Continuous flow photochemical production of Antimalarials

PhD Thesis

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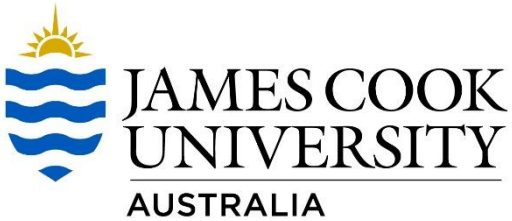

Supervisor:

Associate Professor Michael Oelgemöller

Dedicated to my Teachers

Abstract:

The main aim of this thesis was to investigate the application of continuous flow technology for the photochemical synthesis of the antimalarial agent artemisinin and for photooxygenations of allylic alcohols. The synthesis of novel trioxane compounds was realized in a conventional batch reactor. The suitability of metal-organic-frameworks as sensitizers in photooxygenation reactions was furthermore investigated under batch conditions.

Flow chemistry is a growing field in organic synthesis and has subsequently been adapted by researchers worldwide. Likewise, chemical and pharmaceutical industries are implementing flow reactors in sustainable synthesis.

The industrial semisynthetic production of artemisinin currently depends on a reliable supply of a bioengineered precursor and on conventional batch photochemical methods that are both energy and cost inefficient. Artemisinin production from dihydroartemisinic acid (DHAA) and its mixed-anhydride was thus investigated in the first part of this thesis using flow chemistry. Two-steps and one-pot protocols were first investigated using batch methods in order to optimize the conditions. The protocols were subsequently transferred to flow conditions. Initial flow studies utilized an in-house built capillary reactor and various photosensitizers. When conducted on its own, the flow photooxygenation step showed satisfactory results in terms of conversions, selectivity and yields. In contrast, the combined two-step (in series) operation suffered from an insufficient oxygen supply. The artemisinin synthesis was furthermore explored in a purpose-designed commercially available flow reactor developed by Vapourtec Ltd. The solar synthesis of artemisinin from DHAA was realized for the first time in a simple parabolic trough flow reactor.

In the second part of this thesis, photooxygenations of allylic alcohols, i.e. precursor compounds of potential new antimalarial agents, were examined under flow conditions. Subsequent peroxyacetalization of the oxygenated intermediates generated novel trioxane compounds. The photooxygenation of 4-methylpent-3-en-2-ol was successfully investigated in an in-house built capillary flow reactor as well as the advanced Vapourtec reactor. Another in-house built capillary flow reactor was also employed to investigate the photooxygenations of 4-methylpent-3-en-2-ol, 2, 5-dimethylhex-4-en-3-ol and 2, 6-dimethylhept-2en-4-ol, respectively. Using the hydroperoxy alcohol intermediates, several novel trioxane compounds were synthesized by Lewis-acid catalyzed peroxyacetalization with selected carbonyl compounds. Borontrifluoride hydrate (BF_3) or indium triflate [$In(OTf)_3$] were investigated as

potent catalysts. While all desired products were obtained, their purification proved challenging.

In the third part of this thesis, metal-organic-frameworks (MOFs) were studied as novel sensitizers in photooxygenation reactions. The synthesis of ascaridole from α-terpinene was first explored using PCN224 FN12 39-1, PCN222FN1337-1, MOF525FN1531-1, PCN-222, PCN-224, PCN-224' and PCN-222-Zr-MOF. Of these, only the latter was able to produce the desired product with moderate efficiency. The quality of the supplied MOFs may have greatly affected the success of this study. Subsequent photooxygenations of dihydroartemisinic acid (DHAA) and its mixed-anhydride remained unsuccessful.

Declaration:

I hereby declare that the Ph.D. thesis entitled *"Continuous flow photochemical production of Antimalarials"* is my original work, that the data presented in the thesis are the results of experiments conducted by me except where explicitly stated otherwise in the text. I confirm that to the best of my knowledge in thesis submitted for assessment all sources have been properly acknowledged and cited within the text.

Signed: ID No.:

Date:10/05/2019

Acknowledgement:

I want to express my deep gratitude and thank to my supervisor **A/Prof Michael Oelgemöller** for giving me the opportunity to pursue a Ph.D. at James Cook University. I am very grateful to him for his constant support, guidance, motivation and supervision throughout the entire duration of this study. Despite having a busy schedule, he has been able to help me with the project handling, clarifying research concepts, providing detailed knowledge and thorough discussions, which I highly appreciate. I am very thankful to him for the crucial suggestions that helped me to understand the thesis structure and data compilation. Also, the knowledge I gained while working under him is completely new for me and has certainly helped widen my grasp on the subject.

I would like to thank **Dr. Mark Robertson**, my secondary supervisor, for helping me in all possible ways and for introducing me to the analytical instruments. Beside my advisors, I also thank **Prof. Peter Junk** who allowed me to work in his laboratory to perform some very important synthesis work that was necessary for the partial fulfillment of the thesis. I also take the opportunity to thank **Dr. Jun Wang** and **Dr. Nazli Elsamirad** for their help and support.

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law's family members for their love and faith that gave me strength to make important decisions while staying alone in a foreign country.

Abbreviations:

ACN	acetonitrile
^{13}C-NMR	carbon nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
CA	compressed air
$CDCl_3$	deuterated chloroform
CO_2	carbon dioxide
DCM	dichloromethane
DCA	anthracene-9,10-dicarbonitrile
d	doublet
dd	doublet of a doublet
dddd	doublet of a doublet of a doublet of a doublet
dq	doublet quartet
DHAA	dihydroartemisinic acid
DMF	dimethylformamide
et al.	et alii (and others)
FEP	Fluorinated ethylene propylene
g	gram
GC	gas chromatography
H_2O	distilled water
H_2SO_4	sulphuric acid
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
hυ	light photon
i-Bu	iso butyl group
i-Pr	iso propyl group
i-PrOH	isopropyl alcohol of isopropanol
J	coupling constant
K_2CO_3	potassium carbonate
$LiAH_4$	lithium aluminum hydride
m	multiplet
MB	methylene blue
Me	methyl group

mg	milligram
$MgSO_4$	magnesium sulphate
mL	milliliter
mmol	millimole
mM	millimolar
$NaHCO_3$	sodium bicarbonate
$NaHSO_3$	sodium bisulphite
$NaSO_4$	sodium sulphate
nm	nanometers
NMR	nuclear magnetic resonance
^oC	degree Celsius
ppm	parts per million
p-TSA	para-toluene sulphonic acid
RB	rose bengal
RB-TEA	rose Bengal bis-(triethylammonium) salt
r. t.	room temperature
R.T.	residence time
s	singlet
t	triplet
t-Bu or *t*-butyl	tertiary butyl group
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TPP	tetraphenylporphyrin
T.R.	thermal reaction
UV	ultraviolet

Publications:

1. M. Oelgemöller, T. Goodine, P. Malakar “Flow Photochemistry – A Green Technology with a Bright Future”; in: Sustainable Flow Chemistry – Methods and Applications, L. Vaccaro (Ed.), Wiley-VCh, Weinheim 2017, Chapter 1.
2. M. Oelgemöller, P. Malakar, M. Yaseen, K. Pace, R. Hunter, M. Robertson “Applied and green photochemical synthesis at James Cook University in Townsville Australia” EPA Newslett. 2017, 93, 35 – 41.
3. M. Oelgemöller, M. Bolte, T. Goodine, S. Mumtaz, P. Malakar, A. Dunkerton, R. Hunter “The Eradicate Insect-borne Diseases with Sunlight Initiative at James Cook University in Australia” EPA Newslett. 2015, 88, 85-90.
4. M. Oelgemöller, M. Bolte, T. Goodine, S. Mumtaz, P. Malakar, A. Dunkerton, R. Hunter “TropEco Research Award 2014 – The Eradicate Insect-borne Diseases with Sunlight Initiative at JCU” AITHM Newslett. 2015, April, 12.
5. M. Oelgemöller, M. Bolte, T. Goodine, S. Mumtaz, P. Malakar, A. Dunkerton, R. Hunter “TropEco Research Award 2014 – The Eradicate Insect-borne Diseases with Sunlight Initiative at JCU” Sustainability@JCU Newletters 2014, November (TropEco AwardContribution). http://us8.campaignarchive2.com/?u=52f23e99e66486c756ac8aa72&id=5ea5ddb8ac&e=a1cfe43efa

Presentations:

1. **Poster presentation** on "Slugs versus bugs – Dye sensitized flow photochemical generation of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani Pordanjani, M. Oelgemöller Festival of Science 2017, Townsville (Australia), 8 September 2017.

2. **Oral presentation** (15 minutes) on "Scaling-up Anti-malarial agents in continuous flow reactor" P. Malakar, M. Oelgemöller 2016 Biology in the Tropics Postgraduate Student Conference, Townsville (Australia), 28 – 29. September 2016.

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5. **Poster and oral presentation** (3 minutes) on "Bio-active Organic Compound synthesis from a Novel Capillary Flow Reactor" P. Malakar, M. Oelgemöller 2016 CBMDT and CBTID Retreat, Fitzroy Island (Australia), 15.-17. July 2016.

6. **Poster presentation** on "Slugs versus bugs – Dye sensitized flow photochemical generation of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani Pordanjani, M. Oelgemöller 2016 CSTE Postgraduate Seminar Day, Townsville (Australia), 31. May 2016.

7. **Oral presentation** (3 minutes) on "Bio-active Organic Compound synthesis from a Novel Capillary Flow Reactor" P. Malakar, M. Oelgemöller 2016 CSTE Postgraduate Seminar Day, Townsville (Australia), 31. May 2016.

8. **Poster presentation and oral presentation** (3 minutes) on "Slugs versus bugs – Dye sensitized flow photochemical generation of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani Pordanjani, M. Oelgemöller North Queensland Festival of Life Sciences 2015, Townsville (Australia), 5. November 2015.

9. **Oral presentation** (15 minutes) on "Rolling back Malaria with bubbles and light - Continuous flow synthesis of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani

Pordanjani, M. Oelgemöller North Queensland Festival of Life Sciences 2015, Townsville (Australia), 5. November 2015.

10. **Poster presentation and oral presentation** (3 minutes) on "Slugs versus bugs – Dye sensitized flow photochemical generation of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani Pordanjani, M. Oelgemöller 2015 Australasian Tropical Health Conference – Emerging Priorities in Tropical Health Research, Palm Cove (Australia), 20.-22. September 2015.

11. **Oral presentation** (3 minutes) on "Slugs versus bugs – Dye sensitized flow photochemical generation of antimalarials" P. Malakar, M. Gerhard, H. Mommadkhani Pordanjani, M. Oelgemöller 2015 College of Science Technology Engineering "My Research in Three Minutes" competition, Townsville (Australia), 3. August 2015.

12. **Poster presentation** on "Fighting Parasites with Tropical Flora" P. Malakar, M. Oelgemöller, S. K. Veliyath, A. R. Deb, V. Keshri, S. Sahoo, L. K. Kanthal North Queensland Festival of Life Sciences 2014, Townsville (Australia), 4. November 2014.

13. **Poster presentation and oral presentation** (10 minutes) on "Fighting Parasites with Tropical Flora" P. Malakar, M. Oelgemöller, S. K. Veliyath, A. R. Deb, V. Keshri, S. Sahoo, L. K. Kanthal 2014 Australasian Tropical Health Conference, Palm Cove (Australia), 7.-9. September 2014.

Curriculum Vitae

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Table of Contents

List of Tables

List of Figures

List of Schemes

Chapter 1:

Introduction

1. Introduction

1.1 Photochemistry

Organic synthesis has a long and rich history of utilizing photochemistry to drive chemical processes by the absorption of photons. Thus, the use of UV-light, visible light or sunlight for inducing chemical transformations forms the basis of photochemistry. Absorption of light causes an electronic transition in a molecule, leading to an excited state in which the molecule attains a different electronic configuration compared to that of its ground state. This alters the chemical reactivity and opens a wider range of possible transformations [1, 2]. By the early twentieth century, photochemical pioneers acknowledged sunlight as a cleaner and greener source of energy [3, 4, 5]. However, there has been a reluctant attitude in the chemical industry to adapt photochemical reactions for large-scale production of fine chemicals during that time [6, 7]. The inability of most organic molecules to absorb visible light and the lack of ultraviolet wavelengths within the solar spectrum simply restricted the use of photochemical reactions on any industrial scale [8].

Sunlight induced photoreactions on the earth must have occurred billions of years ago. By the eighteenth and nineteenth century, various synthetic photochemical reactions were discovered, initially by chance and later by design, by early pioneers. H. D. Roth summarized these early investigations on photoreactions that ultimately led to the establishment of photochemistry as a major branch in chemistry [3]. Today, photochemical reactions of heterogeneous gas-liquid media such as photooxygenations or photochlorinations are industrially used for efficient production of chemicals [9, 10]. Over the last decades, ‘green’ techniques were generally adopted in chemical synthesis to minimize waste generation and to reduce reagent needs. As part of this trend, flow chemistry in particular has revolutionized the chemical synthesis process and has ultimately also led to a renewed interest in preparative photochemistry.

1.2 Photooxygenations

Over the past decades, photooxygenations have attracted continuing attention in the field of green chemistry. Singlet oxygen ($^1O_2$) is a powerful reagent for oxygenation reactions and has found applications in photodynamic therapy [11, 12], plant defense mechanisms [13], organic synthesis [14], pharmaceutical drug development [15] and natural product synthesis [16]. Photooxygenations are considered as model gas-liquid reactions, have been studied in detail and have found industrial relevance. These transformations yield oxygenated products under mild conditions using air (oxygen), catalytic amounts of a dye-sensitizer and visible light [10,

17]. Photochemical gas-liquid reactions require an efficient mixing between the liquid and the gas phase. According to Gollnick, photooxygenation may operate via a Type I or Type II reaction mechanism after the initial absorption of light (hv) by a sensitizer (Sens) to attain an excited state (Sens*). In Type I reactions, the electronically excited sensitizer (Sens*) interacts with the ground state substrate molecule by either hydrogen transfer or electron transfer, yielding radicals or radical ions. In contrast, Type II reactions proceed via energy transfer from the excited sensitizer Sens* with ground state oxygen ($^3O_2$) thus producing singlet oxygen ($^1O_2$) that reacts with the substrate molecule to an oxygenated product. A third possible mechanism proceeds by an electron transfer from molecular oxygen to the sensitizer, hence producing the superoxide anion (O_2^-) as the reactive species and an oxidized sensitizer ($Sens_{ox}$) **Figure 1.1** [10, 18].

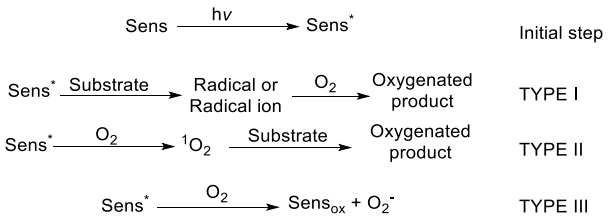
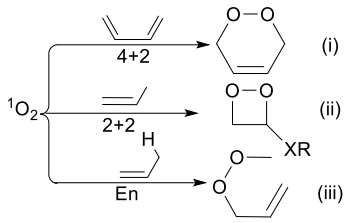


Figure 1.1: Types of Photooxygenation Reactions [18].

Photosensitization of triplet oxygen (Type II) is the most common and suitable method for generation of highly reactive singlet oxygen *in situ*. Singlet oxygen ($^1O_2$) reacts with olefins via three major pathways (**Scheme 1.1**): (i) conjugated dienes react preferably by [4+2] cycloaddition to form endoperoxides, and the reaction is analogous to a photo-induced Diels-Alder reaction in which the oxygen serves as the dienophile; (ii) electron-rich olefins follow [2+2] cycloadditions to produce 1, 2-dioxetanes; strained acetylenes, ketenes, allenes, sulfines, oximes, 1-methylene-2,5-cyclohexadienes, and the analogous *4H*-pyran and thiopyran-4-thiophene molecules also add molecular oxygen via a [2+2] cycloaddition; and (iii) inactivated olefins with allylic hydrogen atoms produce allylic hydroperoxides by undergoing an ene-type reaction [19, 20]. Studies have been conducted extensively to understand the electronic structure, reactivity, sources and applications of singlet oxygen [21, 22, 23].



Scheme 1.1: Interactions of singlet oxygen with olefins.

1.3 Singlet oxygen

Singlet oxygen is a reactive oxygen species (ROS) that plays an important role in the field of organic synthesis. Singlet oxygen $^1\Delta_g$ ($^1O_2$) can be generated by photosensitized methods or chemical reactions. Photosensitized generation of singlet oxygen has advantages over chemical reaction processes in terms of better control and avoidance of side reactions [24]. Due to its high oxidizing ability, singlet oxygen is more electrophilic and rapidly reacts with unsaturated carbon-carbon bonds, neutral electrophiles such as sulfides, amines and anions as well. Thus, singlet oxygen as a versatile synthetic reagent that has found applications in fine chemical synthesis and wastewater treatment [22].

1.4 Photooxygenation reactions and reactor technology

1.4.1 Conventional Photoreactors

Synthetic organic photochemistry is traditionally performed using an immersion well reactor (**Figure 1.2**). The reactor comprises a single low-, medium- or high-pressure mercury lamp in combination with a double jacketed water-cooled immersion well made of quartz glass. This assembly is then usually placed inside a Pyrex reaction flask. Gas is passed into the reaction from the bottom of the reactor and the apparatus is placed inside a light-shielded cabinet [9]. The batch reactor is a proven device for laboratory scale synthesis. However, most of the reaction mixture remains unaffected by light due to its limited penetration into the reaction mixture. Hence, photoreactions typically only occur close to the light source. Poor mixing in most photochemical devices prevents the usage of large volumes. Photoreactions subsequently require extended reaction times, which can unintentionally result in increased impurities due to side or follow-up reactions [25]. These factors also provide a challenge for large-scale industrial manufacturing.

The Rayonet chamber reactor represents another simple, reliable and cost-effective laboratory photoreactor. It consists of a ring of multiple low-pressure fluorescent tubes that provide radiation to a centrally placed reaction flask (**Figure 1.2**). To ensure sufficient cooling, a fan is attached to the bottom of the chamber and an additional cold finger is typically inserted into the reaction flask [8,9]. However, chamber reactors cannot be adopted for large-scale manufacturing due to the low photon output of their fluorescent tubes.

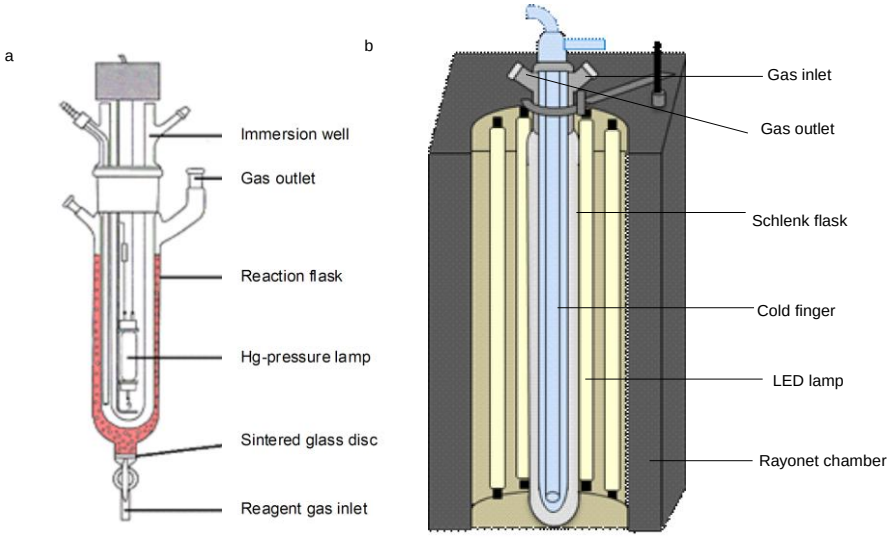


Figure 1.2: Schematic of (a) immersion well reactor and (b) Rayonet chamber with centrally placed three necked Schlenk flask.

In industrial processes, multistep reactions are usually conducted in individual batches to transform starting materials into the desired products [26]. Although this approach is fundamental to modern synthesis, it is time-consuming, wasteful and requires work-up for every intermediate formed [27, 28]. This, coupled with the inefficiencies of large-scale batch photochemical reactors, stresses the need for new and advanced chemical technologies that enable rapid scale-up and sustainable processes.

1.4.2 Microreactors and Continuous Flow techniques

As a result of technical advancement in combinatorial chemistry, the importance of automation and improved technologies has been realized by the chemistry community. Consequently, new techniques that speed up chemical transformations, simplify work-up and enable efficient isolation of products have greatly influenced organic synthesis [6]. Over the past 15 years, the introduction of miniaturization in chemistry (**Figure 1.3**) has led to the development of micro- and microfluidic (or mesofluidic) flow devices that mimic large scale production on laboratory

scale [29]. Flow chemistry involves processing reactions within well-defined reaction channels with dimensions of less than 1000 µm. The laminar flow inside the channels provides better mixing by diffusion, excellent control over reaction times, high surface to volume ratios and efficient temperature regulations. The most attractive feature of continuous flow synthesis is the ease of transferring reaction conditions between reactors and subsequently the ability for scale up to production levels by simply operating multiple systems in parallel. This process is known as "numbering-up" or "scale-out". Moreover, the small volumes of reaction mixture inside the channels ensure safe use of highly toxic solvents or explosive reactants [7, 30, 31]. Particularly in photooxygenations, the intermediate hydroperoxides formed are potentially explosive [32], making flow operation an attractive approach. In practice, the hazardous peroxide intermediates can be rapidly converted to the desired products through in series continuous flow reactions, i.e. using several flow reactors in a row.

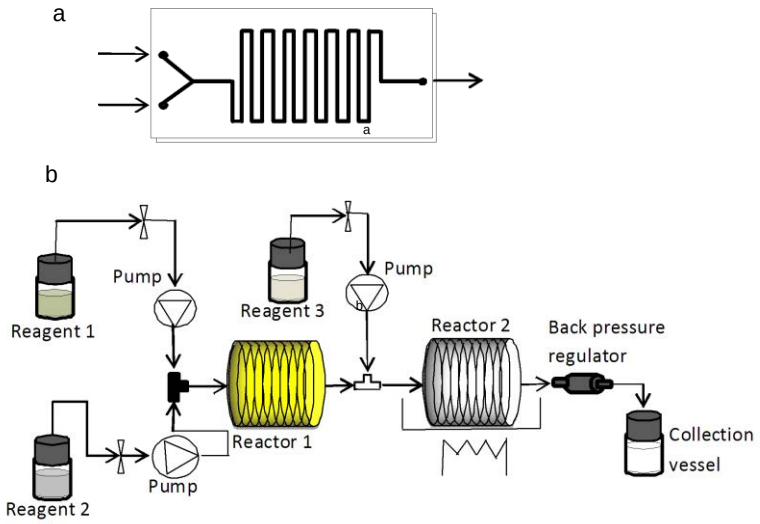
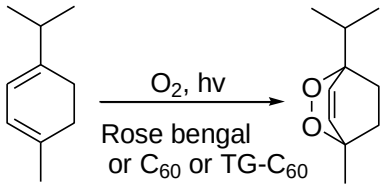


Figure 1.3: Schematic of (a) Chip microflow reactor and (b) Parallelization of Continuous Flow-technique for multi-step organic synthesis.

1.4.3 Photooxygenations in microfabricated glass micro-chip reactors

The dye-sensitized photooxygenation of α-terpinene was first investigated in a micro-scale reactor by Wootton and co-workers (**Scheme 1.2**) [33]. In this reaction singlet oxygen was used in a [4+2] cycloaddition to afford the endoperoxide ascaridole with a relatively low-intensity light source. The glass microchip with a footprint of 5 cm x 2 cm was made in-house and comprised two inlet channels (**Figure 1.4a**), a serpentine irradiation section and an outlet channel. Each microchannel had an average depth of 50 µm and an average width of 150 µm and the serpentine section covered a total length of 50 mm (**Table 1.1**). A solution of α-

terpinene (85%, 0.6 mL) and rose Bengal in methanol (20 mL) was introduced into one inlet at a flow rate of 1 µL min^{-1}. Oxygen gas was passed through the other inlet at 15 µL min^{-1} by a PHD2000 syringe pump. The serpentine section of the chip was irradiated with an overhead 20 W tungsten lamp at a distance of 10 cm. A conversion of 85% after a residence time corresponding to 5 sec irradiations was determined by GC analysis. In comparison, the batch reaction in a round bottom flask containing a solution of α-terpinene and rose Bengal in methanol (40 ml) and irradiation with a 500 W tungsten lamp produced 67% of ascaridole after 4 h.



Scheme 1.2: Photooxygenation of α-terpinene.

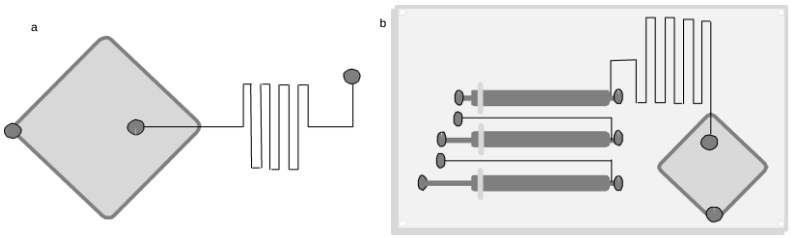


Figure 1.4: Schematic of (a) Glass microreactor [33] and (b) Glass-thiolene Chamber microreactor [34].

Table 1.1: Comparison of ascaridole synthesis in batch vs glass microreactor.

Parameters	Batch Reactor	Micro-flow Reactor
Glassware	Round bottomed flask (100 ml)	Glass micro-chip 50mm length
Tungsten Light source	500 W at 20 cm distance.	20 W at 10 cm distance.
Irradiation time	4 hours	5 seconds
Findings	67% yield (by flash chromatography)	85% conversion (GC)

Maggini *et al.* reported photochemical oxygenations in a fabricated thiolene-based microstructure reactor that was specifically designed to include a solid-supported photosensitizer (**Figure 1.4b**; **Table 1.2**) [34]. This reactor was also used for the photooxygenation of α-terpinene to ascaridole. A homogeneous reaction (**Scheme 1.2**) was initially performed by injecting an oxygen saturated mixture of 1 mmol of α-terpinene, 0.5 mmol tetradecane (internal standard for GC) and 0.012 mmol of C_{60} fullerene in toluene (10 ml) into the microreactor (volume of 0.152 mL). Using a residence time of 180 sec and a 300 W tungsten halogen lamp, a 97% conversion of α-terpinene was achieved at –5°C. The yield of ascaridole was calculated to 51% (by GC) and photochemical degradation of ascaridole was suggested to account for the losses. An increase in temperature (10°C) did not improve the reaction and instead resulted in a decreased yield.

Table 1.2: Key reactor parameter comparisons of homogeneous and heterogeneous microreactors.

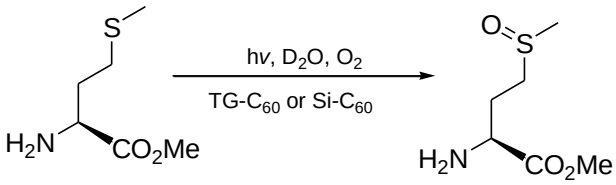
Microreactor	Photo-catalyst	Conversion	
		α-terpinene	**L-methionine**
Serpentine μ-reactor[1] (Homogeneous)	C_{60}	97%	-
Chamber μ-reactor[2] (Heterogeneous)	TG-C_{60}	97%	85%
	Si-C_{60}	-	100%

[1]Glass photochemical reactor (10mL $V_{solution}$); [2]In-house glass-thiolene serpentine oxygenation zone 500 μm (L) with chamber 3 mm x 30mm (W x L), reactor volume of 0.152 mL.

The analogous heterogeneous photooxygenation of α-terpinene (1.5 mmol) in toluene was conducted using Tentagel® resin beads functionalized with C_{60} fullerene (TG-C_{60}) as a solid supported sensitizer with the same light source. The reagents and oxygen were injected into the serpentine oxygenation zone, which then linked into the chamber containing the solid-supported sensitizer. Using a residence time of 54 sec, a 97% conversion and 53% yield of ascaridole were determined. On demand, two or more chambers could be employed in series via connecting Teflon tubing. The reaction times under flow conditions were shorter than the batch process which required approximately an hour with the same light source. The higher conversion was attributed to the narrow channel dimensions of the microreactor, allowing better oxygen diffusion into the reagents.

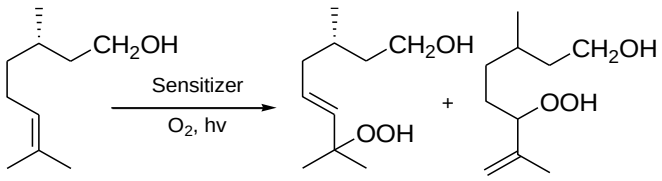
The same authors studied the oxidation of *L*-methionine to methionine sulfoxide in a microreactor (**Scheme 1.3**). Tentagel fullerene (TG-C_{60}) and functionalized fulleropyrrolidine-

SiO_2 hybrid (SiO_2-C_{60}) were used as solid supported sensitizers. The reaction of *L*-methionine (0.120 mmol) in D_2O was initiated using a 300 W tungsten lamp. At 0°C, the conversion of *L*-methionine was reported to be better with the SiO_2-supported (100% conversion to methionine sulfoxide within 33 sec) than the TG-supported fullerene (85% conversion in 102 min). Using a 5 x 3 array of white LEDs as an alternative irradiation source, *L*-methionine was converted in up to 95% at room temperature using the Si-C_{60} photosensitizer. In contrast, LED irradiation was unsuccessful in producing ascaridole from α-terpinene on Si-C_{60} as it was thought that the limited emission range of the LED source affected the photosensitized generation of singlet oxygen. The shorter lifetime of singlet oxygen in toluene compared with D_2O was another possible cause of the unsuccessful reaction.



Scheme 1.3: Photooxygenation of L-methionine.

A study using a glass microreactor (**Figure 1.5**) has been reported by Meyer et al. for the photosensitized oxidation of citronellol (**Scheme 1.4**), a key step in the synthesis of rose oxide [35]. The aim of the investigation was to establish a comparison between efficiencies of both batch and microreactors in terms of their respective space-time yields (STY) and photon efficiencies (**Table 1.3**). The Borofloat microreactor (Little Things Factory GmbH, Ilmenau, Germany) was made of high temperature-residence glass (1 mm ID, 0.27 ml) and the light source used was a LED array consisting of 4 x 10 diodes, specially designed for the Borofloat microreactor (**Figure 1.5**). The double walled storage reservoir was filled with a solution of β-citronellol (0.1 M) and a ruthenium polypyridyl complex [$Ru(^tbpy)_3Cl_2$] (0.001 M) as the sensitizer, fitted with a reflux cooler and flushed with compressed air for 20 min (flow rate 0.393 Lh^{-1}). The reaction mixture was recirculated through the reactor under illumination for 60-70 h with varying light intensities ranging from 1 to 7.98 $mWcm^{-2}$. The results from HPLC analysis showed a somewhat better conversion to the hydroperoxides [(3S)-6hydroperoxy-3,7-dimethyloct-7-en-1-ol and (S, E)-7-hydroperoxy3,7-dimethyloct-5-en-1-ol] and photon efficiency in the microreactor than in a conventional reactor. The space-time yield is directly influenced by the reactor geometry and after 20 minutes of irradiation, the STY of microreactor was found to be one order of magnitude higher than that in the Schlenk-reactor.



Scheme 1.4: Photooxygenation of Citronellol.

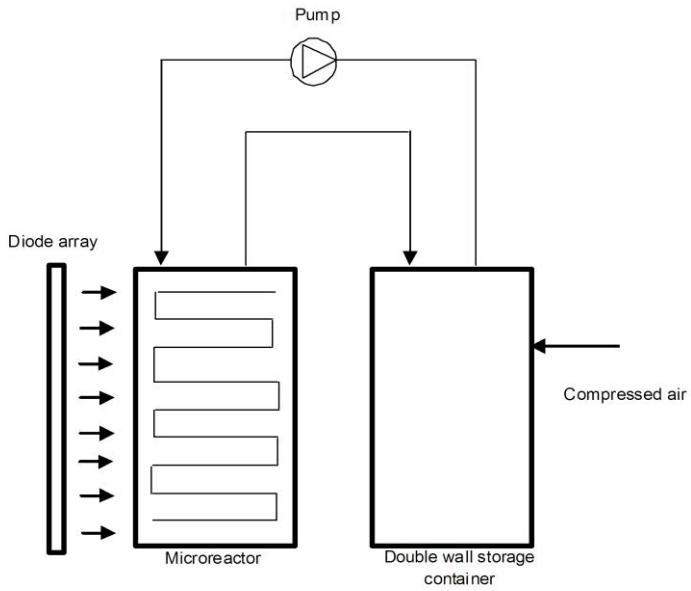


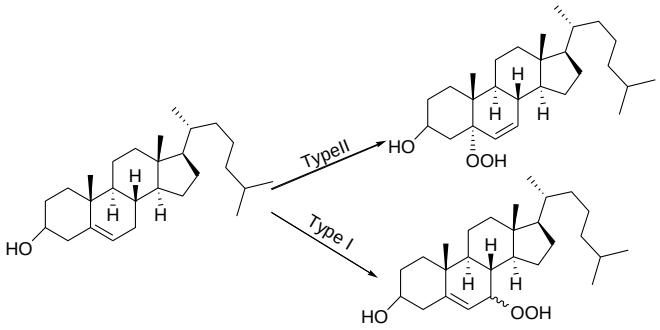
Figure 1.5: Schematic Microreactor setup for Photooxygenation of Citronellol [35].

Table 1.3: The key specifications of batch and micro-flow reactor.

Parameters	**Reactor**	
	Schlenk tube	Borofloat microreactor
Volume	40 mL	0.27 mL in channel.
Illumination area	15.19 cm^2	6.87 cm^2
Light source	2 x 15 LED stick with 6.15 $mWcm^{-2}$ intensity.	4 x 10 Diodes array with 6.15 $mWcm^{-2}$ intensity.
Photon efficiency	0.022	0.048

Boyle and co-workers have also demonstrated that a photoactive porphyrin immobilized inside the glass channels of a microfluidic chip is capable of producing singlet oxygen with high efficiency [36]. The chip was designed with 16 parallel channels [200 µm (W) x 12 mm (L)] originating from three inlets (for gas and reactants) and with one outlet (**Figure 1.6**). The

reactor setup was used for the singlet oxygen photoreaction of cholesterol (**Scheme 1.5**) to 5α-hydroperoxycholesterol and 7α/7β-hydroperoxycholesterol. A batch reaction was conducted with an oxygen saturated mixture of cholesterol (10 mM), photosensitizer (20 μm) in a 10% methanol in dichloromethane solution under a Xe light source (fluence rate = 2376 W cm^{-2}) for 1 hour. Analogous flow experiments with direct injection of oxygen were then conducted with similar concentrations of sensitizer and cholesterol solutions, flow rates of 5 and 2.5 μL min^{-1} and irradiation fluence rates of 10.5 and 21 Wcm^{-2}, respectively. A second series of experiments used the microchip containing the immobilized photosensitizer with a diluted solution of cholesterol (5 mM) under the same flow conditions. HPLC analysis of the resulting solutions revealed a similar STY of oxidized cholesterol products for both flow methods (immobilized and homogenous) at the lower flow rate, with both having much higher STY than the batch reaction. However, the conversion was very poor for both flow modes compared to batch operation. Further photoreactions of α-terpinene (0.15 mM in methanol or hexane) and citronellol (0.15 mM in methanol) in the immobilized microreactor under Xe arc lamp irradiation (fluence rate = 21.0 W cm^{-2}) showed inferior conversions if compared to the batch counterpart. Interestingly, the STY for ascaridole formation was considerably increased on-chip, while the STY of citronellol remained very low. The porphyrin immobilized on the glass channels of a microfluidic chip was reported to be capable of producing singlet oxygen with high efficiency and without photobleaching within the time period of the experiment. However, the chip can only be used for a very small amount of sample.



Scheme 1.5: Type I and Type II photooxidation of Cholesterol.

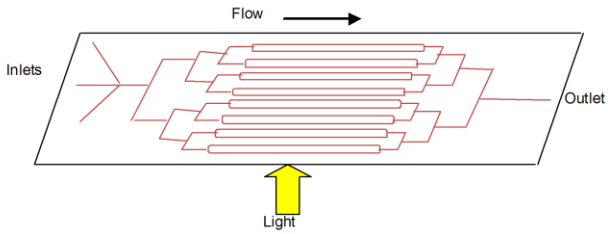
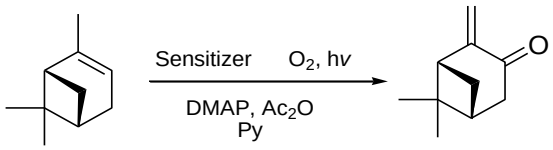


Figure 1.6: Schematic of Porphyrin immobilized microfluidic chip with 16 parallel channels [36].

The photochemical reaction of α-pinene with singlet oxygen to form pinocarvone has been recently reported by Lapkin *et al*. using an annular recirculating photoreactor and a silicon microfluidic chip (**Scheme 1. 6**) [37]. The recirculating reactor (**Figure 1.7a**) contained an annular porous glass membrane fixed at the bottom of reactor for better gas dispersion and was surrounded by an aluminum cylinder. The photoreaction of α-pinene (0.36 M) in the reactor was performed using three different light sources: a 524 nm LED, a 420 nm actinic fluorescent lamp and a Xe arc lamp. The accumulation rate ($\mathbf{r}_{reactor}$) of pinocarvone inside the annular reactor was highest when using the 420 nm fluorescent light source, while a decrease in reaction rate was observed with the LED and further with the Xe arc lamp. The silicon microreactor (microfluidic chip, channel width x depth 500 x 240 µm, length = 199.5 cm, V = 240 µL) included a metal micro heat-exchanger (**Figure 1.7b**) that was operated in three different modes. The continuous flow operation and recirculation mode allowed homogeneous mixing by injecting an oxygen pre-saturated reaction mixture, whereas gas-liquid segmented continuous operation was performed for heterogeneous oxygenation. The microreactor was operated with varying oxygen pressures and with a 524 nm or 416 nm LED, Xe arc lamp or a 250 W metal halide (MH) lamp. The photooxygenation of α-pinene was subsequently examined. In the single pass mode, when an oxygen saturated solution of α-pinene (0.36 M) in dichloromethane was introduced into the microreactor, the majority (97%) remained unreacted. Hence, oxygen presaturation at atmospheric pressure and several recirculation passes were needed to achieve complete conversion. Even in the recirculation mode at elevated oxygen pressure, the reaction required 2 days for complete conversion under illumination from a 416 nm LED array. The data also suggested that higher oxygen pressures increased productivity (**Table 1.4**.). Generally, pre-saturation of a reservoir at elevated pressure is a potential hazard due to the formation of a potentially explosive oxygen-solvent vapor. This was overcome via the use of a gas-liquid segmented flow. This was found to allow safe operation at elevated oxygen pressure due to the short quenching distance, small volume of gas bubbles, efficient

mixing and excellent heat exchange. A quantitative conversion of α-pinene could be achieved in a short time by joining five identical microreactors in series with an independent oxygen feed for each unit. In terms of effectiveness of the light sources, the LEDs were comparable to the more powerful 250 W MH lamp. A conventional batch reactor (immersion well reactor with 125 W medium pressure Hg lamp) was also used to compare performances. However, the rate of product formation was too low because of the poor quantum yield. Based on the actinometrical data postulated by the authors, the microreactor showed 3-7 times higher space time yields. Due to the better light utilization in the microreactor, the intensity of absorbed light, rate and quantum yields were higher than those in the annular recirculating or batch reactors.



Scheme 1. 6: Oxygenation of α-pinene to pinocarvone.

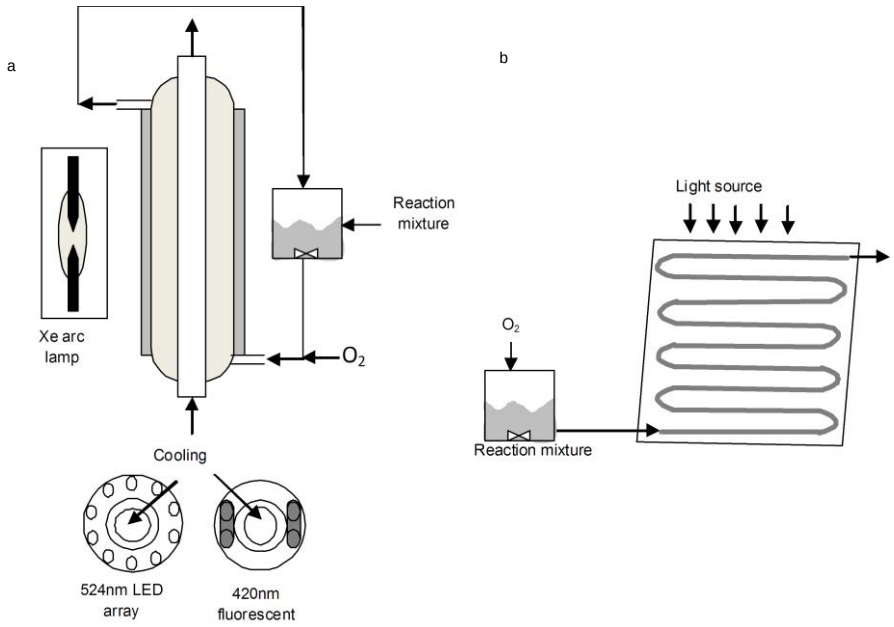


Figure 1.7: Schematic of (a) Recirculating annular photoreactor and (b) a microreactor [37].

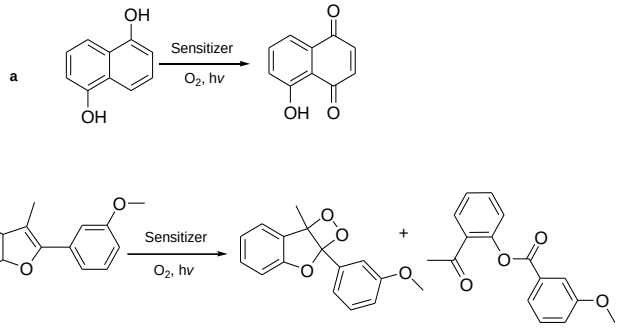
Table 1.4: Photooxygenation of 0.36 M α-pinene 11 in different reactors.

Reactors	**Light**	$\mathbf{I}_a$ (Einst $L^{-1}s^{-1}$)	$\mathbf{r}_{reactor}$ (mol. $L^{-1}s^{-1}$)
Batch	Hg lamp	1.2×10^4	0.076×10^4
Annular photoreactor	420 nm FL	5.7×10^4	1.8×10^4
	524 nm LED	4.6×10^4	1.1×10^4
	Xe arc	2.3×10^4	0.70×10^4
			[a]0.85×10^3
Microreactor	416 nm LED	1.9×10^3	[b]1.1×10^3
			[c]4.1×10^4
	250 W MH	3.6×10^3	[c]11×10^4

[a] Single pass continuous reaction with 6 bar oxygen pressure; [b] Recirculating mode with 6 bar oxygen pressure; [c] Gas-liquid segmented flow; accumulation rate of pinocarvone($\mathbf{r}_{reactor}$), intensity ($\mathbf{I}_a$).

A modular photoreactor was designed with micro structured reactors (μPR) equipped with commercially available OLEDs (organic light emitting diodes) by Ziegenbalg and group [38]. They demonstrated the use of OLEDs as an alternative to already established LED light sources. The three microreactor modules (3 x 1.256 ml volume) connected in a series were made of borosilicate glass with round channels (1 mm ID x 1.6 m length). Each module was equipped with two OLEDs, one irradiating from above and the other from below. Oxygen and reagent were injected with two syringe pumps and merged in a T-junction to form a stable slug flow at 0.5 ml/min of total flow rate. The reactor was evaluated against four benchmark photooxygenation reactions (**Scheme 1.2**, **Scheme 1.4** and **Scheme 1.7**). A 92% conversion was obtained for α-terpinene with a stoichiometric input ratio of oxygen to reactant ($r_{O2/RL}$) of 20. Photooxygenation of citronellol was similar with a slightly lower conversion under the same conditions. However, experiments with 1, 5-dihydroxynaphthalene (**Scheme 1.7a**) showed far lower conversions and the reaction of 2-(3-methyloxyphenyl)-3-methyl-1-benzofurane (**Scheme 1.7b**) required recirculation of reactants. The authors attributed these results to improved photon flux of the light source. The flow photooxygenation of α-terpinene was compared with a batch (250 mL round bottomed flask with 14.3 cm inner diameter) or a FEP (Fluorinated ethylene propylene) tube reactor [39] in terms of productivity ($\acute{n}$) and photonic efficiency of the reactor (ξ_R) (**Table 1.5**). The productivity was found to be independent of the number of OLEDs while the stoichiometric input ratio of oxygen to reactant

($r_{O2/RL}$) was the main factor effecting productivity. The photonic efficiency was greatly affected by the number of OLEDs.



Scheme 1.7: Photooxygenation of 1, 5-dihydroxynaphthalene and 2-(3-mthyloxyphenyl)-3-methyl-1-benzofurane.

Table 1.5: Comparison of efficiency characteristics of different reactors.

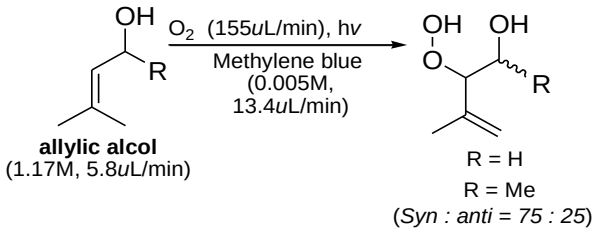
Reactors	Light Source	Power (W)	$\acute{n}$ (nmolJ^{-1})	ξ_R (nmolJ^{-1})
µPR-3 modules	3 OLEDs	2.1	37[a]	252
			20[b]	136
	6 OLEDs	4.2	39[a]	133
			20[b]	68
Batch	3 OLEDs	2.1	44	300
FEP tube	Med-p-Hg	450	41667	265

[a] stoichiometric input ratio of oxygen to reactant $r_{O2/RL}$=10.25; [b] stoichiometric input ratio of oxygen to reactant $r_{O2/RL}$=20; productivity ($\acute{n}$), photonic efficiency of the reactor (ξ_R).

1.4.4 Photooxygenations in membrane microreactor

Recently, a dual-channel microreactor was reported by Park *et al.* [40] for gas-liquid biphasic reactions with improved reaction rate (**Figure 1.8a**). In this reactor, the top and bottom channels are separated by a thin gas permeable polydimethylsiloxane (PDMS) membrane, and gas diffuses from the bottom channel into the solution in the top channel. However, the reported microreactor suffered from swelling problems. To overcome this problem, the authors built a second reactor by shielding the inner surface of the upper channel with polyvinylsilazane (PVSZ) [41]. This newly fabricated reactor's PDMS membrane retained its optical transparency. The photosensitized oxygenation of citronellol (0.1 M solution) through the dual

channel reactor resulted in a 97% yield with a 1.81 mmol daily output after 3 min compared to the batch, which required 180 min. An increased concentration of citronellol in solution (0.35 M) successfully increased production to 6.34 mmol per day in 3 min, whereas in batch the yield decreased and prolonged irradiation (510 min) was required. To establish the feasibility of the reactor for scale-up, the volume of the dual-channel reactor was increased by 7.3 times higher than the original volume of 38.9 µL (**Table 1.6**); the yield was lower but a daily through-put of 45.49 mmol was obtained. An investigation of the reaction parameters in the dual-channel microreactor for the photooxygenation of α-terpinene (0.1M) was performed and produced 91% of ascaridole after 3 min at 105 µL/min oxygen flow rate and at 5ºC. An attempt to increase the concentration to 0.35 M was unsuccessful and it failed to match the yield at lower concentration. Two allylic alcohols were reacted to form two different allylic hydroperoxides in 122 sec with 99% and 97% conversion, respectively (**Scheme 1.8**). The dual-channel reactor was also reported to retain its efficacy and long-term stability even after continuous running for 4 days.



Scheme 1.8: Photooxygenations of Allylic alcohol.

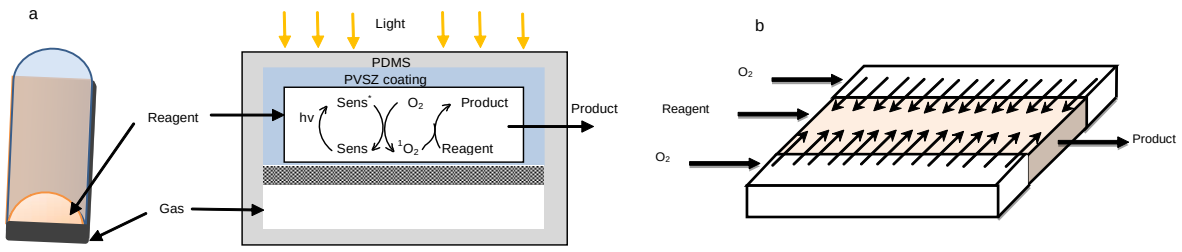


Figure 1.8: Schematic of (a) Dual channel [40] and (b) triple channel microreactor [42].

Table 1.6: Photooxygenation under White 16 W LED lamp in different membrane and batch reactor

Reactors	Reactor Volume	O_2-liquid contact area	Results (%)		
			α-terpinene	Citronellol	Allylic alcohols
Batch	50 mL	15.20 cm^2	82[a]	99[a]	-
Dual Channel	38.9 µL	1.98 cm^2	91[a]	97[a]	99[c]
					20[d]
Triple Channel	3.3 µL	0.825 cm^2	96[b]	99[b]	98[c]
					97[d]

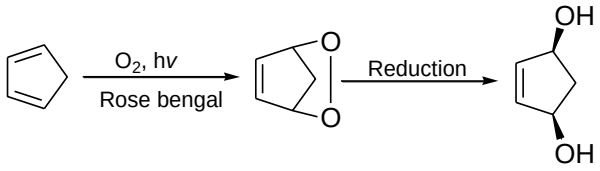
[a] % yield of ascaridole and hydroperoxides from α-terpinene and citronellol, respectively; [b] % Conversion [c] % Conversion of allylic alcohol to hydroperoxide (R = H); [d] % Conversion of alcohol to hydroperoxide (R = CH_3).

The dual-channel microreactor only allows one side of the solution to be saturated with the gas. An advanced triple-channel microreactor was thus designed by Park *et al.* with an increased interfacial area. The microreactor was fabricated from PDMS and the liquid reaction channel was exposed to gas from two sides [42]. The central channel of the reactor (33 cm length x 250 µm width x 40 µm depth) was employed for carrying the reaction solution and the two outer parallel channels (250 µm width x 40 µm depth) for supplying oxygen. The gas and reaction channels were separated by a 100 µm thick membrane (**Figure 1.8b**). The efficacy of the triple-channel reactor for conducting chemical reactions was demonstrated by investigating photooxygenations of α-terpinene (0.2 M) and citronellol (0.2 M) to produce their corresponding oxygenated products with 96% and 99% conversions, respectively. Likewise, the conversions for allylic alcohols (0.2 M) to produce the corresponding hydroperoxides (R = H or CH_3) were 98% and 97%, respectively **Table 1.6**.

1.4.5 Photooxygenations in falling film microreactor

The falling-film microreactor designed by IMM, Germany, was designed for facile photochemical gas-liquid reactions (**Figure 1.9**) [43]. The reactor comprises a bottom housing section with integrated heat exchanger, a reaction plate, a contact zone mask and a top housing with an open space. The reactor is equipped with a transparent quartz window for illuminating the reaction with UV-light. The liquid phase is introduced into the reactor through a horizontal slot and distributed into sub-streams that enter the microchannels through an orifice and flow

downwards. The gas is passed counter currently over the reaction mixture and the reaction occurs at the gas-liquid interface. Photooxygenation of cyclopentadiene (**Scheme 1.9**) produces an explosive intermediate that is immediately reduced to *cis*-2-cyclopenten-1, 4-diol. In the batch reaction described by Kaneko et al. [44] the product yield was reported to be high but the formation of the explosive intermediate in great amounts was found to be a hazard. When this reaction was performed in a falling film reactor with 32 parallel microchannels of 66 mm length, 600 µm width and 300 µm depth and irradiation with a Xe lamp at 10-15ºC, 0.95 g (20% yield) of 2-cyclopenten-1, 4-diol were obtained after reduction. Due to the short residence time, the concentration of the potentially explosive intermediate was low throughout the reaction channel and could be immediately reduced at the outlet of the reactor.



Scheme 1.9: Photooxygenations of cyclopentadiene in a falling film reactor.

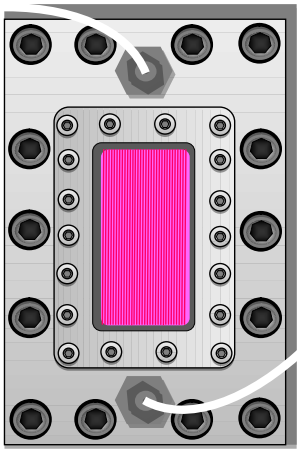


Figure 1.9: Schematic of falling film reactor [43].

Later Oelgemöller *et al.* explored the synthesis of juglone (**Scheme 1.7a**) from the cheap and commercially available 1, 5-dihydroxynaphthalene using the same falling film microreactor [45]. The reaction plate had 16 parallel micro channels of 1200 µm width, 400 µm depth and 78 mm length each. With an air flow rate of 26.5 mL/min and a solution flow rate of 0.08 mL/min, a 31% conversion was achieved after 160 sec of circulation and irradiation with an energy efficient fluorescent bulb (18 W). Replacement of the light source with an LED array

(3 W), however, reduced the conversion to only 9%. In comparison, the reaction in a traditional Schlenk flask (16 x 8 W) in a Rayonet chamber resulted in 14% conversion after 10 min of irradiation. In terms of energy efficiency, the LED array showed a higher value (69.2%$W^{-1}h^{-1}$) than the fluorescent bulb (38.8%$W^{-1}h^{-1}$) but the compact fluorescent lamp furnished complete conversion to juglone in more convenient overall time frame of 80 min. The reaction was reported to be eco-friendly due to the utilization of an energy saving light source and green reagents like aqueous isopropanol (9:1), rose bengal and air.

1.4.6 Photooxygenations in capillary microreactors

To overcome the limitations of large scale organic photochemical synthesis in typical batch reactors, Booker-Milburn and Berry [46] constructed a single pass continuous flow reactor by combining a commercially available immersion well with UV-transparent solvent-resistant fluorinated ethylene propylene (FEP) tubing. The practical reactor consisted of FEP tubing wound around a water-cooled immersion well with an UV lamp at its center. Using this design, Seeberger and Lévesque [39] constructed a simple continuous flow reactor to perform biphasic gas-liquid photoreactions. The FEP tube wrapped immersion well photoreactor containing a medium pressure 450 W mercury lamp that was cooled to 25ºC (**Figure 1.10**). The substrate solution and oxygen were mixed in a polytetrafluoroethylene (PTFE) T-mixer resulting in the formation of large bubbles surrounded by a thick liquid film (slug flow) inside the FEP tube. This slug flow pattern produced a high surface area and enabled efficient mass transfer. Singlet oxygen photoreactions conducted in the newly developed flow reactor were subsequently compared with reactions in a 78 µL silicon-glass microreactor under LED lamp irradiation. The greater mass transfer through the reactor decreased the amount of oxygen supply without affecting the conversion and precise delivery through a mass flow controller enabled easy regulation of flow rates to achieve a stable slug flow formation. The photooxygenation of α-terpinene and citronellol in the FEP tube reactor produced 85% of ascaridole and 88% of hydroperoxides, respectively.

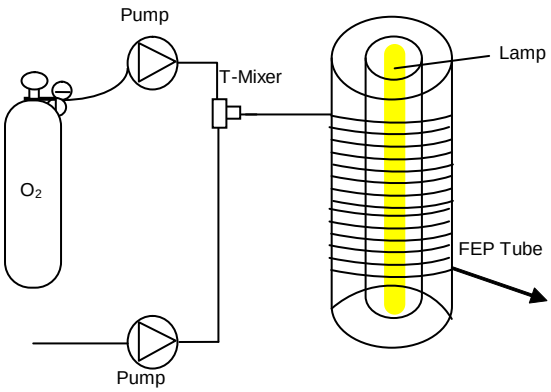
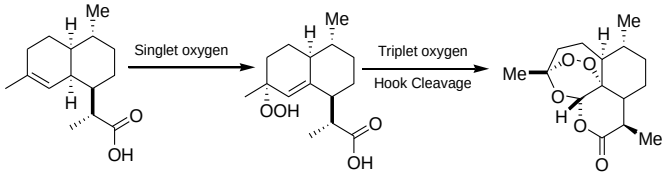


Figure 1.10: FEP tube continuous flow reactor [39].

Photooxygenation is a key-step in the synthesis of artemisinin **(Scheme 1.10**), an antimalarial drug that is very expensive due to its high production costs. Seeberger and Lévesque [47] consequently utilized a FEP continuous flow reactor (**Figure 1.11**) for the photochemical transformation of dihydroartemisinic acid (DHAA) to its corresponding hydroperoxide followed by a Hook cleavage via an acid catalyzed step. To perform the two-step reaction in series, the authors joined an additional thermal PTFE reactor. The reagent mixture containing DHAA and tetraphenylporphyrin (TPP) in dichloromethane (DCM) was pumped (2.5 ml/min) with a HPLC pump and oxygen (7.5 ml/min) was supplied by a mass-flow controller via a T-mixer to form slug flow. Irradiation was conducted at 25ºC with a 450 W medium pressure Hg lamp and the product mixture was mixed with trifluoroacetic acid (TFA) in DCM (0.5 ml/min from an acid resistant pump) via another T-mixer and allowed to pass through a PTFE coil (total volume 26 ml). The first 16 ml of the thermal loop were maintained at room temperature and the remaining 10 ml at 60ºC. A residence time of 2 min in the photoreactor module and of 2.5 min in the PTFE thermal reactor yielded 39% of artemisinin after chromatographic purification. Based on this result, the authors calculated a possible production of 200 g of artemisinin per day. However, irradiation with the energy intensive 450 W Hg lamp generated substantial amounts of heat, which can be a problem for industrial scale-up.



Scheme 1.10: Photooxygenation of Dihydroartemisinic acid.

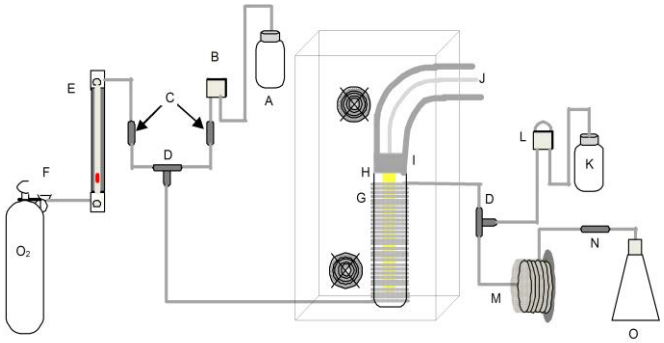


Figure 1.11: Schematic of FEP continuous flow reactor [47].

A) Substrate reservoir, B) HPLC pump, C) Valves, D) T-mixers, E) Mass flow controller, F) Manometer, G) FEP tubing, H) Quartz immersion well, I) Pyrex filter, J) Connection to medium pressure Hg lamp, K) TFA solution reservoir, L) Acid-resistant HPLC pump, M) PTFE thermal reactor N) Back pressure regulator (BPR), O) Collection flask.

In the follow-up studies, the authors successfully produced artemisinin in a one-pot reaction using a LED lamp (72 W) and a novel continuous flow reactor (**Figure 1. 12**) [48a]. The reactor comprised a FEP tube (0.76 mm ID, volume 7.5 ml) wrapped around a glass plate (7 x 9 cm^2) in two layers. This photoreactor module was immersed into a glycol/water (3:2 v/v) bath maintained at –20ºC (Figure 10) and the substrate solution of 250 ml feed volume (mixture of 29.5 g dihydroartemisinic acid, 143 mg of 9, 10-dicyanoanthracene and 4.8 ml of TFA in toluene) was introduced at 1.25 ml min^{-1} with an oxygen supplied at a flow rate of 5 ml/min. This resulted in a short residence time (11.5 min) that was sufficient for to achieve complete photooxygenation. The reaction mixture from the outlet was then brought to 10ºC in a reaction line (0.76 mm ID, 10 ml volume) and then to 25ºC in a second reaction line (1.57 mm ID, 30 ml volume). This method enabled artemisinin synthesis in a good yield (46%) and with satisfactory photon efficiency (24%) with just one pump and an initial oxygen supply in continuous flow. Following the similar protocol from photooxygenation of DHAA in Vapourtec UV-150 photochemical reactor 35% of artemisinin formation was reported. [48b]

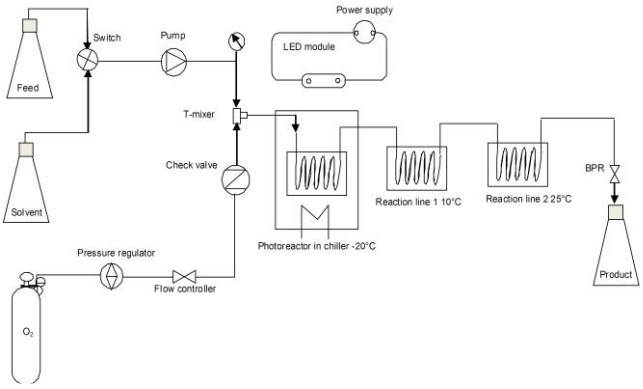
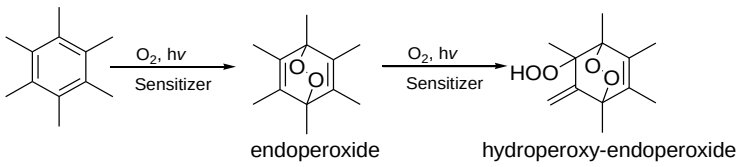


Figure 1. 12: Schematic of continuous flow reactor for one-pot production of Artemisinin [48a].

Recently Park and co-workers conducted the photosensitized oxygenation of hexamethyl benzene in a droplet-based microreactor (**Scheme 1.11**), which resulted in the formation of a mixture of an endoperoxide and a hydroperoxy-endoperoxide [49]. The investigation was performed in an in-house built microreactor; however, no reactor dimensions are mentioned in the study. Two syringes, one filled with hexamethyl benzene (1 mmol) in acetone-d_6 (10 mL) and another filled with a solution of methylene blue (0.01 mmol) in acetone-d_6 (10 mL) were injected through two inlets with oxygen gas being passed through a third inlet (**Figure 1.13**). The microchannel was immersed into a Dewar flask and irradiated with a 16 W LED lamp. At a temperature of 0ºC and a 30 min residence time, yields of endoperoxide of ~10% and of hydroperoxy-endoperoxide of 96.4% were reported. These were far superior over the batch yields of endoperoxide and hydroperoxy-endoperoxide of 1.4% and 3.7%, respectively, after a longer reaction time of 90 min at the same temperature. The low yield in batch is due to the slow diffusion of singlet oxygen. In contrast, the higher yield of the droplet reactor resulted from the short molecular diffusion distance caused by the high surface-to-volume ratio inside a narrow channel.



Scheme 1.11: Photooxygenation of hexamethyl benzene.

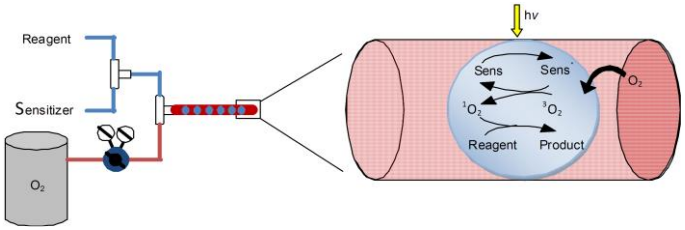
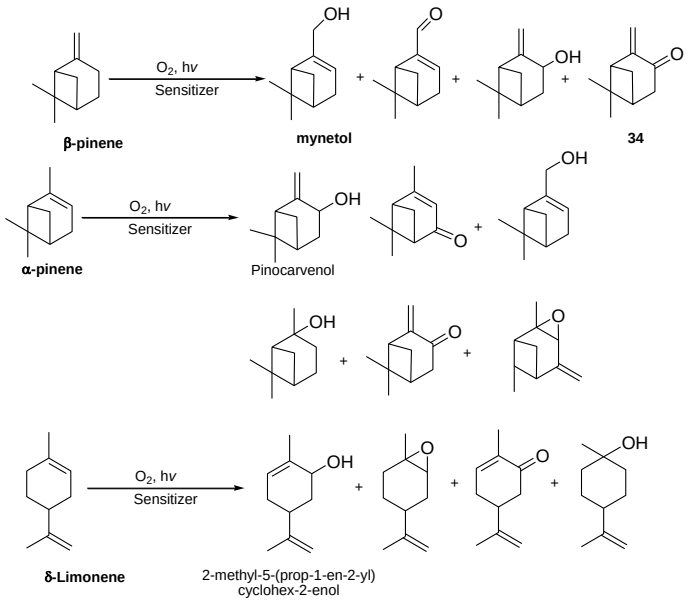


Figure 1.13: Schematic of the Droplet photoreactor [49].

In a follow-up study, the authors investigated photooxygenations of monoterpenes (**Scheme 1.12**) in a mono-channel micro-reactor (MC-MR) and a tube-in-tube (TIT-R) continuous flow reactor (**Figure 1.14**) [50]. The MC-MR was designed for lab-scale preparation, whereas the TIT-R was developed for large-scale productions. The mono-channel reactor comprises of micro tubes and two T-junctions (thru-hole 0.5mm). The sensitizer and reagent solutions were separately injected with syringe pumps and mixed in the first T-junction. Oxygen was delivered through another T-junction and the gas-liquid slug flow was allowed to pass through a FEP tube (0.5 mm ID, 3 m length, reaction volume 0.02 6ml) while being irradiated with a 16 W LED lamp. The photooxygenation section of the reactor was held in a Dewar that maintained a temperature of 5ºC and allowed reflection of light. The tube-in-tube reactor (Figure 12b) had two T-junctions and one gas-permeable inner tube (0.6 mm ID, 3 m length) inserted into an outer light-transparent but non-gas-permeable tube (2.0 mm ID, 3 m length, reaction volume 7.92 ml). The reagent feeds, radiation source and temperature control method were the same as used for the MC-MR. The photooxygenation of a number of model reactions were subsequently studied in these reactors and compared with batch reactions of oxygen presaturated solution in a 50 ml round-bottomed flask (reaction volume 10 ml) under otherwise similar conditions (**Table 1.7**). The photooxygenations of selected monoterpenes were reported to have higher yields in the flow processes than in batch. In terms of productivity, the TIT-MR were superior over the MC-MR. The use of natural sunlight for the photooxygenation of β-pinene to myrtenol in the MC-MR gave a good yield (~68%), but this was significantly lower than that when using LED lamps. The MC-MR and TIT-MR were able to significantly reduce reaction times and gave higher yields than the batch reactor due to improved mass transfer of oxygen into the liquid media.



Scheme 1.12: Photooxygenations of monoterpenes.

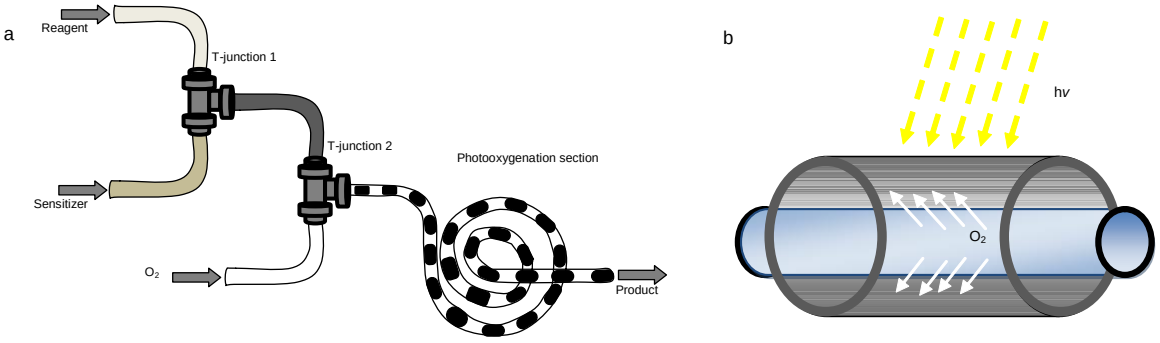


Figure 1.14: Schematic of (a) MC-MR and (b) TIT-MR [50].

Table 1.7: Comparison of products yields in batch, MC-MR and TIT-MR. Reaction time in parentheses.

Products	Reactors under 16W LED lamp, temperature 5ºC		
	Batch yield Time	**MC-MR yield time**	**TIT-R yield time**
Ascaridole	92% 180min	99.9% 4min	87.4% 4min
(3S)-6hydroperoxy-3,7-dimethyloct-7-en-1-ol and (S,E)-7-hydroperoxy3,7-dimethyloct-5-en-1-ol	92% 180min	90.1% 2min	87.7% 2min
Myrtenol	98.9% 1440min	99.9% 60min	87.5% 58min
Pinocarvenol	99.9% 1440min	82.7% 15min	99.9% 20min

2-methyl-5-(prop-1-en-2-yl) cyclohex-2-enol	96.9% 1080min	46.9% 20min	46.1% 20min

1.4.7 Photooxygenations in the microcapillary film

Wootton *et al.* recently reported microcapillary films (MCFs) made of 10 parallel microcapillaries embedded in a FEP film (5 m long). These allow through-wall mass transport of oxygen into the reagents (**Figure 1.15**) [51]. Each capillary in the MCF had an elliptical cross section, with an average hydraulic diameter of 104.2±10.6 μm and an average wall thickness of 61.5±17.1 μm. The utility of MCFs for photooxygenation was demonstrated by synthesizing ascaridole from α-terpinene. The oxygen pressure chamber remained isolated from the reactants by a wall. An increase of the oxygen pressure resulted in a rise in the reaction rate. Oxygen diffused through the FEP film to react with α-terpinene. Using a residence time of 14 min resulted in a good yield of 90%. The STY of the MCF was determined as 6.36% per min, far greater than the STY of the batch reactor [37] with 0.28% per min. Due to its high resistance to chemicals and solvents, the MCF was found to be superior over the PDMS device, which suffered from swelling problems.

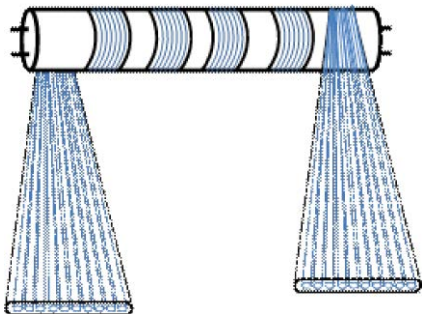


Figure 1.15: Schematic of FEP MCFs consisting of 10 parallel channels [51].

1.4.8 Photooxygenations in a sapphire tubular reactor

Worrall and co-workers realized singlet oxygen generation in supercritical carbon dioxide ($scCO_2$), opening a new opportunity for synthetic photosensitized oxidations. They also showed that $^1O_2$ has a relatively long lifetime in $scCO_2$, which is furthermore dependent on the density of $scCO_2$. Acquiring similarly long lifetimes of $^1O_2$ in conventional solvents necessitates the selection of highly chlorinated solvents that are becoming unacceptable for large scale use [52]. Following this approach, George and Poliakoff investigated the photooxygenation of α-terpinene in $scCO_2$ using 5, 10, 15, 20-tetrakis-(pentafluorophenyl)

porphyrin (TPFPP) in a small batch scale apparatus (**Figure 1.16a**). This comprised of a multi-purpose photochemical and spectroscopic cell with CaF_2 windows, a path length of 2 mm and a volume of 2 mL. The reaction of α-terpinene to ascaridole was carried out by dissolving TPFPP in α-terpinene overnight and diluting O_2 (140 bar, 1.31 mol %) in $scCO_2$ prior to pressurizing the photochemical cell. At 40°C, irradiation with a 300 W xenon lamp gave quantitative conversion of α-terpinene within 160 sec [53]. A preliminary continuous flow option with a sapphire tube resulted in 89% conversion of α-terpinene at a flow rate of 0.1 ml min^{-1}. Later, the authors evaluated the effectiveness of LEDs for this reaction, using a specially designed sapphire reactor tube as an effective continuous flow reactor for performing photo-oxidations [54]. The sapphire tube (7.8 mm ID, 1.2 mm thick wall, 5.7 mL of total volume) was sealed in a stainless-steel holder. Two LED arrays, each containing four 1000 Lumen LEDs and mounted on an aluminum heat sink, were used as light sources. The LEDs were cooled by two 5 cm diameter fans (**Figure 1.16b**). The sapphire cell mounted in the continuous-flow system was supplied with liquid CO_2 at 2.0 mL/min (pump head at -10°C, 48 bar), the organic reactant containing the photosensitizer was pumped at 0.2 mL/min and O_2 was injected at a rate of two molar equivalents of O_2 to organic reactant. A single pass reaction through the reactor showed quantitative conversion and after an 8 h run, 96 mL of ascaridole were obtained, representing a 3000-fold scale-up over the batch setup. A single pass continuous flow reaction of citronellol at 0.1 mL/min substrate flow and 1 mL/min of $scCO_2$ flow with 2 equivalent of O_2 at 180 bar resulted in quantitative conversion with 52% selectivity to (3S)-6-hydroperoxy-3,7-dimethyloct-7-en-1-ol and 48% selectivity to (S,E)-7-hydroperoxy3,7-dimethyloct-5-en-1-ol.

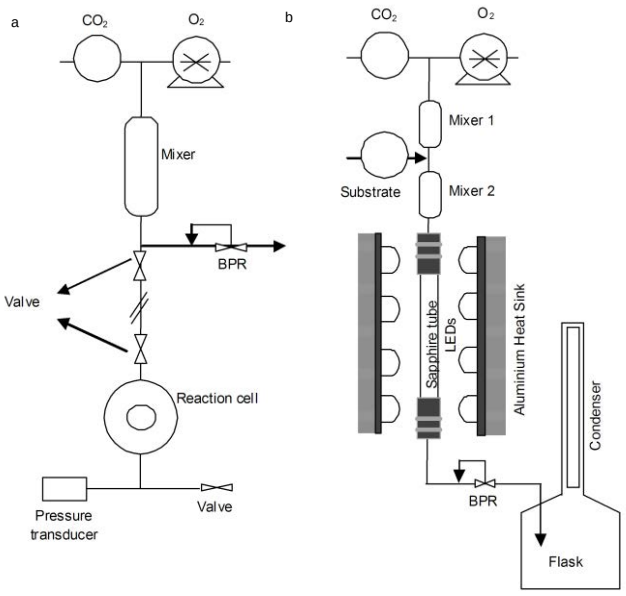


Figure 1.16: Schematic of (a) batch [53] and (b) flow setup for photoreaction with $scCO_2$ [54].

Further $^1O_2$ reactions in $scCO_2$ were subsequently studied with a wide range of photosensitizers and using surfactants and co-solvents [55]. To obtain a photocatalyst-free oxygenated product, a number of photosensitizers with different immobilizations were furthermore investigated in the $scCO_2$ sapphire tube reactor [56]. The four materials studied were (i) commercial polymer-bound rose Bengal (RB), (ii) RB/TPP/Zn-TPP/TDCPP trapped in cast PVC-films, (iii) ionic sensitizers (TDCPP+/TPP+/$[Ru(bpy)_3]^{2+}$) on SiO_2 aerogel support and (iv) TDCPP-COOH coupled to PVC-NH_2. The photooxygenation of α-terpinene and citronellol in the flow reactor was performed by loading the immobilized photosensitizer into the sapphire tube, pressurizing with CO_2 and O_2 (2:1 molar ratio of O_2:substrate) to 140 bars for α-terpinene and 180 bar for citronellol, respectively. Irradiation with two arrays, each with four LEDs, was started while injecting substrate at a flow rate of 0.1 ml/min. For batch reactions, a prefilled spectroscopic cell was pressurized with CO_2 and O_2 and irradiated with white light LEDs mounted on an aluminum heat sink. The covalently bound TDCPP based-photosensitizers on amino-functionalized-PVC (TDCPP-COOH coupled to PVC-NH_2) was found to meet the authors' criteria of catalyst-free products in high yields for a prolonged period of usage. In particular, ascaridole and the corresponding hydroperoxides of citronellol were obtained in yields of 85% and 88%, respectively. The other immobilized photocatalysts were prone to rapid leaching and photobleaching. Nevertheless, the usage of immobilized sensitizers helps to achieve a more efficient utilization of the sensitizer material and additionally avoids separation of sensitizer or co-solvents from the product.

In order to decrease the amount of photocatalyst used in the homogeneous photooxygenation of α-terpinene and citronellol, incorporation of a fluorous biphasic separation using a $scCO_2$ sapphire tube reactor has also been successfully demonstrated [57]. This concept was based on the solubility of the photocatalyst in $scCO_2$ and fluorous solvents rather than in organic solvents. A highly fluorophilic photocatalyst and solvent, i.e. hydrofluoroether (HFE), were employed in a monophasic $scCO_2$ reaction (**Figure 1.17**). At the end of the experiment, the pressure was released to give gaseous CO_2 and a biphasic liquid mixture. The photocatalyst was then collected in the denser fluorous phase. The initial flow reactions were conducted to investigate the effect of pressure on the reaction and biphasic separation of product. More than 99% conversion for α-terpinene was reported at >14 MPa of CO_2/O_2 and for citronellol at >16 MPa of CO_2/O_2, respectively. A clear separation between liquid HFE and ascaridole occurred in the collection flask but some trace amounts of photocatalyst remained in the product. In contrast, less photocatalyst remained in organic phase when citronellol was photooxygenated. When operated in continuous mode for 20 h (10 full cycles), citronellol conversion dropped from 60% to 45% under stressed conditions (citronellol flow rate 0.2 ml/min, pressure 18 MPa, recycling flow rate 0.1 ml/min). Although 88% of the photocatalyst could be recovered, significant amounts of HFE were lost during the venting of CO_2. HFE refill was thus required at periodic intervals, preventing critical high-pressure maintenance and creating a potentially explosive oxygen and organic vapor mixture.

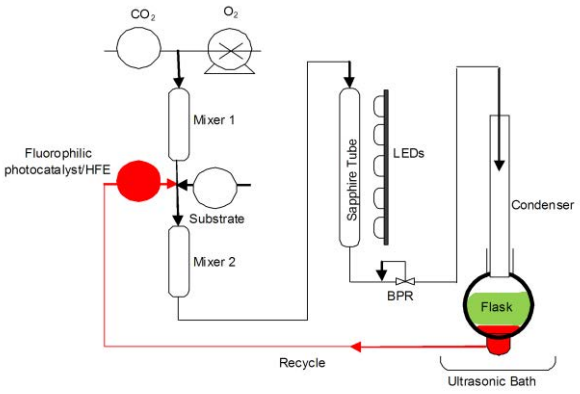


Figure 1.17: Photochemical reactor with continuous fluorous phase recycling [57].

The photooxygenation in tubular reactors was also applied to the synthesis of artemisinin, with the aim of reducing environmental and economic costs [58]. Based on the principle of green chemistry, two strategies were developed for facile artemisinin production. These strategies

included (1) the use of liquid CO_2 (replacing $scCO_2$) as solvent with a recyclable heterogeneous photosensitizer/acid system that acts as a dual catalyst with both the Brønsted acidic and photocatalyst function (**Figure 1.18a**); and (2) the use of recyclable aqueous solvent mixtures containing water soluble acid and photocatalysts. Following the first strategy, all reactions were maintained at 18 MPa pressure and 5ºC with an O_2:DHAA molar ratio of 2:1. To obtain a photocatalyst-free product, immobilized porphyrin was used which was prepared by anchoring meso-tetraphenylporphyrin (TPP) or meso-tetrakis(pentafluorophenyl) porphyrin (TPFPP) onto the sulfonated cross-linked polystyrene ion-exchange resin Amberlyst-15 (Amb). A residence time of ~10 min was obtained using a flow rate of 0.125 ml/min for the co-solvent (EtOAc or toluene) and of 0.525 mL/min for the CO_2/O_2 flow. After 4 cycles, complete conversion of DHAA was achieved, with an isolated yield of 51% for artemisinin. Doubling of the reactor length (240 mm) and hence residence time gave complete conversion in a single pass and furnished a 48% yield of artemisinin (**Table 1.8**). The advantage of this method included minimized by-product formation and the heterogeneous dual catalyst/CO_2 system, which enabled direct accumulation of pure product without further work-up. However, the running time was limited by bleaching of the solid supported photocatalyst. Following the second strategy (**Figure 1.18b**), the oxygen saturated mixture of the substrate DHAA in an aqueous solvent containing sulfuric acid and photocatalyst $[Ru(bpy)_3]Cl_2$ was performed in an *up-flow* mode through glass beads (6 mm diameter) inside the reactor (maintained at 5ºC) under high pressure (1 MPa). This approach resulted in large conversions after ~20 min, but the yield of artemisinin remained below with 50%. More product could be obtained by keeping the product mixture from the continuous flow reaction under an oxygen atmosphere with constant stirring for an additional period of time (at 10 bar O_2 for 16 hours). The second strategy was also used in batch mode and irradiation with a LED lamp for 5 hours (at 5-10ºC). An overall yield of 66% (isolated yield 50%) was obtained using a mixed solvent system (THF:H_2O = 60:40). Both strategies enabled operations at higher temperature and avoided the use of toxic trifluoroacetic acid (TFA). The reaction progress depended on the reactor length in both cases.

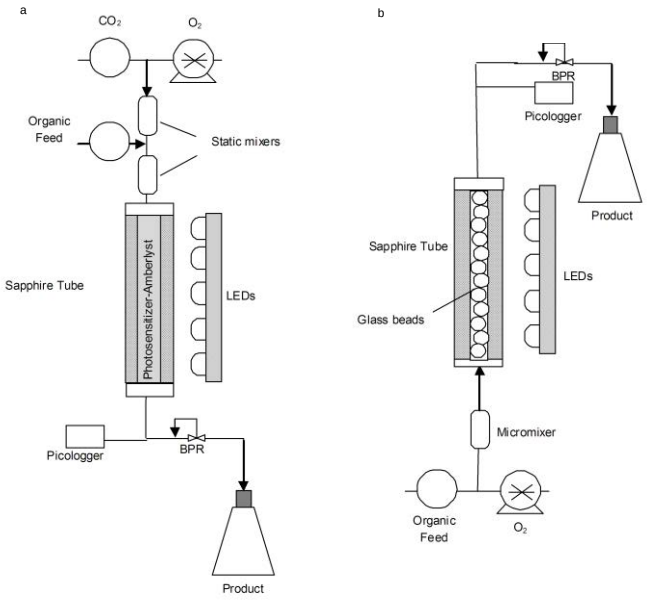


Figure 1.18: Schematic of continuous flow in (a) Strategy 1 setup with tubular reactor containing Photosensitizer-Amberlyst and (b) Strategy 2 setup with up-flow of aqueous solvent and organic reagents [58].

Table 1.8: Conditions and key findings of continuous flow under LEDs and batch reactions for artemisinin synthesis

	Solvent	Photo-catalyst	Yield
Strategy 1	EtOAc: CO_2	TPFPP-Amb	50%[a]
	Toluene:CO_2	TPP-Amb	51%[b]
			48%[c]
Strategy 2 (flow)	EtOH:H_2O[d] 60:40	$[Ru(bpy)_3]Cl_2$ ($2.0x10^{-4}$ $mol.L^{-1}$)	38%
	THF:H_2O[e] 60:40	$[Ru(bpy)_3]Cl_2$ ($1.0x10^{-4}$ $mol.L^{-1}$)	38%
Strategy 2 (batch)[f]	THF:H_2O 60:40	Rose bengal	53%
		TPP	56%
		$[Ru(bpy)_3]Cl_2$	66%

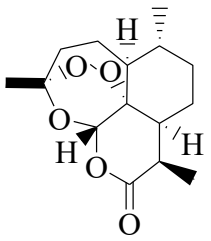
[a] Flow rate of DHAA in co-solvent was 0.05ml/min ; [b] Yield after 4 cycle; [c] Single pass yield by doubling the reactor length; [d] DHAA 0.02$mol.L^{-1}$ and flow rate was 0.25$ml.min^{-1}$; [e] DHAA 0.21$mol.L^{-1}$ and flow rate was 0.12$ml.min^{-1}$; [f] DHAA $5.3x10^{-2}mol.L^{-1}$ and photocatalyst 0.001mmol, acid employed was TFA.

1.5. Malaria and Artemisinin Combination Therapies (ACTs)

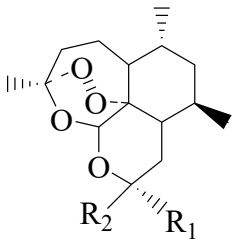
Malaria remains a major global health problem. Malaria, specifically cerebral malaria, caused by the parasite Plasmodium falciparum, claims the lives of 1–3 million people per year in developing countries, many of whom are children under 5 years of age [59]. The control of malaria largely depends on drug therapies, and, to a lesser extent, prophylaxis. Most of the

antimalarial drugs currently available have been in use for decades, but their use is now severely limited by the emergence and spread of drug resistance, primarily in Plasmodium falciparum [60]. For much of the twentieth century, malaria was treated with the fast-acting and inexpensive drugs chloroquine and pyrimethamine–sulphadoxine. From the 1960s onwards, these drugs progressively succumbed to the appearance and spread of resistance around the world. The sesquiterpene endoperoxide artemisinin is currently the most effective treatment against multi-drug resistant Plasmodium species, and artemisinin combination treatments (ACTs) are now first-line drugs, as recommended by the WHO. These are remarkably potent against the asexual blood stage of the parasite's life cycle, during which it replicates inside human red blood cells and causes the disease. Despite intensive resistance prevention campaigns, delayed rates of parasite clearance after administration of ACTs have been already observed near the Thai-Cambodian border [61, 62].

The herb *Artemisia annua L*. has been used in Chinese traditional medicine for centuries. Tu, inspired by artemisia usage described in Ge Hong's ancient book "Zhou Hou Bei Ji Fang", isolated white needles of artemisinin from the ethereal extract of the plant. In addition to artemisinin, several other sesquiterpenes were identified from the ethereal fraction, including arteannuic acid, arteannuin A, arteannuin B, arteannuin C, and amorphane. However, these compounds all show weak or no antimalarial activity. As a distinctive sesquiterpene, artemisinin contains five interweaving oxygen atoms that form a cyclic ether, a peroxy ether, a cyclic acetal and ketal, as well as a lactone. Given the absence of a solubilizing moiety in its structure, artemisinin is insoluble in water, and poorly soluble in lipids. The poor biopharmaceutical properties and low bioavailability of artemisinin restricts its clinical application, even though artemisinin was approved and launched by the Chinese Food and Drug Administration (CFDA) in 1985 [63]. Artemisinin's sesquiterpene trioxane lactone is essential for its activity. The lactone can easily be reduced (with sodium borohydride), resulting in the formation of dihydroartemisinin, which has an even higher antimalarial activity in vitro than artemisinin itself. Many derivatives such as artemether, arteether, artesunate and artelinic acid have been synthesized from dihydroartemisinin, and these are collectively called first-generation derivatives of artemisinin. Artemisinin and its derivatives (**Figure 1.19**) kill all stages of the malaria parasite (including 'young rings') by interacting with heme to produce carbon-centered free radicals that alkylate proteins and damage the microorganelles and membranes of the parasites [64].



Artemisinin

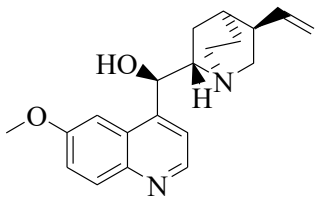


Artemether $R_1 = H, R_2 = OMe$
Arteether $R_1 = H, R_2 = OEt$
Artelinic acid $R_1 = H, R_2 = OCH_2C_6H_5COOH$
Artesunic acid $R_1 = O_2CCH_2CH_2COOH, R_2 = H$

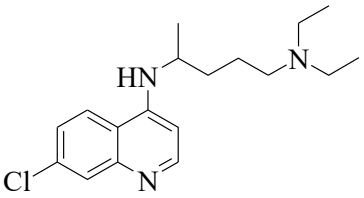
Figure 1.19: Artemisinin and its derivatives.

The first-generation artemisinin derivatives can be grouped into oil-soluble C(10) β-alkyl ethers (artemether and arteether) and water-soluble C(10) β-(substituted) esters (sodium artesunate and sodium artelinate). These drugs possess more oil/water solubility and antimalarial efficacy than the parent drug, artemisinin. Due to these reasons, they have mostly replaced the quinoline-based drugs (**Figure 1.20**) such as quinine (QN), chloroquine (CQ), amodiaquine and mefloquine (MQ) and their combination therapies in the treatment of malaria. Artemether and arteether are more potent than artemisinin but have short half-lives and showed fatal toxicities in animal models. Sodium artelinate, the sodium salt of artelinic acid, is sometimes used in the place of artesunate to overcome the hydrolytic instability experienced with the latter. In comparison to oil-soluble analogs (artemether and arteether), sodium artelinate is not only more stable in aqueous solution but also has a much longer biological half-life (1.5-3.0 h) with less CNS toxicity (in rats). The water-soluble artemisinin derivatives have a rapid onset of action, which makes them especially effective against severe malaria. At the same time, rapid disappearance from the blood may be a key reason behind their slow development of resistance in the malaria parasites. To nevertheless stop the spread of resistance, sodium artesunate is usually given in combination with more slowly eliminated drugs such as lumefantrine, amodiaquine, piperaquine, mefloquine and pyronaridine. This in turn increases the efficiency of treatment in resistant malaria. However, resistance to ACTs (e.g. artesunate-mefloquine) against *P. falciparum* has been observed in many parts of Southeast Asia. Recently, resistance against piperaquine was also found for the *P. falciparum* parasite. Due to this reason, triple ACTs such as artemether + lumefantrine + amodiaquine and artesunate + mefloquine + piperaquine have been recommended by the WHO for treating resistant *P. falciparum* malaria. Some of these combination therapies (e.g. artesunate + mefloquine + piperaquine) have shown positive results in TRACII study. Since mefloquine is active in piperaquine resistant strains and vice versa, this triple-drug combination can be an

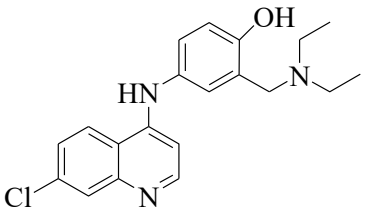
effective therapeutic approach to treat resistant malaria. High treatment costs (relative to chloroquine or quinine), unsatisfactory physicochemical/pharmacokinetic properties (poor lipid-water-partitioning behavior, inadequate bioavailability, short plasma half-life, etc.), toxicities and limited availability from natural sources are some other notable problems associated with artemisinin-based antimalarial agents [65].



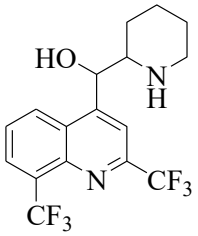
Quinine



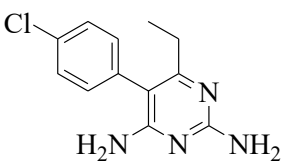
Chloroquine



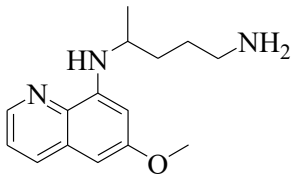
Amodiaquine



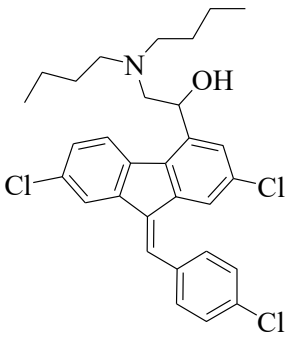
Mefloquine



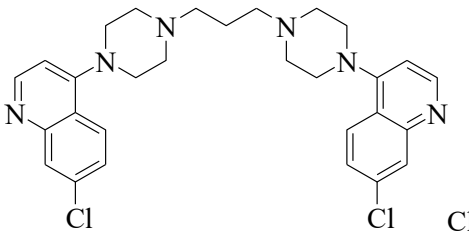
Pyrimethamine



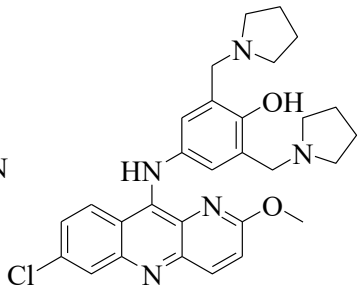
Primaquine



Lumefantrine



Piperaquine



Pyronaridine

Figure 1.20: Structures of some Antimalarial drugs**.**

1.5.1 Recent advances in Artemisinin synthesis

Artemisinin is derived naturally from the sweet wormwood plant Artemisia annua *L* [66, 67]. As the current frontline drug, the demand for artemisinin increases dramatically every year. However, the plant-based production is very slow and consequently, alternative semi-synthetic approaches to artemisinin and its more potent derivatives have been investigated [68, 69, 70]. Artemisinin acid (AA), a simple natural precursor of artemisinin, is 8-10 times more abundant

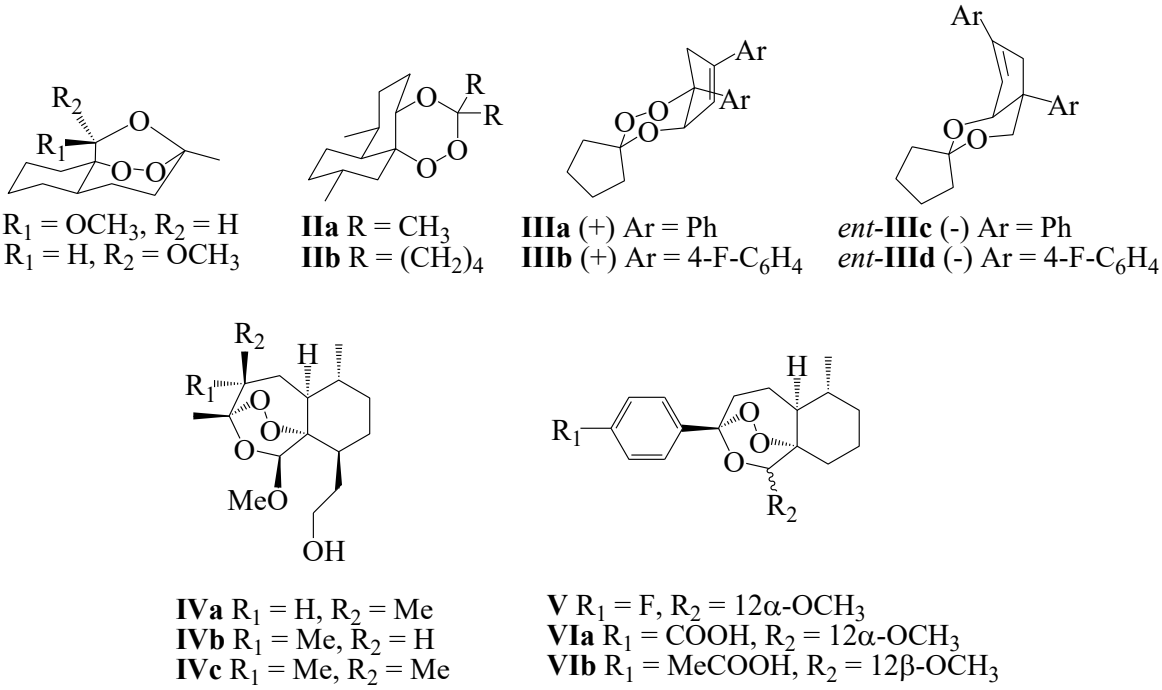
in plants than artemisinin itself [66]. A number of biosynthetic methods for the large-scale production of AA were thus developed in order to ensure a steady supply of artemisinin at low costs. One of the most critical steps during the synthesis of artemisinin is the regio- and diastereoselective reduction of artemisinic acid (AA) to dihydroartemisinic acid (DHAA). Artemisinin is accessible from dihydroartemisinic acid (DHAA) and its methyl ester via hydroperoxidation and rearrangements [69, 71, 72, 73, 74]. The photooxygenation of DHAA to form an intermediate hydroperoxide and its subsequent catalytic cyclization in the presence of a Lewis acid to form artemisinin was first reported by Roth and Acton in 1989 [75, 76, 77]. Keasling and coworkers, in collaboration with Amyris, later achieved the biosynthetic production of AA from yeast [69, 74]. This led to the development of a fully semisynthetic artemisinin manufacturing process on industrial scale (55% isolated yield) by Sanofi [78].

The Seeberger group later developed a continuous flow process for the two-step artemisinin synthesis protocol (photochemical transformation involving singlet oxygen and subsequent Hook cleavage of the intermediate hydroperoxide) that avoided the isolation and purification of the intermediates. The method employed tetraphenylporphyrin as a sensitizer in dichloromethane and a 450 W medium-pressure mercury lamp as a light source to convert DHAA into the intermediate hydroperoxide. The following Hook cleavage in the presence of oxygen resulted in the formation of artemisinin in 30% yield [47]. A year later the authors optimized the one-pot continuous flow production of artemisinin using a 420 nm LED module and 9, 10-dicyanoanthracene (DCA) as a photosensitizer, which increased the isolated yield to 57% [48a]. Rossen, Poliakoff, George and co-workers reported two sustainable approaches to artemisinin using white LED lights. Here, a solution of DHAA in an appropriate solvent is first fed into the reactor and artemisinin is collected directly at the outlet. Solvents and photocatalysts can be effectively recycled [79, 80]. Current research aims at developing shorter reaction times, simplified processes and easy downstream methods in order to ensure a cost-efficient supply of artemisinin.

1.6 1, 2, 4-Trioxanes as potential anti-malarial

The spreading resistance of *Plasmodium falciparum* to most of the current antimalarial drugs, as well as the absence of a vaccine for the protection against malaria, has created an urgent need for new effective, safe and affordable drugs. The difficult supply of artemisinin and its complex structure demand the design of cheaper synthetic endoperoxide-based antimalarials

[81]. It was shown in various studies on artemisinin and its derivatives that the endoperoxide ring was the biologically relevant moiety responsible for the killing of the parasite [82]. Further structure-activity relationship studies suggested that the lactone ring in artemisinin may not be essential for antimalarial activity [83, 84]. Subsequently, there have been a number of studies on synthetic and natural endoperoxide derivatives and simplified synthetic trioxanes (**Figure 1.21**). Of these, 1, 2, 4-trioxane compounds have emerged as effective leads that fulfill the minimal peroxide-based requirements for antimalarial activity [85]. Trioxane **I** and **II** were synthesized by photooxygenation of the appropriate enol-ether precursors. The isomers of **I** showed differences in antimalarial activities against *P. falciparum* strains. Better efficacy was observed for the spirocyclopantenyl substituted derivative **II** than the methyl group containing compound [86]. The high artemisinin-like activities of compounds **IIIa, IIIb, IIIc** and **IIId** suggested that a *cis*-fused bicyclic 1, 2, 4-trioxane moiety carrying an aryl substituent attached to the heterocycle significantly contribute to the activity [87]. A dramatic change in activity was seen in the cyclohexanone-derived trioxanes **IV** due to changes in configuration at one stereocenter. The 4β-methylated **IVa** can undergo 1, 5-hydrogen atom transfer and showed a 100 times higher potency than the 4α-methylated trioxane **IVb** and the 4, 4-dimethylated trioxane **IVc** [88]. The water-insoluble 3-*p*-fluorophenyl trioxane **V** was comparatively safer than artemeether. For the purpose of intravenous administration, water-soluble 3-*p*-carboxyphenyltrioxanes **VI** were synthesized from cyclohexane in five steps and **VIa** was reported to be a promising antimalarial agent [89].



Ia $R_1 = OCH_3$, $R_2 = H$
Ib $R_1 = H$, $R_2 = OCH_3$

IIa $R = CH_3$
IIb $R = (CH_2)_4$

IIIa (+) Ar = Ph
IIIb (+) Ar = 4-F-C_6H_4

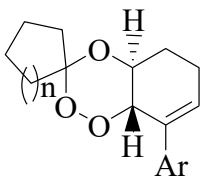
ent-**IIIc** (-) Ar = Ph
ent-**IIId** (-) Ar = 4-F-C_6H_4

IVa $R_1 = H$, $R_2 = Me$
IVb $R_1 = Me$, $R_2 = H$
IVc $R_1 = Me$, $R_2 = Me$

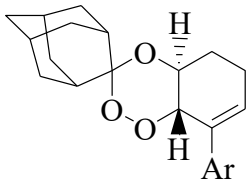
V $R_1 = F$, $R_2 = 12\alpha$-OCH_3
VIa $R_1 = COOH$, $R_2 = 12\alpha$-OCH_3
VIb $R_1 = MeCOOH$, $R_2 = 12\beta$-OCH_3

Figure 1.21: Trioxane compounds of potential antimalarial activity.

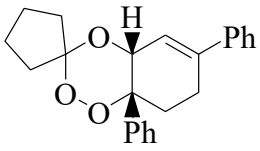
The *trans*-fused bicyclic 1, 2, 4-trioxanes **VII–X** (**Figure 1.22**) were prepared by photooxygenation of 3-aryl-2-cyclohexanols and spirocycloheptane **9** was found to be the most active compound. The poor antimalarial activities of trioxanes **VII–X** suggests that the *trans*-fusion may be unfavorable for artemisinin-like activity [90]. Under the same screening conditions another *trans*-fused trioxane **XI** showed weaker activity than the *cis*-fused **IIa** against the W2 *P. falciparum* clone [91]. Trioxanes **XII–XVI** were successfully synthesized as simple analogues with a sufficient activity for treating malaria. From various starting materials, the β-hydroxyhydroperoxides were obtained which were later coupled to different carbonyl compounds to prepare the desired trioxanes. A series of 6-[α-(3′-aryl-3′-hydroxypropyl) vinyl]-1,2,4-trioxanes (**XII**), showing promising antimalarial activity against multi-drug resistant *Plasmodium yoelii* in mice, were prepared from geranyl acetate [92]. Using cyclopropyl allylic alcohol as a starting material furnished the 1, 2, 4-trioxanes **XIII**. Antimalarial activity was found for the 6-arylvinyl- and 6-adamantylvinyl-substituted 1, 2, 4-trioxanes **XIV**, prepared from aryl substituted allyl alcohols [93]. Photooxygenation of methyl substituted allyl alcohols and subsequent catalysis resulted in the production of trioxanes **XV** and **XVI**, of which the spiroadamantane containing derivative exhibited increased anti-malarial activity [94].



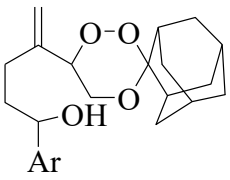
VII n = 1, Ar = 4-PhC_6H_4
VIII n = 2, Ar = 4-PhC_6H_4
IX n = 3, Ar = 4-PhC_6H_4



X Ar = 4-ClC_6H_4

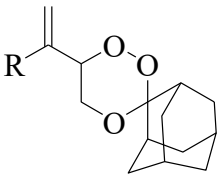


XI

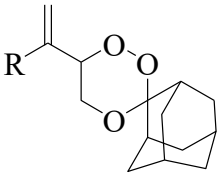


a, Ar = 4-Ph
b, Ar = 4-ClC_6H_4
c, Ar = 1-naphthyl
d, Ar = 4-PhC_6H_4

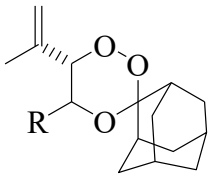
XIIa-d



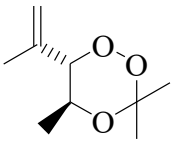
XIIIa R = cyclopropyl
XIIIb R = Ph



XIVa R = 2-tetrahydronaphthyl
XIVb R = 2-Phenanthrenyl
XIVc R = 2-fluorenyl



XVa R = CH_3
XVb R = cyclopropyl
XVc R = *n*-Pr



XVI

Figure 1.22: Some potentially active trioxane compounds.

Chapter: 2 Aims and Objectives

2. Aims and Objectives

2.1 Aims

The aims of the research work were to investigate dye-sensitized photooxygenations to known or potential antimalarial compounds, to adopt new continuous flow tools and to evaluate MOFs as potential photosensitizers.

2.2 Objectives

2.2.1 Photochemical synthesis of artemisinin

In line with literature and industrial processes, the production of artemisinin was envisaged from two different precursors, i.e. dihydroartemisinic acid (DHAA) and its mixed-anhydride. Initially, the synthesis of artemisinin was to be investigated under batch conditions using conventional laboratory equipment. Subsequently, the reaction protocols were to be transferred to an in-house built continuous flow reactor. A comparison of batch and flow operations was sought to demonstrate the superiority of flow reactors over conventional batch reactors.

- In-door photoreactions involved:
    - Tow-step batch conversion from dihydroartemisinic acid (DHAA).
    - One-pot batch conversion from dihydroartemisinic acid (DHAA).
    - Two-step mixed batch and flow process using dihydroartemisinic acid (DHAA).
    - Two-step in series flow reaction using dihydroartemisinic acid (DHAA).
    - One-pot flow process involving dihydroartemisinic acid (DHAA).
    - Batch conversions from the mixed-anhydride of DHAA.
    - Flow conversion using the mixed-anhydride of DHAA.
- Out-door photoreactions involved solar batch and solar flow photochemical transformation of DHAA.

2.2.2 Synthesise of novel 1, 2, 4-trioxane compounds

Since the 1, 2, 4-trioxane moiety in artemisinin is responsible for its antimalarial activity, the synthesis of simplified trioxanes was to be attempted. In particular, the synthesis of novel trioxane target compounds was envisaged from readily available allylic alcohols. Different carbonyl compounds and Lewis-acids were also to be investigated. The considered synthetic approach included:

- Photochemical conversions of allylic alcohols to form hydroperoxyalcohol intermediates were to be explored in batch and flow reactors.

- Peroxyacetalizations of the hydroperoxyalcohol intermediates were to be conducted in batch to obtain the desired 1, 2, 4-trioxanes.

2.2.3 Photooxygenation with Metal-organic-frameworks

The suitability of metal-organic-frameworks (MOFs) as photosensitizers for singlet oxygen generation was to be explored. The photooxygenation of α-terpinene was chosen as a model reaction to test different MOFs samples. Reactions were to be performed in a simple mini-batch reactor using either air or oxygen gas. A commercial solid-supported sensitizer was to be considered as a reference material. Likewise, model compounds that mimic potentially 'leached' photosensitizer from the MOF were to be investigated.

Chapter 3:

Results

3. Results

3.1 Reactors for photochemical synthesis

3.1.1 Batch setup

Batch reactions were conducted in a Pyrex Schlenk flask equipped with a cold finger (**Figure 3. 1**). A stream of air bubbles was supplied from an aquarium pump via a side arm of the Schlenk flask using a FEP tube with a HPLC filter attached to its end. A short FEP tube attached to the second side arm of the flask served as a gas outlet. The flask containing the reaction mixture was placed centrally inside a Rayonet chamber reactor (RPR-200 model, Southern New England Ultraviolet Company, Connecticut) equipped with 16 fluorescent tubes (Sylvania cool white F8T5/CW, 8 W). To monitor the reaction progress, samples were collected in 30 minutes intervals and analyzed by ^{1}H-NMR spectroscopy.

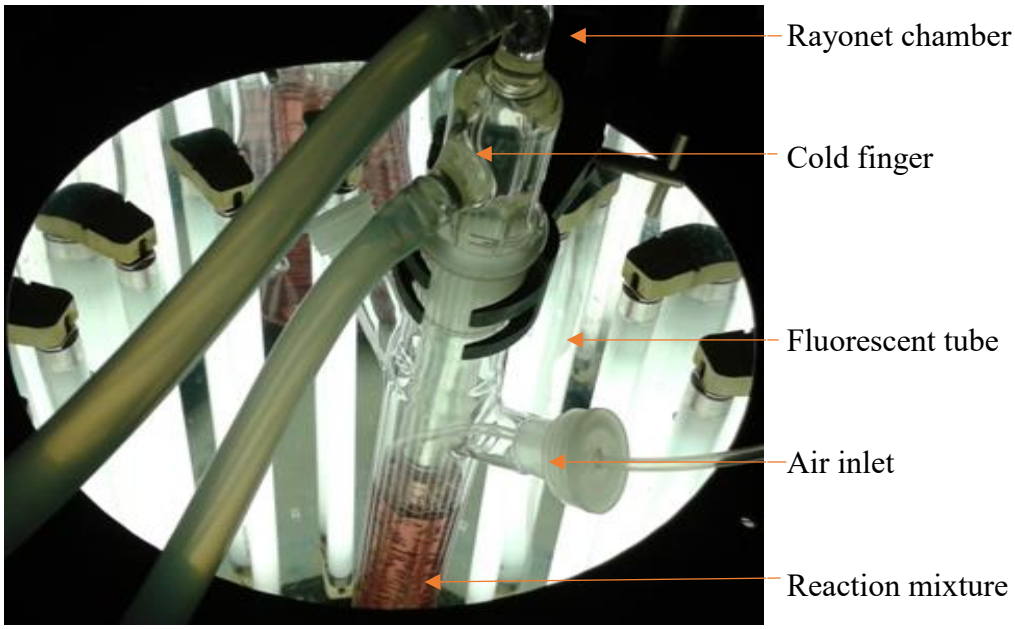


Figure 3. 1: Rayonet Reactor Chamber containing Schlenk flask.

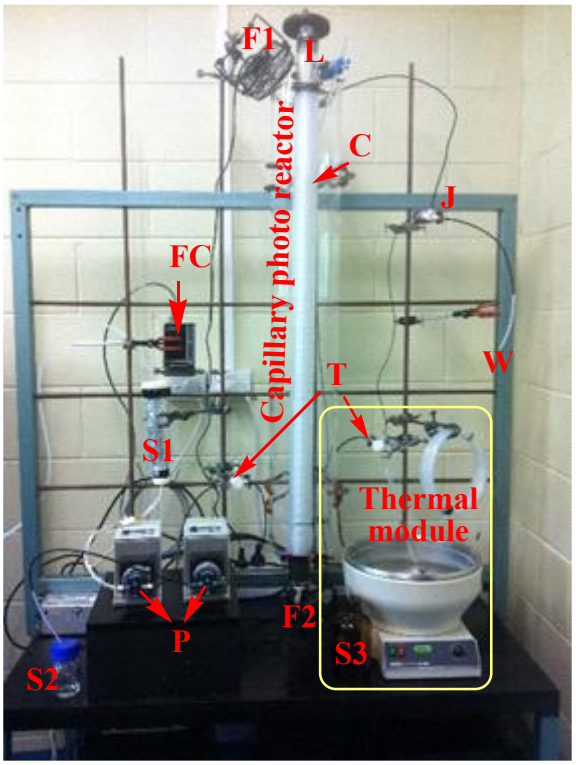
3.1.2 Flow setups

Three different types of flow reactor systems were used for the study of photooxygenation reactions.

3.1.2.1 In-house capillary flow reactor model – 1

The flow-photoreactor, fabricated in-house, comprised of transparent and chemically inert fluorinated ethylene polymer (FEP) tubing wrapped around a Crompton lighting cool white fluorescent tube of 20 W power and a surrounding Pyrex® sleeve shield (**Figure 3. 2**). The

FEP tubing had an inner diameter of 1.58 mm and the exposed tubing had a length of 49 m, resulting in an internal exposed volume of 96.02 mL. The reagents and air were introduced into the reactor via a T-mixer. An Ismatec piston pump was used to supply a steady flow of the liquid fraction, whereas an MKS Type 1179A gas flow controller was chosen to regulate the air flow rate. The combined liquid and air flows produced a slug-flow inside the FEP tubing, which was irradiated with visible light generated from a fluorescent tube. The temperature inside the Pyrex column was controlled by two Nexair cooling fans placed on the top and at the bottom. A T-valve was attached to the outlet of the photoreactor column that allowed for a switch between a product receiver and a secondary thermal reactor loop. For single step reactions, the product mixture was collected in an amber flask. For coupled reactions, the product mixture was allowed to pass through a second T-mixer through which an acid solution could be injected and subsequently through a thermal reactor loop consisting of a FEP tube of 38.64 m length (inner diameter: 1.58 mm).



S1and S2 = Reactants reservior
S3=Product collection reservior
P = Liquid flow controller pump
FC = Gas flow controller
L = Fluorescent Light
C = FEP capillary
F1 and F2 = Fans
T = T-mixer
J= T-junction
W = Waste outflow

Figure 3. 2: In-house built Capillary flow reactor.

3.1.2.2 In-house parabolic solar flow reactor

Solar flow reactions were performed in the parabolic trough concentrating solar reactor. The trough was made from a polished aluminium sheet. A glass tube was positioned in its focal line, which was covered by the reaction capillary. The later consisted of a 27 m long FEP

capillary tube with an internal volume of 53 mL. The temperature of the reaction mixture was controlled by flowing tap water through the center of the glass tube. A slug flow was produced inside the capillary by supplying reagents with an Ismatec piston pump and air with an aquarium pump (DYMAX 30, Charles Austen Pumps Ltd. England) via a T-mixer (**Figure 3. 3**).

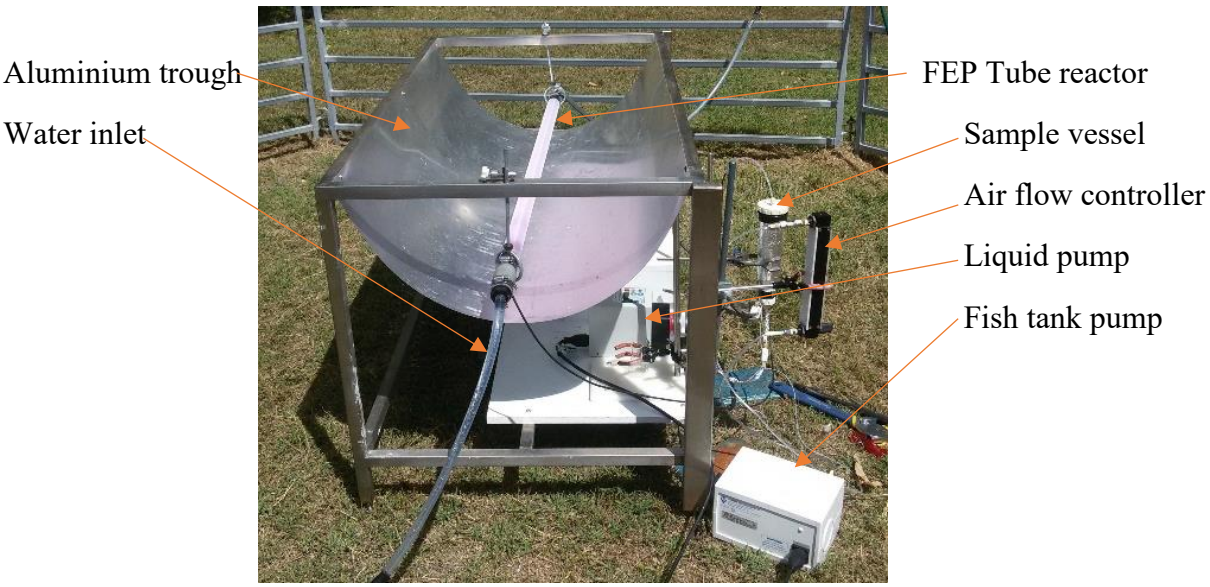


Figure 3. 3: In-house parabolic trough concentrating solar reactor.

3.1.2.3 In-house capillary flow reactor model – 2

The reactor was made of 28 m long (inner diameter: 1.58 mm) chemically inert FEP tubing wrapped around a Pyrex® glass cylinder (outer diameter: 7 cm) (**Figure 3. 4**). The reactor was placed centrally inside a Rayonet chamber photoreactor (RPR-200, Southern New England Ultraviolet Company, Connecticut) equipped with 16 fluorescent tubes (Sylvania cool white F8T5/CW, 8 W). In addition to the exhaust fan inside the reactor's chamber, a second fan (Nexair) was attached at the top to keep the temperature controlled. A slug flow of the liquid reaction mixture and air was produced via a T-junction. A steady liquid flow was maintained by an Ismatec piston pump and an air flow via an Alicat flow controller.

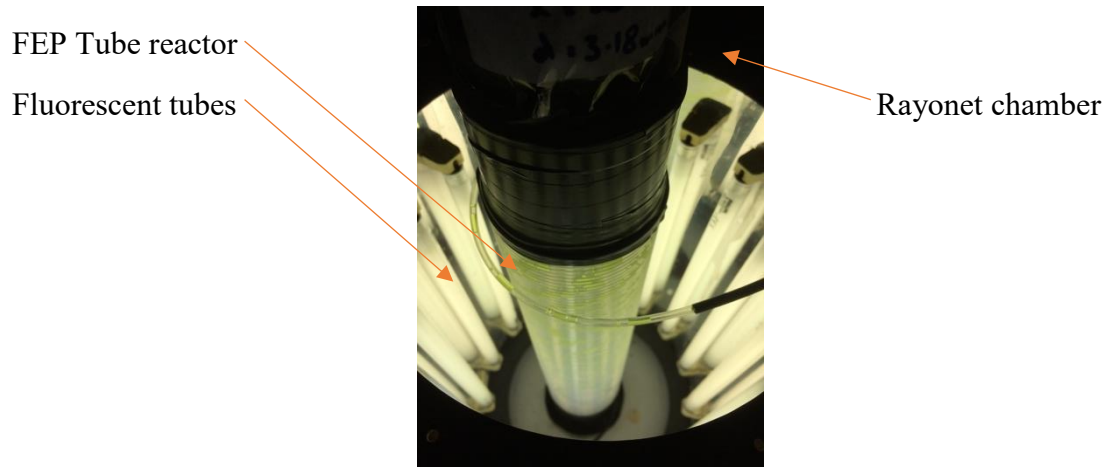


Figure 3. 4: In-house capillary flow set-up placed inside Rayonet chamber.

3.1.2.4 Vapourtec photoreactor

Selected photooxygenations were also realized in the commercially available Vapourtec-easy-photochem E-series reactor, which enabled control of wavelength, flow rate, residence time, temperature and pressure (**Figure 3. 5**). The reactor comprises of three main components: an easy-Scholar pump with control platform, an E-series cooling module and the UV-150 photochemical reactor loop. The easy-Scholar unit incorporates three advanced V3 continuous peristaltic pumps that allow operations at flow rates between 0.10 mL/min and 10 mL/min. The thermal tube reactor cartridge contains a 10 mL perfluoroalkoxy alkane (PFA) reactor coil for optional tandem photochemical-thermal couplings. A reagent and solvent bottle rack are located on the top of the reactor. The easy-Photochem system is also equipped with an adjustable back-pressure regulator (BPR) and a temperature control module. This cooling unit delivers chilled gas, either nitrogen or compressed air, to the UV-150 irradiation chamber. Within the photochemical module, the reactor room is separated and sealed from the lamp region, thus allowing effective cooling. Depending on the application, the reactor temperature can be varied between -5°C and 80°C. The UV-150 Photochemical chamber is fitted with a 3.6 W LED lamp and a 10 mL FEP reactor coil with a wall thickness of 0.15 mm and an internal diameter of 1.30 mm. The whole unit is accompanied by a touchscreen with the necessary control software installed.

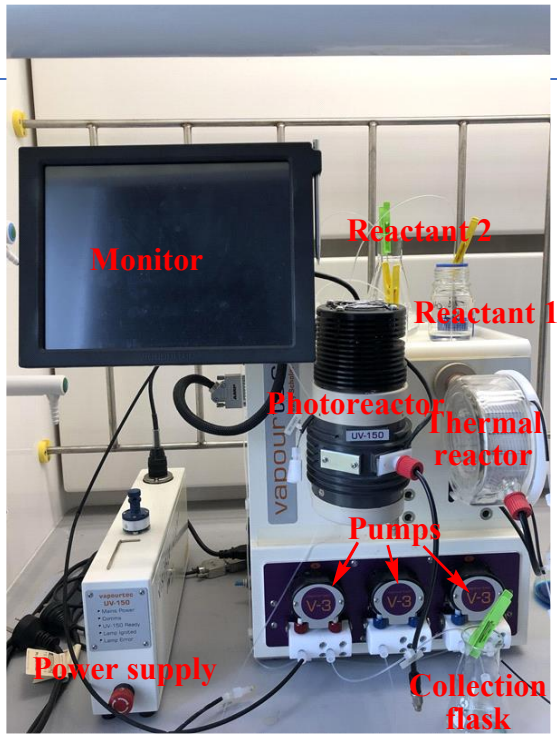
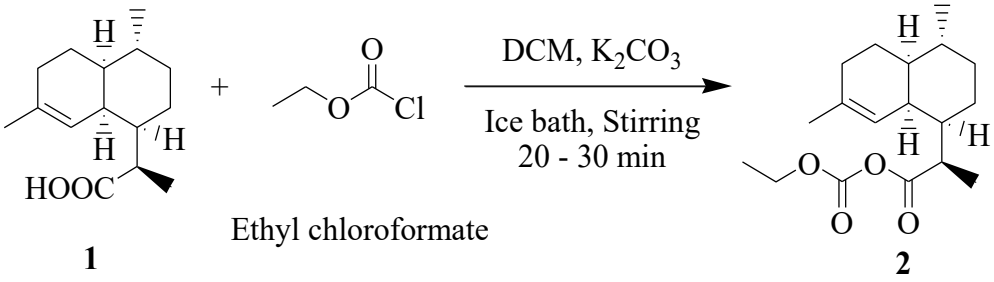


Figure 3. 5 Vapourtec flow photoreactor.

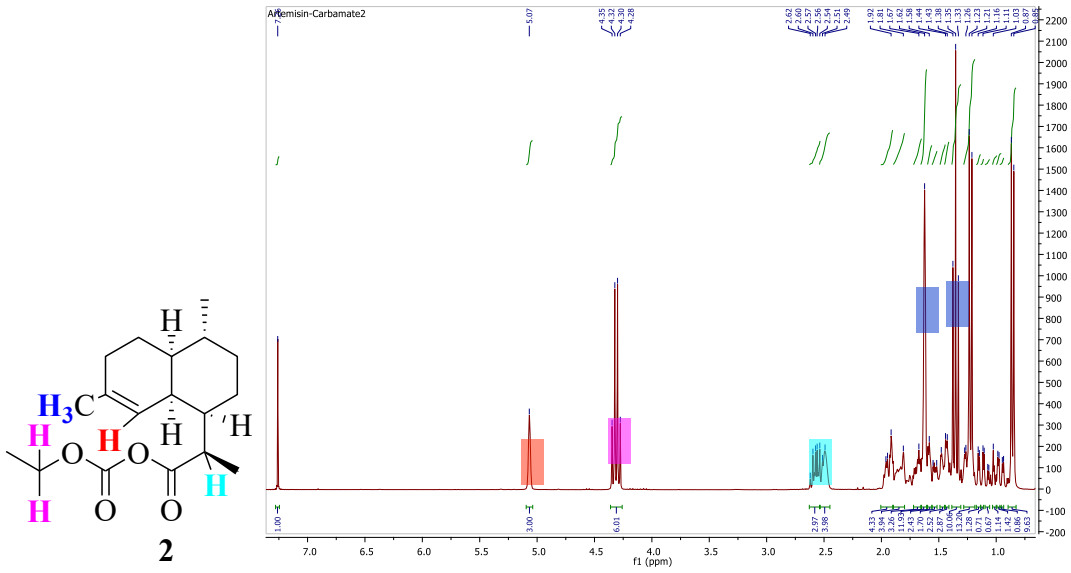
3.2 Artemisinin syntheses

3.2.1 Synthesis of the ethyl mixed carbonate of dihydroartemisinic acid (2)

The mild esterification reaction of dihydroartemisinic acid (**1**) with ethyl chloroformate in the presence of K_2CO_3 (**Scheme 3. 1**) was described by Dhainaut et al. [95]. After workup, (3R)-dihydroarteannuin B acid, ethyl mixed carbonate (**2**) was obtained in 94% yield as a colorless thick oil. The structure of **2** was confirmed by ^{1}H-NMR analysis that showed a characteristic quartet for the –COC$\underline{H_2}$CH$_3$ group at 4.31 ppm (**Figure 3. 6**).



Scheme 3. 1: Esterification of dihydroartemisinic acid **1**.

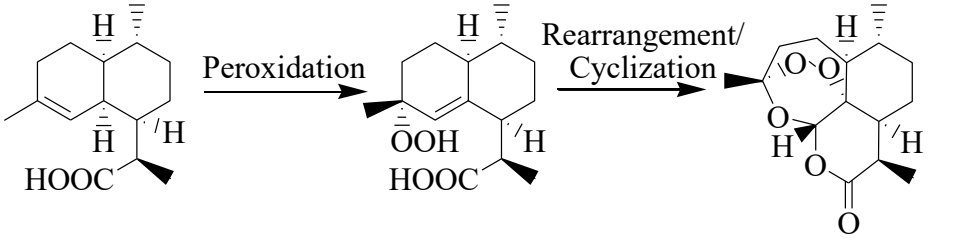


2

Figure 3. 6: [1]HNMR Spectrum of Mixed anhydride of DHAA (**2**).

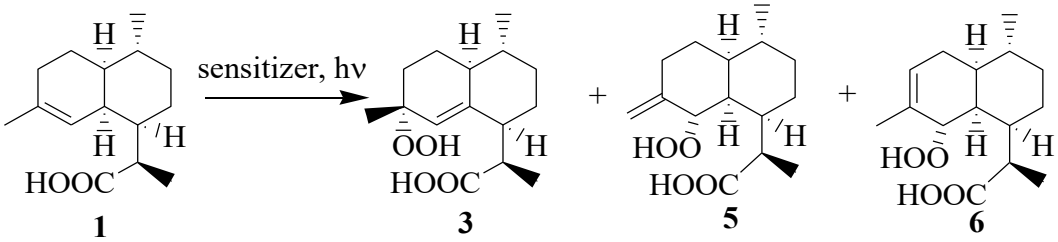
3.2.2 Artemisinin synthesis by photooxygenation of dihydroartemisinic acid

Artemisinin is a naturally occurring antimalarial drug [96, 97], which can be synthesized from dihydroartemisinic acid (DHAA). **Scheme 3. 2** shows the two-step transformation of **1** to artemisinin **4**. In step 1, photooxygenation of **1** forms the tertiary allylic hydroperoxide intermediate **3**. Subsequent Hook Cleavage of **3** in step 2, followed by spontaneous cyclization and rearrangement forms the final product **4**.



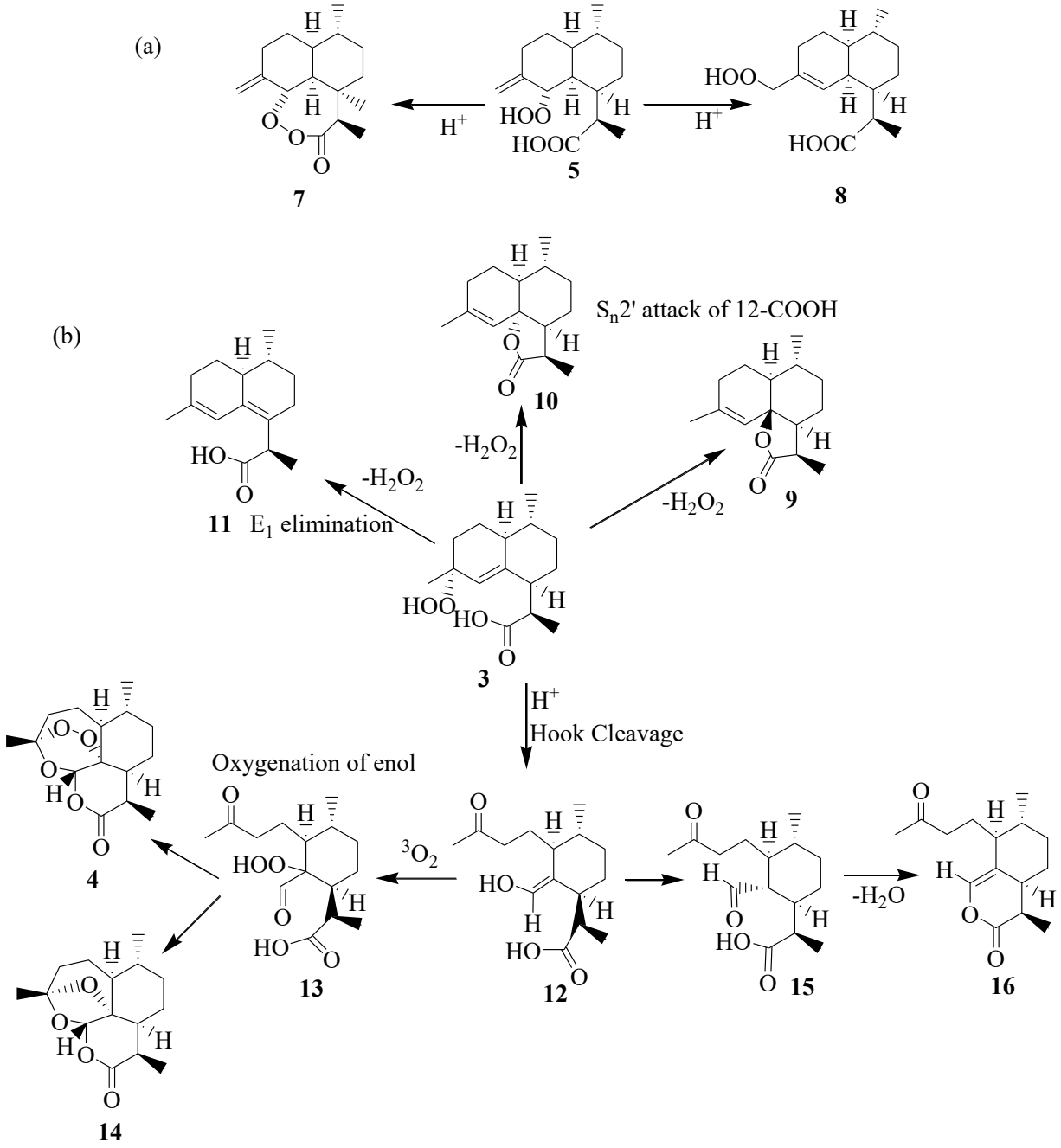
Scheme 3. 2: Synthesis of artemisinin **4** from DHAA **1**.

When **1** undergoes photooxygenation along with the desired hydroperoxide **3** two other minor hydroperoxides **5** and **6** are also formed (**Scheme 3. 3**).



Scheme 3. 3: Photooxygenation products **3**, **5** and **6** from **1**.

Of these, the secondary allylic hydroperoxide **5** undergoes spontaneous oxygenation to form the natural product arteannuin H **7** or 3, 2-allylic rearrangement to the primary allylic hydroperoxide **8** (**Scheme 3. 4a**) [98, 99].



Scheme 3. 4: (a) transformation of secondary allylic hydroperoxide **5** into **7** and **8**; (b) Spontaneous formation of **9**, **10** and **11** from **3**; and acid catalyzed transformation of 3 to form **4**, **14** and **16**.

The tertiary allylic hydroperoxide **3** can form **9**, **10** and **11** through elimination of hydrogen peroxide via different pathways. Upon acid treatment, **3** undergoes Hook cleavage and forms

enol compound **12**, which reacts with molecular oxygen to form the vicinal hydroperoxyl-aldehyde **13**. Spontaneous cyclization of **13** finally forms **4** and **14**, whereas in absence of molecular oxygen tautomerization of enol **12** forms the aldehyde **15**. Subsequent loss of water molecule from **15** furnishes the six-membered lactone **16** (**Scheme 3. 4b**) [100]. The characteristic proton NMR shifts of the three different hydroperoxide **3, 5** and **6** are summarized in **Table 3. 1** and those of the possible by-products from acid catalyzed thermal reactions are shown in **Table 3. 2**.

Table 3. 1: Characteristic ^{1}H-NMR signals of three hydroperoxides **3**, **5** and **6**.

Position	δ (ppm) of hydroperoxides		
	3	**5**	**6**
3	-	-	5.70(s)
5	5.24 (s)	4.72(s) & 4.75(s)	4.37(s) & 4.40(s)
11	2.73(q)	-	-
15	-	5.06(s) & 4.91(s)	-

Table 3. 2: Characteristic ^{1}H-NMR signals of different by-products.

Compounds	Position	δ (ppm)	Peak
7	5-H	5.02	d
8	5-H	5.54	s
9	5-H	5.64	s
10	5-H	5.53	s
11	5-H	6.13	s
13	5-H	9.93	d
14	5-H	5.70	s
15	5-H	9.58	d
16	5-H	6.08	s

3.2.2.1 Batch study

3.2.2.1.1 Two-step batch study for the synthesis of artemisinin

A number of solvents and sensitizers were applied to the photoreaction of **1** under batch conditions in order to find the best conditions for achieving complete conversion and high selectivity. All photoreactions were performed in a Rayonet chamber reactor, followed by TFA treatment in a conventional round-bottom flask. After aqueous workup, artemisinin was (wherever possible) isolated using a known crystallization method. To keep the batch and flow reactions separate all the batch reactions were denoted with Experiment numbers and flow reactions were denoted with Entry numbers in this thesis.

In line with the Seeberger protocol [101], dichloromethane was initially used for all batch photoreactions (**Table 3. 3**) and follow-up acid-cyclization reactions (**Table 3. 4**). Crude products were commonly analyzed by ^{1}H-NMR and their chemical compositions determined by integration of baseline separated signals. The estimated % of intermediate **3**, product **4** or other known byproducts do not represent yields. Significant losses of material were furthermore noticed for a range of experiments. Selected experiments are described below.

The photoirradiation of DHAA **1** in dichloromethane (62.4 mM) in the presence of tetraphenylporphyrin (TPP, 0.244 mM) resulted in complete conversion of **1** and formation of the intermediate hydroperoxide **3** in an estimated amount of 86% (by NMR, **Figure 3. 7**) (Experiment 1). The presence of intermediate **3** was confirmed by NMR analysis of the crude product and its methine (–CH=) proton was found at 5.24 ppm, in line with the literature [100]. Treatment with trifluoroacetic acid (TFA) under air bubbling for 2 hours at room temperature, produced a complex reaction mixture that contained, among numerous byproducts, an estimated amount of 19% of artemisinin **4** (by NMR).

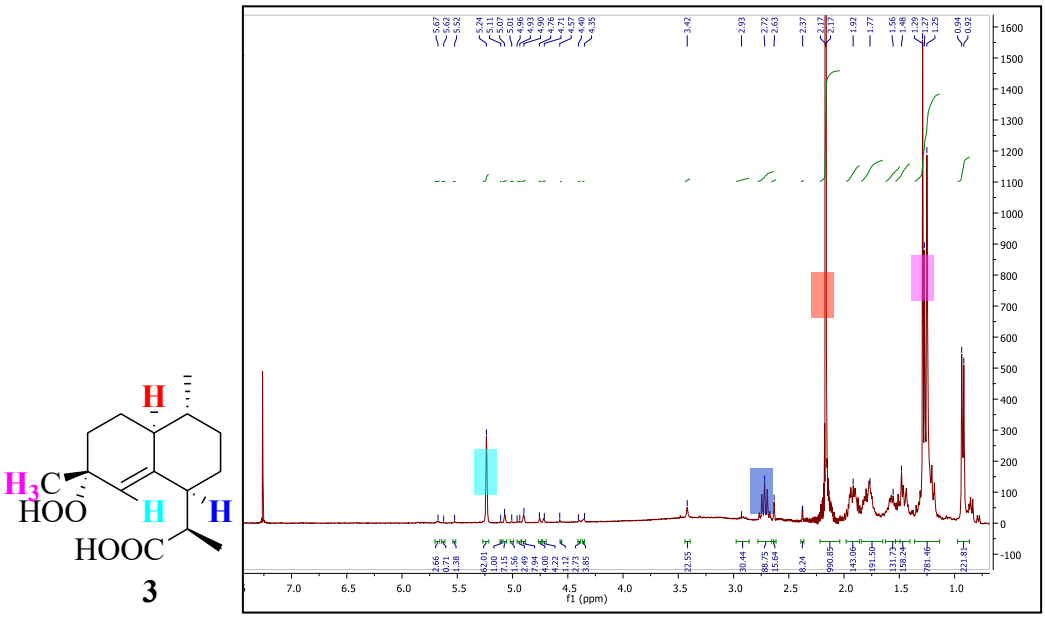


Figure 3. 7 : ^{1}H-NMR spectrum of crude hydroperoxide intermediate (**3**).

The modified Roth protocol [102] involved irradiation of a DHAA (**1**) solution in dichloromethane (10.6 mM) in the presence of methylene blue (0.234 mM) for 4 h (Experiment 5). Surprisingly, NMR analysis of the crude photoirradiation mixture showed no intermediate **3**, but artemisinin instead in an estimated amount of 60% (by NMR). Subsequent treatment with TFA and stirring for 4 days (although later considered unnecessary) somewhat reduced

the amount of artemisinin (**4**) to 54%. From this reaction, pure artemisinin was obtained through crystallization from cyclohexane in a yield of 47%.

When the same photooxygenation method was repeated, the desired intermediate **3** was again not found, with an estimated 21% (by NMR) of artemisinin formed instead. Subsequent thermal acid-treatment and stirring for 24 hours resulted in an estimated amount of **4** of 89% (by NMR). From this crude mixture, artemisinin could be isolated in 35% by crystallization (Experiment 6).

Another photoreaction was performed with a lower concentration of **1** (5.3mM) and methylene blue (0.117 mM) (Experiment 7). TFA was added directly to the crude photoproduct solution and the resulting mixture was stirred for 2 h in the presence of air and at 60°C. Although NMR analysis of the crude product suggested a large proportion of artemisinin of 91% (by NMR), the following crystallization only furnished an isolated yield of **4** of 8%.

When the same photoreaction was repeated (**1**: 5.3 mM; methylene blue: 0.117 mM), NMR analysis of the photoreaction mixture showed no intermediate **3** but the presence of artemisinin in an estimated amount of 21%. Following acid-treatment and stirring for 1 hour at room temperature, the resulting crude product contained an estimated 49% (by NMR) of artemisinin **4**, but which failed to crystallize (Experiment 26).

Photooxygenation of the same reaction mixture (**1**: 5.3 mM; methylene blue: 0.117 mM) for 2 hours gave an estimated amount of 19% of artemisinin (by NMR) but without any intermediate **3** (Experiment 21). Acidic alumina was tested as an alternative to TFA in the second step, but resulted in the formation of various byproducts next to approx. 12% of artemisinin (by NMR).

Using the same conditions, another photoreaction was performed (Experiment 22). 2 Drops of TFA were directly added to the crude photo solution, but resulted in the formation of complex mixture with approx. 47% of **4** (by NMR).

To further improve the selectivity and yield of **4**, additional batch studies were performed with altered conditions. At the end of each irradiation, the crude reaction mixture was filtered through a patch of silica in order to remove the sensitizer dye. TFA was subsequently added to the filtrate (Experiments 23-25 and 27).

Irradiation of DHAA (5.3 mM) in the presence of methylene blue (0.117 mM) for 2 h resulted in an estimated conversion of 40% with an estimated amount of **4** of 18% (by NMR). No intermediate **3** could be identified by NMR analysis (Experiment 23).

The photoreaction of DHAA (10.6 mM) with methylene blue (0.117 mM) for 3 hours showed an estimated conversion of 46% with about 26% of intermediate **3** and trance amounts of

artemisinin (Experiment 24). Subsequent treatment of the reaction mixture with TFA and stirring for 24 h gave artemisinin in an amount of 11% (by NMR).

Photoirradiation of DHAA (10.6 mM) with methylene blue (0.234 mM) for 3.5 h resulted in an estimated conversion of 77% with approx. 25% artemisinin **4** (by NMR) but no intermediate **3** (Experiment 25). Subsequent treatment with TFA gave a crude product that contained approx. 38% of **4** (by NMR).

The same photoreaction (**1**: 10.6 mM; methylene blue: 0.234 mM) conducted for 2.5 hours resulted in a calculated conversion of 95% with approx. 48% of **3** and 4% of artemisinin (by NMR). After the following thermal reaction conducted at room temperature for 1 hour, a crude product containing approx. 24% of artemisinin (by NMR) and other byproducts was isolated (Experiment 27).

To confirm the need for oxygen, a photochemical reaction was performed in the absence of air (Experiment 18). Subsequent NMR analysis confirmed the presence of mainly starting material, although trace amounts of **3** and 2% of artemisinin (by NMR) could be detected as well. After the thermal follow-up reaction, the crude product consisted of 91% of DHAA and 5% of artemisinin (by NMR).

Rose Bengal bis-(triethylammonium) salt (RB-TEA) was furthermore investigated as a sensitizer with improved solubility in dichloromethane. The corresponding photochemical reaction resulted in a conversion of approximately 93%, with 81% of **3** (by NMR). After the succeeding thermal reaction, artemisinin (**4**) could be isolated in a yield of 14% (Experiment 28).

A reduction in the amount of RB-TEA (Experiment 29) resulted in a calculated conversion of 67% with 48% of **3** (by NMR). After the thermal reaction, artemisinin (**4**) was again isolated in a yield of 15%.

Changing the sensitizer amount of RB-TEA to 0.159 mM gave an estimated conversion of 83% with 49% of **3** (Experiment 30). Using a larger amount of TFA in the subsequent thermal step produced a crude product that contained about 38% of artemisinin (by NMR), although further isolation by crystallization was unsuccessful.

Repetition of the same 2-step experiment gave a crude reaction mixture with a calculated amount of 42% (by NMR) for artemisinin (Experiment 31).

Table 3. 3: Conditions for batch photoreactions (step-1) of DHAA **2** with TPP/methylene blue in Dichloromethane (80mL).

Exp	DHAA 1		Sensitizer		Irradiation	Conv.	Compositions [normalized to 100%]								Comment
	[mg]	[mM]	Type	[mM]	[h]	[%]	**1**	**3**	**5**	**6**	**4**	**7**	**8**	**9**	
1	1180	62.4	TPP	0.244	2	100	-	**86**	11	3	**-**	-	-		~10% impurities were excluded while calculating the integrals in all cases and only the genuine know peaks were taken in account. In some cases, after step 1 directly proceeded to step 2 reaction without analyzing the photo-product samples. Hence the conversion and intermediate hydroperoxides were not determined.
5	200	10.6	MB	0.234	4	88	12	**-**	-	-	**60**	6	-	22	
6	200	10.6	MB	0.234	4	69	31	**-**	10	-	**21**	-	-	38	
7	100	5.3	MB	0.117	2	ND				ND					
[Δ]18	200	10.6	MB	0.117	3	7	93	**1**	1	2	**2**	-	-	1	
21	100	5.3	MB	0.117	2	69	31	**-**	9	7	**19**	-	11	23	
22	100	5.3	MB	0.117	2	ND				ND					
23	100	5.3	MB	0.117	2	40	60	**-**	5	2	**18**	-	-	15	
24	200	10.6	MB	0.117	3	46	54	**26**	8	3	**1**	-	4	4	
25	200	10.6	MB	0.234	3.5	77	23	**-**	15	10	**25**	-	8	19	
26	100	5.3	MB	0.117	2	72	28	**-**	11	5	**21**	-	10	25	
27	200	10.6	MB	0.234	2.5	95	5	**48**	6	4	**4**	9	12	12	
28	200	10.6	RB-TEA	0.212	2	93	7	**81**	3	2	**-**	4	2	1	
29	200	10.6	RB-TEA	0.106	2	67	33	**48**	6	6	**1**	3	2	1	
30	200	10.6	RB-TEA	0.159	2	83	17	**49**	12	7	**2**	-	7	6	
31	200	10.6	RB-TEA	0.159	2	ND				ND					

Conversion and compositions were determined by ^{1}H-NMR (±3%); methylene blue (MB), tetraphenylporphyrin (TPP), rose Bengal bis-(triethylammonium) salt (RB-TEA); r.t. (room temperature) ND (not determined); [Δ] A photoreaction without air, but air was supplied in the second thermal reaction step.

Table 3. 4: Conditions for follow-up batch thermal reaction (step-2).

Exp	Acid		Time	Temp.	Wt.	Compositions [normalized to 100%]										Comment
	Type	amount			[mg]	1	4	7	9	10	11	13	14	15	16	
1	§TFA	0.19 mL	2 h	r.t.	513	10	**19**	15	19	-	-	-	-	32	5	~10% impurities were excluded while calculating the integrals in all cases and only the genuine know peaks were taken in account.
5	*TFA	0.2 mL	4 days	r.t.	270	15	**54**	11	11	2	5	-	2	-	-	
					112$^{¤}$		**47$^{\alpha}$**									
6	*TFA	0.2 mL	24 h	r.t.	211	5	**89**	-	4	-	-	-	2	-	-	
					83$^{¤}$		**35$^{\alpha}$**									
7	§TFA	1 drop	24 h	60°C	47	3	**91**	3	3	-	-	-	-	-	-	
					9.7$^{¤}$		**8$^{\alpha}$**									
18	§TFA	0.19 mL	2 h	r.t.	109	91	**5**	-	1	-	-	2	-	-	1	
21	§acidic alumina	catalytic amounts	1 h	50°C	113	8	**12**	6	63	11	-	-	-	-	-	
22	TFA	2 drops	24 h	r.t.	80	20	**47**	12	21	-	-	-	2	-	-	
23	$^{\#}$TFA	1-2 drops	1 h	r.t.	53					ND						
24	$^{\#}$ TFA	0.19 mL	24 h	r.t.	98	65	**11**	10	7	-	-	-	7	-	-	
25	$^{\#}$ TFA solution	1 drop	2 h	55°C	122	26	**38**	8	26	-	-	-	2	-	-	
26	§TFA	1-2 drops	1h	r.t.	78	17	**49**	11	23	-	-	-	-	-	-	
27	$^{\#}$TFA	1-2 drops	1h	r.t.	332	13	**24**	6	52	-	5	-	-	-	-	

28	§TFA	2 drops	2 h	50°C	163	10	**48**	6	13	-	-	-	-	-	23	
					33¤		**14α**									
29	§TFA	2 drops	2 h	50°C	157	29	**49**	11	11	-	-	-	-	-	-	
					35¤		**15α**									
30	§TFA	2 drops	2 h	50°C	168	28	**38**	14	8	-	8	-	3	-	1	
31	§TFA	0.1 ml	2 h	50°C	102	31	**42**	16	3	-	4	-	4	-	-	

Compositions were determined by ^{1}H-NMR (±3%); § after irradiation TFA or acidic alumina was added to the reaction mixture with continuous air bubbling, *Catalysis was done as per Roth and Acton, 1991; # after irradiation the reaction mixture was filtered through silica to remove dye. To the filtrate, in a flask, TFA was added under air bubbling condition and stirred; ¤ Isolated weight; α Isolated yield; Exp 5 and 6 was done in n-hexane and others were in dichloromethane; Exp 5,6, 23, 24, 25, 27- filtration through silica after step 1 reaction (in others filtration through silica after step 2 reaction), not determined (ND).

Further batch photoreactions of **1** (5.6 mM) in combination with methylene blue (0.125 mM) were performed using acetone as a solvent and the results are described in **Table 3. 5**. Acetone was considered a more environmentally friendly solvent compared to dichloromethane. The results from the subsequent thermal reaction are summarized in **Table 3. 6**. Conversions and product compositions were again estimated by NMR analysis. However, the majority of the reactions gave unknown byproducts that were omitted in these estimations. The calculated proportions of **3** and **4** are thus unrealistically high. This becomes evident when comparing the estimated amount of artemisinin in a crude product mixture (as determined by NMR), with actual isolated yields.

Photoirradiation for 4 hours resulted in 100% conversion with an estimated amount of 83% for intermediate **3** (by NMR). The follow-up reaction conducted for 4 days yielded a crude mixture containing approx. 53% of **4** (by NMR), next to other by-products (Experiment 2).

Repetition of the same experiment with 5 hours of irradiation showed complete conversion with a calculated amount of **3** of 89% (by NMR). Subsequent thermal treatment for 4 days resulted in an isolated yield of 19% for artemisinin **4** (Experiment 3). The FTIR analysis of the collected crude intermediate hydroperoxide (**Figure 3. 8a**) showed characteristic bands by the important functional groups which were assigned as abroad peak at around 3300 cm^{-1} due to strong absorption by OH group stretching and the C-H stretching was observed by sharp peak at 2927 cm^{-1} and 2868 $cm^{-}1$. Peaks observed at 1700 cm^{-1} was due to absorption by C=O group. The peaks at 1455 cm^{-1} and 912 cm^{-1} indicated the OH bending vibration. The isolated artemisinin's FTIR spectrum (**Figure 3. 8b**) bands were assigned by comparing the literature data [[103]] The observed medium intensity absorption peak at 2923 cm^{-1} and 2870 cm^{-1} were due to C-H_2 stretching and the other important sharp peak observed at 1705 cm^{-1} which was exerted by the C=O stretching vibration. Peak at 1456 cm^{-1} was by C-H_2 bending and 1374 cm^{-1} may be due to C-H_3 stretching. The stretching vibration due -O- showed peak at 1081 cm^{-1}, -C-O- stretch absorption peaks were at 1031 cm^{-1} and 1012 cm^{-1}. The C-C stretching vibrations were at 992 cm^{-1} 928 cm^{-1} and 832 cm^{-1}.

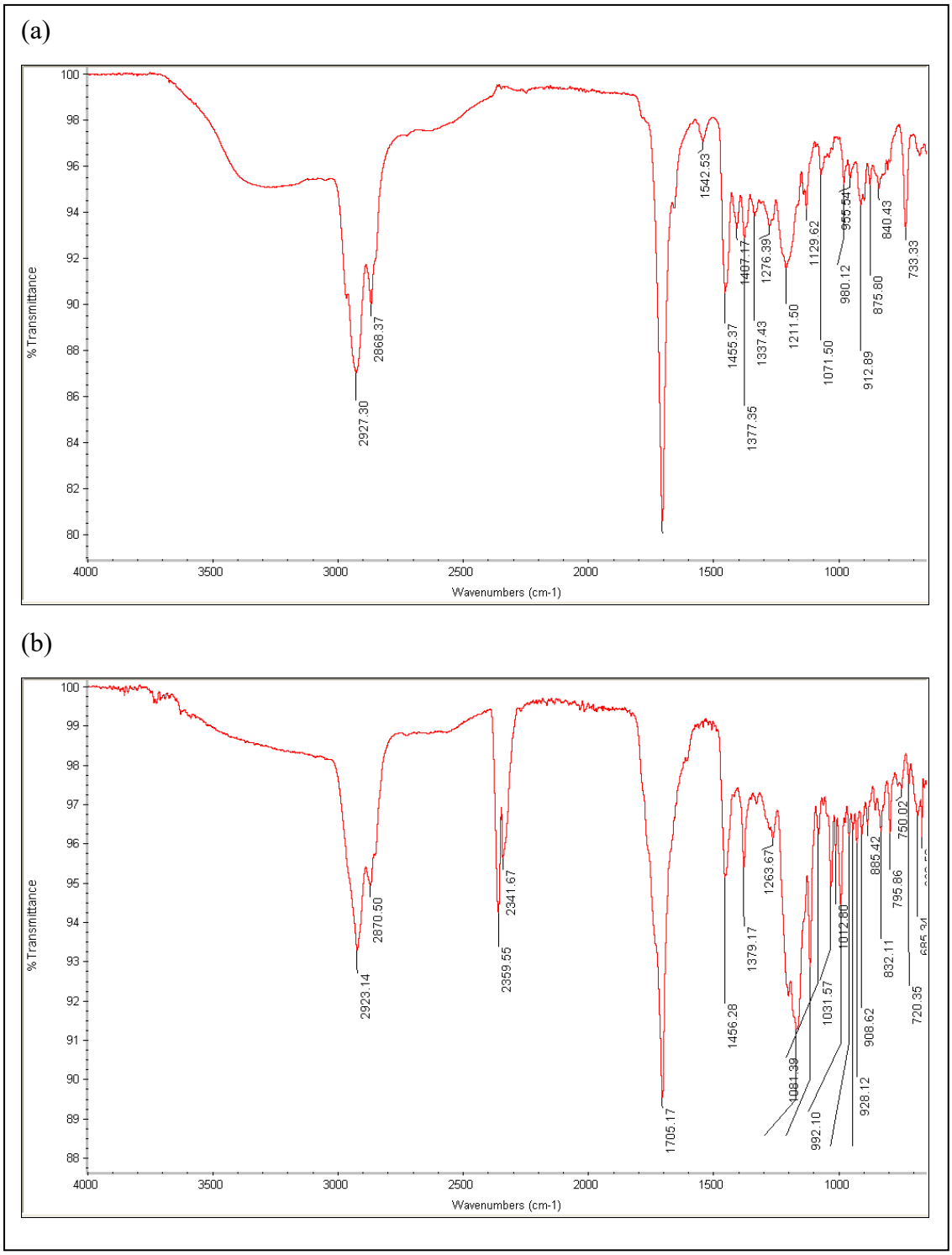


Figure 3. 8: FTIR spectra of (a) intermediate hydroperoxide **3** and (b) artemisinin **4**.

When the same photoreaction was repeated, intermediate **3** was obtained in a calculated amount of 79% (by NMR) and artemisinin **4** was isolated in a yield of 23% (Experiment 4).

Decreasing the irradiation time to 3.5 h resulted in a calculated conversion of 88% with approx. 76% of intermediate **3** formed. Acid treatment for 2 h at 60°C gave product **4** in an isolated yield of 28% (Experiment 8).

However, repetition of the same reaction showed an increase in conversion to approx. 99% with an estimated amount of intermediate **3** of 78% (by NMR). After the subsequent thermal reaction, an amount of artemisinin of approx. 56% in the crude product mixture was calculated (by NMR). Attempts to isolate **4** by crystallization remained unsuccessful (Experiment 11).

A photoirradiation conducted for 3 hours also furthermore performed but the conversion rate and amount of intermediate **3** could not be determined by NMR due to the complex product mixture. The subsequent thermal reaction conducted with *p*-toluenesulfonic acid as catalysis gave a crude product that contained approx. 21% of DHAA (**1**) and 11% of artemisinin (by NMR) (Experiment 12).

Another photoreaction was performed for 2 hours, showing 99% conversion with a calculated amount of **3** of 83%. An approx. amount of 56% of artemisinin was determined in the crude product after 2 h of acid catalyzed treatment at 60°C (Experiment 14).

Table 3. 5: Batch photoreactions of DHAA **1** (5.6 mM, 100 mg) using acetone 75 mL and methylene blue (0.125 mM).

Exp	Irradiation	Conv.	Compositions [normalized to 100%]							
	[h]	[%]	**1**	**3**	**5**	**6**	**4**	**7**	**8**	**9**
2	4	100	-	**83**	10	4	-	-	-	3
3	5	100	-	**89**	9	2	-	-	-	-
4	5	100	-	**79**	5	3	-	-	5	8
8	3.5	88	12	**76**	7	2	-	-	1	2
11	3.5	99	1	**78**	7	11	-	-	-	3
12	3					ND				
14	2	99	1	**83**	9	4	-	-	2	1

Conversion and compositions were determined by ^{1}H-NMR (±3%), not determined (ND).

Table 3. 6: Batch thermal reactions of photo-products of experiments from Table 3.5.

Exp	Acid		Solvent	Wt.	Time	Temp.	Compositions [normalized to 100%]								
	Type	Amount		(mg)			**1**	**4**	**7**	**9**	**11**	**13**	**14**	**15**	**16**
2	*TFA	1 drop	n-hexane	159	4 days	r.t.	-	**53**	31	11	-	-	5	-	-
3	*TFA	1 drop	n-hexane	23[¤]	4 days	r.t.	-	**38**	20	13	-	-	-	-	29
								19 [α]							
4	*TFA	1 drop	Acetone	28[¤]	24 h	r.t.	-	**31**	3	43	16	-	3	-	4
								23 [α]							

8	[§]TFA	1 drop	Acetone	182 33[¤]	2 h	60°C	43	**25** **28** [α]	-	12	7	-	9	-	4
11	[§]TFA	1drop	Acetone	109 38[¤]	2 h	60°C	-	**56**	19	3			19		3
12	[§]p-TSA	Catalytic amount	Acetone	112	2 h	60°C	21	**11**	17	10			38		3
14	[§]TFA	1drop	Acetone	51	2 h	60°C	Trace	**56**	20	6			9		8

Conversion and compositions were determined by ^{1}H-NMR (±3%); * Catalysis was done as per Roth and Acton, 1991; [§] after irradiation complete TFA/ p-TSA (p-Toluenesulfonic acid) was directly added to the final reaction mixture with air bubbling; [¤] Isolated weight; [α] Isolated yield.

Photooxygenations of DHAA (**1**) were furthermore conducted for 5 hours in ethanol as a sustainable solvent using rose Bengal as photosensitizer and the results are shown in **Table 3. 7**. The subsequent results of the corresponding acid-catalyzed cyclization reactions are summarized in **Table 3. 8**. Conversions and product compositions were again calculated from NMR integrations. Unknown byproducts were omitted in these calculations. The estimated amounts of **3** and **4** are thus unreasonably high. This becomes evident when comparing these values with actual isolated yields of artemisinin.

The photoreaction of DHAA (**1**; 11.3 mM) in the presence of rose Bengal (0.274 mM) resulted in a calculated conversion of 92% with an estimated amount of 71% for intermediate **3** (by NMR). After acid treatment and workup, 58% of artemisinin were estimated in the crude product (by NMR). Crystallization from cyclohexane furnished **4** in an isolated yield of 17% (Experiment 13). Its identity was confirmed by ^{1}H-NMR analysis (**Figure 3. 9**).

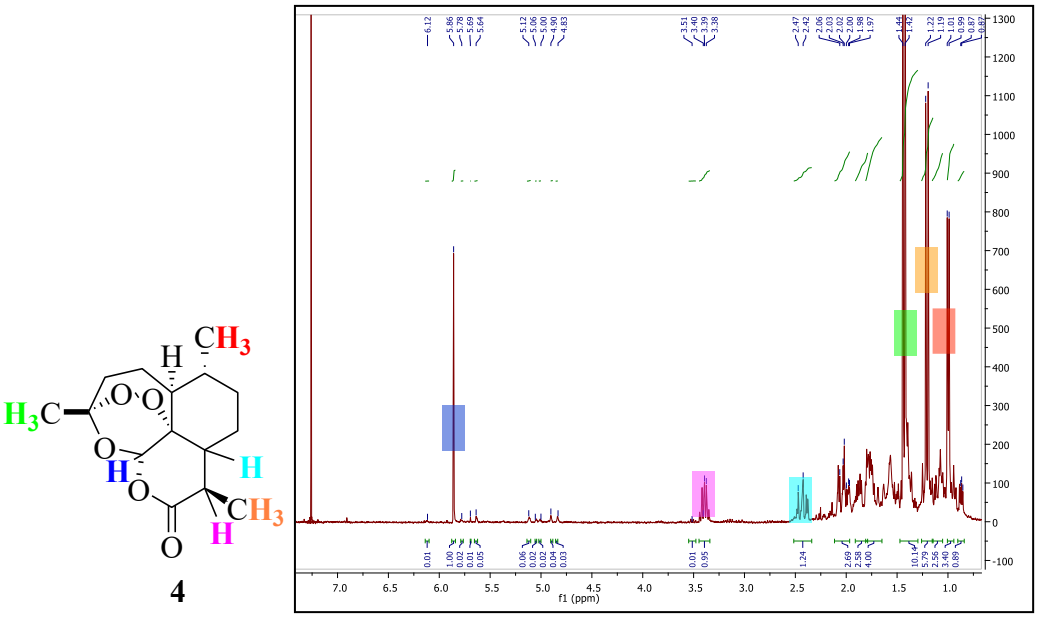


Figure 3. 9: ^{1}H–NMR spectrum of recrystallized artemisinin **4**.

A reaction conducted with a decreased concentration of **1** resulted in a complex mixture and subsequently, conversion and amount of intermediate **3** could not be determined by NMR. However, ^{1}H-NMR analysis at the crude product obtained after TFA-catalyzed cyclization showed the presence of approx. 42% of DHAA **1** and 10% of product **4** (Experiment 15).

A further reaction (**1**: 10.6 mM; rose Bengal: 0.257 mM) furnished a calculated conversion of 96% with an estimated amount hydroperoxide **3** of 85% (by NMR). After treatment with TFA,

the crude product obtained was found to contain approx. 40% of **4**. After crystallization, however, only 4% of artemisinin **4** could be isolated (Experiment 16).

A photooxygenation with reduced amounts of DHAA **1** and rose Bengal resulted in a calculated conversion of 92% with approx. 72% of **3** (by NMR). After the subsequent thermal reaction, an estimated amount of 56% of artemisinin **4** was determined in the crude mixture (by NMR) (Experiment 17).

When the photoreaction of **1** with rose Bengal was performed in the absence of an oxygen source, no intermediate **3** was observed. However, after thermal catalysis upon air bubbling, a 78% conversion with an estimated amount of **4** of 44% was obtained (by NMR) (Experiment 20).

Table 3. 7: Batch photoreactions of **2** in Ethanol.

Exp	DHAA 1		RB	Volume	Conv.	Compositions [normalized to 100%]							
	[mg]	[mM]	[mM]	[mL]	[%]	**1**	**3**	**5**	**6**	**4**	**7**	**8**	**9**
13	200	11.3	0. 274	75	92	8	**71**	7	5	1	-	-	8
15	191.2	10.7	0. 274	75					ND				
16	200	10.6	0.257	80+5 H_2O	96	4	**85**	8	3	-	-	-	-
17	100	3.5	0.171	120	92	8	**72**	7	5	2	-	4	2
[#]20	100	4.2	0.205	100					ND				

Conversion and compositions were determined by ^{1}H-NMR (±3%); All photoreactions were performed for 5 hours; Rose Bengal (RB), [#]Photoreaction without any air or oxygen, not determined (ND).

Table 3. 8: Batch thermal reactions of photo-products of experiments from Table 3.7.

Exp	TFA	Time	Temp.	Wt.	Compositions [normalized to 100%]								
		[h]		[mg]	**1**	**4**	**7**	**9**	**11**	**13**	**14**	**15**	**16**
13	1 drop	2	60°C	104	9	**58**	25	1	-	2	2	-	3
				41 [¤]		**17** [α]							
15	1 drop	1	50°C	101	42	**10**	7	5	1	8	3	1	23
16	0.19mL	2	60°C	218	11	**40**	-	3	-	5	9	2	30
				11 [¤]		**9** [α]							
17	0.19mL	6	r.t.	50	-	**59**	13	3	-	15	-	7	3
20 (air)	1 drop	2	60°C	78	15	**44**	21	2	-	3	2		13

Conversion and compositions were determined by ^{1}H-NMR (±3%); Room temperature (r.t.), [¤] Isolated weight; [α] Isolated yield;

Batch photooxygenations of DHAA in a mixture of isopropanol and water as an environmentally benign medium were also explored and the results are summarized in **Table 3. 9**. Likewise, the results from the subsequent acid-treatment processes are shown in **Table 3. 10**. As before, conversions and product compositions were calculated by NMR analysis, ignoring unknown byproducts.

When a solution of **1** (10.7 mM) was irradiated in the presence of rose Bengal (0.274 mM) for 3.5 hours, a conversion of 97% and an approx. amount of 74% of **3** were calculated by NMR. After acid-catalytic treatment for 2 hours, a crude product with an estimated amount of 71% of product **4** was obtained. Subsequent crystallization gave **4** in an isolated yield of just 7% (Experiment 9).

A thermal acid-catalyzed reaction was also performed using concentrated HCl instead of TFA but no product **4** was obtained (Experiment 10).

Changing the sensitizer to methylene blue (0.0957 mM) and irradiation for 5 hours resulted in an estimated conversion of 58% with approx. 20% of intermediate **3** (by NMR). After acid-catalyzed treatment at room temperature, the crude product obtained showed a calculated amount of artemisinin (**4**) of 25% (Experiment 19).

An additional photoreaction with rose Bengal (0.257 mM) for 3.5 hours showed an estimated conversion of 78% with approx. 62% of intermediate hydroperoxide **3**. After acid-treatment at room temperature overnight, an estimated amount of 38% for product **4** was determined by NMR in the crude reaction mixture (Experiment 33).

Table 3. 9: Batch photoreaction of **2** in isopropanol: water (75:8 Vol%) in combination with rose Bengal (RB) or methylene blue (MB).

Exp	DHAA		Sensitizer		i-PrOH:H_2O	Conv.	Compositions [normalized to 100%]						
	[mg]	[mM]	Type	[mM]		[%]	**1**	**3**	**5**	**6**	**4**	**7**	**9**
9	200	10.7	RB	0. 274	75:8	97	3	**85**	10	2	-	-	-
10	200	10.2	RB	0. 274	75:8	NA	NA	**NA**	NA	NA	NA	NA	NA
19	200	10.8	MB	0.257	72:8	58	42	**20**	-	11	2	16	9
33	200	10.8	RB	0.171	72:8	87	13	**62**	9	9	2	-	5

Conversion and compositions were determined by ^{1}H-NMR (±3%); All photoreactions were performed for 3.5 hours except for Experiment 19 where irradiation was 5 hours; Conversion and yields were calculated as per proton NMR spectra integration of the characteristic peaks, rose Bengal (RB), methylene blue (MB), room temperature (r.t.), not available (NA).

Table 3. 10: Follow up batch thermal reactions of photo-products of experiments from Table 3.9.

Exp	Acid		Time	Temp.	Wt.	Compositions [normalized to 100%]						
	Type	**Amount**	**[h]**		**(mg)**	**1**	**4**	**7**	**9**	**11**	**14**	**16**
9	TFA	2 drops	2	60°C	44	trace	**71**	26	-	-	2	trace
					16[¤]		**7**[α]					
10	HCl	1 drop	2	60°C	-	59	**-**	-	16	22	3	-
19	TFA	0.19 mL	24	60°C to r.t.	100	34	**39**	23	2	-	2	trace
33	TFA	3-4 drops	24	r.t.	146	8	**55**	23	6	-	2	6
					38[¤]		**38**[α]					

Conversion and compositions were determined by ^{1}H-NMR (±3%); [¤] Isolated weight; [α] Isolated yield;

3.2.2.1.2 One-pot batch synthesis of artemisinin

One-pot batch photooxygenations of DHAA (**1**) were preferably conducted in dichloromethane as it caused the least photodegradation of **1**, although toluene and acetonitrile were explored as alternative solvents as well. TPP, anthracene-9, 10-dicarbonitrile or methylene blue were employed as sensitizer. TFA was added into the reaction mixture either at the beginning or after 1-2 hours of irradiation. The results of the combined one-step batch reactions are described in **Table 3. 11**. Conversion rates and product compositions were estimated by NMR analysis. Crystallization of artemisinin was attempted for all reactions, but often failed due to the complexity of the product mixtures.

An estimated conversion of 66% of DHAA **1** and an isolated yield of 36% for artemisinin were obtained after irradiation of **1** (10.6 mM) and TPP (0.122 mM) in dichloromethane for 2 hours, subsequent addition of TFA (0.19 mL) and further irradiation for 1 hour (Experiment 34).

Repetitions of the experiment with similar concentrations of reactants but addition of TFA at the beginning resulted in conversions of **1** of 96% and 100%, respectively (Experiment 35 and 36). In case of Experiment 35, a calculated amount of **4** of 51% was determined (by NMR), but no product could be crystallized. Thus, extraction of the crude mixture obtained from Experiment 36 with boiling n-hexane followed by aqueous workup was successfully trialed and gave product **4** in an isolated yield of 32%.

Addition of 2 drops of a TFA solution (0.13 M) after 1 hour and subsequent irradiation of a total of 5 hours (**1**: 10.6 mM; TPP: 0.122 mM) resulted in an estimated conversion of DHAA of approx. 10% (by NMR). Only artemisinin was identified as a product, although a variety of unknown byproducts were detected as well (Experiment 37).

The photooxygenation conducted with anthracene-9, 10-dicarbonitrile in toluene for 2 hours showed a poor conversion of DHAA of just 5% with an estimated amount of 2% of artemisinin (Experiment 38).

Prolonged irradiation of the same reaction mixture for 13 hours caused an estimated conversion of 6% conversion, but showed no artemisinin but other byproducts instead (Experiment 39).

Using acetonitrile as a solvent and conducting a photoreaction of **1** (5.6 mM), rose Bengal (0.137 mM) with 1 drop of TFA for 2 hours showed complete conversion. However, the crude product was found to contain largely byproducts with an estimated amount of **4** of only 4% (Experiment 40).

The one-step photoreaction with methylene blue in dichloromethane for 3 hours resulted in a calculated conversion of 89% and the crude product mixture obtained after aqueous workup contained an estimated 40% of product **4** (Experiment 41).

Furthermore, experiments conducted with the same reagent composition aimed at varying the amount of TFA added (Experiments 42-47).

A calculated conversion of **1** of approx. 90% and an isolated yield of 50% for artemisinin was obtained with 0.01 mL of TFA and irradiation for 2 hours (Experiment 42). The x-ray crystallography (**Figure 3. 10**) analysis of the isolated compound **4** proved the absolute structure of the synthesized artemisinin

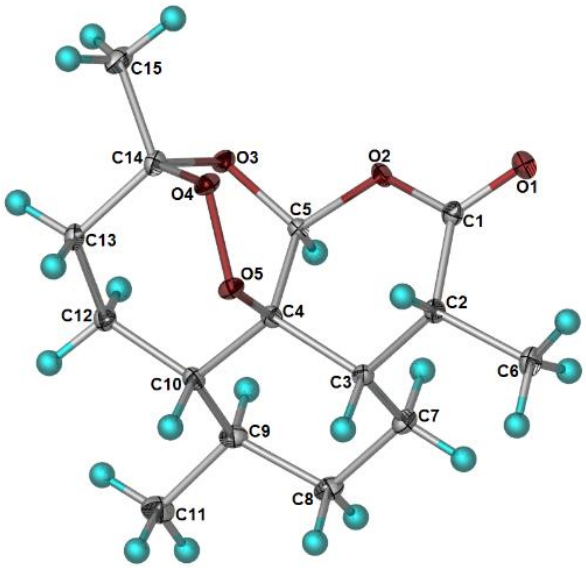


Figure 3. 10: X-ray crystallography structure of artemisinin **4**.

The same reaction but with an increased amount of TFA of 0.05 mL TFA showed an estimated conversion of 92% and furnished artemisinin in an isolated yield of 42% (Experiment 43).

Further increase of TFA to 0.10 mL resulted in an estimated conversion of only 24% conversion and the crude product was found to contain mainly byproducts with an estimated 2% of **4** (Experiment 44).

When 0.15 mL of TFA was added a calculated conversion of 71% was obtained, with the crude product containing approx. 23% of **4** (Experiment 45).

An estimated conversion of 38% with approx. 18% of product **4** were achieved with 0.20 mL of TFA (Experiment 46).

Subsequently, a reaction with 0.50 mL of TFA resulted in a poor conversion of approx. 11% with a very low estimated amount of product **4** of 3% (Experiment 47).

Table 3. 11: One-pot batch synthesis of artemisinin **4**.

Exp	DHAA		Sensitizer		TFA	Solvent	Irradiation	Wt.	Conv.	Composition [normalized to 100%]								
	[mg]	[mM]	Type	[mM]			[h]	[mg]	[%]	1	4	7	9	11	13	14	15	16
[a]34	200	10.6	TPP	0.122	*0.19 mL	DCM	3	248	66	34	**47**	10	8	-	-	-	-	-
								86[¤]			**36**[α]							
[b]35	200	10.6	TPP	0.122	0.19 mL	DCM	3	219	96	4	**51**	26	-	19	-	-	-	-
[b]36	200	10.6	TPP	0.122	0.19 mL	DCM	3	137	100	-	**64**	10	23	-	-	3	-	-
								77[¤]			**32**[α]							
37	200	10.6	TPP	0.122	[#]0.19 mL	*i*-PrOH	5	223	10	90	**10**	-	-	-	-	-	-	-
38	200	10.6	DCA	0.16	0.19 mL	Toluene	2	219	5	95	**2**	2	1	-	-	-	-	-
39	1999.5	99.9	DCA	2.48	1.6 mL	Toluene	13	205	6	94	**-**	1	1	-	4	-	-	-
[a]40	100	5.6	RB	0.137	[#]1 drop	ACN	2	117	100	-	**4**	-	19	28	-	-	2	47
[a]41	110	5.8	MB	0.351	[$]2 drops	DCM	3	52	89	11	**40**	-	41	2	-	2	-	4
[a]42	200	10.6	MB	0.117	0.01 mL	DCM	2	135	90	10	**51**	11	24	2	-	-	1	1
								121[¤]			**50**[α]							
[a]43	200	10.6	MB	0.117	0.05 mL	DCM	2	131	92	8	**51**	14	17	5	-	-	-	5
								99[¤]			**42**[α]							
[a]44	200	10.6	MB	0.117	0.10 mL	DCM	2	93	24	76	**2**	8	6	8	-	-	-	-
[a]45	200	10.6	MB	0.117	0.15 mL	DCM	2	65	71	29	**23**	28	17	2	-	1	-	-
[a]46	200	10.6	MB	0.117	0.20 mL	DCM	2	157	38	62	**18**	7	12	-	-	1	-	-
[a]47	200	10.6	MB	0.117	0.50 mL	DCM	2	130	11	89	**3**	3	5	-	-	-	-	-

Conversion and compositions were determined by ^{1}H-NMR (±3%); Meso-Tetraphenylporphyrin (TPP), DCA (anthracene-9,10-dicarbonitrile), Rose Bengal (RB), Methylene blue (MB), Dichloromethane (DCM), acetonitrile (ACN), Iso-propanol (*i*-PrOH), (room temperature (r.t.); Solvent volume for all reactions were 80 mL except for Exp 39 the volume was 84.6 mL and Exp 40 volume was 75 mL; *TFA was added into the reaction after 2h irradiation and then irradiation was continued. $^{\#}$ TFA was added after 1 hour irradiation and then irradiation continued; $^{\$}$2 drops of 0.1306M TFA solution in DCM; ^{a} Workup method: aqueous workup dichloromethane vs saturated $NaHCO_3$, then washing with brine and drying of $NaSO_4$, followed by filtration over silica; ^{b} Workup method: evaporation of solvent, then extraction with boiling n-hexane followed by aqueous workup with saturated $NaHCO_3$, then washing with brine and drying of $NaSO_4$, followed by filtration over silica; yields were calculated as per proton NMR spectra integration of the characteristic peaks; ^{g} Isolated weight; $^{\alpha}$ Isolated yield.

3.2.2.2 Photooxygenations of dihydroartemisinic acid under flow conditions

For all flow experiments, the in-house built capillary flow reactor-1 (**Figure 3. 3**) was used for both, tandem and one-pot operation. In most cases, compressed air was used as the oxygen source.

3.2.2.2.1 Phototransformation of dihydroartemisinic acid in flow and subsequent acid-catalyzed cyclization in batch

After the photoconversion of **1** in the flow reactor equipped with a 5-psi back pressure regulator, the acid-catalyzed Hook cleavage of the photoproduct **3** was conducted separately under batch conditions. The results are shown in **Table 3. 12** to **Table 3. 15**. Conversions and product compositions were calculated from NMR analysis. Crystallization of artemisinin with cyclohexane was attempted for all reactions.

Flow photooxygenation of a solution of **1** (10 mM) and rose Bengal (0.514 mM) in ethanol (Entry 1) using flow rate of 5 mL/min for both, liquid and gas, and subsequently a residence time of 11 minutes furnished an estimated 23% conversion with approx. 18% of intermediate **3**. The reaction mixture was cooled to 0°C and air was bubbled into the solution for 2 minutes. Successive dropwise addition of TFA (0.19 mL), stirring for 2 hours upon air bubbling and workup gave a crude product that contained an estimated amount of **4** of just 3%.

Another flow reaction of DHAA (4 mM) and rose Bengal (0.514 mM) in ethanol was performed with a liquid flow rate of 2.5 mL/min and an air flow rate of 5 mL/min, resulting in a residence time of 18 minutes (Entry 2). NMR analysis showed an estimated conversion of 60% with approx. 42% of hydroperoxide **3**. Successive TFA-catalyzed treatment gave a crude product that contained ca. 21% of the desired **4**.

The flow reaction of DHAA (6 mM) and methylene blue (0.125 mM) in acetone (Entry 3) was performed with a liquid flow rate of 2 mL/min and an air flow rate of 2.5 mL/min, ensuing a residence time of 25 minutes. NMR analysis showed an estimated 86% conversion with approx. 75% of intermediate **3**. After evaporation of the solvent, the semisolid residue was mixed with 50 mL of diethyl ether and filtered in order to remove most of the sensitizer dye. The filtrate was evaporated and dissolved in n-hexane containing one drop of TFA. The reaction flask was saturated with air, stoppered and allowed to stand for 4 days. At the end of this process, an isolated yield of pure **4** of 35% was obtained.

The analogue reaction in acetone was performed with a liquid flow rate of 2.5 mL/min and an air flow rate of 2.5 mL/min, providing a residence time of 20 minutes (Entry 4). The reaction

furnished a calculated 72% conversion with ca. 60% of intermediate **3**. Following the same thermal procedure as in Entry 3 resulted in an isolated yield of 23% of pure **4** as an off-white solid.

The photooxygenation of **1** (10.5 mM) and tetraphenylporphyrin (0.122 mM) in dichloromethane utilized flow rates of 1.6 mL/min (liquid) and 1 mL/min (air) and resulted in a residence time of 27 minutes (Entry 5). An estimated conversion of **1** of 96% was obtained with approx. 73% of **3** formed. Successive treatment with TFA in dichloromethane produced a crude product mixture that only contained byproducts.

When using DHAA (21 mM) and rose Bengal and a liquid flow rate of 2.5 mL/min and airflow rate of 2.5 mL/min (residence time of 25 minutes), an approx. conversion of 66% with ca. 51% of intermediate **3** was observed (Entry 17). At the outlet of the flow reactor, the photoproduct was continuously added to a flask containing a stirred solution TFA (0.01 mL) in isopropanol (40 mL), which was additionally purged with air. NMR analysis of the crude product mixture showed an estimated presence of 16% of artemisinin with several byproducts, large amounts of unreacted DHAA (**1**).

With the same concentrations and flow rates, the photoreaction in ethanol resulted in ca. 57% conversion with formation of approx. 39% of intermediate **3** (Entry 18). Using the same TFA-treatment protocol, a crude product was isolated that contained an estimated 9% of artemisinin **4** with high amounts of starting material and other byproducts.

A similar reaction conducted in isopropanol (**1**: 21 mM; rose Bengal: 0.234 mM; liquid and air flow rates: 2.5 mL/min; residence time: 25 min) resulted in a calculated conversion of 24% with approx. 10% of intermediate **3** (Entry 19). Direct treatment with TFA as described before produced an estimated 4% of **4** with high amounts of starting material and other byproducts.

Fixing the liquid flow rate to 1 mL/min and air flow rate to 0.5 mL/min without a BPR gave a residence time of 45 minutes. The photoreaction of **1** (10.5 mM) in the presence of methylene blue showed an approx. 43% conversion with an estimated 14% of **3** next to other byproducts (Entry 6). The reaction mixture was filtered through silica to remove the dye and the filtrate was treated with 1 drop of TFA under air bubbling. Stirring for 2 hours at room temperature and workup produced a crude mixture that contained starting material, numerous byproducts and an estimated 4% of **4**.

The photooxygenation of DHAA (10.5mM) with rose Bengal-bis(triethylammonium) salt (RB-TEA) and a 45 minutes residence time resulted in an approx. 69% conversion with ca. 54% **3** (Entry 7). Subsequent acid-cyclization and workup furnished a crude product that contained mostly starting material and byproducts, with an estimated amount of 6% of **4**.

A similar flow reaction (**1**: 7 mM) with RB-TEA and a residence time of 50 min (flow rates: 1 mL/min for liquid and 0.5 mL/min for air) gave an estimated 78% conversion with approx. 60% of **3** (Entry 8). Successive TFA-treatment produced a crude mixture that consisted of starting material, several byproducts and approx. 22% of product **4**.

The photooxygenation of **1** (5 mM) with methylene blue and using a liquid flow rate of 1 mL/min and air of flow rate of 0.5 mL/min created a residence time of 50 minutes (Entry 9). NMR analysis showed only an approx. 31% conversion with trace amounts of artemisinin and other byproducts, but no intermediate **3**. The reaction mixture was transferred into a Schlenk flask and TFA (0.1 mL) was added. This mixture was further irradiated in a Rayonet reactor upon air bubbling for 2 hours. A crude mixture was obtained containing ca. 22% of **4** along with starting material **1** and other byproducts.

When a mixture of **1** (3 mM) and RB-TEA was irradiated (liquid: 1 mL/min; air: 0.5 mL/min; residence time: 50 min) an estimated conversion of 78% with approx. 38% of **3** was achieved (Entry 10). Successive acid-treatment resulted in a crude product mixture that only contained starting material and other byproducts.

A similar photooxygenation (**1**: 5 mM) in the presence of RB-TEA was conducted using a liquid flow rate of 1 mL/min and an oxygen flow rate of 0.5-0.6 mL/min, which gave a residence time of 55 minutes (Entry 11). NMR analysis showed an approximate 94% conversion with ca. 43% of **3** besides an increased number of byproducts. Immediate TFA-treatment by continuous addition of photoproduct furnished a crude product mixture with an estimated 40% of **4**.

A modified reaction (**1**: 21 mM) with RB-TEA and using flow rates of 1 mL/min (liquid) and 0.5 mL/min (air) created a residence time was 55 minutes (Entry 12). NMR analysis revealed an approx. 23% conversion with only ca. 9% of **3**. Subsequent TFA-treatment produced a crude product that contained approx. 11% of artemisinin (**4**).

The flow photoreaction of **1** (42 mM) with RB-TEA and flow rates of 1 mL/min (liquid) and 0.5 mL/min (air) realized a residence time of 75 minutes and gave an estimated 52% conversion with approx. 18% of **3** (Entry 13). The following modified TFA-treatment produced a crude product that contained mostly unreacted starting material **1** and only ca. 4% of artemisinin.

Using a solution of **1** (21 mM) with rose Bengal and flow rates of 1 mL/min (liquid) and 0.5 mL/min (air) generated a residence time of 65 minutes (Entry 14), which gave an approx. 54% conversion of **1** with ca. 30% of intermediate **3**. Subsequent TFA-treatment resulted in a crude product that contained mainly starting material but approx. 13% of artemisinin.

Using a residence time of 65 minutes (liquid: 1 mL/min; air: 0.5 mL/min), an estimated 68% conversion was obtained with a solution of **1** (21 mM) with rose Bengal (Entry 15). NMR analysis showed ca. 51% of intermediate **3**. Treatment with TFA produced a crude product that contained mainly starting material and just ca. 4% of **4**.

Repetition of the previous reaction in isopropanol furnished an approx. conversion of 41% with ca. 27% of intermediate **3** (Entry 16). Follow-up treatment with TFA gave a crude mixture that consisted of mainly starting material, large amounts of byproducts and only ca. 2% of artemisinin.

Table 3. 12: Phototransformation of dihydroartemisinic acid **1** in flow at different flow rates (5 psi BPR).

Entry	Solvent	DHAA 1		Sensitizer		Flow rates [mL/min]		R.T. [min]	Conv. [%]	Composition [normalized to 100%]						
		[mg]	[mM]	Type	[mM]	Liquid	Air			1	3	5	6	4	8	9
1	Ethanol	473	10	RB	0.514	5	5	11	23	77	18	5	-	–		
2	Ethanol	200	4	RB	0.514	2.5	5	18	60	40	42	9	5			4
3	Acetone	200	6	MB	0.125	2	2.5	25	86	14	75	9	2			
4	Acetone	200	6	MB	0.125	2.5	2.5	20	72	28	60	7	4			
5	DCM	200	10.5	TPP	0.122	1.6	1	27	96	4	73	13	7			3
17	[#]*i*-PrOH	200	21	RB	0.514	2.5	2.5	25	66	34	51	8	4		2	1
18	Ethanol	200	21	RB	0.514	2.5	2.5	25	57	43	39	7	6			5
19	*i*-PrOH	200	21	RB	0.234	2.5	2.5	25	24	76	10	5	5	2		2

Conversion and compositions were determined by ^{1}H-NMR (±3%); Methylene blue (MB), Tetraphenylporphyrin (TPP) and Rose Bengal bis-(triethylammonium) salt (RB-TEA), Residence time (R.T.), dichloromethane (DCM), Iso-propanol (*i*-PrOH), back pressure regulator (BPR); * isolated yield; [#] *i*-PrOH was mixed with water (36:4).

Table 3. 13: Follow-up thermal acid-catalyzed treatment of products from Table 3.12.

Entry	TFA	Time	Temp.	Wt.[mg]	Composition [normalized to 100%]								
					1	4	7	9	11	13	14	15	16
1	0.19 mL	2 h	0°C	414	59	3	10	12	5			12	
2	0.19 mL	2 h	0°C	110	57	21	7	14					
3	1 drop	4 days	r.t.	195, 84*	16	60, 35[$]	20	5					

4	1 drop	4 days	r.t.	209, 56*	7	84, 23$	4	3			1		1
5	0.19 mL	#	r.t.	128	28	8	38	10	16				
17	0.01 mL	2h	r.t.	167	52	16	6	15					12
18	0.01 mL	2h	r.t.	132	62	9	3	13					13
19	0.01 mL	2h	r.t.	109	86	4	1	3					6

Conversion and compositions were determined by ^{1}H-NMR (±3%); #The photo-product from flow reactor was directly collected in a flask containing a stirred solution TFA in dichloromethane then subjected to aqueous workup; * Isolated weight; $ isolated yield.

Table 3. 14: Photooxygenations of DHAA **1** at liquid 1 mL/min vs. gas 0.5 mL/min flow rates without BPR.

Entry	**Solvent**	**DHAA 1**		**Sensitizer**		**Gas**	**R.T.**	**Conv.**	**Compositions [normalized to 100%]**						
		[mg]	**[mM]**	**Type**	**[mM]**		**[min]**	**[%]**	**1**	**3**	**5**	**6**	**4**	**8**	**9**
6	DCM	100	10.5	MB	0.234	CA	45	43	57	14	6	3	6	4	11
7	DCM	200	10.5	RB-TEA	0.213	CA	45	69	31	54	4	5		3	3
8	DCM	125	7	RB-TEA	0.213	CA	50	78	22	60	8	4		3	3
9	DCM	100	5	MB	0.234	CA	50	31	69	-	6	5	7		13
10	DCM	50	3	RB-TEA	0.213	CA	50	78	22	32	14	6	7	6	13
11	DCM	100	5	RB-TEA	0.213	O_2	55	94	6	43	12	11	11		17
12	DCM	200	21	RB-TEA	0.425	CA	55	23	77	9	4	2	1	2	6
13	DCM	200	42	RB-TEA	0.856	CA	75	52	48	18	8	7	4	8	7
14	*i-PrOH	200	21	RB	0.514	CA	65	54	46	30	5	5	3	5	5
15	Ethanol	200	21	RB	0.514	CA	65	68	32	51	9	8			
16	i-PrOH	200	21	RB	0.514	CA	64	41	59	27	5	2		1	2

Conversion and compositions were determined by ^{1}H-NMR (±3%); Methylene blue (MB), Tetraphenylporphyrin (TPP) and Rose Bengal bis-(triethylammonium) salt (RB-TEA), Residence time (R.T.), dichloromethane (DCM), Iso-propanol (*i*-PrOH); * *i*-PrOH was mixed with water (36:4).

Table 3. 15: Follow-up thermal acid-catalyzed treatment products from Table 3.14.

Entry	TFA	Time [h]	Temp.	Wt.	Compositions [normalized to 100%]							
				[mg]	1	4	7	9	10	11	14	16
6	1 drop	2	r.t.	47	72	4	1	16		7		
7	0.5 mL	2	Reflux, 50°C	145	76	6		4		12	2	
8	0.1 mL	2	Reflux, 50°C	76	39	22	23	9		4	3	
9	0.1 mL	2	r.t.	86	11	49	20	8	2	10		
10	0.1 mL	24	r.t.	23	Complex NMR							
11	0.01 mL	2	r.t.	49	13	40	14	11				22
12	0.01 mL	1	Reflux, 50°C	138	80	11	3	2		3		1
13	0.01 mL	1	Reflux, 60°C	141	79	4	4	12				1
14	0.05 mL	2	r.t.	109	65	13	6	7				9
15	0.05 mL	2	r.t.	123	84	4	6	3				3
16	0.05 mL	2	r.t.	173	80	2	1	6				11

3.2.2.2.2 Tandem flow synthesis of artemisinin by coupling of photooxygenation and acid-catalysis

The tandem continuous flow system coupled the photochemical flow module with a thermal module, in which the Hook cleavage took place using the residual oxygen from the photooxygenation. TFA was inject into the effluent stream of the photoreactor module. The results and conditions are shown in **Table 3. 16**.

The tandem flow reaction of DHAA (10.5 mM) with tetraphenylporphyrin and using flow rates of 1.6 mL/min (liquid) and 1 mL/min (air) showed a ca. 64% conversion (Entry 20). A TFA solution was injected at 1 mL/min and the reaction mixture was maintained at 40°C in the thermal flow module. NMR analysis showed ca. 18% of artemisinin in the crude product.

Repetition of the same reaction (Entry 21) showed no artemisinin in the final product mixture.

A related flow reaction with methylene blue (**1**: 5.6 mM) at flow rates of 1.6 mL/min (liquid) and 1 mL/min (air) resulted in ca. 90% conversion. The coupled TFA-treatment gave a crude mixture containing approx. 57% of artemisinin (Entry 22).

Repetition of the same reaction (Entry 23) resulted in ca. 55% conversion and approx. 37% of **4**, next to other byproducts.

Further repetition (Entry 24) resulted in an estimated 84% conversion of **1** and gave ca. 79% of artemisinin in the final crude product. This experiment, however, suffered from a paused flow inside the capillary due to back pressure.

A more successful tandem flow reaction performed resulted in approx. 92% conversion after a residence time of 40 minutes and produced an isolated yield of pure product **4** of 24% (Entry 25).

The continuous flow reaction of **1** (10.2 mM) with rose Bengal showed a ca. 62% conversion after a residence time of 48 minutes (Entry 26). Subsequent TFA-treatment gave a crude product that contained approx. 36% of artemisinin next to other byproducts and starting material.

Using an accelerated liquid flow rate of 2 mL/min reduced the residence time to 25 minutes. The flow photoreaction of **1** (10.6 mM) thus showed a decreased conversion of approx. 49%. TFA-catalyzed cyclization furnished a crude product consisting of ca. 26% artemisinin and other byproducts (Entry 27).

The same reaction conducted in chloroform and using a residence time of 35 minutes resulted in only ca. 3% conversion. Consequently, TFA-treatment only produced traces of **4** with several other byproducts (Entry 28).

To increase the residence time and maintain a stable slug-flow, tandem reactions were also conducted at slow flow rates without a back-pressure regulator (**Table 3. 17**).

The flow reaction of **1** (5.3 mM) with methylene blue and flow rates of 2 mL/min (liquid) and 1 mL/min (air) resulted in approx. 54% conversion (Entry 29). Subsequent TFA-catalyzed cyclization furnished an estimated amount of 39% of **4** in the crude product mixture.

The flow photoreaction of **1** (10.6 mM) with rose Bengal in recirculation mode (liquid: 1 mL/min; air: 1 mL/min) resulted in approx. 87% conversion. Follow-up treatment with TFA gave a crude product containing ca. 36% of artemisinin next to other byproducts (Entry 30).

Using flow rates of 1 mL/min (liquid) and 0.75 mL/min (air) and hence a residence time of 60 min, the flow photoreaction of **1** (10.6 mM) with rose Bengal showed ca. 70% conversion (Entry 31). However, subsequent TFA-treatment furnished mainly byproducts with only approx. 3% of artemisinin.

The photoreaction of **1** (5.6 mM) with methylene blue at flow rates of 1.6 mL/min (liquid) and 1 mL/min (air) and hence a residence time of 45 minutes gave an estimated 42% conversion (Entry 32). Follow-up TFA-catalyzed cyclization produced mainly byproducts with only trace amounts of **4**.

Similar flow photoreactions with the same concentrations (Entries 33-35) showed good conversions of **1** but failed to produce any artemisinin after TFA-treatment.

In contrast, the related photooxygenation of **1** (6 mM) with rose Bengal resulted in complete conversion (Entry 37). Subsequent cyclization with TFA resulted in a crude mixture that contained ca. 28% of **4** (next to other byproducts).

The flow photoreaction of **1** (5.3 mM) with TPP and using flow rates of 1.6 mL/min (liquid) and 0.75 mL/min (air) showed an estimated conversion of 99%. Successive TFA-treatment furnished a crude product mixture that contained approx. 56% of product **4** (Entry 36).

Table 3. 16: Tandem photoreaction and thermal reaction with back pressure regulator (5psi).

Entry	Solvent	Volume [mL]	DHAA 1		Sensitizer		Flow rates [mL/min]		R.T. [min]	T. R. Temp.	Wt. [mg]	Conv. [%]	Compositions [normalized to 100%]				
			[mg]	[mM]	Type	[mM]	Liquid	Air					1	4	7	9	16
20	DCM	80	200	10.5	TPP	0.122	1.6	1	27	40°C	83	64	36	18	40	ND	8
21	DCM	80	200	10.5	TPP	0.122	1.6	1	27	40°C	91	-	Complex NMR			-	-
*22	Acetone	75	100	5.6	MB	0.125	1.6	1	45	r.t. to 50°C	48	90	10	57	9	24	1
*23	Acetone	75	100	5.6	MB	0.125	1.6	1	40	r.t. to 50°C	39	55	45	37	17	ND	2
*24	Acetone	75	100	5.6	MB	0.125	1.6	1	40	r.t. to 50°C	41	84	16	79	ND	6	-
*25	Acetone	75	100	5.6	MB	0.125	1.6	1	40	r.t. to 50°C	161 29$	δ		24♣			
*26	*i*-PrOH+ water	75+8	200	10.2	RB	0.247	1.6	1	48	r.t. to 50°C	132	62	38	36	22	4	-
27	DCM	80	200	10.6	MB	0.234	2	1	25	45°C	69	49	51	26	11	13	-
28	$CHCl_3$	80	200	10.6	MB	0.234	2	1	35	45°C	88	3	97	–			3

Conversion and compositions were determined by ^{1}H-NMR (±3%); Methylene blue (MB), Tetraphenylporphyrin (TPP) and Rose Bengal bis-(triethylammonium) salt (RB-TEA), Residence time (R.T.), Thermal reaction (T. R.), room temperature (r.t.), dichloromethane (DCM), Iso-propanol (*i*-PrOH), Back pressure regulator (BPR); * The first

20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. [$] Isolated weight; δ Complex crude NMR; ♣ Isolated yield of pure **4**; [#] Volume of TFA solution: 60mL of respective solvent containing 1mL TFA and injected at 1 mL/min flow rate except in Entry 27 flow of TFA solution was 0.5 mL/min.

Table 3. 17: Tandem photoreaction and thermal reaction without back pressure regulator.

Entry	Solvent	Volume [mL]	DHAA 1 [mM]	Sensitizer		Flow rates [mL/min]		R.T. [min]	T. R.		Wt. [mg]	Conv. [%]	Compositions [normalized to 100%]				
				Type	[mM]	Liquid	Air		Ψ	Temp.			1	4	7	9	16
29	DCM	80	5.3	MB	0.117	2	1	25	[b]1	45°C	43	54	46	39	12	3	-
30	Ethanol	40	10.6	RB	0.257	1	1	40	[c]0.5	r.t.	54	[i]87	13	36	14	8	30
31	Ethanol	40	10.6	RB	0.257	1	0.75	60	[c]0.5	43°C	65	70	30	3	4	14	48
[a]32	Acetone	75	5.6	MB	0.125	1.6	1	45	[d]0.5	r.t. to 50°C	77	42	58	2	-	20	20
[a]33	Acetone	75	5.6	MB	0.125	1.6	1	45	[e]1	r.t. to 50°C	31	64	36	-	-	4	60
[a]34	Acetone	75	5.6	MB	0.125	1.6	1	45	[e]1	r.t. to 50°C	39	-	-	-	-	-	-
[a]35	Acetone	75	5.6	MB	0.125	1.6	1	45	[f]1	r.t. to 50°C	59	73	27	15	15	29	13

[a]36	DCM	80	5.3	TPP	0.122	1.6	0.7 5	45	[g]0.5	r.t. to 50°C	110	99	1	56	27	12	5
37	Acetone	70	6	RB	0.293	1.6	1	45	[h]1	r.t.	33	68	32	28	40	-	-

Conversion and compositions were determined by ^{1}H-NMR (±3%); Amount of DHAA was 100 mg in all cases; Methylene blue (MB), Tetraphenylporphyrin (TPP), Residence time (R.T.), Thermal reaction (T. R.), room temperature (r.t.), dichloromethane (DCM), Iso-propanol (*i*-PrOH), Back pressure regulator (BPR); Ψ flow rate (mL/min) of TFA solution; [a] The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. [b] 0.19mL TFA in 60mL $CHCl_3$; [c] 1drop TFA in 40mL DCM; [d] 0.1mL TFA in 10mL acetone ; [e] 1mL TFA in 60mL acetone; [f] 3drops TFA in 60mL acetone; [g] 1mL TFA in 60mL DCM; [h] 3drops TFA in 60mL n-hexane; [i] conversion after recirculation reaction;

3.2.2.2.3 One-pot continuous flow synthesis of artemisinin under flow conditions

Due to the fluctuating results from the coupled flow processes, a one-pot continuous flow synthesis of artemisinin **4** from DHAA **1** was investigated. The process was realized by pumping a reaction mixture containing substrate **1**, sensitizer and catalytic amounts of trifluoroacetic acid in dichloromethane (unless otherwise stated) directly into the capillary flow reactor. The results of these one-pot continuous flow reactions are shown in **Table 3. 18**.

Using a solution of **1** (5.3 mM) with methylene blue and TFA, and flow rates of 1.6 mL/min (liquid) and 0.75 mL/min (air) a conversion of ca. 73% was achieved. From the reaction, pure artemisinin (**4**) was isolated in a yield of 13% (Entry 40).

The flow reaction of **1** (5.3 mM) with methylene blue in acetone was performed at flow rates of 1.6 mL/min (liquid) and 1 mL/min (air), producing a residence time of 45 minutes. NMR analysis revealed an estimated 32% conversion and only ca. 5% of **4** (Entry 41).

Setting the flow rates to 1 mL/min (liquid) and 0.5 mL/min (air) increased the residence time to 55 minutes. Subsequent one-step flow reaction of **1** (10.6 mM) with methylene blue only gave an approx. 27% conversion with ca. 17% of **4** (Entry 42).

Further reduction of the flow rates to 0.25 mL/min (liquid) and 0.5 mL/min (air) and photooxygenation of **1** (5.3 mM) with methylene blue resulted in approx. 86% conversion. Pure product **4** was obtained by crystallization in yield of 22% (Entry 45).

A conversion of approx. 50% of **1** with ca. 37% of **4** was obtained using a residence time of 60 minutes (liquid: 1 mL/min; air: 0.5 mL/min) and a solution of DHAA **1** (5.3 mM) with methylene blue (Entry 46).

Using RB-TEA as a sensitizer in dichloromethane, the flow reaction of **1** (2.6 mM) at 1 mL/min (liquid) and 0.5 mL/min (air) flow rates showed no conversion (Entry 47).

Photooxygenation of **1** (5.3 mM) with methylene blue using a residence time of 50 minutes (liquid: 1 mL/min; air: 0.5 mL/min) resulted in ca. 42% conversion and approx. 20% of product **4** (Entry 48).

A selected flow reaction was conducted with pure oxygen and high concentrations of DHAA (21.1 mM) and methylene blue (0.469 mM) in dichloromethane containing TFA (5 mL of 0.01 M solution). At flow rates of 1 mL/min (liquid) and 5 mL/min (oxygen) a residence time of 55 minutes was achieved (without back pressure regulator). NMR analysis revealed an estimated 83% conversion with approx. 52% of artemisinin, which could not be crystallized (Experiment 52).

Another flow reaction of **1** (10.6 mM) with methylene blue (0.117 mM) and TFA (0.01 mL) in dichloromethane was injected at flow rates of 1 mL/min (liquid) and 0.5 mL/min (air). NMR analysis revealed an approx. conversion of 32% with ca. 20% of **4** (Experiment 56).

The flow rates were consequently changed to 1 mL/min (liquid) and 0.5 mL/min (air) without a back-pressure regulator (Experiment 67-69).

A flow reaction of **1** (25 mM) and tetraphenylporphyrin (0.098 mM) resulted in approx. 28% conversion after a residence time of 53 minutes, with only traces of artemisinin.

Then the flow reaction was conducted with **1** (21.1 mM) and methylene blue (0.234 mM) and a residence time of 40 minutes, a low conversion of approx. 16% with ca. 11% of **4** were obtained.

Repetition of the same reaction led to ca. 24% conversion with only approx. 12% of artemisinin.

One-pot flow reactions were also performed at higher liquid flow rate of 2.5 mL/min and air flow rates of 1 mL/min in the presence of a 5 psi back pressure regulator (Experiment 58-66 in **Table 3. 19**).

The flow photoreaction of **1** (2.6 mM) with methylene blue (0.117 mM) and a residence time of 15 minutes furnished an estimated conversion of 73% with ca. 37% of artemisinin.

Repetition of the reaction showed ca. 68% conversion and approx. 21% of artemisinin after a slightly longer residence time of 17 minutes (Entry 64).

Repetition of the reaction with an increased concentration of methylene blue (0.234 mM) showed ca. 69% conversion with approx. 44% of artemisinin after a similar residence time of 17 minutes.

Further increase in methylene blue concentration to 0.391 mM resulted in only approx. 48% conversion and ca. 26% of product **4**.

Three flow reactions were furthermore conducted with 4 mM solutions of **1** and varying amounts of methylene blue. Using a methylene blue concentration of 0.117 mM and a residence time of 10 minutes, an estimated 72% conversion of **1** was observed with approx. 37% of artemisinin.

Repetition of the reaction showed ca. 72% conversion and approx. 41% artemisinin after a slightly longer residence time of 20 minutes (Entry 65).

A slight increase in methylene blue concentration to 0.234 mM and a residence time of 18 minutes gave ca. 72% conversion and approx. 45% of artemisinin.

At a similar residence time, an estimated 52% conversion with ca. 32% artemisinin was observed when the methylene blue concentration was further increased to 0.391 mM.

A flow reaction performed with **1** (10.6 mM) and methylene blue (0.117 mM) in showed only approx. 42% conversion after 30 minutes with ca. 27% of artemisinin (Entry 66).
Successive reactions were conducted using flow rates of 2.5 mL/min for both, liquid and air streams and adopting a 5-psi back pressure regulator (Experiment 70-72, **Table 3. 19**).
Under these flow conditions, the photooxygenation of **1** (21.1 mM) and methylene blue (0.234 mM) in acetone showed ca. 47% conversion with approx. 5% of artemisinin after 40 minutes.
The same reaction in dichloromethane showed approx. 19% conversion with ca. 10% of artemisinin after a residence time of 10 minutes.
Repetition of the same reaction resulted in a ca. 30% conversion with an estimated amount of 21% artemisinin due to a longer residence time of 21 minutes.

Table 3. 18: Results of one-pot continuous flow syntheses of artemisinin with slow flow rates and without back pressure regulator.

Entry	DHAA 1		Sensitizer		TFA	Flow rates [mL/min]		R.T. [min]	Wt. [mg]	Conv. [%]	Compositions [normalized to 100%]						
	[mg]	[mM]	Type	[mM]		Liquid	Air				1	4	7	8	9	11	16
40	100	5.3	MB	0.117	1 drop	1.6	1	40	56	73	27	39	17	-	16	-	-
									15			♣13					
41	100	5.3	MB	0.117	1 drop	1.6	1	45	66	32	68	5	10	-	5	5	8
42	100	10.6	MB	0.234	1 drop	1	0.5	55	70	27	73	17	3	-	7	-	-
45	100	5.3	MB	0.117	1 drop	0.25	0.5	88	80	86	14	51	18	-	18	1	-
									27			♣22					
46	50	5.3	MB	0.117	3 drops	1	0.5	60	31	50	50	37	7	3	2	2	-
47	50	2.6	RB-TEA	1.27	0.1 mL	1	0.5	50	77	ND	No change in starting material						
48	100	5.3	MB	0.117	0.1 mL	1	0.5	50	41	42	58	20	7	3	12	-	-
52	100	21.1	MB	0.469	♥5 mL	1	*5	55	61	83	17	52	12	-	18	-	-
56	200	10.6	MB	0.117	0.01mL	1	0.5	55	117	32	68	20	3	-	8		1
67	1180	25	TPP	0.098	0.1mL$^{\theta}$	1	0.5	53	1208	28	72	4	9	-	10		5
68	200	21.1	MB	0.234	0.05mL	1	0.5	40	129	16	84	11	1		4		
69	200	21.1	MB	0.234	0.05mL	1	0.5	40	180	24	76	12	3		5		

Conversion and compositions were determined by ^{1}H-NMR (±3%); In all entries dichloromethane was used as solvent except in Entry-41 the solvent was acetone; Volume of solvents : 80 mL in Entry 40, 45, 47, 48, 56, 75 mL in Entry 40, 40 mL in Entry 42, 46, 68, 69, 20 mL in Entry 52 and 57, 200 mL in Entry 67; Methylene blue (MB), Tetraphenylporphyrin (TPP) and Rose Bengal bis-(triethylammonium) salt (RB-TEA), Residence time (R.T.), room temperature (r.t.), Back pressure regulator (BPR); ♣ Isolated yield; *Pure oxygen was used instead of air; ♥ 0.01M TFA solution; $^{\theta}$ TFA added for 200mL solution of reactants (25 mM **1** and *meso*-tetraphenylporphyrin 0.0.098mM).

Table 3. 19: Results of one-pot continuous flow syntheses of artemisinin with 5 psi BPR.

Entry	DHAA 1		Methylene blue [mM]	TFA	Flow rates [mL/min]		R.T. [min]	Wt. [mg]	Conv. [%]	Compositions [normalized to 100%]						
	[mg]	[mM]			Liquid	Air				1	4	7	8	9	11	16
58	50	2.6	0.117	1 drop	2.5	1	15	25	73	27	37	13	1	22	-	-
59	50	2.6	0.234	1 drop	2.5	1	17	32	69	31	44	7	-	19		
60	50	2.6	0.391	1 drop	2.5	1	17	27	48	52	26	4		13	4	1
61	75	4	0.117	1 drop	2.5	1	10	50	72	28	37	8		25		
62	75	4	0.234	3 drops	2.5	1	18	37	72	28	45	14		13		
63	75	4	0.391	0.1mL	2.5	1	18	34	52	48	32	5		12	2	1
64	500	2.6	0.117	ϕ0.1mL	2.5	1	17	210	68	32	21	23		24		
65	500	4	0.117	*0.066mL	2.5	1	20	230 51♣	72	28	41 8♣	15		14	2	-
66	200	10.6	0.117	0.01mL	2.5	1	30	118	42	58	27	9		4	1	
70	200	21.1	0.234	0.01mL	2.5	2.5	40	189	47	53	5	6		10		27
71	200	21.1	0.234	0.1mL$^{\theta}$	2.5	2.5	10	190	19	81	10	6		3		
72	200	21.1	0.117M	0.05mL	2.5	2.5	21	138	30	70	21	4		4	1	

Conversion and compositions were determined by ^{1}H-NMR (±3%); In all entries dichloromethane was used as solvent except for Entry –70 the solvent was acetone; Volume of solvent : 80 mL in Entry 58 – 63 and 66, 40 mL in Entry 70 – 72, 800 mL in Entry 64 and 533.28 mL in Entry 65; Methylene blue (MB), Residence time (R.T.), Back pressure regulator (BPR); ♣ Isolated yield; * TFA added for 533.28 mL solution of reactants (40mM **1** and methylene blue 0.117mM); ϕ TFA added for 800mL solution of reactants (26mM **1** and methylene blue 0.117mM).

3.2.2.2.4 One-pot continuous flow syntheses of artemisinin via prolonged irradiations

One-pot continuous flow reactions with extended irradiation times were performed to achieve complete conversions and hence higher yields of the desired artemisinin. Prolonged residence times were achieved by keeping the solvent volume low and skipping the pre- and post-run flushing of the reactor with solvent. The gas flow rate was maintained at 0.5 mL/min and the liquid flow rate at 1 mL/min, respectively. The results are shown in **Table 3. 20**.

The flow reaction of a solution of **1** (21.1 mM) with methylene blue (0.469mM) and pure oxygen resulted in an estimated 89% conversion after a residence time of 135 minutes. Pure artemisinin was isolated by crystallization in 23% yield (Entry 51).

A further reaction of the same concentration with air showed a ca. 42% conversion with approx. 35% of product **4**, but which could not be isolated (Entry 53).

However, an isolated yield of **4** of 23% was obtained when the previous reaction was repeated (Entry 54).

Doubling of the substrate concentration failed to produce any conversion or yield (Entry 55).

3.2.2.2.5 Recirculated one-step flow reactions

To achieve higher conversions of **1** and thus yields of **4**, selected one-pot flow reactions were conducted by recirculating the reaction mixture several times through the flow reactor. To achieve this, the outlet tubing was connected to the reservoir holding the starting material. Flow rates of 2.5 mL/min for both liquid and gas (unless otherwise noted) and usage of a 5 psi BPR created a residence time of 15 minutes inside the flow reactor. The results from these flow reactions are shown in **Table 3. 21**.

The reaction of **1** (10.6 mM) with TPP resulted in an incomplete reaction after a single pass (Entry 38). Recirculation of this reaction for four times gave an approx. 92% conversion with approx. 47% of artemisinin, which could not be crystallized.

A flow reaction of the same reaction mixture but with a slightly decreased liquid flow rate of 2.1 mL/min gave a residence time of 20 minutes (Entry 39). Recirculation of the reaction mixture for three times resulted in an approx. 97% conversion and 19% isolated yield of artemisinin **4**.

A previous reaction that had failed to convert any starting material after a single pass was recirculated for 3 hours. However, the conversion remained at approx. 24% due to photobleaching of methylene blue. An estimated amount of 17% of artemisinin was observed (Entry 43).

Another flow reaction with a high amount of TFA resulted in ca. 60% conversion of **1** and approx. 24% of artemisinin **4** after a single pass (Entry 44). Recirculation of this reaction for 215 minutes could neither increase the conversion nor the yield.

A one-pot flow reaction of **1** (5.3 mM) with methylene blue was conducted with pure oxygen and using flow rates of 1 mL/min for both liquid and gas (residence time: 60 min). After recirculation of the reactants for 4 hours an approx. 80% conversion with ca. 43% of product **4** was obtained (Entry 49).

Table 3. 20: One-pot continuous flow syntheses of artemisinin (1 mL/min liquid and 0.5 mL/min gas flow rates).

Entry	DHAA 1		Methylene	TFA	R.T.	Wt.	Conv.	Composition [normalized to 100%]					
	[mg]	[mM]	blue [mM]		[min]	[mg]	[%]	1	4	7	9	11	16
*51	100	21.1	0.469	♠5mL	135	69, 28	89	11	84 ♣23	2	1	1	1
53	100	21.1	0.469	♥5mL	135	86	42	58	35	2	4		
54	100	21.1	0.469	♠5mL	115	65 28	NA		♣23			NA	
55	200	42.3	0.469	♠5mL	125	127	NA					NA	

Conversion and compositions were determined by ^{1}H-NMR (±3%); In all entries 20 mL dichloromethane was used as solvent, total volume of solvent was 25mL in each reaction; Methylene blue (MB), Residence time (R.T.), room temperature (r.t.), Back pressure regulator (BPR); ♣ Isolated yield; *Pure oxygen was used instead of air; ♠ 0.1M TFA solution in dichloromethane; ♥ 0.01M TFA solution in dichloromethane, Not available (NA).

Table 3. 21: Results recirculated flow reactions for artemisinin synthesis.

Entry	DHAA 1		Sensitizer		TFA	Flow rates [mL/min]		BPR 5psi	R.T. [min]/ M.P.	R.T.$^{\delta}$ [min]	Wt. [mg]	Conv. [%]	1	4	7	9	11
	[mg]	[mM]	Type	[mM]		Liquid	Air										
38	400	10.6	TPP	0.122	0.19mL	2.5	2.5	√	15	90$^{\#}$	329	92	8	47	35	10	
39	200	10.6	TPP	0.122	0.19mL	2.5	2.5	√	20	90$^{\#}$	88 45	97	3	66 ♣19	8	23	
43	200	10.6	MB	0.234	3 drops	1	0.5	x	55/3	160	178	24	76	17	3	4	

44	200	10.6	MB	0.234	0.19mL	1	0.5	x	55/4	215	73	60	40	25	8	4	6
49	100	5.3	MB	0.234	0.2mL	1	*1	x	60/4	240	37	80	20	43	21	15	

Conversion and compositions were determined by ^{1}H-NMR (±3%); In all entries dichloromethane was used as solvent, Volume of solvent : 160mL in Entry 38, in Entry 39 – 49 volume was 80mL, 40mL was in Entry 50; Methylene blue (MB), Tetraphenylporphyrin (TPP) and Rose Bengal bis-(triethylammonium) salt (RB-TEA), Residence time (R.T.), Multiple passage (M.P.), room temperature (r.t.), Back pressure regulator (BPR); ♣ Isolated yield; *Pure oxygen was used instead of air; $^{\delta}$ total residence time, $^{\#}$ Recirculation in loop.

3.2.3 Solar syntheses of artemisinin

3.2.3.1 One-pot solar batch reactions

Solar batch reactions were performed in a Schlenk flask exposed to direct sunlight. Air was purged into the reaction mixture from an aquarium tank via a FEP-tubing equipped with a HPLC filter. The results from the solar exposures are summarized in **Table 3. 22**.

Solar exposure of DHAA (10.6 mM) with TPP (0.122 mM) in dichloromethane for 1 hour resulted in complete conversion with approx. 84% of intermediate hydroperoxide **3**. Direct addition of TFA (0.19 mL) to the reaction mixture and further air bubbling for 1 hour in the sun gave approx. 53% of artemisinin in the crude reaction mixture (Experiment 48).

Using a mixture of isopropanol and water as a solvent, solar irradiation of DHAA (10.2 mM) with rose Bengal (0.251 mM) showed approx. 70% conversion with ca. 52% of **3** after 2 hours. Follow-up treatment with TFA resulted in an isolated yield of **4** in 36% (Experiment 49).

The solar reaction of DHAA (5.6 mM) with methylene blue (0.125 mM) in acetone for 2 hours showed ca. 97% conversion with approx. 78% of **3** (Experiment 50). Successive TFA-treatment furnished a crude product containing approx. 75% of artemisinin. Upon crystallization, pure **4** was isolated in a yield of 23%.

Solar photooxygenation of DHAA (11.3 mM) with rose Bengal (0.273 mM) in ethanol for 3 hours resulted in ca. 78% conversion with approx. 56% of **3**. Addition of TFA and further solar exposure for 2 hours showed approx. 86% of **4** in the crude product mixture (Experiment 51).

Repetition of the same reaction showed approx. 65% conversion with ca. 46% of **3** after 1 hour of illumination. Follow-up TFA-treatment increased the conversion to approx. 71%, but with only an estimated amount of 14% of **4** (Experiment 52).

3.2.3.2 Solar flow reactions

Solar flow reactions were conducted in a parabolic flow reactor equipped with an aluminum mirror (**Table 3. 23**).

Using DHAA (10.6 mM) with rose Bengal (0.258 mM) in ethanol and a liquid flow rate of 1.6 ml/min, followed by injecting air, resulted in a residence time of just 7 min. Recirculation for 1.5 h produced complete conversion with approx. 83% of **3**. TFA-catalyzed cyclization under batch conditions resulted in an isolated yield of pure artemisinin of 18% (Entry 114).

Similar reactions in ethanol and isopropanol-water pumped at 5 mL/min flow rate and recirculating for 1 hour showed ca. 96% conversion with approx. 79% of **3** (Entry 115) and complete conversion with ca. 84% of **3** (Entry 116), respectively. Subsequent acid-treatment in flow at 60°C failed to produce larger amounts of products.

Recirculation of a solution of DHAA (10.6 mM) with rose Bengal (0.258 mM) in *i*-PrOH:H_2O (72:8 vol%) at a flow rate of 5 mL/min for 1 hour gave complete conversion with ca. 83% of **3**. Subsequent TFA-cyclization at ambient temperature showed ca. 16% of **4** in the crude product mixture and after recrystallization from cyclohexane 33% of by-product **16** was isolated (Entry 117). The isolated lactone ring compound **16** structure was confirmed by x-ray crystallography (**Figure 3. 11**).

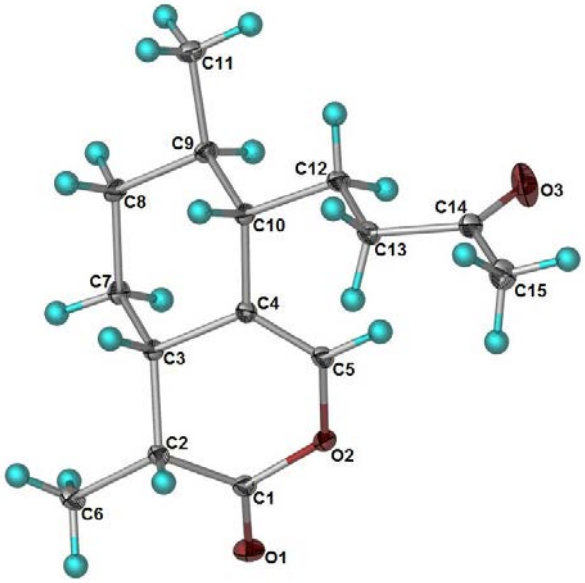


Figure 3. 11: X-ray crystallography structure of lactone ring by-product **16**.

Table 3. 22: Results of batch solar syntheses of artemisinin.

Exp.	DHAA 1		Sensitizer		Solvent	I [h]	Conv. [%]	Composition [normalized to 100%]					TFA	Wt. [mg]	Composition [normalized to 100%]					
	[mg]	[mM]	Type	[mM]				1	3	5	6	9			1	4	7	9	11	16
48	200	10.6	TPP	0.122	DCM	2	[a]100	-	84	11	5	-	*0.19mL	178	-	53	22	13	10	2
49	200	10.2	RB	0.251	[@]*i*-PrOH	3	[b]70	30	52	8	5	5	[$]0.01mL	14787	-	[ε.]36	Crude NMR not available			
50	100	5.6	MB	0.251	Acetone	3	[b]97	3	78	3	15	1	[$] 0.19mL	6628	-	75 [ε.]23	2 3	2	-	-
51	200	11.3	RB	0.273	Ethanol	5	[c]78	22	56	8	7	6	[#]1drop	54	-	86	8	3	-	3
52	200	11.3	RB	0.273	Ethanol	2	[a]64	36	46	14	5	-	*1drop	124	71	14	3	6		6

Conversion and compositions were determined by [1]H-NMR (±3%); Irradiation (I); Methylene blue (MB), Tetraphenylporphyrin (TPP), Rose Bengal (RB), dichloromethane (DCM), isopropanol (*i*-PrOH) ; Volume of solvent: 80mL in Experiment 48, 75mL in Experiment 50 – 52; [@] mixed solvent Iso-propanol: water 75:8 in Experiment 49; [a] Conversion after 1 hour irradiation; [b] Conversion after 2 hours irradiation; [c] conversion after 3 hours irradiation; * TFA was added after 1hour irradiation and then continued irradiation [$] TFA was added after 2 hours irradiation and then continued irradiation; [#] TFA was added after 3 hours irradiation and then continued irradiation; [ε.] Isolated yield.

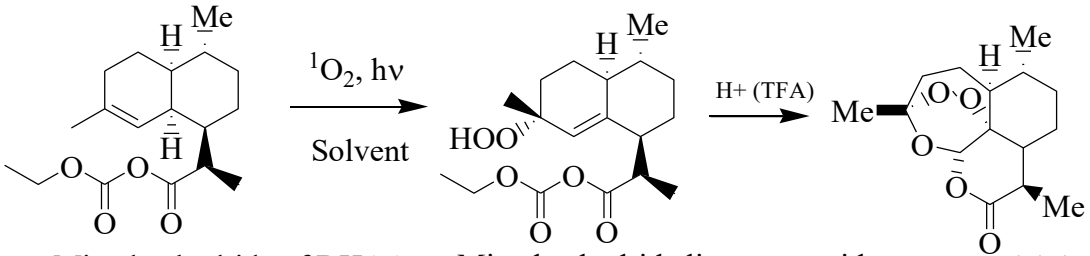
Table 3. 23: Results of solar flow synthesis of artemisinin from DHAA **1** (10.6 mM [200mg]) with rose Bengal (0.258 mM).

Entry	Solvent	Flow rate [mL/min]	R.T. * [min]	Conv. [%]	Composition [normalized to 100%]					Thermal reaction	Wt. [mg]	Composition [normalized to 100%]				
					1	**3**	**5**	**6**	**9**			**1**	**4**	**7**	**9**	**16**
114	*i*-PrOH : H_2O 72:8	1.6	7	100	-	83	12	5	-	0.01mL TFA, 60°C in batch mode	113 42♦	2	14 18♦	15	12	57
♣115	Ethanol	5	7	96	4	79	12	5	-	0.01mL TFA in 60mL Ethanol, 2mL/min, 60°C	14	Complex NMR with numerous by-products.				
♣116	*i*-PrOH : H_2O 72:8	5	7	100	-	84	15	1	-	0.01mL TFA in 30mL *i*-PrOH, 1mL/min, 60°C	-	Complex NMR with numerous by-products.				
♣117	*i*-PrOH : H_2O 72:8	5	7	100	-	83	11	6	-	0.01mL TFA in 40mL *i*-PrOH, 1mL/min	130 81♦	-	16	10	25	49 33♦

Conversion and compositions were determined by ^{1}H-NMR (±3%); Solvent volume was 80mL in each case; Back pressure regulator of 5psi was used; Rose Bengal (RB), Residence time (R.T); Iso-propanol (*i*-PrOH); *Recirculation: Entry 114 for 2hour, Entry 115 – 117 for 1hour and the conversions stated were after recirculation; ♣ Tandem solar flow reaction with thermal capillary reactor 8.4m long; ♦Isolated yield.

3.2.4 Syntheses of artemisinin from the mixed anhydride of dihydroartemisinic acid

The synthesis of artemisinin from the mixed anhydride of DHAA (**2**) was furthermore studied under batch and flow conditions. Upon photooxygenation, **2** forms the linear peroxide mixed anhydride **17** (**Figure 3. 12**), which forms artemisinin (**4**) upon subsequent acid catalysis (**Scheme 3. 5**). The intermediate peroxide **17** shows characteristic chemical shifts at 5.08 ppm (=CH-) and 4.32 ppm (-CH_2-), respectively, as shown in **Figure 3. 12**. Batch protocols included both, two-step and one-pot processes (**Table 3. 24**), whereas, only one-pot reactions were conducted in continuous flow (**Table 3. 25**).



Scheme 3. 5: Synthesis of Artemisinin (**4**) from mixed anhydride of DHAA (**2**).

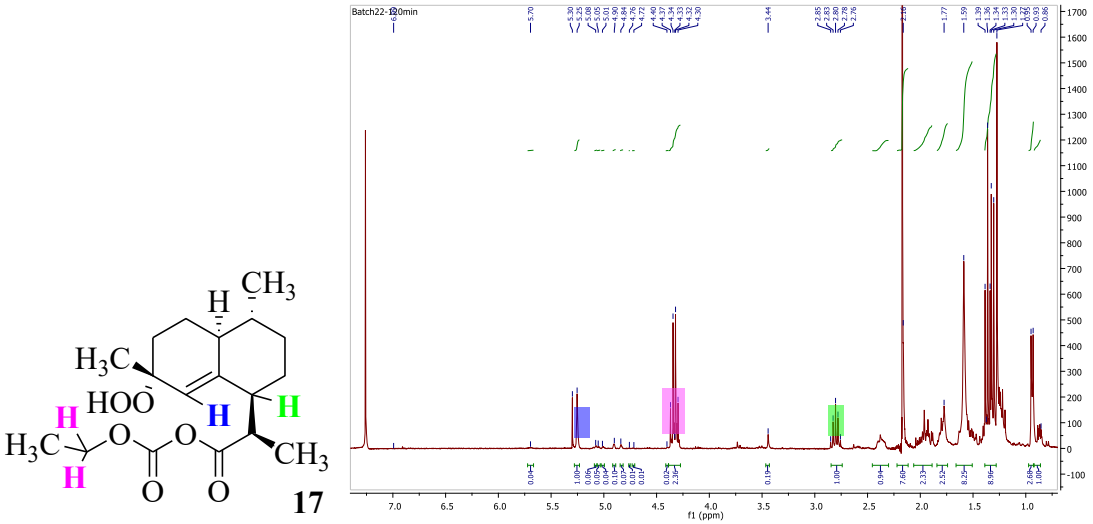


Figure 3. 12: ^{1}H-NMR spectrum of intermediate mixed anhydride linear peroxide (**17**).

3.2.4.1 Batch photoreactions of the mixed anhydride of dihydroartemisinic acid

A one-pot batch photoreaction of the mixed anhydride of DHAA (4 mM) and methylene blue (0.156 mM) in the presence of TFA in dichloromethane resulted in an estimated 92% conversion after 2 hours with approx. 67% of artemisinin in the crude product mixture (Experiment 53).

Photooxygenation of **2** (4.3 mM) with methylene blue (0.125 mM) in acetone for 2 hours resulted in ca. 95% conversion with approx. 86% of intermediate **17** (86%). However, after acid-treatment, no defined products could be detected by NMR analysis of the crude reaction mixture (Experiment 54).

Using ethanol as a solvent, the photooxygenation of **2** (8.6 mM) with rose Bengal (0.274 mM) showed approx. 92% conversion with ca. 77% of **17** after 5 h. Subsequent TFA-catalyzed cyclization furnished approx. 25% of artemisinin in the crude product (Experiment 56).

Repetition of the same experiment gave ca. 86% conversion with approx. 60% of **17**. After TFA-treatment, the final crude product contained only approx. 9% of artemisinin (Experiment 57).

Photooxygenation of **2** (9.8 mM) with rose Bengal (0.274 mM) in a mixture of isopropanol and water resulted in ca. 72% conversion with approx. 37% of **17** after 5 hours. Successive treatment with TFA gave a crude product that contained approx. 25% of artemisinin (Experiment 58).

3.2.4.2 Flow photooxygenations of the mixed anhydride of dihydroartemisinic acid

The one-pot continuous flow reaction of **2** (8.1 mM) with methylene blue (0.156 mM) and TFA (0.01 mL) in dichloromethane and using a residence time of 40 minutes (liquid flow rate: 1 mL/min; air flow rate: 0.5 mL/min) resulted in ca. 43% conversion and approx. 24% artemisinin (Entry 73).

Using a liquid flow rate of 0.5 mL/min and air flow rate of 1 mL/min the same residence time of 40 minutes was achieved. The subsequent flow photooxygenation of **2** (8.1 mM) with methylene blue (0.156 mM) and TFA (0.01 mL) in dichloromethane resulted in ca. 34% conversion with approx. 22% artemisinin (Entry 74).

When air was replaced with pure oxygen at a flow rate of 0.5 mL/min (residence time: 40 min), the flow photoreaction of **2** (5.3 mM) with methylene blue (0.234 mM) and TFA (0.1 mL) in dichloromethane produced ca. 97% conversion with approx. 55% of artemisinin (Entry 75).

Table 3. 24: Results of artemisinin batch syntheses from mixed anhydride of DHAA (**2**).

Exp.	2		Sensitizer		Solvent	T [h]	Conv. [%]	Composition [normalized to 100%]			TFA	Wt. [mg]	Composition [normalized to 100%]				
	[mg]	[mM]	Type	[mM]				2	17	7			2	4	7	9	16
*53	100	4	MB	0.156	DCM	2	92	ND			0.01mL	95 28	8	67 30	21	4	- 8
54	100	4.3	MB	0.125	Acetone	2	95	5	86	9	1 drop	91	Complex NMR with numerous by-products.				
55	100	4.3	MB	0.125	Ethanol	2		ND			1 drop	84	Complex NMR with numerous by-products.				
56	200	8.6	RB	0.274	Ethanol	5	92	8	77	15	1 drop	89	15	25	24	1	35
57	200	8.6	RB	0.274	[#]*i*-PrOH	5	86	14	60	26	1 drop	62	27	9	21	2	40
58	253	9.38	RB	0.274	Acetone	5	72	28	37	35	1 drop	152	24	25	22	3	26

Conversion and compositions were determined by ^{1}H-NMR (±3%); Irradiation (I); For experiment 54 – 58 after photo irradiation acid catalysis was done by adding 1 drop TFA into the solution in presence of air and stirred for 2 h at 60°C (two-step reaction); * One-opt batch reaction, 0.01mL TFA was added at the same time with starting material and sensitizer and irradiated; [#] Solvent mixture Iso-propanol : water 75:8; [@] by ^{1}H-NMR integration, not determined (ND).

Table 3. 25: Results of one-pot flow syntheses of artemisinin from mixed anhydride of DHAA (**2**).

Entry	2		MB	TFA	Flow rate		R.T.	Wt.	Conv.	Composition [normalized to 100%]				
	[mg]	[mM]	[mM]	[mL]	Liquid	Air	[min]	[mg]	[%]	2	4	7	9	16
73	200	8.1	0.156	0.01	1	0.5	40	112	43	57	24	10	4	5
74	200	8.1	0.156	0.01	0.5	1	40	104	34	66	22	9	3	trace
75	130	5.3	0.234	0.1	1	0.5	*40	89	97	3	55	39	3	trace

Conversion and compositions were determined by ^{1}H-NMR (±3%); in all entries 80mL dichloromethane was used as solvent; Methylene blue (MB), Residence time (R.T.); *Pure oxygen was used instead of air; $^{@}$ by ^{1}H-NMR integration.

3.2.5 Synthesis of artemisinin in the Vapourtec reactor

Selected photooxygenation of **1** and **2** were also explored in the advanced Vapourtec flow reactor (capillary volume 10 mL). Air was injected into the liquid stream at 1 mL/min via a T-piece using an Alicat mass flow controller. The reaction mixture was pumped through the capillary at a flow rate of 0.5 mL/min. The reactor temperature was 26-29°C and the pressure inside the capillary 0.6 bar. The gas-liquid slug flow travelled into the photoreactor chamber equipped with a 3.4 W LED panel. At the outlet of the reactor, the product mixture was collected, evaporated and analyzed by NMR spectroscopy (**Table 3. 26**).

The photoreaction of **1** (21.1 mM) with methylene blue (0.468 mM) and a residence time of 6 minutes resulted in approx. 48% conversion with ca. 24% of artemisinin (Entry 118).

Decreasing the concentration of **1** (5.3 mM) and methylene blue (0.117 mM) but maintaining the same residence time furnished ca. 66% conversion with approx. 34% of artemisinin (Entry 119).

Further reduction in concentration of **1** (2.6 mM) without changing the concentration of the sensitizer or residence time gave approx. 64% conversion with an estimated amount of artemisinin of 31% (Entry 120).

Likewise, the flow photooxygenation of **2** (16.2 mM) with methylene blue (0.468 mM) and a 6 minutes residence time showed approx. 33% conversion with ca. 21% of product **4** (Entry 121).

Reduction of concentrations of **2** (4.05 mM) and methylene blue (0.117 mM) while maintaining a residence time of 6 minutes resulted in ca. 73% conversion but only approx. 5% of the desired **4** (Entry 122).

A flow photoreaction of **2** (2.02 mM) with methylene blue (0.117 mM) and 6 minutes residence time resulted in ca. 60% conversion with an estimated amount of artemisinin of 38% (Entry 123).

Table 3. 26: Results of one-pot photoreactions of in the Vapourtec reactor.

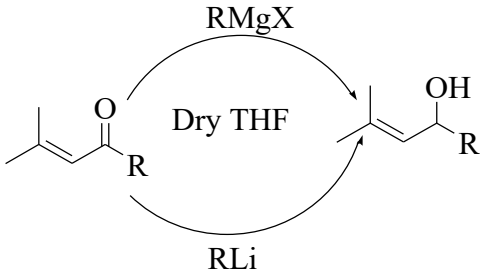
Entry	Starting material			MB	DCM	TFA	R.T.	Wt.	Conv.	Composition [normalized to 100%]					
	Type	[mg]	[mM]	[mM]	[mL]	[mL]	[min]	[mg]	[%]	1	2	4	7	9	16
118	**1**	100	21.1	0.468	20	0.01	6	51	48	52		24	4	20	trace
119	**1**	100	5.3	0.117	80	0.01	6	59	66	34	NA	34	15	16	1
120	**1**	50	2.6	0.117	80	0.01	6	39	64	36		31	17	16	-
121	**2**	100	16.2	0.468	20	0.01	6	44	33		67	21	10	-	2
122	**2**	100	4.05	0.117	80	0.01	6	32	73	NA	27	5*	13	-	11
123	**2**	50	2.02	0.117	80	0.01	6	16	60		40	38	14	-	8

Conversion and compositions were determined by ^{1}H-NMR (±3%); Gas flow rate 0.5mL/min; liquid flow rate1mL/min; no back-pressure regulator was used; Not applicable (NA); Conversion and compositions were determined by ^{1}H-NMR (±3%); *44% unreacted intermediate **17**.

3.3 Syntheses of 1, 2, 4-trioxane

3.3.1 Syntheses of allylic alcohols

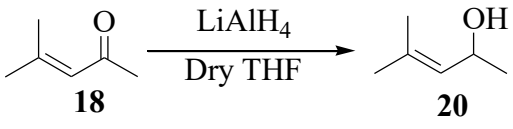
Three different allylic alcohols (**20, 21** and **22**) were prepared from commercially available mesityl oxide (**18**) and 3-methyl-2-butenal (**19**) by reaction with either lithium aluminum hydride or with Grignard reagents in dry THF (**Scheme 3. 6** and **Table 3. 27**).



Scheme 3. 6: Synthesis of allylic alcohols (**20 – 22**).

3.3.1.1 Synthesis of 4-methylpent-3-en-2-ol

The reduction of mesityl oxide (**17**) with lithium aluminum hydride in THF resulted in the formation of almost 42 g of mesitylol (or 4-methylpent-3-en-2-ol, **20**) in a yield of 82% (**Scheme 3. 7**). The satisfactory purity of **20** was confirmed by ^{1}H-NMR analysis **Figure 3. 13**.



Scheme 3. 7: Synthesis of 4-methylpent-3-en-2-ol (**20**) from mesityl oxide (**18**).

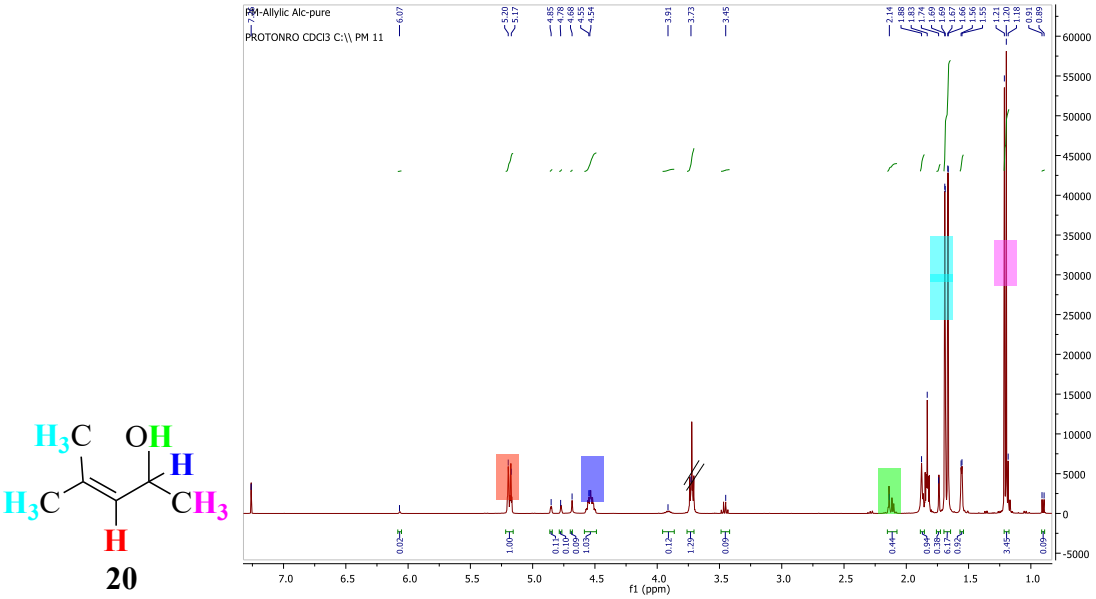
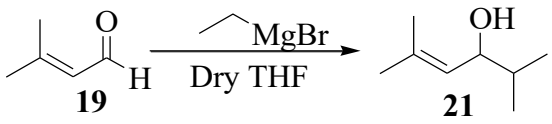


Figure 3. 13: ^{1}H-NMR spectra of 4-Methylpent-3-en-2-ol (**20**).

3.3.1.2 Synthesis of 2, 5-dimethylhex-4-en-3-ol

The reaction of isopropylmagnesium bromide with 3-methyl-2-butenal (**19**) in dry THF resulted in the formation 9.12 g of 2, 5-dimethylhex-4-en-3-ol (**21**) in a good yield (**Scheme 3. 8**). Its identity was confirmed by ^{1}H-NMR analysis (**Figure 3. 14**) and **21** was subsequently used without further purification.



Scheme 3. 8: Synthesis of 2, 5-Dimethylhex-4-en-3-ol (**21**) from 3-methyl-2-butenal (**19**).

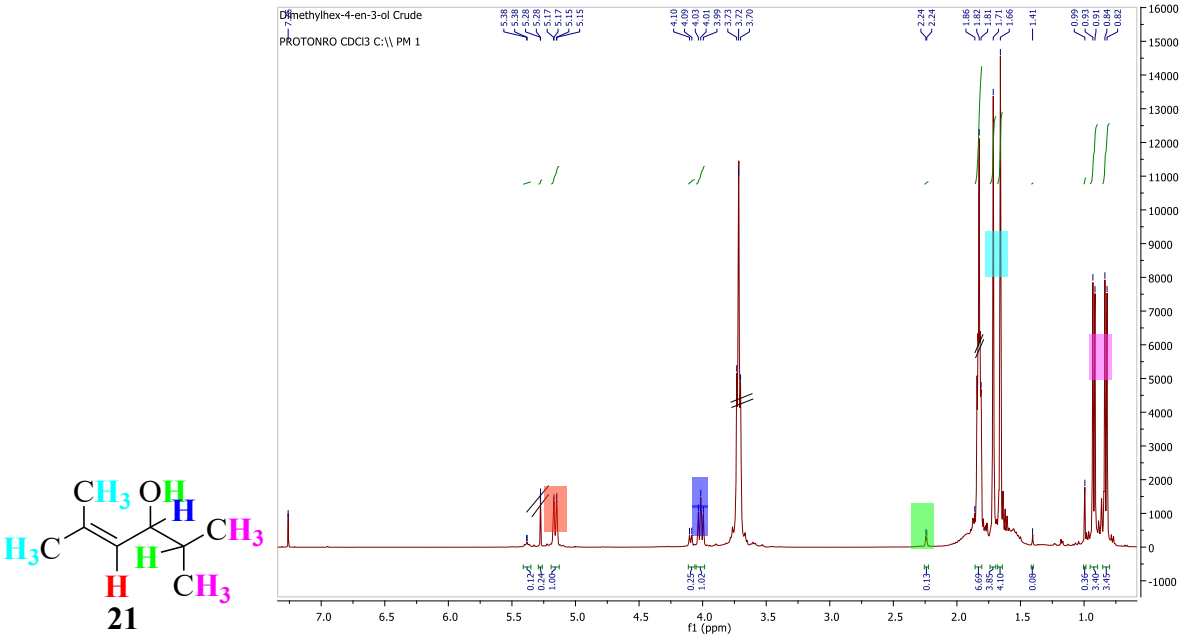
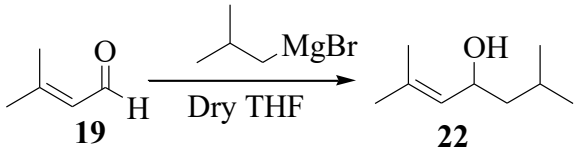


Figure 3. 14: ^{1}H- NMR spectra of 2, 5-Dimethylhex-4-en-3-ol (**21**).

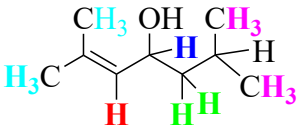
3.3.1.3 Synthesis of 2, 6-dimethylhept-2en-4-ol

The reaction of isobutylmagnesium bromide with 3-methyl-2-butenal (**19**) in dry THF produced 10.34 g of crude **22**, which was further purified by bulb-to-bulb distillation, which yielded 4.16g of 2, 6-dimethylhept-2en-4-ol (**22**) (**Scheme 3. 9**). ^{1}H-NMR analysis confirmed its structure and satisfactory purity (**Figure 3. 15**). Compound **22**, was thus used without further purification.



19 **22**

Scheme 3. 9: Synthesis of 2, 6-Dimethylhept-2en-4-ol (**22**) from 3-methyl-2-butenal (**19**).



22

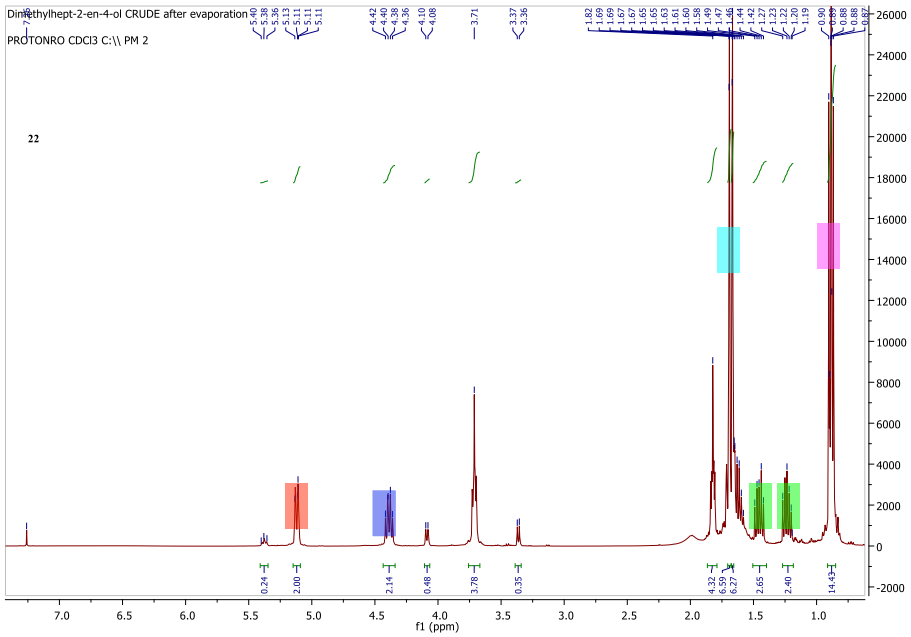


Figure 3. 15: ^{1}H- NMR spectra of 2, 6-Dimethylhept-2en-4-ol (**22**).

Table 3. 27: Characteristic ^{1}H-NMR chemical shifts of allylic alcohols.

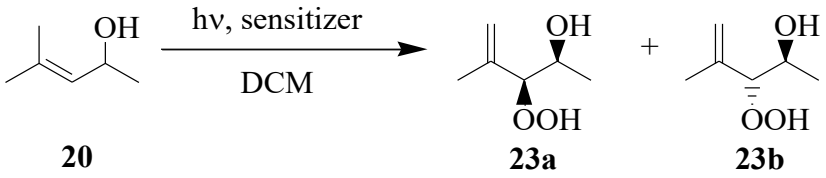
Compound	R	^{1}H-NMR (ppm) in $CDCl_3$		Yields		
		=CH	CH-OH	Crude [g]	Isolated [g]	[%]
20	CH_3	5.19	4.52	57.13	41.99	82
21	*i*-Pr	5.16	4.06	9.12	-	-
22	*i*-Bu	5.12	4.39	10.34	4.16	-

3.3.2 Photooxygenations of allylic alcohols

3.3.2.1 Photooxygenations of 4-methylpent-3-en-2-ol

Photooxygenations of 4-methylpent-3en-2-ol (**20**) were realized in both, a batch reactor and flow reactor. Photoirradiation of **20** in the presence of a $^{1}O_2$ sensitizer leads to the formation of 3-hydroperoxy-4-methylpent-4-en-2-ol (**23**) as a diastereomeric *syn-anti* mixture (**23a** and

23b) (**Scheme 3. 10**). Their ^{1}H-NMR spectrum is shown in **Figure 3. 16** and characteristic chemical shifts are listed in **Table 3. 28**.



Scheme 3. 10: Photooxygenation of 4-methylpent-3-en-2-ol (**20**).

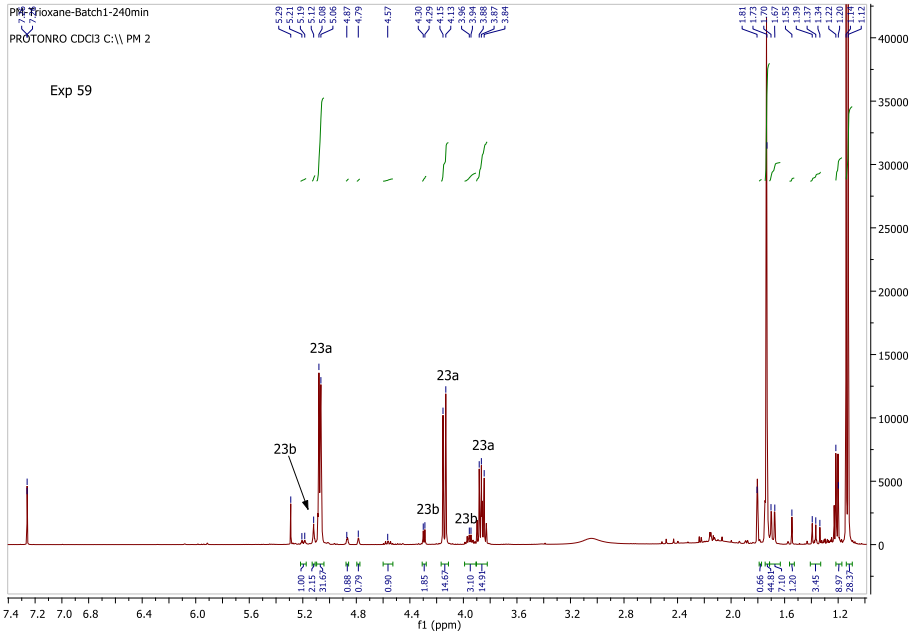


Figure 3. 16: ^{1}H- NMR spectrum of 3-hydroperoxy-4-methylpent-4-en-2-ol (**23**).

Table 3. 28: ^{1}H-NMR chemical shifts of diastereoisomeric 3-hydroperoxy-4-methylpent-4-en-2-ols (**23a** and **b**).

Compound	**^{1}H-NMR (ppm) in $CDCl_3$**		
	C=C<u>H</u>	**C<u>H</u>-OOH**	**C<u>H</u>-OH**
23a	5.08(m)	4.13(d)	4.87(dq)
23b	5.12(m)	4.29(d)	4.94(dq)

3.3.2.1.1 Batch photooxygenations of 4-methylpent-3-en-2-ol

Batch photoreactions of **20** were performed in a Schlenk flask (100 mL) using dichloromethane as a solvent and air as a source of oxygen. Two sensitizers, tetraphenylporphyrin (TPP) and methylene blue (MB), were investigated for this batch study. After mixing, the Schlenk flask

was placed in the center of a Rayonet chamber reactor and air was introduced into the reaction mixture from an aquarium pump. Irradiations were conducted using 16 x 8 W cool white fluorescent tubes. The results of the batch photoreactions are described in **Table 3. 29**. Conversions and diastereoisomeric ratios were determined by NMR-analysis.

The batch irradiation of **20** (50 mM) in the presence of TPP (0.0488 mM) for 4 hours resulted in 95% conversion with 79% of the major isomer **23a** and 16% of the minor isomer **23b** formed (Experiment 59). Repetition experiments resulted in similar conversion of 94% with 72-77% of **23a** and 17-22% of **23b** (Experiments 61 and 69).

A higher concentrated batch reaction of **20** (510 mM) with TPP (51 mM) for 4 hours gave 85% conversion with 65% of **23a** and 20% of **23b** (Experiment 62). Extension of irradiation to 5 hours for the same concentrations gave a high conversion of 95% with a **23a/b** isomeric ratio of 75:20% (Experiment 60). Repetition of the same reaction confirmed a 95% conversion with a **23a/b** ratio of 76:19% (Experiment 70). A further increase of the irradiation time for the same concentration to 6 hours resulted in complete conversion and a **23a/b** isomeric ratio of 82:18% (Experiment 73).

Further photooxygenations were performed with increased concentrations of **20** (100 mM) and TPP (0.0488 mM) and 5 hours of irradiation. NMR analysis showed 91% conversion with 76% of **23a** and 15% of **23b** (Experiment 71).

Another irradiation reaction was performed with 100 mM **20** and 0.0976 mM TPP for 6 hours and gave 98% conversion with 87% of **23a** and 11% of **23b** (Experiment 72). Extending the irradiation time to 7 hours for the same concentration furnished complete conversion with a **23a/b** isomeric ratio of 85:15% (Experiment 74).

The irradiation time was subsequently reduced to 3 hours and photoreactions of **20** (50 mM) were performed with varying concentrations of TPP (Experiments 63-67). Over a TPP concentration range of 0.0976-0.4066 mM, conversions of 87-96% were obtained. The isomeric ratios of **23a/b** were found in the range of 70-83:13-18%.

Following the protocol reported by Singh et al., methylene blue was furthermore used as sensitizer [104]. After 4 hours of irradiation, a solution of **20** (33 mM) and methylene blue (0.0625 mM) was converted in 94% and the diastereoisomeric **23a** and **23b** were formed in 77% and 18%, respectively (Experiment 68).

Table 3. 29: Batch photoreactions of 4-methylpent-3-en-2-ol (**20**).

Exp	20		Sensitizer		DCM	Irradiation	Wt.	Conv.	Composition [normalized to 100%]		
	[mg]	[mM]	Type	[mM]	[mL]	[h]	[mg]	[%]	20	23a *Syn*	23b *anti*
*59	500	50	TPP	0.0488	100	4	550	95	5	79	16
60	500	50	TPP	0.0488	100	5	498	95	5	75	20
61	500	50	TPP	0.0488	100	4	553	94	6	77	17
62	510	51	TPP	0.0488	100	4	622	85	15	65	20
63	500	50	TPP	0.0976	100	3	469	96	4	83	13
64	500	50	TPP	0.1464	100	3	609	87	13	70	18
65	500	50	TPP	0.1627	100	3	543	92	8	74	18
66	500	50	TPP	0.2440	100	3	733	94	6	76	18
67	500	50	TPP	0.4066	100	3	855	93	7	77	16
68	250	33	MB	0.0625	75	4	109	94	6	77	18
69	500	50	TPP	0.0488	100	4	534	94	6	72	22
70	500	50	TPP	0.0488	100	5	607	95	5	76	19
71	1000	100	TPP	0.0488	100	5	966	91	9	76	15
72	1000	100	TPP	0.0976	100	6	1027	98	2	87	11
73	500	50	TPP	0.0488	100	6	358	100	-	82	18
74	1000	100	TPP	0.0976	100	7	1220	100	-	85	15
75	1000	100	TPP	0.0488	100	7	1375	100		94%	6%

Conversion and compositions were determined by ^{1}H-NMR (±3%); Methylene blue (MB), *meso* – Tetraphenylporphyrin (TPP).

3.3.2.1.2 Flow photooxygenations of 4-methylpent-3-en-2-ol

Flow reactions involving **20** were performed in both flow reactor models. Compressed air was used predominantly as oxygen source, although selected reactions were also conducted with pure oxygens. The reactions were carried out in dichloromethane with TPP or methylene blue as photosensitizers. After a set residence time, the crude product was analyzed by ^{1}H-NMR spectroscopy and conversions and diastereoisomeric compositions were determined by integration of baseline separated signals.

When using flow reactor model – 1 equipped with a 5-psi back pressure regulator, the reactants were pumped into the reaction capillary by an Ismatec rotary piston pump. Compressed air or oxygen gas were injected into the liquid stream via a T-mixer. The generated slug-flows were irradiated by a central 20 W fluorescent tube and the photoproducts were collected at the top of the reactor in an amber glass vessel. The results of the photoreactions conducted are shown in **Table 3. 30**.

Using flow rates of 1 mL/min (liquid) and 0.5 mL/min (air), a residence time of 75 minutes was obtained. Photooxygenation of a solution of **20** (50 mM) and TPP (0.0976 mM) gave 60% conversion with 44% of **23a** and 16% of **23b**, respectively (Entry 76).

Using the same flow rates and TPP concentration (0.0976 mM), but a higher concentration of **20** (100 mM) necessitated repeated irradiation. After 4 passages, the final crude showed 65% conversion with 52% of **23a** and 13% of **23b** (Entry 77).

Using the same conditions as in Entry 76 but omitting the back-pressure regulator gave a residence time of 40 min. The subsequent photooxygenation furnished a conversion of 58% with 50% of **23a** and 8% of **23b** (Entry 78).

When the flow rates for both, liquid and compressed air, were set to 5 mL/min and a 5-psi back pressure regulator was utilized, residence times of 6-13 minutes were obtained. The flow reaction of **20** (50 mM) with TPP (0.0976 mM) and a residence time of 12 minutes showed 80% conversion with 62% of **23a** and 18% of **23b** (Entry 79). With a residence time of 10 minutes, a 96% conversion with a **23a/b** ratio of 82:16% was achieved (Entry 80). Complete conversion with 91% of **23a** and 9% of **23b** was observed with a residence time of 13 minutes (Entry 81). However, repletion of the latter reaction showed a poor conversion of 26% (Entry 82), suggesting an uneven slug flow formation due to unstable pressures.

Additional flow photooxygenations were conducted using the same flow conditions and concentration of **20** (50 mM), but varying concentrations of TPP. With 0.1627 mM of TPP, a 22% conversion with 12% of **23a** and 10% of **23b** was observed after a residence time of 6 minute (Entry 84). An increased TPP concentration to 0.2440 mM resulted in 34% conversion

after 10 minutes (Entry 85). A further increase to 0.4066 mM of TPP showed 32% conversion with 22% of **23a** and 10% of **23b** after 10 minutes (Entry 86).

Under the same flow conditions, a flow reaction with pure oxygen was conducted with **20** (50 mM) and TPP (0.0488 mM). generating a residence time of 8 minutes, a 28% conversion was obtained with 18% of **23a** and 10% of **23b** (Entry 83).

Flow reactions of **20** were also performed with higher flow rates of 2.5 mL/min for both, liquid and compressed air streams in the presence of a 5-psi back pressure regulator. When **20** (50 mM) with TPP (0.2440 mM) was irradiated with a residence time after 14 minutes, a 44% conversion with 34% of **23a** and 10% of **23b** was obtained (Entry 87).

A flow reaction with increased TPP concentration (0.4066 mM) and 20 minutes residence time showed 46% conversion with 36% of **23a** and 10% of **23b** (Entry 88).

The concentration of starting material **20** was consequently reduced to 25 mM and flow photooxygenation with TPP (0.2440 mM) for 20 minutes resulted in 49% conversion with 34% of **23a** and 15% of **23b** (Entry 89). Repetition of the same reaction showed a 46% conversion with 32% of **23a** and 14% of **23b** after 16 minutes (Entry 90).

The subsequent reaction with 25 mM of **20** and 0.4066 mM of TPP and a residence time of 20 minutes furnished a conversion of 50% with a **23a/b** isomeric ratio of 34:16% (Entry 91).

Under the same flow conditions, irradiation of **20** (50 mM) with methylene blue (0.1875 mM) in ethanol gave 64% conversion with 34% of **23a** and 30% of **23b** in 25 minutes (Entry 92).

Furthermore, selected flow photoreactions were performed with methylene blue in dichloromethane. Complete conversion with 90% of **23a** and 10% of **23b** was obtained in 15 minutes for a 111 mM solution of **20** with 0.2891 mM of methylene blue (Entry 93).

Increased concentrations of **20** of 125 mM and methylene blue of 0.2345 mM resulted in 90% conversion with a **23a/b** isomeric ratio of 74:16% after 13 minutes (Entry 94).

In Entry 96, the conversion was 16% after 18 minutes and this was as a result of an unstable pressure and uneven gas-liquid flow pattern. Complete conversion with 75% of **23a** and 25% of **23b** was observed with a residence time of 18 minutes (Entry 97). In case of Entry 98 with a residence time of 10 minutes, a 91% conversion with 81% of **23a** and 10% of **23b** was achieved. With a residence time of 12 minutes, a conversion of 83% was obtained with a **23a/b** isomeric ratio of 70:13% (Entry 99).

Selected flow reactions of **20** were also explored in Flow reactor model – 2, which was places inside a Rayonet chamber reactor. The reactants were pumped into the reaction capillary and mixed with compressed air or oxygen via a T-mixer. The gas-liquid slug flow was then allowed to travel through the flow reactor while being irradiated by 16 x 8 W cool white fluorescent

tubes. The photoproduct was collected outside the chamber in an amber glass vessel. NMR analysis was used for the determination of conversions and product compositions. Flow reactions were conducted without a back-pressure regulator and the flow rates were set at 1.5 mL/min for both, gas and liquid streams. The results are summarized in **Table 3. 31**.

Flow photoirradiation of **20** (50 mM) with TPP (0.0488 mM) using compressed air and a residence time of 11 minutes showed 85% conversion with a **23a/b** ratio of 73:12% (Entry 100). Repeating the same reaction with a 4 minutes residence time furnished a 26% conversion with 19% of **23a** and 7% of **23b** (Entry 101). Under the exact conditions (Entry 102), a similar conversion of 28% with a **23a/b** ratio of 22:6% was obtained.

Further reactions were observed to show 86% conversion with 72% of **23a** and 14% of **23b** (Entry 103) and 100% conversion with 93% of **23a** and 7% of **23b** (Entry 104) after 8 minutes residence time.

Selected flow photooxygenation reactions of **20** were also conducted with pure oxygen under the same flow conditions mentioned above. When a solution of **20** (50 mM) with TPP (0.0488 mM) was pumped through the reactor with a residence time of 9 minutes, a 38% conversion with a **23a/b** ratio of 30:8% was obtained (Entry 105).

A similar reaction of **20** (50 mM) with TPP (0.0976 mM) showed 56% conversion with 46% of **23a** and 10% of **23b** after a residence time of 12 minutes (Entry 106).

A subsequent photoreaction with 100 mM of **20** and 0.0488 mM of TPP resulted in a conversion of 46% with a **23a/b** isomeric ratio of 42:4% in 10 minutes residence time (Entry 107).

3.3.2.1.3 Photooxygenations of 4-methylpent -3-en-2-ol in the Vapourtec flow reactor

In the commercial Vapourtec flow reactor (equipped with a 10 mL reaction capillary) the reactants were drawn via pump B and air was injected using an Alicat mass flow controller. The gas-liquid slug flow was irradiated with 3.6 W LED lights and the reactor temperature was kept between 26-29°C. The results of the photoreactions are shown in **Table 3. 32**.

The flow reaction using flow rates of 2.5 mL/min (liquid) and 5 mL/min (air) and 0.3 bar pressure resulted in a short residence time of 1.5 minutes. Under these conditions, a solution of 125 mM of **20** with 0.235 mM of methylene blue furnished only 11% conversion with 7% of **23a** and 4% of **23b** (Entry 124).

By decreasing the flow rates to 1 mL/min for both, liquid and air streams and a pressure of 0.5 bar, a residence time of 5 minutes was achieved. Using the same concentrations as shown

previously, flow photooxygenation gave complete conversion with a **23a/b** ratio of 87:13% (Entry 125).

Then the flow rates were further decreased to 0.5 mL/min for the liquid stream and 1 mL/min for the air stream, a pressure of 0.6 bar and a residence time of 6 were achieved. A flow photoreaction with 50 mM of **20** and 0.0488 mM of TPP resulted in 43% conversion with 33% of **23a** and 10% of **23b** (Entry 126), whereas the reaction with doubled concentration (**20**: 100 mM; TPP: 0.0976mM) showed 25% conversion with a **23a/b** ratio of 15:10% (Entry 127).

Then the reactant concentration was reduced to 25 mM of **20** and 0.0488 mM of TPP, a conversion of 57% with 50% of **23a** and 7% of **23b** was achieved (Entry 128).

Table 3. 30: Results of flow photoreactions of **20** in Flow reactor model – 1.

Entry	20		Sensitizer		Solvent	Volume [mL]	Flow rates [mL/min]		R.T. [min]	Wt. [mg]	Conv. [%]	Composition [normalized to 100%]		
	[mg]	[mM]	Type	[mM]			Liquid	CA				20	23a	23b
76	500	50	TPP	0.0976	DCM	100	1	0.5	75	483	60	40	44	16
77	1000	100	TPP	0.0976	DCM	50	1	0.5	75	394	65*	35	52	13
78	500	50	TPP	0.0976	DCM	100	1	0.5	40	442	58	42	50	8
79	500	50	TPP	0.0976	DCM	100	5	5	12	472	80	20	62	18
80	500	50	TPP	0.0976	DCM	100	5	5	10	451	96	4	82	14
81	500	50	TPP	0.0976	DCM	100	5	5	13	434	100	-	91	9
82	500	50	TPP	0.0976	DCM	100	5	5	13	411	26	74	16	10
83	250	50	TPP	0.0488	DCM	50	5	5 (O_2)	8	260	28	72	18	10
84	500	50	TPP	0.1627	DCM	100	5	5	6	511	22	78	12	10
85	500	50	TPP	0.2440	DCM	100	5	5	10	518	34	66	22	12
86	500	50	TPP	0.4066	DCM	100	5	5	10	519	32	68	22	10
87	500	50	TPP	0.2440	DCM	100	2.5	2.5	14	503	44	56	34	10
88	500	50	TPP	0.4066	DCM	100	2.5	2.5	20	522	46	54	36	10
89	250	25	TPP	0.2440	DCM	100	2.5	2.5	20	232	49	51	34	15
90	250	25	TPP	0.2440	DCM	100	2.5	2.5	16	241	46	54	32	14
91	250	25	TPP	0.4066	DCM	100	2.5	2.5	20	265	50	50	34	16
92	250	50	MB	0.1875	Ethanol	50	2.5	2.5	25	70	64	36	34	30

93	445	111	MB	0.2891	DCM	40	2.5	2.5	15	20	100	-	90	10
94	500	125	MB	0.2345	DCM	40	2.5	2.5	13	188	90	10	74	16
96	500	125	MB	0.2345	DCM	40	2.5	2.5	18	86	16	84	9	7
97	500	125	MB	0.2345	DCM	40	2.5	2.5	18	147	100	-	75	25
98	500	125	MB	0.2345	DCM	40	2.5	2.5	10	26	91	9	81	10
99	500	125	MB	0.2345	DCM	40	2.5	2.5	12	81	83	17	70	13

Conversion and compositions were determined by ^{1}H-NMR (±3%);All reactions were performed under 5psi BPR attached at the end of the flow reactor capillary except for Entry 78 which was performed without BPR; Methylene blue (MB), *meso* – Tetraphenylporphyrin (TPP) Residence time (R.T.); Back pressure regulator (BPR); Compressed air (CA); Entry 92 and 93 the final solution containing crude was treated with silica to remove dye and filtered.; * overall conversion after reinjecting 4 times.

Flow reactor model – 2 results.

Table 3. 31: Results of flow photoreactions of **20** in Flow reactor model – 2.

Entry	**20**		**TPP**	**Flow rates (mL/min)**		**R.T.**	**Wt.**	**Conv.**	**Composition [normalized to 100%]**		
	[mg]	**[mM]**	**[mM]**	**Liquid**	**Gas**	**[min]**	**[mg]**	**[%]**	**20**	**23a**	**23b**
100	500	50	0.0488	1.5	1.5(CA)	11	454	85	15	73	12
101	500	50	0.0488	1.5	1.5(CA)	4	460	26	74	19	7
102	500	50	0.0488	1.5	1.5(CA)	4	260	28	72	22	6
103	500	50	0.0488	1.5	1.5(CA)	8	470	86	14	72	14
104	500	50	0.0488	1.5	1.5(CA)	8	395	100	-	93	7
105	500	50	0.0488	1.5	1.5(O_2)	9	446	38	62	30	8
106	500	50	0.0976	1.5	1.5(O_2)	12	606	56	44	46	10
107	1000	100	0.0488	1.5	1.5(O_2)	10	1102	46	54	42	4

Conversion and compositions were determined by ^{1}H-NMR (±3%); *meso* – Tetraphenylporphyrin (TPP); Residence time (R.T.); Dichloromethane (100mL) was used as solvent in all cases; Back pressure regulator (BPR); Compressed air (CA); Not available (NA).

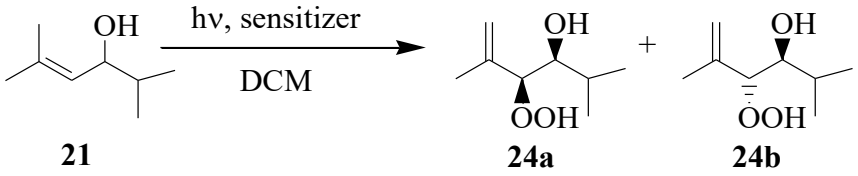
Table 3. 32: Results of flow photoreaction of 20 in the Vapourtec photoreactor module.

Entry	20		Sensitizer		DCM [mL]	Flow rates (mL/min)		R.T. [min]	Wt. [mg]	Conv. [%]	Composition [normalized to 100%]		
	[mg]	[mM]	Type	[mM]		Liquid	CA				20	23a	23b
124	500	125	MB	0.235	40	2.5	5	1.5	483	11	89	7	4
125	500	125	MB	0.235	40	1	1	5	20	100	-	87	13
126	500	50	TPP	0.0488	100	0.5	1	6	471	43	57	33	10
127	500	100	TPP	0.0976	50	0.5	1	6	415	25	75	15	10
128	250	25	TPP	0.0488	100	0.5	1	6	197	57	43	50	7

Conversion and compositions were determined by ^{1}H-NMR (±3%); *meso* – Tetraphenylporphyrin (TPP), methylene blue (MB); Residence time (R.T.); Compressed air (CA).

3.3.2.2 Photooxygenations of dimethylhex-4-en-3-ol

The photooxygenation of dimethylhex-4-en-3-ol (**21**) was performed using the batch photoreactor and flow reactor model – 2. The photoproduct forms a diastereomeric mixture of 4-hydroperoxy-2, 5-dimethylhex-5-en-3-ol (**24**) (**Scheme 3. 11**, **Table 3. 35** and **Figure 3. 17**).



Scheme 3. 11: Photooxygenation of dimethylhex-4-en-3-ol (**21**).

Table 3. 33: Selected ^{1}H-NMR chemical shifts of **24a** and **b**.

Compound	^{1}H-NMR (ppm) in $CDCl_3$		
	C=C**H**	C**H**-OOH	C**H**-OH
24a	5.09 (s)	4.32 (d)	3.50 (m)
24b	5.04 (s)	4.37 (d)	3.56 (d)

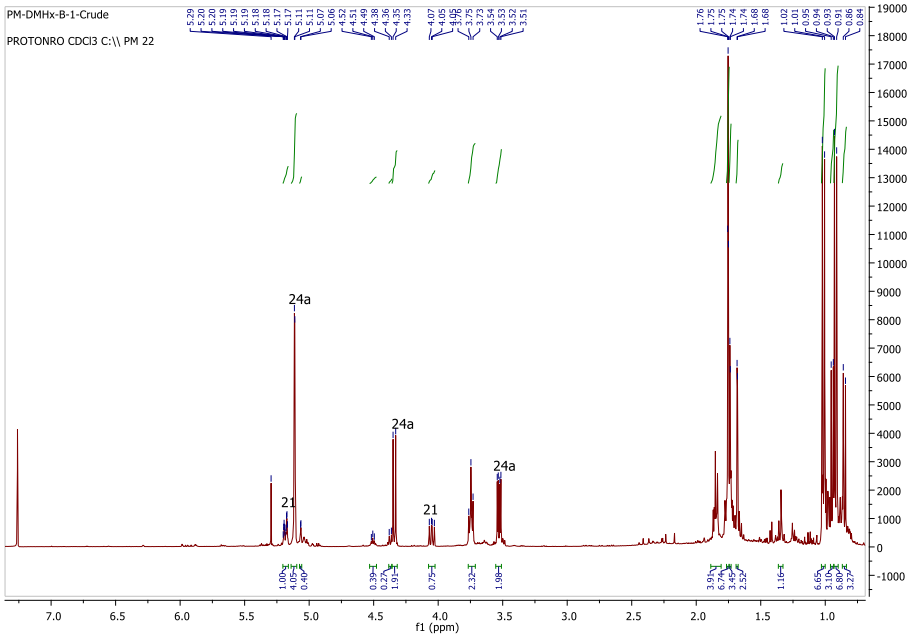


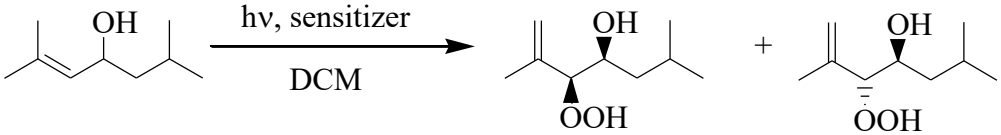
Figure 3. 17: ^{1}H-NMR spectrum of diastereoisomeric 4-hydroperoxy-2, 5-dimethylhex-5-en-3-ols (**24a/b**).

A batch reaction was performed in a Schlenk flask placed inside a Rayonet reactor equipped with 16 x 8W cool white fluorescent tubes. Irradiation of a solution of **21** (36 mM) and TPP (0.0488 mM) in dichloromethane for 5 hours showed 74% conversion with 70% of **24a** and 4% of **24b** minor isomer (Experiment 76).

For the flow reaction a solution with the same reactant concentrations was pumped into flow reactor model – 2 at 1.5 mL/min and oxygen gas were injected at a flow rate of 1.5 mL/min. After a residence time of 11 minutes, a conversion of 21% and a **24a/b** ratio of 19:2% were obtained (Entry 108). The same flow reaction with compressed air and a residence time of 11 minutes furnished a 85% conversion with 74% of **24a** and 12% of **24b** (Entry 109). Another flow reaction conducted with air under the same conditions and a residence time of 10 minutes showed 24% conversion with 21% of **24a** and 3% of **24b** (Entry 110).

3.3.2.3 Photooxygenations of dimethylhept-2-en-4-ol

A series of photooxygenations of dimethylhept-2-en-4-ol (**22**) was performed in the batch photoreactor and in flow reactor model – 2 as well (**Table 3. 36**). The photoproduct forms a diastereomeric mixture of 3-hydroperoxy-2, 6-dimethylhept-1-en-4-ol (**25**) (**Scheme 3. 12** and **Figure 3. 18**).



22 **25a** **25b**

Scheme 3. 12: Photooxygenation of dimethylhept-2-en-4-ol (**22**).

Table 3. 34: Selected ^{1}H-NMR chemical shifts for **25a** and **b**.

Compound	^{1}H-NMR (ppm) in $CDCl_3$		
	C=C**H**	C**H**-OOH	C**H**-OH
25a	5.07 (m)	4.16 (d)	3.75 (dd)
25b	5.03 (m)	4.31 (d)	3.84 (dd)

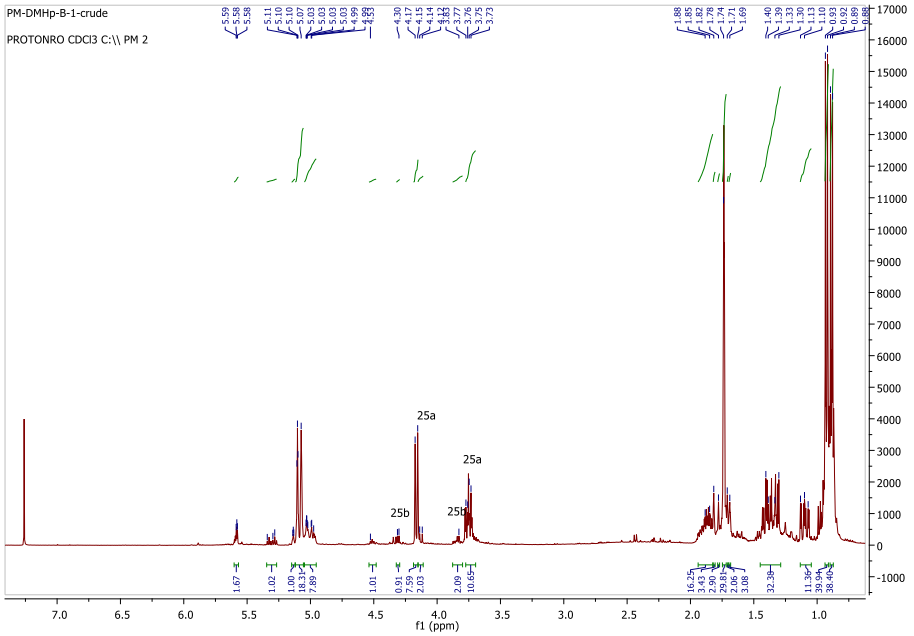


Figure 3. 18: ^{1}H-NMR spectrum of 3-hydroperoxy-2, 6-dimethylhept-1-en-4-ol (**25a/b**).

A batch reaction was again conducted in Schlenk flasks placed in a Rayonet chamber reactor equipped with 16 x 8W cool white fluorescent tubes. The photooxygenation of 32 mM of **22** with 0.0488 mM of TPP in dichloromethane for 5 hours showed complete conversion with 89% of **25a** and 11% of **25b** (Experiment 77).

Selected flow reactions using the same reactants concentrations were performed with flow rates of 1.5 mL/min (liquid) and 1.5 mL/min (gas). With a residence time of 11 minutes and pure oxygen, a 43% conversion was obtained with 38% of **25a** and 5% of **25b** (Entry 111). The same reaction with compressed air and a residence time of 11 minutes was recirculated twice and consequently resulted in a 59% conversion with a **25a/b** ratio of 51:8% (Entry 112). Another flow reaction under the same conditions with air showed 44% conversion with 39% of **25a** and 5% of **25b** minor isomer (Entry 113) after a residence time of 10 minutes.

Table 3. 35: Photooxygenations of dimethylhex-4-en-3-ol in batch and flow reactor model – 2.

Mode	Reactions	21		TPP [mM]	DCM [mL]	Gas	R.T.	Wt. [mg]	Conv. [%]	Composition [normalized to 100%]		
		[mg]	[mM]							21	24a	24b
Batch	Exp 76	500	36	0.0488	100	Air	5h	337	74	26	70	4
Flow	Entry 108	500	36	0.0488	100	O_2	11min	273	21	79	19	2
	Entry 109	500	36	0.0488	100	CA	11min	419	86	14	74	12
	Entry 110	500	36	0.0488	100	CA	10min	392	24	76	21	3

Conversion and compositions were determined by ^{1}H-NMR (±3%); *meso* – Tetraphenylporphyrin (TPP) Residence time (R.T.); * Compressed air (CA); Liquid flow rate 1.5 mL/min; gas flow rate 1.5mL/min.

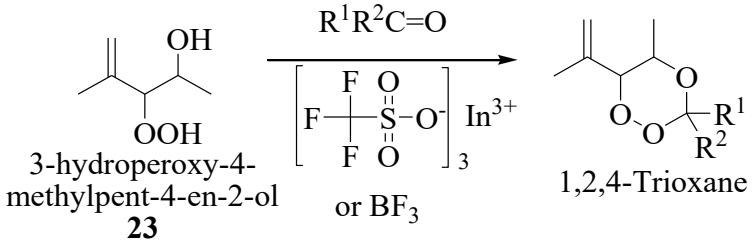
Table 3. 36: Photooxygenations of dimethylhept-2-en-4-ol in batch and flow reactor model – 2.

Mode	Reactions	22		TPP [mM]	DCM [mL]	Gas	R.T.	Wt. [mg]	Conv. [%]	Composition [normalized to 100%]		
		[mg]	[mM]							22	25a	25b
Batch	Exp 77	500	32	0.0488	100	Air	5h	450	100	-	89	11
Flow	Entry 111	500	32	0.0488	100	O_2	11	448	43	57	38	5
	Entry 112	500	32	0.0488	100	CA	11	454	59	41	51	8
	Entry 113	500	32	0.0488	100	CA	6	476	44	56	39	5

Conversion and compositions were determined by ^{1}H-NMR (±3%); *meso* – Tetraphenylporphyrin (TPP) Residence time (R.T.); * Compressed air (CA); Liquid flow rate 1.5 mL/min; gas flow rate 1.5mL/min.

3.3.3 Acid catalyzed reactions to form trioxane compounds

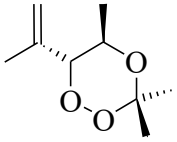
A series of potent or potential antimalarial 1, 2, 4-trioxanes were synthesized using crude 3-hydroperoxyl-4-methylpent-4-en-2-ol (**23**). Lewis-acid catalyzed peroxyacetalization reaction of β-hydroperoxy alcohols with carbonyl compounds in the presence of 0.2 mL of borontrifluoride hydrated (BF_3) or 5-50 mg of indium triflate [$In(OTf)_3$] as catalyst led to the formation of the trioxane compounds **26-36** (**Scheme 3. 13**). The reactions were carried out under standard batch conditions at 0°C for 2 hours and subsequently at room temperature overnight with continuous stirring. The photoproduct β-hydroxy hydroperoxide (**23**) is a diastereoisomeric mixture hence the synthesized 1, 2, 4-trioxane compounds were also diastereomeric mixtures. The identity of the compounds was confirmed using ^{1}H-NMR spectral data from the literature [105].



Scheme 3. 13: General synthesis scheme of 1, 2, 4-trioxanes **26-36**.

The 1, 2, 4-trioxane compounds 26-32 were synthesized by condensing 23 with equivalent amounts of aliphatic ketones in the presence of In(OTf)3 as a catalyst (**Table 3. 37**). Using four different aromatic aldehydes, compounds 33-36 were also synthesized using BF3 hydrated or In(OTf)3 as shown in **Table 3. 38**.

Reaction of a diastereoisomeric 83:17% mixture of **23a/b** with acetone in the presence of $In(OTf)_3$ resulted in formation of compound **26**. After evaporation of the solvent and excess acetone, a crude product containing TPP and catalyst was obtained. Aqueous workup was not performed as the catalyst is known to be insoluble in water [106]. The identity and satisfactory purity of **26** was confirmed by NMR analysis (**Figure 3. 19**).



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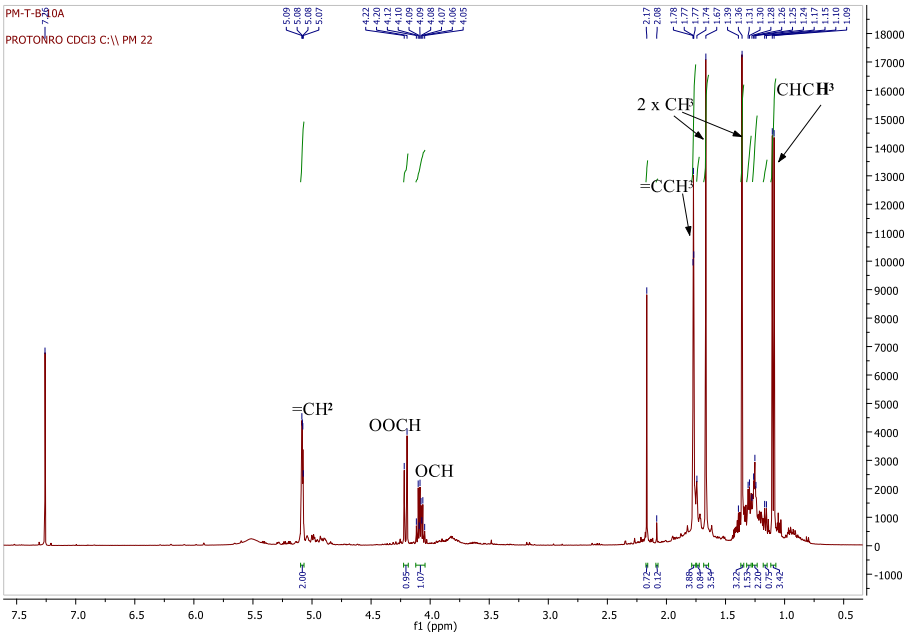
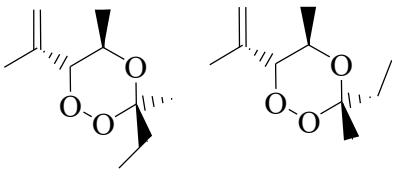


Figure 3. 19: ^{1}H-NMR spectrum of crude **26**.

When a 85:15-mixture of **23** was reacted with 2-butanone in the presence of $In(OTf)_3$, compound **27** was obtained as a mixture of the diastereomers **27a** and **27b**. NMR analysis confirmed the identity and relative purity of the diastereomeric pair (**Figure 3. 20**). Aqueous workup to remove excess ketone led to a complete loss of the product [107]. Likewise, an attempted chromatographic purification with n-hexane and ethyl acetate (9:1 vol%) failed to obtain any product.



27a **27b**

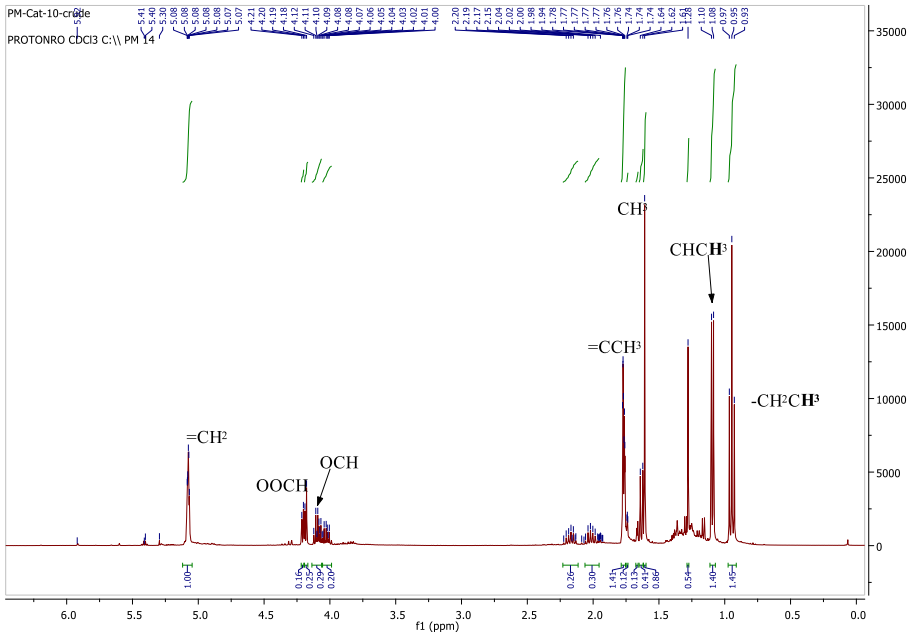
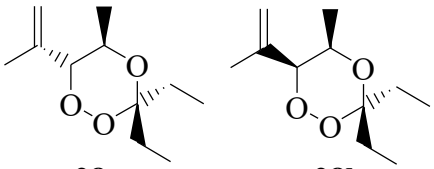


Figure 3. 20: ^{1}H-NMR spectrum of crude **27**.

When a mixture of 3-pentanone and **23** was treated with $In(OTf)_3$, the isomeric compounds **28a** and **b** were generated along with traces of the byproduct **28c**. Proton NMR analysis of the crude product confirmed the identity of **28a/b** as well as **28c** (**Figure 3. 21**). Aqueous washing of the crude product was not performed as the catalyst is insoluble in water [106] and the conditions may decompose the trioxane products [107]. Chromatographic purification was conducted with n-hexane and ethyl acetate (9:1 vol%) as mobile phase but failed to produce any product.



28a **28b**

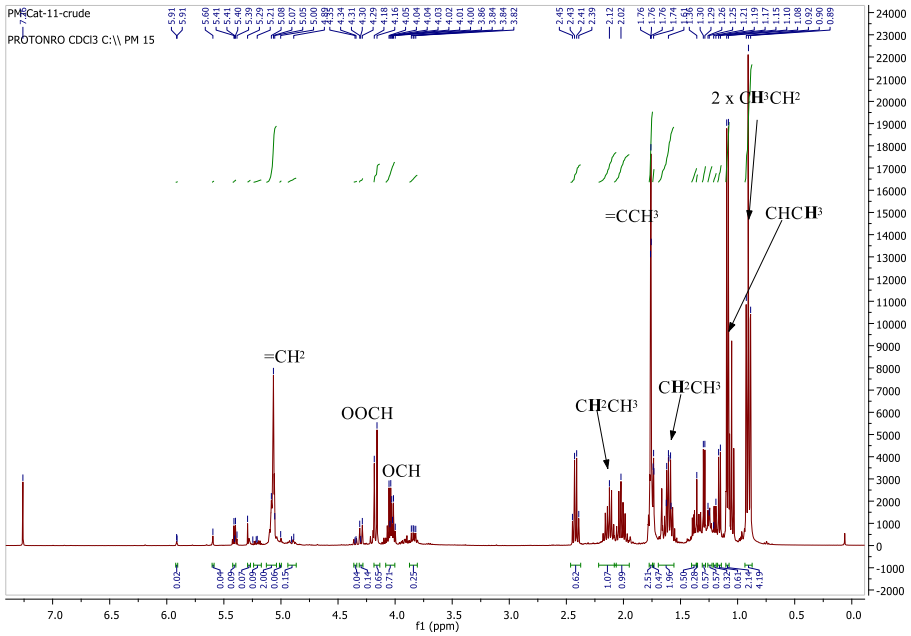
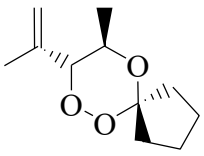


Figure 3. 21: ^{1}H-NMR spectrum of crude **28**.

Upon treatment with cyclopentanone and $In(OTf)_3$, the hydroperoxy alcohol **23** produced compound **29**. NMR analysis of the crude product confirmed the identity and high purity of the desired product (**Figure 3. 22**). To remove excess ketone, catalyst and TPP chromatographic purification was attempted with n-hexane and ethyl acetate (9:1 vol%) as mobile phase, but this led to complete loss of the product. The synthesis was of **29** was subsequently repeated using boron trifluoride hydrate as a catalyst, which can be easily removed by aqueous workup. However, NMR analysis of the crude product obtained showed a very complex reaction mixture with a variety of byproducts. Aqueous workup did not improve the quality of this product. Hence, the synthesis was repeated with indium triflate and the crude product was collected without any further purification.



29

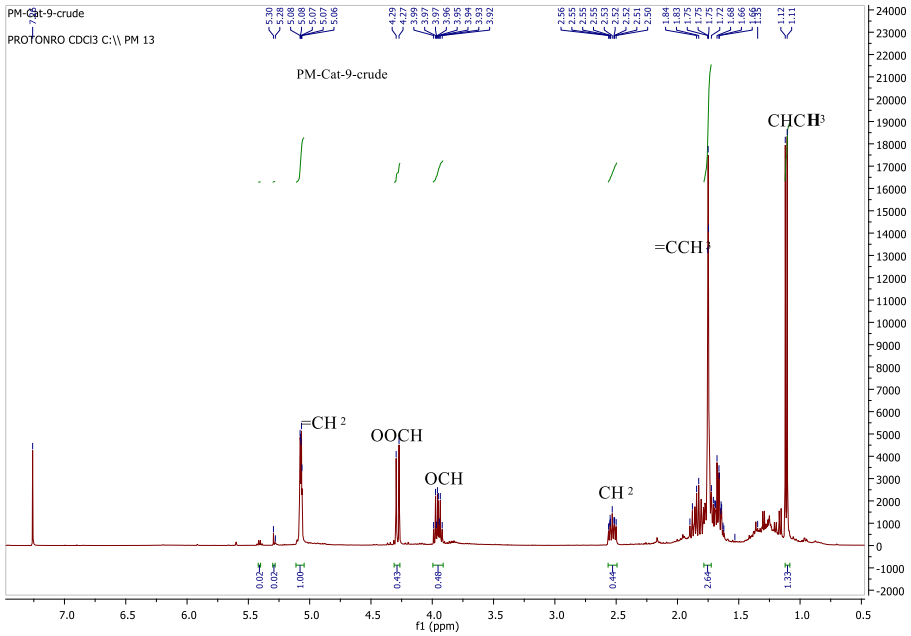
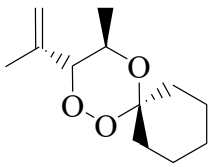


Figure 3. 22: ^{1}H-NMR spectrum of crude **29**.

Similarly, the reaction of **23** with cyclohexanone in the presence of $In(OTf)_3$ resulted in the formation of compound **30**. NMR analysis of the crude product revealed its high purity with very few impurities present **Figure 3. 23**. The crude product was nevertheless subjected to purification in a chromatography station using a slow gradient elution with n-hexane and ethyl acetate (0-5%). However, no product could be collected.



30

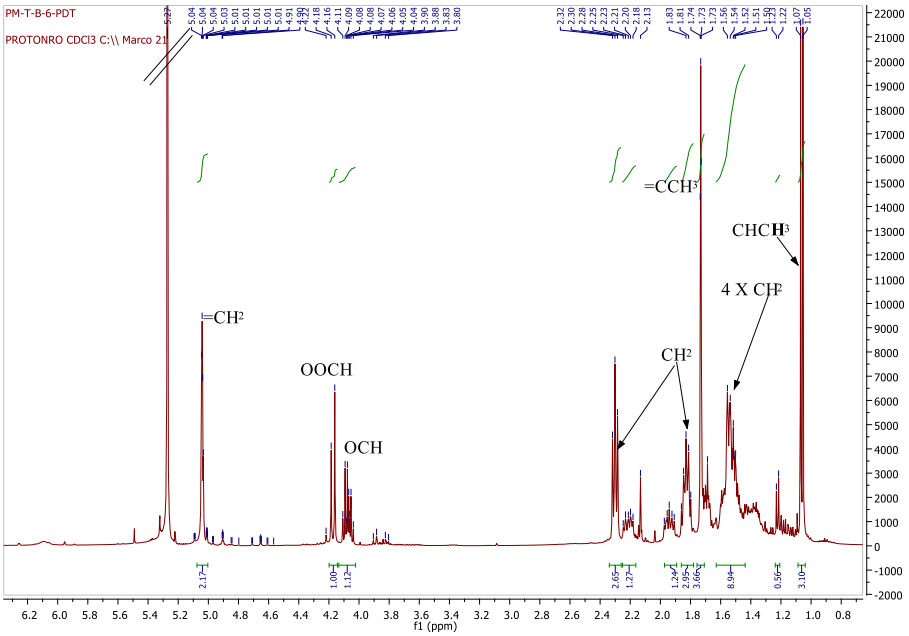
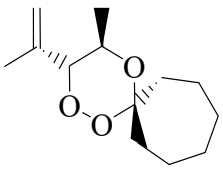


Figure 3. 23: ^{1}H-NMR spectrum of crude **30**.

The reaction of cycloheptanone with **23** using boron trifluoride hydrate as catalyst was thought to produce compound **31**. However, NMR analysis of the crude product showed a complex spectrum, indicating either the presence of numerous byproducts or the population of various conformers of **31** (**Figure 3. 24**). The reaction was repeated with indium triflate but analysis of the crude product gave the same complex NMR spectrum.



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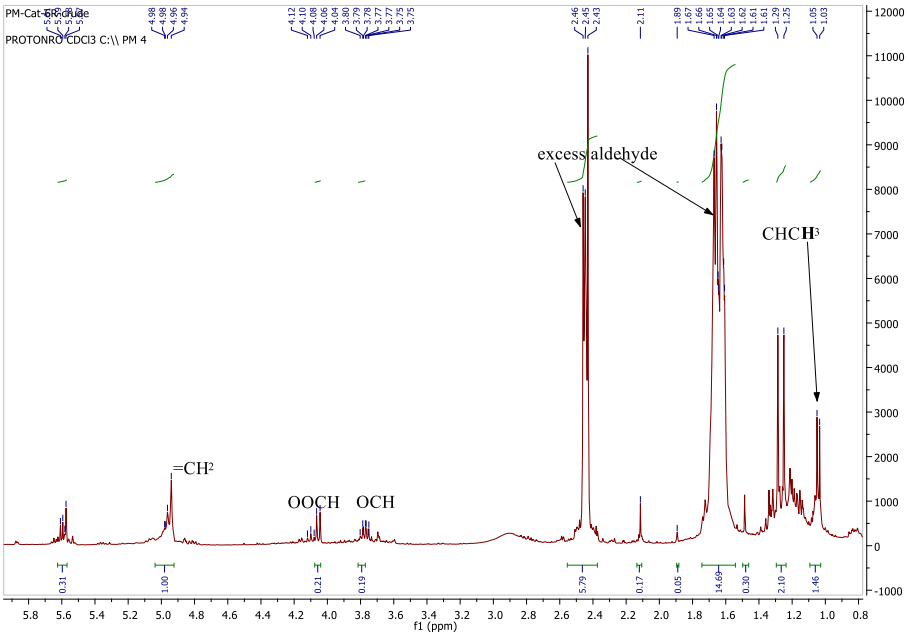
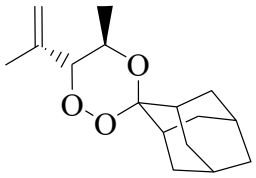


Figure 3. 24: ^{1}H-NMR spectrum of crude **31**.

A similar reaction of **23** with adamantanone in the presence of indium triflate resulted in the formation of compound **32**. Analysis of the crude product suggested a satisfactory purity with few impurities presents (**Figure 3. 25**). An attempt to purify the product by flash chromatography with a slow gradient elution with n-hexane and ethyl acetate (0-5%) led to the loss of all product material.



32

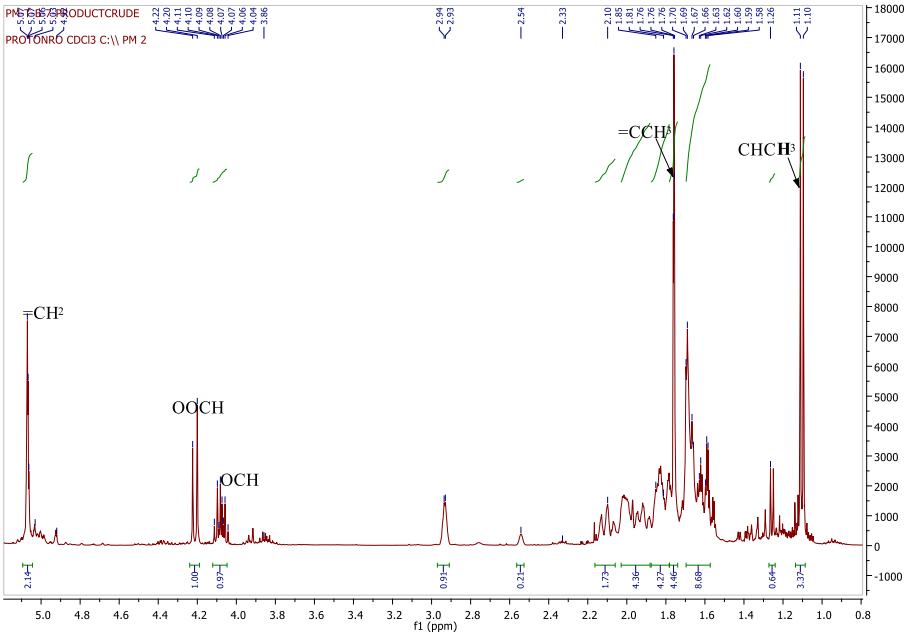
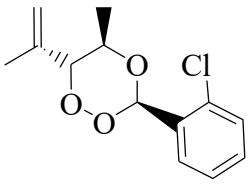


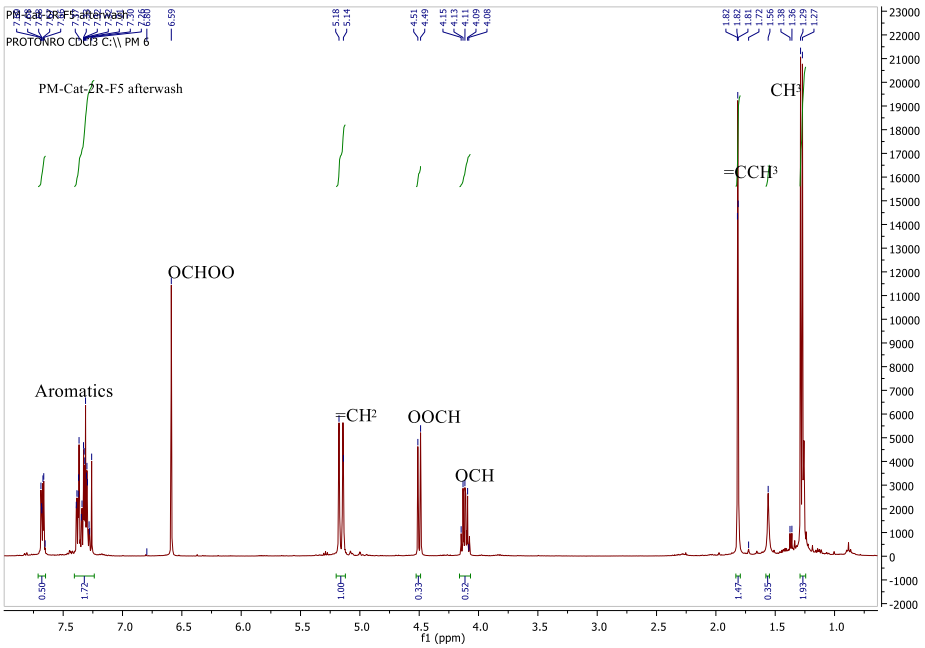
Figure 3. 25: ^{1}H-NMR spectrum of crude **32**.

Compound **33** was synthesized through reaction of hydroperoxyalcohol **23** with 2-chlorobenzaldehyde in the presence of boron trifluoride hydrate as a catalyst. The crude product obtained was found to contain the desired product **33**, excess aldehyde and some impurities. Chromatographic purification was performed with n-hexane and ethyl acetate (9:1 vol%) as mobile phase and fractions collected were found to contain **33** and residual aldehyde. In order to remove the aldehyde, the combined fractions were subjected to aqueous workup as described by Brindle et. al. [107], yielding a small amount of pure **33**. NMR analyses confirmed the presence of a single diastereomer (**Figure 3. 26**).



33

(a)



(b)

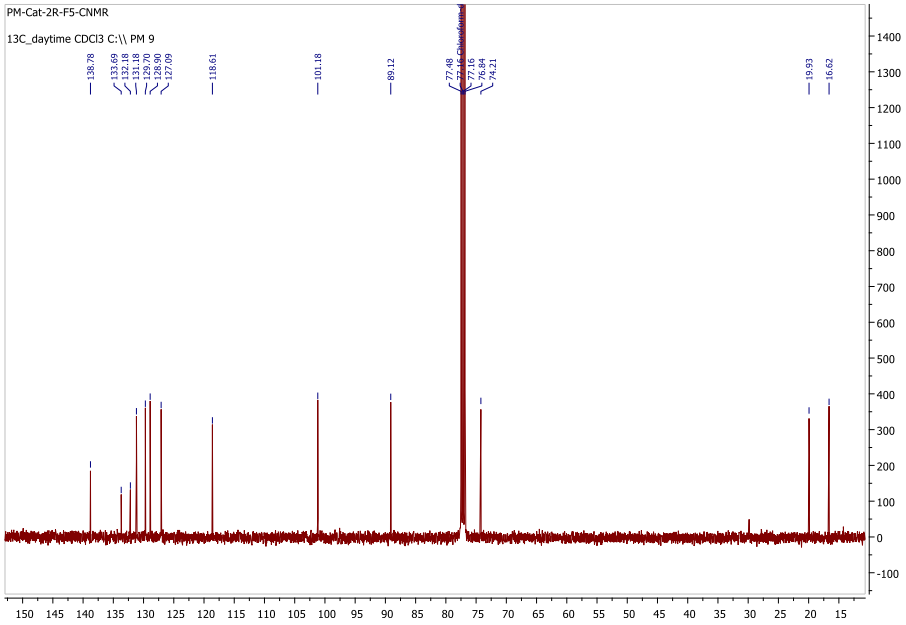
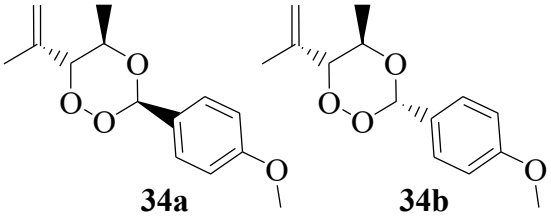


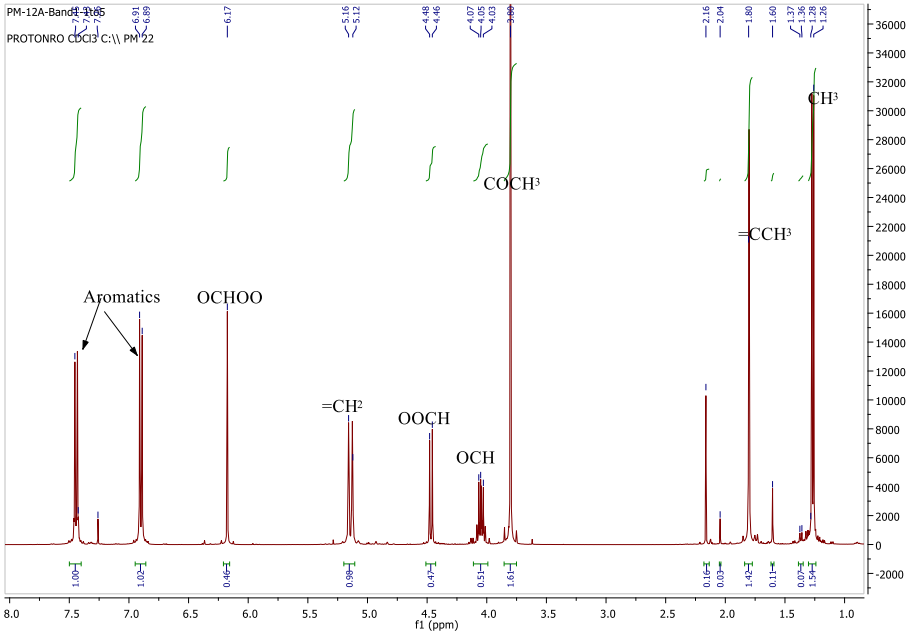
Figure 3. 26: (a) ^{1}H-NMR spectrum and (b) ^{13}C-NMR spectrum of pure **33**.

When the photooxygenation product **23** was treated with 4-methoxybenzaldehyde in the presence of indium triflate, compound **34** was obtained as a pair of diastereomers. Compounds **34a** (major) and **34b** (minor) were generated in a ratio of 93:7 ratio, as determined by NMR analysis (**Figure 3. 27**) and isomer **34a** was obtained by chromatographic separation.



34a **34b**

(a)



(b)

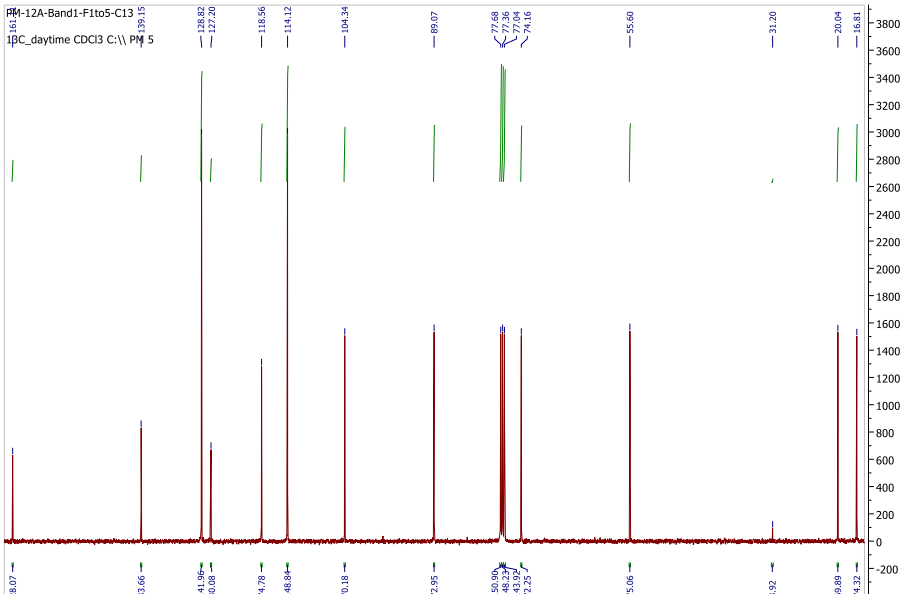
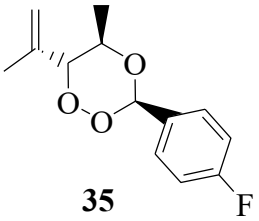


Figure 3. 27: (a) ^{1}H-NMR spectrum and (b) ^{13}C-NMR spectrum of pure **34a**.

Compound **35** was likewise synthesized by reacting **23** with 4-fluorobenzaldehyde in the presence of indium triflate. NMR analysis confirmed the formation of **35** but showed the presence of excess aldehyde along with other minor impurities (**Figure 3. 28**). Aqueous workup was attempted to remove excess aldehyde but the product itself decomposed under these conditions. Repetition of the synthesis followed by column chromatographic purification with n-hexane and ethyl acetate (9:1 vol%) resulted in the isolating a small quantity of product, but this was found to be contaminated with plasticizer.



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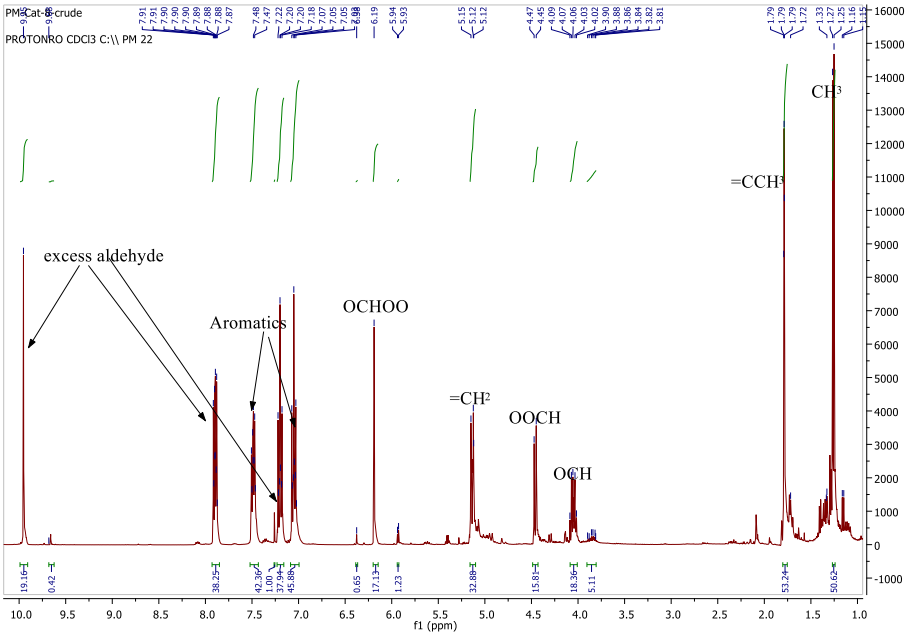


Figure 3. 28: ^{1}H-NMR spectrum of crude **35**.

The final reaction of **23** was conducted with 5-bromo-2-methoxybenzaldehyde and indium triflate as a catalyst in order to obtain the diastereoisomeric pair of trioxanes **36a/b**. The crude product was purified using a chromatography station and an eluent of n-hexane and ethyl acetate (0-10%) as mobile phase. A mixture of the two isomers **36a** (major) and **36b** (minor) was collected as confirmed by NMR-analysis (**Figure 3. 29**). However, the sensitizer TPP could not be entirely removed by this purification method.

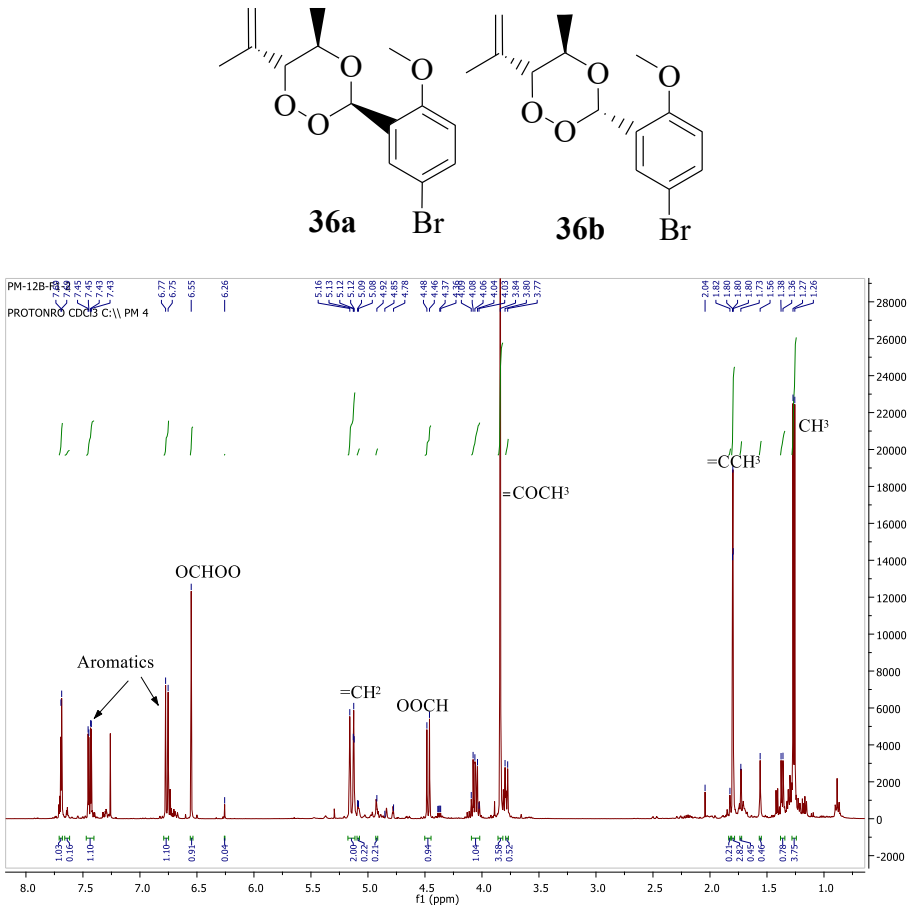


Figure 3. 29: ^{1}H-NMR spectrum of crude **36a/b**.

Table 3. 37: Details of the reactions of **23** with aliphatic ketones and the corresponding products

Sl. No.	DCM [mL]	23		$In(OTf)_3$	Ketones	Amount	Product	Crude
		[mg]	[mol]	[mg]				[mg]
1. PM-T-B-10A	100	270	0.002	10	Acetone	1.64mL	**26**	291
2. PM-Cat-10	100	500	0.0038	30	2 - Butanone	0.338mL	**27**	335
3. PM-Cat-11	100	500	0.0038	30	3 - Pentanone	0.44mL	**28**	413
4. PM-Cat-9	100	500	0.0038	30	Cyclopentanone	0.334mL	**29**	548
5. PM-T-B-6	100	600	0.0046	50	Cyclohexanone	0.48mL	**30**	1034
6. PM-Cat-6R	50	250	0.002	5	Cycloheptanone	0.23mL	**31**	113
7. PM-Cat-7	100	600	0.0046	10	Adamantanone	500mg	**32**	808

Table 3. 38: Details of the reactions of **23** with aldehydes and the corresponding products

Sl. No.	DCM	23		Catalyst		Aldehydes	Amount	Product	Crude [mg]
	[mL]	[mg]	[mol]	Type	Amount				
1. PM-Cat-2R	100	250	0.0019	BF_3 hydrated	0.2mL	2 - Chlorobenzaldehyde	0.231mL	**33**	263 (13mg, Rf=0.76)
2. PM-T-B-12A	100	250	0.0019	$In(OTf)_3$	5mg	4 - Methoxybenzaldehyde	0.22mL	**34**	493 (71mg, Rf=0.43)
3. PM-Cat-8	100	250	0.0019	$In(OTf)_3$	5mg	4 - Fluorobenzaldehyde	0.535mL	**35**	772 (Rf=0.62)
4. PM-T-B-12B	100	250	0.0019	$In(OTf)_3$ 5mg	5mg	5 – Bromo – 2 – methoxybenzaldehyde	393mg	**36**	631 (58mg, Rf=0.40)

Chapter 4:

Discussion

4. Discussion

4.1 Singlet oxygen generation

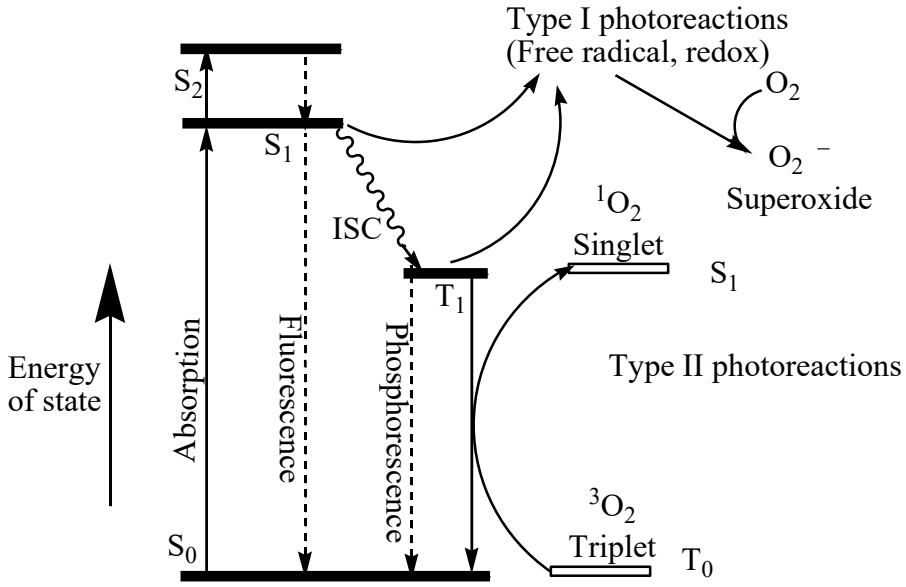
Singlet oxygen ($^1O_2$) is a reactive oxygen species (ROS) that plays an important role in the field of organic synthesis. Molecular oxygen has an open-shell triplet ground state, $^3\sum_g^-$ ($^3O_2$), and there are two low-lying excited states, $^1\Delta_g$ and $^1\sum_g^+$, differing in spin and occupancy of two degenerate anti-bonding orbitals. The second excited state $^1\sum_g^+$ has an identical electronic configuration to that of the ground state, except that two electrons have antiparallel spins. The transition from the $^1\Delta_g$ state to the $^3\sum_g^-$ state is spin forbidden, thus $^1\Delta_g$ is a relatively long-lived species. The second excited state of oxygen, on the other hand, is short-lived due to a spin-allowed transition to the $^1\Delta_g$ state [108]. The $^1\Delta_g$ state has an energy of 94 kJ/mol with an estimated radiative lifetime of 64 min, whereas the $^1\sum_g^+$ has an energy of 157 kJ/mol with a lifetime of 10 sec, respectively (**Table 4.1**). Due to its higher energy and low stability $^1\sum_g^+$ has a significantly shorter lifetime than $^1\Delta_g$. Hence, the term singlet oxygen commonly only refers to $^1\Delta_g$ [109, 110].

Table 4.1: Comparison of three different states of oxygen molecule.

State	π Orbital assignment	Energy level [KJ/mole]	Lifetime
$^1\sum_g^+$	$\underline{\uparrow}$ $\underline{\downarrow}$	157	64min
$^1\Delta_g$	$\underline{\uparrow\downarrow}$ _	94	10sec
$^3\sum_g^-$	$\underline{\uparrow}$ $\underline{\uparrow}$	0	Not applicable

In photooxygenation reactions, singlet oxygen ($^1\Delta_g$) is generated by sensitization (**Scheme 4.1**). On exposure to visible light of an appropriate wavelength, the sensitizer is activated and generates $^1\Delta_g$ through energy transfer from its triplet state. The sensitizer itself returns to its ground state [111]. Due to one photon (hν) transition, the ground state sensitizer (S_0) transforms first into a higher singlet excited state (S_2), which upon internal conversion (IC) relaxes to the lowest singlet excited state (S_1). Intersystem crossing (ISC) generates the triplet state of the sensitizer (T_1). The lifetime of the T_1 state is longer (several µs) than that of the S_1 state (within ns), allowing it to react in two different pathways defined as Types I and II mechanisms. A Type I mechanism involves hydrogen-atom abstraction or electron-transfer between the excited sensitizer and a substrate, yielding free radicals. These radicals can react with triplet oxygen

($^3O_2$) to form reactive oxygen species such as the superoxide radical anion ($O_2^{3\bullet-}$). In a Type II mechanism, singlet oxygen is generated via energy transfer during a collision of the excited sensitizer with triplet oxygen [108].



Scheme 4.1: Jablonski diagram for Type I and Type II photosensitization processes.
[horizontal bars represent energy levels of the different excitation states of the photosensitizer (full bars) or of molecular oxygen (empty bars). S_0 = ground singlet state; S_1 = first excited singlet state; S_2 = second excited singlet state; T_0 = ground triplet state; T_1 = first excited triplet state; ISC = intersystem crossing]

The efficiency of the photooxygenation process is related to the lifetime (τ) of singlet oxygen ($^1\Delta_g$) which is highly dependent on the nature of the solvent. Its lifetime τ is significantly longer in halogenated solvents and in deuterated solvents. In solvents containing five or more –CH- groups, τ reaches a stable value. The participation of -OH, -OO- and –CH- vibrations of the solvents molecules causes deactivation of the energy of singlet oxygen. Thus, in ethanol, water and diethyl ether, the lifetime of singlet oxygen is shorter. In tetrahydrofuran, acetone or ether, τ is in the order of 10^{-5} sec (**Table 4.2**) [112].

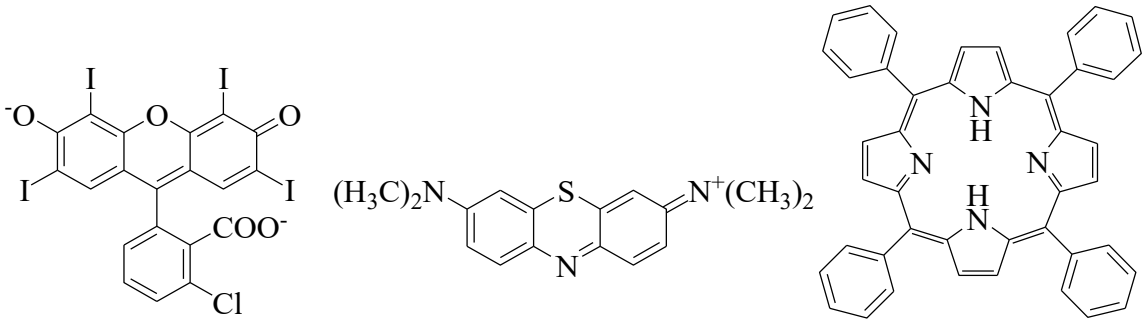
Table 4.2: $^1\Delta_g$ lifetime τ in different solvents.

Sl. No.	Solvents		$^1\Delta_g$ lifetime τ (sec)
1	Carbon tetrachloride	CCl_4	2.6×10^{-2}
2	Chloroform	$CHCl_3$	2.5×10^{-4}
3	Deuterochloroform	$CDCl_3$	8.4×10^{-4}
4	Dichloromethane	CH_2Cl_2	9.1×10^{-5}
5	Tetrachloroethylene	C_2Cl_4	1.2×10^{-3}
6	Trichloroethylene	C_2HCl_3	2.2×10^{-4}
7	Ethylene dichloride	$C_2H_2Cl_3$	7.0×10^{-5}
8	Ethanol	C_2H_5OH	9.7×10^{-6}
9	Deuteroethanol	C_2D_5OD	2.3×10^{-4}
10	Diethyl ether	$(C_2H_5)_2O$	3.4×10^{-5}
11	Acetone	$(CH_3)_2CO$	5.1×10^{-5}
12	Tetrahydrofuran	C_4H_8O	3.0×10^{-5}

4.2 Sensitizer comparison

Several organic dyes or photosensitizers have ability to absorb UV to visible light and can generate singlet oxygen. These photosensitizers must possess certain properties (**Table 4.3**) such as (1) a high absorption coefficient in the spectral region, (2) a triplet state of appropriate energy ($E_T \geq 95$ kJ/mol) to allow for efficient energy transfer to ground state oxygen, (3) a high quantum yield for ISC into the triplet state ($\Phi_T > 0.4$) with a long triplet state lifetime ($\tau_T >$ 1μs), and (4) a high photostability. Methylene blue is a phenothiazine dye with strong absorbance in the range of 550-700 nm, and has a significant quantum yield for $^1O_2$ formation ($\Phi_\Delta = 0.52$ in ethanol). The xanthene dye rose Bengal exhibits intense absorption bands in the green area of the visible light spectrum (480-550 nm) and has a high quantum yield for $^1O_2$ production ($\Phi_\Delta = 0.76$ in methanol). The presence of several heavy halogens substituents in rose Bengal increases its quantum yield for intersystem crossing, which makes this particular dye an efficient photosensitizer. Porphyrin derivatives have the ability to absorb several wavelengths in the UV to visible range. The Soret band in the blue region and the Q-bands in the red region represent their major bands within the visible range. The long-lived triplet states of porphyrins allow high quantum yields. Tetraphenylporphyrin (H_2TPP) shows broad absorption in the 300-700 nm range and has a high quantum yield for $^1O_2$ production ($\Phi_\Delta =$ 0.78 in benzene). However, porphyrins may undergo rapid decomposition in the presence of singlet oxygen (photobleaching). Singlet oxygen is a powerful electrophile and can react rapidly with a variety of substrates. With olefins, it can form dioxetanes via [2+2] cycloaddition or allylic hydroperoxides via ene-reaction. With dienes, it can undergo [4+2] cycloaddition to endoperoxides. These reactions can destroy the conjugation within the porphyrin sensitizers,

which subsequently causes complete suppression of the absorption of visible light and thus inhibits the further generation of singlet oxygen [108].



Rose bengal | Methylene blue | *meso*-Tetraphenylporphyrin

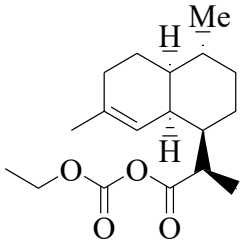
Figure 4.1: Structure of selected photosensitizers

Table 4.3: Photophysical properties of selected photosensitizers.

Sl. No.	Dye	Φ_T	τ_T (μs)	Triplet energy E_T [kJ/mol]	Φ_Δ
1	Methylene blue	-	-	138	0.52 (EtOH)
2	Rose Bengal	-	-	164	0.76 (CH_3OH)
3	H_2TPP	0.82	1380 (300 K)	140	0.78 (C_6H_6)
4	MgTPP		1350 (300 K)	-	0.62 (C_6H_6)
5	ZnTPP	0.88	1200 (300 K)	-	0.83 (C_6H_6)
6	PdTPP	1	380 (300 K)	-	0.88 (C_6H_6)

4.3 Synthesis of the mixed anhydride of dihydroartemisinic acid

Dihydroartemisinic acid (**1**) was successfully converted into its mixed anhydride (**2**) with high yield. The mixed anhydride of DHAA (**2**) represents an activated form of DHAA. Chloroformates are well known in organic chemistry for synthesis of mixed anhydrides as they can easily couple with carboxylic acids in basified organic solvents. The use of the mixed anhydride of DHAA instead of DHAA itself is known to result in much cleaner and improved artemisinin synthesis [113].

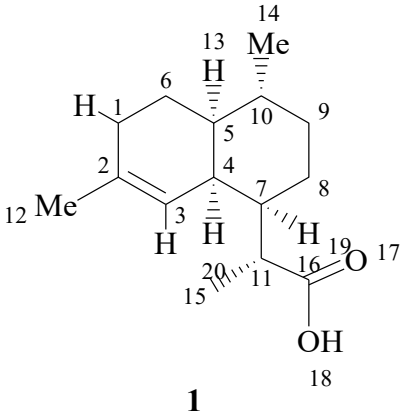


Mixed anhydride of DHAA

2

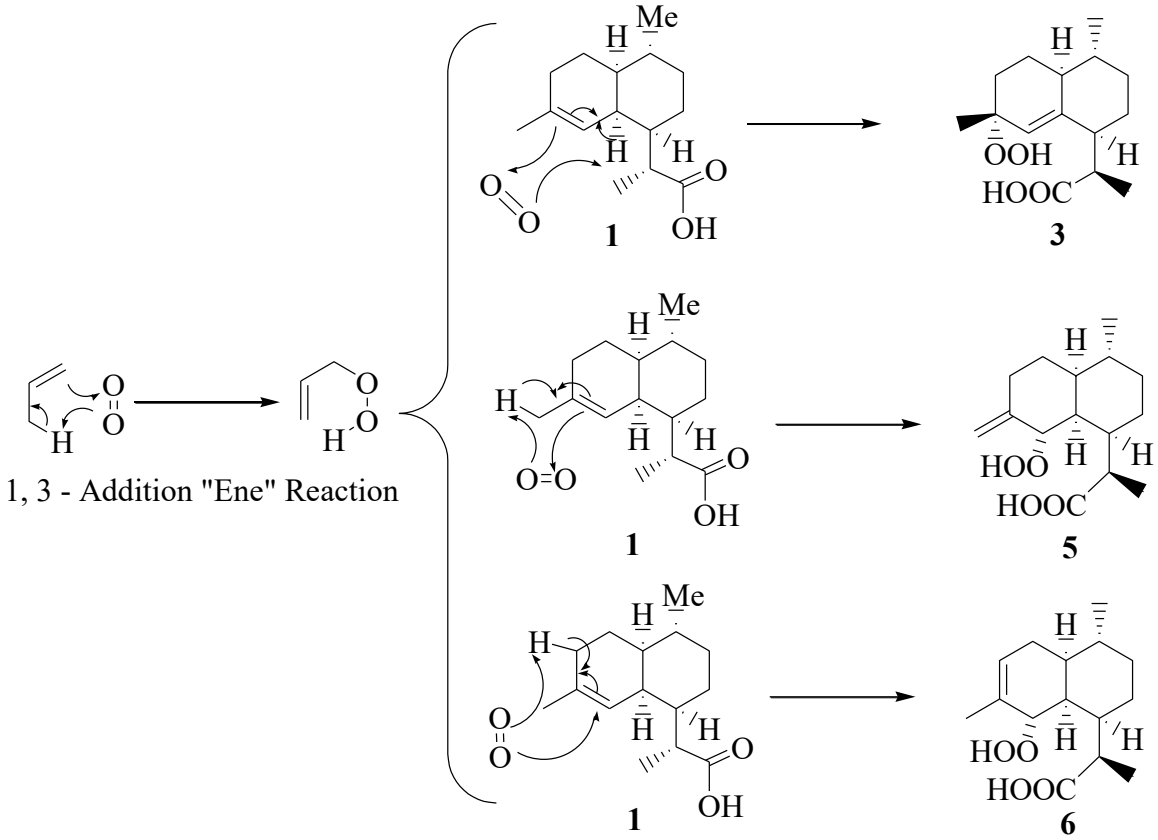
4.4 Artemisinin syntheses via photooxygenation of dihydroartemisinic acid

Artemisinin-based combination therapies (ACTs) represent the best treatment for multi-drug resistant and cerebral malaria [114, 115]. The rising demand for artemisinin can no longer be met by slow and resource demanding plant-based production. While the complete synthesis of artemisinin from simple precursors have been achieved, this lengthy process is not economically viable. Hence, semi-synthetic syntheses of artemisinin have been developed instead [69, 116]. The most efficient way utilizes artemisinin acid (AA), a simple and abundant precursor in plants. A number of biosynthetic methods for the large-scale production of AA have been developed in order to ensure a steady supply of artemisinin at a low price. During the process, artemisinic acid is converted by regio- and diastereoselective reduction to dihydroartemisinic acid (DHAA). Artemisinin is accessible from either DHAA or its methyl ester via hydroperoxidation and rearrangements [69, 117, 118, 119, 120].



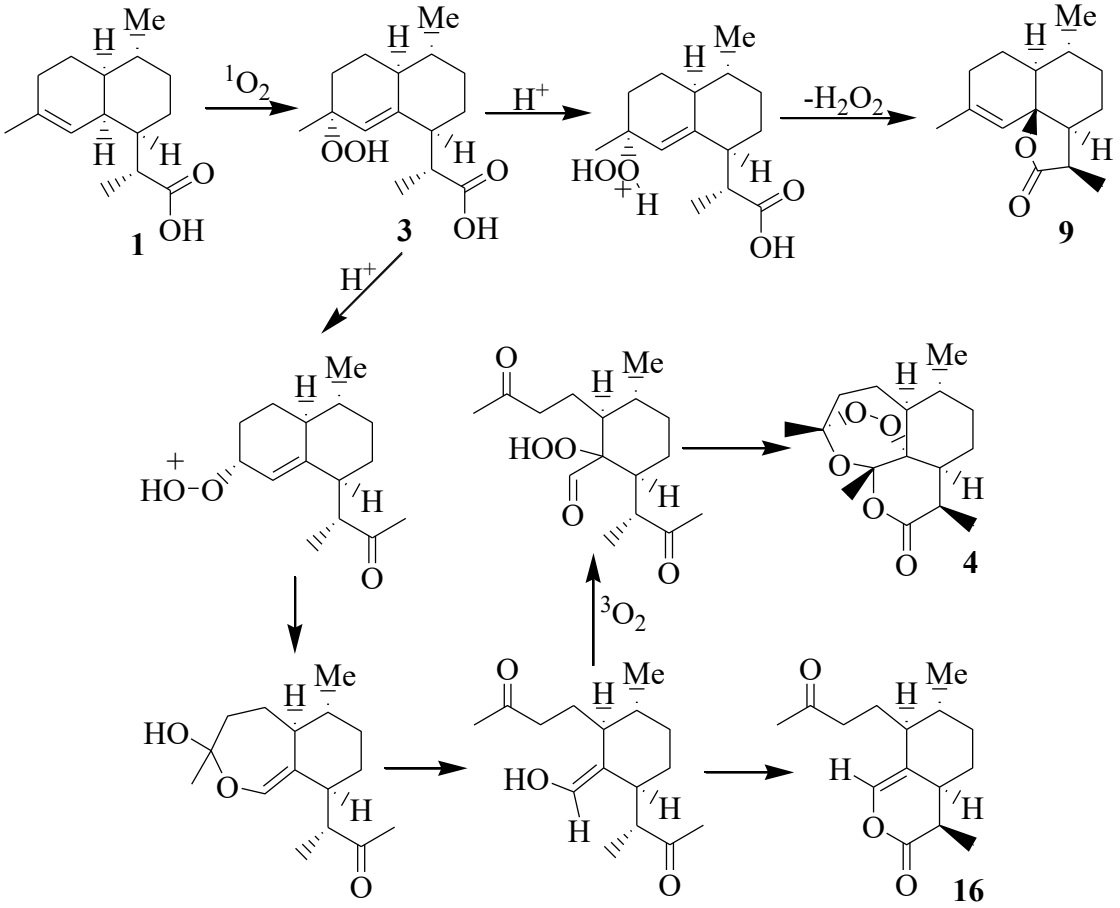
1

The ene-photooxygenation of olefins containing an allylic hydrogen yields allylic hydroperoxides in which the double bond is shifted to an adjacent position [121]. The transformation of dihydroartemisinic acid to artemisinin involves initial peroxidation of DHAA to form the tertiary allylic hydroperoxide **3** as the major product, along with smaller amounts of the isomeric secondary allylic hydroperoxides **5** and **6** (**Scheme 4.2**). Interaction of singlet oxygen with the β-H-atom at position 4 generates the desired hydroperoxide **3**. The latter two hydroperoxides **5** and **6** are formed from two alternative ene-type reactions of molecular oxygen with the α-H-atoms at positions 12 and 1, respectively. Subsequent protonation of hydroperoxide **3** and Hook cleavage leads to the formation of an enol intermediate. This enol reacts with triplet oxygen to form the hydroperoxide which undergo cyclization to form artemisinin [122, 123].



Scheme 4.2: Mechanism of the formation of the various photooxygenation products.

Acid treatment of the initial hydroperoxide photoproducts can form various byproducts along with artemisinin (**Scheme 4.3**). The main byproducts **7** and **8** are formed from hydroperoxide **5** as described in **Chapter 3**. Compound **9** or its isomer **10** are formed from **3** upon prolonged irradiation [123]. Compound **11** results from E_1 elimination reaction of **3**, whereas compounds **13**, **14**, **15** and **16** are formed after Hook cleavage of **3** in the presence or in the absence of triplet oxygen. Acid catalysis under oxygen rich conditions gives the highest amounts of the desired artemisinin **4**, along with small amounts of **14**. In contrast, a lack of triplet oxygen produces more of **16**. The formation of **16** can thus be used an as indicator for the oxygen supply during a reaction.



Scheme 4.3: Mechanism of conversion of intermediate hydroperoxide to artemisinin and other by-products.

The photooxygenation of DHAA and follow up Lewis acid-catalyzed cyclization to form artemisinin was first reported by Roth and Acton in 1989 [124]. The biosynthetic production of AA from yeast was achieved by Keasling and coworkers in collaboration with Amyris [69, 120]. These studies led to the development of the semi-synthetic artemisinin preparation on industrial scale by Sanofi, with a reported 55% isolated yield for the conversion of DHAA into artemisinin [113]. Recent cost pressures have caused a disruption and ultimately sale of the industrial manufacturing plant.

Ensuring a steady supply of artemisinin in minimum time and at low costs thus demands simplified alternative production methods. The synthesis of artemisinin was thus explored by using a simple continuous flow method that can operate on site and on demand and can produce the desired amounts in a flexible and mobile (portable) way. Keeping the cost effectiveness and energy efficiency of the process in mind, an inexpensive capillary flow reactor design and

visible light utilization were envisaged. The usage of compressed air as oxygen source was also desired to satisfy the concept of *Green Chemistry.*

4.4.1 Artemisinin syntheses from DHAA under batch conditions

Batch photooxygenations of DHAA were performed to find a preferable solvent-sensitizer combination in terms of accessibility and costs. Another aim was to achieve maximum conversion within a reasonably short irradiation time. NMR analysis of the crude photoproduct was used as a non-destructive method to determine the presence of the intermediate hydroperoxide. GC-analysis was not suitable due to the thermal instability of most intermediates and byproducts. Likewise, HPLC-analysis was not performed as pure reference samples of intermediates and byproducts were not commercially available. Due to its thermal instability, intermediate **3** was not isolated and was used directly for subsequent acid-catalyzed treatment. The conditions for artemisinin synthesis were investigated in terms of sensitizer, solvent, oxygen source, light source, Lewis acid, temperature and reaction time (**Table 4.4**).

Table 4.4: Parameters optimized for the two-step batch process.

Photooxygenation parameter		**Thermal parameter**	
Sensitizers:	meso-tetraphenylporphyrin (TPP), methylene blue (MB), rose Bengal (RB), rose Bengal bis-(triethyl-ammonium) salt (RB-TEA).	Acid catalysts:	trifluoroacetic acid (TFA), conc. HCl, acidic alumina, p-toluenesulfonic acid.
Solvents:	acetone, dichloromethane, ethanol, isopropanol, acetonitrile.	Temperatures:	Room temperature – 60°C
Concentration:	5-25 mM	Reaction times:	2 hours-4 days.
Irradiation:	2-6 hours.		
Light source:	16 × 8 W cool white fluorescent tubes.	Amount of acid catalysts:	1 drop to 0.2mL

The one-step batch synthesis of artemisinin was investigated by combining all reagents required and photoirradiation. The production of artemisinin in a single run or one-pot reaction naturally represents the most efficient process in terms of solvent and reagent needs, time energy costs.

4.4.1.1 Two-step batch synthesis of artemisinin

These photooxygenations were conducted to find the most suitable solvent-photosensitizer combination for high DHAA conversion with high selectivity towards intermediate **3**. The

lifetime of singlet oxygen is highly dependent on the solvent and $^1O_2$ show a better stability in chlorinated solvents like carbon tetrachloride and dichloromethane [112]. Seeberger tested numerous combinations of solvents, equivalents of oxygen and gas pressures for photooxygenation process screening [125]. Although no details were mentioned for these tests, but the least toxic non-flammable dichloromethane was reported to show high conversion and yield. For this reason, dichloromethane was initially chosen in combination with tetraphenylporphyrin (H_2TPP or TPP) as a nonpolar and hence readily dissolvable sensitizer with excellent absorption in the visible range. The electronic absorption spectrum of porphyrin consists of two regions (**Figure 4.2**). The first involve the transition from the ground state to the second excited state ($S_0 \rightarrow S_2$) and the corresponding band is called the Soret or B band. The range of absorption is between 380 – 500 nm. The second region consists of a weak transition to the first excited state ($S_0 \rightarrow S_1$) in the range between 500 – 750 nm (the Q bands). These favorable spectroscopic features of porphyrins are due to the conjugation of 18 π-electrons and the absorption wavelength perfectly overlaps with visible spectrum of light. [126] Using this combination of DCM and TPP, complete conversion could be achieved in 2 hours. Despite the highly selective formation of **3**, the poor oxygen availability in the successive thermal reaction resulted in the preferential formation of **15** over artemisinin **4** (Experiment 1).

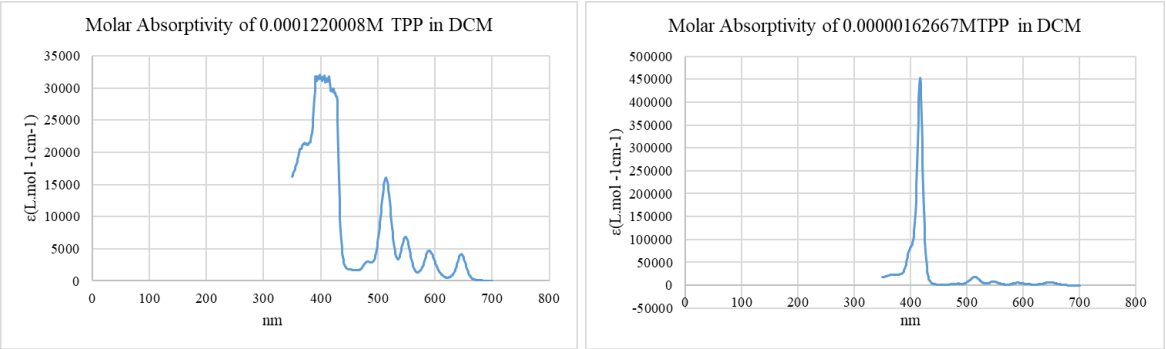


Figure 4.2: UV-visible absorption spectrum of TPP; calculated molar absorption co-efficient (ε) 32040.77 L.mol^{-1}cm^{-1}at 399nm for 0.0001220008M and 452458.089 L mol^{-1}cm^{-1}at 417nm for 0.00000162667M TPP.

In contrast, methylene blue (MB) shows an intense absorption maximum at 654 nm (**Figure 4.3**) and its cationic nature makes it suitable for applications in polar or aprotic solvents. MB turned out to be moderately efficient in terms of conversion. However, in many cases artemisinin **4** was directly formed during photoirradiation, i.e. before addition of any acid, and consequently no intermediate hydroperoxide **3** was detected. The direct formation of

artemisinin **4** has been previously reported for photooxygenations of **1** with methylene blue at -78°C in dichloromethane and subsequent replacement of solvent to petroleum ether followed by standing of the crude reaction mixture at room temperature produced artemisinin. This was explained by the acidic nature of the solvent. However, the addition of a strong acid further increased the yield of artemisinin. The formation of artemisinin in the absence of acid required air oxidation for 4 days, but did not occur in acetone, diethyl ether, acetonitrile or ethanol. Furthermore, a solvent dependency for reaching high conversions was noted. Likewise, additional acid catalysis was found to be beneficial. Yields of <1% in acetonitrile, ethanol or diethyl ether after 3 days and 13% in dichloromethane after 18 hours were reported. Additional acid catalysis with TFA changed the yields to 11% in acetonitrile after 3 days, in diethyl ether to ca. 2% after 18 hours, in petroleum ether to 15% after 1 hour and to 24% after 18 hours and in dichloromethane to 11% after 18 hours, respectively [127]. The formation of artemisinin in the absence of mineral acids has been reported before when acidic copper ions were used as catalyst [128]. The inconsistent formation of artemisinin in varying amounts throughout this study may alternatively suggest the presence of acidic contaminants. Nevertheless, the dichloromethane-methylene blue combination ultimately showed a high conversion of 95% with approx. 48% of **3** after 2.5 hours of irradiation and gave an isolated yield of **4** of 24% after the thermal acid-treatment. An even better result was obtained for the acetone-methylene blue pair, which produced a very effective (2 hours with 99% conversion) and clean photooxygenation with a high selectivity for **3** (83% by NMR) **Table 4.6**. From this, a high proportion of 56% of artemisinin was formed during subsequent acid-treatment.

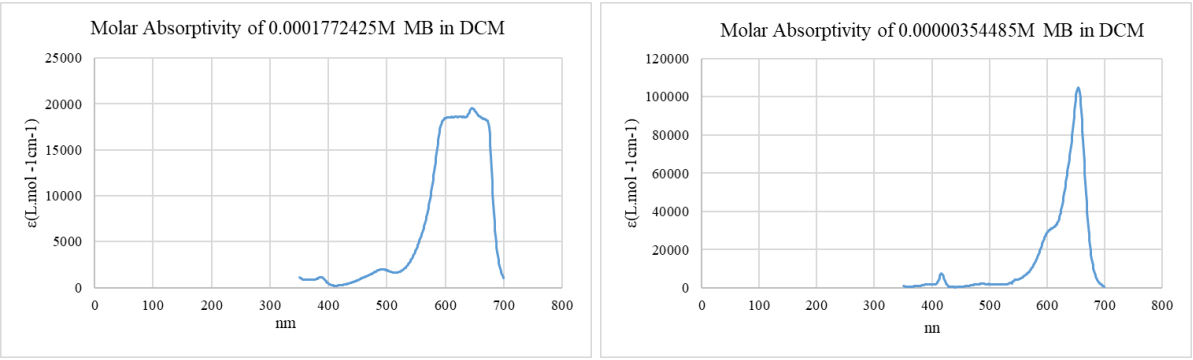


Figure 4.3: UV-visible absorption spectrum of methylene blue; calculated molar absorption co-efficient (ε) 19583.339.$mol^{-1}cm^{-1}$at 646nm for 0.0001772425Mand 107905.962 L $mol^{-1}cm^{-1}$at 654nm for 0.00000354485M methylene blue.

Rose bengal (RB) is an excellent photosensitizer and shows strong absorption in the visible range (490-560 nm) **Figure 4. 4**. It is also used extensively for photooxygenations in industry. Due to the poor solubility of the bis-sodium salt in dichloromethane, its corresponding bis-(triethylammonium) salt (RB-TEA) was employed instead. RB-TEA gave the best result in terms of the formation of **3** with 81% (by NMR **Table 4.6**) although numerous byproducts were noted as well. Successive acid treatment thus produced artemisinin in moderate amounts and accompanied by other byproducts that prevented its crystallization. A disadvantage of RB-TEA is its high price and limited commercial availability. The cheap bis-sodium salt was thus investigated in the polar and more sustainable alcohols ethanol and isopropanol. The latter was mixed with water in order to improve the solubility of RB and hence the transparency of the reaction mixture. While RB presumably showed a good selectivity for hydroperoxide **3**, the presence of numerous unidentified byproducts suggested photochemical or thermal decomposition involving the solvents. Irradiation times were also longer than in dichloromethane or acetone due to the shorter singlet oxygen lifetime in alcohols (in ethanol: 9.7 x 10^{-6} s). In contrast, dichloromethane and acetone show superior singlet oxygen lifetimes of 6.3 x 10^{-5} s and 5.1 x 10^{-5} s, respectively, and were thus preferred over alcohols. Moreover, rose Bengal tends to bleach over longer irradiation periods, especially in the presence of acids. It was thus not found suitable for the desired one-pot synthesis of artemisinin that required the initial presence of TFA.

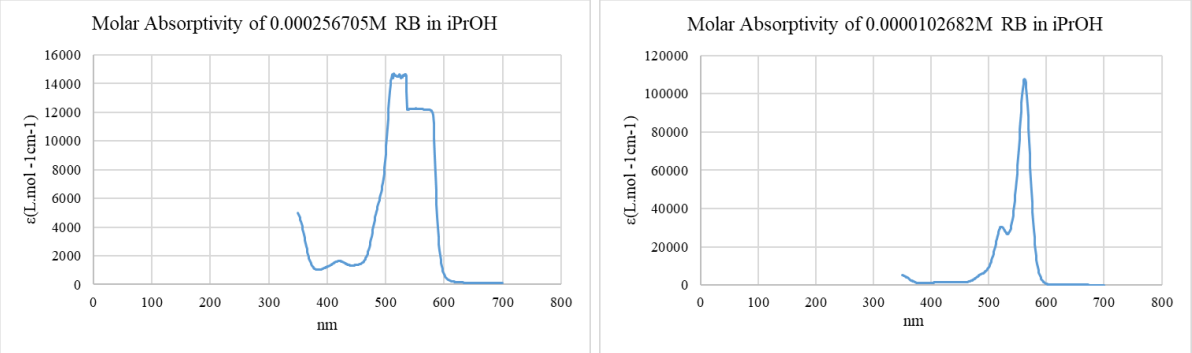


Figure 4. 4:UV-visible absorption spectrum of rose Bengal; calculated molar absorption co-efficient (ε) 14701.7 L.mol^{-1}cm^{-1}at 514nm for 0.000256705M and 107905.962 L mol^{-1}cm^{-1}at 562nm for 0.0000102682M rose Bengal.

Artemisinin synthesis was commonly accompanied by compounds **7** and **9** either during photooxygenation or thermal acid-treatment. The six-membered lactone **16** was also frequently formed after acid-treatment, indicates a deficiency of triplet oxygen in the reaction mixture.

Under batch conditions, the reaction mixture was continuously purged with air as an oxygen supply. The oxygen content of atmospheric air is only 20.95% [129, 130] which may not be sufficient under the given process conditions. In particular, a high amount of dissolved oxygen was required at any time, but the reaction volumes were typically below 100 mL. Evaporation and thus loss of solvent due to constant gas bubbling reduced the amount of solvent and hence oxygen supply medium further. For highly volatile solvents, complete evaporation during long purging periods was commonly observed. This reduced the amount of available oxygen and also caused a concentration of TFA in the residual reaction volume. The lack of oxygen and the increased acid concentration may have thus contributed to decomposition or side reactions. The concentrations of dissolved oxygen (for pure oxygen and air) in various solvents are listed in **Table 4.5**. Values range from 1.25-15.0 mmol/L for pure oxygen and 0.27-3.1 mmol/L for air. For a typical reaction volume of 100 mL and air oxygen source, the amount of available dissolved oxygen was thus just 0.027-0.31 mmol at any given time. As the amount of dissolved oxygen is highest in n-hexane, thermal acid-treatments in this solvent almost always showed the highest amount of artemisinin formed. However, the extreme volatility of n-hexane caused substantial solvent losses and thus a reduction in available dissolved oxygen.

Table 4.5: O_2 Concentration in different solvents.

Entry	Solvent	Temperature °C	$[O_2]$/mmol L^{-1} (1.013 bar O_2)	$[O_2]$/mmol L^{-1} (0.213 bar O_2)
1	Acetone	20	11.4	2.4
		25	11.3	2.4
2	Dichloromethane	20	10.7	2.2
3	Ethanol (95%)	25	7.84	1.64
4	i-Propanol	20	10.3	2.2
		25	10.2	2.1
5	n-Hexane	20	15.0	3.1
		25	14.7	3.1
6	Water	20	1.39	0.29
		25	1.27	0.27

Table 4.6: Best results for the photooxygenation of DHAA.

Exp	Solvent	1 [mM]	Sensitizer		Irradiation [h]	Conv. [%]	3 [%]
			Type	[mM]			
28	DCM	10.6	RB-TEA	0.212	2	93	81
14	Acetone	5.6	MB	0.125	2	99	83
16	EtOH (H_2O)	10.6	RB	0.257	5	96	85
9	iPrOH (H_2O)	10.7	RB	0.274	3.5	97	85

Table 4.7: Best results of the acid catalyzed cyclization of hydroperoxide **3**.

Exp	Solvent	TFA	Time [h]	Major compositions [%]			
				4	**7**	**9**	**16**
28	DCM	2 drops	2	48	6	13	23
14	Acetone	1drop	2	56	20	6	8
16	EtOH (H_2O)	0.19mL	2	40		3	30
9	iPrOH(H_2O)	2 drops	2	71	26	-	trace

Seeberger explored different Brønsted and Lewis acids such as camphorsulfonic acid, copper (II) trifluoromethanesulfonate, DOWEX (an ion exchange resin catalyst), *p*-toluenesulfonic acid, and trifluoroacetic acid in various solvents to find the most efficient conditions for acid catalyzed reaction of **3**. Although no details were mentioned, trifluoroacetic acid (TFA) performed best to induce the desired solvent-dependent Hock cleavage [47]. Existing studies showed that catalysis involving acetic acid can significantly decrease both conversion and selectivity, whereas, strong acid like sulfuric acid can cause very fast acid-catalyzed tautomerization of enol **12** leading to the formation of **16** [48a]. As an alternative to the hazardous and expensive trifluoroacetic acid (TFA), other acid catalysts were trialed for the thermal reaction in this study (**Figure 4.5**). When TFA was used, the highest amounts of artemisinin were most commonly obtained. For example, a crude photooxygenation mixture containing 81% of **3** (by NMR) subsequently gave 48% of artemisinin (**4**) with only 13% of **9**, 6% of **7** and 23% of **16** (by NMR). In contrast, solid acidic alumina predominantly resulted in the formation of compound **9** with significantly reduced amounts of artemisinin (**4**). The heterogeneous solid-liquid-gas system may have prevented sufficient acid release and thus supply for catalysis to occur. In contrast, *p*-toluenesulfonic acid produced predominantly compounds **7**, **9** and **14** with only small quantities of **4**. Likewise, concentrated hydrochloric acid predominantly gave compounds **11** and **9**, with no artemisinin at all. These results confirm that TFA represents the ideal catalyst for the thermal cyclization to artemisinin. This may be due to its superior solubility and acid strength in organic solvents. The same finding has been reported by Seeberger [48a].

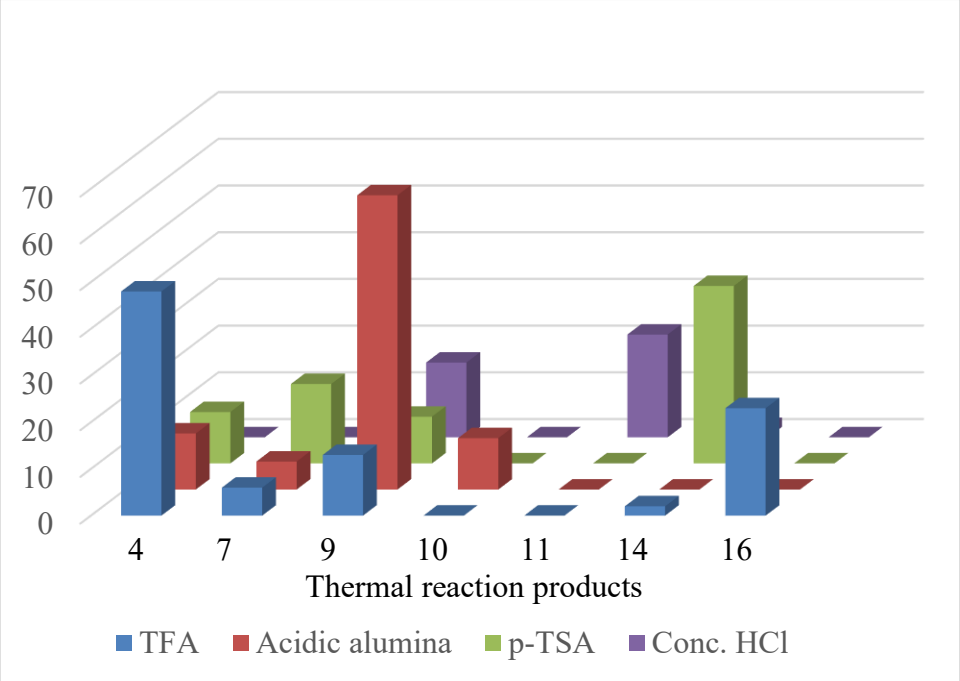


Figure 4.5: Effect of different catalysts towards formation of **4** and other by-products.

Studies conducted with TFA at low concentrations required heating but gave good selectivity, whereas high concentrations led to poor selectivity [48a]. Temperature and the amount of TFA supplied also played a significant role on the thermal cyclization efficiency (**Figure 4.6**). Reactions conducted at higher temperature (50-60°C) with small amounts of TFA showed a higher production of artemisinin (**4**). Likewise, an increase in TFA at room temperature produced more artemisinin as well. The combination of higher temperature (60°C) and amounts of TFA, however, decreased artemisinin formation. The results suggest that a higher degree of dissociation, either achieved by increasing temperature of concentration of TFA, and hence available protons favors cyclization. Excessive amounts of available protons, however, favor alternative reaction pathways. For the ultimately envisaged one-pot synthesis protocol, ambient temperature and a higher amount of TFA were thus viewed preferable.

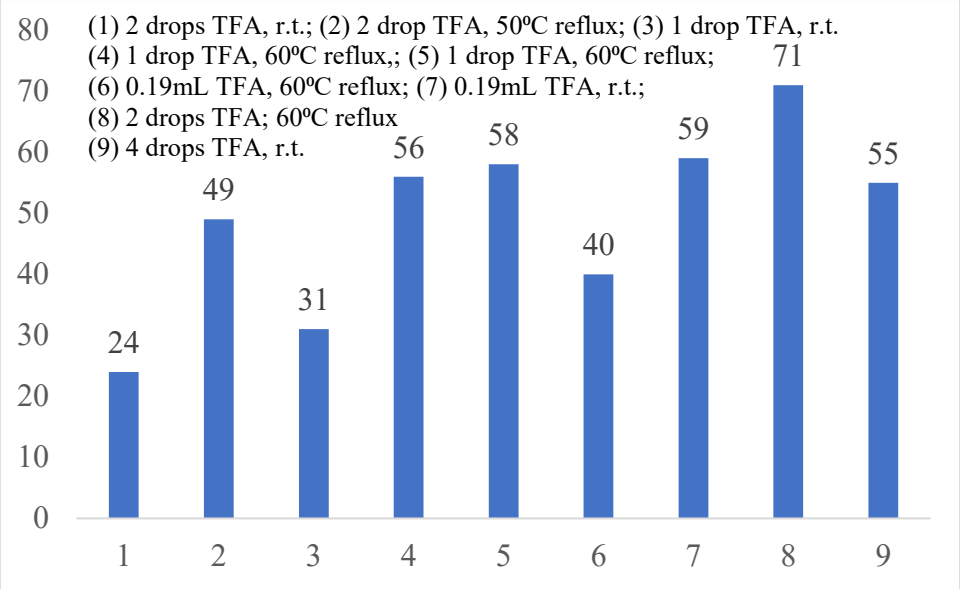


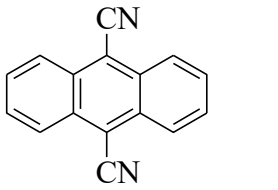
Figure 4.6: Effect of amount of TFA and temperature.

4.4.1.2 One-pot synthesis of artemisinin under batch conditions

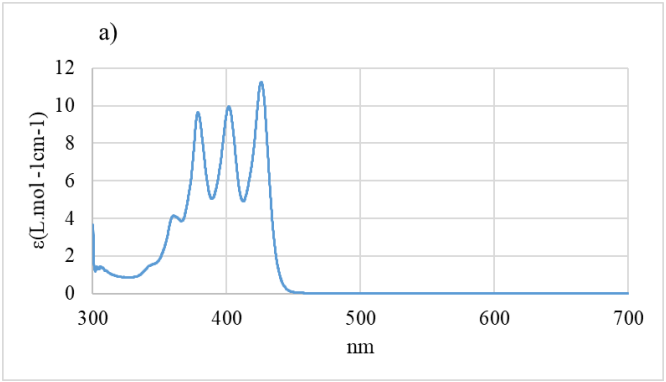
The synthesis of artemisinin (**4**) from DHAA (**1**) was also realized by combining both reaction steps, where all the reactants including TFA were already available during photoirradiation (**Table 4.8**). As reported previously, acid catalysis maintained at 25°C has proven to give high yields [48a] and this finding was crucial for the combined one-pot synthesis in the current study. Following Seeberger's protocol using dichloromethane and TPP [47], two variations were trialed that either supplied TFA after a set irradiation time or from the beginning.

Following the first approach (TFA addition after 2 h of irradiation), low conversion and percentage of artemisinin were obtained. In contrast, the addition of TFA prior to photoirradiation gave complete conversion with a higher amount of artemisinin. This result was surprising as protonation of TPP is known to decrease its singlet oxygen generation efficiency [48a]. It is thus assumed that significant protonation of TPP did not occur and that the immediate availability of acid instead favored rapid conversion of hydroperoxide **3**. This direct conversion may also disfavor any decomposition of intermediate **3**. The formation of the six membered lactone **16** was likewise suppressed, probably due to the better air and thus oxygen supply in the photoreactor setup. The long and narrow Schlenk flask with its central cold finger created a good bubble distribution. In contrast, the much wider round bottom flask created a more localized bubble distribution.

Anthracene-9, 10-dicarbonitrile (DCA) remains stable to pH change. This feature makes DCA (quantum yield of 1.56 in benzene) an ideal sensitizer for the one-pot synthesis of artemisinin. The ZnTPP (quantum yield 0.83 in benzene) at higher concentrations was shown to undergo photobleaching and the selectivity towards the desired hydroperoxide subsequently decreased. On the other hand, despite having a higher quantum yield, DCA showed similar levels of selectivity as TPP. Due to its lower extinction co-efficient, however, higher concentrations of DCA were required. [48a]. Additional reactions were thus performed using the improved Seeberger protocol, i.e. anthracene-9, 10-dicarbonitrile (DCA) in toluene, and by adding TFA but the reactions remained unsuccessful even after 13 hours of irradiation. The measured absorption co-efficient of DCA in toluene was found to be 11.26804L.mol^{-1}cm^{-1} at 426nm absorption maxima (**Figure 4. 7**). The poor absorption of DCA within the emission spectrum of the cool white light source most likely prevents efficient generation of singlet oxygen and hence effective photooxygenation.



Anthracene-9,10-dicarbonitrile or 9,10-Dicyanoanthracene(DCA)



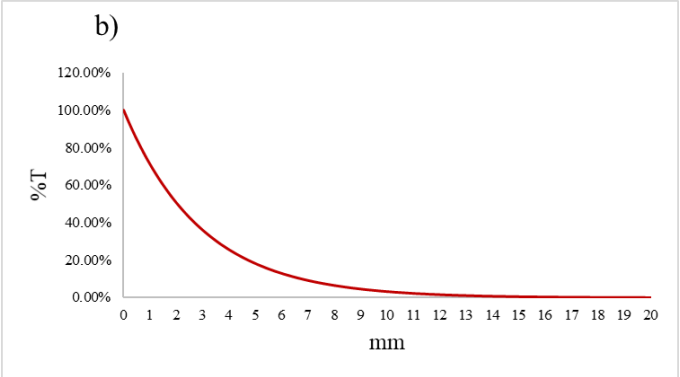
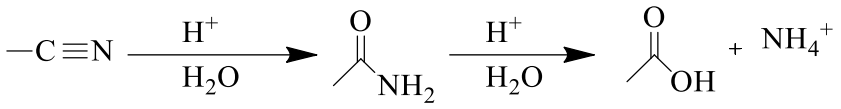


Figure 4. 7: a) Molar Absorptivity of 0.13099M DCA in Toluene with absorption maxima 1.476 at 426nm, 1.302 at 402nm, 1.263 at 379nm and 0.543 at 361nm; b) Light transmission through 0.13099M DCA in toluene at extinction co-efficient 11.26804 L.mol^{-1}cm^{-1} at 426nm absorption maxima.

A selected reaction was furthermore conducted in isopropanol with TPP and delayed addition of TFA. Both, conversion and artemisinin content remained low, possibly due to the significantly reduced lifetime of singlet oxygen in this solvent system.

A similar reaction in acetonitrile with rose Bengal and delayed addition of TFA showed complete conversion, but predominant formation of byproducts **9**, **11** and **16**, with negligible amounts of artemisinin. It is known that in polar aprotic solvents only a low yield of artemisinin was obtained, the main products being the side products, dihydro-epi-deoxyarteannuin B (**9**) and low polarity solvents show higher selectivity [48a]. Moreover, in presence of TFA caused partial hydrolysis of acetonitrile with the formation of acetamide and ethanoic acid (**Scheme 4.4**), which may have formed unknown byproducts.



Scheme 4.4: Hydrolysis of acetonitrile in presence of acid.

Table 4.8: Best results of the one-pot reactions in batch.

Exp	Solvent	Irradiation [h]	Conv. [%]	Yield 4 [%]	
				By ^{1}H-NMR	Isolated
36	DCM	3	100	64	32
40	ACN	2	100	4	-
42	DCM	2	90	51	50
43	DCM	2	92	47	42

Following the protocol by Roth [3] [127], reactions with methylene blue in dichloromethane were performed with different amounts of TFA (**Figure 4.8**). Artemisinin formation peaked with 51% when a small amount (0.01-0.05 mL) of neat TFA was used. These conditions also gave the best isolated yields of 50% and 42%, respectively. Higher amounts of TFA caused a drop in photooxygenation efficiency and hence conversion of **1**, possibly due to acid-catalyzed bleaching of the sensitizer methylene blue.

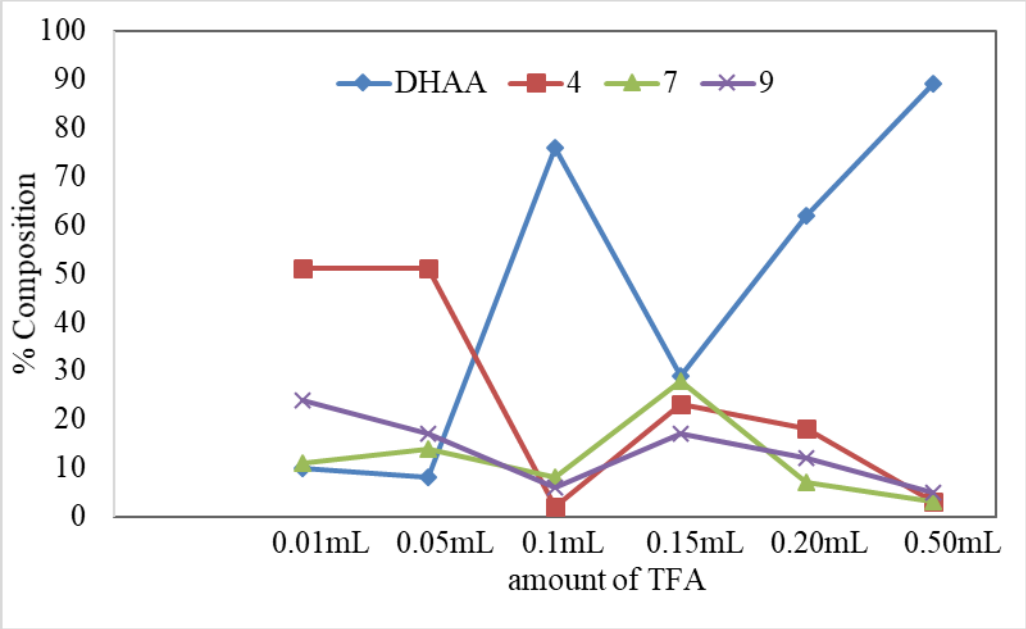


Figure 4.8: Effect of TFA on the amount of artemisinin **4** and byproduct formation at room temperature.

These findings are superior to the reported batch method described by Roth (**Table 4. 9**), that required irradiation for 30 minutes with a 400 W high pressure sodium lamp, followed by thermal catalyzed-cyclization for 4 days and furnished only 36% of artemisinin (**4**). The reaction also required a solvent change from acetone to petroleum ether. In contrast, the developed one-step method provides a much higher yield of **4** of 50% and follows a simple one-pot approach without any solvent switch and thus simpler workup and isolation. While the irradiation time was longer with 2 hours, the concentration of **1** was double and the available light inside the Rayonet chamber was just 128 W.

Table 4. 9: Comparison of batch synthesis of artemisinin with literature.

Batch conditions	**Two-step method Roth *et al.*** [102]	**One-pot synthesis Current work**
Solvent	Acetone	Dichloromethane
Sensitizer	Methylene blue 3mg	Methylene blue 3mg
DHAA **1**	5.6 mM	10.6 mM
Light source/ Irradiation time	Westinghouse Ceramalux high-intensity C400S51 electric discharge street lamp 400 W / 30 minutes	Fluorescent Tubes 16 x 8 W / 2 hours

Thermal catalysis Artemisinin	1 drop TFA in petroleum ether, 4 days 36%	0.01 mL TFA added initially 50%

4.4.2 Photooxygenation of DHAA under flow conditions

Inspired by the optimized reaction conditions obtained in the batch study, the photooxygenation was subsequently conducted under flow conditions. Compressed air and, in selected cases, pure oxygen was used. The usage of oxygen was later abandoned due to a leak in the cylinder valve. The reagent gas was injected into the liquid reagent stream via a T-piece, thus creating gas-liquid slug flows. These slug flows generated thin liquid films with high surface to volume ratios at the periphery of the gas bubbles. This offered fast and efficient gas to liquid mass transfer. Due to the inner rotation of the bubbles and liquid slugs, mixing and continuous circulation favored fast diffusion of oxygen into the liquid media. Due to the small localized concentrations inside the slug-flow, accumulation of potentially explosive hydroperoxide **3** is avoided. The photoreaction product is collected continuously outside the irradiated area and can be readily removed or allowed to enter a subsequent flow reactor attached in series. The general setup of the flow reactor is shown below.

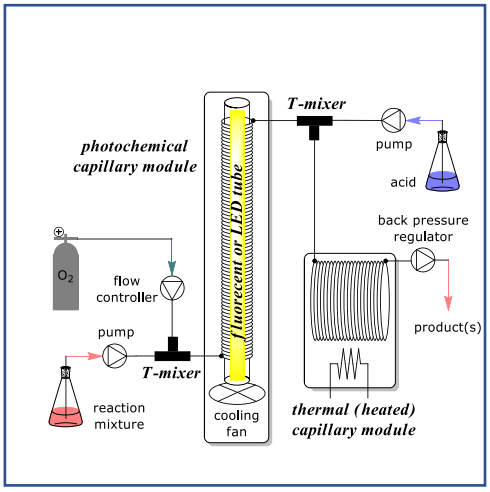


Figure 4. 9: Schematic diagram of in-house built capillary flow reactor.

4.4.2.1 Decoupled photooxygenation of DHAA under flow conditions and subsequent acid-treatment under batch conditions

A crucial necessity of flow photooxygenations was the creation of a stable gas-liquid slug flow. The synthesis of artemisinin was thus initially studied separately in order to determine ideal flow conditions to achieve high conversions and selectivity. As the conversion is naturally

residence time dependent, different gas and liquid flow rates were studied. Likewise, a 5 psi back pressure regulator (BPR) was tested. Adaptation of a BPR increases mass transfer at the gas-liquid contact surface and hence improves conversion rates. However, the BPR could only be used for higher flow rates due to the limitations of the available pumps. At lower flow rates, the presence of the BPR led to a sudden stop of the flow inside the capillary. This may have occurred due to a pressure drop inside the rising capillary and the liquid pump was unable to pump against the pressure of the BPR. Alternatively, the pressure created by the solvent vapor inside the capillary could have contributed to this sudden stop.

The complete photoconversion of **1** requires at least equivalent amounts of oxygen and the oxygen content in the supplied compressed air was 20.5%. Therefore, it was necessary to estimate the amount of oxygen present in the gas bubble and in the liquid phase. The number of moles of oxygen can be calculated from the ideal gas law (**Equation 4.1**). The dissolved oxygen content in the chosen solvents (**Table 4.10**) [131] must be further taken into consideration although the pressure inside the capillary was likely higher than that under batch conditions, even in the absence of a BPR.

Equation 4.1

$$pV = nRT$$

The slug flow formed were maintained in such a way that the liquid bubbles were slightly smaller than the gas bubbles. In almost all successful flow reactions, stable slugs were generated with gas bubble lengths of approx. 1 cm and liquid bubble length of approx. 0.8 cm (**Figure 4.10**) at the injection point. However, larger liquid bubbles were observed towards the end of the flow reactor due to consumption of oxygen and hence reduction in size of the gas bubbles.

Figure 4.10: Gas-liquid slug flow formed inside the reaction capillary.

Table 4.10: Concentration of oxygen in liquid phase of slug flow.

Solvent	**Conc. O_2 in liquid bubble [mol/L]**
Acetone	1.19×10^{-2}
Dichloromethane	1.11×10^{-2}
Ethanol	9.78×10^{-3}
Isopropanol	1.02×10^{-2}

Changes in the liquid flow rates altered the residence time and available oxygen content. This was evident when comparing flow reactions conducted with the ethanol-rose Bengal combination. High flow rates (air and liquid: 5 mL/min) and subsequently a short residence time (11 min) caused an almost complete drop in conversion compared to lower flow rates (liquid: 2.5 mL/min; air: 5 mL/min) and hence longer residence times (18 min), where the conversion was found to be 60% (with 42% of **3** by NMR).

The transparency of the reaction medium also played a crucial role. This was notable from reactions conducted in isopropanol. Neat isopropanol has a significantly lower polarity than ethanol and gave a turbid reaction mixture with low transparency, which consequently resulted in a poor conversion. The addition of water restored transparency and gave 66% conversion with 51% of hydroperoxide **3** (by NMR). However, subsequent acid-catalyzed cyclization gave unsatisfactory product formation with significant amounts of unknown byproducts. It is thus likely that alcohols interfere with the desired transformations and that the estimated amounts

determined by NMR are overestimations. Due to the instability of rose Bengal towards acid, it was not considered suitable for the desired combined one-flow or one-pot-one-flow process. Switching to Roth's methylene blue-acetone combination [3] and simultaneous decrease in air flow rates (2.5 and 2.0 mL/min) and hence increase in residence time (20 and 25 min) resulted in higher conversions (72% and 86%) with good selectivity. Subsequent acid-treatment according to Roth generated artemisinin in good yields.

From **Table 4.11** it can be seen that the flow reaction in dichloromethane with TPP showed the best conversion and amount of **3**, although the amounts of **5** and **6** were slightly increased if compared to the reaction in acetone. The molar ratio factor $[O_2]/[\mathbf{1}]$ varied significantly with the different flow rates at the entry point thus showing variable conversions rates.

The removal of the BPR resulted in consistently stable slug flows and a simultaneous decrease in flow rates enabled longer residence times. Despite this, reactions in alcohol with rose Bengal or in dichloromethane with methylene blue showed no significant improvements. In contrast, the dichloromethane-rose Bengal bis-(triethylammonium) salt (RB-TEA) combination showed good conversion with acceptable selectivity towards **3**, even though the successive artemisinin formation performed poorly. Replacing air with pure oxygen naturally resulted in higher conversions under otherwise similar conditions, although the amounts of byproduct **9** along with undesired hydroperoxide **5** and **6** increased as well. Increasing concentrations of both, **1** or sensitizer does not necessarily improve conversion and thus productivity rates. Higher concentrations of DHAA requires more oxygen and hence larger air (or oxygen) bubbles. An increase in sensitizer eventually reduces the light penetration throughout the reaction capillary and may also cause quenching effects between sensitizer molecules.

For the flow photooxygenation reactions, the productivity of **3** (**Table 4.11**) was calculated based on NMR yields using **Equation 4.2**.

Equation 4.2: $Productivity\ (P) =$

$$\frac{[Substrate\ concentration\ x\ Irradiated\ volume\ x\ NMR\ yield]}{Irradiation\ time\ in\ minutes}$$ [132]

Considering the molar ratio of DHAA **1** and [O] at the injection point the moles of oxygen were relatively low but the conversions were found to be high for aliquots analyzed during flow reactions. The analyzed sample composition contained many by-products along with the desired **3**, this indicates not all used DHAA was converted to **3** and oxygen may be partially consumed for side-reactions. The conversion was the highest using DCM-TPP combination

(Entry 5) which can be attributed to high quantum yield of TPP and longer life time of singlet oxygen in DCM. On the other hand, mole of oxygen was much higher in reaction conducted with pure oxygen thus showing high conversion as well.

A major concern observed were the often-contradictory product compositions between the initial photooxygenation and the subsequent thermal TFA-catalyzed cyclization. Regularly, the determined residual amounts of DHAA (**1**) varied within the same reaction sequence. Likewise, the amounts of intermediate **3** did not convert to similar amounts of artemisinin (**4**). Unstable slug flows and sudden pressure drops may have caused variations of conversion rates inside the capillary. The sample taken for NMR analysis from the flow reactor during photooxygenation may have thus not shown a representative average composition. Unknown byproducts or polymers were furthermore not considered when determining product ratios by NMR.

Table 4.11: Conversion of DHAA 1 in flow reactor at different residence times and productivity of **3**.

Entry	Solvent	Sensitizer	L_f	G_f	*N*	*ṅ*	$[O_2]/[1]$	Conv. [%]	P [moles/day]
3	Acetone	MB	2	2.5(air)	6.94058E-06	1.20E-05	0.5783816	86	0.04
4	Acetone	MB	2.5	2.5(air)	6.94058E-06	1.50E-05	0.4627053	72	0.04
5	DCM	TPP	1.6	1(air)	2.77623E-06	1.68E-04	0.0165252	95	0.033
8	DCM	MB	1	0.5(air)	4.07993E-06	7.00E-06	0.5828477	78	0.0096
9	DCM	RB	1	0.5(air)	4.07993E-06	5.00E-06	0.8159868	31	-
11	DCM	MB	1	0.5(O_2)	1.99021E-05	5.00E-06	3.9804235	94	0.0045

L_f liquid flow rate (mL/min), G_f gas flow rate (mL/min), *n* moles of oxygen and *ṅ* moles of DHAA at the injection point, P is Productivity of **3**.

4.4.2.2 Synthesis of artemisinin by tandem flow operation

Continuous flow reactions in series were performed by attaching another thermal capillary module to the flow photoreactor. TFA was added into the photoproduct stream prior to entering the thermal module. The tandem flow reactions were conducted with and without back pressure regulator (BPR) and different flow rates to achieve optimal conditions for high conversions and artemisinin formations.

Using a BPR and short residence times, reactions in dichloromethane with TPP gave good conversion but unsatisfactory selectivity. Switching to acetone with methylene blue showed good conversion and an encouraging amount of artemisinin in the sample taken, but continuous operation could not be maintained due to pressure problems that caused a collapse of the slug flow and a complete stop of the reaction even before 1/3 of the reaction mixture had been pumped through the reactor. It remains unclear if the differences in polarity and/or viscosity between the solvents contributed to this phenomenon.

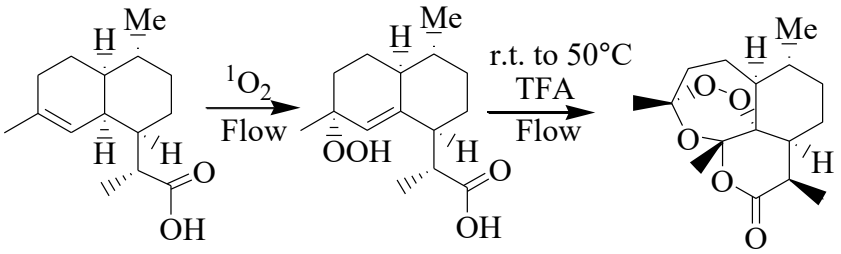
Conversions and selectivity further varied with solvent, sensitizer and/or flow rate changes, although no clear correlation was observed. This makes any interpretation or comparison of the results difficult. However, NMR analysis of flow reactions in the presence of a BPR commonly showed little or **16**, which indicates that sufficient oxygen is maintained in solution to convert hydroperoxide **3** to artemisinin **4**.

Removal of the BPR prevented unstable slug flows or pressure changes. Conversion rates and product selectivity again varied depending on solvent, sensitizer, flow rate ratios and residence times. Commonly, the formation of **16** became dominant, suggesting insufficient dissolved oxygen supply in the thermal reaction step. The best performance was achieved for dichloromethane and TPP with a residence time of 45 minutes, suggesting that this pair successfully combines the advantages properties of the solvent and sensitizer. With the highest molar ration [O_2]/[**1**] factor reaction in DCM with TPP showed maximum conversion (**Table 4.12**).

Table 4.12: Production of artemisinin in sequential continuous flow mode.

Entry	Solvent	Sensitizer	L_f	G_f	R. T. [min]	*n*	$\dot{n}$	$[O_2]/[1]$	Conv. [%]	P [mmol/day]
20	DCM	TPP	1.6	1	27	2.77623E-06	1.68E-05	0.1652519	64	8
26	i-PrOH+H_2O	RB	1.6	1	48	2.77623E-06	1.68E-05	0.1652519	62	9
27	DCM	MB	2	1	25	2.77623E-06	2.12E-05	0.1309543	49	12.7
29	DCM	MB	2	1	25	8.15987E-06	1.06E-05	0.7697989	54	9.5
31	Ethanol	RB	1	0.75	60	6.1199E-06	1.06E-05	0.5773492	70	0.3
36	DCM	TPP	1.6	0.75	45	6.1199E-06	8.48E-06	0.7216864	99	8
37	Acetone	RB	1.6	1	45	8.15987E-06	9.60E-06	0.8499863	68	4

L_f liquid flow rate (mL/min), G_f gas flow rate (mL/min) and compressed air used as gas, *n* moles of oxygen and $\dot{n}$ moles of DHAA at the injection point, P is Productivity of **4**, 5 Psi BPR was employed in Entry 20, 26 and 27.



1 (5.6mM) **3** **4**

Acetone vs 0.125mM MB; 24% **4** (isolated yield)
DCM vs 0.122mM TPP; 56% **4** (by ^{1}H-NMR)

Scheme 4.5: Tandem flow synthesis of artemisinin.

Although the sequential tandem protocol for artemisinin production failed to produce high conversions, high selectivity and high isolated yields of artemisinin, comparison with known literature processes still demonstrated some advantages (**Table 4.13**.). The Seeberger protocol employed tetraphenylporphyrin as the sensitizer in dichloromethane and used an energy-intensive 450 W medium-pressure mercury lamp for the phototransformation. The lamp generates significant amounts of heat and must thus be cooled efficiently. The lamp also produces a broad emission spectrum and destructive wavelengths must be filtered off, while others do not match with the absorption of the sensitizer. Despite these limitations, subsequent in-line Hook cleavage resulted in an isolated yield of 39% for artemisinin [133]. In contrast, the developed method used a single cool white fluorescent tube that does not generate much heat and can be cooled by a simple desk fan. A superior isolated yield of 50% of artemisinin was achieved by George and co-workers [134]. However, their method requires the generation of supercritical carbon dioxide as a solvent using very high pressures and low temperatures, which makes this process very complex and energy-demanding. A sophisticated and hence expensive fluorinated TPP sensitizer is furthermore needed. As it is not recovered, it must be constantly replaced. By contrast, the developed flow reactor operates at atmospheric or 5 psi pressure and uses air as a safer oxygen source.

Table 4.13: Comparison of known sequential processes for artemisinin synthesis.

Parameters	**Seeberger *et al.* 2012**	**M. W. George *et al.* 2015**	**Current work**
Light	medium-pressure Hg lamp (450 W),	LEDs	Fluorescent tube 20W
Photoreactor	FEP tubing (20mL) wrapped around Schlenk	sapphire tube reactor high pressure photo-oxidations, 5°C	FEP tubing (96.02mL) wrapped around Pyrex sleeve
Gas	O_2 (7.5mL/min)	O_2	Air (0.75mL/min)
Sensitizer	TPP	TPFPP	TPP
Solvent	DCM (2.5mL/min)	$scCO_2$ (1.05mL/min) Co-solvent EtOAc	DCM (1.6mL/min)
Residence time	2 min	-	45min
Thermal reaction	TFA in DCM at 0.5 mL/min; r.t. to 60°C	stainless steel packed with amberlyst-15 acid fixed beads, 25°C	FEP tubing 38.64m long, r.t. to 50°C
Artemisinin	39%	50%	56%

The unsatisfactory oxygen supply for both reaction steps, the somewhat difficult operation of coupled processes and the need for additional equipment subsequently called for a simplified one-pot-one-flow process.

4.4.2.3 One-pot continuous flow synthesis of artemisinin

One-pot continuous flow reactions were conducted by simply pumping a solution containing all reagents through the flow photoreactor module. The ultimate aim was to achieve high conversions, excellent selectivity and high isolated yields (>50%). Due to their previously demonstrated superior performances, dichloromethane and acetone were chosen as solvents. To achieve longer residence time with stable slug flows, reactions were performed without any attached BPR.

Based on conversion and amount of artemisinin generated, the dichloromethane-methylene pair gave good results, although the isolated yield and selectivity remained unsatisfactory. The known dichloromethane-TPP system also performed satisfactorily. Increases in residence time,

changes in flow rate ratios, alterations in DHAA and TFA concentrations and the oxygen source all altered the outcome of the reaction. It is impossible to fully understand the impact of all reaction parameters together, individual factor such as the amount of available oxygen (dissolved and in the gas slug) and favorable sensitizer properties ultimately provided important contributions. At low flow rates, uneven droplet flows (liquid segment/air bubble length <0.5cm) were furthermore formed.

To facilitate higher conversion a 5 psi BPR was reintroduced, although it caused pressure drops or gains that constantly changed the residence times within individual reactions. As with previous experiments, conversion rates, selectivity and amounts of artemisinin strongly depended on a variety of conditions. Overall, methylene blue in dichloromethane gave good results and remained stable towards the acidic reaction conditions. Its concentration was also important and a constant increase did not result in better performances in terms of conversions and selectivity, potentially due to poor light penetration and self-quenching effects. Compared to the reactions without BPR, conversions under otherwise similar conditions improved, indicating that the device provides more dissolve oxygen and can hence improve DHAA conversion.

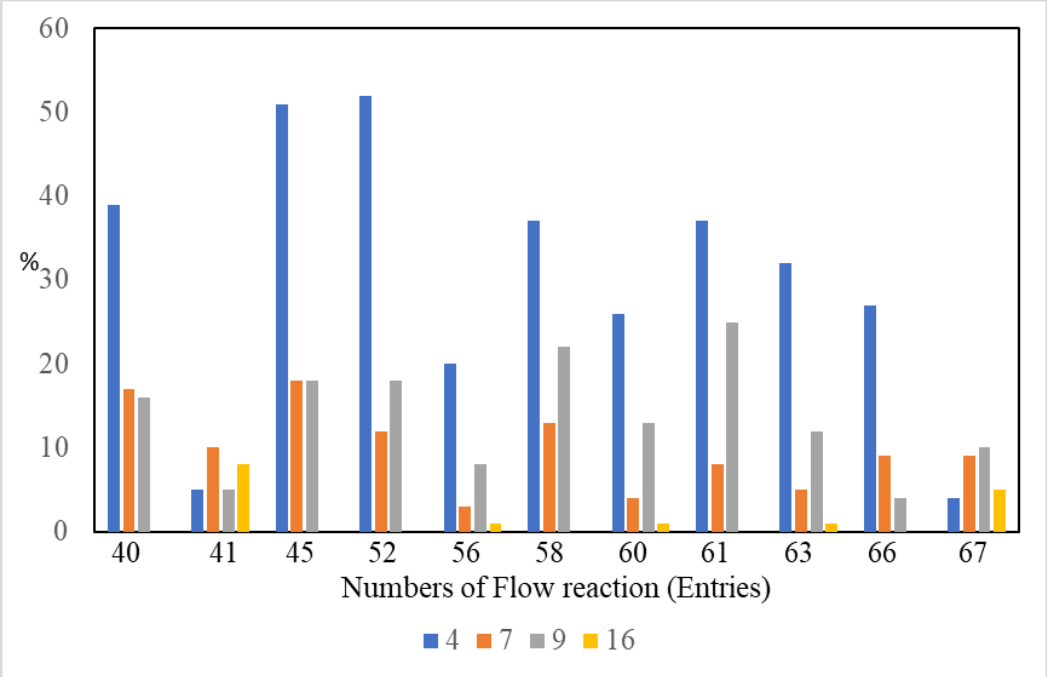


Figure 4. 11: Formation of artemisinin **4** and byproducts **7**, **9** and **16** during one-pot continuous flow reaction.

The data comparison from **Figure 4. 11** shows the presence of by-products **7** and **9** in all reactions, indicating partial oxygen consumption and thus decreasing selectivity for artemisinin synthesis. The molar ratio factor plays an important role to facilitate conversion. Although the molar ratio of $[O_2]/[\mathbf{1}]$ was highest in reactions conducted with pure oxygen (Entry 52) the conversion could not be improved. In contrast, at much lower flow rates compressed air **Table 4.14** mediated flow reaction (Entry 40) showed 73% conversion, where the molar ratio of $[O_2]/[\mathbf{1}]$ was approximately 1. Due to the unstable slug flow, conversion and productivity remained low (Entry 41). For the reaction showing the highest conversion (Entry 45), the oxygen content was high due to very low flow rates that caused droplet formation instead of a stable slug flow inside capillary. At higher concentrations of DHAA **1** (Entry 56 and 67) the conversions were very low, which can be attributed to insufficient oxygen inside the air bubbles. Introducing a BPR should increase conversions and productivity due to better solubility of oxygen into the liquid phase. Thus, higher productivities were observed in Entries 58, 60, 61, 63 and 66, though the conversions varied due to pressure fluctuation that led to uneven slug flows.

Table 4.14: Production of artemisinin from one-pot continuous flow reactions.

Entry	1[mM]	Sensitizer	L_f	G_f	*N*	*ṅ*	$[O_2]/[1]$	Conv. [%]	P [mmol/day]
40	5.3	MB	1.6	1	8.15987E-06	8.48E-06	0.9622486	73	6
41	5.3	MB	1.6	1	8.15987E-06	8.48E-06	0.9622486	32	0.7
45	5.3	MB	0.25	0.5	4.07993E-06	1.33E-06	3.0791955	86	4
52	21.1	MB	1	5(O_2)	1.99E-04	2.11E-05	9.4322831	83	6
56	10.6	MB	1	0.5	4.07993E-06	1.06E-05	0.3848994	32	8
58	2.6	MB	2.5	1	2.77623E-06	6.50E-06	0.4271126	73	7
60	2.6	MB	2.5	1	2.77623E-06	6.50E-06	0.4271126	48	4.6
61	4	MB	2.5	1	2.77623E-06	1.00E-05	0.2776232	72	17
63	4	MB	2.5	1	2.77623E-06	1.00E-05	0.2776232	52	8
66	10.6	MB	2.5	1	2.77623E-06	2.65E-05	0.1047635	42	11
67	25	TPP	1	0.5	4.06003E-06	2.50E-05	0.1624013	28	5

L_f liquid flow rate (mL/min), G_f gas flow rate (mL/min) and compressed air used as gas, *n* moles of oxygen and *ṅ* moles of DHAA at the injection point, P is Productivity of **4**; solvent Dichloromethane in all cases, acetone in Entry 41, 5 Psi BPR was employed in Entry 58, 60, 61, 63 and 66.

The developed one-flow process was attractive in terms of its simplicity although it failed to deliver the desired goals. Nevertheless, the developed protocol shows some advantages if compared to known literature processes (**Table 4.15**). The one-pot continuous flow process by Seeberger [48a] used a 420 nm LED module and 9, 10-dicyanoanthracene (DCA) as photosensitizer with TFA and produced an excellent artemisinin yield of 57%. Although the residence time is very short, the photooxygenation requires low temperature and submerging the reactor into a cooling bath. Likewise, the process still uses a separate thermal reactor maintained at room temperature. The developed method generates artemisinin through a 'real' one-pot reaction without any sophisticated cooling. George and co-workers also reported two strategies for artemisinin synthesis using white LEDs. The first strategy included the use of a dual-function solid acid/photocatalyst with liquid carbon dioxide as solvent and circulation, which resulted in a modest isolated yield of artemisinin of 39%. The second strategy involved aqueous mixtures of organic solvents as media with (tris(bipyridine)ruthenium(II) chloride) as photocatalyst, producing 50% of artemisinin [134]. In comparison to this, the developed flow process is much simpler and does not require working with high pressure, $scCO_2$ and low temperatures.

Table 4.15: Comparison of one-pot continuous flow production for artemisinin production.

Parameters	Seeberger *et al.* 2013	M. W. George *et al.* 2015	Current work
Light	420nm LED module	LEDs	Fluorescent tube 20 W
Photoreactor	7.5 mL volume wrapped around a glass plate in two layers, -20°C	sapphire tube reactor for high pressure photooxidations	FEP tubing (96.02 mL) wrapped around Pyrex sleeve
Gas	O_2 (5 mL/min)	O_2	Air (1 mL/min)
Sensitizer/acid catalyst	DCA/TFA	Strategy-1: dual-function solid acid/photocatalyst (TPP-Amb) Strategy-2: (tris(bipyridine)ruthenium(II) chloride)/TFA	MB/TFA
Solvent	Toluene (1.25 mL/min)	Strategy-1: $scCO_2$, Co-solvent Toluene Strategy-2: THF/H_2O (60/40)	DCM (2.5 mL/min)
Residence time	1.5 min	Strategy-1: 10 min Stategy-2: 5 hours	10 min

Additional thermal reaction Artemisinin	10 to 25°C 57%	Strategy-2: Additional treatment with 10bar O_2 for 16 hours Strategy-1: 39% Strategy-2: 50%	- 37%

To convert solutions with higher DHAA concentrations and hence improve productivity toward artemisinin, recirculation of the reaction medium was investigated. For the dichloromethane-TPP combination, recirculation proved beneficial in terms of conversion and artemisinin content. Naturally, recirculation demands a good stability of the sensitizer towards TFA as well as light. The latter presented a problem for methylene blue, which underwent photobleaching due to the prolonged exposure to light.

4.4.3 Reactor comparison

4.4.3.1 Gas liquid mixing and mass transfer

In bi-phasic gas-liquid reactions the conversion and yield are dependent on proper mixing of the two phases. The traditional batch reactor uses bubbling of gas into the liquid media and therefore, a uniform mixing and gas saturation was not possible. Undissolved gas also exits the reaction vessel and creates solvent/air vapors. Batch reactions were thus run for extended periods of time to reach completions. In flow, the gas was injected into the liquid stream inside a narrow capillary and this resulted in the formation of an advantageous slug flow. The gas liquid slug flow in particular forms a thin liquid film (**Figure 4.12**) around the gas bubble with a large surface area. The consequently large surface to volume ratio enables an efficient mass transfer of oxygen into the liquid film. Due to the flow movement throughout the capillary there is a constant circulation inside the gas and liquid bubbles that facilitates mixing and favors reactions between reagents. The helical capillary coil furthermore increases mass transfer and hence oxygen-saturation of the liquid phase due to radial mixing. The gas is furthermore contained inside the capillary and cannot escape as in the open batch vessel.

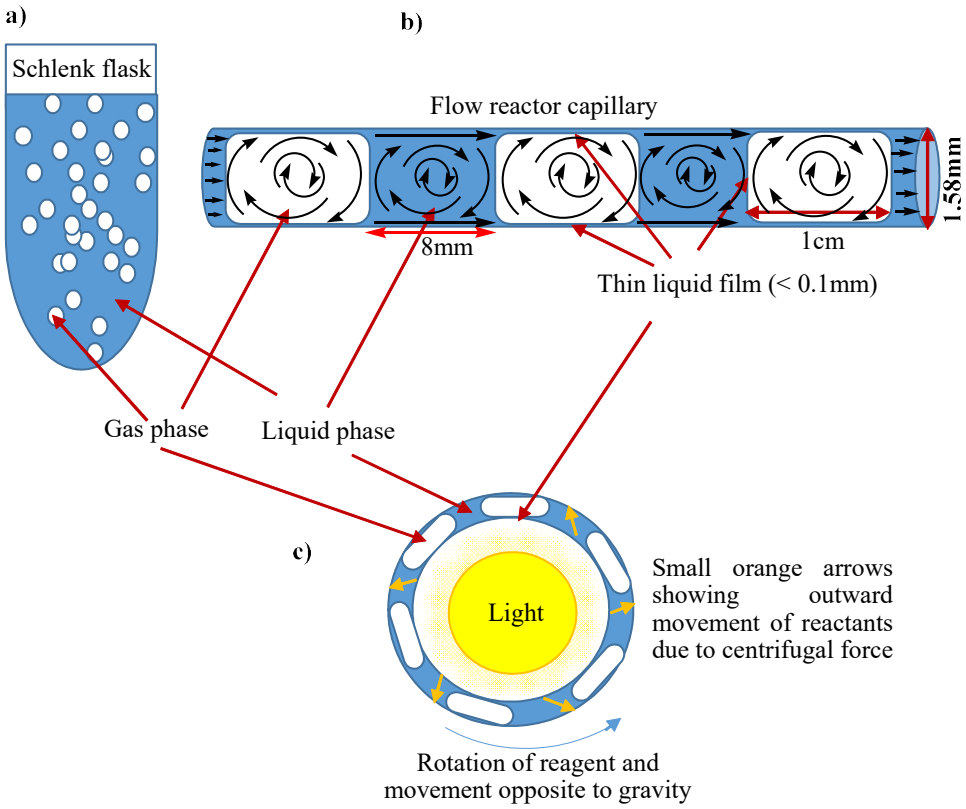


Figure 4.12: Schematic representation of (a) gas bubble formed in liquid under batch condition; (b) gas-liquid slug flow formation inside capillary and circulation of molecules inside gas and liquid phase leading to maximum contacts between reagents and gas on the thin film formed around gas bubble; (c) continuous upward movement of slugs causing reagents to tendency of reagents to scatter away from center.

4.4.3.2 Light utilization

When comparing the light efficiency of the reactors, the batch Rayonet reactor contained 16 fluorescent tubes of 8 W each arranged at the periphery of the chamber (**Figure 4.13**). This outside-in arrangement only partially directs light to the centrally placed Schlenk flask and hence reaction mixture. The majority of the light needs to be reflected by the polished aluminum sheet surrounding the chamber. Reflection and travelled distance, however, reduce the efficiency of the light significantly.

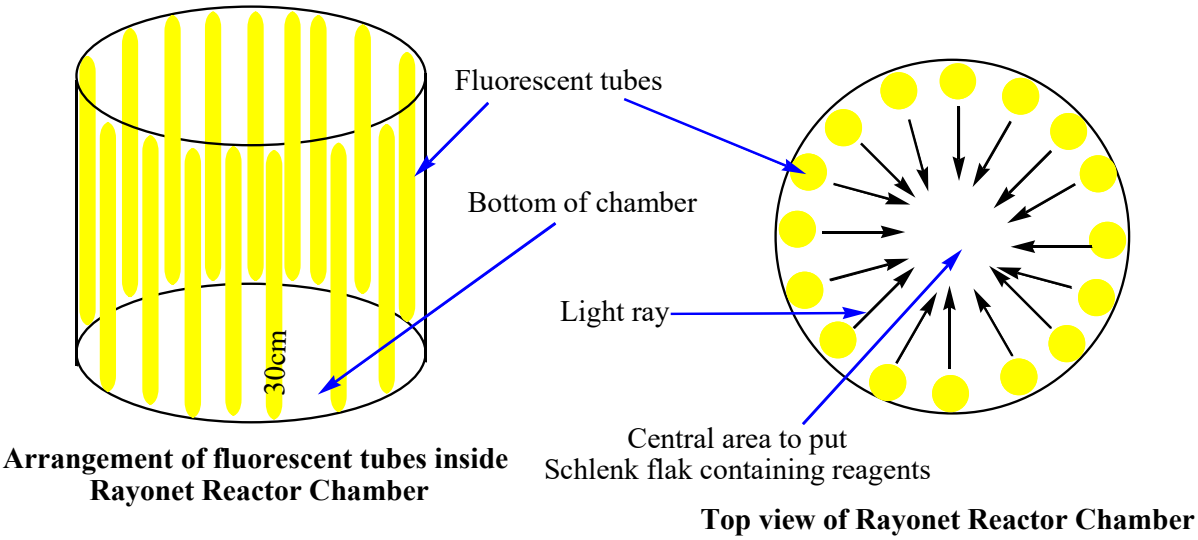


Figure 4.13: Schematic representation of the Rayonet chamber and its light distribution.

For the small-scale batch reactions, the filling height inside the Schlenk flask reached up to 16.5 cm for a standard volume of 100 mL. In comparison, the length of each fluorescent tube was approx. 30.5 cm. Hence, a large amount of light remained unused as it passed underneath the reaction vessel at the bottom of the chamber. The intensity of the light furthermore varied inside the reactor and depended on position and distance with respect to the lamps. The intensity of light was measured as 39 Klux close to the tubes and dropped to 32 Klux near the Schlenk flask due to the distance gap of 10 cm. The light intensity at the top and near the bottom of the reaction vessel were significantly lower with approx. 24 Klux as less light was provided near the ends of the fluorescent tubes (**Figure 4.14**).

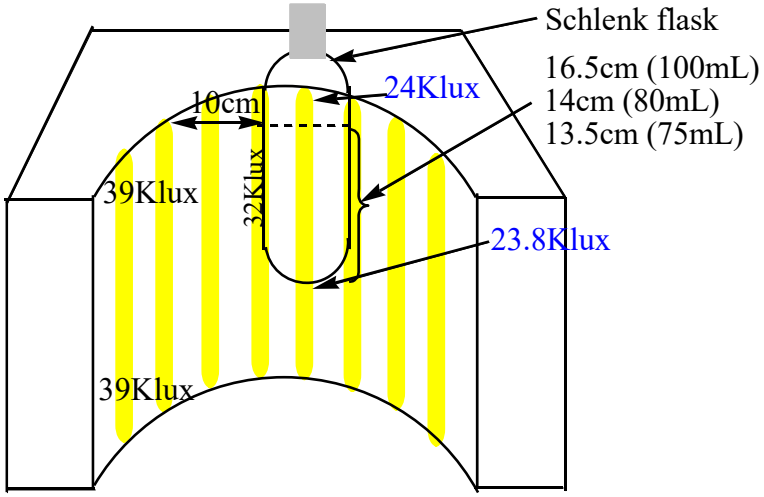


Figure 4.14: Schematic cross section of Rayonet chamber showing Schlenk flask position and differences in light intensity at various points.

In contrast, the fluorescent tube in the flow reactor was placed inside a Pyrex sleeve with the reaction capillary tightly wrapped around it. This inside-out irradiation utilized almost all light emitted from the light source. As the ends of the fluorescent tube are not covered by the Pyrex sleeve, the weaker light emissions in these areas do not contribute to the irradiation. Instead, the entire capillary is irradiated evenly, with only a minimal amount of emitted light remained unused (**Figure 4.15**). The intensity of light was measured to 14 Klux on the fluorescent tube and only decreased to 12 Klux on the Pyrex sleeve. Unlike the batch reactor, the small distance between light source and Pyrex sleeve does not cause any significant light losses.

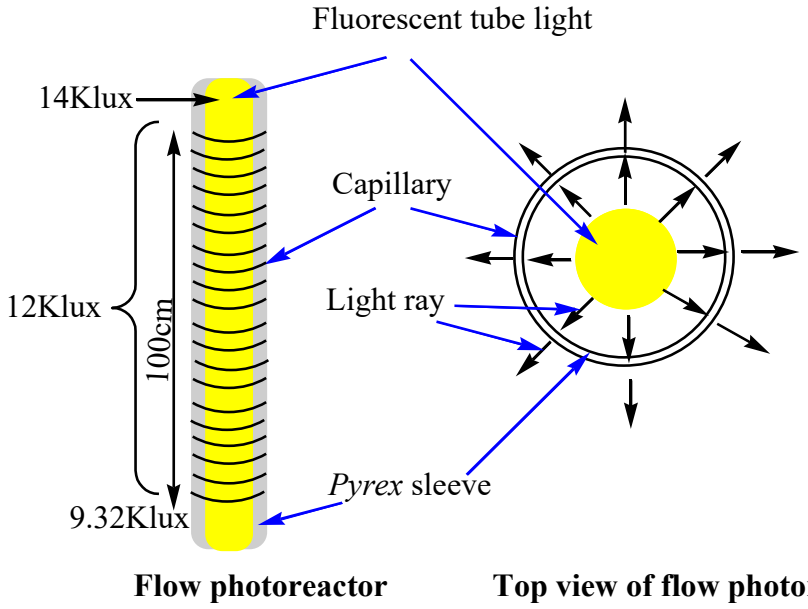


Figure 4.15: Schematic representation of light distribution inside the capillary flow reactor model – 1.

As light has to pass through the Pyrex sleeve first, its transmission spectrum was measured and showed full transmission in the visible range (**Figure 4.16a**). The transmission range also matched with the emission spectrum of the light source (**Figure 4.16b**). Consequently, the Pyrex sleeve in flow and vessel in batch do not reduce the amount of light passing through it.

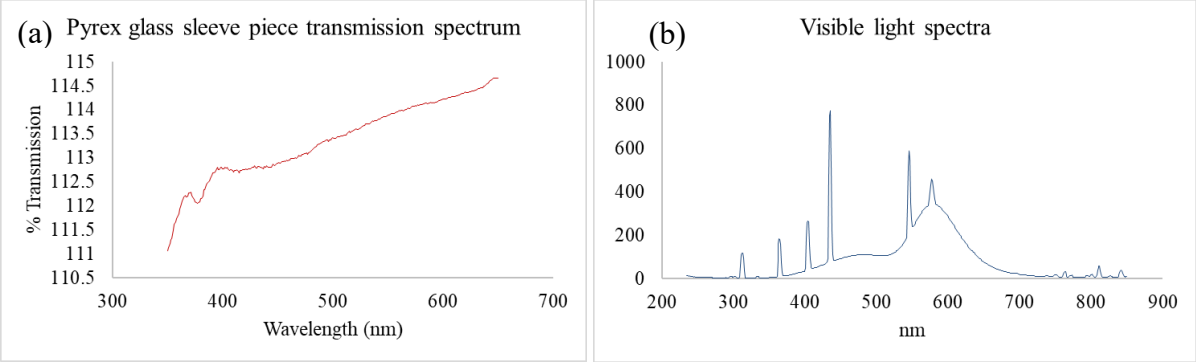


Figure 4.16: (a) Transmission spectrum of Pyrex sleeve and (b) emission spectrum of visible light.

The light attenuation throughout a reaction medium is determined by the path lengths and the concentration of the absorbing species, as described by the Beer-Lambert's law. For the photooxygenation reactions studied, the concentration of the sensitizer and the inner diameters of the capillary or Schlenk flask (the latter must take into account the diameter of the inserted cold finger and the outside-in irradiation) impacted on the light penetration. For the Schlenk flask, the effective path length was 3.5 mm, whereas the flow capillary had a path length of almost half with 1.58 mm. The thickness of the films (and thus path length) created along the gas bubbles of the slug flow was estimated to be 0.1-0.5 mm as it was barely visible. For selected sensitizer concentrations, the light transmissions at 646nm, 514nm and 399 nm were calculated based on the Beer-Lambert's law and using the molar absorptivity values (ε) of 19583.339 $L.mol^{-1}cm^{-1}$ (MB), 14701.7 $L.mol^{-1}cm^{-1}$ (RB) and 32040.7735 $L.mol^{-1}cm^{-1}$ (TPP), respectively (**Figure 4.17**). For all concentrations and sensitizers, complete light penetration was realized, although transmission dropped to below 25% for the batch system. In contrast, the capillary and especially the thin films show very high light transmissions and hence provided more light for effective singlet oxygen generation.

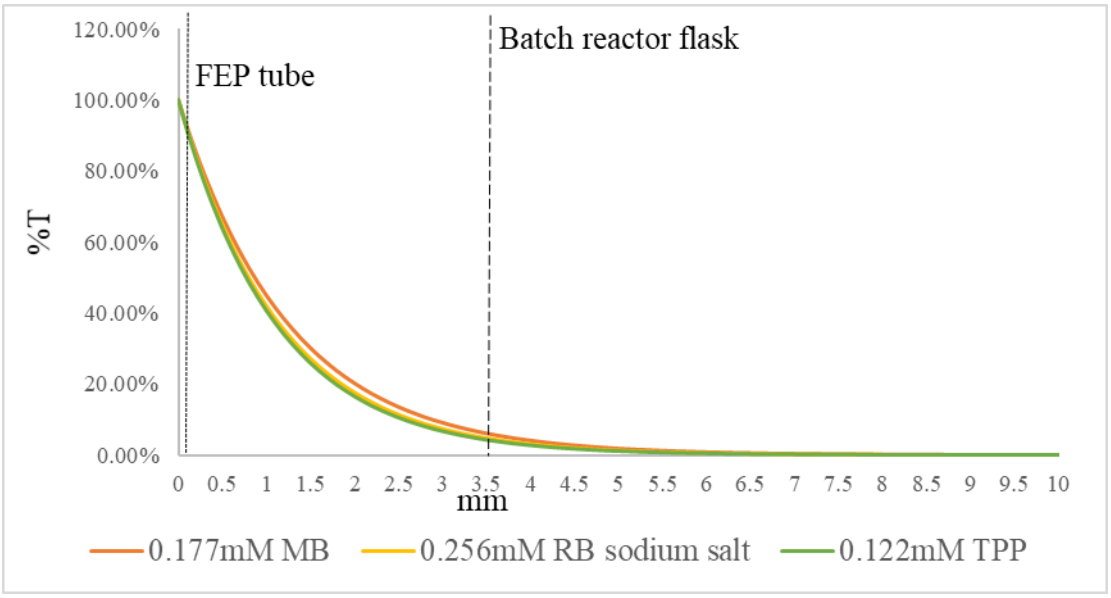


Figure 4.17: Transmission of light through different sensitizer solutions at absorption maximum 646nm and molar extinction co-efficient (ε) 19583.339 $L.mol^{-1}cm^{-1}$ for MB, 514nm and (ε) 14701.7 $L.mol^{-1}cm^{-1}$ for RB, 399 nm and (ε) 32040.7735 $L.mol^{-1}cm^{-1}$ for TPP. The internal diameter of the FEP capillary 1.58mm.

4.4.3.3 Energy efficiency

In terms of energy consumption for the photooxygenation step, the Rayonet batch reactor together with its air supply pump needed more electricity and longer operation times (**Table 4.16**). Furthermore, it was shown that photooxygenation performed at -20°C gave maximum productivity for **3**. With increased temperature the selectivity decreases, however, even at all temperatures almost complete conversion with **3** as major product can be obtained [48a].

Table 4.16: Power consumption details for both reactor setups.

Batch system		**Flow reactor system – 1**	
Electrical parts	**Power consumption [Watts]**	**Electrical parts**	**Power consumption [Watts]**
Lights	128	Light	47
Rayonet reactor	13	Liquid pump	4.1
Aquarium pump	2.7	MKS air pump	11.7
-	-	Fan	15 x 2
Run time	3-5 hours	Run time	10-65 minutes

Hence, in the current study additional cooling of reactors was required to minimize heat generated from light source and maintain ambient temperature. The batch reactor required chilled water for its cold finger, which adds to its energy consumption. In contrast, the flow system had a 1.5 times lower power consuming, required shorter reaction times to achieve high conversions and did not use any chilled water for temperature control.

4.4.4 Solar syntheses of artemisinin

Selected solar illumination of DHAA were explored in different solvents with different sensitizers.

Figure 4.18: Solar reactions under (a) batch and (b) flow conditions.

Batch solar reactions used the same Schlenk flask from the indoor reaction exposed to direct sunlight and gentle air purging. The combination of dichloromethane and TPP gave the best performance in terms of conversion, followed by acetone and methylene blue. However, both solvents were very volatile and constant air purging caused significant losses that required constant refilling of solvent. Batch solar reactions in alcohols (isopropanol and ethanol) in combination with rose Bengal were also found to show moderate conversions and did not suffer from extreme solvent losses. Selectivity again varied depending on the solvent.

Considering the solvent's suitability, solar flow reactions of DHAA were conducted solely in isopropanol with rose Bengal as sensitizer. Recirculation was required to produce meaningful conversions. The lack of oxygen in the subsequent thermal indoor reaction favored the formation of **16**, which could be isolated in 33% yield (**Table 4. 17**). Solar reactions generally give better product qualities in photooxygenation due to the minimal amount of natural UV radiation.

Table 4. 17: Solar reactions of DHAA in isopropanol (mixed with water) and rose Bengal.

Compounds	Batch	Tandem flow
Conversion	70%*	100%[#]
3	52%*	83%[#]
4	36% (isolated)	16%
16	-	33% (isolated)

* After 2 hours; [#] after 1-hour recirculation of reagents;

The solar radiation data for the respective experimental days were recorded at a nearly weather station on the JCU campus in Townsville and the solar illumination data is shown in **Figure 4. 19.** The solar reactions were started from 11 am when the solar irradiation was very intense. The data showed that all reactions were well exposed to sunlight except on the 5th of May 2015, when clouds caused a decrease in solar radiation. A perfect sunny day was the 11th of May 2015, when reactions were conducted with maximum sunlight without any interruption by clouds. However, the conversion rates remained similar for all batch and flow reactions irrespective of the weather conditions.

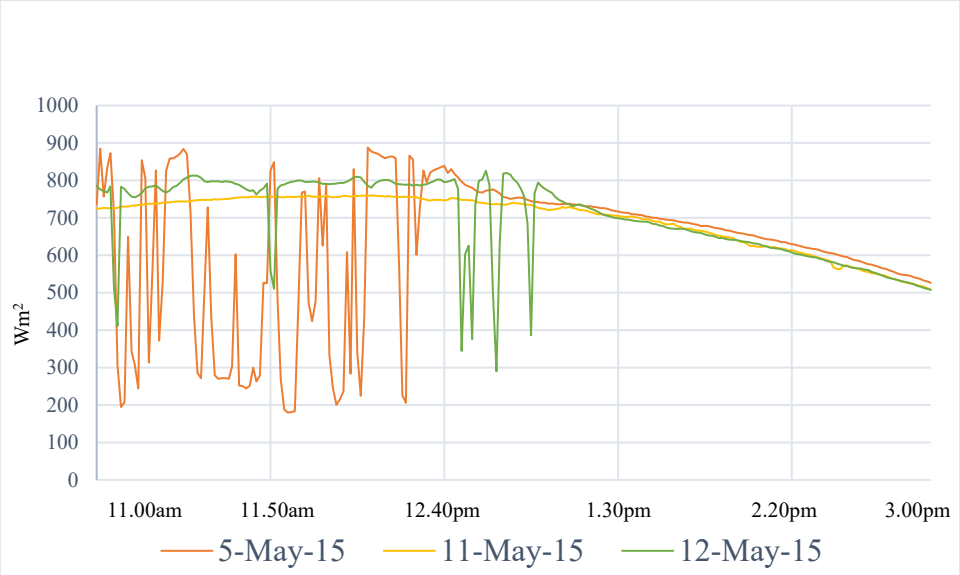


Figure 4. 19: Solar data recorded by photovoltaic station in JCU campus.

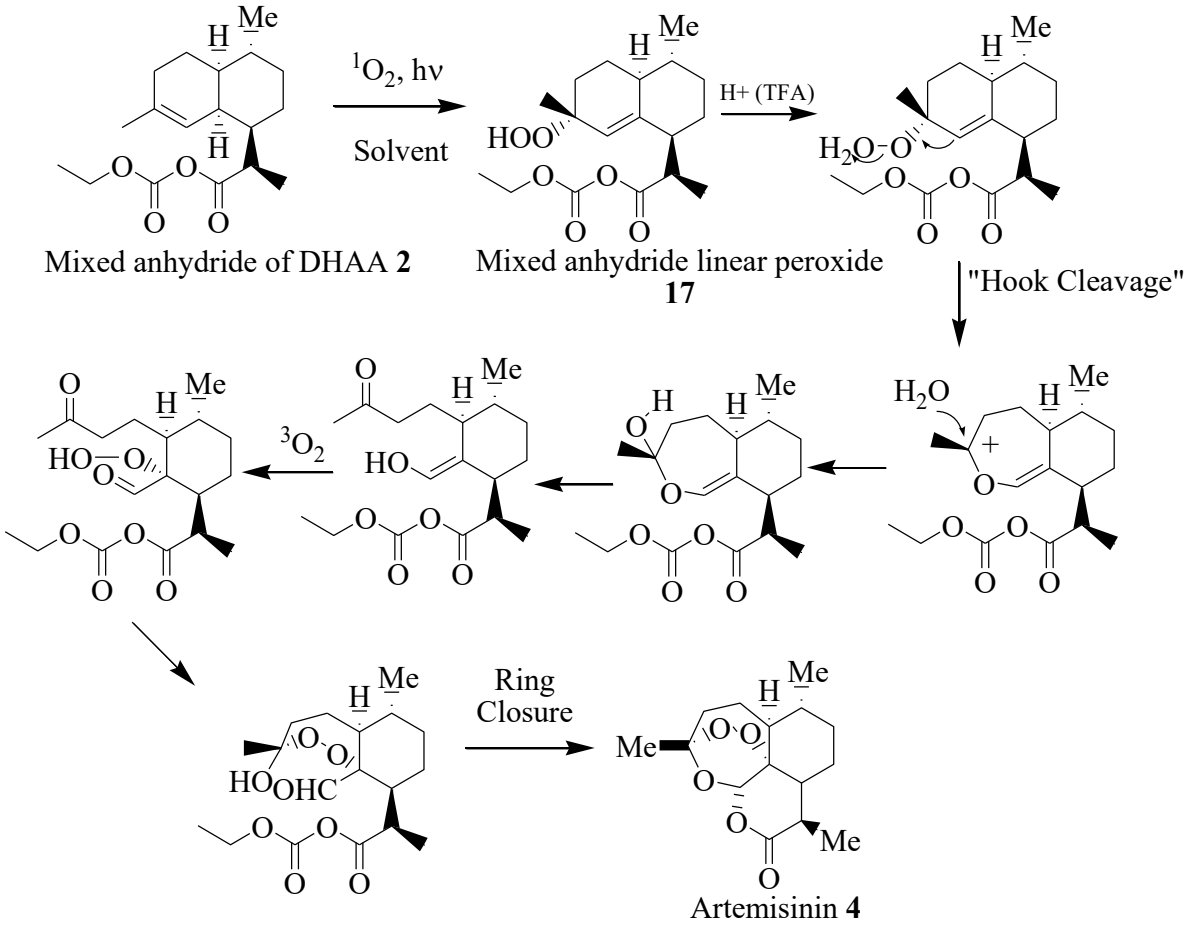
4.5 Synthesis of artemisinin from the mixed anhydride of dihydroartemisinic acid

The mixed anhydride of dihydroartemisinic acid is used industrially as the starting material for artemisinin synthesis. To inhibit the formation of **9** the carboxylic group of DHAA **1** must be masked. However, using the mixed anhydride of dihydroartemisinic acid can considerably

increase **16** despite the suppression of **9** [47, 78]. Hence, the mixed anhydride **2** is preferentially used. Photooxygenation of **2** in the presence of a photosensitizer produces allylic hydroperoxide or mixed anhydride linear peroxide **17** and the mechanism follows the same ene-reaction of singlet oxygen. Subsequently, compound **17** undergoes Hook Cleavage in the presence of an acid catalyst followed by rearrangement to form artemisinin (**Scheme 4.6**). Using the mixed anhydride of DHAA minimizes side reactions and hence improves selectivity (**Table 4.18**).

Table 4.18: Parameters optimized in batch and flow reactions.

Batch reaction parameters		**Flow reaction parameters**	
Sensitizers:	methylene blue (MB), rose Bengal (RB)	Gas:	Oxygen, air
Solvents:	acetone, dichloromethane, ethanol, isopropanol,	Flow rates:	0.5 – 1 mL/min for gas and liquid
Concentration:	4 – 9 mM	Sensitizer concentration:	Methylene blue 0.1 – 0.3 mM
Irradiation:	2-6 hours.		
Light source:	16 × 8 W cool white fluorescent tubes		



Scheme 4.6: Mechanism for the formation of artemisinin from the mixed anhydride of DHAA.

As with the photooxygenations from DHAA itself, the efficiency depended on the solvent-sensitizer combination used. The one-pot batch reaction of **2** in acetone with methylene blue gave the best conversion, selectivity and isolated yield of **4** (**Table 4.19**). When compared to the reported work, the one-step batch production was able to produce a 50% yield after 8 hours of irradiation [135]. Two-step reactions in either acetone or alcohols gave high amounts of byproduct, probably due to their reactions with intermediates. While the formation of **9** was indeed inhibited, an increase in the formation of **16** was found in the two-step protocol, suggesting insufficient oxygen supply during the thermal reaction. One-pot reactions were found more selective for artemisinin formation (**Figure 4.20**) as the oxygen supply system in the Schlenk flask was superior over that in the round bottom flask used for the thermal reaction. The two-step reaction also caused accumulation of the instable linear hydroperoxide and released potentially flammable solvent/air vapor, both representing safety hazards [48a]. Therefore, subsequent flow reactions were only conducted under one-pot conditions.

In flow with both air and oxygen, the formation of **9** and **16** were significantly suppressed, however, the yield of artemisinin could not be improved and no isolated yield could be obtained. The small amounts produced and the complexity of the crude reaction mixtures commonly prevented crystallization.

Despite these limitations, the developed process showed some advantages over the reported protocol described by Burgard and co-workers [135]. In particular, the literature process utilized a 150 W medium-pressure mercury lamp that required light filtering to remove destructive wavelengths as well as effective cooling. The developed process used energy efficient and 'cold' fluorescent tubes instead, that also solely emit visible light.

Table 4.19: One-pot artemisinin formation from the mixed anhydride of DHAA in DCM.

Sl.	Mode	Dye	Gas	TFA	Light	Irradiation	Artemisinin [%] *
1	Batch Burgard *et al.* [135]	TPP	Air	9.9g	150W Hg Lamp	8h	50 (isol.)
2	Batch	MB	Air	0.01ml	8W x 16 Fluorescent tube	2h	67 (30%isol.)
3	Flow	MB	Air	0.01ml	20W Fluorescent tube	40min	24
4	Flow	MB	O_2	0.1ml		40min	55

Liquid flow 1mL/min, gas flow rate 0.5mL/min; * by ^{1}H-NMR (±3%)

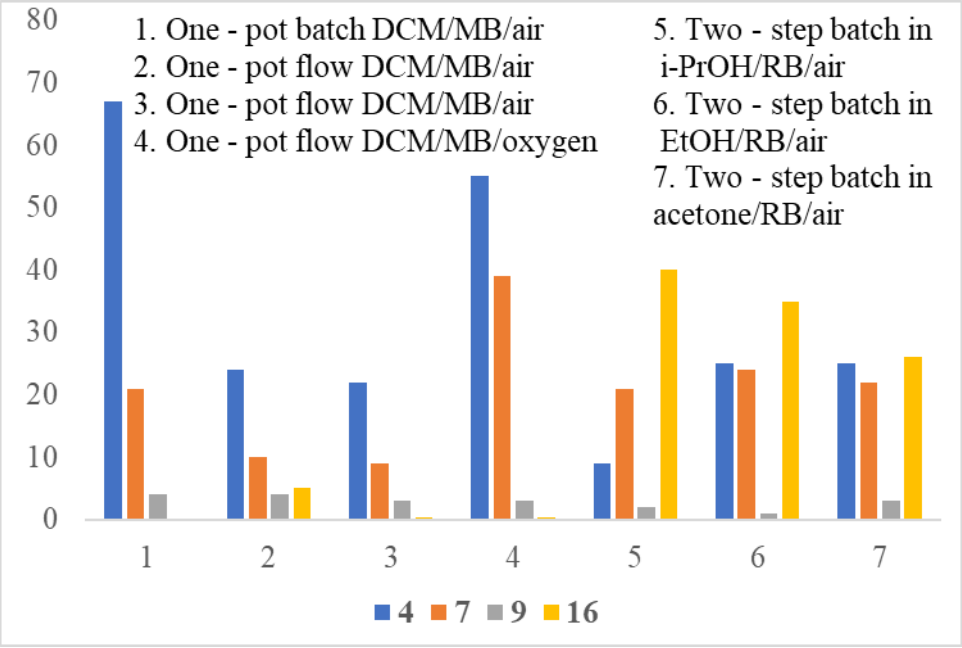


Figure 4.20: Compositions from flow and batch photoreactions of mixed anhydride of DHAA.

4.6 Synthesis of artemisinin in the Vapourtec reactor

It was demonstrated that the E-Series was able to convert dihydroartemisinic acid into artemisinin via photooxidation and a subsequent Hock cleavage/triplet oxygen oxidation. The UV-150 reactor operated at 15 °C while the second reactor was used at room temperature (25 °C) and over approximately 35minutes 35% artemisinin was determined by H^1NMR [48b]. Unlike the reported conditions for artemisinin synthesis protocol the current study is a one-pot continuous flow approach in the Vapourtec E-series photochemical reactor. One-pot continuous flow reactions were performed in the Vapourtec-easy-photochem E-series reactor using methylene blue and dichloromethane for current the study. Despite the short residence times in the small capillary, appreciable conversions, selectivity and amounts of artemisinin were obtained (**Figure 4.21**). The highest amount of artemisinin with 38% (by NMR) was achieved when the mixed anhydride was used. In all reactions byproduct **7** remained within an acceptable range of 4-17%. The use of the mixed anhydride of DHAA completely suppressed the formation of **9**. Generally, only small amounts (or no) **16** were seen. The purpose designed Vapourtec reactor allows for the generation of stable slug-flows (**Figure 4. 22**) and offers an optimal match between the 420 nm LED-array and the sensitizer. The reaction capillary is fully illuminated by the central light source (inside-out irradiation) and temperature is controlled through air flows. These features generate favorable conditions for artemisinin formation.

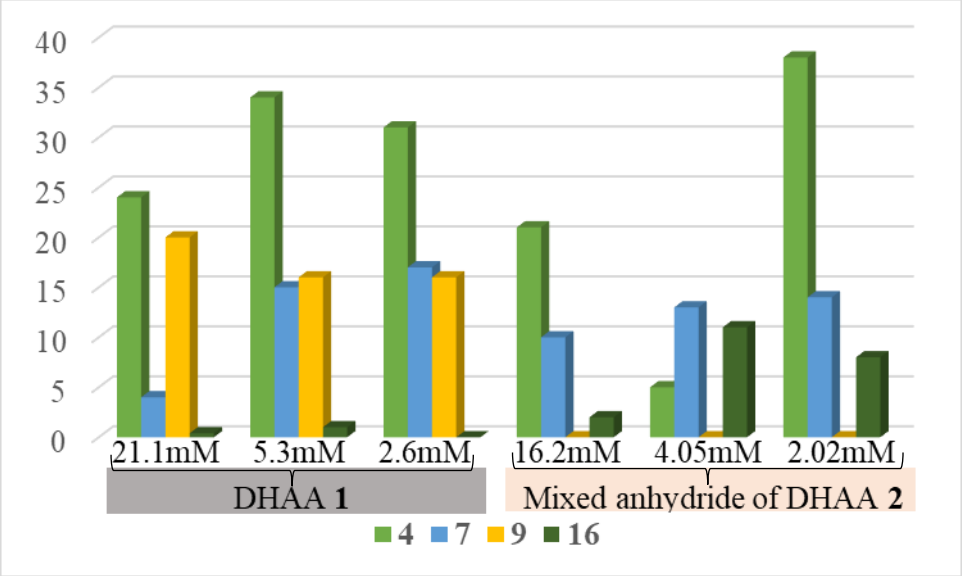


Figure 4.21: Different compositions of crude mixtures collected after photoreactions of DHAA and its mixed anhydride in the Vapourtec flow reactor.

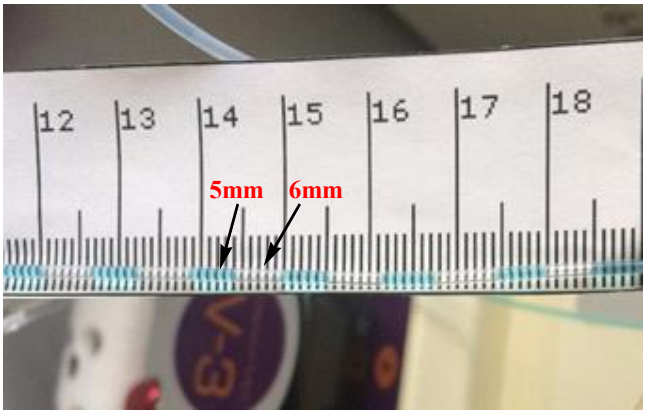
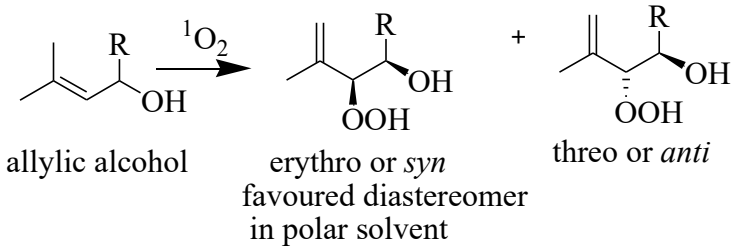


Figure 4. 22: Gas-liquid slug flow formation in the reaction capillary (air: 0.5 mL/min; liquid: 1 mL/min).

4.7 Photooxygenation of allylic alcohols (20 - 22)

The ene-reaction of diastereoisomeric allylic alcohols with singlet oxygen were investigated and produced *syn*-hydroxy allylic hydroperoxide as major diastereomers due to the hydroxy-directing effect of $^1O_2$ in the conformationally fixed substrates [136]. The solvation of the hydroxyl group through hydrogen bonding in polar solvent and thus reduces the oxygen-hydrogen steering effect When the allylic substituent develops unfavorable electronic repulsions with the incoming electrophile becomes highly erythro diastereoselective (**Scheme 4.7**).



Scheme 4.7: Solvent dependant formation of hydroperoxyl alcohol diastereomers.

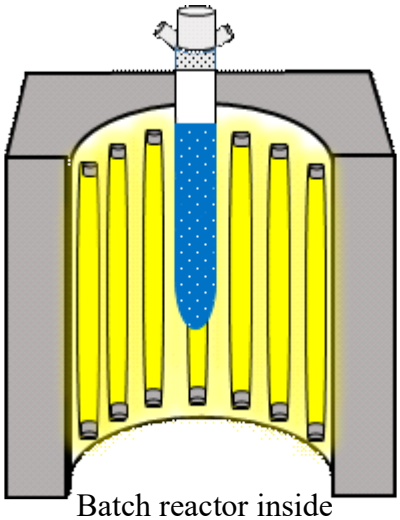
4.7.1 Photooxygenation of 4-methylpent-3-en-2-ol

The photooxygenation of allylic alcohol **20** was explored in batch, flow reactor model – 1 and flow reactor model – 2. The mechanism of the photooxygenation follows the ene-mechanism and forms two isomers **23a** (major) and **23b** (minor), what can be assigned by NMR analysis. The diastereoselectivity of this reaction is significantly high in nonpolar solvents [137], hence, the reactions were investigated solely in dichloromethane. TPP in dichloromethane was found

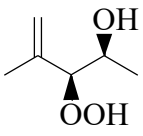
to give high conversions but high sensitizer concentration reduced the efficiency due to poor light penetration and self-quenching. With methylene blue the reaction gave a poor mass balance, suggesting decompositions that result in the loss of material (**Figure 4.23**).

The ene-reaction of **20** was further investigated in the in house-built flow reactor model – 1 at different flow rates of compressed air and the liquid stream in the presence of a 5psi back pressure regulator (BPR). Conversion rates and diastereoisomeric ratios depended on the residence time, flow rate ratios and oxygen source. The PBR played an important role as it controlled the pressure downstream of the reactor and facilitated rapid movement and hence mixing within the slugs inside the capillary [138]. Also, the BPR also helped to maintain a constant flow throughout the length of the tubing at high flow rates, which was difficult in reactions with very low flow rates.

Increased TPP concentrations may have reduced the light transparency and self-quenching thus leading to lower conversions even at higher flow rates. Methylene blue as sensitizer in ethanol showed a reduced selectivity for the *syn* isomer and lower conversions, suggesting hydrogen-bonding between substrate **20** and the solvent that favor different conformations and block the approach of singlet oxygen compared to reactions in dichloromethane.



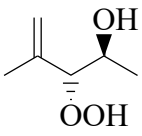
Batch reactor inside Rayonet Chamber



syn

(2*S*,3*S*)-3-hydroperoxy-4-methylpent-4-en-2-ol

23a



anti

(2*S*,3*R*)-3-hydroperoxy-4-methylpent-4-en-2-ol

23b

DCM vs TPP 96% conversion, *syn : anti* 86:14
DCM vs methylene blue 94% conversion, *syn : anti* 81:19

Figure 4.23: Photooxygenation of **20** in batch reactor and formation of **23a** and **23b**.

While operating the photooxygenation using dichloromethane and TPP in both, batch and flow modes, it was noticed that the reaction mixture turned from purple to green within a few minutes. While TPP is known to change color in acidic media due to protonation and

conformational changes, the performed reactions did not utilize or produce any acid. The color change may thus be either caused by oxidation of TPP or by actual protonation due to the presence of trace amounts of hydrochloric acid in dichloromethane. Both possibilities were tested by adding either hydrogen peroxide or conc. hydrochloric acid to solutions of TPP in dichloromethane (**Figure 4.24**). While the hydrogen peroxide solution stayed purple, the solution containing conc. HCl slowly turned green. This suggests that color change during the photooxygenation may have been caused by trace amounts of acid generated from dichloromethane. The green color is due to the formation of the dicationic H_4TPP^{2+} through protonation of the pyrrole nitrogen atoms in the central core of the porphyrin. This protonation changes the conformation of the porphyrin [139, 140]. Despite its absorption in the visible, the dicationic H_4TPP^{2+} species has a much lower efficiency for singlet oxygen formation [141]. Nevertheless, when the current photooxygenation was monitored by NMR analysis, the change of color did not affect the reaction progress and did not cause the formation of other side-reactions.

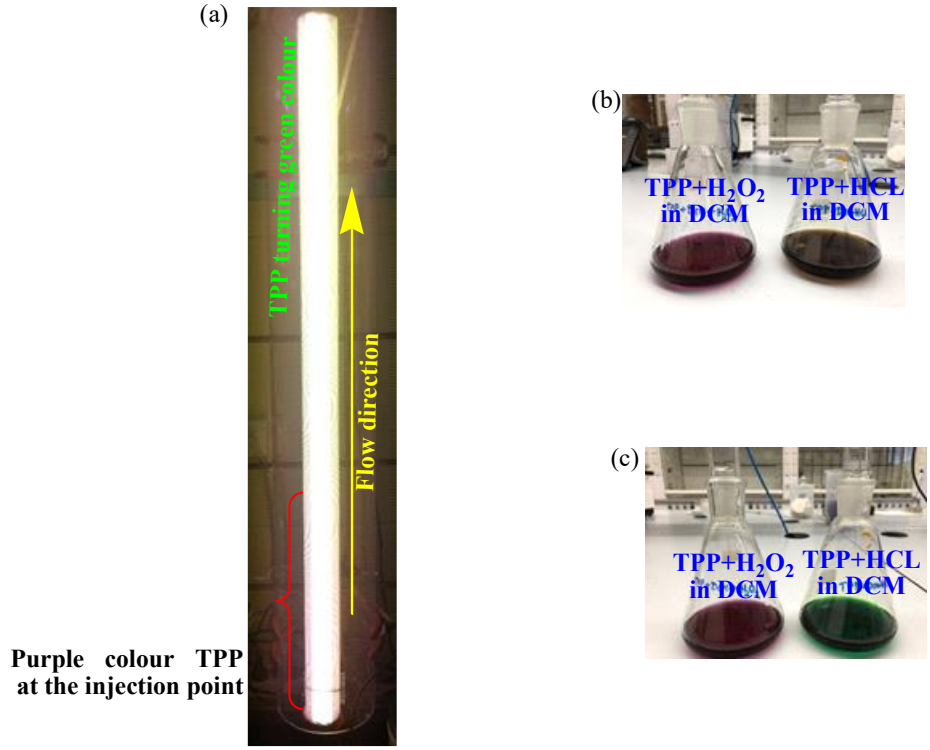


Figure 4.24: Reaction mixture containing TPP showing change in color from purple to green inside the flow reactor capillary; (b) initial solution of TPP in dichloromethane after addition of hydrogen peroxide or conc. hydrochloric acid; (c) after 2 hours of stirring at room temperature.

The photooxygenation was furthermore investigated in the flow reactor model – 2 using TPP and dichloromethane. The reactor's tubing length was shorter and irradiations operated in an outside-in mode inside a Rayonet chamber reactor (**Figure 4.25**). Under even slug flow conditions (**Figure 4.26**), high conversions were achieved with short residence times.

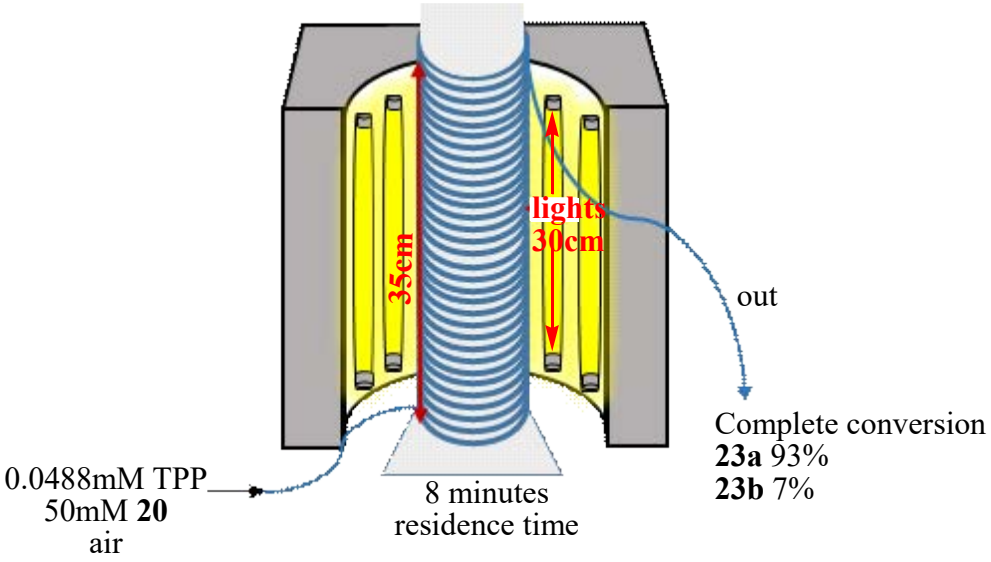
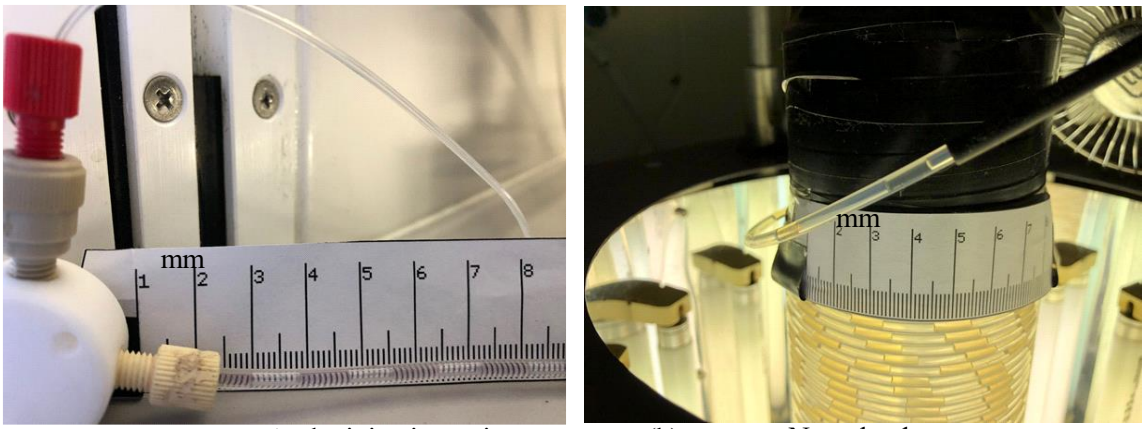


Figure 4.25: Photooxygenation of 20 in continuous flow reactor model – 2 and formation of **23a** and **23b**.



(a) At the injection point liquid slug 9mm air bubble 8mm

(b) Near the downstream liquid slug 9mm air bubble 10.1mm

Figure 4.26: Gas-liquid slug flow formation in continuous flow reactor model – 2; (a) slug flow formation at the entry point and (b) slug-flow ear the outlet of capillary reactor.

The photooxygenation of allylic alcohol **20** was also investigated in the commercial Vapourtec flow reactor equipped with a 3.6 W LED panel. At low flow rates and hence longer residence

times, complete conversions were obtained. The methylene blue-dichloromethane caused significant mass balance losses, suggesting unknown side reactions. In contrast, TPP in dichloromethane gave reasonable conversions with a residence time of 6 minutes, although efficiencies decreased with increasing amount of **20** (**Figure 4.27**). The Vapourtec reactor allowed for an easy adjustment of stable slug flows and showed a good match of the 420 nm LED with the sensitizers.

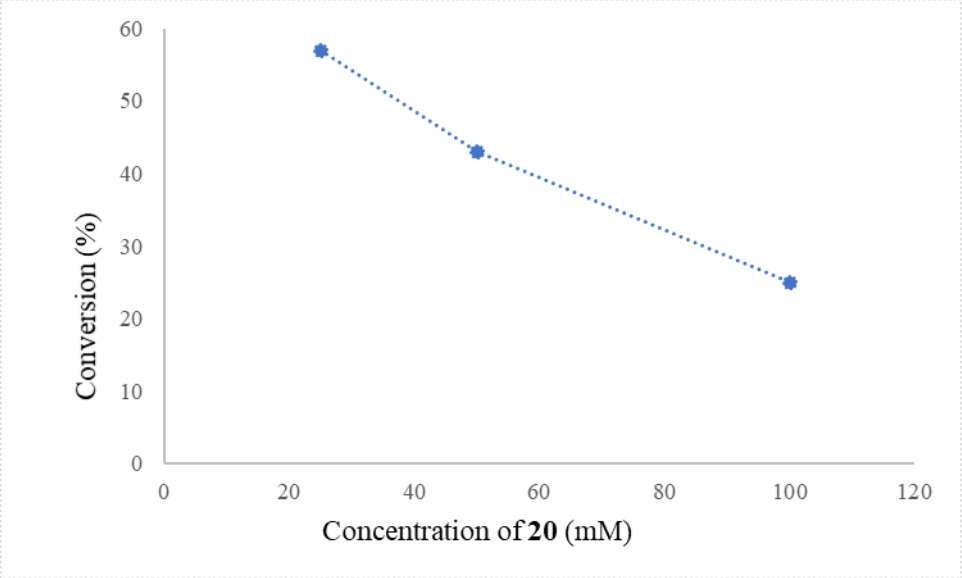


Figure 4.27: Conversion trend of 20 in Vapourtec flow reactor.

When comparing the results with available literature data, the achieved results under flow conditions show some advantages. For example, the photooxygenation of **20** under batch conditions and irradiation for 48 hours in a polymer matrix using a Halogen street lamp furnished a conversion of 83% [105]. The developed flow process can achieve higher conversions in much shorter time.

4.7.2 Photooxygenation of dimethylhex-4-en-3-ol

Photooxygenation of dimethylhex-4-en-3-ol (**21**) with TPP in dichloromethane was investigated in batch and in flow reactor model – 2. The photoreaction produced a diastereoisomeric mixture of **24a** and **24b**, what can be differentiated by NMR analysis. Batch irradiations showed very good diastereoselectivity, although complete conversion could not be achieved. In contrast, continuous flow photooxygenation of **21** with compressed air gave a high conversion in a short residence time although its reproducibility remained a challenge. As the reason for this could not be established, a meaningful discussion cannot be accomplished.

In comparison, the literature reported a conversion of 72% after 48 hours of irradiation using a Halogen street lamp [105]. The developed process thus offers a more energy efficient and cleaner alternative.

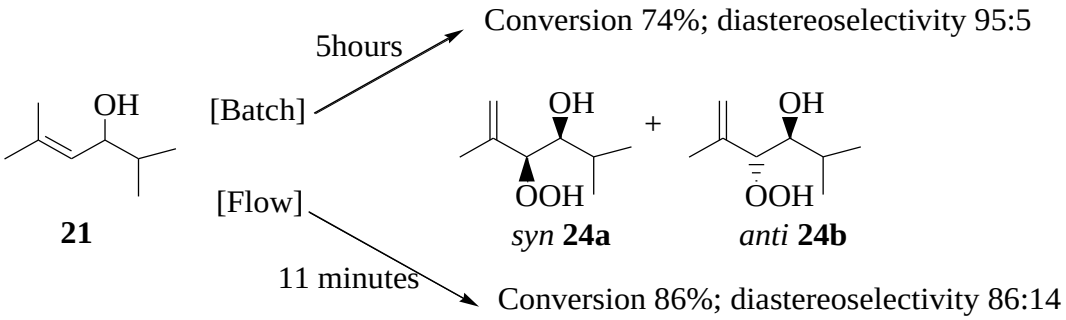


Figure 4.28: Photooxygenation products of dimethylhex-4-en-3-ol in batch vs flow.

4.7.3 Photooxygenation of dimethylhept-2-en-4-ol

Photooxygenations of dimethylhept-2-en-4-ol (**22**) with TPP in dichloromethane were furthermore investigated in batch and in flow reactor model – 2. The reaction produces a diastereoisomeric mixture of **25a** and **25b**, what can be assigned by NMR analysis. The batch reaction in the Rayonet reactor readily gave complete conversion after 5 hours of irradiation. In comparison, the flow reaction in single pass or recirculation mode gave conversions of up to 56%. Back pressure issues caused fluctuations in residence times and hence reaction performances, preventing any meaningful discussion.

However, the literature process gave 77% conversion after 60 hours of irradiation with a Halogen street lamp [105]. Despite its technical performance issues, the developed flow protocol offers an energy-efficient and safer alternative.

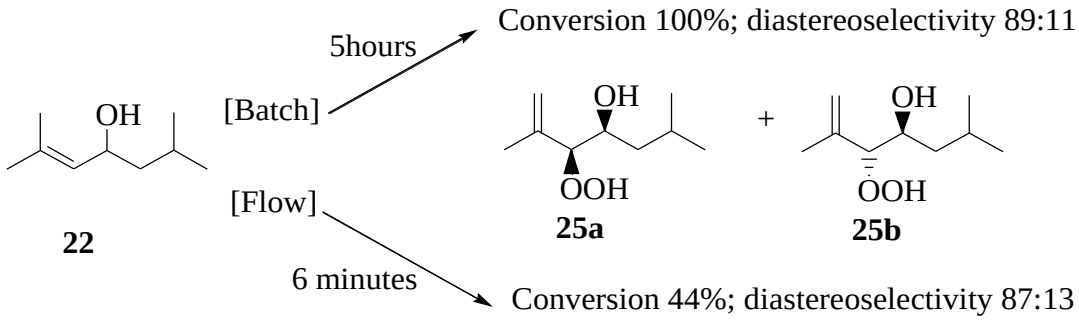
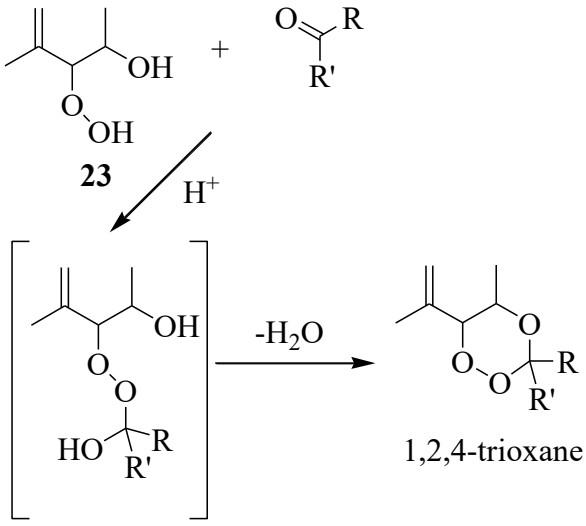


Figure 4.29: Photooxygenation products of dimethylhept-2-en-4-ol in batch vs flow.

4.8 Syntheses of trioxane compounds by acid catalyzed reactions of 23

Photooxygenations of allylic alcohol **20** produced sufficient amounts of crude 3-hydroperoxy-4-methylpent-4-en-2-ol **23** for the synthesis of a small 1, 2, 4-trioxane library. The desired trioxanes were synthesized by treating the β-hydroxy hydroperoxides with catalytic amounts of indium triflate in presence of an appropriate carbonyl compound (**Scheme 4.8**).



Scheme 4.8: Mechanism of 1,2,4-trioxane formation from hydroperoxyl alcohol.

The efficiency of the synthesis varied with the selected carbonyl compound. The removal of excess carbonyl compound and the catalyst also remained an unsolvable challenge. In almost all cases, conventional chromatographic purification methods led to the complete loss of the products. Attempts to remove excess aldehyde or ketones through extractions were also unsuccessful. The trioxane ring is thus suspected to undergo ring opening under acidic (chromatography on silica gel) or aqueous conditions. In fact, thermal, base-catalyzed and acid-catalyzed decompositions and rearrangements of artemisinin and trioxanes have been described in the literature [142, 143, 144].

Chapter 5: MOFs as Potential Sensitizers in Photooxygenations

5 Metal-organic Frameworks as potential sensitizers in photooxygenations

5.1 Background on MOFs

Metal-organic frameworks (MOFs) are a class of porous solid materials consisting of crystalline coordination polymers with channels that permeate the solid. The molecular components used to construct MOFs are rigid organic ligands featuring two or more functional groups that coordinate to transition metal ions. The resulting transition metal complexes serve as higher-order building blocks that continue to self-assemble into one-, two- or three-dimensional networks (i.e., frameworks) that form highly ordered solids. A trademark of MOFs is the presence of continuous channels that impart porosity and result in a variety of topological architectures (e.g., cubic, diamond) that depend on the length, number of coordinating functional groups and rigidity of the organic linking ligand [145]. MOFs show interesting properties such as permanent porosity, high surface area and uniform open cavities. The large variety of potential building blocks, i.e. metals and organic linkers, makes it possible to construct MOFs with designed properties for diverse applications [146]. Since the organic linkers play a crucial role in targeting the functionalities of porous MOFs, porphyrins and metallo-porphyrins have received great attention in building porous porphyrinic framework materials [147]. The porosity imparted by the size and geometry of the linkers, as well as the coordination sphere around the metal clusters give MOFs an increased surface area and a higher density of accessible catalytic sites if compared to traditional catalysts. In particular, MOFs containing porphyrinic macrocycles (**Figure 5.1**) as linkers are attractive due to the photoactive nature of these molecules. Porphyrin-based moieties are ubiquitous in nature and are capable of catalyzing a wide range of reactions. MOFs incorporating free-base and metallo-porphyrins are often limited by their structural stability in polar solvents, particularly water. Recently, this limitation has been addressed by the development of porphyrinic MOFs comprised of highly oxophilic metal ions, such as Zr^{4+} and Al^{3+} (e.g. PCN-222, 223, 224, 225, MOF-525, 545 and Al-PMOF), which provide considerable improvement in structural and chemical stabilities of the resulting frameworks [148, 149].

For the use of MOFs as photocatalysts it is highly desirable to have linkers that absorb in the visible region. Since most conventional arene-linked MOFs absorb in the UV, the presence of substituents with strong bathochromic shifts in the absorption is necessary. The presence of NH_2-groups and polycyclic aromatic compounds (dyes) as linkers indeed shift the absorption

of MOFs into the visible region. In addition, inorganic metal ions or metal oxide nodes can also act as visible-light harvesting centers. MOFs can this play an active role, absorbing photons by the organic linkers and converting the initial ligand-localized exciton into a charge-separate state by single electron transfer from the ligand to the metal nodes. The most common ligands in MOFs are organic polycarboxylates that can, upon photon absorption, transfer an electron to the positive metal ions bound to them. Other linkers can exhibit similar photochemical behavior. Moreover, aromatic compounds have intense absorption bands above 250 nm and, depending on the substituents, can easily move to 300 nm or even into the visible region ($\lambda > 400$ nm). Consequently, MOFs can be designed to exhibit visible-light induced photoreactions [150].

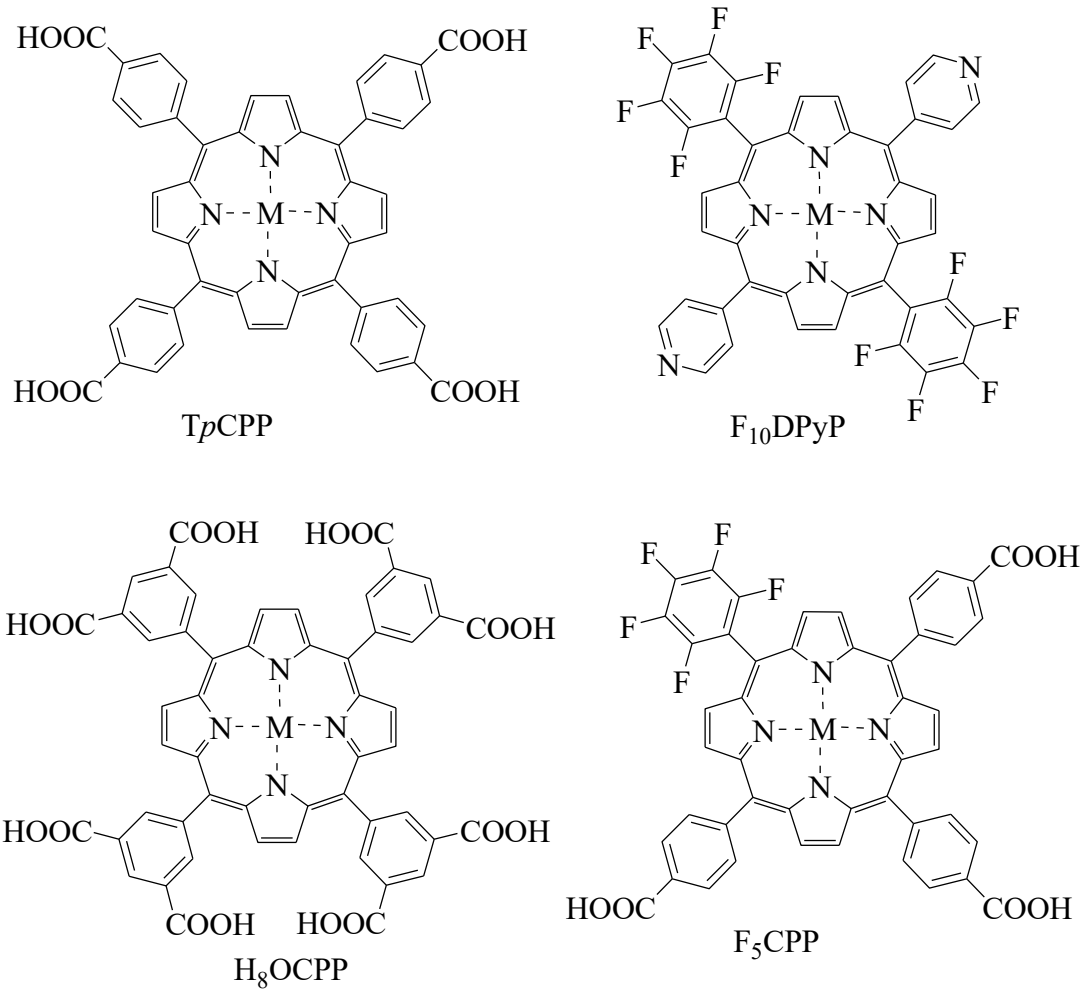


Figure 5.1: Porphyrins used in MOFs preparation as shown by Paz et al. 2016 [149].

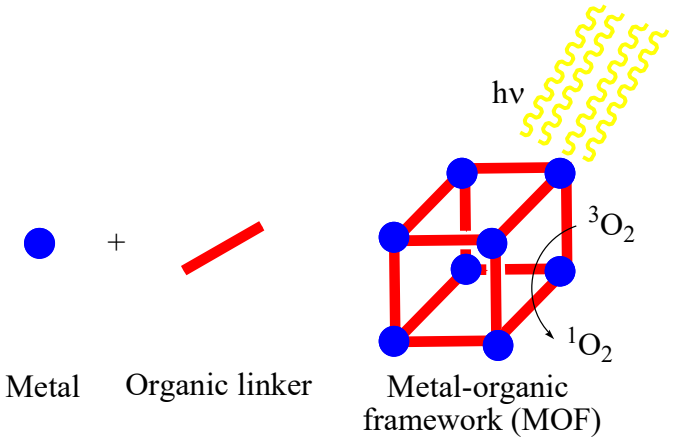


Figure 5.2: Schematic of singlet oxygen generation by MOFs.

Singlet oxygen ($^1O_2$), a mild yet efficient oxidant, has proven to be a versatile reactive oxygen species with applications in multiple organic transformations. As a result, porphyrinic MOFs have been recently reported to be effective photosensitizers for $^1O_2$ generation and to exhibit good catalytic activity for photooxygenation reactions (**Figure 5.2**). Wu and co-workers showed that incorporation of the biomimetic metallo-porphyrins into porous metal-organic frameworks (**Figure 5.3**) does not only sustain a long stability by preventing destructive self-oxidation, but can also enhance its catalytic functions. The photocatalytic activity of $[Zn_2(H_2O)_4Sn^{IV}(TPyP)(HCOO)_2]$·guests immobilized inside MOFs was explored for the photooxygenation of 1, 5-dihydroxynaphthalene and sulfides under visible light irradiation. Almost quantitative conversions and remarkable selectivity (up to >99%) were achieved in heterogeneous phases with outstanding stability of the subsequently recycled catalyst [151].

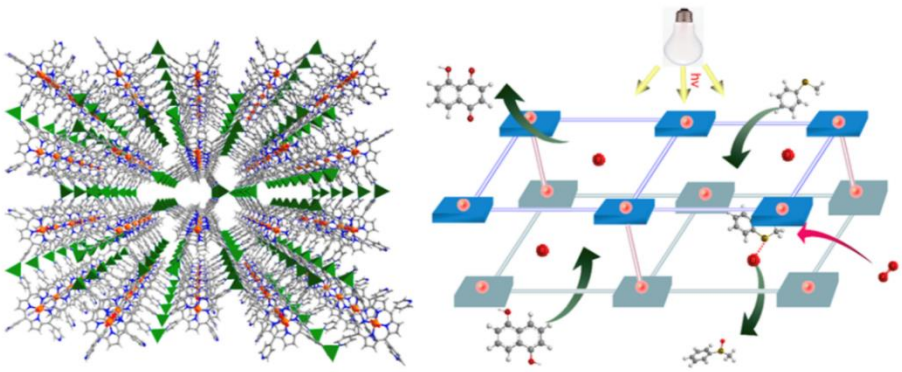


Figure 5.3: Perspective view of the 3D porous framework of $[Zn_2(H_2O)_4Sn^{IV}(TPyP)(HCOO)_2]$·guest down the c axis (left) and schematic representation of the photooxidation of dihydroxynaphthalene and sulfides (right). Color scheme: Sn, orange

balls; Zn, green square-pyramids; O, red; N, blue; C, gray; H, light gray as shown by Wu et al. 2014 [151].

Jiang and co-workers designed and synthesized Pt/PCN-224(M) composites by integration of Pt nanocrystals into porphyrinic metal−organic frameworks (MOFs), PCN-224(M) (**Figure 5.4**). Due to a synergetic photothermal effect and singlet oxygen production, these composites exhibited excellent catalytic performances in the photooxidation of aromatic alcohols at 1 atm O_2 and at ambient temperature. The reactions proceed with excellent selectivity and yields within short reaction times using visible-light irradiation. Among all materials tested, PCN-224(Zn) was reported to exhibit the greatest ability of $^1O_2$ production due to the strongest diamagnetism with the d^{10} configuration of Zn^{2+} among different metals residing in the porphyrin center in the MOF [152, 153].

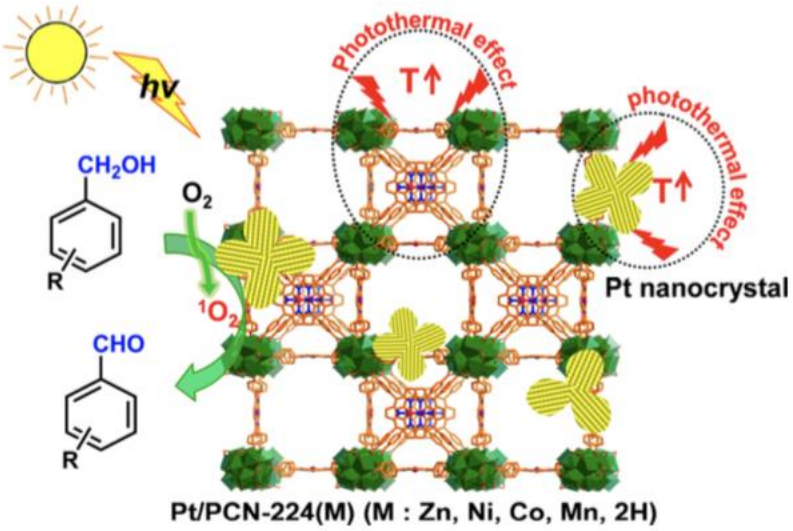


Figure 5.4: Schematic Illustration Showing the Singlet Oxygen-Engaged Selective Oxidation of Alcohols over Pt/ PCN-224(M) Using Molecular Oxygen under Visible-Light Irradiation as shown by Jiang et al. 2017 [152].

Zhou et al. reported that isostructural MOFs with uncoordinated porphyrin and other metalloporphyrins, including Fe, Mn, Co, Ni, Cu, and Zn, affording a new series of stable MOFs (**Figure 5.5**). The PCN-222 series of MOFs possess the largest open channels and are extraordinarily stable. Their powder X-ray diffraction (XRD) patterns remain intact upon immersion in water, boiling water, as well as in 2 M, 4 M, 8 M and even concentrated aqueous HCl solutions for 24 h, suggesting that no phase transition or framework collapse happens during these treatments. Catalytic studies have demonstrated that mesoporous PCN- 222(Fe)

can catalyze the oxidation of a variety of substrates. The integration of a high density of catalytic centers, ultra-large open channels, and the extra-ordinary chemical stability of PCN-222(Fe) suggests a bright future for building MOF-based platforms for enzyme-mimic catalysis [154].

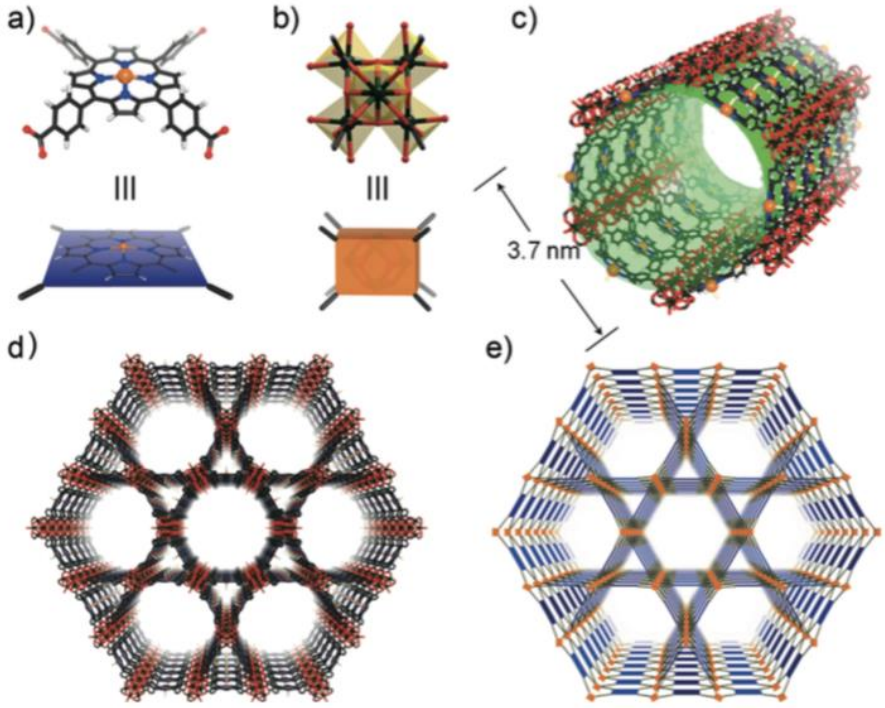


Figure 5.5: Crystal structure and underlying network topology of PCN- 222(Fe). The Fe-TCPP (a; blue square) is connected to four 8-connected Zr6 clusters (b; light orange cuboid) with a twisted angle to generate a 3D network in Kagome-like topology (d,e) with 1D large channels (c; green pillar). Zr black spheres, C gray, O red, N blue, Fe orange. H atoms were omitted for clarity as shown by Zhou et al. 2012 [154].

Targeted photodynamic therapy (PDT) with Zr(IV)-based porphyrinic metal-organic framework PCN-224 nanoparticles was investigated by Zhou and coworkers. Through synthesis of size controllable MOF nanoparticles, a successful tuning of PCN-224 nanoplatforms were established to a range that is of biological interest (30 – 190 nm). Further functionalization with folic acid (FA) onto the Zr^6 cluster in the PCN-224 enhanced the PDT efficacy owing to the active targeting of the modified MOF nanomaterial (**Figure 5.6**). Fabrication of photosensitizer as MOF nanoparticle followed by size optimization may serve as useful tool for specific in desired application. [155].

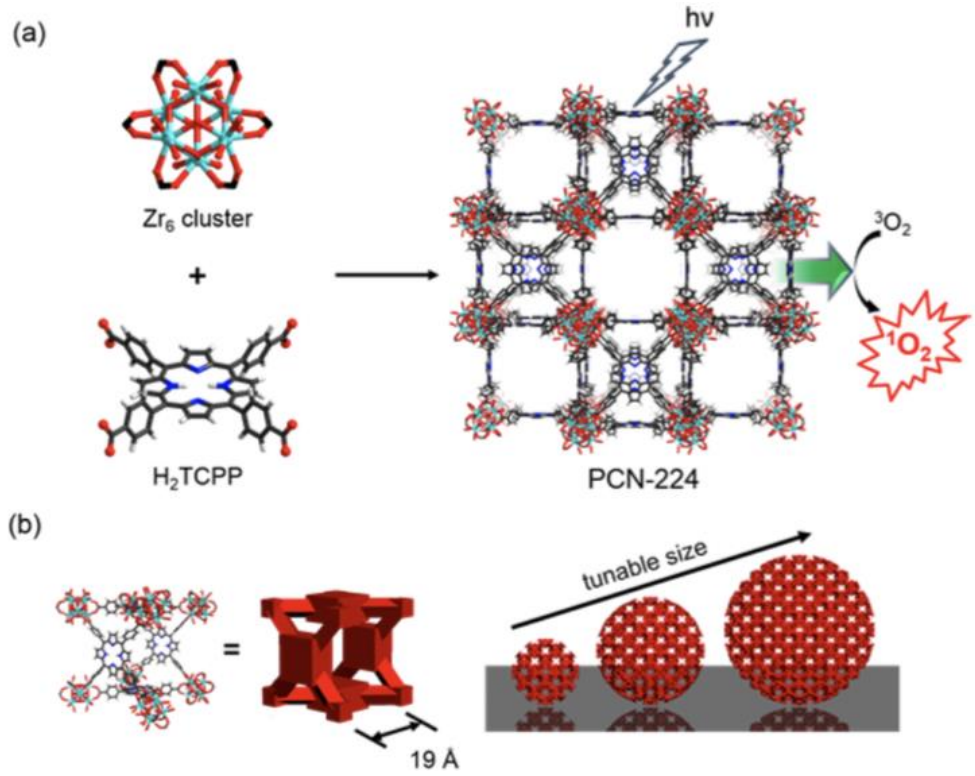
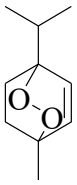


Figure 5.6: Illustration of PCN-224 structure. (a) 6-connected Zr6 cluster (Zr6O4(OH)4(H2O)6(OH)6(COO)6), tetratopic linker (tetrakis (4-carboxyphenyl)porphyrin (H2TCPP)), and 3D nanoporous framework of PCN-224. (b) A cubic unit of PCN-224 and schematic illustration of spherical PCN-224 nanoparticles on the basis of construction of cubic units, yielding different sizes as shown by H – C. Zhou et al, 2016 [155].

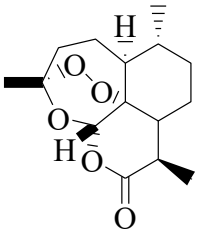
5.2 Selected photooxygenations for the synthesis of bioactive compounds

Singlet oxygen ($^1O_2$) is widely used in organic synthesis for the production of various bioactive components [156]. Molecular oxygen can be introduced into hydrocarbon substrates such as alkenes, leading to allylic alcohols, or 1, 3-dienes, leading to endoperoxides. Both of these synthetic transformations have been used as key-steps in a number of natural-product syntheses [157]. Ascaridole (**38**) is a naturally occurring compound that was first isolated from fresh *Chenopodium ambrosioides*. It has strong antihelmintics activity and also possesses mild anti-plasmodial activity *in-vitro* [158]. The [4+2] photocycloaddition of singlet oxygen to α-terpinene **37** to form ascaridole was first described by Schenck and Zeigler in 1944 [159]. Pure ascaridole **38** was described as a fragrant, freely mobile colorless oil [160]. When extracted from natural sources or impure, ascaridole has been described as a yellow oil instead. The main impurity found in α-terpinene is para-cymene (**39**), which is also formed as a byproduct during the [4+2] cycloaddition of α-terpinene [161]. The sesquiterpene endoperoxide artemisinin (**4**),

isolated from *Artemisia annua*, represents another natural remedy for the treatment of malaria. The semisynthetic production of artemisinin is based on a singlet oxygen reaction [69].



Ascaridole **38**



Artemisinin **4**

5.3 Aims

Due to the need for more sustainable synthesis methods, MOFs represent interesting materials for photooxygenations. There photophysical properties can be tuned on demand and their solid nature allows for easy recovery and recyclability. MOFs may thus be superior over traditional, soluble photosensitizers. Selected MOFs were studied as potential photosensitizers for the synthesis of ascaridole and artemisinin.

Most common current photooxygenation protocols involve a liquid media that carries α-terpinene and a soluble sensitizer. The isolation of pure ascaridole is often a challenge as complete removal of the sensitizer material is very difficult. Traditional purification techniques also frequently cause an increase in byproduct formation, particularly p-cymene as a breakdown product of ascaridole. The photooxygenation step in the synthesis of artemisinin results in complex reaction mixtures that often prevent crystallization of the pure product. Washing with organic solvents in order to remove the soluble photosensitizer likewise cause substantial material losses. To obtain sensitizer-free product and to simplify purification steps, solid supported photocatalysts have thus gained increasing attention.

5.4 Results and discussion

A number of different MOFs were provided by Dr. Christopher Richardson from the Faculty of Science, Medicine and Health at the University of Wollongong, NSW, Australia. Three samples of substandard grade MOFs (PCN_{224} FN_{12} 39-1, PCN_{222} FN_{13} 37-1 and MOF_{525} FN_{15} 31-1) and four high grade MOF samples (PCN-222, PCN-224, PCN-224' and PCN-222-Zr-MOF) were supplied to explore their suitability as sensitizers in selected photooxygenation reactions. Due to the small amounts of materials provided, the reactions were performed exclusively under batch conditions using a Rayonet chamber reactor and reaction progress was monitored by HPLC-, GC- or NMR-analyses.

5.4.1 Reaction setup

All photoreactions with MOFs were performed in a small (25 mL) Pyrex test tube with a small cold finger for circulating chilled water and a sidearm which was used as a gas inlet or outlet. Gas (compressed air or oxygen) was supplied through a FEP capillary tube. The reaction setup was placed inside a Rayonet chamber reactor equipped with 16 fluorescent tubes and an additional cooling fan (**Figure 5. 7**).

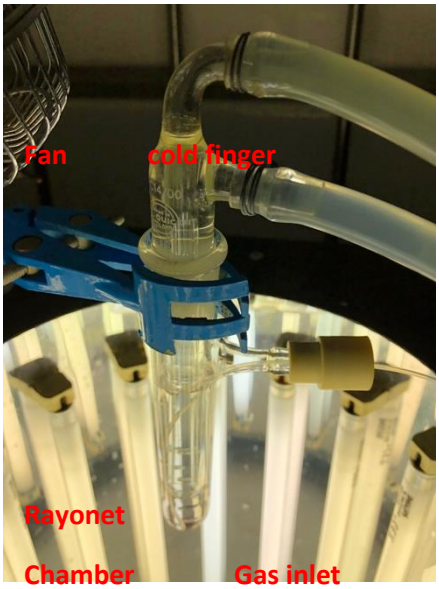


Figure 5. 7: Batch set-up for photooxygenation of **37** with MOFs.

5.4.2 Analytical methods

5.4.2.1 HPLC method

Samples from the photooxygenation reaction of α-terpinene with low-grade MOFs were subjected to HPLC analysis. The instrument used was a Shimadzu HPLC Nexera-i, Lax-2040C 3D, System number- 4-00326 equipped with a Phenomenex, Kinetex 2.6 µ XB-C18, 100F; 150 x 4.60 mm column (**Figure 5.8a**). Samples were analyzed using a detection wavelength of 242 nm and by keeping the oven temperature at 25°C and at 5000 psi pressure. Methanol:water (65:35 Vol%), filtered through 0.22 mm Millipore filtration apparatus and degassed by sonicating for 30 min, was used as mobile phase. Standards of α-terpinene (**37**), ascaridole (**38**) and p-cymene (**39**) were prepared as 1% solutions using methanol as diluent and filtration through a 0.22mm membrane filter. HPLC analyses of the standard solutions gave retention times of 4.2 min for α-terpinene (**37**), 7 min for ascaridole (**38**) and 9.9 min for p-cymene (**39**), respectively. α-Terpinene was of technical grade (≥89%) and subsequently contained

significant amounts of impurities that interfered with HPLC analysis. Previous GC-MS analysis identified p-cymene, α-phellandrene and cineole as main impurities (among others) [161]. It was assumed that these impurities did not interfere with the photoreaction. The molar absorptivity (ε) of ascaridole at 242 nm was determined to 132.2 $M^{-1}cm^{-1}$, 3267 $M^{-1}cm^{-1}$ for α-terpinene and 61 $M^{-1}cm^{-1}$ for p-cymene.

5.4.2.2 GC method

Samples (injection volume 1 µL) from the photooxygenation reaction of α-terpinene with high-grade MOFs were analyzed by gas chromatography (**Figure 5.8b**). An Agilent 7890A GC machine with Agilent software equipped with a 7683B auto-injector and an FID detector (300°C, gas makeup N_2 at 25 $mL.min^{-1}$). The column used was a Phenomenex Zebron ZB-5 (5% phenyl, 95% dimethylsiloxane) with an internal diameter of 0.25 mm and a film thickness of 0.25 µm. Helium was used as carrier gas at 24 psi and the injector temperature was set at 150°C. The initial oven temperature was 100°C (1 min holding), increasing to a final 230°C (5 min holding) at 25°C min^{-1}. The known impurities of α-terpinene were ignored when determining product compositions as they are known to not interfere with the photooxygenation [161].

(a) (b)

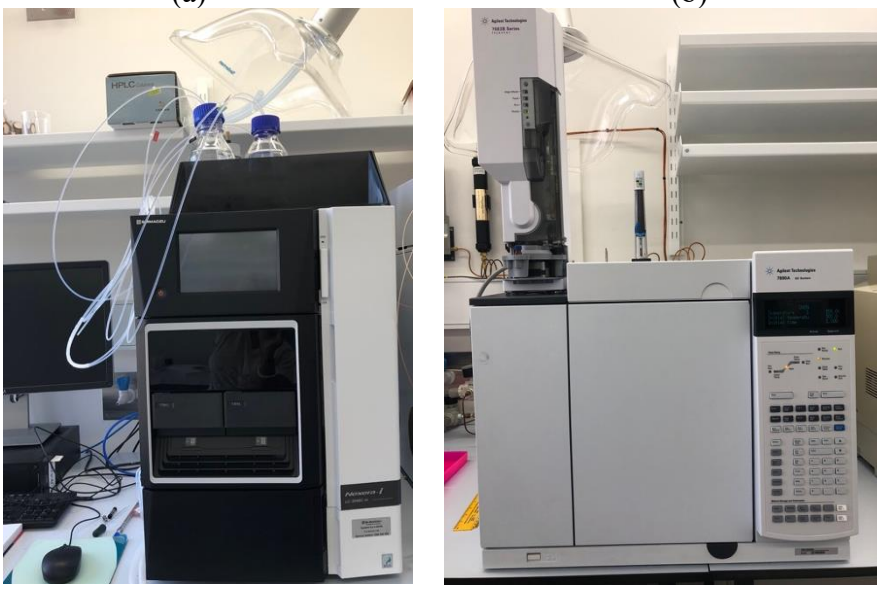
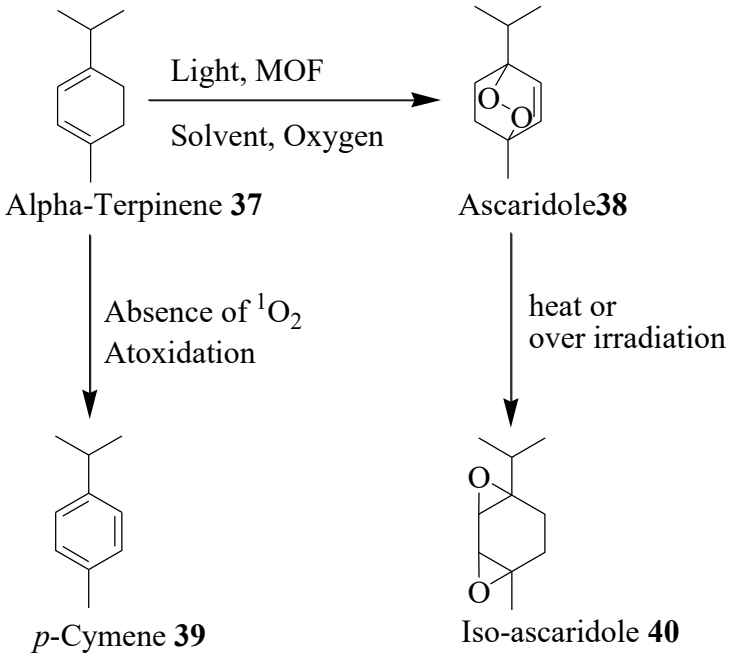


Figure 5.8: (a) HPLC machine and (b) gas chromatography machine.

5.4.3 Photooxygenation reactions of α-terpinene with low-grade MOFs (PCN_{224} FN_{12} 39-1, PCN_{222} FN_{13} 37-1 and MOF_{525} FN_{15} 31-1)

Preliminary photooxygenations were conducted with three sub-standard MOFs, i.e. PCN_{224} FN_{12} 39-1, PCN_{222} FN_{13} 37-1 and MOF_{525} FN_{15} 31-1, respectively. Photooxygenations of α-terpinene (**Scheme 5.1**) with PCN_{224} FN_{12} 39-1 for 40 min and using 419 nm light formed negligible amounts of **38** in only 6%. Similar photooxygenations conducted with PCN_{222} FN_{13} 37-1 for 40 min yielded only 8% of ascaridole, whereas 15% were obtained with MOF_{525} FN_{15} 31-1 (**Table 5.1**, **Figure 5.9**). The yields of ascaridole (**38**) are significantly lower than the reported batch yields that produce complete conversion of α-terpinene after just 10 min of irradiation with visible light in the presence of tetraphenylporphyrin or rose Bengal as sensitizers.



Scheme 5.1 Photooxygenation of α-terpinene **37** with MOFs to form ascaridole **38**; corresponding autoxidation of **37** to p-cymene **39** and thermal or photochemical isomerization of **38** to iso-ascaridole **40**.

Table 5.1: Conditions for Photoreaction of α-terpinene with low-grade MOFs under 419 nm light and HPLC analyzed data.

Expt.	MOFs	Irradiation	Time (min)	Ascaridole
	Type	Amount (mg)		38 (%)
MOF 1	PCN_{224} FN_{12} 39-1	0.0135	40	5.8
MOF 2	PCN_{222} FN_{13} 37-1	0.0081	40	8
MOF 3	MOF_{525} FN_{15} 31-1	0.0094	40	15

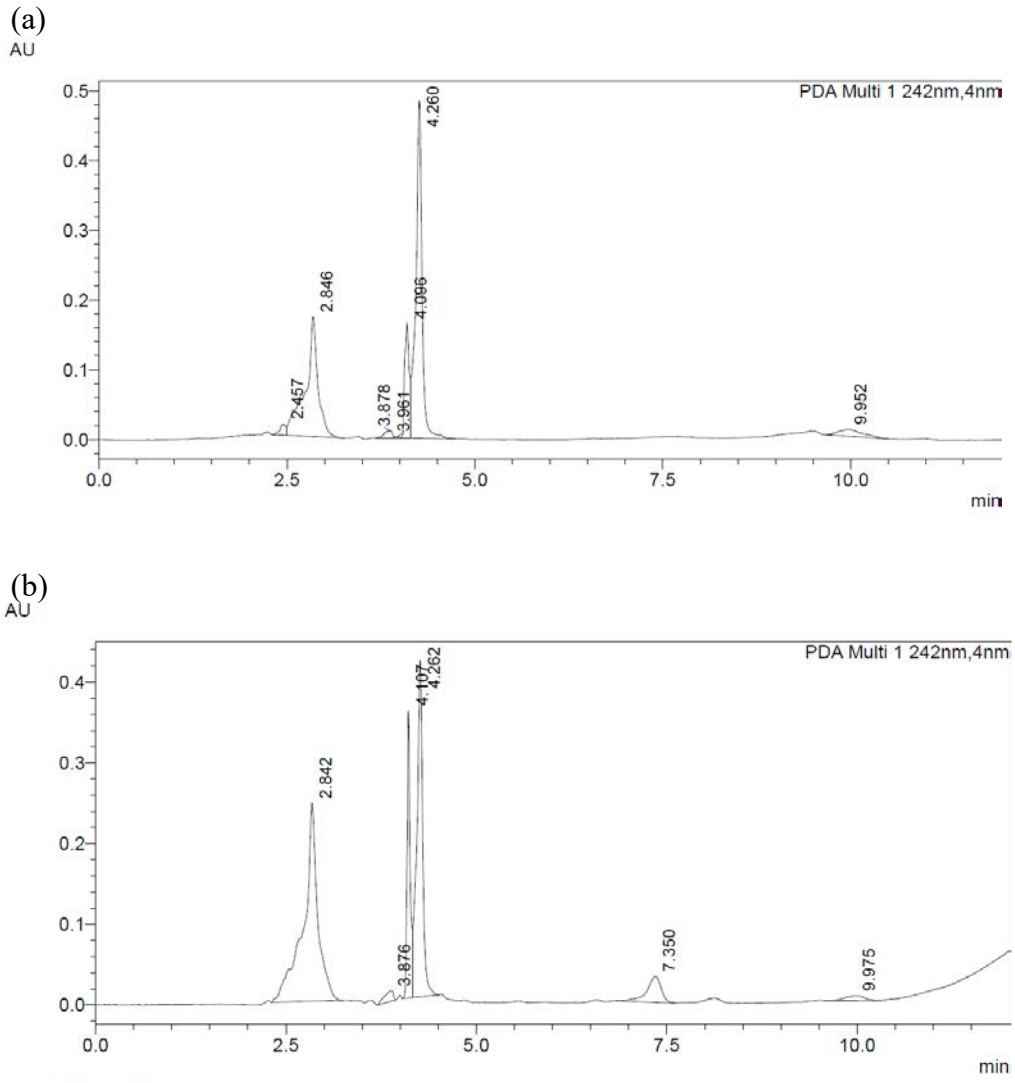


Figure 5.9: Typical chromatograms before and after photoreactions α-terpinene (**37**) with low-grade MOFs (a) 0 min sample and (b) 40 min sample.

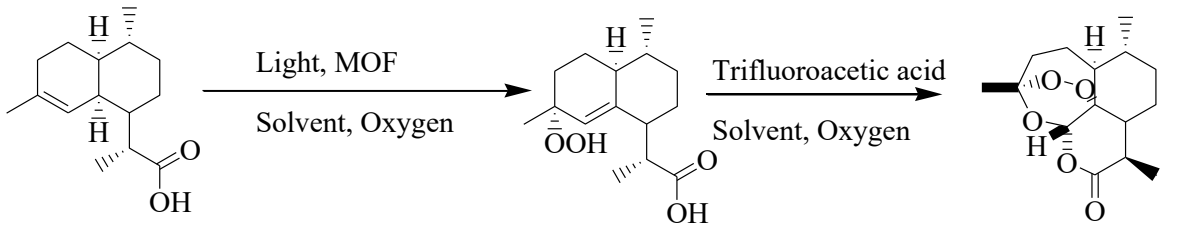
5.4.4 Attempted photooxygenation of dihydroartemisinic acid with low-grade MOFs (PCN_{224} FN_{12} 39-1, PCN_{222} FN_{13} 37-1 and MOF_{525} FN_{15} 31-1)

Photoreactions of dihydroartemisinic acid were also explored with the three sub-standard MOFs samples (**Scheme 5.2**, **Table 5.2**) under batch conditions, but were monitoring by NMR analysis.

Photooxygenation of DHAA (**1**) under visible light with PCN_{224} FN_{12} 39-1 remained unsuccessful and no conversion of **1** was observed even after 3 hours of irradiation. Likewise, photooxygenation of **1** in the presence of the same MOF but using 350 nm UVA light did not produce any detectable intermediate or final product after 5 h of irradiation. Irradiations in the

presence of $PCN_{222}FN_{13}$ 37-1 and $MOF_{525}FN_{15}$ 31-1 type with DHAA (**1**) with 350 nm UVA light produced trace amounts of artemisinin (**4**) after 3 h of irradiation. Prolonged irradiation for up to 10 h resulted in a number of byproducts. Longer irradiation times were considered too energy intensive, especially when compared to the known batch process that produced complete conversion after 3 h under visible light irradiation.

All the above three substandard MOFs ($PCN_{224}FN_{12}$ 39-1, $PCN_{222}FN_{13}$ 37-1 and $MOF_{525}FN_{15}$ 31-1) failed to produce singlet oxygen and drying of these MOFs might the reason. The dry MOFs lack porosity and crystallinity, thus, in the gas-liquid-solid reaction system the oxygen molecules failed to interact with photocatalytic site in MOF.



Dihydroartemisinic acid**1** | Hydroperoxide intermediate **3** | Artemisinin **4**

Scheme 5.2: Photoreaction of dihydroartemisinic acid 1 with MOFs.

Table 5.2: Reaction conditions used for photooxygenation of dihydroartemisinic acid (**1**).

Expt.	MOFs		Light	Irradiation time	**4**
	Type	Amount (mg)			
MOF 1	$PCN_{224}FN_{12}$ 39-1	4.4	Cool Visible	1h	–
MOF 2	$PCN_{224}FN_{12}$ 39-1	11.6	Cool Visible	3h	–
MOF 3	$PCN_{224}FN_{12}$ 39-1	8.7	UVA 350nm	5h	–
MOF 4	$PCN_{222}FN_{13}$ 37-1	5.1	UVA 350nm	10h	Traces
MOF 5	$MOF_{525}FN_{15}$ 31-1	5.9	UVA 350nm	10h	Traces

5.4.5 Photooxygenation reactions with high-grade MOFs (PCN-222 and PCN-224)

Photooxygenations of α-terpinene (**37**) were again explored in the mini-batch vessel with the two high-grade MOFs provided as well as other reference sensitizers. Next to PCN-222 and PCN-224, the well-known commercial solid sensitizer rose Bengal B bound on polystyrene (or RBBP) and free H_2TCPP and H_2TMeCPP were investigated. A standard solution of α-terpinene (0.2 mL) in DCM (20 mL) was used for each reaction (**Table 5.3**). The reaction mixture in the radiation tube was irradiated with 16 x 8 W cool white fluorescent tubes in a

chamber reactor (**Figure 5. 7**) for 2 to 3 hours. Initially, all reactions were performed for 2 hours to establish their conversion rates by GC analyses. The results were subsequently compared to analogue photoreactions using reference photosensitizers (RBBP, H_2TCPP and H_2TMeCPP).

After 2 hours of irradiation in the presence of PCN-222 or PCN-224, ascaridole (**38**) was formed in yields of 57% and 41%, respectively (**Figure 5.10** and **Table 5.4**). Although the conversion rates were encouraging, the increase in p-cymene (**39**) suggested competing autooxidation (**Scheme 5.1**) due to the lack of singlet oxygen formation. In comparison, the formation of other impurities was minimum. Isoascaridole (**40**) is known to form from ascaridole itself.

Table 5.3: Batch reaction condition for photooxygenation of α-Terpinene **37** with MOFs.

Photocatalysts	α-Terpinene 37	Light	Irradiation	Gas
PCN-222, PCN-224 Rose Bengal B bound on polystyrene (or RBBP), H_2TCPP, H_2TMeCPP	0.2mL taken in DCM 20mL for in each reaction with different photocatalysts	Cool white fluorescent tubes	2 – 3 hours	O_2 10sccm

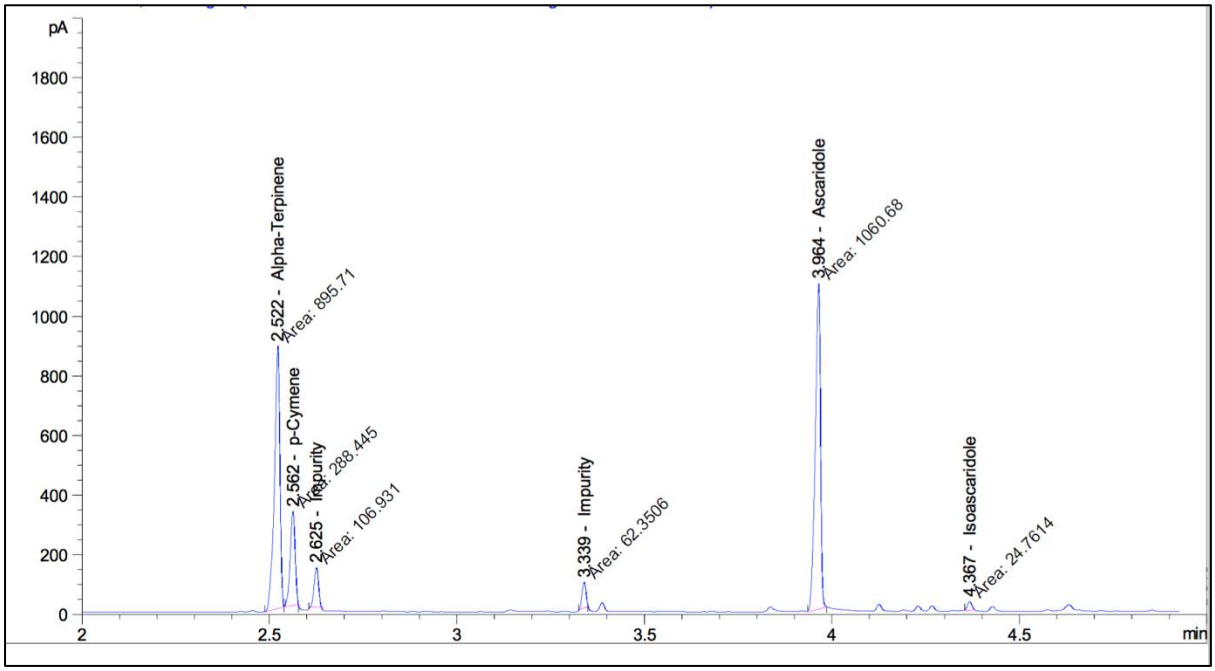


Figure 5.10: A typical chromatogram showing ascaridole **38**, p-cymene **39**, isoascaridole **40** and impurities after 2 hours photoirradiation of α-Terpinene **37** with MOF sample.

Table 5.4: Results of photoreaction of α-terpinene with MOFs after 2 hours irradiation in batch.

MOFs	Time (min)	α-terpinene **37**	Ascaridole **38**	p-cymene **39**	impurity
PCN-222	0	95%	0	2%	3%
	120	30%	57%	7%	4%
PCN-224	0	95%	0	2%	3%
	120	45%	41%	8%	5%

To determine the efficiency of both MOFs as photosensitizers, rose Bengal B bound on polystyrene (RBBP), [4,4',4",4'''-(porphine-5,10,15,20-tetraryl)tetrakis(benzoic acid)] (H_2TCPP) and 5,10,15,20-(4-carboxymethoxyphenyl)porphyrin (H_2TMeCPP) were investigated. Commercial RBBP is frequently used as a reference when designing novel solid-supported sensitizer. H_2TCPP was selected to represent 'leached' photosensitizer from the investigated MOFs, whereas H_2TMeCPP represented its soluble equivalent. Photoirradiation of α-terpinene (**37**) in the presence of all photosensitizers were subsequently conducted for 2 hours each. The results showed good conversions of α-terpinene of 75% for both MOFs (**Figure 5.11a**). In comparison, complete conversion was achieved with the established RBBP. However, when comparing the formation of ascaridole during the course of each photoreaction, the MOFs and RBBP showed similar trends and yielded 54%, 47% and 59% of **38**, respectively (**Figure 5.11b**). Free H_2TCPP remained completely insoluble in the reaction medium and subsequently showed only a low conversion of α-terpinene (**37**) of 25% and poor formation of ascaridole (**38**) of 12%. Leaching of H_2TCPP does therefore not (or only marginally) contribute to the observed photooxygenations of the MOF materials. In contrast, the partially soluble H_2TMeCPP gave almost complete conversion after 20 min and resulted in the formation of 88% of ascaridole.

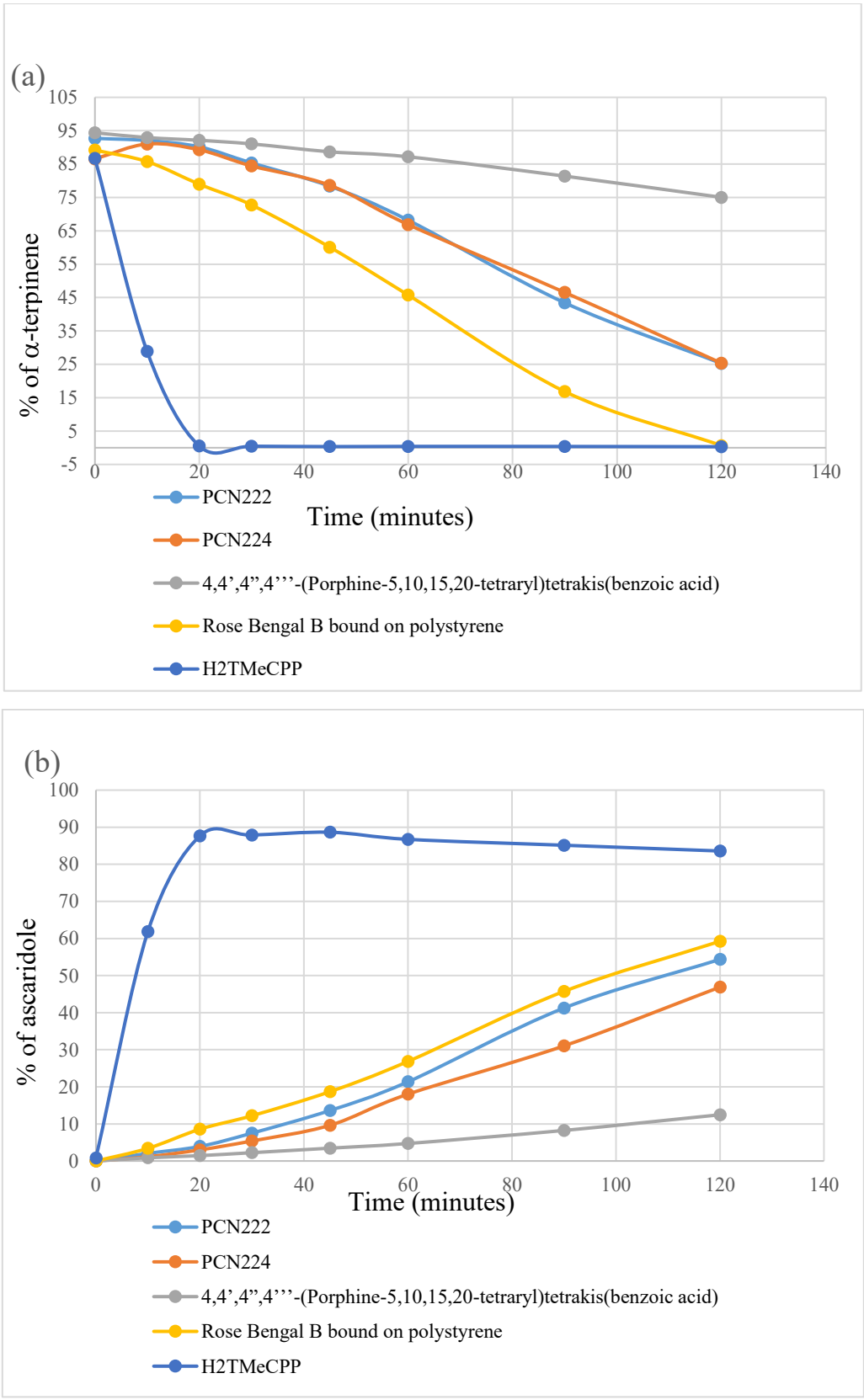


Figure 5.11: (a) Comparison of conversion of α-terpinene after photoreaction with MOFs and other photocatalysts; (b) Comparison of ascaridole yield after photoreaction of α-terpinene with MOFs and other photocatalysts.

A sensitizer-free photoreaction of α-terpinene was performed to evaluate the degree of autooxidation and to confirm the photoactivity of the MOFs for ascaridole production. After 2 hours of irradiation with visible light, only marginal changes in the chemical composition of the starting material were observed by GC analysis. While ascaridole was formed in <1%, the amount of p-cymene (**39**) increased from 2% to 6% due to autooxidation (**Figure 5.12**). Likewise, two dark reactions in the absence of light but with oxygen bubbling were performed with both, PCN222 and PCN224. A similar dark reaction was furthermore conducted in the absence of oxygen and nitrogen bubbling instead for 2 hours (**Table 5.5**). GC analyses of samples taken at 0 minutes and 120 minutes showed no notable changes in the chemical composition of the starting material with complete absence of any ascaridole. Likewise, the control photoreactions under nitrogen bubbling showed no changes in the chemical compositions although ascaridole was detected in one case in a neglectable amount of 2%. Hence, light activation was essential for singlet oxygen production and subsequent photooxygenations.

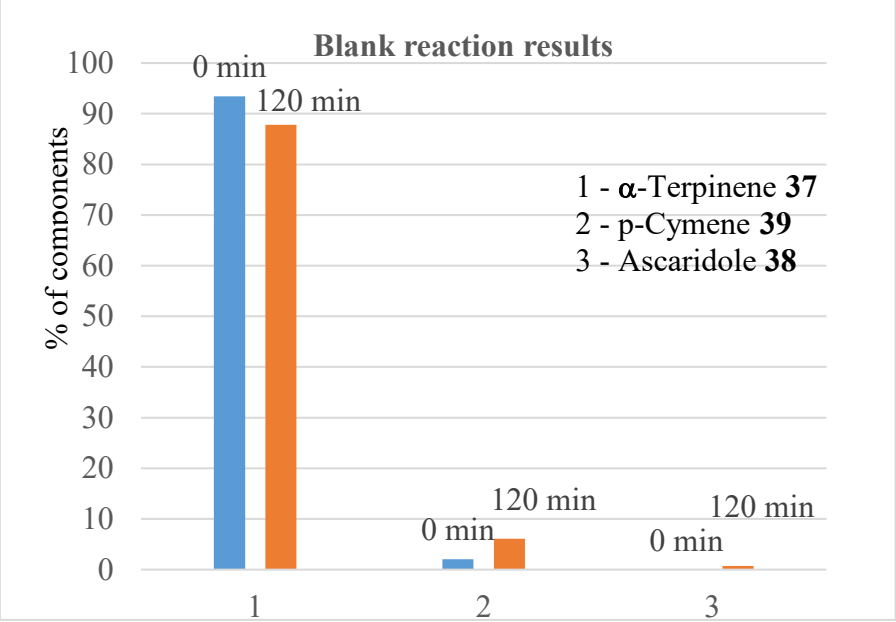


Figure 5.12: Results of Blank reaction of α-terpinene in absence of MOFs or any photocatalysts.

Table 5.5: Results from dark reactions of α-terpinene.

Dark reaction 1		**With PCN222**		**With PCN224**	
α-terpinene 0.2ml DCM 20 ml $N_2$10ml/min No light, no O_2	**Composition**	**0min**	**120min**	**0min**	**120min**
	37	85%	84%	87%	87%
	39	7%	8%	6%	5%
	Impurity	4%	4%	4%	4.%
	38	0	0	0	0
Dark reaction 2		**With PCN222**		**With PCN224**	
α-terpinene 0.2ml DCM 20 ml N_2 10ml/min 8x16W visible light	**Composition**	**0min**	**120min**	**0min**	**120min**
	37	93%	91%	92%	92%
	39	4%	3%	4%	3%
	Impurity	4%	4%	4%	4%
	38	0	2 %	0	2%
Dark reaction 3		**With PCN222**		**With PCN224**	
α-terpinene 0.2ml DCM 20 ml O_2 10ml/min No light MOF used	**Composition**	**0min**	**120min**	**0min**	**120min**
	37	93%	93%	95%	94%
	39	3%	3%	2%	2%
	Impurity	4%	3%	3%	4%
	38	0	0	0	0

As the MOFs were supplied in the form of suspensions, the exact amounts used in each reaction were estimated to approximate 8-10 mg per 1 mL of suspension. To establish the necessary reaction time for complete conversion, batch photoreactions of α-terpinene (**37**) were again performed for a longer period of time (3.5 hours) and by adding more concentrated suspensions of MOFs. In all cases, complete conversion of starting material was achieved within 210 minutes. The highest yields (by GC) of ascaridole (**38**) for both MOFs were found after about 180 minutes with 69% for PCN222 and 66% for PCN224, respectively (**Figure 5.13**). Further irradiation up to 210 minutes caused a drop in ascaridole in favor of the formation of isoascaridole (**40**). This observation suggests photoisomerization of ascaridole (**38**) to isoascaridole (**40**) during prolonged irradiation [161]. There was a slow and steady increase in the amount of p-cymene (**39**), indicating some autoxidation due to the constant purging with oxygen. The triphasic gas-liquid-solid system appears unable to convert all oxygen supplied into $^1O_2$.

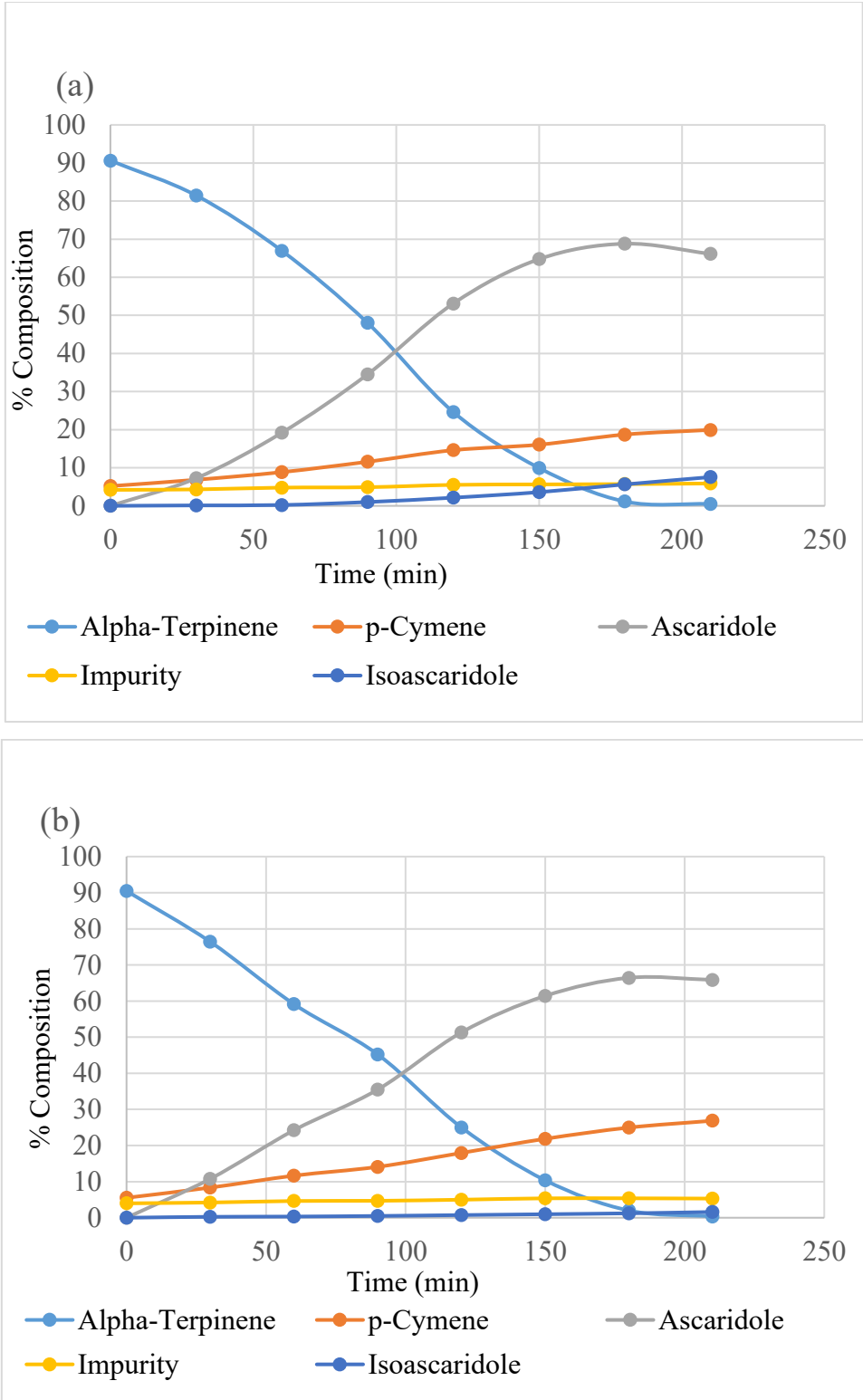


Figure 5.13: Results of 3.5h photoreaction of (a) α-terpinene vs PCN222 and (b) α-terpinene vs PCN224.

5.4.5.1 Leaching studies for PCN-222 and PCN-224

All previous experiments showed satisfactory to complete transformations of α-terpinene under photooxygenation conditions. However, the possibility of leaching of porphyrins from the excited MOFs into the solution could not be ruled out. The mechanical stability of the MOFs was furthermore uncertain. Leaching tests were thus conducted with PCN-222, PCN-224 and free H_2TCPP as a reference. In methanol, H_2TCPP shows an absorption maximum at 415 nm (Soret band) with a shoulder at 396 nm [162] and may thus be photoactivated under the previously used irradiation conditions.

Leaching tests were performed by continuously stirring suspension of MOFs and H_2TCPP in DCM for 3 hours at room temperature in the dark. Both MOFs and H_2TCPP were found insoluble in DCM. The suspensions were subsequently filtered and the filtrates were analyzed by UV-visible spectroscopy in the range of 350-650 nm at 25°C (Shimadzu UV-1800 with 1 cm quartz cell and UVProbe software). The UV-spectra obtained suggested that some PCN224 had leached into the solvent, whereas PCN222 and H_2TCPP remained largely stable or insoluble (**Figure 5.14**).

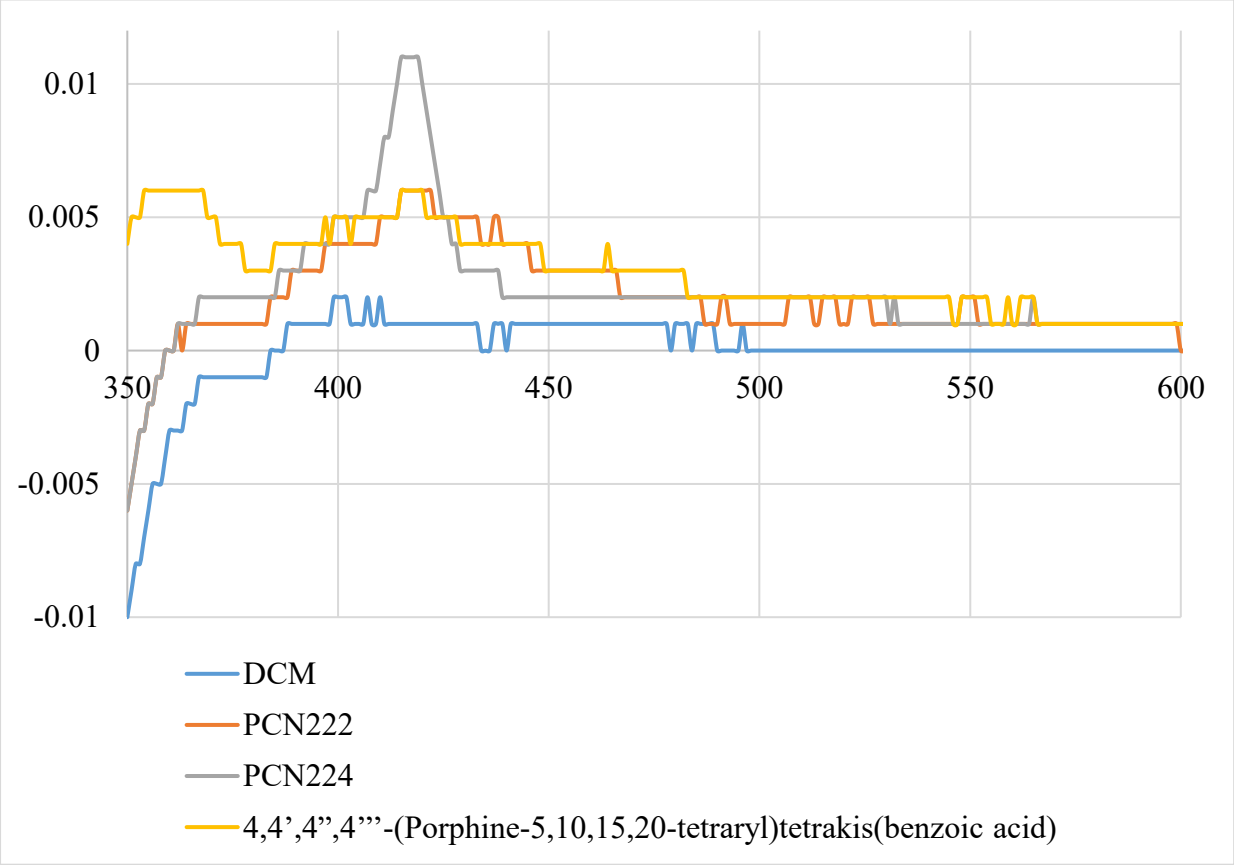


Figure 5.14: UV-visible spectra of filtrates from MOFs and H_2TCPP suspensions.

5.4.5.2 Recyclability tests for PCN-222 and PCN224

As the MOFs were largely insoluble in the reaction media it was possible to investigate their recyclability and reusability. The recovery protocol involved centrifugation of the MOF suspension for 2 minutes at 100 rpm, careful removal of the liquid fraction and washing of the residue with fresh dichloromethane. The protocol was repeated five times to remove any reagents from the previously conducted photoreactions. A recovery of 80-90% of the initially used MOF was proposed for each cycle. The recovered MOFs were subsequently used to sensitize the photooxygenation of α-terpinene (**Table 5.6**).

Table 5.6: Results of photoreactions of α-terpinene with recycled MOFs PCN-222 and PCN-224 after 2 hours of irradiation with visible light.

MOFs	Cycle	α-terpinene 37	ascaridole 38	p-cymene 39	isoascaridole 40
PCN-222	1	29%	47%	16%	2%
	2	31%	45%	16%	3%
	3	0.6%	39%	52%	2%
PCN-224	1	0.5%	67%	25%	2%
	2	0.4%	68%	24%	3%

Reactions with once, twice or three-times recycled PCN-222 showed similar conversions of α-terpinene if compared to the initial reaction with fresh PCN-222. However, a small decrease in ascaridole yield from 47% to 45% and finally 39% was noted with each cycle. This indicates that PCN-222 was able to retain its general photoactivity. However, a purplish coloring of the final reaction mixture was noted at the end of each reaction (**Figure 5.15a-b**). This may suggest photoinduced leaching or, more likely, photobleaching of the porphyrin linker and consequently breakdown of the MOF. Photobleaching of porphyrins have indeed been widely reported earlier [163]. Further material losses during the extensive washing and centrifugation procedure may have also reduced the amount of available MOF for the next photoreaction. Interestingly, the third recycled PCN-222 cycle gave an almost complete conversion and a dramatic increase in p-cymene (**39**) to 52%. This suggests that the available active MOF amount had dropped under a critical threshold. Thermal autooxidation reactions thus dominated this recycling experiment. In contrast, recycled PCN-224 showed complete conversions for both reusing cycles. Strong colorization was again observed (**Figure 5.15c-d**), suggesting excessive leaching or photodegradation of the MOF.

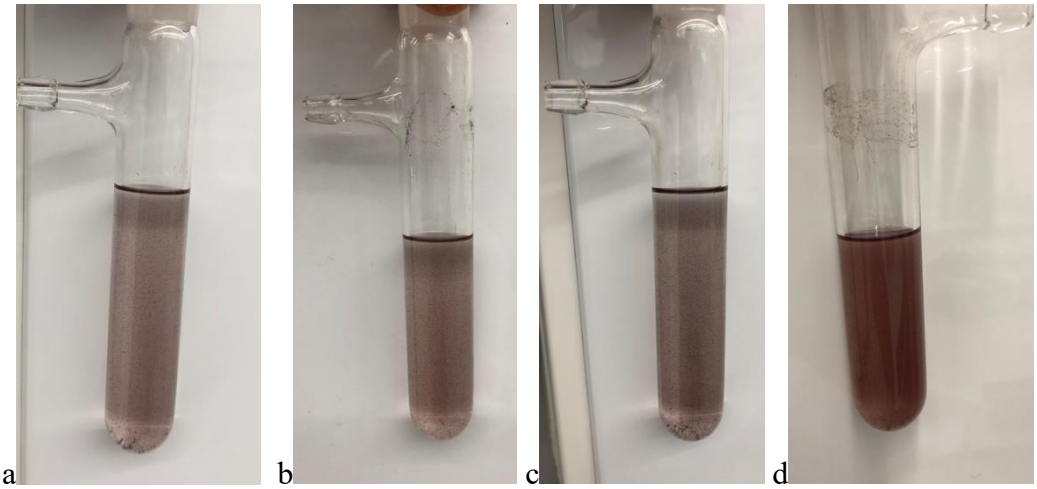
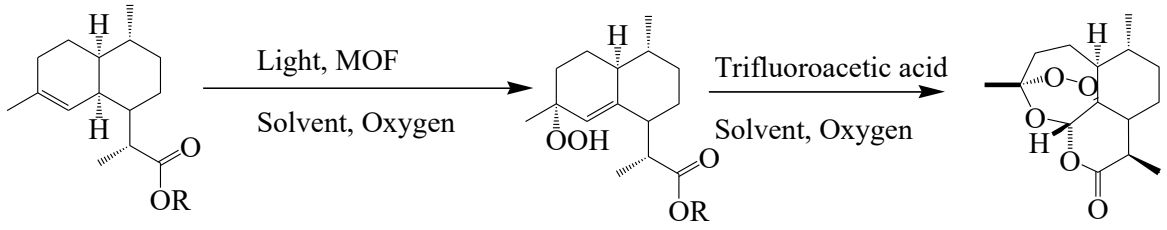


Figure 5.15: (a) Recycled PCN-222 before photoirradiation; (b) Recycled PCN-222 after photoirradiation; (c) Recycled PCN-224 before photoirradiation; (d) Recycled PCN-224 after photoirradiation.

5.4.6 Attempted photooxygenation of dihydroartemisinic acid 1 with high-grade MOFs (PCN-224 and PCN-222)

Two different batch photoreactions were performed with 0.169 mmol of dihydroartemisinic acid (DHAA, **1**) in the presence of PCN222 or PCN224, under oxygen bubbling and with visible light for 5 hours (**Scheme 5.3**). NMR analysis of the final crude reaction mixture obtained with PCN-222 showed no changes in the starting material and thus no traces of the desired products or intermediates. Upon the addition of the MOF to the solvent containing DHAA prior to irradiation, the solution changed color to green. This indicated a thermal breakdown of the MOF, probably caused by the acidic nature of DHAA. Carboxylic acids are indeed known to interact with porphyrins and to consequently change their absorption behavior [164]. Reaction in presence of PCN-224 resulted in formation of trace amounts of artemisinin (**4**) along with other byproducts (**Figure 5.16**). Most of the starting material, however, remained unchanged. This finding again indicates very poor singlet oxygen generation, potentially caused by the deactivation of PCN-224 by the acidic DHAA. Alternatively, the significantly larger size of DHAA, if compared to the much smaller α-terpinene, may have prevented inclusion into or aggregation onto the MOF, preventing oxygenation by any $^1O_2$ formed.



R=H DHAA **1**
R=$COOC_2H_5$ mixed anhydride of DHAA **2**

R=H Hydroperoxide intermediate **3**
R=$COOC_2H_5$ Linear hydroperoxide **17**

Artemisinin **4**

Scheme 5.3: Photoreaction scheme of DHAA **1** and mixed anhydride of DHAA **2**.

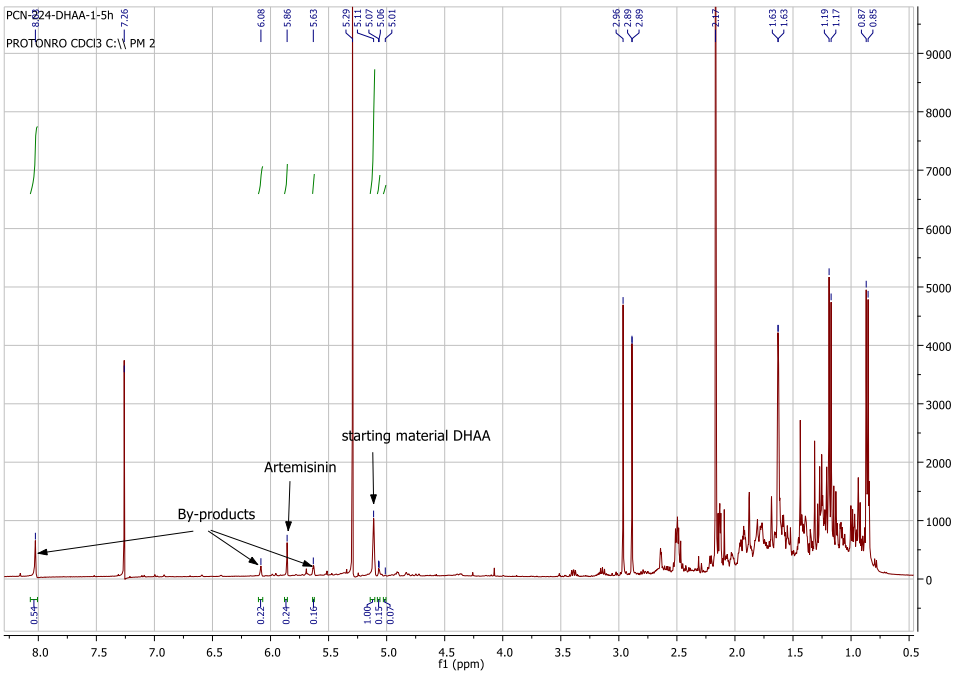


Figure 5.16: NMR after 5 hours photoirradiation of DHAA 1 with PCN-224.

5.4.7 Attempted Photooxygenation of the mixed anhydride of dihydroartemisinic acid 2 with high-grade MOFs (PCN-224 and PCN-222)

To investigate if the acidic nature of DHAA had caused the loss of photooxygenation efficiency, its mixed anhydride was selected as starting material. Two different batch photoreactions were consequently performed with 0.129 mmol of the mixed anhydride of DHAA in the presence of either PCN222 or PCN224 (**Scheme 5.3**). All other conditions were identical to the DHAA reactions. However, NMR analysis of the crude irradiation products showed no changes of the starting material (**Table 5.7**). Steric reasons, rather than the acidic reaction media, may thus be largely responsible for the lack of any photo reactivity. α-Terpinene is also known to undergo photooxygenation rapidly and is thus often used as a model

reaction when investigating new photosensitizers. In contrast, the photooxygenation of DHAA or its mixed anhydride may be much slower and may thus require exhaustive irradiation times.

Table 5.7: Reaction conditions for photooxygenation of **1** and **2** with MOFs.

Solvent	Photocatalysts	Light	Irradiation	Gas	4
20mL dichloromethane	PCN-222 or PCN-224	Cool white fluorescent tubes	5 hours	O_2 10sccm	nil

5.4.8 Photooxygenation of α-terpinene with PCN-224' and PCN-222-Zr-MOF

The latest obtained MOFs samples PCN-224' and PCN-222-Zr-MOF were also investigated using α-terpinene in a mini-batch vessel following the previous reaction conditions (**Table 5.3**). The MOF suspension aliquot remained stable in the reaction media without showing any color. After irradiation with 16 x 8W cool white fluorescent tubes for 3.5 hours, GC analysis of the sample showed 24% of ascaridole **38** with 42% of starting material **37** with PCN-224' (**Figure 5. 17**). The formation of p-cymene **39** in 26% indicates insufficient singlet oxygen generation by the MOF thus favoring autoxidation of **37**.

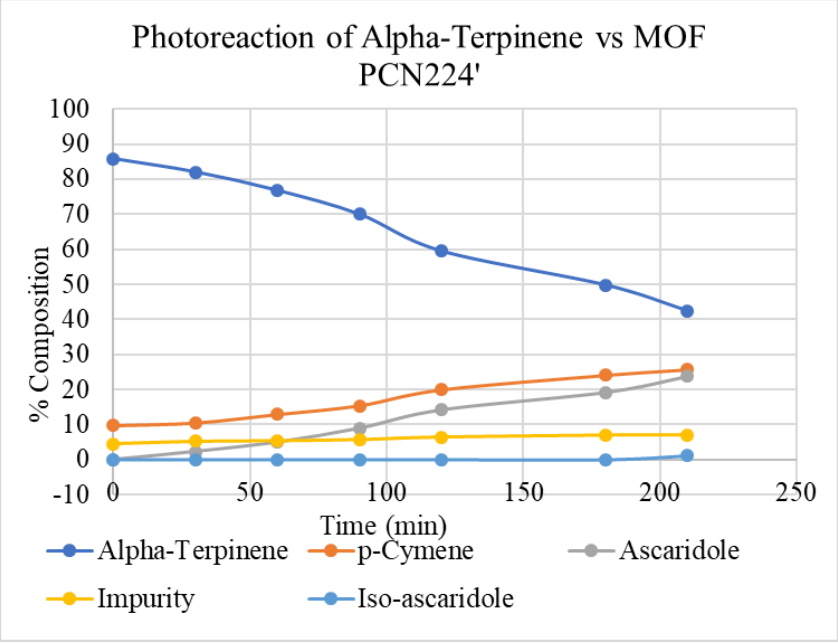


Figure 5. 17: Photooxygenation of α-terpinene with PCN-224'.

Photooxygenation of **37** with PCN-222-Zr-MOF generated 46% of ascaridole after 3.5 hours leaving 29% of α-terpinene in the reaction media. In this case, the p-cymene **39** amount was

found at 20% (**Figure 5. 18**). The MOF sample also remained stable, however, during the irradiation, the reaction solution appeared slightly greenish in color.

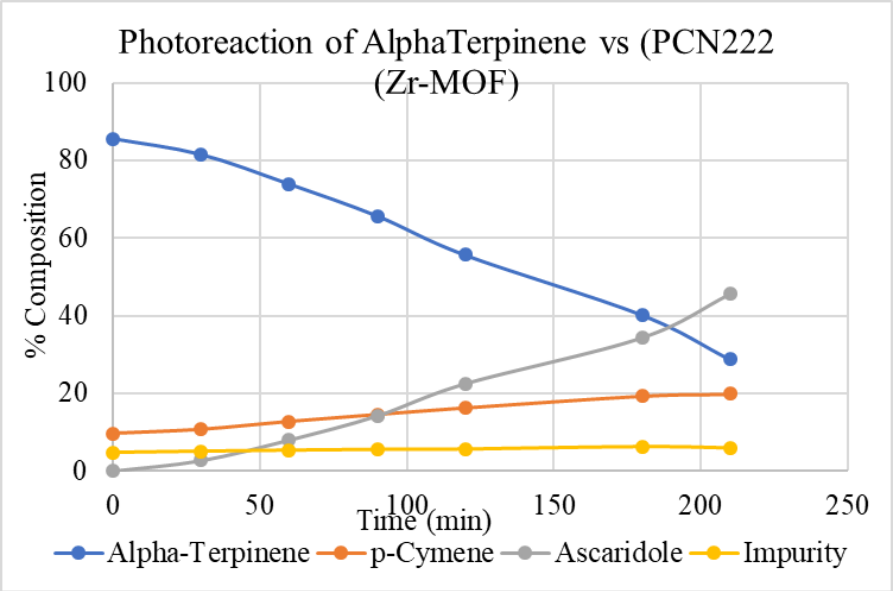
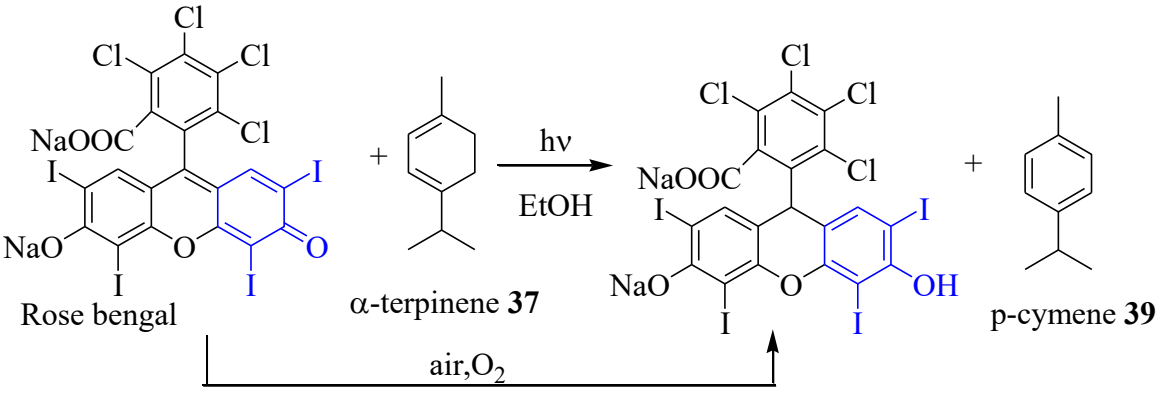


Figure 5. 18: Photooxygenation of α-terpinene with PCN-222-Zr-MOF.

Alternatively, the formation of p-cymene may be caused by photobleaching of the sensitizer. For example, rose bengal bleaching under UV-irradiation was linked to the production of **39** from α-terpinene (**Scheme 5. 4**). In polar solvents, abstraction of hydrogen from α-terpinene reduces the arylxanthene skeleton of rose bengal [165]. Subsequently, the significant increase in p-cymene formation may be attributed to photobleaching of the porphyrins incorporated in the MOF.



Scheme 5. 4: Photobleaching of rose bengal during photooxygenation of α-terpinene leading to p-cymene formation.

5.5 Conclusion

The applications of MOFs PCN-222, PCN-224, PCN-224' and PCN-222-Zr-MOF to the photooxygenation of α-terpinene showed good conversions and efficient ascaridole generation. Isoascaridole formation was found to be small within the first 2 hours of irradiation, but increased upon prolonged irradiation. The formation of p-cymene via autooxidation depended on the chosen MOF, indicating differences in the ability to generate singlet oxygen and poor mixing of the gas-liquid-solid media and hence mass transfer in the simplified mini-batch setup. Recovery tests for both MOFs (PCN-222 and PCN-224) resulted in coloring of the reaction media, presumably due to partial photobleaching of the porphyrin linkers and thus breakdown of the MOF. The results obtained suggest that MOFs may function as novel sensitizers in photooxygenation reactions. However, high-purity MOFs and a more advanced setup are needed for future studies.

Chapter 6: Summary and Outlook

6. Summary and Outlook

6.1 Summary

The synthesis of artemisinin through photooxygenation of dihydroartemisinic acid (DHAA) was demonstrated under both, tandem in series flow and one-pot continuous flow conditions. Choosing an acetone-methylene blue combination and compressed air as oxygen source, an acceptable isolated yield of artemisinin of 24% was achieved with a residence time of just 40 minutes under tandem continuous flow conditions. In contrast, the two-step batch reaction resulted in a 28% isolated yield after 3.5 hours of irradiation followed by 2 hours of thermal catalysis. When switching to dichloromethane and methylene blue, an improved isolated yield of 47% was obtained for the batch reaction, while the tandem flow reaction conducted with a residence time of 25 minutes resulted in 39% of artemisinin (by NMR) that could not be successfully isolated. Overall, the tandem flow reactions suffered from constant pressure drops and thus irregular slug-flows, which subsequently caused large deviations in conversion rates. In addition, the complete consumption of oxygen during the photooxygenation step caused a subsequent deficiency of oxygen in the coupled thermal loop, hence favoring side reactions that lead to increased amounts of the known six-membered lactone by-product. In addition, the reproducibility of tandem reactions was found challenging and thus, a one-pot continuous flow regime was adapted to avoid complicated flow management.

Artemisinin was synthesized by a one-pot continuous flow reaction using a dichloromethane-methylene blue combination, compressed air and a residence time of 88 minutes in an isolated yield of 22%. Under these conditions, however, a small droplet flow was formed in the capillary. A uniform slug-flow formation was achieved using a 5 psi back-pressure-regulator and subsequently, artemisinin was formed in 45% with a residence time of 37 minutes. In the absence of the back-pressure-regulator, artemisinin was determined in an amount of 39% (by NMR) with a slightly higher residence time of 40 minutes. In both cases, however, artemisinin could not be isolated in a pure form. The one-pot protocol favored the immediate formation of oxygenated side products such as a five-membered lactone ring. Replacing compressed air with pure oxygen at higher flow rate generated 52% of artemisinin, but the formation of numerous by-products again prevented its isolation in pure form. In comparison, a remarkably high isolated yield of 50% was obtained under batch conditions with the same solvent-sensitizer combination after 2 hours of irradiation. Overall, the isolation and purification of artemisinin from the often-complex reaction mixture remained the major hurdle.

The solar flow synthesis of artemisinin was realized for the first time, but gave poor yields. Due to the very short residence times in the available flow reactor, recirculation of the reaction mixture was required. Nevertheless, a tandem solar flow reaction with an isopropanol-rose Bengal combination showed 16% of artemisinin by NMR analysis. The lack of available oxygen in the coupled thermal flow reactor, however, led to the formation of major by-products.

To further suppress by-product formation, the artemisinin synthesis was investigated using the mixed-anhydride of DHAA as a starting material. Using a dichloromethane-methylene blue combination, the one-pot batch synthesis of artemisinin produced a 30% isolated yield. In contrast, the corresponding flow reaction furnished less than 25% of the desired product (by NMR). A flow reaction performed with pure oxygen, however, showed 55% of artemisinin by NMR analysis but could not be isolated. Overall, the ratio of selected by-products shifted under both, flow and batch conditions.

Photooxygenation reactions of three different allylic alcohols were also investigated under flow conditions. In the initial flow reactor-1, a complete conversion of allylic alcohol 4-methylpent-3-en-2-ol was realized with a flow rate of 5 mL/min (13 min residence time) and using a 5 psi back-pressure-regulator, compressed air and a dichloromethane-TPP combination. In contrast, the corresponding batch reaction required 6 hours to achieve complete conversion. A flow reaction with pure oxygen in flow reactor-1 showed only 22% conversion, but this was due to a leakage from the gas cylinder that resulted in pressure problems and an uneven slug-flow. Further reactions with oxygen were thus not be performed. Although the use of dichloromethane-methylene blue showed good conversions, the reactions suffered from extreme mass balance losses. Using the second in-house built flow reactor-2 gave an 85% conversion of 4-methylpent-3-en-2-ol after 11 minutes with air, but only a 56% conversion after 12 minutes using pure oxygen. The in-house built second flow reactor-2 showed reasonable photochemical conversions of 2, 5-dimethylhex-4-en-3-ol of 86% (with air) and 21% (with pure oxygen) with a residence time of 11 minutes. Conversions of 2, 6-dimethylhept-2-en-4-ol in the same reactor were 44% (with air) after 6 minutes and 43% (with pure oxygen) after 11 minutes. The reason for the unexpected drops in conversions when using oxygen remained unclear but may be linked to unnoticed gas supply issues in the new Science Place building. To avoid complex inert atmosphere conditions, a series of trioxanes was synthesized using different carbonyl compounds and indium triflate or boron trifluoride hydrate as catalysts. All compounds were obtained as very clean crude products as confirmed by NMR analyses. Further purification was unsuccessful and was linked to the instability of the trioxane

skeleton towards aqueous workup (to remove excess carbonyl compound) and chromatographic separation. Four new compounds were synthesized using different aromatic aldehydes but yields remained low with 9-27% and purification remained a major hurdle.

To evaluate the use of metal-organic-frameworks (MOFs) for photooxygenations, the photoreactions of DHAA, its mixed-anhydride and α-Terpinene were investigated under batch conditions. Supplied samples of PCN_{224} FN_{12} 39-1, PCN_{222} FN_{13} 37-1 and MOF_{525} FN_{15} 31-1 were found to be of poor quality (notification by the supplier at the end of the study) and subsequently, photooxygenations of DHAA and α-terpinene remained largely unsuccessful with these materials. The second batch of supplied MOFs, i.e. PCN-222 and PCN-224, showed almost complete conversion of α-Terpinene after 3 hours of irradiation and gave yields of Ascaridole of 69% and 66%, respectively. However, the photooxygenations of DHAA and the mixed-anhydride of DHAA were unsuccessful even with these materials. The third batch of MOFs i.e. PCN-224' and PCN-222-Zr-MOF showed moderate conversion of α-terpinene and yielded 24% and 46% ascaridole respectively.

6.2 Outlook

The in-house built flow reactors offered a better thermal control and efficient mixing for biphasic gas-liquid photooxygenations if compared to batch reactors that need additional cooling systems to control the heat generation and high dilution. The surface to volume ratio in flow reactor is much higher which leads to efficient mixing of reactants, thus resulting in quick conversion of the starting material. In the flow reactor isolation of potential explosive intermediates is not required because the intermediate can be directly allowed to flow through the second thermal reactor and final product can be obtained from the outlet. Investigations done in this research showed that for artemisinin synthesis in-stead of using series of flow reactor a one-pot flow reaction can be done by combining all reagents of two-step protocol and just by injecting once artemisinin can be synthesized 'on-site' and 'on-demand' within very short period of time and with minimum equipment. Experimentally it was shown that with 10 minutes residence time 17mmol per day of productivity can be obtained from the capillary flow reactor – 1, but in overall the conversion remained poor due to shorter residence time. Also, the flow reactor -1could not be operated by attaching a back-pressure regulator which could led to proper gas-liquid mixing and could thus improve conversion. However, both the conversion and productivity can be increased by increasing the reactor capillary volume that may require another parallel flow setup involving a second light source. This will increase the residence time and flow reactions can be operated at higher flow rates in presence of a back-

pressure regulator. The final product purification by recrystallization also remained challenging. Due to the presence of many by-products artemisinin could not be isolated in most of the cases. To obtain completely by-products free and photosensitizer free artemisinin preparative HPLC can serve as a more efficient method for purification.

Also, for the photooxygenation of allylic alcohols flow reactors 1 and 2 offer much faster reactions than the conventional methods reported. On the other hand, the use of indium triflate or boron trifluoride hydrate enabled the trioxane synthesis much easier in batch with high selectivity. These two combined approaches offer a comparatively simpler method for potential alternative antimalarial trioxane synthesis. Future work can be done on a two-step continuous flow synthesis of trioxane compounds by attaching a second thermal flow reactor at the end of photo flow reactor and by injecting the catalyst solution via a T-mixer. To make the in-series flow reaction successful, photoreactions of allylic alcohols should be first realized in the presence of carbonyl compounds that are required in the second step. Also, apart from the carbonyl compounds used in this project, additional cyclic aldehydes or ketones can be used to produce spiro bi-cyclic trioxanes. The purification of the synthesized trioxanes remained unsuccessful by combi-flash column chromatography and conventional column chromatography. These methods neither removed excess carbonyl compounds nor the sensitizer TPP. Also, the adapted work-up procedure was found to cause complete destruction of the product. For future work, preparative TLC or HPLC can be adapted for purification purpose that can give TPP free products.

The metal-organic-frameworks (MOFs) supplied for this project were of unknown quality and therefore, the recyclability of MOFs samples could not be performed. The utilization of PCN-222 and PCN-224 for the photooxygenation of α-terpinene should be further studied in the future. Since the reactions include three phases (gas, liquid and solid) the photooxygenation could also be conducted under solvent free conditions, e.g. in polymer matrix. This can ensure clean product formation without mechanically disturbing the MOFs.

Chapter 7:

Experimental Part

7. Experimental Part

7.1 General Procedure

7.1.1 Solvents and reagents

All solvents and reagents were commercially available (Sigma-Aldrich or Alfa Aesar) and were used without purification. Dihydroartemisinic acid (100g) was donated by Zagaya. Metal organic frameworks samples were sent by Dr. Christopher Richardson (MRACI CCHEM), Senior Lecturer, School of Chemistry, Faculty of Science, Medicine and Health, University of Wollongong NSW, Australia.

7.1.2 Photochemical Equipment

Photoreactors:

Batch experiments were carried out in a Rayonet RPR-200 photochemical chamber reactor (Southern New England Ultraviolet Company, USA) equipped with 16 × 8 W fluorescent tubes. In-house flow setups were used for both in-door as well as outdoor flow reactions.

Glassware:

All reactions were performed in Pyrex glassware.

7.1.3 Analytical methods

IR:

Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or thin films, and were recorded in the range 600 cm^{-1} - 4000 cm^{-1}. IR peaks are listed in wavenumbers ($\tilde{\nu}$; in cm^{-1}).

NMR:

NMR facilities were used at JCU in Townsville and at the biomolecular analysis laboratory at AIMS. At JCU, NMR spectra were recorded on an Oxford 300 (^{1}H: 300 MHz and ^{13}C: 75 MHz) with a ^{UNITY}INOVA system console using the Varian Software VnmrJ program and Bruker 400 AscendTM (^{1}H: 400 MHz and ^{13}C: 100 MHz). At AIMS, NMR spectra were recorded on a Bruker Avance 300 UltrashieldTM (^{1}H: 300 MHz and ^{13}C: 75 MHz) using the MestReNova v5.3.2-4936 software. Data was acquired using TopSpin 2.1 and 3.0, respectively. Residual solvent peaks served as an internal standard and samples were prepared in $CDCl_3$ (δ = 7.26/77.3 ppm) and acetone-d_6 (δ = 2.09/30.6 ppm). Solvent peaks and impurities were compared with literature values [H. E. Gottlieb, V. Kotlyar, A. Nudelman J. Org. Chem. 1997, 62, 7512].

7.1.4 Chromatographic method

Separations:

Column chromatography was carried out in Pyrex glass columns using Scharlan silica gel 60 (particle size 0.06-0.2 nm) 70-230 mesh ASTM. Mixtures of ethyl acetate and and *n*-hexane were used as mobile phase.

Or flash column chromatography by fraction collector CombiFlash® Rf+ was used for purification purpose. The process operates under high air purge through flash column and mobile phase (ethyl acetate and *n*-hexane) elution can be isocratic or gradient. The system detects UV spectra in real time - during peak elution and the desired fractions can be collected automatically.

TLC:

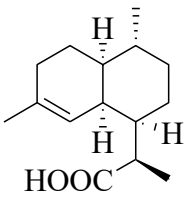
Thin layer chromatography was performed in glass jars on Macherey-Nagel polygram sil G/UV_{254}. Mixtures of ethyl acetate and cyclohexane or ethyl acetate and *n*-hexane were used as mobile phase.

GC:

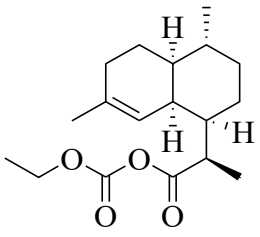
Gas chromatography samples were analyzed on an Agilent 7890A gas chromatograph using the Agilent software, and 7683B auto-injector. The column used during the investigations was a Phenomenex Zebron ZB-5 low polarity (5% phenyl, 95% dimethylsiloxane) column (0.25 mm ID × 0.25 µm film thickness).

7.2 Synthesis of Starting materials

7.2.1 Synthesis of mixed anhydride of DHAA or dihydroarteannuin B acid, ethyl mixed carbonate (2)



1



2

0.4442g (0.4ml) ethyl chloroformate was added dropwise within 5 min. to a stirred solution of 1g (4.232mmol) DHAA **1** and 0.7g potassium carbonate in 50mL dichloromethane in an ice bath. After addition stirring was continued for 30min.

The mixture was then washed thrice with water (3 x 50 mL) and dried over anhydrous magnesium sulphate. The solution was then concentrated to dryness at reduced pressure and 1.2329g of an oily residue **2** was obtained that solidified after storing in fridge. The crude yield was 94.489% and was used as such for further photoreactions.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 7H), 5.07 (s, 21H), 4.31 (q, J = 7.1 Hz, 42H), 2.63 – 2.53 (m, 21H), 2.54 – 2.45 (m, 28H), 2.01 – 1.90 (m, 31H), 1.81 (s, 28H), 1.67 (s, 23H), 1.62 (s, 84H), 1.58 (s, 17H), 1.53 (d, J = 9.5 Hz, 12H), 1.48 (s, 18H), 1.43 (d, J = 4.6 Hz, 20H), 1.35 (t, J = 7.1 Hz, 71H), 1.25 (dd, J = 13.8, 5.0 Hz, 93H), 1.15 (d, J = 3.1 Hz, 9H), 1.11 (s, 5H), 1.07 (d, J = 2.8 Hz, 5H), 1.03 (s, 8H), 0.98 (d, J = 3.1 Hz, 10H), 0.94 (d, J = 3.2 Hz, 6H), 0.86 (d, J = 6.5 Hz, 68H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.55 (s), 149.30 (s), 136.32 (s), 135.96 (s), 119.27 (s), 118.84 (s), 77.45 (s), 77.02 (s), 76.60 (s), 65.55 (s), 43.60 (d, J = 7.7 Hz), 42.58 (s), 42.12 (s), 41.66 (d, J = 3.9 Hz), 36.29 (d, J = 2.0 Hz), 35.14 (d, J = 9.7 Hz), 27.47 (dd, J = 21.2, 6.7 Hz), 26.55 (s), 25.72 (d, J = 3.7 Hz), 23.81 (s), 19.65 (d, J = 3.8 Hz), 15.07 (s), 14.66 (s), 13.93 (s).

7.2.2 Synthesis of allylic alcohols

General Procedure 1:

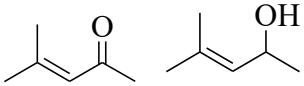
A 250 mL, three-necked, round-bottomed flask equipped with a pressure-equalized dropping funnel, N_2 gas inlet and reflux condenser. The flask was charged with the organolithium compound dissolved in dry THF (75 mL). Then the substrate compound (**18**) was carefully added dropwise at 0 °C under an atmosphere of N_2. After complete addition the mixture was stirred overnight at 0 °C, and then the reaction was quenched with 15 mL ice water followed by addition of 15% NaOH solution (15 mL) and finally 50 mL water. The liquid layer was taken in separatory funnel and the semisolid residue was washed several times with Et_2O. The collected liquid layers in separatory funnel were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL), the combined organic layers were collected, washed with brine (3 x 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by fractional distillation.

General Procedure 2:

A 250 mL, three-necked, round-bottomed flask equipped with a pressure-equalized dropping funnel, N_2 gas inlet and reflux condenser. The flask was charged with the Grignard reagent under inert atmosphere and then the substrate compound (**19**) was carefully added dropwise at

0 °C under an atmosphere of N_2. After complete addition the mixture was stirred at 0 °C for 4 hours, and then the reaction was quenched with cold saturated NH_4Cl solution (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL), the combined organic layers were collected, washed with brine (3 x 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the oily residue was collected.

7.2.2.1 Synthesis of 4-methylpent-3-en-2-ol 20

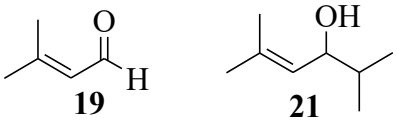


18 **20**

Following **General Procedure 1** 4.9 g (129.11 mmol) of $LiAlH_4$ was mixed in 75 mL dry THF in three-necked flask and 58.3 mL (50.02 g, 0.509 mmol) Mesityl oxide **18** was added dropwise under N_2 atmosphere. Crude yield 57.133g and after fractional distillation under pressure 90 torr 41.9877g pure 4-methylpent-3-en-2-ol **20** (yield 82%) as oil was obtained, boiling point range 87 - 89°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (ddt, J = 8.5, 2.8, 1.4 Hz, 1H), 4.58 – 4.49 (m, 1H), 1.68 (dd, J = 9.7, 1.3 Hz, 1H), 1.20 (d, J = 6.2 Hz, 1H).

7.2.2.2 Synthesis of 2,5-dimethylhex-4-en-3-ol 21

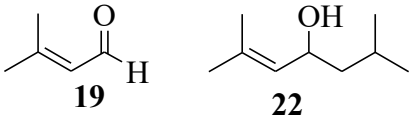


19 **21**

Following **General Procedure 2** 49.966 mL (7.365 g, 50 mmol) of 1M isopropylmagnesium bromide solution in dry THF was taken in a three-necked flask and 3.826 mL (3.36 g, 40 mmol) 3-methyl-2-butenal **19** in 50 mL dry THF was added dropwise under N_2 atmosphere. After the aqueous work-up and evaporation of solvent under reduced pressure 9.1235 g crude oil 2,5-dimethylhex-4-en-3-ol **21** was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ5.16 (dd, *J* = 9.0, 1.3 Hz, 1H), 4.06 – 3.96 (m, 1H), 1.71 (s, 5H), 1.66 (s, 5H), 0.92 (d, *J* = 6.7 Hz, 4H), 0.83 (d, *J* = 6.8 Hz, 4H).

7.2.2.3 Synthesis of 2,6-dimethylhept-2-en-4-ol 22



19 **22**

Following **General Procedure 2** 25 mL (8.066 g, 50 mmol) of 2M isobutylmagnesium bromide solution in dry THF was taken in a three-necked flask and 3.826 mL (3.36g, 40 mmol) 3-methyl-2-butenal **19** in 25 mL dry THF was added dropwise under N_2 atmosphere. After the aqueous work-up and evaporation of solvent under reduced pressure 10.3364 g crude oil **22** was obtained. After fractional distillation under pressure 90 torr 4.1556g pure 2,6-dimethylhept-2-en-4-ol **22** (yield 68%) as oil was obtained, boiling point

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (dd, J = 6.4, 5.1 Hz, 1H), 4.39 (dd, J = 14.9, 7.6 Hz, 1H), 1.69 (d, J = 1.1 Hz, 3H), 1.67 (d, J = 1.2 Hz, 4H), 1.66 – 1.58 (m, 3H), 1.50 – 1.42 (m, 1H), 1.28 – 1.19 (m, 1H), 0.91 – 0.86 (m, 7H).

7.3 Photochemical Reactions

7.3.1 Batch reactions

General Procedure 3: General method for Batch photoreaction of dihydroartemisinic acid 1, mixed anhydride of dihydroartemisinic acid 2 and allylic alcohols (20 – 22)

Batch photoreactions were conducted in a Schlenk flask comprised of *Pyrex*® with a glass sidearm. Using varying concentrations of sensitizers (rose bengal, methylene blue, tetraphenylporphyrin) in dichloromethane or acetone or isopropanol or ethanol, **1** or **2** or the allylic alcohols (**20 – 22**) was irradiated with visible light (16 x 8W cool white fluorescent tubes) inside the Rayonet chamber. Using an aquarium pump, air was gently bubbled through the Schlenk flasks' sidearm. Samples were taken between for NMR analysis to monitor the conversion.

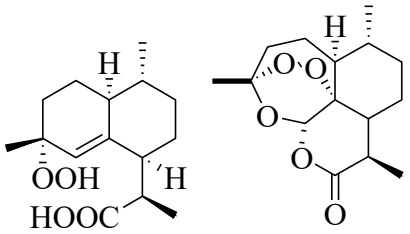
General Procedure 4: General methods for Batch Catalysis of intermediate hydroperoxide 3 for artemisinin synthesis

The reaction mixture containing the photo-product transferred into a 100 mL two-necked flask placed on ice bath or hot water bat maintained at 50 - 60°C or at room temperature. Air was gently bubbled into the mixture for 2 minutes and through the other neck trifluoroacetic acid (TFA) or conc. HCl or acidic alumina was added. The reaction was stirred under continuous air bubbling for 1 – 24 hours. Then the solution volume was reduced to 25 mL in case of dichloromethane or completely evaporated in case of acetone, alcohol and the residue was dissolved in 25 mL dichloromethane. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate

and filtered over silica to remove some sensitizer. Oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and then the crude was subjected to recrystallization from cyclohexane.

General Procedure 5: After the photoreaction was over the solution was transferred into a round bottomed flask and the solvent was evaporated under vacuum to obtain the residue semisolid mixture containing **3**. Then 50 mL diethyl ether was added to the residue and filtered to remove most of the sensitizer dye. After filtration the filtrate was subjected to evaporation of solvent. The residue recovered was analyzed by NMR to confirm the presence of **3**. The to the residue 25 mL n-hexane containing one drop of TFA was added in a two-necked round bottomed flask supplied with air. The reaction flask was stoppered and allowed to stand for 2 hours to 4 days in air at room temperature. Then the supernatant n-hexane was decanted and the residue was extracted thrice with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and concentrated followed by recrystallization from cyclohexane to get pure artemisinin **4**.

7.3.1.1 Batch Photoreactions of Dihydroartemisinic acid 1 followed by catalytic reaction of the intermediate 3 to synthesize artemisinin 4



3 **4**

Experiment 1 (Batch 1):

Following **General Procedure 3** mixture of 1.18g (5 mmol) of **1** and 12mg (0.02 mmol) meso-tetraphenylporphyrin in 200 mL of dichloromethane was irradiated for 2 hours and the conversion to **3** was monitored by NMR analysis. Yield of intermediate **3** 86%.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 0.19 mL trifluoroacetic acid (TFA) was conducted and reaction was allowed to stand for 2 hours at room temperature with continuous stirring. After the aqueous work-up 0.513 g of brown crude product was obtained.

Conversion 100% and intermediate **3** 86% and 19% artemisinin **4** by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: 5.24 (s, 4H), 2.82 – 2.67 (m, 5H), 1.33 – 1.26 (m, 27H), 0.94 (d, J = 5.5 Hz, 9H), 0.86 (d, J = 6.1 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.40 (m, 1H, H-11) (Complex NMR)

Experiment 2 (Batch 2):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 4 hours. Then by following **General Procedure 5** catalysis of intermediate **3** was performed with 1 drop of TFA and stirred in presence of air for 4 days. Finally, 0.159g crude product **4** as sticky solid was obtained.

Conversion 100% and intermediate **3** 83% and 53% artemisinin **4** by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.81 – 2.67 (m, 1H), 1.98 – 1.71 (m, 6H), 1.49 (s, 4H), 1.21 (t, J = 7.0 Hz, 10H), 0.93 (d, J = 5.9 Hz, 3H), 0.86 (d, J = 6.1 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.41 (m, 1H, H-11) (Complex NMR)

Experiment 3 (Batch 3):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 5 hours. Then by following **General Procedure 5** for catalysis of **3** was performed with 1 drop of TFA and stirred in presence of air for 4 days. Finally, 23mg (19%) of product **4** as off-white solid after recrystallization was obtained.

Conversion 100%, intermediate hydroperoxide **3** 89% and Artemisinin **4** 38% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 1.87 (dd, J = 31.6, 11.4 Hz, 5H), 1.63 – 1.35 (m, 4H), 0.94 (d, J = 5.9 Hz, 3H), 0.86 (d, J = 6.3 Hz, 1H).

IR of 3: (film)
$\tilde{\nu}$ (cm^{-1}) = 3300 (O-H), 2927 and 2868 (C-H), 1700 (C=O), 1542, 1455, 1377, 1337, 1276, 1211, 1129, 1071, 980, 955, 912, 875, 840.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (ddd, J = 12.5, 9.9, 7.0 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.07 (d, J = 6.6 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.82 – 1.72 (m, 1H), 1.45 (s, 1H), 1.40 (dd, J = 3.9, 1.3 Hz, 1H), 1.21 (d, J = 9.8 Hz, 1H), 1.13 – 1.05 (m, 1H), 1.00 (d, J = 5.9 Hz, 1H).

IR of 4: (film)

$\tilde{\nu}$ (cm^{-1}) = 2923 and 2870 (C – H), 1705 (C =O), 1456 (CH_2), 1374 (CH_3), 1081 (-O-), 1031 and 1012 (-C-O-), 992, 928 and 832 (C-C).

Experiment 4 (Batch 4):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 5 hours. Then by following **General Procedure 5** for catalysis of **3** was performed with 1 drop of TFA and stirred in presence of air for 24 hours. Finally, 28mg (23%) of product **4** as off-white solid after recrystallization was obtained.

Conversion 100%, hydroperoxide **3** 79% and artemisinin **4** 31% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: 5.24 (s, 1H), 2.88 – 2.66 (m, 1H), 2.00 – 1.76 (m, 7H), 1.62 – 1.34 (m, 6H), 0.94 (d, J = 5.9 Hz, 7H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.39 (m, 1H, H-11).

Experiment 5 (Batch 5):

Following **General Procedure 3** mixture of 200mg (0.84mmol) of **1** and 6mg (0.0187 mmol) methylene blue in 80 mL of dichloromethane was irradiated for 4 hours and the conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 5** Catalytic reaction of **3** in presence of air and 0.2 mL trifluoroacetic acid (TFA) was conducted and reaction was allowed to stand for 4 days with continuous stirring at room temperature. After extraction with n-hexane 270mg crude and after recrystallization from cyclohexane 112mg (47%) product **4** was obtained as green solid.

Conversion 88% and by NMR 54% artemisinin **4**.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed in NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.98 – 5.74 (m, 1H), 3.46 – 3.31 (m, 1H), 2.52 – 2.28 (m, 3H), 2.16 – 1.98 (m, 5H), 1.84 – 1.68 (m, 8H), 1.43 (s, 6H), 1.19 (d, J = 7.3 Hz, 7H), 0.99 (d, J = 5.9 Hz, 5H).

Experiment 6 (Batch 5-Repeat):

Following **General Procedure 3** mixture of 200mg (0.84mmol) of **1** and 6mg (0.0187 mmol) methylene blue in 80 mL of dichloromethane was irradiated for 4 hours and the conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 5** Catalytic reaction of **3** in presence of air and 0.2 mL trifluoroacetic acid (TFA) was conducted and reaction was allowed to stand for 24 hours with continuous stirring at room temperature. After extraction with n-hexane 211mg crude and after recrystallization from cyclohexane 83mg (35%) product **4** was obtained as green solid.

Conversion 69% after first step and y NMR 89% artemisinin **4**.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed in NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.82 (d, J = 24.0 Hz, 1H), 3.39 (t, J = 4.5 Hz, 1H), 2.45 (d, J = 14.6 Hz, 1H), 2.15 – 1.93 (m, 3H), 1.89 – 1.65 (m, 6H), 1.43 (d, J = 6.9 Hz, 10H), 1.21 (d, J = 7.3 Hz, 6H), 1.00 (d, J = 5.6 Hz, 6H).

Experiment 7 (Batch 5R):

Following **General Procedure 3** mixture of 100mg (0.42mmol) of **1** and 3mg (0.0093 mmol) methylene blue in 80 mL of dichloromethane was irradiated for 2 hours and the conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 0.2 mL trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 24 hours with continuous stirring at room temperature. After the aqueous work-up 46.6mg (91% by NMR) crude and after recrystallization from cyclohexane 9.7mg (8%) product **4** was obtained as off-white solid.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: NMR not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.40 – 3.34 (m, 1H), 2.49 – 2.34 (m, 2H), 2.18 – 1.95 (m, 4H), 1.92 – 1.70 (m, 7H), 1.42 (s, 7H), 1.18 (d, J = 7.3 Hz, 7H), 1.12 – 1.04 (m, 3H), 0.98 (d, J = 5.9 Hz, 4H).

Experiment 8 (Batch 14):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 3.5 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.182g crude product and after recrystallization from cyclohexane 33mg (28%) product **4** was obtained as pale solid.

Conversion 88%, NMR yield of **3** 76% and artemisinin **4** 25% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.73 (m, 1H), 2.02 – 1.71 (m, 7H), 1.66 – 1.43 (m, 6H), 0.93 (d, J = 5.9 Hz, 4H), 0.85 (s, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.41 (m, 1H, H-11).

Experiment 9 (Batch 15):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 20mg (2.05408 mmol) of rose bengal in 75 mL of isopropanol combined with 8 mL water was irradiated for 3.5 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 2 drops TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.044g crude product and after recrystallization from cyclohexane 16mg (7%) product **4** was obtained as off white solid.

Conversion 97%, yield of **3** 85% product 71% as per NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.71 (p, J = 6.9 Hz, 1H), 2.01 – 1.70 (m, 6H), 1.64 – 1.37 (m, 5H), 0.93 (d, J = 5.7 Hz, 4H), 0.87 (d, J = 3.1 Hz, 1H), 0.78 (d, J = 3.0 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.46 – 3.30 (m, 1H), 2.42 (dt, J = 13.4, 4.0 Hz, 2H), 2.21 – 1.97 (m, 5H), 1.95 – 1.66 (m, 8H), 1.44 (s, 6H), 1.21 (s, 6H), 0.99 (d, J = 5.7 Hz, 3H), 0.87 (d, J = 6.2 Hz, 2H).

Experiment 10 (Batch 16):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 20mg (2.05408 mmol) of rose bengal in 75 mL of isopropanol combined with 8 mL water was irradiated for 3.5 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop concentrated HCl was conducted at 60°C and reaction was allowed to stand for 2 hours with

continuous stirring. But during evaporation the solution was lost due to spillage in rotary evaporator.

Conversion not determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Complex NMR.

Experiment 11 (Batch 17):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 3.5 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.109g crude product and after recrystallization from cyclohexane 38mg mixed product containing 56% product **4** was obtained.

Conversion 99%, yield of **3** 78% product 56% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.72 (dt, J = 7.8, 6.3 Hz, 1H), 0.92 (d, J = 6.0 Hz, 5H), 0.86 (d, J = 3.0 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.38 (m, 1H, H-11).

Experiment 12 (Batch 18):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 3 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop p-Toluenesulfonic acid was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.112g crude product and after recrystallization from cyclohexane no product.

Conversion not determined after first step, artemisinin **4** 11% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.37 (m, 1H, H-11) Complex NMR.

Experiment 13 (Batch 20):

Following **General Procedure 3** a solution of 200mg (0.84 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated for 5 hours.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.104g crude product and after recrystallization from cyclohexane 41mg (17 %) pure **4** was obtained.

Conversion 92%, yield of **3** 71% product **4** 58% as in NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.70 (m, 1H), 1.99 – 1.70 (m, 4H), 1.71 – 1.45 (m, 3H), 0.96 – 0.89 (m, 2H), 0.79 (d, J = 5.9 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.38 (dt, J = 12.6, 6.3 Hz, 1H), 2.63 – 2.25 (m, 8H), 2.10 – 1.70 (m, 19H), 1.44 (s, 10H), 1.20 (d, J = 7.3 Hz, 13H), 0.99 (d, J = 5.9 Hz, 8H), 0.93 – 0.81 (m, 6H).

Experiment 14 (Batch 21):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 2 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.0.051g crude product and after recrystallization from cyclohexane no product.

Conversion 99%, yield of **3** 83% product **4** 56% as in NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: 1H NMR (300 MHz, cdcl3) δ 5.24 (s, 1H), 2.82 – 2.65 (m, 1H), 2.03 – 1.73 (m, 5H), 1.68 – 1.42 (m, 4H), 0.93 (d, J = 5.7 Hz, 3H), 0.85 (d, J = 6.2 Hz, 1H), 0.79 (d, J = 5.8 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.39 (m, 1H, H-11) Complex NMR.

Experiment 15 (Batch 25):

Following **General Procedure 3** solution of 191.2mg (0.8089 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated for 5 hours.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 50°C and reaction was allowed to stand for 1 hours with continuous stirring and 0.141g crude was obtained. After the aqueous work-up with mixture of dichloromethane and n-hexane 0.101g crude product from DCM fraction and 0.01g crude from n-hexane fraction were collected.

Conversion and yield of **3** not determined and product **4** 10% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.41 (m, 1H, H-11) Complex NMR.

Experiment 16 (Batch 27):

Following **General Procedure 3** solution of 200mg (0.84 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 80 mL ethanol and 5 mL water was irradiated for 5 hours.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 30 minutes with continuous stirring and no product was observed in NMR but by-products. The catalysis was continued by adding 0.19mL TFA for 2 hours in presence of air bubbling and 0.218g crude was obtained which upon recrystallization yielded 11mg (9%) pure **4**.

Conversion 96%, yield of **3** 85% and product **4** 40% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.70 (dq, J = 14.0, 6.8 Hz, 1H), 2.25 – 2.12 (m, 1H), 1.99 – 1.69 (m, 5H), 1.48 (dddd, J = 28.9, 23.6, 17.8, 10.3 Hz, 5H), 0.93 (d, J = 5.4 Hz, 3H), 0.87 (d, J = 3.2 Hz, 1H), 0.79 (d, J = 5.6 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.39 (tt, J = 7.3, 3.6 Hz, 1H), 2.50 – 2.30 (m, 1H), 2.10 – 1.95 (m, 2H), 1.91 – 1.69 (m, 4H), 1.44 (s, 2H), 1.20 (d, J = 7.3 Hz, 3H), 1.11 – 1.00 (m, 3H), 1.00 (d, J = 6.0 Hz, 3H).

Experiment 17 (Batch 28):

Following **General Procedure 3** solution of 100mg (0.42 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 120 mL ethanol for 5 hours in presence of Nitrogen instead of air.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air bubbling and 0.19 mL trifluoroacetic acid (TFA) was conducted at room temperature and reaction was allowed to stand for 6 hours with continuous stirring and 85mg crude was obtained with very less product observed in NMR but more by-products. After workup 49.6mg mixed product showing more **4** in NMR was obtained.

Conversion 92%, yield of **3** 72% product **4** 69% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.70 (p, J = 6.8 Hz, 1H), 2.03 – 1.72 (m, 9H), 1.64 – 1.35 (m, 9H), 0.93 (d, J = 5.7 Hz, 5H), 0.86 (d, J = 6.4 Hz, 1H), 0.79 (d, J = 5.9 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.41 (m, 1H, H-11) Complex NMR.

Experiment 18 (Batch 29 Photoreaction without air):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 80 mL of dichloromethane was irradiated in absence of air for 3 hours. The NMR analysis showed no change of starting material. Then into the reaction air was supplied and after 30 minutes 0.19 mL TFA was added and irradiation was continued for 2 hours. NMR analysis showed no change of starting material. After the aqueous workup as described in **General Procedure 4** 0.109 g of crude containing starting material was recovered.

Conversion 7%, yield of **3** 1% and product **4** 5% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.41 (m, 1H, H-11).

Experiment 19 (Batch 30):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 72 mL of isopropanol and 8 mL water was irradiated for 5 hours. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring and continued for overnight at room temperature. After the aqueous work-up 0.100g mixed crude product and after recrystallization from cyclohexane no pure product.

Conversion 58%, yield of **3** 20% product **4** 39% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5), 2.73 (m, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.38 (m, 1H, H-11).

Experiment 20 (Batch 31 Reaction without air):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 20mg (0.02085 mmol) Rose bengal in 100 mL of ethanol was irradiated for 5 hours in presence of Nitrogen instead of air. The conversion to **3** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **3** in presence of air and 1 drop TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring and continued for overnight at room temperature. After the aqueous work-up 0.078g mixed crude product and after recrystallization from cyclohexane no pure product.

Conversion and yield of **3** not determined, product **4** 44% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.41 (m, 1H, H-11).

Experiment 21 (Batch 34):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 2 hours. The NMR analysis did not show presence of intermediate **3**.

Then following **General Procedure 4** Catalytic reaction in presence of air and acidic alumina was conducted at 50°C and reaction was allowed to stand for 1 hours with continuous stirring. Crude weight was 113mg after evaporation of solvent. NMR analysis of crude showed 12% of **4** but more by-products.

Conversion 69% after first step and product **4** 12% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.39 (m, 1H, H-11).

Experiment 22 (Batch 35):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 2 hours. The NMR analysis did not show presence of intermediate **3**.

Then following **General Procedure 4** Catalytic reaction in presence of air and TFA 2 drops was conducted at room temperature and reaction was allowed to stand overnight with continuous stirring. Later additional 2 drops neat TFA was added.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 80 mg of mixture of **4** and by-products.

Conversion and **3** were not determined, product **4** 47% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.40 (m, 1H, H-11).

Experiment 23 (Batch 37):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 40 mL of dichloromethane was irradiated for 2 hours. Then the reaction mixture was filtered through silica to remove dye. To the filtrate, in a flask, 1 – 2 drops of TFA was added under air bubbling condition at room temperature and stirred for 1 hour. Then solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate. After solvent evaporation 53.4mg crude was obtained.

Conversion 40%.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), c; Complex NMR.

Experiment 24 (Batch 38):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 3 hours. Then the reaction mixture was filtered through silica to remove dye. To the filtrate, in a flask, 0.19 mL of TFA was added under air bubbling condition at room temperature and stirred overnight (24hours).

Then solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate. After solvent evaporation 98.1mg crude was obtained.

Conversion 46%, yield of **3** 26% and product **4** 11% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: 5.24 (s, 1H, H-5) 2.73 (m, 1H, H-11)

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5) 3.37 (m, 1H, H-11); Complex NMR.

Experiment 25 (Batch 39):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 6mg (0.0186 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 3.5 hours. Then the reaction mixture was filtered through silica to remove dye. To the filtrate, in a flask, 1 drop of TFA solution (2 – 3 drops neat TFA in 10 mL n-hexane) was added under air bubbling condition at 55°C and stirred for 2 hours. Then solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate. After solvent evaporation 121.8mg crude was obtained.

Conversion 77%, yield of **3** none and product **4** 38% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5) 3.37 (m, 1H, H-11); Complex NMR.

Experiment 26 (Batch 40):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 1 – 2 drops TFA was conducted at room temperature and reaction was allowed to stand 1 hour with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed

by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 78.4 mg of mixed products.

Conversion 72%, yield of product **4** 49% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5) 3.39 (m, 1H, H-11); Complex NMR.

Experiment 27 (Batch 41):

Following **General Procedure 3** mixture of 1.145g (4.8445 mmol) of **1** and 6mg (0.0186 mmol) of methylene blue in 80 mL of dichloromethane was irradiated for 2.5 hours. Then the reaction mixture was filtered through silica to remove dye. To the filtrate, in a flask, 1 - 2 drops of TFA was added under air bubbling condition at room temperature and stirred 1 hour. Then solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate. After solvent evaporation 0.332g crude was obtained containing **4** and by-products.

Conversion 95%, yield of **3** 48% product 24% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: 5.24 (s, 1H, H-5) 2.76 (m, 1H, H-11)

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5) 3.39 (m, 1H, H-11); Complex NMR.

Experiment 28 (Batch 42):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 20mg (0.017 mmol) of rose bengal bis(triethylammonium)salt in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 2 – 3 drops TFA was conducted at 50°C and reaction was allowed to stand 2 hours with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate

and filtered through silica. Crude weight was 162.5 mg of mixed products which upon recrystallization from cyclohexane yielded 32.6mg (14%) pure **4**.

Conversion 93%, yield of **3** 81% and product **4** 48% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.23 (s, 1H, H-5), 2.79 – 2.67 (m, 1H, H-11), 2.17 – 1.42 (m, 4H), 1.29 (s, 1H), 1.26 (d, J = 6.8 Hz, 1H), 0.93 (d, J = 5.9 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.48 – 3.29 (m, 1H, H-11), 2.48 – 2.36 (m, 1H), 2.10 – 1.97 (m, 2H), 1.87 (ddd, J = 16.1, 8.4, 4.8 Hz, 2H), 1.83 – 1.67 (m, 4H), 1.43 (s, 6H), 1.19 (d, J = 7.3 Hz, 6H), 0.99 (d, J = 5.9 Hz, 5H).

Experiment 29 (Batch 43):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 10mg (0.0085 mmol) of rose bengal bis(triethylammonium)salt in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 2 – 3 drops TFA was conducted at 50°C and reaction was allowed to stand 2 hours with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 156.8 mg of mixed products which upon recrystallization from cyclohexane yielded 34.6mg (15%) pure **4**.

Conversion 67%, yield of **3** 48% and product **4** 49% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.21 (s, 1H, H-5), 2.74 – 2.66 (m, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.38 (dd, J = 7.3, 5.3 Hz, 1H), 2.54 – 2.36 (m, 1H), 2.03 (dd, J = 19.1, 9.2 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.81 – 1.71 (m, 3H), 1.42 (d, J = 10.1 Hz, 5H), 1.20 (d, J = 7.3 Hz, 4H), 0.99 (d, J = 5.9 Hz, 4H).

Experiment 30 (Batch 44):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 15mg (0.0128 mmol) of rose bengal bis(triethylammonium)salt in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 2 – 3 drops TFA was conducted at 50°C and reaction was allowed to stand 2 hours with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 167.7 mg of mixed products, upon recrystallization from cyclohexane pure **4** could not been isolated.

Conversion 83%, yield of **3** 49% and product **3** 38% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5), 2.79 – 2.68 (m, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.42 – 3.29 (m, 1H, H-11).

Experiment 31 (Batch 45):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 15mg (0.0128 mmol) of rose bengal bis(triethylammonium)salt in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 0.1 mL TFA was conducted at 50°C and reaction was allowed to stand 2 hours with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 102.3 mg of mixed products, upon recrystallization from cyclohexane pure **4** could not been isolated.

Conversion and yield of **3** were not determined, product **4** 42% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.42 – 3.38 (m, 1H, H-11).

Experiment 32 (Batch 45-Repeat):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 15mg (0.0128 mmol) of rose bengal bis(triethylammonium)salt in 80 mL of dichloromethane was irradiated for 2 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 2 – 3 drops TFA was conducted at 50°C and reaction was allowed to stand 2 hours with continuous stirring.

Then after evaporation of the solvent the residue was extracted with boiling n-hexane thrice (3 x 25 mL) and the washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane and organic fractions were dried over sodium sulphate or magnesium sulphate and filtered through silica. Crude weight was 127.6 mg of mixed products, upon recrystallization from cyclohexane pure **4** could not been isolated.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Not available.

Experiment 33 (Batch 53):

Following **General Procedure 3** mixture of 200mg (0.84 mmol) of **1** and 20mg (0.02085 mmol) of rose bengal in 72 mL of isopropanol and 8 mL water was irradiated for 3.5 hours.

Then following **General Procedure 4** Catalytic reaction in presence of air and 3 – 4 drops TFA was conducted at room temperature and reaction was allowed to stand over night with continuous stirring and air bubbling.

Then after evaporation of the solvent the residue was dissolved in 25 mL dichloromethane and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate. After solvent evaporation 0.147.5g crude was obtained containing **4** and by-products; after recrystallization from cyclohexane 59mg (38%) product **4** was obtained mixed with by-products and DHAA.

Conversion 87%, yield of **3** 62% and product **4** 55% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H, H-5), 2.76 – 2.65 (m, 1H, H-11).

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.41 – 3.32 (m, 1H), 2.50 – 2.26 (m, 2H), 2.07 (d, J = 48.8 Hz, 7H), 1.77 (s, 8H), 1.41 (s, 7H), 1.18 (d, J = 7.3 Hz, 4H), 0.98 (d, J = 6.0 Hz, 6H), 0.85 (d, J = 6.3 Hz, 2H).

7.3.1.2 One-pot Batch synthesis of artemisinin by direction addition of TFA during photoreaction

General Procedure 6: In the Schlenk flask *Pyrex*® with glass sidearm containing specified amount of sensitizer and **1** or **2** were taken in suitable solvent and TFA was added at the time of starting irradiation or after 1-2 hours of irradiation. Into the Schlenk flask placed inside the Rayonet chamber air was gently bubbled in solution from an aquarium pump. Cold finger was inserted inside the flask and then the 16 x 8W visible light tubes of reactor were turned on to start the photoreaction.

General Procedure 7: After the photoreaction the solvent was evaporated under reduced pressure and the residue was extracted thrice with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate and filtered over silica to remove some sensitizer. Oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and then the crude was subjected to recrystallization from cyclohexane.

General Procedure 8: After finishing the photoreaction solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate and filtered over silica to remove some sensitizer. Oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and then the crude was subjected to recrystallization from cyclohexane.

Experiment 34 (Batch 6):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 6mg (0.01 mmol) TPP in 80 mL dichloromethane was irradiated. After completion of 2 hours irradiation 0.19 mL TFA was added into the reaction and continued irradiation up to 3 hours. Then following **General Procedure 7** a crude semisolid of 0.245g was obtained which upon recrystallization from cyclohexane resulted in formation of 86mg (36%) pure product **4** as brown solid.

Conversion -66% and product **4** 47% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.39 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.44 – 2.32 (m, 5H), 2.11 – 2.00 (m, 4H), 1.87 (s, 3H), 1.78 (d, *J* = 10.0 Hz, 6H), 1.46 – 1.36 (m, 12H), 1.21 (d, *J* = 7.3 Hz, 9H), 1.00 (d, *J* = 5.8 Hz, 8H).

Experiment 35 (Batch 7):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 6mg (0.01 mmol) TPP and 0.19 mL TFA in 80 mL dichloromethane was irradiated for 3 hours. Then by following **General Procedure 8** oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and then the crude was subjected to recrystallization. A crude semisolid of 0.219g was obtained which upon recrystallization from cyclohexane no pure product was obtained.

Conversion -96% and product **4** 51% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H, H-5), 3.47 – 3.33 (m, 1H, H-11).

Experiment 36 (Batch 7-Repeat):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 6mg (0.01 mmol) TPP and 0.19 mL TFA in 80 mL dichloromethane was irradiated for 3 hours. Then by following **General Procedure 8** a crude semisolid of 0.137g was obtained which upon recrystallization from cyclohexane yielded 77mg (32%) brown colored product was obtained.

Conversion -100% and product **4** 64% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.45 – 3.31 (m, 1H, H-11).

Experiment 37 (Batch 8):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 6mg (0.01 mmol) TPP in 80 mL isopropanol was irradiated. After completion of 1hour irradiation 0.19 mL TFA was

added into the reaction and continued irradiation up to 5 hours. NMR analysis showed incomplete conversion and 0.223g recovered.

Conversion -10% and product **4** 10% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H, H-5), 3.39 (m, 1H, H-11).

Experiment 38 (Batch 12):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.01314 mmol) anthracene-9,10-dicarbonitrile and 0.19 mL (0.0024 mmol) TFA in 80 mL toluene was irradiated for 2 hours. No product was found and only starting material recovered 0.219g as solid.

Conversion -5% and product **4** 2% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5).

Experiment 39 (Batch 13):

Following **General Procedure 6** solution of 1.9995g (8.46 mmol) of **1**, 47.93mg (0.20998 mmol) anthracene-9,10-dicarbonitrile and 1.615 mL (21.0927 mmol) TFA in 84.6 mL toluene was irradiated for 13 hours. No product was found and only starting material recovered 0.205g as solid. (sample lost while transferring)

Conversion -5% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: Not observed.

Experiment 40 (Batch 32):

Following **General Procedure 6** mixture of 100mg (0.42 mmol) of **1** and 10mg (0.10425 mmol) of rose bengal in 75 mL of acetonitrile was irradiated for 2 hours. NMR analysis of 1hour sample showed complete conversion. After 1 hour of irradiation 1 drop TFA was added into the flask and irradiation was continued for 2 hours. Following **General Procedure 8** 0.117g crude product containing only by-product was obtained.

Conversion -100% and product **4** 4% by NMR.

^{1}H NMR (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.73 (dt, J = 14.3, 7.0 Hz, 1H), 1.97 – 1.47 (m, 8H), 1.32 – 1.24 (m, 8H), 0.93 (d, J = 5.7 Hz, 3H).

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H, H-5).

Experiment 41 (Batch 36):

Following **General Procedure 6** solution of 110mg (0.4654 mmol) of **1**, 9mg (0.02814 mmol) methylene blue in 80 mL dichloromethane was irradiated for 3 hours with 8W x 8 cool visible light fluorescent tubes and 2 drops of 0.1306M TFA (in dichloromethane) was added into the reaction right after lights were turned on. Then following **General Procedure 8** for workup 52mg of mixed crude was obtained.

Conversion -89% and product **4** 40% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.38 (dd, J = 12.3, 7.5 Hz, 1H, H-11).

Experiment 42 (Batch 46):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL (0.0149g, 0.13 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 134.6mg of mixed crude was obtained and after recrystallization from cyclohexane 121.2mg (50%) of pure off-white **1** was isolated.

Conversion -90% and product **4** 51% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.83 (s, 1H), 3.40 – 3.30 (m, 1H), 2.40 (ddd, J = 14.6, 10.8, 4.4 Hz, 2H), 2.14 – 1.94 (m, 4H), 1.90 – 1.81 (m, 2H), 1.73 (ddd, J = 14.1, 7.7, 4.0 Hz, 4H), 1.41 (s, 6H), 1.17 (d, J = 7.3 Hz, 6H), 0.97 (d, J = 5.9 Hz, 4H), 0.85 (d, J = 6.2 Hz, 1H).

Experiment 43 (Batch 47):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.05 mL (0.0745g, 0.653 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 131.2mg of mixed crude was obtained and after recrystallization from cyclohexane 99.1mg (42%) of pure off-white **1** was isolated.

Conversion 92% and product **4** 51% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.83 (s, 1H), 3.39 – 3.31 (m, 1H), 2.47 – 2.33 (m, 1H), 2.09 – 1.90 (m, 3H), 1.85 (dd, J = 5.9, 3.1 Hz, 1H), 1.81 – 1.67 (m, 3H), 1.40 (d, J = 8.0 Hz, 5H), 1.17 (d, J = 7.3 Hz, 4H), 0.97 (d, J = 5.9 Hz, 4H), 0.85 (d, J = 6.3 Hz, 1H).

Experiment 44 (Batch 48):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.1 mL (0.149g, 1.3 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 93mg of crude was obtained containing starting material and by-product.

Conversion -24% and product **4** 2% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: Complex NMR.

Experiment 45 (Batch 49):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.15 mL (0.2235g, 1.96 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 65mg of crude was obtained containing starting material and by-product.

Conversion 71% and product **4** 23% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.42-3.36 (m, 1H, H-11).

Experiment 46 (Batch 50):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.2 mL (0.298g, 2.614 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 157mg of crude was obtained containing starting material and by-product.

Conversion 38% and product **4** 18% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H, H-5), 3.37 (m, 1H, H-11).

Experiment 47 (Batch 51):

Following **General Procedure 6** solution of 200mg (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.5 mL (0.745g, 6.534 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 129.5mg of crude was obtained containing starting material and by-product.

Conversion -11% and product **4** 3% by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.42-3.36 (m, 1H, H-11).

7.3.1.3 Solar one-step batch synthesis of artemisinin 4 from 1

General procedure 9: In the Schlenk flask *Pyrex*® with glass sidearm containing specified amount of sensitizer and **1** in suitable solvent were mixed and TFA was added at the time of starting irradiation or after 1-2 hours of irradiation under sunlight. Into the Schlenk flask air was gently bubbled in solution from an aquarium pump and cold finger was inserted inside the flask and then the flask was placed under sunlight to start the photoreaction. After finishing the photoreaction, the solution concentrated to 25 mL (in case of dichloromethane) or completely evaporated in case of acetone, ethanol and isopropanol and the residue was dissolved in dichloromethane 25 mL. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate or Magnesium sulphate and filtered over silica to remove some sensitizer. Oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and then the crude was subjected to recrystallization from cyclohexane.

Experiment 48 (Batch 9):

Following **General procedure 9** solution of 200mg (0.84 mmol) of **1**, 6mg (0.01 mmol) TPP in 80 mL dichloromethane was irradiated in sunlight. NMR analysis after 1 hours showed complete conversion. After completion of 1hour irradiation 0.19 mL TFA was added into the reaction and continued irradiation for 1 hours more. After solvent evaporation 267mg of crude and after workup 178mg crude was obtained but after workup the final product was lost in rotary evaporator.

Conversion -100%, yield of **3** 84% and product **4** 53% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.81 – 2.63 (m, 1H), 2.15 (td, J = 11.8, 4.4 Hz, 2H), 1.97 – 1.70 (m, 6H), 1.58 – 1.42 (m, 3H), 0.94 (d, J = 5.8 Hz, 3H), 0.87 (s, 1H), 0.79 (d, J = 2.0 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H), 3.47 – 3.34 (m, 1H), 2.52 – 2.24 (m, 7H), 2.11 – 1.89 (m, 10H), 1.81 (dd, J = 38.6, 18.9 Hz, 17H), 1.45 (s, 3H), 1.21 (d, J = 7.1 Hz, 10H), 1.00 (d, J = 6.0 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H).

Experiment 49 (Batch 10):

Following **General procedure 9** solution of 200mg (0.84 mmol) of **1**, and 20.3mg (0.02085 mmol) Rose bengal in 75 mL isopropanol with 8 mL water was irradiated in sunlight. After completion of 2 hours irradiation 0.01 mL TFA was added into the reaction and continued irradiation for 1 hours more. After solvent evaporation and workup 147mg of crude was obtained and 86.5mg (36%) pure **4** was obtained as pinkish solid.

Conversion -70% and yield of **3** 52% after 2 hours by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H, H-5), 2.70 (s, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.44 – 3.35 (m, 1H), 2.42 (dd, J = 19.1, 10.5 Hz, 2H), 2.24 – 1.95 (m, 6H), 1.80 (t, J = 20.3 Hz, 12H), 1.42 (s, 3H), 1.21 (d, J = 7.3 Hz, 10H), 1.00 (d, J = 5.8 Hz, 8H).

Experiment 50 (Batch 11):

Following **General procedure 9** solution of 100mg (0.42 mmol) of **1** and 3mg (0.0093 mmol) methylene blue in 75 mL acetone was irradiated in sunlight. After completion of 2 hours irradiation 0.19 mL TFA was added into the reaction and continued irradiation for 1 hours more. After solvent evaporation and workup 0.066g of crude was obtained and 28mg (23.439%) pure **4** was obtained as off-white.

Conversion -97% and yield of **3** 78% after 2 hours, product **4** 75% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.80 – 2.66 (m, 1H), 1.29 (d, J = 4.4 Hz, 5H), 1.26 (d, J = 0.6 Hz, 2H), 0.93 (d, J = 5.9 Hz, 3H), 0.88 (d, J = 5.9 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.48 – 3.31 (m, 1H), 2.43 (dt, J = 9.6, 5.9 Hz, 1H), 2.12 – 1.94 (m, 4H), 1.94 – 1.74 (m, 6H), 1.42 (d, J = 5.8 Hz, 5H), 1.19 (d, J = 7.3 Hz, 4H), 0.99 (d, J = 5.9 Hz, 4H).

Experiment 51 (Batch 19):

Following **General procedure 9** solution of 200mg (0.84 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated in sunlight. After completion of 3 hours irradiation 1 drop TFA was added into the reaction and continued irradiation for 2 hours more. After solvent evaporation and workup 0.054g of crude was obtained and after recrystallization 28mg pale sticky material obtained.

Conversion 78% and yield of **3** 56% after 3 hours, product **4** 86% after 5 hours by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5), 2.72 (s, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.42 – 3.35 (m, 1H), 2.47 – 2.35 (m, 2H), 2.05 (dddd, J = 12.7, 9.3, 6.0, 1.6 Hz, 8H), 1.95 – 1.68 (m, 13H), 1.43 (d, J = 1.1 Hz, 8H), 1.19 (d, J = 7.3 Hz, 8H), 1.15 – 1.05 (m, 7H), 0.99 (d, J = 5.9 Hz, 5H).

Experiment 52 (Batch 26):

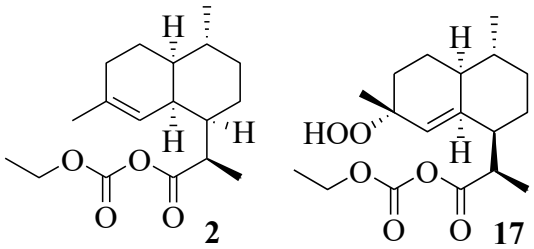
Following **General procedure 9** solution of 200mg (0.84 mmol) of **1**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated in sunlight for 1 hour and 1 drop TFA was added into the reaction and continued irradiation for 1 hours more. After solvent evaporation 0.249g crude and after workup 0.124g of crude was obtained and no pure product could be recrystallized.

Conversion 64% and yield of **3** 46% after 1hour, product **4** 14% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5), 2.71 (s, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H, H-5), 3.43 – 3.32 (m, 1H, H-11).

7.3.1.4 Batch photoreactions of 2 to synthesize artemisinin 4



Experiment 53 (PM-Ester-batch-1):

Following **General Procedure 6** solution of 100mg (0.3242 mmol) of **2**, 4mg (0.0125 mmol) methylene blue and 0.01 mL (0.0149g, 0.13 mmol) TFA in 80 mL dichloromethane was irradiated for 2 hours. Then following **General Procedure 8** for workup 95mg of crude was obtained and 27.8mg (30%) pure **4** was recovered by recrystallization.

Conversion 92% and product **4** 67% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.44 – 3.32 (m, 1H), 2.44 (ddd, J = 14.6, 13.0, 3.9 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.92 – 1.72 (m, 3H), 1.45 (s, 3H), 1.21 (d, J = 7.3 Hz, 3H), 1.00 (d, J = 6.0 Hz, 3H).

Experiment 54 (Batch 22):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **2** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 2 hours. The conversion **17** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **17** in presence of air and 1 drop TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 91mg crude product and after recrystallization from cyclohexane no product.

Conversion 98% and yield of **17** 86% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 17: δ 5.25 (s, 1H), 4.33 (dt, J = 7.1, 5.6 Hz, 2H, -C$\underline{H_2}$-O-C=O), 2.80 (p, J = 7.0 Hz, 1H), 1.77 (s, 2H), 1.41 – 1.36 (m, 3H), 1.33 (d, J = 3.3 Hz, 3H), 1.30 (s, 1H), 1.27 (s, 4H), 0.94 (d, J = 6.0 Hz, 3H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Complex NMR

Experiment 55 (Batch 22- Repeat):

Following **General Procedure 3** mixture of 100mg (0.42 mmol) of **2** and 3mg (0.0093 mmol) of methylene blue in 75 mL of acetone was irradiated for 2 hours. The conversion to **17** was monitored by NMR analysis.

Then following **General Procedure 4** Catalytic reaction of **17** in presence of air and 1 drop TFA was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.084g crude product and after recrystallization from cyclohexane no product.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 17: Not available.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Complex NMR

Experiment 56 (Batch 23):

Following **General Procedure 3** solution of 200mg (0.65 mmol) of **2**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated for 5 hours.

Then following **General Procedure 4** Catalytic reaction of intermediate in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring and 0.212g crude residue was collected after solvent

evaporation. After the aqueous work-up 89mg mixed product was obtained and no pure product recovered by recrystallization.

Conversion -92%, **17** 77% and product **4** 25% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 17: δ 5.26 (s, 1H), 4.33 (qd, J = 7.1, 3.2 Hz, 2H), 2.80 (t, J = 6.9 Hz, 1H), 2.37 (d, J = 5.8 Hz, 1H), 1.62 (d, J = 9.4 Hz, 7H), 1.38 (d, J = 7.4 Hz, 8H), 1.36 (s, 6H), 1.33 (d, J = 14.8 Hz, 12H), 1.28 (t, J = 9.0 Hz, 22H), 0.87 (d, J = 6.4 Hz, 6H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Complex NMR

Experiment 57 (Batch 23-Repeat):

Following **General Procedure 3** solution of 200mg (0.65 mmol) of **2**, and 20mg (0.02085 mmol) Rose bengal in 75 mL ethanol was irradiated for 5 hours.

Then following **General Procedure 4** Catalytic reaction of intermediate in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring and 0.175g crude residue was collected after solvent evaporation. After the aqueous work-up 62mg mixed product was obtained and no pure product recovered by recrystallization.

Conversion 86%, intermediate **17** 60% and product **4** 9% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 17: δ 5.25 (s, 1H), 4.41 – 4.25 (m, 2H, -C$\underline{H_2}$-O-C=O), 2.83 – 2.68 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), Complex NMR.

Experiment 58 (Batch 24):

Following **General Procedure 3** solution of 253mg (0.82 mmol) of **2**, and 20mg (0.02085 mmol) Rose bengal in 75 mL isopropanol and 8 mL water was irradiated for 5 hours.

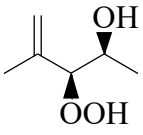
Then following **General Procedure 4** Catalytic reaction of intermediate in presence of air and 1 drop trifluoroacetic acid (TFA) was conducted at 60°C and reaction was allowed to stand for 2 hours with continuous stirring. After the aqueous work-up 0.278g crude which was further extracted with boiling n-hexane (3 x 25mL) and 0.152g mixed product was obtained and no pure product recovered by recrystallization.

Conversion 86%, intermediate **17** 60% and product **4** 9% by NMR.

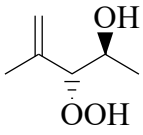
^{1}H-NMR: (300 MHz, $CDCl_3$) of 17: δ 5.25 (s, 1H), 4.32 (m, 2H, -C$\underline{H_2}$-O-C=O), 2.74 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.40 (m, 1H, H-11) Complex NMR.

7.3.1.5 Batch photoreactions of 4-methylpent-3-en-2-ol 20 to synthesize hydroperoxyalcohol 23



syn
(2*S*,3*S*)-3-hydroperoxy-4-methylpent-4-en-2-ol
23a



anti
(2*S*,3*R*)-3-hydroperoxy-4-methylpent-4-en-2-ol
23b

Experiment 59 (PM-T-B-1):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.00488 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 4 hours 95% conversion was obtained and crude weight was 0.550g containing **23** as mixture of 83:17 *syn*:*anti* diastereomers.

Conversion 95%, yield of **23a** 79% and **23b** 16% by NMR.

(2S,3S)-3-hydroperoxy-4-methylpent-4-en-2-ol (*Syn*) 23a (major):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (m, 2H), 4.14 (d, *J* = 8.4 Hz, 1H), 3.90 – 3.82 (m, 1H), 1.76 – 1.71 (m, 3H), 1.20 (d, *J* = 0.9 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 3H).

(2S,3R)-3-hydroperoxy-4-methylpent-4-en-2-ol (*anti*) 23b (minor):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (m, 2H), 4.29 (d, *J* = 5.0 Hz, 1H), 4.02 – 3.90 (m, 1H), 1.80 (m, 3H), 1.22 (d, *J* = 1.3 Hz, 3H).

Experiment 60 (PM-T-B-2):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.00488 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 5 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 5 95%

conversion was obtained and crude weight was 0.4979g containing **23** as mixture of 79:21 *syn*:*anti* diastereomers.

Conversion 95%, yield of **23a** 75% and **23b** 20% by NMR.

(*2S,3S*)-3-hydroperoxy-4-methylpent-4-en-2-ol (*Syn*)23a (major):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (dd, *J* = 3.7, 2.3 Hz, 15H), 4.14 (d, *J* = 8.4 Hz, 7H), 3.86 (dq, *J* = 8.4, 6.4 Hz, 1H), 1.76 – 1.72 (m, 2H), 1.20 (s, 1H), 1.13 (d, *J* = 6.4 Hz, 1H).

(*2S,3R*)-3-hydroperoxy-4-methylpent-4-en-2-ol (*anti*)23b (minor):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 – 5.11 (m, 2H), 4.29 (d, *J* = 5.0 Hz, 1H), 3.94 (dd, *J* = 10.3, 6.7 Hz, 1H), 1.80 (s, 3H), 1.25 – 1.23 (m, 1H), 1.23 – 1.21 (m, 3H).

Experiment 61 (PM-T-B-3):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.00488 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 4 hours 94% conversion was obtained and crude weight was 0.5533g containing **23** as mixture of 82:18 *syn*:*anti* diastereomers.

Conversion 94%, yield of **23a** 77% and **23b** 17% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 62 (PM-T-B-4):

Following **General Procedure 3** 0.51g (5.0919 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.00488 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 4 hours 85% conversion was obtained and crude weight was 0.622g containing **23** as mixture of 76:24 *syn*:*anti* diastereomers.

Conversion 85%, yield of **23a** 65% and **23b** 20% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 63 (PM-T-B-5):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 6mg (0.00976 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 3 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 3 hours 96% conversion was obtained and crude weight was 0.4689g containing **23** as mixture of 86:14 *syn*:*anti* diastereomers.

Conversion 96%, yield of **23a** 83% and **23b** 13% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 64 (PM-T-B-6):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 9mg (0.014640 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 3 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 3 hours 87% conversion was obtained and crude weight was 0.6092g containing **23** as mixture of 79:21 *syn*:*anti* diastereomers.

Conversion 87%, yield of **23a** 70% and **23b** 18% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 65 (PM-T-B-7):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 10mg (0.016267 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 3 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 3 hours 92% conversion was obtained and crude weight was 0.5432g containing **23** as mixture of 80:20 *syn*:*anti* diastereomers.

Conversion 92%, yield of **23a** 74% and **23b** 18% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 66 (PM-T-B-8):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 15mg (0.024400 mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 3 hours 94% conversion was obtained and crude weight was 0.7329g containing **23** as mixture of 81:19 *syn*:*anti* diastereomers.

Conversion 94%, yield of **23a** 76% and **23b** 18% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 67 (PM-T-B-9):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 25mg (0.040660mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 3 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 3 hours 93% conversion was obtained and crude weight was 0.8546g containing **23** as mixture of 83:17 *syn*:*anti* diastereomers.

Conversion 93%, yield of **23a** 77% and **23b** 16% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 68 (PM-T-B-13):

Following **General Procedure 3** 0.250g (2.496 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 1.5mg (0.00469mmol) methylene blue in 75 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 4 hours 94% conversion was obtained and crude weight was 0.109g containing **23** as mixture of 81:19 *syn*:*anti* diastereomers.

Conversion 94%, yield of **23a** 77% and **23b** 18% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 69 (PM-T-B-14):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was

irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 4 hours 94% conversion was obtained and crude weight was 0.8546g containing **23** as mixture of 77:23 *syn*:*anti* diastereomers.

Conversion 94%, yield of **23a** 72% and **23b** 22% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 70 (PM-T-B-15):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 5 hours 95% conversion was obtained and crude weight was 0.6068g containing **23** as mixture of 80:20 *syn*:*anti* diastereomers.

Conversion 95%, yield of **23a** 76% and **23b** 19% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 71 (PM-T-B-16):

Following **General Procedure 3** 1g (9.984 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 5 hours 91% conversion was obtained and crude weight was 0.9663g containing **23** as mixture of 84:16 *syn*:*anti* diastereomers.

Conversion 91%, yield of **23a** 76% and **23b** 15% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 72 (PM-T-B-17):

Following **General Procedure 3** 1g (9.984 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 6mg (0.00976mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 6 hours

98% conversion was obtained and crude weight was 1.027g containing **23** as mixture of 89:11 *syn*:*anti* diastereomers.

Conversion 98%, yield of **23a** 87% and **23b** 11% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 73 (PM-T-B-18):

Following **General Procedure 3** 0.5g (4.99 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 4 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 6 hours 100% conversion was obtained and crude weight was 0.3576g containing **23** as mixture of 82:18 *syn*:*anti* diastereomers.

Conversion 100%, yield of **23a** 82% and **23b** 18% by NMR.

^{1}H NMR: Similar to Experiment 59.

Experiment 74 (PM-T-B-19):

Following **General Procedure 3** 1g (9.984 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 6mg (0.00976mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 7 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 7 hours 100% conversion was obtained and crude weight was 1.22g containing **23** as mixture of 85:15 *syn*:*anti* diastereomers.

Conversion 100%, yield of **23a** 85% and **23b** 15% by NMR.

^{1}H NMR: Similar to Experiment 59.

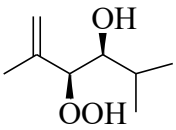
Experiment 75 (PM-T-B-20):

Following **General Procedure 3** 1g (9.984 mmol) of 4-methylpent-3-en-2-ol **20** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 7 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **20** to **23** was determined by NMR analysis of the reaction samples. After 7 hours 100% conversion was obtained and crude weight was 1.375g containing **23** as mixture of 94:6 *syn*:*anti* diastereomers.

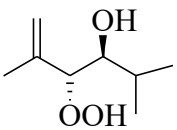
Conversion 100%, yield of **23a** 94% and **23b** 6% by NMR.

^{1}H NMR: Similar to Experiment 59.

7.3.1.6 Batch photoreactions of 2,5-Dimethylhex-4-en-3-ol 21



24a



24b

Experiment 76 (PM-DMHx-B-1):

Following **General Procedure 3** 0.500g (3.8998 mmol) of 2,5-Dimethylhex-4-en-3-ol **21** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane was irradiated under visible light for 5 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **21** to **24** was determined by NMR analysis of the reaction samples. After 5 hours 74% conversion was obtained and crude weight was 0.337g containing **24** as mixture of 95:5 *syn*:*anti* diastereomers.

Conversion 74%, yield of **24a** 70% and **24b** 4% by NMR.

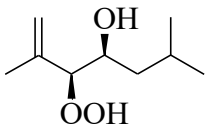
(*3S,4S*)-4-hydroperoxy-2,5-dimethylhex-5-en-3-ol (*syn*) 24a (major):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.32 (d, *J* = 8.3 Hz, 1H), 3.55 – 3.50 (m, 1H), 1.76 – 1.71 (m, 3H), 1.67 (d, *J* = 1.2 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 2H), 0.90 (d, *J* = 6.8 Hz, 2H).

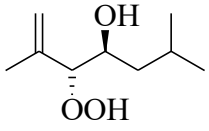
(*3S,4R*)-4-hydroperoxy-2,5-dimethylhex-5-en-3-ol (*anti*) 24b (minor):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.37 (d, *J* = 6.4 Hz, 1H), 3.56 (d, *J* = 2.6 Hz, 1H), 1.77 (s, 2H), 0.93 (d, *J* = 6.7 Hz, 9H), 0.84 (d, *J* = 6.8 Hz, 6H).

7.3.1.7 Batch photoreactions of 2,5-Dimethylhept-2-en-4-ol 22



25a



25b

Experiment 77 (PM-DMHp-B-1):

Following **General Procedure 3** 0.500g (3.5151 mmol) of 2,5-Dimethylhept-2-en-4-ol **22** was mixed with 3mg (0.0044880mmol) *meso*-tetraphenylporphyrin in 100 mL of dichloromethane

was irradiated under visible light for 5 hours in Schlenk flask placed inside Rayonet reactor. Conversion of **22** to **25** was determined by NMR analysis of the reaction samples. After 5 hours 100% conversion was obtained and crude weight was 0.4494g containing **25** as mixture of 89:11 *syn*:*anti* diastereomers.

Conversion 100%, yield of **25a** 89% and **25b** 11% by NMR.

(*3S,4S*)-3-hydroperoxy-2,6-dimethylhept-1-en-4-ol (*syn*) 25a (major):

^{1}H NMR (400 MHz, CDCl3) δ 5.10 – 5.00 (m, 1H), 4.16 (d, J = 8.1 Hz, 1H), 3.75 (dd, J = 10.3, 5.7 Hz, 1H), 1.74 (s, 1H), 1.36 (dd, J = 31.1, 10.0 Hz, 1H), 1.14 – 1.06 (m, 1H), 0.93 (d, J = 6.7 Hz, 2H), 0.88 (s, 2H).

(*3R,4S*)-3-hydroperoxy-2,6-dimethylhept-1-en-4-ol (*anti*) 25b (minor):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 – 5.01 (m, 1H), 4.31 (d, *J* = 4.8 Hz, 1H), 3.84 (dd, *J* = 7.5, 2.5 Hz, 1H), 1.78 (s, 1H), 0.87 (d, *J* = 1.7 Hz, 2H).

7.1.3.8 Batch Catalytic reactions of 23 for synthesis of Trioxanes

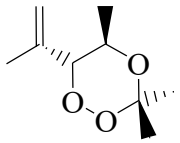
General procedure 10: 0.2 mL of Boron trifluoride hydrate or catalytic amount of In(III)$(OTf)_3$ was added to a round bottomed flask containing stirred solution of β-hydroperoxyalcohol (**23**). The mixture was stirred on ice-bath maintained at 0 – 5°C for 2 hours then stirred overnight at room temperature. Then the solvent was evaporated under reduced pressure and the collected crude was dissolved in 10mL DMF. Followed by mixing with 25mL saturated sodium bisulphite solution and shaking for 30 seconds. Then 25mL water was added and the aqueous layer was extracted with 10% ethyl acetate/n-hexane (3 x 25 mL) and organic layers were collected and washed three times with water 25mL followed by washing with brine solution 25mL. Then dried over Sodium sulphate or Magnesium sulphate. Oily or semisolid crude mixture was obtained after evaporation of solvent in rotary evaporator and NMR analysis was performed for crude and then subjected to chromatographic separation or stationary phase fraction collector.

7.1.3.8.1 (*5R,6R*)-3,3,5-trimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 26:

Experiment 78 (PM-T-B-10A):

Following **General procedure 10** 270mg (2.08mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 1.64mL (2.08mmol) acetone and 10mg In(III)$(OTf)_3$ in 100mL

dichloromethane in a round bottomed flask kept at 0℃ and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 291mg of crude containing **26** was obtained. The crude was analyzed by NMR spectroscopy. Followed by aqueous workup with saturated sodium bisulphite solution the final mixture analysis showed complete absence of product.



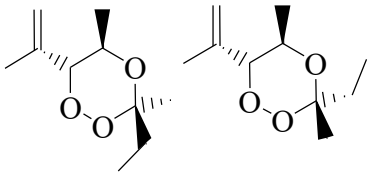
26

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (dd, 2H, *J* = 3.2, 1.6 Hz, =C$\underline{H}_2$), 4.21 (d, 1H, *J* = 9.5 Hz, OOC$\underline{H}$), 4.08 (dq, 1H, *J* = 9.5, 6.2 Hz, OC$\underline{H}$), 1.79 – 1.75 (m, 3H, =CCH_3), 1.67 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.10 (d, 3H*J* = 6.2 Hz, C$\underline{H}_3$CH).

7.1.3.8. 2 (*3R,5R,6R*)-3-ethyl-3,5-dimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 27a and (*3S,5R,6R*)-3-ethyl-3,5-dimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 27b:

Experiment 79 (PM-Cat-10):

Following **General procedure 10** 500mg (3.784mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.338mL (3.784mmol) 2 - butanone and 30mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0℃ and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 335mg of crude containing 1,2,4-trioxane compound was obtained containing a mixture of diastereomers **27a** and **27b** with 61:39 ratio as shown by NMR spectroscopy. Followed by aqueous workup with saturated sodium bisulphite solution the final mixture analysis showed complete absence of product.



27a **27b**

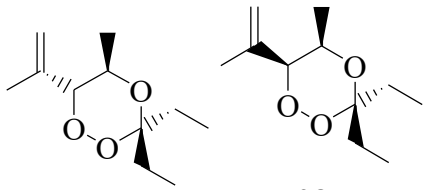
^{1}H NMR (400 MHz, $CDCl_3$) of major diastereomer 27a: δ 5.13 – 5.04 (m, 2H, =CH_2), 4.18 (d, *J* = 4.9 Hz, 1H, OOCH), 4.13 – 4.06 (m, 1H, OCH), 1.79 – 1.76 (m, 3H, CH_3C=), 1.63 (d, *J* = 7.6 Hz, 3H, C$\underline{H}_2$$CH_3$), 1.61 (s, 3H, CH_3), 1.09 (d, *J* = 6.1 Hz, 8H, C$\underline{H}_3$CH), 0.95 (t, *J* = 7.6 Hz, 9H, CH_2C$\underline{H}_3$).

^{1}H NMR (400 MHz, $CDCl_3$) of minor diastereomer 27b: δ 4.21 (d, *J* = 4.9 Hz, 1H, OOCH), 4.06 – 3.99 (m, 1H, OCH), 1.75 – 1.73 (m, 1H, CH_3C=), 1.28 (s, 3H, CH_3).

7.1.3.8. 3 (*5R,6R*)-3,3-diethyl-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 28a and (*5R,6S*)-3,3-diethyl-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 28b:

Experiment 80 (PM-Cat-10):

Following **General procedure 10** 500mg (3.784mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.44mL (3.784mmol) 3 - pentanone and 30mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 413mg of crude containing 1,2,4-trioxane was obtained containing a mixture of diastereomers **28a** and **28b** with 89:11 ratio as shown by NMR spectroscopy. Followed by aqueous workup with saturated sodium bisulphite solution the final mixture analysis showed complete absence of product.



28a **28b**

^{1}H NMR (400 MHz, $CDCl_3$) of major diastereomer 28a: δ 5.10 – 5.04 (m, 2H, $=CH_2$), 4.17 (d, *J* = 9.5 Hz, 1H, OOCH), 4.07 – 4.00 (m, 1H, OCH), 2.19 – 1.94 (m, 2H, $C\underline{H_2}CH_3$), 1.77 – 1.75 (m, 3H, $C\underline{H_3}C$=), 1.64 – 1.54 (m, 2H, 2H, $C\underline{H_2}CH_3$), 1.09 (d, *J* = 6.2 Hz, 3H, CH_3CH), 0.90 (t, *J* = 7.6 Hz, 6H, 2 x $C\underline{H_3}CH_2$).

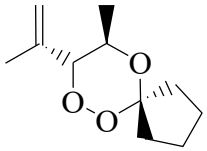
^{1}H NMR (400 MHz, $CDCl_3$) of minor diastereomer 28b: δ 4.98 – 4.87 (m, 2H, $=CH_2$), 4.20 (d, *J* = 9.6 Hz, 1H, OOCH), 3.87 – 3.81 (m, 1H, OCH), 1.04 (d, *J* = 7.4 Hz, 3H, $C\underline{H_3}CH$).

7.1.3.8. 4 (*8RS,9RS*)-8-Isopropenyl-9-methyl-6,7,10-trioxa-spiro[4.5]decane 29:

Experiment 81 (PM-Cat-9):

Following **General procedure 10** 500mg (3.784mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.334mL (3.784mmol) cyclopentanone and 30mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 548mg of crude containing 1,2,4-trioxane **29** was obtained and the crude was

analyzed by NMR spectroscopy. Followed by column chromatography with 9:1 n-hexane and ethyl acetate no product could be recovered.



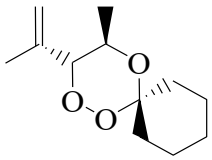
29

^{1}H NMR (400 MHz, $CDCl_3$) of 29: δ 5.12 – 5.04 (m, 2H, $=CH_2$), 4.28 (d, *J* = 9.4 Hz, 1H, OOCH), 3.95 (dq, *J* = 9.4, 6.3 Hz, 1H, OCH), 2.58 – 2.47 (m, 1H, CH_2), 1.78 – 1.72 (m, 3H, $CH_3C=$), 1.62 – 1.90 (m, 7H, CH_2)1.11 (d, *J* = 6.3 Hz, 3H, $C\underline{H_3}CH$).

7.1.3.8. 5 (*3RS,4RS*)-3-Isopropenyl-4-methyl-1,2,5-trioxa-spiro[5.5]undecane 30:

Experiment 82 (PM-T-B-6):

Following **General procedure 10** 600mg (4.6mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.48mL (4.6mmol) cyclohexanone and 30mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 1034mg of crude containing 1,2,4-trioxane **30** was obtained and the crude was analyzed by NMR spectroscopy. Followed by column chromatography with 9:1 n-hexane and ethyl acetate no product could be recovered.



30

^{1}H NMR (400 MHz, $CDCl_3$) of 30: δ 5.06 – 5.02 (m, 2H, $=CH_2$), 4.17 (d, *J* = 9.6 Hz, 1H, OOCH), 4.11 – 4.03 (m, 1H, OCH), 2.25 – 2.18 (m, 1H, CH_2), 1.98 – 1.89 (m, 1H, CH_2), 1.74 – 1.71 (m, 3H, $CH_3C=$), 1.52 (dd, *J* = 11.9, 9.9 Hz, 8H, 4 x CH_2), 1.06 (d, *J* = 6.1 Hz, 3H, CH_3CH).

7.1.3.8. 6 (*3RS,4RS*)-3-Isopropenyl-4-methyl-1,2,5-trioxa-spiro[5.6]dodecane 31:

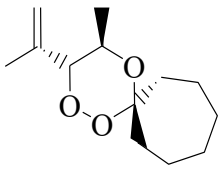
Experiment 83 (PM-Cat-6):

Following **General procedure 10** 250mg (1.892mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.23mL (1.892mmol) cycloheptanone and 0.2mL Boron trifluoride hydrate (BF_3 hydrate) in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24

hours. After solvent evaporation 137mg of crude containing 1,2,4-trioxane **31** was obtained and the crude was analyzed by NMR spectroscopy showed a complex mixture containing no product.

Experiment 84 (PM-Cat-6R):

Following **General procedure 10** 250mg (1.892mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.23mL (1.892mmol) cycloheptanone and 5mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 113mg of crude containing 1,2,4-trioxane **31** was obtained and the crude was analyzed by NMR spectroscopy showed a complex mixture containing little product. Followed by column chromatography with 9:1 n-hexane and ethyl acetate no product could be recovered.



31

^{1}H NMR (400 MHz, $CDCl_3$) of 30 (significant signals in complex NMR): δ 5.01 – 4.91 (m, 2H, $=CH_2$), 4.05 (d, J = 8.2 Hz, 1H, OOCH), 3.81 – 3.74 (m, 1H, OCH), 2.13 – 2.10 (m, 2H, $C\underline{H_2}CH_3$), 1.04 (d, J = 6.4 Hz, 3H, $C\underline{H_3}CH$).

7.1.3.8. 7 (*5RS,6RS*)-5-Methyl-6-(prop-1-en-2-yl)-spiro[1,2,4-trioxacyclohexane-3,2'-adamantane] 32:

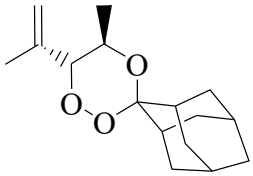
Experiment 85 (PM-T-B-5):

Following **General procedure 10** 469mg (3.54mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 533mg (3.54mmol) adamantanone and 0.2mL Boron trifluoride etherate (BF_3 etherate) in 100mL dry dichloromethane in a round bottomed flask kept at 0°C under inert atmosphere and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 971mg of crude containing and the crude was analyzed by NMR spectroscopy showed a complex mixture containing no product.

Experiment 86 (PM-Cat-7):

Following **General procedure 10** 600mg (4.6mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 500mg (3.3mmol) adamantanone and 10mg In(III)$(OTf)_3$ in 100mL

dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 808mg of crude containing 1,2,4-trioxane **32** was obtained and the crude was analyzed by NMR spectroscopy showed a clean product formation.



32

^{1}H NMR (400 MHz, $CDCl_3$) of 32: δ 5.10 – 5.05 (m, 6H), 4.21 (d, *J* = 9.5 Hz, 3H), 4.08 (dq, *J* = 9.5, 6.2 Hz, 3H), 2.93 (d, *J* = 2.5 Hz, 3H), 1.79 – 1.73 (m, 15H), 1.73 – 1.56 (m, 30H), 1.10 (d, *J* = 6.2 Hz, 10H).

7.1.3.8. 8 (*3R,5R,6R*)-3-(2-chlorophenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 33:

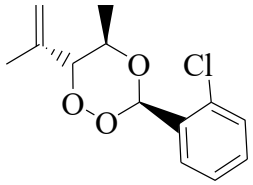
Experiment 87 (PM-Cat-2):

Following **General procedure 10** 500mg (3.785mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.426mL (532mg, 3.785mmol) 2-chlorobenzaldehyde and 5mg In(III)$(OTf)_3$ in 50mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation the crude sample was analyzed by NMR spectroscopy showing a complex spectrum and no desired product was present.

Experiment 88 (PM-Cat-2R):

Following **General procedure 10** 250mg (1.892mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.213mL (266mg, 1.892mmol) 2-chlorobenzaldehyde and 0.2 mL BF_3 hydrate in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 263mg of crude containing 1,2,4-trioxane **33** was obtained and the crude was analyzed by NMR spectroscopy showed a clean product formation along with leftover aldehyde and little impurities. The work-up was skipped and the crude was subjected to separation process directly. Followed by column chromatography with 9:1 n-hexane and ethyl acetate 39.3mg product was obtained mixed with aldehyde. The mixed product was the

subjected to aqueous work-up with sodium bisulphite solution and the NMR analysis showed complete removal of aldehyde leaving only 13mg (0.0504mmol, 27%) pale oily product **33**.



33

^{1}H NMR (400 MHz, $CDCl_3$) of 33: δ 7.76 – 7.16 (m, 1H), 6.59 (s, 1H), 5.15 (dd, *J* = 8.2, 6.7 Hz, 1H), 4.50 (d, *J* = 9.1 Hz, 1H), 4.11 (dq, *J* = 9.1, 6.3 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) of 33: δ 138.78 (s), 133.69 (s), 132.18 (s), 131.18 (s), 129.30 (d, *J* = 80.2 Hz), 127.09 (s), 118.61 (s), 101.18 (s), 89.12 (s), 74.21 (s), 19.93 (s), 16.62 (s).

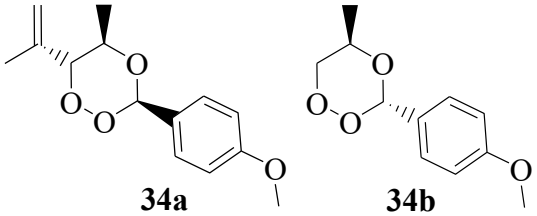
Molecular weight: 245.72 g/mol

Rf value: 0.76

7.1.3.8. 9 (*3R,5R,6R*)-3-(4-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 34a and (*3S,5R,6R*)-3-(4-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 34b:

Experiment 89 (PM-T-B-12A):

Following **General procedure 10** 250mg (1.892mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.222mL (249mg, 1.892mmol) 4-methoxybenzaldehyde and 5mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 493mg of crude containing 1,2,4-trioxane **34** was obtained and the crude was analyzed by NMR spectroscopy showed a clean product formation along with leftover aldehyde and impurities. The work-up was skipped and the crude was subjected to separation process directly. Followed by Combi flash separation method with slow gradient n-hexane and (5 – 10%) ethyl acetate 71mg (0.2803mmol, 15%) purple color oily product was obtained as diastereomeric mixture. The TPP mixed with **23** from photooxygenation step could not be removed.



34a **34b**

^{1}H NMR (400 MHz, $CDCl_3$) of 34a (major): δ 7.48 – 6.80 (m, 1H), 6.17 (s, 1H), 5.14 (d, *J* = 14.1 Hz, 1H), 4.47 (d, *J* = 9.1 Hz, 1H), 4.09 – 3.98 (m, 1H), 1.86 – 1.76 (m, 1H), 1.27 (d, *J* = 10.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) of 34a (major): δ 161.11 (s), 139.15 (s), 128.82 (s), 127.20 (s), 118.56 (s), 114.12 (s), 104.34 (s), 89.07 (s), 74.16 (s), 55.60 (s), 31.20 (s), 20.04 (s), 16.81 (s)

^{1}H NMR (400 MHz, $CDCl_3$) of 34b (minor): δ 6.35 (s, 1H), 1.71 (s, 14H), 1.32 (d, *J* = 11.4 Hz, 51H).

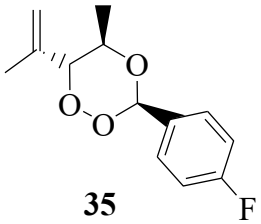
Molecular Weight: 253.31g/mol

Rf value: 0.43

7.1.3.8. 10 (*3R,5R,6R*)-3-(4-fluorophenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 35:

Experiment 90 (PM-Cat-8):

Following **General procedure 10** 500mg (3.785mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 0.405mL (469.75mg, 3.785mmol) 4 – fluorobenzaldehyde and 5mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 771.5mg of crude containing 1,2,4-trioxane **34** was obtained and the crude was analyzed by NMR spectroscopy showed a clean product formation along with leftover aldehyde and impurities. The work-up was skipped and the crude was subjected to separation process directly. Followed by Column chromatographic purification with 9:1 n-hexane and ethyl acetate only 6mg slightly pinkish oily product was obtained along with leftover aldehyde. The TPP mixed with **23** from photooxygenation step could not be removed.



35

^{1}H NMR (400 MHz, $CDCl_3$) of 35: δ 7.49 (ddd, *J* = 8.3, 5.2, 2.5 Hz, 1H), 7.05 (ddd, *J* = 9.5, 5.8, 2.4 Hz, 1H), 6.38 (s, 1H), 6.19 (s, 1H), 5.17 – 5.09 (m, 1H), 4.46 (d, *J* = 9.1 Hz, 1H), 4.11 – 3.99 (m, 1H), 1.80 – 1.78 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 1H).

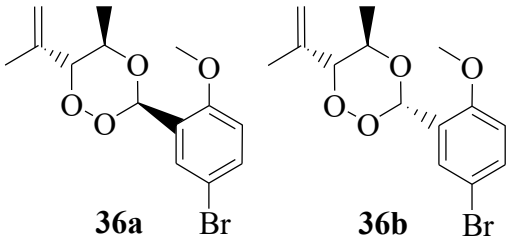
Molecular Weight: 241.28g/mol

Rf value: 0.58

7.1.3.8. 11 (*3R,5R,6R*)-3-(5-bromo-2-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 36a and (*3S,5R,6R*)-3-(5-bromo-2-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane 36b:

Experiment 91 (PM-T-B-12B):

Following **General procedure 10** 250mg (1.892mmol) of 3-hydroperoxy-4-methylpent-4-en-2-ol **23** was mixed with 393.3mg (1.892mmol) 5-Bromo-2-methoxybenzaldehyde and 5mg In(III)$(OTf)_3$ in 100mL dichloromethane in a round bottomed flask kept at 0°C and stirred. The reaction was allowed to attain room temperature with continuous stirring for 24 hours. After solvent evaporation 631mg of crude containing 1,2,4-trioxane **36** was obtained and the crude was analyzed by NMR spectroscopy showed a clean product formation along with leftover aldehyde and impurities. The work-up was skipped and the crude was subjected to separation process directly. Followed by Combi flash separation method with slow gradient n-hexane and (5 – 10%) ethyl acetate 58mg (0.175mmol, 9%) purple color oily product was obtained as diastereomeric mixture along with little other impurities. The TPP mixed with **23** from photooxygenation step could not be removed.



36a **36b**

^{1}H NMR (400 MHz, $CDCl_3$) of 36a (major): δ 7.69 (d, *J* = 2.6 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.55 (s, 1H), 5.13 (dd, *J* = 8.4, 6.9 Hz, 2H), 4.47 (d, *J* = 9.1 Hz, 1H), 3.84 (s, 3H), 1.80 – 1.79 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 4H).

^{1}H NMR (400 MHz, $CDCl_3$) of 36b (minor): δ 6.26 (s, 1H), 1.82 (s, 1H), 1.73 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 1H).

Molecular Weight: 331.20g/mol

Rf value: 0.40

7.3.2 Flow reactions

7.3.2.1 Photoreactions in capillary flow Reactor – 1

General Procedure 11: Prior to every flow reaction the light was turned on and the flow reactor was first flushed with 100mL of solvent along with air into the solvent stream at the desired flow rates to get stabilized gas-liquid slug flow. When the solvent was about to finish the sample vessel was filled with reaction mixture containing specified amount of sensitizer and substrate (**2** or **4** or **20**) in required volume of solvent and the real reaction continued without any break in slug-flow. Likewise, just before ending of every reaction the sample vessel was again filled with 50mL of solvent and the reactor was flushed out continuously to collect adhered reactants on the wall of capillary.

7.3.2.1.1 Photo transformation of Dihydroartemisinic acid (DHAA) 1 in flow reactor – 1 and follow-up catalysis in batch to synthesize artemisinin 4

Entry 1 (Artemisinin flow 1):

Following **General Procedure 11** at 5 mL/min flow rate (average of combined air and liquid flow) a solution of 0.473g (2.001 mmol) of **1** and 100mg (0.09826 mmol) rose bengal in 200 mL ethanol was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. After 11 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed 18% of intermediate **3** was observed.

The reaction mixture was cooled at 0°C and air was bubbled in to the solution with an aquarium pump for 2 minutes. Then 0.19 mL (2.482 mmol) of TFA was added dropwise into the stirred solution and catalysis was continued for 2 hours with air bubbling. After solvent evaporation 0.414g of crude was obtained and traces of product **4** was seen to be present.

Conversion 23%, intermediate **3** 18% and product **4** 3% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H, H-5), 2.74 (m, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.38 (m, 1H, H-11).

Entry 2 (Artemisinin flow 2):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.200g (0.84 mmol) of **1** and 100mg (0.09826 mmol) rose bengal in 200 mL ethanol was injected into the

capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 18 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis showed presence of intermediate **3** (42%).

The reaction mixture was cooled at 0°C and air was bubbled in to the solution with an aquarium pump for 2 minutes. Then 0.19 mL (2.482 mmol) of TFA was added dropwise into the stirred solution and catalysis was continued for 2 hours with air bubbling. After solvent evaporation and workup 0.110g of crude was obtained containing 21% **4** with other by-products and **1**.

Conversion 60%, intermediate **3** 42% and product **4** 21% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H, H-5), 2.72 (m, 1H, H-11).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H, H-5), 3.40 (m, 1H, H-11).

Entry 3 (PM-1):

Following **General Procedure 11** at 2 mL/min liquid flow rate a solution of 0.200g (0.84 mmol) of **1** and 6mg (0.0186 mmol) methylene blue in 150 mL acetone was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 25 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis showed 88% conversion and presence of 64% intermediate **3**.

Following **General Procedure 5** catalysis of photo-product was conducted and 0.195g crude was obtained that yielded 84mg (35%) off-white pure **4** upon recrystallization from cyclohexane.

Conversion 86%, intermediate **3** 75% and product **4** 60% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.82 – 2.68 (m, 1H), 2.00 – 1.76 (m, 13H), 1.58 (dd, J = 24.6, 19.1 Hz, 8H), 1.29 (dd, J = 9.8, 5.9 Hz, 11H), 0.93 (d, J = 5.7 Hz, 3H), 0.87 (d, J = 6.3 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.46 – 3.34 (m, 1H), 2.58 – 2.36 (m, 2H), 1.21 (d, J = 7.3 Hz, 6H), 1.00 (d, J = 5.9 Hz, 4H), 0.88 (d, J = 4.4 Hz, 4H).

Entry 4 (PM-2):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.200g (0.84 mmol) of **1** and 6mg (0.0186 mmol) methylene blue in 150 mL acetone was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 20 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of intermediate **3**.

Following **General Procedure 5** catalysis of photo-product was conducted and 0.209g crude was obtained that yielded 56mg (23%) off-white pure **4** upon recrystallization from cyclohexane.

Conversion 72%, intermediate **3** 60% and product **4** 84% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.82 – 2.69 (m, 1H), 2.04 – 1.76 (m, 8H), 1.67 – 1.41 (m, 11H), 1.19 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 5.8 Hz, 3H), 0.86 (d, J = 2.7 Hz, 2H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, J = 13.2 Hz, 1H), 3.42 – 3.33 (m, 1H), 2.52 – 2.29 (m, 2H), 2.03 (d, J = 13.2 Hz, 3H), 1.92 – 1.67 (m, 5H), 1.42 (s, 7H), 1.18 (d, J = 7.3 Hz, 5H), 1.01 (dd, J = 25.7, 4.0 Hz, 5H).

Entry 5 (PM-6):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.00976 mmol) *meso*-tetraphenylporphyrin in 80 mL dichloromethane was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. After 27 minutes residence time in flow reactor the photo-product was collected in a flask containing a stirred solution of 0.19 mL (2.482 mmol) TFA in 10 mL dichloromethane. After evaporating solvent 0.266g crude was obtained which was dissolved in 25 mL ethyl acetate. Then the mixture was washed with saturated solution of sodium hydrogen carbonate 25 mL followed by addition of 20 mL water. The organic layer was separated and the aqueous layer was washed thrice with 3 x 25 mL ethyl acetate. Organic layers were combined and washed with 25 mL brine solution and then dried over anhydrous sodium sulphate. After that the solution was filtered through silica and then ethyl acetate was evaporated. A crude mixture of 0.128g was obtained.

Conversion 96%, intermediate **3** 73% and product **4** 8% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.79 – 2.66 (m, 1H), 2.01 – 1.71 (m, 6H), 1.64 – 1.38 (m, 5H), 1.31 – 1.24 (m, 7H), 0.93 (d, J = 5.9 Hz, 3H), 0.86 (d, J = 6.2 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s,1H), complex NMR.

Entry 6 (PM-28):

Following **General Procedure 11** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. After 45 minutes residence time the reaction mixture was continuously collected in a flask. Then the mixture was filtered through silica to remove dye and to the filtrate 1 drop TFA was added in presence of air bubbling in it. The reaction was continued for 2 hours at room temperature. Later the solvent volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 46.5mg mixed crude was obtained.

Conversion 43%, intermediate **3** 14% and product **4** 4% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.74 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s,1H), 3.38 (m, 1H), complex NMR.

Entry 7 (PM-33):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 45 minutes the reaction end-product was collected continuously in a flask and 0.5 mL TFA was added in presence of air bubbling in the flask. The reaction was continued for 2 hours at 50°C. Later the solvent was evaporated and to the residue 25 mL n-hexane was added, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 144.8mg mixed crude was obtained.

Conversion 69%, intermediate **3** 54% and product **4** 6% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.83 – 2.64 (m, 1H), 2.19 – 2.06 (m, 1H), 1.88 (ddd, J = 36.3, 20.1, 6.1 Hz, 8H), 1.60 – 1.39 (m, 6H), 0.86 (d, J = 6.4 Hz, 2H), 0.80 (d, J = 9.0 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s,1H), 3.39 (m, 1H), complex NMR.

Entry 8 (PM-34):

Following **General Procedure 11** a mixture of 0.125g (0.528 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask and 0.1 mL TFA was added in presence of air bubbling in the flask. The reaction was continued for 2 hours at 50°C and stirred at room temperature for 4 days. Later the solvent was evaporated and to the residue 25 mL n-hexane was added, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 76mg mixed crude was obtained.

Conversion 87%, intermediate **3** 60% and product **4** 22% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.73 (dt, J = 12.2, 6.0 Hz, 1H), 2.02 – 1.73 (m, 11H), 1.53 (dd, J = 28.5, 19.2 Hz, 8H), 1.30 – 1.22 (m, 12H), 0.93 (d, J = 5.9 Hz, 4H), 0.86 (d, J = 6.5 Hz, 2H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s,1H), 3.36 (m, 1H), complex NMR.

Entry 9 (PM-35):

Following **General Procedure 11** a mixture of 0.100g (0.42 mmol) of **1**, 6mg (0.0186 mmol) methylene blue in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask and transferred into a Schlenk flask followed by addition of 0.1 mL TFA in presence of air bubbling in the flask and photo irradiation continued in Rayonet chamber for 2 hours. Later the solvent was evaporated and the residue was extracted with boiling n-hexane (3 x 25 mL).

Then the hexane fractions were combined and evaporated. A crude mixture of 86.3mg was obtained which on further recrystallization could not yield pure **4**.

Conversion 31%, intermediate **3** none and product **4** 49% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: Not observed.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.37 (dd, J = 7.2, 5.4 Hz, 1H), 2.47 – 2.31 (m, 3H), 2.14 – 1.87 (m, 16H), 1.45 – 1.38 (m, 19H), 1.19 (d, J = 9.7 Hz, 17H), 0.98 (d, J = 5.7 Hz, 10H).

Entry 10 (PM-36):

Following **General Procedure 11** a mixture of 0.050g (0.21 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask and catalysis was conducted by adding 0.1 mL TFA into the flask in presence of air bubbling and continued over night at room temperature. Later the solvent volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 23.4mg crude was obtained.

Conversion 87%, intermediate **3** 32% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.73 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Complex NMR.

Entry 11 (PM-39):

Following **General Procedure 11** a mixture of 0.100g (0.42 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by a mass flow controller (Alicat) pure oxygen was introduced into the reactants at 0.5 – 0.6 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask and catalysis was conducted by adding 0.01 mL TFA into1 the flask in presence of air bubbling and continued 2 hours at room temperature. Later the solvent volume was reduced to 25 mL and

washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 49.3mg crude was obtained.

Conversion 94%, intermediate **3** 43% and product **4** 40% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.23 (s, 1H), 2.72 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.88 (s, 1H), 3.39 (m, 1H). Complex NMR.

Entry 12 (PM-49):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask and catalysis was conducted by adding 0.01 mL TFA into the flask in presence of air bubbling and continued for 1 hour at 60°C and 1 hours at room temperature. Later the solvent volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 138mg crude was obtained.

Conversion 23%, intermediate **3** 9% and product **4** 11% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.73 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.39 (m, 1H). Complex NMR.

Entry 13 (PM-50):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 75 minutes the reaction end-product was collected continuously in a flask and catalysis was conducted by adding 0.01 mL TFA into the flask in presence of air bubbling and continued for 1 hour at 60°C and 1 hours at room

temperature. Later the solvent volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 141mg crude was obtained.

Conversion 52%, intermediate **3** 18% and product **4** 4% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.73 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.37 (m, 1H). Complex NMR.

Entry 14 (PM-62):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) rose bengal in 36 mL isopropanol and 4 mL water was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the outlet of reactor. Residence time was 65 minutes. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.05 mL TFA in 40 mL isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 108.8mg crude was obtained.

Conversion 54%, intermediate **3** 30% and product **4** 13% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.71 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.37 (m, 1H). Complex NMR.

Entry 15 (PM-63):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) rose bengal in 40 mL ethanol was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the outlet of reactor. Residence time was 65 minutes. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.05 mL TFA in 40 mL

isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 123mg crude was obtained.

Conversion 68%, intermediate **3** 51% and product **4** 4% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.26 (s, 1H), 2.72 (dd, J = 9.5, 5.2 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.00 – 1.74 (m, 6H), 1.61 – 1.42 (m, 5H), 1.33 – 1.20 (m, 13H), 0.87 (d, J = 6.5 Hz, 2H), 0.80 (d, J = 6.1 Hz, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 16 (PM-64):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) in 40 mL isopropanol was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the outlet of reactor. Residence time was 64 minutes. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.05 mL TFA in 40 mL isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 173mg crude was obtained.

Conversion 41%, intermediate **3** 27% and product **4** 2% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.74(m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.37 (m, 1H).

Entry 17 (PM-69):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) rose bengal in 36 mL isopropanol and 4 mL water was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the outlet of reactor. Residence time was 25 minutes. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.01 mL TFA in 40 mL isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 167mg crude was obtained.

Conversion 66%, intermediate **3** 51% and product **4** 16% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.74 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.37 (m, 1H), complex NMR.

Entry 18 (PM-70):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) rose bengal in 40 mL ethanol was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the outlet of reactor. Residence time was 25 minutes. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.01 mL TFA in 40 mL isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 132.2mg crude was obtained.

Conversion 57%, intermediate **3** 39% and product **4** 9% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.74 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.37 (m, 1H).

Entry 19 (PM-71):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue in 40 mL isopropanol was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the outlet of reactor. Residence time was 25 minutes and conversion were 25% with 11% **3**. The photo-irradiated reagents were continuously collected in a flask containing stirred solution 0.01 mL TFA in 40 mL isopropanol with air bubbling supplied in it. The catalysis was continued for 2 hours at room temperature. Then the solvent was evaporated and the residue was dissolved in dichloromethane 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 109mg crude was obtained containing majority of starting material with traces of product.

Conversion 24%, intermediate **3** 10% and product **4** 4% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 3: δ 5.25 (s, 1H), 2.73 (m, 1H).

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), Complex NMR.

7.3.2.1.2 Tandem photoreaction and thermal reaction in capillary flow Reactor – 1 to synthesize Artemisinin 4 from DHAA 1

General Procedure 12: Prior to every flow reaction the light was turned on and the flow reactor was first flushed with 100mL of solvent along with air into the solvent stream at the desired flow rates to get stabilized gas-liquid slug flow. When the solvent was about to finish the sample vessel was filled with reaction mixture containing specified amount of sensitizer and substrate **1** in required volume of solvent and the photo-product then entered into another capillary thermal reactor attached to the outlet of the main photoreactor with the help of a T-junction. A solution of trifluoroacetic acid was then injected into the stream of photo-product via the T-junction and allowed to travel through the thermal reactor maintained at desired temperature. After every reaction was over the sample vessel was again filled with 50mL of solvent and the reactor was flushed out continuously to collect adhered reactants on the wall of capillary.

Entry 20 (PM -7):

Following **General Procedure 12** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.00976 mmol) *meso*-tetraphenylporp3hyrin in 80 mL dichloromethane was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 27 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL DCM containing TFA 1 mL solution was pumped into the flow stream via another T-valve. The thermal module was maintained at 40°C in a water bath. The finally collected mixture was concentrated and 0.318g crude was obtained that was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 83.3mg mixed crude was obtained.

Conversion 64% and product **4** 18% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), Complex NMR.

Entry 21 (PM -8):

Following **General Procedure 12** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.00976 mmol) *meso*-tetraphenylporphyrin in 80 mL dichloromethane was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 27 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL DCM containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The thermal module was maintained at 40°C in a water bath. The finally collected mixture was concentrated and 0.324g crude was obtained that was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 91mg mixed crude was obtained.

Conversion and product could not be determined, complex NMR.

Entry 22 (PM-9):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and 0.117g crude was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 48mg mixed crude was obtained containing 56% product.

Conversion 90% and product **4** 56% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 23 (PM-10):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **2**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and 0.105g crude was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25

mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 39mg mixed crude was obtained containing 37% product.

Conversion 55% and product **4** 37% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.88 (s, 1H), 3.40 (m, 1H).

Entry 24 (PM-11):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 40 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and 0.141g crude was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 41mg mixed crude was obtained containing 79% product.

Conversion 84% and product **4** 79% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.88 (s, 1H), 3.45 – 3.35 (m, 1H), 2.53 – 2.18 (m, 23H), 2.06 – 1.62 (m, 19H), 1.44 (s, 7H), 1.21 (d, J = 7.2 Hz, 8H), 1.00 (d, J = 5.8 Hz, 5H), 0.88 (d, J = 6.1 Hz, 2H).

Entry 25 (PM-12):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After

40 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 0.161g crude mixture was collected, 29mg (24%) pure **4** was isolated after recrystallization from cyclohexane.

Conversion and product could not be determined as the crude NMR was very complex.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.50 – 3.31 (m, 1H), 2.52 – 2.38 (m, 1H), 2.14 – 1.94 (m, 3H), 1.83 (dd, J = 27.5, 8.0 Hz, 6H), 1.42 (t, J = 7.3 Hz, 12H), 1.20 (d, J = 7.3 Hz, 4H), 1.12 – 1.04 (m, 2H), 0.99 (d, J = 5.9 Hz, 5H).

Entry 26 (PM-13):

Following **General Procedure 12** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal in 75 mL isopropanol and 8 mL water was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 48 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL isopropanol containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and isopropanol was evaporated and the 0.251g residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 131.6mg crude mixture containing 36 % of artemisinin **4** was collected, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 62% and product **4** 36% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.36 (m, 1H).

Entry 27 (PM-14):

Following **General Procedure 12** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.0186 mmol) methylene blue in 80 mL dichloromethane was injected into the flow reactor – 1 at 2 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 25 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL dichloromethane containing TFA 1 mL solution was pumped (0.5 mL/min) into the flow stream via another T-valve. The first full length of thermal reactor was in a water bath at 45°C. The end product from reactor was collected in a flask and isopropanol was evaporated and the 0.212g residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 69mg crude mixture 26 % of artemisinin **4** was collected, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 49% and product **4** 26% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.37 (m, 1H).

Entry 28 (PM-15):

Following **General Procedure 12** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.0186 mmol) methylene blue in 80 mL chloroform was injected into the flow reactor – 1 at 2 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 35 minutes of residence time the photo-product mixture was recirculated once again in the photoreactor. After that the mixture of photo-products from flow reactor – 1 were allowed to enter into the thermal module (capillary 38.64m long) and 60 mL chloroform containing TFA 1 mL solution was pumped (1mL/min) into the flow stream via another T-valve. The first full length of thermal reactor was in a water bath at 45°C. The end product from reactor was collected in a flask and chloroform was evaporated and the residue was found which was

dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 88.3mg crude mixture was collected, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 3% and no product **4** seen by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Not observed.

Entry 29 (PM-16):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue in 80 mL dichloromethane was injected into the flow reactor – 1 at 2 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No BPR was used in this case. After 25 minutes of residence time when the photo-product mixture from flow reactor – 1 continuously entered into the thermal module (capillary 38.64m long) and 60 mL chloroform containing TFA 0.19 mL solution was pumped (1mL/min) into the flow stream via another T-valve. The first full length of thermal reactor was in a water bath at 45°C. The end product from reactor was collected in a flask and solvent was evaporated and the 0.113g residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 42.7mg crude mixture was collected showing 39% **4**, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 54% and product **4** 39% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H), 2.57 – 2.34 (m, 8H), 2.22 – 2.07 (m, 10H), 1.84 (ddd, J = 18.9, 16.4, 6.4 Hz, 34H), 1.47 (d, J = 8.6 Hz, 5H), 1.23 (d, J = 10.3 Hz, 29H), 0.87 (d, J = 6.4 Hz, 22H).

Entry 30 (PM-17):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 10mg (0.01027 mmol) Rose bengal in 40 mL ethanol was injected into the flow reactor – 1 at 1 mL/min flow

rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No BPR was used in this case. After 40 minutes of residence the photo-product mixture was recirculated once again in the photoreactor. After that the mixture of photo-products from flow reactor – 1 were allowed to enter into the thermal module (capillary 8.4m long) and 40 mL dichloromethane containing 1 drop TFA solution was pumped (0.5 mL/min) into the flow stream via another T-valve. The full length of thermal reactor maintained at room temperature. The end product from reactor was collected in a flask and solvent was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 54mg crude mixture was collected containing 36% artemisinin with other by-products, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 87% and product **4** 36% after recirculation by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.38 (m, 1H).

Entry 31 (PM-18):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 10mg (0.01027 mmol) Rose bengal in 40 mL ethanol was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.75 mL/min flow rate via the T-mixer. No BPR was used in this case. After 60 minutes of residence the photo-product mixture from flow reactor – 1 continuously enter into the thermal module (capillary 8.4m long) and 40 mL dichloromethane containing 1 drop TFA solution was pumped (0.5 mL/min) into the flow stream via another T-valve. The full length of thermal reactor maintained at 43°C in water bath. The end product from reactor was collected in a flask 25 mL saturated sodium hydrogen carbonate solution supplied with gentle air bubbling in it from a fish tank pump. Workup was followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 65.3mg crude mixture was collected, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 70% and product **4** 3% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H), 3.40 (m, 1H).

Entry 32 (PM-19):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 10 mL acetone containing TFA 0.1 mL solution was pumped (0.5 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 0.77g crude mixture was collected, no pure **4** was isolated after recrystallization from cyclohexane.

Conversion 42% and product **4** 2% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.38 (m, 1H), complex NMR.

Entry 33 (PM-20):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and

organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 31.3mg crude mixture was collected.

Conversion 64% and no product **4** was seen by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Not observed.

Entry 34 (PM-21):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. Also, additional air from fish tank pump was injected into thermal reaction via the same T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 39mg crude mixture was collected.

Conversion and product **4** were not determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Not observed, complex NMR.

Entry 35 (PM-22):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.00937 mmol) methylene blue in 75 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL acetone containing 3 drops TFA

solution was pumped (1 mL/min) into the flow stream via another T-valve. Also, additional air from fish tank pump was injected into thermal reaction via the same T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and kept it stirred with air bubbling in it for overnight. Then acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 59mg crude mixture was collected showing 15% **4** with by-products.

Conversion 73% and product **4** 15% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 36 (PM-23):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 6mg (0.00976 mmol) *meso*-tetraphenylporphyrin in 80 mL dichloromethane was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 0.75 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL DCM containing TFA 1 mL solution was pumped (1 mL/min) into the flow stream via another T-valve. The first 20.4m length of thermal reactor was thermal module was at room temperature and remaining 18.24m was in a water bath at 50°C. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 110.1mg crude mixture was collected showing 56% **4** with by-products.

Conversion 99% and product **4** 56% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.83 (s, 1H), 3.43 – 3.31 (m, 1H), 2.38 (dd, J = 11.6, 2.8 Hz, 2H), 2.18 – 1.95 (m, 8H), 1.88 – 1.62 (m, 14H), 1.42 (s, 4H), 1.19 (d, J = 7.3 Hz, 7H), 0.97 (d, J = 5.9 Hz, 4H).

Entry 37 (PM-26):

Following **General Procedure 12** a mixture of 0.100g (0.42 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal in 70 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. No 5psi BPR was attached between the end of flow reactor capillary and the thermal reactor inlet. After 45 minutes of residence time when the photo-product mixture from flow reactor – 1 entered into the thermal module (capillary 38.64m long) 60 mL n-hexane containing 4 – 5 drops TFA solution was pumped (1 mL/min) into the flow stream via another T-valve. The full length of thermal reactor was thermal module was at room temperature. The end product from reactor was collected in a flask and acetone was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 33mg crude mixture was collected containing 28% of **4**.

Conversion 68% and product **4** 28% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.83 (s, 1H), 3.38 (m, 1H), complex NMR.

7.3.2.1.3 One-pot continuous flow synthesis of Artemisinin 4 in flow Reactor – 1

General Procedure 13: Prior to every flow reaction the light was turned on and the flow reactor was first flushed with 100mL of solvent along with air into the solvent stream at the desired flow rates to get stabilized gas-liquid slug flow. When the solvent was about to finish the sample vessel was filled with reaction mixture containing specified amount of sensitizer, substrate **1** or **2** and trifluoroacetic acid in required volume of solvent and the end product was collected. After every reaction was over the sample vessel was again filled with 50mL of solvent and the reactor was flushed out continuously to collect adhered reactants on the wall of capillary.

Entry 38 (PM-4):

Following **General Procedure 13** a mixture of 0.400g (1.692 mmol) of **1**, 12mg (0.01952 mmol) *meso*-tetraphenylporphyrin and 0.19 mL (2.482 mmol) TFA in 160 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the end of the flow reactor capillary. The residence time was 15 minutes and the reaction were continued by circulating in a loop for 90 minutes. After finishing the photoreaction solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and 0.329g of crude was obtained containing 47% artemisinin mixed with other by-products.

Conversion 92% and product **4** 47% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.44 – 3.37 (m, 1H), 2.60 – 2.25 (m, 9H), 1.44 (s, 4H), 1.21 (d, J = 8.5 Hz, 7H), 0.88 (d, J = 6.1 Hz, 4H).

Entry 39 (PM-5) :

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.00976 mmol) *meso*-tetraphenylporphyrin and 0.19 mL (2.482 mmol) TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.1 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the end of the flow reactor capillary. The residence time was 20 minutes and the reaction were continued by circulating in loop for 90 minutes. After finishing the photoreaction solution volume was reduced to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 0.088g of crude was obtained. After recrystallization from cyclohexane 45mg (19% yield) brown colored **4** was isolated.

Conversion 97% and product **4** 66% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.47 – 3.32 (m, 1H), 2.54 – 2.34 (m, 1H), 2.21 – 1.95 (m, 4H), 1.90 – 1.61 (m, 7H), 1.45 (s, 6H), 1.21 (d, J = 7.7 Hz, 6H), 1.00 (d, J = 5.8 Hz, 4H).

Entry 40 (PM-24):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 1 drop of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 0.75 mL/min flow rate via the T-mixer. The residence time was 40 minutes the reaction end-product was allowed to travel through a capillary thermal reactor (8.4m) where additional air was injected via a T-valve. After finishing the reaction final mixture was collected continuously in a flask and solvent was evaporated and residue was dissolved in n-hexane 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with n-hexane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 56mg of crude was obtained. After recrystallization from cyclohexane 15mg (13% yield) white colored **4** was isolated.

Conversion 73% and product **4** 39% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.39 (dt, J = 14.5, 7.3 Hz, 1H), 2.43 (t, J = 20.1 Hz, 2H), 2.25 – 1.94 (m, 8H), 1.84 (d, J = 40.8 Hz, 10H), 1.43 (s, 7H), 1.20 (d, J = 7.3 Hz, 8H), 0.99 (d, J = 6.0 Hz, 5H).

Entry 41 (PM-25):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 1 drop of TFA in 80 mL acetone was injected into the flow reactor – 1 at 1.6 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. The residence time was 45 minutes the reaction end-product was collected continuously in a flask and solvent was evaporated and residue was dissolved in dichloromethane 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 66mg of crude was obtained. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 32% and product **4** 5% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.40 (m, 1H).

Entry 42 (PM-27):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 1 drop of 0.13M TFA solution in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask and solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 70mg of crude was obtained containing 17% product mixed with other compounds. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 27% and product **4** 17% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 43 (PM-29):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.0186 mmol) methylene blue and in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask and then 3 drops of TFA was mixed into it, then the reaction mixture was circulated 3 times into the photoreactor upto 160min.

Then the solvent was evaporated and the residue was extracted with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and evaporated, 176.7mg crude was obtained containing starting material with traces of product and no pure **4** was found.

Conversion 24% and product **4** 17% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H), 3.41 (m, 1H).

Entry 44 (PM-30):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 6mg (0.0186 mmol) methylene blue and 0.19 mL (2.482 mmol) of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5

mL/min flow rate via the T-mixer. The residence time was 55 minutes and the reaction end-product circulated 4 times into the photoreactor till 215 minutes.

Then the solvent was evaporated and the residue was extracted with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and evaporated, 72.8mg crude was obtained containing 25% of product **4** with other by-products, no pure **4** was found by recrystallization.

Conversion 60% and product **4** 25% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.39 (m, 1H).

Entry 45 (PM-31):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 1 drop of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 0.25 mL/min flow rate (with a Syringe flow injector pump) and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 88 minutes the reaction end-product was collected continuously in a flask and solvent was evaporated and residue was extracted with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and evaporated, 76.9mg crude was obtained and after recrystallization from cyclohexane 26.6mg (22%) pure **4** was found as white crystals.

Conversion 86% and product **4** 51% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.37 (tt, J = 7.3, 3.6 Hz, 1H), 2.51 – 2.34 (m, 1H), 2.12 – 1.93 (m, 2H), 1.91 – 1.65 (m, 4H), 1.43 (s, 5H), 1.19 (d, J = 7.3 Hz, 4H), 0.99 (d, J = 5.9 Hz, 3H).

Entry 46 (PM-32):

Following **General Procedure 13** a mixture of 0.050g (0.21 mmol) of **1**, 1.5mg (0.0046 mmol) methylene blue and 2 – 3 drops of TFA in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 60 minutes the reaction end-product was collected continuously in a flask and solvent was evaporated and residue was extracted with boiling n-hexane (3 x 25 mL). The n-hexane fractions were combined and evaporated, 42mg crude was obtained containing 37% **4** and after recrystallization from cyclohexane no pure **4** was found.

Conversion 50% and product **4** 37% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H), 3.45 – 3.35 (m, 1H), 2.58 – 2.31 (m, 7H), 2.23 – 1.74 (m, 29H), 1.44 (s, 6H), 1.20 (d, J = 7.0 Hz, 15H), 0.99 (d, J = 5.5 Hz, 9H).

Entry 47 (PM-37):

Following **General Procedure 13** a mixture of 0.050g (0.21 mmol) of **1**, 20mg (0.017 mmol) Rose bengal – bis(triethylammonium) salt and 0.1 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask. NMR analysis showed no change of starting material and 77.1mg crude containing DHAA **1** was collected after solvent evaporation.

Conversion and product **4** could not be determined.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: Not determined.

Entry 48 (PM-38):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.1 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 40.6mg of crude was obtained containing 20% **4**. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 42% and product **4** 20% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.41(m, 1H).

Entry 49 (PM-40):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 6mg (0.0186 mmol) methylene blue and 0.2 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by a mass flow controller (Alicat) pure oxygen was introduced into the reactants at 1 mL/min flow rate via the T-mixer. The residence time was 60 minutes the reaction end-product was collected continuously in a flask. NMR analysis showed very less

conversion so the reactants were circulated 4 times in flow reactor for 4 hours. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 37mg of crude was obtained containing 43% **4**. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 80% and product **4** 43% by NMR.

^{1}H-NMR: (300 MHz, $CDCl_3$) of 4: δ 5.87 (s, 1H), 3.41 (m, 1H).

Entry 50 (PM-42):

Following **General Procedure 13** a mixture of 0.050g (0.21 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.02 mL TFA in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by a mass flow controller (Alicat) pure oxygen was introduced into the reactants at 0.36 – 0.44 mL/min flow rate via the T-mixer. The residence time was 100 – 120 minutes the reaction end-product was collected continuously in a flask. In this case the pre and post-reaction flushing was skipped so only 40mL solution mixed with gas was travelling through the reactor to get maximum time of irradiation. NMR analysis showed very less conversion so the reactants were circulated again in flow reactor. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 31.6mg of crude was obtained. After recrystallization from cyclohexane no pure **4** could be isolated.

NMR not available

Entry 51 (PM-43):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 5 mL of 0.1M TFA solution in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by aa mass flow controller (Alicat) pure oxygen was introduced into the reactants at 0.50 – 0.80 mL/min flow rate via the T-mixer. The residence time was 135 minutes the reaction end-product was collected continuously in a flask. In this case the pre and post-reaction flushing was skipped so only 20mL solution mixed with

gas was travelling through the reactor to get maximum time of irradiation. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 69mg of crude was obtained. After recrystallization from cyclohexane 28mg (23%) pure **4** could be isolated.

Conversion 89% and product **4** 84% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.39 (qd, J = 7.3, 5.4 Hz, 1H), 2.54 – 2.35 (m, 2H), 2.10 – 1.95 (m, 3H), 1.91 – 1.71 (m, 5H), 1.43 (s, 4H), 1.20 (d, J = 7.3 Hz, 4H), 0.99 (d, J = 6.0 Hz, 3H).

Entry 52 (PM-44):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 5 mL of 0.01M TFA solution in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by a mass flow controller (Alicat) pure oxygen was introduced into the reactants at 3.5 – 6 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask. In this case the post-reaction flushing was done with 20mL dichloromethane. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 61mg of crude was obtained. After recrystallization from cyclohexane 46.5mg crude containing 52% **4** was obtained but pure product could not be isolated.

Conversion 83% and product **4** 52% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.38 (q, J = 7.2 Hz, 1H), 2.53 – 2.29 (m, 2H), 2.21 – 1.94 (m, 5H), 1.91 – 1.73 (m, 5H), 1.43 (s, 5H), 1.20 (d, J = 7.4 Hz, 6H), 0.99 (d, J = 5.8 Hz, 5H).

Entry 53 (PM-45):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 5 mL of 0.01M TFA solution in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5

mL/min flow rate via the T-mixer. The residence time was 135 minutes the reaction end-product was collected continuously in a flask. In this case the pre and post-reaction flushing was skipped so only 20mL solution mixed with gas was travelling through the reactor to get maximum time of irradiation. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 86mg of crude was obtained. After recrystallization from cyclohexane 34mg crude obtained containing 35% of artemisinin and pure product could not be isolated.

Conversion 42% and product **4 3**5% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.45 – 3.34 (m, 1H), 1.20 (d, J = 7.3 Hz, 5H), 0.99 (d, J = 5.9 Hz, 4H).

Entry 54 (PM-46):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 5 mL of 0.1M TFA solution in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 115 minutes the reaction end-product was collected continuously in a flask. In this case the pre and post-reaction flushing was skipped so only 20mL solution mixed with gas was travelling through the reactor to get maximum time of irradiation. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 65mg of crude was obtained. After recrystallization from cyclohexane 28.2mg (23%) pure **4** could be isolated.

Conversion and product **4** were not determined.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: Not available.

Entry 55 (PM-47):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 5 mL of 0.1M TFA solution in 20 mL dichloromethane was injected into

the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 125 minutes the reaction end-product was collected continuously in a flask. In this case the pre and post-reaction flushing was skipped so only 20mL solution mixed with gas was travelling through the reactor to get maximum time of irradiation. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 127mg of crude was obtained. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion and product **4** were not determined.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: Not available.

Entry 56 (PM-48):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected continuously in a flask. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 117mg of crude was obtained containing 20% artemisinin mixed with starting material. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 32% and product **4 3**5% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.42 – 3.33 (m, 1H), 2.44 – 2.35 (m, 1H), 2.20 – 1.99 (m, 5H), 1.98 – 1.71 (m, 20H), 1.43 (s, 9H), 1.20 (d, J = 7.7 Hz, 11H), 1.00 (s, 6H).

Entry 57 (PM-51):

Following **General Procedure 13** a mixture of 0.100g (0.42 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 20 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 55 minutes the reaction end-product was collected

continuously in a flask. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 58mg of crude was obtained and no pure **4** could be isolated. All samples were lost.

Conversion and product **4** were not determined.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: Not available.

Entry 58 (PM-52):

Following **General Procedure 13** a mixture of 0.50g (0.21 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 15 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 25mg of crude was obtained containing 37% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 73% and product **4** 37% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.42 – 3.36 (m, 1H), 2.45 – 2.38 (m, 1H), 2.17 – 2.09 (m, 2H), 2.09 – 1.95 (m, 6H), 1.48 – 1.43 (m, 6H), 1.20 (dt, J = 7.3, 2.6 Hz, 9H), 1.00 (d, J = 6.0 Hz, 5H).

Entry 59 (PM-53):

Following **General Procedure 13** a mixture of 0.050g (0.21 mmol) of **1**, 6mg (0.0186 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 17 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated

sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 31.7mg of crude was obtained containing 44% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 69% and product **4** 44% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.42 – 3.34 (m, 1H), 2.48 – 2.33 (m, 2H), 2.17 – 1.99 (m, 4H), 1.99 – 1.70 (m, 9H), 1.43 (s, 6H), 1.20 (d, J = 5.8 Hz, 7H), 0.99 (d, J = 6.0 Hz, 4H).

Entry 60 (PM-54):

Following **General Procedure 13** a mixture of 0.050g (0.21 mmol) of **1**, 10mg (0.03126 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 15 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 27mg of crude was obtained containing 26% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 48% and product **4** 26% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.44 – 3.32 (m, 1H), 2.44 – 2.37 (m, 1H), 2.10 – 2.00 (m, 3H), 1.98 – 1.84 (m, 7H), 1.44 (s, 4H), 1.19 (d, J = 0.7 Hz, 3H), 0.99 (d, J = 5.9 Hz, 3H).

Entry 61 (PM-55):

Following **General Procedure 13** a mixture of 0.075g (0.318 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The

residence time was 10 minutes the reaction end-product was collected continuously in a flask. Then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 50mg of crude was obtained containing 37% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 72% and product **4** 37% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40(m, 1H).

Entry 62 (PM-56):

Following **General Procedure 13** a mixture of 0.075g (0.318 mmol) of **1**, 6mg (0.0186 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 18 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 37mg of crude was obtained containing 45% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 72% and product **4** 45% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.46 – 3.30 (m, 1H), 2.45 – 2.36 (m, 1H), 2.18 – 2.05 (m, 3H), 1.92 – 1.73 (m, 7H), 1.44 (s, 4H), 1.20 (d, J = 7.3 Hz, 5H), 1.00 (d, J = 6.0 Hz, 4H).

Entry 63 (PM-57):

Following **General Procedure 13** a mixture of 0.075g (0.318 mmol) of **1**, 10mg (0.03126 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor.

The residence time was 18 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 34mg of crude was obtained containing 32% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 52% and product **4** 32% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.46 – 3.33 (m, 1H), 2.45 – 2.36 (m, 1H), 2.16 – 2.04 (m, 2H), 1.94 – 1.73 (m, 9H), 1.44 (s, 4H), 1.20 (d, J = 7.5 Hz, 6H), 0.99 (d, J = 5.9 Hz, 4H).

Entry 64 (PM-58):

Following **General Procedure 13** a mixture of 0.500g (2.1245 mmol) of **1**, 30mg (0.093794 mmol) methylene blue and 0.1 mL of TFA in 800 mL dichloromethane (reagents are same as used in PM-52) was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 17 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 210mg of crude was obtained containing 21% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 68% and product **4** 21% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.38 (m, 1H).

Entry 65 (PM-59):

Following **General Procedure 13** a mixture of 0.500g (2.1245 mmol) of **1**, 20mg (0.062529 mmol) methylene blue and 0.066 mL of TFA in 533.28 mL dichloromethane (reagent concentrations are same as PM-55) was injected into the flow reactor – 1 at 2.5 mL/min flow

rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 20 minutes the reaction end-product was collected continuously in a flask. The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 230mg of crude was obtained containing 41% of artemisinin. After recrystallization from cyclohexane only 8% pure **4** could be isolated.

Conversion 72% and product **4** 41% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.45 – 3.34 (m, 1H), 2.51 – 2.35 (m, 1H), 2.11 – 1.96 (m, 2H), 1.93 – 1.67 (m, 4H), 1.44 (s, 7H), 1.21 (d, J = 7.3 Hz, 5H), 0.99 (s, 4H).

Entry 66 (PM-60):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. A 5 psi BPR was attached at the outlet of the capillary flow reactor. The residence time was 30 minutes the reaction end-product was collected continuously in a flask (conversion 35%, artemisinin16%). But due pressure problem the reaction movement was stopped and it was recirculated without BPR (50% conversion). The solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and digested in activated charcoal then filtered. Only 74.2mg of crude was obtained. After repeating extraction of aqueous layer with dichloromethane total 118.2mg crude was recovered containing 27% of artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 42% and product **4** 27% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.44 – 3.35 (m, 1H), 2.45 – 2.37 (m, 2H), 2.07 (dddd, J = 18.0, 11.7, 7.0, 3.6 Hz, 8H), 1.99 – 1.73 (m, 25H), 1.44 (s, 18H), 1.20 (d, J = 7.5 Hz, 13H), 1.00 (d, J = 5.9 Hz, 12H).

Entry 67 (PM-61):

Following **General Procedure 13** a mixture of 1.18g (5 mmol) of **1**, 12mg (0.02 mmol) *meso*-tetraphenylporphyrin and 0.1 mL of TFA in 200 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the end of reactor, but another FEP capillary coil (0.58mm ID, 10 mL volume) was attached. The residence time was 53 minutes the reaction end-product was collected continuously in a flask. Negligible conversion was seen and 1.211g residue containing mostly **1** was obtained. Then the reaction was recirculated 4 times by adding 12gm *meso*-tetraphenylporphyrin more and 80 mL dichloromethane to the residue with increased the flow rates (air 1 mL/min and liquid 2 mL/min). After that the solvent was evaporated to concentrate to 25 mL and then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 1.208g of crude was obtained containing 28% artemisinin mixed with by-products. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 28% and product **4** 4% after 53 minutes residence time by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.38 (m, 1H).

Entry 68 (PM-65):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.05 mL of TFA in 40 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the end of reactor. The residence time was 40 minutes the reaction end-product was collected continuously in a flask. Then solvent was concentrated to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 129mg of crude was obtained containing majority of starting material and 11% artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 16% and product **4** 11% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 69 (PM-66):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.05 mL of TFA in 40 mL acetone was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. No BPR was attached at the end of reactor. The residence time was 40 minutes the reaction end-product was collected continuously in a flask. Then solvent was evaporated and residue was dissolved in dichloromethane 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 180mg of crude was obtained containing majority of starting material and 12% artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 24% and product **4** 12% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.39 (m, 1H).

Entry 70 (PM-67):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 40 mL acetone was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the end of reactor. The residence time was 40 minutes the reaction end-product was collected continuously in a flask. Then solvent was evaporated and residue was dissolved in dichloromethane 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 188.8mg of crude was obtained containing majority of starting material and by-product and only 5% artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 47% and product **4** 5% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (m, 1H).

Entry 71 (PM-68):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 40 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the end of reactor. The residence time was 10 minutes the reaction end-product was collected continuously in a flask. Then solvent was concentrated to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 190.2mg of crude was obtained containing majority of starting material and 10% artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 19% and product **4** 10% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.39 (m, 1H).

Entry 72 (PM-72):

Following **General Procedure 13** a mixture of 0.200g (0.84 mmol) of **1**, 3mg (0.0093 mmol) methylene blue and 0.01 mL of TFA in 40 mL dichloromethane was injected into the flow reactor – 1 at 2.5 mL/min flow rate and air was introduced into the reactants at 2.5 mL/min flow rate via the T-mixer. A 5psi BPR was attached at the end of reactor. The residence time was 21 minutes the reaction end-product was collected continuously in a flask. Then solvent was concentrated to 25 mL and washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 138mg of crude was obtained containing majority of starting material and 21% artemisinin. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 30% and product **4** 21% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.43 – 3.32 (m, 1H), 2.43 – 2.34 (m, 1H), 2.10 – 1.95 (m, 4H), 1.89 (tdd, J = 9.4, 7.7, 4.6 Hz, 10H), 1.42 (s, 11H), 1.18 (d, J = 7.6 Hz, 7H), 0.98 (d, J = 5.9 Hz, 5H).

7.3.2.1.4 Flow reactions of mixed anhydride of DHAA 2

Entry 73 (PM-EsterFlow-1):

Following **General Procedure 13** a mixture of 0.200g (0.65 mmol) of **2**, 8mg (0.025 mmol) methylene blue and 0.01 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and air was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 40 minutes the reaction end-product was collected continuously in a flask. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 112mg of crude was obtained. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 43% and product **4** 24% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.43 – 3.34 (m, 1H), 2.09 – 1.94 (m, 8H), 2.00 – 1.72 (m, 21H), 1.44 (s, 9H), 1.24 (d, J = 10.3 Hz, 12H), 1.00 (d, J = 5.9 Hz, 7H).

Entry 74 (PM-EsterFlow-2):

Following **General Procedure 13** a mixture of 0.200g (0.65 mmol) of **2**, 8mg (0.025 mmol) methylene blue and 0.01 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 0.5 mL/min flow rate and air was introduced into the reactants at 1 mL/min flow rate via the T-mixer. The residence time was 40 minutes the reaction end-product was collected continuously in a flask. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 103.7mg of crude was obtained. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 34% and product **4** 22% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.84 (s, 1H), 3.41 – 3.34 (m, 1H), 2.43 – 2.35 (m, 1H), 2.13 – 1.97 (m, 5H), 1.99 – 1.75 (m, 18H), 1.42 (s, 13H), 1.23 (d, J = 5.1 Hz, 11H), 0.98 (d, J = 5.9 Hz, 6H).

Entry 75 (PM-41):

Following **General Procedure 13** a mixture of 0.130g (0.42 mmol) of **2**, 6mg (0.0186 mmol) methylene blue and 0.1 mL TFA in 80 mL dichloromethane was injected into the flow reactor – 1 at 1 mL/min flow rate and by aa mass flow controller (Alicat) pure oxygen was introduced into the reactants at 0.5 mL/min flow rate via the T-mixer. The residence time was 50 minutes the reaction end-product was collected continuously in a flask. Then the solvent was concentrated to 25 mL, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate and filtered over silica, 89mg of crude was obtained containing 55% product with other by-products. After recrystallization from cyclohexane no pure **4** could be isolated.

Conversion 97% and product **4** 55% by NMR.

^{1}H-NMR: (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.43 – 3.33 (m, 2H), 2.48 – 2.37 (m, 2H), 2.10 – 1.95 (m, 5H), 1.93 – 1.73 (m, 11H), 1.43 (s, 3H), 1.20 (d, J = 5.8 Hz, 7H), 0.99 (d, J = 6.0 Hz, 4H).

7.3.2.1.5 Flow reactions of allylic alcohol 4-Methylpent -3-en-2-ol 20

Entry 76 (PM-T-F-1):

Following **General Procedure 11** at 1 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 0.5 mL/min flow rate. After 75 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 60%. The reagents were reinjected 4 times in flow reactor but the conversion remained the same. Finally, 0.4831g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 73:27 was obtained after solvent evaporation under reduced pressure.

Conversion 60%, yield of **23a** 44% and **23b** 16% by NMR.

^{1}H NMR (400 MHz, $CDCl_3$) of 23a (major): δ 5.12 – 5.08 (m, 2H), 4.15 (d, J = 8.3 Hz, 1H), 3.91 – 3.84 (m, 1H), 1.76 – 1.74 (m, 1H), 1.15 (d, J = 6.4 Hz, 1H).

^{1}H NMR (400 MHz, $CDCl_3$) of 23b (minor): δ 5.17 – 5.14 (m, 2H), 4.28 (d, J = 5.2 Hz, 1H), 3.98 – 3.91 (m, 1H), 1.85 – 1.80 (m, 3H), 1.23 (d, J = 6.4 Hz, 4H).

Entry 77 (PM-T-F-2):

Following **General Procedure 11** at 1 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 50 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 0.5 mL/min flow rate. After 75 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 81% and hence the reactants were reinjected 3 times into the flow reactor to obtain complete conversion of **20**, but the overall conversion was 65%. Finally, 0.3944g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*: *nti* 80:20 was obtained after solvent evaporation under reduced pressure.

Conversion 65%, yield of **23a** 52% and **23b** 13% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 78 (PM-T-F-3):

Following **General Procedure 11** at 1 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 and no back pressure regulator (BPR) was attached near the outlet. To the reactant stream air was injected via T-valve at 0.5 mL/min flow rate. After 40 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 58% and hence the reactants were recirculated thrice into the flow reactor and conversion of **20** was 86%. Finally, 0.4424g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 87:13 was obtained after solvent evaporation under reduced pressure.

Conversion 58%, yield of **23a** 50% and **23b** 8% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 79 (PM-T-F-4):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 12 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 80%. Finally, 0.472g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 76:24 was obtained after solvent evaporation under reduced pressure.

Conversion 80%, yield of **23a** 62% and **23b** 18% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 80 (PM-T-F-5):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 10 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 96% and hence the reactants were recirculated into the flow reactor again to obtain complete conversion of **20**. Finally, 0.4514g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 85:15 was obtained after solvent evaporation under reduced pressure.

Conversion 96%, yield of **23a** 82% and **23b** 14% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 81 (PM-T-F-6):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 13 minutes of residence time the solution of photo-product was

collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 100% and hence the reactants were recirculated into the flow reactor again to obtain complete conversion of **20**. Finally, 0.4340g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 91:9 was obtained after solvent evaporation under reduced pressure.

Conversion 100%, yield of **23a** 91% and **23b** 9% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 82 (PM-T-F-7):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 13 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 26% and hence the reactants were recirculated 5 times into the flow reactor and 96% conversion of **20** was obtained. Finally, 0.411g of crude mixture containing starting material and diastereomeric mixture of **20** *syn*:*anti* 84:16 was obtained after solvent evaporation under reduced pressure.

Conversion 26%, yield of **23a** 16% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 83 (PM-T-F-8):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.250g (2.496 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 50 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream pure oxygen was injected via T-valve at 5 mL/min flow rate. After 8 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 28% and 0.2597g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 64:36 was obtained after solvent evaporation under reduced pressure.

Conversion 28%, yield of **23a** 18% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 84 (PM-T-F-9):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 10mg (0.016267 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 6 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 22% and hence the reactants were recirculated 4 times into the flow reactor and 66% conversion of **20** was obtained. Finally, 0.5114g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 74:26 was obtained after solvent evaporation under reduced pressure.

Conversion 22%, yield of **23a** 12% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 85 (PM-T-F-10):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 15mg (0.024400 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 10 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 34% and hence the reactants were recirculated twice into the flow reactor and 81% conversion of **20** was obtained. Finally, 0.5184g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 84:16 was obtained after solvent evaporation under reduced pressure.

Conversion 34%, yield of **23a** 22% and **23b** 12% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 86 (PM-T-F-11):

Following **General Procedure 11** at 5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 25mg (0.040660 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 5 mL/min flow rate. After 10 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 32% and hence the reactants were recirculated twice into the flow reactor and 69% conversion of **20** was obtained. Finally, 0.519g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 80:20 was obtained after solvent evaporation under reduced pressure.

Conversion 32%, yield of **23a** 22% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 87 (PM-T-F-12):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 15mg (0.024400 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 14 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 44% and hence the reactants were recirculated once again into the flow reactor and 64% conversion of **20** was obtained. Finally, 0.5032g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 77:23 was obtained after solvent evaporation under reduced pressure.

Conversion 44%, yield of **23a** 34% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 88 (PM-T-F-13):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 25mg (0.040660 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at

2.5 mL/min flow rate. After 20 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 46% and hence the reactants were recirculated once again into the flow reactor and 100% conversion of **20** was obtained. Finally 0.5217g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 80:20 was obtained after solvent evaporation under reduced pressure.

Conversion 46%, yield of **23a** 36% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 89 (PM-T-F-14):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.250g (2.496 mmol) of **20** and 15mg (0.024400 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 20 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 49% and 0.2321g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 69:31 was obtained after solvent evaporation under reduced pressure.

Conversion 49%, yield of **23a** 34% and **23b** 15% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 90 (PM-T-F-14R):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.250g (2.496 mmol) of **20** and 15mg (0.024400 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 20 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 46% and 0.241g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 70:30 was obtained after solvent evaporation under reduced pressure.

Conversion 46%, yield of **23a** 32% and **23b** 14% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 91 (PM-T-F-15):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.250g (2.496 mmol) of **20** and 25mg (0.040660 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 20 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 50% and 0.2651g of crude mixture containing starting material and diastereomeric mixture of **23** *syn*:*anti* 68:32 was obtained after solvent evaporation under reduced pressure.

Conversion 50%, yield of **23a** 34% and **23b** 16% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 92 (PM-T-F-17):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.250g (2.496 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 50 mL ethanol was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 25 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 64% and after recirculating once again into the flow reactor 100% conversion was seen. The final solution was treated with silica to remove dye and filtered and 70mg crude containing diastereomeric mixture of **23** *syn*:*anti* 72 : 28 was obtained after solvent evaporation under reduced pressure.

Conversion 64%, yield of **23a** 34% and **23b** 30% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 93 (PM-T-F-18):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.445g (4.4429 mmol) of **20** and 3.7mg (0.0115679 mmol) methylene blue in 40 mL dichloromethane was

injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 15 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 100% and the final solution was treated with silica to remove dye and filtered and 20mg crude containing diastereomeric mixture of **23** *syn*:*anti* 90:10 was obtained after solvent evaporation under reduced pressure.

Conversion 100%, yield of **23a** 90% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 94 (PM-T-F-19):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 13 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 90% and 0.188g crude containing diastereomeric mixture of **23** *syn*:*anti* 82:18 was obtained after solvent evaporation under reduced pressure.

Conversion 90%, yield of **23a** 74% and **23b** 16% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 95 (PM-T-F-20):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.445g (4.4429 mmol) of **20** and 3.7mg (0.0115679 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 9 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion could not be determined as the NMR was very complex and after recirculating once again 32% conversion was shown 3.7mg crude containing diastereomeric mixture of **23** *syn*:*anti* 56:44 was obtained after solvent evaporation under reduced pressure.

Conversion 32%, yield of **23a** and **23b** not known.

^{1}H NMR: Same as Entry 76.

Entry 96 (PM-T-F-21):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 18 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 16% and recirculated thrice to get maximum conversion, NMR showed 88% conversion. Total 86mg crude containing diastereomeric mixture of **23** *syn*:*anti* 67:33was obtained after solvent evaporation under reduced pressure.

Conversion 16%, yield of **23a** 9% and **23b** 7% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 97 (PM-T-F-22):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 18 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The NMR analysis showed 100% conversion and 0.1468g crude containing diastereomeric mixture of **23** *syn*:*anti* 75:25 was obtained after solvent evaporation under reduced pressure.

Conversion 100%, yield of **23a** 75% and **23b** 15% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 98 (PM-T-F-23):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR)

attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 10 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The 10 minutes sample analysis showed conversion was 91% but due to BPR created pressure problem the final sample showed incomplete reaction. The reagents were recirculated four times to get 100% conversion and 26mg crude containing diastereomeric mixture of **23** *syn*:*anti* 83:17 was obtained after solvent evaporation under reduced pressure.

Conversion 91%, yield of **23a** 81% and **23b** 10% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 99 (PM-T-F-25):

Following **General Procedure 11** at 2.5 mL/min liquid flow rate a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.0093794 mmol) methylene blue in 40 mL dichloromethane was injected into the capillary flow Reactor – 1 containing 5 psi back pressure regulator (BPR) attached near the outlet. To the reactant stream air was injected via T-valve at 2.5 mL/min flow rate. After 12 minutes of residence time the solution of photo-product was collected in a flask and NMR analysis was performed to check any presence of **23**. The conversion was 83% and recirculated once again to get complete conversion. 0.0813g crude containing diastereomeric mixture of **23** *syn*:*anti* 86:14 was obtained after solvent evaporation under reduced pressure.

Conversion 83%, yield of **23a** 70% and **23b** 13% by NMR.

^{1}H NMR: Same as Entry 76.

7.3.2.2 Flow reactions in Flow reactor – 2

General Procedure 14: Solution of allylic alcohol (**20** or **21** or **22**) and sensitizer (methylene blue or *meso*-tetraphenylporphyrin) in dichloromethane was injected into the flow reactor – 2 by a ischemic liquid flow controller pump at 1.5 mL/min flow rate and into the liquid stream gas (air or oxygen) was introduced via a T-mixture at 1.5 mL/min flow rate by Alicat mass flow controller. The flow reaction was under visible light (8 W x 16) in Rayonet chamber and the end product from the reactor was collected in a collection flask. No back-pressure regulator (BPR) was used in this reactor for any of the flow reactions.

7.3.2.2.1 Flow reaction of 20

Entry 100 (PM-T-F-26):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air was used as source of oxygen. After 11 minutes of residence time in flow reactor the conversion was 85% and 0.4535g crude collected after solvent evaporation containing starting material diastereomeric mixture of **23** *syn*:*anti* 86:14 ratio.

Conversion 85%, yield of **23a** 73% and **23b** 12% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 101 (PM-T-F-27):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air was used as source of oxygen. After 4 minutes of residence time in flow reactor the conversion was 26% and 0.4597g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 73:27 ratio.

Conversion 26%, yield of **23a** 19% and **23b** 7% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 102 (PM-T-F-28):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air was used as source of oxygen. After 4 minutes of residence time in flow reactor the NMR analysis of 4 minutes sample showed conversion 100%, but the final crude sample from the collection flask showed 28% conversion. 0.2603g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 79:21 ratio. (Note: after evaporation while transferring half of the sample was lost.)

Conversion 28%, yield of **23a** 22% and **23b** 6% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 103 (PM-T-F-29):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air was used as source of oxygen. After 8 minutes of residence time in flow reactor

the conversion was 86% and 0.4703g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 84:16 ratio.

Conversion 86%, yield of **23a** 72% and **23b** 14% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 104 (PM-T-F-30):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air was used as source of oxygen. After 8 minutes of residence time in flow reactor the conversion was 100% and 0.3952g crude collected after solvent evaporation containing diastereomeric mixture of **23** *syn*:*anti* 93:7 ratio.

Conversion 100%, yield of **23a** 93% and **23b** 7% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 105 (PM-T-F-31):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 9 minutes of residence time in flow reactor the conversion was 38% and then the reactants were reinjected in flow reaction. Complete conversion (100%) was obtained and 0.446g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 93:7 ratio.

Conversion 30%, yield of **23a** 30% and **23b** 8% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 106 (PM-T-F-32):

Following **General Procedure 14** a solution of 0.500g (4.992 mmol) of **20** and 6mg (0.009760 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 12 minutes of residence time in flow reactor the conversion was 56% then the reactants were reinjected in flow reaction. Complete conversion (100%) was obtained and 0.6061g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 91:9 ratio.

Conversion 56%, yield of **23a** 50% and **23b** 6% by NMR.

^{1}H NMR: Same as Entry 76.

Entry 107 (PM-T-F-33):

Following **General Procedure 14** a solution of 1g (9.984 mmol) of **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 10 minutes of residence time in flow reactor the conversion was 46% and 1102mg crude collected after solvent evaporation containing starting material and diastereomeric mixture of **23** *syn*:*anti* 91:9 ratio.

Conversion 46%, yield of **23a** 42% and **23b** 4% by NMR.

^{1}H NMR: Same as Entry 76.

7.3.2.2.2 Flow reaction of Dimethylhex-4-en-3-ol 21

Entry 108 (PM-DMHx-F-1):

Following **General Procedure 14** a solution of 0.500g (3.8998 mmol) of **21** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air as oxygen source was used for photooxygenation. After 11 minutes of residence time in flow reactor the conversion was 21% and 0.2727g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **24** *syn*:*anti* 90:10 ratio.

Conversion 21%, yield of **24a** 19% and **24b** 2% by NMR.

^{1}H NMR: Same as Experiment 76.

Entry 109 (PM-DMHx-F-2):

Following **General Procedure 14** a solution of 0.500g (3.8998 mmol) of **21** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 11 minutes of residence time in flow reactor the conversion was 86% and 419mg crude collected after solvent evaporation containing starting material and diastereomeric mixture of **24b** *syn*:*anti* 86:14 ratio.

Conversion 86%, yield of **24a** 74% and **24b** 12% by NMR.

^{1}H NMR: Same as Experiment 76.

Entry 110 (PM-DMHx-F-3):

Following **General Procedure 14** a solution of 0.500g (3.8998 mmol) of **21** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 10 minutes of residence time in flow reactor the conversion was 24% and 392mg crude collected after solvent evaporation containing starting material and diastereomeric mixture of **24** *syn*:*anti* 86:14 ratio.

Conversion 24%, yield of **24a** 21% and **24b** 3% by NMR.

^{1}H NMR: Same as Experiment 76.

7.3.2.2.3 Flow reaction of Dimethylhept-2-en-4-ol 22

Entry 111 (PM-DMHp-F-1):

Following **General Procedure 14** a solution of 0.500g (3.5151 mmol) of **22** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Compressed air as oxygen source was used for photooxygenation. After 11 minutes of residence time in flow reactor the conversion was 43% and 0.4474g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **25** *syn*:*anti* 88:12 ratio.

Conversion 43%, yield of **25a** 38% and **25b** 5% by NMR.

^{1}H NMR: Same as Experiment 77.

Entry 112 (PM-DMHp-F-2):

Following **General Procedure 14** a solution of 0.500g (3.5151 mmol) of **22** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 11 minutes of residence time in flow reactor, however NMR spectra was difficult to analyze due to poor shimming. Then the collected solution was reentered into flow reactor and the conversion was 59%. After solvent evaporation 0.4537g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **25** *syn*:*anti* 86:14 ratio.

Conversion 59%, yield of **24a** 51% and **24b** 8% by NMR.

^{1}H NMR: Same as Experiment 77.

Entry 113 (PM-DMHp-F-3):

Following **General Procedure 14** a solution of 0.500g (3.5151 mmol) of **22** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was irradiated in flow reactor. Pure oxygen gas was used for photooxygenation. After 6 minutes of residence time in flow reactor the conversion was 44% and 0.476g crude collected after solvent evaporation containing starting material and diastereomeric mixture of **25** *syn*:*anti* 87:13 ratio.

Conversion 44%, yield of **24a** 39% and **24b** 5% by NMR.

^{1}H NMR: Same as Experiment 77.

7.3.2.3 Solar flow reactions of DHAA 1 in parabolic flow reactor – 3

Entry 114 (SF-PM-1 Repeat):

Following **General Procedure 11** a mixture of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal in 72 mL isopropanol and 8 mL water was injected into the flow reactor – 3 at 1.6 mL/min flow rate and air was introduced into the reactants at from a fish tank pump via the T-mixer at 1mbar pressure. A 5psi BPR was attached at the end of flow reactor capillary. After 7 minutes of residence time the photo-product mixture from flow reactor – 2 was collected in flask and recirculated for 2 hours. The catalytic reaction was performed in batch following **General Procedure 4** by adding 0.01 mL TFA in the mixture and stirred it for 2 hours at 60°C with air bubbling. The solvent was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 113mg crude mixture was collected. After recrystallization from cyclohexane 42mg (18%) pure **4** was isolated.

Conversion 100% and **3** 83% after 2 hours recirculation, product **4** 14% by NMR.

^{1}H NMR (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.75 – 2.64 (m, 1H), 2.28 – 2.12 (m, 1H), 2.00 – 1.70 (m, 5H), 1.62 – 1.39 (m, 4H), 1.30 – 1.24 (m, 8H), 0.93 (d, J = 5.6 Hz, 2H).

^{1}H NMR (300 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.38 (m, 1H).

Entry 115 (SF-PM-2):

Following **General Procedure 12** a solution of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal in 80 mL ethanol was injected into the flow reactor – 3 at 5 mL/min flow rate and

air was introduced into the reactants at from a fish tank pump via the T-mixer at 5 – 6 mbar pressure. Residence time was 7 minutes. A 5psi BPR was attached at the end of flow reactor capillary and the tube outlet was attached to a capillary thermal reactor (8.4m) via another T-junction through which 60 mL ethanol mixed with 0.01 mL TFA was injected at 2 mL/min by a syringe pump into the photo-product stream. The thermal reactor was maintained at 60°C in a water bath. The final product solution was collected continuously in a flask containing stirred solution of saturated sodium hydrogen carbonate 25 mL. The final solution was extracted with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 14mg crude mixture was collected.

Conversion 96% and **3** 79% after 1hour recirculation by NMR.

^{1}H NMR (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.72 (p, J = 6.8 Hz, 1H), 2.16 (dt, J = 14.9, 7.3 Hz, 1H), 2.05 – 1.70 (m, 5H), 1.64 – 1.42 (m, 4H), 1.24 (dd, J = 15.9, 5.8 Hz, 10H), 0.93 (d, J = 5.8 Hz, 3H).

^{1}H NMR (300 MHz, $CDCl_3$) of 4: Complex NMR, could not be determined.

Entry 116 (SF-PM-3):

Following **General Procedure 12** a solution of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal 72 mL isopropanol and 8 mL water was injected into the flow reactor – 3 at 5 mL/min flow rate and air was introduced into the reactants at from a fish tank pump via the T-mixer at 5 – 6 mbar pressure. Residence time was 7 minutes. A 5psi BPR was attached at the end of flow reactor capillary and the tube outlet was attached to a capillary thermal reactor (8.4m) via another T-junction through which 30 mL isopropanol mixed with 0.01 mL TFA was injected at 1 mL/min by a syringe pump into the photo-product stream. The thermal reactor was maintained at 60°C in a water bath. The final product solution was collected continuously in a flask containing stirred solution of saturated sodium hydrogen carbonate 25 mL. The final solution was extracted with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation no crude could be recovered.

Conversion 100% and **3** 84% after 1hour recirculation by NMR.

^{1}H NMR (300 MHz, $CDCl_3$) of 3: δ 5.23 (s, 1H), 2.78 – 2.60 (m, 1H), 2.16 (m, 1H), 2.03 – 1.68 (m, 4H), 1.50 (dd, J = 24.3, 14.5 Hz, 4H), 1.34 – 1.16 (m, 13H), 0.93 (d, J = 5.3 Hz, 3H).

^{1}H NMR (300 MHz, $CDCl_3$) of 4: Complex NMR, could not be determined.

Entry 117 (SF-PM-4):

Following **General Procedure 12** a solution of 0.200g (0.84 mmol) of **1**, 20mg (0.0205 mmol) Rose bengal 72 mL isopropanol and 8 mL water was injected into the flow reactor – 3 at 5 mL/min flow rate and air was introduced into the reactants at from a fish tank pump via the T-mixer at 5 – 7 mbar pressure. Residence time was 7 minutes. A 5psi BPR was attached at the end of flow reactor capillary and the tube outlet was attached to a capillary thermal reactor (8.4m) via another T-junction through which 40 mL isopropanol mixed with 0.01 mL TFA was injected at 1 mL/min by a syringe pump into the photo-product stream. The final product solution was collected continuously in a flask and later solvent was evaporated and the residue was found which was dissolved in 25 mL DCM, then washed with 25 mL saturated sodium hydrogen carbonate solution followed by addition of 20 mL water and organic layer was collected. The aqueous layer was washed with Dichloromethane (3 x 25 mL). Organic layers were collected and washed with brine solution 25 mL then dried over Sodium sulphate. Filtered over silica and after evaporation 130mg crude mixture was collected showing 13% **4** in NMR analysis. After recrystallization from cyclohexane 81mg (33%) pure by-product **16** was isolated as oil that formed white crystals after storage in fridge.

Conversion 100% and **3** 83% after 1hour recirculation and product **4** 13% by NMR.

^{1}H NMR (300 MHz, $CDCl_3$) of 3: δ 5.24 (s, 1H), 2.80 – 2.65 (m, 1H), 2.16 (s, 2H), 2.06 – 1.74 (m, 6H), 1.66 – 1.42 (m, 5H), 1.31 – 1.18 (m, 17H), 0.93 (d, J = 5.8 Hz, 3H).

^{1}H NMR (300 MHz, $CDCl_3$) of 4: δ 5.83 (s, 1H), 3.37 (m, 1H).

^{1}H NMR (300 MHz, $CDCl_3$) of 16: δ 6.07 (s, 1H), 3.01 – 2.86 (m, 1H), 2.70 – 2.55 (m, 1H), 2.52 – 2.36 (m, 1H), 2.14 (s, 3H), 2.08 – 1.96 (m, 1H), 1.91 – 1.74 (m, 2H), 1.64 (d, J = 9.6 Hz, 1H), 1.55 – 1.38 (m, 1H), 1.21 (d, J = 7.0 Hz, 4H), 1.12 (d, J = 10.6 Hz, 2H), 0.98 (d, J = 5.7 Hz, 3H).

^{13}C NMR (75 MHz $CDCl_3$) of 16: δ 208.53 (s), 171.73 (s), 131.97 (s), 124.57 (s), 77.82 – 77.40 (m), 77.40 – 77.01 (m), 76.97 – 76.59 (m), 47.33 (s), 42.74 (s), 41.80 (s), 41.29 (s), 36.66 (s), 35.52 (s), 30.18 (s), 28.64 (s), 20.97 (s), 20.08 (s), 11.63 (s).

7.3.2.4 Photoreactions in Vapourtec

7.3.2.4.1 Photooxygenation of DHAA (1) and mixed anhydride of DHAA (2) in Vapourtec reactor

General Procedure 15: Specified amount of **1** or **2** was dissolved in dichloromethane containing sensitizer (methylene blue) and trifluoroacetic acid in a flask. The reagent mixture was pumped through the capillary with the help of Pump B at 0.5 mL/min flow rate and air was injected into the liquid stream at 1 mL/min flow rate by Alicat mass flow controller. The gas-liquid slugs formed inside capillary then travelled into the Vapourtec photoreactor and irradiated by LED 3.6W panel. After the irradiation was finished the final mixture was collected continuously to a flask from the outlet capillary.

After NMR analysis the final solution was concentrated to 25 mL and washed with saturated sodium hydrogen carbonate solution 25 mL and then 20 mL water was added to the mixture. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 x 25 mL), then the organic layers were combined and washed with 25 mL Brine solution and the organic layer was collected, dried over sodium sulphate and crude was collected after solvent evaporation under reduced pressure.

Entry 118 (PM-Vap-DHAA-1R):

Following **General Procedure 15** a solution of 0.100g (0.42 mmol) of **1**, 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 20 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **1** was 48% and after aqueous workup and solvent evaporation 51.3mg of crude was collected containing 24% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.39 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.19 – 2.02 (m, 4H), 1.99 – 1.87 (m, 7H), 1.83 – 1.74 (m, 6H), 1.49 – 1.41 (m, 9H), 1.19 (t, *J* = 7.2 Hz, 10H), 1.00 (d, *J* = 5.8 Hz, 4H).

Entry 119 (PM-Vap-DHAA-2):

Following **General Procedure 15** a solution of 0.100g (0.42 mmol) of **1** 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 80 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **1** was 66% and after aqueous workup and solvent evaporation 58.7mg of crude was collected containing 34% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.38 (dt, J = 14.1, 7.1 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.14 (d, J = 3.5 Hz, 8H), 1.94 – 1.58 (m, 27H), 1.41 (d, J = 12.0 Hz, 9H), 1.22 – 1.17 (m, 9H), 0.98 (d, J = 5.7 Hz, 6H).

Entry 120 (PM-Vap-DHAA-3):

Following **General Procedure 15** a solution of 0.050g (0.21 mmol) of **1**, 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 80 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **1** was 64% and after aqueous workup and solvent evaporation 39.1mg of crude was collected containing 31% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.44 – 3.30 (m, 1H), 2.41 (ddd, J = 17.5, 14.9, 5.7 Hz, 2H), 2.47 – 2.31 (m, 3H), 2.25 – 2.03 (m, 7H), 1.98 – 1.73 (m, 15H), 1.45 (d, J = 15.4 Hz, 7H), 1.20 (d, J = 7.4 Hz, 7H), 0.99 (d, J = 5.8 Hz, 4H).

Entry 121 (PM-Vap-mixedanhydride-1R):

Following **General Procedure 15** a solution of 0.100g (0.324 mmol) of **2**, 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 20 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **2** was 33% and after aqueous workup and solvent evaporation 44.2mg of crude was collected containing 21% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H), 3.43 – 3.33 (m, 2H), 2.45 – 2.34 (m, 2H), 2.13 – 1.98 (m, 7H), 1.99 – 1.70 (m, 25H), 1.42 (s, 7H), 1.20 (dd, J = 11.7, 7.1 Hz, 20H), 0.98 (d, J = 6.0 Hz, 8H).

Entry 122 (PM-Vap-mixedanhydride-2):

Following **General Procedure 15** a solution of 0.100g (0.324 mmol) of **2**, 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 80 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **2** was 73% and after aqueous workup and solvent evaporation 34.2mg of crude was collected containing 5% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.85 (s, 1H). Other peaks could not be identified.

Entry 123 (PM-Vap-mixedanhydride-3):

Following **General Procedure 15** a solution of 0.050g (0.162 mmol) of **2**, 3mg (mmol) of methylene blue and 0.01 mL trifluoroacetic acid in 80 mL dichloromethane was irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **2** was 60% and after aqueous workup and solvent evaporation 16.2mg of crude was collected containing 38% artemisinin **4** as per NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) of 4: δ 5.86 (s, 1H), 3.40 (dt, *J* = 12.7, 7.4 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.19 – 2.08 (m, 3H), 2.03 – 1.93 (m, 4H), 1.44 (s, 4H), 1.23 (dd, *J* = 6.9, 3.9 Hz, 5H), 1.03 – 0.97 (m, 5H).

7.3.2.4.2 Photooxygenation of 4-methylpent-3-en-2-ol (20) in Vapourtec flow reactor

General procedure 16: Specified amount of **20** was dissolved in dichloromethane containing sensitizer (*meso*-tetraphenylporphyrin) in a flask. The reagent mixture was pumped through the capillary with the help of Pump B and air was injected into the liquid stream at by Alicat mass flow controller. The gas-liquid slugs formed inside capillary then travelled into the Vapourtec photoreactor and irradiated by LED 3.6W panel. After the irradiation was finished the final mixture was collected continuously to a flask from the outlet capillary.

Entry 124 (PM-T-F-24):

Following **General Procedure 16** a solution of 0.500g (4.992 mmol) **20** and 3mg (0.009379 mmol) methylene blue in 40 mL dichloromethane was injected at 2.5 mL/min flow rate and air was introduced via T-mixer at 5 mL/min flow rate. The resulted slug flow of reagents and air irradiated in Vapourtec flow reactor at ambient temperature. After 1.5 minutes of residence time NMR analysis showed 11% conversion of **20**. After solvent evaporation 483mg crude obtained containing starting material and diastereomeric mixture of **23** *syn*:*anti* 64:36 ratio.

Conversion 11%, yield of **23a** 7% and **23b** 4% by NMR.

Entry 125 (PM-T-F-24R):

Following **General Procedure 16** a solution of 0.500g (4.992 mmol) **20** and 3mg (0.009379 mmol) methylene blue in 40 mL dichloromethane was injected at 1 mL/min flow rate and air was introduced via T-mixer at 1 mL/min flow rate. The resulted slug flow of reagents and air irradiated in Vapourtec flow reactor at ambient temperature. After 5 minutes of residence time NMR analysis showed complete conversion of **20** and after solvent evaporation 20mg of crude was collected containing **23** as diastereomeric mixture *syn*:*anti* 87:13 as per NMR analysis.

Conversion 100%, yield of **23a** 87% and **23b** 13% by NMR.

Entry 126 (PM-Vap-1):

Following **General Procedure 16** a solution of 0.500g (4.992 mmol) **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL was injected at 0.5 mL/min flow rate and air was introduced via T-mixer at 1 mL/min flow rate. The resulted slug flow of reagents and air irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **20** was 43% and the reactants were reinjected in vapourtec reactor. After the second injection 56% conversion was observed and then followed by solvent evaporation 0.471mg of crude was collected containing **23** as diastereomeric mixture *syn*:*anti* 75:25 as per NMR analysis.

Conversion 43%, yield of **23a** 33% and **23b** 10% by NMR.

Entry 127 (PM-Vap-2):

Following **General Procedure 16** a solution of 0.500g (4.992 mmol) **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 50 mL dichloromethane was injected at 0.5 mL/min flow rate and air was introduced via T-mixer at 1 mL/min flow rate. The resulted slug flow of reagents and air irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **20** was 25% and after solvent evaporation 0.415mg of crude was collected containing **23** as diastereomeric mixture *syn*:*anti* 60:40 as per NMR analysis.

Conversion 25%, yield of **23a** 15% and **23b** 10% by NMR.

Entry 128 (PM-Vap-3):

Following **General Procedure 16** a solution of 0.250g (2.496 mmol) **20** and 3mg (0.004880 mmol) *meso*-tetraphenylporphyrin in 100 mL dichloromethane was injected at 0.5 mL/min flow rate and air was introduced via T-mixer at 1 mL/min flow rate. The resulted slug flow of reagents and air irradiated in Vapourtec flow reactor at ambient temperature. After 6 minutes of residence time NMR analysis showed conversion of **20** was 57% and after solvent evaporation 0.197mg of crude was collected containing **23** as diastereomeric mixture *syn*:*anti* 88:12 as per NMR analysis.

Conversion 57%, yield of **23a** 50% and **23b** 7% by NMR.

7.4 Photooxygenation reactions with MOFs

General Procedure 17: Specified amount of starting material and catalytic amount of MOFs suspension was mixed in dichloromethane and transferred into a small 25 mL volume Pyrex test tube with a sidearm. Through the sidearm air/oxygen was introduced by a FEP capillary to create gentle bubbling in solution to keep the MOFs floating and a cold finger was inserted to keep the reaction temperature low. Prior to turning on the lights in Rayonet chamber the reactants were purged with air/oxygen for 15 minutes and then irradiated under specific light sources. Reaction completion was monitored by sampling for HPLC, NMR or GC analysis.

7.4.1 Phototransformation of Alpha-Terpinene (37)

Experiment 92 (MOF-1 PCN_{224} FN_{12} 39-1 vs α-terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN_{224} FN_{12} 39-1 (approximately 0.0135mg) were mixed in 20 mL of dichloromethane and irradiated under 419nm light source with air bubbling for 40 minutes. HPLC analysis showed presence of 5.8% ascaridole **38**.

Retention times on HPLC: α-terpinene **37** at 4.28min, ascaridole **38** at 7.42 min and p-cymene **39** at 10.05min.

Experiment 93 (MOF-2 PCN_{222} FN_{13} 37-1 vs α-terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN_{222} FN_{13} 37-1 (approximately 0.0081mg) were mixed in 20 mL of dichloromethane and irradiated under 419nm light source with air bubbling for 40 minutes. HPLC analysis showed presence of 8% ascaridole **38**.

Retention times on HPLC: α-terpinene **37** at 4.29min, ascaridole **38** at 7.4 min and p-cymene **39** at 10.06min.

Experiment 94 (MOF-3 PCN_{525} FN_{15} 31-1 vs α-terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37**(89% purity) and 1mL suspension of PCN_{525} FN_{15} 31-1 (approximately 0.0094mg) were mixed in 20 mL of dichloromethane and irradiated under 419nm light source with air bubbling for 40 minutes. HPLC analysis showed presence of 15% ascaridole **38**.

Retention times on HPLC: α-terpinene **37** at 4.27min, ascaridole **38** at 7.38 min and p-cymene **39** at 10.04min.

Experiment 95 (PM-PCN-224-1):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37**(89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with air bubbling for 60 minutes. GC analysis showed 32% conversion of α-terpinene and presence of 20% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min.

Experiment 96 (PM-PCN-224-2):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37**(89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.94 psi pressure for 120 minutes. GC analysis showed 55% conversion of α-terpinene and presence of 41% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min, iso-ascaridole **40** at 4.37min.

Experiment 97 (PM-PCN-224-3):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.94 psi pressure for 120 minutes. GC analysis showed 75% conversion of α-terpinene and presence of 47% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min, ascaridole **38** at 3.97 min and p-cymene **39** at 2.57min, iso-ascaridole **40** at 4.37min.

Experiment 98 (PM-PCN-224-4):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.96 psi pressure for 3.5 hours. GC analysis showed complete conversion of α-terpinene and presence of 66% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.97 min and p-cymene **39** at 2.57min, iso-ascaridole **40** at 4.38min.

Experiment 99 (PM-PCN-222-1):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.94 psi pressure for 120 minutes. GC analysis showed 70% conversion of α-terpinene and presence of 57% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.97 min and p-cymene **39** at 2.56min, iso-ascaridole **40** at 4.37min.

Experiment 100 (PM-PCN-222-2):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.94 psi pressure for 120 minutes. GC analysis showed 75% conversion of α-terpinene and presence of 54% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.55min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.58min, iso-ascaridole **40** at 4.37min.

Experiment 101 (PM-PCN-222-3):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.94 psi pressure for 3.5 hours. GC analysis showed complete conversion of α-terpinene and presence of 66% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.97 min and p-cymene **39** at 2.56min, iso-ascaridole **40** at 4.38min.

Experiment 102 (Blank Reaction):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) was mixed in 20 mL of dichloromethane and without adding any MOFs sample irradiated under

cool visible light source with pure oxygen bubbling at 10 mL/min flow rate, 14.90 psi pressure for 120 minutes. GC analysis showed 87% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52minand p-cymene **39** at 2.56min.

Experiment 103 (Dark Reaction 1 with PCN 224):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and Nitrogen gas was purged at 10 mL/min flow rate, 14.98 psi pressure for 120 minutes in absence of light. GC analysis showed 87% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min and p-cymene **39** at 2.56min.

Experiment 104 (Dark Reaction 1 with PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and Nitrogen gas was purged at 10 mL/min flow rate, 14.97 psi pressure for 120 minutes in absence of light. GC analysis showed 84% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min and p-cymene **39** at 2.57min.

Experiment 105 (Dark Reaction 2 with PCN 224):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with Nitrogen gas was purged at 10 mL/min flow rate, 14.95 psi pressure for 120 minutes. GC analysis showed 90.67% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min and p-cymene **39** at 2.57min.

Experiment 106 (Dark Reaction 2 with PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with Nitrogen gas was purged

at 10 mL/min flow rate, 14.96 psi pressure for 120 minutes. GC analysis showed 91% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min and p-cymene **39** at 2.57min.

Experiment 107 (Dark Reaction 3 with PCN 224):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure for 120 minutes in absence of light. GC analysis showed 94% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min and p-cymene **39** at 2.57min.

Experiment 108 (Dark Reaction 3 with PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure for 120 minutes in absence of light. GC analysis showed 93% of α-terpinene and no presence of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min and p-cymene **39** at 2.57min.

Experiment 109 [4,4',4",4'" – (Porphine – 5,10,15,20 – tetraryl) tetrakis (benzoic acid)] vs α-Terpinene:

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 10mg (0.0126 mmol) of [4,4',4",4'" – (Porphine – 5,10,15,20 – tetraryl) tetrakis (benzoic acid)] were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.96 psi pressure for 120 minutes. GC analysis showed 75% of α-terpinene and presence of 12% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.53min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min.

Experiment 110 (H_2TMeCPP vs α-Terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 10mg (0.0136 mmol) of [5,10,15,20 – Tetrakis(4 – carboxymethoxy phenyl)porphyrin] were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure for 120 minutes. GC analysis showed complete conversion of α-terpinene and presence of 84% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min and iso-ascaridole at 4.37min.

Experiment 111 (H_2TMeCPP vs α-Terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mg (0.00136 mmol) of [5,10,15,20 – Tetrakis(4 – carboxymethoxy phenyl)porphyrin] were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure for 120 minutes. GC analysis showed complete conversion of α-terpinene and presence of 81% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min and iso-ascaridole at 4.37min.

Experiment 112 (Sensitox vs α-Terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 10mg of Rose bengal B bound on polystyrene were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed complete conversion of α-terpinene and presence of 59% ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.52min, ascaridole **38** at 3.96 min and p-cymene **39** at 2.56min and iso-ascaridole at 4.38min.

7.4.2 Recyclability tests of MOFs (PCN 222 and PCN 224)

General Procedure 18: MOFs from the above general photoreactions were recycled by centrifugation at 100rpm for 2 minutes and washed five times with dichloromethane. Then the recycled MOFs samples were mixed with 2 mL dichloromethane in glass vial and stored in fridge for further use.

Experiment 113 (Test 1 Recycled PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 2mL suspension recycled PCN 222 were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed 60% conversion of α-terpinene and presence of 47% ascaridole **38**. Following **General Procedure 18** the PCN 222 was recycled and stored.

Experiment 114 (Test 2 Recycled PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 2mL suspension recycled PCN 222 were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed 58% conversion of α-terpinene and presence of 45% ascaridole **38**. Following **General Procedure 18** the PCN 222 was recycled and stored.

Experiment 115 (Test 3 Recycled PCN 222):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 2mL suspension recycled PCN 222 were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed 58% conversion of α-terpinene and presence of 39% ascaridole **38**. Following **General Procedure 18** the PCN 222 was recycled and stored.in fridge for further use.

Experiment 116 (Test 1 Recycled PCN 224):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 2mL suspension recycled PCN 224 were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed 60% conversion of α-terpinene and presence of 67% ascaridole **38**. Following **General Procedure 18** the PCN 224 was recycled and stored fridge for further use.

Experiment 117 (Test 2 Recycled PCN 224):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 2mL suspension recycled PCN 224 were mixed in 20 mL of dichloromethane and

irradiated under cool visible light source with pure oxygen gas was purged at 10 mL/min flow rate, 14.92 psi pressure for 120 minutes. GC analysis showed 60% conversion of α-terpinene and presence of 68% ascaridole **38**. Following **General Procedure 18** the PCN 224 was recycled and stored.

7.4.3 Phototransformation of DHAA (1) with MOFs

Experiment 118 [MOF-1 (PCN_{224} FN_{12} 39-1vs DHAA)]:

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN_{224} FN_{12} 39-1 (approximately 4.4mg) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with air bubbling for 60 minutes. NMR analysis showed no change of starting material.

Experiment 119 [MOF-2 (PCN_{224} FN_{12} 39-1 vs DHAA)]:

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN_{224} FN_{12} 39-1 (approximately 11.6mg) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with air bubbling for 3 hours. NMR analysis showed no change of starting material.

Experiment 120 [MOF-3 (PCN_{224} FN_{12} 39-1 vs DHAA)]:

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN_{224} FN_{12} 39-1 (approximately 8.7mg) were mixed in 20 mL of dichloromethane and irradiated under UVA 350nm light source with air bubbling for 5 hours. NMR analysis showed no change of starting material.

Experiment 121 [MOF-4 (PCN_{222} FN_{13} 37-1 vs DHAA)]:

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN_{222} FN_{13} 37-1 (approximately 5.1mg) were mixed in 20 mL of dichloromethane and irradiated under UVA 350nm light source with air bubbling for 10 hours. NMR analysis showed traces of **4**.

Experiment 122 [MOF-5 (PCN_{525} FN_{15} 31-1 vs DHAA)]:

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN_{525} FN_{15} 31-1 (approximately 5.9mg) were mixed in 20 mL of dichloromethane and irradiated under UVA 350nm light source with air bubbling for 10 hours. NMR analysis showed traces of **4**.

Experiment 123 (PM-PCN-224-DHAA-1):

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min rate, pressure 14.96 psi for 5 hours. NMR analysis showed no change of starting material.

Experiment 124 (PM-PCN-222-DHAA-1):

Following **General Procedure 17** 40mg (0.169 mmol) dihydroartemisinic acid (**1**) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min rate, pressure 14.98 psi for 5 hours. NMR analysis showed no change of starting material.

7.4.4 Phototransformation of mixed-anhydride of DHAA (2)

Experiment 125 (PM-PCN-224-mixedanhydride of DHAA-1):

Following **General Procedure 17** 40mg (0.129 mmol) mixed anhydride of dihydroartemisinic acid (**2**) and 1mL suspension of PCN224 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min rate, pressure 14.91 psi for 5 hours. NMR analysis showed no change of starting material.

Experiment 126 (PM-PCN-222- mixedanhydride of DHAA-1):

Following **General Procedure 17** 40mg (0.129 mmol) mixed anhydride of dihydroartemisinic acid (**2**) and 1mL suspension of PCN222 (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and irradiated under cool visible light source with pure oxygen bubbling at 10 mL/min rate, pressure 14.97 psi for 5 hours. NMR analysis showed no change of starting material.

7.4.5 Photooxygenation of α-terpinene 37 with PCN-224' and PCN-222-Zr-MOF

Experiment 127 (PCN-224' vs α-terpinene):

Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN-224' (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure

and for 210 minutes irradiated under 16 x 8W cool white fluorescent tube light. GC analysis showed 24% of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.58min, ascaridole **38** 4.04min and p-cymene **39** at 2.63min.

Experiment 128 (PCN-222-Zr-MOF vs α-terpinene)

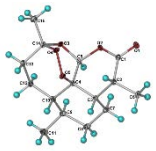
Following **General Procedure 17** 0.2 mL (0.167g, 0.001 mmol) α-terpinene **37** (89% purity) and 1mL suspension of PCN-222-Zr-MOF (approximately 8 – 10 mg/mL) were mixed in 20 mL of dichloromethane and pure oxygen gas was purged at 10 mL/min flow rate, 14.98 psi pressure and for 210 minutes irradiated under 16 x 8W cool white fluorescent tube light. GC analysis showed 46% of ascaridole **38**.

Retention times on GC: α-terpinene **37** at 2.58min, ascaridole **38** 4.04min and p-cymene **39** at 2.63min.

7.5 X-ray crystallographic data

X-Ray crystallographic analyses were performed on a Bruker APEX-II CCD diffractometer. Key crystallographic data is compiled in **Table 7. 1** [166].

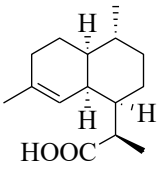
Table 7. 1: Key crystallographic data.

Parameter	**4**	**16**
		
Formula	$C_{15}H_{22}O_5$	$C_{15}H_{22}O_3$
M_w (g/mol)	282.32	250.32
a (Å)	6.3060(13)	4.8800(10)
b (Å)	9.2910(19)	12.478(3)
c (Å)	23.922(5)	22.559(5)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
Volume (Å^3)	1401.6(5)	1373.7(5)
Z	4	4
δ_{calc} (g/cm^3)	1.338	1.210
Crystal system	orthorhombic	orthorhombic

Space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1
Reflections collected	3219	3131
Reflections unique	3076	3063
R_1	0.0517	0.0509
wR_2	0.1311	0.1307
Goodness of Fit	1.069	1.071

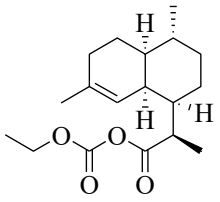
Chapter 8:
List of Compounds

8. List of Compounds



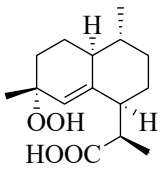
1

(*R*)-2-((1*R*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-octahydro-1,6-dimethylnaphthalen-4-yl)propanoic acid



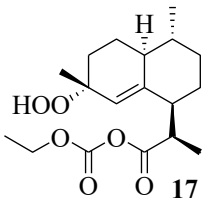
2

(*R*)-2-((1*R*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-octahydro-1,6-dimethylnaphthalen-4-yl) propanoyl ethyl carbonate



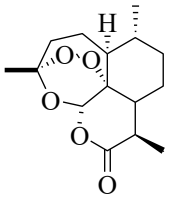
3

(*R*)-2-((1*R*,4*S*,6*R*,8a*S*)-1,2,3,4,6,7,8,8a-octahydro-6-hydroperoxy-1,6-dimethylnaphthalen-4-yl)propanoic acid



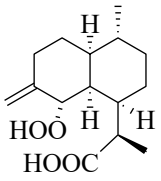
17

(*R*)-2-((1*R*,4*S*,6*R*,8a*S*)-1,2,3,4,6,7,8,8a-octahydro-6-hydroperoxy-1,6-dimethylnaphthalen-4-yl)propanoyl ethyl carbonate



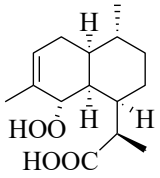
4

Artemisinin



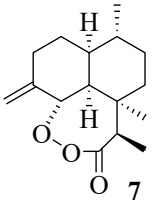
5

(*R*)-2-((1*S*,4a*S*,5*R*,8*R*,8a*S*)-decahydro-1-hydroperoxy-5-methyl-2-methylenenaphthalen-8-yl) propanoic acid



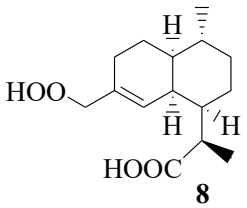
6

(*R*)-2-((1*R*,4*R*,4a*S*,5*S*,8a*S*)-1,2,3,4,4a,5,8,8a-octahydro-5-hydroperoxy-1,6-dimethylnaphthalen-4-yl)propanoic acid



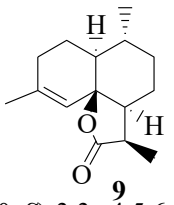
7

(1*S*,4*R*,4a*R*,7*R*,7a*S*,10a*S*)-decahydro-4,4a,7-trimethyl-10-methylenenaphtho[1,8-*cd*][1,2]dioxepin-3(1*H*)-one



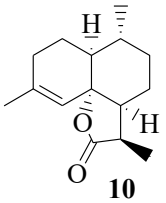
8

(*R*)-2-((1*R*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-octahydro-6-(hydroperoxymethyl)-1-methylnaphthalen-4-yl)propanoic acid



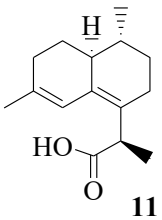
9

(3*R*,3a*S*,6*R*,6a*S*,10a*S*)-3,3a,4,5,6,6a,7,8-octahydro-3,6,9-trimethylnaphtho[1-*b*]furan-2-one



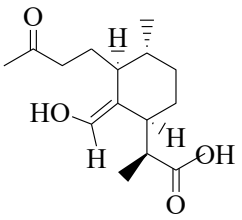
10

(3*R*,3a*S*,6*R*,6a*S*,10a*R*)-3,3a,4,5,6,6a,7,8-octahydro-3,6,9-trimethylnaphtho[1-*b*]furan-2-one

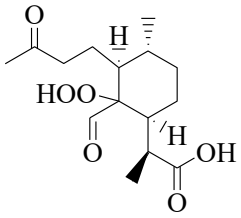


11

(*R*)-2-((1*R*,8a*S*)-1,2,3,7,8,8a-hexahydro-1,6-dimethylnaphthalen-4-yl)propanoic acid



12



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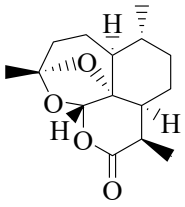

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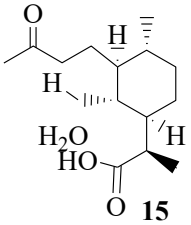
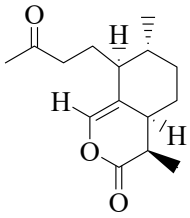


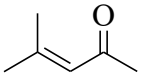
15

(*R*)-2-((1*R*,2*R*,3*S*,4*R*)-2,4-dimethyl-3-(3-oxobutyl) cyclohexyl)propanoic acid hydrate

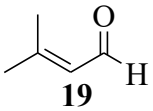


16

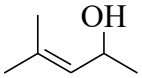
(4*R*,4a*S*,7*R*,8*S*)-4,4a,5,6,7,8-hexahydro-4,7-dimethyl-8-(3-oxobutyl)isochromen-3-one



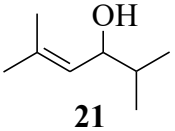
18
4-methylpent-3-en-2-one



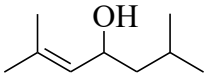
19
3-methylbut-2-enal



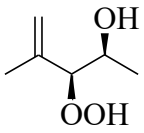
20
4-methylpent-3-en-2-ol



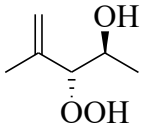
21
2,5-dimethylhex-4-en-3-ol



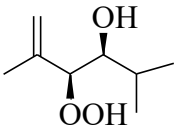
22
2,6-dimethylhept-2-en-4-ol



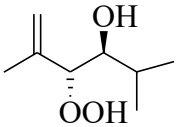
23a
(2*S*,3*S*)-3-hydroperoxy-4-methylpent-4-en-2-ol



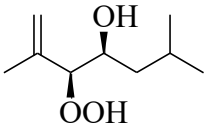
23b
(2*S*,3*R*)-3-hydroperoxy-4-methylpent-4-en-2-ol



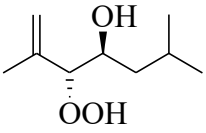
24a
(3*S*,4*S*)-4-hydroperoxy-2,5-dimethylhex-5-en-3-ol



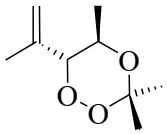
24b
(3*S*,4*R*)-4-hydroperoxy-2,5-dimethylhex-5-en-3-ol



25a
(3*S*,4*S*)-3-hydroperoxy-2,6-dimethylhept-1-en-4-ol

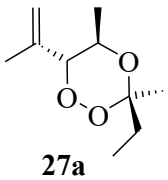


25b
(3*R*,4*S*)-3-hydroperoxy-2,6-dimethylhept-1-en-4-ol



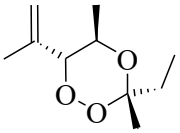
26

(5*R*,6*R*)-3,3,5-trimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



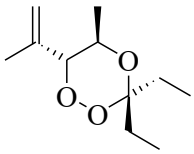
27a

(3R,5R,6R)-3-ethyl-3,5-dimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



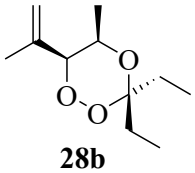
27b

(*3S,5R,6R*)-3-ethyl-3,5-dimethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



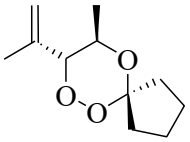
28a

(*5R,6R*)-3,3-diethyl-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



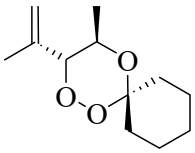
28b

(5R,6S)-3,3-diethyl-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



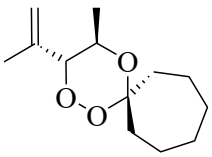
29

(*8RS,9RS*)-8-Isopropenyl-9-methyl-6,7,10-trioxa-spiro[4.5]decane



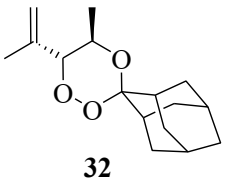
30

(*3RS,4RS*)-3-Isopropenyl-4-methyl-1,2,5-trioxa-spiro[5.5]undecane

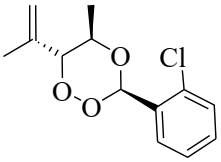


31

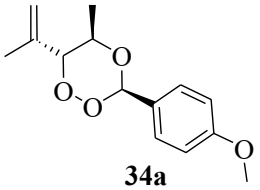
(*3RS,4RS*)-3-Isopropenyl-4-methyl-1,2,5-trioxa-spiro[5.6]dodecane



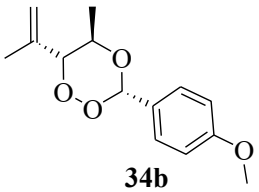
32
(*5RS,6RS*)-5-Methyl-6-(prop-1-en-2-yl)-spiro[1,2,4-trioxacyclohexane-3,2'-adamantane]



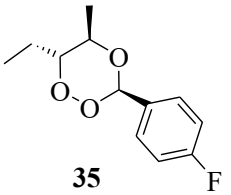
33
(*3R,5R,6R*)-3-(2-chlorophenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



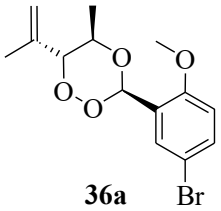
34a
(*3R,5R,6R*)-3-(4-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



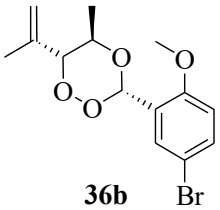
34b
(3*S*,5*R*,6*R*)-3-(4-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



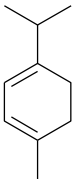
35
(*3R,5R,6R*)-3-(4-fluorophenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



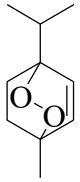
36a
(*3R,5R,6R*)-3-(5-bromo-2-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



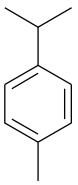
36b
(*3S,5R,6R*)-3-(5-bromo-2-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane



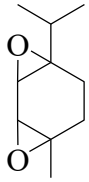
Alpha-Terpinene **37**



Ascaridole **38**



p-Cymene **39**



Iso-ascaridole **40**

Chapter 9: References

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