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Semisynthetic Artemisinin, the Chemical Path to Industrial Production

Joël Turconi,*[,†] Frédéric Griolet,[†] Ronan Guevel,[‡] Gilles Oddon,[§] Roberto Villa,[∥] Andrea Geatti,[∥] Massimo Hvala,[∥] Kai Rossen,[⊥] Rudolf Göller,[⊥] and Andreas Burgard*[,⊥]

[†]Sanofi, Sisteron Plant, 45 chemin de Météline, B.P. 15 Sisteron, France

[‡]Sanofi, Pasteur Campus, Merieux -1541, Avenue Marcel Merieux - 69280 Marcy L'Etoile, France

[§]Sanofi Chimie, 31-33 quai Armand Barbès, 69583 Neuville-sur-Saône cedex, France

[∥]Miglioram Processi, Sanofi-Aventis, Via Roberto Lepetit, 142, 12075 Garessio (CN), Italy

[⊥]Chemistry and Biotechnology Development, Frankfurt Chemistry, Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, Building G 838, 65926 Frankfurt am Main, Germany

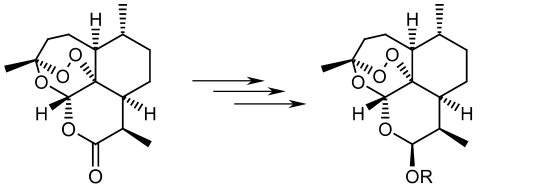
ABSTRACT: A new commercial-scale alternative manufacturing process to produce a complementary source of artemisinin to supplement the plant-derived supply is described by conversion of biosynthetic artemisinic acid into semisynthetic artemisinin using diastereoselective hydrogenation and photooxidation as pivotal steps. This process was accepted by Prequalification of Medicines Programme (PQP) in 2013 as a first source of nonplant-derived-artemisinin in industrial scale from Sanofi production facility in Garessio, Italy.

1. INTRODUCTION

Malaria is a disease that affects millions of people, mostly in tropical and subtropical regions. The human and economic toll is devastating, e.g. an estimated 300 million children are infected every year, with often debilitating effects.[1]

A global effort is under way to fight malaria using preventative measures and through vaccine development, but also through the provision of cost-efficient treatment options. Artemisinin and its derivatives (dihydroartemisinin, artemether, artesunate) are essential to modern malaria therapy, thus requiring an efficient access to these compounds (Scheme 1).

Scheme 1. Artemisinin and its derivatives



Artemisinin

R = H, Dihydroartemisinin
R = Methyl, Artemether
R = Succinate, Artesunate

Guided by the knowledge of traditional medicine, artemisinin was discovered, identified, and brought to the patient by Chinese scientists at the beginning of the 1970s. Artemisinin is found in the plant *Artemisia annua*, which contains highly variable amounts in its leaves. Until recently, extraction provided the only efficient access to artemisinin, which resulted in large price fluctuations and therefore an unstable supply.[2]

A major break-through was the discovery by Keasling of a biosynthetic pathway for the preparation of artemisinic acid (AA), an advanced precursor of artemisinin, in yeast.[3] On the basis of the fundamental work of Acton, Roth[4] and Brown, et al.[5] the company Amyris managed to convert artemisinic acid (AA) into artemisinin, and this laboratory synthesis gave for the first time hope and guidance for a viable industrial process that would allow the large-scale preparation of artemisinin independent from the extractive process. The work of Keasling and Amyris has recently been described[6] (Scheme 2), and we will now detail the efforts undertaken at Sanofi in the years 2008−2013 to turn these initial results into a fully implemented industrial process that is resulting in 35 t of artemisinin in 2013, increasing to 60 tons in 2014. This development work has been supported by the Bill and Melinda Gates Foundation with the goal of leading to a consistent source of artemisinin using a "no profit, no loss" cost model for Sanofi. The implementation of this process successfully addressed environmental, cost, safety, quality, and regulatory aspects, both for the scale-up of the fermentation of artemisinic acid (AA) and for its subsequent conversion to artemisinin. The fermentation will be detailed in a separate publication; this paper will focus on the steps necessary to convert artemisinic acid (AA) to artemisinin, i.e. the development of a homogeneously catalyzed highly diastereoselective hydrogenation, a photochemical singlet oxygenation, and a subsequent complex rearrangement—clearly all serious challenges, especially keeping in mind that artemisinin is a peroxide requiring a careful attention to safety on scale. The synthetic sequence towards artemisinin as implemented by Sanofi is thus an excellent example of combining synthetic biology, homogeneous catalysis, and photochemistry to achieve an efficient, large-scale access to an important drug for a price that is at least competitive with a simple extraction from the plant. Bearing major breakthroughs

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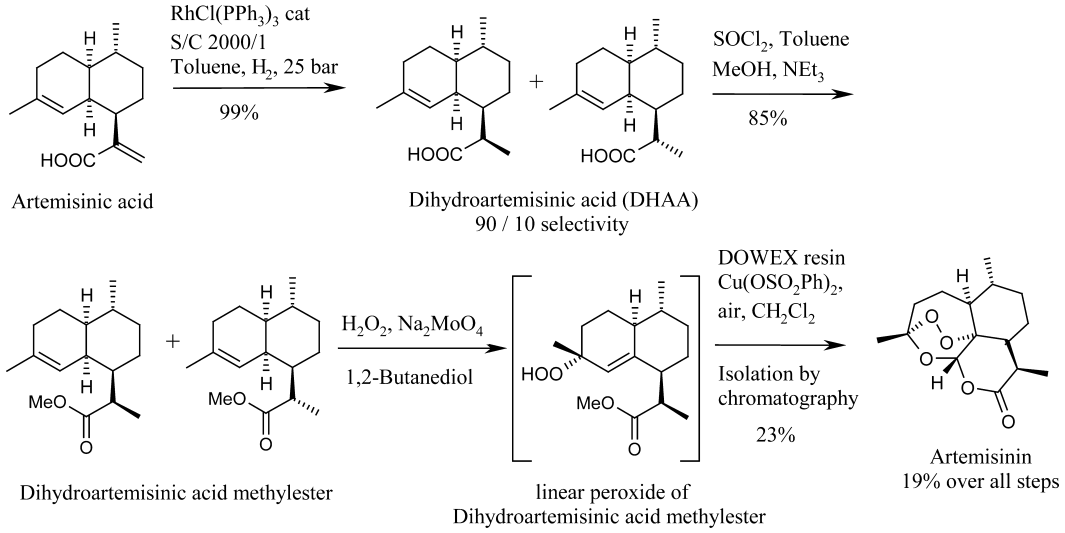
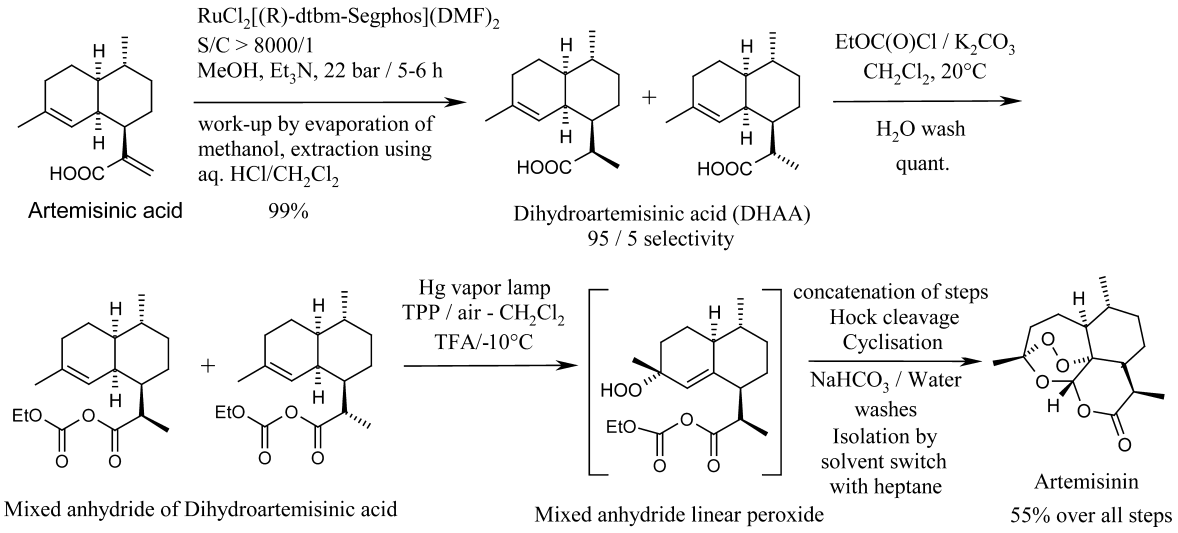
Scheme 2. Initial chemistry path by Amyris



Scheme 3. New generation process by Sanofi



in synthetic methodology, we are confident that this hybrid approach is far superior to a total synthesis and none of the many total syntheses published[7−12] appear to even approach providing a basis for a potentially viable process. The synthetic sequence applied by Sanofi[13,14] follows a strategy that is closely related to the mechanism used by the *Artemisia annua* plant and is summarized in Scheme 3.

Interestingly, the Seeberger group[15] recently described a useful extension of this chemistry by performing the photooxidation step in a full flow system, rather than in the semibatch process that Sanofi implemented in the factory. The inherent advantages of using flow chemistry, especially as applied to photochemical reactions, are highlighted by other Seeberger publications,[16−19] pointing to potential future improvements.

2. DIASTEREOSELECTIVE HYDROGENATION

The first challenge is the diastereoselective hydrogenation of the acrylate system of artemisinic acid (AA) to dihydroartemisinic acid (DHAA). While it was known that this could be achieved using, e.g., Ni borohydride in very moderate diastereoselectivity (3:2), the use of Wilkinson catalyst was described by Amyris[6] as giving a near quantitative conversion with surprisingly high 90:10 diastereoselectivity for the desired stereochemistry. Combining the inherent diastereoselectivity of artemisinic acid (AA) with an appropriately matched chiral hydrogenation catalyst should allow for better selectivity. In addition, the high loading required for the Wilkinson catalyst and the high cost of Rh makes its use impractical for any industrial production. Indeed, a comprehensive screen of catalysts and ligands performed at Takasago for Sanofi provided the $RuCl_2[(R)\text{-DTBM-Segphos}](DMF)_n$ catalyst.[20] At 22 bar H_2 a 95:5 selectivity is obtained, and even S/C levels of 8.000 give complete hydrogenation in a few hours. S/C levels of 16.000 are also successfully feasible but take more time (Scheme 3). It is notable that a Ru phanephos catalyst performs essentially identically, but none of the catalysts or systems screened led to perfect diastereoselectivity. We recently published in the literature a paper about a remarkably diastereoselective hydrogenation of artemisinic acid (AA) with diimide, which resulted in diastereoselctivities ≥97:3 and excellent yields of >90% (including the crystallization, isolation, and drying step). The implementation of this hydrogenation on

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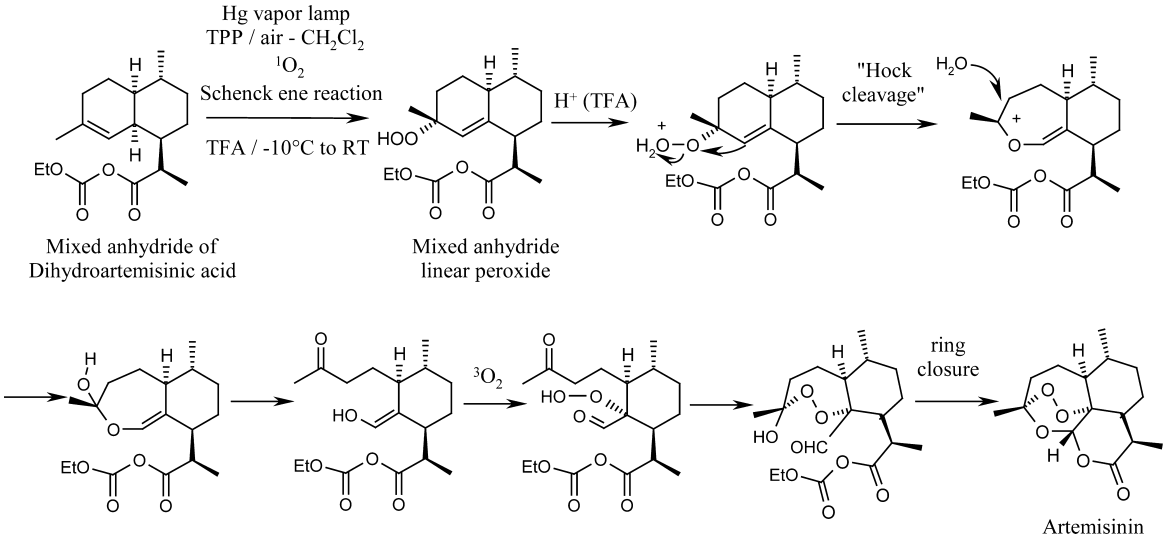
Scheme 4. New-generation process by Sanofi: proposed photooxidation mechanism



scale achieved the hydrogenation by using air and hydrazine hydrate in an alcoholic solvent.[21−23]

3. PHOTOOXIDATION TO ARTEMISININ

With dihydroartemisinic acid (DHAA) available, the subsequent conversion of dihydroartemisinic acid (DHAA) to artemisinin involves complex oxidation/rearrangements. Mechanistically, it is assumed that a regioselective Schenck ene reaction between singlet oxygen and the double bond takes place, followed by a Hock cleavage and a subsequent oxygenation and cyclization. This mechanistic sequence had been proposed and supported with experimental evidence by Brown[5] and is also assumed to be the mechanism taking place in *Artemisia annua*. In view of the complexity of the transformations it is not surprising that numerous impurities can and do arise. Initially, we followed the lead set by Amyris and obtained the singlet oxygen in the Aubry decomposition of H_2O_2 with molybdates[24] and induced the subsequent Hock cleavage with copper sulfonate salts. Gratifyingly, a yield as high as 41% could be obtained for the complex sequence when solvents and reaction conditions were carefully controlled. However, all attempts to improve this yield failed, despite significant efforts invested into the isolation and elucidation of reaction impurities to allow a better understanding of the reaction.

The utility of the Aubry reaction allows the generation of singlet oxygen, and thus the Schenck ene reaction, while avoiding the need for photochemical equipment. While in principle highly attractive, photochemical reactions are rarely practiced in industry[25] and there is even less precedence for the large-scale application of the Schenck ene reaction with photochemically generated singlet oxygen. This is easily understood, as the hurdles to the implementation of a large-scale Schenck ene reaction are significant. Apart from the lack of experience and equipment, the choice of permissible solvents is very limited, the resulting products are inherently unsafe hydroperoxides, and the chemical engineering aspects such as mixing, gas transfer, and light transmission are unusually complex on scale. In the case of the synthesis of artemisinin, the situation is even more complex as the Schenck ene reaction is just the beginning of a complex reaction cascade that requires several subsequent chemical steps (Hock cleavage, additional oxygenation, ring closure) as illustrated in Scheme 4.

Fully cognizant of the issues, we decided to perform the Schenck ene reaction in methylene chloride using tetraphenylporphyrin (TPP) as a sensitizer. The choice of these classical reaction conditions is dictated by safety concerns (nonhalogenated solvents are not compatible with the oxygenation conditions) and implies significant capital investment to ensure the complete containment and recycling of methylene chloride. With these constraints, the use of methylene chloride is environmentally acceptable. Tetraphenylporphyrin (TPP) is not only readily available but also a highly efficient sensitizer for the photochemical conversion of triplet oxygen to singlet oxygen.

An additional constraint for devising a reaction sequence was discovered when we examined the safety data for the initially formed Schenck ene hydroperoxide. An exothermal decomposition of the hydroperoxide of dihydroartemisinic acid at +15 °C ruled out any sequence that led to a significant accumulation of this compound, particularly in the consideration that metallic surfaces in the production equipment could accelerate the decomposition of hydroperoxides. Consequently, the only viable option to obtain the desired sequence would have to implement a one-pot sequence from dihydroartemisinic acid (DHAA), or a derivative thereof, to artemisinin, comprising at least four distinct chemical steps. We examined dihydroartemisinic acid (DHAA) and several derivatives of dihydroartemisinic acid (DHAA) in this direct conversion, using TFA as an acid. A reasonable working hypothesis as to the mechanism of the final closure to the tricyclic system of artemisinin led us to propose the use of activated esters (mixed anhydride) accomplished by ethyl chloroformate/potassium carbonate in the hope that these would facilitate the final ring closure. The use of readily available mixed anhydrides leads to a much cleaner and improved reaction, resulting in a highly satisfactory *overall yield* of 55% *isolated* artemisinin from the starting material artemisinic acid (AA) (i.e., comprising the diastereoselective hydrogenation, the formation of the mixed anhydride, and the final photochemical reaction sequence, including the final isolation of artemisinin as a pure, crystalline compound) as depicted in Scheme 3.

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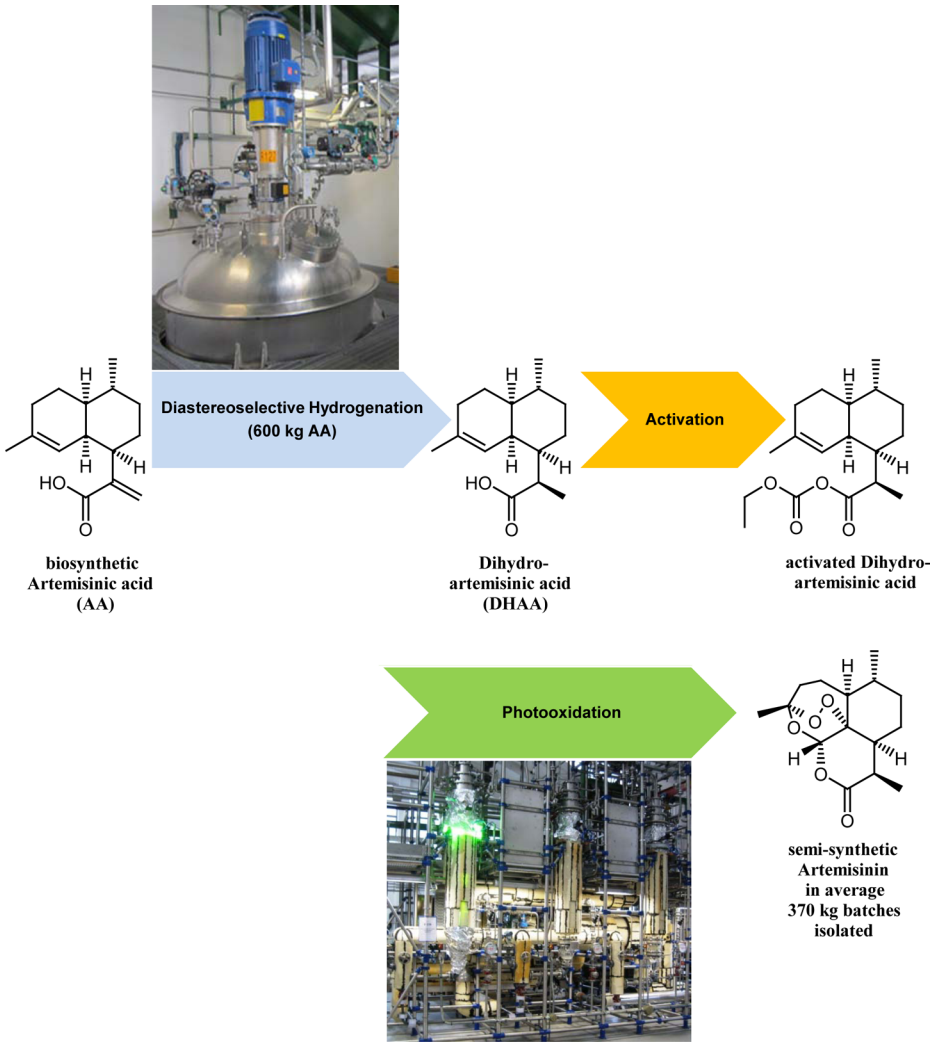
Scheme 5. Manufacturing of semisynthetic artemisinin in production scale



On the basis of these results, a dedicated pilot unit was set up at Sanofi facility, Neuville (France). We selected a semibatch mode concept with a recirculation loop, which is possible as artemisinin is very stable under the reaction conditions and it offers optimal conditions versus energy consumption and the transformation rate. In addition to the other chemical engineering challenges, critical parameters included construction materials that minimize the loss of light (optimizing the quantum photonic yield) and the choice of a lamp with the optimal spectral distribution of emitted spectrum (medium-pressure mercury/gallium lamp). The unit must also ensure a good turbulence of the recirculating fluid and allow a good gas−liquid transfer, while maintaining the internal temperature at −10 °C.

A significant effort was dedicated to finding conditions that allowed a safe and reliable isolation of crystalline artemisinin from this reaction mixture; artemisinin is a peroxide with a DSC onset temperature of 160 °C and a release of 840 J/g. To this end, the reaction mixture has to be washed several times to remove the TFA, using aq sodium bicarbonate, and filtered over a specific absorbent to remove traces of tetraphenylporphyrin (TPP). This treatment is mandatory as a safe solvent switch to heptane for the isolation of crystalline artemisinin is not trivial, and the development and implementation of a reliably safe and reproducible isolation procedure is challenging for such a compound. Nevertheless, we managed to define a safe operating range for the isolation and set up a strict safety management process for the operation on scale. The first pilot batch was successful at 50-kg scale in 2011 in Neuville (filter dryer and centrifuge technologies).

4. INDUSTRIALIZATION

Of obvious critical importance is the compliance of the isolated material with the required purity specifications. Prequalification of Medicines Programme (PQP) announced the acceptability of the first source of nonplant-derived-artemisinin, manufactured by Sanofi, for use in manufacture of API submitted to WHO in May 2013.[26]

The ultimate goal of all process development activities is the implementation of laboratory and pilot-plant results into commercial equipment. Indeed, guided by the results from the Neuville pilot plant, the investment into large-scale equipment was undertaken at the Sanofi facility in Garessio, Italy. The equipment and process were validated by 2012 and is producing commercial quantities of artemisinin since 2013, with 35 tons expected for 2013, ramping up to 60 tons in 2014 (batch size is on average 370 kg isolated artemisinin). On the basis of the work described in part above, the material meets

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the quality and purity requirements for a drug and is being used to make drug product (Scheme 5).

5. CONCLUSION

In summary, we can report the successful completion of a long story: the sole reliance on artemisinin isolated from the plant *Artemisia annua* can be supplemented by a reliable and plannable supply chain that uses a combination of synthetic biology, sophisticated homogeneous catalysis and complex photochemistry to produce industrial quantities of an important drug.

6. EXPERIMENTAL SECTION

Step 1: Hydrogenation of Artemisinic Acid to Dihydroartemisinic Acid (DHAA). Artemisinic acid (600 kg) was dissolved in 1200 kg methanol; 259 kg triethylamine and 480 g ruthenium-Segphos catalyst were added. The homogeneous mixture was hydrogenated using 22 bar at 25 °C to yield dihydroartemisinic acid as triethylammonium salt dissolved in methanol. The hydrogenation was monitored by HPLC. Dihydroartemisinic acid (DHAA) triethylammonium salt solution was distilled under vacuum to remove methanol before 2000 kg dichloromethane were added. Water (1800 kg) was added to the dichloromethane solution of DHAA, and with 270 kg conc. hydrochloric acid, the pH of the aqueous phase was adjusted until pH was 1−2. After phases were separated, the organic phase was washed a second time with 2000 kg water. The combined organic phases were treated with 30 kg silica gel in order to remove ruthenium traces and were filtered and directly used in the next step. The dihydroartemisinic acid (DHAA) was not isolated before the next step.

Step 2: Activation of Dihydroartemisinic Acid (DHAA) with Ethylchloroformate to Mixed Anhydride (DHAEMC). Potassium carbonate (410 kg) was added to the dichloromethane solution of dihydroartemisinic acid before 306 kg ethylchloroformate was introduced to perform the reaction at 20−30 °C to mixed anhydride (DHAEMC). The reaction was monitored by HPLC. As soon as the reaction was accomplished, 2230 kg water was added. After phase separation, the organic phase was cooled at about −10 °C to remove residual water as ice in the organic phase before the subsequent photooxidation.

Step 3: Photooxidation of Mixed Anhydride (DHAEMC) to Artemisinin. To the solution of DHAEMC were added 2570 kg dichloromethane and 300 g tetraphenylporphyrin (TPP) before the solution was exposed to light irradiation using photoreactors containing mercury vapour lamps and ambient air bubbling at about −10 to −15 °C. In the beginning of the irradiation 132 kg trifluoroacetic acid was added to the reaction mixture. The reaction was monitored by HPLC. As soon as the reaction was completed, the solution was treated twice with 720 L aqueous solution of sodium bicarbonate and was subsequently washed with 1440 kg water. The washed organic phase was treated with 30 kg activated charcoal and filtered. Before the crystallisation step, the ADT_{24h} of the reaction mixture was checked.

Step 4: Crystallization of Artemisinin. By the organic solution of artemisinin coming from the photooxidation, dichloromethane was partially removed by distillation under vacuum, while 2700 kg *n*-heptane was added in order to maintain a constant volume in the reactor. During the solvent switch artemisinin was crystallized. The *n*-heptane suspension of artemisinin was added with 180 kg ethanol, and then it was cooled at about 20 °C to accomplish the crystallization. The wet product was isolated by centrifugation, and washed twice with 1200 kg mixture of *n*-heptane/ethanol. The artemisinin was dried under reduced pressure at a temperature not exceeding 36 °C. About 370 kg of artemisinin as crystalline white powder was typically obtained for a batch size of 600 kg of artemisinic acid.

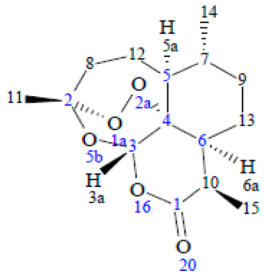
Analytical Data of Semisynthetic Artemisinin. Optical Rotation: $[\alpha]^{20}_{D}$ = +74−78 [10 mg/mL in ethanol].

The melting point of the crystalline artemisinin was found to be about 159 °C.

The theoretical mass of $[M + H]^+$ is 283.1545 amu. The high-resolution mass spectrum shows the $[M + H]^+$ at m/z = 283.1557 amu. This measured mass is consistent with the $[M + H]^+$ formula $C_{15}H_{22}O_5$ within an deviation of 4.2 ppm. (amu: atomic mass unit)

Data acquisition of all NMR spectra was achieved using a spectrometer operating at a proton resonance frequency of 600 MHz and a carbon 13 resonance frequency of 150 MHz (see Table 1). The NMR spectra were recorded using a solution in deuterated dimethyl sulfoxide (DMSO-d_6). Calibration was performed using the residual solvent signal.

Table 1. NMR spectral data



assignment	^{13}C [ppm]	C-type	^{1}H [ppm][a]	mh[b]
1	171.34	C=O	–	–
2	104.62	C-quat.	–	–
3	93.20	CH	6.11	singlet
4	79.48	C-quat.	–	–
5	49.43	CH	1.34	multiplet
6	43.85	CH	1.79	dt
7	36.02	CH	1.54	multiplet
8	35.42	CH_2	2.28, 2.06	multiplet
9	33.07	CH_2	1.65	multiplet
10	32.44	CH	3.17	multiplet
11	24.85	CH_3	1.36	singulet
12	24.28	CH_2	1.34, 1.94	multiplet
13	22.36	CH_2	1.15, 1.73	dq
14	19.46	CH_3	0.93	doublet
15	12.30	CH_3	1.08	doublet

[a]Proton chemical shifts are given in approximations. [b]The proton multiplicities are annotated according to their obvious appearance in the spectrum.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: Andreas.Burgard@sanofi.com

*E-mail: Joel.Turconi@sanofi.com

Notes

The authors declare no competing financial interest.

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