

An Improved Synthesis of the “Miracle Nutrient” Coenzyme Q₁₀

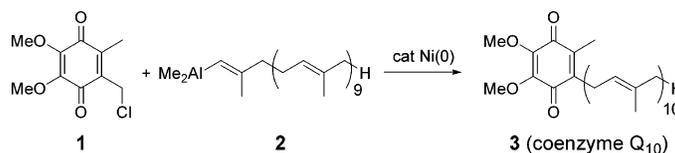
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ABSTRACT



A new route to the key coupling partner, chloromethylated CoQ₀ (1), allows for direct formation of CoQ₁₀ (3) via nickel-catalyzed cross-coupling with the side chain in the form of an in situ-derived vinyl alane (2).

Coenzyme Q₁₀ (also known as ubiquinone; CoQ₁₀, **3**) is a vital human nutrient responsible for shuttling electrons through the respiratory chain. CoQ₁₀ is used, in reduced form, by all cells as an antioxidant, quenching free radicals and thereby fighting the aging process. The extent of CoQ₁₀ in tissue has been linked to energy levels, and the benefits for cardiac patients are especially well documented.¹ With the demand for CoQ₁₀ 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 sequence² (Scheme 1) relies on the nickel-mediated coupling^{3,4} of **2** with readily available benzylic chloride **4**. Since **4** derives from inexpensive trimethoxy-

toluene **5**, the most expensive ingredient in our CoQ₁₀ 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 CoQ₁₀.

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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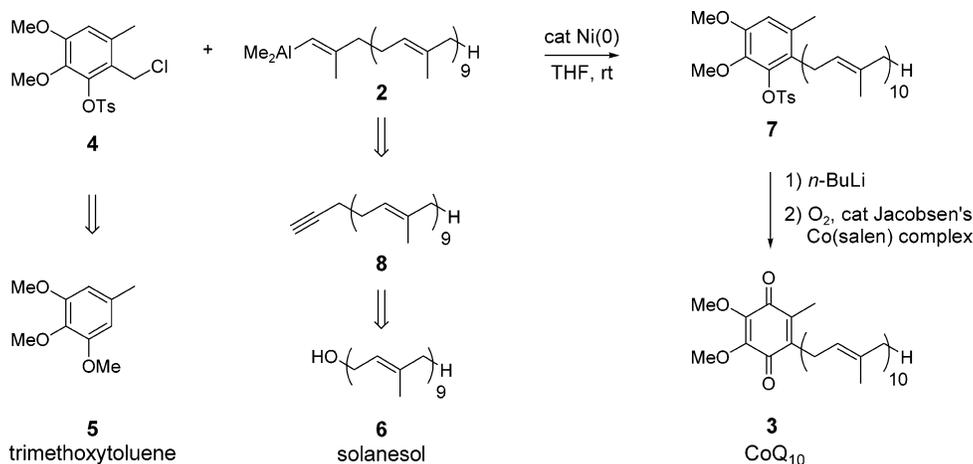
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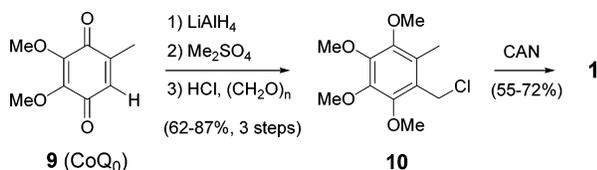
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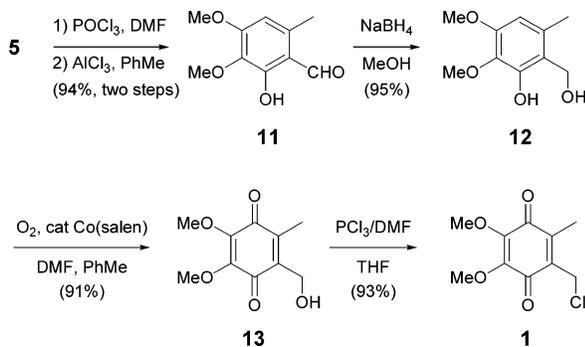
Scheme 1. Previous Synthesis of CoQ₁₀ Proceeding through Tosylate **7**

sought to devise a strategy that would provide CoQ₁₀ 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 CoQ₃₋₈⁸ and recently applied by Negishi to CoQ₁₀.⁹

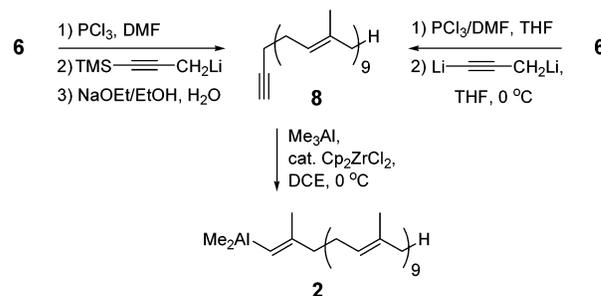
The existing sequence to quinone **1** (Scheme 2) is less than ideal in that it starts with far more expensive CoQ₀ (**9**)

Scheme 2. Previous Synthesis of **1** Starting from CoQ₀

and requires four steps to install the chloromethyl functionality, including a final modest-yielding reoxidation from a protected hydroquinone **10** employing (NH₄)₂Ce(NO₃)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 AlCl₃^{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***original work**new route*

functionality using 0.26 equiv of NaBH₄ 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).

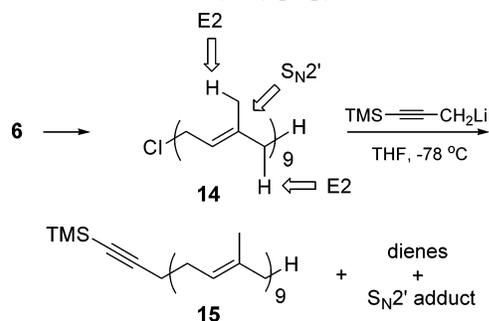
Although quinone **1** can be readily converted to CoQ₁₀ by existing technology,^{7,8} we endeavored to improve the three-step process leading from solanesol to alkyne **8**, the 48-carbon precursor to vinyl alane **2** (Scheme 4). Thus, solanesyl chloride **14** could be made by preformation of the Vilsmeier salt (0.66 equiv of POCl₃, 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 $\text{E}2$ elimination and, to a lesser degree, $\text{S}_{\text{N}}2'$ 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 $0\text{ }^\circ\text{C}$ to room temperature rather than the far lower temperatures (-78 to $-20\text{ }^\circ\text{C}$) 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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