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Graphical Abstract

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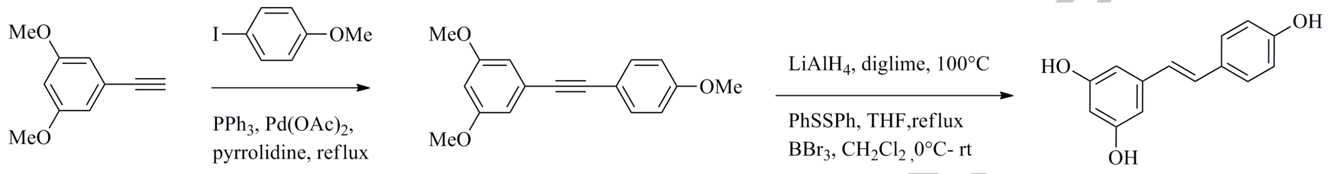

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A new synthesis of resveratrol

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ABSTRACT

Resveratrol was synthesized in a 4-step synthesis using a simple Sonogashira type reaction with 93% yield using commercially available 3,5-dimethoxy-1-ethynyl-benzene and 4-iodoanisole, followed by reduction, isomerization and deprotection and with overall yield of 63%.

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Resveratrol **1**, a naturally occurring polyphenolic non-flavonoid antioxidant, is a phytoalexin compound that has been isolated from grape skin, vine bark, nuts, berries and many other plants. This compound has various health benefits, including chemo-preventive effects against cancer, inflammation, aging, obesity, cardiovascular diseases and neurodegeneration. Antioxidative, antibacterial and antifungal activities have also been attributed to this molecule[1, 2].

A current area of research is related to synthesis of resveratrol oligomers which present in many cases higher antioxidant properties and better activities for different types of diseases than the same resveratrol. These new results triggered a big interest in the field, which can be appreciated for the great number of research papers and reviews recently published[2].

Many synthetic approaches for resveratrol have been reported primarily through Wittig-type reactions[3, 4] and Horner–Emmons[5, 6], but they usually require relatively long synthetic routes with variable diastereoselectivity. Additionally, approaches involving Pd-catalyzed Heck[7-14] or Susuki[15] reactions or Ru-catalyzed cross metathesis[16,17] have also been published. In most cases using the Heck reaction, preparation of the required precursor takes several steps or it involves the use of expensive catalysts.

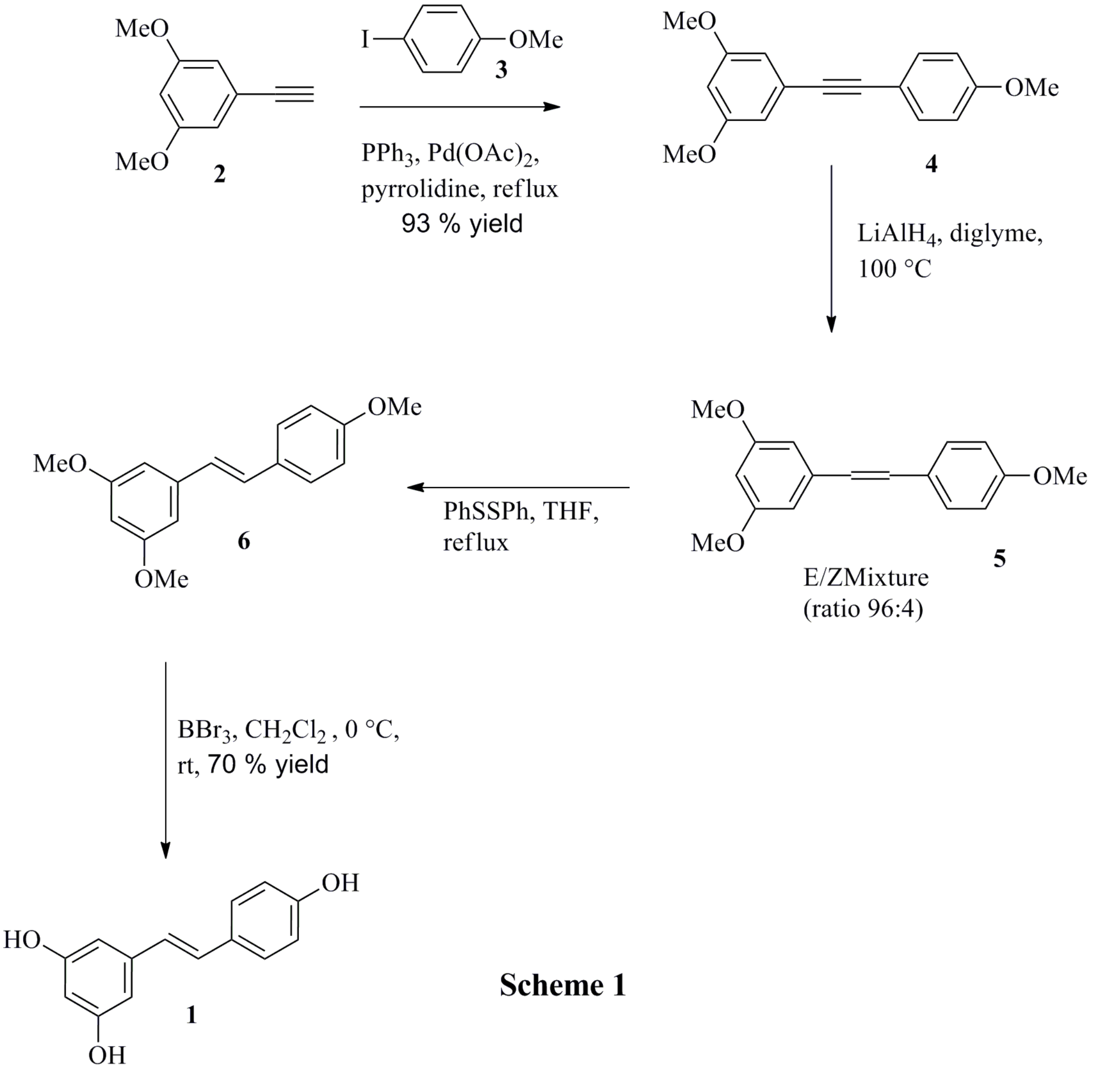
Other methodologies involving lithiation-condensation[18], Perkins[19], Ramberg-Bäcklund[20] or Diels-Alder-Wittig[21] reactions have also been reported. In many cases, however, the synthetic sequence is rather long, consequently leading to low product yields, and controlling the stereo- and regiochemistry of the process can also be difficult. The development of new strategies seems to be necessary.

In a previous report concerning the synthesis of combretastatin A4 and AVE-8062A, we developed a simple and successful method based on the use of palladium complexes to conduct cross coupling among terminal alkynes and aryl halides, without a copper salt catalyst, in refluxing pyrrolidine[22].

Therefore, we now apply the same procedure to synthesize (**1**) in a 4-step synthesis from commercial reactants and simple catalysts.

The synthetic strategy we use is reported in Scheme 1, and it consists of the Sonogashira coupling of 3,5-dimethoxy-1-ethynyl-benzene (**2**) with 4-iodoanisole (**3**) according to our previous paper[22]. These reaction conditions using $Pd(OAc)_2$ and triphenylphosphine in refluxing pyrrolidine afforded in a very simple way the precursor **4** in 93% isolated yield. To avoid hydrogenation on Lindlar´s catalyst or metal ammonia reduction, we tried stereospecific reduction by $LiAlH_4$[23], but in spite of the *trans* addition of the hydride to the triple bond occurring mainly to obtain **6**, we observed a minor *cis* addition product, giving an E/Z mixture **5**, in a ratio of 96:4, in quantitative yield. Double bond isomerization[24] of the crude mixture **5** with a catalytic amount of diphenyl disulfide in refluxing tetrahydrofuran gave solely the trans isomer **6**; deprotection (BBr_3, CH_2Cl_2, 0 °C at room temperature)[18] afforded the desired resveratrol (**1**).

In conclusion, we have developed a simple synthesis of resveratrol (**1**) with an overall yield of 62% over four steps.



Scheme 1

*Procedure for the preparation of 1,3-Dimethoxy-5-(4-methoxy-phenylethynyl)-benzene (**4**)* To a solution of 1.5 g (9.2 mmol) of 1-ethynyl-3,5-dimethoxybenzene and 2.16 g (9.2 mmol) of 4-iodoanisole in 10.0 mL of pyrrolidine, 64 mg (0.246 mmol) of triphenylphosphine and 27 mg (0.123 mmol) of $Pd(OAc)_2$ were added. The mixture was stirred under an Ar stream and heated at reflux temperature for 1.0 hour. The mixture was frozen and poured into 60 mL of saturated ammonium chloride solution and then extracted with 30 mL of CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). After filtration, the residue was purified by flash column chromatography on silica gel, with hexane-EtOAc, 9:1 as the eluent, to give pure (**4**) in 93% yield.

*(E/Z) 3´,4,5´-trimethoxy-stilbene (**5**),* To a solution of 200 mg (0.745 mmol) of 1,3-dimethoxy-5-(4-methoxy-phenylethynyl)-benzene in 6.0 mL of diglyme, under Ar stream 56.5 mg (1.49 mmol) of lithium aluminum hydride was added, and the mixture was stirred and heated at 90 to 100 °C for 1.0 hour. The solution was quenched with 20 mL of cold EtOAc and 30 mL of ammonium chloride saturated solution. The aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the residue was subjected to the next step without purification. The HPLC analysis of the mixture gave an E/Z ratio of 96:4. The analysis was performed using a column Synergi of 4 μ hydro RP 80A, with a mobile phase of methanol: acetonitrile: buffer (63:30:7), the buffer was dibasic potassium phosphate/H_3PO_4 to pH of 6.8 to temperature of 40 °C

(E)-3´,4,5´-trimethoxy-stilbene (**6**). The mixture of (E/Z) isomers (200 mg, 0.745 mmol) and 30 mg (1.49 mmol) of $(PhS)_2$ in 15.0 mL of anhydrous THF was refluxed under Ar for 2 h. After cooling, the solvent was evaporated under reduced pressure to dryness, and the residue was purified by flash column chromatography on silica gel, with hexane-EtOAc 8:2 to give pure **6** (190 mg, 95%) as a colorless oil.

*(E)-3´,4,5´-trihydroxy-stilbene (**1**),* BBr_3 (1.38 g, 5.52 mmol) was added dropwise into methylated stilbene (**6**) (190 mg, 0.745 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, then stirred for 5 h and left at room temperature over one hour. The mixture was poured onto ice, and the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x10 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous sodium sulfate and evaporated under reduced pressure to dryness. The solid was recrystallized from MeOH-CH_2Cl_2, to afford pure Resveratrol (**1**) (112 mg, 70% yield) as an off-white powder; mp 258-260 °C.

The products were analyzed by ^1H and ^{13}C NMR, IR and mass spectra. All the spectra are contained in Supplementary Material

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25. 1,3-dimethoxy-5-(4-methoxy-phenylethynyl)-benzene (**4**), IR (KBr) cm^{-1}: 2936.2, 2837.5, 2208.6, 1585.5, 1509.5, 1454.7, 1418.6, 1245.8, 1153.5.^{1}H RMN ($CDCl_3$) δ ppm: 3.8 (s, 6H, 2 CH_3), 3.82 (s, 3H, CH_3), 6.44 (t, 1H, H4´), 6.67 (d, 2H, H2´, H6´), 6.87 (dt, 2H, H3, H5), 7.46 (dt, 2H, H2, H6). ^{13}C RMN ($CDCl_3$) δ ppm: 55.277 (OCH_3), 55.408 (2 OCH_3), 88.042 (**C**≡C), 88.951 (C≡**C**), 101.507 (C4´), 109.154 (C2´, C6´), 113.979 (C3, C5), 115.122 (C2, C6), 124.834 (C1), 133.102 (C1´), 159.645 (C4), 160.478 (C3´, C5´). MS (EI, 70 eV) m/z (rel. int.): [M+] 268 (100), 253 (18), 225 (10), 210 (6), 195 (4), 182 (4), 152 (10), 134 (10). HRMS-DART calculated for $C_{17}H_{17}O_3$ [M+H$^+$] 269.11777, found: 269.11689
26. A sample of the mixture (**5**) was purified by column chromatography and spectral data of the Z isomer are the following: IR (KBr) cm^{-1}: 2834.3, 1588.7, 1508.9, 1455.9, 1425.5, 1248.1, 1203.6, 1153.8, 862.3, 835.0.1H RMN ($CDCl_3$) δ ppm: 3.77 (s, 9H, 3 CH_3), 6.31 (t, 1H, H4´), 6.43 (d, 2H, H2´, H6´), 6.45 (d, J=12.3 Hz, C**H**=CH), 6.52 (d, J=12.33 Hz, CH=C**H**), 6.76 (dt, 2H, H3, H5), 7.21 (dt, 2H, H2, H6).^{13}C RMN (CDCl3) δ ppm: 55.205 (3 OCH_3), 99.623 (C4´), 106.606 (C2´, C6´), 113.516 (C3, C5), 126.667 (**C**H=CH), 129.549 (C1), 130.140 (CH=**C**H), 130.263 (C2, C6), 139.471 (C1´), 158.731 (C4), 160.556 (C3´, C5´). MS (EI, 70 eV) m/z (rel. int.): [M+] 270 (100), 269 (23), 239 (10), 224 (10), 212 (9), 196 (12), 195 (10), 181 (10), 165 (10), 152 (15), 144 (8), 141 (10), 115 (10). HRMS-DART calculated for $C_{17}H_{19}O_3$ [M+H$^+$] 271.13342, found: 271.13268
27. (*E*)-3´,4,5´-trimethoxy-stilbene (**6**), IR (KBr) cm^{-1}: 2834.1, 1587.5, 1509.4, 1455.5, 1424.4, 1249.2, 1147.7, 958.5, 827.3, ^{1}H RMN (CDCl3) δ ppm: 3.82 (s, 9H, 3 CH_3), 6.37 (t, 1H, H4´), 6.65 (d, 2H, H2´, H6´), 6.89 (dt, 2H, H3, H5), 6.905 (d, J=16.2 Hz, C**H**=CH), 7.03 (d, J=16.25 Hz, CH=C**H**), 7.44 (dt, 2H, H2, H6). 13C RMN (CDCl3) δ ppm: 55.389 (3 OCH_3), 99.623 (C4´), 104.358 (C2´, C6´), 114.152 (C3, C5), 126.564 (**C**H=CH), 127.794 (C2, C6), 128.731 (CH=**C**H), 129.921 (C1), 139.689 (C1´), 159.391 (C4), 160.959 (C3´, C5´). MS (EI, 70 eV) m/z (rel. int.): [M+] 270 (100), 269 (25), 239 (8), 224 (10), 212 (10), 196 (10), 195 (9), 181 (8), 165 (10), 152 (15), 141 (10), 115 (10). HRMS-DART calculated for $C_{17}H_{19}O_3$ [M+H$^+$] 271.13342, found: 271.13329.
28. (*E*)-3´,4,5´-trihydroxy-stilbene (**1**), IR (KBr) cm^{-1}:3299.0, 1585.5, 1383.5, 1147.7. 1H RMN (Metanol-d4) δ ppm: 6.18 (t, 1H, H4´), 6.46 (d, 2H, H2´, H6´), 6.76 (dt, 2H, H3, H5), 6.79 (d, J=16.2 Hz, C**H**=CH), 6.95 (d, J=16.25 Hz, (CH=C**H**), 7.34(dt, 2H, H2, H6). ^{13}C RMN ($CDCl_3$) δ ppm: 102.640 (C4´), 105.779 (C2´, C6´), 116.473 (C3, C5), 126.946 (**C**H=CH), 128.757 (C2, C6), 129.379 (CH=**C**H), 130.354 (C1), 141.269(C1´), 158.280 (C4), 159.545 (C3´, C5´). MS (EI, 70 eV) m/z (rel. int.): [M+] 228 (100), 227 (13), 211 (8), 181 (18), 165 (8), 152 (8), 144 (5), 141 (5), 128 (5), 115 (8), 114 (5). HRMS-DART calculated for $C_{14}H_{13}O_3$ [M+H$^+$] 229.08647, found: 229.08662

Highlights

It has been developed a synthesis of resveratrol with good yields and high purity

Resveratrol has been synthesized by an effective and simple reaction

Was produced in 4-step including a simple Sonogashira type reaction with 93 % yields