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An Efficient Method for Determining the Relative Configuration of Furofuran Lignans by ^{1}H NMR Spectroscopy

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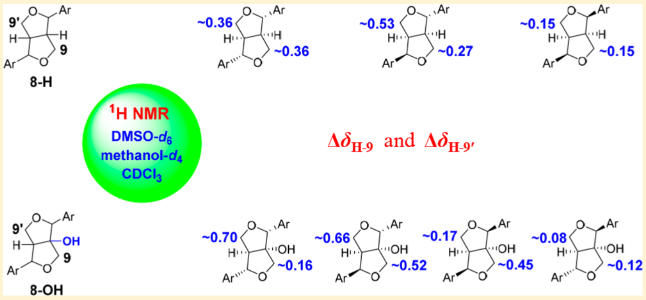
Supporting Information

ABSTRACT: An efficient ^{1}H NMR spectroscopic approach for determining the relative configurations of lignans with a 7,9′:7′,9-diepoxy moiety has been established. Using the chemical shift differences of H_2-9 and H_2-9′ ($\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$), the configurations of 8-H and 8-OH furofuran lignans can be rapidly and conveniently determined. The rule is applicable for data acquired in DMSO-d_6, methanol-d_4, or $CDCl_3$. Notably, the rule should be applied carefully when the C-2 or C-6 substituent of the aromatic rings may alter the dominant conformers of the furofuran moiety.



Lignans are a large class of natural products that are widely distributed in plants and are derived from the oxidative coupling of two C_6−C_3 units.[1] Of these compounds, furofuran lignans are an important group of molecules with a characteristic 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton;[2] that is, they possess a 7,9′:7′,9-diepoxy moiety. Numerous furofuran lignans have been isolated from various plants, and their bioactivities have been evaluated. They have been found to exhibit antiviral,[1−3] antitumor,[2] antioxidant,[4] calmodulin-inhibitive,[5] and antihypertensive activities.[6]

Generally, the 8-H and 8-OH patterns are the two main distinguishing characteristics of furofuran lignans. Because of the presence of four stereogenic carbons and the variability of the conformers of the fused ditetrahydrofuran moieties bearing aromatic rings, it is difficult to define their C-7/C-8 and C-7′/C-8′ relative configurations. Several studies have focused on this problem, and solutions have included applying chiral silylation reagents to particular structures,[7] examining the coupling constants of the protons,[8] examining the chemical shifts of the carbons,[9−11] analysis of the ROESY NMR spectrum,[3] and X-ray crystallographic analysis.[12] Among these methods, NMR spectroscopy is a useful technique for identifying and analyzing the relative configurations of naturally occurring compounds. However, both the coupling constants of the protons and the ROESY spectrum were inconclusive for determining the relative configurations of the fused ditetrahydrofuran moieties. Some research teams reported an empirical coupling constant method (in $CDCl_3$) in which a small coupling constant ($J \approx 4$ Hz) of 7-H/8-H or 7′-H/8′-H corresponds to a *trans* configuration and a large coupling constant ($J \approx 7$ Hz) corresponds to a *cis* configuration.[8] However, further studies suggested the coupling constants have no clear relationship with the relative configuration of the furofuran stereocenters.[9,13] The ROESY spectrum was also ambiguous due to variations in the conformations of the furofuran units, which are caused by differences in the orientation of the two aromatic rings. Therefore, finding a convenient and reliable approach is urgently needed.

RESULTS AND DISCUSSION

The nine 8-H furofuran lignans sesamin (**1**),[12] (+)-pinoresinol (**2**),[14] (+)-sesartemin (**3**),[15] asarinin (**4**),[12] (+)-epipinoresinol (**5**),[16] (+)-episesartemin A (**6**),[15] (+)-diasyringaresinol (**7**),[17] lirioresinol-C dimethyl ether (**8**),[18] and (+)-disaesartemin (**9**)[15] were analyzed as model compounds (Figure 1). The configurations of **1** and **4** were determined by single-crystal X-ray crystallography.[12] Since the 7,9′:7′,9-diepoxy moiety is in a *cis*-fused configuration in naturally occurring furofuran lignans,[12−18] the challenge is in determining the relative configurations of C-7/C-8 and C-7′/C-8′.

Structurally, these nine 8-H type furofuran lignans were classified into three types: (I) 7-H/8-H *trans*, 7′-H/8′-H *trans* (**1**−**3**); (II) 7-H/8-H *trans*, 7′-H/8′-H *cis* (**4**−**6**); and (III) 7-H/8-H *cis*, 7′-H/8′-H *cis* (**7**−**9**) (Figure 1). After full assignment of their ^{1}H NMR data in $CDCl_3$, an interesting phenomenon was observed. The H_2-9 and H_2-9′ diastereotopic methylene protons of compound **1** resonated at δ_H 4.23 (H-9a), 3.86 (H-9b), 4.23 (H-9′a), and 3.86 (H-9′b), while the corresponding protons of compound **4** resonated at δ_H 4.09 (H-9a), 3.81 (H-9b), 3.83 (H-9′a), and 3.29 (H-9′b) (Table S5, Supporting Information). The literature data of compound **7** indicated that the methylene proton resonances of **7** resonated at δ_H 3.73 (H-9a) and 3.57 (H-9b) and at δ_H 3.73 (H-9′a) and 3.57 (H-9′b).[17] There were distinct differences in the chemical shifts of the two pairs of methylene protons of

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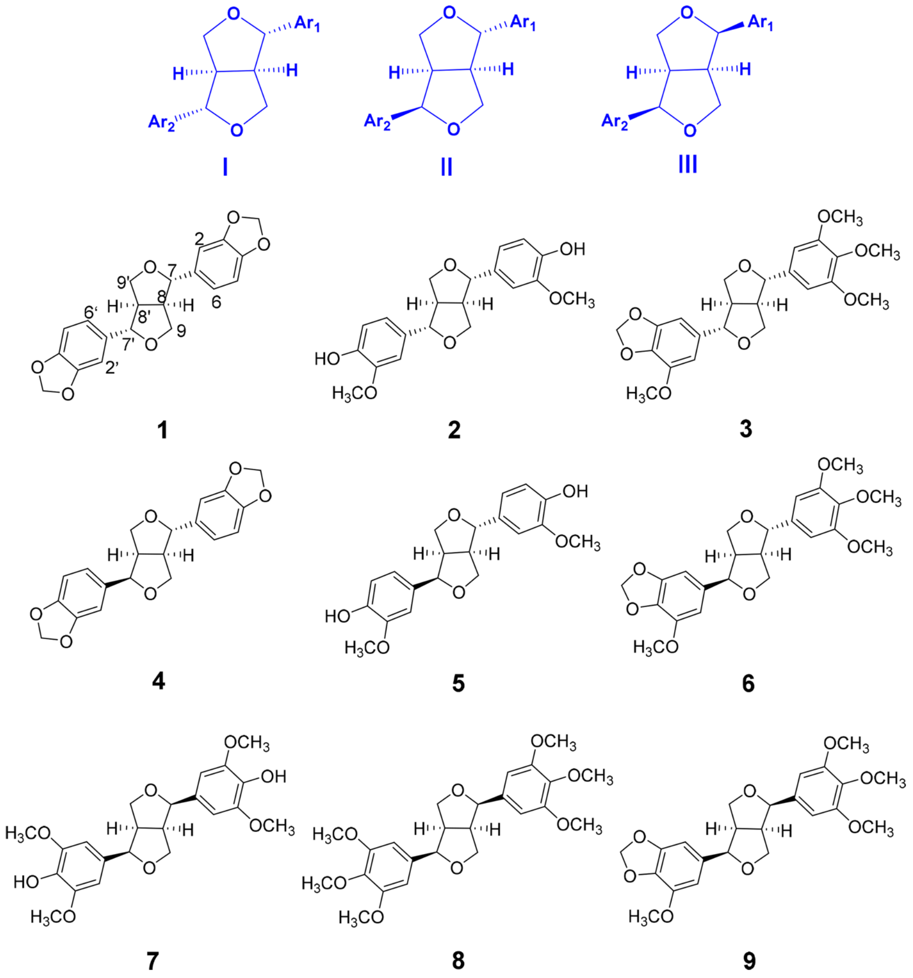

Figure 1. Structures of 8-H furofuran lignans.

compounds **1**, **4**, and **7**. In compound **1**, the chemical shift differences of H_2-9 and H_2-9′ ($\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$) have medium values (0.37). In compound **4**, one of the methylene protons had a medium value ($\Delta\delta_{H\text{-}9}$ = 0.28) and the other had a large value ($\Delta\delta_{H\text{-}9'}$ = 0.54). Unlike in **1** and **4**, the values of the protons in compound **7** were both small ($\Delta\delta_{H\text{-}9}$ = 0.16 and $\Delta\delta_{H\text{-}9'}$ = 0.16). Similar chemical shift differences were also observed in compounds **2**, **3**, **5**, **6**, **8**, and **9** (Tables S8 and S10, Supporting Information). Thus, the chemical shifts of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ of the three types of 8-H furofuran lignans are a direct result of the relative configurations of C-7/C-8 and C-7′/C-8′.

To review the relative configurations of 8-OH-type furofuran lignans, 1-hydroxypinoresinol (**10**),[19] pseuderesinol (**11**),[20,21] (+)-1-hydroxy-6-epipinoresinol (**12**),[19] (+)-6-epifraxiresinol 4′,4″-di-*O*-methyl ether (**13**),[19] (1*R**,2*R**,5*R**,6*R**)-2,6-bisphenyl-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane (**14**),[22] (+)-gmelinol (**15**),[22] 1-hydroxyfurofuran (**16**),[23] neogmelinol (**17**),[9] (+)-1-hydroxy-2,6-bisepipinoresinol (**18**),[24] and dipsalignan A (**19**)[24] (Figure 2) were selected as model compounds. The configuration of **14** was determined from its single-crystal X-ray crystallography.[22] Since their 7,9′:7′,9-diepoxy moiety also possesses a *cis*-fused configuration,[19−24] these compounds can be classified into four groups according to the orientations of the two aromatic rings: (IV) 7-H/8-OH *trans*, 7′-H/8′-H *trans* (**10**, **11**); (V) 7-H/8-OH *trans*, 7′-H/8′-H *cis* (**12**−**15**); (VI) 7-H/8-OH *cis*, 7′-H/8′-H *cis* (**16**); and (VII) 7-H/8-OH *cis*, 7′-H/8′-H *trans* (**17**−**19**).

Their ^{1}H NMR data were assigned, and the values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ of these compounds were calculated. The results showed that the chemical shift differences of H_2-9 and H_2-9′ ($\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$) in 8-OH-type furofuran lignans did not follow the same rule as those in 8-H-type furofuran lignans. Compound **10** (type IV) had a small value for $\Delta\delta_{H\text{-}9}$ (0.15) and a large value for $\Delta\delta_{H\text{-}9'}$ (0.70). Compound **12** (type V) had large values for both $\Delta\delta_{H\text{-}9}$ (0.49) and $\Delta\delta_{H\text{-}9'}$ (0.67). For compound **16** (type VI), a synthesized furofuran lignan with *cis*-oriented aromatic rings, the values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ were 0.45 and 0.17, respectively.[23] Only a few type VII compounds have been isolated from natural sources. The chemical shifts of H_2-9 and H_2-9′ of these compounds could not be confidently assigned. Compound **17** showed only a small value of $\Delta\delta_{H\text{-}9}$ (0.18), while the value of $\Delta\delta_{H\text{-}9'}$ could not be determined because the chemical shifts of H-9′a and H-9′b have not been assigned.[9] The literature reports of furofuran lignans **18** and **19** suggest they both contain *cis*-oriented aromatic rings.[24] However, both compounds had small values of both $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ ($\Delta\delta_{H\text{-}9}$ = 0.12, $\Delta\delta_{H\text{-}9'}$ = 0.11 in **18**; $\Delta\delta_{H\text{-}9}$ = 0.13, $\Delta\delta_{H\text{-}9'}$ = 0.06 in **19**). These results did not match the corresponding data of compound **16** (type VI). The *cis* relative configurations of H-7′/H-8′ in **18** and **19** were assigned based on the magnitude of the coupling constants ($J_{H\text{-}7',8'}$ = 7.8 Hz), despite the fact that the coupling constants are not indicative of

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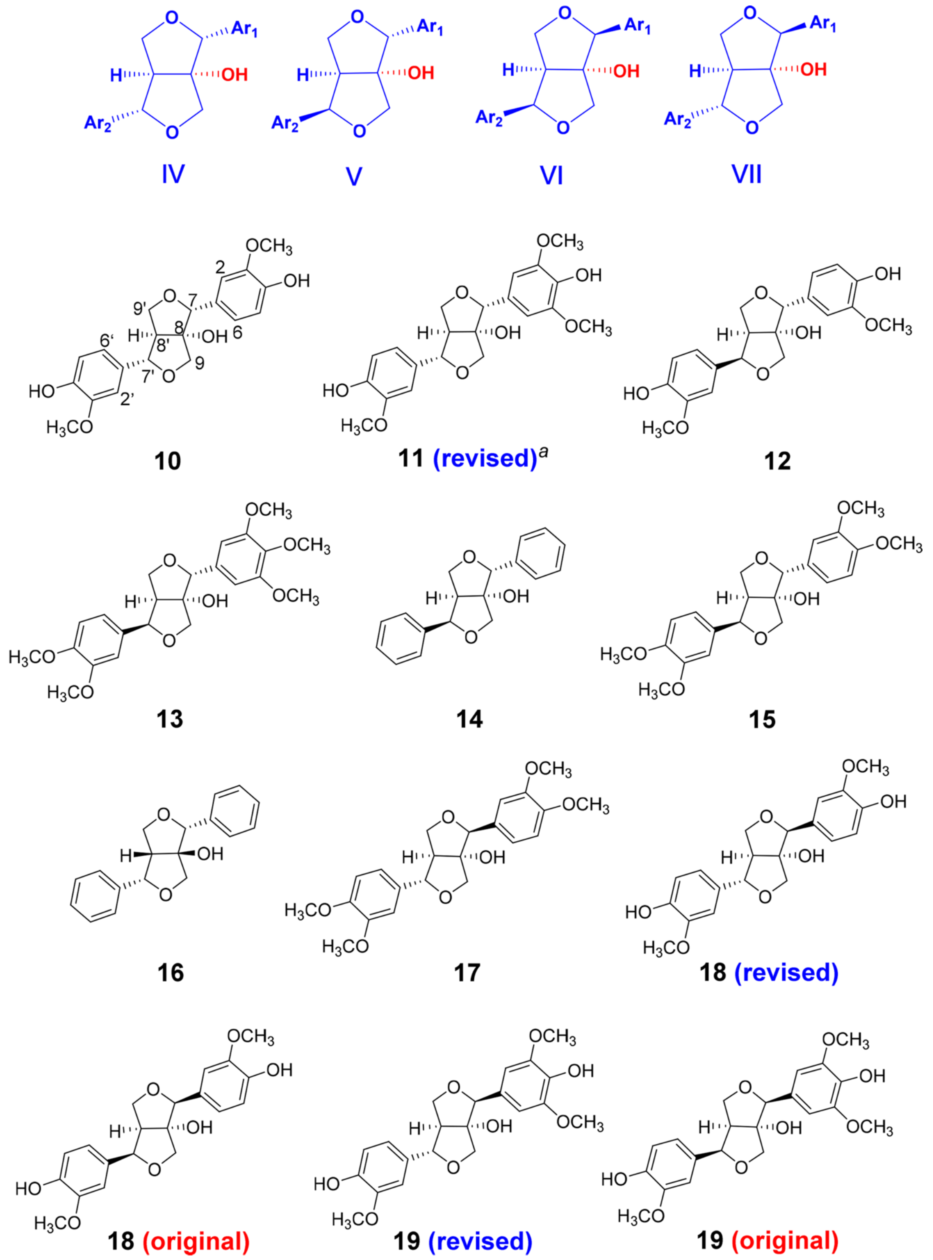

Figure 2. Structures of 8-OH furofuran lignans. [a]The hydroxy group of **11** was moved from C-5′ to C-4′ according to ref 21.

the configurations of the furofuran lignans.[9,13] Thus, compounds **18** and **19** should have the same relative configurations as **17**. The relative configurations of H-7′/H-8′ of **18** and **19** should, thus, be revised as shown (Figure 2). Similarly, the expected chemical shift differences were observed in compounds **11**, **13**, **14**, and **15** (Table S10, Supporting Information). Thus, the relative configurations of the 8-OH furofuran lignans may be confidently assigned using the values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$.

Considering that deuterated solvents have a major impact on the chemical shifts of methylene protons, the NMR spectra of compounds **1**, **4**, **10**, and **12** were recorded in different solvents, namely, DMSO-d_6, methanol-d_4, and $CDCl_3$ (Figure 3). Although the chemical shifts of H_2-9 and H_2-9′ varied in different deuterated solvents, the values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ in these solvents fluctuated only slightly and did not impact the identification of the relative configurations based on the values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ (Table S8, Supporting Information).

Except for the aforementioned aglycones, seven plant-derived 8-H and 8-OH furofuran lignan glucosides, **A**−**G**,[4,10,25−28] were also studied (Figure S1, Supporting Information). Their ^1H NMR spectra were recorded in DMSO-d_6 and methanol-d_4. The values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ of these glucosides also obeyed the rule (Table S9, Supporting Information). Other reported 8-H and 8-OH furofuran lignan glucosides displayed the same trend.[19,30]

The values of $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ of the 8-H furofuran lignans are shown in Figure 4. The 7-H/8-H *trans*, 7′-H/8′-H *trans* compounds showed two medium values ($0.25 < \Delta\delta < 0.40$); the 7-H/8-H *trans*, 7′-H/8′-H *cis* compounds had a large ($\Delta\delta > 0.40$) and a medium value; and the 7-H/8-H *cis*, 7′-H/8′-H *cis* compounds showed two small values ($\Delta\delta < 0.25$). The $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ values of these three types of compounds were

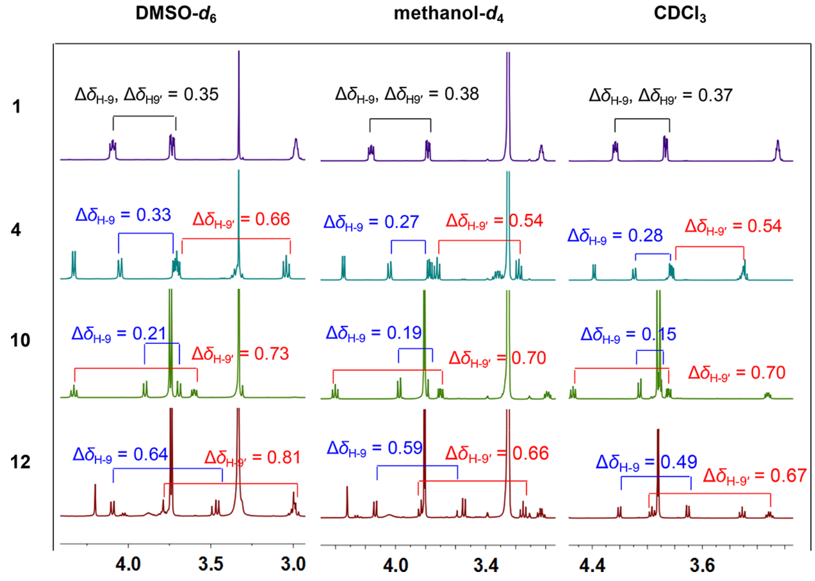

Figure 3. Differences in the chemical shifts of H-9 and H-9′ of compounds **1**, **4**, **10**, and **12** in different deuterated solvents.

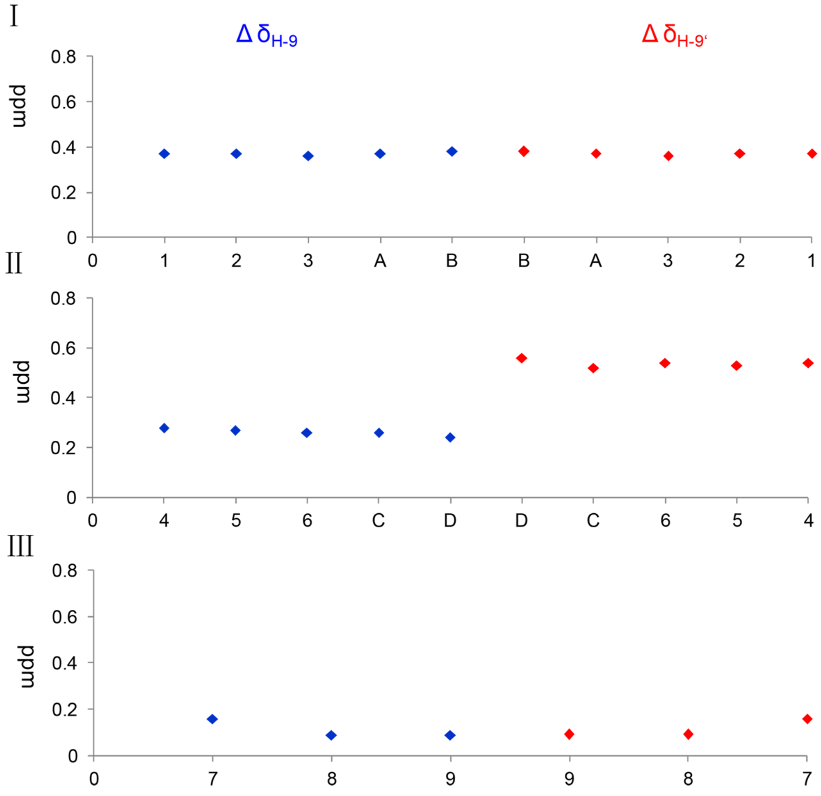

Figure 4. $\Delta\delta_{H-9}$ and $\Delta\delta_{H-9'}$ values for the 8-H furofuran lignans. The NMR spectra of compounds **1**−**9** were recorded in $CDCl_3$. The NMR spectra of compounds **A**−**D** were recorded in methanol-d_4.

significantly different and may be used to define the relative configurations. The values of $\Delta\delta_{H-9}$ and $\Delta\delta_{H-9'}$ of the 8-OH-type furofuran lignans are shown in Figure 5. The results showed that 7-H/8-OH *trans*, 7′-H/8′-H *trans* compounds had a small and a large value; the 7-H/8-OH *trans*, 7′-H/8′-H *cis* compounds showed two large values; the 7-H/8-OH *cis*, 7′-H/8′-H *cis* compounds had a large and a small value; and the 7-H/8-OH *cis*, 7′-H/8′-H *trans* compounds showed two small values. Thus, the values of $\Delta\delta_{H-9}$ and $\Delta\delta_{H-9'}$ of 8-H or 8-OH furofuran lignans could be used to assign the relative configurations of C-7/C-8 and C-7′/C-8′.

Based on the ^{1}H NMR data of the 25 furofuran lignans, a relationship between the chemical shift differences ($\Delta\delta_{H-9}$ and $\Delta\delta_{H-9'}$) and their corresponding relative configurations may be summarized as follows:

(1) For the 8-H-type furofuran lignans (Figure 4):
  type I (7-H/8-H *trans*, 7′-H/8′-H *trans*): $\Delta\delta_{H-9}$ and $\Delta\delta_{H-9'}$ = 0.30−0.40

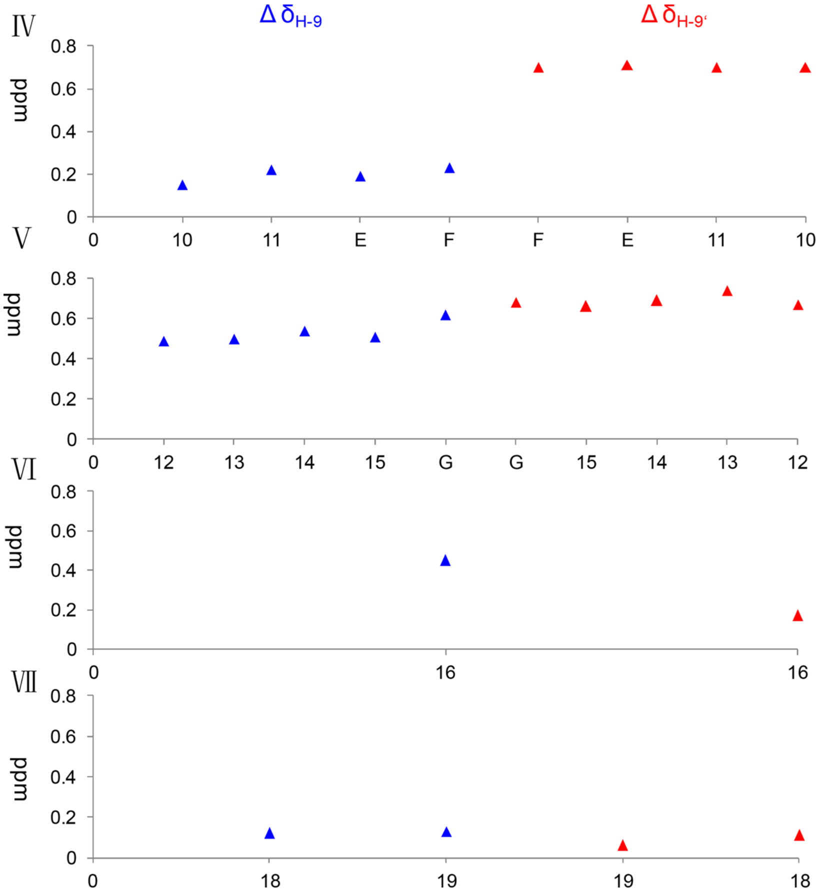

Figure 5. $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ values of 8-OH furofuran lignans. The NMR spectra of compounds **10**−**16** were recorded in $CDCl_3$. The NMR spectra of compounds **18**, **19**, and **E**−**G** were recorded in methanol-d_4.

type II (7-H/8-H *trans*, 7′-H/8′-H *cis*): $\Delta\delta_{H\text{-}9} = 0.205–0.36$, $\Delta\delta_{H\text{-}9'} > 0.50$

type III (7-H/8-H *cis*, 7′-H/8′-H *cis*): $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'} < 0.20$

(2) For the 8-OH type furofuran lignans (Figure 5):

type IV (7-H/8-OH *trans*, 7′-H/8′-H *trans*): $\Delta\delta_{H\text{-}9} < 0.25$, $\Delta\delta_{H\text{-}9'} > 0.65$

type V (7-H/8-OH *trans*, 7′-H/8′-H *cis*): $\Delta\delta_{H\text{-}9} > 0.45$, $\Delta\delta_{H\text{-}9'} > 0.65$

type VI (7-H/8-OH *cis*, 7′-H/8′-H *cis*): $\Delta\delta_{H\text{-}9} \approx 0.45$, $\Delta\delta_{H\text{-}9'} \approx 0.15$

type VII (7-H/8-OH *cis*, 7′-H/8′-H *trans*): $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'} < 0.20$

The common feature of the naturally occurring 8-H- and 8-OH-type furofuran lignans is that they all have a 7,9′:7′,9-diepoxy moiety bearing two aromatic rings. Generally, there are always substituents, including hydroxy, methoxy, methylenedioxy, monosaccharide, and disaccharide groups, at C-3, C-4, and/or C-5 of the aromatic rings.[29−35] Because these substituents are far away from the H_2-9 and H_2-9′ positions, they have little effect on the chemical shift differences ($\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$). However, when the substituents are located at C-2 or C-6 of the aromatic rings, the rules should be applied with care because the dominant conformers of the bicycle of such furofuran lignans may be altered. For instance, the values of $\Delta\delta_{H\text{-}9}$ (0.48) and $\Delta\delta_{H\text{-}9'}$ (0.52) of 6-epiterminaloside K were highly different from those of type II.[36]

■ EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured with a JASCO P-2000 polarimeter (JASCO, Easton, MD, USA). UV and IR spectra were measured on a JASCO V650 spectrometer and a Nicolet 5700 spectrometer (Thermo Scientific, Waltham, MA, USA), respectively. NMR spectra were recorded by a Bruker 500 MHz NMR spectrometer (Bruker-Biospin, Billerica, MA, USA), and the values are given in ppm. ESIMS data were acquired on an Agilent 1100 series LC/MSD ion trap mass spectrometer. Preparative HPLC was performed on a Shimadzu LC-10AT equipped with an SPD-10A detector (Shimadzu Corp., Tokyo, Japan) and a YMC-Pack ODS-A column (250 mm × 20 mm, 5 μm; YMC Corp., Kyoto, Japan). Column chromatography was performed on Sephadex LH-20 (Pharmacia Fine Chemicals, Uppsala, Sweden) and macroporous resin (Diaion HP-20, Mitsubishi Chemical Corp., Tokyo, Japan).

Plant Material. The fruits of *Forsythia suspensa* were collected in December 2011 from Yuncheng City of Shanxi Province, People's Republic of China. The plant material was identified by Lin Ma (Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences). A voucher specimen numbered ID-S-2597 was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Chinese Academy of Medical Sciences.

Extraction and Isolation. The dried powder of fruits of *F. suspensa* (90 kg) was extracted with 75% $EtOH–H_2O$ three times under reflux and filtered to produce a crude extract (12.6 kg). The extract was suspended in water (12 L) and successively extracted by petroleum ether, EtoAc, and *n*-BuOH, respectively. The *n*-BuOH fraction (4 kg) was suspended in water (40 L) to obtain an aqueous layer. The layer was concentrated to yield a water-soluble portion (1.5 kg), which was chromatographed on macroporous adsorption resin

(HP-20) using a mixture of EtOH−H_2O (0, 15, 30, 50, and 95%) to afford five fractions.

The 30% fraction (460 g) was subjected to a Sephadex LH-20 column and eluted with MeOH−H_2O in a mixture gradient (10−60%) to give 111 fractions (1−111). Fraction 50 was purified by reversed-phase preparative HPLC with 30% MeOH−H_2O to yield **A** (20 mg) and **E** (8 mg). Fraction 62 was purified by reversed-phase preparative HPLC with 40% MeOH−H_2O to give **G** (28 mg). The 50% fraction (370 g) was chromatographed over macroporous adsorption resin (HP-20) by a mixture of MeOH−H_2O (0, 15, 30, 40, 50, and 95%) to afford six fractions (I−VI). Fraction IV (175g) was separated by a Sephadex LH-20 column and eluted with MeOH−H_2O in a mixture gradient (20−60%) to obtain 223 fractions (1−223). Fractions 89−96 were purified using reversed-phase preparative HPLC with 45% MeOH−H_2O to obtain **B** (37 mg), **C** (232 mg), and **D** (13 mg). Fraction 204 was purified using reversed-phase preparative HPLC with 45% MeOH−H_2O to yield **2** (7 mg) and **5** (16 mg).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00044.

Additional figures and tables (PDF)

NMR and MS spectra for compounds **1**, **2**, **4**, **5**, **10**, **12**, **A−E**, and **G**; ECD spectra for compounds **2**, **5**, **10**, and **12** (PDF)

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Notes

The authors declare no competing financial interest.

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