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New convenient synthesis of iridol. An approach to the synthesis of ubiquinones

Paolo Bovicelli,[a,*] Roberto Antonioletti,[a] Maurizio Barontini,[a] Giorgio Borioni,[a] Roberta Bernini[b] and Enrico Mincione[b]

[a]*C.N.R. Istituto di Chimica Biomolecolare—Sezione di Roma, c/o Dipartimento di Chimica, Università di Roma 'La Sapienza', p.le A. Moro 5, Box 34 Roma 62, I-00185 Roma, Italy*
[b]*Dipartimento A.B.A.C., Università della Tuscia. V. S. Camillo de Lelli, 1, I-01100 Viterbo, Italy*

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Abstract—A strategy for the synthesis of ubiquinones, in which iridol is the key intermediate, has been developed, together with a new convenient synthesis of iridol (2,3-dimethoxy-5-methylphenol) starting from the easily available 4-methylphenol and using mild conditions and friendly and high-yielding reactions.

In most cases, degenerative pathologies and aging process are strictly correlated to oxidative stress. This condition is the result of a lost equilibrium between oxidative processes and systems of defence, usually due to an overproduction of free radicals or to a low level of antioxidants in the organism.[1]

Antioxidant systems of defence are of two types: enzymatic, including peroxy dismutase, catalase, glutathione peroxydase and chemically included, α-tocopherol, ascorbic acid, β-carotene, polyisoprenoids, polyphenols (flavonoids, ubiquinones, etc.). Ubiquinones, for their antioxidant and free-radical scavenging properties, are compounds well studied in recent years.[1]

Ubiquinones, also known as coenzyme Q_n (n = number of isoprene units in the side chain) are lipophilic molecules constituted by a highly functionalised benzoquinone moiety and an all-*trans* polyisoprene hydrophobic chain, which assures their solubility in organic media. In a redox system these compounds are present as *p*-benzoquinones (ubiquinones, CoQ) and *p*-hydroquinones (ubiquinonols, $CoQH_2$) (Scheme 1).[2]

Ubiquinones are present in many natural systems in which they function as antioxidants and scavengers of free radicals.[3] Natural CoQ_n are those with n from 6 to 10, the minor members of the family being synthetic. In the human system, CoQ_{10} is of fundamental importance since it is involved in the production of ATP.[4]

Since the discovery of their properties, CoQ_{10} and the other ubiquinones are targets of total synthesis in many laboratories.[5–8] CoQ_{10} can be obtained by fermentative processes but its growing demand in therapy prompted many workers to explore new ways for its production.

Classical syntheses of ubiquinones start from CoQ_0,[6] synthesised from natural aromatic compounds in low yields, by a Claisen rearrangement and a final low-yield oxidation to quinone.[7] Today, the best synthesis of CoQ_{10} is that reported by Lipshutz, in which the key-step is the coupling between a benzyl chloride derivative and an allyl-dimethyl-alane, previously prepared from solanesol.[8] In this synthesis, the final oxidative step was improved by using Co(salen) as catalyst, but difficulties reside in the preparation of the reagents.

In this paper we revisited a strategy for the synthesis of ubiquinones, in which iridol **6** (Scheme 2) is the key intermediate. To the best of our knowledge, today the most direct syntheses of iridol are those starting from

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* Corresponding author. Tel.: +39 06490422; fax: +39 0649913628; e-mail: paolo.bovicelli@icb.cnr.it

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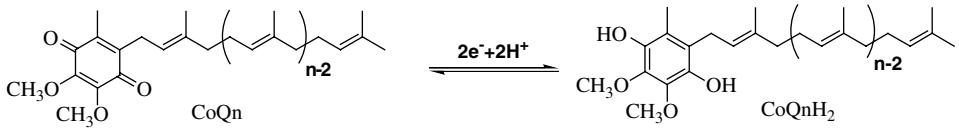
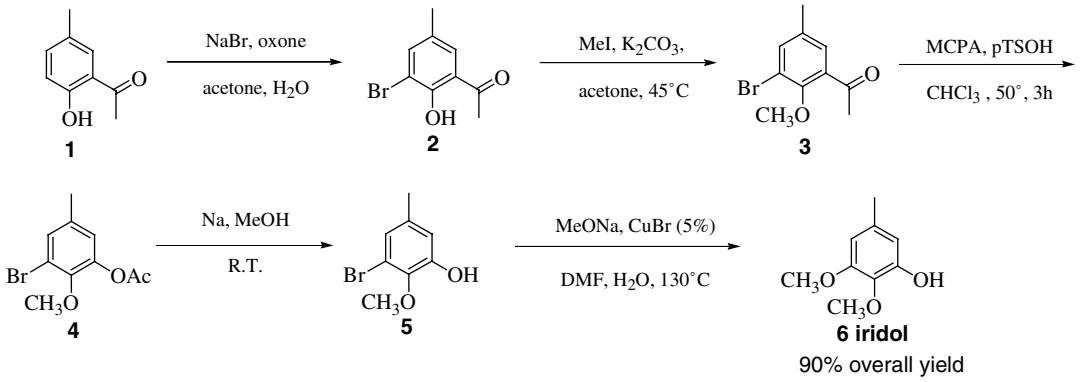


Scheme 1. Redox equilibrium of CoQ_n.



Scheme 2. Synthesis of iridol.[11]

3(MeO)-benzaldehyde in an eight-step procedure and 52% overall yield,[7] and from vanillin.[9] Exploiting our experiences in the synthesis of polyphenols we developed a simple, efficient and economically convenient synthesis of iridol.

Recently we found an efficient and selective halogenation of activated aromatic compounds by using dimethyldioxirane (DMD), both in isolated form or generated in situ, as an oxidant of halide anions. 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 with this method.[10] The halogenation of aromatics results compatible with sensitive functional groups and the amount of the added oxidant determines the degree of halogenation. This halogenation method does not need the use of molecular halogen and of metal catalysts and can be considered as non polluting.

In the scheme developed by us for the synthesis of iridol, the bromination of 2-hydroxy-5-methylacetophenone, **1**, commercially available at low price, was the first step, a practical, eco-friendly and quantitative reaction, which occurs under mild conditions (Scheme 2).

Compound **2** was methylated by using MeI under basic condition. The next step was a Bayer–Villiger reaction, which was carried out, at first, as usual at 25 °C affording, in a week, a 70–80% yield of the desired product. Later on we found that by simply warming the reaction at 50 °C it was complete after 24 h and **4** was obtained in quantitative yield. Transesterification in methanol by using a catalytic amount of sodium metal led to **5**. The substitution of bromine with a methoxy group eventually afforded the final product.

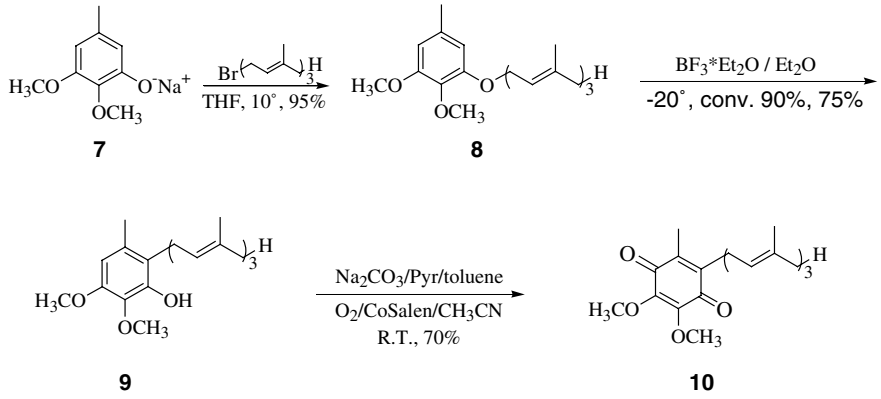
The method for carrying out the latter reaction described in the literature[12] proved ineffective and needed a careful revisitation in order to render the transformation a general and useful one. After several trials we found that the substitution reaction must be carried out paying attention to three factors: (a) the sodium methoxide used to bring about the nucleophilic substitution should be completely free from methanol;[13] (b) the copper(I) bromide should be prepared freshly, purified by precipitating it from a saturated solution of sodium bromide and dried under a vacuum overnight. It should also be noted that not every batch of CuBr is reactive enough. The purified salt should look as a powder of light blue-green colour; (c) DMF should contain some water. If DMF is used anhydrous the reaction does not start at all. With a 5% water content the best result was obtained.

If these conditions are strictly observed, the reaction is of undoubted general value since every substrate we reacted gave the corresponding methoxy derivative,[14] the only limit being the relatively high temperature, at which not every compound is stable.

The overall yield of 90%, the use of friendly reactions, the low cost of the reagents, and the compatibility with the environment make this process of high value in the preparation of iridol, a useful intermediate in the synthesis of *p*-quinone derivatives.

As an example of the usefulness of **6** we developed an approach to ubiquinones. The oxidation of **6** by the system O_2/Co(salen) gave the corresponding *p*-quinone (CoQ_0), already used as a key intermediate in the synthesis of CoQ_n, but the yields of the oxidation step were not very satisfactory.

Iridol can be directly functionalised by a Claisen type rearrangement. For this aim, **8** was prepared by etherification of sodium phenoxide, **7**, with farnesyl bromide, previously prepared by treating farnesol with PBr_3 (Scheme 3).



Scheme 3. Synthesis of CoQ_3.

By treating **8** with BF_3 etherate at −20 °C an almost complete conversion of it into two compounds occurred, resulting from the shift of the alkenyl chain to the *ortho* (75%) and *para* (25%) positions, with respect to the initial position of the ethereal moiety. From the crude, product **9** could be easily separated by flash chromatography and submitted to the oxidation reaction promoted by Co(salen).[15]

The final step was much more efficient than previously observed in the case of iridol and gave high yields of CoQ_3 **10**, the ubiquinone with the farnesyl side chain.

The exploitation of the same strategy in the synthesis of higher order ubiquinones by using suitable polyisoprenols is presently our main purpose. Besides, iridol has the correct functionalities for acting as a good scavenger of free radicals, and a number of derivatives can be prepared with this objective.

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11. A Varian Mercury 300 MHz instrument was used to record NMR spectra. All compounds were isolated as oils. Significant data for key compounds. **3**: ^{1} NMR δ (ppm): 7.50 (1H, d, J = 2.2 Hz, Ar–H), 7.33 (1H, d, J = 2.2 Hz, Ar–H), 3.81 (3H, s, CH_3O); ^{18}C NMR δ (ppm): 199.6 (C=O), 153.8 (ArC–OCH_3), 129.3 (ArC–CO), 117.8 (ArC–Br), 62.2 (CH_3O), 30.4 (CH_3CO), 20.3 (CH_3). **4**: ^{1}H NMR δ (ppm): 7.23 (1H, d, J = 2.2 Hz, Ar–H), 6.82 (1H, d, J = 2.2 Hz, Ar–H), 2.32 (3H, s, CH_3CO); ^{13}C NMR δ (ppm): 168.8 (COO), 147.0 (ArC–O), 144.2 (ArC–OCO), 117.2 (ArC–Br), 60.9 (CH_3O), 20.6 (CH_3COO). **6**: ^{1}H NMR δ (ppm): 6.42 (1H, d, J = 1.5 Hz, Ar–H), 6.29 (1H, d, J = 1.5 Hz, Ar–H), 3.85 (3H, s, CH_3O), 3.84 (3H, s, CH_3O), 2.26 (3H, s, $ArCH_3$); ^{13}C NMR δ (ppm): 152.0 and 149.0 (ArC–OH and ArC–O), 134.0 and 133.4 (ArC–O and ArC–Me), 60.8 (CH_3O), 55.7 (CH_3O). **8**: ^{1}H NMR δ (ppm): 6.40 (2H, bs, 2Ar–H), 5.11 (1H, t, J = 6.6 Hz, C–CH=C), 4.60 (2H, d, J = 6.6 Hz, O–CH_2–C=C); ^{13}C NMR δ (ppm): 65.5 (Ar–O–CH_2), 60.2 (CH_3O), 55.5 (CH_3O). **9**: ^{1}H NMRδ (ppm): 6.27 (Ar–H), 3.88 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 3.30 (2H, d, J = 6.6 Hz, Ar–CH_2–C). ^{13}C NMR δ (ppm): 60.9 (CH_3O), 55.7 (CH_3O), 16.1 (Ar–CH_2).
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