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## High-Yielding Preparation of a Stable Precursor of Hydroxytyrosol by Total Synthesis and from the Natural Glycoside Oleuropein

AUGUSTO GAMBACORTA,<sup>\*,§</sup> DANIELA TOFANI,<sup>§</sup> ROBERTA BERNINI,<sup>‡</sup> AND ANTONELLA MIGLIORINI<sup>†</sup>

Dipartimento di Ingegneria Meccanica e Industriale, Università degli studi "Roma Tre", via della Vasca Navale 79, 00146 Roma, Italy; Dipartimento di Agrobiologia ed Agrochimica, Università della Tuscia, Via S. Camillo de Lellis, 01100 Viterbo, Italy; and Dipartimento di Chimica, Università "La Sapienza", P.le Aldo Moro 5, 00185 Rome, Italy

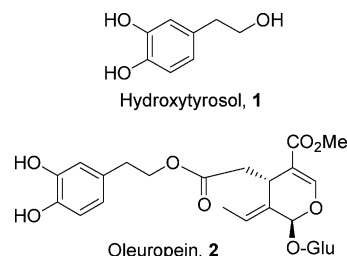
The unprecedented acetonide of the antioxidant hydroxytyrosol has been synthesized by a two-step high-yielding procedure and found to be both purifiable by chromatography and stable over a wide pH range. The protection stabilizes hydroxytyrosol against oxidation, thereby allowing long-term storage. The protection can quantitatively be removed, under nonaqueous conditions, to afford pure hydroxytyrosol suitable for use as an additive in food and cosmetic preparations. Extension of the same methodology to the natural and easily accessible glycoside oleuropein, followed by saponification of the resulting complex mixture of acetonides, allowed hydroxytyrosol acetonide to be recovered in high yield. This constitutes a new interesting methodology to obtain the antioxidant hydroxytyrosol.

**KEYWORDS:** Hydroxytyrosol; hydroxytyrosol acetonide; oleuropein; catechol stabilization; antioxidants

### INTRODUCTION

Hydroxytyrosol **1** [or 2-(3,4-dihydroxyphenyl)ethanol or 3,4-DHPEA; **Figure 1**] is a strong antioxidant (*1*). It is the hydrolysis product of the glycoside oleuropein **2** (*2*), an antifeedant (*3*) secondary metabolite, present in considerable amounts in all parts of olive trees (6–9% w/w in dry leaves) (*4*) and responsible for the bitter taste of unprocessed olives. In oleuropein the hydroxytyrosol moiety is esterified by elenolic acid. During the milling process for olive oil production (*5*) the released endogenous  $\beta$ -glycosidases hydrolyze the ester bond present in **2** and afford **1**, which is partitioned between the oil and water phases. The same hydrolysis occurs under basic conditions used in the debittering process for green table olive manufacturing (*6*). Therefore, **1** is found in small amounts in virgin olive oil (*5*), where it is responsible for oil stability, and in higher amounts in process waters originating from both olive oil production (OMWW) and table olive debittering (*6*).

Due to the presence of the catechol moiety, the antioxidant efficiency of **1** in water is comparable to that of ascorbic acid, whereas in lipidic medium it is 4 times higher (*7*), this behavior being known as the "polar paradox" (*8*). Moreover, **1** is an amphiphilic molecule ( $\log P = 0.02$ ) (*9*) and is bioavailable (*10*) so that it can penetrate cell membranes (*11*), where it exerts many biological activities (*12*). Hydroxytyrosol has been shown



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

to protect cells against oxidative stress (*13*), to have antimicrobial (*14*) and anticancer (fat-related) activity (*5b*, *15*), and, mainly, to reduce heart disease pathogenesis (*16*).

Therefore, it is not surprising that many chemical efforts have been made to collect pure hydroxytyrosol, either by synthesis or from natural sources, to use it as a dietary supplement or as a stabilizer in foods and cosmetic preparations (*17*). Synthetic approaches are based on simple reduction of commercial 3,4-dihydroxyphenylacetic acid (*18*) or the corresponding methyl ester (*19*), whereas recovery from natural sources is based on both chemical (*20*) and enzymatic (*21*) treatments of oleuropein- or tyrosol-containing wastewaters that originate from olive processing.

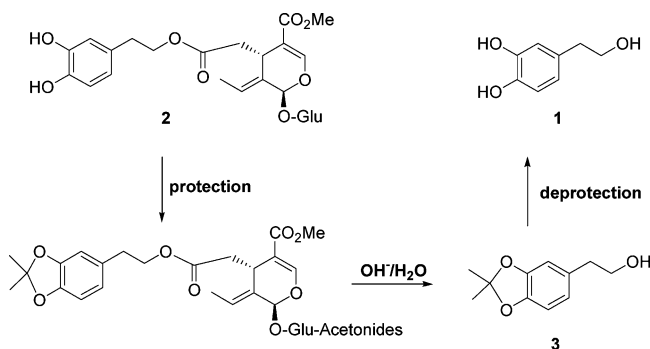
However, none of the above-mentioned processes provides hydroxytyrosol in high amount and purity. Indeed, compound **1** is such a good antioxidant that it undergoes quick self-oxidation in the air, particularly on silica gel and in alkaline medium (*18b*), to afford a black polymeric material. This behavior does not allow either long-term storage or high-yielding

\* Author to whom correspondence should be addressed (telephone +390655173280; fax +390655173327; e-mail gambacor@uniroma3.it).

<sup>§</sup> Università degli studi "Roma Tre".

<sup>‡</sup> Università della Tuscia.

<sup>†</sup> Università "La Sapienza".

**Scheme 1.** Plan for Hydroxytyrosol **1** Recovery from Oleuropein **2**

chromatographic purification, and it prevents simple saponification of **2** (**22**).

Therefore, we focused our attention on the possibility of stabilizing **1** by suitable protection of the catechol function (i.e., the acetonide group), which would pave the way for chromatographic purification, long-term storage, and deprotection under mild conditions. Moreover, extension of the same protection to the easily obtainable and abundant oleuropein **2**, followed by saponification, purification, and deprotection (**Scheme 1**), might allow a high-yielding recovery of pure hydroxytyrosol **1**.

Acetates (**18a**) or benzyl ethers (**23**) have been reported as protective groups for **1**, but they were not suited for our purposes in view of either they saponify under basic conditions (**Scheme 1**) or require hydrogenolytic conditions for benzyl ether removal. Thus, we chose the acetonide moiety, unprecedented in practical use, as a suitable protective group. We report here the synthesis and stability of the acetonide **3** together with its recovery from oleuropein **2**.

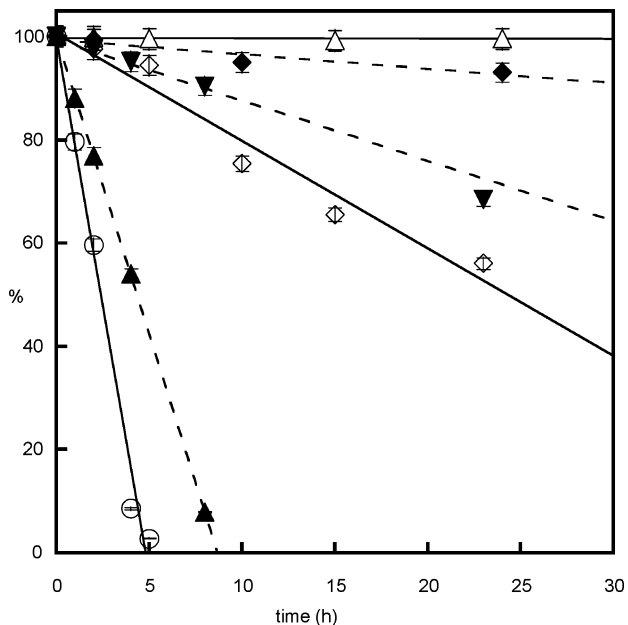
## MATERIALS AND METHODS

**Materials.** Freshly extracted oleuropein **2** was supplied by Prof. Troisi (University of Lecce, Italy). HPLC control showed a 47% purity (see **Figure 3A**). The main unidentified impurity ( $t_R = 23.83$  min) was not further investigated and probably comes from oleuropein oxidation. Chromatographic purification was not suitable because of substantial loss of material. Therefore, **2** was used without further purification. All chemicals used were of analytical grade. 3,4-Dihydroxyphenylacetic acid was purchased from Sigma Aldrich as were all other solvents and reagents. 2-Methoxypropene and 2,2-dimethoxypropane (DMP) were used directly after distillation. When specified, solvents were dried over common drying agents (**24**) and then distilled. Silica gel 60 F254 plates and silica gel 60 were purchased from Fluka. Petroleum ether used for chromatographic separations was the 40–60° fraction.

**HPLC Analyses.** Chromatographic analyses were performed on a TSP Spectra Series P200 apparatus equipped with a Thermo Hypersil BDS  $C_{18}$  column (250  $\times$  4.6 mm, 5  $\mu$ m) at  $\lambda = 280$  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 pure  $CH_3CN$  within the following 20 min.

**Spectroscopic Data.**  $^1H$  and  $^{13}C$  NMR were recorded in  $CDCl_3$  (99.8% in deuterium) using a Gemini 200 spectrometer. All chemical shifts are expressed in parts per million ( $\delta$  scale) and are referenced to either the residual protons or carbon of the solvent. FT-IR spectra were recorded in  $CHCl_3$  on a Bruker Vector 22 spectrometer. GC-MS analyses were obtained on a Fisons GC 8000 gas chromatograph equipped with a capillary column (Supelco Equity 5, 30 m long, i.d. = 0.25 mm, film thickness = 0.25  $\mu$ m) and coupled with a Fisons MD800 mass detector. HRMS were recorded with a Micromass Q-TOF *micro* mass spectrometer (Waters). Only the spectral data of new compounds are reported here.

**2-(3,4-Dihydroxyphenyl)ethanol **1** from Oleuropein **2**.** Compound **2** (328 mg, purity = 47%, 0.29 mmol) was dissolved in 6 M NaOH (5 mL), under argon atmosphere in the dark, and the solution was stirred



**Figure 2.** Acid hydrolyses of **3**: (○) 2 N HCl, 37 °C; (◇) pH 1, 37 °C; (△) pH 2, 37 °C; (▲) 6 N HCl, 25 °C; (▼) pH 0, 25 °C; (◆) pH 1, 25 °C. Each point represents the average value of three independent runs. The percent error ( $\pm 2\%$ ) is also reported.

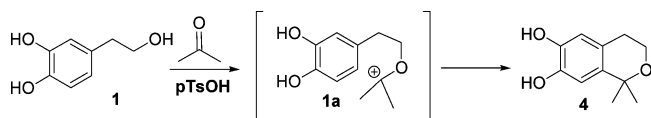
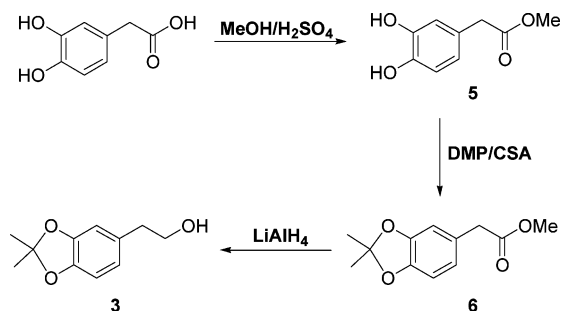
for 2 h. The solution was acidified to pH 3 with 2 M HCl and extracted with EtOAc. The organic extracts were dried over  $Na_2SO_4$  and evaporated in vacuo to afford a residue (30 mg) containing 55% of **1** (HPLC analysis). Purification on silica gel (20:1, w/w) by elution with  $CHCl_3/MeOH$  (80:20, v/v) gave a pure standard of **1** (5 mg; 0.03 mmol; yield 11%). Spectroscopic data were consistent with those reported in the literature (**25**).

**1,1-Dimethylisochroman-6,7-diol **4**.** Under argon atmosphere in the dark, a solution of **1** (100 mg, 0.65 mmol) and *p*-toluenesulfonic acid (pTsOH, 15 mg, 0.09 mmol) in dry acetone (20 mL) was refluxed for 3 h. The resulting solution was evaporated in vacuo, and the residue was redissolved in EtOAc and washed with acidified (pH 3) brine. The organic phase was dried over  $Na_2SO_4$  and evaporated under reduced pressure, and the residue (110 mg) was purified over silica gel (20:1, w/w) by elution with hexane/EtOAc (70:30, v/v) to afford pure **4** (75 mg, 0.39 mmol, yield 60%).

Spectroscopic data were in agreement with those reported in the literature (**26**).

**(3,4-Dihydroxyphenyl)acetic Acid Methyl Ester **5**.** A few drops of concentrated  $H_2SO_4$  were added to a solution of 3,4-dihydroxyphenylacetic acid (2.70 g, 16.07 mmol) in MeOH (250 mL) under argon atmosphere in the dark, and the reaction was refluxed for 2 h. After solvent evaporation in vacuo, the residue was redissolved in EtOAc and washed with  $NaHCO_3$  (saturated solution). The aqueous phase was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over  $Na_2SO_4$ , and evaporated under reduced pressure to give the ester **5** (2.70 g, 14.83 mmol, yield = 96%). The material was clean enough (94% via GC-MS) to be directly used in the next step. Spectroscopic data were in agreement with those reported in the literature (**27**).

**2-(2,2-Dimethylbenzo[1,3]dioxol-5-yl)acetic Acid Methyl Ester **6**.** Under argon atmosphere in the dark, 2,2-dimethoxypropane (16.0 mL, 130 mmol) and camphorsulfonic acid (0.56 g, 2.4 mmol) were added to a solution of **5** (2.70 g, 14.83 mmol) in anhydrous  $CHCl_3$  (150 mL), and the solution was refluxed for 8 h. The reaction mixture was neutralized by shaking with  $NaHCO_3$  (saturated solution), and the resulting aqueous phases were extracted three times with portions of  $CHCl_3$ . The combined organic extracts were dried over  $Na_2SO_4$  and evaporated in vacuo. The crude residue was purified on silica gel (20:1, w/w) by elution with petroleum ether/Et<sub>2</sub>O (9:1, v/v) to furnish pure **6** (2.99 g, 13.47 mmol, yield 91%):  $^1H$  NMR ( $CDCl_3$ ),  $\delta$  6.80–6.60 (m, 3H, aromatic H), 3.69 (s, 3H,  $OCH_3$ ), 3.51 (s, 2H,  $Ph-CH_2$ ), 1.66

**Scheme 2.** Formation of Isochromane **4****Scheme 3.** Synthesis of Acetonide **3** from 3,4-Dihydroxyphenyl-acetic Acid

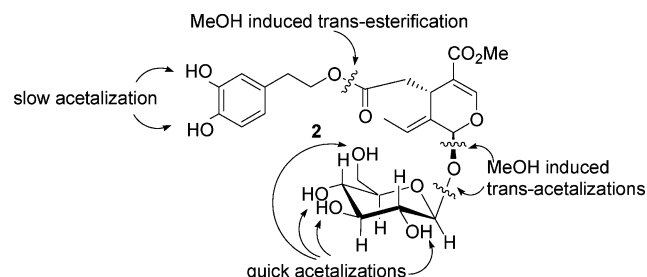
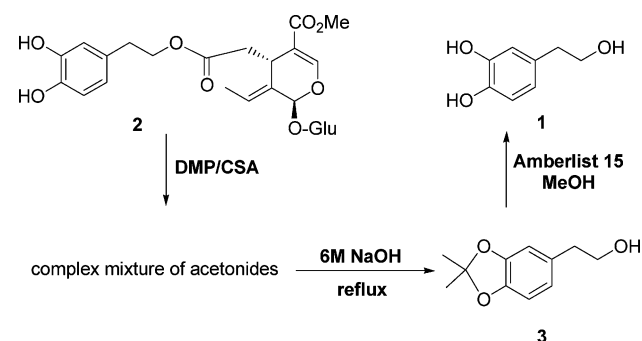
[s, 6H, C(CH<sub>3</sub>)<sub>2</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>), δ 172.31 (C<sup>1</sup>), 147.70 (C<sup>5</sup>), 146.67 (C<sup>6</sup>), 126.94 (C<sup>3</sup>), 121.80 (C<sup>8</sup>), 118.03 [C(CH<sub>3</sub>)<sub>2</sub>], 109.55 (C<sup>7</sup>), 108.15 (C<sup>4</sup>), 52.05 (OCH<sub>3</sub>), 40.92 (C<sup>2</sup>), 25.94 [C(CH<sub>3</sub>)<sub>2</sub>]; IR<sub>max</sub> (CHCl<sub>3</sub>), 1734, 1498, 1257, 1237 cm<sup>-1</sup>; MS, *m/z* (%) 222 (M<sup>+</sup>, 48), 207 (100), 163 (70), 123 (37), 77 (15). HRMS: found, 222.0894; C<sub>12</sub>H<sub>14</sub>O<sub>4</sub> requires 222.0892.

**2-(2,2-Dimethylbenzo[1,3]dioxol-5-yl)ethanol 3.** Under argon atmosphere in the dark LiAlH<sub>4</sub> (160 mg, 4.21 mmol) was added to a solution of ester **6** (1.87 g, 8.42 mmol) in anhydrous THF (250 mL). The suspension was refluxed for 3 h. The mixture was then cooled, and excess hydride was cautiously decomposed by adding first wet Et<sub>2</sub>O in small portions and then water, until the formation of a white precipitate occurred. After removal of the precipitate by filtration under reduced pressure, the solution was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to obtain a crude mixture. The material was purified over silica gel (20:1, w/w) by elution with petroleum ether/Et<sub>2</sub>O (90:10, v/v) to give pure **3** (1.55 g, 8.0 mmol, yield = 95%). Samples of **3** were left for 2 months at room temperature in the light and found unchanged as judged by HPLC and GC-MS analyses. <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ 6.68–6.58 (m, 3H, H aromatic H), 3.79 (t, 6.6 Hz, 2H, CH<sub>2</sub>–OH), 2.75 (t, 6.6 Hz, 2H, CH<sub>2</sub>Ph), 2.03 (s, 1H, OH), 1.66 [s, 3H, C(CH<sub>3</sub>)<sub>2</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>), δ 147.65 (C<sup>5</sup>), 146.06 (C<sup>6</sup>), 131.42 (C<sup>3</sup>), 121.23 (C<sup>8</sup>), 117.68 [C(CH<sub>3</sub>)<sub>2</sub>], 109.00 (C<sup>7</sup>), 108.09 (C<sup>4</sup>), 63.75 (C<sup>1</sup>), 38.90 (C<sup>2</sup>), 25.81 [C(CH<sub>3</sub>)<sub>2</sub>]; IR<sub>max</sub> (CHCl<sub>3</sub>), 3620, 3446, 1497, 1255, 1235 cm<sup>-1</sup>; MS, *m/z* (%) 194 (M<sup>+</sup>, 50), 179 (50), 163 (95), 123 (100), 77 (25). HRMS: found, 194.0944; C<sub>12</sub>H<sub>14</sub>O<sub>4</sub> requires 194.0943.

**Hydroxytyrosol 1 from 2-(2,2-Dimethylbenzo[1,3]dioxol-5-yl)-ethanol 3.** Amberlyst 15 (50 mg) was added to a solution of **3** (100 mg, 0.51 mmol) in MeOH (5 mL), and the suspension was refluxed under stirring for 3 h while the reaction progress was monitored by HPLC. At the end, the resin was removed by filtration, and the resulting solution was evaporated under reduced pressure to afford **1** (76 mg, 0.49 mmol, yield = 97%, purity = 99% via HPLC and GC-MS). Spectroscopic data were superimposable with those of the pure standard of **1**.

**Effect of pH and Temperature on the Acid Hydrolysis of 3.** A standard solution was prepared by dissolving **3** (388 mg, 2 mmol) in EtOH (5 mL). Small portions (30 μL) of this solution were added to HCl solutions (1 mL) at pH 2, 1, 0, and 2 M HCl, respectively, under argon atmosphere in the dark to reach a 12 mmol/L final concentration of **3**. Hydrolyses were carried out either at room temperature or at 37 °C and were monitored by regularly collecting small samples of the solution, neutralizing to pH 7 with solid NaHCO<sub>3</sub>, and analyzing by HPLC the percent decrease of **3** with respect to residual **3** and product **1** formed. Results are shown in Figure 2; each point represents the average value from three independent runs (±2% error).

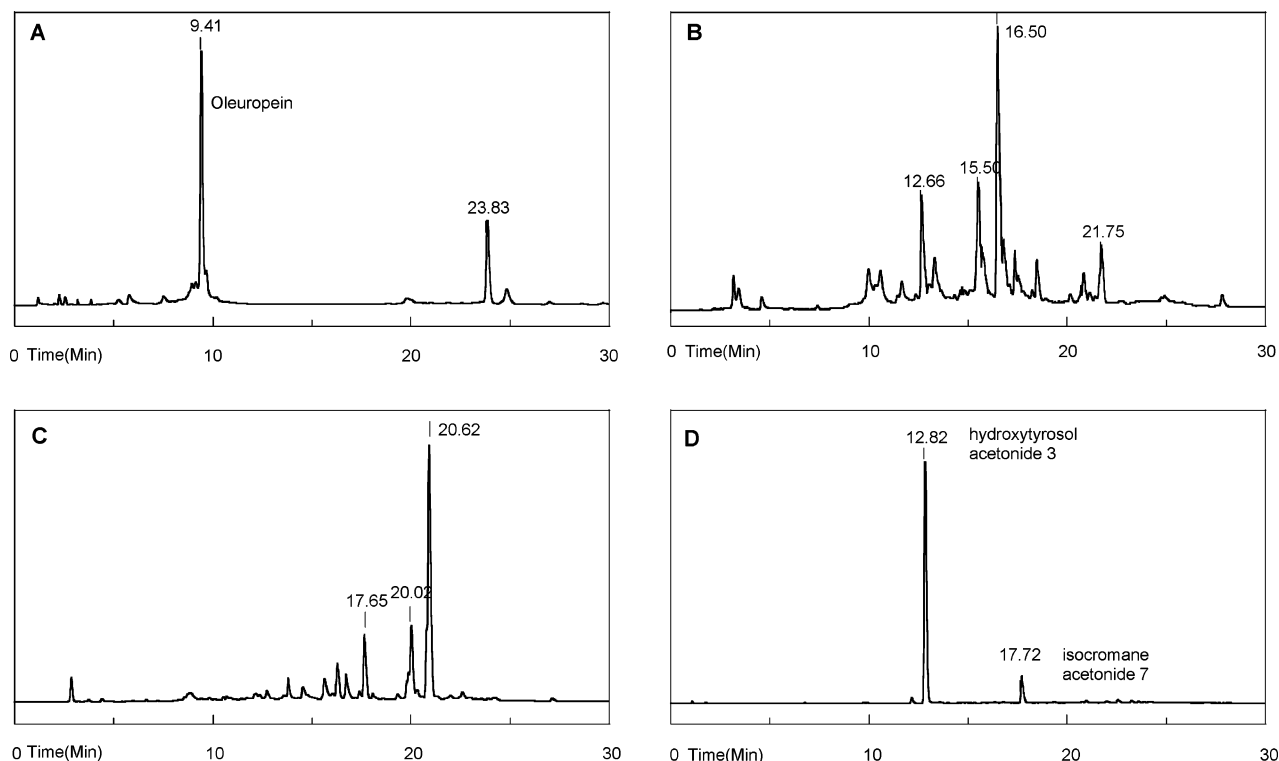
**2-(2,2-Dimethylbenzo[1,3]dioxol-5-yl)ethanol 3 from Oleuropein 2.** Under argon atmosphere and in the dark, 2,2-dimethoxypropane (0.18 mL, 1.44 mmol) was dissolved in anhydrous CHCl<sub>3</sub> (5 mL) in a

**Scheme 4.** Possible Competitive Reactions in the Acetalization of Oleuropein**Scheme 5.** Preparation of Hydroxytyrosol **1** from Oleuropein **2**

flask connected to a Dean–Stark apparatus, where the condensation funnel was filled with 4 Å molecular sieves to absorb the MeOH fraction (**24**) from the distilling azeotropic CHCl<sub>3</sub>/MeOH mixture (**28**). Oleuropein (**2**) (100 mg, purity = 47% via HPLC, corresponding to 0.087 mmol of pure **2**) and camphorsulfonic acid (4.2 mg, 0.018 mmol) were added, and the resulting suspension was refluxed by monitoring the reaction progress by HPLC (see Figure 3). After 6 h, the reaction mixture was neutralized by shaking with NaHCO<sub>3</sub> (saturated solution), and the separated aqueous phases were re-extracted three times with Et<sub>2</sub>O. The collected organic extracts were dried over dry Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo, obtaining a crude mixture (180 mg), which was directly used in the subsequent reaction. The mixture was suspended in 6 M NaOH (5 mL) and refluxed for 2 h. The solution was then adapted to pH 9 with 6 M HCl. The aqueous phases were separated and re-extracted three times with portions of Et<sub>2</sub>O, and the combined organic extracts were dried over dry Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to afford the crude saponification mixture (63 mg). GC-MS analysis showed the presence of **3** together with a minor component tentatively identified as **2,2,5,5-tetramethyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]-isochromene 7** [MS, *m/z* (%) 234 (M<sup>+</sup>, 12), 219 (100), 179 (12), 43 (89)]. Chromatographic purification on silica gel (20:1, w/w) using petroleum ether/Et<sub>2</sub>O (80:20, v/v) as eluent gave pure **3** (13 mg, 0.067 mmol, yield = 77% with reference to the starting substrate **2**), which was identical to the material obtained by synthesis.

## RESULTS AND DISCUSSION

In preliminary experiments, we tried to obtain acetonide **3** directly from hydroxytyrosol **1**, obtained in turn by alkaline hydrolysis of oleuropein **2** as described by Uccella et al. (22). However, in our hands, the procedure furnished **1** in only poor yield (55% via HPLC), as expected in view of the above-mentioned lack of stability of **1** under basic conditions (**18b**). The yield was further reduced to 11% after chromatographic purification. Moreover, hydroxytyrosol **1** turned out not to be a suitable starting material for direct acetalization of the catechol moiety because it afforded the isochromane **4** (Scheme 2) as the main product, under acidic conditions (pTsOH) in acetone. Formation of **4** from **1** has been already reported by Guiso et al. (26) under different conditions. This transformation was explained in terms of an oxa-Pictet Spengler cyclization of the



**Figure 3.** HPLC profiles of the acetalization reaction of oleuropein 2: (A) substrate; (B) after 2 h of heating; (C) after 5 h of heating; (D) after saponification of the crude mixture.

cationic intermediate **1a**, generated by the addition of the more nucleophilic primary alcohol group to acetone.

Therefore, we ruled out the direct acetalization of **1** as a way to obtain **3** and alternatively focused on substrates where the catechol function cannot compete with more nucleophilic groups.

Therefore, acetonide **3** was easily prepared starting from methyl ester **5** (see Materials and Methods) (27) of the commercially available 3,4-dihydroxyphenylacetic acid (Scheme 3). Introduction of the acetonide protection in compound **5** was obtained in high yield (91%) by means of a transacetalization reaction using 2,2-dimethoxypropane (DMP) and camphorsulfonic acid (CSA) in  $\text{CHCl}_3$ . It has to be noted that the use of either acetone or 2-methoxypropene resulted in low yields or formation of substantial amounts of polymers. Subsequent  $\text{LiAlH}_4$  reduction of the protected ester **6** gave hydroxytyrosol acetonide **3** in almost quantitative yield (95%). Compound **3** was stable on silica, and this allowed quantitative recovery of the product, with a high grade of purity, after chromatographic purification. In addition, **3** was recovered unchanged after 2 months of exposure to air and light.

With acetonide **3** in hand, we studied its hydrolytic behavior at 25 and 37 °C under acid catalysis. This was done to study the steadiness of protection under acidic conditions and particularly to show if **3** is cleaved by gastric juices. The effect of bases was not examined, in view of the well-known stability of acetals under basic conditions. The experiments were carried out under argon atmosphere and in the dark. HPLC measurements showed a decrease of the substrate and the contemporary formation of hydroxytyrosol **1**. Results are given in Figure 2, where only the percentual decrease of substrate is listed (see Materials and Methods).

As clearly shown in Figure 2, this process is accelerated with increased acidity as well as rising temperature. Acetonide **3** is

almost stable at pH 2 at 37 °C, whereas it undergoes slow hydrolysis at pH 1 ( $t_{1/2} > 140$  h at 25 °C and  $t_{1/2} = 40$  h at 37 °C) and fast hydrolysis at pH 0 ( $t_{1/2} = 42$  h at 25 °C and  $t_{1/2} = 3$  h with 2 N HCl at 37 °C).

These results stress the importance of derivate **3** as a suitably stabilized form of hydroxytyrosol whenever this compound has to be purified and long-term storage is required before industrial use. Moreover, the high stability makes this protection appropriate for obtaining of **3** from oleuropein **2** (Scheme 1).

On the other hand, protection of **1** would be worthless, unless a mild and high-yielding procedure for releasing free hydroxytyrosol were to be found. Moreover, in view of the previously mentioned amphiphilic character of **1** (9), the use of aqueous media for deprotection could result in substantial loss of hydroxytyrosol **1**. Therefore, we tested various nonaqueous heterogeneous acidic conditions that could allow recovery of **1** by simple filtration. Using Amberlyst 15 in MeOH, **3** was easily converted into **1** with complete recovery of the pure product after simple filtration and evaporation of the solvent. The yield of hydroxytyrosol (97%) and its purity (99%) make this procedure a highly useful method.

Consequently, we extended this procedure to oleuropein **2** to obtain stabilized hydroxytyrosol **3** directly from an abundant natural source. However, the first step, the oleuropein acetalization step, deserves some preliminary considerations in view of the complex structure of glycoside **2**.

As shown in Scheme 4 many possible reactions can compete with the desired acetalization of the catechol moiety. First, the hydroxyl groups of the glucose subunit can undergo quicker acetalization as they show higher nucleophilicity in comparison with those of the catechol subunit. Many different acetonides of the glucose moiety can be expected. Other competing reactions can occur after the release of methanol, as a reaction



byproduct. This can produce either transacetalization at the glycoside moiety or transesterification processes at the ester bond.

Therefore, oleuropein **2** was acetalized (**Scheme 5**) under the same conditions described for the preparation of compound **6**. The only difference was the use of a Dean–Stark apparatus in which the condensation funnel was filled with 4 Å molecular sieves, to selectively remove methanol (**24**) distilled as azeotrope with  $\text{CHCl}_3$  (**28**). This setup minimizes the methanol-induced transesterification and transacetalization processes. The reaction progress was followed by HPLC without isolating any intermediates, and the process was carried on until a steady chromatographic profile was obtained. Results are reported in **Figure 3**.

As expected, oleuropein **2** (**Figure 3A**,  $t_R = 9.42$  min) quickly reacted to afford a complex mixture with a lower polarity. The retention times of main peaks ranged between 13 and 17 min (**Figure 3B**). These peaks are probably related to acetalization and/or polyacetalization processes of the glucose moiety in **2**. However, prolonged reaction times (3 h, **Figure 3C**) resulted in a change of the chromatographic profile in favor of products with higher retention times (20–21 min), likely derived from exhaustive acetalization. Further heating of the mixture did not affect the chromatographic profile, and the crude mixture was directly saponified to afford acetone **3** together with a small amount (8%) of an unknown compound (**Figure 3D**,  $t_R = 17.72$  min). This was tentatively identified as the isochromane acetone **7** on the bases of the similarity between the GC-MS spectra of **7** (see Materials and Methods) and **4**. Compound **7** was probably derived from acetalization of the isochromane **4**, produced in turn by cyclization of hydroxytyrosol **1** (see **Scheme 2**). The latter compound is the expected product of oleuropein **2** transesterification in the presence of methanol (see **Scheme 4**). After chromatographic purification over silica, the pure acetone **3** was obtained in high yield (76% referred to **2**) and quantitatively converted into hydroxytyrosol **1** as described above.

To the best of our knowledge, this is the first high-yielding procedure to produce stabilized acetone **3** from the abundant (**4**) and easily extractable (**2**) natural glycoside oleuropein. Because deprotection affords pure hydroxytyrosol in high yield, the overall procedure can be regarded as a suitable alternative of previous methods that access **1** from **2** by chemical or enzymatic processes (20–22).

In conclusion, we have found that the natural and unstable antioxidant hydroxytyrosol **1** can be stabilized if the catechol function is protected as acetone **3**. This novel compound is highly stable in air and under light, over silica, and in a wide range of basic and acidic conditions. It can be purified and stored long-term. In addition, we have reported an easy and mild method for deprotection so that the acetone **3** can be regarded as a stable source of hydroxytyrosol **1**.

However, the protection cannot be introduced directly; therefore, **3** must be prepared either by a high-yielding two-step process or by chemical elaboration of the natural and abundant glycoside oleuropein **2**. In view of both the high amount of oleuropein in olive leaves and the easy extraction, this procedure constitutes a new interesting route to antioxidant **1**.

As a final consideration, the high stability of **3** can also be regarded to cause trouble as it is aimed to deprotect the catechol function under very mild physiological conditions (derma or gastric pH). Further work is in progress to answer this question.

## LITERATURE CITED

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