An Efficient Stereoselective Synthesis of Co-enzyme Q_{10}

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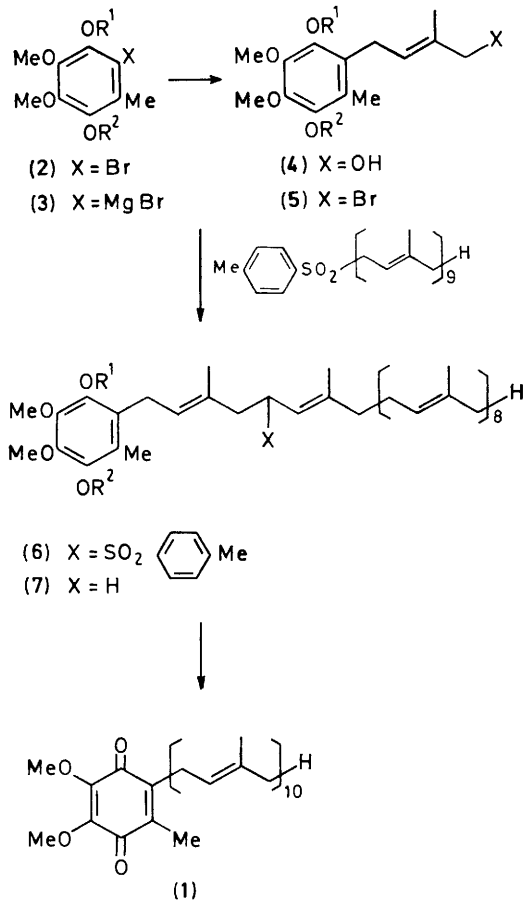
Co-enzyme Q_{10} was efficiently synthesised by stereo- and regio-selective prenylation of the protected hydroquinone (**2**) with isoprene epoxide and solanesyl *p*-tolyl sulphone in a good overall yield.

Co-enzyme Q_{10} (**1**) plays a pivotal role in several metabolic sequences and there is an increasing need for an efficient preparative method for this substance owing to its remarkable physiological and clinical activity.[1] Most of the existing methods involve alkylation of a protected or unprotected hydroquinone or quinone precursor with decaprenyl compounds.[2,3] However, the alkylating agents, such as decaprenol and decaprenyl bromide, from which other alkylating agents can be prepared, are usually obtained as a mixture of *cis* and *trans* isomers from natural solanesol.[2] Therefore the utility of these methods is diminished by the difficulty in isolating a single isomer of the pure alkylating reagent. Another approach to (**1**) was reported by Terao *et al.*[4] using a sulphone-functionalised prenylhydroquinone and solanesyl bromide; however, the stereoselective synthesis of the former component requires multi-step procedures.

Recently[5] we reported a stereoselective synthetic route to all-*trans*-decaprenol from geraniol *via* the coupling of polyprenyl sulphones and a halide, and subsequent reductive elimination of the sulphone group. This methodology has now been applied to the stereoselective synthesis of (**1**).

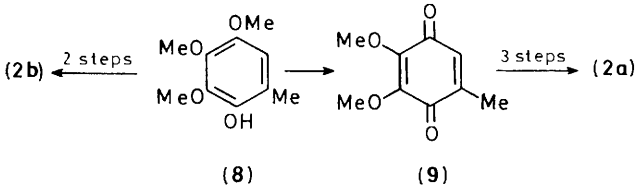
The bromide (**2a**)[6] was converted into the Grignard reagent (**3a**) and treated with isoprene epoxide in the presence of a catalytic amount of copper(I) chloride in tetrahydrofuran (THF) at -50 °C to afford the *trans*-allylic alcohol (**4a**) in 77% yield. The stereochemistry of the alcohol was confirmed by the n.m.r. spectrum of the aldehyde (δ_{CHO} 9.31)[7] obtained by Collins oxidation of (**4a**). The alcohol (**4a**) was converted (BuLi, *p*-$MeC_6H_4SO_2Cl$, and LiBr; 89% yield) into the bromide (**5a**), which was then coupled with the anion of solanesyl *p*-tolyl sulphone to give the product (**6a**) in a good yield.

The reductive elimination of the sulphone group in (**6a**)



a; $R^1 = R^2 = MeOCH_2$
b; R^1 = Me, $R^2 = PhCH_2$

by the usual method[8] (lithium–ethylamine, −78 °C) did not afford any desired product. The normal product (**7a**), however, was obtained when (**6a**) was subjected to the modified Bouvault-Blanc reduction[9] (8 equiv. of metallic sodium and 10 equiv. of ethanol in THF at room temp.). Simple acid-catalysed deprotection of (**7a**) followed by neutralisation and air oxidation furnished co-enzyme Q_{10} (**1**) in nearly quantitative yield. Pure all-*trans*-(**1**) was obtained by silica gel column chromatography (10% THF–hexane) and recrystallisation from ethanol, m.p. 48—49 °C, in 83% yield.



A similar reaction sequence was successfully applied to give another synthesis of (**1**) starting from the bromide (**2b**). The final step consisted of the modified Bouvault-Blanc reduction (*vide supra*) of (**6b**), and reductive elimination of the benzyl protecting group in (**7b**) (Li–$EtNH_2$, −78 °C), followed by mild oxidation of the *p*-methoxyphenol ($FeCl_3$, ethyl acetate–isopropyl ether).

Considering that (**2a**) is made from 2,3-dimethoxy-5-methylbenzoquinone (**9**) in three steps, and that (**2b**) is obtained in two steps from 2,3,4-trimethoxy-6-methylphenol (**8**),[10] an intermediate in the synthesis of (**9**), the latter route, *i.e.* (**2b**) → (**4b**) → (**6b**) → (**1**), seems to provide the most effective synthesis of co-enzyme Q_{10} (**1**).

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