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Concise synthesis of artemisinin from a farnesyl diphosphate analogue

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ABSTRACT

Artemisinin is one of the most potent anti-malaria drugs and many often-lengthy routes have been developed for its synthesis. Amorphadiene synthase, a key enzyme in the biosynthetic pathway of artemisinin, is able to convert an oxygenated farnesyl diphosphate analogue directly to dihydroartemisinic aldehyde, which can be converted to artemisinin in only four chemical steps, resulting in an efficient synthetic route to the anti-malaria drug.

1. Introduction

Malaria affects almost 50% of the world's population and causes hundreds of thousands of deaths each year.[1] Isolated from the plant *Artemisia annua* (qinghaosu), the sesquiterpene artemisinin (**1**) exhibits excellent anti-malaria activity and kills the parasite at most of its asexual stages of development in human blood.[2] Artemisinin-based combination treatments (ACTs) are widely used as the first-line treatment for malaria.[3] Although several synthetic routes to artemisinin (**1**) have been developed,[4] the chemical synthesis is lengthy and low yielding due to the highly complex structure of the sesquiterpene endoperoxide. The worldwide supply of artemisinin (**1**) relies predominantly on the extraction of (**1**) from the plant *Artemisia annua*[5] and as a consequence the world market price is highly volatile ranging from US $350 to $1700 per kilogram.[6] Most countries affected by malaria epidemics are in the developing world, and therefore a stable and affordable supply of artemisinin (**1**) is highly desirable.

Currently the most efficient synthetic route to produce artemisinin is the combination of a biosynthetic process with several chemical steps (Scheme 1). The biosynthesis of artemisinin is well understood[7] and the key step to this synthesis involves the class I sesquiterpene cyclase amorphadiene synthase (ADS). This enzyme catalyses the cyclisation of (*E*,*E*)-farnesyl diphosphate (FDP, **2**) to amorpha-4-11-diene (**3**), a bicyclic intermediate with four stereocentres. **3** can be converted to the advanced synthetic intermediate dihydroartemisinic acid (DHAA, **4**) either chemically[8a] or enzymatically using engineered yeast (Scheme 1).[8b,c] The latter method has been developed into a semi-synthetic production of artemisinin (**1**). Engineered yeast containing ADS and five other enzymes produce artemisinic acid (**5**), which is subsequently reduced to DHAA (**4**) by a transition metal-catalysed hydrogenation.[8a,9] DHAA (**4**) can then be converted to artemisinin (**1**) in three well-established steps.[10] The pharmaceutical company Sanofi developed a commercial route for biosynthetically produced artemisinin in 2014, but this process has now discontinued due to strong market forces.[11] Alternative routes for the low-cost production of artemisinin (**1**) are therefore urgently required.

Here we report a novel synthetic route to artemisinin (**1**) starting from the oxygenated farnesyl diphosphate analogue 12-hydroxyfarnesyl diphosphate (**6**) (Scheme 2). Amorphadiene synthase (ADS) is able to convert **6** in a single step to dihydroartemisinic aldehyde (DHAAl, **7**), an advanced intermediate of artemisinin.[12] This route does not proceed *via* amorphadiene (**3**) and therefore avoids several redox steps. Increasing the oxidation state at the linear precursor stage produces a two-step synthesis of **4**, which significantly shortens the synthesis of artemisinin (**1**).

2. Enzymatic reaction

ADS catalyses the Mg^{2+}-dependent, highly chemo- and stereoselective cyclisation of FDP (**2**) to amorphadiene (**3**) (Scheme 3).[13] ADS cleaves the C—O bond in **2** and generates diphosphate and a carbocation, which rearranges through a series of ring closures

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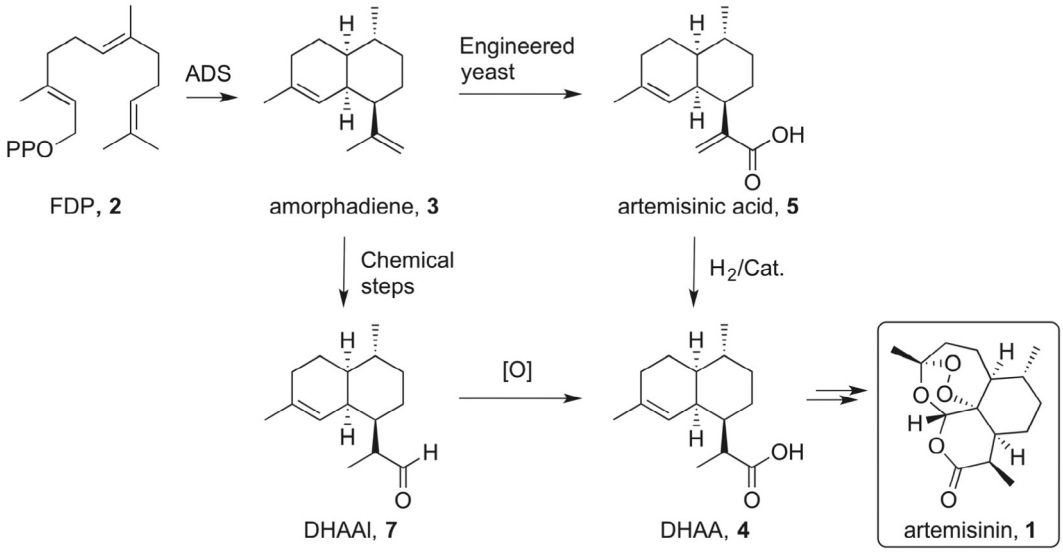
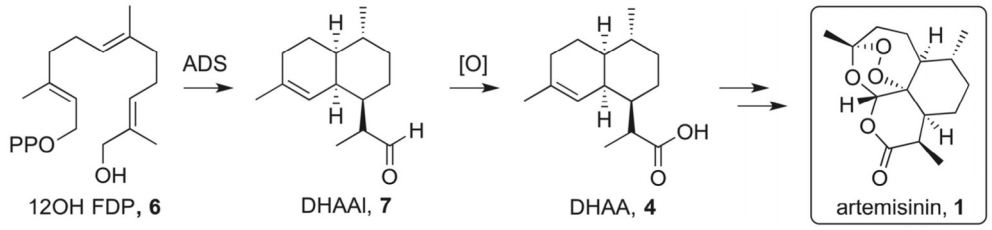
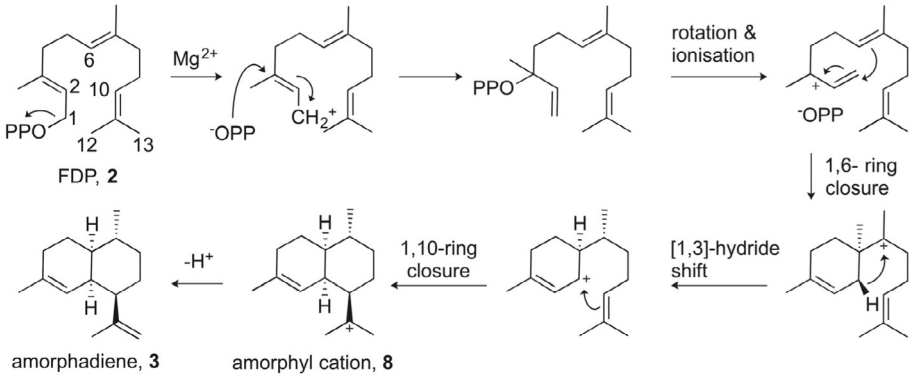


Scheme 1. Synthesis of artemisinin (**1**) from farnesyl diphosphate (**2**).



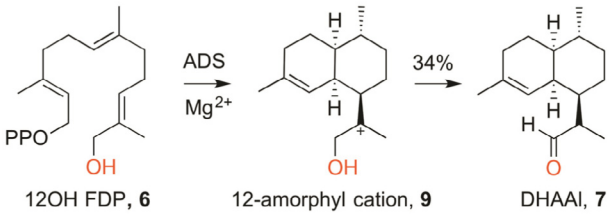
Scheme 2. Schematic synthesis of artemisinin (**1**) from 12-hydroxyfarnesyl diphosphate (**6**).



Scheme 3. Biosynthetic pathway to amorpha-4,11-diene (**3**).

and hydride transfer processes. The last step in the enzymatic sequence is the deprotonation of amorphyl cation (**8**) to yield amorphadiene (**3**) (Scheme 3).

The enzyme's remarkable ability to convert a linear precursor to a structurally and stereochemically complex cyclic product offers a very efficient synthetic route to terpenes. Sesquiterpene synthases are not only highly effective and often stereospecific in the reactions they catalyse, many of them also display some degree of substrate promiscuity and some analogues of FDP (**2**) can be converted to modified terpenoids.[14] As an example, it has been shown that ADS catalyses the cyclisation of 12-hydroxy FDP (**6**) to produce dihydroartemisinic aldehyde (**7**) (Scheme 4) with a 34% yield.[12] The seemingly moderate yield is common for sesquiterpene cyclases as the reaction is limited by the release of the hydrocarbon



Scheme 4. ADS-catalysed cyclisation of 12-hydroxyfarnesyl diphosphate (**7**).

products from the aqueous incubation media.[15] Aldehyde **7** is a well-established intermediate in the biosynthesis of artemisinin (**1**).[7] In contrast to the three redox steps required to convert (**3**)