A New Synthesis of Stilbene Natural Product Piceatannol

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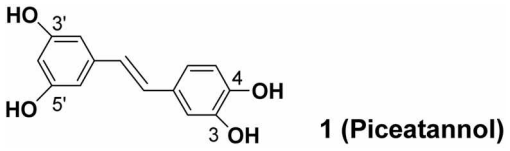
Hydroxylated (*E*)-stilbene natural products are widely present in nature and show a variety of biological activities including anti-inflamatory,[1] antioxidative,[2] lipid-lowering,[3] radical scavenging,[4] neuroprotection,[5] anticarcinogenic[6] and antiviral[7] activities. (*E*)-3,3',4,5'-tetrahydroxystilbene (piceatannol, **1**, Figure 1) was isolated from *Rheum undulatum* which has been widely used in China and Korea for the treatment of blood platelet aggregation.[8] It was reported that 0.3 g of pure piceatannol was isolated from 1 kg of dry root of *Rheum undulatum*.[9] The limited supply of piceatannol from nature has prevented the diverse characterization of its biological activities. Several syntheses of (*E*)-stilbene have been reported by using Wittig-Horner,[10] Heck[11] and Suzuki[12] coupling reactions. However, the polyhydroxy (*E*)-stilbenes are difficult to prepare due to oxidizing sensitivity of the polyphenolic groups, and due to inherent difficulties of controlling trans-selectivity. We report herein the new total synthesis of piceatannol (**1**) in 6 steps from vanillin by using Sonogashira coupling reaction.

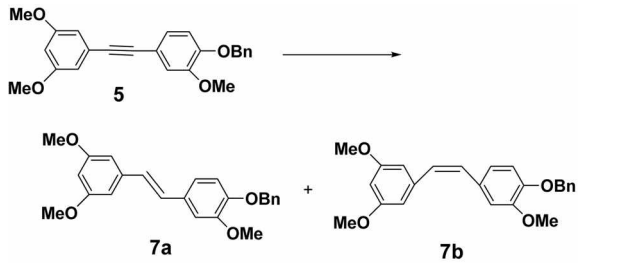
Vanillin (**2**) in acetone at reflux with benzyl bromide and potassium carbonate produced 95% yield of benzylated vanillin **3** which was then reacted with trimethylsilyl diazomethane and *n*-buthyllithium in THF at −78 °C to give ethynylbenzene **4** in 99% yield by Colvin rearrangement[13] (Scheme 1). Sonogashira coupling of **4** with 1-iodo-3,5-dimethoxybenzene by using $PdCl_2(PPh_3)_2$/CuI/Et_3N in DMF yielded **5** in 97% yield. Direct reduction of **5** to give (*E*)-stilbene produced no reaction (entries 1-6) or afforded only (*Z*)-stilbene **7b** in 80% yield by using Zn/HCl in acetonitrile (entry 7) as shown in Table 1. In order to produce (*E*)-stilbene, **5** was reacted with bromine at −78 °C and gave only the desired (*E*)-dibromostilbene **6** in 80% yield through the cyclic bromoniun intermediate (Scheme 2). Reductive debromination of **6** with Zn/KI/HCl in ethanol (entry 3) yielded 80% of (*E*)-stilbene **7a** as shown in Table 2. However, LAH and *n*-BuLi (entries 4 and 6) in reductive debromination reaction produced only the acethylene **5** back, and *t*-BuLi (entry 5) gave the 1:1 mixture of **5** and **7a**. Finally, dealkylation of **7a** by BBr_3 in methylene chloride gave piceatannol (**1**) in 50% yield. Polymethoxy aryl ether has been known to difficult for demethylation by using BBr_3 or other reagents probably due to susceptibility for oxidation of polyphenolic substances.[14]



1 (Piceatannol)

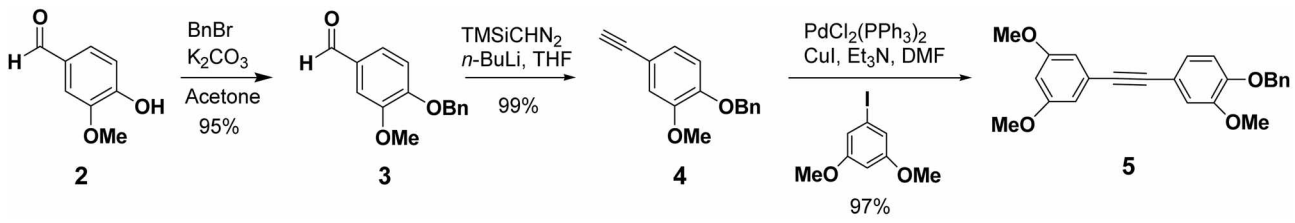
Figure 1. Chemical structure of piceatannol.

Table 1. Direct reduction of 1-benzyloxy-4-(3,5-dimethoxyphenyl)-ethynyl-2-methoxybenzene

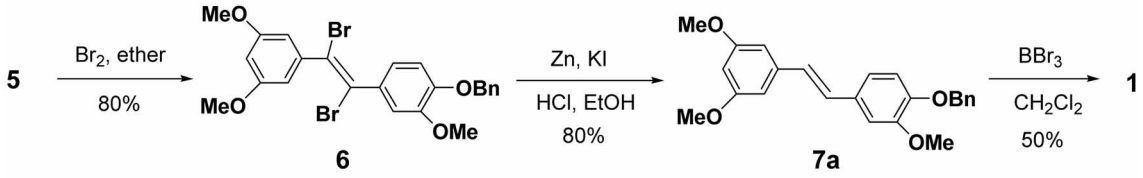


Entry	Reagent[a]	Solvent	Time (h)	Yield (%)[b] (**7a**:**7b**)
1	In	H_2O:EtOH(10:1)	48	-
2	$NaBH_3CN$	THF	48	-
3	Na/NH_3	Dioxane	48	-
4	LAH	THF	48	-
5	Zn	AcOH	48	-
6	Zn/HCl	THF	48	-
7	Zn/HCl	CH_3CN	48	80(0:100)

[a]All reflux conditions except entry 3 at room temperature. [b]Isolated and purified yield.

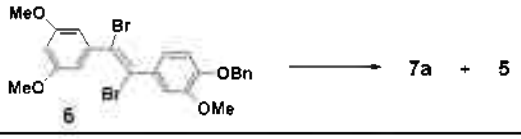


Scheme 1



Scheme 2

Table 2. Reductive debromination of (*E*)-1-benzyloxy-4-[1,2-dibromo-2-(3,5-dimethoxyphenyl)vinyl]-2- methoxybenzene



Entry	Reagent	Solvent	Time (h)	Yield (%)[a] (**7a**:**5**)
1	Zn/HCl	THF	24	–
2	Zn/HCl/KI	THF	24	–
3	Zn/HCl/KI	EtOH	24	80(100:0)
4	LAH	THF	1	60(0:100)
5	*t*-BuLi	THF	0.5	50(50:50)
6	*n*-BuLi	THF	1	36(0:100)

[a]Isolated and purified yield.

In conclusion, the 6 steps reaction procedure including benzylation, Covin rearrangement, Sonogashira coupling, bromination, reductive debromination and dealkylation gave piceatannol in 29% overall yield. This compound is now under investigation for its biological activities.

Experimental Section

All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR for ^{1}H and 75 MHz for ^{13}C, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Flash chromatography was carried out using silica gel Merck 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected.

4-Benzyloxy-3-methoxybenzaldehyde (3). To a solution of vanillin (**1**) (5.00 g, 32.9 mmol) in acetone (100 mL) under nitrogen atmosphere was added K_2CO_3 (13.6 g, 98.6 mmol) and stirred for 0.5 h at rt and refluxed for 1 h after addition of benzyl bromide (3.9 mL, 32.9 mmol). Solvent was removed by evaporation and the organic product was extracted with ethyl acetate, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:7) to give the white solid **3** (7.56 g, 95%). R_f 0.37 (EtOAc:Hexane = 1:3); mp 60-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (3H, s, OCH_3), 5.24 (2H, s, benzyl CH_2), 6.98 (1H, d, J = 8.4 Hz, 5-H), 7.34-7.42 (7H, m), 9.82 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.38 (OCH_3), 71.14 (benzyl CH_2), 109.47 (C2), 112.54 (C5), 126.85 (C6), 127.39, 128.41, 128.93, 131.35 (C1), 136.11, 150.01 (C3), 153.94 (C4), 191.03 (C=O).

1-Benzyloxy-4-ethynyl-2-methoxybenzene (4). To a solution of trimethylsilyldiazomethane (2 M solution in dichloromethane, 6 mL) in THF (45 mL) under nitrogen atmosphere was added *n*-butyllithium (1.6 M solution in hexane, 5.1 mL) at −78 °C and stirred for 0.5 h. Saturated NH_4Cl (30 mL) solution was added to this reaction bottle at rt and extracted with diethyl ether, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:7) to give the yellow solid **4** (2.90 g, 99%). R_f 0.63 (EtOAc:Hexane = 1:3); mp 80-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (1H, s, acetylene), 3.87 (3H, s, OCH_3), 5.15 (2H, s, benzyl CH_2), 6.79 (1H, br d, J = 8.1 Hz, 5-H), 7.00 (1H, br s, 3-H), 7.01 (1H, d, J = 8.1 Hz, 6-H), 7.32-7.39 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.30 (OCH_3), 71.13 (benzyl CH_2), 76.09 (acetylene CH), 84.03 (acetylene C), 113.65 (CH), 114.86 (C), 115.40 (CH), 125.54 (CH), 127.43 (x2), 128.18 (CH), 128.81 (x2), 136.81 (C), 149.12 (C), 149.33 (C).

1-Benzyloxy-4-(3,5-dimethoxyphenyl)ethynyl-2-methoxybenzene (5). The mixture of ethynylbenzene (**4**, 0.41 g, 1.7 mmol), 1-iodo-3,5-dimethoxybenzene (0.3 g, 1.1 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.02 g, 0.034 mmol), copper(I) iodide (0.015 g, 0.057 mmol), TEA (0.5 mL) in DMF under nitrogen atmosphere was stirred for 5 h at rt. The solvent was removed by evaporation and the organic product was extracted with CH_2Cl_2, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:2) to give the yellow solid **5** (0.41 g, 97%). R_f 0.45 (EtOAc:Hexane = 1:3); mp 86-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (6H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.17 (2H, s, benzyl CH_2), 6.43 (1H, t, J = 2.4 Hz, 4'-H), 6.66 (2H, d, J = 2.1 Hz, 2',6'-H), 6.83 (1H, d, J = 8.7 Hz, 6-H), 7.05 (2H, m, 3,5-H), 7.31-7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.76 (2 x OCH_3), 56.32 (OCH_3), 71.13 (benzyl CH_2), 88.30 (acetylene), 89.31 (acetylene), 101.84 (C4'), 109.40 (C2',6'), 113.69, 114.87, 115.87, 124.88, 125.02, 127.45 (x2), 128.17 (x2), 128.81 (x2), 136.84, 148.78, 149.31, 160.62 (x2).

(*E*)-1-Benzyloxy-4-[1,2-dibromo-2-(3,5-dimethoxyphenyl)vinyl]-2-methoxybenzene (6). To the solution of **5** (0.10 g, 0.27 mmol) in diethyl ether (5 mL) was added bromine (0.014 mL, 0.27 mmol) and stirred for 1 h at −78 °C. The reaction mixture was extracted with ethyl acetate, washed

with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:4) to give the yellow solid **6** (0.12 g, 80%). R_f 0.17 (EtOAc:Hexane = 1:3); mp 174-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (6H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.17 (2H, s, benzyl CH_2), 6.43 (1H, J = 2.1 Hz, 4'-H), 6.66 (2H, d, J = 2.4 Hz, 2',6'-H), 6.83 (1H, d, J = 8.4 Hz, 6-H), 7.05 (2H, m, 3,5-H), 7.33-7.41 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.09 (OCH_3), 56.55 (2 x OCH_3), 70.74 (benzyl CH_2), 96.72, 103.21, 112.31, 112.68, 115.81, 121.91, 122.08 (x2), 127.03 (x2), 127.74 (x2), 128.40 (x2), 131.54, 136.49, 142.22, 148.67, 148.77, 156.20.

(*E*)-3,3',5'-Trimethoxy-4-benzyloxystilbene (7a). To the solution of dibromostilbene **6** (0.30 g, 0.56 mmol) in EtOH (30 mL) was added zinc dust < 10 micron (1.73 g, 26.5 mmol), potassium iodide (0.63 g, 3.82 mmol), 4% HCl (1.5 mL) under nitrogen atmosphere and refluxed for 6 h at 80-90 °C. The solvent was removed by evaporation and the organic product was extracted with CH_2Cl_2, washed with brine, dried and filtered using Celite® 545. The solvent was removed by evaporation and the organic product was chromatographed (EtOAc:Hexane=1:7) to give the yellow solid **7a** (0.17 g, 80%). R_f 0.43 (EtOAc:Hexane = 1:3); mp 112-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.11 (2H, s, benzyl CH_2), 6.37 (2H, brd, J = 10.8 Hz, 5,6-H), 6.51 (1H, d, J = 17 Hz), 6.53 (1H, d, J = 17 Hz), 6.70 (3H, br s, 2',4',6'-H), 7.25-7.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.57 (2 x OCH_3), 56.00 (OCH_3), 71.14 (benzyl CH_2), 99.91, 106.86 (x2), 112.59, 113.70, 122.11, 127.42 (x2), 128.02 (x2), 128.72 (x2), 129.12, 130.46, 137.25, 139.66, 147.50, 149.14, 160.73 (x2).

Piceatannol (1). To the solution of alkoxystilbene **7** (0.10 g, 0.19 mmol) in CH_2Cl_2 (10 mL) was added boron tribromide (1.0 M solution in dichloromethane, 1.13 mL) at −20 °C under nitrogen atmosphere and stirred for 1 h. After the reaction mixture was stirred for 2 h at rt, the solvent was removed by evaporation and the organic product was extracted with ethyl acetate, washed with brine, dried and concentrated to give the solid. The solvent was removed by evaporation and the organic product was chromatographed (EtOAc:Hexane = 1:1) to give the pale yellow solid **1** (0.023 g, 50%). R_f 0.47 (diethyl ether); mp 228 °C dec.; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.31 (1H, t, J = 2.1 Hz, 4'-H), 6.57 (2H, d, J = 1.8 Hz, 2',6'-H), 6.82 (1H, d, J = 16.2 Hz, olefinic H), 6.83 (1H, d, J = 9.0 Hz, 5-H), 6.90 (1H, dd, J = 8.4, 1.8 Hz, 6-H), 6.95 (1H, d, J = 16.5 Hz, olefinic H), 7.10 (1H, d, J = 1.8 Hz, 2-H), 8.15 (4H, br s, OH); ^{13}C NMR (75 MHz, acetone-d_6) δ 102.12 (C4), 105.21 (C2',6'), 113.25 (C2), 115.71 (C5), 119.52 (C6), 126.23 (olefinic), 128.78 (olefinic), 130.05 (C1), 140.17 (C1'), 145.24 (C4), 145.27 (C3), 158.64 (C3', 5').

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References and Notes

1. Kimura, Y.; Okuda, H.; Arichi, S. *Biochim. Biophys. Acta* **1985**, *834*, 275.
2. Stivala, L. A.; Savio, M.; Carafoli, F.; Perucca, P.; Bianchi, L.; Maga, G.; Forti, L.; Pagoni, U. M.; Albini, A.; Prosperi, E.; Vannini, V. *J. Biol. Chem.* **2001**, *276*, 22586.
3. Frankel, E. N.; Waterhouse, A. L.; Kinsella, J. E. *Lancet* **1993**, *341*, 1103.
4. Rho, H. S.; Baek, H. S.; You, J. W.; Kim, S. J.; Kim, M.-K.; Kim, D. H.; Chang, I. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 837.
5. Gupta, Y. K.; Chaudhary, G.; Srivastava, A. K. *Pharmacology* **2002**, *65*, 170.
6. Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnworth, R. N.; Kinghorn, A. D.; Metha, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218.
7. Doherty, J. J.; Fu, M. M. H.; Stiffler, B. S.; Limperos, R. J.; Pokabla, C. M.; DeLucia, A. L. *Antiviral Res.* **1999**, *43*, 145.
8. Ko, S. K.; Lee, C. R.; Lee, H. S.; Kim, H.; Baek, K. H.; Tokuoka, K.; Chung, S. H. *Kor. J. Pharmacogn.* **2003**, *34*, 25.
9. Ko, S. K.; Lee, S. M.; Whang, W. K. *Arch. Pharm. Res.* **1999**, *22*, 401.
10. Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875.
11. Botella, L.; Najera, C. *Tetrahedron* **2004**, *60*, 5563.
12. Cho, C.-H.; Park, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 1159.
13. Colvin, E. W.; Hamill, B. J. *J. Chem. Soc. Perkin Trans. 1* **1977**, 869.
14. Drewes, S. E.; Fletcher, L. P. *J. Chem. Soc. Perkin Trans. 1* **1974**, 961.