Four New Sesquiterpenoids from the Fruits of *Alpinia oxyphylla*

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Two new norsesquiterpenoids, oxyphyllenotriol A (1) and oxyphyllone G (2), and two new sesquiterpenoids, oxyphyllol D (3) and oxyphyllol E (4), together with two known compounds (5, 6) were isolated from the fruits of *Alpinia oxyphylla*. Their structures were determined on the basis of spectroscopic analysis, including high resolution electrospray ionization mass spectrometry (HR-ESI-MS), 1D- and 2D-NMR, and the absolute configurations of 2 and 4 were determined by theoretical calculation of electronic circular dichroism (ECD) and comparison with the experimental ECD spectra.

Key words *Alpinia oxyphylla*; sesquiterpenoid; electronic circular dichroism

The Zingiberaceae plant *Alpinia oxyphylla* Miq. is widely cultivated in South China. The fruits of this plant have been used as Traditional Chinese Medicine (TCM) for the treatment of intestinal disorders, urosis and diuresis, and were coded in Chinese Pharmacopeia[1] as an aromatic stomachic. Previous chemical investigations of *A. oxyphylla* have reported sesquiterpenoids, some of which showed inhibitory effects on nitric oxide (NO) production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages and release of β-hexosaminidase from RBL-2H3 cells.[2—6] In our continuing endeavor to discover new bioactive natural products from TCM, four new compounds including two 14-norcadinane-type sesquiterpenoids (**1**, **2**) and two eudesmane-type sesquiterpenoids (**3**, **4**), together with two known compounds oxyphyllol C (**5**)[3] and epinootkaol (**6**)[7] were isolated from the fruits of *A. oxyphylla* (Fig. 1). This paper reports the isolation and the structure elucidation of the new sesquiterpenoids.

Results and Discussion

Compound **1** was isolated as light yellow viscous oil. The high resolution electrospray ionization mass spectrometry (HR-ESI-MS) exhibited a pseudo-molecular ion peak $[M-H]^-$ at *m*/*z* 235.1329 (Calcd for $C_{14}H_{19}O_3$, 235.1340) corresponding to the molecular formula of $C_{14}H_{20}O_3$, indicating 5 degrees of unsaturation. The IR spectrum revealed the presence of hydroxyl group (3451 cm^{-1}) and phenolic group (1640, 1461 cm^{-1}).[8] The ^{1}H-NMR spectrum of **1** (Table 1) showed two *ortho*-aromatic proton signals at δ_H 7.14 (1H, d, J=8.5 Hz), 6.80 (1H, d, J=8.5 Hz), and a methyl signal at δ_H 1.51 (3H, s). A set of signals at δ_H 3.39 (1H, m), 1.30 (3H, d, J=7.0 Hz) and 1.23 (3H, d, J=7.0 Hz) revealed the presence of one isopropyl group.

The ^{13}C-NMR chemical shifts for **1** along with the information obtained from the ^{1}H-detected heteronuclear single-quantum coherence spectrum (HSQC) experiment (Tables 1, 2) revealed 14 carbon resonances, suggesting a norsesquiterpenoid: six carbons at δ_C 134.0, 141.7, 124.5, 114.8, 121.9 and 151.2 indicating an aromatic moiety, three signals for isopropyl group at δ_C 27.5, 24.1 and 25.3, one methyl group at δ_C 26.5, two methylenes at δ_C 19.6, 27.9, one signal for the oxygenated methine at δ_C 70.7, and one quaternary carbon oxygenated at δ_C 71.2. Considering the five units of unsaturation required for the molecular formula $C_{14}H_{20}O_3$ and the identification of one aromatic ring, a bicyclic compound was deduced.

The structure of **1** was elucidated from HSQC, ^{1}H–^{1}H shift correlation spectroscopy (^{1}H–^{1}H COSY) and heteronuclear multiple bond coherence spectroscopy (HMBC) studies. HMBC correlations from H-11 (δ_H 3.39), H_3-12 (δ_H 1.30) and H_3-13 (δ_H 1.23) to C-6 (δ_C 141.7) indicated that the isopropyl was connected to the aromatic ring at C-6 (Fig. 2), which was further confirmed by up-shift H-11 (δ_H 3.39) attributed to the isopropyl group (Fig. 2). In addition, the HMBC cross-peaks of H_3-15 (δ_H 1.51) with C-2 (δ_C 27.9), C-3 (δ_C 71.2) and C-4 (δ_C 70.7), H-8 (δ_H 6.80) and H-1 (δ_H

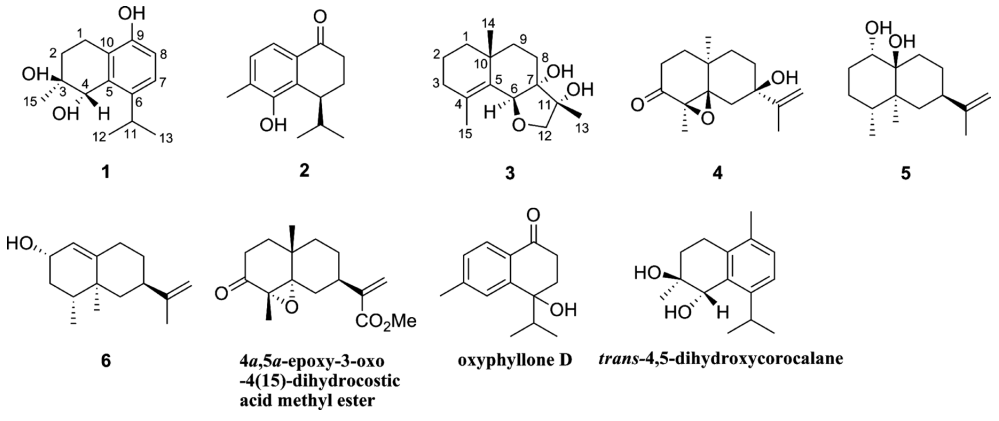

Fig. 1. Structures of Sesquiterpenoids

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Table 1. ^{1}H-NMR Spectral Data of **1**—**4** (500 MHz, δ in ppm, J in Hz)

No.	**1**[a)]	**2**[a)]	**3**[a)]	**3**[b)]	**4**[a)]	**4**[b)]
1	2.76 m; 2.83 m	7.55 d (8.0)	1.46 m; 1.37 m	1.34 m; 1.25 m	1.31 m; 2.07 m	1.21 m; 1.93 m
2	1.86 m; 2.07 m	7.09 d (8.0)	1.63 m; 1.80 m	1.47 m; 1.59 m	2.45 m; 2.37 m	2.35 m; 2.24 m
3			2.01 m; 2.09 m	1.94 m; 1.99 m		
4	4.54 s					
5						
6		2.83 m	4.72 d (1.5)	4.57 d (1.2)	1.46 d (2.0); 2.35 s	1.29 m; 2.26 m
7	7.14 d (8.5)	2.32 m; 2.05 m				
8	6.80 d (8.5)	2.75 m; 2.53 m	1.80 m; 1.52 m	1.62 m; 1.36 m	1.68 m; 1.92 m	1.48 m; 1.85 m
9			1.42 m; 1.51 m	1.24 m; 1.28 m	1.47 m; 2.05 m	1.32 m; 1.90 m
10						
11	3.39 m	1.86 m				
12	1.30 d (7.0)	1.09 d (6.5)	3.88 d (1.5)	3.72 d (9.5); 3.61 d (9.5)	5.10 s; 4.89 s	5.00 s; 4.75 s
13	1.23 d (7.0)	0.90 d (6.5)	1.24 s	1.06 s	1.84 s	1.75 s
14			1.12 s	1.03 s	1.07 s	0.97 s
15	1.51 s	2.31 s	1.77 s	1.63 s	1.39 s	1.23 s
7-OH				4.08 s		4.29 s
11-OH				4.50 s		

a) Spectra were measured in $CDCl_3$. *b*) Spectra were measured in DMSO-d_6.

Table 2. ^{13}C-NMR Spectral Data of **1**—**4** (125 MHz, $CDCl_3$, δ in ppm)

No.	**1**	**2**	**3**	**4**
1	19.6	119.9	39.9	31.5
2	27.9	128.6	18.4	35.9
3	71.2	128.8	33.5	207.7
4	70.7	150.9	137.3	63.2
5	134.0	134.1	129.7	70.9
6	141.7	37.9	77.8	33.2
7	124.5	24.9	78.8	74.5
8	114.8	33.4	26.1	30.6
9	151.2	198.7	36.7	33.0
10	121.9	131.7	33.0	33.5
11	27.5	31.6	79.4	150.5
12	24.1	21.4	76.6	110.0
13	25.3	21.3	18.5	18.8
14			25.8	20.4
15	26.5	16.7	19.4	11.3

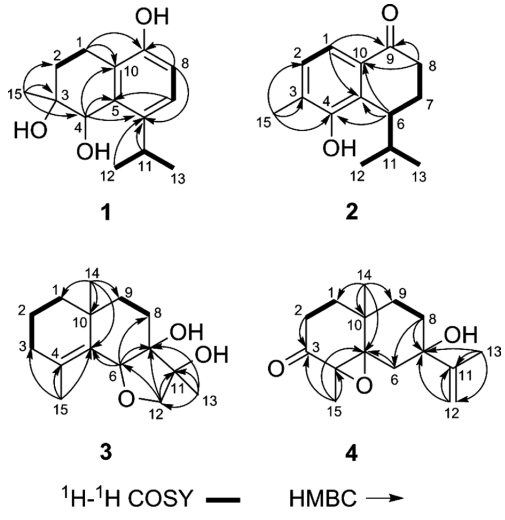

Fig. 2. ^{1}H–^{1}H COSY and Key HMBC Correlations for **1**—**4**

2.76) with C-9 (δ_C 151.2) suggested that three hydroxyl groups were determined to be at C-3, C-4 and C-9, respectively (Fig. 2). The above total data showed that compound **1**

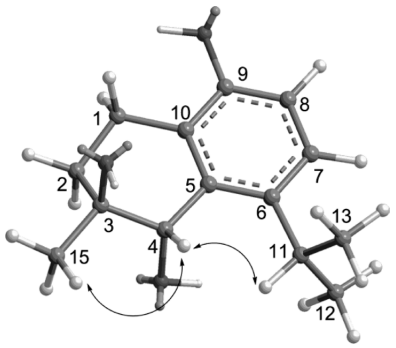

Fig. 3. Key ROESY Correlations for **1**

was a 14-norcadinane-type sesquiterpenoid, which was analogous to *trans*-4,5-dihydroxycorocalane[9] except that the CH_3-14 was replaced by a hydroxyl group.

The relative configuration of compound **1** was established by the rotating frame Overhauser effect spectroscopy (ROESY) experiment.[9] H-4 showed ROESY correlation with H-11 indicated that H-4 was in an equatorial orientation. CH_3-15 was assigned as a pseudo equatorial, due to correlation with H-4 and no ROESY correlation with H-1β (Fig. 3). Hence, compound **1** was identified as 3β,4α,9-trihydroxy-14-norcadina-5,7,9-triene, and named oxyphyllenotriol A.

Compound **2** was obtained as light yellow viscous oil. The molecular formula of $C_{14}H_{18}O_2$ was deduced from the HR-ESI-MS ion peak $[M-H]^-$ at *m*/*z*: 217.1241 (Calcd for $C_{14}H_{17}O_2$, 217.1234). The ^{1}H-, ^{13}C-NMR and HSQC spectra (Tables 1, 2) analysis indicated that compound **2** also displayed 14 carbon signals, including six 1,2,3,4-tetrasubstituted aromatic carbons at δ_C 119.9, 128.6, 128.8, 134.1, 131.7 and 150.9, one carbonyl carbon at δ_C 198.7, one isopropyl group (δ_C 31.6, 21.4, 21.3), one methyl group at δ_C 16.7, two methylenes at δ_C 24.9, 33.4, and one methine at δ_C 37.9.

Compared with **1**, the isopropyl of **2** connected with aliphatic C-6 (δ_C 37.9) but not with aromatic ring, which was evidenced by down-shift proton H-11 (δ_H 1.86) of the isopropyl group, as well as the ^{1}H–^{1}H COSY spin system H-

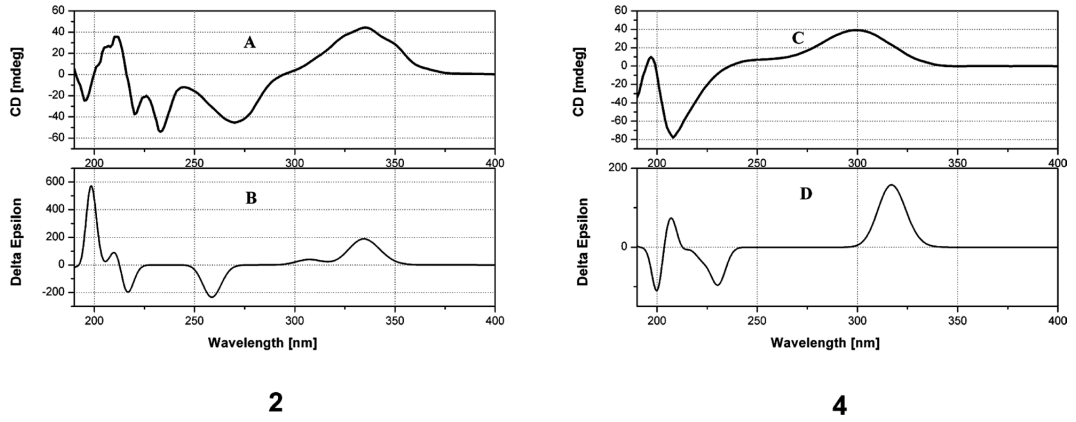

Fig. 4. Experimental ECD Spectra (A, C) and Calculated ECD Spectra (B, D) of **2** and **4**

6/H-11/H_3-12/H_3-13 (Fig. 2). Above information indicated that the structure of **2** was a 14-norcadinane-type sesquiterpenoid whose skeleton is identical to oxyphyllone D.[4] The HMBC correlations from H_3-15 (δ_H 2.31) and H-6 (δ_H 2.83) to C-4 (δ_C 150.9), and from H-1 (δ_H 7.55) and H-8 (δ_H 2.75) to C-9 (δ_C 198.7) established that a phenolic function and carbonyl group were located at C-4, C-9 (Fig. 2), respectively.

The absolute configuration of **2** was determined by comparison of its theoretically calculated electronic circular dichroism (ECD) spectrum with the experimental ECD spectrum.[10,11] The geometry was built on the basis of a *S*-configuration based on a 3D-structure of **2**. Then, the conformational analysis was performed by means of the semiempirical PM3 method, as implemented in the program package Q-Chem, starting from preoptimized geometries generated by the MM2 force-field in Chem 3D software. After that, the ECD spectrum was calculated in the gas phase using time-dependent density functional theory (TDDFT) at the B3LYP/6-31G(d) level. The calculated ECD spectrum displayed negative and positive Cotton effects (CEs) which showed good agreement with the experimental ECD spectrum (Fig. 4), allowing the assignment of the absolute configuration of **2** as depicted. Thus, the structure of **2** was deduced to be (6*S*)-4-hydroxy-14-norcadina-1,3,5-triene-9-one, and named oxyphyllone G.

Compound **3** was isolated as white power. The molecular formula was determined as $C_{15}H_{24}O_3$ by HR-ESI-MS ion peak at *m*/*z*: 251.1662 $[M-H]^-$ (Calcd for $C_{15}H_{23}O_3$, 251.1653). The IR spectrum showed the absorption bands of hydroxyl group (3434 cm^{-1}) and olefinic bond (1650 cm^{-1}). The ^{1}H-NMR spectrum (Table 1) revealed three methyls at δ_H 1.24, 1.12 and 1.77, one oxymethylene signal at δ_H 3.88 (2H, d, J=1.5 Hz) and an oxymethine proton at δ_H 4.72 (1H, d, J=1.5 Hz). The ^{13}C-NMR and the distorsionless enhancement by polarization transfer (DEPT) spectrum (Table 2) of **3** showed 15 carbon signals, including three methyls, six methylenes (one oxygenated at δ_C 76.6), one oxygenated methine at δ_C 77.8, and five quaternary carbons (two olefinic carbons at δ_C 137.3, 129.7 , two oxygenated at δ_C 78.8, 79.4).

According to further analysis of 2D-NMR experiments including ^{1}H–^{1}H COSY, HSQC and HMBC (Tables 1, 2 and Fig. 2), compound **3** was fully assigned as an eudesmane-type sesquiterpenoid.[12—14] The ^{1}H–^{1}H COSY spectrum of **3** suggested the existence of two proton spin units as showed in Fig. 2. The oxymethylene was linked with C-6 by *O*-bond to form an tetrahydrofuran ring in an angular positions at C-6, C-7, and two hydroxyl groups at C-7 and C-11, which were clarified by analysis of the obvious HMBC correlations of H_3-13 (δ_H 1.24) with C-7 (δ_C 78.8), C-11 (δ_C 79.4) and C-12 (δ_C 76.6), and H-12 (δ_H 3.88) with C-6 (δ_C 77.8), C-7 (δ_C 78.8) and C-11 (δ_C 79.4) (Fig. 2), respectively.

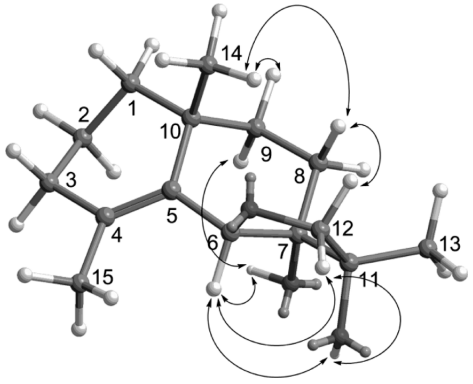

Fig. 5. Key ROESY Correlations for **3**

The relative configuration of **3** was determined by ROESY spectrum. Assuming CH_3-14 to be β-orientation, as it is the case for most natural eudesmanes isolated from high plants, the correlations of H-6 with OH-7 (δ_H 4.08) and OH-11 (δ_H 4.50), and absence of correlation of CH_3-14/H-6 revealed that H-6, OH-7 and OH-11 were α-orientation (Fig. 5). Therefore, the structure of **3** was elucidated as (13β-methyl,14β-methyl,6α-H)-4,5-dehydroeudesman[2,1-*b*] tetrahydrofuran-7α,11α-diol, and named oxyphyllol D.

Compound **4** was obtained as colorless viscous oil. Its molecular formula $C_{15}H_{22}O_3$ was deduced on the basis of HR-ESI-MS ion peak at *m*/*z* 273.1471 $[M+Na]^+$ (Calcd for $C_{15}H_{22}O_3Na$, 273.1461). The NMR data (Tables 1, 2) suggested that **4** also possessed an eudesmane skeleton.[12,15,16] A terminal double bond was located between C-11 (δ_C 150.5) and C-12 (δ_C 110.0) by the HMBC correlations from H-12 (δ_H 5.10) to C-13 (δ_C 18.8) and C-7 (δ_C 74.5, oxygenated) (Fig. 2). In addition, a carbonyl carbon at C-3 and an epoxy bridge at C-4, C-5 were confirmed through comparing the ^{13}C-NMR data of **4** with the known compound 4α,5α-epoxy-

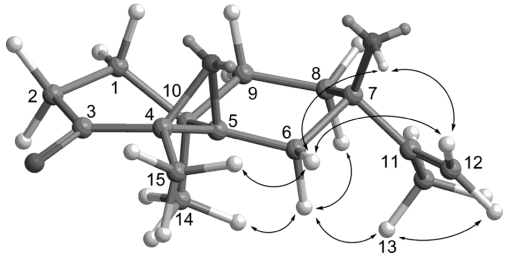

Fig. 6. Key ROESY Correlations for **4**

3-oxo-4(15)-dihydrocostic acid methyl ester.[16] This was further evidenced by HMBC cross-peaks of H_3-15 (δ_H 1.39) to C-3 (δ_C 207.7), C-4 (δ_C 63.2) and C-5 (δ_C 70.9), and H_3-14 (δ_H 1.07) to C-5 (δ_C 70.9).

The relative configuration of **4** was established by the ROESY experiment and ^{1}H-, ^{13}C-NMR data. As showed in Fig. 6, the ROESY correlations of H-6α/CH_3-14, H-6α/H-8α suggested that H-6α and H-8α were α-orientation if CH_3-14 was assumed to be α-orientation. OH-7 (δ_H 4.29) showed correlation with H-6β, but no ROESY correlation with H-6α, indicating β-orientation of OH-7. The epoxy bridge was deduced as β-orientation by comparison with spectral data of literature.[16] The ECD calculation (Fig. 4) confirmed the absolute configuration as depicted. Thus, the structure of **4** was concluded as (4*R*,5*R*,7*R*,10*R*)-7-hydroxyl-4,5-epoxy-11,12-dehydroeudesman-3-one, and named oxyphyllol E.

Experimental

General Experimental Procedures Optical rotations were measured with a JASCO P-1020 polarimeter. CD spectra were carried out on a JASCO 810 spectropolarimeter. IR (KBr disks) spectra were recorded on a Bruker Tensor 27 spectrometer. UV spectra were obtained on a Shimadzu UV-2450 spectrometer. NMR spectra were recorded on a Bruker ACF-500 NMR instrument (^{1}H: 500 MHz, ^{13}C: 125 MHz), with tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on a MS Agilent 1100 Series LC/MSD ion-trap mass spectrometer (ESI-MS) and HR-ESI-MS was done on a Mariner time-of-flight mass spectrometer with an electrospray interface, respectively. Silica gel (Qingdao Haiyang Chemical Co., Ltd., China), Sephadex LH-20 (Pharmacia, U.S.A.) and RP-C_{18} (40—63 μm, Fuji, Japan) were used for column chromatography. Preparative HPLC was carried out using an Agilent 1100 Series instrument with a Shim-pack reversed-phase C_{18} column (20×200 mm) and a 1100 Series multiple wavelength detector.

Plant Material The air-dried fruits of *A. oxyphylla* were collected from Guangdong Province, People's Republic of China, in September 2009, and were authenticated by Professor Mian Zhang, Research Department of Pharmacognosy, China Pharmaceutical University. A voucher specimen (No. 20091010) has been deposited in the Department of Natural Medicinal Chemistry, China Pharmaceutical University.

Extraction and Isolation The air-dried fruits of *A. oxyphylla* (3.5 kg) were extracted by refluxing with 95% ethanol three times and concentrated under reduced pressure (215 g). The residue was suspended in H_2O, and then extract with CH_2Cl_2 and EtOAc to give 180 g and 4 g extracts, respectively. The CH_2Cl_2 extract was subjected to a silica gel column chromatography (CC) eluted with petroleum ether–acetone in a gradient (1 : 0 to 1 : 1), to afford 14 fractions (Fr. 1—14). Fr. 5 eluted with a gradient of petroleum ether–EtOAc (10 : 1 to 1 : 2) on a silica gel CC to give 6 subfractions (Fr. 5.1—5.6). Fr. 5.3 was chromatographed continuously into 5 subfractions (Fr. 5.3.1—5.3.5) using an RP-C_{18} column with a gradient of MeOH–H_2O (6 : 4 to 1 : 0). Fr. 5.3.3 was further separated by preparative HPLC using MeOH–H_2O (75 : 35, 10 ml/min) as the mobile phase to give **6** (4 mg). Fr. 6 over a Sephadex LH-20 column using MeOH–CH_2Cl_2 (1 : 1) as the eluting solvent to obtain 3 subfractions (Fr. 6.1—6.3). Fr. 6.2 was purified by preparative HPLC using MeOH–H_2O (70 : 30, 10 ml/min) as the mobile phase to obtain **2** (5 mg) and **4** (7 mg). Fr. 8 was applied to a silica gel CC with MeOH–CH_2Cl_2 (1 : 100 to 1 : 10) to afford 4 subfractions (Fr. 8.1—8.4). Fr. 8.3 was separated by RP-C_{18} column following purification with preparative HPLC [MeOH–H_2O (65 : 35, 10 ml/min)] to give **1** (4 mg), **3** (4 mg) and **5** (7 mg).

Oxyphyllenotriol A (**1**): Light yellow, viscous oil; $[\alpha]_D^{23}$ +13.2 (c=0.4, $CHCl_3$); UV λ_{max} ($CDCl_3$) nm (log ε): 241 (3.7), 280 (3.6); IR (KBr) ν_{max} cm^{-1}: 3451, 2957, 2925, 2852, 1640, 1461, 1378; ^{1}H-NMR ($CDCl_3$, 500 MHz) see Table 1 and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Table 2; ESI-MS m/z: 237 $[M+H]^+$; HR-ESI-MS m/z: 235.1329 $[M-H]^-$ (Calcd for $C_{14}H_{19}O_3$, 235.1340).

Oxyphyllone G (**2**): Light yellow, viscous oil; $[\alpha]_D^{23}$ +41.5 (c=0.4, $CHCl_3$); CD λ_{max} (c=0.25, CH_3OH) nm ($\Delta\varepsilon$): 195.2 (−24.6), 211.3 (+35.7), 220.1 (−37.5), 233.2 (−54.0), 270.1 (−45.3), 335.0 (+44.4); UV λ_{max} ($CDCl_3$) nm (log ε): 265 (3.9), 310 (3.5); IR (KBr) ν_{max} cm^{-1}: 3443, 2960, 2927, 1662, 1462, 1635, 1332, 1290, 1237; ^{1}H-NMR ($CDCl_3$, 500 MHz) see Table 1 and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Table 2; ESI-MS m/z: 219 $[M+H]^+$; HR-ESI-MS m/z: 217.1241 $[M-H]^-$ (Calcd for $C_{14}H_{17}O_2$, 217.1234).

Oxyphyllol D (**3**): White power; $[\alpha]_D^{23}$ −1.4 (c=0.1, $CHCl_3$); UV λ_{max} ($CDCl_3$) nm (log ε): 243 (2.9); IR (KBr) ν_{max} cm^{-1}: 3434, 2979, 2939, 2872, 1650, 1454, 1383, 1352, 1017; ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{1}H-NMR (DMSO-d_6, 500 MHz) see Table 1, and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Table 2; ESI-MS m/z: 251 $[M-H]^-$; HR-ESI-MS m/z: 251.1662 $[M-H]^-$ (Calcd for $C_{15}H_{23}O_3$, 251.1653).

Oxyphyllol E (**4**): Colorless, viscous oil; $[\alpha]_D^{23}$ +26.8 (c=0.4, $CHCl_3$); CD λ_{max} (c=0.22, CH_3OH) nm ($\Delta\varepsilon$): 197.1 (+9.8), 208.2 (−78.0), 295.5 (+38.0); UV λ_{max} ($CDCl_3$) nm (log ε): 245 (2.4); IR (KBr) ν_{max} cm^{-1}: 3460, 2960, 2936, 1701, 1653, 1453, 1409, 1382, 901; ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{1}H-NMR (DMSO-d_6, 500 MHz) see Table 1, and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Table 2; ESI-MS m/z: 249 $[M-H]^-$; HR-ESI-MS m/z: 273.1471 $[M+Na]^+$ (Calcd for $C_{15}H_{22}O_3Na$, 273.1461).

Theory and Calculation Details The calculations were performed by the Q-Chem program package and the Chem 3D software. MM2 molecular mechanics force-field calculations were employed to search the possible conformations. All ground-state geometries were optimized at the B3LYP/6-31G(d) level, and harmonic frequency analysis was computed to confirm the minima. TDDFT at the same level in the gas phase was employed to calculate excitation energy and rotatory strength R. The ECD spectra were then simulated by overlapping Gaussian functions for each transition according to:

$$\Delta\varepsilon = \frac{2}{2.296\times10^{-39}} \times \frac{1}{\sqrt{\pi}\,w} \sum_i \Delta E_{0i} R_{0i} e^{-[2(E-\Delta E_{0i})/w]^2}$$

Where w is the bandwidth at 1/e peak height and expressed in energy units. ΔE_{0i} and R_{0i} are the excitation energies and rotator strengths for the transition from 0 to i, respectively.[17]

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