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Studies on the Synthesis of a Natural Product-Piceatannol and its Analogs

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Abstract: Piceatannol, (E)-3, 3′, 4, 5′-tetrahydroxy stilbene, a natural polyhydroxy stilbene, possesses many biological activities, its synthesis has been reported. We designed another route of its synthesis, which can be controlled more easily. The synthetic product was characterized by elemental analysis, IR, MS and ^{1}H-NMR. Its analogs were synthesized by the similar method.

Keywords: Total synthesis, piceatannol, analogs.

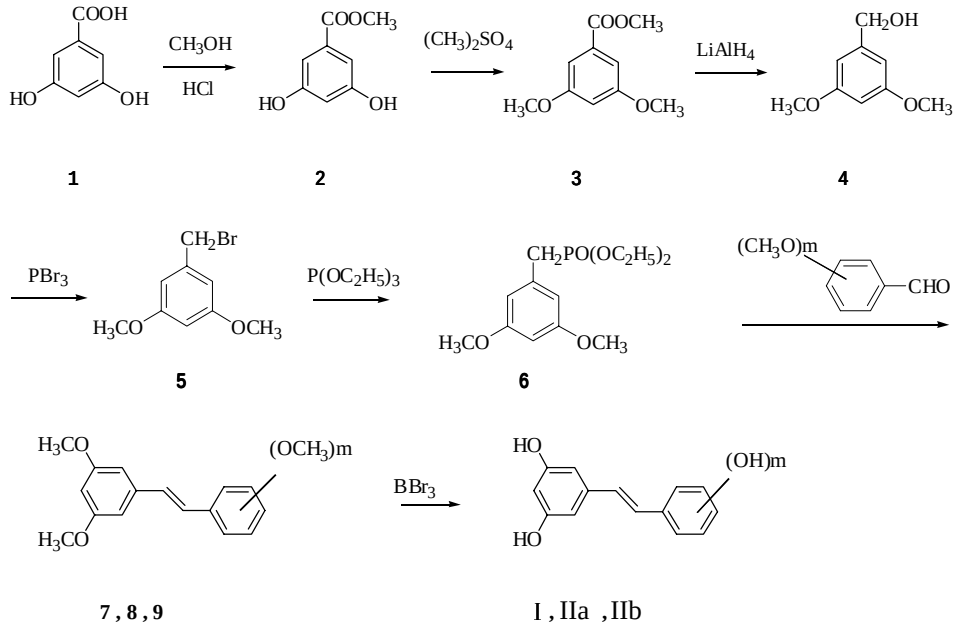
Piceatannol(Ⅰ), (E)-3, 3′, 4, 5′-tetrahydroxy stilbene, which was first isolated by F.E. King[1],is a natural polyhydroxy stilbene found in several traditional chinese herbs[2,3], it has been proved that piceatannol has many biological activities such as antimicrobial activity[4], protein tyrosine kinase inhibition[5] and so on. These polyhydroxy compounds are difficult to prepare, due to the polyphenolic groups are liable to oxidize in air. Several total synthesis methods of piceatannol have been reported[6,7,8]. In order to synthesize enough piceatannol and its analogs with the hydroxy groups locating in different positions of the benzene ring for biological evaluation, we developed another synthetic route, which was used in the synthesis of resveratrol in our early work[9]. In our synthetic strategy, methoxy groups were used to protect the hydroxy groups instead of benzyl groups which were usually used in the literature[10]. The methoxy protecting groups were easily removed by boron tribromide[11,12,13]. The synthetic route of piceatannol is shown in **Scheme 1**.

Starting from 3, 5-dihydroxybenzoic acid **1**, through 5 steps, we obtained compound **6** which was condensed with 3, 4-dimethoxy benzalaldehyde in THF/NaH using Wittig-Horner reaction to give the precursor **7**, (E)-3, 3′, 4, 5′-tetramethoxy stilbene. Finally, the methoxy groups in **7** were removed by BBr_3 in dichloromethane at room temperature under nitrogen. The target product I was purified by column chromatography and characterized by elemental analysis, IR, MS and ^{1}H-NMR. The spectral data were identical with the corresponding natural product according to the literature[8]. The total yields based on **1** is 26%.

For the purpose of seeking structure-activity relationship of piceatannol, we prepared its analogs. By a similar procedure, we have synthesized two polyhydroxyl stilbenes II**a** and II**b** as shown in **Scheme 1**. The total yields were 34% and 43% for

IIa, IIb, respectively. IIb is also a natural[1,6] product. Its activity has not been reported.

Scheme 1 Synthetic route of piceatannol and its analogs

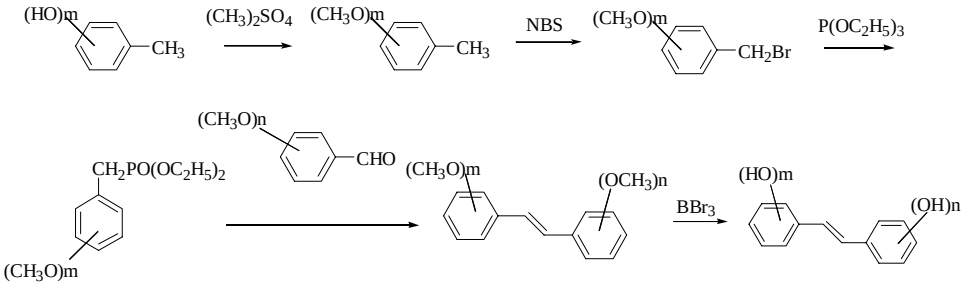


7	m=3, 4-OCH_3	I	m=3, 4-OH
8	m=3-OCH_3	IIa	m=3-OH
9	m=3, 4, 5-OCH_3	IIb	m=3, 4, 5-OH

Compounds IIc～IIf were synthesized as shown in **Scheme 2** .

Methylation of (*m*- or *p*-)methyl phenol with dimethyl sulfate and potassium carbonate in dry acetone, followed by bromination with NBS, gave the *p*(*m*)-methoxy benzyl bromide, which reacted with triethyl phosphite to afford diethyl [*p*(*m*)-methoxy benzyl] phosphonate(**10**, **11**) respectively. The phosphonate (**10**, **11**) were condensed with methoxy group substituted benzaldehyde by Wittig-Horner reaction in the presence of THF/NaH to gain corresponding precursor (**12**, **13**, **14**, **15**). Finally the protective methoxy groups were removed by similar method to give compound IIc, IId, IIe and IIf, which were purified by column chromatography.

Scheme 2 Synthetic route of analogs of piceatannol



10,11 **12,13,14,15** **IIc, IId, IIe, IIf**

10	m=4-OCH_3	**12**	m=4-OCH_3	n=3, 4-OCH_3	**IIc**	m=4-OH	n=3, 4-OH
11	m=3-OCH_3	**13**	m=3-OCH_3	n=3, 4-OCH_3	**IId**	m=3-OH	n=3, 4-OH
		14	m=3-OCH_3	n=3-OCH_3	**IIe**	m=3-OH	n=3-OH
		15	m=3-OCH_3	n=4-OCH_3	**IIf**	m=3-OH	n=4-OH

The biological evaluation of the target compounds(I, II**a~f**) are under going.

Acknowledgment

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14. For compound **7**, (E)-3,3′,4,5′-tetramethoxy stilbene , mp 65-67°C (lit.,[1] 68-69°C); ^{1}H-NMR (300MHz ,$CDCl_3$) δ ppm : 7.054 (brd, 1H, J=8.1Hz, H-6); 7.011 (s, 1H, H-2); 6.864 (d, 1H, J=8.1Hz, H-5); 6.660 (d, 2H, J=2.4Hz, H-2′,6′); 6.385 (t, 1H, J=2.4Hz, H-4′); 3.952, 3.908(s, each 3H, OCH_3-3,4); 3.835 (s,6H, OCH_3-3′,5′); 7.039, 6.904 each 1H(d,J=16.2Hz,H-α,β). For compound **I**,piceatannol, (E)-3,3′,4,5′-tetrahydroxy stilbene, mp 222°C dec. (lit.,[1] 229°C, dec); its ^{1}H-NMR, IR, MS data are identical with the literature[1,6,10].
15. For compound **IIa**, (E)-3,3′,5-trihydroxy stilbene, mp 237°C (dec); ^{1}H-NMR, (300MHz, DMSO-d_6) δ ppm: 7.125(t, 1H, J=8.1Hz, H-5′); 6.965(brd, 1H, J=8.1Hz, H-6′); 6.916(d, 1H, J=2.1Hz, H-2′); 6.652(dd, 1H, J=8.1,2.1Hz, H-4′); 6.404(d, 2H, J=2.1Hz, H-2,6); 6.141(t, 1H, J=2.1Hz, H-4); 6.909(s, 2H, H-α,β), 9.242,9.086(s, D_2O exchangeable, OH-3,5,3′). elemental analysis: $C_{14}H_{12}O_3$ •0.4H_2O calcd. C 71.47% H 5.48% Found: C 71.94% H 5.54% . MS: *m/z*

228(M^+, 100), 211, 181.

16. For compound **IIb**, (E)-3,3′,4,5,5′-pentahydroxy stilbene, mp 236°C dec (lit.,[1] 245°C, dec); its analytical data are identical with the literature[1,6].
17. For compound **IIc,** (E)-3,4,4′-trihydroxy stilbene, mp (carbonify); ^{1}H-NMR: (300MHz, DMSO-d_6) 7.316(d, 2H, J=8.7Hz, H-2′,6′); 6.910(d, 1H, J=2.1Hz, H-2); 6.775(dd, 1H, J=8.1,2.1Hz, H-6); 6.719(d, 2H, J=8.7Hz, H-3′,5′), 6.684(d, 1H, J=8.1Hz, H-5); 6.785(s, 2H, H-α,β); 9.305, 8.797, 8.698(s, D_2O exchangeable, OH). elemental analysis: $C_{14}H_{12}O_3$:calcd. C 73.67% H 5.30% . Found: C 74.01% H 5.33%. MS: *m/z* 228(M^+, 100), 211, 181.
18. For compound **IId**, (E)-3,3′,4-trihydroxy stilbene, mp 176-178°C ; ^{1}H-NMR: (300MHz, DMSO-d_6) 7.135(t, 1H, J=8.1Hz, H-5′); 6.965-6.885(m, 4H, H-2,2′,6′, one of H-α,β); 6.832(dd, 1H, J=8.4,1.8Hz, H-6), 6.706(d, 1H, J=8.4Hz,H-5), 6.614(dd, 1H, J=8.1,2.4Hz, H-4′), 6.799(d, 1H,J=16.2Hz ,one of H-α,β); 9.298, 9.037, 8.868(s, D_2O exchangeable, OH-3,4,3′). elemental analysis: $C_{14}H_{12}O_3$ $0.1H_2O$: calcd. C 73.10% H 5.34% Found: C 72.94% H 5.37%.
19. For compound **IIe**, (E)-3,3′-dihydroxy stilbene, mp 142-146°C; ^{1}H-NMR: (300MHz, DMSO-d_6) 7.145 (t, 2H, J=7.8Hz, H-5,5′); 7.116(brd, 2H, J=7.8Hz, H-6,6′); 6.941 (t, 2H, J=2.4Hz, H-2,2); 6.662(brdd, 2H, J=7.8,2.4Hz, H-4,4′); 7.043(s, 2H, H-α,β); 9.411(s, D_2O exchangeable, OH). MS: 212(M^+, 100), 195, 165.
20. For compound **IIf**, (E)-3,4′-dihydroxy stilbene, mp 202-208°C; ^{1}H-NMR: (300MHz, CD_3COCD_3-d_6), 7.432(d, 2H, J=8.4Hz, H-2′,6′); 7.152(t, 1H, J=7.8Hz, H-5); 7.006(brd, 1H, J=7.8Hz, H-6); 7.006(t, 1H, J=2.1Hz, H-2); 6.836(d, 2H, J=8.4Hz, H-3′,5′); 6.707(brdd, 1H, J=7.8,2.1Hz, H-4); 7.094, 6.960 each 1H(d, J=16.5Hz, H-α,β); 8.520, 8.339(s, D_2O exchangeable, OH-3,4′). elemental analysis:$C_{14}H_{12}O_2$: :calcd. C 79.23% H 5.70% Found: C 79.01% 5.66%.

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