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# A two-step process for the synthesis of hydroxytyrosol

Paolo Ziosi,[a,b] Claudio Paolucci,[a] Francesco Santarelli,[a] Tommaso Tabanelli,[a] Sauro Passeri,[c] Fabrizio Cavani*[a,b] and Paolo Righi*[a]

**Abstract:** Here we report about a new process for the synthesis of hydroxytyrosol (3,4-dihydroxyphenylethanol), the most powerful natural antioxidant currently known, by means of a two-step approach. Catechol is first reacted with 2,2-dimethoxyacetaldehyde in basic aqueous medium, to produce the corresponding mandelic derivative with > 90% conversion of the limiting reactant and about 70% selectivity to the desired para-hydroxyalkylated compound. Thereafter, the intermediate is hydrogenated to hydroxytyrosol using a Pd/C catalyst, with total conversion of the mandelic derivative and 68% selectivity. This two-step process is the first example of a synthetic pathway for hydroxytyrosol which does not involve the use of halogenated components or of reduction methodologies that produce stoichiometric waste. It also avoids the complex procedure currently used for hydroxytyrosol purification when it is extracted from wastewater of olive oil production.

## Introduction

Hydroxytyrosol (**1**, 3,4-dihydroxyphenylethanol) is the most powerful natural antioxidant currently known.[1] It can be found in leaves and fruits of olive, extra virgin olive oil and it is particularly abundant in olive oil mill wastewaters from where it can be recovered.[2] Hydroxytyrosol is a metabolite of oleuropein (**2**), another major phenolic component of olive products; they both give to extra-virgin olive oil its bitter and pungent taste (Figure 1).

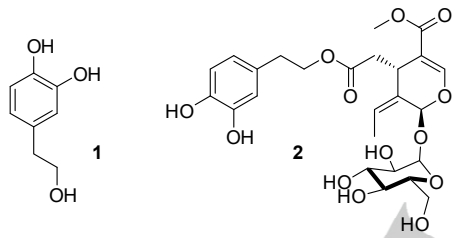

**Figure 1.** Structures of hydroxytyrosol (**1**) and oleuropein (**2**).

Well-documented studies confirm its anti-inflammatory, antibacterial, antioxidant health benefits, its anticancer (fat-related) activity, it improves the quality of life for osteoporosis patients and, mainly, it reduces heart disease pathogenesis.[3] Although still relatively new to most people, **1** promises to soon become a staple in natural health care. More active than antioxidant vitamins and synthetic antioxidants, **1** is an amphiphilic molecule that is rapidly absorbed into the bloodstream and tissues, where it can perform its free radical scavenging duties. It is the only phenolic compound that is able to cross the blood-brain barrier, which allows it to also absorb free radicals throughout the central nervous system. [3f, 3g] It is also a metabolite of the neurotransmitter dopamine, which means it may play a role in neuroprotection. Therefore, **1** is employed in food (stabilizer for vegetable oils, beverages, margarines, yogurts, etc.), pharmaceutical (supplements) and cosmetic industries (sun screens, lotions, shampoos, deodorizers etc). It is not surprising that many chemical efforts have been made to collect pure **1**, either by synthesis or from natural sources.[2]

There are several synthetic approaches[1b,4] but they have important disadvantages because they are generally based on simple reduction of commercial 3,4-dihydroxyphenylacetic acid (or the corresponding methyl ester, or the mono/bis *O*-methylated catechol derivatives) using halogenated reactants and stoichiometric reductants ($NaBH_4$ or $LiAlH_4$). Other examples start from tyrosol (or derivatives such as homovanillyl alcohol) but this is a highly costly reactant and a two-step 2-iodoxybenzoic acid (IBX) oxidation/$Na_2S_2O_4$-reduction is necessary. More recently, commercially available 3,4-dihydroxybenzaldehyde was used as the starting material, but again it is not a cheap reactant and a multi-step process is required, which also employs halogenated reactants/solvents.

There are several patents issued on the synthesis of **1**: some use expensive starting materials (such as tyrosol or its derivatives) [4b] or carcinogenic reactants (such as epoxides derivatives,[4c] safrole[4d]). There are examples of total synthesis of **1** starting from cheaper materials (such as catechol), but again the problems are related to multi-step synthetic sequences, the use of halogenated reactants (which release HCl) and stoichiometric reductants.[4d-4f] In a recent patent, a natural-identical hydroxytyrosol is obtained through a synthetic procedure starting from 2-(3,4-dimethoxyphenyl)ethanol.[4g] At last, there are examples based on enzymatic treatments of natural sources, such as oleuropein or tyrosol-containing wastewaters from olive processing.[4h,4i,4o]

Nowadays the only way to obtain **1** at an industrial scale is by means of extraction (or in some cases by membrane filtration) from wastewater of olive oil production industry. The more relevant issues are the low extraction yield, the use of large amounts of organic solvents (such as hexane, ethyl acetate) and the several and expensive purification steps.[4j,4k]

However, none of the above-mentioned processes provides **1** in high amount and purity or the processes are very expensive.

In the present work, we report a more sustainable and convenient process for the synthesis of **1**: our aim was to develop a two-step reaction starting from cheap reactants, avoiding halogenated or stoichiometric reductants, and using only water as solvent. The detailed study underpinning such

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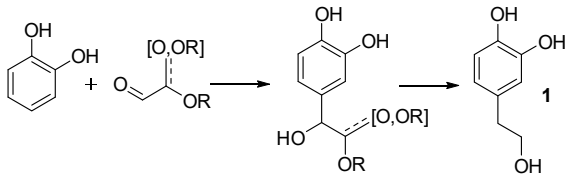
achievements, namely the studies on the parameters affecting the yield and selectivity to **1**, is also reported.
The idea behind the new process reported here is to hydroxyalkylate catechol with an oxygenated $C_2$ compound to obtain the corresponding para-substituted product. The second step is the one-pot hydrogenation of this intermediate to **1** using $H_2$ as reductant and a metal supported catalyst (Scheme 1).




**Scheme 1.** A novel two-step hydroxyalkylation/reduction access to **1** from catechol.

Nowadays, catechol is industrially produced by hydroxylation of phenol with hydrogen peroxide in the presence of a catalyst such as phosphoric and perchloric acid (Rhone-Poulenc process), [5a] ferrocene and cobalt salts (Brichima process),[5b] organic peroxides and acid (Ube process)[5c] and titanium silicalite (TS-1) (EniChem, now CFS Europe).[5d] However, the current research is focused on the development and improvement of new synthetic pathways starting from lignin. In particular, catechol can be produced as a by-product by means of pyrolysis, hydrogenolysis and hydrothermal cracking.[5e,5f,5g] Recently, an LCA analysis of these innovative routes compared to the traditional ones revealed an overall reduction in environmental impacts for the lignin route compared to the fossil-based ones.[5h]

## Results and Discussion

### Hydroxyalkylation step

Preliminary experiments were aimed at finding the conditions for the aqueous base-promoted hydroxyalkylation under which high substrate conversion into the 4-substituted intermediate was achieved.
We carried out several tests in order to screen which reactants and reaction conditions were the most promising ones. The reactions were usually followed by TLC, HPLC and $^1$H-NMR.
Glyoxylic acid (**3**),[6a] glyoxal (**4**) and 2,2-dimethoxyacetaldehyde (**5**) (Figure 2) were tested as the oxygenated $C_2$ compound in the hydroxyalkylation step. In the case of hydroxyalkylation with **3** we obtained the desired mandelic derivative with good yield (48 %) and we purified it by means of a chromatographic column.

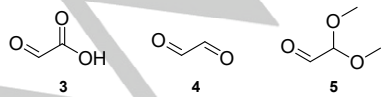
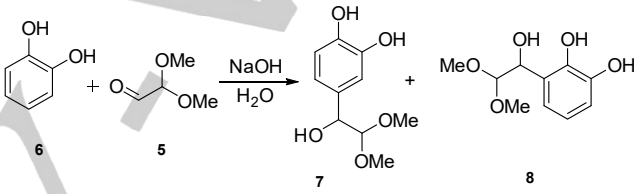



**Figure 2.** Structures of glyoxylic acid (**3**), glyoxal (**4**) and 2,2-dimethoxy-acetaldehyde (**5**).

However, we later found (*vide infra*) that the carboxylic group of this mandelic derivative cannot be properly hydrogenated to the desired product **1**; therefore we abandoned **3** as the reactant for the hydroxyalkylation of **6**. The use of **4** was also abandoned because the yields to the desired product were lower than 4%. In fact, in basic aqueous solution **4** undergoes a fast intramolecular Cannizzaro reaction,[6b] forming sodium glycolate. We thought that the use of **5** could solve the problem of reactant disproportionation; in fact, **5** has one aldehydic group which is needed for the hydroxyalkylation, while the second is masked by the acetal group, which in basic aqueous solution is stable and cannot react forming by-products. This reactant can also be easily prepared by reacting glyoxal dissolved in methanol in the presence of an acid catalyst.[6b]
The reaction is depicted in Scheme 2, showing the desired 4-substituted catechol derivative (**7**) as opposed to the undesired 3-substituted catechol derivative **8**.




**Scheme 2.** Reaction between **6** and **5** to form the desired 4-substituted catechol derivative **7**. The structure of the undesired 3-subtituted catechol derivative **8** is also shown.

We started with the screening of the reaction temperature at a given molar feed ratio (**6** : **5** : NaOH = 1 : 1 : 1) (entries 1, 6 and 7 in Table 1). From rt to 80°C the selectivity to the desired product was satisfactory, between 65 and 71%. At 80°C the reaction was complete in 5-6 hours, whereas at lower temperatures it was not complete even after 24 h. We noticed that the NaOH : **6** molar ratio influences the products distribution, independently from the amount of **5** used. In fact, with a NaOH : **6** molar ratio of 0.5 or less, the selectivity to **7** was always close to 70% (entries 2, 4, 5, 8 and 9 in Table 1).

**Table 1.** Results of the hydroxyalkylation reaction of **6** with **5**.

| | molar feed ratio[a] | | | **6** | Selectivity (%) | | **5** |
|---|---|---|---|---|---|---|---|
| entry | **5** | NaOH | T (°C) | X (%) | **7** | **8** | X (%)[b] |
| 1 | 1 | 1 | 80 | 75 | 60 | 40 | 79 |
| 2 | 1 | 0.5 | 80 | 62 | 69 | 31 | 65 |
| 3 | 0.5 | 1 | 80 | 45 | 53 | 47 | 96 |
| 4 | 0.5 | 0.5 | 80 | 44 | 69 | 31 | 96 |
| 5 | 0.5 | 0.25 | 80 | 37 | 70 | 30 | 79 |
| 6 | 1 | 1 | rt | 60 | 66 | 34 | 65 |
| 7 | 1 | 1 | 40-60 | 70 | 65 | 35 | 74 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | 0.5 | 0.5 | 40-60 | 34 | 71 | 29 | 69 |
| 9 | 0.5 | 0.5 | 60 | 37 | 69 | 31 | 79 |

[a] With respect to **6**; **5** = 2,2-dimethoxyacetaldehyde. X=conversion. [b] calculated as sum of yields to products with respect to the initial amount of **5**.

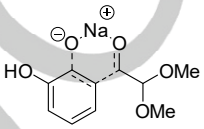
When we used a NaOH : **6** ratio of 1.0, the selectivity decreased down to 53-60%. The amount of **5** used, instead, clearly influenced the reaction efficiency; in fact, high **5** conversion could be achieved at low **5** : **6** ratio, that is, under conditions at which **5** was the limiting reactant, while using a NaOH : **6** ratio of at least 0.5 : 1 and temperature 80 °C (entries 3, 4 in Table 1).
Bases other than NaOH were tested, namely LiOH, KOH, and $Cs_2CO_3$, while using the same conditions as for entry 4 (Table 1). The same products distribution as with NaOH was obtained, with selectivity to **7** equal to 67-69% and **6** conversion of 41%. An exception was the experiment with KOH, which gave 23% **6** conversion only. We also used MgO and $Ca(OH)_2$, but in this case we obtained a lower selectivity, between 44 and 51%.
Some experiments were carried out in organic solvents (Table 2), replacing NaOH with NaOMe. The results showed an opposite selectivity compared to the experiments carried out in water: with methanol the *ortho* product, **8**, was obtained with 82-85% selectivity (as opposed to 30% only in water).

**Table 2.** Results of the hydroxyalkylation reaction between catechol and DMA in organic solvents.

| entry[a] | solvent | **5**[b] | T (°C) | X (%) | **7** | **8** | X (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | MeOH | 1 | Reflux | 68 | 18 | 82 | 73 |
| 2 | MeOH | 0.5 | Reflux | 49 | 18 | 82 | 100 |
| 3 | MeOH | 0.5 | 60 | 44 | 15 | 85 | 90 |
| 4 | THF | 0.5 | 80[d] | 47 | 9 | 91 | 96 |

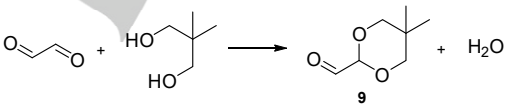
[a] All experiments were carried out with NaOMe as the base, with a **6** : base molar ratio equal to 1 : 1. [b] Molar ratio with respect to **6**. [c] calculated as sum of yields to products with respect to the initial amount of **5**. [d] test in sealed tube.

This value was even higher when the reaction was carried out in THF, for which the selectivity to **8** was as high as 93%. Similarly to the Kolbe-Schmitt reaction,[6c-6e] we hypothesized that in this case the reaction proceeded via an intermediate alkali metal **6**-**5** complex (see Scheme 3), finally favoring the *ortho* hydroxyalkylation. In fact, organic solvents cannot solvate efficiently the sodium catecholate, which coordinates the aldehyde carbonyl in **5** allowing the formation of the complex. On the contrary, when the reaction is carried out in water, the solvent can solvate and "isolate" the sodium catecholate, hence reducing the contribution of the Kolbe-Schmitt mechanism.
Attempts to improve the selectivity to the desired *para* isomer **7** were carried out by replacing NaOH with alkylammonium hydroxide, which could form hindered salts of the catechol so preventing *ortho* hydroxyalkylation.[6f] We first employed tetralkylammonium hydroxides, such as tetramethyl- or tetrabutylammonium hydroxide (TMA and TBA, respectively). In the first case, we did not obtain any improvement in selectivity to **7**, which still was close to 70%, moreover conversion of **6** was low (< 30%), even after 23 h reaction time. The use of TBA brought about only a slight improvement of selectivity to **7**, which rose up to 77-78%. On the other hand, the use of tetralkylammonium hydroxides gave rise to problems both during the reaction ~~because of its low solubility in water (in methanol the reaction did not take place),~~ and ~~during~~ the separation of the products, because of their amphiphilic feature. For these reasons this strategy was abandoned.




**Scheme 3.** Hypothesis of activation of **5** to ortho hydroxyalkylation by sodium catecholate.

As a final attempt to improve the selectivity, we tried to employ a more hindered acetal, such as 5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**9**) which can be obtained from 2,2-dimethyl-1,3-propanediol (Scheme 4) (see Experimental for the synthesis of this compound[6b]).

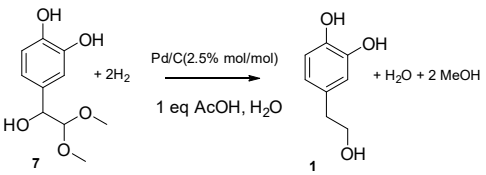



**Scheme 4.** Glyoxal monoacetalization with 2,2-dimethyl-1,3-propanediol.

We carried out some tests using **9** under the optimized conditions for **5**. The final conversion of **6** was about 40% (the theoretical one being 49%), and the selectivity to the corresponding 4-substituted catechol isomer was 75%. Given this modest selectivity improvement we decided to abandon this strategy.
Overall, the best yield to **7** was equal to 46% (selectivity 65% at 70% conversion of **6**), achieved at mild temperature (40-60°C).

**Hydrogenation step**

The mandelic derivative 7 was isolated from the reaction mixture of the first step by means of flash chromatography.
An in-depth kinetic and optimization study of the reduction of catechol hydroxyacetal **7** to **1** was then underpinned (Scheme 5).




**Scheme 5.** Hydrogenation of 4-(hydroxyalkylacetal) catechol derivative **7** to **1**.

We identified and isolated three reaction intermediates and two by-products (Figure 3).

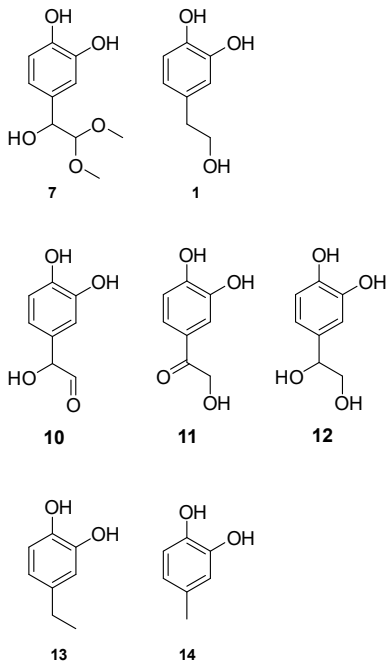



**Figure 3.** Structure of compounds isolated and identified during the hydrogenation of **7**. Top: starting material and hydroxytyrosol; middle: intermediates; bottom: by-products.

The first tests were carried out with one equivalent of acetic acid, 3 bars of $H_2$, Pd as the metal catalyst (10% w/w over carbon, 2.5% mol/mol with respect to **7**), at 150 °C. Figure 4 compiles conversion of **7** and yields to products.

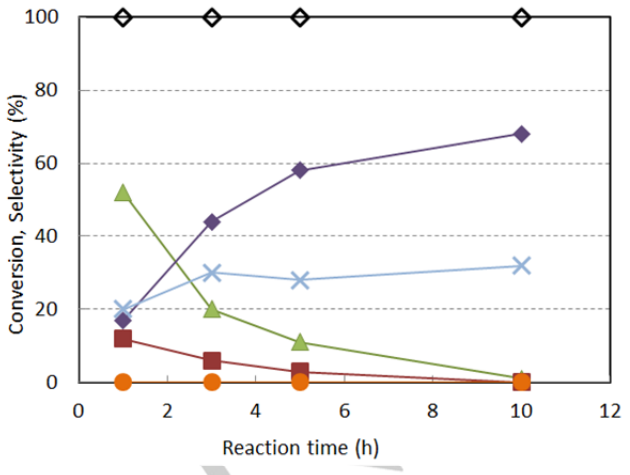



**Figure 4.** Effect of reaction time on **7** conversion (◇), selectivity to **11** (▲), **12** (■), **1** (◆), **14** (×), and **13** (●). Reaction conditions: T = 150 C; **7**:Pd:acetic acid 1:0.025:1 molar ratio; 3 bars of hydrogen.

After one hour reaction, **7** was completely converted and all products shown in Figure 3 were formed (except **13**). From the experimental trends we could notice that compound **11** (the major product at short reaction time) and **12** were reaction intermediates which were completely converted after about 10 h. Conversely, yields to **1** and **14** increased during time, until the final value of about 68% and 35%, respectively. The diol **12** was formed by hydrogenation of **11**.

The formation of **14** might involve a decarbonylation step;[6g] indeed, CO was formed, as inferred by sampling the gas-phase of the autoclave at the end of the reaction.

Experiments were also carried out using different $H_2$ pressure (Figures S1 and S2 in Supporting Information). At reduced pressure, the yield to **14** was similar to that one obtained at 3 bars, but in the former case it was obtained in correspondence of a greater yield to intermediate products (compare for example the **14**:**11** yield ratio after 1 h for the test at 3 bars $H_2$ and after 5 h for the test at 1 bar $H_2$), and a much lower yield to **1**. At 6 bars $H_2$ pressure, the formation of **14** was considerably decreased; the higher pressure might have both disfavored the decarbonylation and accelerated the reduction of **10** (and **11**), so subtracting these compounds from further decarbonylation. At high $H_2$ pressure, however, C balance was close to 75-80% (while it was 95-100% at 1 and 3 bars), suggesting the formation of some unidentified compound, probably deriving from the hydrogenolysis of intermediates. In another test, carried out by increasing $H_2$ pressure up to 8 bars, the reaction was complete after 3 hours only, but the selectivity to **1** and **14** did not change compared to results shown in Figure S1. Overall, the best yield to **1** was obtained at 3 bar $H_2$ pressure.

Results shown in Figure 4 also demonstrate that **1** is a stable compound with the Pd catalyst; in fact, its yield did not decrease for prolonged reaction times, after total consumption of reaction intermediates **11** and **12** (see HPLC chromatograms Figure S7). This also allowed us to confirm that **13** and **14** were not formed by consecutive hydrogenolysis of **1**.

In order to investigate on the reaction pathway, we decided to slow down the reaction rate, by decreasing the temperature down to 90 °C, while maintaining one equivalent of acid and 3 bar $H_2$ pressure (Figure 5).

Again, **7** was quickly converted and after 1 h the only visible product was **11**; **12** and **1** started to form more slowly. Only when a significant amount of **12** was formed (about 20% yield), also **14** started to form. This might suggest that **14** indeed forms from **12**. We also noticed an important lack in the C balance, particularly at the beginning of the reaction, which decreased during time. Indeed, in the HPLC we observed the appearance of another peak (not visible in the analysis of previous experiments carried out at higher temperature), the intensity of which decreased on increasing reaction time. Identification of this compound was possible by carrying out an experiment in deuterated water, loading equimolar amounts of **7** and acetic acid.

We left the vial at 60°C for three days and finally we analyzed the reaction mixture by means of $^1$H-NMR (see Figure 6, in which the corresponding products signals are indicated).

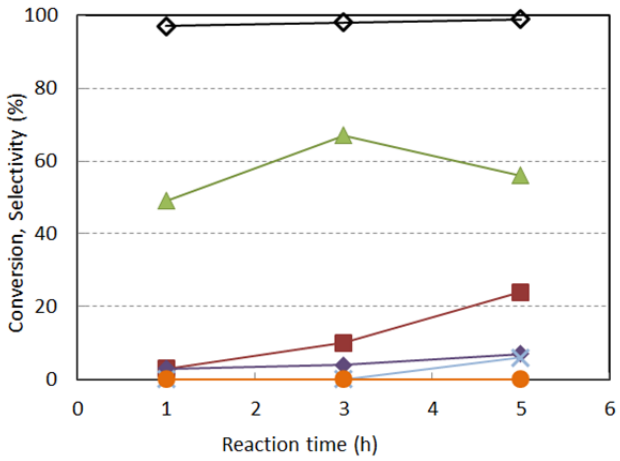



**Figure 5.** Effect of reaction time on **7** conversion (◇), selectivity to **11** (▲), **12** (■), **1** (◆), **14** (×) and **13** (●). Reaction conditions: T = 90 C; **7**: Pd:acetic acid 1:0.025:1 molar ratio; 3 bar hydrogen.

We found a conversion of **7** of about 56% with a yield to the hydrated hydroxyaldehyde of 55%. This experiment allowed us to attribute the unidentified compound to intermediate **10**.

At this point, we could delineate the reaction pathway for the transformation of **7** to **1** (Scheme 6). Hydrolysis of **7** occurs very rapidly, with release of two equivalents of methanol and formation of the hydroxyaldehyde, **10**, which quickly undergoes a double tautomeric equilibrium with formation of **11**, through the ene-diol. Therefore, the intermediate compound **11**, which because of the conjugation of the C=O bond with the aromatic ring is more stable than **10**, can be considered as the true reactant of this reaction (at least for the experiments carried out at 150°C). Then the reduction of the ketone to **12** is followed by hydrogenolysis of the benzylic alcohol to **1**. Obviously, the formation of **12** could originate directly from **10**, at least in part. In fact, it is even possible that **12** is produced via the ene-diol, which can form at high temperature and be easily reduced.

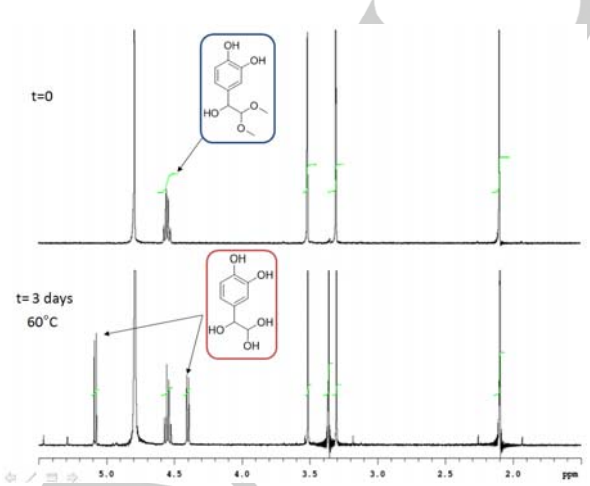
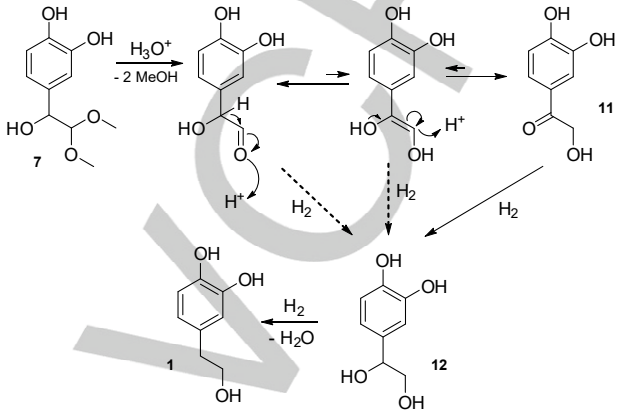



**Figure 6.** $^{1}$H-NMR spectra of HAC (time zero, top) and reaction crude (bottom). Reaction conditions: T = 60°C; **7** : acetic acid = 1 : 1 molar ratio, in $D_2O$.

Given that **14** does not form by consecutive hydrogenation of **1**, which is a stable product, and does not undergo consecutive transformations, it may form either by decarbonylation of **10** (which was not isolated in experiments carried out at 150 °C, but is in equilibrium with **11**), or by hydrogenolysis of **12**.




**Scheme 6.** Possible reaction pathway from catechol derivative **7** to **1**.

To gain more insight into the mechanism by which **14** is formed, we tried the reduction of the ketone **11**, which we prepared and isolated separately. This reduction was carried out in the absence of any acid, in order to slow down the reaction rate. The results obtained further support the previous hypothesis, in fact, as shown in Figure 7, **14** only start to form after 1 h, when quite a lot of **12** is already formed. However, the C balance was lower than 100% (i.e., between 73 and 95%), probably because of the formation of some unidentified compound.

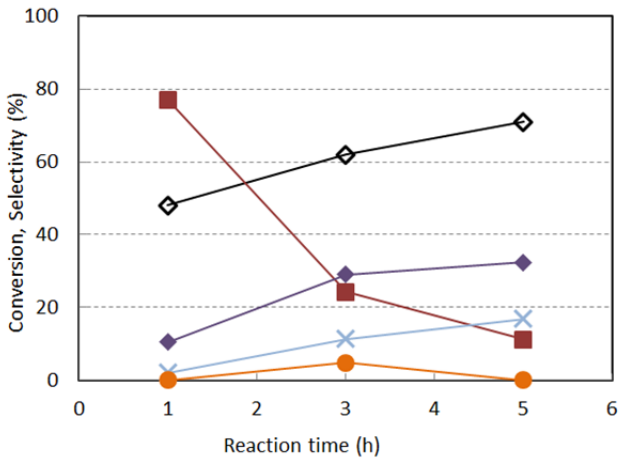
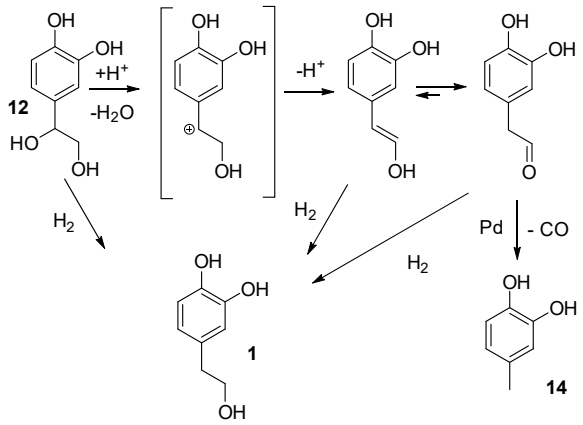



**Figure 7.** Effect of reaction time on **11** conversion (◇), selectivity to **12** (■), **1** (◆),**13** (●) and **14** (×). Reaction conditions: T = 150 C; **11**/Pd 1/0.025 molar ratio, with no acetic acid; 3 bars hydrogen.

Finally, we carried out a reduction test starting from **12** (Figure S2). As expected, we found that also in this case **14** was formed, although it was less than 5%.

All these tests demonstrated that **14** was formed from **12**, and likely involved a decarbonylation step. Based on these results, we could hypothesize the formation pathway of **14** as illustrated in Scheme 7. First, the dehydration of the benzylic hydroxyl group in **12** occurs forming a carbocation which releases a proton forming the enol; then it undergoes a tautomeric equilibrium forming the aldehyde. Obviously, each of these intermediates can be directly and quickly reduced to **1**, but, at last, the aldehyde formed could undergo decarbonylation.




**Scheme 7.** Possible mechanisms for the formation of **14** starting from **12**.

We also investigated the effect of the acid amount on catalytic performance; we carried out experiments with 0.05 and 0 equivalents of acetic acid, under the same conditions as those used in Figure 4. The presence of acetic acid did not affect **7** conversion (the transformation of **7** was very quick at 150°C, and we always achieved total conversion), and in both cases final yields to products were obtained in 10 h reaction time; however, the acid had a remarkable effect on the distribution of products. This is shown in Figures S3 and S4, plotting the selectivity ratio **1**/(**10**+**11**+**12**), and indicator of how fast is the transformation of intermediates **10**, **11** and **12** into the desired product **1**, and the selectivity ratio **1**/(**13**+**14**), an indicator of the relative rates for the two parallel reactions leading from **12** either to **1** or to the by-products **13** and **14**, respectively. It is shown that in both cases the presence of an equivalent of acetic acid had positive effects; in fact, it favored the transformation of intermediates to **1**, and limited the undesired formation of **13** and **14** compared to **1**. The role of the acid may be that of facilitating the hydrolysis and tautomerisation steps from **7** to **12** (Scheme 6), and the dehydration and tautomerisation steps from **12** to **1** (Scheme 7). In an experiment carried out at 8 bar $H_2$, without acetic acid, the final yield to **1** was reached in a shorter reaction time (5 h instead of 10 h), but yield to **1** was 55% only with a yield to **14** equal to 20%. It is also worth noting that in the absence of acetic acid we observed the formation of **13** (not observed with one equivalent of acid), with ca 10% yield after 10 h; moreover, the mass balance was ca 85% only. To avoid the need of any homogenous acid, we also tried to use 10% Pd/H-ZSM5 as an acidic support, but, unfortunately, these tests led to very poor mass balances.

Finally, we compared the reactivity of carbon-supported Pd, Pt, Rh and Ru catalysts (all commercial catalysts, see Experimental).

Pt and Rh had similar behavior: the conversion of **7** was complete within 1 hour, but even after 5 hours the yield to **1** was 30% only.

In the case of Ru we found a completely different reactivity (Figure 8): after 1 hour the conversion of **7** was complete, but there was no accumulation of **11**. There were only **1** and **12**, and minor amounts of **13** and **14**. However, an important lack in the C balance was found, which was maintained all over the experiment time; $^1$H-NMR analysis showed the presence of new aliphatic signals, suggesting the reduction of the aromatic ring may occur under these more drastic conditions. Even when the hydrogen pressure was decreased down to 1.5 bars, we found a consistent accumulation of **11** (80% selectivity at complete conversion of **7**) with low yield to **1** (Figure S5). However, in this case C balance was close to 100%.

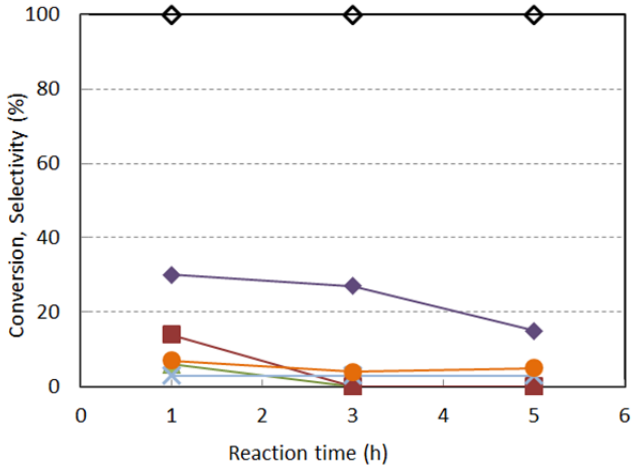


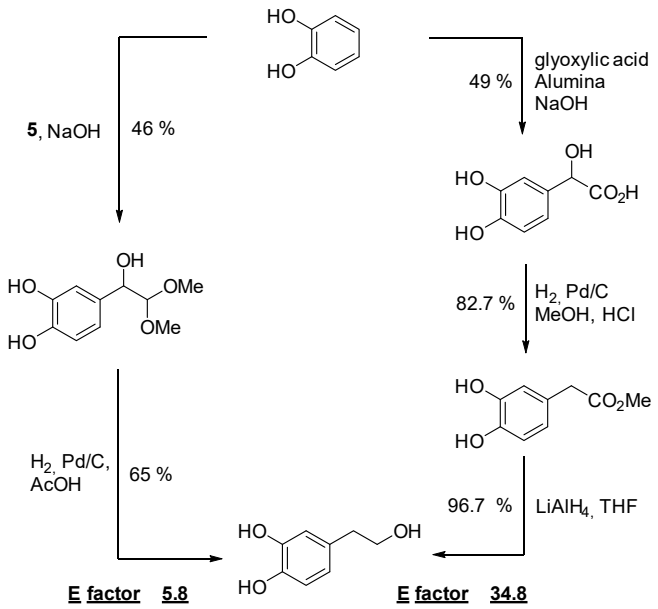

**Figure 8.** Effect of reaction time on **7** conversion (◇), selectivity to **11** (▲), **12** (■), **1** (◆), **14** (×) and **13** (●). Reaction conditions: T = 150°C; **7**:Ru 1:0.025 molar ratio; 8 bar hydrogen.

On the other hand, by keeping 8 bars of hydrogen and reducing the reaction temperature down to 120 °C (Figure S6), we found again important lacks in the carbon balance, although if **7** conversion was not complete even after 5 h reaction time; moreover, accumulation of **12** was also observed.

**Green metrics: a comparison with a patented process to hydroxytyrosol**

In 2007, DSM patented a process[7] in which catechol is first reacted with glyoxylic acid, to produce 3,4-dihydroxymandelic acid; then the latter is hydrogenated with $H_2$ and a Pd/C in the presence of methanol to produce (3,4-dihydroxyphenil)-acetic

acid methyl ester, which is finally reduced with $NaBH_4$ or $LiAlH_4$ to hydroxytyrosol (Scheme 8).




**Scheme 8.** Comparison of the two processes to hydroxytyrosol: this paper (left) and the 3-step process claimed by DSM (right).

In fact, the mandelic derivative cannot be hydrogenated to hydroxytyrosol with $H_2$, because the aromatic ring is hydrogenated instead of the carboxylic acid.

In order to circumvent this problem and avoid the use of stoichiometric reducing agents, we adopted the strategy of changing the nature of the intermediate, i.e., via the acetal instead of the mandelic compound (Scheme 1).

The optimized process was compared to the previous reference by means of Sheldon's E factor.[9] The comparison between the two processes was carried out considering the charge of all input materials for each step.[9,10] Both processes afforded crude hydroxytyrosol of comparable purity (HPLC or NMR) and the comparison was therefore done at the crude stage, where all data were available for both processes. The results of this comparison are summarized in Table 3. The first step, the hydroxyalkylation step, has an almost equal impact on the E factor of both processes (3.54 g/g of hydroxytyrosol produced for the literature process against 3.80 g/g for the hydroxylation step with MAG). The use of stoichiometric $LiAlH_4$ as the final reducing agent of the literature process makes necessary to transform the carboxylic acid moiety into an ester group. To achieve this, the second step of the literature process needs to be run in MeOH which result in significant contribution to the E factor (13.2 g/g of final hydroxytyrosol). Finally, $LiAlH_4$ requires the use of an additional organic solvent (dry THF) in the third step of the process which also adds a great contribution to the E factor (16.97 g/g). This has to be compared with the single reduction step of our process which is run in water and therefore has no significant contribution to the overall E factor.[9] Even though the literature process has a slightly better overall yield, this is obtained at the expenses of less practical three-step process which requires a stoichiometric hydride reducing agent and above all at the expenses of a worse E factor, 34.8 g/g compared to 5.8 g/g of our process.

**Table 3.** Comparison of the E factor for the two processes (Scheme 8).

| ***Literature process***[7] | | ***present work*** | |
|---|---|---|---|
| Substance | Amount[a] | Substance | Amount[a] |
| catechol | 1.82 | catechol | 2.39 |
| NaOH | 1.21 | NaOH | 0.88 |
| alumina | 0.73 | MAG (**5**) | 2.66 |
| glyoxylic acid | 1.28 | | |
| **Waste of step 1** | **3.54** | | **3.80** |
| HCl | 0.06 | Pd | 0.03 |
| MeOH | 13.20 | C | 0.24 |
| Pd | 0.01 | AcOH | 0.60 |
| C | 0.16 | | |
| **Waste of step 2** | **14.31** | | **2.01** |
| dry THF | 16.97 | | |
| $LiAlH_4$ | 0.37 | | |
| **Waste of step 3** | **16.96** | | |
| **E factor** | **34.81** | | **5.80** |
| Overall yield (%) | 39 | | 30 |

[a] all values are expressed as mass amount normalized to the same mass unit of desired hydroxytyrosol (g/g)

## Conclusions

We developed a two-step reaction for the synthesis of hydroxytyrosol consisting of the hydroxyalkylation of catechol to the corresponding mandelic derivative followed by the one-pot reduction to the desired product.

After a wide screening of reactants and reaction conditions, we found that best results were obtained with catechol as the starting aromatic, 2,2-dimethoxyacetaldehyde as alkylating agent and NaOH as the catalyst with a relative molar feed ratio of 1:0.5:0.5. These reactions were carried out in water at 80 °C and they were complete in few hours. We found that a selectivity to the desired product as high as 70% with respect to the limiting reagent could be achieved at complete conversion of catechol. The second step is the one-pot reduction of the intermediate. We tested several reaction conditions and catalysts, reaching 70% yield of hydroxytyrosol at complete conversion of the acetal in few hours. The reaction solvent was water. We investigated

the reaction pathway, identifying the mechanism of formation for all the reaction by-products and intermediates.
Finally, we can assert that this is a new approach to the synthesis of hydroxytyrosol, which could be an alternative to the current industrial process.

## Experimental Section

**General.** Products were purified from the reaction mixture by flash chromatography (230–400 mesh) using as the eluent a petroleum ether/ethyl acetate mixture (vol. ratios from 8/2 to 7/3). Then, the products were identified by means of ESI-MS and 1H and 13C NMR and, whenever possible, by comparison with authentic commercial samples. ESI-MS spectra (positive or negative) were recorded using a Waters Micromass ZQ 4000, equipped with a capillary probe (3.54 kV), with a cone voltage of 20 volts and direct injection (20 μL min−1). Unless otherwise stated, $^{1}H$ and $^{13}C$ NMR spectra were recorded in deuterated chloroform at 25 °C on a Varian Inova 300, at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) for $^{1}H$ and $^{13}C$ are given in ppm. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; bs, broad signal. HPLC method: the instrument was equipped with Kinetex 5μm EVO C18 100A column, 100x4.6 mm, with UV detector set at λ=270 nm. In a general procedure, 60μL of the reaction mixture were sampled and diluted with distilled water to obtain a final volume of 2 mL; then the solution is filtered with a syringe equipped with a 0,45 μm PTFE filter and injected for the HPLC analysis. The injection volume is 20 μL. After the injection a 1,5 mL/min of A was eluted for 5 minutes, then the flow was increased to 2 mL/min and the composition gradually changed to 100% of B in 30 seconds, then 2 mL/min of 100% of B was maintained for 14 minutes. Solvents: A: $H_2O$/Methanol vol. ratio of 98/2 +0.2% wt of formic acid; B: $H_2O$/Methanol vol. ratio of 80/20 +0.2% wt of formic acid

**Materials.** Catechol, glyoxylic acid, glyoxal and 2,2-dimethoxyacetaldehyde, 2,2-dimethyl-1,3-propanediol, glacial acetic acid, **12** and NaOH were purchased from Sigma-Aldrich and used as such, without further purifications.

**Catalysts**. Pd, Pt, Rh, Ru catalysts were all supported over carbon: Pd was 10% w/w, while Pt, Rh and Ru were 5% w/w. All catalysts were purchased from Sigma-Aldrich.

**Hydroxyalkylation step.** 4-(1-hydroxy-2,2-dimethoxyethyl)benzene-1,2-diol (**7**) The reactions were carried out in 5 mL closed cap vials. In a standard procedure, 130 mg of catechol, 98 mg of DMA solution (60% w/w in water), 23 mg of NaOH and 1.8 mL of water were added in the vial; then the vial was closed and the temperature increased to the desired one (e.g. 80°C). The reaction was carried out under autogenic pressure. With the aim of isolating enough amount of 7 for the subsequent studies, few reactions were performed at a bigger scale, in this way 3 g of crude were collected, the solvent (water) was evaporated in vacuum and the products were solubilized in methanol. The mandelic derivative **7** was isolated from this crude by means of flash chromatography, using 50 g of silica in a 4.5 cm (inner diameter) column, using an eluent gradient of petroleum ether/ethyl acetate mixture from 70/30 to 60/40 (vol. ratio) obtaining a brownish oil. $^{1}H$ NMR (400 MHz, $D_2O$) δ (ppm): 3.27 (3H, s), 3.49 (3H, s), 4.50 (1H, d, J=6.6 Hz), 4.54 (1H, dd, J=8.2, 2.0 Hz), 6.83 (1H, d, J=8.2 Hz), 6.89 (1H, d, J= 2.0 Hz). $^{13}C$ NMR (100 MHz, acetone-d6) δ (ppm): 55.92 (CH3), 56.34 (CH3), 73.70 (CH), 107.59 (CH), 115.71 (CH), 116.74 (CH), 120.67 (CH), 132.41 (CH), 144.56 (CH), 144.66 (CH).

**Hydrogenation step**. The reactions were generally carried out loading in a stainless steel autoclave and under a nitrogen atmosphere 50 mg of **7**, 6.2 mg of Pd (10% w/w carbon supported), 14 mg of acetic acid, 10 mL of water. The system was evacuated and flushed with hydrogen for three times, then the temperature was set at 150 °C and the hydrogen pressure kept at 6 bars for 7 h reaction. Thereafter, the crude reaction mixture was cooled down and the autoclave carefully evacuated. Purity (A%) of **1** was assessed by HPLC in the following way: 60 μL of the crude reaction mixture were withdrawn and taken up with water in a 2 mL volumetric flask. HPLC analysis showed a purity grade of around 70% (A/Atot %). Analytically pure samples of **1** were obtained by flash chromatography on silica gel eluting with hexane : ethyl acetate = 50 : 50. $^{1}H$ NMR (400 MHz, $D_2O$) δ (ppm): 2.75 (2H, dt, J=6.6, 1.2 Hz), 3.79 (2H, dt, J=6.6, 2.2 Hz), 6.75 (1H, dd, J=8.2, 2.0 Hz), 6.84 (1H, d, J=2.3 Hz), 6.88 (1H, d, J=7.8 Hz). $^{13}C$ NMR (100 MHz, $D_2O$) δ (ppm): 37.79, 63.41, 117.00, 117.49, 122.03, 132.66, 142.97, 143.76, 144.59.

**Synthesis of 5,5-dimethyl-1,3-dioxane-2-carbaldehyde (9).** In a 100 mL Dean-Stark system, 10 g glyoxal solution (40% w/w in water), 6.8 g 2,2-dimethyl-1,3-propanediol, 0.244 g of *p*-toluenesulphonic acid were dissolved in 35 mL of toluene and then the mixture was heated and refluxed for 7 h (7.5 mL of water were collected, about the theoretical amount calculated). After cooling the crude, 1.5 g of $NaHCO_3$ were added and the new mixture was left under magnetic agitation at room temperature overnight. The day after, the crude was filtered over celite and the solvent was removed by the use of a rotary evaporator and a vacuum pump. Finally, the distillation of the filtered solution (using a Vigreaux column under at about 80 °C at 30 mbar) allow to isolate 0.7 g of DDC as a pale yellow liquid. $^{1}H$ NMR (400 MHz, $CDCl_3$): 0.75 (3H, s), 1.17 (3H, s), 3.50 (2H, d, J=11.3 Hz), 3.71 (2H, d, J=11.3 Hz), 4.65 (1H, s), 9.40 (1H, s). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 21.51 (CH3), 22.50 (CH3), 30.36 (C), 76.84 (CH2), 76.87 (CH2), 98.44 (CH), 194.33 (CHO).

**Synthesis of 1-(3,4-dihydroxyphenyl)-2-hydroxyethan-1-one (11)**. The reactions were carried out loading in a stainless steel autoclave 200 mg of **7**, 10 mL $H_2O$, under nitrogen atmosphere. The temperature was set at 150°C for 1 h reaction. The crude was dried under vacuum and the product was isolated from the mixture by flash chromatography using as the eluent a $CHCl_3/CH_3OH$ mixture with a 95/5 vol. ratio. $^{1}H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.93 (2H, s), 6.97 (1H, d, J=8.6 Hz), 7.42 (1H, d, J=2.3 Hz), 7.45 (1H, dd, J=8.2, 2.0 Hz). $^{13}C$ NMR (100 MHz, $CD_3OD$) δ (ppm): 66.65 (CH2), 116.23 (CH), 116.86 (CH), 123.18 (CH), 128.57 (CH), 147.53 (CH), 153.46 (CH), 199.45 (CH).

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**Keywords:** hydroxytyrosol, hydroxyalkylation, hydrogenation, 2,2-dimethoxy-acetaldehyde (DMA), catalysis

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[9] To achieve meaningful comparisons of processes, water is generally excluded from the calculation of the E factor. See: a) M. Lancaster, *Green Chemistry: An Introductory Text,* Royal Society of Chemistry, Cambridge, 2002; and b) ref. 7d.

[10] It was not possible to include in this comparison the materials used for work-ups, since amounts of those materials are not available for the literature process.

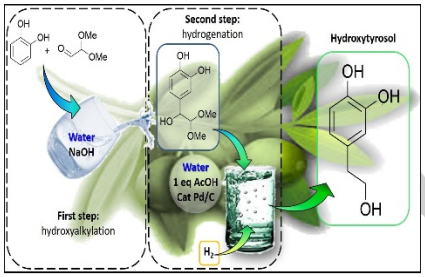
**Entry for the Table of Contents** (Please choose one layout)

Layout 1:

# FULL PAPER

Table of Contents

A two-step innovative process for the synthesis of hydroxytyrosol is reported. Both steps are conducted in water and mild conditions.




*Paolo Ziosi, Claudio Paolucci, Francesco Santarelli, Tommaso Tabanelli, Sauro Passeri] Fabrizio Cavani* and Paolo Righi*

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**A new process for the synthesis of hydroxytyrosol**