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Capillary Electrophoresis Determination, Synthesis, and Stability of Resveratrol and Related 3-*O*-β-D-Glucopyranosides

VINCENZO BRANDOLINI,* ANNALISA MAIETTI, PAOLA TEDESCHI, ELISA DURINI, SILVIA VERTUANI, AND STEFANO MANFREDINI*

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, via Fossato di Mortara 17-19, I-44100 Ferrara, Italy

Because of the health implications of resveratrol and piceid, which are widely present in foods, we focused our attention on the development of a highly efficient methodology for their characterization and measurement. On the basis of our experience in capillary electrophoresis for separation of polyphenolic compounds, we developed a general analytical method for piceid identification which was also applicable to complex natural mixtures such as red wine. In view of its very limited availability from natural sources, we first directed our attention to the development of a synthetic route suitable to produce an adequate amount of polydatin (piceid or resveratrol 3-*O*-β-D-glucopyranoside). The latter was synthesized by a new one-step procedure which afforded the expected product in a good yield. The studied compounds were also investigated for their stability to UV irradiation.

KEYWORDS: Resveratrol; polydatin; red wine; synthesis; capillary electrophoresis (CE)

INTRODUCTION

In recent years, several scientific studies have attracted considerable attention to the fact that moderate but regular red wine consumption is correlated with beneficial effects on human health (*1*). Epidemiological studies have shown a negative correlation between moderate wine consumption and the risk of coronary heart disease (CHD) (*2*). Moreover, wine consumption has been recently related to reduced rates of cancer and degenerative disorders, such as Alzheimer's disease and dementia (*3*, *4*).

Polyphenolic compounds, which are present in the skin of grapes and red wine, are proposed to be responsible for these activities, particularly stilbene compounds such as *trans*-resveratrol, its glucoside polydatin (piceid or resveratrol 3-*O*-β-D-glucopyranoside), and their less effective isomeric forms. Resveratrol, first identified in red wine in 1992 (*5*), is suggested to reduce CDH mortality on the basis of (i) its ability to inhibit platelet aggregation by impairment of eicosanoid synthesis (*6*); (ii) protection from oxidation of the human LDL (low-density lipoproteins) by acting as radical scavenger and antioxidant (7); and (iii) hypotensive activity, acting through an estrogen-like mechanism (*8*). A moderate anticarcinogenic activity, by inhibition of cellular events associated with tumor initiation, promotion, and progression, has been also ascribed to resveratrol (9). The *trans*-piceid isomer shows similar properties; biological studies have revealed its role as an antioxidant, anticlotting, and antiinflammatory agent (*10*, *11*). However, *trans*-piceid has been observed to be less active than *trans*-resveratrol in reducing lipid levels and inhibiting eicosanoid synthesis (*12*, *13*).

Recently, typical red wine stilbene compounds have been found in considerable amounts in *Polygonum cuspidatum* root, a plant widely used in ancient Chinese and Japanese herbal medicine for a variety of therapeutic purposes. In particular, the powder from dried *P. cuspidatum* roots has been used in Asia to treat atherosclerosis as well as other medical ailments including cough, asthma, hypertension, and cancer, thereby supporting the beneficial effects of stilbene compounds (*14*).

Because of the health implications of resveratrol and piceid, several researchers have focused their attention on the development of methodologies for their characterization and measurements in foods and other natural products. These include gas chromatography/mass spectrometry (GC/MS) (*15*) and high-performance liquid chromatography (HPLC) (*16*, *17*). The introduction of the capillary electrophoresis (CE) technique has made available a new method to investigate separation of *cis*- and *trans*-resveratrol isomers (*18*−*20*). Advantages over chromatographic techniques, in particular HPLC, are small sample size requirement, lower costs in view of the reduced organic solvent consumption and inexpensive capillary instead of expensive HPLC or GC columns, and high efficiency of separation and speed. These properties make CE a valuable technique for analysis of complex mixtures of natural origin as well as newly synthesized products (*21*). In all these methods, *trans*-resveratrol identification was performed by comparison with a standard from chemical synthesis, whereas the c*is*-resveratrol standard was generated by exposure to UV radiation of a *trans*-resveratrol standard solution (*22*). To date, only a few methodologies have been described for identification and separation of the corresponding glycosidic forms of resveratrol because of the lack of standard piceids. In fact, extracts of *P. cuspidatum* roots are usually used to perform piceid determinations.

* To whom correspondence should be addressed (fax +39-532-29-1296, E-mail bnv@unife.it and mv9@unife.it).

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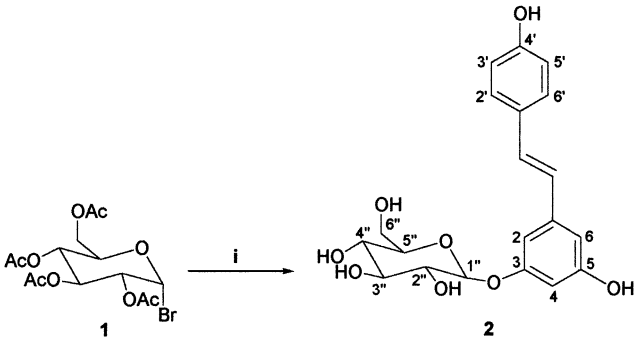

Figure 1. Synthetic route for resveratrol 3-*O*-*β*-D-glycopyranoside. (i) MeOH, MeONa, (*E*)-resveratrol, 40 °C.

To develop a general CE analytical method for piceid identification, and in view of the limited availability of piceid from natural sources, we first directed our attention to the development of a synthetic route suitable to produce an adequate amount of polydatin. In this regard, Orsini and co-workers have described the preparation of polydatin through a multistep synthesis (*11*). From literature reports and our experience in the field of glycosylation protocols (*23*−*26*), we have developed a simple synthetic strategy for preparation of the targeted glycoside. We now present a simple and direct one-step synthesis of *trans*-piceid (**2**) (**Figure 1**) and optimized conditions for separation of resveratrol, piceid, and their isomers. A study of the effect of UV irradiation on *trans*-polydatin as well as the extension of the method to a complex natural mixture (wine) will be also described.

MATERIALS AND METHODS

General Methods. Reaction courses were routinely monitored by thin-layer chromatography (TLC) on Duracil-25 precoated silica gel (Macherey-Nagel, Düren, Germany) with detection under a 254-nm UV lamp and/or by spraying the plates with 10% H_2SO_4/CH_3OH and heating. Column chromatography was performed with 70−230 mesh silica gel (Macherey-Nagel). Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra were obtained on a HPG2025A mass spectrometer (Helwett-Packard, Boise ID) operating in a positive linear mode. Nuclear magnetic resonance spectra were determined in DMSO-d_6/D_2O solution with an AC-200 spectrometer (Brucker, Karlsruhe, Germany), and chemical shifts are presented in ppm from tetramethylsilane as an internal standard. Optical rotations were determined with a P-1010 polarimeter (Jasco, Tokyo, Japan). Melting points were determined by a Kofler melting point apparatus (Thermovar, C. Reichert AG, Vienna, Austria) and are uncorrected. All drying operations were performed over anhydrous sodium sulfate or magnesium sulfate.

Chemicals. Reagent-grade MeOH was refluxed over Mg and I_2, distilled, and stored over 3 Å molecular sieves. α-Bromotetra-*O*-acetyl-D-glucose was purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI); (*E*)-resveratrol for the synthetic studies and an authentic sample of polydatin for comparison purposes were kindly supplied by Laila Impex (Viajawada, India).

Standard *trans*-resveratrol was purchased from Sigma (Aldrich Chemical Co., Inc.); *trans*-resveratrol glucoside (piceid) extract from *P. cuspidatum* was kindly supplied by Laila Impex (Viajawada, India). *cis*-Resveratrol and *cis*-piceid standards were obtained from the trans isomers' standard solutions by UV irradiation. UV irradiation was performed with a UV lamp (Camag, Muttenz, Switzerland) at 254 nm. Absorbance of irradiated solutions was analyzed by a UVICON 922 spectrophotometer (Kontron Instruments, Milan, Italy). Standard solutions of *trans*-resveratrol and *trans*-piceid, 100 ppm each, were prepared and subdivided into six aliquots of 1 mL each. The vials were stored in a freezer and irradiated by UV lamp for 0, 5, 10, 20, 40, and 60 min, respectively.

Chemical reagents were purchased from Carlo Erba (Milan, Italy) (sodium hydroxide, methanol, ethyl acetate, sodium lauryl sulfate, sodium sulfate anhydrous) or Fluka (Aldrich Chemical Co., Inc.) (sodium tetraborate decahydrate, polyethyleneglycol 400). HPCE water was purchased from Merck (Darmstadt, Germany).

(*E*)-Resveratrol 3-*O*-*β*-D-Glycopyranoside (2). To a stirred solution of NaOMe (230 mg, 10 mmol) in anhydrous MeOH (40 mL) was added dropwise, under argon atmosphere, a solution of (*E*)-resveratrol (2.28 g, 10 mmol) in MeOH (40 mL). After 1.5 h at room temperature, to the (*E*)-resveratrol monosodium salt solution was slowly added α-bromotetra-*O*-acetyl-D-glucose (2.1 g, 5 mmol), previously dissolved in anhydrous MeOH (20 mL). The resulting solution was heated at 40 °C, under argon atmosphere, for 1 h (TLC, CH_2Cl_2/MeOH 8:2). The dark brown solution was evaporated to dryness and the residue treated with Et_2O. The suspension was filtered and the organic phase evaporated to dryness. The crude residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH 8.5:1.5, to afford 170 mg of compound **2** together with 1.1 g of starting (*E*)-resveratrol.

Compound **2**: yield 25% (based on recovered starting material); yellow solid; mp 225−228 °C [lit. (*22*) mp 228−230 °C]; $[\alpha]^{25}_D$ = −62.2 (*c* 0.32, MeOH) [lit. (*23*) $[\alpha]^{25}_D$ = − 65.26]; ^{1}H NMR (DMSO-d_6) δ 9.49 (br s, 1H, OH phenolic), 9.38 (br s, 1H, OH phenolic), 7.39 (d, 2H J = 8.5 Hz, H2′ and H6′), 7.03 (d, 1H, J = 16.9 Hz, H-b, vinyl), 6.85 (d, 1H, J = 16.9 Hz, H-a, vinyl), 6.75 (d, 2H, J = 8.5 Hz, H3′ and H5′), 6.71 (dd, 1H, J = 1.8 Hz, H-2), 6.53 (dd, 1H, J = 1.8 Hz, H-6), 6.30 (dd, 1H, J = 1.8 Hz, H-4), 5.30 (d, 1H, OH), 5.12 (d, 1H, OH), 5.03 (d, 1H, OH), 4.80 (d, 1H, J = 7 Hz, H-1″), 4.61 (t, 1H, OH), 3.70 (dd, 1H, J = 12.1, 1.8 Hz, H-6″B), 3.63−3.13 (m, 5H, H″, H3″, H4″ H5″, H6″A); ^{13}C NMR (DMSO-d_6) δ 158.9 (s, C-3 or C-5), 158.4 (s, C-3 or C-5), 157.3 (s, C-4′), 139.4 (s, C-1), 130.0 (s, C-1′), 128.6 (d, C-*β*), 128.0 (d, C-2′ and C-6′), 125.2 (d, C-α), 115.6 (d, C-3′ and C-5′), 107.2 (d, C-6), 104.7 (d, C-4), 102.8 (d, C-2), 100.7 (d, C-1″), 77.2 (d, C-5″), 76.7 (d, C-3″), 73.3 (d, C-2″), 69.8 (d, C-4″), 60.7 (t, C-6″); MALDI-TOF MS m/z 391 $(M + H)^+$, 413 $(M + Na)^+$, and 429 $(M + K)^+$ ($C_{20}H_{22}O_8$ requires 390.13).

(*Z*)-Resveratrol 3-*O*-*β*-D-Glycopyranoside: ^{1}H NMR (DMSO-d_6) δ 6.30 and 6.42 (AB system, 2H, J = 11.8 Hz, H-a and H-b, vinyl) (*11*).

Analytical Method. The instrument used for analyses was a P/ACE 5500 (Beckman, Fullerton, CA) with a diode array detector. Data collection and analyses were performed by using P/ACE Station software. The separation was obtained with a 57 cm × 75 μm i.d. fused silica capillary maintained in a cartridge with a detector window of 800 μm × 100 μm. The capillary was conditioned prior to its first use by flushing with 0.1 M NaOH for 5 min, then with water for 15 min, and finally with buffer for 10 min. The buffer was composed of 20 mM $Na_2B_4O_7$, 25 mM PEG 400, and 25 mM SDS with addition of 10% methanol just before use. The sample was injected into the capillary by pressure injection for 5 s. Separation was obtained at 28 kV and 25 °C for 15 min. A good linear relationship, ranging from 1 to 50 ppm, between peak area and concentration of *trans*-resveratrol and *trans*-piceid was found. The limit of detection in the real sample was 0.05 ppm in wine, thus ensuring the desired high efficiency for the method.

Solid-Phase Extraction (SPE). In the case of the wine sample, SPE extraction was conducted with a 500 mg, 10 mL Isolute MF C18 cartridge (Stepbio, Bologna, Italy). The cartridge was conditioned before use with 10 mL of ethyl acetate, 10 mL of methanol, and 10 mL of water. The sample, 10 mL of red wine, was then loaded and eluted with 10 mL of ethyl acetate. The eluate was filtered through an anhydrous sodium sulfate cartridge and evaporated to dryness. The residue was dissolved in 0.5 mL of methanol and injected in the CE system.

RESULTS AND DISCUSSION

We have previously investigated the effectiveness of the capillary electrophoresis technique for the separation of the *cis*- and *trans*-resveratrol isomers (*20*, *27*). With the aim of extending the separation technique to glycoside derivatives of resveratrol, the analysis conditions and the buffer concentration were varied

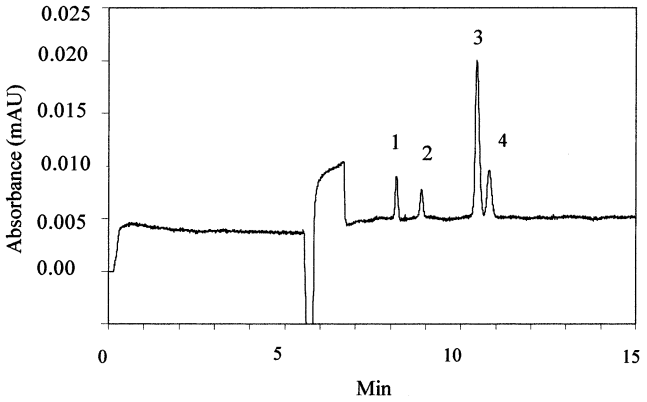

Figure 2. Electropherogram of a standard mixture of *trans*-resveratrol (1), *cis*-resveratrol (2), *trans*-piceid (3), and *cis*-piceid (4).

as described in the Analytical Method section. The optimization of these conditions permitted good separations of mixtures of *trans*-resveratrol, *cis*-resveratrol, *trans*-piceid, and *cis*-piceid, as shown in **Figure 2**.

To develop the analytical separation conditions, considerable amounts of pure isomers were required, and, because of the limited availability of these compounds from natural sources, their preparation was undertaken. Orsini et al. (*11*) described a multistep synthesis of the polydatin, obtained through the preparation of the stilbene skeleton by the Wittig reaction and then glycosylation using α-bromotetra-*O*-acetyl-D-glucose in aqueous phase, under phase-transfer catalysis. This required prior protection of the hydroxyl group at the 4′ position as the methoxy derivative. Polydatin was obtained in good yield but only after several synthetic steps. With the aim of obtaining polydatin by a simpler synthetic methodology, we developed a method of direct glycosylation. From our experience in the field (*22*, *23*), from established glycosylation protocols (*25*, *26*), and by exploiting the low reactivity of phenolic moieties, we obtained resveratrol 3-*O*-*β*-D-glucopyranoside in a one-step reaction. The synthesis was simply performed on *trans*-resveratrol monosodium salt, by the addition of α-bromotetra-*O*-acetyl-D-glucose (**1**). The reaction proceeded with concomitant deprotection of the hydroxyl functions on the sugar moiety to provide the expected 3-*O*-glycosylated derivative (**2**) in a satisfactory yield (**Figure 1**).

Of the two possible anomers, only the *β*-anomer was obtained when the glycosylation was carried out under strictly controlled reaction conditions (concentration, temperature, and time) in the presence of a 2:1 molar ratio of *trans*-resveratrol and α-bromotetra-*O*-acetyl-D-glucose. Under these conditions, no traces of the corresponding 3,5-diglucoside and 4′-glucoside derivatives were recovered, whereas consistent amounts of starting *trans*-resveratrol were always isolated (50−60%). However, the one-step reaction allowed compound **2** to be obtained in 25% yield after purification. Compound **2** was characterized by spectroscopic analysis, by comparison with literature data (*11*, *17*), and found to be identical in all respects to an authentic sample isolated from a natural source (*P. cuspydatum* from Laila Impex, Viajawada, India). Moreover, the electropherograms of both compounds, synthetic and natural, showed the same migration time, the corresponding peaks, and the same absorption spectra (**Figure 3**).

In general, *cis*-resveratrol and the corresponding glycoside are less well represented in natural products than the isomeric forms, thereby leading to a lack of analytical standards and to difficulties in their identification and quantification. The possibility of converting the trans isomers into the cis isomers by UV irradiation has previously been described (*22*). Therefore, *trans*-resveratrol and *trans*-piceid solutions were irradiated for different times (5−60 min), and the total absorbance was determined. On the basis of isomerization experiments, a calibration curve was obtained, assuming that the reduction of the trans isomers achieved by UV irradiation was the result of cis isomer generation. The electrophoretic analysis was conducted by following and further developing a method previously reported by us (*20*), optimized in view of the report by Gu et al. (*18*). In the present study, the analytical method was improved in order to obtain concomitant separation and determination of *cis*- and *trans*-resveratrol and of the corresponding glycosides (**Figure 2**). The electropherograms were analyzed in detail by identification of all peaks and by calculation of peak areas. The effect of the irradiation time on the isomerization of *trans*-resveratrol and *trans*-piceid is shown in **Figure 4**: in the first 5 min, 50% *trans*- to *cis*-resveratrol isomerization was obtained. Equilibrium was achieved after 20 min of exposure, with a 90% final conversion.

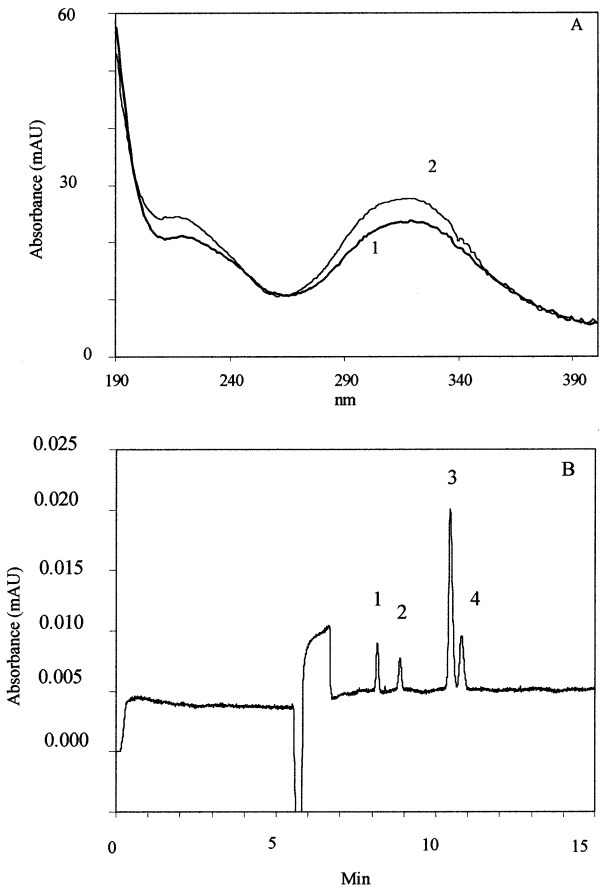

Figure 3. (A) Comparison between the absorption spectrum of synthesized compound (1) and the absorption spectrum of standard *trans*-piceid from *P. cuspidatum* roots (2). (B) Electropherogram of synthesized compound (1).

To further assess the procedure, the method was also applied, under the same experimental conditions, to complex natural mixtures such as wine. Resveratrol and piceid isomers were identified in a sample of wine by comparison to corresponding standards. The electropherogram of red wine extract is shown in **Figure 5**. Peaks 1 and 2 correspond to *trans*- and *cis*-piceid, and peaks 3 and 4 correspond to *trans*- and *cis*-resveratrol, respectively. SPE extraction was necessary to obtain clear and concentrated samples.

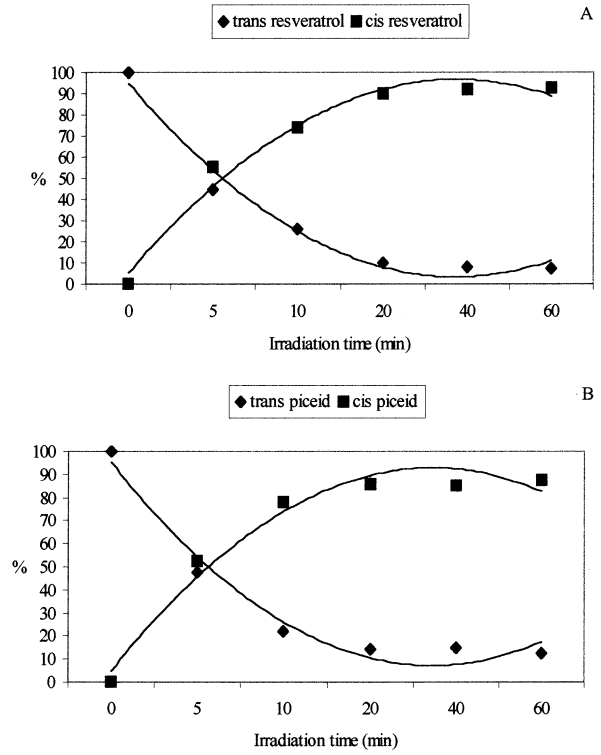

Figure 4. (A) Isomerization curves upon irradiation of *trans*-resveratrol standard solution (100 ppm) by UV lamp at 254 nm. (B) Isomerization curves upon irradiation of *trans*-piceid standard solution (100 ppm) by UV lamp at 254 nm.

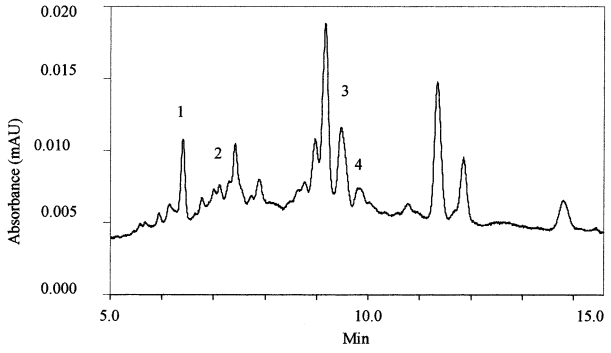

Figure 5. Electrophoretic separation of red wine extract obtained by SPE extraction. Peaks 1 and 2 correspond to *trans*- and *cis*-piceid, and peaks 3 and 4 correspond to *trans*- and *cis*-resveratrol.

In conclusion, in vivo and in vitro studies have shown that *trans*-resveratrol and *trans*-piceid are interesting compounds because of their pharmacological properties. The presence of the above compounds in foods and natural extracts has produced an increase in demand for analytical techniques specific for their qualitative and quantitative determinations. Among the available techniques, CE, with diode array detection, represents an efficient method for the determination and separation of cis and trans isomers; analysis is sensitive, low in cost, fast, and reliable. On the basis of our experience in the use of the CE technique for the separation and characterization of natural derivatives, we have developed a specific protocol to identify and separate resveratrol isomers and their corresponding glycosides, piceids, from synthetic as well as natural sources. Furthermore, a study on UV irradiation of *trans*-polydatin, aimed at obtaining the corresponding cis isomer, has been also conducted, leading to 90% final conversion. Moreover, to define the correct elution conditions, in view of the very limited availability from natural sources of the above-mentioned isomers, we directed our efforts to achieving a considerable amount of polydatin by a synthetic route. The synthetic strategy proposed in this study represents an improvement over already known procedures for *trans*-polydatin preparation because the latter is now achievable through a one-step reaction, starting from commercially available materials. Therefore, we propose this one-step synthesis as a method for the preparation of the larger amounts of the compound necessary for the study of the biological properties of this important class of molecules (*28*, *29*).

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