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A Short, Highly Efficient Synthesis of Coenzyme Q_{10}

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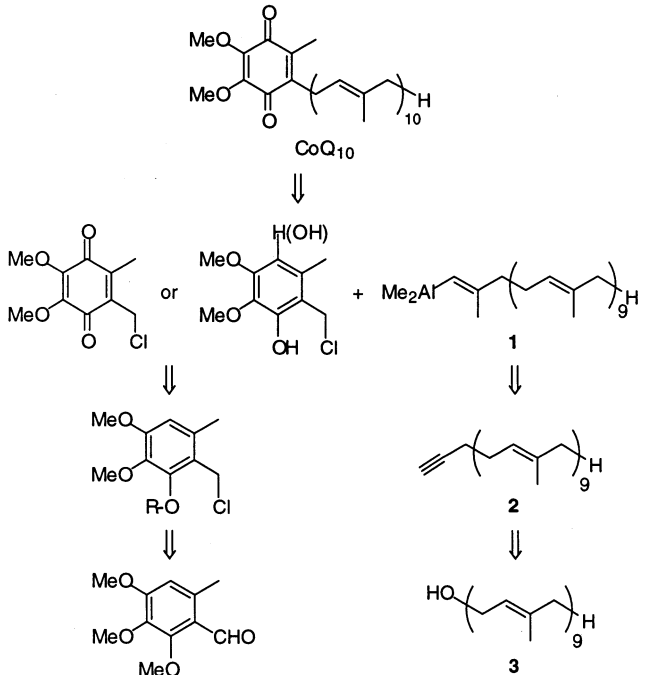
Open any textbook on basic biochemistry and there is likely to be considerable discussion devoted to the essential roles played by coenzyme Q_{10}.[1] Its presence in virtually every cell in the human body accounts for its alternative name: ubiquinone. With close to three decades of biomedical science to its credit, the combination of a polar headgroup attached to a 50 carbon tail is a remarkable construct of evolution. Oftentimes referred to as the "miracle nutrient",[2] CoQ_{10} plays a vital role in maintaining human health and vigor. Its involvement in mitochondrial processes such as respiration, cellular production of ATP, maintenance of heart muscle strength, quenching of free radicals in the battle against aging, and enhancement of the immune system are only a few of its many virtues.[3] Although much of society is unaware of the importance of ubiquinone, chemists on the other hand have devoted considerable effort in attempting to devise economically viable routes to this nutraceutical,[4] as well as its lower homologues.[5] In this report, we describe our ongoing work in this field which has led to a very short and highly efficient synthesis of CoQ_{10}.

Attachment of the two subsections of the target, that is, a polar quinone or aromatic precursor, and a (49 carbon) lipophilic hydrocarbon side chain, was anticipated to occur via a nickel(0)-catalyzed cross-coupling involving in-situ-derived vinyl alane **1** (Scheme 1), as previously developed for related couplings.[6] Starting with solanesol (**3**), isolated in quantity from tobacco leaves,[7] acetylene **2** could be prepared as illustrated in Scheme 2. Thus, conversion of **3** to the corresponding chloride **4** (96%) is best done using PCl_3 in DMF, which gives rise to material of excellent quality simply upon workup. Treatment of **4** with lithiated TMS-propyne (1.2 equiv)[8] in THF gives intermediate **5** in 87% isolated yield. Exposure of **5** to warm sodium ethoxide in ethanol (or 95% EtOH) led essentially quantitatively to terminal alkyne **2**.

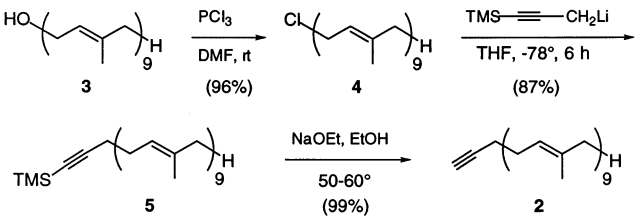
The quinone section of CoQ_{10} was initially planned starting with the readily available and inexpensive crystalline benzaldehyde derivative **6**,[9] because selective demethylation with $AlCl_3$ is known[10] and could be effected in high yield (94%; Scheme 3). After tosylation (98%), the resulting crystalline aldehyde **7** was smoothly converted in one pot to an ideal coupling partner, the derived benzylic chloride **8** (95%; mp 110−110.5 °C). Given the inexpensive nature of both **6** and **7**, and the newly developed process for direct conversion of **7** to **8**, this benzylic chloride is now offered in quantity.[9]

With **2** available in three steps and **8** provided commercially, the coupling could be carried out using nickel catalysis in standard fashion (Scheme 4).[6] Initial Negishi carboalumination[11] of **2** led to intermediate **1**. Exposure of **1** (1.3 equiv) to 3 mol percent Ni(0) and halide **8** (1 equiv) provided the CoQ skeleton **9**. This oily product could then be detosylated using 2 equiv of *n*-BuLi at 0 °C, thereby generating free phenol **10** as a stable crystalline solid (92%; mp 49−50.5 °C). Oxidation of **10** using catalytic amounts of Jacobsen's[12] Co(salen) complex[13] under an oxygen atmosphere at ambient temperature[14] afforded yellow-orange, all-*E*, CoQ_{10} in 94% isolated yield.

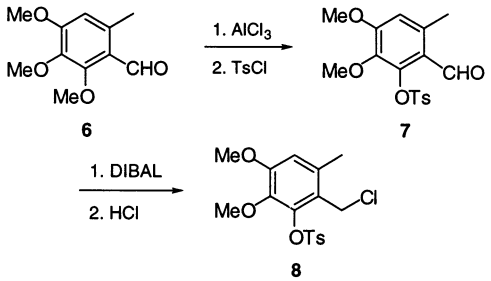
Scheme 1. Retrosynthetic Analysis of CoQ_{10}



Scheme 2. Preparation of Alkyne **2**



Scheme 3. Generation of Coupling Partner **8**



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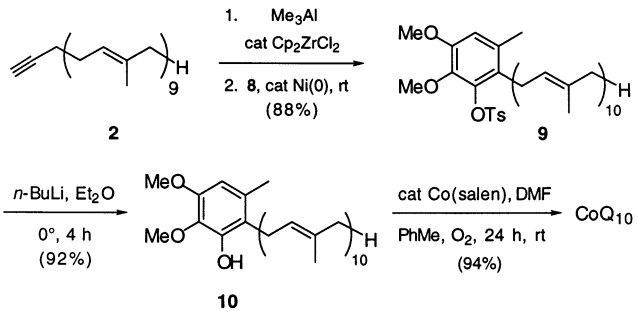
Scheme 4. Cross-Coupling and Final Conversion to CoQ_{10}



In summary, a novel route to CoQ_{10} has been realized, which calls for six total operations (**3** → **4** → **5** → **2** → **9** → **10** → CoQ_{10}) to arrive at ubiquinone in 64% overall yield, which constitutes the most efficient synthesis reported to date.[4,15] Synthetic CoQ_{10} was identical to authentic material in all respects.[16] Particularly noteworthy is the fact that by virtue of the synthetic sequence outlined herein, typical impurities such as the corresponding cis-isomer and CoQ_9, oftentimes found in CoQ_{10} which is produced industrially almost entirely by fermentation,[17] are completely averted.

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Note Added in Proof: Results from a recently completed study by the NIH on the beneficial effects of CoQ_{10} on those who suffer from Parkinson's disease have been disclosed; see www.msnbc.com/news/821158.asp?0si=-.

Supporting Information Available: Experimental procedures and spectroscopic data for all intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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