An efficient synthesis of resveratrol and a hydroxyl derivative via the Perkin reaction: *cis* to *trans* isomerisation in a demethylation process

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Two *trans* polyphenolic stilbenes, Resveratrol and 3,4,4',5- *trans*-tetrahydroxystilbene, were prepared in three steps from 4-methoxy phenylacetic acid and methoxylated benzaldehydes via a Perkin reaction. An interesting *cis* to *trans* isomerisation occured in the demethylation process in the presence of AlI_3 and acetonitrile to give resveratrol and 3,4,4',5-*trans*-tetrahydroxystilbene with overall yields of 51% and 48% respectively.

Keywords: polyphenolic stilbenes, Perkin reaction, resveratrol, 3,4,4',5- *trans*-tetrahydroxystilbene, isomerisation

Resveratrol (3,4',5-*trans*-trihydroxystilbene) **1a** is an outstanding polyphenolic stilbene which in recent years has aroused the attention of not only biologists and chemists, but also the general public. Resveratrol exerts many effects on cellular events associated with cancer initiation, promotion and progression.[1] It is an antioxidant, antimutagen, and apoptosis inducer. It promotes the clearance of Alzheimer's disease amyloid-peptides and affords neuroprotective properties.[2] It has been shown that resveratrol can inhibit cyclooxygenase, hydroperoxidases, protein kinase C, Bcl-2 phosphorylation, Akt, focal adhesion kinase, NFκB, matrix metalloprotease-9, and cell cycle regulators.[3] Studies reported by Sinclair and colleagues have confirmed that resveratrol is a potent lead compound for a new medicinal category called small molecule sirtuin activators(STACs) which exerts antiaging properties through calorie restriction mimic.[4] Recently resveratrol has been shown to extend the lifespan of evolutionarily distant species including *S. cerevisiae, C. elegans* and *D. melanogaster* in a Sir2-dependent manner, improve health and extend maximum lifespan by 59% in a vertebrate fish.[5] Recent studies have also shown that resveratrol improves the health and survival of mice on a high-calorie diet.[6]

Hydroxylated resveratrol analogues, which in recent studies possessed a higher activity than resveratrol, are important targets.[7-9] Hydroxylated resveratrol analogues showed selective cyclooxygenase-2 inhibition,[10] increased antioxidant, prooxidant activity and cytotoxicity.[8] 3,4,4',5-*Trans*-tetrahydroxystilbene **1b**, a resveratrol derivative, exhibits potent growth inhibitory effect against transformed human cells,[11] differentially induces pro-apoptotic p53/Bax gene expression and inhibits the growth of transformed cells but not their normal counterparts.[12]

The most common synthetic method to prepare resveratrol and its analogues involves a Wittig reaction,[13] which forms a mixture of *cis*- and *trans*-stilbenes. Hence the conversion of *cis*- to *trans*- stilbene was needed, which sometimes involved relatively harsh reaction conditions. A palladium-catalysed Heck-based route has been reported that utilised 3,5-dihydroxybenzaldehyde as the starting material, through series of reactions to form the 3,5-diacetoxy-styrene intermediate,[14] but the overall yield was poor. Guy Solladié *et al.*[15] synthesised resveratrol by Perkin reaction in which *i*-propyl ethers were used as protecting groups and an extremely expensive reagent BCl_3 was used to eliminate them in the last stage at low temperature condition (–78°C). Chromatographic purification was also required to obtain the final product. Starting from 4-methoxyphenylacetic acid and methoxylated benzaldehydes, we report a convenient synthetic route for resveratrol **1a** and 3,4,4',5-*trans*-tetrahydroxystilbene **1b** via Perkin reaction methodology in only three steps with good yields (Scheme 1).

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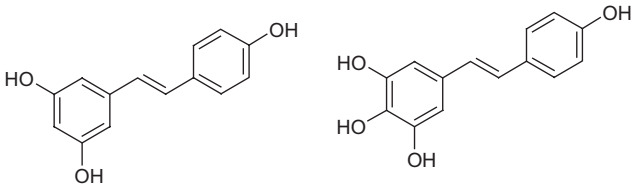


1a **1b**

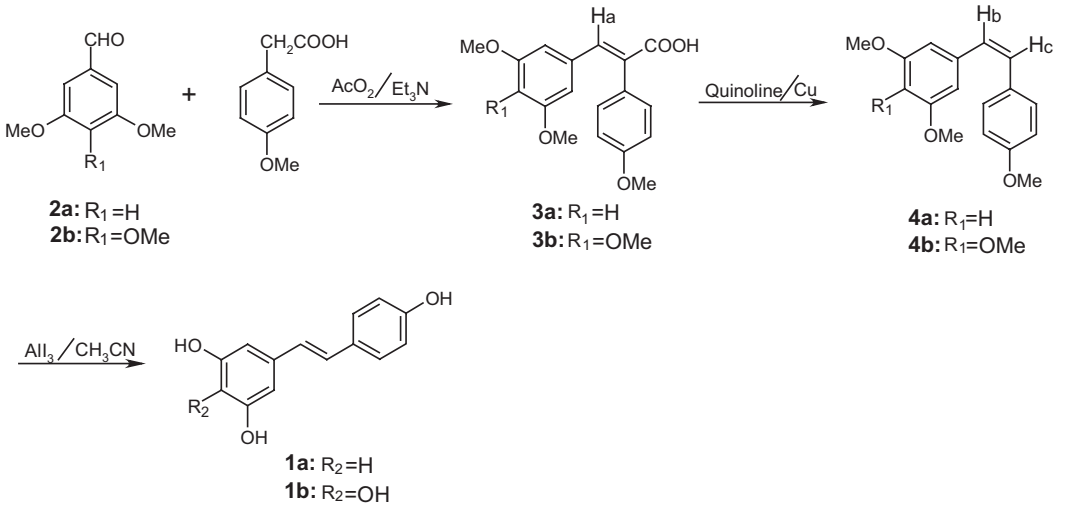
Fig.1 The chemical structure of resveratrol and 3,4,4',5-*trans*-tetrahydroxystilbene.

Also, we have found that, in demethylation process, the *cis*-stilbenes were simultaneously and completely converted to *trans*-stilbenes. The one-pot demethylation and isomerisation process has not been reported in the literature. This is the most efficient synthetic route for resveratrol **1a** and 3,4,4',5-*trans*-tetrahydroxystilbene **1b** starting from commercial materials.

Results and discussion

The Perkin condensation between 4-methoxyphenylacetic acid and methoxylated benzaldehydes in the presence of acetic anhydride and triethylamine at 110°C gave the 1,2-diarylacrylic acids **3a–b** in 86.4% and 84% yields respectively, in which the *cis*-stilbene isomer (the *E* isomer by IUPAC rules) was the main product (*cis*-stilbene/*trans*-stilbene = 11/1). The *cis*-stilbene configuration was established by the ^{1}H NMR spectrum, in which the field effect of carboxylic group in the *cis*-stilbene resulted in a noticeable low-field shift of the alkene H-atom. This field effect was not found in *trans*-stilbene (the *Z* isomer by IUPAC rules). This can be confirmed by chemical shift of alkene H-atom of the isomers, for **3a**, δ_{Ha} = 7.81 ppm, and for *trans*-stilbene isomer (Z)-**3a**, δ_{Ha} = 6.91 ppm (Figure 2).

The decarboxylation was carried out in the presence of quinoline and copper powder at 220°C under nitrogen, to give the polymethoxy stilbenes **4a–b** in 70.6% and 70% yields respectively in which the *cis*-stilbene was the main product. The geometrical configuration of **4a** and **4b** were also determined by ^{1}H NMR, the J_{bc} = 12 Hz for *cis*-stilbene whereas the J_{bc} = 16 Hz for *trans*-stilbene. The last step, demethylation, was performed in the presence of AlI_3 and acetonitrile, to give polyphenolic stilbenes **1a–b**, with a *trans*-stilbene structure were obtained in 83.8% and 82% yields respectively. In this step, AlI_3 was used to remove the methyl groups, and to our surprise, when the methyl groups were removed, the configuration of stilbene was simultaneously and completely isomerised from *cis* to *trans*. This was novel and made the synthetic process highly efficient. Several explanations may account for the demethylation and isomerisation process. (Scheme 2).



Scheme 1 Synthesis of polyphenolic stilbenes.

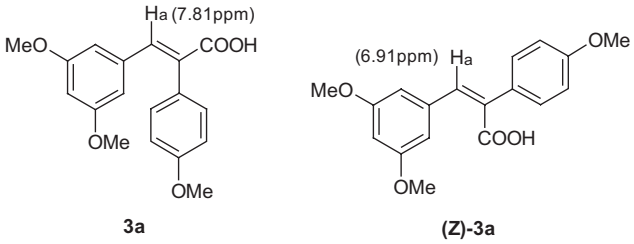


Fig. 2 Chemial shift of alkene H-atom.

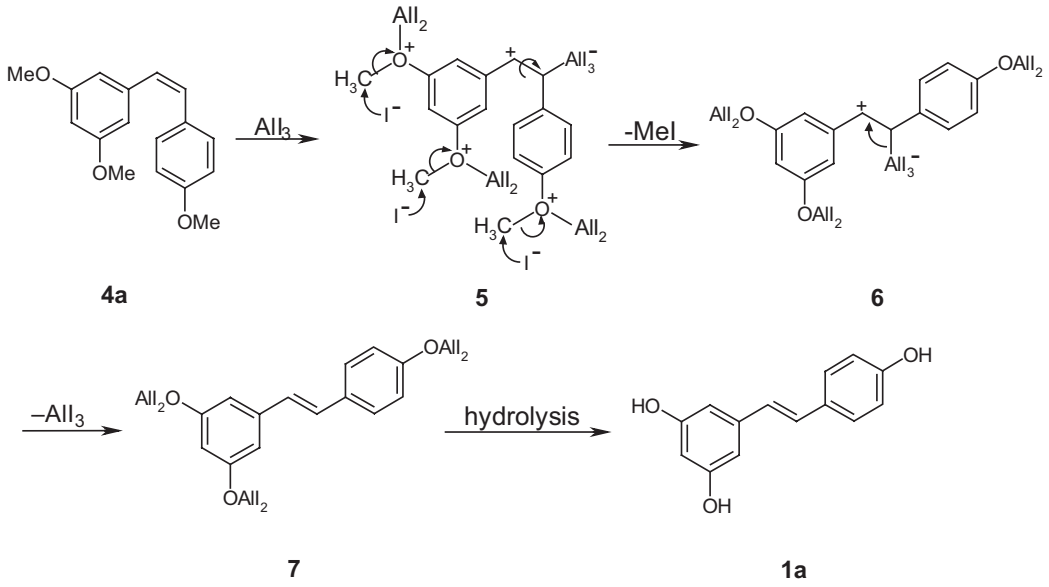
Demethylation process occured when **4a** undergone electrophilic attack by AlI_3, and at the same time, the intermediate **5** can rotate around the carbon-carbon single bond to acquire a more favourable configuration, then with the loss of MeI and AlI_3 to give the more stable *trans*-stilbene **7,** finally, **1a** was obtained by hydrolysis.

The reaction temperature (82°C) is perhaps another reason for the isomerisation of double bond, when *cis*-stilbene is heated at certain temperature with sufficient energy to overcome the activation energy of isomerisation, *cis*-stilbene will be converted to the more stable *trans*-isomer.

In the Perkin condensation, we took advantage of the fact that the product is an acid, and used a basification/extraction/acidification procedure as an easy way to isolate the solid product and remove any nonacidic impurities in the crude product. The product was obtained in a yield of 84%. The yield reported by Guy Solladié *et al.,* in the Perkin reaction was only 70%.

In the decarboxylation reaction, dark oily byproducts in the mixture made the purification difficult. In order to purify the crude product, column chromatography is usually needed. TLC analysis showed that compounds **4a–b** were poorly lipophilic, whereas the byproducts were highly lipophilic. Thus, we used petroleum ether to extract compounds **4a–b** from the dark oily reaction mixtures and leaving the byproducts alone. The product was thus readily purified without using column chromatography. The crude products **4a–b** can also be purified by vacuum distillation (180–185°C/0.2 mmHg).

In summary, we have developed an effective process for syntheses of *trans* polyphenolic stilbenes in good yields. Starting from 4-methoxyphenylacetic acid and methoxylated benzaldehydes, resveratrol **1a** and 3,4,4',5-tetrahydroxy-*trans*-stilbene **1b** were successfully prepared in only three steps with overall yields of 51% and 48.2% respectively.



Scheme 2 Proposed mechanism for demethylation/isomerisation process.

Purification of compounds was improved and the *cis* to *trans* isomerisations in demethylation process made the procedure a highly efficient one.

Experimental

All reagents were obtained from commercial suppliers and were used without further purification. The melting points were uncorrected and determined on Thiele apparatus. IR spectra were recorded on an Analect RFX-65A IR spectrometer. ^{1}H NMR were obtained from a Brucker DRX-400 MHz spectrometer with TMS as an internal standard. EI-MS analysis was performed using a Shimadzu GCMS-QP5050A mass spectrometer. Elemental analyses were carried out by Elementar Vario EL element analyser.

General procedure for the synthesis of (**3a–b**): **2a–b** (60 mmol), 4-methoxyphenyl-acetic acid (60 mmol), acetic anhydride (16.6 ml, 176 mmol), and triethylamine (25.5 ml, 185 mmol) were added to a 100 ml three-neck round-bottom flask equipped with a reflux condenser. The solution was stirred at 120°C for 5 h. The reaction mixture was poured into ice-water, stirred and stored for a few hours. A yellow solid was obtained by filtration, and was dissolved in 5% NaOH-soln.(100 ml), extracted with ethyl acetate and the organic layers were separated. Hydrochloric acid (V/V = 1 : 1) was added to the aqueous phase to pH 2–3, to precipitate a pale yellow solid which was filtered, and recrystallised from EtOH to afford **3a–b**. Moreover, in the synthesis of **3a**, a trace amount of (*Z*)-**3a** (*trans*-stilbene isomer of **3a**) can also be obtained by fractional recrystallisation and provides spectral data for structure identification. Compound **3a**: colourless crystal (86.4% yield); m.p. 140–142°C; IR (KBr, cm^{-1}): 3432 (OH), 3008, 2951, 2851, 1672 (C=O). ^{1}H NMR ($CDCl_3$, 400 MHz) δ3.54 (s, 6H, $2OCH_3$), 3.80 (s, 3H, OCH_3), 6.26 (d, 2H, 2,6-ArH, *J* = 2.0 Hz), 6.33 (t, 1H, 4-ArH, *J* = 2.0 Hz), 6.91 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 7.17 (d, 2H, 2',6'-ArH, *J* = 8.8 Hz), 7.81 (s, 1H, C=CH), 11.53 (s, 1H, COOH, D_2O exchangeable). EI-MS: 314 (M^+), 283, 269, 254, 239, 224, 148, 120. Anal. Calc. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.96; H, 5.80%. Compound (Z)-**3a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 6H, $2OCH_3$), 3.82 (s, 3H, OCH_3), 6.41 (t, 1H, 4-ArH, *J* = 2.0 Hz), 6.60 (d, 2H, 2,6-ArH, *J* = 2.0 Hz), 6.90 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 6.91 (s, 1H, C=CH), 7.42 (d, 2H, 2',6'-ArH, *J* = 8.8 Hz), 11.60 (s, 1H, COOH, D_2O exchangeable). Compound **3b**: colourless crystal (84% yield); m.p. 208–209°C. IR (KBr, cm^{-1}): 3438 (OH), 2967, 2940, 1680(C=O). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56 (s, 6H, $2OCH_3$), 3.80 (s, 6H, $2OCH_3$), 6.35 (s, 2H, 2,6-ArH), 6.94 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 7.19 (d, 2H, 2',6'-ArH, *J* = 8.8 Hz), 7.81 (s, 1H, C=CH), 10.11 (s, 1H, COOH, D_2O exchangeable). EI-MS: 344 (M^+), 329, 269, 225, 210, 169, 148, 127, 113. Anal. Calc. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.42; H, 5.80%.

General procedure for the synthesis of (**4a–b**): The reaction was carried out under a dry nitrogen atmosphere. Copper powder (6.00 g, 94.4 mmol) was added to a solution of **3a–b** (20 mmol) and quinoline (55 ml, 466 mmol). The mixture was stirred at 220°C for 4 h. Then the copper power was filtered off, hydrochloric acid (1 : 1, V/V) was added to the filtrate, which was extracted with ethyl acetate. The combined organic layers were washed with water. After drying with anhydrous $MgSO_4$ and evaporation of the solvent, a dark oil was obtained which was then extracted with petroleum ether to afford a pale yellow oil **4a–b**. Compound **4a**: pale yellow oil (70.6% yield); IR (cm^{-1}): 3002, 2956, 2835, 1595, 1510, 1458. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.65 (s, 6H, $2OCH_3$), 3.76 (s, 3H, OCH_3), 6.30 (t, 1H, 4-ArH, *J* = 2.4 Hz), 6.41 (d, 2H, 2,6-ArH, *J* = 2.4 Hz), 6.42–6.51 (q, 2H, CH=CH, *J* = 12 Hz), 6.75 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 7.20 (d, 2H, 2',6'-ArH, *J* = 8.8 Hz). EI-MS: 270 (M^+), 255, 239, 224, 196, 181, 152, 127. Compound **4b**: pale yellow oil (70% yield); IR (cm^{-1}): 3003, 2938, 1577, 1508, 1459, 1417. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 6H, $2OCH_3$), 3.77 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.40–6.49 (q, 2H, CH=CH, *J* = 12 Hz), 6.48 (s, 2H, 2,6-ArH), 6.77 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 7.22 (d, 2H, 2',6'-ArH, *J* = 8.8 Hz). EI-MS: 300 (M^+), 285, 225, 210, 165, 152, 128.

3,4',5-Trans-trihydroxystilbene (resveratrol) (**1a**): a solution of **4a** (2.70 g, 10 mmol) in 5 ml CH_3CN was added dropwise to a solution of AlI_3 (15.22 g, 37.3 mmol) and CH_3CN (75 ml). The mixture was stirred at 82°C for 3 h. The resulting mixture was concentrated to obtain a yellow solid, which was added into water, then filtered to afford a pale yellow solid which was recrystallised from EtOH/H_2O to yield white crystal **1a** (1.91 g, 83.8%). M.p. 263–265°C. (lit.,[13] 256–259°) IR (KBr, cm^{-1}): 3291(OH), 3019, 1606, 1587, 1511, 1462, 1444. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.10 (t, 1H, 4-ArH, *J* = 2.0 Hz), 6.37 (d, 2H, 2,6-ArH, *J* = 2.0 Hz), 6.74 (d, 2H, 3',5'-ArH, *J* = 8.4 Hz), 6.80–6.92 (q, 2H, CH=CH, *J* = 16 Hz), 7.38 (d, 2H, 2',6'-ArH, *J* = 8.4 Hz), 9.20 (s, 2H, 2OH, D_2O exchangeable), 9.55 (s, 1H, OH, D_2O exchangeable). EI-MS: 228 (M^+), 211, 199, 181, 152, 91, 76, 55. Anal. Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.46; H, 5.40%. It was identified by comparison of the ^{1}H NMR spectrum.[13]

3,4,4',5-Trans-tetrahydroxystilbene (**1b**): To a solution of AlI_3 (19.18 g, 47 mmol) and CH_3CN (80 ml), a solution of **4b** (3.00 g, 10 mmol) in 5 ml CH_3CN was added dropwise. The mixture was stirred at 82°C for 3 h. The resulting mixture was concentrated to obtain a red solid, which was added into sat. NaCl soln., then extracted with ethyl acetate. The combined organic layers were washed with water, dried with anh. $MgSO_4$, and concentrated to obtain a pale yellow solid, which was recrystallised from EtOH/H_2O to yield white crystals of **1b** (2.00 g, 82%). M.p. 258–260°C. IR (KBr, cm^{-1}): 3473(OH), 3309, 1604, 1538, 1446. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 6.60 (s, 2H, 2,6-ArH), 6.80 (d, 2H, 3',5'-ArH, *J* = 8.8 Hz), 6.82 (s, 1H), 6.83 (s, 1H), 7.36(d, 2H, 2',6'-ArH, *J* = 8.8 Hz), 7.36 (s, 1H, OH, D_2O exchangeable), 7.81 (s, 2H, 2OH, D_2O exchangeable), 8.36 (s, 1H, OH, D_2O exchangeable). EI-MS: 244 (M^+), 225, 197, 181, 169, 141, 115. Anal. Calc. for $C_{14}H_{12}O_5 \cdot H_2O$: C, 64.12; H, 5.38. Found: C, 63.86; H, 5.45%.

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