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Sarcanolides A and B: two sesquiterpenoid dimers with a nonacyclic scaffold from *Sarcandra hainanensis*

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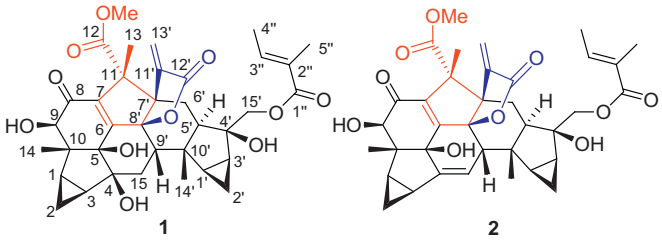
ABSTRACT

Two novel lindenane-type sesquiterpenoid dimers, sarcanolides A (**1**) and B (**2**), were isolated from the whole plants of *Sarcandra hainanensis*. These compounds feature a new nonacyclic scaffold in which the bond formation of C-11–C-7′ imposed the five-membered lactone ring in a full β-direction. Their structures, including the absolute configuration, were determined by NMR analysis, CD exciton chirality method, and ECD calculation.

1. Introduction

Lindenane-type sesquiterpenoid dimers are important secondary metabolites of the plants of Chloranthaceae family.[1–5] They are widely believed derived from the enzymatic Diels–Alder reaction of two lindenane-type sesquiterpenes forming the linkages of C-15–C-9′ and C-6–C-8′.[2–4] This class of highly complex compounds displayed a wide spectrum of biological activities, such as antifungal,[6] cytotoxicity,[7] hepatoprotective activity,[7] and inhibition of cell adhesion molecules expression.[8] In our previous study, quite a few lindenane-type sesquiterpenoid dimers isolated from *Chloranthus spicatus* were found to exhibit potent and selective inhibition on the delayed rectifier (I_K) K^+ current.[2,9] *Sarcandra hainanensis* (Pei) Swamy et Bailey (Chloranthaceae), an evergreen subshrub growing in southern China, has been used as a folk medicine to treat inflammation and bone fracture.[10] A recent chemical investigation on this species has led to the isolation of two flavonoid derivatives showing weak inhibition against HIV-1 integrase.[11] Recently, several cytotoxic sesquiterpenoids and dimeric sesquiterpenoids were isolated from *Sarcandra glabra* belonging to the same genus *Sarcandra* by our group.[12] In our continuing chemical study on the plants of Chloranthaceae family, two novel lindenane-type sesquiterpenoid dimers, sarcanolides A (**1**) and B (**2**), featuring an unprecedented carbon framework via the formation of C-11–C-7′ bond were isolated from the whole plants of *S. hainanensis*. We present herein the details of isolation and structural elucidation of these compounds.



2. Results and discussion

Sarcanolide A (**1**) was obtained as a colorless gum. The HRESIMS displayed a sodiated molecular ion peak at *m/z* 673.2636 $[M+Na]^+$ consistent with a molecular formula $C_{36}H_{42}O_{11}$ (calcd for $C_{36}H_{42}O_{11}Na$, 673.2625) requiring 16 degrees of unsaturation. The IR spectrum indicated the presence of hydroxyl (3446 cm^{-1}) and carbonyl (1743 and 1709 cm^{-1}) groups. In accordance with the

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molecular formula, all the 36 carbons were resolved in the ^{13}C NMR spectrum (one overlapped with the solvent signals was distinguished in the HMBC spectrum), which were further classified by DEPT experiments as four carbonyls (δ_C 198.1, 172.9, 167.9, and 167.5), three double bonds (one exocyclic, one trisubstituted, and one persubstituted), five sp^3 methylenes (one oxygenated), seven sp^3 methines (one oxygenated), six methyls (one *O*-methyl), and eight sp^3 quaternary carbons (four oxygenated) (Table 1). These functionalities accounted for 7 out of the 16 degrees of unsaturation, the remaining 9 degrees of unsaturation required compound **1** nonacyclic. The ^1H NMR spectrum showed two upfield-shifted proton resonances at δ_H 0.65 (m, 1H) and 0.72(m, 2H) diagnostic for the presence of cyclopropane rings. Three proton signals (δ_H 2.79, 3.27, and 3.43), which did not correlate with any carbons in the HSQC spectrum were only assignable to the exchangeable protons (Table 1). A tiglyl moiety was readily recognized by the NMR data [δ_H 6.88 (q, J=7.0 Hz) and δ_C 167.9, 138.1, and 128.2][4] as well as the intense peak at m/z 83 in the EIMS. The aforementioned data, including ^1H and ^{13}C NMR, suggested that compound **1** was a lindenane-type sesquiterpenoid dimer.[1–9,12] However, its nonacyclic backbone and NMR patterns implied some significant differences in structure as compared with the common octacyclic lindenane-type sesquiterpenoid dimers.[1–9,12]

Table 1
^1H and ^{13}C NMR spectroscopic data of **1** and **2**[a]

No.	1		2	
	δ_H (mult., J in Hz)	δ_C	δ_H (mult., J in Hz)	δ_C
1	1.99 (m)	28.0	2.14 (d, 3.8)	28.4
2α	0.72 (m, 2H)	7.1	0.97 (m)	12.3
2β			1.22 (m)	
3	1.82 (m)	29.6	2.12 (d, 4.0)	22.1
4		79.8		148.9
5		77.2		72.1
6		150.8		150.7
7		140.7		137.2
8		198.1		198.3
9	4.25 (d, 4.0)	81.0	4.07 (d, 3.1)	80.9
10		55.1		56.6
11		63.0		63.8
12		172.9		172.6
13	1.33 (s, 3H)	25.6	1.33 (s, 3H)	25.5
14	1.00 (s, 3H)	13.8	1.11 (s, 3H)	11.8
15α	1.49 (dd, 13.8, 13.8)	34.5	6.14 (d, 1.5)	118.1
15β	2.47 (dd, 13.8, 3.5)			
1′	1.70 (m)	27.0	1.83 (m)	28.2
2′α	0.65 (m)	10.7	0.68 (m)	10.5
2′β	1.15 (m)		1.20 (m)	
3′	1.70 (m)	29.1	1.77 (m)	29.3
4′		78.6		78.6
5′	1.78 (m)	52.7	1.64 (dd, 14.1, 3.3)	53.4
6′α	1.94 (m)	32.8	1.88 (m)	32.5
6′β	1.78 (m)		1.81 (m)	
7′		57.1		57.9
8′		96.9		95.0
9′	3.02 (dd, 13.8, 3.5)	49.2	3.14 (brs)	54.4
10′		41.2		42.8
11′		142.9		143.7
12′		167.5		167.7
13′a	5.71 (s)	126.9	5.75 (s)	125.9
13′b	6.54 (s)		6.56 (s)	
14′	0.89 (s, 3H)	23.7	0.93 (s, 3H)	23.1
15′a	4.07 (d, 11.0)	69.5	4.04 (d, 11.0)	68.7
15′b	3.92 (d, 11.0)		3.90 (d, 11.0)	
1″		167.9		167.8
2″		128.2		128.2
3″	6.88 (q, 7.0)	138.1	6.86 (qq, 7.3, 1.0)	138.2
4″	1.82 (d, 7.0, 3H)	14.4	1.82 (dq, 7.3, 1.0, 3H)	14.5
5″	1.85 (s, 3H)	12.1	1.84 (q, 1.0, 3H)	12.1
OMe	3.77 (s, 3H)	53.1	3.67 (s, 3H)	52.8
4-OH	2.79 (br s)			
5-OH	3.27 (br s)		2.43 (br s)	
9-OH	3.43 (d, 4.0)		3.41 (d, 3.8)	

[a] Data were recorded in $CDCl_3$ at 400 and 100 MHz for ^1H and ^{13}C, respectively.

The partial structures of two lindenane-type sesquiterpenoid components A and B were established by comprehensive analysis of the 1D and 2D NMR spectra, especially HMBC (Fig. 1). For the component A, the HMBC correlations from CH_3-14 to C-1, C-5 (δ_C 77.2), C-9 (δ_C 81.0) and C-10, in particular, the correlations between OH-5 at δ_H 3.27 (br s) and C-5, and between OH-9 at δ_H 3.43 (d, J=4.0 Hz) and C-9 placed two hydroxyls at C-5 and C-9, respectively; a conjugated keto group at δ_C 198.1 was assigned to C-8 by the HMBC correlations of H-9/C-8, and OH-9/C-8; the multiple HMBC correlations from OH-4 at δ_H 2.79 (br s) to C-4 and C-15, from OH-5 to C-4 and C-6, from CH_3-13 to C-7, C-11 and C-12, and from OCH_3 to C-12 revealed the presence of OH-4, Δ^6 double bond, and a carboxylic methyl ester at C-11. For the component B, the exocyclic $\Delta^{11'(13')}$ double bond was incorporated by the HMBC correlations from H_2-13′ to C-7′, C-11′ and C-12′; the quaternary carbon resonance at δ_C 78.6 correlated with H-3′, H-5′, and H_2-15′ in the HMBC was attributed to C-4′ bearing a hydroxy; the tiglyloxy group was attached to C-15′ by the HMBC correlations between H_2-15′ and C-1″; the oxygenated quaternary carbon at δ_C 96.9 was assigned to C-8′ on the basis of the HMBC correlations from H-9′ and H_2-6′ to C-8′. The down field shifted C-8′, with the concomitant presence of the C-12′ ester carbonyl at δ_C 167.5 suggested the formation of an α,β-unsaturated γ-lactone. The component B was hence established.

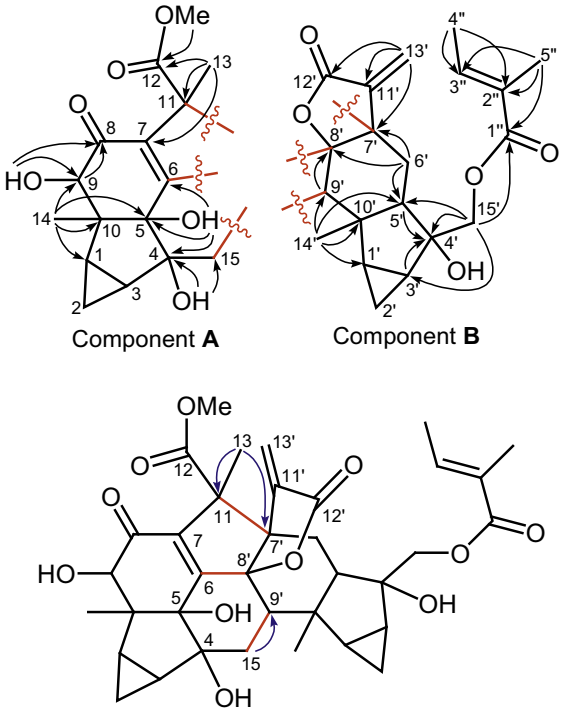


Fig. 1. Key HMBC correlations (H→C) of **1**.

The components A and B occupied seven rings of nonacyclic compound **1**, the remaining two rings must be generated from the connection of the two components. The ^1H–^1H COSY correlations between H_2-15 and H-9′ (see Supplementary data) and the key HMBC correlations from CH_2-15 to C-9′ assigned the linkage between C-15 and C-9′ (Fig. 1). The HMBC correlations from CH_3-13 to C-11 and C-7′ connected C-11 and C-7′ (Fig. 1). Consequently, the last linkage between components A and B came from the bonding of the only two loose ends, C-6 and C-8′. The planar structure of **1** was thus established.

The relative configuration of **1** was established on the basis of a ROESY experiment (Fig. 2). The ROESY correlations of CH_3-14/H_β-2, CH_3-14/OH-5, CH_3-14/OH-9, OH-4/H_β-2, H-9′/OH-4, H-9′/CH_3-14′,

and CH_3-14′/H_β-2′ indicated that they were co-facial, and were arbitrarily assigned in a β-configuration. In consequence, the ROESY cross-peaks of H-1/H-9, H-9/H_α-15, H_α-15/H-3, H-1′/H_α-2′, H-3′/H_α-2′, H_2-15′/H-3′, and H_2-15′/H-5′ revealed that they were α-oriented. The 12′,8′-lactone ring was arranged in a β-direction by the strong ROESY correlation between H_a-13′ and H_β-6′, and the weak correlation between H_a-13′ and H_α-6′. The strong ROESY correlation between CH_3-13 and H_a-13′ indicated that CH_3-13 also took a β-configuration.

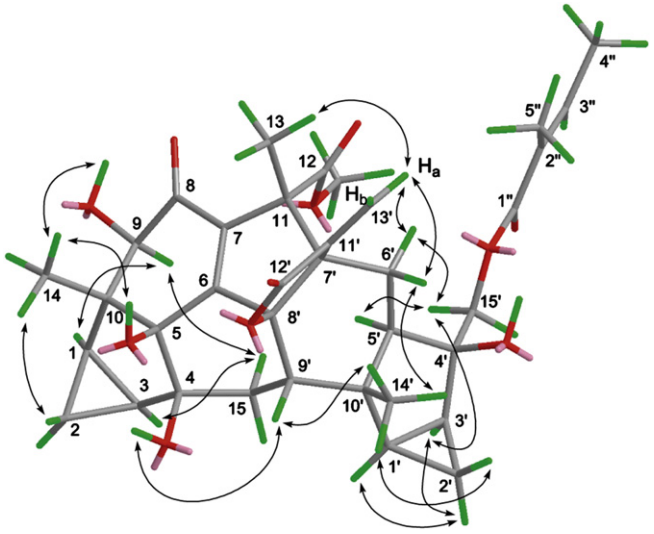


Fig. 2. Selected ROESY correlations (H↔H) of **1**.

Sarcanolide B (**2**), a colorless gum, showed the molecular formula of $C_{36}H_{40}O_{10}$ as determined by HRESIMS at *m*/*z* 655.2515 $[M+Na]^+$ (calcd for $C_{36}H_{40}O_{10}Na$, 655.2519), which was 18 mass units less than that of **1**. The ^1H and ^{13}C NMR spectra of compound **2** shared many similarities with those of **1**, except for the presence of an additional trisubstituted double bond (δ_C 148.9 and 118.1; δ_H 6.14, d, *J*=1.5 Hz), and the concomitant absence of an oxygenated sp^3 quaternary carbon and an sp^3 methylene, suggesting that compound **2** was likely one of the dehydration products of **1** by loss of a molecule of water. This was finalized by analysis of the HMBC spectrum of **2**, in which the correlations from OH-5 to C-10, C-6, C-5, and C-4 (δ_C 148.9), as well as the correlations from H-15 (δ_H 6.14, d, *J*=1.5 Hz) to C-3, C-4, C-5, C-8′, C-9′, and C-10′ furnished a $\Delta^{4(15)}$ double bond. The complete structural assignment of **2** was fully achieved on the basis of spectral analysis, especially 2D NMR (see Supplementary data).

The absolute configuration of compounds **1** and **2** was determined by applying the CD exciton chirality method.[13] Sarcanolide A (**1**) showed CD split in the region of 200–230 nm corresponding to a positive chirality, which arose from the exciton coupling of the two chromophores of the α,β-unsaturated γ-lactone (C-7′, C-11′, and C-13′) and the α,β-unsaturated ketone (C-6, C-7 and C-8) (Fig. 3). The absolute configuration of **1** (1*R*,3*S*,4*S*,5*S*,9*R*,10*R*,11*R*,1′*R*,3′*S*,4′*S*,5′*R*,7′*S*,8′*R*,9′*S*,10′*S*) was therefore assigned as depicted. The CD split pattern of **2** exhibited a little bit complex as compared with **1** due to the involvement of the $\Delta^{4(15)}$ double bond. However, the distinguishable positive chirality (centered around 200–210 nm) arose from the exciton coupling of the two chromophores of the α,β-unsaturated γ-lactone and the α,β-unsaturated ketone still allowed the assignment of the absolute configuration of **2** (1*R*,3*S*,5*R*,9*R*,10*R*,11*R*,1′*R*,3′*S*,4′*S*,5′*R*,7′*S*,8′*R*,9′*S*,10′*S*) as shown.

The calculation of electronic circular dichroism (ECD) has demonstrated great values in determining the absolute configuration of natural products in recent years.[14,15] To verify the absolute configuration assigned by the CD exciton chirality method, ECD calculations using time-dependent density functional theory (TDDFT) at the PBEPBE/6-31G* level were carried out on compounds **1** and **2**, and their enantiomers (Fig. 4). The calculated ECD spectra of compounds **1** and **2** in both gas phase and MeOH closely matched the experimental ECD curves of **1** and **2**, respectively. While the calculated ECD spectra of the enantiomers of **1** and **2** in both gas phase and MeOH were opposite to the experimental ECD curves of **1** and **2**, respectively. The ECD calculations of compounds **1** and **2** further validated the absolute configuration of two compounds as assigned by CD exciton chirality method.

The possible biosynthetic pathways for compounds **1** and **2** are postulated in Scheme 1. Enzymatic Diels–Alder cycloaddition of two lindenane-type sesquitepenoids **ia** and **ib** to form intermediate **ii** is widely believed as the key step in the biosynthesis of this class of sesquitepenoid dimers.[4,9] The key intermediate **iv** would be produced by an acid catalyzed rearrangement on the intermediate **ii** that involved a process of protonation and discharge.[16] The intermediate **iv** would readily convert to **v** via a cascade of oxidative chemistry. Acylation of intermediate **v** finally yielded compound **1**, which would then transform into **2** by loss of one molecule of water

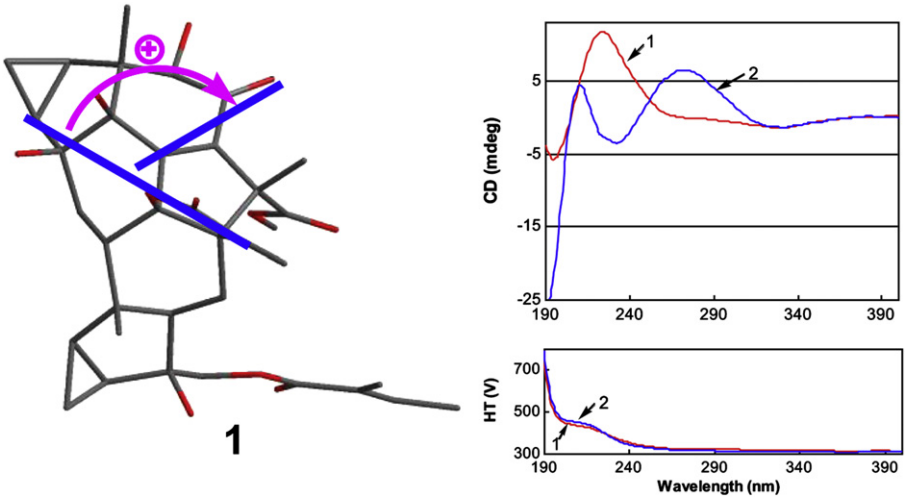


Fig. 3. CD and UV spectra of **1** and **2** (in MeOH), and the stereoview of **1**, bold lines (blue) denote the electric transition dipole of the coupling chromophores of **1**.

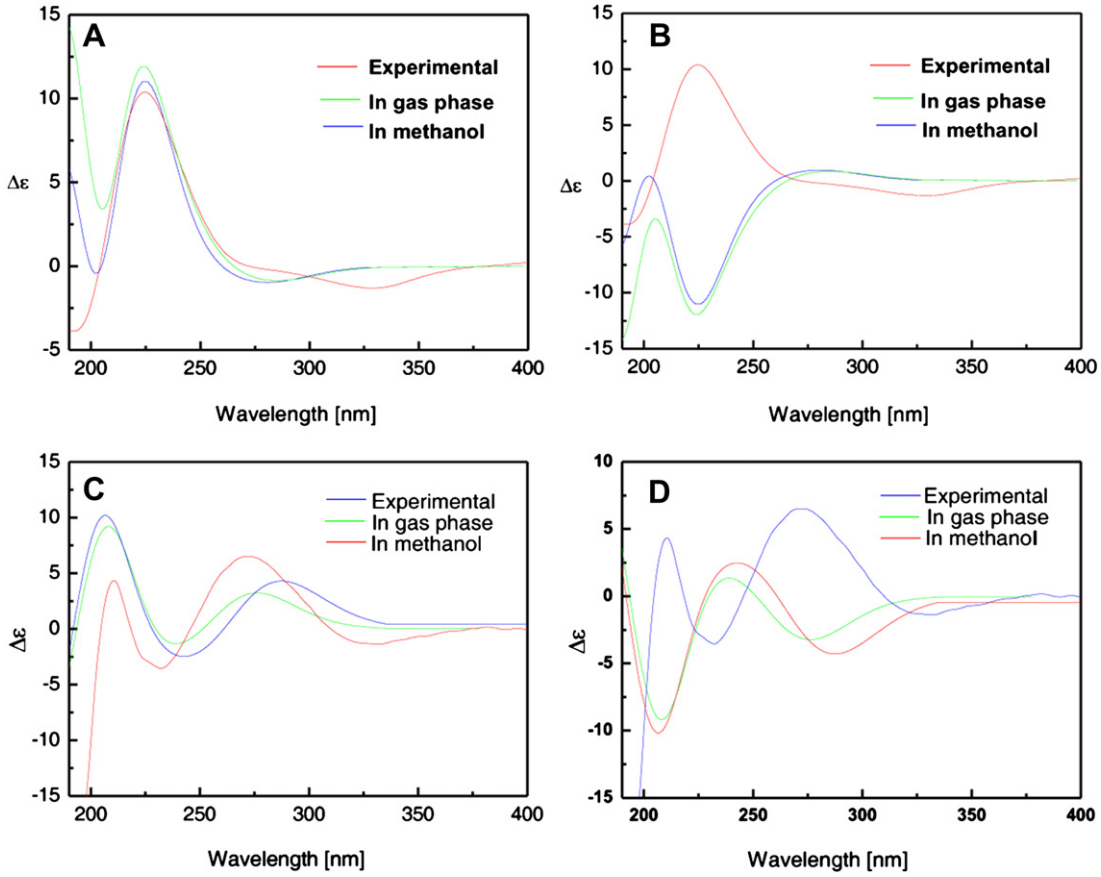
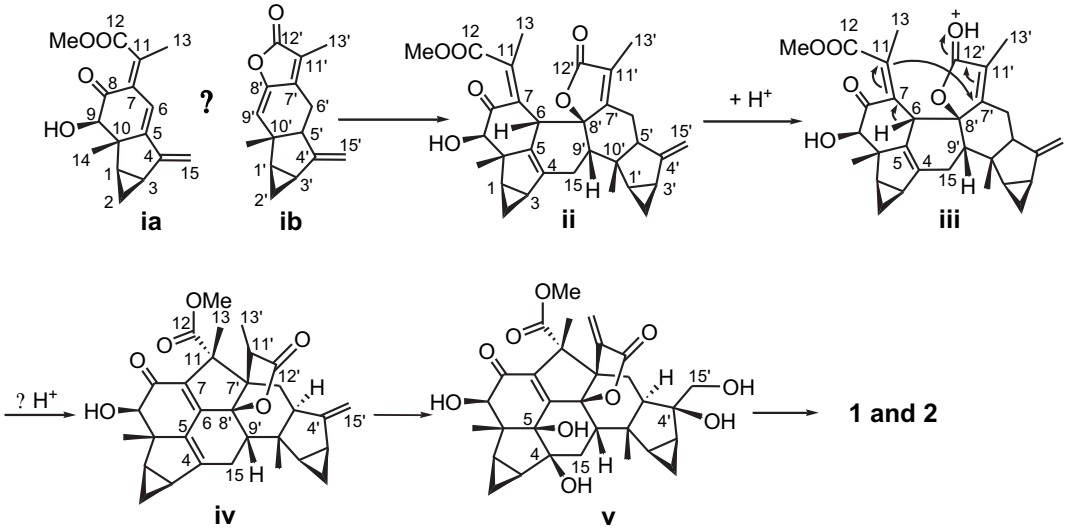


Fig. 4. (A) Experimental ECD spectrum of **1** (red), and calculated ECD spectra of **1** in gas phase (green) and MeOH (blue). (B) Experimental ECD spectrum of **1** (red), and calculated ECD spectra of its enantiomer in gas phase (green) and MeOH (blue). (C) Experimental ECD spectrum of 2 (blue), and calculated ECD spectra of **2** in gas phase (green) and MeOH (red). (D) Experimental ECD spectra of 2 (blue), and calculated ECD spectra of its enantiomer in gas phase (green) and MeOH (red).



Scheme 1. Hypothetical biogenetic pathway proposed for **1** and **2**.

to form the $\Delta^{4(15)}$ double bond. This biogenetic pathway fully supports the structures, including stereochemistry, of the two compounds as assigned.

To the best of our knowledge, sarcanolides A and B represent a complex nonacyclic backbone without precedent among the family of known dimeric lindenane-type sesquitepenoids. We propose to name this carbon scaffold sarcanolide.

The cytotoxic activities of compounds **1** and **2** were evaluated against the HL-60 cell line by using the MTT method,[17] and against the A-549 and BEL-7402 cell lines by using the SRB method,[18] and with pseudolaric acid B[19] as the positive control (IC_{50}=4.2 μM against HL-60, 1.6 μM against A-549, and 1.3 μM against BEL-7402). Unfortunately, neither of the two compounds showed inhibitory activity on the three tested cell lines.

3. Experimental section

3.1. General experimental procedures

Optical rotations were obtained on a Perkin–Elmer 341 polarimeter. UV spectra were recorded on a Shimadzu UV-2550 spectrophotometer. CD spectra were recorded on a JASCO 810 spectrophotometer. IR spectra were recorded on a Perkin–Elmer 577 spectrometer with KBr discs. NMR spectra were recorded on a Bruker AM-400 spectrometer. EIMS (70 eV) and HREIMS were measured on a Finnigan MAT-95 mass spectrometer in *m/z* (rel %), and ESI-MS and HRESIMS were measured on an Esquire 3000plus (Bruker Daltonics) and a Waters-Micromass Q-TOF Ultima Global electrospray mass spectrometer, respectively. All solvents used were of analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China). Silica gel (200–300 mesh), silica gel H60, Sephadex LH-20 (Amersham Biosciences), reversed-phase C_{18} silica gel (150–200 mesh, Merck), and MCI gel (CHP20P, 75–150 μm, Mitsubishi Chemical Industries Ltd.) were used for column chromatography. Pre-coated silica gel GF_{254} plates (Qingdao Haiyang Chemical Co. Ltd. Qingdao, People's Republic of China) were used for TLC.

3.2. Plant material

The whole plants of *S. hainanensis* were collected in April of 2005 from Hainan Province of PR China. The plant was authenticated by Prof. S. M. Huang, Department of Biology, Hainan University of China. A voucher specimen has been deposited in Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Sciences (access number: DHTS-2005-4E).

3.3. Extraction and isolation

The air-dried powder of the plant material (2.0 kg) was percolated with 95% EtOH three times (each 5 L) at rt. The filtrate was collected and concentrated under reduced pressure to give a residue (120 g), which was then suspended in water (1 L) and partitioned successively with petroleum ether and EtOAc. The EtOAc soluble fraction (30 g) was subjected to a column of MCI gel (MeOH/H_2O, 3:7 to 9:1) to give four fractions 1–4. Fraction 2 (8 g) was separated on a silica gel column (petroleum ether/acetone 20:1 to 3:1) to afford four fractions 2a–2d. Fraction 2c (1.3 g) was chromatographed over a column of reversed-phase C_{18} silica gel (MeOH/H_2O, 50%–90%) to give three fractions 2c1–2c3. Fraction 2c1 (230 mg) was then separated on a silica gel column (CH_2Cl_2/MeOH 100:1 to 70:1) to give four fractions 2c1a–2c1d. Both fractions 2c1a (35 mg) and 2c1b (15 mg) were purified by preparative TLC (CH_3Cl/MeOH 20:1), followed by a Sephadex LH-20 column (EtOH) to yield compounds **1** (10 mg) and **2** (8 mg), respectively.

*3.3.1. Sarcanolide A (**1**).* Colorless gum; $[\alpha]_{D^{20}}$ −16 (*c* 0.09, MeOH), UV (MeOH) λ_{max} (log ε) 208 (4.27) nm. IR (KBr, disc) λ_{max} 3446, 2931, 1743, 1709, 1649, 1458, 1381, 1279, 1130, 970 cm^{-1}; for ^1H and ^{13}C NMR data see Table 1; ESI-MS *m/z* 673.3 $[M+Na]^+$; EIMS 70 eV *m/z* (relative intensity) 650 $[M]^+$ (6), 514 (6), 454 (6), 270 (52), 166 (100), 138 (39), 83 (62), 55 (37); HRESIMS *m/z* 673.2636 $[M+Na]^+$ (calcd for $C_{36}H_{42}O_{11}Na$, 673.2625).

*3.3.2. Sarcanolide B (**2**).* Colorless gum; $[\alpha]_{D^{20}}$ −72 (*c* 0.12, MeOH), UV (MeOH) λ_{max} (log ε) 214 (4.12) nm. IR (KBr, disc) λ_{max} 3433, 2922, 1743, 1705, 1637, 1383, 1269, 1130, 1080 cm^{-1}; for ^1H and ^{13}C NMR data see Table 1; ESI-MS *m/z* 655.3 $[M+Na]^+$, 671.2 $[M+K]^+$; EIMS 70 eV *m/z* (relative intensity) 632 $[M]^+$ (16), 514 (12), 454 (10), 235 (15), 209 (8), 83 (100), 55 (42); HRESIMS *m/z* 655.2515 $[M+Na]^+$ (calcd for $C_{36}H_{40}O_{10}Na$, 655.2519).

3.4. Computational methods

The ECD computational methods were the same as described in the Supplementary data of the previous publication of our group.[20]

Acknowledgements

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Supplementary data

Spectroscopic spectra for **1** and **2**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.021. These data include MOL files and InChiKeys of the most important compounds described in this article.

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