

Efficient Synthesis of Natural Polyphenolic Stilbenes: Resveratrol, Piceatannol and Oxyresveratrol

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The practical synthesis of important natural polyphenolic stilbenes, including resveratrol, piceatannol and oxyresveratrol, through Perkin methodology is described. Starting from 3,5-dihydroxyacetophenone (1), the common intermediate 3,5-dimethoxyphenylacetic acid (3) can be obtained *via* methylation and Willgerodt–Kindler reaction. Perkin condensations between (3) and substituted phenylaldehydes 4 furnished *E*-2,3-diarylacrylic acids 5, followed by decarboxylation in Cu/quinoline giving stilbene intermediates 6 which bear the *Z*-configuration. Finally, through a simultaneous demethylation/isomerization process in $\text{AlI}_3/\text{CH}_3\text{CN}$ system, the target compounds 7a–c can be obtained respectively in good to high overall yields. The synthetic method proved to be more concise, *trans*-specific, mild, economical and commonly applicable.

Key words polyphenolic stilbene; Willgerodt–Kindler reaction; Perkin reaction; demethylation; isomerization

Natural *trans* polyphenolic stilbenes were known to have numerous remarkable biological properties including beneficial effects on patients with cancers, cardiovascular diseases, viral infections, diabetes, dementia, and central nervous system (CNS) disorders. Among them, resveratrol, piceatannol and oxyresveratrol are recognized to be the representatives of *trans*-polyphenolic stilbenes (Fig. 1).

Resveratrol (*trans*-3,4',5-trimethoxystilbene) is a phytoalexin isolated from more than 70 plant species such as grapes, peanuts, and berries.¹⁾ It is now commercially produced from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese medicine for centuries. The biological activity of resveratrol has been well documented in recent years through a number of physiological and pharmacological studies which indicate that resveratrol plays an important role in prevention of cancers,^{2–5)} heart diseases,⁶⁾ neurodegenerative diseases⁷⁾ and inflammations.⁸⁾ Moreover, the radical scavenging,⁹⁾ antiviral,¹⁰⁾ antioxidant,¹¹⁾ lipid modification¹²⁾ as well as platelet aggregation inhibition activities¹³⁾ associated with resveratrol have also been reported. Recently, resveratrol has been shown to extend lifespan of yeasts, *Caenorhabditis elegans* and *Drosophila melanogaster* through activation of sirtuins (SIRT-1, 2), a nicotinamide adenine dinucleotide (NAD) dependent histone deacetylase that has been shown to directly correlate with cellular longevity,¹⁴⁾ and to improve health and survival of mice on a high-calorie diet.¹⁵⁾

Piceatannol (*trans*-3,3',4',5-tetramethoxystilbene) is a tetrahydroxystilbene and a close analog of resveratrol with an additional aromatic hydroxyl group. It has been isolated from grapes together with resveratrol and several other traditional Chinese herbs.^{16,17)} Studies showed that piceatannol inhibits

several tyrosine kinases involved in cell proliferation.^{18–21)} The anti-tyrosinase activity of piceatannol ($\text{IC}_{50}=1.53\ \mu\text{M}$) was significantly higher than that of resveratrol ($\text{IC}_{50}=63.2\ \mu\text{M}$). In addition, recent studies indicated that the cancer preventative agent resveratrol is converted to anticancer agent piceatannol by cytochrome P450 enzyme CYP1B1²²⁾ and piceatannol protects PC12 cells from hydrogen-peroxide- and peroxynitrite-induced apoptosis by blocking the activation of c-Jun N-terminal kinase (JNK) and the down-regulation of Bcl-XL.²³⁾

Oxyresveratrol (*trans*-2',3,4',5-tetramethoxystilbene), available from *Morus alba* Linne *Artocarpus lakoocha* Roxb and mulberry wood, is another hydroxylated analog of resveratrol with high similarity. It has been known that oxyresveratrol is transported to tissues at high rates resulting in a bioavailability of about 50%.²⁴⁾ Pharmacological studies have demonstrated that oxyresveratrol can be used as an active ingredient in dermatology,^{25,26)} and exhibiting potent inhibitory effects on cyclooxygenase,^{27,28)} rat liver mitochondrial ATPase activity²⁹⁾ and dihydroxyphenylalanine (DOPA) oxidase activity.²⁷⁾ It has also been revealed that oxyresveratrol is neuroprotective^{30–33)} and inhibits the apoptotic cell death in transient cerebral ischemia.³⁰⁾ Oxyresveratrol also shows a strong potential for practical use in food industry as an antibrowning agent for cloudy apple juices and fresh-cut apples.³⁴⁾

Plants produce resveratrol and its hydroxylated analogues as phytoalexins and the contents of which are extremely poor and only produced in response to stress situations such as fungal infection or injury. For this reason they can hardly be obtained in large quantities by herb extraction, also, the so called “commercial availability” from roots of wild *Polygonum cuspidatum* is far from sustainable and environmentally benign. Therefore, highly efficient synthetic methods for large-scale preparation of these stilbenes are greatly desired. At present, many synthetic approaches for resveratrol and analogues have been designed through Wittig,^{35,36)} Horner,³⁷⁾ Emmons–Wadsworth,³⁸⁾ and Heck³⁹⁾ reactions. Other methodologies involve lithiation-condensation,⁴⁰⁾

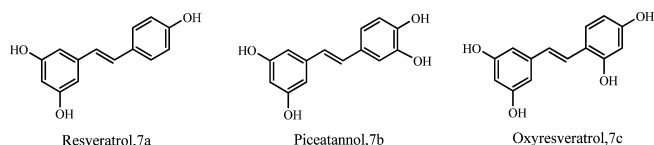


Fig. 1. Chemical Structures of Resveratrol, Piceatannol and Oxyresveratrol

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Perkin,⁴¹⁾ Ramberg–Bäcklund,⁴²⁾ or Diels–Alder/Wittig⁴³⁾ reactions. The formation of carbon–carbon double bond in *trans*-configuration is the key step in the synthetic process. Classical approaches such as Wittig and Heck reaction methods usually require relatively long synthetic sequences and use of expensive catalyst and reagents. In many cases, an extra work is required to transform the mixture of *cis*–/*trans*–isomers to *trans*–stilbenes. These shortcomings consequently result in low product yields and hinder the application of these approaches in large-scale synthesis. Moreover, very few studies on the synthesis of piceatannol^{44–48)} and oxyresveratrol⁴⁵⁾ have been reported so far. Hence, the synthetic method of **7a–c** which is more concise, *trans*-specific, mild and commonly applicable remains to be an important goal.

As part of our ongoing efforts to synthesize naturally occurring stilbene and derivatives, we herein reported a conventional and efficient methodology for the synthesis of resveratrol, piceatannol and oxyresveratrol based on Perkin-type reactions. Starting from the cheap and commercially available 3,5-dihydroxyacetophenone (**1**), synthesis of the common intermediate 3,5-dimethoxyphenylacetic acid (**3**) was achieved through methylation and Willgerodt–Kindler reaction. Perkin condensations between **3** and methoxylated phenylaldehydes **4** gave *E*-2,3-diarylacrylic acids **5**, which were then decarboxylated by means of copper powder in quinoline yielding *Z*-stilbene intermediates **6**. Finally, through a simultaneous demethylation/isomerization process in the presence of AlI_3 , the title compounds of *trans*-polyphenolic stilbenes were obtained in high overall yields (Chart 1).

Experimental

Melting points of compounds were uncorrected and measured on Thiele apparatus. ^1H - and ^{13}C -NMR spectra were measured on Bruker DRX-400 spectrometers. Chemical shifts are reported as δ values with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a RFX-65A spectrometer. Mass spectrometry was performed on a Shimadzu GCMS-QP5050A and VG ZAB-MS mass spectrometers in electron ionization mode.

3,5-Dimethoxyacetophenone (2) DMS (2.5 ml, 25 mmol, dimethyl sulfate) and 10% aqueous NaOH (1.20 g, 30 mmol) were added simultaneously and drop wise to a solution of 3,5-dihydroxyacetophenone (**1**) (1.52 g, 10 mmol) in water at room temperature. The resulting mixture was stirred at room temperature for another 1 h, and then poured into ice-water, stirred and stored for a few hours, a great deal of brown solid **2** was obtained by filtration (1.69 g, 93.8%). mp 34–36 °C; ^1H -NMR (CDCl_3) δ : 2.55 (3H, s), 3.81 (6H, s), 6.62 (1H, t, $J=2.4$ Hz), 7.06 (2H, d, $J=2.4$ Hz); IR (KBr) cm^{-1} : 3010, 2840, 1677; MS (m/z): 180 (M^+). The brown solid **2** was employed in the next step without further purification.

3,5-Dimethoxyphenylacetic Acid (3) A mixture of 3,5-dimethoxyacetophenone (**2**) (1.80 g, 10 mmol), sulfur (0.48 g, 15 mmol), TsOH (0.086, 0.5 mmol, *p*-toluenesulfonic acid) and morpholine (10 ml) was stirred and heated at 120–130 °C for 6 h. Upon cooling, 20% aqueous NaOH (2.0 g, 50 mmol) and TBAB (0.16 g, 0.50 mmol, tetrabutylammonium bromide) were added to the resulting mixture, and hydrolysis was carried out for a further 6 h at 100–110 °C. The resulting mixture was cooled to room temperature, and the aqueous phase was adjusted to pH=6–7 with aqueous HCl ($V/V=1:1$). The black oil-like impurity was removed by filtration. After the filtrate was acidified to pH=2, a large amount of precipitate was observed in the solution. The mixture was stored for a few hours and filtered. The solid was recrystallized from H_2O to afford white crystal **3** (1.58 g, 80.6%). mp 95–97 °C; ^1H -NMR (CDCl_3) δ : 3.56 (2H, s), 3.76 (6H, s), 6.36 (1H, t, $J=2.0$ Hz), 6.41 (2H, d, $J=2.0$ Hz); IR (KBr) cm^{-1} : 3018, 2836, 1702, 1608, 817, 734, 651; MS (m/z): 196 (M^+), 151, 166.

General Procedure for the Preparation of *E*-2,3-diarylacrylic acid (5) A mixture of 3,5-dimethoxyphenylacetic acid (**3**) (1.96 g, 10 mmol) and substituted phenylaldehyde **4** (10 mmol) in acetic anhydride (2.82 ml, 30 mmol) and triethylamine (2.78 ml, 20 mmol) was stirred at 120 °C for 5 h. The resulting mixture was poured into ice-water, stirred and stored for a few hours, a great deal of yellow solid precipitated from the solution. The yellow solid was dissolved in 5% aqueous NaOH (50 ml) and extracted with ethyl acetate. After adjusting the aqueous phase to pH=2–3 with aqueous HCl ($V/V=1:1$), a great deal of pale yellow solid appeared. The remaining solid was recrystallized from EtOH to afford a colorless crystal.

***E*-2-(3,5-Dimethoxyphenyl)-3-(4-methoxyphenyl)-acrylic Acid (5a):** Colorless crystal (2.73 g, 86.3%). ^1H -NMR (CD_3COCD_3) δ : 3.74 (6H, s), 3.75 (3H, s), 6.38 (2H, d, $J=2.0$ Hz), 6.46 (1H, t, $J=2.0$ Hz), 6.68 (2H, d, $J=8.8$ Hz), 7.05 (2H, d, $J=8.8$ Hz), 7.84 (1H, s); IR (KBr) cm^{-1} : 3434, 2935, 1666, 1598; MS (m/z): 316 (M^+), 285.

***E*-2-(3,5-Dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-acrylic Acid (5b):** Colorless crystal (2.93 g, 85.1%). ^1H -NMR (CD_3COCD_3) δ : 3.46 (3H, s), 3.73 (6H, s), 3.83 (3H, s), 6.42 (2H, d, $J=2.0$ Hz), 6.45 (1H, t, $J=2.0$ Hz), 6.56 (1H, d, $J=2.0$ Hz), 6.71 (1H, d, $J=8.4$ Hz), 6.86–6.89 (1H, dd, $J=8.8$ Hz), 7.83 (1H, s); IR (KBr) cm^{-1} : 3438, 2834, 1668, 1596; MS (m/z): 344 (M^+), 313.

***E*-2-(3,5-Dimethoxyphenyl)-3-(2,4-dimethoxyphenyl)-acrylic Acid (5c):** Colorless crystal (2.81 g, 81.6%). ^1H -NMR (CD_3COCD_3) δ : 3.71 (6H, s), 3.74 (3H, s), 3.87 (3H, s), 6.18–6.21 (1H, dd, $J=8.8$ Hz), 6.35 (2H, d, $J=2.4$ Hz), 6.43 (1H, t, $J=2.4$ Hz), 6.53 (1H, d, $J=2.4$ Hz), 6.74 (1H, d, $J=8.8$ Hz), 8.12 (1H, s); IR (KBr) cm^{-1} : 3434, 2838, 1673 1596; MS (m/z): 344 (M^+), 313.

3-(3',5'-Dihydroxyphenyl)-7-hydroxycoumarin (10c) A solution of 3,5-dihydroxyphenylacetic acid (**8**) (1.68 g, 10 mmol) and 2,4-dihydroxybenzaldehyde (**9c**) (1.38 g, 10 mmol) in acetic anhydride (2.82 ml, 30 mmol) and triethylamine (2.78 ml, 20 mmol) was stirred at 110–120 °C for 6 h. The resulting mixture was poured into ice-water, stirred and stored for a few hours, a great deal of yellow solid precipitated from the solution. The remaining solid was recrystallized from ethyl acetate to afford a white solid **10c** (2.43 g, 90%). mp >280 °C, ^1H -NMR (CD_3COCD_3) δ : 3.95 (3H, s), 6.38 (1H, t, $J=2.0$ Hz), 6.73 (2H, d, $J=2.0$ Hz), 7.03 (1H, d, $J=8.8$ Hz), 7.20 (1H, d, $J=8.8$ Hz), 7.94 (1H, s), 8.33 (2H, s), 8.34 (1H, s); ^{13}C -NMR (CD_3COCD_3) δ : 55.8, 103.4, 108.0, 109.2, 115.2, 119.5, 125.2, 134.2, 138.1, 141.2, 142.9, 151.1, 159.1, 160.3; IR (KBr) cm^{-1} : 3168, 1683, 1469;

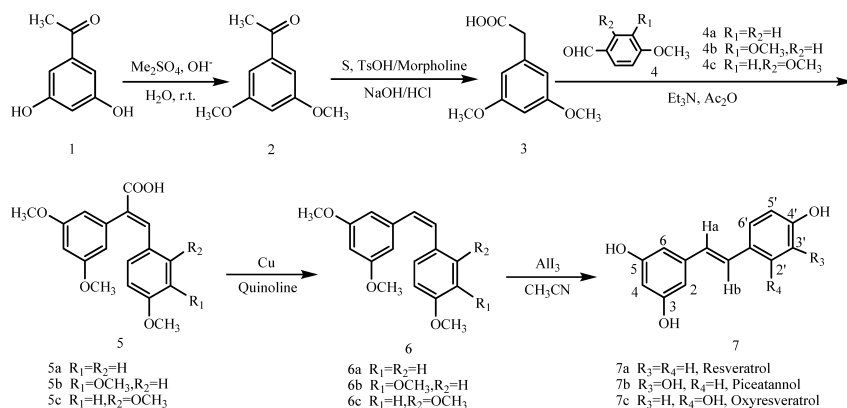


Chart 1. The Synthetic Route of Resveratrol and Its Derivatives

ESI-MS (m/z): 270 (M^+), 269.

General Procedure for the Preparation of *cis*-Polymethoxystilbene Intermediates (6**)** The reaction was carried out under dry nitrogen atmosphere. A solution of **5** (5 mmol), quinoline (15 ml, 100 mmol) and copper powder (2.56 g, 40 mmol) was stirred at 220 °C for 3 h. Then the copper powder was filtered out, and aqueous HCl (V/V = 1 : 1) was added into the filtrate, extracted with ethyl acetate, dried over $MgSO_4$, and evaporated. The dark oily substance was extracted with petroleum ether to afford yellow oil **6**, which was used without further purification.

cis-3,4',5'-Trimethoxystilbene (**6a**): Yellow oil (1.01 g, 74.2%) 1H -NMR ($CDCl_3$) δ : 3.65 (6H, s), 3.76 (3H, s), 6.29–6.30 (1H, t, $J=2.4$ Hz), 6.40–6.43 (1H, d, $J=12.0$ Hz), 6.41–6.43 (2H, d, $J=2.4$ Hz), 6.49–6.52 (1H, d, $J=12.0$ Hz), 6.73–6.76 (2H, dd, $J=8.8$, 2.0 Hz), 7.18–7.20 (2H, dd, $J=8.8$, 2.0 Hz); IR (KBr) cm^{-1} : 3003, 1595, 1425; MS (m/z): 272 (M^+), 257, 241.

cis-3,3',4',5'-Tetramethoxystilbene (**6b**): Yellow oil (1.13 g, 75.3%) 1H -NMR ($CDCl_3$) δ : 3.63 (3H, s), 3.66 (3H, s), 3.66 (3H, s), 3.83 (3H, s), 6.29–6.30 (1H, t, $J=2.0$ Hz), 6.43–6.44 (2H, d, $J=2.0$ Hz), 6.43–6.46 (1H, d, $J=12.4$ Hz), 6.48–6.51 (1H, d, $J=12.4$ Hz), 6.72–6.74 (1H, d, $J=8.0$ Hz), 6.81–6.83 (1H, dd, $J=8.0$, 2.0 Hz), 6.83–6.83 (1H, d, $J=2.0$ Hz); IR (KBr) cm^{-1} : 3002, 1604, 1460; MS (m/z): 300 (M^+), 285.

cis-2',3,4',5'-Tetramethoxystilbene (**6c**): Yellow oil (1.07 g, 70.6%) 1H -NMR ($CDCl_3$) δ : 3.52 (6H, s), 3.58 (3H, s), 3.67 (3H, s), 6.29 (1H, t, $J=2.4$ Hz), 6.41 (1H, d, $J=9.6$ Hz), 6.49 (1H, d, $J=9.6$ Hz), 6.49 (1H, d, $J=12$ Hz), 6.73 (1H, t, $J=8.8$ Hz), 6.73 (1H, d, $J=2.4$ Hz), 7.18 (1H, d, $J=8.8$ Hz); IR (KBr) cm^{-1} : 3002, 1600, 1459; MS (m/z): 300 (M^+), 269.

General Procedure for the Preparation of *trans*-Phenolic Stilbenes (7**)** To a solution of AlI_3 (20.40 g, 50 mmol) in CH_3CN (100 ml) at 82 °C was added drop wise the solution of **6** (10 mmol) in CH_3CN (20 ml), and stirred for 3 h. The resulting mixture was concentrated, and a yellow solid appeared. The remaining solid was added into water, a pale yellow solid was obtained, which was recrystallized from EtOH/ H_2O to afford a white crystal.

trans-3,4',5'-Trimethoxystilbene (Resveratrol, **7a**): White crystal (1.68 g, 73%). mp 224–226 °C (lit⁴⁹) 233–235 °C; 1H -NMR ($CDCl_3$) δ : 6.27 (1H, t, $J=2.0$ Hz), 6.54–6.55 (2H, d, $J=2.0$ Hz), 6.83–6.85 (2H, d, $J=8.8$ Hz), 6.87–6.91 (1H, d, $J=16.4$ Hz), 7.00–7.04 (1H, d, $J=16.4$ Hz), 7.41–7.43 (2H, d, $J=8.8$ Hz), 8.20 (2H, s, D_2O exchangeable), 8.43 (1H, s, D_2O exchangeable); IR (KBr) cm^{-1} : 3292, 1587, 1444; MS (m/z): 230 (M^+). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.46; H, 5.40.

trans-3,3',4',5'-Tetramethoxystilbene (Piceatannol, **7b**): White crystal (1.73 g, 70.9%). mp 231–234 °C; 1H -NMR ($DMSO-d_6$) δ : 6.08–6.09 (1H, t, $J=2.0$ Hz), 6.35–6.35 (2H, d, $J=2.0$ Hz), 6.67–6.71 (1H, d, $J=16.4$ Hz), 6.68–6.70 (1H, d, $J=8.0$ Hz), 6.80–6.83 (1H, dd, $J=8.0$, 2.0 Hz), 6.81–6.85 (1H, d, $J=16.4$ Hz), 6.93–6.94 (1H, d, $J=2.0$ Hz), 8.91 (1H, s, D_2O exchangeable), 9.08 (1H, s, D_2O exchangeable), 9.17 (2H, s, D_2O exchangeable); IR (KBr) cm^{-1} : 3392, 1600, 1481; MS (m/z): 244 (M^+), 227.

trans-2',3,4',5'-Tetramethoxystilbene (Oxyresveratrol, **7c**): White crystal (1.67 g, 68.4%). mp 202–205 °C; 1H -NMR (CD_3COCD_3) δ : 6.21 (1H, t, $J=2.0$ Hz), 6.34–6.37 (1H, dd, $J=8.4$ Hz), 6.41 (1H, d, $J=2.0$ Hz), 6.49 (2H, d, $J=2.0$ Hz), 6.83 (1H, d, $J=16.4$ Hz), 7.27 (1H, d, $J=16.4$ Hz), 7.35 (1H, d, $J=8.4$ Hz), 8.57 (2H, s, D_2O exchangeable), 8.78 (1H, s, D_2O exchangeable), 8.96 (1H, s, D_2O exchangeable); ^{13}C -NMR (CD_3COCD_3) δ : 102.1, 103.4, 105.2, 108.1, 117.0, 124.3, 126.1, 128.1, 141.5, 156.7, 158.9, 159.3; IR (KBr) cm^{-1} : 3208, 1590, 1513; MS (m/z): 244 (M^+), 226.

Results and Discussion

The Perkin reaction has been characterized as favorable atom economy, relatively high yields and simple operations. We therefore based our strategy on Perkin-type reactions to form the stilbene skeleton. It could be noticed that the 3,5-dihydroxyphenyl group (usually referred to as A ring of stilbene) is a common subunit for target compounds **7a–c**, so a common intermediate can serve as starting material. 3,5-Dihydroxyphenylacetic acid (**8**) was initially taken into consideration as the starting material but this compound is not commercially available and is difficult to prepare. Therefore we started with 3,5-dihydroxyacetophenone (**1**), which was cheap and readily available, and obtained 3,5-dimethoxyphenylacetic acid (**3**) as the common intermediate through methylation and Willgerdt–Kindler rearrangement in 80.6% yield.

The procedure has several advantages such as simple operations, short reaction time and high purity of product. It is noteworthy that the direct Willgerdt–Kindler rearrangement of 3,5-dihydroxyacetophenone (**1**) under identical reaction conditions has also been investigated but failed to afford 3,5-dihydroxyphenylacetic acid (**8**).

Perkin condensations between 3,5-dimethoxyphenylacetic acid (**3**) and substituted phenylaldehydes **4a–c** in the presence of acetic anhydride and triethylamine at 120 °C selectively gave *E*-2,3-diarylacrylic acids **5a–c** in yields of 86.3%, 85.1%, and 81.6%, respectively. We can't detect the *Z*-isomer of **5a–c** only after single crystallization. The *E*-configuration with a *cis*-relationship of phenyl rings can be clearly corroborated by 1H -NMR spectrum (Fig. 2, for example **5c**), which has been well established in our previous studies.^{50,51)}

The field-effect of carboxyl group in **5a–c** resulted in a remarkable down-field shift of the olefinic proton ($H\beta$): $\delta=7.84$ for **5a**, $\delta=7.83$ for **5b**, $\delta=8.12$ for **5c**, as compared with the olefinic proton of *cis*-isomer ($\delta\approx 6.90$), suggesting that the down-field shift of olefinic proton is a typical character of *E*-2,3-diarylacrylic acid (**5**). Moreover, the 2'-methoxy group of **5c** may also exert an additional field-effect to the olefinic proton, leading to a even higher chemical shift. The $H(2,6)$ proton of **5c** appears as a doublet at δ 6.35 ppm and $H(4)$ as a triplet at δ 6.43 ppm with a coupling constant $J=2.4$ Hz. The $H(5')$, $H(6')$ proton signals of B ring appear at δ 6.20 and δ 6.74 ppm, respectively, with the triple-bond coupling constant $J=8.8$ Hz; δ 6.53 ppm corresponds to the $H(3')$ proton of B ring with a W-type long-range coupling constant of $J=2.4$ Hz.

Decarboxylation reactions of **5a–c** were carried out in the presence of Cu/quinoline at 220 °C under the protection of N_2 to give the *Z*-stilbene intermediates **6a–c** in yields of 74.2%, 75.3%, and 70.6%, respectively. Results determined by 1H -NMR spectrum clearly indicate that, despite the high reaction temperature, the decarboxylation process maintained the original *cis*-relationship of phenyl rings and gave the corresponding *cis*-products **6a–c** with a typical coupling constant of $J=12.4$ Hz.

Demethylation process of **6a–c** took place smoothly in the presence of AlI_3 in acetonitrile. Interestingly and fortunately, a simultaneous *cis*- to *trans*-isomerization was also taking place during the demethylation process, giving high yields for the target compounds **7a–c**. We tried a number of

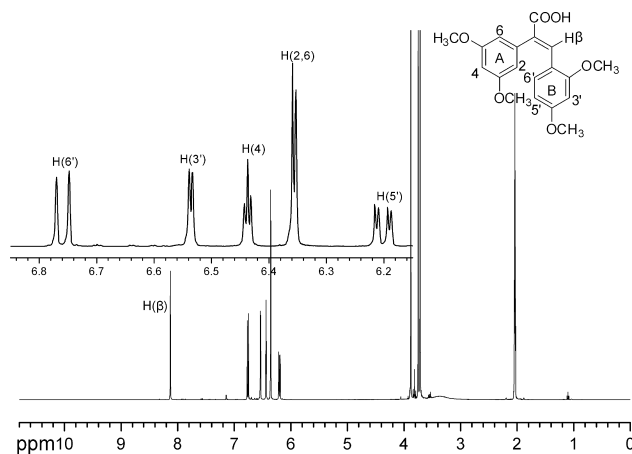
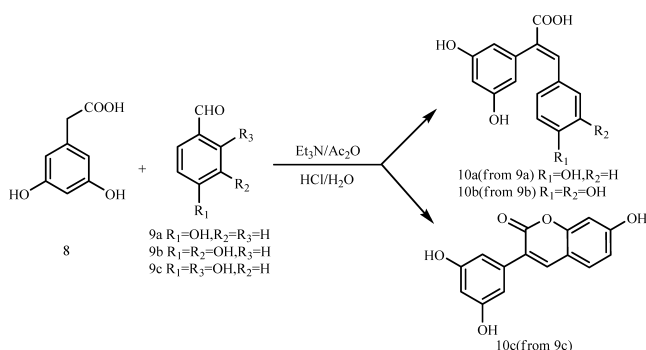


Fig. 2. The 1H -NMR Spectrum of Compound **5c**

Table 1. ^1H -NMR (400 Hz, δ/ppm) Spectra for Target Compounds **7a**, **7b**, and **7c** at 298K^{a)}

Position	Resveratrol (7a) ^{b)}	Piceatannol (7b) ^{c)}	Oxyresveratrol (7c) ^{d)}
Ha	7.00 (1H, d, $J=16.4$ Hz)	6.81 (1H, d, $J=16.4$ Hz)	6.83 (1H, d, $J=16.4$ Hz)
Hb	6.87—6.91 (1H, d, $J=16.4$ Hz)	6.67—6.71 (1H, d, $J=16.4$ Hz)	7.27 (1H, d, $J=16.4$ Hz)
2,6	6.54—6.55 (2H, d, $J=2.0$ Hz)	6.35—6.35 (2H, d, $J=2.0$ Hz)	6.49 (2H, d, $J=2.0$ Hz)
3,5(2 $\times$ -OH)	8.20 (2H, s, D ₂ O exchangeable)	9.17 (2H, s, D ₂ O exchangeable)	8.57 (2H, s, D ₂ O exchangeable)
4	6.27 (1H, t, $J=2.0$ Hz)	6.08 (1H, t, $J=2.0$ Hz)	6.21 (1H, t, $J=2.0$ Hz)
2'	7.41—7.43 (2H, d, $J=8.8$ Hz)	6.93—6.94 (1H, d, $J=2.0$ Hz)	8.96 (1H, s, D ₂ O exchangeable)
3'	6.83—6.85 (2H, d, $J=8.8$ Hz)	8.91 (1H, s, D ₂ O exchangeable)	6.41 (1H, d, $J=2.0$ Hz)
4'(-OH)	8.43 (1H, s, D ₂ O exchangeable)	9.08 (1H, s, D ₂ O exchangeable)	8.78 (1H, s, D ₂ O exchangeable)
5'	6.83—6.85 (2H, d, $J=8.8$ Hz)	6.68—6.70 (1H, d, $J=8.0$ Hz)	6.34—6.37 (1H, dd, $J=8.4$ Hz)
6'	7.41—7.43 (2H, d, $J=8.8$ Hz)	6.80—6.83 (1H, dd, $J=8.0, 2.0$ Hz)	7.35 (1H, d, $J=8.4$ Hz)

a) Number of hydrogens, multiplicity, and J values in Hz are given in parentheses. b) CDCl_3 as the solvent. c) $\text{DMSO}-d_6$ as the solvent. d) CD_3COCD_3 as the solvent.

Chart 2. The Different Regioselectivity Results of Perkin Reaction between **8**+**9a, b** and **8**+**9c**

other solvents such as THF, EtOAc, $\text{C}_5\text{H}_5\text{N}$, and 1,4-dioxane, but none of them afforded the desired product. The proposed mechanism of demethylation/isomerization had been reported in our previous work.⁵¹⁾

The target compounds have been characterized by IR, EI-MS and NMR analyses. The observed ^1H -NMR spectral pattern and the ratio of integrated intensities lend evidence to the structure of **7a**—**c**. For example, the ^1H -NMR spectrum of **7a**—**c** exhibited a typical AB system at 6.81—7.27 ppm with a coupling constant of $J=16.4$ Hz, readily assigned to the *trans* olefinic unit. The active hydrogens of **7a**—**c** disappeared through D_2O exchange of ^1H -NMR, in agreement with the proposed structure. The ^1H -NMR spectral data were shown in Table 1.

Additionally, due to our interest on the substitution effect concerning Perkin reactions, we used 3,5-dihydroxyphenylacetic acid (**8**) instead of 3,5-dimethoxyphenylacetic acid (**3**) as the starting material to explore Perkin condensations with hydroxylated phenylaldehydes **9** (Chart 2). Our results show that the reactions between **8** and **9a, b** produced *E*-2,3-diacylacrylic acids **10a, b** as the main products as expected, whereas the reaction between **8** and **9c** afforded a novel cyclized stilbene derivative with a molecular formula of

$\text{C}_{15}\text{H}_{10}\text{O}_5$, namely 3-arylcoumarin **10c**. The regioselectivity formation of **10c** may come out of isomerization and subsequent lactonization of *ortho*-hydroxylated *E*-2,3-diarylacrylic acid. The later was a intermediate of Perkin reaction. As the backbone of this kind of compounds bear the resemblance to stilbenes, coumarins as well as isoflavones, the biological properties of which are of great interest. Further results associated with this methodology will be reported in due course.

Conclusion

A facile and practical synthesis of *trans* polyphenolic stilbenes including resveratrol, piceatannol and oxyresveratrol were achieved under Perkin strategy in high overall yields. Starting from 3,5-dihydroxyphenylacetic acid (**1**), the common intermediate 3,5-dimethoxyphenylacetic acid (**3**) was prepared through methylation and Willgerodt–Kindler reaction. Perkin condensation and decarboxylation reactions gave methoxylated *cis*-stilbenes **6** in good yields. Finally, the simultaneously occurred demethylation/isomerization process catalyzed by AlI_3 in acetonitrile made the procedure a highly efficient one. The present results have provided a conventional, cost-effective and commonly viable process for synthesis of *trans* polyphenolic stilbenes.

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