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Radical-scavenging polyphenols: new strategies for their synthesis

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Abstract

New strategies for the synthesis of polyphenols, compounds with antioxidant properties contained in every kind of plants, are discussed. Syntheses of different classes of polyphenols, namely ubiquinones, present in many natural systems in which electron-transfer mechanisms are involved, hydroxytyrosol, one of the main components of the phenol fraction in olives, and flavonoids, widespread in the plant kingdom, were approached by simple and environmentally sustainable methods.

Introduction

Many chronic degenerative diseases in adults and the parallel aging process are in many cases directly related to oxidative stress. This condition is the result of an imbalance between oxidative processes and defence systems (Kaikkonen et al 1997). It occurs because of an overproduction of free radicals in the organism, a deficit in the defence system, or, most commonly, both factors together.

Natural antioxidants can be divided into two types: enzymatic (including peroxy dismutase, catalase, glutathione peroxidase) and non-enzymatic (Gatto et al 2002). From the latter, relatively small molecules are believed able to prevent development of some pathologies, and to protect tissues from biological damage caused by the formation of free radicals. Many beverages and plant extracts, as well as vegetables and some types of fruit, are therefore believed to be important dietary constituents because they contain antioxidant compounds.

Ascorbic acid (vitamin C), tocopherols (vitamin E), carotenoids, phenolic and polyphenolic substances are particularly important among these compounds. Currently, the most widely used preservatives are synthetic (*t*-butylhydroxyanisole, toluene, *t*-butylhydroquinone, etc.), whereas it would be desirable to use natural substances or their derivatives to preserve products intended for human use or animal feed.

Unfortunately, the production of natural substances invariably requires their extraction from the organisms of origin, which may not be viable either because of the small amount of extract that can be obtained and/or the high costs of extraction procedures. Furthermore, every extraction procedure involves the destruction of a product meant for human and/or animal consumption. Recovery from waste products or using modestly polluting synthetic methods is therefore preferred to extraction, and may also control or improve yields. The availability of controlled methods for the synthesis of these compounds is preferable since it opens up the possibility of obtaining derivatized molecules with improved or specific properties for the preservation of a given product.

Polyphenols are molecules with antioxidant properties contained in every kind of plant. The specific properties of these molecules are due to the presence of aromatic moieties and of many hydroxyl groups (Fernandez-Bolanos et al 1998). The antioxidant effect may be brought about in many ways, one of which is the so-called 'free-radical scavenging' mechanism, whereby the unpaired electron becomes delocalized over the aromatic ring, acquiring the possibility of forming strong hydrogen bonds. Natural antioxidants endowed with such structural characteristics (such as flavonoids, gallic acid, resveratrol, ubiquinones and hydroxytyrosol) are important for their potential use in foods and drugs.

In the last few years we have reviewed strategies for simple, efficient and economically viable syntheses of bioactive polyphenols, such as ubiquinones, hydroxytyrosol and

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derivatives, together with flavonoid derivatives. Recently, we developed an efficient and selective method for halogenating activated aromatic compounds by using dimethyldioxirane (Bovicelli et al 2002), both in its isolated form or generated in-situ, as an oxyfunctionalizing reagent or as an oxidant of halide anions to produce electrophilic species. The method was applied to a range of complex natural compounds, such as flavones and flavanones, with excellent results, and a number of halogenated flavonoids have been prepared using this method (Bovicelli et al 2001). Halogenation of aromatics proved compatible with sensitive functional groups, and the amount of the added oxidant determines the degree of halogenation (Mincione et al 2003). Halogenated derivatives of aromatic systems are the key intermediates for the preparation of higher oxidized compounds and derivatives. In particular, a bromination–methoxylation pathway, developed in our laboratories over recent years, for introducing oxygenated functions into aromatic rings allows already known or promising powerful antioxidant polyhydroxylated aromatic derivatives to be obtained.

Synthesis of ubiquinones

Ubiquinones, also known as coenzyme Q_n (CoQn; n = number of isoprene units in the side chain), are lipophilic molecules comprising a highly functionalized benzoquinone moiety and an all-*trans* polyisoprene hydrophobic chain, which ensures solubility in organic media. In a redox system, these compounds are present as *p*-benzoquinones (CoQ) and *p*-hydroquinones (ubiquinonols, $CoQH_2$) (Lipshutz et al 2002) (Figure 1).

Ubiquinones are present in many natural systems in which electron-transfer mechanisms are involved (Anderson et al 2005) and they also function as antioxidants and scavengers of free radicals (Kalen et al 1987; Mordente et al 1993; Georgellis et al 2001). Natural CoQ_n are those with n from 6 to 10, the minor members of the family being synthetic. CoQ_{10} is the endogenous compound in humans. All other members of the family are known as powerful antioxidants and could be used as dietary supplements, and as anti-aging factors and nutrients in creams to preserve the epithelium from damage due to aggressive environmental oxidants.

Many methods are known to produce ubiquinones, including the fermentation process for CoQ_{10}, and syntheses starting from CoQ_0 (Lipshutz et al 2005), with a final low-yield oxidation to quinone (Merz & Rauschel 1993). Today, the best synthesis of CoQ_{10} is that reported by Lipshutz & Mollard (2003), in which the key step is the coupling between a benzyl chloride derivative and an allyl-dimethyl-alane, previously prepared from solanesol. The limitations of this method are probably the high cost of the starting materials and the difficulties in preparing the reagents.

Our approach to the synthesis of these compounds makes use of iridol as a key intermediate, exploiting a Lewis-acid-promoted shift of an ethereal allyl chain. Iridol is a naturally occurring phenol (De Laire & Tiemann 1893) and is commercially available, but at high cost. To make our approach economically viable we needed to develop a low-cost synthesis of iridol, since the syntheses reported to date use severe conditions and expensive and environmentally unfriendly reagents (Merz & Rauschel 1993).

We proposed a high-yield synthesis based on simple reactions, using environmentally sustainable and affordable reagents (Figure 2) (Bovicelli et al 2005).

Bromination of activated aromatic rings by the oxone/NaBr system to produce a highly electrophilic halogenating species has been developed over recent years and applied to a series of natural compounds, showing high efficiency and selectivity (Bovicelli et al 2001, 2002). This method does not require the use of molecular halogen or metal catalysts and can be considered as non-polluting. The methoxylation step, in which a bromine atom is substituted by a methoxy group, was likewise developed by strictly controlling the reaction conditions, since the procedure previously described in the literature (Capdevielle & Maumy 1993) proved ineffective on our substrates.

To verify the usefulness of iridol in the synthesis of ubiquinones, we described the synthesis of CoQ_3 (Figure 3). The sodium salt of iridol was etherificated by reaction with bromofarnesyl, previously prepared by treatment of farnesol with PBr_3. Treatment of the ether obtained with a Lewis acid such as etherate BF_3 in very mild conditions afforded an allyl shift to the relative *ortho* position. The final step, an oxidation promoted by Co(salen) (Lipshutz 2002) yielded a good amount of ubiquinone Q_3.

Good yields of the rearranged product were accomplished by the shift of the allyl chain into the relative *para* position. This rearrangement became much more important when longer chains were used, such as when a solanesyl group was used to synthesize CoQ_9, in which case the *para* shift was the only observed phenomenon.

To improve the efficiency of our approach based on the allyl shift, we changed strategy and followed a scheme in which 3,4,5-trimethoxytoluene, submitted to a formylation–oxidation procedure, gave the suitable phenol derivative so that the only free position for the allyl chain to migrate to is the relative ortho (alpha) position (Figure 4) (Bovicelli et al 2006). The sodium salt of the new phenol was reacted with a suitable allyl bromine to give the corresponding ether, and further

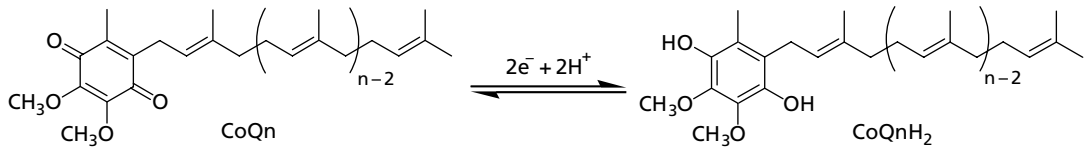

Figure 1 Redox equilibrium of coenzyme Q (CoQ_n) and ubiquinonols ($CoQnH_2$); n = number of isoprene units in the side chain.

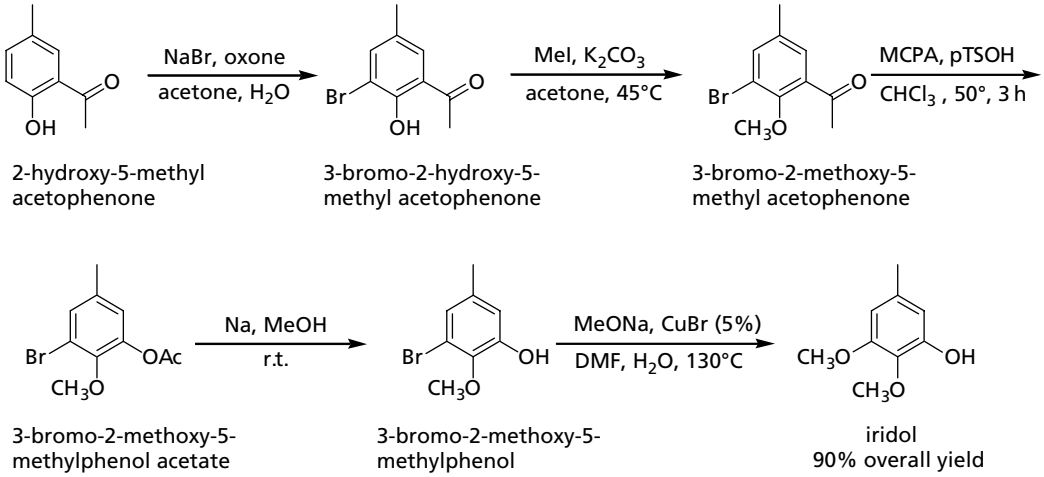

Figure 2 Synthesis of iridol.

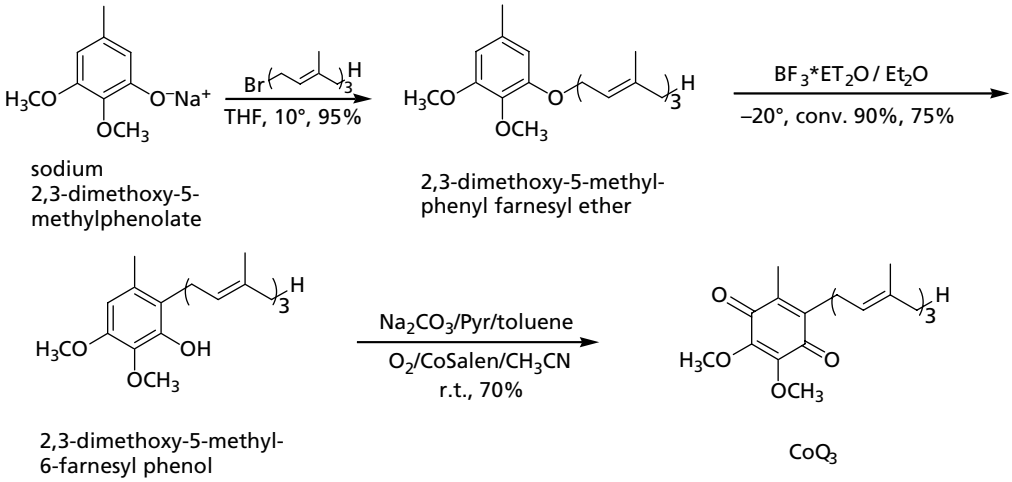

Figure 3 Synthesis of ubiquinone Q_3.

treatment with a Lewis acid led to the correct product, rearrangement occurring only on the free position. Using this strategy we obtained good results for every allyl side chain we used. In the case of the solanesyl group, yields were lower than obtained with shorter chains but were still good. Worthy of note is that in no case was there evidence of epimarization of the allyl chain from our analytical methods.

Synthesis of hydroxytyrosol and its derivatives

Hydroxytyrosol (3,4-dihydroxy-phenethyl alcohol) is believed to be the antioxidant with the highest free-radical-scavenging capacity: double that of quercetin and more than three times that of epicatechin. Hydroxytyrosol is one of the main components of the phenol fraction identified in the fruit of the olive, a widespread tree in the Mediterranean. It is present as a free molecule or as a substructure of more complicated compounds, such as oleuropein, present in large quantities in the leaves and in unripe olives. Unfortunately, being a hydrophilic molecule and thus poorly soluble in lipid matrices, most of the hydroxytyrosol contained in the fruits ends up in the waste water at the end of the manufacturing process (Visioli et al 1999). In olive oil, in which it plays an important role as an antioxidant preserving against the degradation of fatty acids, it is present in very small quantity, the least being in extra-virgin olive oil (Gutfinger 1981).

Hydroxytyrosol may be extracted from waste water, but the process does not seem economically viable (Fernandez-Bolanos et al 2004), or may be obtained by synthetic processes, including reduction of 3,4-dihydroxyphenylacetic acid (Tuck et al 2000), hydrolysis of oleuropein (Alcudia Gonzalez et al 2004) and by enzymatic conversion of tyrosol

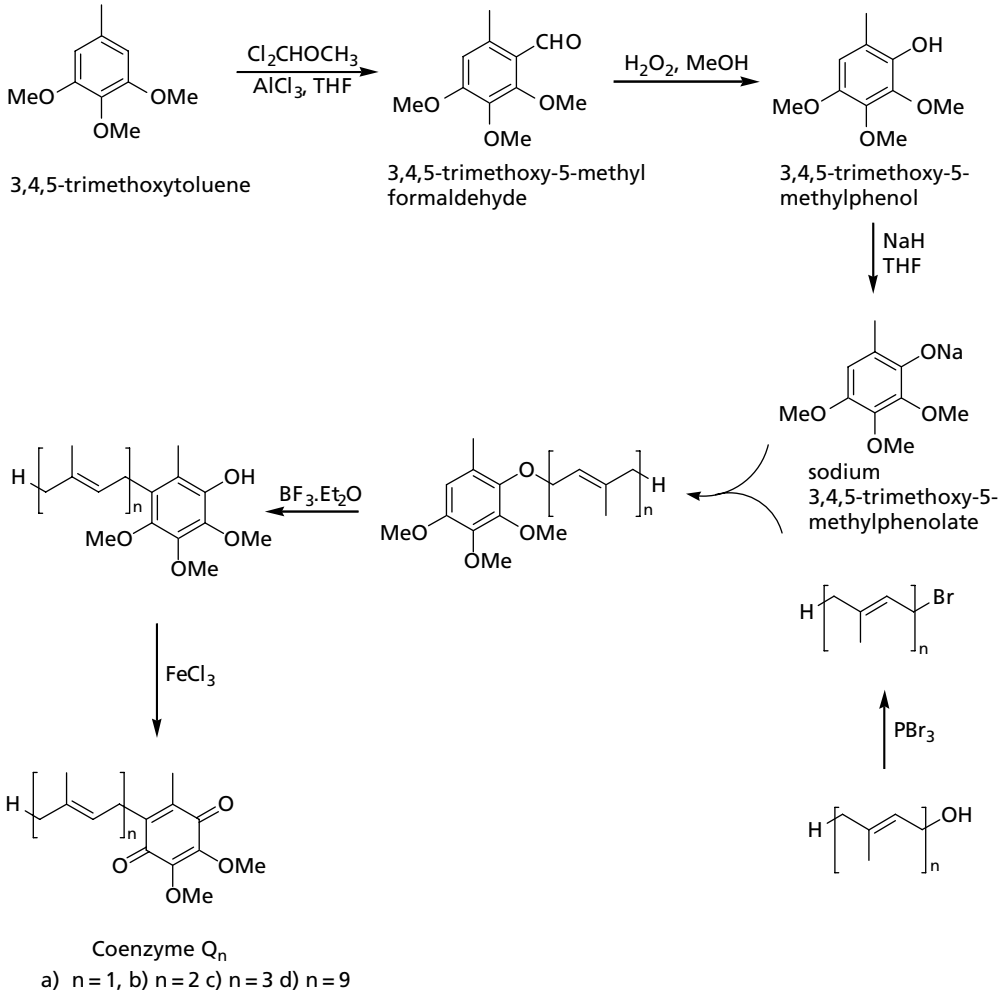

Figure 4 Improved synthesis of ubiquinones starting from 3,4,5-trimethoxytoluene.

(Espin et al 2001) and oleuropein (Briante et al 2004). None of the methods described is suitable for industrial applications, partly because of the high cost of the starting materials, increasing the market price of these molecules.

Tyrosol (4-hydroxy-phenethyl alcohol) is also widely present in the waste water. It is easily separated from these waters as a solid material but this material is acidic and highly polluting and must therefore be destroyed before disposal, which is expensive. Tyrosol is not biologically active and, being a phenol and thus an acidic material, is considered a pollutant. The development of simple systems to transform tyrosol into hydroxytyrosol is therefore attractive for the added value it might give to waste water.

Using our expertise in oxyfunctionalization of aromatic rings, we proposed a synthetic scheme using easy transformation and highly eco-friendly, economically and environmentally sustainable processes (Figure 5) (Bovicelli et al 2007). By this method, hydroxytyrosyl acetate and any other ester derivative can be synthesized, giving the possibility of obtaining prodrugs, since the esters are easily transformed into the parent alcohols by a number of hydrolases present in the organism. One of the most critical problems in using hydroxytyrosol as preservative or drug, as well as its high cost, is its ready degradation in the presence of external oxidants, light and base media. The corresponding ester derivative on the side chain proved to be very stable for long periods in almost any conditions except in hydrolytic or reducing media. For this reason, such derivatives can be used in formulations as precursors of the active principle.

A new compound with promising biological properties has been synthesized by a similar procedure (Figure 6). 2,5-Dihydroxytyrosol has been shown to have powerful antibacterial activity, and, owing to its structure, is a potentially good antioxidant. The biological properties of this new molecule are currently being investigated.

Derivatives of natural flavonoids

Compounds acting as free-radical scavengers are able to produce stable radical species. Many studies on the effect of substituents on the aromatic moiety have been reported

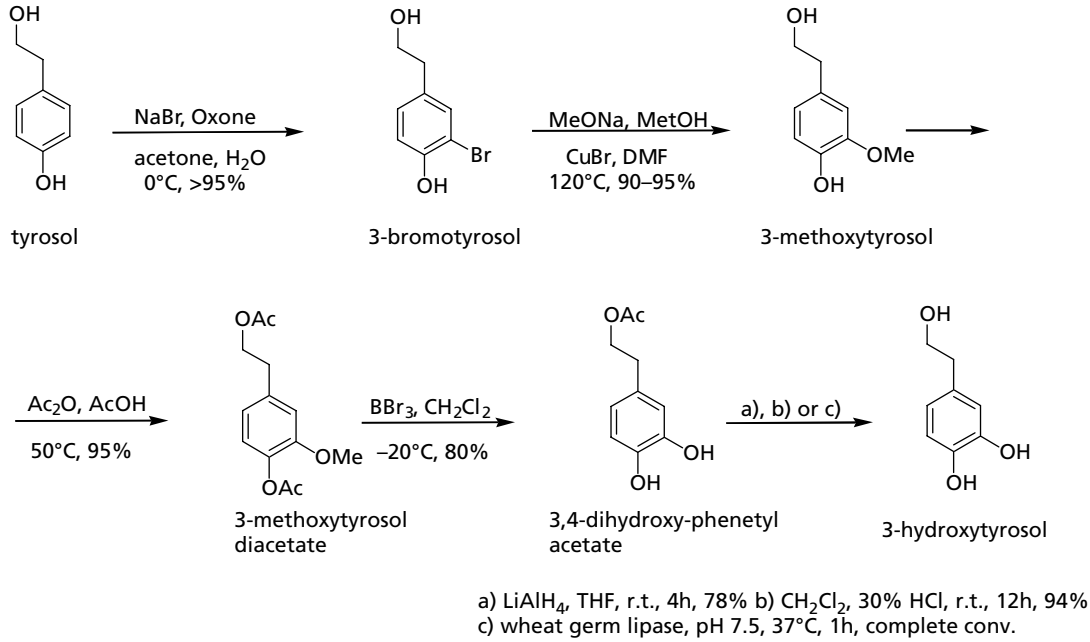

Figure 5 Synthesis of hydroxytyrosol from tyrosol.

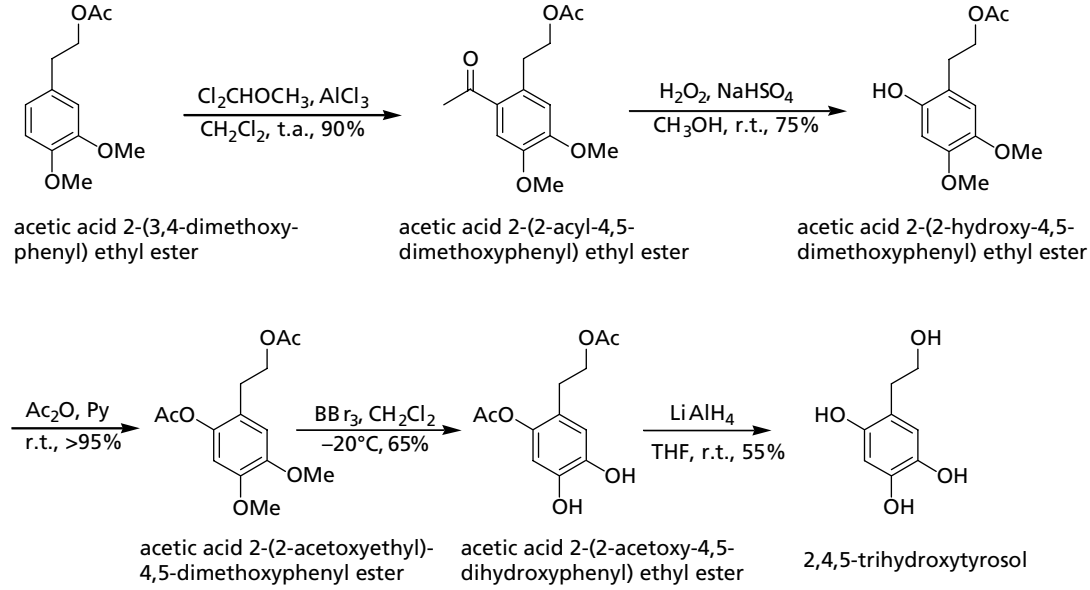

Figure 6 Synthesis of 3,5-dihydroxytyrosol.

(Balasundram et al 2006), with the main focus on oxygenated groups and their relative positions. All the factors able to stabilize a radical species contribute to improving the scavenging properties of the molecule, and from these factors the closeness between a hydroxyl group with other oxygenated moieties (hydroxyl, methoxyl, etc.) seems to be of great importance. This situation is often found in natural compounds (Hotta et al 2001; Leopoldini et al 2004), including the flavonoid class (Heim et al 2002).

Flavonoids are widespread in nature, occurring in many vegetables (Geissman 1962), and in particular in grapes (Amiot et al 1986), olive leaves (Heimler et al 1992) and plants of the citrus genus (Kefford & Chandler 1970).

Over 4000 flavonoids have been identified in the vegetable kingdom, and every plant possesses a complex mixture of these compounds, which describes a characteristic chemical profile. Flavonoids participate in many physiological and biochemical processes, for example as enzyme inhibitors, in

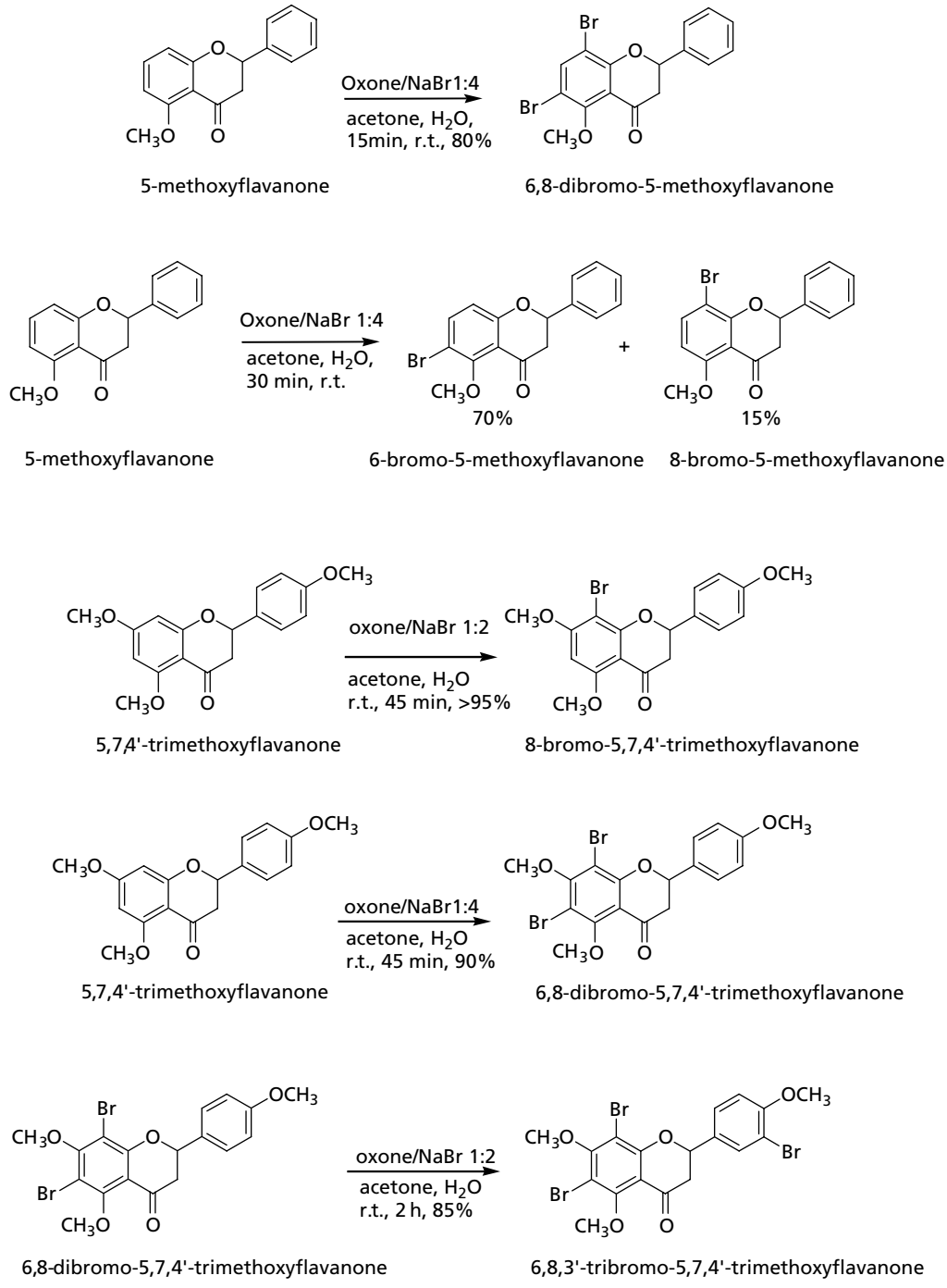

Figure 7 Selective bromination of flavanones.

defending plants from bacteria and fungi, in fixing nitrogen, in growth regulation and in oxy-reductive processes in cells (Harborne 1982).

Given that flavonoids are present in many beverages and food, they are constituents of the human diet (Kyle & Duthie 2006; Nemeth & Piskula 2007). They carry out several biological functions in the organism (Kyriakydis et al 1986; Okura et al 1988; Ferriola et al 1989), including that as antioxidant (Lemanska et al 2001). Because of the increasing interest in these molecules, methods for their synthesis and structural modification are the goals of several research groups. Our interest in this field is to exploit our experience in the functionalization of aromatic compounds to prepare new flavonoids that are potentially useful as drugs or food preservatives. Synthesis of flavonoids is usually performed by the ring closure of chalcones (Stermitz et al 1975; Sanicanin & Tabakovic 1986); however, yields are not always satisfactory.

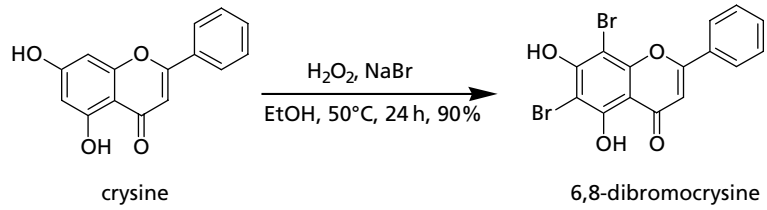

Figure 8 Soft bromination of flavanones.

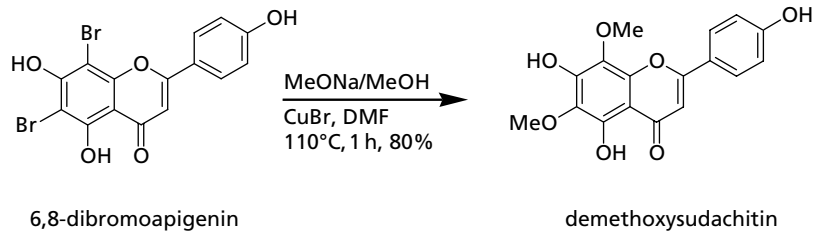

Figure 9 Methoxylation of bromoflavanones.

Given the high degree of aromatic ring oxygenation, the bromination–methoxylation procedure already used in the synthesis of ubiquinones and hydroxytyrosol was then considered in the oxy-functionalization of natural flavonoids in order to obtain more active molecules.

The bromination procedure proved efficient and selective on flavanones (Figure 7), and a number of derivatives were prepared. However, this failed when applied to flavones, because of the sensitivity of the enonic double bond on the C ring to the reaction conditions.

Bromo-flavanones were easily converted into the corresponding flavones by an I_2/DMSO-promoted oxidation (Fatma et al 1984). When the A ring is sufficiently activated for electrophilic attack, a softer method can be used for bromination to avoid the interaction with the enonic double bond, and the H_2O_2/NaBr system in ethanol successfully converted chrysine to the corresponding dibromo derivative (Figure 8).

All these bromo-flavanones were converted into the corresponding methoxy-derivatives by an improved substitution procedure of the bromine atoms (Figure 9). Until now, this reaction was not reproducible and thus little used in synthesis, its success being dependent on the nature of the substrates. With our optimized procedure the reaction is suitable for almost every transformation, including for very sensitive substrates such as flavanoids. In practice, a blue resulting mixture between MeONa, CuBr (the catalyst) and DMF was prepared separately at room temperature and added to the warm solution of the substrate in DMF. In this way the decomposition of DMF was prevented and the reagent worked correctly.

The closeness of methoxyl and hydroxyl groups on aromatic rings is a common situation in natural compounds, which provides several biological properties (Saroglou et al 2005; Nakagawa et al 2006). Such a situation is readily achieved using the procedure that we propose. In spite of their importance for human health, studies on biological activities of flavonoids are inadequate, because of their scarcity and high cost, apart from some very common compounds. With our approach a number of rare or new flavanoids can be prepared starting from cheap material.

Conclusion

The development of simple sequences of reactions, such as bromination–methoxylation and formylation–oxidation procedures, allows selective functionalization of aromatic compounds and gains access to classes of highly biologically active products for which the previous syntheses are complex or low yielding. Some of the compounds that we prepared are expensive, and our approach makes it possible to obtain them at low cost with eco-friendly reactions, readily manipulated reagents, and almost always environmentally sustainable processes. Three classes of compounds – ubiquinones, hydroxytyrosol derivatives and flavonoids – can be obtained using the chemistry introduced here.

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