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A re-investigation of resveratrol synthesis by Perkins reaction. Application to the synthesis of aryl cinnamic acids

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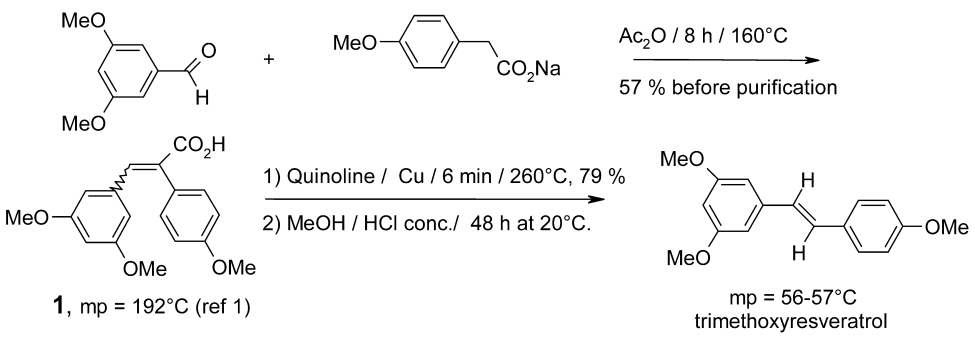
Abstract—A re-investigation of resveratrol synthesis by Perkins reaction allowed to improve this method and to determine the configuration of the intermediates. The results were applied to the synthesis of several aryl cinnamic acids for biological evaluation. © 2003 Elsevier Science Ltd. All rights reserved.

Resveratrol is a natural polyphenol which has been isolated from more than 70 plant species. In 1992 it was reported that resveratrol had antioxidant and antimutagenic properties,[1a–c] a result which is probably at the origin of a tremendous amount of work to synthesize many resveratrol analogues.[1d]

The first synthesis of resveratrol with identification of the synthetic material by comparison with the natural product was reported in 1941 by Späth and Kromp.[1e] This synthesis was indeed based on a report of Takaoka[2] who isolated resveratrol from roots of *Veratrum grandifluorum*. It described a synthesis of resveratrol dimethyl and trimethyl ether but the synthetic material could not be compared with the natural product derivatives because it never crystallized. This synthesis, a Perkins type condensation of *p*-anisyl acetic acid sodium salt with 1,3-dimethoxy benzaldehyde in acetic anhydride, was reinvestigated by Späth and Kromp[1] who purified a small sample of the resulting trimethoxystilbene carboxylic acid **1** by sublimation and after decarboxylation they isolated the trimethyl ether of resveratrol which was identical to the natural product derivative reported by Takoaka (Scheme 1).

In this reaction the configuration of **1** was not determined. After decarboxylation the product could not be crystallized and finally the trimethyl ether of resveratrol (*trans* configuration) was isolated by crystallisation in 48 h from a mixture of MeOH and conc. HCl, experimental conditions which could isomerise *cis* to *trans* resveratrol.

Later on, this Perkins type reaction was described in presence of a base for the synthesis of *cis*-stilbene from benzaldehyde and phenylacetic acid.[3] *cis*-Stilbene was obtained by decarboxylation of the adduct and this result



Scheme 1.

Keywords: cinnamic acid; *cis–trans* isomerization; Perkins reaction.

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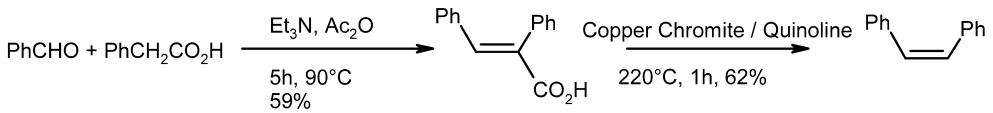
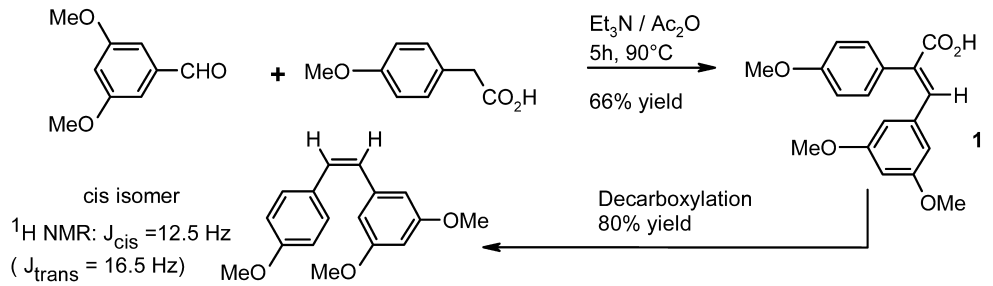


Scheme 2.



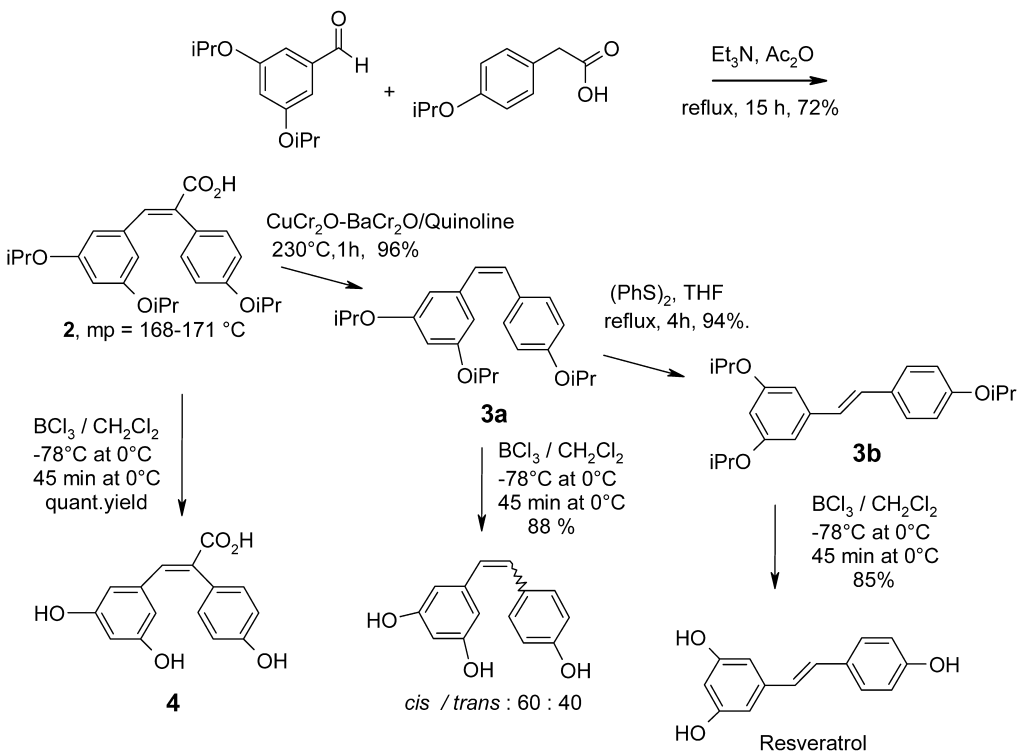
Scheme 3.

Table 1. Temperature effect on the decarboxylation of **1**

Catalyst	Solvent	*T* (°C) (time)	*cis–trans* ratio (GPC)
Cu Chromite	Quinoline	210 (1 h)	57:43
		210 (1 h 30 min)	75:25
		230 (1 h)	86:14
Cu powder	Quinoline	230 (1 h)	79:21
No catalyst	Quinoline	230 (4 h)	No reaction

allowed the authors to assume that the carboxylic acid intermediate had also the same configuration (Scheme 2). Wood and Mallory[4] applied also the method to *p*-anisaldehyde.

We report in this paper a re-investigation of the Perkins reaction for application to the synthesis of resveratrol and analogues. We also report the synthesis of several



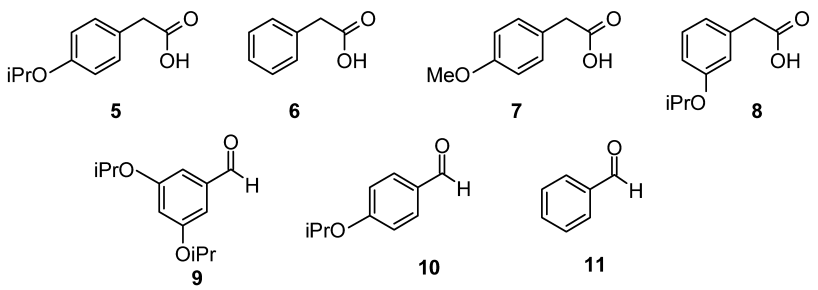
Scheme 4.

Table 2. Isomerization of *cis* and *trans* resveratrol in the NMR tube in acetone D_6

Time	*cis–trans* ratio
0	72:28
12 h	59:41
36 h	55:45
3 days	26:74

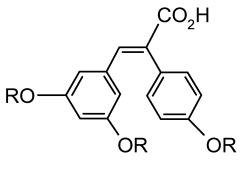
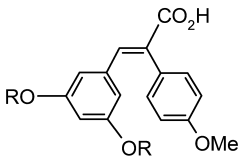
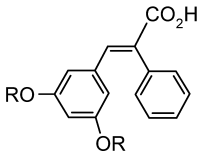
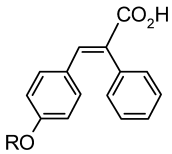
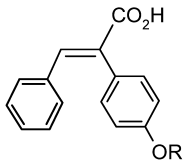
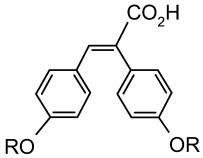
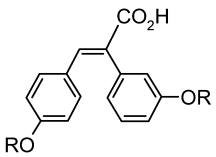
substituted aryl cinnamic acids, the first intermediate isolated in the Perkins condensation, for biological evaluation.

We started our study with Perkins condensation of *p*-anisyl acetic acid to 3,5-dimethoxybenzaldehyde in presence of acetic anhydride and triethylamine at 90°C. We obtained in 72% yield only one isomer of the resulting carboxylic acid



Scheme 5.

Table 3. Synthesis of aryl cinnamic acids by Perkins condensation

Aryl acetic acid	Aromatic aldehyde	Perkins adduct R=*i*-Pr	After deprotection with BCl_3, R=H
5	**9**	 **2**,72%	45 min at 0°C; **4**, 98%
7	**9**	 **12a**,70%	1 h at 25°C; **12b**, 86%
6	**9**	 **14**, 63%	Degradation
6	**10**	 **15a**, 58%	30 min at 25°C; **15b**, 89%
5	**11**	 **16a**, 54%	30 min at −10°C; 63%; isomerization *trans*–*cis*: 80:20
5	**10**	 **17a**, 32%	2 h at 25°C; **17b**, 97%
8	**10**	 **18a**, 30%	4 h at 0°C; **18b**, 90%

1. However the configuration of **1** was not determined in this experiment (Scheme 3).

The decarboxylation was then carried out in presence of copper chromite[3] and we found a clear temperature effect as shown in Table 1: *cis–trans* mixtures were obtained from a single carboxylic acid isomer and the *cis* isomer was always the main product. With the catalyst used by Späth and Kromp, copper powder, we isolated a 79:21 *cis–trans* mixture at 230°C showing that the pure *trans* isomer isolated by the authors resulted from isomerization during the acidic treatment they used.

Aware of the difficulties of resveratrol purification after cleavage of the methyl ethers due to degradation products, we decided to use isopropyl ethers which are known[5] to be cleaved at lower temperature than methyl ethers and should avoid the isomerization of the product.

Condensation of isopropyl ethers of *p*-hydroxyphenyl acetic acid and 3,5-dihydroxybenzaldehyde in the previous Perkins conditions (Scheme 4) led in 72% yield to only one isomer of the carboxylic acid **2** which was identified by RMN NOESY as the *cis* isomer. Gas chromatography analysis of the corresponding methyl ester showed the absence of the *trans* isomer. Decarboxylation with copper chromite at 230° afforded in 96% yield a 95:5 *cis–trans* mixture of the substituted stilbenes **3**. *cis–trans* Isomerization of this mixture in refluxing THF with phenyldisulfide led in 94% yielded the pure *trans* substituted stilbene; the isopropyl ethers were cleaved in high yield with BCl_3 below 0°C.

Attempts to isolate pure *cis*-resveratrol from the isopropyl ether 95:5 *cis–trans* mixture **3** in the same conditions and below −10°C failed giving always a 60:40 *cis–trans* mixture of resveratrol (Scheme 4). This results confirms the easy *cis–trans* isomerization[6] of resveratrol in presence of Lewis acid.

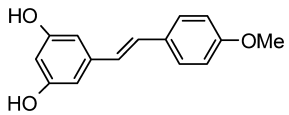
We also observed in the NMR tube a slow isomerization of *cis* resveratrol. We however, could not completely isomerise the *cis* isomer to the *trans* because of degradation in presence of acid at room temperature (Table 2).

However, the cleavage of *i*-propyl ethers in acid **2** with BCl_3 below 0° worked quantitatively without any isomerization.

It is clear that the use of *i*-propylether was an improvement in the purification of resveratrol which can be now obtained in four high yield steps.

We then applied this method to the preparation of analogues of phenyl-cinnamic acid. The starting materials used for the Perkins reaction (in the conditions used in the Scheme 4) are shown in Scheme 5, and yields in Table 3.

The deprotection conditions with BCl_3 were adapted to each compound with reaction times and temperatures between 30 min at −10°C and 2 h at 25°C (Table 3). The results listed in this Table 3 showed that the stability of the polyhydroxy cinnamic acids after cleavage of the protecting isopropyl ethers is strongly depending on the position of the phenol groups on the aromatic rings, an experimental observation which is difficult to explain at the present time (Scheme 6).



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Scheme 6.

It must be pointed out that decarboxylation of the acid **12a**, followed by deprotection with BCl_3 in the conditions described in Scheme 4, gave the mono-methoxy resveratrol **19** only in the *trans* configuration and not the usual *cis–trans* mixture; the isomerization occuring during the acidic cleavage of the *i*-propyl ethers (methyl ethers being stable in these conditions).

In conclusion, our results showed that resveratrol and analogues can be readily obtained by Perkins condensation. All the compounds listed in Table 3 are under biological evaluation.

1. Experimental

1.1. Data for compounds

1.1.1. 4-Isopropoxyphenylacetic acid (5). 10 g of 4-hydroxyphenylacetic acid, 30 g of potassium carbonate (3.3 equiv.) and 28 mL of isopropyl bromide (4.6 equiv.) in 100 mL of DMF were heated to reflux during 29 h. After cooling down to room temperature, 100 mL of water were added in order to dissolve the carbonate and 100 mL of HCl 2 M to acidify the solution. The aqueous layer was extracted by ethyl acetate (3×50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. 20 g of LiOH (14 equiv.), 100 mL of water and 100 mL of THF were added. After refluxing for 15 h, THF was evaporated. 50 mL of ether were added and the solution was acidified to pH=1 at 0°C by HCl 2 M (150 mL). The aqueous layer was extracted with ether (4×100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was recrystallized in hexane/ethyl acetate (9:1) to give 10.5 g of a colourless solid. Yield for the two steps: 85%. R_f=0.35 (hexane/ethyl acetate 1:1). Mp: 57–61°C. ^{1}H NMR ($CDCl_3$):7.00 (AB, $4H_{arom}$, J_{AB}=8.6 Hz, $\Delta\nu$=66.6 Hz), 4.52 (sept., $1H_{CH}$, J=6 Hz), 3.58 (s, $2H_{benz.}$), 1.32 (d, $6H_{(CH3)_2}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 178.2, 157.3, 130.5, 125.1, 118.0, 70.0, 40.2, 22.1.

1.1.2. 3-Isopropoxyphenylacetic acid (8). The title compound was prepared following the same procedure as for 4-isopropoxyphenylacetic acid **5** from 3-hydroxyphenylacetic acid. Yield for two steps: 73% (2.6 g). R_f=0.37 (hexane/ethyl acetate 1:1). Oil at 25°C, solide at 6°C. ^{1}H NMR ($CDCl_3$): 7.21 (m, $1H_{arom}$), 6.83 (m, $3H_{arom}$), 4.55 (sept., $1H_{CH-iPr}$, J=6.1 Hz), 3.61 (s, $2H_{benzylique}$), 1.33 (d, $6H_{CH3-iPr}$, J=6.1 Hz). ^{13}C NMR ($CDCl_3$): 177.4, 157.9, 134.7, 129.5, 121.4, 116.9, 114.5, 69.7, 40.2, 22.1.

1.1.3. 3,5-Diisopropoxybenzaldehyde (9). To 1 g of 3,5-dihydroxybenzaldehyde in DMF (10 mL) isopropyl bromide (3.1 mL, 4.5 equiv.) and then anhydrous potassium carbonate (3.3 g, 3.3 equiv.) were added at room temperature. The mixture was heated for 2.5 h at 55°C, cooled to room temperature, and quenched with water (15 mL). The organic layer was extracted with ethyl acetate (3×15 mL), dried over $MgSO_4$, filtrated and concentrated. The resulting deep red oil was purified by chromatography on silica gel (hexane/ethyl acetate 9:1) to give a pale yellow oil (1.5 g). Yield: 94%. R_f=0.67 (hexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): 9.77 (s, $1H_{(-COH)}$), 6.85 (d, 2H, J=2.4 Hz), 6.56 (t, $1H_{arom}$, J=2.3 Hz), 4.49 (sept., $2H_{(iPr)}$, J=6 Hz), 1.25 (d, $12H_{CH3(iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 192.1, 159.6, 138.4, 118.6, 110.3, 70.3, 22.0.

1.1.4. 4-Isopropoxybenzaldehyde (10). The title compound was prepared following the same procedure as for 3,5-diisopropoxybenzaldehyde **9**. Pale yellow oil (2.2 g). Yield: 82%. R_f=0.71 (hexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): 9.70 (s, $1H_{(-COH)}$), 7.49 (AB, $4H_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=225 Hz), 4.65 (sept., $1H_{(H-OiPr)}$, J=6 Hz), 1.37 (d, $6H_{(CH3-OiPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 190.2, 162.9, 131.7, 129.4, 115.4, 70.0, 21.6.

1.2. General procedure for the Perkins reaction

1.2.1. α-(*p*-Isopropoxyphenyl)-*m*,*m*-diisopropoxycinnamic acid (2). Under argon, 2.12 g of 3,5-diisopropoxybenzaldehyde (1 equiv.), 1.85 g of 4-isopropoxyphenyl-acetic acid (1 equiv.), 1.62 mL of acetic anhydride (1.8 equiv.) and 0.94 mL of triethylamine (0.7 equiv.) were heated at 110°C during 12 h, cooled at room temperature, diluted in 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated. A deep yellow solid (4.24 g) was purified by chromatography on silica gel (hexane/ethyl acetate 9:1). 300 mg (16%) of the aldehyde were recovered and 3 g of solid were recrystallized in hexane to give 2.38 g of acid **2**. Yield: 72%. **R_f=0.46 (hexane/ethyl acetate 1:1). Mp: 168–171°C. ^{1}H NMR ($CDCl_3$): 7.79 (s, $1H_{vinylic}$), 7.02 (AB, $4H_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=51.7 Hz), 6.30 (t, $1H_{arom}$, J=2 Hz), 6.23 (d, $2H_{arom}$, J=2 Hz), 4.52 (sept., $1H_{(1×iPr)}$, J=6 Hz), 4.16 (sept., $1H_{(2×iPr)}$, J=6 Hz), 1.32 (d, $6H_{(1×iPr)}$, J=6 Hz), 1.17 (d, $6H_{(2×iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 173.7, 158.7, 157.8, 142.6, 136.2, 131.5, 131.1, 127.5, 115.9, 110.2, 106.2, 69.9, 69.8, 22.2, 22.1. For $C_{24}H_{30}O_5$ were calculated 72.36 %C, 7.54 %H and found 72.34 %C, 7.81 %H.

1.3. General procedure for decarboxylation

1.3.1. *cis* 3,4′,5-Triisopropoxystilbene (3a). To 4.19 g of the acid **2**, were added 15 mL of quinoline (11 equiv.) and 214 mg of copper chromite. The reaction flask was heated at 230–240°C during 1 h. The mixture was then cooled, filtrated over celite which was washed with 2×20 mL of ethyl acetate. The organic layer was washed with 2×20 mL of HCl 2 M, dry over $MgSO_4$ and concentrated. 4.60 g of a black oil were purified by chromatography on silica gel (hexane/ethyl acetate 9.5:0.5) to give a pale yellow oil (3.55 g). Yield: 96%. R_f=0.38. ^{1}H NMR ($CDCl_3$): 6.97 (AB, $4H_{arom}$, J_{AB}=8.6 Hz, $\Delta\nu$=90 Hz), 6.46 (AB, $2H_{vinylic}$, J_{AB}=12.2 Hz, $\Delta\nu$=15 Hz), 6.38 (d, $2H_{arom}$, J=2.2 Hz), 6.28 (t, $1H_{arom}$, J=2.2 Hz), 4.50 (sept, $1H_{(1×iPr)}$, J=6.0 Hz), 4.34 (sept, $2H_{(2×iPr)}$, J=6.0 Hz), 1.31 (d, $6H_{(1×iPr)}$, J=6.0 Hz), 1.23 (d, $12H_{(2×iPr)}$, J=6.0 Hz). ^{13}C NMR ($CDCl_3$): 158.9, 157.0, 139.5, 130.3, 130.0, 129.6, 129.0, 115.6, 108.4, 103.4, 69.9, 22.1. For $C_{23}H_{30}O_3$ were calculated 77.96 %C, 8.47 %H and found 77.73 %C, 8.71 %H.

1.4. General procedure for isopropyl ether cleavage

1.4.1. α-(*p*-Hydroxyphenyl)-*m*,*m*-dihydroxycinnamic acid (4). To 450 mg of acid **2** in 8 mL of dichloromethane, were added at −78°C, 7.4 mL of BCl_3 (1 M in CH_2Cl_2). The mixture was maintained 1.5 h between −30 and −60°C then 45 min at 0°C. After addition of the borane, a deep yellow precipitate appeared and remained during all the reaction. By quenching with water (10 mL), the colour disappeared. 15 mL of ethyl acetate were added at 0°C, (to dissolve the precipitate) and 10 mL of 2 M sodium hydroxide were added (pH=1). The aqueous layer was extracted with ethyl acetate (3×10 mL), the organic layer was dried over $MgSO_4$ and concentrated. 330 mg of a colourless powder were obtained. Yield: 98%. Mp: 254–257°C. ^{1}H NMR ($CDCl_3$): 8.50 (bs, 1H), 8.30 (bs, 2H), 7.55 (s, $1H_{vinylic}$), 6.85 (AB, $4H_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=52 Hz), 6.15 (t, $1H_{arom}$, J=2.1 Hz), 6.04 (d, $2H_{arom}$, J=2.1 Hz). ^{13}C NMR ($CDCl_3$): 168.9, 158.6, 157.4, 139.8, 137.4, 133.1, 131.4, 127.6, 115.5, 109.4, 103.9.

1.4.2. *trans* 3,4′,5-Triisopropoxystilbene (3b). 2.5 g of *cis*-triisopropoxystilbene **3a** in THF (40 mL) and diphenyldisulfide (0.34 g, 0.2 equiv.) were heated under reflux for 4 h. The THF was evaporated, 2.94 g were purified by chromatography on silica gel (ethyl acetate/hexane 1:19), to give 2.4 g of a yellow oil. Yield: 96%. R_f=0.33 (hexane/ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$): 7.14 (AB, $4H_{arom}$, J_{AB}=8.8 Hz, $\Delta\nu$=108 Hz), 6.93 (AB, $2H_{vinylic}$, J_{AB}=16.2 Hz, $\Delta\nu$=26.4 Hz), 6.61 (d, $2H_{arom}$, J=2.1 Hz), 6.34 (t, $1H_{arom}$, J=2.1 Hz), 5.57 (sept, $2H_{(1×iPr)}$, J=6.0 Hz), 5.56 (sept, $1H_{(2×iPr)}$, J=6.0 Hz), 1.33 (d, $18H_{(3×iPr)}$, J=6.0 Hz). ^{13}C NMR ($CDCl_3$): 159.3, 157.7, 139.7, 129.9, 128.6, 127.8, 126.7, 116.1, 106.3, 103.0, 70.0, 22.2.

1.4.3. *trans* 3,4′,5-Trihydroxystilbene (resveratrol). To 200 mg of triisopropoxystilbene, in dichloromethane (20 mL), at −78°C, were added 3.4 mL of BCl_3 1 M in CH_2Cl_2. The temperature was allowed to reach −10°C, and maintained for 1 h at −10°C. The reaction was quenched with 20 mL of water, the pink solution turned to pale. 20 mL of ethyl acetate were added and then 8 mL of a 10% potassium carbonate solution to reach pH=6. In order to be in slightly acidic conditions (pH=1.5), 0.25 mL of HCl 2 M were added. The aqueous layer was extracted with ethyl acetate (3×10 mL). After drying over $MgSO_4$, concentrating, the slightly coloured powder obtained (169 mg) was dissolved in 4 mL of ethyl acetate. Adding 5 mL of hexane induced a precipitation. After filtration, 109 mg of a colourless powder were obtained. Yield: 85%. Mp: 255–260°C. R_f=0.24 (hexane/ether 1:3). ^{1}H NMR ($CDCl_3$): 8.50 (s, $1H_{phenol}$), 8.23 (s, $2H_{phenol}$), 7.13 (AB, $4H_{arom}$, J_{AB}=8.6 Hz, $\Delta\nu$=117 Hz), 6.96 (AB, $2H_{vinylic}$, J_{AB}=16.4 Hz, $\Delta\nu$=26.0 Hz), 6.54 (d, $2H_{arom}$, J=2.1 Hz),

6.27 (t, 1H$_{arom}$, J=2.1 Hz). ^{13}C NMR ($CDCl_3$): 159.1, 157.6, 140.4, 129.5, 128.6, 128.3, 126.4, 115.9, 105.2, 102.2.

1.4.4. *cis* 3,4′,5-Trihydroxystilbene. Following the same procedure as for *trans*-triisopropoxystilbene, the *cis* 3,4′,5-triisopropoxystilbene (200 mg) was deprotected to give 114 mg of 3,4′,5-trihydroxystilbene-*cis* and 3,4′,5-trihydroxystilbene-*trans* in 60:40 to 50:50 mixtures. Yield: 88%. R_f=0.17 (hexane/ether 1:3). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H$_{phenol}$), 8.14 (s, 2H$_{phenol}$), 6.90 (AB, 4H$_{arom}$, J_{AB}=8.8 Hz, $\Delta\nu$=88.1 Hz), 6.37 (AB, 2H$_{vinylic}$, J_{AB}=12.3 Hz, $\Delta\nu$=15.6 Hz), 6.29 (d, 2H$_{arom}$, J=2.2 Hz), 6.22 (t, 1H$_{arom}$, J=2.2 Hz).

1.4.5. α-(Methoxyphenyl)-*m*,*m*-dimethoxycinnamic acid (1). The title compound was prepared following the general Perkins procedure. Yield: 66% (1.25 g). R_f=0.20 (hexane/ethyl acetate 1:1). Mp: 171–174°C. ^{1}H NMR ($CDCl_3$): 7.83 (s, 1H$_{vinyl}$), 7.06 (AB, 4H$_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=50 Hz), 6.35 (t, 1H$_{para}$, J=2 Hz), 6.27 (d, 2H$_{ortho}$, J=2 Hz,), 3.82 (s, 3H$_{(1\times OMe)}$), 3.56 (s, 6H$_{(2\times OMe)}$). ^{13}C NMR ($CDCl_3$): 172.3, 160.3, 159.5, 142.2, 136.2, 131.5, 131.2, 127.6, 114.3, 108.6, 102.6, 55.4. For $C_{18}H_{17}O_5$, calculated 68.94 %C, 5.43 %H, and found 69.20 %C, 5.69 %H.

1.4.6. 3,4′,5-Trimethoxystilbene-*cis*. From (**1**) by the decarboxylation procedure. Yield: 80% (215 mg). Yellow oil. R_f=0.57 (hexane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): 6.99 (AB, 4H$_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=90 Hz), 6.49 (AB, 2H$_{vinyl}$, J_{AB}=12.5 Hz, $\Delta\nu$=20 Hz), 6.44 (d, 2H$_{ortho}$, J=2 Hz), 6.32 (t, 1H$_{meta}$, J=2 Hz), 3.78 (s, 3H$_{(OMe)}$), 3.67 (s, 6H$_{(2\times OMe)}$). ^{13}C NMR ($CDCl_3$): 161.1, 159.3, 140.0, 130.8, 130.8, 129.2, 130.7, 114.1, 107.2, 100.2, 55.8. For $C_{17}H_{17}O_3$, calculated 75.75 %C, 6.31 %H, and found 75.83 %C, 6.58 %H.

1.4.7. 3,4′,5-Trimethoxystilbene-*trans*. Following the general isomerization procedure, yield: 91% (176 mg). R_f=0.48 (hexane/ethyl acetate 1:1). Mp: 54–56°C (lit.: 56–57°C). ^{1}H NMR ($CDCl_3$): 7.19 (AB, 4H$_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=110 Hz), 7.03 (AB, 2H$_{vinyl}$, J_{AB}=16.5 Hz, $\Delta\nu$=25 Hz), 6.68 (d, 2H$_{meta}$, J=2 Hz), 6.40 (t, 1H$_{ortho}$, J=2 Hz), 3.84 (s, 3H$_{(3\times OMe)}$). ^{13}C NMR ($CDCl_3$): 161.1, 159.5, 139.8, 128.8, 127.9, 126.7, 114.2, 104.4, 130.0, 99.7, 55.4, 55.4.

1.4.8. α-(*p*-Methoxyphenyl)-*m*,*m*-diisopropoxycinnamic acid (12a). Yield: 70% (3.83 g). R_f=0.36 (hexane/ethyl acetate 1:1). Mp: 172–177°C. ^{1}H NMR ($CDCl_3$): 7.81 (s, 1H$_{vinyl}$), 7.05 (AB, 4H$_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=50 Hz), 6.31 (t, 1H$_{arom}$, J=2 Hz), 6.22 (d, 2H$_{arom}$, J=2 Hz), 4.16 (sept, 1H$_{(1\times iPr)}$, J=6 Hz), 3.81 (s, 3H$_{(OMe)}$,), 1.17 (d, 12H$_{(2\times iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 173.0, 159.8, 159.1, 142.9, 136.4, 131.5, 131.4, 128.1, 114.6, 110.5, 106.5, 70.3, 55.7, 22.4. For $C_{22}H_{26}O_5$, calculated 71.26 %C, 7.02 %H, and found 71.04 %C, 6.98 %H.

1.4.9. α-(*p*-Methoxyphenyl)-*m*,*m*-dihydroxycinnamic acid (12b). Yield: 86% (320 mg). R_f=0.20 (hexane/ether 1:9). Mp: 176–183°C. ^{1}H NMR ($(CD_3)_2CO$): 8.27 (bs, 2H$_{phenol}$), 7.66 (s, 1H$_{vinyl}$), 7.03 (AB, 4H$_{arom'}$, J_{AB}=9 Hz, $\Delta\nu$=45 Hz), 6.26 (t, 1H$_{para}$, J=2.1 Hz), 6.17 (d, 2H$_{ortho}$, J=2.1 Hz), 3.82 (s, 3H$_{(OMe)}$). ^{13}C NMR ($(CD_3)_2CO$): 169.0, 129.3, 160.1, 114.5, 159.1, 109.9, 140.6, 104.5, 137.8, 55.7, 133.5, 131.9. IR: 3352, 3210, 1695, 1618, 1600, 1513, 1447, 1370, 1331.

1.4.10. α-Phenyl-*m*,*m*-diisopropoxycinnamic acid (14). Yield: 63% (1.35 g). R_f=0.37 (hexane/ethyl acetate 1:1). Mp: 149–156°C. ^{1}H NMR ($CDCl_3$): 7.84 (s, 1H$_{vinyl}$), 7.37 (m, 3H$_{arom}$), 7.27 (m, 2H$_{arom}$), 6.31 (t, 1H$_{arom}$, J=2 Hz), 6.20 (d, 2H$_{arom}$, J=2 Hz), 4.11 (sept, 2H$_{(2\times iPr)}$, J=6 Hz), 1.15 (d, 12H$_{(2\times iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 173.1, 158.6, 142.7, 135.7, 131.5, 129.7, 128.7, 127.9, 110.2, 106.3, 69.8, 22.0. For $C_{21}H_{24}O_4$, calculated 74.09 %C, 7.11 %H, and found 73.96 %C, 7.22 %H.

1.4.11. α-(Phenyl)-*p*-isopropoxycinnamic acid (15a). Yield: 58% (1.05 g). R_f=0.42 (hexane/ethyl acetate 1:1). Mp: 148–156°C. ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H$_{vinyl}$), 7.37 (m, 3H$_{arom}$), 7.25 (m, 2H$_{arom}$), 6.82 (AB, 4H$_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=65 Hz), 4.50 (sept, 1H$_{(1\times iPr)}$, J=6 Hz), 1.29 (d, 6H$_{(2\times iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 173.5, 159.2, 142.3, 136.0, 132.9, 129.9, 129.0, 128.9, 127.9, 126.6, 115.3, 69.9, 22.0.

1.4.12. α-(Phenyl)-*p*-hydroxycinnamic acid (15b). Colourless powder. Yield: (89%). R_f=0.47 (ether). Mp: 190–193.5°C. ^{1}H NMR ($(CD_3)_2CO$): 8.79 (bs, 1H$_{phenol}$), 7.80 (s, 1H$_{vinyl}$), 7.37 (m, 3H$_{arom}$), 7.23 (m, 2H$_{arom}$), 6.85 (AB, 4H$_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=65 Hz). ^{13}C NMR ($(CD_3)_2CO$): 169.0, 159.5, 140.9, 138.1, 133.4, 134.2, 130.7, 129.4, 128.3, 127.1, 116.1.

1.4.13. α-(*p*-Isopropoxyphenyl)-cinnamic acid (16a). Yield: 54% (1.45 g). R_f=0.36 (hexane/ethyl acetate 1:1). Mp: 142–149°C. ^{1}H NMR ($CDCl_3$): 7.90 (s, 1H$_{vinyl}$), 7.15 (m, 5H$_{arom}$), 7.04 (AB, 4H$_{arom}$, J_{AB}=9 Hz, $\Delta\nu$=60 Hz), 4.52 (sept, 1H$_{(1\times iPr)}$, J=6 Hz), 1.36 (d, 6H$_{(1\times iPr)}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 173.5, 157.8, 142.2, 134.7, 131.4, 131.2, 130.9, 129.4, 128.3, 127.1, 116.1, 69.8, 22.0.

1.4.14. α-(*p*-Hydroxyphenyl)-cinnamic acid (16b). Colourless powder. Yield: 63%. Mp: 191–194°C/212–214°C. ^{1}H NMR ($(CD_3)_2CO$): *cis*: 8.52 (bs, 1H$_{phenol}$), 7.80 (s, 1H$_{vinyl}$), 7.21 (m, 5H$_{arom}$), 6.96 (AB, 4H$_{arom}$, J_{AB}=4.5 Hz, $\Delta\nu$=40 Hz). *trans*: 8.66 (bs, 1H$_{phenol}$), 7.69 (s, 1H$_{vinyl}$), 7.21 (m, 5H$_{arom}$), 7.01 (AB, 4H$_{arom}$, J_{AB}=4.5 Hz, $\Delta\nu$=120 Hz). ^{13}C NMR ($(CD_3)_2CO$): *cis*: 168.6, 157.5, 139.4, 135.7, 133.6, 131.4, 130.7, 129.1, 128.5, 127.6, 115.7. *trans*: 168.6, 157.8, 136.0, 135.9, 133.6, 131.3, 130.5, 128.7, 128.6, 128.4, 116.5.

1.4.15. α-(*p*-Isopropoxyphenyl)-*p*-isopropoxycinnamic acid (17a). Yield: 32% (1.41 g). R_f=0.36 (hexane/ethyl acetate 1:1). Mp: 153–156.5°C. ^{1}H NMR ($CDCl_3$): 7.84 (s, 1H$_{vinyl}$), 7.02 (AB, 4H$_{arom}$, J_{AB}=8.8 Hz, $\Delta\nu$=150 Hz), 6.85 (AB, 4H$_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=75 Hz), 4.54 (sept, 2H$_{2\times iPr}$, J=6.1 Hz), 1.34 (d, 6H$_{1\times iPr}$, J=6.1 Hz), 1.29 (d, 6H$_{1\times iPr}$, J=6.1 Hz). ^{13}C NMR ($CDCl_3$): 173.6, 159.1, 157.6, 142.0, 132.8, 131.1, 128.6, 127.7, 126.8, 116.2, 115.3, 70.0, 69.9, 22.2, 22.0. IR: 2979, 2932, 2624, 1666, 1598, 1564, 1504, 1465, 1421. For $C_{21}H_{24}O_4$, calculated 74.09 %C, 7.11 %H, and found 73.82 %C, 7.09 %H.

1.4.16. α-(*p*-Hydroxyphenyl)-*p*-hydroxycinnamic acid (17b). Yield: 97% (260 mg). R_f=0.18 (hexane/ether 1:5).

Mp: 153.5–159°C. ^{1}H NMR ($(CD_3)_2CO$): 8.75 (bs, $1H_{phenol}$), 8.45 (bs, $1H_{phenol}$), 7.74 (s, $1H_{vinyl}$), 6.96 (AB, $4H_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=40 Hz), 6.85 (AB, $4H_{arom}$, J_{AB}=8.8 Hz, $\Delta\nu$=70 Hz). ^{13}C NMR ($(CD_3)_2CO$): 169.4, 159.3, 157.9, 140.4, 133.3, 131.9, 130.6, 128.7, 127.5, 116.3, 116.0. IR: 3217, 1659, 1600, 1509, 1420.

1.4.17. α-(*m*-Isopropoxyphenyl)-*p*-isopropoxycinnamic acid (18a). Yield: 30% (1.30 g). R_f=0.36 (hexane/ethyl acetate 1:1). Mp: 122.5–127°C. ^{1}H NMR ($CDCl_3$): 7.88 (s, $1H_{vinyl}$), 7.30 (t, $1H_{meta'}$, J=8.2 Hz), 6.90 (ddd, $1H_{para'}$, J=8.2 Hz, J=2.4 Hz, J=0.9 Hz), 6.86 (AB, $4H_{arom}$, J_{AB}=8.8 Hz, $\Delta\nu$=25 Hz), 6.82 (dd, $1H_{ortho'}$, J=2.4 Hz, J=0.9 Hz), 6.80 (m, $1H_{ortho''}$), 4.52 (sept, $2H_{2\times i\mathrm{Pr}}$, J=6.1 Hz), 1.17 (d, $12H_{2\times i\mathrm{Pr}}$, J=6.1 Hz). ^{13}C NMR ($CDCl_3$): 173.6, 159.3, 158.3, 142.3, 137.2, 133.0, 130.0, 128.9, 126.6, 122.0, 117.0, 116.0, 115.4, 70.0, 69.9, 22.1, 22.0. IR: 2973, 2934, 2549, 1673, 1595, 1564, 1507, 1487, 1470, 1437, 1424, 1383, 1373. For $C_{21}H_{24}O_4$, calculated 74.09 %C, 7.11 %H, and found 74.08 %C, 7.16 %H.

1.4.18. α-(*m*-Hydroxyphenyl)-*p*-hydroxycinnamic acid (18b). Yield: 90% (340 mg). R_f=0.16 (hexane/ether 1:9). Mp: 199–204°C. ^{1}H NMR ($(CD_3)_2CO$): 8.80 (s, $1H_{phenol}$), 8.38 (s, $1H_{phenol}$), 7.35 (s, $1H_{vinyl}$), 7.23 (t, $1H_{meta'}$), 6.86 (AB, $4H_{arom}$, J_{AB}=6.5 Hz, $\Delta\nu$=25 Hz), 6.84 (ddd, $1H_{arom}$, J=8.2 Hz, J=2.4 Hz, J=1.2 Hz), 6.70 (m, $2H_{arom}$). ^{13}C NMR ($(CD_3)_2CO$): 168.4, 158.9, 158.0, 140.1, 138.8, 132.9, 130.1, 130.0, 126.6, 121.2, 116.9, 115.5, 114.8. IR: 3336, 3209, 2952, 2924, 2854, 2627–2511, 2260, 1707, 1660, 1594, 1582, 1510, 1492, 1440, 1415. For $C_{15}H_{12}O_4$, calculated 77.20 %C, 7.96 %H, and found 76.96 %C, 8.18 %H.

1.4.19. 3,5-Diisopropoxy-4′-methoxystilbene-*cis*. Oil. Yield: 84% (1.8 g). R_f: *cis* R_f=0.54 (hexane/ethyl acetate 4:1). *Trans* R_f=0.46 (hexane/ethyl acetate 4:1). ^{1}H NMR ($CDCl_3$): 6.99 (AB, $4H_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=90 Hz), 6.47 (AB, $2H_{vinyl}$, J_{AB}=12 Hz, $\Delta\nu$=15 Hz), 6.38 (d, $2H_{arom}$, J=2 Hz), 6.29 (t, $1H_{arom}$, J=2 Hz), 4.35 (sept, $2H_{(2\times i\mathrm{Pr})}$, J=6 Hz), 3.78 (s, $3H_{(OMe)}$), 1.24 (d, $12H_{(2\times i\mathrm{Pr})}$, J=6 Hz). ^{13}C NMR ($CDCl_3$): 159.0, 159.0, 139.5, 130.3, 129.9, 129.8, 129.1, 113.7, 108.4, 103.4, 69.9, 55.3, 22.2. For $C_{21}H_{26}O_3$, calculated 77.20 %C, 7.96 %H, and found 76.96 %C, 8.18 %H.

1.4.20. 3,5-Dihydroxy,4′-methoxystilbene-*trans* (19). Colourless powder. Yield: 90%. R_f: *cis* R_f=0.30; *trans* R_f=0.20 (hexane/ether 1:3). Mp: 158–166°C. ^{1}H NMR ($(CD_3)_2CO$): 8.25 (bs, $2H_{phenol}$), 7.21 (AB, $4H_{arom}$, J_{AB}=8.5 Hz, $\Delta\nu$=115 Hz), 6.99 (AB, $2H_{vinyl}$, J_{AB}=16 Hz, $\Delta\nu$=20 Hz), 6.56 (d, $2H_{arom}$, J=2 Hz), 6.29 (t, $1H_{arom}$, J=2 Hz), 3.80 (s, $3H_{(OMe)}$). ^{13}C NMR ($(CD_3)_2CO$): 159.9, 159.1, 140.2, 130.5, 128.2, 128.0, 127.1, 114.4, 105.2, 102.3, 55.1.

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