

# Phenolic Natural Compounds with Chromanic Structure

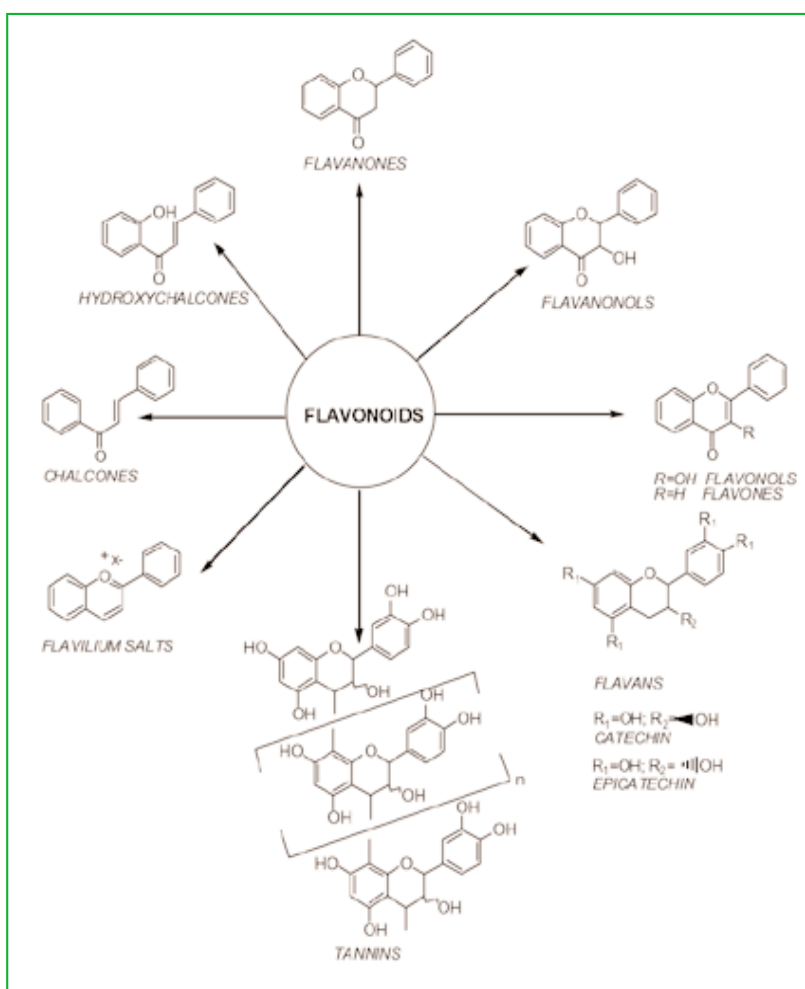
## Their Valorisation by *Green Chemistry* Oxidative Methodologies

by Enrico Mincione, Roberta Bernini, Raffaele Saladino and Paolo Bovicelli

The research group of the Chemistry of the Natural Organic Products operating in the University of Viterbo (Responsible: E. Mincione) has been experienced from some years in oxidative and benign methodologies to convert natural available molecules into fine-chemicals and bioactive compounds (*Green Chemistry*). We report here some examples of oxidative modifications of the chromanic structure, present in two largely available families of natural phenolic compounds such the flavonoids and the tocopherols.

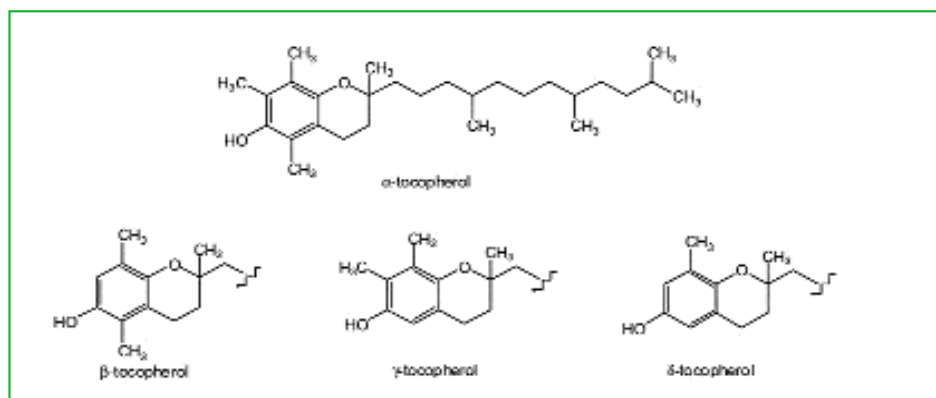
**F**lavonoids are a very large and important group of polyphenolic natural products, universally distributed in higher plants. They also occur in many lower plants group and rarely in fungi. Over 4,000 flavonoids have been identified in plant sources [1]. Chemically, they are phenylchromones with a wide variety of basic structures (Scheme 1). Some products are intensely coloured such as anthocyanins and provide a wide range of red to blue colours in flowers, fruits and leaves. Others, like the flavones, are essentially colour-less and yet they provide the "whiteness" of white flowers but act as copigments to the widespread anthocyanins. Besides their contribution to plant colour, the flavonoids have a variety of other roles in the growth and development of plants: they are involved in photosensitization and energy and act as antioxidants, enzyme

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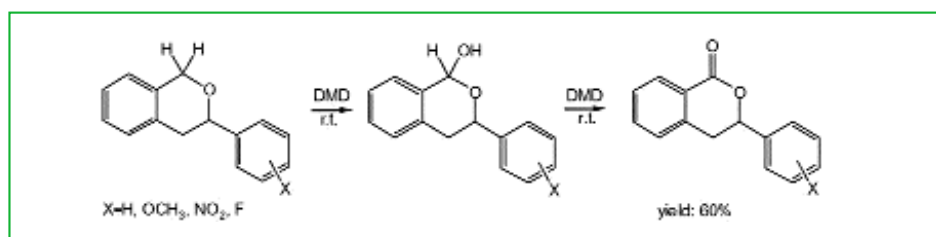


Scheme 1 - Flavonoidic structures

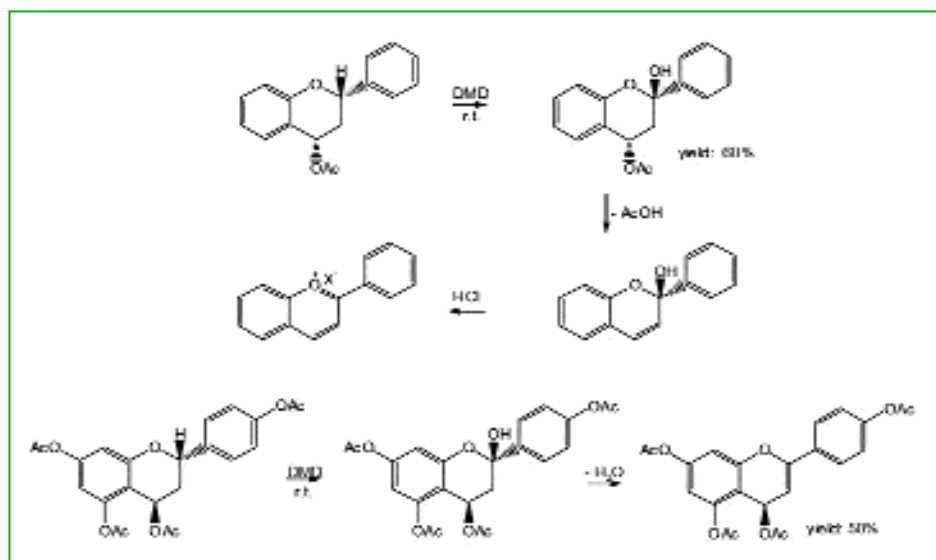
inhibitors, precursors of toxic substances, defence against microbial infections. Flavonoids are found in fruits, especially in citrus fruits but they are present also in vegetables, nuts, seeds, stems. On average, the human diet contains approximately one gram of mixed flavonoids, a quantity that could provide pharmacologically significant concentrations in body fluids and tissues [2]. In fact, flavonoids have long been recognised to possess a wide range of biological and pharmacological properties such as antioxidant, anticancer, anti-inflammatory, antiviral activities [3].



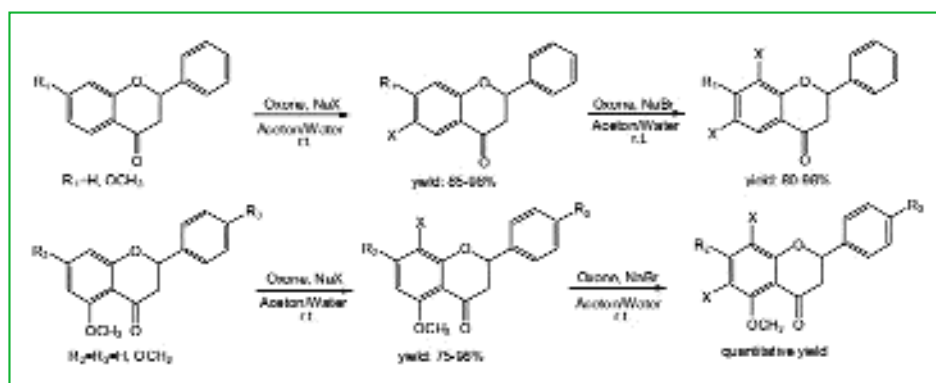
Scheme 2 - Tocopherols present in Vitamin E



Scheme 3 - Benzylic oxyfunctionalization of the substituted isochromans by dimethyldioxirane (DMD)



Scheme 4 - Conversion of the flavans into flavenes by DMD



Scheme 5 - Selective halogenation of flavanones with DMD or oxone/NaX

Tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , Scheme 2) are the components of the Vitamin E and are diffused in some vegetables such as cereals and tomato's seeds. They represent therefore a large waste in the manufacture of the tomato juices. The ratio  $\beta/\gamma/\delta$  changes in different sources. The  $\alpha$ -tocopherol is the more important of these and it's commercially utilised as acetate as antioxidant in the diet and to prevent the alteration of the fats [4].

#### Selective benzylic oxyfunctionalization of isochromans and flavans with dimethyldioxirane (DMD)

DMD is a chemo and regioselective oxidant agent, generated by a commercial cheap product, the oxone, and able to insert oxygen atoms into C-H bonds. This reagent has been recovered to be efficient in the benzylic oxyfunctionalization of cyclic systems such the isochromans and the flavans [5-7]. Isochromans are converted "one step" into isocoumarins (Scheme 3), compounds isolated from a wide variety of microbial, plant and insect sources, which display a wide range of biological activities acting as antifungals, phytotoxics, plant growth regulators, diuretics, antihypertensive and anticancer agents [8]. Flavans are converted into flavenes (Scheme 4) which in acidic conditions produced the corresponding anthocyanidins, the aglicons of the anthocyanins, responsables of the colours of the flowers and utilised as natural food colours [9].

#### Selective halogenation of the phenolic ring of flavanones with DMD or oxone and halide salts

The oxidation of halogen anions by DMD solution in acetone produced reactive species able to halogenate, in acidic media, the phenols [10]. The oxone/sodium bromide (or chloride) is the same efficient to halogenate, by *in situ* generation of DMD, the flavanones with high regioselectivity (Scheme 5, [11]). This methodology avoided the use of polluting agent and the difficulties connected with the handling of the corrosive agent commonly used for the halogenation of the aromatic compounds. On the other hand, with other benign

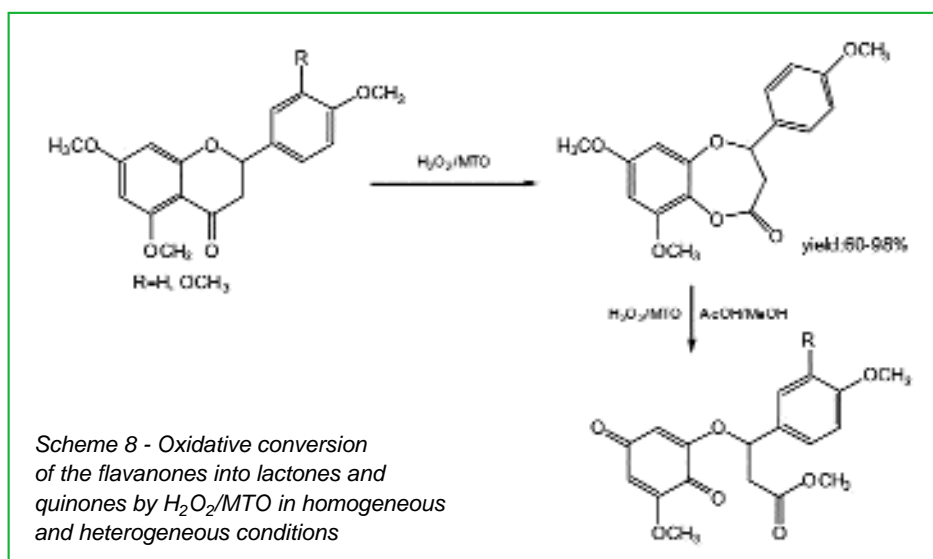
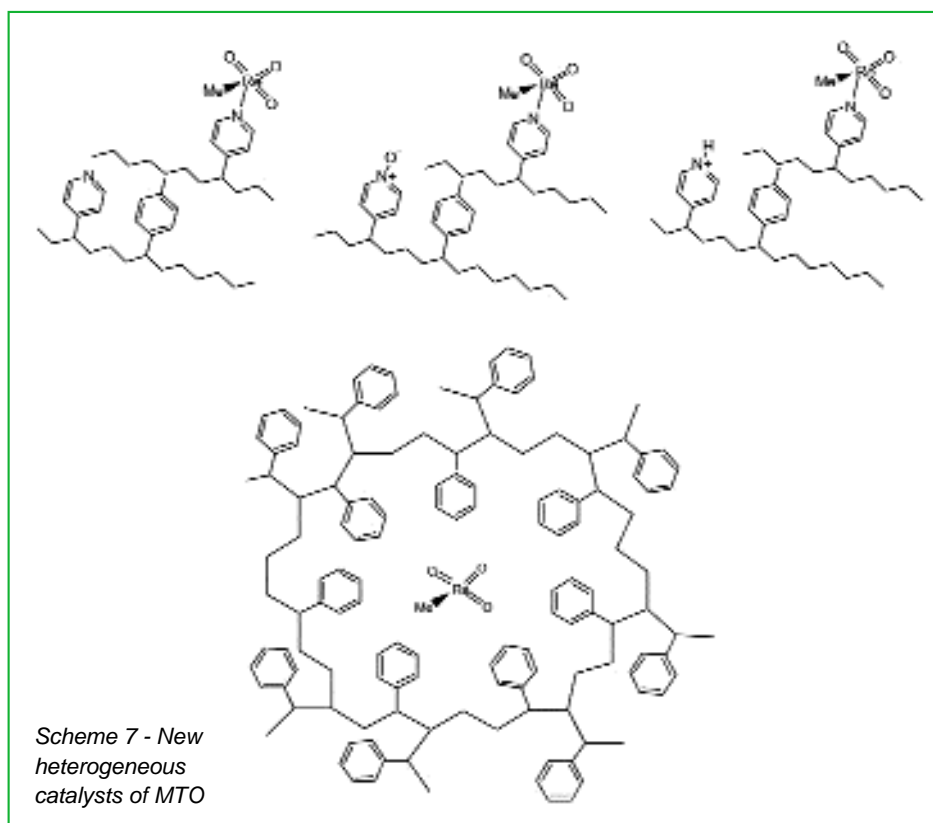
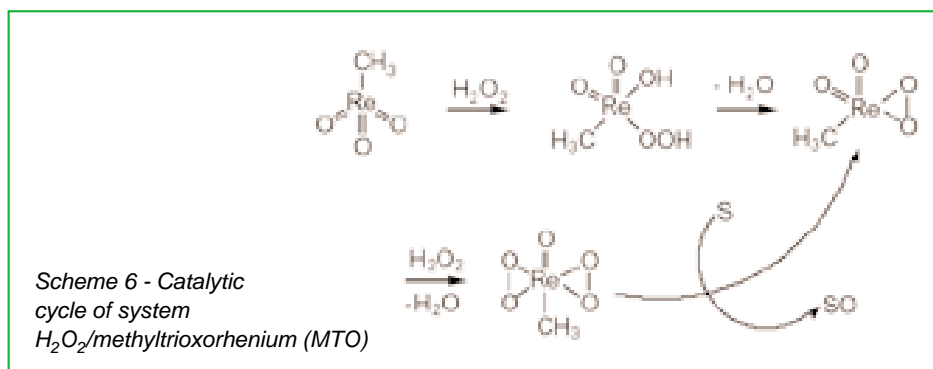
methodologies as the enzymatic, the halogenation of the flavonoids proceeds in very low yields [12]. The halo-flavonoids are recognised to possess anxiolytic and myorelaxant activities [13]. Work is in progress to utilise these halo-compounds to introduce functionalized lateral chains by catalytic palladium reagents\*. The obtained compounds will be tested in order to their bioactivity.

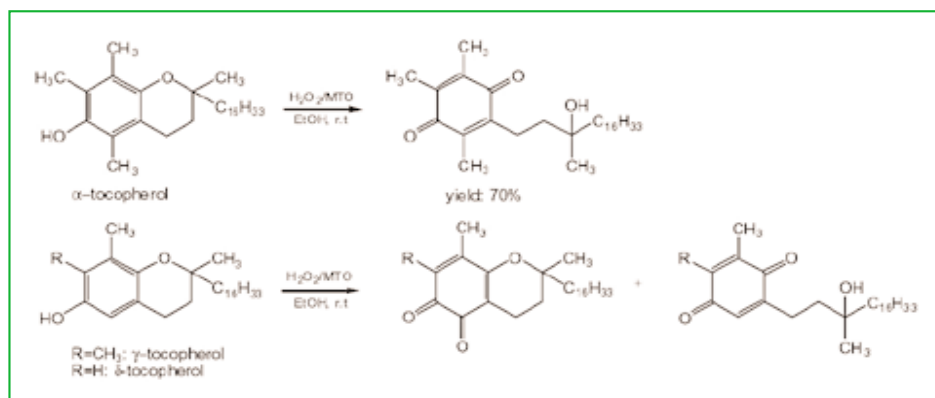
### Conversion of flavanones to lactones and quinones via Baeyer-Villiger reaction

Methyltrioxorhenium (MTO) is a useful catalyst able to activate the hydrogen peroxide, a cheap and benign oxidant agent, producing a diperoxorhenium intermediate (Scheme 6) responsible of the oxidation reactions and acting as nucleophilic as well electrophilic specie. MTO has been chemically linked on a matrix of polyvinilpyridine or mechanically encapsulated in a matrix of polystyrene (Schemes 7), allowing efficient oxidations also in heterogeneous conditions [14]. We reported here the first catalytic Baeyer-Villiger rearrangement of the flavanones by hydrogen peroxide/MTO to get the corresponding lactones (benzodioxepin-2-one, Schemes 8, [15]) in homogeneous as well heterogeneous conditions. The new obtained compounds were recognised by the genetists of our university as bioactives.

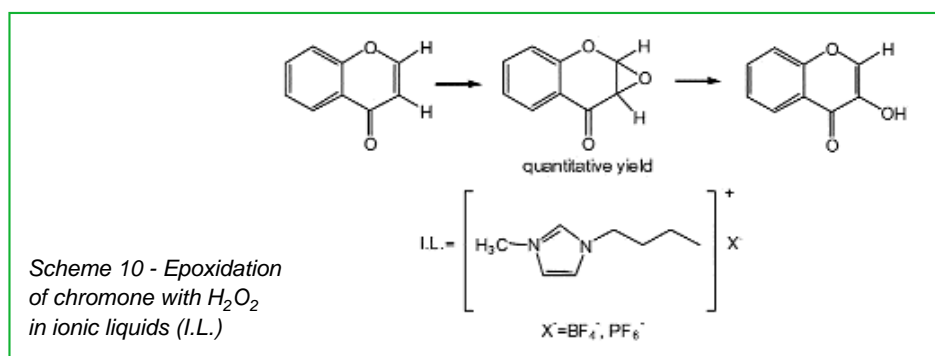
Experimental results show that they have cytostatic and cytotoxic activities and cause apoptosis in cellular tumoral lines, producing a stop of metaphases [16]. They have been also tested by the botanics of university of Naples 2. Some of these show a selective herbicide activity at the level of the commercial products [15]. The heterogeneous catalytic Baeyer-Villiger oxidation has been also extended on simple cyclic ketones. Efficient conversions were obtained with the cyclobutanone. These results (to be published) appear interesting for a successful applications in the field of the synthesis of ciclopentane lactones, molecules responsables of many fragrances.

\* Work in collaboration with S. Cacchi and G. Fabrizi, University of Rome "La Sapienza"





Scheme 9 - Oxidative conversion of the tocopherols into quinones by  $H_2O_2$ /MTO in homogeneous and heterogeneous conditions



Scheme 10 - Epoxidation of chromone with  $H_2O_2$  in ionic liquids (I.L.)

#### Oxidative conversion of tocopherols to quinones by $H_2O_2$ /MTO

This catalytic system has been also utilised to convert the family of the tocopherols into the corresponding quinones that have been recognised to possess many biological activities. The oxidation operates in homogeneous as well heterogeneous conditions (Scheme 9, [17]).

The obtained products have been also reduced to the corresponding hydroquinones which show a strong antioxidant activity. By comparing the different reaction conditions utilized, we can conclude for an improvement of the conversions and the yields of quinones in heterogeneous conditions. The best results have been obtained in the oxidation of the  $\alpha$ -tocopherols. With the  $\gamma$ - and  $\delta$ -tocopherols, the ratio of the *ortho* and *para*-quinones is strongly depending from the catalytic system utilised (results to be published).

#### Epoxidation of the olefinic double bond of the chromenic structure with $H_2O_2$ in ionic liquids

The introduction of the epoxidic ring in chromanic compounds is very useful to get, by further hydrolysis with water, the corresponding enolic function, very important for the bioactivity of these compounds (Scheme 10). We report an efficient epoxidation operated on the chromone via an "environmentally

friendly" oxidation system, using hydrogen peroxide in presence of base catalysis or urea hydrogen peroxide (UHP)/ MTO and ionic liquids as green solvents [18]. Obtained results showed that these new solvents enhance the reactivity of the oxidant agent and the kinetic of the reactions (results to be published). Work is in progress to extend this methodology to the epoxidation of specific double bonds of other classes of natural products.

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