Synthesis of non-symmetrical dispiro 1,2,4,5-tetraoxanes and 1,2,4-trioxanes catalyzed by Silica Sulfuric Acid

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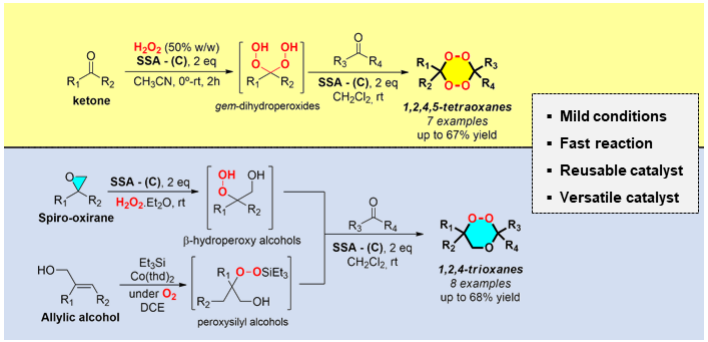


ABSTRACT

A novel protocol for the preparation of non-symmetrical 1,2,4,5-tetraoxanes and 1,2,4-trioxanes, promoted by the heterogeneous Silica Sulfuric Acid (SSA) catalyst, is reported. Different ketones react under mild conditions with *gem*-dihydroperoxides or peroxysilyl alcohols/β-hydroperoxy alcohols, to generate the corresponding endoperoxides in good yields. Our mechanistic proposal, assisted by molecular orbital calculations, at the ωB97XD/def2-TZVPP/PCM(DCM)//B3LYP/6-31G(d) level of theory, enhances the role of SSA in the cyclocondensation step. This novel procedure differs from previously reported methods by using readily available and inexpensive reagents, with recyclable properties, therefore establishing a valid alternative approach for the synthesis of new biologically active endoperoxides.

INTRODUCTION

Artemisinin combination therapies (ACT's) have been used as the first-line treatments against *Plasmodium falciparum* malaria during the last decades.[1–6] Disturbingly, the rise of resistance to artemisinin and its semi-synthetic derivatives (ARTs, **1a**, **Figure 1**) in South East Asia and the synthetic limitations of the ART scaffold have pushed the course of research towards the development of entirely synthetic endoperoxide-based antimalarials.[7–10] Several classes of synthetic endoperoxides have been scrutinized in this context, including 1,2-dioxanes, 1,2,4-trioxanes, 1,2,4-trioxolanes, and 1,2,4,5-tetraoxanes.[11–13] Among these classes, 1,2,4-trioxolanes and 1,2,4,5-tetraoxanes were extensively explored, notably yielding four antimalarial candidates (ozonides OZ277[14] (**2a**) and OZ439[15,16] (**2b**); 1,2,4,5-tetraoxanes RKA182[17] (**3a**) and E209[18] (**3b**), **Figure 1**).

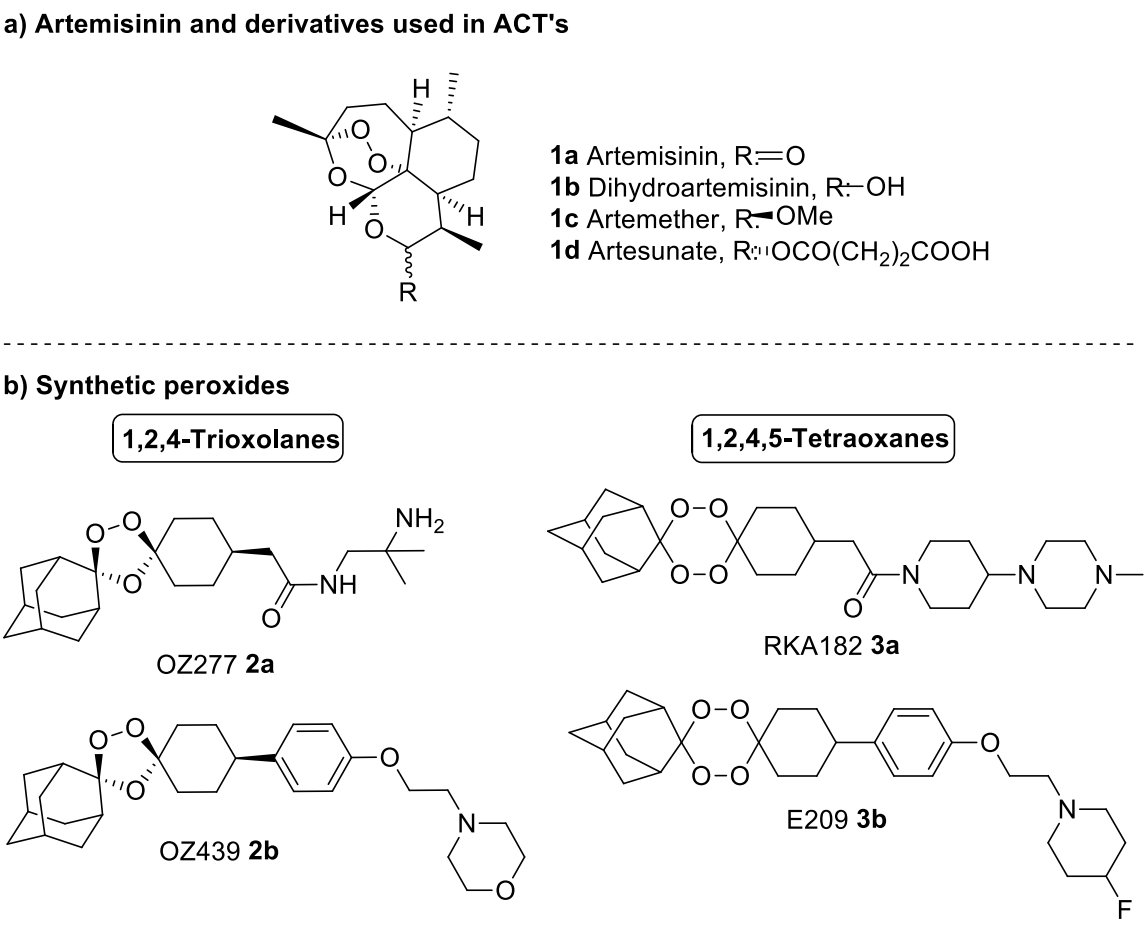


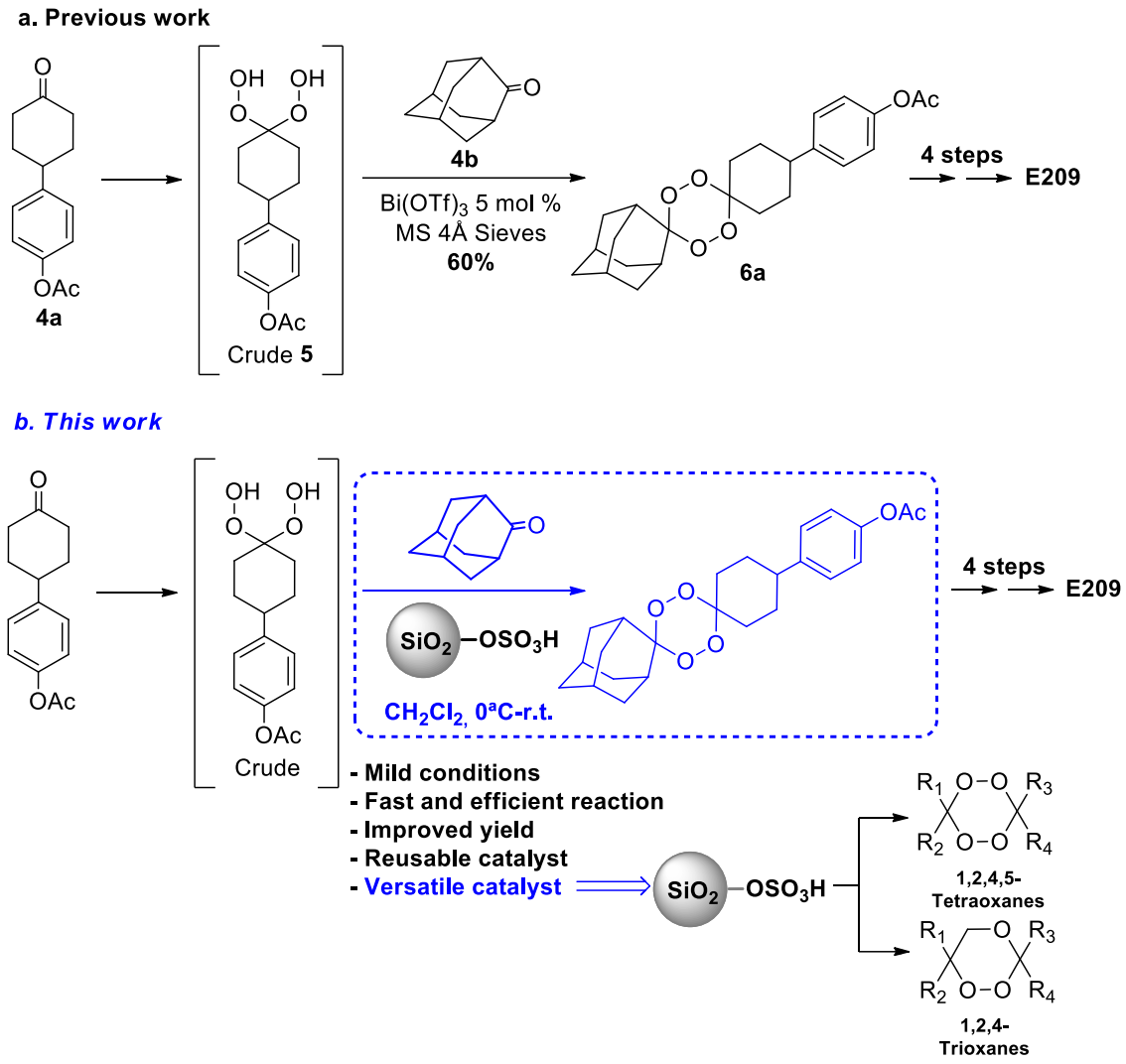
Figure 1. Representative endoperoxide-based antimalarial drugs or candidates. Artemisinin and semi-synthetic derivatives (**1a-d**), 1,2,4-trioxolanes OZ277 (**2a**), OZ439 (**2b**) and 1,2,4,5-tetraoxanes RKA182 (**3a**) and E209 (**3b**).

O'Neill's group reported E209, the newest 1,2,4,5-tetraoxane antimalarial under development. This candidate displays superior pharmacokinetic and pharmacodynamic properties, together with potent nanomolar efficacy against multiple strains of *P. falciparum* and *P. vivax*, *in vitro* and *in vivo*.

E209 also shows reduced cross-resistance with the C580Y mutation in transgenic parasites expressing variant forms of K13, known as the primary liability for artemisinin resistance.[19]

Notwithstanding the promising properties shown by the novel antimalarial candidate E209, the synthetic approach to its preparation demands improvement (**Scheme 1**). Preparation of E209 involves a six step-synthesis comprising the generation of the 1,2,4,5-tetraoxane core present in precursor **6a**, which requires the use of moisture-sensitive catalysts such as Re_2O_7 or $Bi(OTf)_3$, affording a maximum yield of around 60% (when using $Bi(OTf)_3$) (**Scheme 1**, **a**)[18]. During attempts to improve this synthetic step we successfully explored a new methodology for synthesizing the 1,2,4,5-tetraoxane subunit, involving the use of readily available and low-cost silica sulfuric acid (SSA) as catalyst. Silica-supported catalysts have attracted attention in recent years due to their promising reactivity and recoverable and reusable properties, leading to economic and environmental benefits[20,21]. Silica sulfuric acid was reported by Azarifar *et al*.[22] as an effective catalyst for the preparation of *gem*-dihydroperoxides. Peroxyacetalization is the first step in the most broadly used method for synthesizing 1,2,4,5-tetraoxanes, which involves the acid-catalyzed cyclocondensation of a ketone or aldehyde with an active *gem*-dihydroperoxide intermediate prepared *in situ*. Generally, *gem*-dihydroperoxides are generated from the reaction of a carbonyl compound with hydrogen peroxide (30 or 50 wt %), in the presence of a catalyst.[23] It has been reported that several catalysts known to promote peroxyacetalization of ketones and aldehydes (e.g. MTO[24], iodine (I_2)[25], Re_2O_7[26], PMA[27], $Bi(OTf)_3$[28], $ClSO_3H$[29], HPA/NaY[30], ADA-MNPs[31], $H_{3+x}PMo_{12}$-$x^{+6}Mo_x^{+5}O_{40}$[32]) can also induce selective cyclocondensation of these intermediates with ketones/aldehydes, generating 1,2,4,5-tetraoxanes.

Given the attractive properties of SSA, we decided to explore the potential of silica-supported catalysts to promote the cyclocondensation of the 1,2,4,5-tetraoxane ring. Our methodology involves a 'two-pot' procedure, whereby the *gem*-dihydroperoxide generated immediately reacts with the partner carbonyl compound to achieve the cyclocondensation step (**Scheme 1**, **b**).



Scheme 1. (a) Synthetic approach and conditions used in previous preparation of E209; (b) Improved conditions proposed in this work and scope evaluation of the methodology.

RESULTS AND DISCUSSION

Preparation of the intermediate *gem*-dihydroperoxide **5** followed the method reported by Azarifar *et al.*[22], with some adjustments, 4-(4-oxocyclohexyl)phenyl acetate **4a** was reacted with aqueous hydrogen peroxide 50% (w/w) in acetonitrile (4:1 molar ratio of H_2O_2 to the starting ketone), in the presence of the SSA catalyst, at room temperature (**Table 1**). A solvent extraction workup followed, to remove excess of H_2O_2, intended for safety purposes and optimization in the overall yield.

Concerning the preparation of the SSA catalysts, different proportions of sulfuric acid were used (SSA-(**A-D**): 1, 2, 3, and 4 mL of H_2SO_4 (> 95%), respectively). The procedure for preparing each catalyst was identical (**Figure 2**) and is described in detail in the Experimental Section. The molarity of sulfuric acid adsorbed on the silica gel was determined by acid-base titration. The results,

summarized in **Figure 3-A**, indicate that the amount of H_2SO_4 adsorbed by silica appears to be directly proportional to the amount of H_2SO_4 added to both SSA-**(A)** and SSA-**(B)** (3.85 ± 0.04 and 6.10 ± 0.03 mmol in 1 g of SSA, respectively), in contrast to what was observed with SSA-**(C)** and SSA-**(D)** (7.54 ± 0.04 and 8.40 ± 0.04 mmol in 1 g of SSA), demonstrating a saturation tendency on the silica gel surface after continuous addition of H_2SO_4.

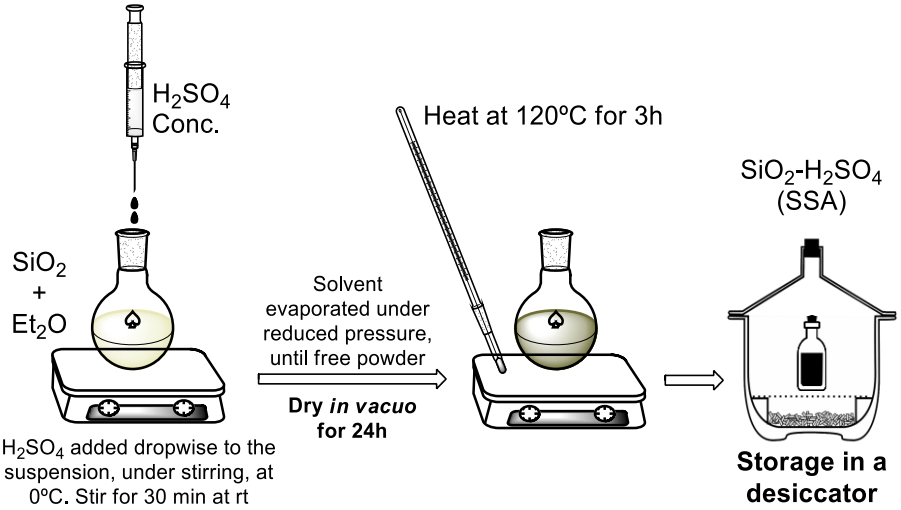


Figure 2. Representation of the procedure followed for the preparation of the SSA-(**A-D**) catalysts.

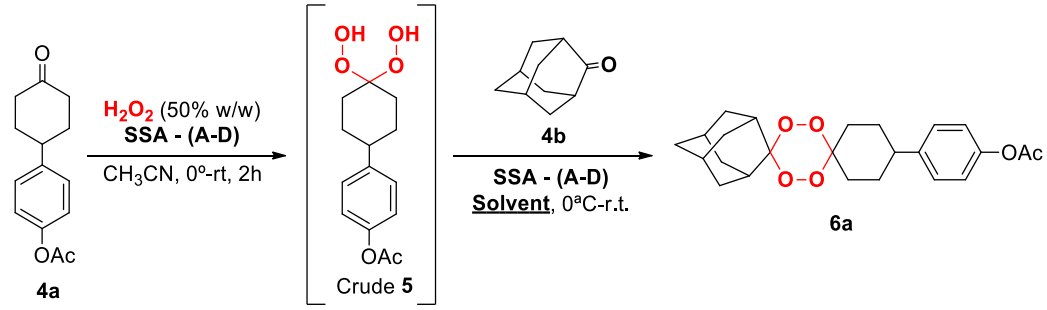
The reaction of the crude *gem*-dihydroperoxide with 2-adamantanone **4b**, in the presence of the SSA catalyst, was selected as the model to finding the optimized reaction conditions for the cyclocondensation step. The factors analyzed were the nature of the solvent as well as the amount and the type of catalyst, namely the ratio of H_2SO_4:SiO_2 (SSA-(**A-D**) (see **Table 1**). Analysis of the data shows that when using a 2:1 molar ratio of SSA-**(C)** to 4-(4-oxocyclohexyl)phenyl acetate **4a**, in anhydrous dichloromethane, at room temperature, *p*-(dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2"-tricyclo[3.3.1.1^{3,7}]decan]-4yl)phenyl acetate **6a** is selectively produced with the highest observed yield (67%), after 60 min (**Table 1**, entry 19). Increasing the reaction time (12h) (**Table 1**, entry 20) and using a higher molar ratio of SSA-**(C)** (3 equivalents, **Table 1**, entry 21) did not improve the efficacy of the model reaction. SSA-**(C)** seemed to outperform in efficiency, compared to the other SSA batches, in the same equivalency (**Table 1**, entries 4-7). Conduction of the model reaction using silica gel, or in the absence of catalyst, did not lead to **6a,** even when extending the reaction time for 48 h, showing the importance of SSA for the reaction's success (**Table 1**, entries 1, 2). Reaction with H_2SO_4 (1 equivalent) afforded the desired 1,2,4,5-tetraoxane **6a**, though in a much lower yield than using the silica-supported-H_2SO_4 catalyst (**Table 1**, entry 3). Solvent effects were also investigated. As shown from the data presented in **Table 1**, anhydrous dichloromethane is the most efficient solvent.

The reaction failed when solvents DMSO, and DMF were used (**Table 1**, entries 16 and 17). This observation is explained by the hygroscopic nature of these solvents. The presence of moisture in the reaction mixture could entail the following results: 1) water may affect the SiO_2-$H_2SO_4 \Leftrightarrow SiO_2$-$H_2O$ conversion equilibrium, altering the catalytic capabilities of SSA by adsorbing on its surface, interfering with the cyclocondensation step, and also promoting the hydrolysis of the intermediate *gem*-dihydroperoxide (DHP) with the regeneration of the corresponding starting ketone; 2) water itself may also hydrolyze the DHP, thus regenerating to its starting ketone. Even though DMSO and DMF had a commercial purity of >98%, these solvents were not freshly distilled prior to use. The use of ethereal solvents such as diethyl ether or 1,4-dioxane strongly inhibited the ability of SSA to promote cyclocondensation to the tetraoxane core (**Table 1**, entries 15 and 18). The yield decreased considerably when the reaction was performed under non-anhydrous conditions (**Table 1**, entries 11-14), revealing that anhydrous conditions favor the cyclocondensation of the 1,2,4,5-tetraoxane core by avoiding decomposition of the *gem*-dihydroperoxide to its starting material. The cyclocondensation was achieved even with minimal amounts of SSA-**(C),** such as 0.01 equivalent, although with 11% yield (**Table 1**, entry 24), demonstrating its catalytic capacity.

A series of 1,2,4,5-tetraoxanes **6a-g** were synthesized using the optimal conditions (**Table 1**, entry 19), thereby demonstrating the methodology's tolerance to a range of functional groups and structural features (**Table 2**). We also applied the methodology to the synthesis of non-symmetrical 1,2,4,5-tetraoxanes and, under heterogeneous conditions, the required compounds were generated with yields ranging from 5 to 67%. The reactions, performed in presence of two equivalents of SSA-**(C)** and using an excess of the second ketone (1.5 mmol) relatively to the starting one, were usually completed in the period of 1 to 6 hours. Homodimeric byproducts were occasionally formed during the cyclocondensation step, especially during the preparation of **6g**. The symmetric 1,2,4,5-tetraoxane byproduct could be differentiated by TLC and was obtained in lower proportion for ketones in which both structures varied substantially between each other, in polarity or composition. These circumstances could be avoided by isolating the DHP through column chromatography and then reacting it with an excess of the second ketone (2 mmol) in the cyclocondensation step. 1,2,4,5-Tetraoxane **6e** was generated in very low yield (5%), which may be ascribed to the use of a very bulky ketone, 2-adamantanone **4b**, which preferentially undergoes a Baeyer-Villiger rearrangement during the cyclocondensation step, originating its corresponding lactone. In fact, 4-oxahomoadamantan-5-one was isolated in a higher amount than the desired 1,2,4,5-tetraoxane **6e**. Hydroperoxidation of aromatic aldehyde **4c** was achieved easily with SSA-**(C)** during the first step. Although cyclocondensation with **4b** was observed, the *gem*-dihydroperoxide decomposed back to **4c**, suggesting some instability of the *gem*-dihydroperoxide in the reaction medium. An attempt to generate the corresponding tetraoxane

from 4,4-difluorocyclohexanone (**4d)** and **4b** was disrupted during purification. It appears that strong electron-withdrawing groups close to the tetraoxane ring, such as the fluorine, favour its instability, promoting decomposition (**Table 2**).

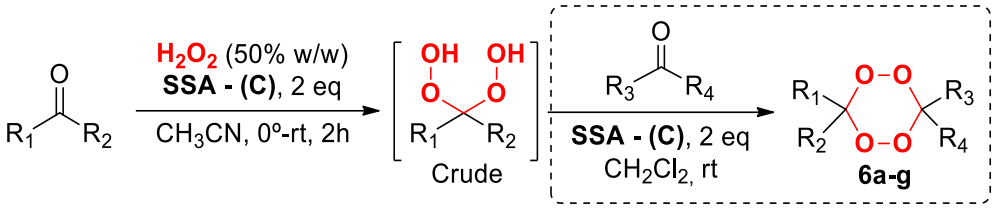
Table 1. Screening of reaction parameters for the formation of 1,2,4,5-tetraoxane **6a**

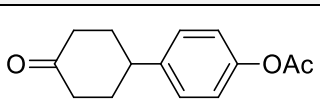
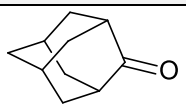
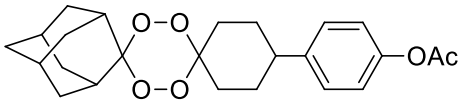
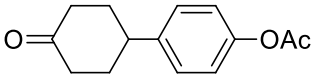
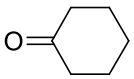
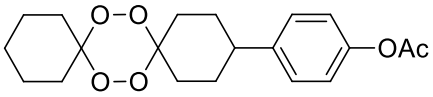
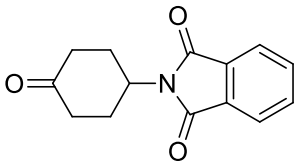
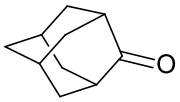
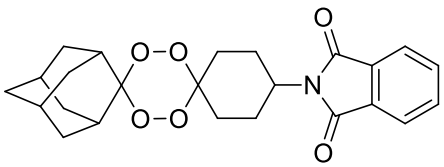
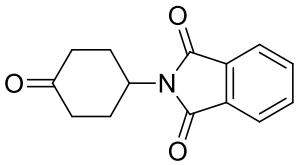
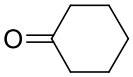
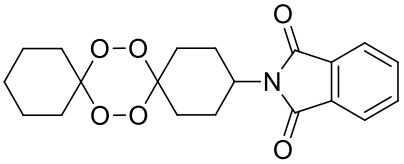
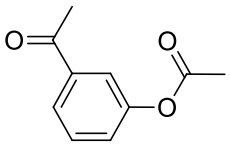
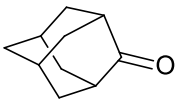
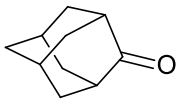
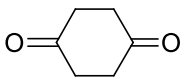
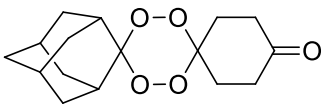
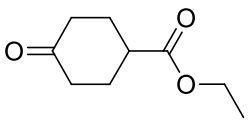
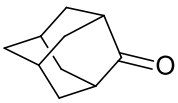
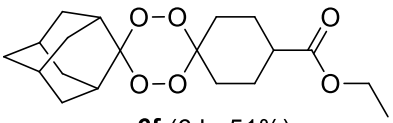
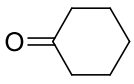
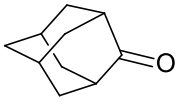
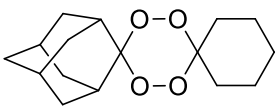
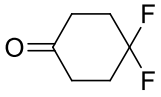
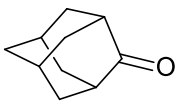


Entry	Catalyst	Solvent	Molar ratio SSA/ST[a]	*t* (min)	Yield(%)
1	None	CH_2Cl_2	-	48h	nr
2	SiO_2	CH_2Cl_2	1[d]	48h	nr
3	H_2SO_4	CH_2Cl_2	1[d]	12h	13
4	SSA - **(A)**	CH_2Cl_2	1	60	48
5	SSA - **(B)**	CH_2Cl_2	1	60	58
6	SSA - **(C)**	CH_2Cl_2	1	60	62
7	SSA - **(D)**	CH_2Cl_2	1	60	53
8	SSA - **(C)**[b]	CH_2Cl_2	1	60	56
9	SSA - **(C)**	CH_3CN	1	75	51
10	SSA - **(C)**	CH_3CN/CH_2Cl_2 (1:1)	1	75	53
11	SSA - **(C)**	CH_2Cl_2[c]	1	75	52
12	SSA - **(C)**	CH_3CN[c]	1	90	48
13	SSA - **(C)**	CH_3CN/CH_2Cl_2 (1:1)[c]	1	90	52
14	SSA - **(C)**	CH_3CO_2Et[c]	1	120	24
15	SSA - **(C)**	Et_2O	1	180	12
16	SSA - **(C)**	DMSO	1	48h	nr
17	SSA - **(C)**	DMF	1	48h	nr
18	SSA - **(C)**	1,4-Dioxane	1	48h	nr
19	***SSA - (C)***	***CH_2Cl_2***	***2***	***60***	***67***
20	SSA - **(C)**	CH_2Cl_2	2	12h	63
21	SSA - **(C)**	CH_2Cl_2	3	60	62
22	SSA - **(C)**	CH_2Cl_2	0.5	60	57
23	SSA - **(C)**	CH_2Cl_2	0.1	120	34
24	SSA - **(C)**	CH_2Cl_2	0.01	12h	11
	Re_2O_7	CH_2Cl_2	-	60	46[18]
	$Bi(OTf)_3$	CH_2Cl_2	-	120	61[18]

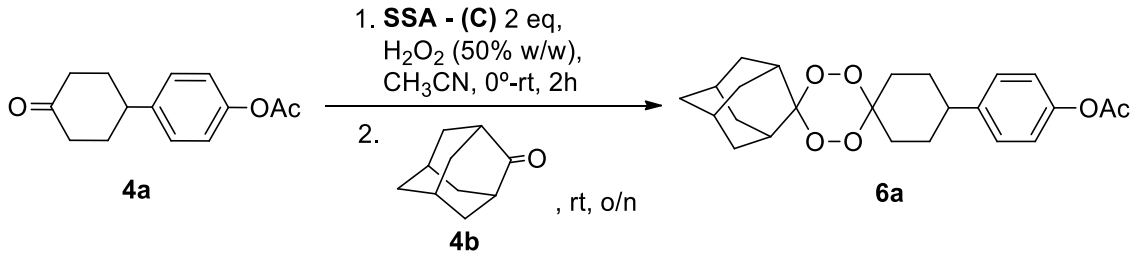
[a]*ST*: Starting material; [b]Formic acid used in the first step, instead of SSA-(C); [c]Not anhydrous; [d]1 equivalent of SiO_2 or H_2SO_4; nr = no reaction; SSA-(**A-D**): 1, 2, 3, and 4 mL of H_2SO_4 (> 95%), respectively).

153 **Table 2.** Scope evaluation in the SSA-promoted formation of 1,2,4,5-tetraoxanes.



Entry	Ketone 1	Ketone 2	Product (reaction time, yield)
1	 **4a**	 **4b**	 **6a** (1 h, 67%)
2			 **6b** (1.5 h, 57%)
3			 **6c** (1 h, 63%)
4			 **6d** (1 h, 47%)
5	 **4c**		(Mostly unreacted **4c**)
6			 **6e** (4 h, 5%)
7			 **6f** (6 h, 51%)
8			 **6g** (2 h, 64%)
9	 **4d**		(Decomposition during purification)

A one-pot approach to synthesize the 1,2,4,5-tetraoxanes was also carried out in order to understand if the performance would match the two-step protocol. The procedure involved addition of two equivalents of SSA-**(C)** and 50% aqueous H_2O_2 (4 mmol) to a solution of the starting ketone (1.0 mmol), in acetonitrile. After consumption of the starting material, 2-adamantanone (1.5 mmol) was added, and the final mixture left stirring overnight (**Scheme 2**). Under these conditions, the desired 1,2,4,5-tetraoxane was obtained in poor yields (8%). Evaporation of the solvent after the peroxidation step was not considered because it would lead to a dangerous concentration of free hydrogen peroxide, highly explosive.



Scheme 2. Conditions for one-pot synthesis of 1,2,4,5-tetraoxanes, using SSA-**(C)**.

The recycling properties of SSA were also thoroughly analyzed. Following each run of the cyclocondensation step of **6a**, SSA-(**C**) was removed from the reaction mixture by filtration and rinsed several times with dichloromethane, to remove contaminants adsorbed on the surface of SSA, and subsequently dried in a vacuum oven at 60°C, for 24h. The recovered SSA-(**C**) was reused in the next run. Analysis of the results displayed in **Figure 3-B**, shows that the catalyst SSA-(**C**) can be used up to two times with only a slight loss in the yield of **6a** (67% to 62%). When using the catalyst in the synthesis of **6a** for five consecutive times, we observed that the yield decreases considerably from the third, the fourth and fifth runs (41%, 27%, and 12%, respectively), which is probably due to the gradual catalyst contamination by the starting materials and byproducts and the slow loss of H_2SO_4. The amount of sulfuric acid loaded on the recovered SSA-**(C)** was also evaluated using the acid-base titration method to better understand the molarity exchanges that occurred during the reaction and recovery process of the compound. **Figure 3-B** shows that the molarity of H_2SO_4 on the silica surface decreases in the recovered catalyst with each run (**run 1**: 7.54 ± 0.04; **run 2**: 4.20 ± 0.08; **run 3**: 3.17 ± 0.06; **run 4**: 1.14 ± 0.05 and **run 5:** 0.53 ± 0.01 mmol in 1 g of SSA) and this decrease is directly related to the yield of the corresponding run's yield (**Figure 3-C**, $r = 0.921$, $p < 0.001$).

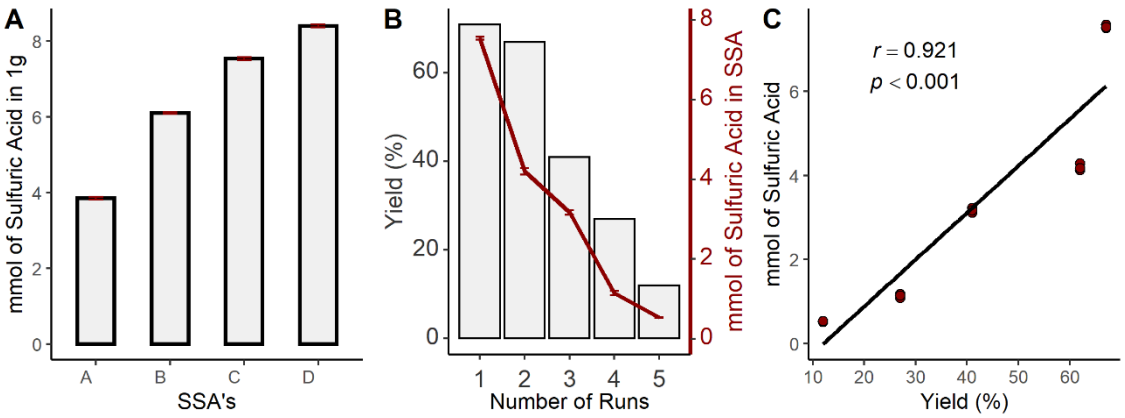


Figure 3. (A) Molarity of H_2SO_4 in SSA-(**A-D**). Bars represent mean values of molarity of H_2SO_4 triplicates ± standard deviation (SD); (B) Reusability SSA-(**C**) in the generation of **6a** (***red line*** corresponds to the molarity of H_2SO_4 in 1 g of SSA, in each run); (C) Pearson correlation coefficient between the yield of each run and the molarity of H_2SO_4, in 1g of SSA.

Mechanistic study for the formation of 1,2,4,5-tetraoxanes

A proposed mechanism for the formation of 1,2,4,5-tetraoxanes is provided in **Figure 4**. The role of SSA as an acid promoter was investigated by density functional theory (DFT) calculations, at the ωB97XD/def2-TZVPP/PCM(DCM)//B3LYP/6-31G(d) level of theory. 2-Adamantanone (**4b**) and 1,1-cyclohexanediyl dihydroperoxide (**5g**) were selected as model substrates and two molecules of $Si(OH)_3(SO_3H)$ were considered, to mimic the SSA. Calculations predict a thermodynamically favoured process, globally. The proposed mechanism involves protonation of the carbonyl group of **4b** by SSA; followed by 1,2-addition of a hydroperoxide of **5g** to the protonated ketone, with concomitant proton abstraction by SSA, *via* TS1 (11.4 kcal mol^{-1}); then protonation of the hydroxyl moiety by SSA; and, finally, a S_N1-type reaction to form the 1,2,4,5-tetraoxane **6g**. The S_N1 reaction occurs *via* water dissociation (TS2, rate-limiting step, 12.4 kcal mol^{-1}) to form a tertiary carbocation that reacts with the second hydroperoxide of **5g** (TS3, 10.5 kcal mol^{-1}), generating **6g** after proton abstraction by SSA. The calculations also suggest that all steps are reversible, except the last one (TS3), the dissociation of the product **6g** from SSA-H_2O being thermodynamically favoured.

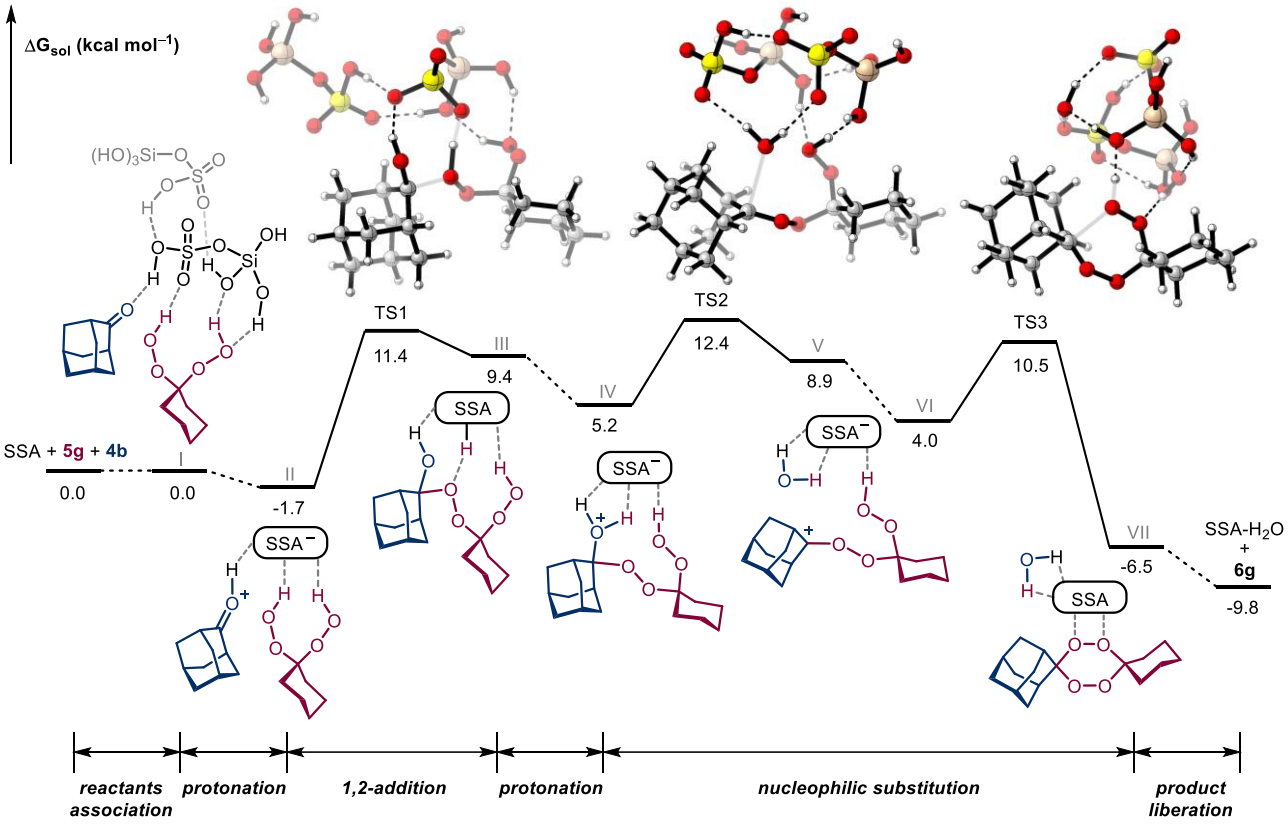
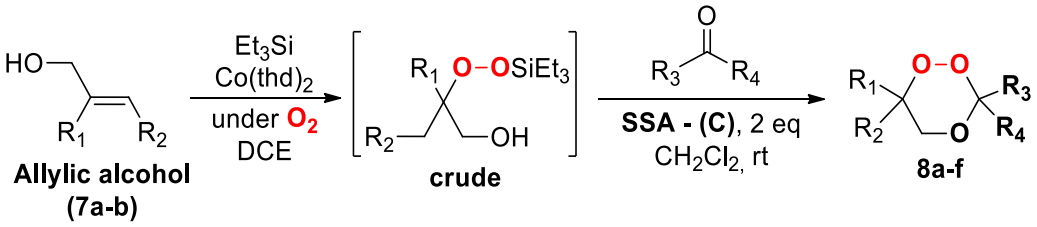


Figure 4. Free energy profile for the formation of 1,2,4,5-tetraoxane **6g** promoted by SSA (modelled by two molecules of $Si(OH)_3(SO_3H)$). DFT calculations were performed at the ωB97XD/Def2-TZVPP/PCM(DCM)//B3LYP/6-31G(d) level of theory (energy values in kcal mol^{-1}).

Inspired by the results obtained for the synthesis of 1,2,4,5-tetraoxanes, we decided to evaluate the SSA catalyst's potential in the cyclocondensation process to generate 1,2,4-trioxanes. Two methods were used: (A) Hydroperoxysilylation of allylic alcohols **7a-b**, followed by cyclocondensation to 1,2,4-trioxanes, in the presence of SSA. The 1,2,4-trioxane moiety (**8a-f**) could be easily constructed in moderate yields (38-68%, **Table 3**), through a milder approach, in the sequence of a Co(II)-mediated peroxysilylation of allylic alcohols (through a Isayama and Mukaiyama hydroperoxysilylation[33,34]); (B) Perhydrolysis of spiro-oxiranes, followed by cyclocondensation to 1,2,4-trioxanes, through reaction with the corresponding ketones, at room temperature, in the presence of SSA. We also explored SSA as a potential catalyst for the perhydrolysis step, since it has been previously reported as a promoter in the alcoholysis and hydrolysis of epoxides[35] and regioselective ring-opening of epoxides by the thiocyanate anion to yield thiocyanohydrins[36]. Perhydrolysis of spiro-oxiranes **9a-b** was achieved with SSA, in the presence of ethereal H_2O_2. A simple solvent extraction workup was performed to remove the H_2O_2 excess, and the crude *β*-hydroperoxy alcohols were used immediately in the next step without further purification. Subsequent cyclocondensation with the corresponding

ketones yielded the 1,2,4-trioxanes **10a-b** in reasonable yields (47-63%, **Table 4**). These results highlight the versatility of SSA for promoting selective cyclocondensation to different six-membered endoperoxide core structures.

Table 3. Hydroperoxysilylation of allylic alcohols, followed by SSA mediated cyclocondensation to 1,2,4-trioxanes.



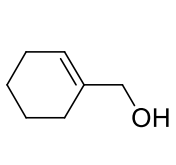
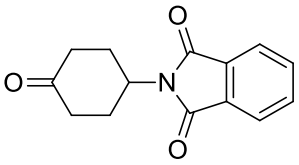
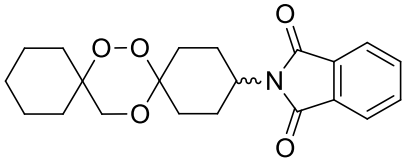
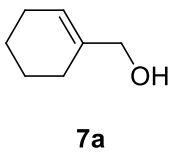
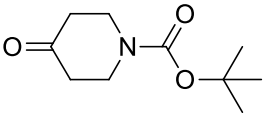
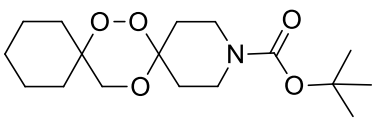
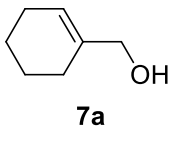
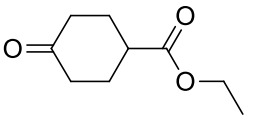
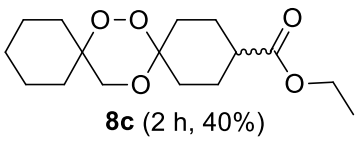
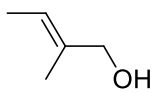
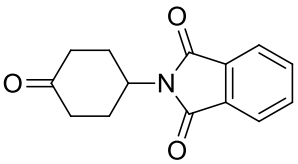
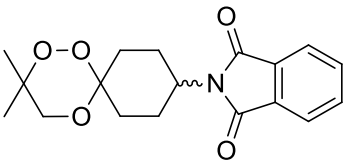
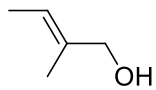
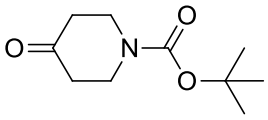
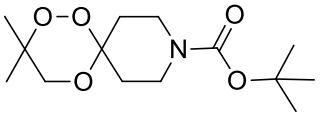
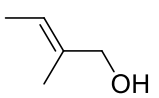
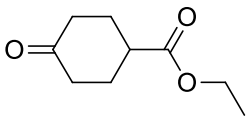
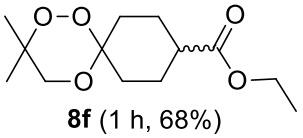
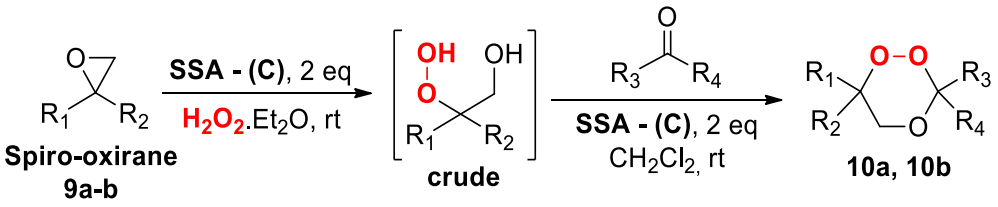
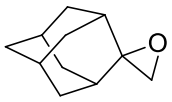
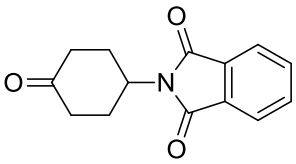
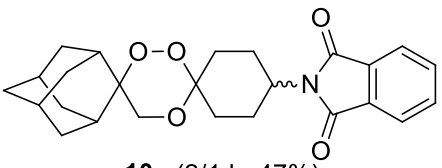
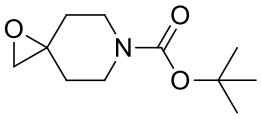
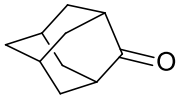
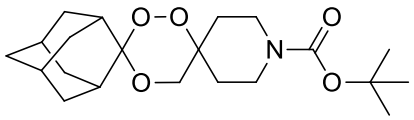
Entry	Allylic Alcohol	Ketone	Product (reaction time, yield)
1	 **7a**		 **8a** (2 h, 46%)
2	 **7a**		 **8b** (2 h, 38%)
3	 **7a**		 **8c** (2 h, 40%)
4	 **7b**		 **8d** (1 h, 62%)
5	 **7b**		 **8e** (1 h, 58%)
6	 **7b**		 **8f** (1 h, 68%)

Table 4. Perhydrolysis of spiro-oxiranes, followed by SSA mediated cyclocondensation to 1,2,4-trioxanes.



Entry	Spiro-oxirane	Ketone	Product (reaction time*, yield)
1	 **9a**		 **10a** (2/1 h, 47%)
2	 **9b**		 **10b** (2/2 h, 63%)

*Reaction time (Step 1/Step 2, hours)

CONCLUSION

The cyclocondensation of a representative library of ketones with *gem*-dihydroperoxides or silyl peroxysilyl alcohols/β-hydroperoxy alcohols to afford the corresponding unsymmetrical 1,2,4,5-tetraoxanes or 1,2,4-trioxanes, mediated by the SSA catalyst, was systematically investigated. The elementary steps governing the cyclocondensation pathway were investigated through molecular orbital calculations, using the DFT method, at the ωB97XD/def2-TZVPP/PCM(DCM)//B3LYP/6-31G(d) level of approximation. The results support a mechanistic proposal that highlights the catalytic role of SSA, where initial protonation of the ketone carbonyl group by SSA emerges as a key step in the mechanism. This novel approach involving the silica-supported catalyst offers several advantages, namely tolerance to a wide range of reagents. In addition, easy preparation, recyclability, and eco-friendly properties of the SSA catalyst are features that make this method an appealing tool in broadening the design of new biologically active endoperoxides. This improved methodology was successfully applied to the preparation of *p*-(dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decan]-4-yl)-phenyl acetate, an instrumental 1,2,4,5-tetraoxane intermediate scaffold for the synthesis of the antimalarial candidate E209.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Chemicals. All reagents and solvents used were of analytical grade and were used without further purification. 2-Adamantanone (**4b**), 4,4-difluorocyclohexanone (**4d**) and 2-methylprop-2-en-1-ol (**7b**) were purchased and used without additional purification. When necessary, solvents were freshly distilled from appropriate drying agents prior to use. Analytical thin layer chromatography (TLC) was carried out using TLC Silica gel 60 F254 aluminium sheets (AL TLC 20x20). Column chromatography was carried out using technical grade Silica Gel 60 (0.04 – 0.063 mm).

Analytical equipment. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded using a Bruker AMX400 spectrometer or a 500 MHz JEOL system equipped with a Royal HFX probe, in solution, using the deuterated solvents described in each experimental procedure. The chemical shifts (δ) are described in parts per million (ppm) downfield from an internal standard of tetramethylsilane (TMS). Melting points (°C) were obtained on an SMP30 melting point apparatus and are uncorrected. High Resolution Mass Spectrometry (HRMS) was recorded using the analytical services within the Chemistry Department at the University of Liverpool (UoL), and within the Centre of Marine Sciences (CCMar). HRMS was conducted on a VG analytical 7070E machine, Frisons TRIO mass spectrometer, or Agilent QTOF 7200, using chemical ionisation (CI) or electrospray (ESI) (UoL), and on Thermo Scientific High Resolution Mass Spectrometer (HRMS), model Orbitrap Elite, capable of MSn, n up to 10 (CCMar). Elemental analysis (%C, %H, %N and %S where specified) were determined by the University of Liverpool Microanalysis Laboratory.

Safety. Organic peroxides are potentially hazardous compounds (inflammable and explosive) and must be handled carefully: 1) a safety shield should be used for all reactions involving H_2O_2; 2) direct exposure to strong heat or light, mechanical shock, oxidizable organic materials or transition-metal ions should be avoided.

Computational Details. Density functional theory (DFT) calculations were performed using the Gaussian 09 software package[37] and structural representations were generated with *CYLview.*[38] All the geometry optimizations were carried out using the standard B3LYP functional and the valence double-zeta 6-31G(d) basis set. All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition states (a single imaginary frequency corresponding to the desired reaction coordinate). Single-point energy calculations on the optimized geometries were then evaluated using the long-range corrected hybrid functional ωB97XD developed by Head-Gordon and co-workers[39] and the valence triple-zeta Def2-TZVPP basis set, with solvent effects (dichloromethane) calculated by means of the Polarizable Continuum Model (PCM) initially devised

by Tomasi and coworkers,[40-43] with radii and non-electrostatic terms of the SMD solvation model, developed by Truhler and co-workers.[44] The free energy values presented along the manuscript and SI were derived from the electronic energy values obtained at the ωB97XD/Def2-TZVPP//B3LYP/6-31G(d) level, including solvent effects, and corrected by using the thermal and entropic corrections based on structural and vibration frequency data calculated at the B3LYP/6-31G(d) level.

Statistical Analysis. The values in this study are expressed as means ± SD. The Shapiro–Wilk test was used for verification of the normality of the data. Graphics and statistical analysis were generated with manual R scripts in RStudio (Version 1.4.1106), using ggplot2 libraries for the graphic figures.

General procedure for preparation of silica sulfuric acid (SSA): Adapted from Roy *et al.*[45], with slight modifications. To a slurry of silica gel (10 g, 230–400 mesh, pore size 60 Å) in dry diethyl ether (50 mL) was added concentrated H_2SO_4 (>95%, 3 mL) under strong stirring, for 30 min, at 0°C. The solvent was evaporated under reduced pressure, resulting in free-flowing silica sulfuric acid that was dried *in vacuo* for 24 hours. Then, it was heated at 120°C for 3 h (using a hot plate), affording the catalyst **SSA-(C).** The prepared catalyst was stored inside in a desiccator. The molarity of sulfuric acid adsorbed on the silica gel was determined by the acid−base titration method. 10 mL of purified water were added to 0.01 g of SSA and the mixture was stirred for 1 hour, at room temperature. The suspension was then titrated with a solution of NaOH (0.0025 M).

Procedure for catalyst regeneration. Following the cyclocondensation process with SSA, the catalyst was filtered out of the reaction mixture and washed several times with dichloromethane to remove any remaining organic contaminants (5 x 25 mL). Drying in a vacuum oven, at 60°C, for 24h, regenerates the catalyst.

General Procedure 1: Synthesis of 1,2,4,5-Tetraoxanes (6a-g). ***Step 1:*** Carbonyl compound **1** (1 mmol) was dissolved in acetonitrile (3 mL) and **SSA-(C)** (2 mmol) was added to the mixture. Hydrogen peroxide 50 wt. % in H_2O (4 mmol) was slowly added, over an ice bath, then the mixture was left to stir at room temperature until consumption of the starting material. To this mixture was added distilled water, then the catalyst was filtered and rinsed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 × 30 mL), dried over with $MgSO_4$, and concentrated under reduced pressure, at low temperature (30-35°C), to obtain the *gem*-dihydroperoxide semi-crude, which was used immediately, without further purification. ***Step 2:*** The *gem*-dihydroperoxide semi-crude was dissolved in anhydrous CH_2Cl_2 (5 mL), followed by addition of the second carbonyl compound **2** (1.5 mmol). The mixture was cooled over an ice bath, prior to addition of **SSA-(C)** (2 mmol). The mixture was then warmed and left to stir at room

temperature until consumption of the starting material. The resulting solution was then filtered, rinsed with CH_2Cl_2, and concentrated under reduced pressure. The residue was purified by flash chromatography using an EtOAc−hexane gradient (unless specified differently) to afford pure 1,2,4,5-tetraoxanes.

General Procedure 2: Synthesis of 1,2,4-Trioxanes (8a-f): *Via* Hydroperoxysilylation of allylic alcohols, followed by cyclocondensation to 1,2,4-trioxane. ***Step 1: Hydroperoxysilylation of Allylic Alcohols.*** Procedure as described by O'Neill *et al.*[46] To a solution of allylic alcohol (1 mmol) in 1,2-dichloroethane (DCE) (10 mL) was added $Co(thd)_2$ (0.03 mmol) at room temperature, and the solution allowed to stir, while bubbling with oxygen. After a couple of minutes, triethylsilane (2 mmol) was added and the reactants were allowed to react under an oxygen atmosphere. The original purple/brown solution became green and the reaction was followed by TLC until completion. The reaction mixture was then filtered through a plug of celite in a sinter funnel, under pressure. The celite was washed with ethyl acetate and the resulting filtrate was then concentrated under reduced pressure to give the semi-crude peroxysilyl alcohol, which was used immediately in the next step without further purification. ***Step 2: Cyclocondensation of the peroxysilyl alcohol to 1,2,4-trioxanes.*** *The* peroxysilyl alcohol semi-crude (1 mmol) and the carbonyl compound (1.5 mmol) were dissolved in anhydrous dichloromethane (5 mL). The mixture was cooled to below 5°C and then **SSA-(C)** (2 mmol) was added. The mixture was then warmed and left to stir at room temperature until completion of the reaction (usually 30-60 min). The resulting solution was then filtered, rinsed with dichloromethane, and concentrated under reduced pressure. Purification by flash chromatography using a mixture of EtOAc/*n*-Hexane (unless specified differently), gave the pure product.

Preparation of the $Co(thd)_2.H_2O$ Catalyst. Procedure as described by O'Neill *et al.*[46] To an aq. solution (95 mL) of NaOH (0.43g, 10 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (thd) (4.0 mL, 19.17 mmol) was slowly added a solution (15 mL) of cobalt (II) chloride (1.34 g, 10.35 mmol). After stirring for 3 hours at 60°C (using an oil bath), and filtering, the product was washed with water and stored under reduced pressure as a purple powder (3.55 g, 40%). The prepared catalyst was stored inside in a desiccator.

General Procedure 3: Synthesis of 1,2,4-Trioxanes (10a and 10b): *Via* perhydrolysis of spiro-oxiranes, followed by cyclocondensation to 1,2,4-trioxanes. ***Step 1:*** To a spiro-oxirane (1 mmol) solution of $MgSO_4$ dried H_2O_2–Et_2O (15 mL, see note below), **SSA-(C)** (2 mmol) was added, at 0°C. The reaction mixture was then allowed to warm at room temperature and stirred until completion (usually 1 h). The reaction mixture was then washed with water (1 × 100 ml) and brine (1 × 100 mL).

The combined aqueous layers were extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were concentrated under *vacuum*, affording the *β*-hydroperoxy alcohol crude, which was immediately used in the next step without any further purification. ***Step 2*: Cyclocondensation of the β-hydroperoxy alcohol to 1,2,4-trioxanes.** The β-hydroperoxy alcohol semi-crude (1 mmol) and the carbonyl compound (1.5 mmol) were dissolved in anhydrous dichloromethane (5 mL). The mixture was cooled to below 5°C and then **SSA-(C)** (2 mmol) was added. The mixture was then warmed and left to stir at room temperature until completion or the reaction (usually 30-60 min). The resulting solution was then filtered, rinsed with dichloromethane and concentrated under *vacu*um. Purification by flash chromatography using a EtOAc−hexane gradient (unless specified differently), gave the pure 1,2,4-trioxane compound.

Method to dry H_2O_2–Et_2O. Procedure as described by Sabbani *et al.*[47]. At 0°C, hydrogen peroxide peroxide (H_2O_2, 42 ml, 50 wt% in H_2O) was dissolved in anhydrous diethyl ether (395 mL). Constant stirring was used to add anhydrous $MgSO_4$ until a thick white slurry sank to the bottom of the flask. The supernatant was then decanted and dried with anhydrous $MgSO_4$ and filtered again, producing an ethereal solution of H_2O_2 with a concentration of approximately 1.5 M. The solution was used immediately thereafter. The solution cannot be stored for later use, due to safety hazards.

General Procedure 4: Corey–Chaykovsky epoxidation. The procedure was adapted from Sabbani *et al.*[47], with slight modifications. A suspension of potassium *tert*-butoxide (1.5 mmol) in anhydrous 1,2-dimethoxyethane or tetrahydrofuran (5 mL) was treated with trimethylsulfoxonium iodide (1.5 mmol) and the mixture was stirred at reflux (using an oil bath) under nitrogen for 2 h. The mixture was then cooled to room temperature and treated dropwise, over 2 min., with a solution (2 mL) of the corresponding ketone (1 mmol) and then left stirring under reflux (using an oil bath), overnight or until completion of the reaction. The mixture was cooled to room temperature and then quenched with water. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under *vacuum.* Purification by flash chromatography using a EtOAc-hexane gradient (unless specified differently), gave the pure spiro-epoxide.

4-(4-Oxocyclohexyl)phenyl acetate (4a). Procedure adapted from by O'Neill *et al.*[18] with slight modifications. To a stirred solution of 4-(4-hydroxyphenyl)cyclohexanone (2.00 g, 10.51 mmol) and triethylamine (2.90 mL, 20.8 mmol) in anhydrous dichloromethane (20 mL) was added acetic anhydride (3.00 mL, 31.74 mmol), dropwise, at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 3 hours, until reaction's completion. The final reaction mixture was washed with water (3 × 20 mL), sodium bicarbonate (3 × 20 mL) and brine (20 mL). The organic layer

was dried with $MgSO_4$, filtered and then concentrated under reduced pressure. Recrystallization of the solid residue from acetone gave the ester (2.20 g, 90% yield) as a white solid. M.p. = 101-103°C. Spectral data are in accordance with the reported in the literature[18]. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 3.08 – 2.98 (m, 1H), 2.50 (dd, *J* = 10.6, 4.6 Hz, 4H), 2.29 (s, 3H), 2.22 (dt, *J* = 14.6, 3.0 Hz, 2H), 1.93 (dt, *J* = 22.7, 10.6 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 210.9, 169.6, 149.2, 142.3, 127.7, 121.6, 42.2, 41.3, 34.0, 21.1 ppm. HRMS (ESI+, *m/z*) calcd $C_{14}H_{16}O_3Na$ $(M+Na)^+$: 255.0992; found 255.0992.

3-Acetylphenyl acetate (4c). This compound was synthesised following the procedure described previously by O'Neill *et al.*[18], using 3′-hydroxyacetophenone. Colourless solid (1.12 g, 86% yield). Spectral data are in accordance with the reported in the literature[48]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.67 (t, *J* = 2.0 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.30 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.1, 169.4, 151.0, 138.6, 129.8, 126.6, 125.9, 121.6, 26.8, 21.2. HRMS (ESI^+, *m/z*) calcd for $C_{10}H_{10}O_3Na$ $(M+Na)^+$: 201.05222; found 201.05185.

p-(Dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decan]-4-yl)-phenyl acetate (6a). This compound was synthesised in accordance with general procedure 1 using 4-(4-oxocyclohexyl)phenyl acetate **4a** (for the peroxidation step) and 2-adamantanone **4b** (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 2.5:97.5, v/v) provided a white solid (278 mg, 67% yield). M.p. = 195-197°C. Spectral data are in accordance with the reported in the literature[18]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 3.35 – 2.94 (m, 2H), 2.54 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.22 (s, 3H), 2.08 – 1.66 (m, 14H), 1.65 – 1.49 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.8, 149.0, 143.5, 127.9, 121.5, 110.6, 107.6, 43.2, 37.0, 34.4, 33.3, 32.0, 30.2, 29.8, 27.2, 21.3. HRMS (ESI^+, *m/z*) calcd $C_{24}H_{30}O_6Na$ $(M+Na)^+$: 437.19346; found 437.19229.

p-(7,8,15,16-Tetraoxa-3-dispiro[5.2.5.2]hexadecyl)phenyl acetate (6b). This compound was synthesised in accordance with general procedure 1 using **4a** (for the peroxidation step) and cyclohexanone (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 2.5:97.5, v/v) provided a white solid (207 mg, 57% yield). M.p. = 93-95°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 3.25 (s, 1H), 2.59 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.32 (d, *J* = 22.7 Hz, 1H), 2.27 (s, 3H), 1.87 – 1.55 (m, 13H), 1.53 – 1.39 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.8, 149.0, 143.5, 127.9, 121.5, 108.5, 107.7, 43.2, 31.9, 31.7, 29.6, 25.5, 22.4, 21.2. HRMS (ESI^+, *m/z*) calcd $C_{20}H_{26}O_6Na$ $(M+Na)^+$: 385.16216; found 385.16165.

2-(Dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decan]-4-yl)-1,3-isoindolinedione (6c). This compound was synthesised in accordance with general procedure 1 using 2-(4-oxocyclohexyl)isoindoline-1,3-dione (for the peroxidation step) and **4b** (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) provided a white solid (268 mg, 63% yield). M.p. = 174-176°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 4.22 (tt, *J* = 12.5, 3.8 Hz, 1H), 3.25 (br d, 2H), 2.55 (s, 2H), 2.15 – 1.84 (m, 8H), 1.79 – 1.61 (m, 10H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.2, 134.0, 132.0, 123.3, 110.7, 106.7, 49.8, 37.0, 34.4, 33.2, 31.2, 30.2, 29.0, 27.2, 25.6, 24.8. HRMS (ESI$^+$, *m/z*) calcd $C_{24}H_{27}NO_6Na$ $(M+Na)^+$: 448.17306; found 448.17273.

2-(7,8,15,16-Tetraoxa-3-dispiro[5.2.5.2]hexadecyl)-1,3-isoindolinedione (6d). This compound was synthesised in accordance with general procedure 1 using 2-(4-oxocyclohexyl)isoindoline-1,3-dione (for the peroxidation step) and cyclohexanone (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) provided a white solid (175 mg, 47% yield). M.p. = 177-179°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.21 (tt, *J* = 12.5, 3.8 Hz, 1H), 3.30 (s, 1H), 2.53 (s, 2H), 2.30 (d, *J* = 31.9 Hz, 2H), 1.90 (s, 1H), 1.79 – 1.61 (m, 6H), 1.60 – 1.42 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.2, 134.0, 132.0, 123.3, 108.6, 106.9, 49.7, 31.9, 31.2, 29.6, 28.8, 25.5, 24.7, 22.3, 21.9. HRMS (ESI$^+$, *m/z*) calcd $C_{20}H_{23}NO_6Na$ $(M+Na)^+$: 396.14176; found 396.14148.

Dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decan]-4-one (6e). This compound was synthesised in accordance with general procedure 1 using **4b** (for the peroxidation step) and 1,4-cyclohexanedione (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 2.5:97.5, v/v) provided a white solid (14.7 mg, 5% yield). M.p = 156-158ºC. Spectral data are in accordance with the reported in the literature[49]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.20 (br s, 1H), 2.72 (s, 2H), 2.48 (br d, 4H), 2.10 – 1.86 (m, 9H), 1.82 – 1.59 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 209.4, 111.1, 106.7, 37.0, 36.5, 35.7, 34.4, 33.2, 30.5, 30.2, 28.0, 27.1. HRMS (ESI$^+$, *m/z*) calcd $C_{16}H_{22}O_5Na$ $(M+Na)^+$: 317.13594; found 317.13599.

Ethyl dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decane]-4-carboxylate (6f). This compound was synthesised in accordance with general procedure 1 using 2-ethyl 4-oxocyclohexanecarboxylate (for the peroxidation step) and **4b** (for the cyclocondensation step). Purification by flash chromatography (EtOAc: *n*-hexane, 1:99, v/v) provided a white solid (178 mg, 51% yield). M.p. = 67-69°C. Spectral data are in accordance with the reported in the literature[50]. ^{1}H NMR (500 MHz, $CDCl_3$): 4.12 (q, *J* = 7.1 Hz, 2H), 3.02 (br d, *J* = 118.6 Hz, 2H), 2.41 – 2.34 (m, 1H), 2.08 – 1.60 (m, 19H), 1.50 (s, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.8,

110.6, 107.3, 60.5, 41.8, 39.4, 37.0, 34.4, 33.2, 30.2, 30.2, 28.3, 27.1, 24.8, 23.9, 14.3. HRMS (ESI^+, *m/z*) calcd $C_{19}H_{28}O_6Na$ $(M+Na)^+$: 375.17781; found 375.17725.

Dispiro[cyclohexane-1,3'-[1,2,4,5]tetraoxane-6',2''-tricyclo[3.3.1.1^{3,7}]decane] (6g). This compound was synthesised in accordance with general procedure 1 using cyclohexanone (for the peroxidation step) and **4b** (cyclocondensation step). Purification by flash chromatography (*n*-hexane, 100%, v/v) provided a white solid (179 mg, 64% yield). M.p = 57-59ºC. Spectral data are in accordance with the reported in the literature[28]. ^1H NMR (500 MHz, $CDCl_3$): δ 3.17 (s, 1H), 2.30 (s, 2H), 2.04 – 1.44 (m, 21H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 110.4, 108.1, 37.1, 37.1, 34.4, 33.3, 33.2, 31.9, 30.2, 29.7, 27.2, 25.5, 22.4. HRMS (MALDI-TOF, *m/z*) calcd for $C_{16}H_{24}O_4K$ $(M+K)^+$: 318,1311; found 318.3302.

Cyclohex-1-enyl-methanol (7a). Procedure by Kwiatkowski et al.[51] with slight modifications. 1-Cyclohexene-1-carboxylic acid (1 g, 7.93 mmol) in diethyl ether (40 mL) was added dropwise to a suspension of $LiAlH_4$ (0.57 g, 23.78 mmol) in anhydrous ether at 0°C (5 mL). The reaction mixture was stirred at 0°C for 60 minutes, and after successively quenched with H_2O (10 mL) and NaOH (6M, 10 mL) allowing to warm to room temperature while stirring. Anhydrous Na_2SO_4 (2 g) was added, the mixture was stirred for 30 minutes, filtered over a pad of celite and washed with EtOAc (3 × 30 mL). The combined organic layers were concentrated under reduced pressure to afford the desired product as a colourless oil (0.81 g, 91% yield). Spectral data are in accordance with the reported in the literature[51]. ^1H NMR (400 MHz, $CDCl_3$): δ 5.71 – 5.65 (m, 1H), 3.97 (s, 2H), 2.03 (dd, *J* = 7.0, 4.3 Hz, 4H), 1.67 – 1.56 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 137.6, 123.1, 67.7, 25.6, 24.9, 22.5, 22.4. HRMS (CI, *m/z*) calcd for $C_7H_{14}N$ $(M+NH_4)^+$: 112.1121; found 112.1124.

2-(7,8,15-Trioxa-12-dispiro[5.2.5.2]hexadecyl)-1,3-isoindolinedione (8a). This compound was synthesised in accordance with general procedure 2 using **7a** and 2-(4-oxocyclohexyl)isoindoline-1,3-dione. Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) followed by recrystallization with acetone provided a white solid (171 mg, 46% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.79 (m, 2H), 7.73 – 7.68 (m, 2H), 4.19 (ddt, *J* = 12.2, 9.8, 3.9 Hz, 1H), 3.66 (s, 2H), 3.11 – 2.21 (m, 3H), 2.04 – 1.23 (m, 15H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.2, 168.1, 133.9, 133.8, 132.0, 123.1, 100.9, 100.7, 77.9, 77.7, 66.4, 66.0, 50.0, 49.9, 25.9, 25.2, 21.3. Duplicate peaks on $^{13}C\{^1H\}$ NMR, it is due to the mixture of isomers *cis* or *trans*. HRMS (ESI+, *m/z*) calcd $C_{21}H_{25}NO_5Na$ $(M+Na)^+$: 394.1625; found 394.1626. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77, found: C, 67.51; H, 7.03; N, 3.58.

Tert-Butyl 7,8,16-trioxa-3-aza-3-dispiro[5.2.5.2]hexadecanecarboxylate (8b). This compound was synthesised in accordance with general procedure 2 using **7a** and 1-boc-4-piperidone. Purification by

flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) provided a white solid (124 mg, 38% yield). ^{1}H NMR (400 MHz, CD_3CN): δ 3.87 – 3.48 (m, 2H), 3.48 – 3.26 (m, 4H), 2.27 (dd, *J* = 12.0, 5.4 Hz, 1H), 1.93 (d, *J* = 1.7 Hz, 22H). $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3CN): δ 154.9, 100.9, 79.6, 78.3, 66.0, 40.8, 30.5, 32.2, 34.5, 28.1, 26.1, 21.6. HRMS (ESI+, *m/z*) calcd $C_{17}H_{29}NO_5Na$ $(M+Na)^+$:350.1938 found 350.1942.

Ethyl 7,8,15-trioxa-12-dispiro[5.2.5.2]hexadecanecarboxylate (8c). This compound was synthesised in accordance with general procedure 2 using **7a** and ethyl 4-oxocyclohexanecarboxylate. Purification by flash chromatography (EtOAc: *n*-hexane, 2.5:97.5, v/v) provided a colorless oil (119 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (qd, *J* = 7.1, 5.4 Hz, 2H), 3.84 – 3.34 (m, 2H), 2.86 – 2.30 (m, 2H), 1.93 – 1.27 (m, 17H), 1.24 (td, *J* = 7.1, 5.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 175.0, 174.9, 101.4, 101.3, 77.7, 77.6, 66.2, 65.9, 60.3, 60.3, 42.2, 41.7, 32.9, 29.9, 25.9, 25.9, 24.8, 24.4, 21.3, 14.2. Duplicate peaks on $^{13}C\{^{1}H\}$ NMR, it is due to the mixture of isomers *cis* or *trans*. HRMS (ESI+, *m/z*) calcd for $C_{16}H_{26}O_5Na$ $(M+Na)^+$: 321.1672; found 321.1676.

2-(3,3-Dimethyl-1,2,5-trioxa-9-spiro[5.5]undecyl)-1,3-isoindolinedione (8d). This compound was synthesised in accordance with general procedure 2 using 2-methylprop-2-en-1-ol (**7b**) and 2-(4-oxocyclohexyl)isoindoline-1,3-dione. Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) provided a white solid (205 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 2H), 7.70 (td, *J* = 5.4, 3.0 Hz, 2H), 4.20 (tt, *J* = 12.4, 4.0 Hz, 1H), 3.69 (m, 2H), 3.18 – 2.37 (m, 3H), 1.84 – 1.03 (m, 11H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 168.2, 168.1, 133.9, 133.8, 132.0, 123.1, 100.7, 100.6, 76.9, 67.0, 66.6, 49.9, 33.3, 27.4, 25.5, 25.1, 22.3. Duplicate peaks on $^{13}C\{^{1}H\}$ NMR, it is due to the mixture of isomers *cis* or *trans*. HRMS (ESI+, *m/z*) calcd for $C_{18}H_{21}NO_5Na$ $(M+Na)^+$: 354.1312; found 354.1317. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23, found: C, 65.14; H, 6.37; N, 4.22.

Tert-Butyl 3,3-dimethyl-1,2,5-trioxa-9-aza-9-spiro[5.5]undecanecarboxylate (8e). This compound was synthesised in accordance with general procedure 2 using **7b** and 1-boc-4-piperidone. Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) provided a white solid (189 mg, 58% yield). M.p = 69-70ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 – 3.57 (m, 2H), 3.56 – 3.20 (m, 4H), 2.42 – 1.71 (m, 3H), 1.59 – 1.02 (m, 16H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 154.6, 100.4, 80.0, 77.2, 66.6, 40.3, 34.4, 28.4, 22.6. HRMS (ESI+, *m/z*) calcd $C_{14}H_{25}NO_5Na$ $(M+Na)^+$: 310.1625; found 310.1627.

Ethyl 3,3-dimethyl-1,2,5-trioxa-9-spiro[5.5]undecanecarboxylate (8f). This compound was synthesised in accordance with general procedure 2 using **7b** and ethyl 4-oxocyclohexanecarboxylate. Purification by flash chromatography (EtOAc: *n*-hexane, 2.5:97.5, v/v) provided a colorless oil (176 mg, 68% yield). Spectral data are in accordance with the reported in the literature[52]. ^{1}H NMR (400

MHz, $CDCl_3$): δ 4.12 (d, *J* = 7.1 Hz, 2H), 3.91 – 3.36 (m, 2H), 2.85 – 2.28 (m, 2H), 1.94 – 1.68 (m, 5H), 1.61 – 1.27 (m, 6H), 1.27 – 1.22 (m, 3H), 1.21 – 1.06 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 175.9, 174.9, 101.2, 101.1, 77.0, 76.9, 66.7, 66.5, 60.3, 60.3, 42.1, 41.7, 35.2, 27.1, 26.4, 26.1, 24.8, 24.4, 22.3, 14.2, 14.2. Duplicate peaks on $^{13}C\{^1H\}$ NMR, it is due to the mixture of isomers *cis* or *trans*. HRMS (ESI+, *m/z*) calcd $C_{13}H_{22}O_5Na$ $(M+Na)^+$: 281.1359; found 281.1361.

Spiro[adamantane-2,2'-oxirane] (9a). This compound was synthesised in accordance with general procedure 4 using **4b** and 1,2-dimethoxyethane as the solvent. Purification by flash chromatography (EtOAc: *n*-hexane, 1:99, v/v) provided a white solid (0.91g, 83% yield). M.p = 176 - 178ºC. Spectral data are in accordance with the reported in the literature[47]. ^1H NMR (400 MHz, $CDCl_3$): δ 2.64 (s, 2H), 2.05 – 1.75 (m, 12H), 1.40 (t, *J* = 3.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 64.6, 54.8, 37.1, 36.9, 35.9, 35.1, 27.1, 27.0. HRMS (CI, *m/z*) calcd for $C_{11}H_{17}O$ $(M+H)^+$: 165.1274; found 165.1275.

Tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (9b). This compound was synthesised in accordance with general procedure 4 using 1-boc-4-piperidone and 1,2-dimethoxyethane as the solvent. Purification by flash chromatography (EtOAc:*n*-hexane, 5:95, v/v) provided a white solid (1.85 g, 58% yield). M.p = 50–52ºC. Spectral data are in accordance with the reported in the literature[47]. ^1H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 2H), 3.43 (ddd, *J* = 13.3, 9.4, 3.7 Hz, 2H), 2.69 (s, 2H), 1.80 (td, *J* = 9.4, 4.7 Hz, 2H), 1.48 (s, 9H), 1.44 (d, *J* = 4.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.8, 79.8, 57.2, 53.8, 42.6, 33.0, 28.4. HRMS (ESI+, *m/z*) calcd for $C_{11}H_{19}NO_3Na$ $(M+Na)^+$: 236.1257; found 236.1256

2-(Dispiro[cyclohexane-1,3'-[1,2,4]trioxane-6',2''-tricyclo[3.3.1.1^{3,7}]decan]-4-yl)-1,3-isoindolinedione (10a). This compound was synthesised in accordance with general procedure 3 using spiro[adamantane-2,2'-oxirane] (**9a**) and 2-(4-oxocyclohexyl)isoindoline-1,3-dione. Purification by flash chromatography (EtOAc: *n*-hexane, 5:95, v/v) followed by recrystallization with acetone provided a white solid (199 mg, 47% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.20 (tt, *J* = 12.4, 4.0 Hz, 1H), 4.04 – 2.88 (m, 2H), 2.77 – 2.00 (m, 5H), 1.94 – 1.38 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.2, 133.9, 132.0, 123.1, 100.7, 81.4, 63.8, 49.9, 37.8, 33.7, 32.0, 27.5, 27.4, 24.7. HRMS (ESI+, *m/z*) calcd $C_{25}H_{29}NO_5Na$ $(M+Na)^+$: 446.1938; found 446.1925.

Tert-butyl dispiro[piperidine-4,3'-[1,2,4]trioxane-6',2''-tricyclo[3.3.1.1^{3,7}]decane]-1-carboxylate (10b). This compound was synthesised in accordance with general procedure 3 using *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (**9b**) and **4b**. Purification by flash chromatography (EtOAc: *n*-hexane, 4:96, v/v) provided a white solid (239 mg, 63% yield). M.p = 74–76ºC. Spectral data are in

accordance with the reported in the literature[47]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (br s, 3H), 3.53 – 2.36 (m, 4H), 2.21 – 1.62 (m, 14H), 1.58 – 1.47 (m, 3H), 1.46 – 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 154.8, 104.6, 79.6, 75.7, 65.3, 39.3, 37.1, 34.9, 33.4, 28.5, 27.1, 27.1, 27.0. HRMS (ESI+, *m/z*) calcd $C_{21}H_{33}NO_5Na$ $(M+Na)^+$: 402.2251; found 402.2254.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org:

- Copies of ^{1}H, $^{13}C\{^{1}H\}$ NMR and HRMS spectra for all compounds and detailed information concerning the DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

Author Contributions

PSMA conceived the original working hypothesis and wrote the first draft of the manuscript. PSMA performed the synthesis and other experiments. LMTF and JASC projected the reaction mechanisms, performed the computations and analysed the data. PMO and MLSC supervised the research and validated the work. All authors co-wrote the final version of the manuscript.

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REFERENCES

(1) Faurant C. From bark to weed: The history of artemisinin. *Parasite.* **2011**, *18*, 215-218. doi:10.1051/parasite/2011183215

(2) Abdulla, S.; Sagara, I.; Borrmann, S.; D'Alessandro, U.; González, R.; Hamel, M.; Ogutu, B.; Mårtensson, A.; Lyimo, J.; Maiga, H.; Sasi, P.; Nahum, A.; Bassat, Q.; Juma, E.; Otieno, L.; Björkman, A.; Beck, H. P.; Andriano, K.; Cousin, M.; Lefèvre, G.; Ubben, D.; Premji, Z. Efficacy and Safety of Artemether-Lumefantrine Dispersible Tablets Compared with Crushed Commercial Tablets in African Infants and Children with Uncomplicated Malaria: A Randomised, Single-Blind, Multicentre Trial. *Lancet* **2008**, *372*, 1819-1827. https://doi.org/10.1016/S0140-6736(08)61492-0

(3) Djimdé, A. A.; Tekete, M.; Abdulla, S.; Lyimo, J.; Bassat, Q.; Mandomando, I.; Lefèvre, G.; Borrmann, S. Pharmacokinetic and Pharmacodynamic Characteristics of a New Pediatric Formulation of Artemether-Lumefantrine in African Children with Uncomplicated *Plasmodium falciparum* Malaria. *Antimicrob. Agents Chemother.* **2011,** *55*, 3994-3999. https://doi.org/10.1128/AAC.01115-10

(4) John, C. C. Primaquine plus Artemisinin Combination Therapy for Reduction of Malaria Transmission: Promise and Risk. *BMC Medicine*. **2016,** *14*, 1-3. https://doi.org/10.1186/s12916-016-0611-9

(5) WHO. *Guidelines for the Treatment of Malaria, 2021* (16 February 2021). WHO Global Malaria Programme.

(6) Rawe, S. L. *Artemisinin and Artemisinin-Related Agents*; Elsevier Ltd, 2020. pp 99-132. https://doi.org/10.1016/B978-0-08-101210-9.00004-4

(7) Ashley, E. A.; Dhorda, M.; Fairhurst, R. M.; Amaratunga, C.; Lim, P.; Suon, S.; Sreng, S.; Anderson, J. M.; Mao, S.; Sam, B.; Sopha, C.; Chuor, C. M.; Nguon, C.; Sovannaroth, S.; Pukrittayakamee, S.; Jittamala, P.; Chotivanich, K.; Chutasmit, K.; Suchatsoonthorn, C.; Runcharoen, R.; Hien, T. T.; Thuy-Nhien, N. T.; Thanh, N. V.; Phu, N. H.; Htut, Y.; Han, K. T.; Aye, K. H.; Mokuolu, O. A.; Olaosebikan, R. R.; Folaranmi, O. O.; Mayxay, M.; Khanthavong, M.; Hongvanthong, B.; Newton, P. N.; Onyamboko, M. A.; Fanello, C. I.; Tshefu, A. K.; Mishra, N.; Valecha, N.; Phyo, A. P.; Nosten, F.; Yi, P.; Tripura, R.; Borrmann, S.; Bashraheil, M.; Peshu, J.; Faiz, M. A.; Ghose, A.; Hossain, M. A.; Samad, R.; Rahman, M. R.; Hasan, M. M.; Islam, A.; Miotto, O.; Amato, R.; MacInnis, B.; Stalker, J.; Kwiatkowski, D. P.; Bozdech, Z.; Jeeyapant, A.; Cheah, P. Y.; Sakulthaew, T.; Chalk, J.; Intharabut, B.; Silamut, K.; Lee, S. J.; Vihokhern, B.; Kunasol, C.; Imwong, M.; Tarning, J.; Taylor, W. J.; Yeung, S.;

Woodrow, C. J.; Flegg, J. A.; Das, D.; Smith, J.; Venkatesan, M.; Plowe, C. V.; Stepniewska, K.; Guerin, P. J.; Dondorp, A. M.; Day, N. P.; White, N. J. Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria. *N. Engl. J. Med.* **2014**. *371*, 411-423. https://doi.org/10.1056/NEJMoa1314981

(8) Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; An, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P. J.; Lindegardh, N.; Socheat, D.; White, N. J. Artemisinin Resistance in *Plasmodium falciparum* Malaria. *N. Engl. J. Med.* **2009**, *361*, 455–467. https://doi.org/10.1056/NEJMoa0808859

(9) WHO. Status Report on Artemisinin and ACT Resistance (December 2019)

(10) Rosenthal, M. R.; Ng, C. L. *Plasmodium falciparum* Artemisinin Resistance: The Effect of Heme, Protein Damage, and Parasite Cell Stress Response. *ACS Infect. Dis.* **2020**, *6*, 1599–1614. https://doi.org/10.1021/acsinfecdis.9b00527

(11) O'Neill, P. M.; Posner, G. H. Perspective A Medicinal Chemistry Perspective on Artemisinin and Related Endoperoxides. *J. Med. Chem.* **2004**, *47*, 2945–2964. https://doi.org/10.1021/jm030571c

(12) Tang, Y.; Dong, Y.; Vennerstrom, J. L. Synthetic Peroxides as Antimalarials. *Med. Res. Rev.* **2004**, *24*, 425–448. https://doi.org/10.1002/med.10066

(13) Kumar, N.; Singh, R.; Rawat, D. S. Tetraoxanes: Synthetic and Medicinal Chemistry Perspective. *Med. Res. Rev.* **2010**, *32*, 581–610. https://doi.org/10.1002/med.20223

(14) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Santo Tomas, J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. Identification of an Antimalarial Synthetic Trioxolane Drug Development Candidate. *Nature* **2004**, *430*, 900–904. https://doi.org/10.1038/nature02779

(15) Charman, S. A; Arbe-Barnes, S.; Bathurst, I. C.; Brun, R.; Campbell, M.; Charman, W. N.; Chiu, F. C. K.; Chollet, J.; Craft, J. C.; Creek, D. J.; Dong, Y.; Matile, H.; Maurer, M.; Morizzi, J.; Nguyen, T.; Papastogiannidis, P.; Scheurer, C.; Shackleford, D. M.; Sriraghavan, K.; Stingelin, L.; Tang, Y.; Urwyler, H.; Wang, X.; White, K. L.; Wittlin, S.; Zhou, L.; Vennerstrom, J. L. Synthetic Ozonide Drug Candidate OZ439 Offers New Hope for a Single-Dose Cure of Uncomplicated Malaria. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 4400–4405. https://doi.org/10.1073/pnas.1015762108

(16) Phyo, A. P.; Jittamala, P.; Nosten, F.; Pukrittayakamee, S.; Imwong, M.; White, N. J.; Duparc, S.; Macintyre, F.; Baker, M.; Möhrle, J. Antimalarial Activity of Artefenomel (OZ439), a Novel

Synthetic Antimalarial Endoperoxide, in Patients with *Plasmodium falciparum* and *Plasmodium vivax* Malaria : An Open-Label Phase 2 Trial. *Lancet Infect. Dis.* **2016**, *16*, 61–69. https://doi.org/10.1016/S1473-3099(15)00320-5

(17) O'Neill, P. M.; Amewu, R. K.; Nixon, G. L.; ElGarah, F. B.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A.; Bousejra ElGarah, F.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A.; ElGarah, F. B.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A. Identification of a 1,2,4,5-Tetraoxane Antimalarial Drug-Development Candidate (RKA 182) with Superior Properties to the Semisynthetic Artemisinins. *Angew. Chemie - Int. Ed.* **2010**, *49*, 5693–5697. https://doi.org/10.1002/anie.201001026

(18) O'Neill, P. M.; Sabbani, S.; Nixon, G. L.; Schnaderbeck, M.; Roberts, N. L.; Shore, E. R.; Riley, C.; Murphy, B.; McGillan, P.; Ward, S. A.; Davies, J.; Amewu, R. K. Optimisation of the Synthesis of Second Generation 1,2,4,5 Tetraoxane Antimalarials. *Tetrahedron* **2016**, *72*, 6118–6126. https://doi.org/10.1016/j.tet.2016.08.043

(19) O'Neill, P. M.; Amewu, R. K.; Charman, S. A.; Sabbani, S.; Gnädig, N. F.; Straimer, J.; Fidock, D. A.; Shore, E. R.; Roberts, N. L.; Wong, M. H. L. H.-L.; Hong, W. D.; Pidathala, C.; Riley, C.; Murphy, B.; Aljayyoussi, G.; Gamo, F. J.; Sanz, L.; Rodrigues, J.; Cortes, C. G.; Herreros, E.; Angulo-Barturén, I.; Jiménez-Díaz, M. B.; Bazaga, S. F.; Martínez-Martínez, M. S.; Campo, B.; Sharma, R.; Ryan, E.; Shackleford, D. M.; Campbell, S.; Smith, D. A.; Wirjanata, G.; Noviyanti, R.; Price, R. N.; Marfurt, J.; Palmer, M. J.; Copple, I. M.; Mercer, A. E.; Ruecker, A.; Delves, M. J.; Sinden, R. E.; Siegl, P.; Davies, J.; Rochford, R.; Kocken, C. H. M. M.; Zeeman, A.-M. M.; Nixon, G. L.; Biagini, G. A.; Ward, S. A. A Tetraoxane-Based Antimalarial Drug Candidate That Overcomes PfK13-C580Y Dependent Artemisinin Resistance. *Nat. Commun.* **2017**, *8*, 1–10. https://doi.org/10.1038/ncomms15159

(20) Das, B.; Thirupathi, P. A Highly Selective and Efficient Acetylation of Alcohols and Amines with Acetic Anhydride Using $NaHSO_4{\cdot}SiO_2$ as a Heterogeneous Catalyst. *J. Mol. Catal. A Chem.* **2007**, *269*, 12–16. https://doi.org/10.1016/j.molcata.2006.12.029

(21) Sardarian A. R.; Inaloo I. D.; Modarresi-Alam A. R.; Kleinpeter E.; Schilde U. Metal-Free Regioselective Monocyanation of Hydroxy-, Alkoxy-, and Benzyloxyarenes by Potassium Thiocyanateand Silica Sulfuric Acid as a Cyanating Agent. *J. Org. Chem.* **2019**, *84*, 1748–1756. https://doi.org/10.1021/acs.joc.8b02191

(22) Azarifar, D.; Najminejad, Z.; Khosravi, K. Synthesis of *gem*-Dihydroperoxides from Ketones and Aldehydes Using Silica Sulfuric Acid as Heterogeneous Reusable Catalyst. *Synth. Commun.* **2013**, *43*, 826–836. https://doi.org/10.1080/00397911.2011.610549

(23) Yadav, N.; Sharma, C.; Awasthi, S. K. Diversification in the Synthesis of Antimalarial Trioxane and Tetraoxane Analogs. *RSC Adv.* **2014**, *4*, 5469–5498. https://doi.org/10.1039/c3ra42513d

(24) Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. One-pot synthesis of non-symmetric tetraoxanes with the H_2O_2/MTO/fluorous alcohol system. *Tetrahedron Lett.* **2003**, *44*, 6309–6312. https://doi.org/10.1016/S0040-4039(03)01472-2

(25) Kumar, N.; Khan, S. I.; Sharma, M.; Atheaya, H.; Rawat, D. S. Iodine-catalyzed one-pot synthesis and antimalarial activity evaluation of symmetrically and asymmetrically substituted 3,6-diphenyl[1,2,4,5]tetraoxanes. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1675–1677. https://doi.org/10.1016/j.bmcl.2009.01.103

(26) Ghorai, P.; Dussault, P. H. Broadly Applicable Synthesis of 1,2,4,5-Tetraoxanes. *Org. Lett.* **2009**, *11*, 213–216. https://doi.org/10.1021/ol8023874

(27) Yan, X.; Chen, J.; Zhu, Y. T.; Qiao, C. Phosphomolybdic Acid Catalyzed Synthesis of 1,2,4,5-Tetraoxanes. *Synlett* **2011**, *19*, 2827–2830. doi: 10.1055/s-0031-1289864

(28) Sashidhara, K. V.; Avula, S. R.; Singh, L. R.; Palnati, G. R. A facile and efficient Bi(III) catalyzed synthesis of 1,1-dihydroperoxides and 1,2,4,5-tetraoxanes. *Tetrahedron Lett.* **2012**, *53*, 4880–4884. https://doi.org/10.1016/j.tetlet.2012.07.001

(29) Khosravi, K.; Asgari, A. An Efficient Synthesis of *gem*-Dihydroperoxides and 1,2,4,5-Tetraoxanes Catalyzed by Chlorosulfonic Acid as a New Catalyst. *J. Adv. Chem.* **2015**, *11*, 3381–3390. https://doi.org/10.24297/jac.v11i3.866

(30) Khosravi, K.; Zendehdel, M.; Naserifar, S.; Tavakoli, F.; Khalaji, K.; Asgari, A. Heteropoly Acid/NaY Zeolite as a Reusable Solid Catalyst for Highly Efficient Synthesis of *gem*-Dihydroperoxides and 1,2,4,5-Tetraoxanes. *J. Chem. Res.* **2016**, *40*, 744–749. https://doi.org/10.3184/174751916X14792244600532

(31) Khosravi, K.; Karimi, A. R.; Naserifar, S. Alkanedisulfamic acid functionalized silica-coated magnetic nanoparticles as a reusable efficient nanocatalyst for synthesis of *gem*-dihydroperoxides and 1,2,4,5-tetraoxanes. *Iran. J. Catal.* **2017**, *7*, 11–20. http://ijc.iaush.ac.ir/article_587163.html

(32) Yaremenko, A. I. A.; Radulov, P. S.; Belyakova, Y. Y.; Demina, A. A.; Fomenkov, D. I.; Barsukov, D. V; Subbotina, I. R.; Fleury, F.; Terent'ev, A. O. Catalyst Development for the Synthesis of Ozonides and Tetraoxanes under Heterogeneous Conditions. Disclosure of an Unprecedented Class of Fungicides for Agricultural Application. *Chem. - A Eur. J.* **2020**, *26*,

4734–4751. https://doi.org/10.1002/chem.201904555

(33) Isayama, S.; Mukaiyama, T. Novel Method for the Preparation of Triethylsilyl Peroxides from Olefins by the Reaction with Molecular Oxygen and Triethylsilane Catalyzed by Bis(1,3-Diketonato)Cobalt(II). *Chem. Lett.* **1989**, *18*, 573–576. https://doi.org/10.1246/cl.1989.573

(34) O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, A.; Park, B. K. Regioselective Mukaiyama Hydroperoxysilylation of 2-Alkyl- or 2-Aryl-Prop-2-En-1-Ols : Application to a New Synthesis of 1,2,4-Trioxanes. *Tetrahedron Lett.* **2001**, *42*, 4569–4571. https://doi.org/10.1016/S0040-4039(01)00791-2

(35) Salehi, P.; Dabiri, M.; Zolfigol, A.; Fard, A. B. Silica Sulfuric Acid; An Efficient and Reusable Catalyst for Regioselective Ring Opening of Epoxides by Alcohols and Water. *Phosphorus, Sulfur, and Silicon.* **2004**, *179*, 1113–1121. doi: 10.1080/10426500490459722

(36) Kiasat, A. R.; Fallah-Mehrjardi, M. $B(HSO_4)_3$: a Novel and Efficient Solid Acid Catalyst for the Regioselective Conversion of Epoxides to Thiocyanohydrins under Solvent-Free Conditions. *J. Braz. Chem. Soc*. **2008**, *19*, 1595–1599. https://doi.org/10.1590/S0103-50532008000800020

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Jr., J. A. M.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Ö. Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. GAUSSIAN 09 (Revision D.01), Gaussian, Inc.: Wallingford CT, 2009.

(38) CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)

(39) Chai, J.-D.; Head-Gordon, M., Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. *Physical Chemistry Chemical Physics* **2008,** *10*, 6615-6620. https://doi.org/10.1039/B810189B

(40) Cances, E.; Mennucci, B.; Tomasi, J., A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. *J Chem Phys* **1997,** *107*, 3032-3041. https://doi.org/10.1063/1.474659

(41) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J., Ab initio study of ionic solutions by a polarizable continuum dielectric model. *Chem Phys Lett* **1998,** *286*, 253-260. https://doi.org/10.1016/S0009-2614(98)00106-7

(42) Mennucci, B.; Tomasi, J., Continuum solvation models: A new approach to the problem of solute's charge distribution and cavity boundaries. *J Chem Phys* **1997,** *106*, 5151-5158. https://doi.org/10.1063/1.473558

(43) Tomasi, J.; Mennucci, B.; Cammi, R., Quantum mechanical continuum solvation models. *Chem Rev* **2005,** *105*, 2999-3093. https://doi.org/10.1021/cr9904009

(44) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J Phys Chem B* **2009,** *113*, 6378-6396. https://doi.org/10.1021/jp810292n

(45) Roy, B.; Mukhopadhyay, B. Sulfuric Acid Immobilized on Silica: An Excellent Catalyst for Fischer Type Glycosylation. *Tetrahedron Lett.* **2007**, *48*, 3783–3787. https://doi.org/10.1016/j.tetlet.2007.03.165.

(46) O'Neill, P. M. ; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, A.; Stocks, P. A. $Co(thd)_2$: A Superior Catalyst for Aerobic Epoxidation and Hydroperoxysilylation of Unactivated Alkenes: Application to the Synthesis of Spiro-1,2,4-Trioxanes. *Tetrahedron Lett.* **2003**, *44*, 8135–8138. https://doi.org/10.1016/j.tetlet.2003.09.033

(47) Sabbani, S.; Stocks, P. A.; Ellis, G. L.; Davies, J.; Hedenstrom, E.; Ward, S. A.; O'Neill, P. M. Piperidine Dispiro-1,2,4-Trioxane Analogues. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5804–5808. https://doi.org/10.1016/j.bmcl.2008.09.052.

(48) Li, W-R.; Yo, Y-C.; Lin, Y-S.; One-Pot Formation of Amides from Benzyl Carbamates: Application to Solid-Phase Synthesis. *Tetrahedron.* **2000**, *56*, 8867–8875. https://doi.org/10.1016/S0040-4020(00)00850-4

(49) Marti, F.; Chadwick, J.; Amewu, R. K.; Burrell-Saward, H.; Srivastava, A.; Ward, S. A.; Sharma, R.; Neil, B. and O'Neill, P. M. Second generation analogues of RKA182: synthetic tetraoxanes with outstanding *in vitro* and *in vivo* antimalarial activities. *Med. Chem. Commun*. **2011**, *2*, 661–665. https://doi.org/10.1039/c1md00102g.

(50) Oliveira, R.; Newton, A. S.; Guedes, R. C.; Miranda, D.; Amewu, R. K.; Srivastava, A.; Gut, J.; Rosenthal, P. J.; O'Neill, P. M.; Ward, S. A.; Lopes, F.; Moreira, R. An Endoperoxide-Based Hybrid Approach to Deliver Falcipain Inhibitors Inside Malaria Parasites. *ChemMedChem* **2013**, *8*, 1528–1536. https://doi.org/10.1002/cmdc.201300202

(51) Kwiatkowski, M. R.; Alexanian, E. J. Synthetic Methods Nickel-Catalyzed Mizoroki – Heck-

Type Reactions of Unactivated Alkyl Bromides. *Angew. Chemie - Int. Ed.* **2018**, *57*, 16857–16860. https://doi.org/10.1002/anie.201810757

(52) Laurent, S. A.; Boissier, J.; Coslédan, F.; Gornitzka, H.; Robert, A.; Meunier, B. Synthesis of "Trioxaquantel"® Derivatives as Potential New Antischistosomal *Drugs. European J. Org. Chem.* **2008**, *5*, 895–913. https://doi.org/10.1002/ejoc.200700975