Pergamon

Tetrahedron 58 (2002) 9045–9048

TETRAHEDRON

Structure of orientanone from *Alisma orientalis*, a novel sesquiterpene originating from guaiane-type carbon skeleton by isopropyl shift

Guo-Ping Peng,[a,*] Feng-Chang Lou,[b] Xian-Feng Huang[a] and Gang Tian[a]

[a]*Nanjing University of Traditional Chinese Medicine, Nanjing 210029, People's Republic of China*
[b]*China Pharmaceutical University, Nanjing 210029, People's Republic of China*

Received 18 June 2002; revised 9 August 2002; accepted 5 September 2002

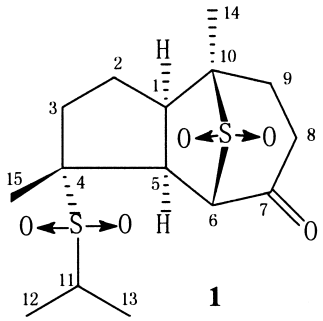
Abstract—A new sesquiterpene, named orientanone (**1**), was isolated from *Alisma orientalis* Juzep. The structure was elucidated by various spectroscopic methods and X-ray crystallography. Orientanone has a carbon skeleton originating from a guaiane-type carbon skeleton by an isopropyl shift. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The dried tuber of *Alisma orientalis* Juzep is commonly used in Chinese medicine and has been recorded in various editions of Pharmacopoeias in China. The plant, which has been prescribed for diuretic and anti-inflammatory purposes in traditional Chinese medicine, contains mainly a series of triterpenoids and sesquiterpenoids. The previous studies of the chemical constituents of *A. orientalis* and *A. japanese* have led to the isolation of 13 sesquiterpenes.[1–5] We earlier reported the isolation and identification of three guaiane-type sesquiterpenes, alismal, alismoxide, orientalol E and one oplopanane-type sesquiterpene, oplopanone.[6,7] As a part of our continuing study, the following describes the isolation and the structure of another new sesquiterpene named orientanone (**1**) derived from a guaiane-type carbon skeleton by an isopropyl shift.

2. Results and discussion

Compound **1** was obtained as colorless prisms from MeOH/H_2O, mp 241–242°C, which reacted negatively (105°C) under 5% H_2SO_4/C_2H_5OH on a TLC plate. The EI-MS did not display a molecular ion, but major fragment ions could be seen at *m/z* 241, 177, 159. In the negative-ion ESI-MS of compound **1**, a quasimolecular ion peak was observed at *m/z* 383 $[M+Cl]^-$, while its positive-ion ESI-MS showed quasimolecular ion peaks at *m/z* 371 $[M+Na]^+$ and *m/z* 387 $[M+K]^+$.



1

HR-MS analysis of the quasimolecular ion peak 349.1132 $[M+H]^+$ (calcd 349.1138) in the positive-ion ESI-MS revealed the molecular formula of **1** to be $C_{15}H_{25}S_2O_5$. The ^{13}C NMR spectrum showed 15 carbon resonances; INEPT analysis indicated the presence of 4 primary, 4 secondary, 4 tertiary and 3 quaternary carbons. One quaternary carbon (δ_C 196.99) was a carbonyl, the other downfield quaternary carbons (δ_C 71.83, 60.79) and two tertiary carbons (δ_C 69.97, 50.07) downfield might be connected to S or O. Considering the molecule of **1**, there should be two sulfonyl groups (S_2O_4) in its structure. The ^1H NMR spectrum exhibited signals assignable to an isopropyl group at δ 3.37 (1H, sept, J=7.1 Hz), 1.39 (3H, d, J=7.1 Hz) and δ 1.35 (3H, d, J=7.1 Hz) together with the signals due to two singlet methyls at δ 1.69 (3H, s) and δ 1.46 (3H, s). These spectral features suggested **1** to be a sesquiterpene. After comparison of the ^1H and ^{13}C NMR data for **1** and the other guaiane-type sesquiterpenes we found that **1** exhibited some marked differences. For instance, **1** contains a carbonyl and two sulfonyl groups, a singlet methyl group (δ 1.46) showed a significant upfield shift (δ_C 13.36). From the ^1H–^1H COSY spectrum of **1**, the proton sequences from H-3 to H-6,

Keywords: *Alisma orientalis*; sesquiterpene; orientanone; X-ray crystallography.

* Corresponding author. Tel.: +86-25-6798186; fax: +86-25-6522534; e-mail: guopingpeng@sohu.com; guopingpeng@sina.com.cn

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)01128-6

Table 1. ^{1}H, ^{13}C NMR, $^{1}H-^{1}H$COSY, NOESY and HMBC spectral data of compound **1** (400 MHz, δ, ppm, $CDCl_3$ as solvent)

No.	^{13}C	^{1}H	Mult, *J* (Hz)	$^{1}H-^{1}H$COSY	NOESY	HMBC
1	48.88 (d)	2.88	dd, 12.0, 3.8	H-5, H-2α, H-2β	H-5, Me-14, H-2α, H-9α	C-2, C-5, C-9, C-10
2	26.84 (t)	α 2.02	m	H-1, H-3α, H -3β	H-1, Me-14	C-1, C-3, C-4, C-6
		β 2.28	m	H-1, H-3α, H -3β	Me-14	
3	36.11 (t)	α 1.99	m	H-2α, H-2β	Me-15	C-1, C-2, C-4, C-5, C-15
		β 2.42	ddd, 12.7, 12.6, 6.4	H-2α, H-2β		
4	71.83 (s)					
5	42.61 (d)	3.47	d, 12.0	H-1, H-6	H-1, H-6, H-8α	C-1, C-2, C-4, C-6, C-7, C-15
6	69.97 (d)	3.92	s	H-5, H-8β	H-5, H-13, Me-15	C-1, C-4, C-5, C-7, C-8, C-10
7	196.99 (s)					
8	34.32 (t)	α 2.82	m	H-9α, H-9β	H-5, H-9α	C-6, C-7, C-9, C-10
		β 2.60	dd, 13.0, 6.3	H-6, H-9α, H-9β	H-9β	
9	32.54 (t)	α 1.88	m	H-8α, H-8β	H-8α, Me-14	C-1, C-7, C-8, C-10, C-14
		β 2.25	dd, 11.8, 6.5	H-8α, H-8β	H-8β, Me-14	
10	60.79 (s)					
11	50.07 (d)	3.37	m	Me-12, Me-13	Me-12, Me-13, Me-15	C-12, C-13
12	16.71 (q)	1.39	d, 3H, 7.1	H-11, Me-13	H-11, Me-15	C-11, C-13
13	16.20 (q)	1.35	d, 3H, 7.1	H-11, Me-12	H-6, H-11, Me-15	C-11, C-12
14	13.36 (q)	1.46	s, 3H		H-1, H-9, H-2	C-1, C-9, C-10
15	18.84 (q)	1.69	s, 3H		H-3β, H-6, H-11, Me-12, Me-13	C-3, C-4, C-5

H-8 to H-9 and H-11 to H-13 were established. The three spin systems were further confirmed by the TOCSY spectrum, which indicated that C-7 position is a quarternary carbon. The long-range correlations between H-5, H-6, H-9, H-8 and C-7, being observed in HMBC experiment, revealed that the C-7 position was oxygenated to be a carbonyl. Therefore, the isopropyl group must shift. Considering an isopropyl group and two sulfonyl groups were connected to C-4, C-10 and C-6, the isopropyl group should shift to a sulfonyl group. Based on the above analyses, together with $^{1}H-^{1}H$ COSY, HMQC and HMBC spectra, most of the structural fragments for **1** were identified (Table 1).

The HMBC spectrum revealed long-range correlations between H-14 and C-10, C-1, C-9; H-15 and C-4, C-3, C-5; H-5, H-6, H-9, H-8 and C-7. In addition, the long-range correlation between H-6 and C-10 was also observed, which indicated C-6 and C-10 was connected through a sulfonyl group. Meanwhile, the HMBC spectrum did not show the correlations between the protons of the isopropyl group and any carbon, which revealed the isopropyl group was not directly linked to the carbons, but rather through a sulfonyl group. This was also confirmed by the downfield shift of C-11 (δ_C 50.07) and C-4 (δ_C 71.83). Thus, the structure was represented as **1**, and this very unusual structure was formed by the isopropyl shift and the C-7 position was oxygenated to be a carbonyl.

Considering the rarity of group shift and sulfonyl groups in the structure of sesquiterpenes, and in order to reconfirm the structure of **1**, crystalline plates suitable for X-ray

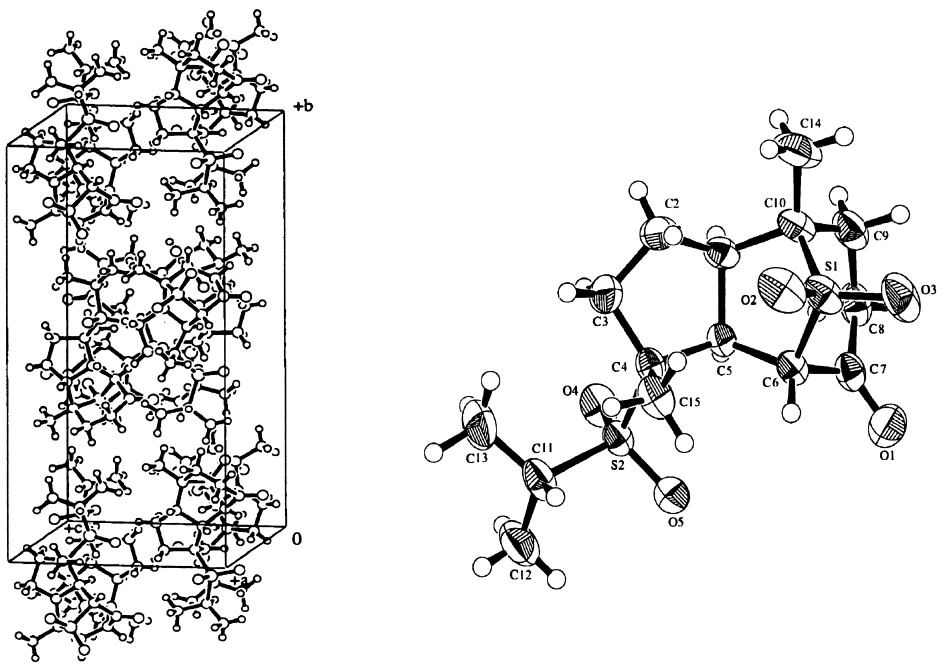


Figure 1. The X-ray structure of **1**.

Table 2. Intramolecular bond angles (°) involving the non-hydrogen atoms

Atom			Angle	Atom			Angle
O(2)	S(1)	O(3)	117.5	C(5)	C(4)	C(15)	116.2
O(2)	S(1)	C(6)	111.5	C(1)	C(5)	C(4)	106.3
O(2)	S(1)	C(10)	111.0	C(1)	C(5)	C(6)	108.9
O(3)	S(1)	C(6)	110.3	C(4)	C(5)	C(6)	118.6
O(3)	S(1)	C(10)	111.9	S(1)	C(6)	C(5)	105.2
C(6)	S(1)	C(10)	91.8	S(1)	C(6)	C(7)	103.3
O(4)	S(2)	O(5)	116.9	C(5)	C(6)	C(7)	110.3
O(4)	S(2)	C(4)	108.6	O(1)	C(7)	C(6)	121.7
O(4)	S(2)	C(11)	108.2	O(1)	C(7)	C(8)	123.2
O(5)	S(2)	C(4)	106.5	C(6)	C(7)	C(8)	115.1
O(5)	S(2)	C(11)	107.1	C(7)	C(8)	C(9)	115.9
C(4)	S(2)	C(11)	109.5	C(8)	C(9)	C(10)	115.7
C(2)	C(1)	C(5)	104.9	S(1)	C(10)	C(1)	102.5
C(2)	C(1)	C(10)	118.3	S(1)	C(10)	C(9)	105.8
C(5)	C(1)	C(10)	109.1	S(1)	C(10)	C(14)	110.3
C(1)	C(2)	C(3)	103.5	C(1)	C(10)	C(9)	111.6
C(2)	C(3)	C(4)	103.6	C(1)	C(10)	C(14)	114.8
S(2)	C(4)	C(3)	112.9	C(9)	C(10)	C(14)	111.1
S(2)	C(4)	C(5)	104.1	S(2)	C(11)	C(12)	112.8
S(2)	C(4)	C(15)	108.3	S(2)	C(11)	C(13)	106.1
C(3)	C(4)	C(5)	102.2	C(12)	C(11)	C(13)	112.3
C(3)	C(4)	C(15)	112.9				

Table 3. Intramolecular distances (Å) involving the nonhydrogen atoms

Atom		Distance	Atom		Distance
S(1)	O(2)	1.438	C(2)	C(3)	1.525
S(1)	O(3)	1.441	C(3)	C(4)	1.543
S(1)	C(6)	1.795	C(4)	C(5)	1.572
S(1)	C(10)	1.801	C(4)	C(15)	1.529
S(2)	O(4)	1.438	C(5)	C(6)	1.540
S(2)	O(5)	1.447	C(6)	C(7)	1.535
S(2)	C(4)	1.820	C(7)	C(8)	1.512
S(2)	C(11)	1.804	C(8)	C(9)	1.533
O(1)	C(7)	1.198	C(9)	C(10)	1.533
C(1)	C(2)	1.513	C(10)	C(14)	1.527
C(1)	C(5)	1.571	C(11)	C(12)	1.512
C(1)	C(10)	1.546	C(11)	C(13)	1.527

crystallographic analysis were grown in methanol solution. The X-ray structure (Fig. 1) was consistent with the above structure.

As shown in Tables 2 and 3, the bond angle and bond length indicated that the oxygen atom on the C-7 position to be a carbonyl, the carbon–sulfur–oxygen bond (rather than carbon–silicon–oxygen bond according to the molecular formula) suggested **1** to be the derivative of a sulfone. From the X-ray structure, H-14 showed a significant γ-effect with H-2 and H-9, which was the proper explanation for the upfield shifts of C-14, C-2 and C-9, and the corresponding splitting peaks could not be observed clearly in the ^{1}H NMR spectrum due to the torsion angles of H-6–C-6–C-5–H-5 and H-8–C-8–C-9–H-9 being nearly 90° resulting from cyclic tension. Furthermore, the NOESY data (Fig. 2) was also compatible with the X-ray structure. Therefore, the stereochemistry of **1** was elucidated unambiguously. Compound **1** is a new type of sesquiterpene formed by an isopropyl shift and with two sulfonyl groups named orientanone.

The most interesting question about compound **1** is how it is formed in this plant. It has been reported that Chinese *A. orientalis* contains germacrene C as the major sesquiterpene

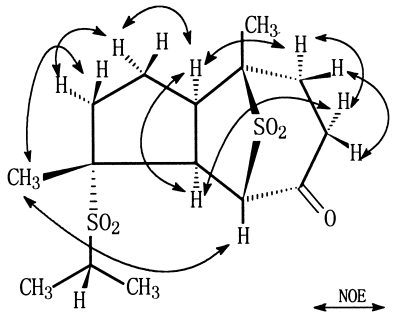
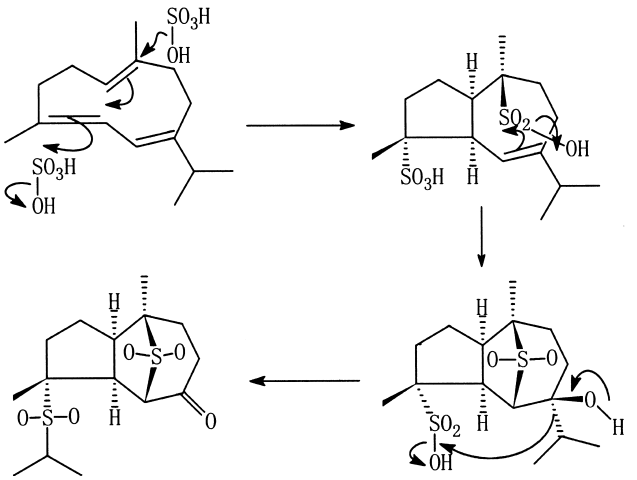


Figure 2. Selected NOE correlations of **1**.



Scheme 1. Possible biosynthetic route of **1** via germacrene C.

constituent together with small amounts of alismol and alismoxide. Germacrene C is fairly unstable, and is readily converted to alismol and alismoxide, which were considered to be secondary products formed during processing.[8] Masayuki proposed that the guaiane-type sesquiterpenes from *A. orientalis* came from alismol during the processing procedure of this crude drug.[3] The 14 guaiane-type sesquiterpenes, which are most likely to be biogenetically derived from alismol, have a *trans* geometry of H-1/H-5. However, this biogenetic hypothesis is not able to reasonably explain the inversion of the H-1/H-5 configuration in compound **1**, since the X-ray structure showed the *cis* geometry of H-1/H-5. Herein we proposed **1** should be sulfonated before cyclization rather than being derived from alismol (Scheme 1). Clearly, in this biogenetic hypothesis the *cis* product is more likely to be formed due to the steric hindrance of the sulfonic acid groups.

3. Experimental

3.1. General

The following instruments were used to obtain physical data: melting points, PHMK 79/2212 micro-melting apparatus (values are uncorrected); IR spectra (KBr discs), Necolet IR-5DX FT IR spectrophotometer; NMR spectra, Bruker ASR-400 NMR spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz, with TMS as an internal standard); EI-MS, Nicolet FTMS-2000 mass spectrometer; ESI-MS,

HPLC/MSD System and PE LC/MS. For column chromatography, silica gel (Qingdao Haiyang Chemical Co. Ltd) were used.

3.2. Plant material

The whole plant was collected in Sichuan Province, China, and identified by Dr Qi-Nan Wu, Nanjing University of Traditional Chinese Medicine, Nanjing, China.

3.3. Extraction and isolation

The fresh plant material (13 kg) was crushed, and percolated with 75% EtOH. The crude extract was concentrated under reduced pressure, giving an oily solid and a solution. The solution was dissolved in EtOAc. The EtOAc-soluble fraction was subjected to silica gel chromatography, step gradient with $CHCl_3$–CH_3OH to afford **1** (80 mg).

3.4. X-Ray crystallography of 1

Suitable colorless prisms of **1** were obtained from a solution in MeOH. The crystal ($0.20\times0.20\times0.30$ mm^3) belongs to the orthorhombic system, space group *Pbca*(61) with a=13.328(3) Å, b=22.302(4) Å, V=3318(1) Å, Z=8, D_{calcd}=1.395 g cm^{-3}, F_{000}=1488.00, μ (Mo Kα)=3.41 cm^{-1} Intensity data were measured on Rigaku ACF7R diffractometer up to 2θ of 55.5°. All 4282 unique reflections were collected by the ω–2θ scan type with 16.0 min^{-1} (in ω)—up to 4 scan rate and (1.15+0.30 tan θ) scan width. The structure was solved by direct method (SHELXS86) and refined by a full-matrix least-squares procedure. The non-hydrogen atoms were given anisotropic thermal parameters. The refinement converged to a final R=0.047, R_W=0.059 for 2671 observed reflections [$I>3.000(I)$] and 200 variable parameters. Full crystallography data are deposited at the Cambridge Crystallography Data Center, 12 Union Road, Cambridge CB2 1EZ, UK, CCDC 190664.

3.4.1. Compound 1. Colorless prisms, mp 241–242°C. EIMS *m/z*: 241(56), 177(32), 159(18), 149(12), 133(10), 97(16), 58(34), 40(100); ESI-MS *m/z*: 371 $[348+Na]^+$, 387 $[348+K]^+$, 383 $[348+Cl]^-$. HR-ESIMS: $C_{15}H_{25}S_2O_5$, 349.1132 $[M+H]^+$ (req. 349.1138). IR ν_{max}: 2997, 2978, 2929, 1730, 1456, 1294, 1260, 1148, 1127, 1116, 1074, 1057, 696, 669, 637, 616, 598, 567, 543 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.88 (dd, J=12.0, 3.8 Hz, H-1), 2.28 (m, H-2), 2.02 (m, H-2), 2.42 (ddd, J=12.7, 12.6, 6.4 Hz, H-3), 1.99 (m, H-3), 3.47 (d, J=12.0 Hz, H-5), 3.92 (s, H-6), 2.82 (m, H-8), 2.60 (dd, J=13.0, 6.3 Hz, H-8), 2.25 (m, H-9), 1.88 (dd, J=11.8, 6.5 Hz, H-9), 3.37 (m, J=7.1 Hz, H-11), 1.39 (3H, d, J=7.1 Hz, H-12), 1.35 (3H, d, J=7.1 Hz, H-13), 1.46 (3H, s, H-14), 1.69 (3H, s, H-11).

Acknowledgements

We thank Dr Qi-Nan Wu (Nanjing University of Traditional Chinese Medicine, Nanjing, China) for identification of the plant and Shanghai Institute of Organic Chemistry (Shanghai, Chinese Academy of Sciences, China) for measuring the NMR spectra and determining the X-ray structure. This work was partially supported by National Key Technologies R&D Program during Five Year Plan Period from Ministry of Science and Technology of the People's Republic of China (96-903-02-03).

References

1. Oshima, Y.; Iwakawa, T.; Hikino, H. *Pytochemistry* **1983**, *22*, 183–185.
2. Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Fukuda, Y.; Murakami, N.; Yamahara, J. *Chem. Pharm. Bull.* **1992**, *40*, 2582–2584.
3. Yoshikawa, M.; Fukuda, Y.; Hatakeyama, S.; Tanaka, N.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1993**, *41*, 1194–1196.
4. Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Fukuda, Y.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1993**, *41*, 1948–1954.
5. Nakajima, Y.; Satoh, Y.; Katsumata, M.; Tsujiyama, K.; Ida, Y.; Shoji, J. *Pytochemistry* **1994**, *36*, 119–127.
6. Peng, G.-P.; Lou, F.-C. *Nat. Prod. Res. Dev. (China)* **2001**, *13*, 1–3.
7. Peng, G.-P.; Lou, F.-C. *Nat. Prod. Res. Dev. (China)* **2001**, *13*, 1–4.
8. Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Matsuoka, T.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1993**, *41*, 2109–2112.