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Photochemical Hydrothiolation of Amorphadiene and Formal Synthesis of Artemisinin via a Pummerer Rearrangement

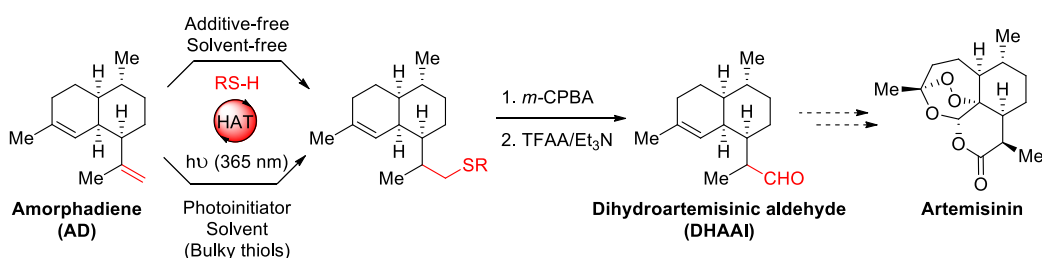
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Supporting Information Placeholder



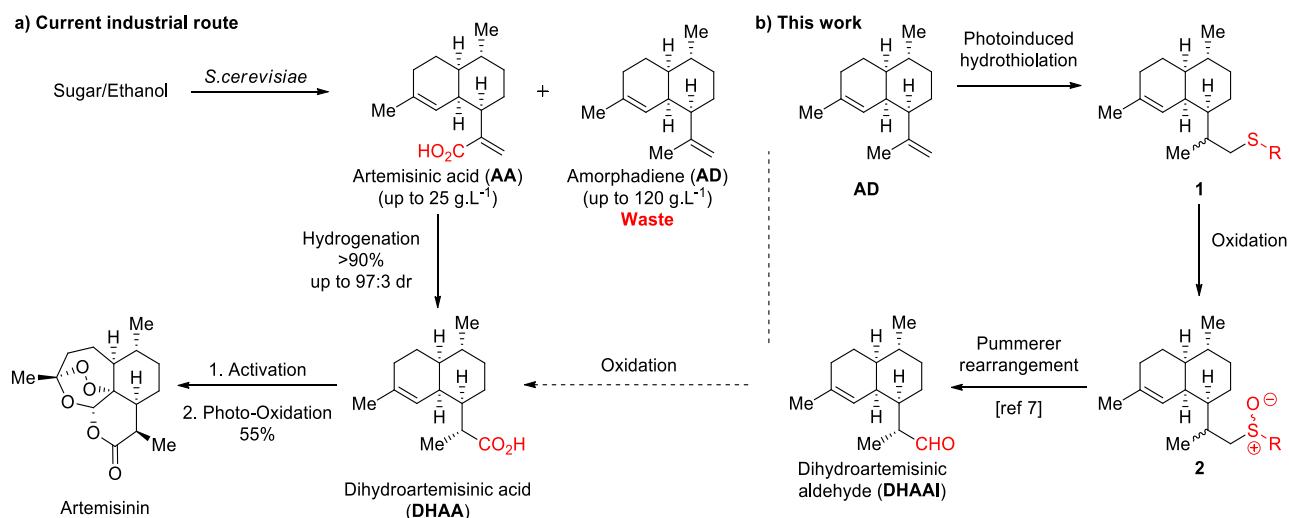
ABSTRACT: A new access to artemisinin is reported based on a selective photochemical hydrothiolation of amorphadiene, a waste product of the industrial semi-synthetic route. This study highlights the discovery of two distinctive activation pathways, under solvent-free conditions or using a photocatalyst promoting H-abstraction. Subsequently, a chemoselective oxidation of the resulting photochemically generated thio-ether, followed by a Pummerer rearrangement afford dihydroartemisinic aldehyde, a key intermediate in the synthesis of artemisinin.

The development of new cost-competitive manufacturing routes to the antimalarial drug artemisinin represents a major strategy to fight malaria.¹ Plant extraction has long been the only commercial source, but the increase in global demand has raised the need for alternative production methods.² This challenge has fueled impressive developments in synthetic biology and organic chemistry which have led to a new large-scale semi-synthesis where the key metabolic intermediate, artemisinic acid, is obtained by fermentation using bioengineered yeasts (*Saccharomyces cerevisiae*), and is then transformed into artemisinin by means of synthetic chemistry (Scheme 1a).²⁻³

Artemisinic acid (AA) is obtained at around 25 g/L and is then converted into dihydroartemisinic acid (DHAA) by a quantitative and diastereoselective hydrogenation utilizing a transition metal chiral catalyst.^{2a} DHAA is then transformed into artemisinin in a complex reaction cascade initiated by a photooxidation process involving singlet oxygen.^{2a,4} These developments have successfully complemented plant extraction, but have failed to provide a cheaper access to artemisinin (Scheme 1a). In this context, a critical look at the cost determining issues of the current semi-synthesis of artemisinin is key to understand which variables need to be addressed to provide a genuinely low-

cost access to this antimalarial drug. This goal could be achieved by performing chemical transformations on a considerably cheaper and less advanced fermentation intermediate than AA. Part of this solution relies on the valorization of amorphadiene (AD), a high yielding fermentation intermediate treated as a waste in the current semi-synthetic production and likely to be available at very high titers (up to 120 g/L) and on industrial scale.⁵ To date, the conversion of AD to DHAA has been reported either using hydroboration,^{5b,6a} hydrosilylation,^{6b} epoxidation^{5a} or allylic chlorination.^{6c} However, these procedures feature important drawbacks such as the use of costly catalysts or reagents, or involve protection/deprotection steps of the internal double bond.

Scheme 1: Current semi-synthesis of artemisinin and proposed semi-synthetic route to dihydroartemisinic aldehyde (**DHAAI**) from amorphaadiene (**AD**).



Herein, we report our preliminary developments of a metal-free and protecting group-free approach which relies on the use of very low cost reagents. This approach implies a three-step sequence involving a key regioselective photochemical hydrothiolation which should, in principle, be compatible with the currently operated large scale photooxidation process to access artemisinin (Scheme 1b).^{2a} The photo-hydrothiolation of **AD** would produce a thio-ether **1** which would then be oxidized to the corresponding sulfoxide **2**. The last step of the sequence would rely on a Pummerer reaction which, when applied to sulfoxide **2**, would give rise to the key artemisinin intermediate **DHAAI**. This intermediate was previously transformed into diastereomerically pure **DHAA** in good yields.^{6,7}

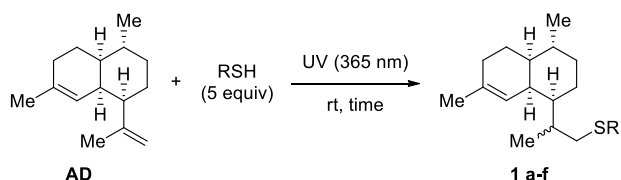
The anti-Markovnikov hydrothiolation of alkenes (also called thiol-ene reaction) has been extensively studied and is known to proceed through addition of a thiyl radical which is either generated by hydrogen abstraction from a thiol (Hydrogen Atom Transfer process, HAT) or by the homolytic cleavage of a disulfide.⁸ As a consequence, hydrothiolations are typically initiated by thermal decomposition of radical precursors, such as *tert*-butyl peroxide or azo-*bis*-isobutyronitrile (AIBN),⁸ or by photochemical activation either by UV irradiation,^{7,9} or visible-light photocatalysis.¹⁰ Photochemistry is in principle appealing since the current industrial synthesis of artemisinin already operates with large scale semi-batch photochemical reactors irradiated with medium pressure mercury lamps emitting in the near-UV to visible-light regions of the electromagnetic spectrum.^{2a} In addition, while radical initiators are often used in excess and, at elevated temperatures, photochemical activation is very attractive since photons are traceless initiators “operating” at close to room temperature.¹¹

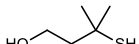
We started our investigations in the development of a photochemical hydrothiolation addition of **AD** by screening literature conditions using UV or visible-light irradiation. Reactions were performed in a commercially available photochemical screening device (PhotoRedOx Box[®]; see ESI, part 2)¹¹ with alkyl- and arylthiols in either polar or

non-polar solvents, as well as under air or under degassed conditions. However, these preliminary efforts were vain as no traces of the desired thio-ethers were detected in these experiments. Instead, under UV and blue light irradiation, variable amounts of **AD** isomers were formed together with the corresponding disulfide as a result of the dimerization of the thiols (5 equiv of thiol were used in each case).¹³ Interestingly, no isomerization occurred in the absence of thiol using the same photochemical conditions. These results seem to indicate that the generation of a thiyl radical might actually occur under such conditions but the thiol is promoting isomerization of **AD** instead of undergoing hydrothiolation. We therefore speculated that increasing the concentration of **AD** could favor the addition of the thiol onto the double bond.¹⁴ Indeed, this hypothesis was confirmed by running the experiment with thiophenol (5 equiv) and **AD**, under solvent-free conditions and irradiation at 365 nm. To our delight, we observed the formation of the desired adduct **1a** with 18% selectivity at 36% **AD** conversion together with several unidentified side products and diphenylsulfide (detected by GC/MS). However, despite our efforts, product **1a** could not be isolated, and its presence was only detected by GC/MS and ¹H NMR analysis.¹⁵ By monitoring the reaction with an excess of PhSH (5 equiv) under UV irradiation (365 nm), we obtained a selectivity of 53% in favor of **1a** after 4 h irradiation, with 71% **AD** conversion (Table 1, entry 1). However, pure **1a** could not be isolated, as the isomerization of the double bond followed by hydrothiolation occurred systematically and the resulting isomers could not be separated. Longer reaction times led to a decrease in selectivity as the hydrothiolation took place on the two double bonds (detected by GC/MS). Lowering the reaction temperature from 25 °C to 0 °C did not improve the selectivity toward the desired thio-ether (25% conversion of **AD** and 16% selectivity after 1 h). We also attempted to improve the selectivity of the process by using either electron-rich or electron-poor thiophenol derivatives but this also turned out to be unsuccessful.

We therefore investigated the addition of alkyl thiols under similar conditions [5 equiv of RSH under UV irradiation LED (365 nm) at 25 °C and under solvent-free conditions]. To our delight, the use of alkyl thiols gave, in all cases, very clean conversion of **AD** to **1b-e** compared to thiophenol (Table 1), thus enabling the selective functionalization of the exocyclic double bond. The use of ethylthiol (EtSH) resulted in an excellent conversion of **AD** after 18 h, and the corresponding adduct **1b** was isolated in 73% yield (Table 1, entry 2). Mercaptoethanol and 3-thiopropyl-1-ol exhibited higher reactivity compared to EtSH, as high **AD** conversions were observed after only 1 h and 3 h, providing the corresponding products with 81% and 77% isolated yields, respectively (Table 1, entries 3 and 4). The secondary thiol, 2-propanethiol, furnished 78% conversion of **AD**, and **1e** was isolated in 75% yield although, a longer reaction time, 44 h, was required to obtain a high conversion (Table 1, entry 5). On the other hand, very poor conversion of **AD** was observed with *t*-butylthiol (*t*-BuSH) or with 3-mercapto-3-methylbutan-1-ol, even after a prolonged reaction time (Table 1, entries 6 and 7), clearly indicating that increasing the bulkiness of the thiol disfavors this addition process. In all cases, the diastereoselectivity was modest (*dr* ~ 60:40) which would ultimately lead to a low yield in (*1R*)-**DHAAI**. However, this low *dr* is not a limiting factor since we recently disclosed an efficient epimerization procedure using the Betti base as a mediator for a Crystallization Induced Diastereoselective Transformation process (CIDT), enabling the conversion of the undesired isomer [(*1S*)-**DHAAI**] into the desired one [(*1R*)-**DHAAI**].⁷

Table 1. Screening of thiols in the hydrothiolation of **AD under solvent-free conditions.**



entry	RSH	time (h)	AD conversion ^[a]	1	yield ^[b]
1	C ₆ H ₅ SH	4	71%	1a	53% ^[c]
2	EtSH	18	96%	1b	73%
3	HO(CH ₂) ₂ SH	1	99%	1c	81%
4	HO(CH ₂) ₃ SH	3	80%	1d	77%
5	<i>i</i> PrSH	44	78%	1e	75%
6	<i>t</i> -BuSH	24	9%	1f	-
7		24	n.d.	1g	-

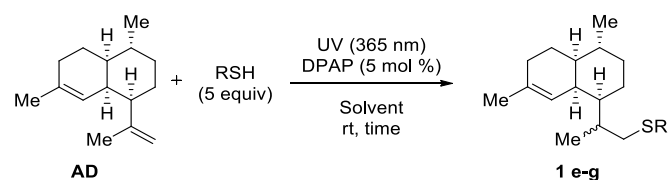
Reactions were performed on a 0.59 mmol scale of **AD** using 5 equiv of thiol. ^[a] Determined by GC/MS analysis. ^[b] Isolated yields after purification on silica gel chromatography. ^[c] Isolated with unidentified by-products with the same mo-

lecular weight according to GC/MS analysis, presumably isomers originating from an isomerization/hydrothiolation process.

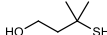
According to literature precedents, H-abstraction (or HAT) could occur in the absence of a photocatalyst or a photoinitiator thanks to the formation of a weak Electron-Donor-Acceptor complex (EDA) between the thiol and **AD**.¹⁶ This type of pre-complexation would preferentially occur under neat conditions facilitating the addition step. However, in our case, we were not able to ascertain this hypothesis using absorption spectroscopy.^{16b, c}

To enable the addition of sterically hindered thiols, we extended our screening to photocatalytic conditions using radical photoinitiators. Gratifyingly, we identified that in the presence of 5 mol % of 2,2-dimethoxy-2-phenylacetophenone (DPAP), the addition of secondary and tertiary thiols was significantly accelerated (Table 2).¹⁷ Under UV-light, DPAP undergoes a Norrish type I fragmentation to give a benzoyl radical which can initiate a radical chain process by H-abstraction.^{8e, 17} As a result, the coupling between **AD** and *i*PrSH delivered the corresponding thio-ether **1e** in 77% yield in a significantly shorter reaction time compared to the initiator-free method (3 h *versus* 44 h) (Table 2, entry 2 *versus* Table 1, entry 2). Interestingly, under these photoinitiated conditions, the hydrothiolation also worked well under diluted conditions (0.5 M), with good selectivity, albeit with slower conversion rates (Table 2, entries 3-5). DPAP also enabled the more challenging hydrothiolation of **AD** by *t*-BuSH, yielding the desired product in 45% isolated yield after 24 h and 68% yield after 72 h (Table 2, entries 6 and 7). All reactions were run on a 0.59 mmol scale and were monitored by GC/MS analysis before purification. The reaction was then carried out on gram scale (1 g, 4.90 mmol) using 20 mol % of DPAP and required longer reaction time to reach high conversion (Table 2, entry 7). Similar results were obtained with 3-mercapto-3-methylbutan-1-ol (Table 2, entry 8). It is important to note that the addition of thiophenol remained problematic under these catalytic conditions, which might be due to a competition between the addition of aryl thiyl radicals and the isomerization of **AD**.

Table 2. Screening of thiols in the hydrothiolation of **AD in the presence of DPAP as a photoinitiator.^[a]**



entry	RSH	solvent	time (h)	AD conversion ^[a]	1 , yield ^[b]
1	<i>i</i> PrSH	-	1	47%	1e , 45%
2	<i>i</i> PrSH	-	3	87%	1e , 77%
3	<i>i</i> PrSH	THF	1	11%	1e , 8%
4	<i>i</i> PrSH	MeCN	1	17%	1e , 13%

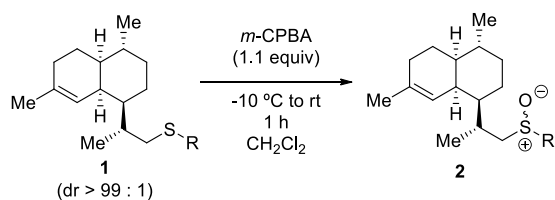
5	<i>i</i> PrSH	PhCl	1	23%	1e , 18%
6	<i>t</i> -BuSH	-	24	60%	1f , 46%
7	<i>t</i> -BuSH	-	72	90%	1f , 68% ^[a,c]
8		-	24	69%	1g , 48%

Reactions were performed on a 0.59 mmol scale of **AD** using 5 equiv of thiol. ^[a]Determined by GC/MS analysis. ^[b]Isolated yields after purification by silica gel flash chromatography, the diastereoselectivity (60:40) was estimated by ¹H NMR analysis. ^[c]The reaction was carried out on gram scale using 20 mol % of DPAP.

According to these results, it is likely that two distinctive photochemical activation pathways occur during the **AD** hydrothiolation. One pathway would rely on the direct absorption of light at 365 nm by either an EDA complex or a solvated charge transfer (CT) complex,^{16b} or even induced by small amounts of impurities^{16c} which could initiate the radical process. In this scenario, no reaction occurs with bulky thiols for which UV irradiation in the presence of DPAP is crucial. Therefore, the efficiency of the thiol radical seems to be dictated by the concentration of the thiol radical and, for less reactive thiols, such as *t*-BuSH, DPAP enables to restart the radical chain propagation which is otherwise disfavored. Interestingly, the reaction proceeds with shorter reaction time in the presence of DPAP than without which could also be due to lower inner filtering effects related to the difference in light absorption.

Having successfully prepared a range of thio-ethers with moderate to high yields, we next evaluated the transformation of **1** to the desired aldehyde, **DHAAI**. Our first attempts to develop a single step transformation of **1** to **DHAAI** using chlorinating reagents failed, either using sulfonyl chloride or *N*-chlorosuccinimide.¹⁸ We therefore decided to develop a two-step process involving a chemoselective sulfoxidation followed by a Pummerer rearrangement.^{19,20} In a preliminary study, we synthesized diastereomerically enriched thio-ethers prepared from pure iododihydroartemisinin (*11R*)-**A** (see ESI, Section 2.4).²² The thio-ethers (*S*)-**1a**, (*S*)-**1e** and (*S*)-**1f** were oxidized to the corresponding sulfoxides **2a**, **2e**, **2f**, after treatment with *m*-CPBA (1.1 equiv) in CH₂Cl₂ at -10 °C for 1 h, and these latter were isolated in up to 87% yield as a mixture of two diastereomers in a ratio 1 to 1 (Table 3).

Table 3: Synthesis of sulfoxides 2a, 2e and 2f.

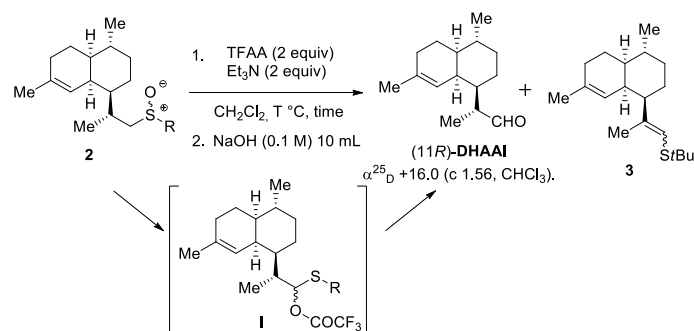


entry	1 (R group)	2 , yield
1	1a (Ph)	2a , 87%
2	1e (<i>i</i> Pr)	2e , 70%
3	1f (<i>t</i> -Bu)	2f , 87%

With the sulfoxides in hand, the investigation of the Pummerer rearrangement started using literature conditions.^{19,20} With acetic anhydride or benzoic anhydride, no reaction was observed. On the other hand, the reaction proceeded very selectively when performed with trifluoroacetic anhydride (TFAA) in the presence of trimethylamine (Et₃N) (Table 4). In this case, full conversion of the sulfoxide **2a** into a diastereomeric mixture of α -substituted sulfide intermediates **I** was observed by ¹H NMR at room temperature (see ESI, Section 3.2). After workup with a saturated aqueous solution of NaHCO₃, **DHAAI** was isolated in 57% yield from **2a**. This result was significantly improved to 71% yield, without epimerization of the (*11R*)-stereocenter, by realizing the workup with a NaOH aqueous solution (0.1 M) (Table 4, entry 1). However, when subjecting **2e** or **2f** under the same room temperature Pummerer conditions, only traces of **DHAAI** were detected. A temperature screening revealed that **DHAAI** can be obtained from alkyl sulfoxides by conducting the experiment at lower temperature. Indeed, **DHAAI** was isolated in 18% yield from **2e** at -10 °C and in 59% from **2f** when the reaction was performed at -20 °C (Table 4, entries 3 and 4). Lowering the temperature to -40 °C did not help to improve the yield. The major side product, isolated from the Pummerer rearrangement of **2f**, was the thioenol compound **3** (see ESI, part 3.4). Noteworthy, in the case of alkyl sulfoxides possessing α -CH next to the sulfur atom (**2e**, R = *i*Pr), the selectivity was lower than in the case of **2a** (**2a**, R = Ph) or **2f** (**2f**, R = *t*-Bu).

Once the feasibility of each step was demonstrated, the entire sequence to access **DHAAI** from **AD** was performed as a proof of concept using *t*-BuSH on gram scale (see ESI, Section 3.4).

Table 4: Pummerer rearrangement of sulfoxides 2.



entry	2 (R)	T °C	time	DHAAI , yield
1	2a (Ph)	rt	2.5 h	71%
2	2e (<i>i</i> Pr)	rt	1.0 h	traces
3	2e (<i>i</i> Pr)	-10 °C	1.0 h	18%
4	2f (<i>t</i> -Bu)	-20 °C	0.5 h	59%

All reactions gave full conversion of **2**

In conclusion, we have investigated the development of an original route towards artemisinin from **AD**, relying on a chemoselective photochemical hydrothiolation step. We

have demonstrated experimentally that this step can proceed with high selectivity when performed at ambient temperature and under solvent-free conditions with non-sterically hindered alkyl thiols. We also provided evidence that this step does not require additives to be initiated, probably due to the formation of a EDA/CT complex or to weakly absorbing species. In addition, we have been able to extend this study to the addition of bulkier thiols by adding DPAP as a radical photoinitiator. We demonstrated, as a proof of concept, that the thio-ether intermediate **1** can be converted to **DHAAI** by a chemoselective sulfoxidation using *m*-CPBA, followed by a Pummerer rearrangement using TFAA. This study provides encouraging results towards the development of a potentially cost-competitive process for the synthesis of artemisinin from **AD**. We are currently investigating potential strategies to increase the overall yield in **DHAAI**, through the development of a continuous flow process.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, and spectra copies of ¹H and ¹³C NMR (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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