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Cryptoacetalide and Epicryptoacetalide, Novel Spirolactone Diterpenoids from *Salvia miltiorrhiza*

Fumika ASARI, Takenori KUSUMI, Guo-Zhi Zheng,[+] Ying-Zhou Cen,[++] and Hiroshi KAKISAWA*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305

Two novel spirolactone diterpenoids have been isolated from the roots of Chinese medicinal plant, *Salvia miltiorrhiza*. Their structures were established by spectroscopic means including 2D-NMR methods.

Dan-shen is the dried roots of a medicinal plant, *Salvia miltiorrhiza* (Labiatae), which is commonly used in China. A number of diterpenoid pigments have been isolated from Dan-shen and identified as physiologically active natural products.[1] In the course of our study on the minor components of this plant,[2] two new diterpenoids have been isolated. In this paper we describe the structures of the novel constituents, cryptoacetalide (**1**) and epicryptoacetalide (**2**).

Cryptoacetalide (**1**) and epicryptoacetalide (**2**), $C_{18}H_{22}O_3$ (HRMS, *m/z* 286.1571), were isolated as an inseparable mixture (**1** : **2** = 3 : 1), together with danshenspiroketallactone,[3] and its epimer.[4,5] In the ^1H and ^{13}C NMR spectra (Table 1 and 2), the signals of the major (**1**) and the minor (**2**) components were clearly identified, and the similarity in the pattern of the signals showed that they were stereoisomers. The IR spectrum exhibited absorption band of a lactone group (1745 cm^{-1}). The ^{13}C NMR of the major isomer (**1**) indicated the presence of an ester carbonyl (δ 168.12), a tetrasubstituted benzene ring [δ 148.85 (s), 144.50 (s), 138.56 (s), 132.91 (d), 124.07 (s), 119.04 (d)]. The unsaturation degree suggested that there must be two more rings other than the benzene and lactone rings. The ^1H-^1H COSY experiment suggested the three partial structures -CH_2-CH_2-CH_2-C(CH_3)$_2$-, -O-CH_2-CH(CH_3)-CH_2-,and -CH=CH- (of the benzene ring) for both **1** and **2**. The carbon signal at δ 112.80 (s) in the ^{13}C NMR spectrum strongly inferred the presence of an acetal linkage in the molecule. In the 2D COLOC experiment (Table 2), the following correlation peaks appeared for **1**; the *gem*-dimethyl protons (δ 1.27 and 1.28) and an aromatic proton (δ 7.62, H-7) showed correlation with an aromatic carbon (δ 148.85, C-5). The other aromatic proton (δ 7.24, H-6) as well as the methylene protons (δ 3.17, H_2-1) were coupled with another sp^2 carbon (δ 138.56, C-10). By these signals as well as the correlation peaks of H-6 to C-8, H-7 to C-9, and H_2-1 to C-9 was deduced the presence of a tetrahydronaphthalene ring system. A methylene proton (δ 1.95, H_a-16) was correlated with an aromatic carbon (C-8) and a quaternary carbon (δ 112.80, C-13). The coupling of this quaternary carbon with H-7 and its chemical shift suggested that this carbon should be an acetal carbon. Therefore, a spiroacetallactone moiety was deduced for cryptoacetalide, and the structure (1) was proposed for this compound. The structure was further confirmed by the sharp singlet nature (free

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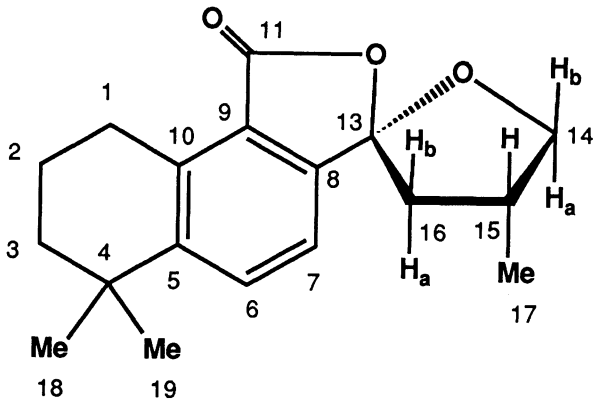
[+] Present address: Suntory Bioorganic Institute, Osaka.
[++] Present address: Department of Chemistry, Jinan University, Guang Zhou, P. R. China.

from $^{2}J_{CH}$ and $^{3}J_{CH}$) of the ester carbon (δ168.12, C-11) in the proton coupled ^{13}C NMR spectrum. The structures of epicryptoacetalide (**2**) is elucidated in the same way as described for **1**.

Stereochemistry of **1** and **2** were determined by the phase-sensitive NOESY spectrum. In the major component (**1**) the NOE was observed between H-7 and H_a-16. Because H_a-16 shows NOE to H_3-17, the syn relationship of the methyl and the benzene ring with respect to the tetrahydrofuran ring has been established. Also the following NOE correlation peaks were observed in the 2D spectrum: H_3-17 to H_a-14, H_b-14 to H-15, and H-15 to H_b-16. Thus the structure of cryptoacetalide including stereochemistry is elucidated as **1**. On the other hand, epicryptoacetalide (**2**) showed the NOE correlation from H_a-16 to H-7 as well as the one from H_a-16 to H-15. Therefore, the methyl and the benzene ring should be located in an anti relation. Other NOE peaks are; H-15 to H_a-14, H_b-14 to H_3-17, and H_3-17 to H_b-16. These findings led to the stereochemistry of cryptoacetalide and epicryptoacetalide as show in **1** and **2**, respectively.



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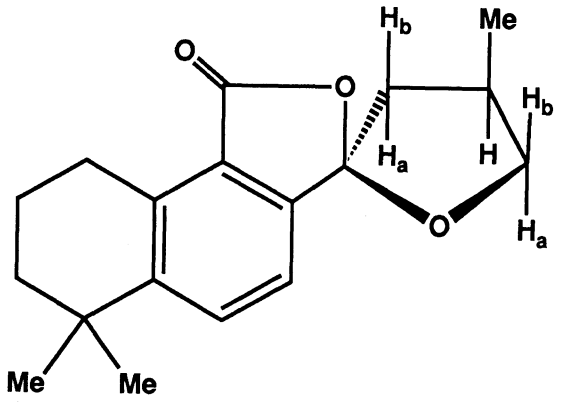

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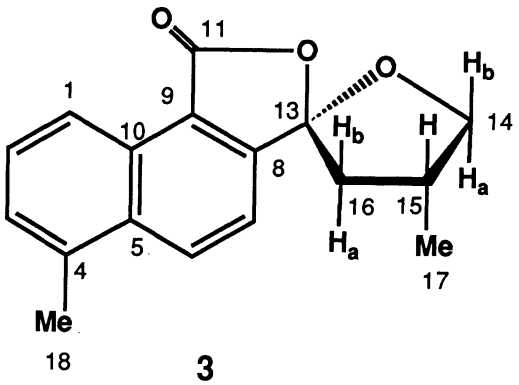

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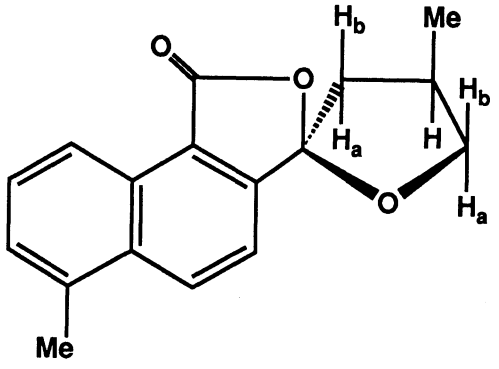

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Table 1. ^{1}H NMR data of **1** and **2** ($CDCl_3$)

position	**1** δ	multiplicity[b]	number	coupling[c] constant	**2** δ	multiplicity	number	coupling constant
1	3.17	m	2H		3.17	m	2H	
2	1.80	m	2H		1.80	m	2H	
3	1.68	m	2H		1.68	m	2H	
6	7.62	d	1H	J=8.1	7.62	d	1H	J=8.1
7	7.24	d	1H	J=8.1	7.20	d	1H	J=8.1
14a	3.71	t	1H	J=8.1	4.31	t	1H	J=8.1
14b	4.36	t	1H	J=8.1	3.81	dd	1H	J=7.0, 8.1
15	2.86	m	1H		2.68	m	1H	
16a	1.95	dd	1H	J=10.5, 13.1	2.58	dd	1H	J=9.4, 13.3
16b	2.43	dd	1H	J=6.8, 13.1	2.10	dd	1H	J=4.5, 13.3
17	1.18	d	3H	J=7.0	1.24	d	3H	J=7.0
18[a]	1.27	s	3H		1.27	s	3H	
19[a]	1.28	s	3H		1.28	s	3H	

a) Assignments are interchangeable.

b) s; singlet, d; doublet, t; triplet, m; multiplet, dd; doublet of doublets.

c) J is expressed in Hz.

Table 2. ^{13}C NMR data of **1** and **2** and the correlations observed in the COLOC experiments (J = 7 Hz; $CDCl_3$)

position	**1** carbon	proton[a]	**2** carbon	proton[a]	position	**1** carbon	proton[a]	**2** carbon	proton[a]
1	δ 25.84	2, 3	δ 25.84	2, 3	10	δ 138.56	1, 6	δ 138.43	1, 6
2	18.30	1, 3	18.30	1, 3	11	168.12		168.33	
3	39.21	18, 19	39.21	18, 19	12	-		-	
4	33.98	18, 19	33.98	18, 19	13	112.80	7, 16a	112.80	7, 16b
5	148.85	3, 7, 18, 19	148.75	3, 7, 18, 19	14	76.90	17	76.90	17
					15	32.33	16, 17	33.23	16, 17
6	132.91	7	133.01	7	16	45.34	17	44.37	17
7	119.04	6	118.92	6	17	17.27		17.99	
8	144.50	6, 16a	145.30	6	18,19	31.64	18, 19	31.64	18, 19
9	124.07	1, 7	123.61	7					

a) The number of proton which shows a cross peak to the carbon in the same row.

References

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3) D. Kong, X, Liu, M. Teng, and X. Rao, *Acta Pharm. Sin.*, **20**, 747 (1985).

4) H. Luo, S. Chen, J. Lee, and J. K. Snyder, *Phytochemistry*, **27**, 290 (1988).

5) The structure of danshenspiroketallactone had been determined by X-ray crystallography as to be **3**, and the epimer of this spiroketallactone, epidanshenspiroketallactone (**4**) has been recently reported (Ref. 4). However, the structures of **1** and **2** in the paper seem to have been mistakenly exchanged. We independently determined the relative stereochemistry of **3** and **4** by the NOE experiments. Our NMR data for **3** are identical with those of danshenspiroketallactone reported in Ref. 3. To eliminate all the confusions, we will show our NMR data of **3** and **4**. Danshenspiroketallactone (**3**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.84 (1H, d, J=8.5 Hz, H-1), 7.56 (1H, dd, J=8.5, 7.0 Hz, H-2), 7.44 (1H, d, J=7.0 Hz, H-3), 8.32 (1H, d, J=8.6 Hz, H-6), 7.53 (1H, d, J=8.6 Hz, H-7), 4.45 (1H, t, J=8.1 Hz, H-14b), 3.79 (1H, t, J=8.1 Hz, H-14a), 2.95 (1H, m, H-15), 2.51 (1H, dd, J=12.9, 6.8 Hz, H-16b), 2.09 (1H, dd, J=12.9, 10.5 Hz, H-16a), 1.23 (3H, d, J=7.0 Hz, H_3-17), 2.72 (3H, s, H_3-18). ^{13}C NMR (125 MHz; $CDCl_3$) δ 121.98 (C-1), 128.79 (C-2), 128.33 (C-3), 134.95 (C-4), 133.30 (C-5), 131.77 (C-6), 118.05 (C-7), 146.96 (C-8), 122.02 (C-9), 129.08 (C-10), 168.26 (C-11), 113.09 (C-13), 77.23 (C-14), 32.49 (C-15), 45.22 (C-16), 17.24 (C-17), 19.68 (C-18). Epidanshenspiroketallactone (**4**): ^{1}H NMR ($CDCl_3$) δ 8.84 (1H, d, J=8.5 Hz, H-1), 7.56 (1H, dd, J=8.5, 7.0 Hz, H-2), 7.44 (1H, d, J=7.0 Hz, H-3), 8.31 (1H, d, J=8.6, H-6), 7.51 (1H, d, J=8.6 Hz, H-7), 4.40 (1H, t, J=8.1 Hz, H-14a), 3.91 (1H, dd, J=8.1, 6.9 Hz, H-14b), 2.73 (1H, m, H-15), 2.67 (1H, dd, J=13.1, 9.4 Hz, H-16a), 2.19 (1H, dd, J=13.4, 4.1 Hz, H-16b), 1.29 (3H, d, J=7.0 Hz, 17-H_3), 2.72 (3H, s, H_3-18). ^{13}C NMR ($CDCl_3$) δ 121.99 (C-1), 128.79 (C-2), 128.33 (C-3), 134.95 (C-4), 133.24 (C-5), 131.89 (C-6), 117.98 (C-7), 147.66 (C-8), 121.52 (C-9), 128.99 (C-10), 168.47 (C-11), 113.09 (C-13), 77.23 (C-14), 33.35 (C-15), 44.16 (C-16), 18.02 (C-17), 19.68 (C-18).

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