Tetrahedron Letters 55 (2014) 2455–2458

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile and sustainable synthesis of the natural antioxidant hydroxytyrosol

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ARTICLE INFO

Article history:
Received 28 January 2014
Revised 19 February 2014
Accepted 28 February 2014
Available online 12 March 2014

Keywords:
Hydroxytyrosol
Eugenol
Antioxidant
Chemical synthesis

ABSTRACT

Hydroxytyrosol [**1**, 2-(3,4-dihydroxyphenyl)ethanol], an olive-derived potent natural antioxidant was conveniently prepared from the clove-derived and commercially available eugenol (**8**, 4-allyl-2-methoxyphenol) using inexpensive reagents in a two-pot four-step process, which successively encompasses a reductive ozonolysis into homovanillyl alcohol (**4**, 4-hydroxy-3-methoxyphenethanol) and a sodium periodate-mediated oxidative demethylation using a reductive workup.

Among the wide variety of bioactive components found in olive oil, several phenolic compounds have been reported to express beneficial effects on human health.[1,2] The concentration of phenolics in the olive fruit varies a lot depending on cultivar, climate, and degree of maturation, although they largely remain in waste waters of olive oil mill process.[3] Nevertheless, the average concentration of phenolics can rise up to 1 g/kg in the first-pressed 'extra virgin' type olive oil.[4] Hydroxytyrosol [**1**, 2-(3,4-dihydroxyphenyl)ethanol] is one of the major phenolic compounds present in the olive fruit and olive oil, together with tyrosol (**2**) and oleuropein (**3**), from which **1** can be generated by hydrolysis (Fig. 1).[2]

Hydroxytyrosol (**1**) is a simple catecholic compound, often wrongly referred to as belonging to the plant polyphenol family of natural products.[5] Its remarkable antioxidation activity[6] makes it a highly promising alternative to synthetic antioxidants such as 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT), 2- and 3-*tert*-butyl-4-hydroxyanisoles (BHA), or ethoxyquin, which are still commonly used as food and/or feed preservatives in spite of their confirmed toxicity.[7] It has notably been shown that **1** contributes to the stability of virgin oil against rancidity caused by oxidation,[8] hence demonstrating the potentiality of its utilization as a natural and non-toxic food preservative. Numerous biological evaluations of **1** have also been performed with the aim of rationalizing observations made on the protective effects of olive oil-rich Mediterranean-type diets against degenerative diseases such as atherosclerosis and cancer.[1,2] For example, **1** has been shown to inhibit the autoxidation of human low-density lipoproteins (LDL),[9] and to inhibit the aggregation of platelets.[10] Hydroxytyrosol is a scavenger of reactive oxygen species,[9c] and hence can confer protection to cells against reactive oxygen species-induced cytotoxicity,[11] as well as against oxidative damages that could be responsible for the initiation and promotion of tumorigenesis.[2c] Antibiotic activities of **1** against some gram-positive and gram-negative bacteria causing infections in the respiratory and intestinal tracts have also been evidenced.[12]

Any further consideration of the potential application of **1** as an alternative non-toxic food/feed preservative capable of expressing additional human health-protecting properties has been thwarted by the lack of access to **1** in sufficiently large quantities at low cost. The only industrial source of **1** so far remains its recovery from olive oil by-products.[13] At best, 4 to 5 kg of crude **1** can be obtained from 1000 kg of 'alperujo', a by-product of modern olive oil mill processing.[13b] A few (bio)chemical syntheses of **1** have been reported (vide infra), but all methods are either low-yielding or rely on the use of relatively expensive starting materials (Fig. 1) or reagents.[2] Therefore, a convenient, economical, and scalable access to **1** still constitutes a valuable objective for the agro-food chemical industry. Here, we wish to report a facile and sustainable synthesis that starts from eugenol as a renewable raw material and that should be readily amenable to an industrial-scale production of **1**.[14]

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http://dx.doi.org/10.1016/j.tetlet.2014.02.134
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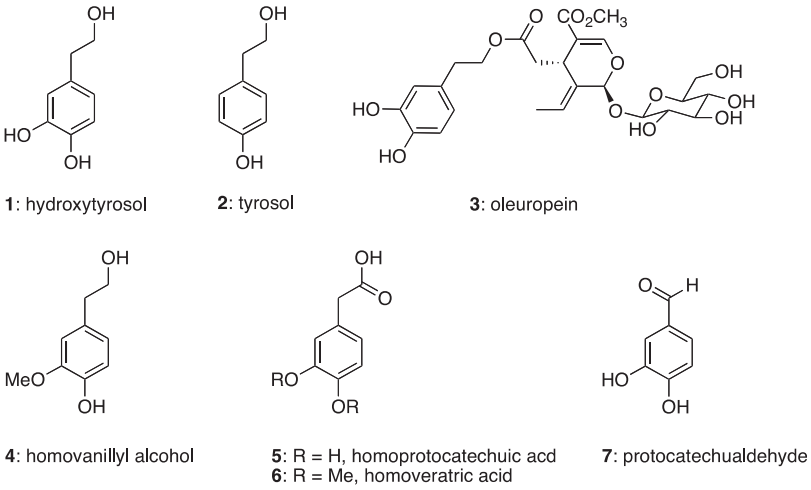

Figure 1. Chemical structures of hydroxytyrosol (**1**) and its main precursors.

Several methods have been reported for the (bio)chemical synthesis of **1** from various natural or synthetic precursors (Fig. 1).[2] Among these procedures, transformation of tyrosol (**2**) is probably the one that has received the most attention from researchers in recent years. Enzymatic oxygenation of **2** using tyrosinases under reductive conditions[15] or via bacterial synthesis[16] catalyzes the *ortho*-monohydroxylation of **2** to furnish **1** in relatively high yields.[15,16] The alternative chemical oxygenation of **2** using the hypervalent iodine (V) reagent 2-iodylbenzoic acid (IBX) under reductive workup conditions using sodium dithionite afforded **1** only in a moderate isolated yield of 30%.[17] However, the use of a polymer-supported variant of IBX enabled the conversion of **2** into **1** in a quantitative yield.[18] Monohydroxylation of **2** was also performed using a wet hydrogen peroxide photocatalytic oxidation system to generate **1** in an optimum yield of 64%.[19] Two other recent synthesis approaches to **1** from **2** have been reported[20] to rely on an indirect installation of the additional hydroxyl group either via a five-step sequence involving an initial *ortho*-bromination of **2** for a subsequent oxygenation by methoxylation,[20a] or via a four-step sequence involving an *ortho*-formylation followed by a Bayer–Villiger oxygenative cleavage step.[20b] Both syntheses required protection and deprotection of the primary alcohol function of **2**.[20] The olive metabolite oleuropein (**3**, Fig. 1) constitutes another important natural precursor from which **1** can be obtained by either chemical[21] or enzymatic[22] hydrolysis. Unfortunately, the supply of both tyrosol (**2**) and oleuropein (**3**) from their natural sources or from their recovery from olive oil mill wastewaters is quantitatively limited, which impedes the development of industrial (bio)chemical processes aimed at generating **1** in large quantities from such precursors.

Demethylation of homovanillyl alcohol (**4**, Fig. 1), a metabolite of **1**, has also been considered as a starting material for the chemical synthesis of **1**, notably by using IBX again, its non-explosive formulation (SIBX, for Stabilized IBX) or its polymer-supported variant to promote the required (oxygenative) demethylation reaction.[18,23] Even though such a chemical transformation can be developed into a high-yielding process using polymer-supported IBX,[18a] the short supply and high cost of **4** combined with the use of a relatively expensive iodane reagent do not meet the criteria for an economical access to **1**. Chemical synthesis of **1** can also be more classically done by reducing 3,4-dihydroxyphenylacetic acid (**5**, *syn*. homoprotocatechuic acid, Fig. 1) or its esters in high yields using various hydrides such as $LiAlH_4$, $NaBH_4$, as well as tetrabutylammonium boronate.[24] Such rapid and efficient syntheses are certainly convenient for producing **1** in the laboratory, but the cost of the starting acid **5**, which is prepared from 3,4-dimethoxyphenylacetic acid (**6**, *syn*. homoveratric acid, Fig. 1),[24c] again precludes their development as a satisfactory supply source of **1** at the industrial scale. Qiao and co-workers very recently reported yet another method for the synthesis of **1** in 5 steps in 60% overall yield via a one-carbon homologation of a protected form of 3, 4-dihydroxybenzaldehyde (**7**, *syn*. protocatechualdehyde, Fig. 1),[25] which is again a relatively costly starting material. Fishman and Brouk also recently reported an enzymatic synthesis of **1** that relies on the use of a bioengineered toluene monooxygenase to induce a regioselective double hydroxylation of 2-phenylethanol.[26] This compound is an inexpensive and abundant substrate, but unfortunately, this highly promising biotransformation has so far only been carried out at the analytical scale.

This long-standing challenge of developing an industrially feasible and economical access to hydroxytyrosol (**1**) led us to explore practical solutions to its chemical synthesis, which we confidentially achieved a few years ago by starting from the natural phenylpropenoid eugenol (**8**).[14] The continued and still growing interest in such a structurally simple yet powerful phenolic antioxidant incited us to disclose herein this method of preparation of hydroxytyrosol (**1**). Eugenol (**8**) is a major aromatic constituent of clove oil (up to approximately 80% by weight of oil), which is commonly produced by hydrodistillation, steam distillation, or Soxhlet (ethanol) extraction from leaves, buds, and stems of clove trees (Myrtaceae).[27,28] Eugenol is commercially available in large quantities and its market price is around US$ 5 per kg, making it an economically realistic feedstock.[29] It is widely used in dentistry, as a flavoring agent in cosmetic and food products, and as a key ingredient in Indonesian kretek cigarettes.[27]

The chemical conversion of eugenol (**8**) into hydroxytyrosol (**1**) can in principle simply rely on a three-step two-pot reaction sequence. We thus initially thought to cleave the allylic side-chain of **8** into a hydroxyethyl unit by ozonolysis with an in situ hydride reduction of the ozonide intermediate, and to cleave the methyl aryl ether bond using a metallic Lewis acid. The question that arose was in which order these transformations should be conducted. We first chose to cleave the methyl aryl ether bond of **8** and opted to rely on the alkyl aryl ether cleavage methodology introduced by Bhatt and Babu.[30] This cleavage reaction makes use of aluminum iodine (AlI_3), which is easily formed by mixing aluminum powder and iodine in a refluxing solvent, such as acetonitrile, prior to the addition of the ether substrate. Andersson later found that the efficiency of this process can be improved by adding a catalytic amount of tetra-*n*-butylammonium iodine (TBAI) and by running