

The Biosynthesis and Synthetic Biology of Artemisinin

BY JOSEPH R. STEPHENSON CLARK
UNIVERSITY OF READING

Abstract

Artemisinin is a frontline antimalarial drug that occurs naturally in the native Chinese herb Artemisia annua. This natural product has a complex structure featuring an unusual 1,2,4-trioxane ring which is responsible for its powerful antimalarial activity. The natural biosynthesis and recent advances in the synthetic biology of artemisinin are discussed in this review. The biosynthesis is divided into three phases. The first involves the head-to-tail linkage of five-carbon allylic pyrophosphates to form a longer (fifteen-carbon) chain pyrophosphate intermediate, which is then cyclized to the bicyclic amorphane skeleton of artemisinin, amorpha-4,11-diene (A-4,11-D). In phase two A-4,11-D undergoes both oxidation and reduction to dihydroartemisinic acid (DHAA). The mechanism of the third and final phase is still subject to some controversy, though it must involve oxidative cleavage of the C-4 double bond in one of the rings of DHAA. It is also possible that this final step is a spontaneous autoxidation and that the 1,2,4-trioxane ring of artemisinin is generated non-enzymatically. Over the past decade there has been much interest in synthetic biological approaches to the production of artemisinin, which employ many of the enzymes that have been described from the biosynthetic pathway to artemisinin in A. annua. In the industrial process, as it is currently practiced, the genes that code for these enzymes are expressed in the chassis organism Saccharomyces cerevisiae (yeast). This produces artemisinic acid (AA), a close relative of DHAA, which is then converted to artemisinin by chemical synthesis.

Introduction

Malaria is an aggressive and highly infectious parasitic disease that is prevalent throughout more than 100 equatorial and subtropical countries. In 2006, 86% of documented cases of malaria occurred in Africa; over half of these were reported in Nigeria, Ethiopia, the Democratic Republic of the Congo, Kenya, and the United Republic of Tanzania.¹ This figure was reported by the World Health Organization (WHO) to have increased to 90% in 2016. Since malaria is largely a Third-World disease, a cheap and effective cure is in great demand.

Due to rising concerns about chloroquine-resistant strains of the malarial parasite *Plasmodium falciparum* during the Vietnam War, a project to screen traditional Chinese medicines (TCM) for antimalarial agents was commissioned by the Chinese government² (historically this was parallel to the U.S. discovery of mefloquine).³ The potent antimalarial activity of *A. annua*, for which usage in TCM dates as far back as 168 B.C.E., was recognized by a team led by the pharmaceutical chemist Youyou Tu. Professor Tu was subsequently awarded the 2015 Nobel Prize for Physiology or Medicine for her contribution to the development of artemisinin. The Chinese scientists characterized artemisinin as a sesquiterpene (fifteen-carbon) lactone containing an endoperoxide. It was noted that this endoperoxide group was essential to

its antimalarial function. In clinical trials artemisinin demonstrated 100% effectiveness towards chloroquine-resistant strains of the *P. falciparum* parasite.⁴

In its natural setting artemisinin probably functions as a chemical defense for *A. annua* against attack by herbivores and insects.^{5,6} It is quite common for natural products with such an “ecological” role to be useful in the treatment of human diseases; in addition to its powerful antimalarial function, artemisinin also shows antiviral and anticancer activity.⁷

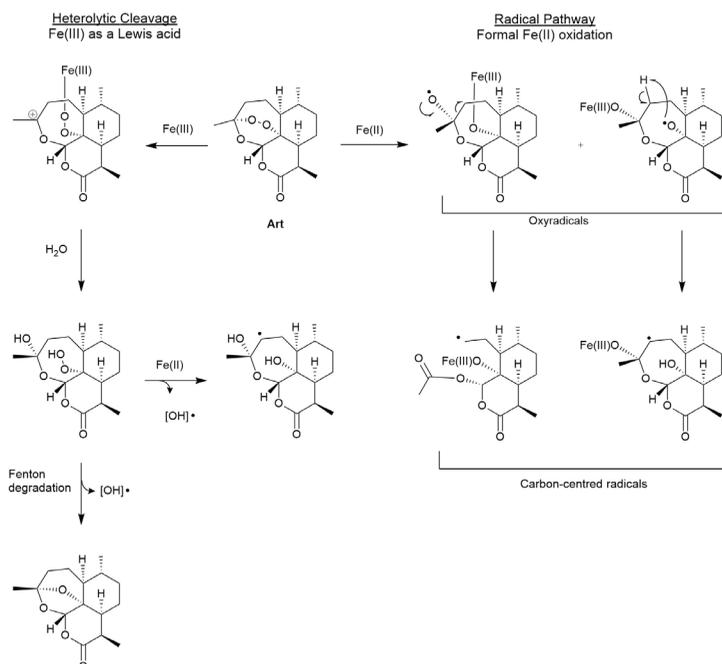
Two main pathways have been proposed for the mode of action of artemisinin (Art). In both, the endoperoxide group is involved in the *in vivo* activation of the drug *via* interaction with iron(II) atoms. These may come from free heme groups released by the digestion of hemoglobin by the parasite, although there is evidence for bio-activation by both heme iron and non-heme iron(III).⁸ In one pathway the endoperoxide group of Art is heterolytically cleaved in a reaction facilitated by the Lewis acidity of iron, followed by interaction with water, which generates a hydroperoxide capable of directly oxidizing protein residues.⁸ This hydroperoxide can also undergo Fenton degradation, thereby expelling a hydroxyl radical (Scheme 1). In the second radical pathway iron(II) is oxidized by either of the endoperoxide oxygen atoms, generating an oxyradical which re-

arranges to a carbon-centered radical capable of both heme- and protein-alkylation (Scheme 1). Some of the proposed carbon-centered radical intermediates have been detected by EPR and spin-trapping studies.⁹

An alternative model involves depolarization of the parasite’s mitochondrial and plasma membranes *via* lipid peroxidation by a reactive oxygen species that is also generated from iron bio-activation of the endoperoxide.^{8,10} There is experimental evidence that physiological levels of artemisinin can depolarize parasite plasma ($\Delta\Psi_p$) and mitochondrial ($\Delta\Psi_m$) membrane potentials.⁸

In practice it is normal to use chemically-modified derivatives of artemisinin in place of the parent compound due to its poor solubility and unfavorable metabolic and hydrolytic stabilities. Generally such an artemisinin derivative is administered alongside another antimalarial in a treatment known as artemisinin-based combination therapy (ACT). ACT is advantageous in that treatment times are reduced and the evolution of drug-resistant strains of the malarial parasite is hindered. ACTs are now recommended by the WHO as the treatment of choice for *falciparum* malaria.

Since its discovery the main problem with this drug has been that the worldwide market for artemisinin is highly unstable due to its dependence on agriculturally-produced artemisinin from an annual crop



Scheme 1: Heterolytic and radical cleavage mechanisms proposed for the iron-catalyzed bio-activation of artemisinin in vivo.⁸

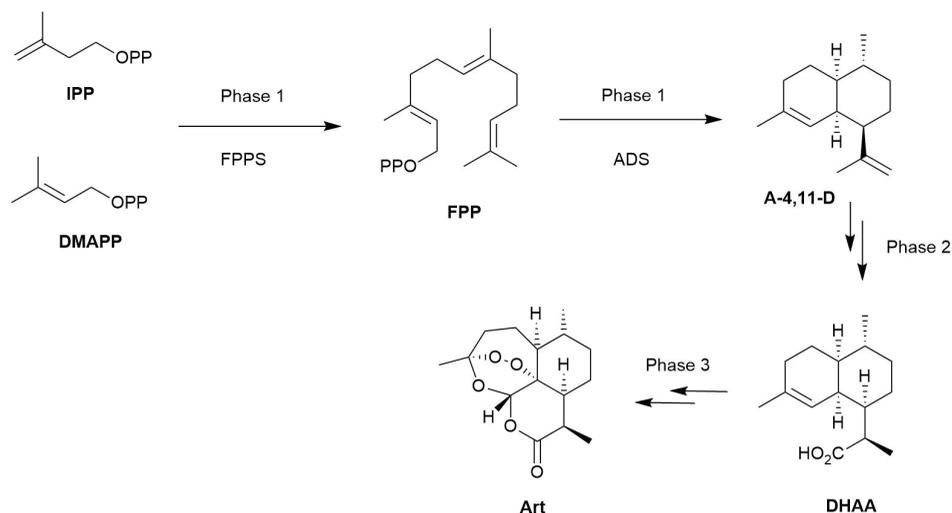
cycle. However, in recent years, a promising development towards a stable supply of the antimalarial drug has come from the emerging science of synthetic biology, in which artemisinin precursors are produced from simpler single-celled organisms in a fermentation process. As discussed below the effectiveness of synthetic biology as an alternative to the agricultural production of artemisinin is intimately linked to our understanding of its biosynthesis in *A. annua*, the natural source.

Biosynthesis

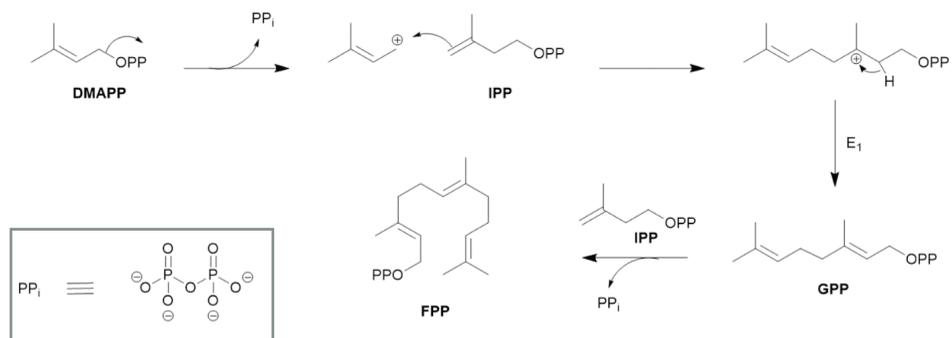
The biosynthesis of artemisinin (Art) in *A. annua* is typically considered in three phases, as shown in Scheme 2.

Phase 1: Biosynthesis of amorpha-4,11-diene (A-4,11-D)

Phase one of the biosynthesis was established first and is the best understood of the three phases. Most of the enzymes involved in phase one have been isolated and fully characterized directly from *A. annua*, providing evidence for their involvement in the proposed biosynthetic pathway. Artemisinin is sequestered in biserial glandular trichomes on the surface of the leaves of *A. annua* since it is highly autotoxic to the plant. Substantial evidence has now been presented to suggest that these enzymes are also located in the trichomes, which are the sites in which the majority of the biosynthesis takes place.^{5,6,11}



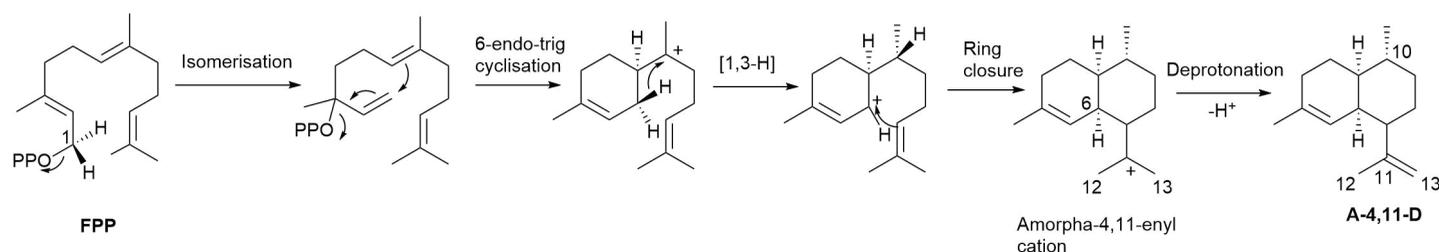
Scheme 2: The three phases in the biosynthesis of artemisinin.



Scheme 3: Stepwise chain extension of DMAPP to FPP by the enzyme FPPS.

Carbon-14 labelling experiments have proven that the hemiterpenoid (five-carbon) isopentenyl pyrophosphate (IPP) is one of the first biogenic precursors to artemisinin.¹² The enzyme farnesyl pyrophosphate synthase (FPPS) catalyzes the successive head-to-tail linkage of two units of IPP with its isomer, dimethylallyl pyrophosphate (DMAPP), in order to generate farnesyl pyrophosphate (FPP) via the intermediate geranyl pyrophosphate (GPP) (Scheme 3). This pseudo-oligomerization process is driven by the stability of the pyrophosphate (PP) leaving group. When the stable pyrophosphate moiety is expelled from DMAPP, an allylic carbocation is formed which is subsequently attacked by the double bond of IPP. This is followed by an E₁ elimination step which reforms the alkene. The same mechanism is then repeated with GPP as the substrate and a second unit of IPP. Both the hemiterpenoid precursors IPP and DMAPP are biosynthesized predominantly via the non-mevalonate (DXP) pathway in *A. annua*,³ although there is evidence for some cross-talk with the alternative mevalonate pathway.¹³

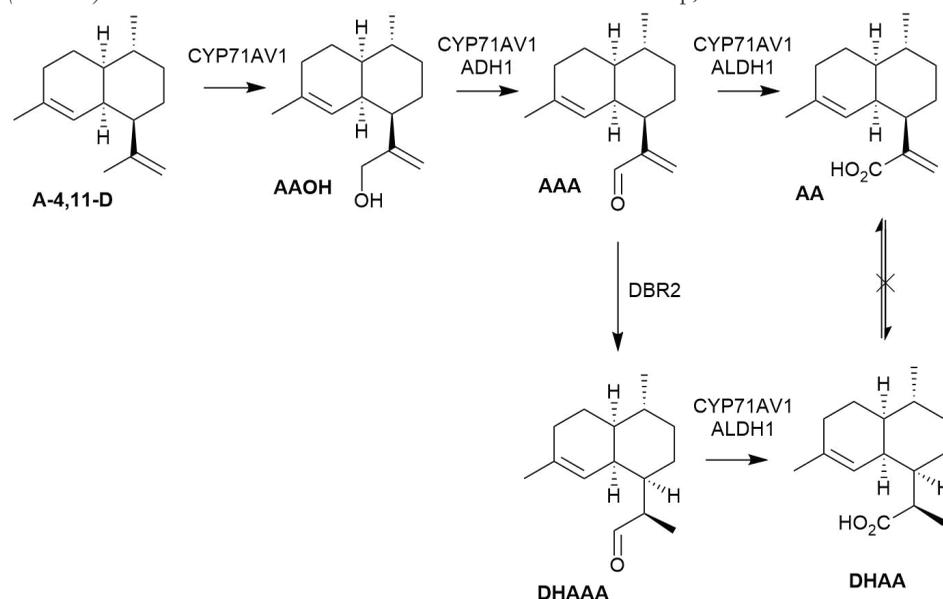
Next, FPP is cyclized to key intermedi-



Scheme 4: Mechanism of the ADS-catalyzed cyclisation of FPP to amorpha-4,11-diene (A-4,11-D).

ate amorpha-4,11-diene (A-4,11-D) by the enzyme amorphadiene synthase (ADS). Like FPPS, ADS is most highly expressed in the glandular secretory trichomes of *A. annua*.¹⁰ The mechanism of ADS catalysis was first demonstrated by the Kim group in 2006 from experiments using deuterium-labeled FPP. They showed that following isomerization of the pyrophosphate group in FPP, this group is lost in a concerted 6-endo-trig cyclization which generates a tertiary carbocation. H-1 of FPP then migrates to the 10-position of amorpha-4,11-diene (Scheme 4). It was possible to identify which of the two diastereotopic C-1 hydrogens underwent this 1,3-hydride shift [1,3-H] by using singly-labeled FPP.¹⁴ Thus, experiments using both enantiomers of singly-labeled [1-²H] FPP confirmed that while one hydrogen migrates to the 10-position of A-4,11-D, the other remains in its place as the H-6 of the amorpha-4,11-enyl cation.¹⁴ The final deprotonation step can occur either from C-12 or C-13 of the amorpha-4,11-enyl cation, resulting in the product, amorpha-4,11-diene (A-4,11-D).³

Phase 2: Biosynthesis of dihydroartemisinic acid (DHAA)



Scheme 5: Key intermediates in phase 2 of the conversion of A-4,11-D to AA or DHAA.

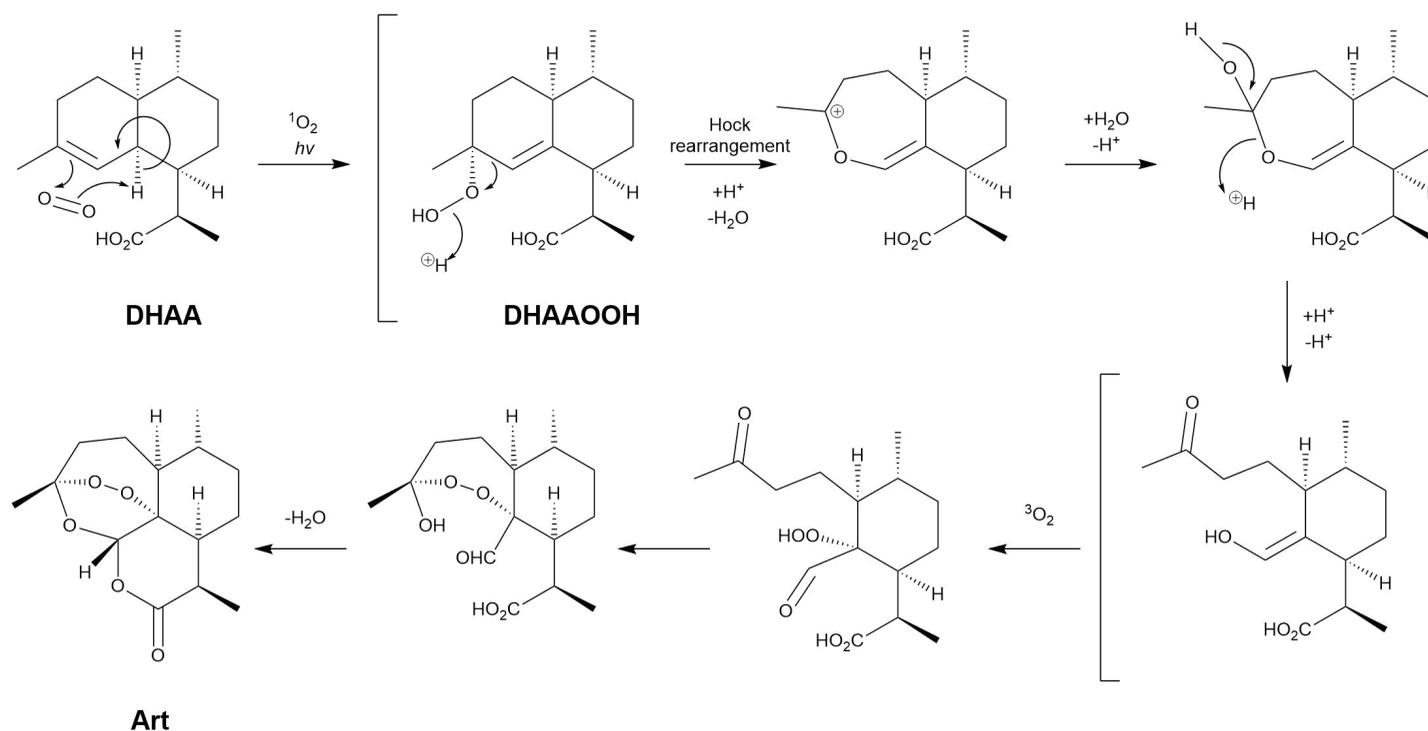
More recently it has become well-established that the oxidative transformation of A-4,11-D yields two alternative products — artemisinic acid (AA) and dihydroartemisinic acid (DHAA). Several of the steps that potentially feature in the conversion of amorpha-4,11-diene to AA and DHAA are inferable from natural products which have been isolated directly from the plant. Thus, the characterization of artemisinic alcohol (AAOH) and artemisinic aldehyde (AAA) from *A. annua* are both consistent with a biosynthetic pathway that involves the oxidation of the isopropylidene functionality in A-4,11-D, as shown in Scheme 5.

For many years AA was assumed to be the biogenic precursor to artemisinin in phase 3, though it is now thought to be a by-product of the biosynthesis, with DHAA as the true precursor. Significant evidence has now accumulated for the route to DHAA that is shown in Scheme 5, which involves two sequential oxidations of A-4,11-D at the C-12 position to AAA, followed by a reduction of the 11,13-double bond to dihydroartemisinic aldehyde (DHAAA). DHAAA is then oxidized once again at C-12 to form DHAA. The gene DBR2, which catalyzes the reduction step, has been demonstrated

to be highly expressed in the glandular secretory trichomes, which are the likely site of artemisinin production in *A. annua*.^{5,6,11} Recombinant DBR2 has also been demonstrated to be relatively specific for the reduction of AAA — for example, it is not capable of reducing the 11,13-double bond in some closely related natural products from *A. annua*, such as AA, AAOH, arteannuin B, and artemisitene.^{13,15} Although DBR2 exhibits activity towards a few small α,β -unsaturated carbonyl compounds (as would be expected for a member of the enoate reductase family of enzymes), it was shown to be unreactive to several others including coniferyl aldehyde, 2*E*-nonenal, and 12-oxophytodienoic acid.^{11,13} Similarly a cDNA for the cytochrome P450 enzyme CYP71AV1 has been shown to be capable of effecting all three of the oxidations of A-4,11-D featured in Scheme 5, in combination with a P450 reductase, and both have been demonstrated to increase artemisinin content in transgenic *A. annua* plants significantly.¹³ Most recently a cDNA encoding the aldehyde dehydrogenase homolog ALDH1, which is capable of facilitating the final oxidation of DHAAA, has also been characterized and demonstrated to be highly expressed in the trichomes.¹³

One of the reasons that AA has been discounted as a biogenic precursor to artemisinin over recent years has been the observation that there is little correlation between AA and artemisinin contents when comparing different transgenic *A. annua* strains.¹⁶ In contrast, levels of artemisinin are found to be positively correlated to levels of DHAA across a number of genotypes of *A. annua* (*i.e.* the more DHAA that is observed in a strain, the more artemisinin that strain is capable of producing).¹⁶ In addition there is also a direct negative correlation between DHAA and artemisinin content *within* any given strain (*i.e.* the less DHAA that is observed in any given specimen, the more artemisinin is present). This negative correlation is most readily rationalized by the assumption that DHAA can be converted to artemisinin and is one piece of evidence that DHAA is the biogenic precursor to artemisinin in the next phase of the biosynthesis.

Note, however, that AA and DHAA



Scheme 6: A possible mechanism for the spontaneous autoxidation of dihydroartemisinic acid to artemisinin.

contents are positively correlated to one another, as would be expected from their relationship in Scheme 5.

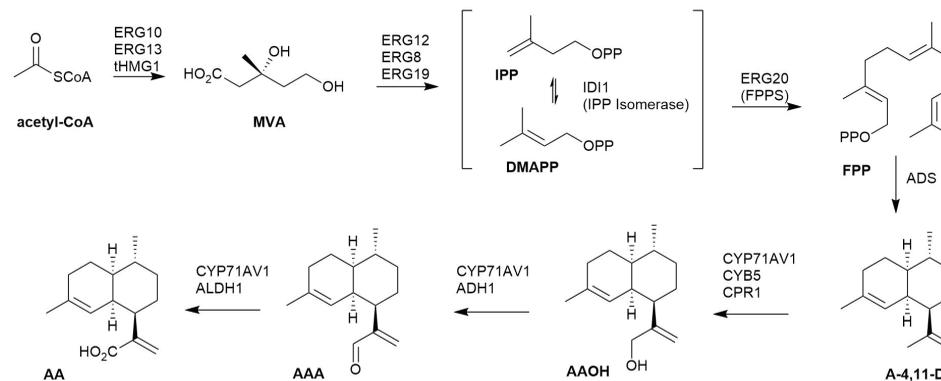
Phase 3: Biosynthesis of artemisinin (Art)

The third and final phase of artemisinin biosynthesis is the least understood, although there is some evidence to suggest that the third phase can proceed non-enzymatically in the plant.¹⁷ Under experimental conditions mimetic of chloroplasts, Wallaart *et al.* have proven that singlet oxygen ($^1\text{O}_2$) enhances yields of artemisinin, although chlorophyll is not necessary for the conversion, which is thought to take place in the trichomes.^{17,18} The proposed pathway involves photooxidation of DHAA by an ene-type mechanism to dihydroartemisinic acid hydroperoxide (DHAAOOH) (Scheme 6), which was identified in Wallaart's experiments, and is a known natural product from *A. annua*.^{18,19} Hock rearrangement of the allylic hydroperoxide generates an oxacyclic intermediate that is ring-opened to an enol.^{15,18} This then undergoes a second oxygenation by triplet oxygen ($^3\text{O}_2$) to generate a hydroperoxy-aldehyde, which is cyclized to the 1,2,4-trioxane system. The comparative ease by which DHAA can be converted to artemisinin *via* DHAAOOH *in vitro* provides circumstantial evidence for a non-enzymatic route for the third phase of natural production.¹⁹

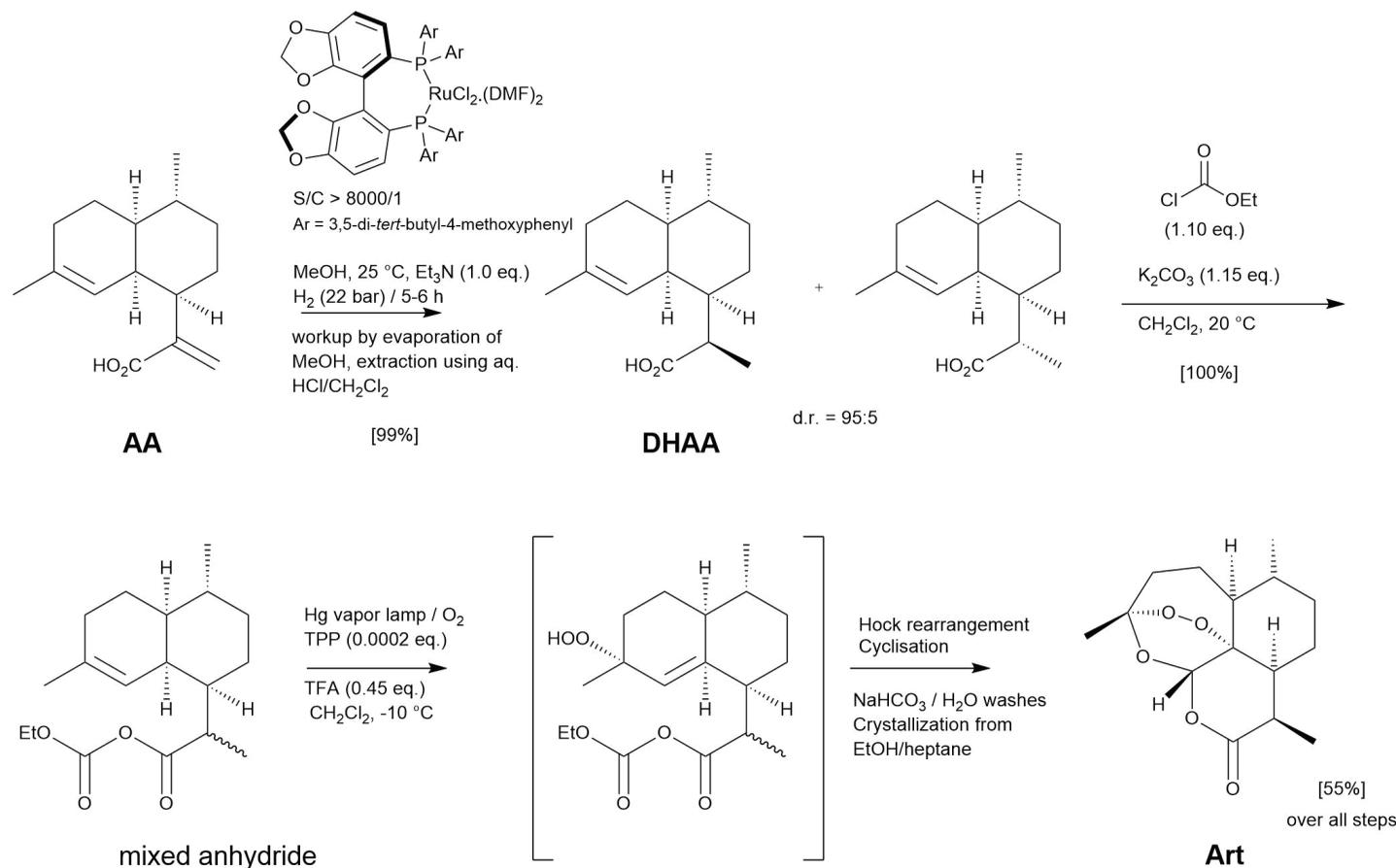
Synthetic biology

Synthetic biology is the genetic engineering of simple organisms to construct useful and exploitable biological systems. Recombinant DNA programming can be used to manipulate metabolic networks in order to transform a microbial host, such as *Saccharomyces cerevisiae* (yeast) or *Escherichia coli* (a bacterium), into a cheap "chemical factory" for the production of natural products.²⁰ Natural products are good targets for synthetic biology since their biosynthetic pathways have often been studied and documented in detail. Additionally, many natural products are expensive and available only in limited quantities from the natural source.

The mean concentration of artemisinin in dry *A. annua* leaves is typically less than 0.5%,²¹ although Swiss-developed transgenic strains have reached almost 2% dry-leaf artemisinin content.²² Direct metabolic engineering of the plant is therefore demonstrably feasible and, as such, offers the most convenient means for increasing yields of agriculturally-produced artemisinin, as well as providing potential routes to novel alternative sesquiterpenes.^{17,22} Synthetic biology, by contrast, holds out the promise of much higher yields of artemisinin, even though it is a technically more demanding approach that requires not only the transfer of relevant genes from the natural source to the micro-



Scheme 7: Conversion of acetyl-CoA to AA in *S. cerevisiae* - the genetically-engineered component of the industrial semi-synthesis of artemisinin



Scheme 8: Chemical transformations of AA to artemisinin (Art) in the chemical synthesis component of Sanofi's artemisinin semi-synthetic process.²⁹

bial host, but also the enhancement of gene expression in that host by the editing of gene promoters and terminators.^{23,24}

Promoters are sequences in DNA which influence the transcription of a gene by providing a binding site for RNA polymerase. Promoters thereby regulate the production of mRNA, thus controlling protein levels inside a cell.²⁴ Useful promoters are typically obtained by constructing libraries of synthetic promoters that cover a range of incrementally increasing activities, thereby permitting quantitative tuning of gene expression in bioengineering.²⁵

In 2003 Prof. Jay Keasling published the first landmark semi-synthesis of artemisinin using genetically engineered organisms (the term "semi-synthesis" emphasizes that his procedure incorporated elements of both synthetic biology and chemical synthesis). Capitalizing on the success of his small team at the University of California, Berkeley, Keasling then co-founded the biotechnology firm Amyris Inc. and began "The Semi-Synthetic Artemisinin Project," with the intent of delivering a new and cheap alternative source of the drug to stabilize worldwide

demand. The Project involved the bio-engineering of the microbial host *S. cerevisiae* to produce artemisinic acid (AA). *S. cerevisiae* was preferred as the host for the microbial biosynthesis of AA since the yield was greater than in *E. coli* (40 g/L as compared with 25 g/L) – ultimately, this was because the latter suffered from issues in the oxidation of A-4,11-D.²⁰

After mechanical recovery of AA from the yeast's cell wall, it was converted to artemisinin by chemical synthesis. In 2008 Amyris granted the recipe for their semi-synthetic procedures royalty-free to French pharmaceutical company Sanofi, in order to set up a large-scale production facility. In 2014, Sanofi was able to distribute over 1.7 million doses of microbially-derived ASAQ (an ACT) to six African countries, including Niger, Nigeria and Liberia.²⁶

The genetically-engineered component of the artemisinin semi-synthesis

In the industrial process it is the mevalonate pathway that is naturally present in yeast that provides the sole source of IPP and DMAPP. This pathway is fundamentally

different from the DXP pathway in *A. annua* and is named after the six-carbon intermediate (R)-mevalonic acid (MVA), which is biosynthesized from acetyl-CoA by three enzymes (ERG10, ERG3, tHMG1), and is then decarboxylated to the hemiterpenes IPP and DMAPP by ERG12, ERG8 and ERG19 (Scheme 7). All these ERG genes (as well as IDI1 and tHMG1 in Scheme 7), code for enzymes in the ergosterol biosynthetic pathway (ergosterol is an essential steroidal component of fungal membranes).²⁰ It is also possible to transfer the genes encoding the "natural" *A. annua* DXP pathway for isoprenoid synthases – indeed, these have been successfully over-expressed in *E. coli* in order to accelerate isoprenoid synthesis in this microbial host.

Next, FPP is bio-synthesized from IPP and DMAPP by ERG20 (farnesyl pyrophosphate synthase, catalyzing the same reaction as in *A. annua* — see Schemes 2 and 3). All the genes used in the industrial process in yeast subsequent to FPP synthesis are derived from *A. annua*. Thus FPP is cyclized to amorphadiene (A-4,11-D) by ADS (see Schemes 2 and 4) and A-4,11-D undergoes

three successive oxidations by CYP71AV1 derived from *A. annua* (as in Scheme 5). These oxidations are facilitated by CYB5 and CPR1, which significantly boost the yield of microbial artemisinic acid (AA),²⁷ as in the plant. Amyris have also reported that the over-expression of genes encoding ERG20 biosynthesis doubles AA yields in *S. cerevisiae*.²⁸

The chemical synthesis component of the artemisinin semi-synthesis

The chemical processing that is required for the conversion of microbial AA to artemisinin involves two steps: an initial reduction of the 11,13-double bond in AA to form DHAA, followed by introduction of the 1,2,4-trioxane ring. In the industrial process the challenging diastereoselective hydrogenation of AA to DHAA has been optimized using a chiral ruthenium catalyst under H₂ at a pressure of 22 bar, to afford 95% selectivity for the natural product (Scheme 8). The photo-catalyzed second step proceeds by the same complex mechanism that is thought to occur non-enzymatically in *A. annua*, as is shown in Scheme 6. However the industrial oxidation reaction is performed in dichloromethane using tetraphenylporphyrin (TPP) as a sensitizer for the photochemical conversion of ³O₂ to ¹O₂, rather than in the lipophilic environment of a trichome. In addition the natural intermediate DHAAOOH was found to be too unstable for the industrial one-pot process. It was discovered that prior derivatization of DHAA to a mixed anhydride facilitated a cleaner conversion to the requisite transient allylic hydroperoxide, with no hazardous accumulation of this intermediate in the complex reaction cascade required for the subsequent oxidation that forms the 1,2,4-trioxane ring (Scheme 8).²⁹

It is worth noting that even though the current method of chemical synthesis affords a 55% overall yield (which represents a considerable improvement on 19% for the original synthetic conversion of AA to artemisinin),²⁹ the complicated chemical steps that are shown in Scheme 8 still account for most of the production costs of semi-synthetic artemisinin.³⁰ As a result optimization of the chemical steps of the Sanofi semi-synthesis is the most studied approach to improving industrial artemisinin yields.

Current approaches to improving industrial artemisinin production

Recently a greener method using liquid CO₂ solvent has been presented as an alternative to the above photooxidation — however, it is lower yielding and thus more expensive.^{30,31} It could be argued that, in the case of artemisinin, decreasing the cost of treatments is more important than environ-

mental considerations.

Despite the expected safety issues Sanofi developed a diimide-based reduction as a metal-free alternative to the catalytic hydrogenation shown in Scheme 8. This approach used the reaction of oxygen and hydrazine monohydrate to generate diimide *in situ*, which effected the desired reduction of AA to DHAA in >90% yield with excellent diastereoselectivity (d.r. ≥ 97:3).³² This method was successful on the kilogram scale and presents a viable alternative to the traditional catalytic hydrogenation.³²

The Seeberger group developed a continuous-flow method as an alternative to the Sanofi photooxidation of DHAA.³³ One of the greatest limitations of large-scale photochemistry is that light can only penetrate a short distance through a solution before it is absorbed by a photosensitizer; thus the use of large vessels results in reduced conversion rates. Seeberger's flow system circumvented this limitation to photochemical generation of ¹O₂ by wrapping a tube around a lamp to maximize light absorbance. In addition to the usual benefits granted by the use of flow chemistry (such as good control over reaction parameters, easy scale-up and safety) Seeberger's method allowed the conversion of DHAA to artemisinin in a continuous process requiring no isolation or purification of intermediates.³³ Improvements on the original continuous-flow setup resulted in a system capable of producing 165 g of artemisinin per day.³⁴ Unfortunately this process may not be commercially viable due to the yield and the requirement for chromatographic purification of the product.³¹

Very recently a novel semi-synthesis of artemisinin was published which uses A-4,11-D as the chemical precursor.³¹ A-4,11-D is formed earlier than AA in the bioengineered pathway and in twice the molar yield;³¹ thus chemical synthesis of artemisinin from A-4,11-D presents a promising alternative to the currently practiced semi-synthesis. A cost-effective semi-synthetic route was devised which could produce artemisinin from A-4,11-D in 6 steps in 60% yield. It was predicted that this novel approach could reduce global artemisinin costs from 200 USD/kg (2016) to around 100 USD/kg.³¹

Conclusion

It can be argued that the development of the industrial process reflects the progress that has been made in our understanding of the three phases of the biosynthesis of artemisinin. Thus the genetically-engineered component of the synthetic biology approach to artemisinin has benefitted greatly from our discoveries regarding phases 1 and 2 of its biosynthesis. By contrast there is still much uncertainty in our understanding of

the details of phase three of the biosynthesis; this finds a parallel in the requirement for a chemical synthesis component the industrial process (in particular, the chemical step that mimics the mechanism of the spontaneous autoxidation described in the plant). As a result, although microbially-sourced artemisinin is now providing a viable alternative source of this drug that is already supporting the improving worldwide supply of ACT treatments, it is no cheaper than agriculturally-produced artemisinin. This may change in the future as improvements in our understanding of the natural biochemistry continue to inform the development of key steps in the industrial process.

One obvious prediction is that we should expect to see a continuation of research into the transfer of DBR2 and ALDH1, the two most recently discovered genes from phase 2 of the biosynthesis in *A. annua* (Scheme 5), to a microbial host. This is expected to be a fruitful line of enquiry because the successful expression of DBR2 and ALDH1 in *S. cerevisiae* could result in a genetically-engineered component of the industrial process that produces DHAA rather than AA. This should, in turn, lead to a substantial reduction in the cost of industrial artemisinin production because it would obviate the need for the first (reductive) step in the chemical synthesis component of the process. (As shown in Scheme 8, this is one of two obligatory chemical steps for the chemical conversion of artemisinic acid to artemisinin, both of which are low-yielding and expensive in comparison with the genetically-engineered component). In contrast semi-synthesis from the earlier biogenic precursor A-4,11-D could present a cost-effective alternative to the current industrial process.

Looking further into the future it may also be possible that a better understanding of phase 3 of the natural biosynthesis in *A. annua* could inspire a more fundamental revolution in the industrial production of artemisinin. If it were discovered that an enzyme exists which can catalyze phase 3 of the biosynthesis (in addition to the spontaneous autoxidation pathway that has already been described), the industrial synthesis may be developed to eliminate the need for the expensive chemical conversion of DHAA. This might be a specific protein from *A. annua* that is capable of converting DHAA to artemisinin, or, alternatively, a family of oxidases from some other species that fulfils this same function. Much effort would surely then follow in the attempt to transfer the gene(s) for this enzyme to a microbial host. If this were achieved, in combination with the transfer of genes for DBR2 and ALDH1 that is currently in progress, then it could one day become possible to express the

entire biosynthetic pathway to artemisinin in a microorganism. This would be a great triumph for synthetic biology: an industrial process that is based solely on genetic engineering - inevitably greener than the current process and certainly cheaper than agricultural methods - making artemisinin more accessible than ever.

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