

A Novel Dimeric Diterpene from *Salvia prionitis*

Mai Li,[†] Jin-Sheng Zhang,^{*,†} and Ming-Qin Chen[‡]

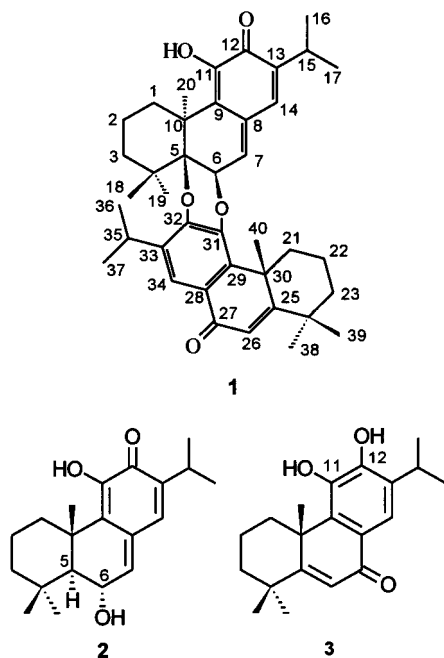
Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, People's Republic of China, and Center of Analysis & Measurement, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China

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A novel dimeric abietane diterpene, hongencaotone (**1**), has been isolated from the roots of *Salvia prionitis*, and its structure was determined by spectral data interpretation and X-ray analysis. Hongencaotone (**1**) is the first ether-linked heterodimeric diterpene to have been isolated from the genus *Salvia*.

Chemical studies on the folk medicinal plant *Salvia prionitis* (Lamiaceae) have yielded various tanshinones,¹ abietane and 4,5-seco rearranged abietane diterpenes,^{1–5} a triterpenoid,¹ and miscellaneous compounds,² of which a few have shown interesting bioactivities.^{1,3,6} In the course of our study on the nonpolar constituents of this plant, a new dimeric abietane diterpene, named hongencaotone (**1**), was isolated for the first time and its structure was determined by 1D and 2D NMR techniques and X-ray analysis. Hongencaotone (**1**) is the first ether-linked heterodimeric diterpene to have been isolated from the genus *Salvia*.

6.9 Hz) together with their coupled methyl signals at δ_{H} 0.99, 1.04, and 0.88, 1.13 ($J = 6.8$ and 6.9 Hz) were observed in ¹H NMR spectrum, indicating there were two isopropyl groups in the molecule. The signal at δ_{H} 7.51 was the resonance of a conjugated enolic proton, as shown from the HMQC spectrum. In the HMBC spectrum, the carbonyl signal at δ_{C} 181.80 correlated with signals at δ_{H} 7.51, 6.46, and 2.92, while the methine signal at δ_{C} 134.60 (δ_{H} 6.46) correlated with an isopropyl proton (δ_{H} 2.92) and an olefinic proton (δ_{H} 5.97). In turn, the oxygenated quaternary carbon at δ_{C} 83.66 correlated with signals at δ_{H} 5.97, 1.42, 1.34, and 0.95, suggesting that **1** should have a quinone methide moiety similar to that of taxodone (**2**).⁷ Analysis of the remaining spectral data resulted in the assignment of a structural fragment quite similar to that of salvinolone (**3**) isolated from the same species.³ Since there were altogether five oxygen atoms (HREIMS) in the molecule, and a total of 50 protons had been designated through the above spectral analyses; hence the two monomeric units must be linked via two ether bridges. The correlation between δ_{H} 5.97 and δ_{H} 1.76 in the NOESY spectrum revealed that C-7 and C-40 were sterically close. The two ether linkages should be located between C-6 and C-31 and C-5 and C-32, respectively. The single-crystal X-ray analysis of **1** verified all above spectroscopic structure assignments involving two monomeric abietane units in the molecule, and there were two molecules in the asymmetric unit. Furthermore, the relative configurations at C-10, C-30, C-5, and C-6 were also determined by X-ray crystallography, which confirmed the structure of the dimeric abietane diterpene hongencaotone as **1**. In contrast to the significant tumor-inhibitory activity of taxodone (**2**)⁸ and salvinolone (**3**),³ hongencaotone (**1**) was ineffective when evaluated against the HL-60 and BEL-7402 tumor cell lines, suggesting that blocking the C-5 and C-6 positions in taxodone (**2**) and the C-11 and C-12 positions in salvinolone (**3**) decreases their antitumor activity.



Compound **1** was obtained as transparent yellow plates from cyclohexane, mp 191–192 °C, $[\alpha]_{\text{D}}^{25}$ 588° (*c* 0.05, MeOH). The molecular composition was determined to be C₄₀H₅₀O₅ from the HREIMS (M^+ , m/z found 610.3671, calcd 610.3658). The ¹H and ¹³C-DEPT NMR spectra revealed that there were 10 methyls, six methylenes, seven methines, and 17 quaternary carbons in the molecule. Two one-proton septets at δ_{H} 2.92 and 3.04 ($J = 6.8$ and

Experimental Section

General Experimental Procedures. The melting point measurements were carried out on a Kofler hot-stage apparatus and are uncorrected. The optical rotation was obtained on a DIP-181 digital polarimeter. The UV spectra were recorded on a Beckman DU-600 spectrophotometer, and the IR spectra on a Perkin-Elmer spectrophotometer. The ¹H, ¹³C, HMQC, and HMBC NMR spectra were recorded on a Bruker AM-400 (¹H) or a Bruker AC-100 (¹³C) spectrometer. Mass spectra were obtained on a MAT 711 mass spectrometer.

Plant Material. The roots of *Salvia prionitis* were collected at Shangrao, Jiangxi Province, People's Republic of China, in

* To whom correspondence should be addressed. Tel: 0086-21-64311833. Fax: 0086-21-64370269. E-mail: jszhang@mail.shcnc.ac.cn.

[†] Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

[‡] Center of Analysis & Measurement, Fudan University.

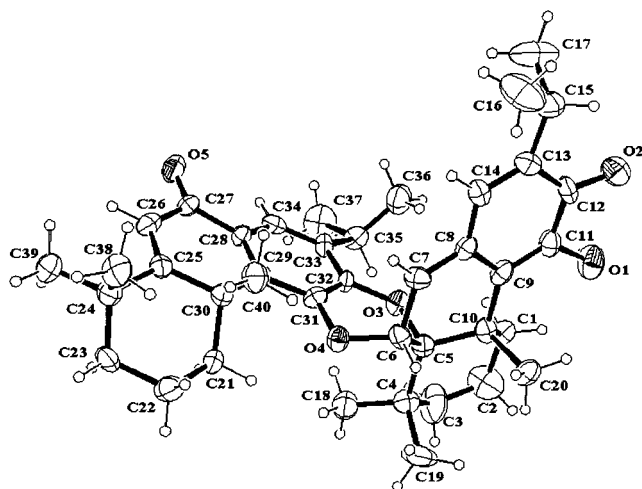


Figure 1. Perspective ORTEP drawing for molecule 1.

Table 1. NMR Data of **1** (δ , CDCl_3)^a

position	¹ H (mult., <i>J</i> in Hz)	¹³ C	HMBC
1	1.26 1.86 (2H, m)	38.87 t	H-20
2	1.68 (2H, m)	18.46 t	H-1
3	2.40 2.76 (2H, m)	31.92 t	H-19
4		46.76 s	H-3, H-19
5		83.66 s	H-7, H-18, H-19, H-20
6	5.54 (1H, d, 2.5)	70.62 d	
7	5.97 (1H, d, 2.5)	138.37 d	
8		134.49 s	H-6, H-7, H-14
9		123.73 s	H-7, H-14, OH
10		40.39 s	H-20
11		144.42 s	OH
OH-11	7.51 (1H, s) ^b		
12		181.80 s	H-14, H-15, OH
13		142.24 s	H-15, H-16, H-17
14	6.46 (1H, s)	134.60 d	H-7, H-15
15	2.92 (1H, septet, 6.8)	26.98 d	H-14, H-16, H-17
16	0.99 (3H, d, 6.8)	20.96 q	H-15, H-16
17	1.04 (3H, d, 6.8)	21.58 q	H-17
18	1.34 (3H, s)	24.35 q	H-3
19	1.42 (3H, s)	24.44 q	H-3
20	0.95 (3H, s)	30.59 q	
21	1.36 3.18 (2H, m)	34.57 t	H-23, H-40
22	1.98 (2H, m)	18.74 t	H-23
23	1.40 1.64 (2H, m)	40.12 t	H-21, H-38, H-39
24		38.06 s	H-23, H-26, H-38, H-39
25		173.73 s	H-21, H-26, H-38, H-39, H-40
26	6.45 (1H, s)	123.92 d	
27		185.47 s	H-34
28		122.94 s	H-26
29		139.47 s	H-21, H-34, H-40
30		42.09 s	H-21, H-26, H-40
31		138.41 s	
32		148.16 s	H-34, H-35
33		135.02 s	H-35, H-36, H-37
34	7.62 (1H, s)	117.56 d	H-35
35	3.04 (1H, septet, 6.9)	27.63 d	H-34, H-36, H-37
36	0.88 (3H, d, 6.9)	21.53 q	H-36
37	1.13 (3H, d, 6.9)	22.31 q	H-35, H-37
38	1.25 (3H, s) ^c	29.74 ^c q	H-23, H-38
39	1.38 (3H, s) ^c	33.30 ^c q	H-23, H-39
40	1.76 (3H, s)	25.25 q	H-21

^a Spectra was recorded in CDCl_3 . Assignments were made by ^{13}C , ^1H NMR, HMQC, and HMBC data. Multiplicity was established from DEPT data. ^b D_2O exchangeable. ^c The assignments may be interchanged in any vertical column.

July 1997 and authenticated by Professor Xiu-Lan Huang, of Shanghai Institute of Materia Medica. A voucher specimen

(No. SIMMP95068) has been deposited in the Herbarium of the Shanghai Institute of Materia Medica.

Extraction and Isolation. Dried roots of *Salvia prionitis* (5 kg) were extracted with EtOAc for 6 days at room temperature. The solvent was removed in vacuo to yield 320 g of a gummy residue, which was subjected to Si gel column chromatography (200–300 mesh) and eluted with cyclohexanes–ethyl acetate (20:1). Repeated Si gel chromatography and preparative TLC of fractions gave hongencaotone (**1**, 15 mg) and the four known compounds 8,11,13-dehydroabietane (12 mg),⁹ royleanone (17 mg),⁷ sapriparaquinone (16 mg),¹⁰ and ferruginol (25 mg).¹¹

Hongencaotone (1): crystallized as transparent yellow plates from cyclohexane; mp 191–192 °C; $[\alpha]_D^{25}$ 588° (*c* 0.05, MeOH); UV λ_{max} (MeOH) (log ϵ) 249 (4.22), 315 (4.42) nm; IR (KBr) ν_{max} 3446, 2929, 1651, 1599, 1466, 1362, 1309, 1252, 1121 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), and HMBC data, see Table 1; EIMS m/z 610 [M]⁺ (50), 572 (74), 541 (48), 298 (50), 229 (100); HREIMS m/z 610.3671 (calcd for $\text{C}_{40}\text{H}_{50}\text{O}_5$, 610.3658).

Crystal data for 1: $\text{C}_{40}\text{H}_{50}\text{O}_5$, $M_r = 610.80$, pale yellow prismatic crystal with dimensions 0.30 × 0.20 × 0.20 mm, tetragonal, space group $P4_1$ or $P4_3$, $T = 20 \pm 1$ °C, $a = b = 12.979(4)$ Å, $c = 39.863(9)$ Å, $V = 6715$ Å³, $Z = 8$, $F(000) = 2640$, $d_{\text{calcd}} = 1.208$ g cm^{-3} , $\mu(\text{Mo K}\alpha) = 0.078$ cm^{-1} .

Data Collection and Structure Refinement. Intensities of 4741 reflections were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71069$ Å) using the ω - 2θ scan technique to a maximum 2θ value of 50° at the room temperature of 20 ± 1 °C. Of these, 2643 with $I > 2\sigma(I)$ were considered observed and used for refinement. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located by geometry and riding on the relative atoms. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.275 and -0.301 e⁻/Å³, respectively. The final agreement factors are $R_1 = 0.0862$ and $wR_2 = 0.2296$ for observed reflections. All calculations were performed on a PC computer using SHELX97 (Sheldrick, 1997).

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Supporting Information Available: X-ray crystallographic data for **1** including atomic coordinates, bond lengths and angles, and thermal parameters. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- Yang, B.-J.; Huang, X.-L.; But, P.-H.; Zhuang, G.-F.; Huang, Y.; Wang, X.-M.; Lin, L.-Z. *Acta Bot. Sin.* **1988**, *30*, 524–527.
- Lin, L.-Z.; Wang, X.-M.; Huang, X.-L.; Huang, Y.; Yang, B.-J. *Planta Med.* **1988**, *54*, 443–444.
- Lin, L.-Z.; Blasko, G.; Cordell, G. A. *Phytochemistry* **1989**, *28*, 177–181.
- Zhang, J.-S.; Huang, Y. *Nat. Prod. Res. Dev.* **1995**, *7*, 1–4.
- Li, M.; Zhang, J.-S.; Ye, Y.-M.; Fang, J.-N. *J. Nat. Prod.* **2000**, *64*, 139–141.
- Huang, X.-L.; Wang, X.-M.; Zhang, J.-S.; Lin, L.-Z. *Acta Bot. Sin.* **1990**, *32*, 490–491.
- Kupchan, S. M.; Karim, A.; Marcks, C. J. *J. Org. Chem.* **1969**, *34*, 3912–3918.
- Hanson, R. L.; Lardy, H. A.; Kupchan, S. M. *Science* **1970**, *168*, 378–380.
- Kitadani, Masayuki; Yoshikoshi, Akira; Kitahara, Yoshio; de Paiya Campello, J.; McChesney, J. D.; Watts, D. J.; Wenkert, E. *Chem. Pharm. Bull.* **1970**, *18*, 402–405.
- Lin, Z.-L.; Wang, X.-M.; Huang, X.-L.; Huang, Y. *Acta Pharm. Sin.* **1990**, *25*, 154–156.
- Nakanishi, T.; Miyasaka, H.; Nasu, M.; Hashimoto, H.; Yoneda, K. *Phytochemistry* **1983**, *22*, 721–723.

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