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Davidiol D, First Naturally Occurring Resveratrol Pentamer Isolated from *Sophora davidii*

**Masayoshi Ohyama, Michie Ichise, Toshiyuki Tanaka,
Munekazu Iinuma* and Charles L. Burandt, Jr.¶**

*Department of Pharmacognosy, Gifu Pharmaceutical University, Mitahora-higashi 5-6-1,
Gifu 502, Japan. ¶Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University
of Mississippi, University, MS 38677, U. S. A.*

Abstract: Davidiol D isolated from the roots of *Sophora davidii* was the first natural instance of a resveratrol pentamer. The structure and relative configuration were established by means of 2D-NMR spectroscopy. Copyright © 1996 Elsevier Science Ltd

From the chemosystematic point of view, we have clarified the close relationship between the morphological classification of the genus *Sophora* and the occurrence of flavonoids and stilbenoids, which suggested that stilbene oligomers were abundant in the section Pseudosophora and sect. Sophora (series Sericeae).[1] For example, from the roots of *S. leachiana* which belongs to the series mentioned above, we have already reported the identification of several oligomers consisting of a resveratrol (3,5,4'-trihydroxystilbene) such as leachianol C.[2] Further investigation on the roots of *S. davidii* which was classified into sect. Pseudosophora, resulted in the isolation of a resveratrol pentamer named davidiol D (**1**) as the first instance of a naturally occurring compound, together three new stilbene oligomers, davidiols A - C.[3]

The roots of *S. davidii* were collected at Texas, U. S. A., in May 1994. An acetone extract (50 g) of the dried and pulverized roots (900 g) was subjected to column chromatography on silica gel (C_6H_6-acetone = 15:1, gradient) for division into eight fractions. Further purification of the acetone eluent by Sephadex LH-20 c.c. (MeOH or acetone) and successive vacuum liquid chromatography ($CHCl_3$-MeOH = 5:1, gradient) resulted in the isolation of **1** (15 mg), and davidiols A (200 mg), B (30 mg) and C (55 mg), respectively.

Davidiol D (**1**), $[\alpha]_D^{27}$ -135° (MeOH) obtained as a brown solid, showed a $[M-H]^-$ ion at *m/z* 1133 ($C_{70}H_{53}O_{15}$) in the negative ion FABMS, which was further confirmed by HR negative ion FABMS 1133.3364 ($[M-H]^-$, -2.0 mmu dev.). In the UV spectrum, absorption bands were observed at 209, 220sh and 282 nm. The ^{1}H-NMR and HH-COSY spectral data indicated that the presence of five 4-hydroxyphenyl groups (designated aromatics A_1-E_1) (Fig. 1), two 3,5-dihydroxyphenyl groups (A_2 and E_2), two 3,5-dioxygenated-1,2-disubstituted benzene rings (B_2 and C_2), a 1,5-dioxygenated-2,3,4-trisubstituted benzene ring (D_2) and four sets of mutually coupling methine protons (H-7a/H-8a, H-7b/H-8b, H-7c/H-8c and H-7e/H-8e) in addition to a set of *trans*-olefinic protons (H-7d/H-8d). The ^{1}H-NMR spectrum also showed the presence of thirteen hydroxyl groups (TABLE 1). These partial structures were also supported by the aid of CH-COSY spectrum.

Table 1 ^{1}H and ^{13}C NMR spectral data of davidiol D (**1**)

No.	δH	δC	No.	δH	δC
1a		134.8	1d		130.1
2(6)a	7.16 (d, 9.0)	127.6	2(6)d	6.84 (d, 8.8)	128.8
3(5)a	6.90 (d, 9.0)	116.0	3(5)d	6.70 (d, 8.8)	116.1
4a		157.8^{a}	4d		157.4
7a	5.11 (d, 2.0)	93.2	7d	5.70 (d, 16.6)	134.6
8a	3.71 (d, 2.0)	54.8	8d	6.16 (d, 16.6)	125.2
9a		149.1	9d		139.3
10a	5.78 (d, 2.0)	106.8	10d		120.9
11a		159.7	11d		159.9
12a	6.24 (t, 2.0)	101.7*	12d	6.39 (s)	97.6
13a		159.7	13d		157.0
14a	5.78 (d, 2.0)	106.8	14d		127.0
1b		136.2	1e		134.3
2(6)b	5.98 (d, 8.8)	129.6	2(6)e	7.19 (d, 8.8)	128.2
3(5)b	6.03 (d, 8.8)	115.1	3(5)e	6.82 (d, 8.8)	116.2
4b		155.2	4e		158.0^{a}
7b	4.01 (br s)	53.7	7e	5.20 (d, 4.6)	93.6
8b	3.02 (br s)	54.7	8e	4.15 (d, 4.6)	58.2
9b		149.4	9e		148.1
10b		118.6	10e	5.88 (d, 2.4)	106.7
11b		161.7	11e		159.5
12b	6.22 (d, 2.0)	95.2	12e	6.13 (t, 2.4)	101.5
13b		160.0	13e		159.5
14b	6.04 (d, 2.0)	104.9	14e	5.88 (d, 2.4)	106.7
1c		136.7	OH	7.60, 7.61, 7.74, 7.94, 8.02 (x2), 8.03 (x2), 8.28, 8.30, 8.36, 8.40, 8.57	
2(6)c	6.72 (d, 8.5)	131.4			
3(5)c	6.14 (d, 8.5)	115.6			
4c		155.5^{a}			
7c	3.84 (d, 12.0)	52.9			
8c	4.52 (d, 12.0)	56.7			
9c		151.9			
10c		122.4			
11c		155.0			
12c	6.37 (d, 2.2)	101.7*			
13c		158.4			
14c	5.83 (d, 2.2)	106.4			

^{1}H- and ^{13}C-NMR spectra were measured in acetone-d_6 at 400 and 100 MHz, respectively.
All protons and carbons were assigned by means of CH COSY and COLOC spectra.
* : overlapping; ^{a} : interchangeable.

In the COLOC spectrum, ^{13}C-^{1}H long-range correlations between C-2(6)a/H-7a, C-10(14)a/H-8a, C-2(6)b/H-7b and C-14b/H-8b were observed, demonstrating that A_1, B_1 and A_2, B_2 were attached to C-7 and C-8 positions at the respective methine groups. Three-bonded correlations [C-11b/H-7a, C-11b/H-8a] indicated that C-8a and C-7a were linked at C-10a and an oxygen adhering at C-11b, respectively. The linkage of C_2 was suggested by the long-range couplings [C-10c/H-7b, C-10c/H-8b] to connect between C-10c and C-7b. Considering the correlation between C-2(6)c and H-7c, C_1 was attached at C-7c. Furthermore, as the

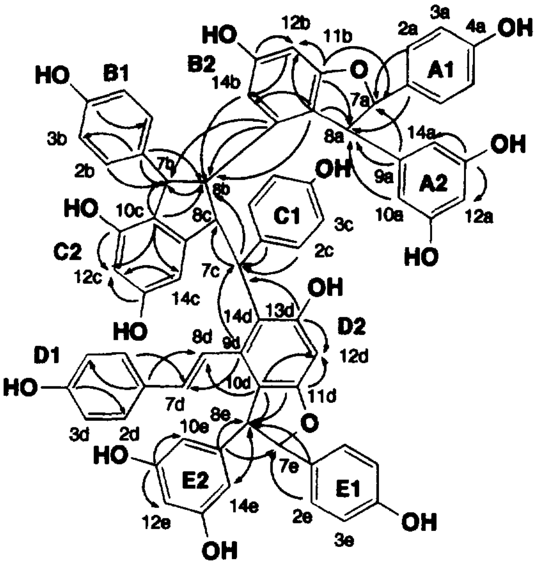

Fig. 1 CH long-range correlations in the COLOC spectrum (J = 8 Hz) of 1

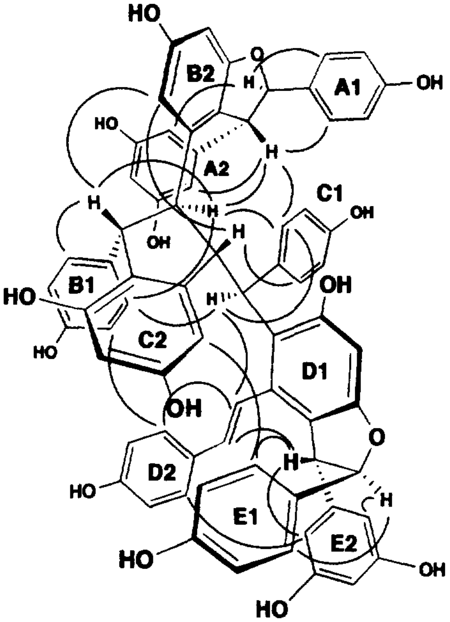

Fig. 2 NOE interactions in the PSNOESY of 1

correlations were observed between C-7c/H-8b and C-7c/H-8c, the position of C-7c was linked at C-8b *via* ^{3}J through C-8c. The olefinic protons (H-7d and H-8d) exhibited the long-range couplings between C-2(6)d and C-10d, respectively. Two quaternary carbons assigned to C-9d, 13d were coupled with H-7c, indicating that $\mathbf{D_2}$ was attached at C-7c. Taking the correlations [C-2(6)e/H-7e, C-10(14)e/H-8e] into account, $\mathbf{E_1}$ and $\mathbf{E_2}$ adhered to C-7e and C-8e, respectively. The additional correlations [C-10d/H-8e, C-11d/H-8e] and the chemical shift at 7e (δ_H 5.20, δ_C 93.6) indicated the presence of a dihydrofuran moiety consisting of C-7e, C-8e, C-10d, C-11d and an oxygen at C-11d. As **1** must comprise five resveratrol units on the basis of the biogenetic pathway, C-8c was considered to connect at C-9c, though there were no ^{13}C-^{1}H long-range correlations between those two carbons. Consequently, the planar structure was determined as shown in Fig. 1.

Coupling constants [J (H-7a/H-8a) = 2.4 Hz and J (H-7e/H-8e) = 4.6 Hz)] due to the dihydrobenzofuran rings suggested that the location of $\mathbf{A_1}$ and $\mathbf{E_1}$ were *trans*-orientation against $\mathbf{A_2}$ and $\mathbf{E_2}$, respectively.[4] In the phase sensitive NOESY spectrum (Fig. 2), NOE interactions [H-2(6)a/H-8a, H-10(14)a/H-7a, H-2(6)e/H-8e and H-10(14)e/H-7e] were observed, which also supported the *trans*-orientation at the furan ring moieties. Additional NOE interactions were observed between H-7b/H-14b and H-8c/H-14b, substantiating that the location of $\mathbf{B_2}$, H-7b and H-8c were *cis*-orientation. NOEs [H-2(6)b/H-7c, H-2(6)b/H-8b and H-2(6)c/H-8b] indicated that $\mathbf{B_1}$, $\mathbf{C_1}$, H-8b and H-7c were settled in a *cis*-orientation. The NOE interactions between H-8a/H-8b and H-8a/H-2(6)c were fully explained when H-8b and H-2(6)c were located in close proximity to H-8a. The NOE enhancements observed between H-3(5)b/H-2(6)d also indicated the spatial proximity between $\mathbf{B_1}$ and $\mathbf{D_1}$. Hence, an unusual chemical shift found in a higher field [δ_H 5.98 (H-2b,6b) and 6.03 (H-3b,5b); $\mathbf{B_1}$] was attributable to the shielding effect caused by $\mathbf{D_1}$. NOEs between H-14c/H-2(6)e can be observed when $\mathbf{C_2}$ was situated in a spatial proximity to $\mathbf{E_1}$. Therefore, the relative configuration of **1** was substantiated to be *rel*-(7a*R*, 8a*R*, 7b*S*, 8b*S*, 7c*S*, 8c*R*, 7e*R*, 8e*R*).

Up to now, some resveratrol oligomers have been reported from the family such as Vitaceae[5] and Cyperaceae[6]. All of these resveratrol oligomers were, however, composed of less than the tetrameric unit. Hence, this occurrence of a resveratrol pentamer is the first instance in a natural product.

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