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An Improved Synthesis of the "Miracle Nutrient" Coenzyme Q_{10}

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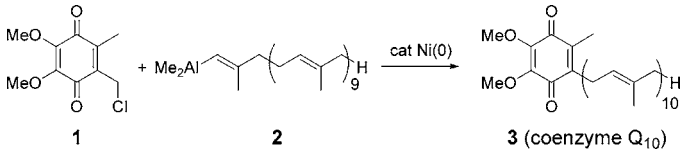
ABSTRACT



1 2 3 (coenzyme Q_{10})

A new route to the key coupling partner, chloromethylated CoQ_0 (1), allows for direct formation of CoQ_{10} (3) via nickel-catalyzed cross-coupling with the side chain in the form of an in situ-derived vinyl alane (2).

Coenzyme Q_{10} (also known as ubiquinone; CoQ_{10}, **3**) is a vital human nutrient responsible for shuttling electrons through the respiratory chain. CoQ_{10} is used, in reduced form, by all cells as an antioxidant, quenching free radicals and thereby fighting the aging process. The extent of CoQ_{10} in tissue has been linked to energy levels, and the benefits for cardiac patients are especially well documented.[1] With the demand for CoQ_{10} as a dietary supplement already exceeding worldwide supply, there is considerable incentive to find an efficient synthetic route for its preparation. Herein we describe an improved synthesis of key coupling partners chloromethylquinone **1** and vinylalane **2**. As previously described,[2] these reactive species combine under nickel catalysis to generate ubiquinones directly.

Our prior sequence[2] (Scheme 1) relies on the nickel-mediated coupling[3,4] of **2** with readily available benzylic chloride **4**. Since **4** derives from inexpensive trimethoxytoluene **5**, the most expensive ingredient in our CoQ_{10} synthesis is solanesol **6**, notwithstanding its status as a waste product of tobacco.[5] Isolation of this 45-carbon allylic alcohol in both quantity and in high (>90%) purity is challenging and can be costly depending upon the method of purification.[6] Thus, an ideal synthesis would seek to minimize the extent to which intermediates based on solanesol are manipulated en route to CoQ_{10}.

In proceeding through intermediate **7**, two additional operations are required to arrive at the natural product: (1) treatment with *n*-BuLi to effect detosylation and (2) autoxidation mediated by catalytic amounts of racemic Jacobsen's Co(salen) complex.[7] Although the yields are quite high, we

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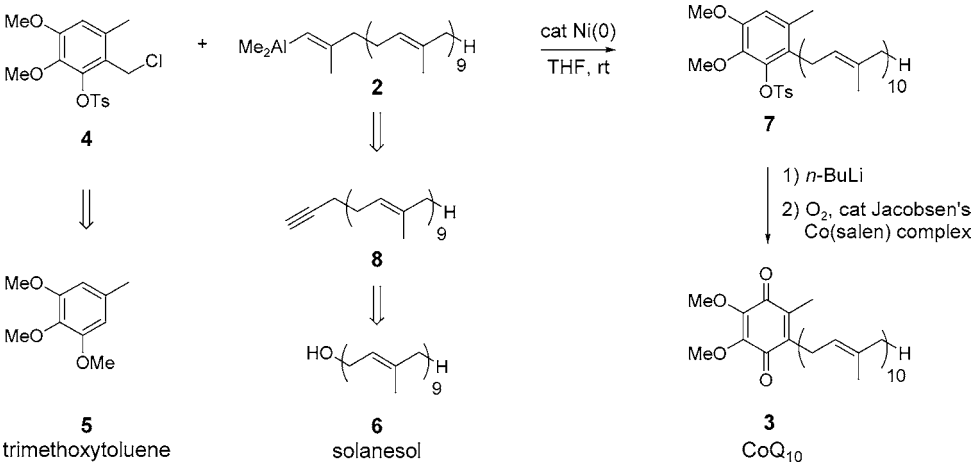
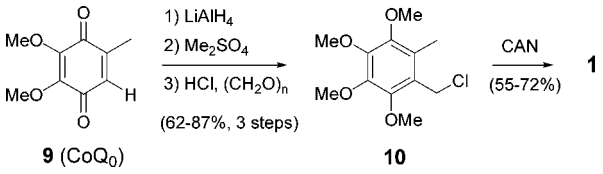
Scheme 1. Previous Synthesis of CoQ_{10} Proceeding through Tosylate **7**



sought to devise a strategy that would provide CoQ_{10} in a single coupling reaction. To realize this goal, efficient entry to coupling partner **1** is needed such that the Ni-catalyzed cross-coupling reaction serves as the final step. This concept was developed for the syntheses of CoQ_{3-8}[8] and recently applied by Negishi to CoQ_{10}.[9]

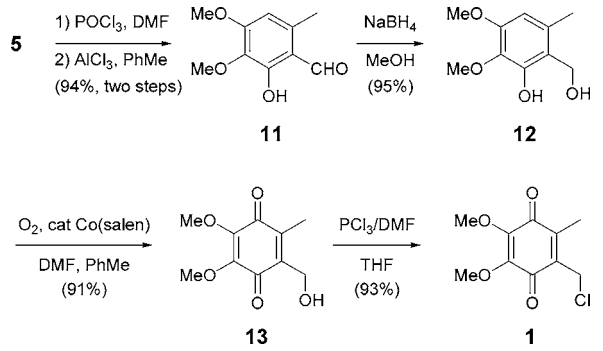
The existing sequence to quinone **1** (Scheme 2) is less than ideal in that it starts with far more expensive CoQ_0 (**9**)

Scheme 2. Previous Synthesis of **1** Starting from CoQ_0



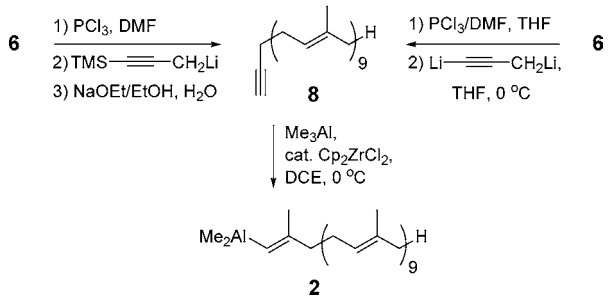
and requires four steps to install the chloromethyl functionality, including a final modest-yielding reoxidation from a protected hydroquinone **10** employing $(NH_4)_2Ce(NO_3)_6$.[3] We now describe a new and concise series of reactions beginning with inexpensive trimethoxytoluene **5** that very efficiently leads to chloromethylated *para*-quinone **1** (Scheme 3).

Scheme 3. New Route to **1** Based on Trimethoxytoluene **5**



Standard Vilsmeier formylation of aromatic **5** followed by regioselective demethylation with $AlCl_3$[3a,10] proceeded smoothly to afford phenol **11** in 94% yield over two steps (Scheme 4). Reduction of the newly inserted aldehyde

Scheme 4. Synthesis of Solanesylalkyne **8**



functionality using 0.26 equiv of $NaBH_4$ in MeOH led to benzylic alcohol intermediate **12** in 95% yield. We were pleased to discover that phenolic oxidation can now be carried out under the influence of the less expensive *parent* Co(salen) complex to produce **13** in 91% yield. The final step in this sequence employs a modified Vilsmeier chlorination to convert quinone alcohol **13** to the corresponding chloride coupling partner **1** (five steps, 76% overall yield).

Although quinone **1** can be readily converted to CoQ_{10} by existing technology,[7,8] we endeavored to improve the three-step process leading from solanesol to alkyne **8**, the 48-carbon precursor to vinyl alane **2** (Scheme 4). Thus, solanesyl chloride **14** could be made by preformation of the Vilsmeier salt (0.66 equiv of PCl_3, 0.66 equiv of DMF neat) to which was then added THF followed by substrate **6**,

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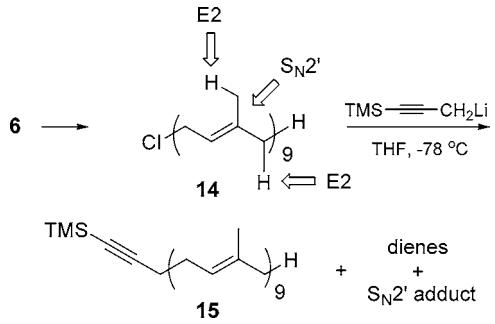
Scheme 5. Competing Processes in the Alkylation of Lithiated Trimethylsilylpropyne



thereby minimizing both reagents and avoiding the use of DMF as a solvent. Prior formation of the salt, followed by use of an alternative solvent, appears to be, to the best of our knowledge, an unprecedented procedure.

While displacement of allylic chloride **14** with lithiated trimethylsilylpropyne leads to protected alkyne **15** in 87% yield,[3] the remaining mass is composed of products of E2 elimination and, to a lesser degree, S_N2' addition (Scheme 5). The similar nature of the byproducts to the alkyne makes separation difficult. Remarkably, use of dilithiopropyne,[11] generated in situ by bubbling propyne gas through a controlled amount of *n*-BuLi, afforded the desired terminal alkyne **8** directly without observable byproduct formation (cf. Scheme 4). This modification not only increases alkyne purity but also shortens the sequence by one step (i.e., no desilylation of **15** to **8** is required). Moreover, the alkylation can be run at 0 °C to room temperature rather than the far lower temperatures (−78 to −20 °C) used previously.[3a]

In summary, several major improvements have been made in the synthesis of the nutraceutical coenzyme Q_{10}. A new sequence has been developed leading to the substituted *para*-quinone headgroup **1**, thereby reducing the extent of manipulation of the (relatively costly) side-chain and eliminating two synthetic steps late in the synthesis. In addition, a shortened route to the side-chain precursor, alkyne **8**, has been realized. Taken together, these advances significantly enhance opportunities for potential industrial scale-up of this essential vitaminlike compound.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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