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Complete NMR data of methoxylated *cis*- and *trans*-stilbenes as well as 1,2-diphenylethanes

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Resveratrol is a polyphenol isolated from many natural sources including grapes, mulberries, eucalyptus, spruce, lilies, and peanuts. The hydroxyl groups in polyphenols can be substituted with various functional groups, allowing production of multiple derivatives. NMR spectroscopy is used to identify new derivatives. Since the complete NMR data of the known derivatives can be useful for identification of the newly isolated derivatives, here, we report the synthesis of 14 methoxylated stilbenes and four 1,2-diphenylethanes and their NMR data.

Keywords: ^{1}H NMR; ^{13}C NMR; 2D NMR; flavonoids; stilbenes

Introduction

Polyphenols such as stilbenes (C6–C2–C6) are classified based on their carbon skeleton. Resveratrol (*trans*-3,5,4′-trihydroxystilbene), a stilbene found in many natural sources, including grapes, mulberries, eucalyptus, spruce, lilies, and peanuts,[1] is produced by plants as a defense mechanism. In humans, it acts as a treatment for cardiovascular diseases and as an anti-oxidative and anticancer agent.[2] After the discovery of its target proteins, research into resveratrol derivatives gained considerable interest.[3] However, their application is limited because of poor oral bioavailability, which results in rapid excretion from the body. Methoxylation can overcome low bioavailability and increase metabolic stability.[4] In addition, because small structural changes can cause a large change in biological activity, various derivatives are being prepared still.[5]

The complete NMR data of the known derivatives can be useful for identification of the newly isolated derivatives. Therefore, we report the synthesis of 14 methoxylated stilbenes and four 1,2-diphenylethanes and their complete NMR data.

Experimental

Synthesis

All the methoxylated stilbene and 1,2-diphenylethane derivatives (**1–18**) were synthesized as shown in Scheme 1. 3,5-Dimethoxybenzaldehyde (**I**) was reduced to 3,5-dimethoxybenzylalcohol (**II**), which was chlorinated to 3,5-dimethoxybenzylchloride (**III**) as described in the literature.[6] 3,5-Dimethoxybenzylchloride (**III**) was treated with triphenylphosphine to produce phosphonium salt (**IV**), which was used in the Wittig reaction along with methoxybenzaldehydes under basic conditions to produce a mixture of *cis* and *trans* isomers of stilbene derivatives (**V**). The *cis* and *trans* isomers were separated by flash column chromatography. The mixture of *cis* and *trans* isomers (**V**) was hydrogenated using a palladium catalyst to produce the reduced products (**VI**).

NMR spectra

All synthetic derivatives were dissolved in $CDCl_3$. Their concentrations were adjusted to approximately 50 mM, and they were transferred to a 5-mm NMR tube. All NMR data were collected on a Bruker Avance 400 spectrometer system (9.4 T; Bruker, Karlsruhe, Germany) at a temperature of 298 K. For the ^{1}H NMR experiment, the relaxation delay and 90° pulse were 1 s and 10.2 μs, respectively. For the ^{13}C NMR experiments, the relaxation delay and 90° pulse were 3 s and 10.3 μs, respectively. Two-dimensional experiments, such as COSY, TOCSY, HMQC, and HMBC, were performed by acquiring 2048 data points for t_2 and 256 data points for t_1. The long-range coupling time for HMBC was 70 ms. Prior to Fourier transformation, zero-filling of 2 K and the sine-squared bell window function were applied using XWin-NMR (Bruker).[7] Analysis of the NMR data was carried out using SPARKY.[8]

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Table 1. ^{1}H NMR chemical shifts of the methoxylated stilbene and 1,2-diphenylethane derivatives **1–18** (ppm) in $CDCl_3$ and values in parentheses are $^{1}H,^{1}H$ coupling constants *J* (in Hz)[a]

Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
2	6.47 (d, 2.2)	6.65 (d, 2.2)	6.39 (d, 2.3)	6.66 (d, 2.2)	6.43 (d, 2.3)	6.70 (d, 2.2)	6.48 (d, 2.3)	6.69 (d, 2.3)	6.47 (d, 2.3)
4	6.34 (t, 2.2)	6.38 (d, 2.2)	6.27 (t, 2.3)	6.37 (t, 2.2)	6.33 (t, 2.3)	6.40 (t, 2.2)	6.35 (t, 2.3)	6.42 (t, 2.3)	6.36 (t, 2.3)
6	6.47 (d, 2.2)	6.65 (d, 2.2)	6.39 (d, 2.3)	6.66 (d, 2.2)	6.43 (d, 2.3)	6.70 (d, 2.2)	6.48 (d, 2.3)	6.69 (d, 2.3)	6.47 (d, 2.3)
7	6.51 (d, 12.2)	6.88 (d, 16.1)	6.49 (d, 12.2)	6.95 (d, 16.5)	6.61 (d, 12.3)	7.06 (d, 16.3)	6.47 (d, 12.2)	7.07 (d, 16.3)	6.61 (d, 12.3)
8	6.42 (d, 12.2)	7.02 (d, 16.1)	6.61 (d, 12.2)	7.30 (d, 16.5)	6.77 (d, 12.3)	7.43 (d, 16.3)	6.55 (d, 12.2)	6.93 (d, 16.3)	6.56 (d, 12.3)
2′	7.15 (d, 8.5)	7.38 (d, 8.6)	–	–	–	–	7.24 (d, 8.7)	7.46 (d, 8.7)	6.87 (t, 2.5)
3′	6.78 (d, 8.5)	6.87 (d, 8.6)	–	–	–	–	6.79 (d, 8.7)	6.91 (d, 8.7)	–
4′	–	–	–	–	6.82 (dd, 1.8, 11.3)	6.84 (dd, 1.3, 8.0)	–	–	6.77 (dd, 2.5, 7.9)
5′	6.78 (d, 8.5)	6.87 (d, 8.6)	6.47 (d, 8.7)	6.69 (d, 8.8)	6.90 (t, 7.8)	7.05 (d, 8.0)	6.79 (d, 8.7)	6.91 (d, 8.7)	7.18 (t, 7.9)
6′	7.15 (d, 8.5)	7.38 (d, 8.6)	6.89 (d, 8.7)	7.29 (d, 8.8)	6.84 (dd, 1.8, 11.3)	7.23 (dd, 1.3, 8.0)	7.24 (d, 8.7)	7.46 (d, 8.7)	6.90 (d, 7.9)
3-OMe	3.66 (s)	3.83 (s)	3.62 (s)	3.82 (s)	3.66 (s)	3.84 (s)	3.79 (s)	3.83 (s)	3.66 (s)
5-OMe	3.66 (s)	3.83 (s)	3.62 (s)	3.82 (s)	3.66 (s)	3.84 (s)	3.79 (s)	3.83 (s)	3.66 (s)
2′-OMe	–	–	3.86 (s)	3.89 (s)	3.87 (s)	3.85 (s)	–	–	–
3′-OMe	–	–	3.86 (s)	3.88 (s)	3.89 (s)	3.88 (s)	–	–	3.69 (s)
4′-OH	4.92 (s)	5.02 (s)	–	–	–	–	–	–	–
4′-OMe	–	–	3.79 (s)	3.87 (s)	–	–	3.69 (s)	3.81 (s)	–
5′-OMe	–	–	–	–	–	–	–	–	–

Position	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
2	6.67 (d, 2.2)	6.43 (d, 2.3)	6.69 (d, 2.3)	6.48 (d, 2.3)	6.68 (d, 2.3)	6.34 (d, 2.2)	6.36 (d, 2.3)	6.43 (d, 2.3)	6.35 (d, 2.4)
4	6.40 (t, 2.2)	6.31 (t, 2.3)	6.38 (t, 2.3)	6.35 (t, 2.3)	6.42 (t, 2.3)	6.31 (t, 2.2)	6.33 (t, 2.3)	6.37 (t, 2.3)	6.31 (t, 2.4)
6	6.67 (d, 2.2)	6.43 (d, 2.3)	6.69 (d, 2.3)	6.48 (d, 2.3)	6.68 (d, 2.3)	6.34 (d, 2.2)	6.36 (d, 2.3)	6.43 (d, 2.3)	6.35 (d, 2.4)
7	7.06 (d, 16.4)	6.58 (d, 12.2)	7.04 (d, 16.4)	6.56 (s)	7.03 (s)	2.84 (m)	2.88 (m)	2.89 (m)	2.84 (s)
8	7.01 (d, 16.4)	6.73 (d, 12.2)	7.45 (d, 16.4)	6.56 (s)	7.03 (s)	2.84 (m)	2.89 (m)	2.94 (m)	2.84 (s)
2′	7.04 (d, 2.6)	–	–	6.48 (d, 2.3)	6.68 (d, 2.3)	7.10 (d, 8.5)	6.76 (m)	–	6.35 (d, 2.4)
3′	–	6.89 (dd, 0.8, 7.8)	6.89 (dd, 0.7, 7.8)	–	–	6.84 (d, 8.5)	–	6.90 (dd, 1.0, 7.5)	–
4′	6.82 (dd, 2.6, 8.1)	7.21 (dt, 1.7, 7.8)	7.24 (dt, 1.7, 7.8)	6.35 (t, 2.3)	6.42 (t, 2.3)	–	6.80 (d, 7.5)	7.23 (dt, 1.7, 7.5)	6.31 (t, 2.4)
5′	7.27 (t, 8.1)	6.80 (dt, 0.8, 7.8)	6.96 (dt, 0.7, 7.8)	–	–	6.84 (d, 8.5)	7.21 (d, 7.5)	6.92 (dt, 1.0, 7.5)	–
6′	7.10 (m)	7.25 (dd, 1.7, 7.8)	7.58 (dd, 1.7, 7.8)	6.48 (d, 2.3)	6.68 (d, 2.3)	7.10 (d, 8.5)	6.74 (m)	7.15 (dd, 1.7, 7.5)	6.35 (d, 2.4)
3-OMe	3.82 (s)	3.62 (s)	3.82 (s)	3.69 (s)	3.85 (s)	3.76 (s)	3.76 (s)	3.80 (s)	3.76 (s)
5-OMe	3.82 (s)	3.62 (s)	3.82 (s)	3.69 (s)	3.85 (s)	3.76 (s)	3.76 (s)	3.80 (s)	3.76 (s)
2′-OMe	–	3.83 (s)	3.88 (s)	–	–	–	–	3.86 (s)	–
3′-OMe	3.84 (s)	–	–	3.69 (s)	3.85 (s)	–	3.78 (s)	–	3.76 (s)
4′-OH	–	–	–	–	–	–	–	–	–
4′-OMe	–	–	–	–	–	3.78 (s)	–	–	–
5′-OMe	–	–	–	3.69 (s)	3.85 (s)	–	–	–	3.76 (s)

[a] Signal multiplicities: s, singlet; d, doublet; t, triplet.

Results and Discussion

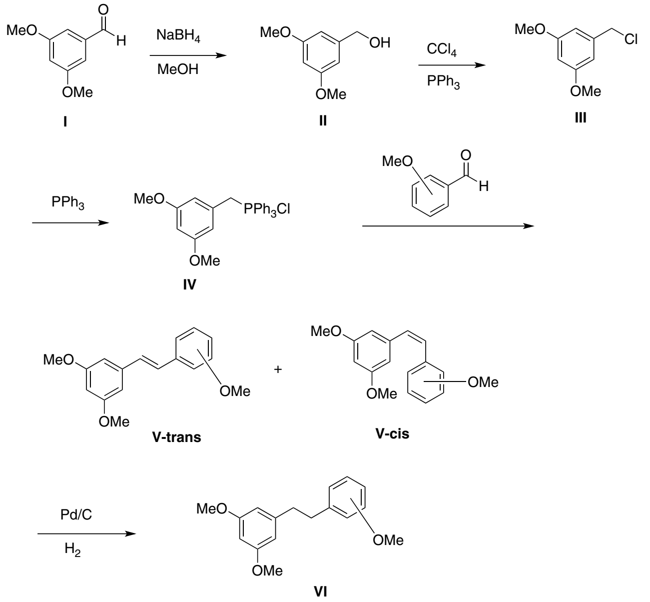
The structures and nomenclature of the methoxylated stilbene and 1,2-diphenylethane derivatives (**1–18**) are shown in Fig. 1. Among the 18 compounds, **3**, **4**, and **5** are novel. The ^{13}C NMR spectrum for **3** had 16 peaks because of its symmetrical A ring. The carbon atoms were identified using DEPT experiments. Among the four quaternary carbons between $\delta = 55$ and 65 ppm, the ^{13}C peak at $\delta = 55.4$ ppm was assigned to 3-OMe/5-OMe of A-ring because of its double intensity. C-3/C-5 and C-2/C6 were assigned in the same manner. H-2/H-6 were identified using HMQC data ($\delta = 6.39$ ppm). The long-range coupling between the ^{1}H peak at $\delta = 6.39$ ppm and the ^{13}C peak at $\delta = 99.8$ ppm observed in the HMBC spectrum indicated that the ^{13}C peak was C-4. Two ^{13}C peaks at $\delta = 126.0$ and 130.0 ppm were attached to two ^{1}H peaks at $\delta = 6.61$ and 6.49 ppm, respectively, and they were assigned to the carbons of the double bond, C-7 or C-8. HMBC data showed that the ^{13}C peak at $\delta = 130.0$ ppm was long-range coupled to H-2/H-6; thus, it was identified as C-7. The ^{13}C peak at $\delta = 139.5$ ppm showed long-range coupling with H-8 at $\delta = 6.61$ ppm; thus, it was identified as C-1. In the same manner, the ^{1}H peak at $\delta = 6.89$ ppm was identified as H-6′ of the B-ring because it was long-range coupled to C-8. Based on the interpretation of the COSY data, the ^{1}H peak at

Table 2. ^{13}C NMR chemical shifts of methoxylated stilbene and 1,2-diphenylethane derivatives **1**–**18** (ppm) in $CDCl_3$

Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	139.8	140.0	139.5	140.2	139.0	139.9	139.7	139.8	139.3
2	106.9	104.6	107.0	104.7	107.1	105.0	106.9	104.4	107.0
3	160.9	161.2	160.7	161.1	160.6	161.2	160.8	161.1	160.8
4	99.9	99.9	99.8	99.8	99.9	100.1	99.9	99.7	100.2
5	160.9	161.2	160.7	161.1	160.6	161.2	160.8	161.1	160.8
6	106.9	104.6	107.0	104.7	107.1	105.0	106.9	104.4	107.0
7	128.5	126.6	130.0	128.1	130.9	130.1	128.9	128.8	130.8
8	130.6	129.1	126.0	124.5	126.3	123.8	130.4	126.6	130.7
1′	129.1	130.0	124.3	123.7	131.9	131.6	129.8	130.0	138.8
2′	130.5	128.2	152.2	152.0	153.0	147.3	130.5	127.9	114.2
3′	115.4	116.0	142.4	142.6	147.4	153.3	113.8	114.2	159.7
4′	156.0	156.0	153.3	153.6	111.6	111.7	159.0	159.5	113.5
5′	115.4	116.0	107.3	108.0	123.7	124.3	113.8	114.2	129.4
6′	130.5	128.2	124.9	121.0	122.4	118.2	130.5	127.9	121.8
3-OMe	55.4	55.6	55.4	55.5	55.3	55.6	55.4	55.4	55.4
5-OMe	55.4	55.6	55.4	55.5	55.3	55.6	55.4	55.4	55.4
2′-OMe	–	–	61.3	61.5	60.9	61.3	–	–	–
3′-OMe	–	–	61.2	61.1	55.9	56.1	–	–	55.3
4′-OMe	–	–	56.2	56.2	–	–	55.4	55.3	–
5′-OMe	–	–	–	–	–	–	–	–	–
					δ of ^{13}C				
Position	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	139.5	139.2	140.2	139.1	139.3	144.5	144.3	145.0	144.3
2	104.8	106.8	104.8	106.9	104.8	106.7	106.6	106.7	106.7
3	161.2	160.2	161.1	160.6	161.2	160.9	160.9	160.8	161.0
4	100.3	99.9	100.0	100.0	100.3	98.1	98.1	98.0	98.2
5	161.2	160.2	161.1	160.6	161.2	160.9	160.9	160.8	161.0
6	104.8	106.8	104.8	106.9	104.8	106.7	106.6	106.7	106.7
7	129.9	130.3	129.3	130.7	129.4	37.0	37.9	36.6	38.2
8	129.3	126.5	124.2	130.7	129.4	38.7	38.2	32.4	38.2
1′	138.8	126.2	126.4	139.1	139.3	134.0	143.5	130.3	144.3
2′	113.7	157.6	157.21	106.9	104.8	129.5	114.5	157.6	106.7
3′	160.1	110.7	111.1	160.6	161.2	113.9	159.8	110.4	161.0
4′	112.0	128.8	129.0	100.0	100.3	158.1	121.0	127.3	98.2
5′	129.2	120.3	120.9	160.6	161.2	113.9	129.4	120.5	161.0
6′	119.5	130.4	126.7	106.9	104.8	129.5	111.4	130.0	106.7
3-OMe	55.6	55.2	55.6	55.3	55.6	55.4	55.3	55.3	55.5
5-OMe	55.6	55.2	55.6	55.3	55.6	55.4	55.3	55.3	55.5
2′-OMe	–	55.6	55.7	–	–	–	–	55.4	–
3′-OMe	55.5	–	–	55.3	55.6	–	55.2	–	55.5
4′-OMe	–	–	–	–	–	55.4	–	–	–
5′-OMe	–	–	–	55.3	55.6	–	–	–	55.5

$\delta = 6.47$ ppm was H-5′. The long-range coupling between the ^{13}C peak at $\delta = 124.3$ ppm and H-7 observed in HMBC identified the C-1′ carbon. Because the ^{13}C peak at $\delta = 152.2$ ppm was long-range coupled to H-8 and H-6′, it was assigned to C-2′. Likewise, two ^{13}C peaks at $\delta = 142.4$ and 153.3 ppm showed two long-range couplings with H-5′ and H-6′, respectively, and they were identified as C-3′ and C-4′, respectively. Based on three long-range couplings observed in the HMBC spectrum, 2′-OMe, 3′-OMe, and 4′-OMe were identified. The coupling constant between H-7 and H-8 was 12.2 Hz; thus, this derivative had a *cis* configuration. The ^{1}H and ^{13}C chemical shifts for all 18 compounds were assigned completely, and their ^{1}H and ^{13}C NMR data are listed in Tables 1 and 2, respectively.

Among the 18 compounds, the ^{1}H NMR data of **1**, **2**, and **13**–**15** and the ^{1}H and ^{13}C NMR data of **7**–**12** and **16**–**18** had been previously reported, and their literature spectra agreed well with the NMR data in this study.[9–13] Here, we report the ^{1}H and ^{13}C NMR data of **3**–**6**, including the three novel compounds, and the ^{13}C NMR data of **1**, **2**, and **13**–**15**. In conclusion, the results in this study provide a useful tool for structural analysis of various methoxylated stilbene and 1,2-diphenylethane derivatives.



Scheme 1. Synthesis of methoxylated stilbene and 1,2-diphenylethane derivatives **1**–**18**.

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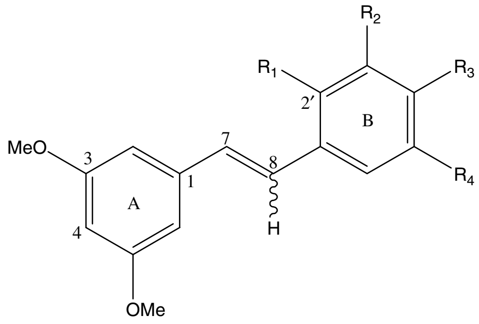

derivatives	C7- C8	configuration	R$_1$	R$_2$	R$_4$	R$_4$
1	Double	*cis*	H	H	OH	H
2	Double	*trans*	H	H	OH	H
3	Double	*cis*	OMe	OMe	OMe	H
4	Double	*trans*	OMe	OMe	OMe	H
5	Double	*cis*	OMe	OMe	H	H
6	Double	*trans*	OMe	OMe	H	H
7	Double	*cis*	H	H	OMe	H
8	Double	*trans*	H	H	OMe	H
9	Double	*cis*	H	OMe	H	H
10	Double	*trans*	H	OMe	H	H
11	Double	*cis*	OMe	H	H	H
12	Double	*trans*	OMe	H	H	H
13	Double	*cis*	H	OMe	H	OMe
14	Double	*trans*	H	OMe	H	OMe
15	Single	–	H	H	OMe	H
16	Single	–	H	OMe	H	H
17	Single	–	OMe	H	H	H
18	Single	–	H	OMe	H	OMe

Figure 1. Structures and nomenclature of methoxylated stilbene and 1,2-diphenylethane derivatives **1**–**18**.

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