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A Concise Synthesis of (+)-Artemisinin

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Supporting Information

ABSTRACT: Malaria represents one of the most medically and economically debilitating diseases present in the world today. Fortunately, there exists a highly effective treatment based on the natural product artemisinin. Despite the development of several synthetic approaches to the natural product, a streamlined synthesis that utilizes low-cost chemical inputs has yet to materialize. Here we report an efficient, cost-effective approach to artemisinin. Key to the success of the strategy was the development of mild, complexity-building reaction cascades that allowed the use of readily available, affordable cyclohexenone as the key starting material.

Malaria infects over 200 million people each year with up to one million, mostly children, perishing from the infection.[1] Currently, the most effective treatment against malaria-causing *Plasmodium* parasites is artemisinin-based combination therapy (ACT). The key ingredient for the production of ACTs, artemisinin (**1**, Figure 1), is a natural

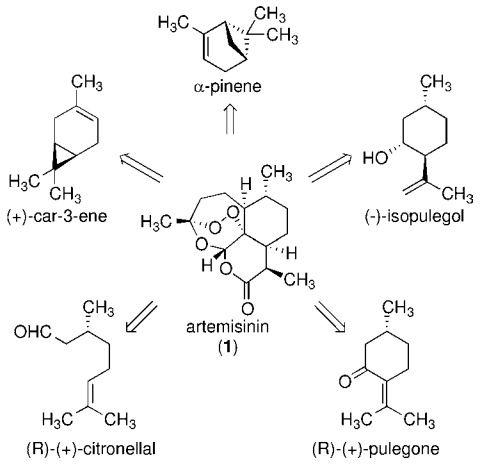


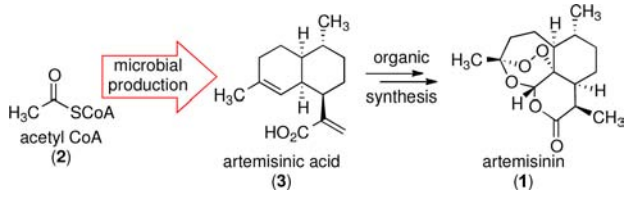
Figure 1. Structures of (+)-artemisinin (**1**) and the various terpene starting materials used in previous total syntheses.

product extracted on an industrial scale from the sweet wormwood plant, *Artemesia annua*. Unfortunately, artemisinin is currently too expensive to meet the distribution needs of the world. Moreover, crop disruptions caused by natural disasters, poor planning, and geopolitical events have led to shortages and price fluctuations. In the last 10 years, there have been two primary approaches to combat these issues: using synthetic biology to produce a chemical precursor of artemisinin in microbes[2] and breeding new varieties of *A. annua* with improved growth and/or production traits.[3] While advances have been made in both areas, these strategies have yet to make a contribution to the world's artemisinin supply. Interestingly, the literature over the past decade reveals a disappointing lack of effort focused on discovering a de novo synthesis of **1** and its derivatives from inexpensive, readily available chemicals—a significantly more affordable and timely research proposition. Herein we describe a concise strategy for the enantioselective total synthesis of (+)-artemisinin (**1**) in as few as five pots. This robust approach provides a step-economical blueprint for the low-cost production of **1** and its derivatives.[4]

Soon after the initial report of the structure and antimalarial activity of artemisinin, chemists began working toward a feasible chemical synthesis of this unprecedented endoperoxide-containing natural product.[5] This work culminated in several total syntheses of **1** between 1979 and 1996.[6] While impressive from a chemical "proof-of-principle" perspective, these early syntheses have done little to address the supply problem of **1** because of the high costs inherent to long reaction sequences, excessive protecting group schemes, and expensive terpene-based starting materials (Figure 1). Even clever modern syntheses of **1** could not compete on price with isolation from natural sources.[7] These problems have driven the perception that a laboratory synthesis of **1** is untenable.[8]

Since 2004, the most promising, high-profile approach to affordable artemisinin production has been the effort to realize microbial production of chemicals that can be used in the semisynthesis of artemisinin (Scheme 1).[2b,9] While direct

Scheme 1. A Semisynthetic Approach to 1



microbial production of **1** represents the most desirable biosynthetic approach, the gene or genes responsible for the conversion of artemisinic acid (**3**) to **1** remain elusive. Recent work by Levesque and Seeberger[10b] described an elegant laboratory conversion of **3** to **1** using a photochemical flow-chemistry approach based on the batch system developed by a Sanofi-Aventis process group.[10a] However, even with the extraordinary resources dedicated to the microbial approach,[11]

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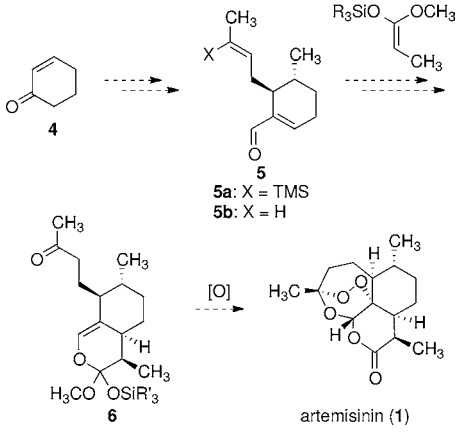
the issue of reliable, low-cost production of **1** remains. The de novo synthesis of **1** reported here offers an attractive alternative.

A robust synthesis of artemisinin requires cheap, readily available chemical inputs, step economy, and overall efficiency. To realize such a strategy, we abstained from protecting groups and relied on cascade reactions to build in significant molecular complexity in each step. The synthetic plan for our synthesis of **1** is detailed in Scheme 2. Starting from cheap, widely available

Scheme 2. Synthetic Plan for the Synthesis of 1

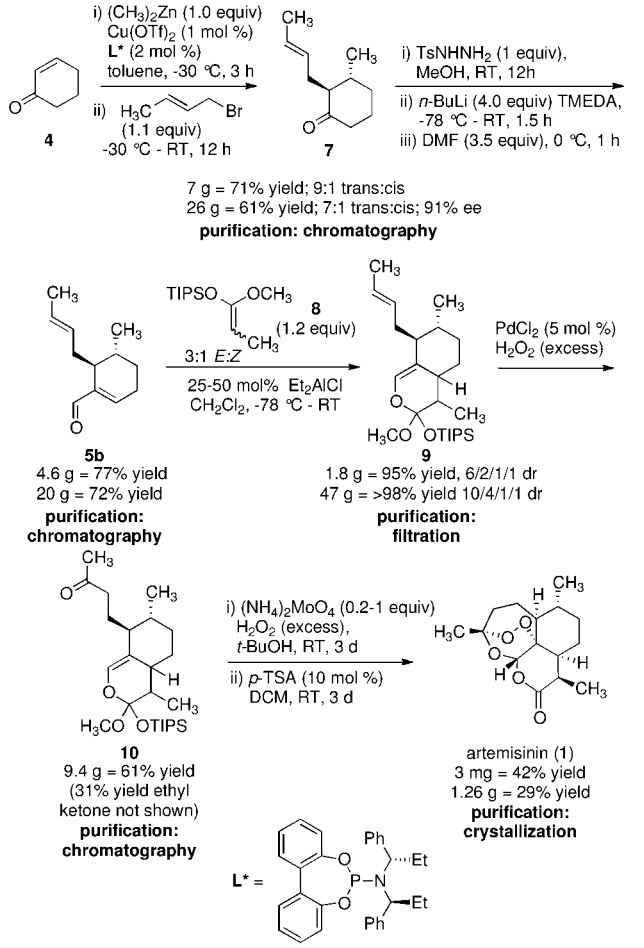


cyclohexenone (**4**), the synthesis of an α,β-unsaturated aldehyde **5** bearing a masked methyl ketone four-carbon chain would provide the opportunity to study various [4 + 2] annulation strategies en route to **6**. After the unusual [4 + 2] reaction between α,β-unsaturated aldehyde **5** and a silyl ketene acetal, unmasking of the methyl ketone side chain would provide ortho ester **6**. Under the coercion of the appropriate oxidation conditions, **6** would undergo oxidative rearrangement to furnish **1**.

Central to the goal of a concise synthesis of **1** was the judicious choice of the four-carbon side chain that would eventually become a methyl ketone. The goal of an economically viable synthesis precluded the use of many common methyl vinyl ketone (MVK) equivalents. While our initial studies directed toward the synthesis of **1** employed the Stork–Jung vinylsilane[12] (see **5a** in Scheme 2), the high cost associated with its preparation[13] (both in terms of chemical inputs and synthetic steps), combined with the difficulties encountered during attempts to unravel the vinylsilane to form a ketone, led us to explore the crotyl group as a novel MVK equivalent (see **5b** in Scheme 2). This choice allowed for the use of crotyl bromide as an exceedingly cost-effective four-carbon feedstock while simultaneously necessitating the development of mild Wacker-type oxidation conditions for internal olefins.

Our synthesis of **1** began with the conversion of cyclohexenone (**4**) to ketone **7** in 61% yield (7:1 trans:cis, 91% ee) via a one-pot conjugate addition/alkylation sequence (Scheme 3).[14] The treatment of **7** with *p*-toluenesulfonylhydrazide in methanol at room temperature provided the corresponding hydrazone. After replacing the solvent, exposure of the hydrazone to *n*-BuLi at low temperature provided a vinyl anion that was quenched with *N*,*N*-dimethylformamide (DMF).[15] This one-pot sequence resulted in the production of α,β-unsaturated aldehyde **5b** in 72% overall yield.

Scheme 3. Synthesis of (+)-Artemisinin (1)



An unusual [4 + 2] reaction was envisioned for the installation of the six-membered lactone of **1**. The use of an α,β-unsaturated aldehyde with silyl ketene acetal **8** for the [4 + 2] reaction required careful control of alternate, unproductive reaction pathways (e.g., Mukaiyama aldol, Mukaiyma Michael, and [2 + 2]).[16] An extensive investigation of acid catalysts revealed the unique ability of dialkylaluminum chloride salts to catalyze the preferential formation of the [4 + 2] product relative to Mukaiyama aldol or Michael products. Consequently, the reaction of silyl ketene acetal **8** and α,β-unsaturated aldehyde **5b** in the presence of low-cost dimethyl- or diethylaluminum chloride provided ortho ester **9** in ≥95% yield as an inseparable mixture of four diastereomers (10:4:1:1). Additional additives to alter the diastereoselectivity were unnecessary because two of the three stereogenic centers proved irrelevant to the synthesis of **1**, thereby allowing the mixture to be used directly in subsequent chemistry.

With ortho esters **9** available in large quantities (~50 g), the investigation of suitable oxidation conditions to produce methyl ketone **10** could proceed. Extensive experimentation led to the discovery of exceptionally straightforward oxidation conditions for internal olefins. Simple stirring of **9** in aqueous hydrogen peroxide with a palladium catalyst resulted in the oxidation of the internal olefin of **9** in greater than 90% yield, producing methyl ketone **10** in 61% yield as a diastereomeric mixture. While these conditions provided the fewest number of side products, extended reaction times were required to achieve full conversion, presumably because of the poor solubility of both

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the substrate and the catalyst in water. Efforts to address the solubility by incorporating cosolvents or phase-transfer catalysts resulted in increased conversion with substantially lower yield in comparison with water alone. While improved regioselectivity of the oxidation would enhance the yield of the desired product, low-cost additives that improve methyl ketone formation remain elusive. Fortunately, the operational simplicity and potential for palladium recycling compensates for the undesired ethyl ketone formation.

In an effort to convert methyl ketone **10** to **1**, a number of disparate oxidative rearrangement strategies were evaluated. Unfortunately, our proposals were rebuffed with complicated mixtures of ring-opened products and no trace of **1**. Success came in the form of carefully controlled generation of singlet oxygen. The final oxidative rearrangement to **1** utilized the in situ formation of singlet oxygen from the decomposition of H_2O_2 by ammonium molybdate to oxidize the enol olefin of **6**.[17] Following oxidation, several oxidized intermediates converged to **1** in 29−42% yield in the presence of acid.

In conclusion, a cost-effective total synthesis of (+)-artemisinin has been achieved on a gram scale from a widely available, inexpensive starting material, cyclohexenone. Salient features of the synthesis include zinc enolate alkylation, an unconventional [4 + 2] annulation, and a high-yielding oxidation of an internal olefin. Current studies seek to further reduce the cost of synthetic artemisinin and enable its large-scale production.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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