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Synthesis of Non-symmetrical Dispiro-1,2,4,5-Tetraoxanes and Dispiro-1,2,4-Trioxanes Catalyzed by Silica Sulfuric Acid

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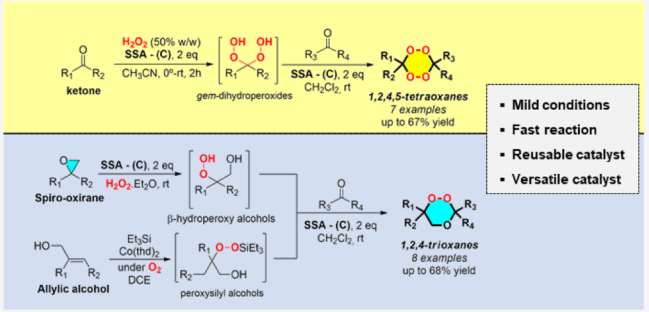
ABSTRACT: A novel protocol for the preparation of non-symmetrical 1,2,4,5-tetraoxanes and 1,2,4-trioxanes, promoted by the heterogeneous silica sulfuric acid (SSA) catalyst, is reported. Different ketones react under mild conditions with *gem*-dihydroperoxides or peroxysilyl alcohols/*β*-hydroperoxy alcohols to generate the corresponding endoperoxides in good yields. Our mechanistic proposal, assisted by molecular orbital calculations, at the *ω*B97XD/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, thereby establishing a valid alternative approach for the synthesis of new biologically active endoperoxides.



INTRODUCTION

Artemisinin combination therapies 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 toward 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**) and 1,2,4,5-tetraoxanes RKA182[17] (**3a**) and E209[18] (**3b**), Figure 1).

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 *Plasmodium 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 1a).[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 a 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] SSA was reported by Azarifar *et al.*[22] as an effective catalyst for the preparation of *gem*-dihydroperoxides (DHPs). 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 DHP intermediate prepared *in situ*. Generally, DHPs 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] and $H_{3+x}PMo_{12-x}{}^{+6}Mo_x{}^{+5}O_{40}$[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

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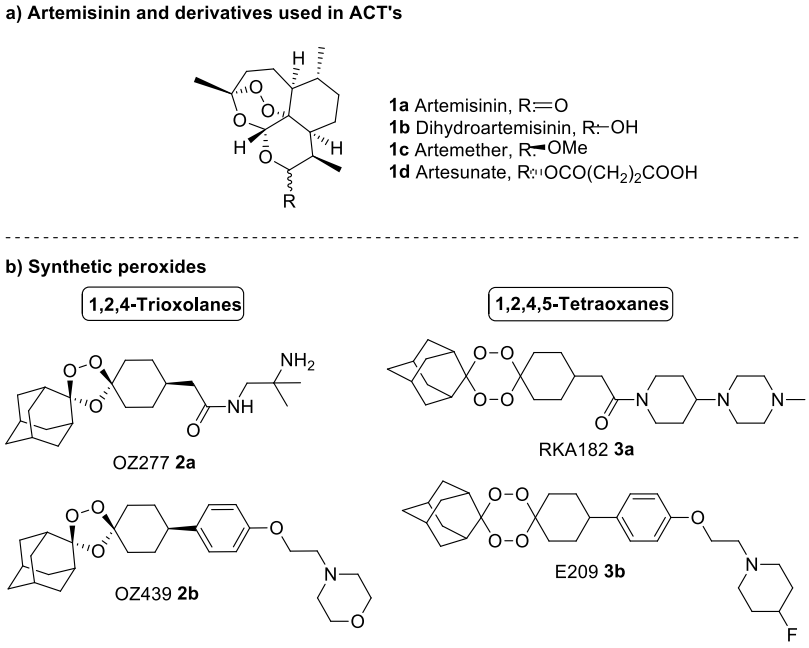
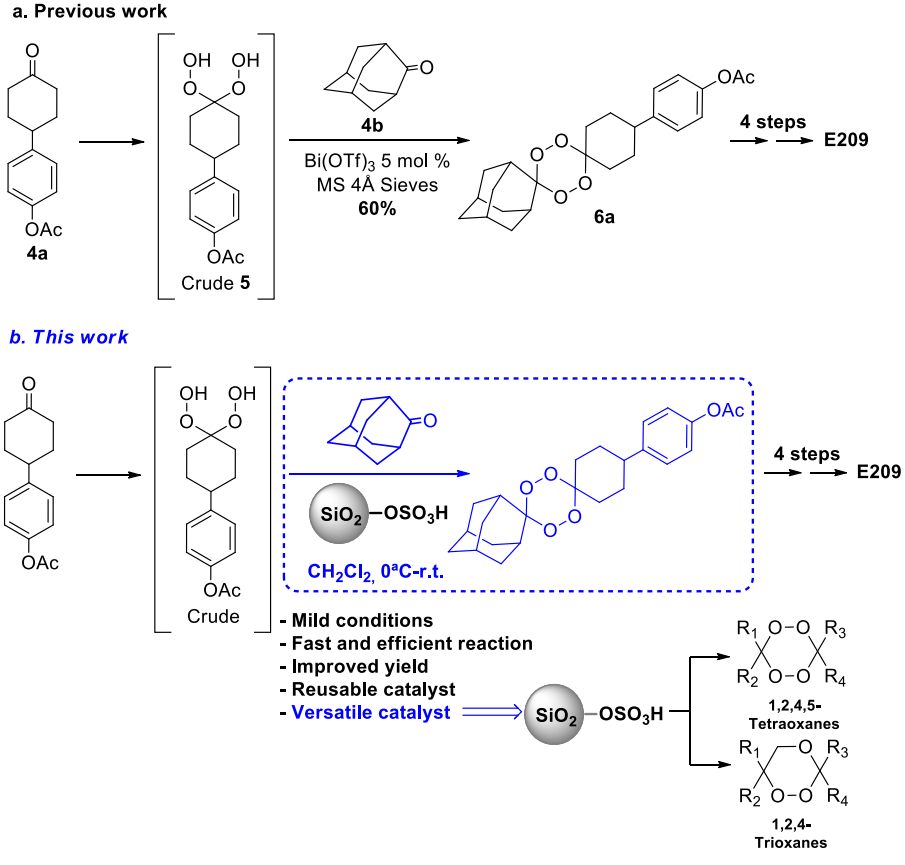


Figure 1. Representative endoperoxide-based antimalarial drugs or candidates. Artemisinin and semi-synthetic derivatives (**1a–d**); 1,2,4-trioxolanes OZ277 (**2a**) and OZ439 (**2b**); and 1,2,4,5-tetraoxanes RKA182 (**3a**) and E209 (**3b**).

Scheme 1. (a) Synthetic Approach and Conditions Used in Previous Preparation of E209 and (b) Improved Conditions Proposed in This Work and Scope Evaluation of the Methodology



cyclocondensation of the 1,2,4,5-tetraoxane ring. Our methodology involves a "two-pot" procedure, whereby the DHP generated immediately reacts with the partner carbonyl compound to achieve the cyclocondensation step (Scheme 1b).

RESULTS AND DISCUSSION

Preparation of the intermediate DHP **5** followed the method reported by Azarifar *et al.*[22] with some adjustments. 4-(4-Oxocyclohexyl)phenyl acetate **4a** was reacted with aqueous

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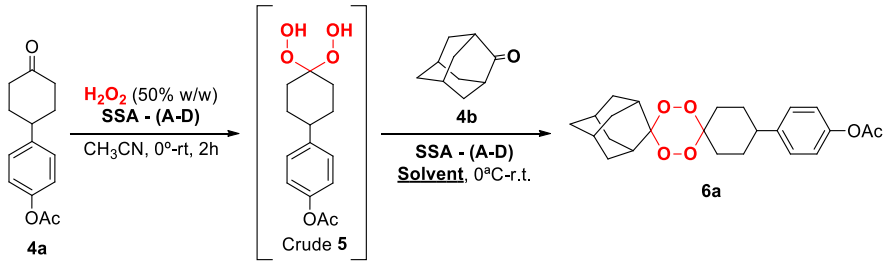
Table 1. Screening of Reaction Parameters for the Formation of 1,2,4,5-Tetraoxane 6a



entry	catalyst	solvent	molar ratio SSA/ST[a]	t (min)	yield (%)
1	none	CH_2Cl_2		48 h	nr
2	SiO_2	CH_2Cl_2	1[d]	48 h	nr
3	H_2SO_4	CH_2Cl_2	1[d]	12 h	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	48 h	nr
17	SSA-(**C**)	DMF	1	48 h	nr
18	SSA-(**C**)	1,4-dioxane	1	48 h	nr
19	***SSA-(C)***	***CH_2Cl_2***	***2***	***60***	***67***
20	SSA-(**C**)	CH_2Cl_2	2	12 h	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	12 h	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 equiv 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.

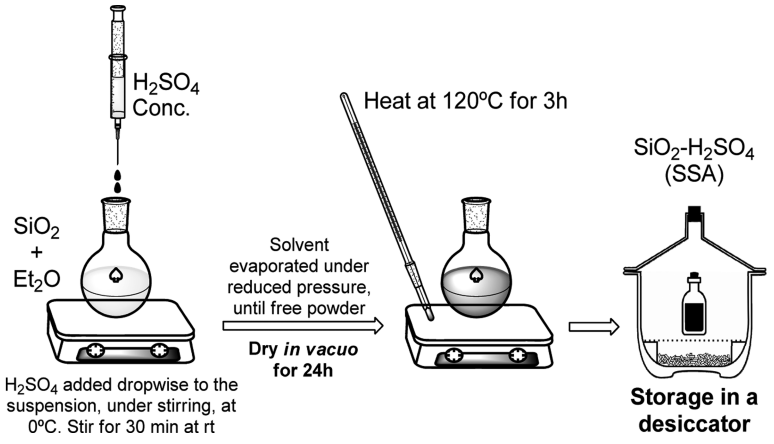


Figure 2. Representation of the procedure followed for the preparation of SSA-(**A**–**D**) catalysts.

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 was followed to remove excess 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 and Computational Details section.

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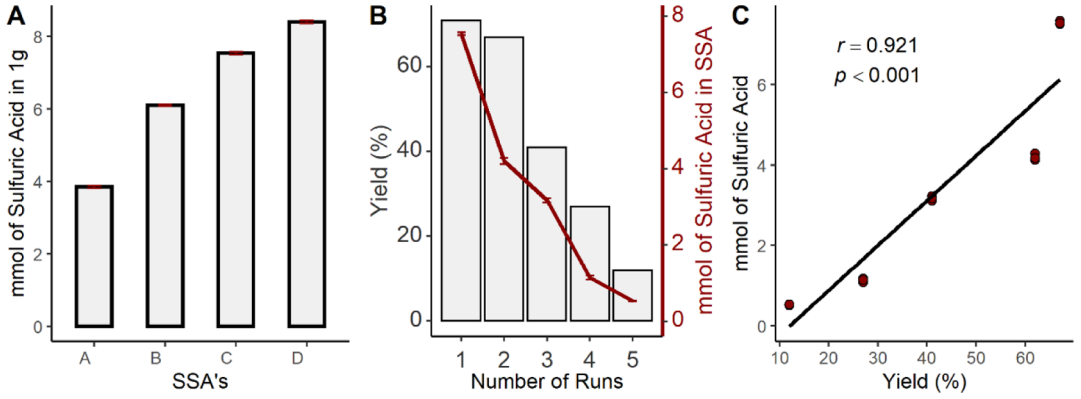

Figure 3. (A) Molarity of H_2SO_4 in SSA-(**A**–**D**). Bars represent the mean values of molarity of H_2SO_4 triplicates ± SD; (B) reusability of SSA-(**C**) in the generation of **6a** (the red line corresponds to the molarity of H_2SO_4 in 1 g of SSA in each run); and (C) Pearson correlation coefficient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

The molarity of sulfuric acid adsorbed on the silica gel was determined by acid–base titration. The results, summarized in Figure 3A, 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.

The reaction of the crude DHP with 2-adamantanone **4b**, in the presence of SSA catalyst, was selected as the model to find 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 the 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 (12 h) (Table 1, entry 20) and using a higher molar ratio of SSA-(**C**) (3 equiv, 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 and 2). Reaction with H_2SO_4 (1 equiv) 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 dimethyl sulfoxide (DMSO) and dimethylformamide (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 ⇔ 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 DHP with the regeneration of the corresponding starting ketone, and (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 DHP to its starting material. The cyclocondensation was achieved even with minimal amounts of SSA-(**C**), such as 0.01 equiv, 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 the presence of 2 equivalents of SSA-(**C**) and using excess of the second ketone (1.5 mmol) relatively to the starting one, were usually completed in the period of 1–6 h. 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 thin-layer chromatography (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 excess of the second ketone (2 mmol) in the cyclocondensation step. 1,2,4,5-Tetraoxane **6e** was generated in a 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 DHP decomposed back to **4c**, suggesting some instability of the DHP in the reaction medium. An attempt to generate the corresponding tetraoxane from 4,4-difluorocy-

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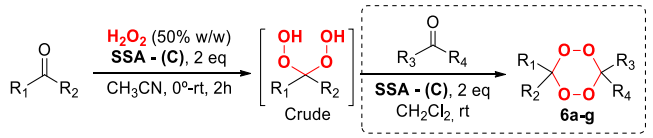
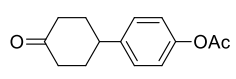
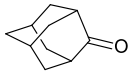
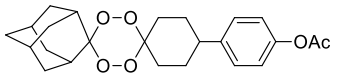
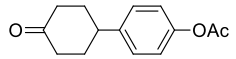
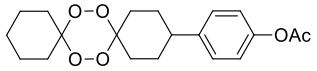
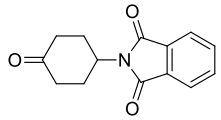
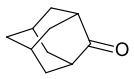
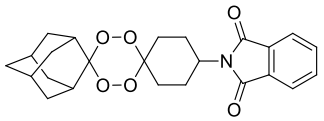
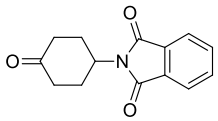
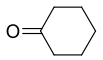
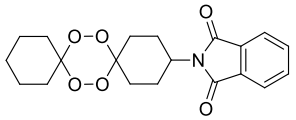
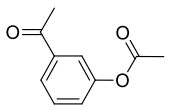
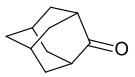
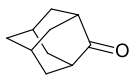
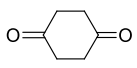
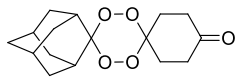
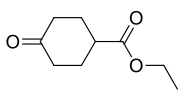
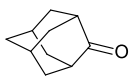
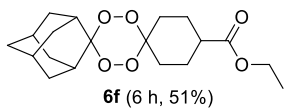
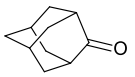
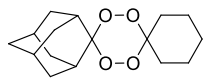
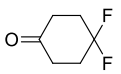
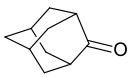
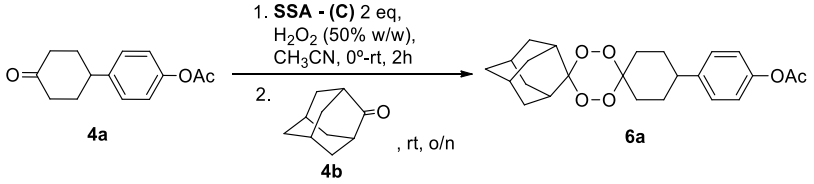
Table 2. Scope Evaluation in the SSA-Promoted Formation of 1,2,4,5-Tetraoxanes



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)

Scheme 2. Conditions for One-Pot Synthesis of 1,2,4,5-Tetraoxanes Using SSA-(C)



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

A one-pot approach to synthesize 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 2 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 for 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

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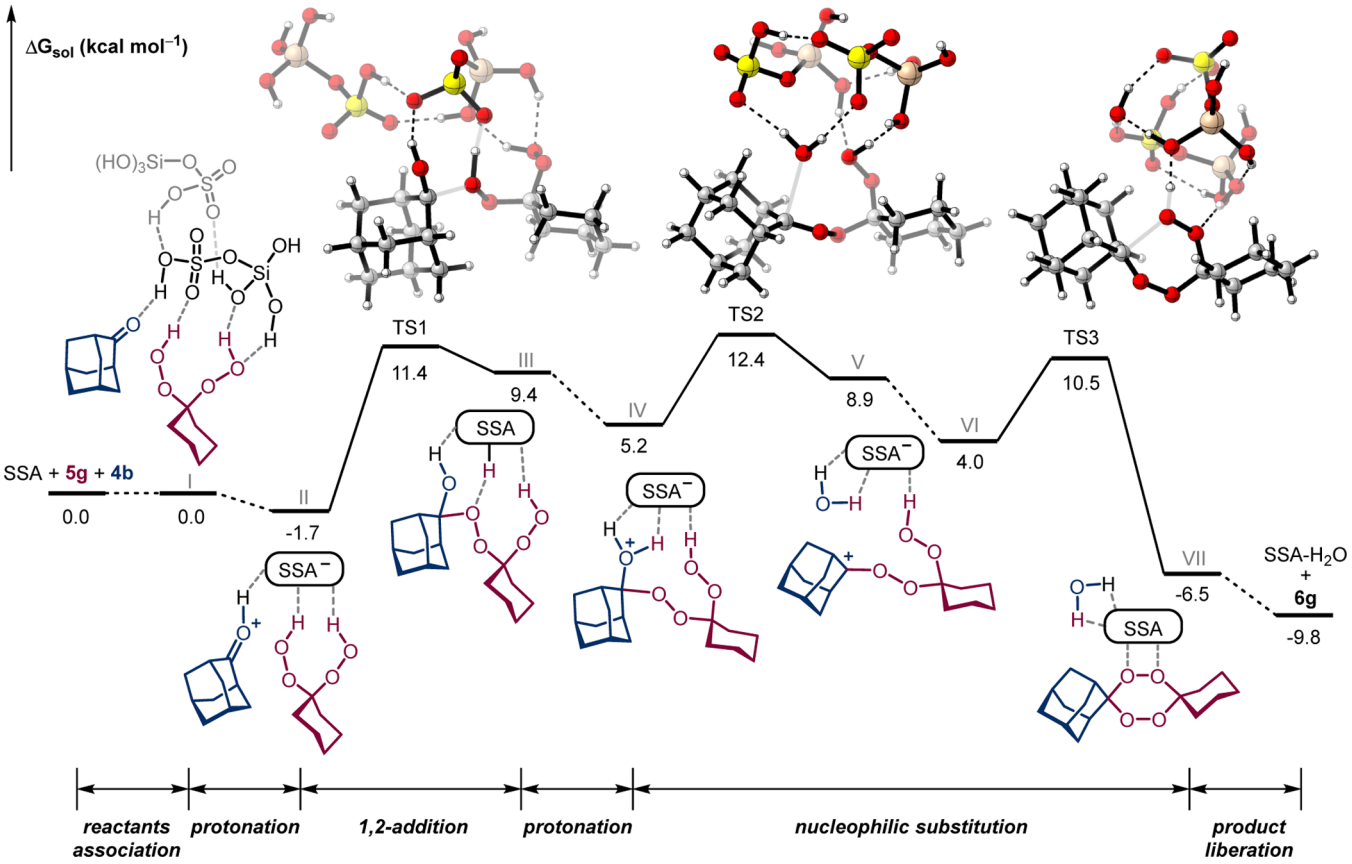

Figure 4. Free energy profile for the formation of 1,2,4,5-tetraoxane **6g** promoted by SSA [modeled by two molecules of $Si(OH)_3(SO_3H)$]. DFT calculations were performed at the ωB97XD/Def2-TZVPP/PCM(DCM)//B3LYP/6-31G(d) level of theory (energy values in kcal mol^{-1}).

considered because it would lead to a dangerous concentration of free hydrogen peroxide, highly explosive.

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 the contaminants adsorbed on the surface of SSA and subsequently dried in a vacuum oven at 60 °C for 24 h. The recovered SSA-(**C**) was reused in the next run. Analysis of the results displayed in Figure 3B shows that the catalyst SSA-(**C**) can be used up to 2 times with only a slight loss in the yield of **6a** (67−62%). When using the catalyst in the synthesis of **6a** for five consecutive times, we observed that the yield decreases considerably from the third, 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 3B 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 3C, $r = 0.921$, $p < 0.001$).

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 favored 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 favored.

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]); and (B) perhydrolysis of spiro-oxiranes, followed by cyclocondensation

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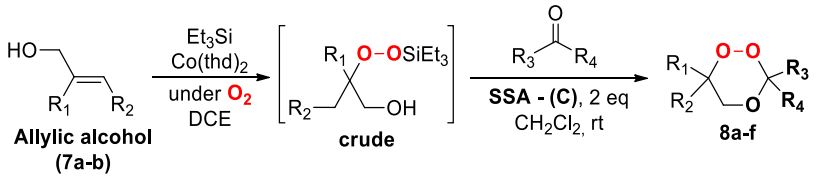
Table 3. Hydroperoxysilylation of Allylic Alcohols, Followed by SSA-Mediated Cyclocondensation to 1,2,4-Trioxanes



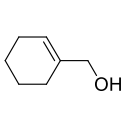
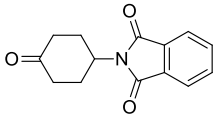
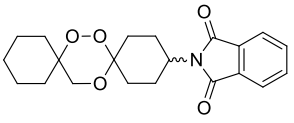
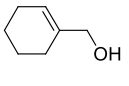
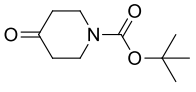
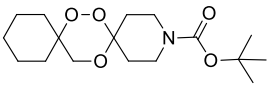
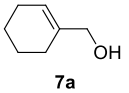
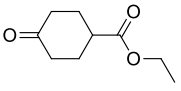
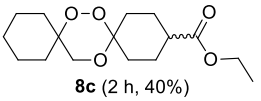
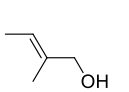
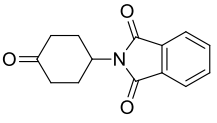
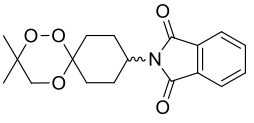
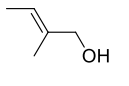
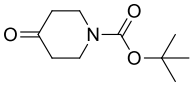
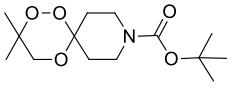
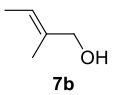
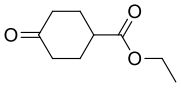
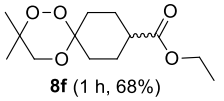
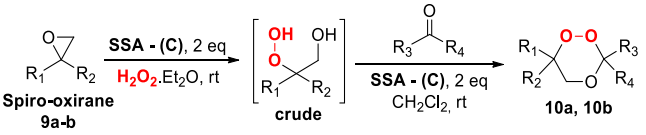
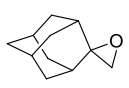
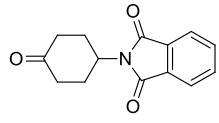
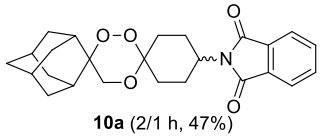
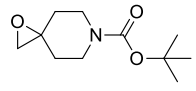
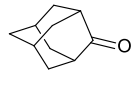
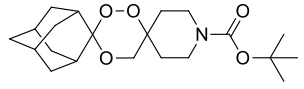
Entry	Allylic Alcohol	Ketone	Product (reaction time, yield)
1	 **7a**		 **8a** (2 h, 46%)
2	 **7a**		 **8b** (2 h, 38%)
3	 **7a**		 **8c** (2 h, 40%)
4	 **7b**		 **8d** (1 h, 62%)
5	 **7b**		 **8e** (1 h, 58%)
6	 **7b**		 **8f** (1 h, 68%)

Table 4. Perhydrolysis of Spiro-oxiranes, Followed by SSA-Mediated Cyclocondensation to 1,2,4-Trioxanes



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

[a]Reaction time (step 1/step 2, hours).

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

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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 excess H_2O_2, 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.

CONCLUSIONS

The cyclocondensation of a representative library of ketones with DHPs 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 TLC was carried out using TLC Silica gel 60 F254 aluminum sheets (AL TLC 20 × 20). 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. 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, a Frisons TRIO mass spectrometer, or an Agilent QTOF 7200 using chemical ionization (CI) or electrospray (ESI) (UoL) and on a Thermo Scientific high-resolution mass spectrometer (HRMS), model Orbitrap Elite, capable of MS*n*, *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 and (2) direct exposure to strong heat or light, mechanical shock, oxidizable organic materials, or transition metal ions should be avoided.

Computational Details. 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 Chai and Head-Gordon[39] and the valence triple-zeta Def2-TZVPP basis set with solvent effects (dichloromethane) calculated by means of the polarizable continuum model initially devised by Tomasi and co-workers,[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 Supporting Information 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 ± standard deviation (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 SSA. The general procedure was adapted from Roy and Mukhopadhyay[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 SSA that was dried *in vacuo* for 24 h. 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. Purified water (10 mL) was added to 0.01 g of SSA, and the mixture was stirred for 1 h 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 × 25 mL). Drying in a vacuum oven at 60 °C for 24 h 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, and then the mixture was left to stir at room temperature until consumption of the starting material. To this mixture was added distilled water, and 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 DHP semi-crude, which was used immediately, without further purification. **Step 2:** The DHP 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.

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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 was 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 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) afforded the pure product.

Preparation of the $Co(thd)_2{\cdot}H_2O$ Catalyst. Procedure as described by O'Neill *et al.*[46] To an aq. solution (95 mL) of NaOH (0.43 g, 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 h 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 vacuum. Purification by flash chromatography using a EtOAc−hexane gradient (unless specified differently) afforded 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 (H_2O_2, 42 mL, 50 wt % in H_2O) was dissolved in anhydrous diethyl ether (395 mL). Constant stirring was carried out 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 to stir 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), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under *vacuum*. Purification by flash chromatography using an EtOAc-hexane gradient (unless specified differently) afforded the pure spiro-epoxide.

*4-(4-Oxocyclohexyl)phenyl Acetate (**4a**).* The procedure was 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 h until the completion of the reaction. 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 afforded the ester (2.20 g, 90% yield) as a white solid. mp 101−103 °C. Spectral data are in accordance with that 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. $^{13}C\{^1H\}$ 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 synthesized following the procedure described previously by O'Neill *et al.*[18] using 3′-hydroxyacetophenone. Colorless solid (1.12 g, 86% yield). Spectral data are in accordance with that 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). $^{13}C\{^1H\}$ 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 synthesized 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). mp 195−197 °C. Spectral data are in accordance with that 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). $^{13}C\{^1H\}$ 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 synthesized 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). mp 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). $^{13}C\{^1H\}$ 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 synthesized 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%

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yield). mp 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 synthesized 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). mp 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 synthesized 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). mp 156−158 °C. Spectral data are in accordance with that 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 synthesized 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). mp 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 synthesized in accordance with general procedure 1 using cyclohexanone (for the peroxidation step) and **4b** (for the cyclocondensation step). Purification by flash chromatography (*n*-hexane, 100%, v/v) provided a white solid (179 mg, 64% yield). mp 57−59 °C. Spectral data are in accordance with that reported in the literature.[28] ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.17 (s, 1H), 2.30 (s, 2H), 2.04−1.44 (m, 21H). ^{13}C{^{1}H} 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**).* The procedure was adapted from Kwiatkowski and Alexanian[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 min and then successively quenched with H_2O (10 mL) and NaOH (6 M, 10 mL) allowing it to warm to room temperature while stirring. Anhydrous Na_2SO_4 (2 g) was added, and the mixture was stirred for 30 min, 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 colorless oil (0.81 g, 91% yield). Spectral data are in accordance with that reported in the literature.[51] ^{1}H 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{^{1}H} 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-isoindoline-dione (**8a**).* This compound was synthesized 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). ^{1}H 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{^{1}H} 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{^{1}H} NMR 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]hexadecane-carboxylate (**8b**).* This compound was synthesized 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 synthesized 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 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 synthesized 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]undecane-carboxylate (**8e**).* This compound was synthesized 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). mp 69−70 °C. ^{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]undecane-carboxylate (**8f**).* This compound was synthesized 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 that 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),

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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 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 synthesized 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 (0.91 g, 83% yield). mp 176−178 °C. Spectral data are in accordance with that 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 synthesized 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). mp 50−52 °C. Spectral data are in accordance with that 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 synthesized 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 synthesized 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). mp 74−76 °C. Spectral data are in accordance with that reported in the literature.[47] ^1H 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). $^{13}C\{^1H\}$ 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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01258.

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

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Author Contributions

P.S.M.A. conceived the original working hypothesis and wrote the first draft of the manuscript. P.S.M.A. performed the synthesis and other experiments. L.M.T.F. and J.A.S.C. projected the reaction mechanisms, performed the computations, and analyzed the data. P.M.O. and M.L.S.C. supervised the research and validated the work. All authors co-wrote the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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