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Convenient Synthesis of Hydroxytyrosol and Its Lipophilic Derivatives from Tyrosol or Homovanillyl Alcohol

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Hydroxytyrosol, a naturally occurred *o*-phenolic compound exhibiting antioxidant properties, was synthesized by a three-step high-yielding procedure from natural and low-cost compounds such as tyrosol or homovanillyl alcohol. First, the efficient chemoselective protection of the alcoholic group of these compounds was performed by using dimethyl carbonate (DMC) as reagent/solvent; second, the oxidation with 2-iodoxybenzoic acid (IBX) or Dess−Martin periodinane reagent (DMP) and in situ reduction with sodium dithionite ($Na_2S_2O_4$) allowed the preparation of carboxymethylated hydroxytyrosol; finally, by a mild hydrolytic step, hydroxytyrosol was obtained in high yield and purity, as confirmed by NMR spectra and HPLC profile. By using a similar methodology, lipophilic hydroxytyrosol derivatives, utilized as additives in pharmaceutical, food, and cosmetic preparations, were prepared. In fact, at first the chemoselective protection of the alcoholic group of tyrosol and homovanillyl alcohol was performed by using acyl chlorides without any catalyst to obtain the corresponding lipophilic derivatives, and then these compounds were converted in good yield and high purity into the hydroxytyrosol derivatives by oxidative/reductive pathway with IBX or DMP and $Na_2S_2O_4$.

KEYWORDS: Hydroxytyrosol; lipophilic hydroxytyrosol; oxidation; 2-iodoxybenzoic acid (IBX); Dess−Martin periodinane (DMP)

INTRODUCTION

Hydroxytyrosol **1** [or 2-(3′,4′-dihydroxyphenyl)ethanol; **Figure 1**] is a natural phenolic compound found in olive fruits, leaves, virgin olive oil (*1*), and olive oil waste waters, also known as vegetable waters (*2*). It is released by hydrolysis of the glycoside oleuropein **2** (**Figure 1**) by means of cellular esterases or acidic catalysis during olive storage and pressing (*3*). A recent study has identified and quantified hydroxytyrosol in several Italian white and red wines.

The antioxidant property of hydroxytyrosol has been claimed in more papers, and it has been attributed to the *o*-diphenolic moiety (*4*). Moreover, it possesses many biological and pharmacological properties. For example, hydroxytyrosol protects human erythrocytes against oxidative damages and low-density lipoprotein (LDL) oxidation (*5*); it induces cytochrome *c*-dependent apoptosis (*6*) and prevents cardiovascular diseases (*7*), certain types of cancer (*8*), and platelet aggregation (*9*). Hydroxytyrosol is also utilized for the treatment of inflammations and protection against neurodegenerative diseases (*10*) and in cosmetic applications such as skin care preparations and bathing agents (*11*). The industrial applications of hydroxytyrosol have been extended using its lipophilic derivatives that are, generally, hydroxytyrosol esters with 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 (*12*). The simplest of these derivatives is hydroxytyrosol acetate [2-(3′,4′-dihydroxyphenyl)ethyl acetate **3**; **Figure 1**] found in olive oil (*13*). The antioxidant activity of this compound in oil and emulsions is much higher than those of α-tocopherol and oleuropein and similar to that of hydroxytyrosol (*14*). Recently, it has been reported that lipophilic phenol derivatives having amphiphilic structure and self-organizing properties are potentially interesting for possible applications in nanotechnology (*15*).

Up until some years ago, hydroxytyrosol was commercially unavailable. More recently, it has been commercialized by some chemical companies but at high prices. Several protocols have been optimized to recover hydroxytyrosol from olive oil waste waters (*16*). Sometimes, it is isolated in a mixture with other phenolic compounds, in particular, with tyrosol **4** [or 2-(4′-hydroxyphenyl)ethanol; **Figure 1**]. Several synthetic procedures of hydroxytyrosol have been reported in the literature, but many of them required various steps and proceeded with no satisfactory yields (*17*). Recently, some enzymatic or chemical conversions of natural oleuropein **2** (*18*) or tyrosol **4** into hydroxytyrosol have been described (*19*). In fact, tyrosol **4** is a very

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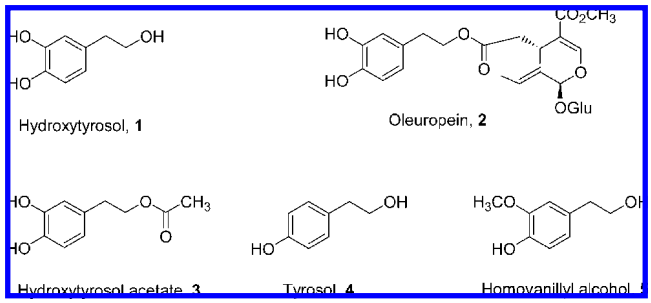


Figure 1. Chemical structures of some low molecular weight phenolic compounds present in olive oil and in olive oil waste waters.

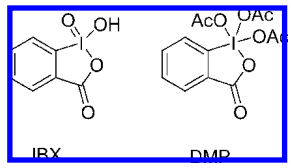


Figure 2. Chemical structures of IBX and DMP.

attractive natural starting material, being the monophenolic precursor of hydroxytyrosol.

Considering the industrial applications of hydroxytyrosol as well its studies on the biological properties, it is important to have at hand simple and efficient synthethic procedures at competitive prices to prepare this compound. Therefore, in this paper we report a new convenient oxidative procedure to obtain hydroxytyrosol as well as its lipophilic derivatives starting from either tyrosol **4** or homovanillyl alcohol **5** [2-(4′-hydroxy-3′-methoxyphenyl)ethanol], natural phenols present in olive oil mill waste waters (*20*), and commercially available inexpensive chemicals. The critical step, that is, the selective protection of the alcoholic hydroxyl group in the presence of phenolic hydroxyl group, was accomplished by using dimethyl carbonate (DMC) as reagent/solvent as well as acyl chlorides. The oxidants of choice were 2-iodoxybenzoic acid (1-hydroxy-1-oxo-1*H*-1λ^5-benz[*d*][1,2]iodoxol-3-one, IBX; **Figure 2**) and the corresponding 1,1,1-triacetoxy derivative (Dess−Martin periodinane, DMP; **Figure 2**) (*21*). Some examples of reactivity of IBX and DMP include oxidative demethylation of simple phenolic methyl aryl ethers (*22*) and oxidation of phenols to *o*-quinones (*23*). When the use of IBX or DMP has been combined with an in situ reduction, several natural and synthethic catecholic compounds have been prepared (*24*). Therefore, the utilization of IBX and DMP and in situ reduction permitted an efficient selective conversion of either protected tyrosol or homovanillyl alcohol into the corresponding hydroxytyrosol derivatives. In fact, we observed that IBX and DMP oxidized the phenolic compounds with a selectivity similar to that of a polyphenol oxidase. Furthermore, we optimized a one-pot synthesis of carboxymethylated hydroxytyrosol. The new procedures described in the present paper have been deposited for two patents (*25*).

MATERIALS AND METHODS

Reagents. Tyrosol [2-(4′-hydroxyphenyl)ethanol], homovanillyl alcohol [2-(4-hydroxy-3-methoxyphenyl)ethanol] were purchased from Sigma Aldrich as were all other solvents and reagents. All chemicals used were of analytical grade. IBX and DMP were prepared in the laboratory as described in the literature (*26, 27*). Silica gel 60 F254 plates and silica gel 60 were furnished by Merck.

Instrumental Analysis. HPLC analyses were performed on a Varian Prostar 325 apparatus equipped with a Varian Pursuit 5u C_{18} column (150 × 4.6 mm) and a dual wavelength UV−vis detector selected on $\lambda = 280$ nm. Elutions were carried out at a 1 mL/min flow rate using a H_2O/CH_3CN mixture (90:10, v/v) for the first minute and a gradient to 40:60 during the following 30 min. GC-MS analyses were performed on a Shimadzu VG 70/250S apparatus equipped with a CP-SIL 8 CB-MS column (25 m × 0.25 mm and 0.25 mm film thickness). The analyses were performed using an isothermal temperature profile of 100 °C for 2 min, followed by a 10 °C/min temperature gradient to 280 °C for 15 min. The injector temperature was 280 °C. HRMS were recorded with a Micromass Q-TOF micro mass spectrometer (Waters). ^{1}H 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. All chemical shifts are expressed in parts per million (δ scale) and are referenced to either the residual protons or carbon of the solvent. Only the spectral data of new compounds are described here, but all ^{1}H and ^{13}C NMR data of lipophilic phenols are available as Supporting Information.

Carboxymethylation of Tyrosol 4 and Homovanillyl Alcohol 5. This reaction was performed following two different methods.

Method a. Either tyrosol **4** (138 mg, 1.0 mmol) or homovanillyl alcohol **5** (168 mg, 1.0 mmol) was dissolved in DMC (3 mL), and then H_2SO_4 96% (10.7 μL, 0.2 mmol) was added. The solution was stirred at reflux ($T = 90$ °C) for 7 h until disappearance of the substrate. At the end, it was cooled to room temperature, and DMC was evaporated under vacuum as an azeotropic mixture with methanol (DMC/CH_3OH = 1:3) boiling at 64 °C. The residue was extracted with ethyl acetate, washed with a saturated solution of NaCl, and dried over Na_2SO_4. After filtration and evaporation under vacuum, 2-(4′-hydroxyphenyl)ethyl methyl carbonate **6** and 2-(4′-hydroxy-3′-methoxyphenyl)ethyl methyl carbonate **7** were obtained as colorless oils in quantitative yields.

Method b. A mixture of either tyrosol **4** (138 mg, 1.0 mmol) or homovanillyl alcohol **5** (168 mg, 1 mmol), DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene, 1.2 mmol), and DMC (3 mL) was heated to reflux (T = 90 °C) for 7 h. The reaction was monitored by thin layer chromatography (TLC) and by gas−mass analysis (GC-MS). After the disappearance of the substrate, the reaction mixture was cooled to room temperature, and DMC was evaporated under vacuum with methanol. The residue was extracted with ethyl acetate and washed with a solution of 1N HCl. The organic extracts were treated with a saturated solution of NaCl and dried over Na_2SO_4, then filtered and concentrated under vacuum. Compounds **6** and **7** were isolated as colorless oils in quantitative yields. Their spectroscopic data have been already described by us (*28*).

Esterification of Tyrosol 4 and Homovanillyl Alcohol 5. Either tyrosol **4** (138 mg, 1.0 mmol) or homovanillyl alcohol **5** (168 mg, 1.0 mmol) was dissolved in DMC (3 mL), and then acyl chloride (acetyl, hexanoyl, palmitoyl, oleoyl, linoleyl chloride, 1.2 mmol) was added. The solution was stirred at room temperature for 24 h until disappearance of the substrate. DMC was evaporated under vacuum to afford a mixture that was solubilized with ethyl acetate and washed with a saturated solution of NaCl. The aqueous phase was extracted with ethyl acetate, washed with a saturated solution of NaCl, and dried over Na_2SO_4. Purification on silica gel of the mixture by elution with hexane/ethyl acetate = 2:1 gave 2-(4′-hydroxyphenyl)ethyl acetate **9** (white solid, 90% yield); 2-(4′-hydroxy-3′-methoxyphenyl)ethyl acetate **10** (colorless oil, quantitative yield); 2-(4′-hydroxyphenyl)ethyl hexanoate **11** (yellow oil, 80% yield); 2-(4′-hydroxy-3′-methoxyphenyl)ethyl hexanoate **12** (yellow oil, 83% yield); 2-(4′-hydroxyphenyl)ethyl palmitate **13** (colorless oil, 75% yield); 2-(4′-hydroxy-3′-methoxyphenyl)ethyl palmitate **14** (colorless oil, 75% yield); 2-(4′-hydroxyphenyl)ethyl oleate **15** (yellow oil, 86% yield); 2-(4′-hydroxy-3′-methoxyphenyl)ethyl oleate **16** (yellow oil, 75% yield); 2-(4′-hydroxyphenyl)ethyl linoleate **17** (yellow oil, 60% yield); and 2-(4′-hydroxy-3′-methoxyphenyl)ethyl linoleate **18** (yellow oil, 70% yield). NMR data of compounds **9**, **10**, **14**, **15**, and **17** were coherent with those reported in the literature (*29*−*33*).

*2-(4′-Hydroxyphenyl)ethyl hexanoate **11**:* ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3H, CH_3), 1.19−1.32 (m, 4H, 2 × CH_2), 1.50−1.65 (m, 2H, CH_2), 2.24 (t, 2H, J = 7.7 Hz, $COCH_2$), 2.83 (t, 2H, J = 7.1 Hz, Ph-CH_2), 4.23 (t, 2H, J = 7.1 Hz, CH_2O), 6.76 (d, 2H, J = 8.4 Hz, *H*-ar), 7.06 (d, 2H, J = 8.4 Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 24.6, 31.2, 34.2, 34.3, 65.2, 115.4, 129.6, 130.0, 154.5, 174.5. HRMS found: 236.3120; $C_{14}H_{20}O_3$ requires 236.3122.

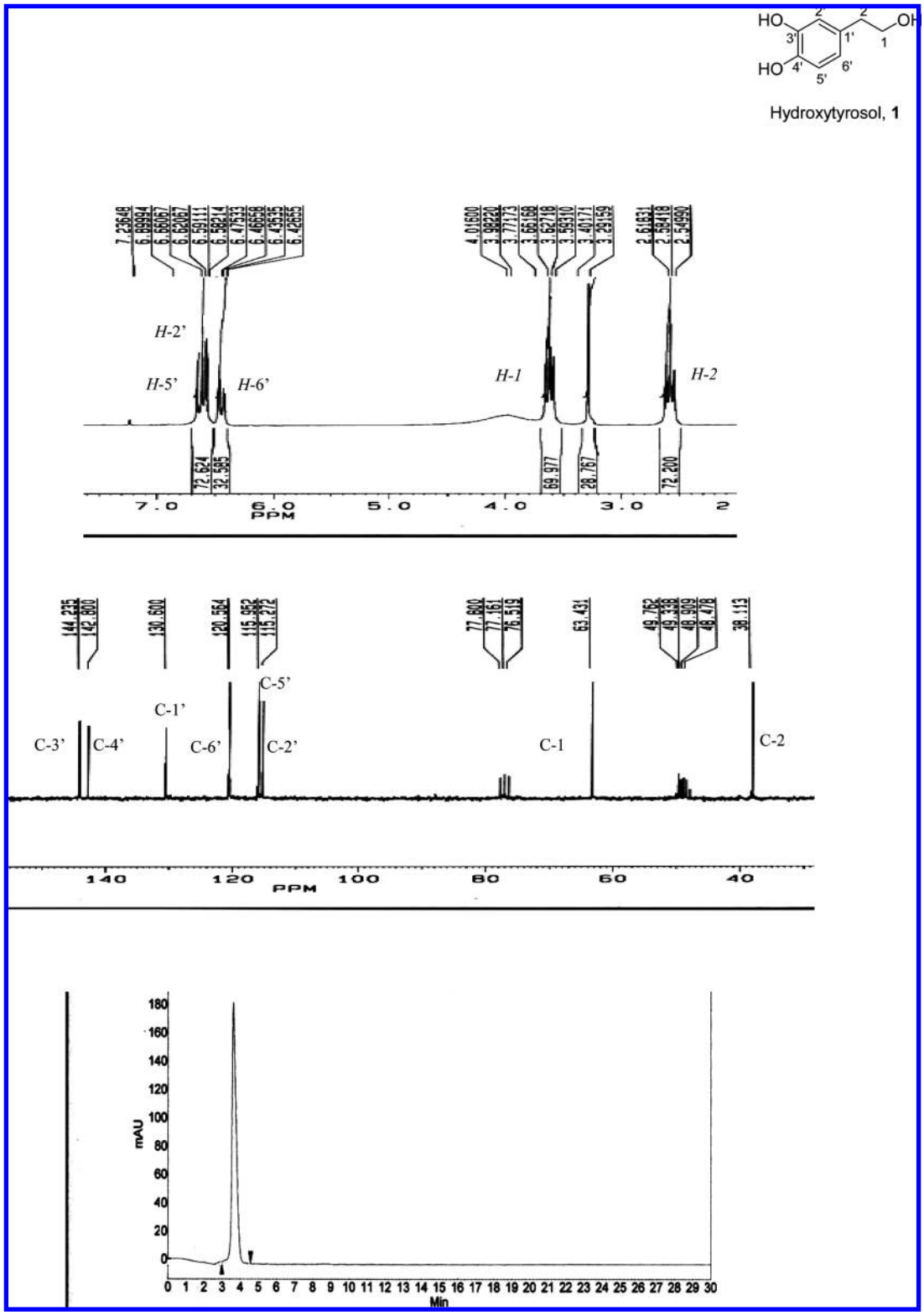


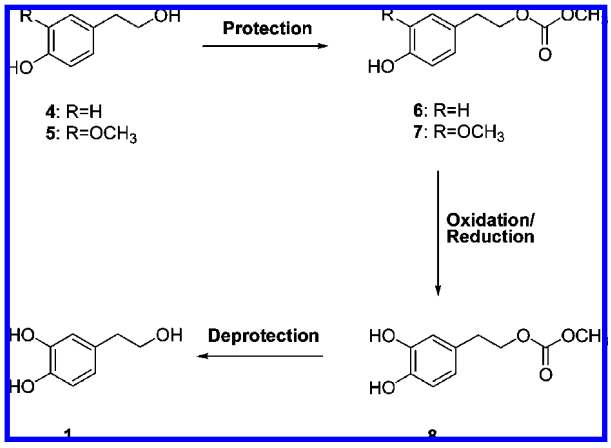
Figure 3. ^{1}H NMR, ^{13}CNMR, and HPLC profiles of hydroxytyrosol **1** synthesized as reported in **Scheme 1**.

2-(4′-Hydroxy-3′-methoxyphenyl)ethyl hexanoate ***12****:* ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, m, CH_3), 1.20−1.29 (4H, m, 2 × CH_2), 1.53−1.61 (2H, m, CH_2), 2.25 (2H, t, J = 7.7 Hz, $COCH_2$), 2.82 (2H, t, J = 7.1 Hz, Ph-CH_2), 3.81 (3H, s, OCH_3), 4.22 (2H, t, J = 7.1 Hz, CH_2O), 6.66 (2H, m, J = 8.4 Hz, *H*-ar), 6.82 (d, 1H, J = 7.2 Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 24.6, 31.2, 34.3, 34.8, 56.0, 64.9, 111.4, 114.5, 121.6, 129.6, 144.3, 146.5, 173.8. HRMS found: 266.3388; $C_{15}H_{22}O_4$ requires 266.3386.

2-(4′-Hydroxyphenyl)ethyl palmitate ***13****:* ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, m, CH_3); 1.24−1.29 (24H, m, 12 × CH_2), 1.55 (2H, m, CH_2), 2.28 (2H, t, J = 7.3 Hz, $COCH_2$), 2.84 (2H, t, J = 7.1 Hz, Ph-CH_2), 4.23 (2H, t, J = 7.1 Hz, CH_2O), 6.75 (2H, d, J = 8.5 Hz, *H*-ar), 7.03 (2H, d, J = 8.5 Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 24.9, 29.1, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 34.2, 34.4, 65.3, 115.4, 129.5, 130.0, 154.6, 174.6. HRMS found: 376.5825; $C_{24}H_{40}O_3$ requires 376.5822.

2-(4′-Hydroxy-3′-methoxyphenyl)ethyl oleate ***16****:* ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, m, CH_3), 1.15−1.25 (20H, m, 10 × CH_2), 1.97 (4H, m, 2 × CH_2), 1.60 (2H, m, CH_2), 2.26 (2H, t, J = 7.6 Hz, $COCH_2$), 2.83 (2H, t, J = 7.1 Hz, Ph-CH_2), 3.85 (3H, s, OCH_3), 4.23 (2H, t, J = 7.1 Hz, CH_2O), 5.33 (2H, m, CH=CH), 6.67−6.70 (2H, m, *H*-ar), 6.82

Scheme 1. Synthetic Procedure To Obtain Hydroxytyrosol **1** from Tyrosol **4** or Homovanillyl Alcohol **5**



(d, 1H, $J = 8.6$ Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.9, 27.1, 27.2, 29.0, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 34.3, 34.8, 55.8, 64.9, 111.3, 114.3, 121.6, 129.6, 129.7, 130.0, 144.3, 146.4, 173.8. HRMS found: 432.6470; $C_{27}H_{44}O_4$ requires 432.6466.

*2-(4′-Hydroxy-3′-methoxyphenyl)ethyl linoleate **18**:* ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, m, CH_3), 1.27−1.37 (14H, m, 7 × CH_2), 1.58 (2H, m, CH_2), 2.01 (4H, m, 2 × CH_2), 2.27 (2H, t, $J = 7.7$ Hz, CH_2), 2.76 (2H, t, $J = 5.9$ Hz, CH_2), 2.84 (2H, t, $J = 7.1$ Hz, Ph-CH_2), 3.84 (3H, s, OCH_3), 4.23 (2H, t, $J = 7.1$ Hz, CH_2O), 5.24−5.38 (4H, m, 2 × CH═CH), 6.65−6.70 (2H, m, *H*-ar), 6.81 (1H, d, $J = 8.6$ Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 25.0, 25.7, 27.2, 29.1, 29.2, 29.3, 29.6, 31.1, 34.3, 34.8, 55.8, 65.0, 111.3, 114.4, 121.6, 127.9, 128.0, 129.6, 130.0, 130.2, 144.3, 146.4, 173.7. HRMS found: 430.6310; $C_{27}H_{44}O_4$ requires 430.6306.

Oxidation of Compounds 6, 9, 11, 13, 15, and 17 with IBX. Substrate (1.0 mmol) was dissolved in CH_3OH (4 mL), and then IBX (336 mg, 1.2 mmol) was added. The solution was stirred at 0 °C until disappearance of the substrate (30 min). At the end, water (4 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol) were added, and the solution was stirred for 5 min at room temperature. After evaporation of the solvent under vacuum, the residue was solubilized with ethyl acetate and treated with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, 2-(3′,4′-dihydroxyphenyl)ethyl methyl carbonate **8** (colorless oil, 86% yield), 2-(3′,4′-dihydroxyphenyl)ethyl acetate **3** (colorless oil, 85% yield), 2-(3′,4′-dihydroxyphenyl)ethyl hexanoate **19** (yellow oil, 84% yield), 2-(3′,4′-dihydroxyphenyl)ethyl palmitate **20** (orange oil, 88% yield), 2-(3′,4′-dihydroxyphenyl)ethyl oleate **21** (orange oil, 89% yield), and 2-(3′,4′-dihydroxyphenyl)ethyl linoleate **22** (orange oil, 73% yield) were obtained. To recover 2-iodobenzoic acid, the aqueous phase deriving from the oxidation reaction was acidified with HCl 37% until pH 1 and then extracted with ethyl acetate. The organic phase was dried on Na_2SO_4. After filtration, the solvent was evaporated under vacuum. 2-Iodobenzoic was recovered in 85% yield.

*2-(3′,4′-Dihydroxyphenyl)ethyl hexanoate **19**:* ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, m, CH_3), 1.18−1.27 (4H, m, 2 × CH_2), 1.49−1.64 (2H, m, CH_2), 2.26 (2H, t, $J = 7.6$ Hz, $COCH_2$), 2.78 (2H, t, $J = 7.1$ Hz, Ph-CH_2), 4.18 (2H, t, $J = 7.1$ Hz, CH_2O), 6.58 (1H, dd, $J = 8.0$ and 1.9 Hz, *H*-ar), 6.70 (2H, d, $J = 1.9$ Hz, *H*-ar), 6.76 (2H, d, $J = 8.0$ Hz, *H*-ar); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.3, 24.6, 31.2, 34.4, 65.2, 115.3, 115.8, 121.2, 130.3, 142.5, 143.8, 174.9. HRMS found: 252.3120; $C_{14}H_{20}O_4$ requires 252.3116. NMR data of compounds **3** and **20**−**22** were consistent with those reported in the literature (*13, 34*).

Oxidation of Compounds 7, 10, 12, 14, 16, and 18 with IBX. The experimental procedure is the same. After evaporation of the solvent, 2-(3′,4′-dihydroxyphenyl)ethyl methyl carbonate **8** (colorless oil, 78% yield), 2-(3′,4′-dihydroxyphenyl)ethyl acetate **3** (colorless oil, 80% yield), 2-(3′,4′-dihydroxyphenyl)ethyl hexanoate **19** (yellow oil, 60% yield), 2-(3′,4′-dihydroxyphenyl)ethyl palmitate **20** (orange oil, 85% yield), 2-(3′,4′-dihydroxyphenyl)ethyl oleate **21** (orange oil, 68% yield), and 2-(3′,4′-dihydroxyphenyl)ethyl linoleate **22** (orange oil, 62% yield) were obtained.

Oxidation of Compounds 6, 9, 11, 13, 15, and 17 with DMP. Substrate (1.0 mmol) was dissolved in THF (4 mL), and then DMP (509 mg, 1.2 mmol) was added. The solution was stirred at room temperature until disappearance of the substrate (1 h). At the end, H_2O (4 mL) and $Na_2S_2O_4$ (348 mg, 2.0 mmol) were added, and the solution was under stirring for 5 min. After evaporation of the solvent under vacuum, the residue was solubilized with ethyl acetate and treated with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried on Na_2SO_4. After evaporation of the solvent, 2-(3′,4′-dihydroxyphenyl)ethyl methyl carbonate **8** (colorless oil, 85% yield); 2-(3′,4′-dihydroxyphenyl)ethyl acetate **3** (colorless oil, 80% yield), 2-(3′,4′-dihydroxyphenyl)ethyl hexanoate **19** (yellow oil, 82% yield), 2-(3′,4′-dihydroxyphenyl)ethyl palmitate **20** (orange oil, 92% yield), 2-(3′,4′-dihydroxyphenyl)ethyl oleate **21** (orange oil, 89% yield), and 2-(3′,4′-dihydroxyphenyl)ethyl linoleate **22** (orange oil, 77% yield) were obtained.

Oxidation of Compounds 7, 10, 12, 14, 16, and 18 with DMP. The experimental procedure is the same. After evaporation of the solvent, 2-(3′,4′-dihydroxyphenyl)ethyl methyl carbonate **8** (colorless oil, 85% yield), 2-(3′,4′-dihydroxyphenyl)ethyl acetate **3** (colorless oil, 72% yield), 2-(3′,4′-dihydroxyphenyl)ethyl hexanoate **19** (yellow oil, 62% yield), 2-(3′,4′-dihydroxyphenyl)ethyl palmitate **20** (orange oil, 88% yield), 2-(3′,4′-dihydroxyphenyl)ethyl oleate **21** (orange oil, 65% yield), and 2-(3′,4′-dihydroxyphenyl)ethyl linoleate **22** (orange oil, 58% yield) were obtained.

One-Pot Synthesis of Compound 8 in Dimethyl Carbonate. Tyrosol **4** (138 mg, 1.0 mmol) was dissolved in DMC, and then H_2SO_4 96% (10.7 μL, 0.2 mmol) was added. The solution was stirred at reflux ($T = 90$ °C) for 7 h until disappearance of the substrate. After cooling at room temperature, H_2O (2 mL) and DMP (1.2 mmol) were added. After 50 min, $Na_2S_2O_4$ (2.0 mmol) was added, and the mixture was carried out under magnetic stirring for 5 min. After evaporation of the solvent at reduced pressure, the residue was solubilized with ethyl acetate and treated with a saturated solution of $NaHCO_3$. The aqueous phase was washed with ethyl acetate; then the organic phases were washed with a saturated solution of NaCl until neutral pH and dried over Na_2SO_4. After evaporation of the solvent, compound **8** was isolated as yellow oil (82% yield).

Hydrolysis of 2-(3′,4′-Dihydroxyphenyl)ethyl Methyl Carbonate 8. To a solution of substrate (226 mg, 1.0 mmol) in THF was added KOH 1 M (3 mL, 3.0 mmol). The mixture was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was solubilized with ethyl acetate and treated with 1 M HCl. The aqueous phase was extracted with ethyl acetate. Organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of solvent, colorless oil was obtained (85% yield). Spectroscopic data are reported in **Figure 3** and were consistent with those reported in the literature (*16b*).

Validation of Experimental Data. All conversions and yields are the average of at least five different experiments.

RESULTS AND DISCUSSION

The procedure optimized to obtain hydroxytyrosol **1** is depicted in **Scheme 1**. To avoid a possible competitive oxidation on the alcoholic chain of tyrosol **4** and homovanillyl alcohol **5**, the first step was the chemoselective protection of this functional group. We performed it by using DMC, a cheap and green carboxymethylating agent having properties as an ecofriendly solvent as well as an environmentally benign substitute for hazardous and toxic reagents such as phosgene, methyl halides, and methyl sulfate (*35*). In our experimental conditions, by using catalytic amounts of sulfuric acid or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), we obtained 2-(4′-hydroxyphenyl)ethyl methyl carbonate **6** (tyrosol carboxymethylated) and 2-(4′-hydroxy-3′-methoxyphenyl)ethyl methyl carbonate **7** (homovanillyl alcohol

Scheme 2. Synthetic Procedure To Obtain Lipophilic Phenols from Tyrosol **4** or Homovanillyl Alcohol **5**

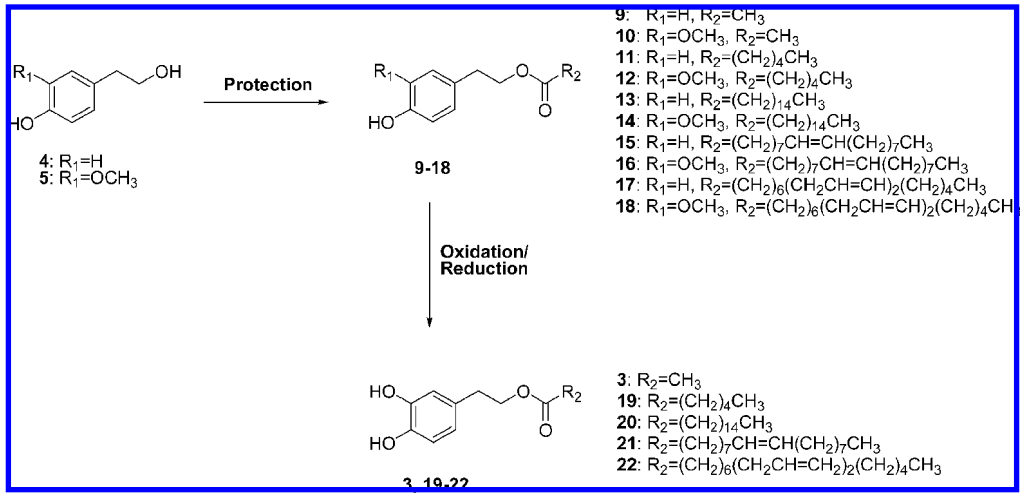


Table 1. Chemoselective Esterification of Tyrosol **4** and Homovanillyl Alcohol **5**[a]

entry	substrate	acylating agent	yield (%)
1	**4**	CH_3COCl	**9**: 90
2	**5**	CH_3COCl	**10**: 100
3	**4**	$CH_3(CH_2)_4COCl$	**11**: 80
4	**5**	$CH_3(CH_2)_4COCl$	**12**: 83
5	**4**	$CH_3(CH_2)_{14}COCl$	**13**: 75
6	**5**	$CH_3(CH_2)_{14}COCl$	**14**: 75
7	**4**	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$	**15**: 86
8	**5**	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$	**16**: 75
9	**4**	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COCl$	**17**: 60
10	**5**	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COCl$	**18**: 70

[a] Experimental conditions: substrate (1.0 mmol); acylating agent (1.2 mmol); DMC (3 mL); rt; 24 h; conversions > 98%.

Table 2. Oxidation of Compounds **9**−**18** with IBX and DMP[a]

entry	substrate	oxidant	yield (%)
1	**9**	IBX	**3**: 85
2	**10**	IBX	**3**: 80
3	**11**	IBX	**19**: 84
4	**12**	IBX	**19**: 60
5	**13**	IBX	**20**: 88
6	**14**	IBX	**20**: 85
7	**15**	IBX	**21**: 89
8	**16**	IBX	**21**: 68
9	**17**	IBX	**22**: 73
10	**18**	IBX	**22**: 62
11	**9**	DMP	**3**: 80
12	**10**	DMP	**3**: 72
13	**11**	DMP	**19**: 82
14	**12**	DMP	**19**: 62
15	**13**	DMP	**20**: 92
16	**14**	DMP	**20**: 88
17	**15**	DMP	**21**: 89
18	**16**	DMP	**21**: 65
19	**17**	DMP	**22**: 77
20	**18**	DMP	**22**: 58

[a] Experimental conditions: (a) oxidation with IBX, substrate (1.0 mmol), CH_3OH (3 mL), IBX (1.2 mmol), $T = 0$ °C, 30 min; (b) oxidation with DMP, substrate (1.0 mmol), THF (3 mL), IBX (1.2 mmol), rt, 1 h; (c) reduction, H_2O (4 mL), $Na_2S_2O_4$ (2.0 mmol), rt, 5 min. Conversions are quantitative.

carboxymethylated) in quantitative conversions and yields (*28*). In these reactions, sulfuric acid increased the electrophilic character of the carbonyl group of DMC; DBU raised the nucleophilic character of the alcoholic function. Afterward, compounds **6** and **7** were oxidized with IBX in methanol at room temperature. The following in situ reduction with sodium dithionite ($Na_2S_2O_4$) allowed the isolation of the corresponding oxidation product, 2-(3′,4′-dihydrophenyl)ethyl methyl carbonate **8** (hydroxytyrosol carboxymethylated), in 86 and 78% yields, respectively. The oxidation proceeded with a high selectivity on the ortho-position. The only byproduct of the oxidation was 2-iodobenzoic acid, which we recovered from the solution and reused for the regeneration of IBX. When the oxidation of **6** and **7** was performed with DMP as oxidant, we observed a similar efficiency; in fact, hydroxytyrosol carboxymethylated **8** was obtained in 85% yield.

Successively, we optimized the one-pot synthesis using the same DMC as carboxymethylating reagent in the first step as well as solvent in the oxidative/reductive step with DMP and $Na_2S_2O_4$. Without any workup and chromatographic purifications, we isolated the final product in quantitative conversion and 82% yield. The final step of the synthethic procedure reported in **Scheme 1** was the deprotection of the alcoholic chain of the hydroxytyrosol carboxymethylated **8**. Acidic conditions (6 M HCl, THF) were ineffective, whereas in basic conditions (1 M KOH, THF) hydroxytyrosol **1** was obtained in 85% yield. The ^1H and ^{13}C NMR spectra and the HPLC profile of the synthesized hydroxytyrosol **1** are reported in **Figure 3**. On the basis of the antioxidant activity of hydroxytyrosol carboxymethylated **8** measured by the DPPH reduction method (*28*) and owing to its lipophilic properties, this compound appears to be a new antioxidant useful for cosmetic and nutraceutical applications.

Finally, we extended this procedure for the preparation of lipophilic hydroxytyrosol derivative (**Scheme 2**), up until now prepared by lipase- or acid-catalyzed esterification of the precious and expensive hydroxytyrosol (*12*). We performed the selective esterification of tyrosol **4** and homovanillyl alcohol **5** with acyl chlorides in DMC as solvent. For example, 2-(4′-hydroxyphenyl)ethyl acetate **9** and 2-(4′-hydroxy-3′-metho xyphenyl)ethyl acetate **10** were prepared in 90% and quantitative yields by using only a little excess of acetyl chloride in DMC without any catalyst (**Table 1**, entries 1 and 2). The chemoselective acylation of the aliphatic hydroxyl group is an important and frequently used transformation in organic synthesis (*36*). Typically, it was performed in dry conditions under homogeneous catalysis with acetic acid or acetyl chloride or acetic anhydride (*37*). Probably, in our experimental conditions, operating in no-dry conditions, the in situ generation of traces of hydrochloric acid deriving from the hydrolysis of the acetyl chloride (*38*) and the greater nucleophilicity of the aliphatic hydroxyl group, compared to the phenolic group, drove the

protection on the alcoholic function of **4** and **5**. We have observed a similar selectivity by using several saturated or unsaturated acyl chloride having longer chains such as hexanoyl chloride, palmitoyl chloride, oleoyl chloride and linoleoyl chloride. The corresponding 2-(4′-hydroxyphenyl)ethyl hexanoate **11**, 2-(4′-hydroxy-3′-methoxyphenyl)ethyl hexanoate **12**, 2-(4′-hydroxyphenyl)ethyl palmitate **13**, 2-(4′-hydroxy-3′-methoxyphenyl)ethyl palmitate **14**, 2-(4′-hydroxyphenyl)ethyl oleate **15**, 2-(4′-hydroxy-3′-methoxyphenyl)ethyl oleate **16**, 2-(4′-hydroxyphenyl)ethyl linoleate **17**, and 2-(4′-hydroxy-3′-methoxyphenyl)ethyl linoleate **18** were isolated in satisfactory yields (**Table 1**, entries 3−10). The following oxidative step with IBX and reduction with $Na_2S_2O_4$ of compounds **9**−**18** allowed us to obtain the corresponding hydroxytyrosol derivatives such as 2-(3′,4′-dihydroxyphenyl)ethyl acetate **3**, 2-(3′,4′-dihydroxyphenyl)ethyl hexanoate **19**, 2-(3′,4′-dihydroxyphenyl)ethyl palmitate **20**, 2-(3′,4′-dihydroxyphenyl)ethyl oleate **21**, and 2-(3′,4′-dihydroxyphenyl)ethyl linoleate **22** in high yields (**Table 2**). In general, the oxidation of tyrosol derivatives proceeded with higher yields compared to homovanillyl derivatives (**Table 2**, compare entries 1, 3, 5, 7, and 9 with entries 2, 4, 6, 8, and 10). As previously observed, the use of DMP did not modify the efficiency and selectivity of the oxidation (**Table 2**, compare entries 1−10 with entries 11−20).

In conclusion, in this paper we described a short, efficient, and low-cost synthetic procedure to obtain hydroxytyrosol as well as its lipophilic derivatives starting from commercially available and natural compounds such as tyrosol as well as homovanillyl alcohol. Reactions proceeded quickly, and the final products were obtained in satisfactory yields and high purity.

SAFETY

IBX was reported to be explosive under impact or heating to >200 °C (*39*). Dess and Martin suggested that the explosive properties of some samples of IBX were due to the presence of impurities of potassium bromate utilized during its preparation, that is, the oxidation of 2-iodobenzoic acid in acidic medium (*40*). A safe and convenient preparation of IBX involves the utilization of oxone in water (*26*).

Supporting Information Available: ^1H and ^{13}C NMR spectra of lipophilic tyrosol, homovanillyl alcohol, and hydroxytyrosol. This material is available free of charge via the Internet at http://pubs.acs.org.

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