Full Papers

Norsesquiterpenes from the Brown Alga *Dictyopteris divaricata*

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Three bisnorsesquiterpenes (**1**−**3**) with novel carbon skeletons and a norsesquiterpene (**4**) have been isolated from the brown alga *Dictyopteris divaricata*. By means of spectroscopic data including IR, HRMS, 1D and 2D NMR techniques, single-crystal X-ray diffraction, and CD, their structures including absolute configurations were proposed as (+)-(1*R*,6*S*,9*R*)-1-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0]non-4-en-3-one (**1**), (−)-(1*S*,6*S*,9*R*)-1-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0] non-4-en-3-one (**2**), (+)-(5*S*,6*R*,9*S*)-5-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0]non-1-en-3-one (**3**), and (−)-(1*R*,7*S*,10*R*)-1-hydroxy-11-norcadinan-5-en-4-one (**4**). Biogenetically, the carbon skeleton of **1**−**3** may be derived from the co-occurring cadinane skeleton by ring contraction and loss of two carbon units, and compound **4** from the oxidation of cadinane derivatives. Compounds **1**−**4** were inactive (IC$_{50}$ > 10 μg/mL) 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.

Sesquiterpene-substituted phenols,[1−4] sesquiterpenes,[5−10] and C$_{11}$ hydrocarbons[11−13] have been reported from species of the genus *Dictyopteris*. As part of our program to systematically assess the chemical and biological diversity of seaweeds distributed in the gulf of the Yellow Sea, China,[14,15] we have previously reported seven cadinane sesquiterpenoids and other compounds[16−18] from the ethanolic extract of *D. divaricata*. Interestingly, the structures of these compounds were completely different from those previously reported from the same species collected in Japan.[6−9] Continuing our investigations on this genus, we report here the isolation and structural elucidation including the absolute configuration of three bisnorsesquiterpenes (**1**−**3**) and one norsesquiterpene (**4**). From a biogenetic point of view, the carbon skeleton of **1**−**3** may be derived from the co-occurring cadinane skeleton by ring

contraction and loss of two carbon units,[16] and compound **4** may come from the oxidation of a cadinane derivative.

1   **2**   **3**   **4**
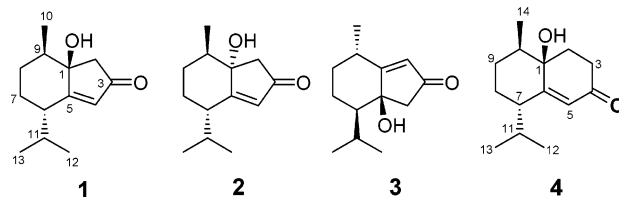
Results and Discussion

Compound **1** was obtained as colorless prisms (Me$_2$CO) and displayed absorption bands for hydroxyl (3373 cm^{-1}) and conjugated carbonyl functionalities (1684 and 1610 cm^{-1}) in the IR spectrum. The EIMS exhibited a molecular ion at *m/z* 208 [M]$^+$, and the molecular formula was determined as C$_{13}$H$_{20}$O$_2$ by HREIMS. The ^{1}H NMR spectrum (Me$_2$CO-d_6) of **1** showed three methyl doublets at δ 0.93 (*J* = 7.0 Hz, CH$_3$-12), 0.98 (*J* = 6.5 Hz, CH$_3$-13), and 1.03 (*J* = 6.5 Hz, CH$_3$-10), an olefinic doublet at δ 5.68 (*J*

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Table 1. ^{1}H NMR Data for Compounds **1**−**4**^{a}

no.	1	2	3	4
2α	2.42 d (18.5)	2.24 d (18.5)	5.80 s	2.07 ddd (13.5,10.0,4.5)
2β	2.28 d (18.5)	2.56 d (18.5)		2.14 ddd (13.5,7.0,4.5)
3α				2.38 ddd (16.0,7.0,4.5)
3α				2.26 ddd (16.0,10.0,4.5)
4α	5.68 d (1.5)	5.83 s	2.20 d (18.5)	
4β			2.80 d (18.5)	
5				5.61 br s
6	2.46 ddd (12.5,6.5,4.0)	2.29 dd (10.5,5.5)	1.99 ddd (12.0,6.5,5.0)	
7α	1.13 dddd (12.5,12.5,12.5,4.0)	1.85 ddd (14.0,4.0,4.0)	2.02 ddd (12.5,5.0,5.0,4.0)	
7β	1.98 dddd (12.5,4.0,4.0,4.0)	1.70 dddd (14.0,14.0,5.5,4.0)	1.35 dddd (12.5,12.5,12.0,4.0)	2.53 ddd (13.0,6.5,5.0)
8α	1.55 dddd (12.5,4.0,4.0,4.0)	2.38 dddd (14.0,14.0,4.5,4.0)	1.80 dddd (13.5,12.5,12.5,4.0)	1.05 dddd (13.0,13.0,13.0,4.0)
8β	1.65 dddd (12.5,12.5,12.5,4.0)	1.22 dddd (14.0,4.0,4.0,4.0)	1.71 dddd (12.5,5.0,4.0,4.0)	2.00 dddd (13.0,5.0,4.0,4.0)
9α	1.47 m	2.24 m		1.53 dddd (13.0,4.0,4.0,4.0)
9β			2.83 dq (13.5,7.0)	1.69 dddd (13.0,13.0,13.0,4.0)
10	1.03 d (6.5)	0.83 d (7.0)	1.33 d (7.0)	1.73 m
11	1.94 m	2.42 m	1.87 m	1.87 m
12	0.93 d (7.0)	0.85 d (6.5)	0.73 d (6.5)	0.90 d (6.5)
13	0.98 d (6.5)	0.96 d (6.5)	0.97 d (6.5)	0.92 d (6.5)
14				1.00 d (6.0)
1-OH	4.10 s	4.23 br s		3.91 s
5-OH			4.15 s	

^{a} ^{1}H NMR data were measured in acetone-d_6 at 500 MHz. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HMQC, and HMBC experiments.
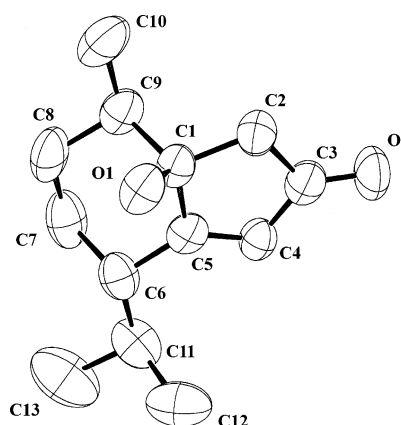
Table 2. ^{13}C NMR Data for Compounds **1**−**4**^{a}

	1	2	3	4
1	79.3 C	80.3 C	185.7 C	72.2 C
2	49.7 CH$_2$	49.0 CH$_2$	129.1 CH	34.3 CH$_2$
3	205.3 C	204.9 C	206.1 C	34.6 CH$_2$
4	125.4 CH	131.7 CH	48.4 CH$_2$	198.2 C
5	186.3 C	181.5 C	80.6 C	122.0 CH
6	44.1 CH	48.5 CH	49.6 CH	171.2 C
7	29.8 CH$_2$	23.5 CH$_2$	20.4 CH$_2$	46.0 CH
8	30.1 CH$_2$	24.6 CH$_2$	29.5 CH$_2$	30.6 CH$_2$
9	44.3 CH	40.1 CH	33.8 CH	30.4 CH$_2$
10	15.9 CH$_3$	14.4 CH$_3$	22.2 CH$_3$	42.0 CH
11	29.2 CH	28.6 CH	29.6 CH	27.5 CH
12	19.0 CH$_3$	21.9 CH$_3$	18.4 CH$_3$	22.1 CH$_3$
13	21.9 CH$_3$	22.7 CH$_3$	23.6 CH$_3$	19.1 CH$_3$
14				15.1 CH$_3$

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

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

= 1.5 Hz, H-4), a characteristic AB coupling system attributed to an isolated methylene group at δ 2.42 (J = 18.5 Hz, H-2α) and 2.28 (J = 18.5 Hz, H-2β), and an exchangeable hydroxyl singlet at δ 4.10 (s, 1-OH), as well as several complex multiplets from δ 1.00 to 2.50 (see Table 1). The ^{13}C NMR and DEPT spectra showed 13 carbon signals including three methyls, three methylenes, four methines (one sp^2 hybrid), one quaternary sp^2 carbon, one carbonyl, and one oxygen-bearing quaternary carbon (Table 2). With four unsaturation degrees, **1** apparently contained two rings besides the carbonyl and the double-bond groups.

The planar bicycle carbon skeleton of **1** was established by 2D NMR experiments. The proton and protonated carbon signals in the NMR spectra of **1** were unequivocally assigned by the HMQC experiment (Tables 1 and 2). In the ^{1}H−^{1}H COSY spectrum homonuclear coupling correlations from H-6 through H$_2$-7 and H$_2$-8 to H-9, and then to H$_3$-10, and correlations from H-11 to H-6, H$_3$-12, and H$_3$-13 revealed the presence of the six-membered ring moiety with a methyl at C-9 and an isopropyl at C-6. In combination with the chemical shift value of C-1, the HMBC correlations between the hydroxy proton and C-1, C-2, C-5, and C-9 and between H$_2$-2 and C-1, C-5, and C-9 clearly indicated that the hydroxylated C-1 was directly connected with C-2, C-5, and C-9, while correlations between H-4 and C-1 and C-6 and between H-11 and C-5

established the connectivity between C-5 and C-6 to form the left six-membered ring. In addition, in the HMBC spectrum correlations of the carbonyl carbon (C-3) with H$_2$-2 and H-4, and the sp^2 methine carbon (C-4) with H$_2$-2, revealed that the carbonyl was located between C-2 and C-4 to form the right five-membered ring. Thus, compound **1** is 1-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0]non-4-en-3-one.

The relative configuration of **1** was elucidated by an analysis of the coupling constants (Table 1) and NOE difference experiments. In the ^{1}H NMR spectrum, the large vicinal coupling constants of 12.5 Hz characteristic of a *trans* diaxial relationship between H-6 and H-7α, as well as between H-8β and H-9, indicated both equatorial orientations of the isopropyl group at C-6 and the methyl group at C-9. In the NOE difference spectrum of **1**, H$_3$-10 and the hydroxy proton were enhanced by irradiation of H-2β, indicating β-orientations of the hydroxy at C-1 and the methyl at C-9. Finally, the structure and the relative configuration of **1** were further confirmed by X-ray crystallographic analysis. The ORTEP drawing, with the atom-numbering scheme indicated, is shown in Figure 1.

The absolute configuration of **1** was proposed from the CD spectrum (Figure 2a) and biogenetic consideration. Although the X-ray structure analysis of **1** indicated that the torsion angle between the double bond and the ketone group is 179.2°, close to 180°, in the crystal state, molecular
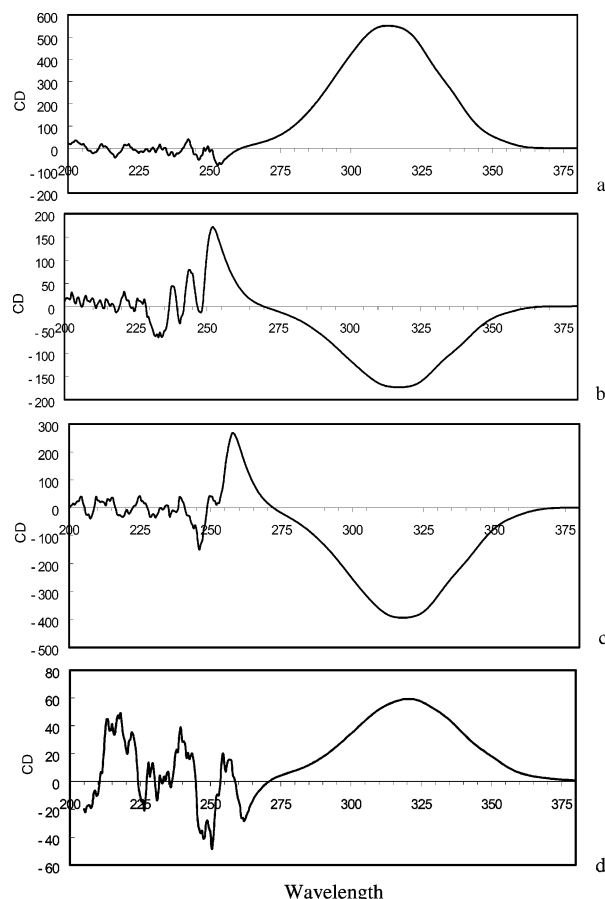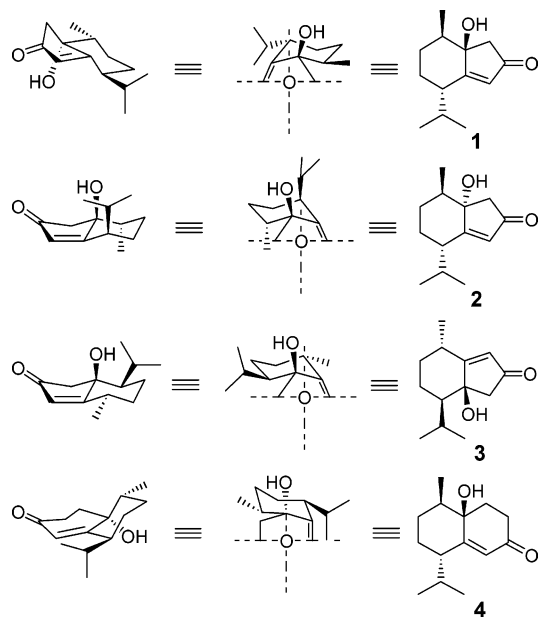
Figure 2. CD spectra of compounds **1**−**4** (a−d).

Figure 3. Proposed absolute configurations of compounds **1**−**4**.

modeling using the MM2 program indicated that the torsion angle between the double bond and the ketone group is 177.9° for the lowest energy conformation of **1**. Based on the octant rule for the cyclopentenone,[19] the positive Cotton effect at 313 nm ($\Delta\epsilon_{max}$ +11.26) for n → π* and negative Cotton effect at 253 nm ($\Delta\epsilon_{max}$ −0.41) for π → π* suggested that the configuration of **1** is as depicted in Figure 3. From the biogenetic point of view, the stereochemistry of the six-membered ring moiety in **1** should be identical with that of the co-occurring cadinane derivatives,

of which the absolute stereochemistry has been proposed.[16] Therefore, the structure of **1** was proposed as (+)-(1*R*,6*S*,9*R*)-1-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0]non-4-en-3-one.

Compound **2** was obtained as a colorless gum with $[\alpha]_D^{20}$ −16° (*c* 0.10, MeOH). The IR, EIMS, and NMR spectral features were very similar to those of **1**, indicating that **2** is an isomer of **1**. This was further confirmed by HREIMS. The 2D NMR experiments including ¹H−¹H COSY, HSQC, and HMBC revealed that **2** possessed the planar structure identical with **1**. Meanwhile, these experiments led to unambiguous assignments of the NMR spectral data of **2** (Tables 1 and 2). In the ¹H NMR spectrum of **2**, the splitting patterns and chemical shifts of H-6, H-7α, H-7β, H-8α, H-8β, and H-9 are obviously different from those of **1**. The coupling split analyses of **2** indicated that the coupling constants between H-6 and H-7β (axial) and between H-9 and H-8α (axial) were 5.5 ($J_{6,7\beta}$) and 4.5 ($J_{8\alpha,9}$) Hz, respectively. The coupling constants between H-6 and H-7α (equatorial) and between H-9 and H-8β (equatorial) were too small to be resolved, indicating that the dihedral angles between these two pairs of vicinal protons were close to 90°. This was confirmed by weak cross-peaks between H-6 and H-7α and between H-9 and H-8β in the ¹H−¹H COSY spectrum of **2**. This evidence demonstrated that both the isopropyl at C-6 and the methyl at C-9 were axial in **2** instead of equatorial in **1**. In the NOE difference experiments, an irradiation of H-2β enhanced H₃-10, while an irradiation of the hydroxy proton enhanced the H-2α and H₃-12, revealing an β-orientation (axial) of the methyl at C-9 and an α-orientation (axial) of the hydroxy at C-1. In addition, the enhancement of H-7α (equatorial) by the irradiation of H₃-13 confirmed the α-orientation of the isopropyl (axial) at C-6. Based on the octant rule for the cyclopentenone,[19] a negative Cotton effect at 317 nm ($\Delta\epsilon_{max}$ −7.88) and a positive cotton effect at 252 nm ($\Delta\epsilon_{max}$ +5.91) in the CD spectrum of **2** (Figure 2b) suggested that the absolute configuration of **2** is as depicted in Figure 3. The biogenetic consideration supported the suggestion, although molecular modeling using the MM2 program indicated that the torsion angle between the double bond and the ketone group is −179.3°, close to planar, for the lowest energy conformation of **2**. Therefore, the structure of **2** was proposed as (−)-(1*S*,6*S*,9*R*)-1-hydroxyl-6-isopropyl-9-methylbicyclo[4.3.0]non-4-en-3-one.

Compound **3** was obtained as a colorless gum with $[\alpha]_D^{20}$ +102° (*c* 0.12, MeOH). The IR, EIMS, and NMR spectral data indicated that **3** is another isomer of **1**, which was confirmed by the 2D NMR spectral analyses of **3**. Based on the assignments of the NMR data (Tables 1 and 2) by the ¹H−¹H COSY, HSQC, and HMBC spectrum, a comparison of the ¹H NMR data of **3** and **1** (or **2**) indicated that the chemical shift values of H-9 and H₃-10 of **3** were significantly downfield shifted to δ 2.83 (1H, dq, *J* = 13.5.0 and 7.0 Hz) and 1.33 (3H, d, *J* = 7.0 Hz), respectively, and H-6 was upfield shifted to δ 1.99 (1H, ddd, *J* = 12.0, 6.5, and 5.0 Hz), suggesting that the double bond was located between C-1 and C-2 in **3** instead of between C-4 and C-5 in **1** (or **2**), while the hydroxyl was at C-5 of **3** rather than at C-1 in **1** (or **2**). This suggestion was confirmed by the HMBC correlations from the methyl doublet (H₃-10) to the quaternary sp² carbon (C-1) of the double bond and from the hydroxy proton to C-1, C-5, and C-6, of which in turn C-6 correlated with the two methyl doublets of the isopropyl. The coupling patterns of H-6 ($J_{6,7\beta}$ = 12.0 Hz, $J_{6,7\alpha}$ = 5.0 Hz) and H-9 ($J_{8\alpha,9}$ = 13.5 Hz, $J_{8\beta,9}$ = 4.0 Hz) indicated that both the isopropyl at C-6 and the methyl at C-9 were

equatorial in **3**. In the NOE difference spectrum of **3** the proton signals of the isopropyl moiety and the hydroxy proton were enhanced by the irradiation of H-4β and H-9, demonstrating a β-orientation of the hydroxy group. Molecular modeling using the MM2 program indicated that the torsion angle between the double bond and the ketone group is 176.0° for the lowest energy conformation of **3**. A negative Cotton effect at 317 nm ($\Delta\epsilon_{max}$ −9.92) and a positive Cotton effect at 258 nm ($\Delta\epsilon_{max}$ +5.16) in the CD spectrum of **3** (Figure 2c) suggested that **3** possessed the absolute configuration as depicted in Figure 3. Therefore, the structure of **3** was proposed as (+)-(5S,6R,9S)-5-hydroxy-6-isopropyl-9-methylbicyclo[4.3.0]non-1-en-3-one.

Compound **4** was obtained as a white amorphous solid with [α]$_D^{20}$ −28° (*c* 0.30, MeOH) and showed IR absorption bands for hydroxy (3471 cm^{-1}) and conjugated carbonyl (1664, 1612 cm^{-1}) groups. The EIMS showed a molecular ion peak at *m/z* 222 [M]$^+$, and the molecular formula $C_{14}H_{22}O_2$ was determined by HREIMS at 222.1617 [M]$^+$. The ^1H NMR spectrum showed three methyl doublets at δ 0.90 (3H, d, *J* = 6.5 Hz, H-12), 0.92 (3H, d, *J* = 6.5 Hz, H-13), and 1.00 (3H, d, *J* = 6.0 Hz, H-14) and an olefinic proton singlet at δ 5.61 (1H, br s, H-5), as well as multiplets attributed to aliphatic methylenes and methines (Table 1). The ^{13}C NMR and DEPT spectra displayed 14 signals for three methyls, four methylenes, four methines (one sp^2 hybrid), one olefinic quaternary carbon, one carbonyl, and one quaternary sp^3 carbon-bearing oxygen (Table 2). The structure of **4** was mainly established by 2D NMR experiments. In the ^1H and ^{13}C NMR spectra the proton and their attaching carbon signals were unambiguously assigned by the HMQC experiment. The presence of the two structural segments (CH$_3$)$_2$CHCHCH$_2$CH$_2$CHCH$_3$ and CH$_2$CH$_2$ was readily established by the ^1H–^1H COSY spectrum, which showed homonuclear correlations from both H$_3$-12 and H$_3$-13 to H-11, which in turn correlated with H-7, and the coupling chain continued from H-7 through H$_2$-8 and H$_2$-9 to H-10 and then to H$_3$-14, as well as correlations from H$_2$-2 to H$_2$-3 without coupling extension. In the HMBC spectrum of **4**, correlations of the oxygenated quaternary carbon (C-1) with H$_2$-2, H$_2$-3, H-9, and H$_3$-14 and C-10 with H$_2$-2 demonstrated that C-10 and C-2 of the two segments were connected through C-1, while correlations of the olefinic quaternary carbon (C-6) with H$_2$-2, H-7, H$_2$-8, H-10, and H-11, and C-1, C-6 and C-7 with the olefinic proton (H-5), demonstrated that C-6 was directly connected with both C-1 and C-7 to form the left six-membered ring. In addition, HMBC correlations from H$_2$-2 and H$_2$-3 to the carbonyl carbon (C-4) and from H-5 to C-3 unequivocally revealed the direct attachments of both C-3 and C-5 to C-4 to form the right six-membered ring. Therefore, the planar structure of **4** is 1-hydroxy-11-norcadinan-5-en-4-one. The relative configuration of **4** was deduced from an analysis of the coupling constants and NOE difference experiments. The equatorial orientations of both the isopropyl at C-7 and the methyl at C-10 were indicated by the characteristic diaxial coupling constants between H-7 and H-8α (*J* = 13.0 Hz) and between H-10 and H-9β (*J* = 13.0 Hz). In the NOE difference spectrum H$_3$-14 was enhanced by the irradiation of the hydroxyl proton, indicating that the hydroxy was axial. The absolute configuration of **4** was proposed from the CD spectrum (Figure 2d). Molecular modeling using the MM2 program indicated that the torsion angle between the double bond and the ketone group is −172.4° for the lowest energy conformation of **4**. Based on the octant rules for the cyclohexenones,[19,20] the positive Cotton effect at 320 nm ($\Delta\epsilon_{max}$ +6.26) for n → π^* and the negative Cotton effect

at 251 nm ($\Delta\epsilon_{max}$ −2.51) for π → π^* suggested that **4** possessed the absolute configuration as depicted in Figure 3. Thus, the structure of **4** was proposed as (−)-(1R,7S,10R)-1-hydroxy-11-norcadinan-5-en-4-one. The possible enantiomer of **4** was synthesized, and its structure with an undetermined configuration was assigned from a mixture.[21]

From the biogenetic point of view, the carbon skeleton of **1**−**3** may be derived from the co-occurring cadinane skeleton[16] by the ring contraction accompanied by loss of two carbon units, and **4** may come from the oxidation of cadinane derivatives.

Compounds **1**−**4** were tested for cytotoxicity against lung adenocarcinoma (A549), stomach cancer (BGC-823), breast cancer (MCF-7), hepatoma (Bel7402), and colon cancer (HCT-8) cell lines by using the MTT method,[22,23] but were found to be 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. The CD spectra were recorded on a Jasco J-715 spectropolarimeter. 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 and HREIMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. 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** 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°, 2θ ≤ 50°] and were corrected by Lorentz and polarization. Altogether 3594 reflections were collected, of which 1140 with |F|^2 ≥ 8σ|F|^2 were observed, and 1501 reflections were independent. The structure was solved by direct methods and refined by full matrix least-squares procedures to R_f = 0.058, R_w = 0.059 [w = 1/σ|F|^2]. Hydrogen positions were found from difference Fourier maps and geometric calculations. All calculations were carried out on a PC by using the NOMCSDP program system.[24]

Material. The brown alga *Dictyopteris divaricata* Okam. was collected at 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) is deposited at the Herbarium of the Institute of Oceanology.

Extraction and Isolation. The alga *Dictyopteris 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 water 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$_2$CO (0−100%) in petroleum ether, and separated into 24 fractions (I−XXIV) on the basis of TLC analyses. Fraction XII was separated by column chromatography over Sephadex LH-20 using petrolium ether−CHCl$_3$−MeOH (5: 5: 1) as the eluent to give six corresponding subfractions. The third subfraction of XII was purified by reversed-phase preparative HPLC using MeOH−H$_2$O (80: 20) to give compounds **2** (21 mg) and **3** (36 mg). The fourth subfraction of XII was purified by reversed-phase preparative HPLC using MeOH−H$_2$O (80: 20) to yield compounds **4** (39 mg) and **1** (19 mg).

(+)-(1*R*,6*S*,9*R*)-1-Hydroxyl-6-isopropyl-9-methylbicyclo-[4.3.0]non-4-en-3-one (1): colorless prisms (Me$_2$CO), mp 146.0−147.5 °C; [α]$_D^{20}$ +23° (*c* 0.10, MeOH); IR (KBr) ν_{max} 3373, 2954, 2879, 1684, 1610, 1468, 1398, 1244, 1190, 1065, 1012, 987, 858 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz), see Tables 1 and 2; EIMS *m/z* (%) 208 (13) [M]$^+$, 165 (12), 137 (27), 109 (8), 58 (33), 43 (100); HREIMS *m/z* 208.1461 (calcd for C$_{13}$H$_{20}$O$_2$, 208.1463).

Crystal data of 1: C$_{13}$H$_{20}$O$_2$, *M*$_r$ 208.30, orthorhombic, space group *P*2$_1$2$_1$2$_1$, *a* = 7.131(1) Å, *b* = 10.111(1) Å, *c* = 17.009(1) Å; *V* = 1226.4(1) Å^3, *Z* = 4, *D*$_c$ = 1.128 g cm^{-3}, *F*(000) = 456; crystal dimensions 0.10 × 0.20 × 0.30 mm.

(−)-(1*S*,6*S*,9*R*)-1-Hydroxyl-6-isopropyl-9-methylbicyclo-[4.3.0]non-4-en-3-one (2): [α]$_D^{20}$ −16° (*c* 0.10, MeOH); IR (KBr) ν_{max} 3426, 2960, 2868, 1716, 1687, 1612, 1466, 1385, 1228, 1169, 1059, 1018, 970, 856 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz), see Tables 1 and 2; EIMS *m/z* 208 (10) [M]$^+$, 180 (10), 165 (13), 137 (22), 125 (6), 109 (8), 58 (40), 43 (100); HREIMS *m/z* 208.1459 (calcd for C$_{13}$H$_{20}$O$_2$, 208.1463).

(+)-(5*S*,6*R*,9*S*)-5-Hydroxyl-6-isopropyl-9-methylbicyclo-[4.3.0]non-1-en-3-one (3): colorless gum, [α]$_D^{20}$ +102° (*c* 0.12, MeOH); IR (KBr) ν_{max} 3425, 2960, 2931, 2871, 1714, 1689, 1618, 1456, 1388, 1371, 1296, 1240, 1173, 1016, 978, 856 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz), see Tables 1 and 2; EIMS *m/z* 208 (12) [M]$^+$, 180 (4), 165 (17), 137 (25), 125 (16), 109 (18), 95 (13), 81 (11), 67 (10), 58 (27), 43 (100); HREIMS *m/z* 208.1460 (calcd for C$_{13}$H$_{20}$O$_2$, 208.1463).

(−)-(1*R*,7*S*,10*R*)-1-Hydroxy-11-norcadinan-5-en-4-one (4): colorless gum, [α]$_D^{20}$ −28° (*c* 0.30, MeOH); IR (KBr) ν_{max} 3471, 2972, 2887, 1664, 1612, 1471, 1388, 1309, 1275, 1217, 1182, 1117, 1005, 982, 962, 926, 885 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz), see Tables 1 and 2; EIMS *m/z* (%) 222 (48) [M]$^+$, 194 (32), 179 (100), 161 (26), 151 (37), 137 (48), 123 (17), 109 (21), 55 (31), 43 (61); HREIMS *m/z* 222.1617 (calcd for C$_{14}$H$_{22}$O$_2$ 222.1620).

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

References and Notes

(1) Fenical, W.; Sims, J. J.; Squatrito, K.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383−2386.
(2) Fenical, W.; McConnel, O. *Experientia* **1975**, *31*, 1004−1005.
(3) Cimino, G.; De Stefano, S.; Fenical, W.; Minale, L.; Sims, J. J. *Experientia* **1975**, *31*, 1250−1251.
(4) Ochi, M.; Kotsuki, H.; Muraoka, K.; Tokoroyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 629−630.
(5) Fenical, W.; Sims, J. J.; Wing, R. M.; Radlick, P. C. *Phytochemistry* **1972**, *11*, 1161−1163.
(6) Kajiwara, T.; Hatanaka, A.; Tanaka, Y.; Kawai, T.; Ishihara, M.; Tsuneya, T.; Fujimura, T. *Phytochemistry* **1989**, *28*, 636−639.
(7) Suzuki, M.; Kowata, N.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2366−2368.
(8) Suzuki, M.; Kowata, N.; Kobayashi, H.; Tanaka, I. *Chem. Lett.* **1990**, *228*, 2187−2190.
(9) Segawa, M.; Yamano, K.; Shirahama, H. *Phytochemistry* **1990**, *29*, 973−974.
(10) Koenig, G. M.; Wright, A. D. *Magn. Reson. Chem.* **1995**, *33*, 178−183.
(11) Boland, W.; Muller, D. G. *Tetrahedron Lett.* **1987**, *28*, 307−310.
(12) Yamada, K.; Ojika, M.; Tan, H. *Chem. Lett.* **1980**, 1633−1634.
(13) Moore, R. E.; Pettus, J. A. J.; Mistysyn, J. *J. Org. Chem.* **1974**, *39*, 2201−2207.
(14) Fan, X.; Xu, N. J.; Shi, J. G. *J. Nat. Prod.* **2003**, *66*, 455−458.
(15) Xu, N. J.; Fan, X.; Yang, Y. C.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 807−809.
(16) Song, F. H.; Fan, X.; Xu, X. L.; Zhao, J. L.; Yang, Y. C.; Shi, J. G. *J. Nat. Prod.* **2004**, *67*, 1644−1649.
(17) Song, F. H.; Fan, X.; Xu, X. L.; Zhao, J. L.; Han, L. J.; Shi, J. G. *Chin. Chem. Lett.* **2004**, *15*, 316−318.
(18) Song, F. H.; Fan, X.; Xu, X. L.; Zhao, J. L.; Han, L. J.; Shi, J. G. *J. Asian Nat. Prod. Res.* **2005** (in press).
(19) Ye, X. L. *Sterochemistry*; Beijing University Express: Beijing, 1999; pp 257−259.
(20) De Pascual Teresa, J.; Moreno Valle, M. A.; Gonzalez, M. S.; Bellido, I. S. *Tetrahedron* **1984**, *40*, 2189−2195.
(21) Bhonsle, J. B. *Synth. Commun.* **1995**, *25*, 289−300.
(22) Mosumann, T. *J. Immunol. Methods* **1983**, *65*, 55−63.
(23) Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936−942.
(24) Wu, B. M.; Lu, Y. *Chin. Chem. Lett.* **1992**, *3*, 637−640.

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