 br dd (17.0, 3.0)	1.22 m	1.24 ddd (13.5, 13.5, 5.0)	1.58 ddd (13.5, 13.0, 4.0)	2.24 m
2β	2.55 ddd (19.0, 5.0, 1.5)	2.22 br dd (17.0, 6.5)	2.22 dd (17.0, 6.0)	2.10 m	2.17 ddd (13.5, 5.0 2.0)	1.76 ddd (13.5, 4.0, 3.5)	2.11 ddd (12.0, 3.5, 3.5)
3α				2.69 ddd (14.0, 14.0, 5.0)	1.94 ddd (13.5, 5.0, 2.0)	1.34 m	1.38 ddd (12.0, 12.0, 3.5)
3β	6.34 m	5.31 br d (6.5)	5.50 d (6.0)	2.13 m	2.31 ddd (13.5, 13.5, 5.0)	1.92 ddd (14.0, 13.0, 4.0)	2.24 m
5		3.79 dd (8.0, 7.0)	4.09 d 8.0	4.33 dd (5.0, 2.0)	4.02 d (11.0)	3.51 dd (8.0, 2.0)	6.88 d (2.0)
6	2.47 d (11.0)	1.39 dd (12.0, 7.0)	1.92 dd (12.0, 8.0)	1.17 dd (12.0, 2.0)	1.16 dd (12.0, 11.0)	1.69 dd (12.0, 2.0)	2.13 br d (12.0)
7	1.92 dddd (13.0, 11.0, 6.5, 3.5)	1.66 dddd (12.0, 12.0, 6.5, 3.5)	1.68 dddd (12.5, 12.0, 6.5, 3.0)	1.94 dddd (12.5, 12.0, 6.5, 3.0)	1.87 ddd (12.0, 12.0, 3.5)	1.85 dddd (12.0, 12.0, 6.5, 3.0)	1.74 dddd (13.0, 12.0, 6.5, 3.0)
8α	1.08 dddd (13.0, 13.0, 13.0, 3.5)	1.06 dddd (12.0, 12.0, 12.0, 3.5)	1.08 dddd (12.5, 12.5, 12.5, 3.0)	1.04 dddd (13.0, 12.5, 12.0, 3.0)	1.16 dddd (13.0, 12.0, 12.0, 3.5)	1.06 dddd (12.5, 12.5, 12.0, 3.5)	1.16 dddd (13.0, 13.0, 13.0, 3.0)
8β	1.63 dddd (13.0, 3.5, 3.5, 3.5)	1.64 dddd (12.0, 3.5, 3.5, 3.5)	1.64 dddd (12.5, 3.5, 3.5, 3.0)	1.66 dddd (12.5, 3.5, 3.5, 3.0)	1.65 dddd (13.0, 3.5, 3.5, 3.5)	1.65 dddd (12.5, 3.5, 3.5, 3.0)	1.69 dddd (13.0, 3.0, 3.0, 3.0)
9α	1.35 dddd (13.0, 3.5, 3.5, 3.5)	1.37 dddd (12.0, 3.5, 3.5, 3.5)	1.40 dddd (12.5, 3.0, 3.0, 3.0, 3.0)	1.39 dddd (13.0, 3.5, 3.5, 3.5)	1.49 dddd (12.0, 3.5, 3.5, 3.5)	1.51 dddd (12.5, 3.5, 3.5, 3.5)	1.48 dddd (13.0, 3.0, 3.0, 3.0)
9β	1.45 dddd (13.0, 13.0, 13.0, 3.5)	1.48 dddd (12.0, 12.0, 12.0, 3.5)	1.50 dddd (12.5, 12.5, 12.5, 3.0)	1.54 dddd (13.0, 13.0, 12.5, 3.5)	1.47dddd (12.0, 12.0, 12.0, 3.5)	1.40 dddd (12.5, 12.5, 12.5, 3.5)	1.58 dddd (13.0, 13.0, 13.0, 3.0)
10	1.53 m	1.30 m	1.33 m	1.23 m	1.32 m	1.25 m	1.43 m
11a	1.67 m	1.71 br.s	1.70 br.s	4.70 t (2.0)	4.57 br s	1.24 s	9.46 s
11b				4.77 br s	4.72 br s		
12	2.40 m	2.49 m	2.24 m	2.14 m		2.05 m	2.23 m
13	0.64 d (7.0)	0.81 d (7.5)	0.84 d (7.0)	0.74 d (7.0)	1.01 s	0.73 d (7.5)	0.81 d 7.0
14	0.91d (7.0)	0.92 d (6.5)	0.91 d (7.5)	0.93 d (7.0)	1.25 s	0.91 d (6.5)	0.96 d 7.0
15	0.89 d (7.0)	0.86 d (7.0)	0.86 d (6.5)	0.85 d (7.0)	0.88 d 7.0	0.83 d (6.5)	0.91 d 7.0
1-OH	3.15 s	2.59 s		4.20 s	3.11 s	3.27 s	
4-OH						3.79 d (4.5)	
5-OH		3.15 br d (8.0)		4.60 br d (5.0)		4.47 d (8.0, 4.5)	

[a] ^{1}H NMR data were measured in acetone-d_6 at 500 MHz. Coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HMQC, and HMBC experiments.

Table 2. ^{13}C NMR Data for Compounds **1**−**7**[a]

	1	2	3	4	5	6	7
1	76.8 s	73.8 s	74.3 s	74.0 s	72.2 s	74.6 s	71.4 s
2	40.0 t	38.0 t	37.7 t	39.2 t	39.0 t	32.9 t	31.7 t
3	137.1 d	120.4 d	124.3 d	26.2 t	30.5 t	29.4 t	19.0 t
4	135.9 s	137.9 s	134.6 s	152.3 s	151.3 s	71.5 s	141.9 s
5	201.4 s	73.4 d	86.7 d	73.1 d	76.7 d	74.4 d	150.0 d
6	56.3 d	52.3 d	45.4 d	50.7 d	60.2 d	43.5d	48.4 d
7	37.2 d	44.6 d	44.3 d	38.3 d	47.3 d	38.0 d	39.5 d
8	23.4 t	25.2 t	25.1 t	24.6 t	27.0 t	24.7 t	25.0 t
9	29.4 t	31.4 t	31.3 t	31.1 t	31.9 t	31.2 t	30.7 t
10	42.6 d	42.4 d	42.3 d	42.6 d	41.8 d	42.4 d	41.0d
11	15.9 q	20.2 q	20.3 q	108.4 t	101.0 t	28.4 q	194.6 d
12	27.8 d	27.6 d	27.6 d	26.2 q	82.8 s	26.1 d	26.8 d
13	15.7 q	16.5 q	16.2 q	15.3 q	30.5 q	15.2 q	21.6 q
14	21.8 q	22.6 q	22.5 q	21.8 q	25.3 q	21.8 q	15.2 q
15	14.4 q	15.0 q	15.0 q	14.9 q	13.9 q	14.7 q	15.1 q

[a] ^{13}C NMR data were measured in acetone-d_6 at 125 MHz. The assignments were based on DEPT, $^1H-^1H$ COSY, HMQC, and HMBC experiments.

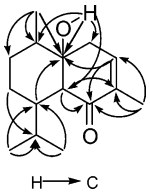

Figure 1. Key HMBC correlations of compound **1**.

heteronuclear correlations of the carbonyl carbon (C-5, δ 201.4) with H-3, H-6, and H-11 established the connectivity of C-5 with C-4 (δ 135.9) and C-6 (δ 56.3). HMBC correlations of the quaternary carbon bearing oxygen (C-1, δ 76.8) with H-2α, H-2β, H-3, H-6, H-9α, H-9β, and H-15, and C-6 with H-2α and H-2β, demonstrated the connectivity of C-1 with C-2, C-6, and C-10, which was further confirmed by correlations from the hydroxyl proton to C-1, C-2, C-6, and C-10.

The relative configuration of **1** was elucidated by an analysis of the coupling constants and NOE difference experiments. In the ^1H NMR spectrum, the large (11.0 Hz) coupling constant of H-6 characteristic of a diaxial relationship with H-7 (dddd, $J_{6,7} = 11.0$, $J_{7,8\alpha} = 13.0$, $J_{7,8\beta} = 3.5$, and $J_{7,12} = 6.5$), and the large vicinal coupling constant of 13.0 Hz between H-9β and H-10 (dq, $J_{9\beta,10} = 13.0$, $J_{10,15} = 7.0$) demonstrated that the methyl group at C-10 was equatorial also. This was confirmed by NOE effects between H-8α and H-10 on one hand and H-6 on the other, as well as an NOE between H-9β and H-7. In addition, the OH signal was strongly enhanced by irradiation of H-7, indicating that the two six-membered rings were *trans*-fused.

Finally, the structure of **1** was confirmed by an X-ray crystallographic analysis. The ORTEP drawing, with the atom-numbering scheme indicated, is shown in Figure 2. The absolute configuration of **1** was determined from the CD spectrum (Figure 3). Molecular modeling using the MM2 program indicated that the torsion angle between the double bond and the ketone group is 163.6° (or −16.4°) for the lowest energy conformation of **1**. In addition, the X-ray structure analysis of **1** indicated that the torsion angle is 166.2° (or −13.8°) in the crystal state. These demonstrated that the enone moiety of **1** was not planar. On the basis of the octant rule for cyclohexenones[26] and related reports,[27,28] the positive Cotton effect at 331 nm ($\Delta\epsilon_{max}$ +6.37) for n→π* and the negative Cotton effect at 251 nm ($\Delta\epsilon_{max}$ −1.26) for π→π* indicated that the configuration of **1** is as depicted in Figure 4. Therefore, the absolute configurations at the chiral centers of **1** are 1*R*, 6*S*, 7*S*, and 10*R*. Accordingly,

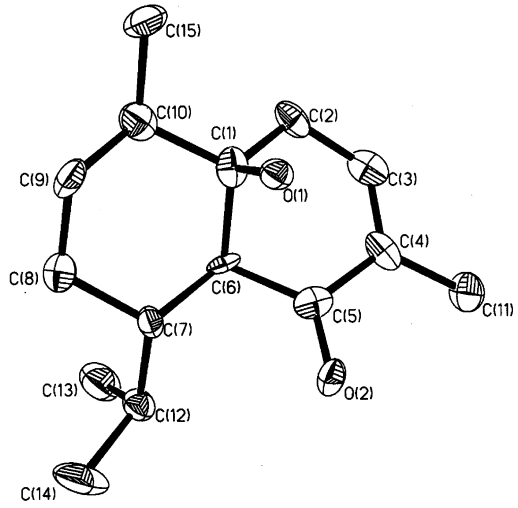

Figure 2. ORTEP drawing of compound **1**.

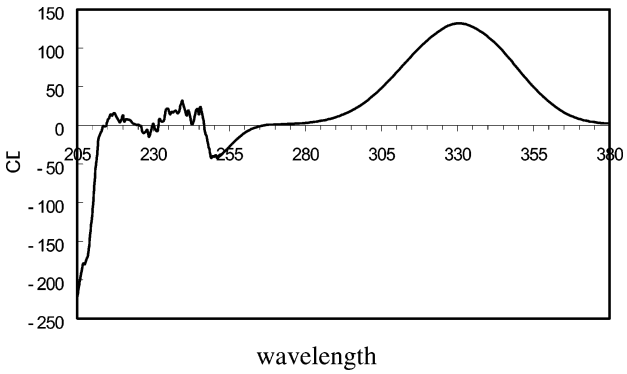

Figure 3. CD spectrum of compound **1**.

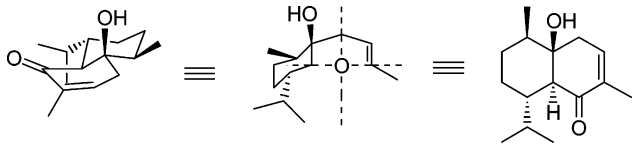

Figure 4. Absolute configuration of compound **1**.

the structure of **1** was identified as (−)-(1*R*,6*S*,7*S*,10*R*)-1-hydroxycadinan-3-en-5-one (**1**).

Compound **2** was obtained as a colorless gum with $[\alpha]_D^{20}$ +29 (*c* 0.15, MeOH) and showed a strong broadened IR absorption band for hydroxyls (3464 cm^{-1}). The FABMS gave a pseudomolecular ion peak at *m*/*z* 239 $[M + H]^+$. The molecular formula was determined as $C_{15}H_{26}O_2$ by the HRFABMS at *m*/*z* 239.2017 in combination with the NMR spectral data of **2** (Table 1). The NMR spectra of **2** were similar to those of **1** except that the carbonyl signal of **1** was replaced by oxymethine signals at δ_H 3.79 (H-5) and δ_C 73.4 (C-5) of **2**. In the ^1H NMR spectrum of **2** (acetone-d_6) the appearance of two exchangeable hydroxyl proton signals at δ_H 3.15 (OH-5) and 2.59 (OH-1) indicated the presence of two hydroxyl groups. All of the above data suggested that **2** possesses the basic structure of cadinan-3-ene-1,5-diol, which was confirmed by $^1H-^1H$ COSY, HMQC, HMBC, and NOESY experiments of **2**. In the $^1H-^1H$ COSY spectrum vicinal couplings between H-2 (δ 2.22, H-2β; δ 1.92, H-2α) and H-3 (δ 5.31) and between H-5 and H-6 (δ 1.39), together with long-range couplings of H-11 (δ 1.71) with H-3 and H-5 confirmed the presence of the hydroxyl group at C-5. In the HMBC spectrum of **2**, correlation of the oxygenated quaternary carbon (C-1, δ 73.8) with H-2, H-3, H-6, H-7, and H-15 confirmed that

the remaining hydroxyl group was located at C-1. Moreover, in the ^{1}H NMR spectrum of **2**, H-6 appeared as a double doublet with coupling constants of 12.0 and 7.0 Hz, while the splitting of H-5 (7.0 Hz) indicated that the larger coupling of H-6 must be caused by H-7. These data proved the presence of a *trans*-fused ring system for **2** and equatorial orientation of the isopropyl at C-7.[25] In addition, the large vicinal coupling constant of 12.0 Hz between H-9β and H-10 revealed that the methyl group at C-10 was equatorial. Thus, the relative configuration of the left ring moiety of **2** was identical to that of **1**. In the NOESY spectrum of **2** correlations between H-5 with H-6 and H-12 established that they are on the same side of the ring system, indicating β orientation for the hydroxyl group at C-5. Because of biogenetic considerations, the absolute configurations at C-1, C-7, and C-10 of **2** were assumed to be identical with those of **1**. Therefore, the structure of **2** was identified as (+)-(1*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-3-ene-1,5-diol.

Compound **3** was obtained as colorless plates from acetone with $[\alpha]_D^{20}$ +54 (*c* 0.15, MeOH) and showed IR, FABMS, and NMR spectra features very similar to those of **2**. The ^{1}H−^{1}H COSY, HMQC, and HMBC spectroscopic analyses of **3** revealed that it possesses a planar structure identical with that of **2** and led to unambiguous assignments of the NMR data for **3** (Tables 1 and 2). By comparing the NMR data of **2** and **3**, the chemical shift values of H-5 and H-6 as well as C-3 and C-5 of **3** were deshielded by $\Delta\delta_H$ 0.3 and 0.53 ppm and $\Delta\delta_C$ 3.9 and 13.3 ppm, respectively, whereas C-4 and C-6 of **3** were shielded by $\Delta\delta_C$ 3.3 and 6.9 ppm, respectively. These shifts suggested that **3** was an epimer at C-5 of **2**. Though the coupling constants between H-5 and H-6 of **3** were almost the same as those of **2**, the NOESY spectrum of **3** showed NOE correlations between H-10 and both H-6 and H-9α and between H-6 and both H-2α and H-12, but not between H-5 and H-6, confirming that H-2α, H-6, H-10, and H-12 are on the same side of the ring system and H-5 on the other side. Therefore, and in view of biogenetic considerations, the structure of **3** was identified as (+)-(1*R*,5*R*,6*R*,7*S*,10*R*)-cadinan-3-ene-1,5-diol.

Compound **4** was obtained as white needles (acetone) with $[\alpha]_D^{20}$ +51 (*c* 0.17, MeOH) and exhibited quasi-molecular ion peaks at *m*/*z* 239 $[M + H]^+$ and 261 $[M + Na]^+$. On the basis of the HRFABMS ion peak at *m*/*z* 261.1850 $[M + Na]^+$ the molecular formula was determined as $C_{15}H_{26}O_2$, which is identical with those of **2** and **3**. The NMR data (Table 1) indicated that **4** was another isomer of **2**. Comparison of the ^{1}H and ^{13}C NMR spectra of **4** with those of **2** indicated that signals of the endocyclic double bond and the methyl group attached to the double bond of **2** were replaced by signals of an exocyclic double bond and an additional methylene (C-3) of **4**. These data demonstrated that the double bond of **4** was located between C-4 and C-11 instead of between C-3 and C-4 as in **2**. The ^{1}H−^{1}H COSY, HMQC, and HMBC experiments of **4** led to unambiguous assignments of the NMR data and confirmed that the structure of **4** was cadinan-4(11)-ene-1,5-diol. The coupling patterns of H-5, H-6, and H-9 (Table 1) revealed that the ring junction and the relative configurations at C-7 and C-10 of **4** were identical with those of **2**. Irradiation of H-5 produced enhancements of H-6, H-12, and H-13, demonstrating that the hydroxyl at C-5 and the isopropyl at C-7 were on different sides of the ring system. The structure of **4** was further confirmed by X-ray crystallographic analysis. The PLUTO drawing, with the atom-numbering scheme indicated, is shown in Figure 5. On

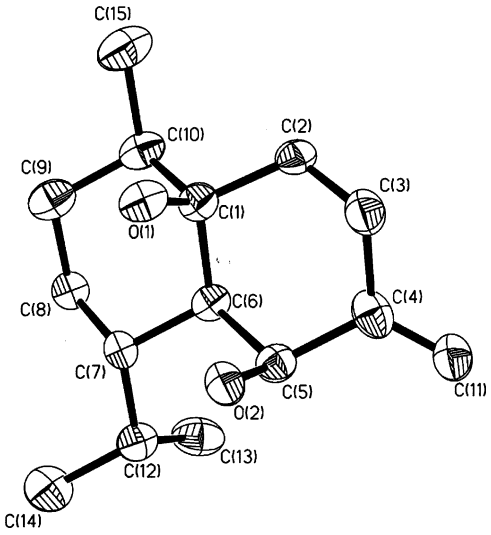

Figure 5. ORTEP drawing of compound **4**.

biogenetic considerations, the absolute configuration of the left ring moiety of **4** was assumed to be identical with that of **1**−**3**. Thus, the structure of **4** was identified as (+)-(1*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-4(11)-ene-1,5-diol.

Compound **5** was obtained as a colorless gum with $[\alpha]_D^{20}$ +55 (*c* 0.29, MeOH) and showed a broadened IR absorption band for hydroxyl groups (3485 cm^{-1}). The positive FABMS gave a quasi-molecular ion peak at *m*/*z* 255 $[M + H]^+$, and the molecular formula was determined as $C_{15}H_{26}O_3$ by the HRFABMS ion at *m*/*z* 255.1946 $[M + H]^+$. The NMR data of **5** (Tables 1 and 2) were similar to those of **4**, except that two methyl doublets of H-13 and H-14 for **4** were replaced by two methyl singlets (δ_H 1.01 and 1.25) of **5** and that the methine carbon of C-12 assigned to the isopropyl unit of **4** was replaced by an oxygenated quaternary carbon (δ_C 82.8). These data suggested that **5** was an analogue of **4** with one more hydroxyl at C-12, which was further confirmed by 2D NMR analyses of **5**. The ^{1}H NMR and protonated ^{13}C NMR data were unambiguously established by a combination of the ^{1}H−^{1}H COSY and HMQC analyses of **5**, with the quaternary carbons being assigned by the HMBC experiment (Tables 1 and 2). In the ^{1}H NMR spectrum, H-6 (δ 1.16) appeared as a double doublet with two large diaxial coupling constants of 11.0 and 12.0 Hz, indicating that the two six-membered rings were *trans*-fused and that the hydroxyl at C-5 and the 2-hydroxyisoproyl at C-7 were equatorial. The coupling pattern of H-9β (δ 1.47, dddd, $J_{9\beta,10} = J_{9\alpha,9\beta} = J_{9\beta,8\alpha} = 12.0$ Hz) indicated that the methyl at C-10 was equatorial also. The relative configuration of **5** was further confirmed by an NOE difference experiment showing strong enhancements of H-7 (δ 1.87) and H-3β (δ 2.31) on irradiation of H-5 (δ 4.02). Accordingly, the structure of **5** was deduced as (+)-(1*R*,5*R*,6*R*,7*R*,10*R*)-cadinan-4(11)-ene-1,5,12-triol.

Compound **6** was obtained as white needles (acetone) with $[\alpha]_D^{20}$ −4.0 (*c* 0.77, $CHCl_3$) and exhibited a molecular ion at *m*/*z* 256 $[M]^+$ in the EIMS and a strong broadened absorption band for hydroxyls (3377 cm^{-1}) in the IR spectrum. The molecular formula was established as $C_{15}H_{28}O_3$ on the basis of the HREIMS ion peak at *m*/*z* 256.2019 $[M]^+$. The ^{1}H NMR spectrum of **6** in acetone-d_6 showed three methyl doublets at δ 0.73 (H-13), 0.83 (H-15), and 0.91 (H-14), one methyl singlet at δ 1.24 (H-11), an oxymethine doublet at δ 3.50 (H-5), and three exchangeable hydroxyl proton signals at δ 4.47, 3.79, and 3.50. In addition, there were several complex multiplets from δ 1.00 to 2.10 (Table 1). The ^{13}C NMR and DEPT spectra (Table

2) showed 15 carbon signals including four methyls, four methylenes, five methines (one oxygenated), and two quaternary oxygenated carbons. These data revealed the structure of a saturated cadinantriol for **6**. The NMR data and locations of the three hydroxyls on the cadinane skeleton were unambiguously assigned by using $^1H-^1H$ COSY, HMQC, and HMBC techniques. In the $^1H-^1H$ COSY spectrum the homonuclear vicinal coupling correlation between the oxymethine proton (H-5) and H-6 (δ 1.69), and long-range coupling correlations between H-5 and H_3-11 and H_2-3 (δ 1.92, H-3β; δ 1.34, H-3α), unequivocally established that two hydroxyls were located at C-4 and C-5 of the cadinane skeleton, respectively. This was further confirmed by two- and three-bond heteronuclear correlations between H-5 and C-1, C-3, C-4, and C-6 and between H-11 and C-3, C-4, and C-5 in the HMBC spectrum. The location of the remaining hydroxyl was assigned to C-1 on the basis of the HMBC correlations of C-1 with H-3, H-5, H-6, H-7, and H-15. The relative configuration of **6** was deduced from analysis of the coupling constants and the NOE difference experiment. In the ^1H NMR spectrum the splitting patterns of H-5 (dd, $J_{5,OH} = 8.0$ Hz, $J_{5,6} = 2.0$ Hz) and H-6 (dd, $J_{5,6} = 2.0$ Hz, $J_{6,7} = 12.0$ Hz) indicated the presence of an equatorial−axial coupling between H-5 and H-6 and a diaxial coupling between H-6 and H-7, demonstrating the *trans*-junction of the two six-membered rings, and axial and equatorial orientations for the hydroxyl at C-5 and the isopropyl at C-7, respectively. These deductions were confirmed by the NOE enhancements of H-6 and H-12 on irradiation of H-5. An NOE enhancement of H_3-11 was also observed when H-5 was irradiated, while H_3-11 was not enhanced on irradiation of H-3β (axial), indicating an equatorial orientation of the hydroxyl at C-4. In addition, the large diaxial coupling constant of 12.5 Hz between H-9β and H-10 (Table 1) established that the C-10 methyl was equatorial. On biogenetic grounds, the absolute configuration of the left ring was again assumed to be identical to those of the earlier compounds. Consequently, the structure of **6** was identified as (−)-(1*R*,4*R*,5*S*,6*R*,7*S*,10*R*)-cadinan-1,4,5-triol.

Compound **7** was obtained as a colorless gum with $[\alpha]_D^{20}$ −33 (*c* 0.10, MeOH) and showed IR absorption bands for hydroxyl (3483 cm^{-1}) and conjugated carbonyl (1684, 1643) groups. The EIMS showed a molecular ion at *m*/*z* 236 $[M]^+$. The NMR data (Tables 1 and 2) indicated that **7** is a cadinane derivative also. In the ^1H NMR spectrum of **7** a characteristic aldehyde resonance at δ 9.46 (H-11) and a broadened olefinic singlet at δ 6.88 (H-5) indicated the presence of an aldehyde and a trisubstituted double bond, which was confirmed by signals at δ 194.6 (d, C-11), 150.0 (d, C-5), and 141.9 (s, C-4) in the ^{13}C NMR spectrum. After geminal protons with different chemical shifts were recognized by the HMQC spectrum, the $^1H-^1H$ COSY spectrum indicated that the left ring of the cadinane carbon skeleton was identical with those of **1**−**6**. In addition, in the $^1H-^1H$ COSY spectrum vicinal couplings among H-2β (δ 2.11), H-2α, H-3β (δ 2.24, overlapping), and H-3α (δ 1.38) and long-range coupling between H-3 and the olefinic proton (H-5) revealed that the aldehyde and the double bond were located at C-4 and between C-4 and C-5, respectively. This was confirmed by three-bond correlations between the aldehyde carbon (C-11) and H-5. The *trans* ring fusion and the equatorial orientations of the isopropyl at C-7 and the methyl at C-10 were elucidated from the coupling constants between H-6 and H-7 ($J_{6,7} = 12.0$ Hz) and between H-9β and H-10 ($J_{9\beta,10} = 13.0$ Hz). Orientations were further confirmed by an NOE correlation between H-6 and H-10 in the NOESY spectrum of **7**. Therefore, the structure of **7** was (−)-(1*R*,6*R*,7*S*,10*R*)-11-oxo-cadinan-4-en-1-ol.

In in vitro cytotoxic assays using the MTT method[29,30] against several human cancer cell lines including lung adenocarcinoma (A549), stomach cancer (BGC-823), breast cancer (MCF-7), hepatoma (Bel7402), and colon cancer (HCT-8) cell lines, compounds **1**−**7** were inactive (IC_{50} > 10 μg/mL).

Experimental Section

General Experimental Procedures. Melting points were determined on an XT-4 micro melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. 1D- and 2D-NMR spectra were obtained at 500 and 125 MHz for ^1H and ^{13}C, respectively, on an Inova 500 MHz spectrometer in acetone-d_6 with solvent peaks as references. EIMS, FABMS, HREIMS, and HRFABMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. The CD spectrum was recorded on a Jasco J-715 spectropolarimeter. Column chromatography was performed with silica gel (200−300 mesh) and Sephadex LH-20. TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light or by spraying with 7% sulfuric acid in EtOH followed by heating. HPLC was performed using an Alltima C18 10 μm preparative column (22 × 250 mm).

X-ray diffraction intensity data of **1** and **4** were collected on a MAC DIP-2030K diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) by the ω scan technique [scan width 0−180°, $2\theta \leq 50°$] and were corrected by Lorentz and polarization. Altogether 1814 and 1748 reflections were collected, of which 1392 and 1413 with $|F|^2 \geq 8\sigma|F|^2$ were observed for **1** and **4**, respectively. Their structures were solved by direct methods and refined by block-matrix least-squares procedure to $R = 0.082$, $R_w = 0.062$ [$w = 1/\sigma|F|^2$] of **1**, and $R = 0.086$, $R_w = 0.059$ [$w = 1/\sigma|F|^2$] of **4**. Hydrogen positions were found from difference Fourier maps and geometric calculations. All calculations were carried out on a PC computer by using the NOMCSDP program system.

Material. The brown alga *Dictyopteris divaricata* Okam. was collected on the coast of Qingdao, China, in May 2002, and identified by Dr. Kui-Shuang Shao (Institute of Oceanology, Chinese Academy of Sciences, Qingdao, 266071, China). A voucher specimen (No. 200223) was deposited at the Herbarium of the Institute of Oceanology.

Extraction and Isolation. *D. divaricata* Okam. (4.40 kg) was extracted with EtOH at room temperature for 3 × 72 h. After the solvent was removed under reduced pressure at <40 °C, a dark residue was obtained. The residue was suspended in H_2O and then partitioned with EtOAc. The EtOAc fraction (120.3 g) was chromatographed over silica gel (1200 g), eluting with a gradient of increasing Me_2CO (0−100%) in petroleum ether, and separated into 24 fractions (I−XXIV) on the basis of TLC analyses. Fractions VI−X were separated by column chromatography over Sephadex LH-20 using petroleum ether−$CHCl_3$−MeOH (5: 5: 1) as the eluent to give corresponding subfractions. The first subfraction of VI was recrystallized from acetone to yield compound **1** (174 mg), and the fifth subfraction of VI was purified by reversed-phase preparative HPLC using MeOH−H_2O (80: 20) to give compound **3** (20 mg). The third subfraction of VII was purified by reversed-phase preparative HPLC using MeOH−H_2O (80: 20) to yield compounds **2** (24 mg) and **4** (54 mg). The third subfraction of VIII and the second subfraction of X were separately purified by reversed-phase preparative HPLC using MeOH−H_2O (80: 20) to yield compounds **5** (32 mg), **6** (45 mg), and **7** (14 mg).

(−)-(1*R*,6*S*,7*S*,10*R*)-1-Hydroxycadinan-3-en-5-one (1): colorless prisms (Me_2CO); mp 179−180 °C; $[\alpha]_D^{20}$ −47 (*c* 0.18, MeOH); IR (KBr) ν_{max} 3512, 2962, 2870, 1664, 1460, 1369, 1354, 1273, 1194, 1130, 1063, 997, 920, 843 cm^{-1}; ^1H NMR

(acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; EIMS *m/z* (%) 236 (7) $[M]^+$, 218 (8) $[M - H_2O]^+$, 193 (3), 175 (6), 125 (100), 111 (7), 110 (6), 58 (6), 55 (7), 43 (30); HREIMS *m/z* 236.1761 (calcd. for $C_{15}H_{24}O_2$, 236.1776).

Crystal data of 1: $C_{15}H_{24}O_2$, M_r 236.35, orthorhombic, space group $P2_12_12_1$, $a = 9.581(1)$ Å, $b = 10.494(1)$ Å, $c = 13.806(3)$ Å; $V = 1388.1(3)$ Å^3, $Z = 4$, $D_c = 1.092$ g cm^{-3}, $F(000) = 520$; crystal dimensions 0.15 × 0.15 × 0.40 mm.

(−)-(1*R*,5*S*,6*R*,7*S*,10*R*)-Cadinan-3-ene-1,5-diol (2): colorless gum, $[\alpha]_D^{20}$ +29 (*c* 0.15, MeOH); IR (KBr) ν_{max} 3464, 2960, 2933, 2881, 1464, 1371, 1211, 1134, 1003, 976, 901, 885, 868 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; FABMS *m/z* 239 $[M + H]^+$; HRFABMS *m/z* 239.2017 (calcd for $C_{15}H_{27}O_2$, 239.2011).

(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-Cadinan-3-ene-1,5-diol (3): colorless plates (Me_2CO); mp 154−156 °C; $[\alpha]_D^{20}$ +54 (*c* 0.15, MeOH); IR (KBr) ν_{max} 3500, 3276, 2960, 2927, 2884, 1466, 1387, 1198, 1132, 1034, 995, 906, 887, 816 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; FABMS *m/z* 239 $[M + H]^+$; HRFABMS *m/z* 239.2021 (calcd for $C_{15}H_{27}O_2$, 239.2011).

(+)-(1*R*,5*S*,6*R*,7*S*,10*R*)-Cadinan-4(11)-ene-1,5-diol (4): white needles (Me_2CO); mp 139−140 °C; $[\alpha]_D^{20}$ +51 (*c* 0.17, MeOH); IR (KBr) ν_{max} 3365, 3251, 2958, 2922, 2854, 1442, 1321, 1271, 1084, 1024, 926 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; positive FABMS *m/z* 261 $[M + Na]^+$, 239 $[M + H]^+$, 221, 203; HRFABMS *m/z* 261.1850 $[M + Na]^+$ (calcd for $C_{15}H_{26}O_2Na$ 261.1830).

Crystal data of 4: $C_{15}H_{24}O_2$, M_r 238.37, orthorhombic, space group $P2_12_12_1$, $a = 6.697(1)$ Å, $b = 9.031(1)$ Å, $c = 24.173(3)$ Å; $V = 1462.0(3)$ Å^3, $Z = 4$, $D_c = 1.083$ g cm^{-3}, $F(000) = 528$; crystal dimensions 0.15 × 0.20 × 0.20 mm.

(+)-(1*R*,5*R*,6*R*,7*R*,10*R*)-Cadinan-4(11)-ene-1,5,12-triol (5): colorless gum, $[\alpha]_D^{20}$ +55 (*c* 0.29, MeOH); IR (KBr) ν_{max} 3485, 2968, 2931, 2858, 1660, 1630, 1456, 1365, 1259, 1115, 1041, 982, 881, 839 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; FABMS *m/z* 255 $[M + H]^+$; HRFABMS *m/z* 255.1946 (calcd for $C_{15}H_{27}O_3$ 255.1960).

(−)-(1*R*,4*R*,5*S*,6*R*,7*R*,10*R*)-Cadinan-1,4,5-triol (6): colorless needles (Me_2CO); mp 146−147 °C; $[\alpha]_D^{20}$ −4.0 (*c* 0.77, $CHCl_3$); IR (KBr) ν_{max} 3377, 2958, 2927, 2873, 1464, 1402, 1371, 1218, 1078, 1011, 941 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; EIMS *m/z* (%) 256 (12) $[M]^+$, 238 (8), 220 (17), 213 (15), 205 (11), 195 (12), 185 (100), 177 (13), 167 (5), 159 (7), 149 (12), 137 (10), 121 (8), 111 (14), 109 (16), 107 (10), 95 (16), 83 (14), 81 (11), 69 (13), 55 (15); HREIMS *m/z* 256.2019 $[M]^+$ (calcd for $C_{15}H_{26}O_2$ 256.2038).

(−)-(1*R*,6*R*,7*S*,10*R*)-11-Oxocadinan-4-en-1-ol (7): colorless gum, $[\alpha]_D^{20}$ −33 (*c* 0.10, MeOH); IR (KBr) ν_{max} 3483, 2958, 2933, 2873, 1684, 1643, 1460, 1387, 1369, 1250, 1198, 1124, 1068, 995, 951, 926, 876 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Tables 1 and 2; EIMS *m/z* (%) 236 (8) $[M]^+$; HREIMS *m/z* 236.1759 (calcd for $C_{15}H_{24}O_2$ 236.1776).

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Supporting Information Available: ^{1}H, ^{13}C NMR and DEPT spectra of compounds **1**−**7**; X-ray crystallographic data of compounds **1** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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