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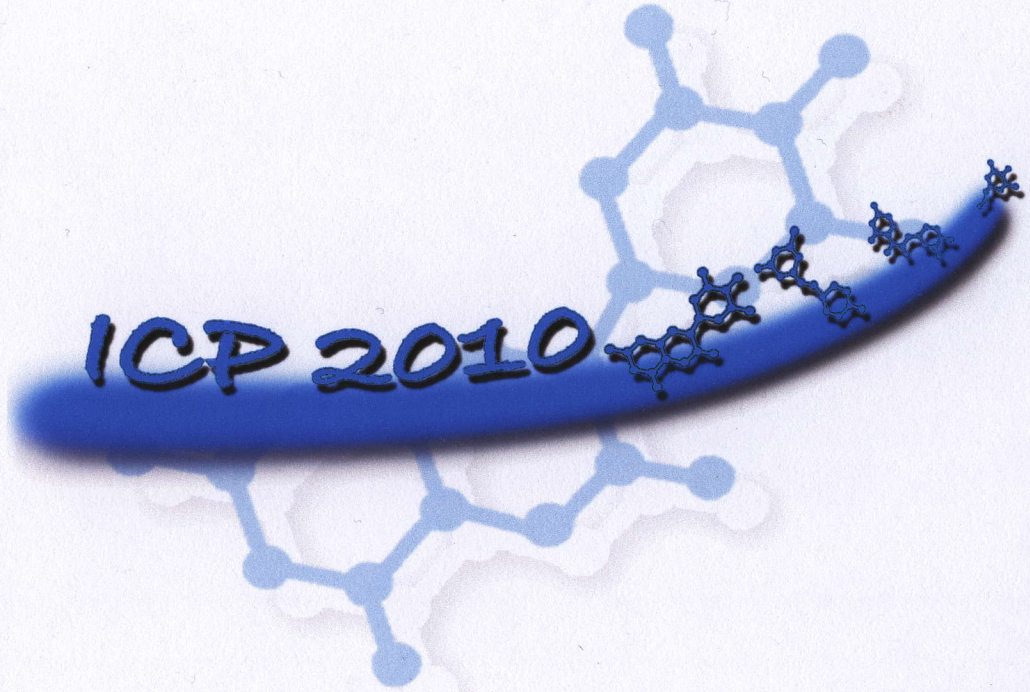

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New and efficient syntheses of hydroxytyrosol and its lipophilic derivatives

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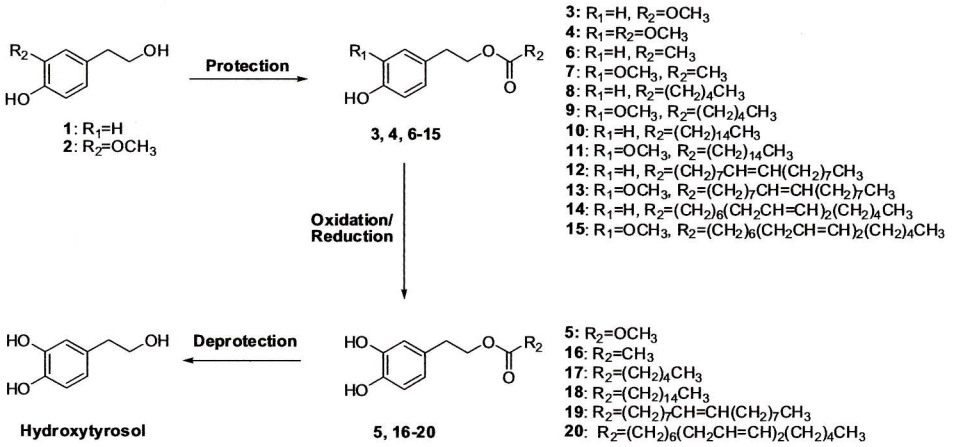
Abstract. New and efficient oxidative procedures to synthesize hydroxytyrosol and its lipophilic derivatives are described. Starting materials are available and natural compounds such as tyrosol and homovanillyl alcohol. The oxidant of choice is homogeneous as well heterogeneous 2-iodoxybenzoic acid (IBX) able to perform the aromatic hydroxylation and the oxidative demethylation of phenolic compounds with a chemo and regioselectivity similar to that of the polyphenol oxidase and cytochrome P450. The reactions proceed quickly and the final products are isolated in good yields and high purity. After the first oxidation, heterogeneous IBX (IBX-polystyrene) is recovered by simple filtration, regenerated and reused for more cycles of oxidation reactions without loss of efficiency.

Introduction. Hydroxytyrosol [2-(3',4'-dihydroxyphenyl)ethanol] is a natural compound found in olive fruits, leaves, virgin olive oil [1], and olive oil waste waters, also known as vegetable waters [2]. The antioxidant property of this molecule has been claimed in more papers, and it has been attributed to the *o*-diphenolic moiety [3]. Moreover, hydroxytyrosol possesses many biological and pharmacological properties. Its industrial applications are increased after the preparation of the corresponding lipophilic derivatives that are, generally, esters having long saturated or unsaturated alkylic chains. These compounds show a good solubility in oils and emulsions and are used as additives in food and cosmetic products as well as in pharmaceutical preparations. Up until some years ago, hydroxytyrosol was commercially unavailable; more recently, it is commercialized by some chemical companies but at high prices. Several protocols have been optimized to recover hydroxytyrosol from olive oil waste waters but sometimes, it is isolated in mixture with other phenolic compounds; synthetic procedures have been reported in the literature, but many of them require various steps and proceed with no satisfactory yields. In this communication we describe our recent results on the synthesis of hydroxytyrosol and its lipophilic derivatives. The methodology is based on the aromatic hydroxylation of tyrosol [2-(4'-hydroxyphenyl)ethanol] or oxidative demethylation of homovanillyl alcohol [2-(4'-hydroxy-3'-methoxyphenyl)ethanol] derivatives with 2-iodoxybenzoic acid (IBX) under homogeneous as well as heterogeneous conditions. The oxidation reactions proceeded with high chemo and regioselectivity; the final products were isolated in good yield and high purity.

Material and Methods. Reagents and solvents were purchased from Sigma Aldrich. IBX was prepared in our laboratory as described [4]. IBX-polystyrene was furnished from Novabiochem. HPLC analyses were performed on a Varian Prostar 325 apparatus equipped with an UV-Vis detector selected on λ=280 nm. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (99.8% in deuterium) and in CD_3OD (99.8% in deuterium) using a Bruker 200 MHz spectrometer. Silica gel 60 F254 plates and silica gel 60 were furnished by Merck.

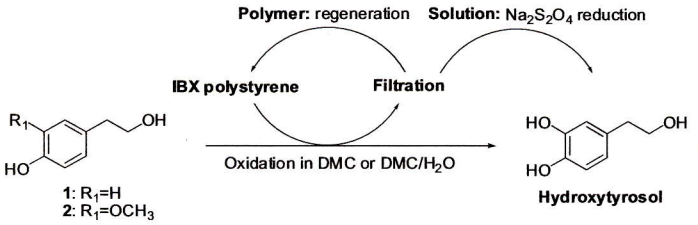
Results and Discussion. Tyrosol **1** is a very attractive starting material for the preparation of hydroxytyrosol, being its monophenolic precursor. Unfortunately, the direct chemo and regioselective oxidation of compound **1** with IBX followed by an in situ reduction with sodium dithionite ($Na_2S_2O_4$) proceeded in only 30% yield. This result was due to practical problems of extraction of the final product from the aqueous medium after the reductive step. Similar results were obtained after the oxidative demethylation of homovanillyl alcohol **2**. Under these experimental conditions, a chemoselective protection of the alcoholic group of compounds **1** and **2** was necessary to diminish the hydrophilic character of the catecholic compounds. We performed it by using dimethyl carbonate (DMC), an ecofriendly chemical used as reagent/solvent, to obtain the corresponding carboxymethylated derivatives **3** and **4**; their oxidation/reduction with IBX and $Na_2S_2O_4$ allowed the isolation of carboxymethylated hydroxytyrosol **5** in quantitative yield. Finally, hydroxytyrosol was obtained in high yield and purity by a mild hydrolytic step under basic conditions (Scheme 1).

When the chemoselective protection of the alcoholic group of tyrosol **4** and homovanillyl alcohol **5** was performed with saturated and unsaturated acyl chlorides (acetyl, hexanoyl, palmitoyl, oleoyl, linoleyl chloride), the corresponding lipophilic hydroxytyrosol esters **16-20** were isolated in high yields (70-98%).



Scheme 1. Oxidative/reductive pathway of tyrosol and homovanillyl alcohol derivatives under homogeneous conditions.

As an alternative route, hydroxytyrosol was prepared by direct oxidation of tyrosol **1** or homovanillyl alcohol **2** by using IBX-polystyrene (Scheme 2). The use of the polymer-supported reagent facilitated the work-up of the reaction. In fact, after the first oxidation, the reagent was separated from final product by simple filtration and hydroxytyrosol was recovered in quantitative yield. IBX-polystyrene was regenerated and reused for at last five cycles of oxidation reactions without loss of efficiency [6].



Scheme 2. Oxidative/reductive pathway of tyrosol and homovanillyl alcohol under heterogeneous conditions.

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