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I. An Improved Procedure for Alkene Ozonolysis. II. Exploring a New Structural Paradigm for Peroxide Antimalarials.

Charles Edward Schiaffo
University of Nebraska-Lincoln

I. An Improved Procedure for Alkene Ozonolysis.

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By

Charles E. Schiaffo

A DISSERTATION

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I. An Improved Procedure for Alkene Ozonolysis.

II. Exploring a New Structural Paradigm for Peroxide Antimalarials.

Charles E. Schiaffo, Ph.D.

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Advisor: Patrick H. Dussault

The use of ozone for the transformation of alkenes to carbonyls has been well established. The reaction of ozone with alkenes in this fashion generates either a 1,2,4-trioxolane (ozonide) or a hydroperoxyacetal, either of which must undergo a separate reduction step to provide the desired carbonyl compound. There is considerable interest in being able to perform a reductive ozonolysis to directly provide the carbonyl. Previous reports from the Dussault lab have shown that amine N-oxides are able to perform a reductive ozonolysis. In the course of efforts to expand this reaction to other oxyanions it was realized that water was also able to efficiently perform a net reductive ozonolysis via nucleophilic capture of the carbonyl oxide. This transformation was investigated for a variety of substrates and was shown to offer a useful alternative to conventional ozonolysis conditions.

Malaria is a global health epidemic that affects between 300-500 million people annually, with the most deadly strain being P. *falciparum*. The current treatment for malaria is artemisinin combination therapy, but the development of artemisinin-resistant strains of malaria has spurred the need for the development of new treatments. 1,2,4-Trioxolanes exhibit high efficacy against malaria, but concerns remain about their

thermal and serum stability. Our analysis of the likely mechanism of action of ozonides guided our development of structurally related 3-alkoxy-1,2-dioxolanes as a potential treatment for malaria. This class of compounds has shown to possess high levels of activity against P. *falciparum in vitro*. The synthesis of these dioxolanes required the development of new synthetic routes, which will be discussed in detail, as will efforts to optimize the activity of 3-alkoxy-1,2-dioxolanes. In addition, the synthesis and evaluation of 1,2,4-trioxepanes as potential antimalarials was explored.

In the course of our investigation into the synthesis of 3-alkoxy-1,2-dioxolanes, we found Re (VII) oxide to be an effective catalyst for the transetherification of 3-alkoxy-1,2-dioxolanes. Re (VII) oxide was briefly explored as a catalyst for allylation or etherification reactions that involve stabilized carbocations as intermediates.

Acknowledgements

First, I would like to thank my advisor, Professor Patrick Dussault for his help and guidance. I am grateful for all the time he spent helping me and his patience. I believe that he has helped me become a better scientist.

I would like to thank the members of my committee: Prof. Takacs, Prof. Du, Prof. Nickerson, Prof. Redepenning, and Prof. Choe. I am indebted to the help that Joe Dumais and Sara Basiaga provided on the NMR and the other small instruments. Without the help of Sergio Wittlin and Matthias Rottman, who performed the antimalarial screening, and Tony Lloyd, from EHS who helped with the shipments, I would have no biological data and I thank them. I also thank Prof. Jonathan Vennerstrom and Yuxiang Dong at the University of Nebraska-Medical Center for there guidance on medicinal chemistry.

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I am fortunate for having parents who have been supportive of me through this journey. They never doubted me and provided encouragement at all the right times. Finally, I would like to thank my fiancée Van Nguyen Mai for her help, support, and guidance. She has been a true pillar of stability for me during this journey.

Chapter 1

Improved procedure for alkene ozonolysis

This chapter discusses the mechanism of ozonolysis and the trapping of the carbonyl oxide by various nucleophiles. In addition, the use of water in a reductive ozonolysis fashion will be discussed.

Section 1: Mechanism of ozonolysis and previous work involving trapping of the carbonyl oxide

Section 2: Trapping of the carbonyl oxide with water

Section 3: References

Section 1

Section 1.1: Mechanism of ozonolysis

Section 1.2: Issues with O_3 in synthesis

Section 1.3: Reductive ozonolysis using N-oxides

Section 1.4: Reductive ozonolysis using water

Ozonolysis is a powerful synthetic tool for the cleavage of alkenes to their corresponding carbonyl compounds. The use of ozonolysis in synthesis and as a synthetic tool has been extensively reviewed.[1-5] In this chapter, I will review the mechanism of ozonolysis with a focus on trapping of the carbonyl oxide.

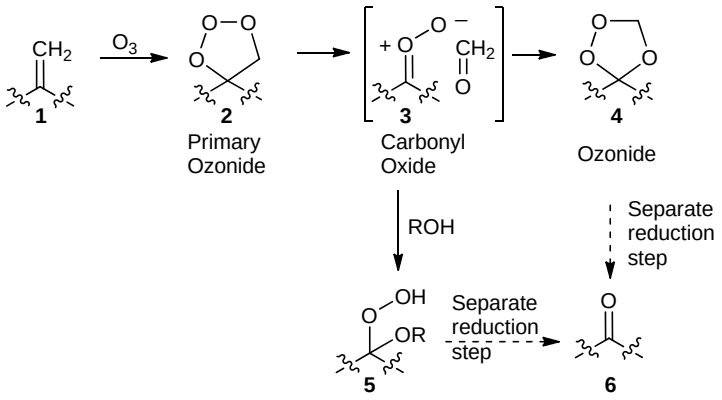
Section 1.1

Mechanism of ozonolysis

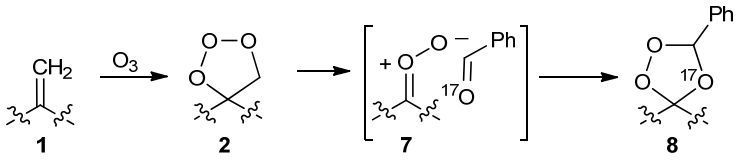
The postulated mechanism of ozonolysis has been extensively reviewed.[6-10]

The Criegee mechanism for ozonolysis is now widely accepted. The first step of, the Criegee mechanism of ozonolysis is the cycloaddition of ozone to an alkene generating a 1,2,3-trioxolane (primary ozonide), **2**. The primary ozonide is a short lived species that undergoes fragmentation to the carbonyl oxide (**3**) and carbonyl. The carbonyl oxide can undergo cyclization with a carbonyl group, either the co-generated species or an exogenously added reagent, to form a 1,2,4-trioxolane (secondary ozonide), **4**. The rate of this cycloaddition is related to the dipolarophilicity of the carbonyl, with aldehyde and electron-poor ketones reacting most rapidly.[9] Alternatively, in the presence of a nucleophile the carbonyl oxide will be trapped forming a hydroperoxy acetal (**5**). The best nucleophile for the trapping of the carbonyl oxide is a primary alcohol.[6] The

ozonides and hydroperoxyacetals are often reduced in a separate step to furnish carbonyl products.



Recent isotopic labeling studies directly support the Criegee mechanism. In 1998, Berger reported NMR studies of the trapping of ^{17}O-labeled benzaldehyde in ozonolysis. Isotopically labeled ozonide **8** with the ^{17}O in the ether was the sole ozonide isolated and gives support for the intermediacy of the carbonyl oxide during ozonolysis.[11] The lack of ^{17}O in the peroxide argues against some more complicated mechanisms, which have been proposed as an alternative to the Criegee mechanism.[10,12,13]



Section 1.2

Issues with O_3 in synthesis

The use of ozonolysis as a synthetic tool is to some degree limited by the need to employ a separate reduction step to convert the ozonide or peroxide intermediates to the desired carbonyl compound. The use of powerful reducing agents such as BH_3,[14] Zn/HOAc,[15] and $LiAlH_4$[16] can lead to compatibility issues with other functional groups. The use of a milder reducing agent such as Me_2S[17] can lead to incomplete reduction of

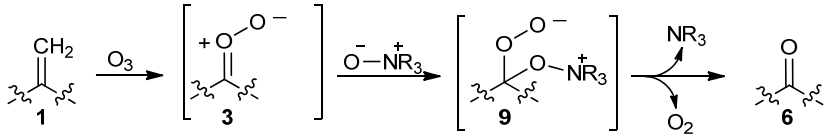
the ozonide. The use of PPh_3 usually leads to complete reduction of the ozonide, but the resulting $O=PPh_3$ needs to be removed from the final product.[18]

Section 1.3

Reductive ozonolysis using N-oxides

The development of a reductive ozonolysis approach is desired as it would eliminate the need for a separate reduction step. A second advantage to this approach is that the reduction takes time, while with reductive ozonolysis the reduction is complete when the ozonolysis is complete. The Dussault lab has an interest in affecting the outcome of ozonolysis through intercepting the carbonyl oxide. It was postulated that since alcohols[9] are capable of trapping the carbonyl oxide it possible that another oxygen nucleophile would also be successful. The use of dimethyl sulfoxide had been previously reported and prompted the exploration of other oxyanions.[19,20]

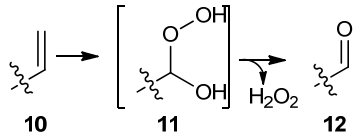
In the course of these explorations, our lab has shown that a variety of N-oxides are able to trap the carbonyl oxide and produce the desired carbonyl in a one-pot manner.[21,22] The postulated mechanism for this reaction involves addition of N-oxide to carbonyl oxide **3** to form tetrahedral intermediate **9**. Intermediate **9** then undergoes fragmentation to provide aldehyde **6**. The only byproducts of this reaction are oxygen and the corresponding amine.



Section 1.4

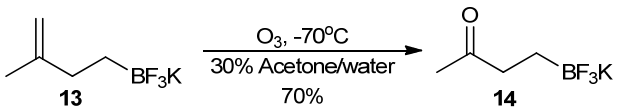
Reductive ozonolysis using water

These results, in conjunction with the known reactivity of alcohols and carbonyl oxides, made us wonder if water was able to trap the carbonyl oxide. A literature search revealed that trapping of the carbonyl oxide with water has been mainly reported in the literature related to atmospheric (gas phase) ozonolysis reactions.[23-26] There are a handful of relevant examples in solution. Pryor and Church reported that the ozonolysis of fatty acids in emulsions produced aldehydes and a stoichiometric amount of hydrogen peroxide.[27,28] In 1998, Von Sonntag explored the ozonolysis of ethene and its derivatives and found a similar result.[29] In 1982, Niki explored the relative reactivity of various protic solvents towards the carbonyl oxide.[30] The ozonolysis of tetramethylethylene with methanol and water revealed that methanol was a superior trap of the carbonyl oxide. In all of the literature the proposed mechanism involves intermediate **11**, which fragments to generate the aldehyde and one equivalent of hydrogen peroxide.



10 **11** **12**

In 2007, Molander reported the cleavage of alkene **13** to ketone **14**.[31] What is notable about this approach is the high yield obtained even at -70°C. This substrate formed stable ozonides, that were difficult to reduce, and this procedure was one of several explored. The use of this procedure on another alkene (styrene analog of **13**) led to a mixture of products and this reaction was not explored.



13 **14**

Section 2

This section describes my attempts to trap the short lived carbonyl oxide intermediate generated in ozonolysis to directly provide a carbonyl in a "reductive" ozonolysis.

Section 2.1: Rationale

Section 2.2: Initial phase transfer studies

Section 2.3: Anhydrous tetrabutyl ammonium salts

Section 2.4: Water as a trap

Section 2.5: Substrate scope

Section 2.6: Conclusions

Section 2.7: Experimentals

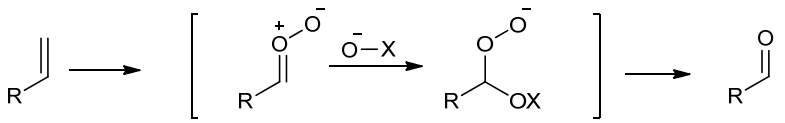
Section 2.8: References

Section 2.1

Rationale

Previous research in the Dussault lab had demonstrated that trapping of carbonyl oxides by nucleophilic amine oxides led to the direct formation of carbonyl groups by the formation and decomposition of an unstable tetrahedral intermediate containing a peroxyanion as well as an oxyammonium salt (Section 1.3). I became interested in whether this process was limited to oxyammonium species or was general for species containing a nucleophilic oxygen connected weakly to another heteroatom (periodate for example). As will be discussed below, my results suggest that the reductive fragmentation may be possible for other fragments combining a nucleophilic oxygen with

an easily cleaved oxygen-heteroatom bond. However, in the course of this work I discovered conditions for the highly efficient trapping of water to afford the desired carbonyl compound.



Initially, sodium periodate was chosen to test this hypothesis as it possess a nucleophilic oxyanion, is commercially available, and is cheap. $NaIO_4$ would be solubilized in water and the interaction with the carbonyl oxide of decene would be facilitated by a phase transfer agent.

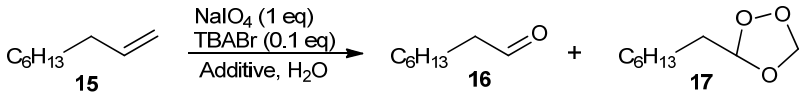
Section 2.2

Initial phase transfer studies

As expected under aprotic ozonolysis conditions, the ozonide was formed as the major product (Table 1.1 entry 1). To my delight, ozonolysis in the presence of water, CH_2Cl_2, a phase-transfer agent, and periodate switched the selectivity and aldehyde was isolated as the major product (Entry 2). CCl_4, a non-polar aprotic solvent, was not suitable and led to the ozonide being formed as the major product. Commercial bleach (Entry 4) and oxone (Entry 5) could be used as additives to afford aldehyde **16**. To rule out periodate performing a Hon fragmentation[32] (E_1CB), pure ozonide was resubjected to the reaction conditions and no further reaction was observed.

A control reaction which included water and a phase-transfer catalyst but which omitted the oxyanion nucleophile also produced aldehyde in good yield (Entry 6). This suggests that water is able to trap the carbonyl oxide. This result led me to question the relative contributions of water and the oxyanion nucleophile in promoting the apparent

fragmentation. Water appears capable of trapping the carbonyl oxide and the resulting intermediate undergoes decomposition to the desired product. When water and $NaIO_4$ are used together it is unclear which species is trapping the carbonyl oxide. To answer this question two different approaches were taken.



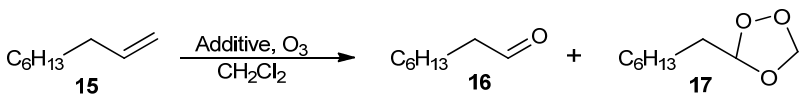
Entry	Additive (eq)	H_2O (eq)	TBABr (eq)	Solvent	Yield (%) **16**	Yield (%) **17**
1	None	0	0	CH_2Cl_2	13	72
2	$NaIO_4$ (1)	92	0.1	CH_2Cl_2	32	8
3	$NaIO_4$ (1)	92	0.1	CCl_4	3	34
4	NaOCl (1)	0	0.1	CH_2Cl_2	42	11
5	Oxone (1)	92	0.1	CH_2Cl_2	30	9
6	None	92	(0.3)	CH_2Cl_2	42	9

Table 1.1
Initial screen of various additives and decene

Section 2.3

Anhydrous tetrabutyl ammonium salts

A variety of anhydrous oxyanions solubilized with a bulky quaternary ammonium salt were screened to determine if a oxyanion is capable of trapping the carbonyl oxide (Table 1.2). It was found that various anhydrous oxyanions are able to trap the carbonyl oxide to form nonanal, **16**, in a one pot manner (Entries 4-7). For reasons of economy $TBAIO_4$ was chosen to find optimal conditions. Increasing the equivalents of O_3 (Entry 2 vs. 3) improved the yield of aldehyde. The reason for this improvement is unclear as previous reactions all appeared to go to completion. In the presence of super stoichiometric amounts of $TBAIO_4$ the yield of aldehyde is tripled (Entry 4). This method is capable of providing a synthetically useful yield of nonanal, but the need for a large excess of reagent complicates purification.



Entry	Additive (eq)	Ozone (eq)[A]	Yield (%) **16**	Yield (%) **17**
1	None	1.2	13	72
2	$TBAIO_4$ (1)	1.2	35	ND
3	$TBAIO_4$ (1)	1.7	55	ND
4	$TBAIO_4$ (3)	1.7	72	17
5	$TBANO_2$ (1)	1.2	38	13
6	$TBANO_3$ (1)	1.2	38	13
7	TBAOCN (1)	1.2	32	25
8	TEMPO (1)	1.2	None by TLC	Present by TLC

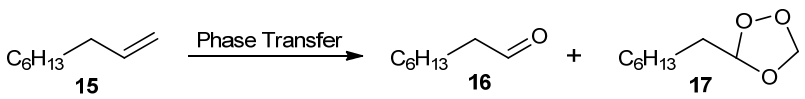
Table 1.2 Screen of various anhydrous salts and their ability to influence the formation of aldehyde

[A]Based upon calibration of delivery against a known substrate

Section 2.4

Water as a trap

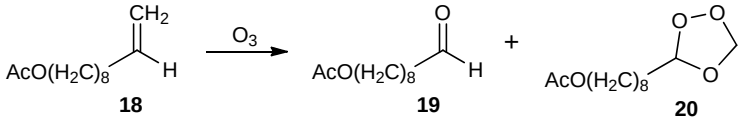
With the knowledge that water is able to trap the carbonyl oxide, it became necessary to determine the optimum trapping conditions (Table 1.3). A screen was performed based upon monitoring (NMR) the relative yields of nonanal (**16**) vs. decene ozonide (**17**) derived upon ozonolysis of decene under a given set of conditions. It was found the addition of water in the absence of a phase transfer agent led to a lower yield of both aldehyde and ozonide (Entry 2). Widely varying results for the reaction in CH_2Cl_2 vs. CCl_4 suggests a key factor could be solvent polarity and/or the amount of solubilized water (Entries 3-5). We therefore hypothesized that higher yields of aldehyde should be obtained in a water-miscible solvent such as acetone or acetonitrile. This hypothesis was found to be true (Entries 7-9). When water immiscible ethyl acetate was employed the yield of aldehyde decreased (Entry 10).



Entry	Phase Transfer (eq)	Water (eq)	Solvent	Yield (%) **16**	Yield (%) **17**
1	None	None	DCM	13[a]	72[a]
2	None	18	DCM	8	21
3	TBABr (1)	92	DCM	54	ND
4	$TBAHSO_4$ (.1)	92	DCM	33	9
5	TBABr (0.1)	92	CCl_4	12	59
7	None	92	Acetone	46	2.9
8	None	18	Acetone	67	6
9	None	18	MeCN	42	8
10	None	18	EtOAc	35	6

Table 1.3 [a] Isolated yields
Yields determined by NMR

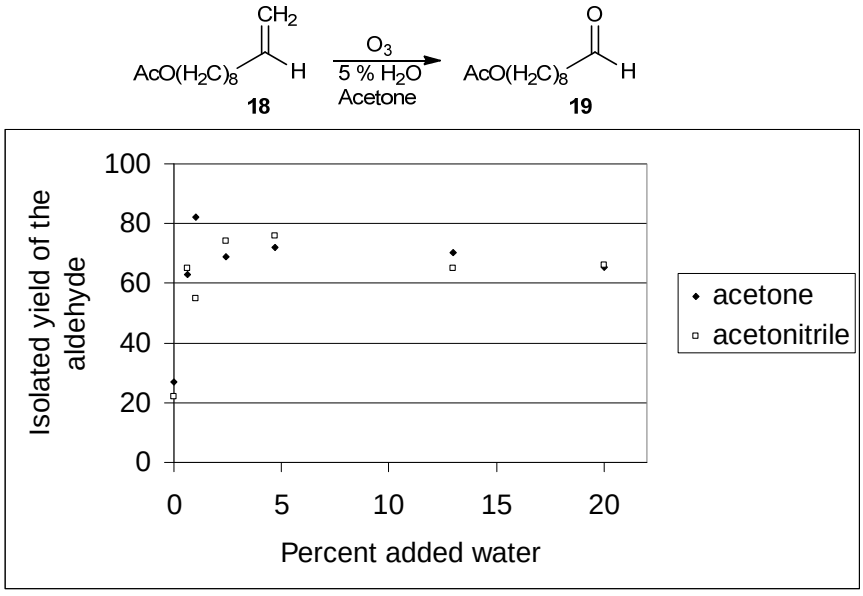
The relative volatility of nonanal led to relatively low isolated yields, and we developed a screen based upon the oxidation of 9-decenyl acetate, which would generate a less volatile product. This approach led to similar trends as those present in Table 1.4, namely, that the use of a non-polar solvent led to poor yields (Entry 4), while the use of more polar CH_2Cl_2 led to good yields (Entries 2-4) in the presence of a phase transfer agent. As was expected the use of acetone led to good yield of aldehyde (Entry 6).



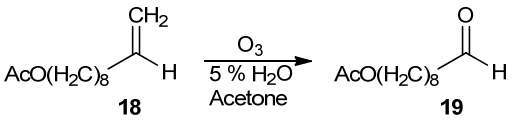
Entry	Phase Transfer (eq)	Water (eq)	Solvent	Yield (%) **19**	Yield (%) **20**
1	None	None	DCM	13	72
2	TBABr (0.1)	92	DCM	42	9
3	TBABr (1)	92	DCM	72	17
4	TBABr (0.1)	92	CCl4	12	59
5	TBABr (0.1)[a]	92	DCM	63	9
6	None	18	Acetone	72	14

Table 1.4 Use of 9-decenylacetate as an ozonolysis substrate
[a]$NaHCO_3$ added

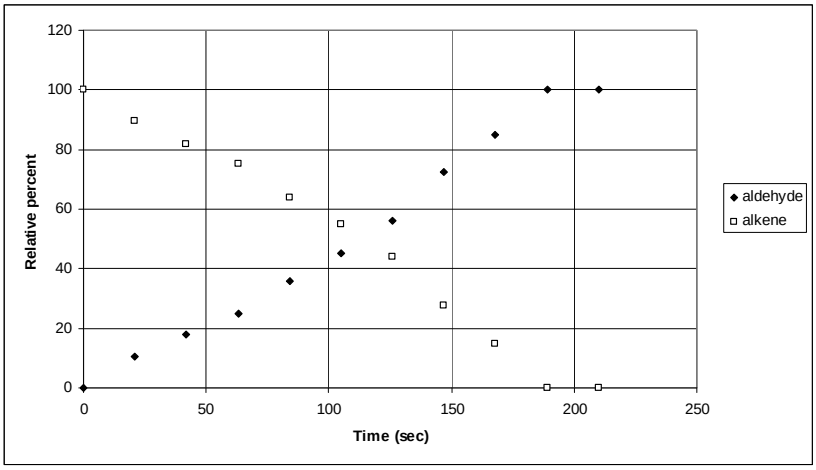
It was unknown what effect varying amounts of solubilized water would have on the reaction. To determine this, I investigated the ozonolysis of alkene **18** in acetonitrile and acetone containing varying amounts of solubilized water. New bottles of solvent were utilized for this screen, but the solvent underwent no additional drying. As little as 0.6% added water led to a remarkable increase in the yield of aldehyde and this high yield was maintained up to 20% added water. It is expected that at a certain point the solvent mixture is able to no longer solubilize both the alkene and water, resulting in a decline in yield of the aldehyde. Based upon these results 5% added water (v/v) was used for all further experiments.



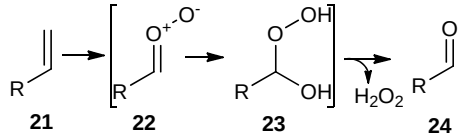
I wanted to verify that the consumption of the alkene was linearly related to the formation of aldehyde. Thus **18** was subjected to ozonolysis and aliquots were taken every 33 seconds and filtered through a silica plug. ^{1}H NMR was taken and showed **18** and **19**, but no ozonide. A graph of the calculated relative amounts of the consumed alkene vs. the generated products shows a linear trend.



18 19



The hypothesis, which is supported by previous literature, is that solubilized water is able to trap the carbonyl forming hydroperoxyacetal intermediate, **23**. This type of trapping has been reported in the literature for atmospheric chemistry (gas phase) and has not been previously applied as a general synthetic method to solution chemistry.[23,24] For more complete coverage of this field see Section 1.4. Tetrahedral intermediate **23** undergoes *in situ* fragmentation giving the desired carbonyl, **24**, and hydrogen peroxide as a byproduct. To test this hypothesis, I performed the ozonolysis of **18** in 95:5 acetone/water (v/v) and collected the aqueous layer remaining after extraction with CH_2Cl_2. Testing this layer with calibrated peroxide test strips indicated that hydrogen peroxide was present in stoichiometric amounts.

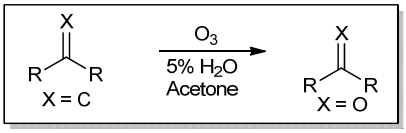


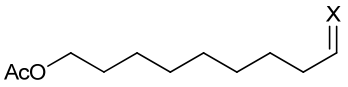
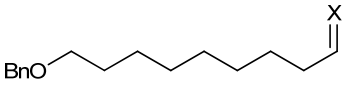
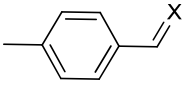
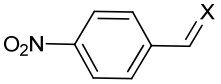
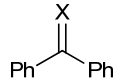
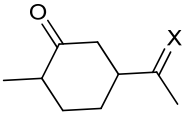
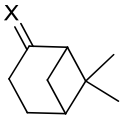
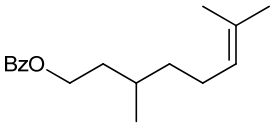
21 22 23 24

Section 2.5

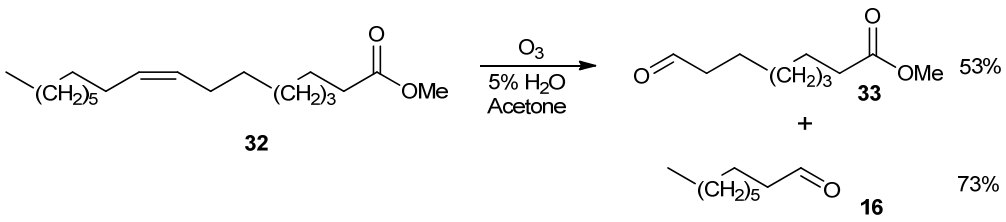
Substrate scope

A variety of alkenes were subjected to ozonolysis under these conditions to determine substrate scope. Some of the initial yields were in our opinion lower than would be expected. It was thought that excess ozone might be problematic and as a solution to this indicator Sudan Red III was employed.[33] As was expected from the screening studies the ozonolysis of **18** and **25** proceeded in good yield. Likewise, ozonolysis of styrenes **26** and **27** proceeded in moderate to excellent yield. Styrene **27** was chosen as an alkene which undergoes ozonolysis to give the aldehyde and formaldehyde O-oxide. Therefore, the quantitative yield indicates that the water is able to trap the formaldehyde carbonyl oxide before recombination with **27** can occur. The ozonolysis of structurally more complicated terpene **29** proceeded in quantitative yield. Ozonolysis of β-pinene (**30**) produced the ozonide as the major product.



Substrate	Structure	No Sudan Red III (%)	Sudan Red III (%)
18		72	NA
25		NA	72
26		NA	73
27		NA	quant.
28		NA	52
29		76	quant.
30		NA	19
31		54	75

Methyl oleate, **32**, was used to determine if the two chemically different aldehydes could be isolated. Both aldehydes **33** and **16** were isolated, however, the yield for **33** was depressed.



Section 2.6

Conclusions

This work has shown two new methodologies for the formation of aldehydes or ketones directly from alkenes. The first is utilizing oxyanions as a new method for the "reductive" ozonolysis of alkenes. This route requires a large excess of reagents that must be removed making this approach less than ideal. The second is the use of water to directly trap the carbonyl oxide giving the desired carbonyl compound. The advantage of this route is the need for no elaborate purification. The disadvantage is the generation of a stoichiometric amount of hydrogen peroxide

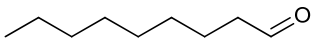
Section 2.7

Experimentals

All reagents were used as received from commercial vendors, with the exception of CH_2Cl_2, which was distilled from calcium hydride, and THF, which was distilled from sodium/benzophenone. All reactions were conducted under an atmosphere of N_2 except where noted; "RBF" indicates round-bottom flask. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% *N*,*N*'-dimethyl-*p*-phenylenediamine solution in 1:20:100 acetic acid/water/methanol (specific for peroxides);[34] 1% aq. $KMnO_4$ (for unsaturated compounds);. "Standard drying and purification" refers to drying of organic extracts over Na_2SO_4, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. ^1H /^{13}C NMR spectra were recorded

at 300 (75), 400(100), or 500(125) MHz in $CDCl_3$ unless otherwise indicated; peaks are reported as: chemical shift (multiplicity, J couplings in Hz, number of protons).

We experienced no safety issues in the course of performing this research. Ozonides and peroxides can be explosive and dangerous and all prudent safety precautions should be taken.[35,36]



Nonanal (16):

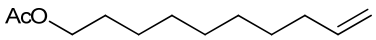
Representative procedure for ozonolysis in CH_2Cl_2 in the presence of H_2O, a phase transfer agent, and $NaIO_4$

To a flame-dried RBF containing a solution of decene (3 mmol) in CH_2Cl_2 (20 mL) was added sequentially $NaIO_4$ (3 mmol) in H_2O (5 mL) and phase transfer agent (0.1-1mmol) and cooled to 0^oC. A stream of O_3/O_2 was passed through the reaction for the allotted amount of time and the reaction flask was purged with a stream of O_2 for 2 min. H_2O (25 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (25 mL) and dried with $NaSO_4$. The residue obtained upon concentration *in vacuo* was subjected to column chromatography with 10 % EA/hex to afford **16** as a colorless oil. R_f (10 % EA/hex): 0.56. ^1H NMR (300 MHz): 9.71 (t, J = 1.8, 1H), 2.82 (dt, J = 1.7, 7.3, 2H), 1.6 (m, 2H), 1.45-1.13 (10H), 0.83 (t, J = 6.9, 3H).

Also formed is 3-octyl-1,2,4-trioxolane as a colorless oil. ^1H NMR (300): 5.20 (s, 1H), 5.13 (t, J = 3.2, 1H), 5.04 (s, 1H), 1.72 (m, 2H), 1.51-1.20 (12H), 0.89 (t, J = 6.8, 3H).

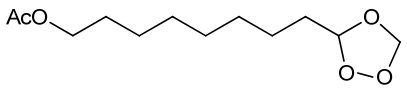
Representative procedure for the ozonolysis in CH_2Cl_2 /H_2O in the presence of a phase transfer agent

To a flame-dried RBF containing a solution of decene (3 mmol) in CH_2Cl_2 (20 mL) was added sequentially H_2O (5 mL) and phase transfer agent (0.1-1 mmol). The solution was cooled to 0°C and a stream of O_3/O_2 was passed through the reaction for the allotted amount, after which the reaction was purged with a stream of O_2 for 2 min. H_2O (25 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (25 mL) and subjected to standard drying and purification with 10 % EA/hex to afford **16** as a colorless oil. For yields see Table 1.2.



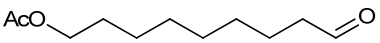
9-decenenyl acetate (18):

To a flame-dried RBF containing a solution of 9-decen-1-ol (4.0135g, 26 mmol) in pyridine (40 mL) was added sequentially Ac_2O (2.86 mL, 39 mmol) and DMAP (319.8 mg, 2.6 mmol) and reaction was stirred overnight. 2 N HCl (80 mL) was added and the resulting suspension was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 80 mL), brine (80 mL), and were subjected to standard drying and purification with 5% EA/hex to afford **18** (4.6201 g, 90%) as a colorless oil. R_f (5 % EA/hex): 0.44. ^{1}H NMR (300 MHz): 5.79 (ddt, J = 17.0, 10.2, 6.7, 1H), 4.95 (m, 2H), 4.03 (t, J = 6.7, 2H), 2.08 – 1.97 (5H), 1.66 – 1.53 (2H), 1.43 – 1.22 (10H). ^{13}C (75 MHz): 171.3, 139.2, 114.3, 64.7, 33.9, 29.5, 29.3, 29.1, 29.0, 28.7, 26.0, 21.1. The NMR spectra matched those previously reported.[37]



8-(1,2,4-trioxolan-3-yl)octyl acetate (20):

In a flame-dried RBF containing **18** (0.5281g, 2.6 mmol) was added in CH_2Cl_2 (20 mL). The solution was cooled to -78 ^oC and a stream of O_3/O_2 was passed through the solution until blue and the flask was purged with O_2 for 2 min. The solution was concentrated *in vacuo* and purified via flash chromatography with 10% EA/hex to afford **20** (416.6mg, 63%) as a colorless oil. R_f (10% EA/hex) = 0.4. ^1H NMR (400 MHz): 5.043 (s, 1H), 4.977 (t, J = 4.95, 1H), 4.871 (s, 1H), 3.908 (t, J = 6.74, 2H), 1.884 (s, 3H), 1.57 (m, 2H), 1.49 (m, 2H), 1.31-1.19 (10H). ^{13}C NMR (100 MHz): 170.6, 103.5, 93.8, 64.2, 31.4, 30.9, 29.1, 28.9, 28.4, 25.7, 23.6, 20.6. HRMS: calc for $C_{12}H_{23}O_5$: 247.1546; found: 247.1545.

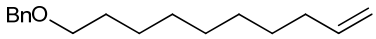


9-oxononyl acetate (19):

Representative procedure for the ozonolysis in CH_2Cl_2 /H_2O in the presence of a phase transfer agent

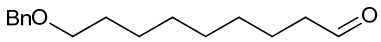
To a flame-dried RBF containing a solution of **18** (3 mmol) in CH_2Cl_2 (20 mL) was added sequentially H_2O (5 mL) and phase transfer agent (0.1-1 mmol). The flask was cooled to 0^oC and a stream of O_3/O_2 was passed through the reaction for the allotted amount of time. The reaction flask was purged with a stream of O_2 for 2 min. H_2O (25 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (25 mL) and subjected to standard drying and purification with 10 % EA/hex to afford **19** as a colorless oil. R_f (10% EA/hex): 0.33. ^1H NMR (300 MHz): 9.72 (t, J = 1.7, 1H), 4.0 (t, J = 4, 2H), 2.38 (dt, J =

1.7, 7.2, 2H), 2.0 (2, 3H), 1.65 – 1.49 (4H), 1.37 – 1.23 (8H). ^{13}C (75 MHz): 202.9, 171.3, 64.6, 43.9, 29.3, 29.1, 29.0, 28.6, 25.9, 22.1, 21.1. The NMR spectra matched those previously reported.[38]



((dec-9-en-1-yloxy)methyl)benzene:

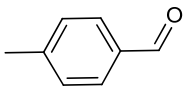
A suspension of NaH (630 mg, 15.8 mmol, 60% in mineral oil) in a flame-dried RBF was washed with THF (10 mL) and suspended in THF (20 mL). 9-decen-1-ol (2.074 g, 13.3 mmol) and benzyl bromide (2.44 g, 14.3 mmol) were added sequentially and the reaction was stirred overnight. H_2O (20 mL) was added and extracted with EA (2 x 30 mL) and washed with brine (30 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford ((dec-9-en-1-yloxy)methyl)benzene (1.3305 g, 41%) as a yellow oil. R_f (10 % EA/hex): 0.86. ^1H NMR (400 MHz): 7.41 – 7.26 (5H), 5.84 (ddt, J = 17.0, 10.2, 6.7, 1H), 2.50 (m, 2H), 5.0 (m, 2H), 4.53 (s, 2H), 3.49 (t, J = 6.8, 2H), 2.11- 2.02 (2H), 1.69 – 1.59 (2H), 1.45 – 1.26 (10H). ^{13}C (100 MHz): 139.3, 138.9, 128.5, 127.8, 127.6, 114.3, 73.0, 70.7, 33.9, 29.6, 29.3, 29.1, 26.4. The NMR spectra matched those previously reported.[39]



9-(Benzyloxy)nonanal (25):

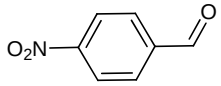
To a flame-dried RBF containing a solution of 9-dencenyl benzylether (748.5 mg, 3.04 mmol) in acetone (20 mL) was added sequentially added H_2O (1 mL, 56 mmol) and Sudan Red III (trace). The solution was cooled to 0^oC and mixture of O_3/O_2 was passed through the flask until the red color dissipated. The reaction was purged with O_2 for 2 min. H_2O (25 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2

x 25 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to EA to afford **25** (545.3 mg, 72%) as a yellow oil. R_f (10% EA/hex): 0.34. ^{1}H NMR (400 MHz): 9.77 (t, J = 1.8, 1H), 7.40-7.26 (5H), 4.52 (s, 2H), 3.48 (t, J = 6.6, 2H), 2.43 (dt, J = 1.9, 7.4, 2H), 1.66 – 1.58 (4H), 1.44 – 1.27 (9H). ^{13}C (100 MHz): 203.0, 138.8, 128.4, 127.7, 127.6, 72.9, 70.5, 44.0, 29.9, 29.4, 29.3, 29.2, 26.2, 22.1. The NMR spectra matched those previously reported.[40]



4-Methyl-benzaldehyde (26):

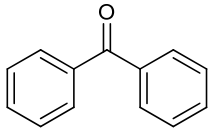
To a flame-dried RBF containing a solution of 4-methylstyrene (369.8 mg, 3.1 mmol) in acetone (20 mL) was added H_2O (1.0 mL, 56 mmol) and Sudan Red III (trace). The solution was cooled to 0^{o}C and O_3/O_2 was passed through the flask until the red color dissipated. H_2O (25 mL) was added and the suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **26** (275.9 mg, 73%) as a yellow oil. R_f (10% EA/hex): 0.52. ^{1}H NMR (400 MHz): 9.95 (s, 1H), 7.76 (d, J = 8.1, 2H), 7.32 (d, J = 8.1, 2H), 2.42 (s, 3H). NMR spectra matched commercially available samples.



4-nitrobenzaldehdye (27):

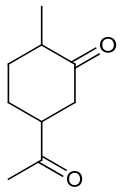
To a flame-dried RBF containing a solution of 4-nitrostyrene (307.5 mg, 2.1 mmol) in acetone (13 mL) was added H_2O (0.66 mL, 37 mmol) and Sudan Red III (trace). The solution was cooled to 0^{o}C and O_3/O_2 was passed through the flask until the red color dissipated. H_2O (25 mL) was added and the suspension was extracted with CH_2Cl_2 (2 x

25 mL). The combined organic layers were subjected to standard drying and purification with 30% Et_2O/pent to afford **27** (312.3 mg, quantitative) as a white solid. R_f (30% Et_2O/pent): 0.57. ^1H NMR (400 MHz): 10.17 (s, 1H), 8.41 (d, J = 8.4, 2H), 8.09 (d, J = 8.4, 2H). ^{13}C (100 MHz): 190.5, 151.3, 140.2, 130.7, 124.5. The NMR spectra matched those previously reported. [41]



Benzophenone (28):

To a flame-dried RBF containing a solution of 1,1-Diphenylethylene (578.7 mg, 3.2 mmol) in acetone (20 mL) was added H_2O (1.0 mL, 56 mmol) and Sudan Red III (trace). The solution was cooled to 0^oC and O_3/O_2 was passed through the flask until the red color dissipated. H_2O (25 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **28** (303.5 mg, 52%) as a white solid. Rf (10% EA/hex): 0.43. ^1H NMR (300 MHz): 7.87 – 7.79 (4H), 7.64 – 7.56 (2H), 7.53 – 7.45 (4H). ^{13}C (75 MHz): 196.9, 137.7, 132.5, 130.2, 128.4. The NMR spectra matched those previously reported.[42]



5-acetyl-2-methyl-cyclohexanone (29):

Small Scale (3 mmol):

To an oven dried RBF containing a solution of dihydrocarvone (396.3 mg, 3 mmol) in acetone (17 mL) was added sequentially H_2O (0.9 mL, 49.5 mmol) and Sudan Red III (trace). The solution was cooled to 0°C and a stream of O_3/O_2 was passed through the flask until the red color dissipated. The flask was purged with O_2 for 2 min. H_2O (25 mL) was added and the suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were subjected to standard drying and purification with 40 % Et_2O/hex to afford **29** (401.9 mg, quant.) as a yellow oil. ^1H NMR (300 MHz): 2.78 (m, 1H), 2.43 (d, J = 9, 2H), 2.34 (apparent sextet, J = 6.3, 1H), 2.15 (s, 3H), 2.2-2.05 (2H), 1.68 (apparent qd/ddd, J = 13.3, 3.4, 1H), 1.39 (apparent qd/ddd, J = 13.1, 3.4, 1H), 0.98 (d, J = 9.5, 3H). ^{13}C NMR (75 MHz): 211.5, 208.3, 52.0, 44.5, 42.7, 34.5, 28.3, 27.8, 14.3. HRMS: calc for $C_9H_{15}O_2$: 155.1072; found: 155.1066.

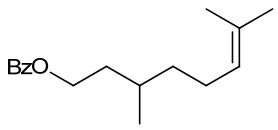
Large Scale Procedure (Chromatographic purification):

To an oven dried RBF containing a solution of dihydrocarvone (3g, 20 mmol) in acetone (133 mL) was added H_2O (6.8 mL, 378 mmol) and Sudan Red III (trace). The solution was cooled to 0°C and O_3/O_2 was passed through the flask until the red color dissipated. The flask was purged with O_2 for 2 min. H_2O (150 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (2 x 130 mL). The combined organic

layers were subjected to standard drying and purification with 40 % Et_2O/hex to afford **29** (2.6249g, 86%) as a yellow oil.

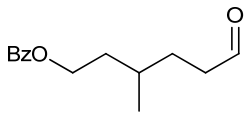
Large Scale procedure (purification by distillation):

To a flame-dried RBF containing a solution of dihydrocarvone (4.9395g, 32 mmol) in acetone (213 mL) was added H_2O (10 mL, 556 mmol) and Sudan Red III (trace). The solution was cooled to 0°C and O_3/O_2 was passed through the flask until the red color dissipated. The flask was purged with O_2 for 2 min. H_2O (100 mL) was added and extracted with CH_2Cl_2 (1 x 130 mL and 1 x 30 mL). The combined organic layers were washed with H_2O (30 mL) and dried with Na_2SO_4. The residue obtained upon concentration *in vacuo* was purified by Kugelrohr (bulb-to-bulb) distillation (245 °C @ 90 torr) to afford **29** as a yellow oil (3.9331g, 78%).



Citronellyl benzoate:

In a flame-dried RBF containing a solution of B-citronellol (2.1399g, 13.7 mmol) in pyridine (20 mL) was added benzoyl chloride (2.0705g, 14.1 mmol). The reaction was stirred for 4 hours. Et_2O (40 mL) was added and the organic layer was washed sequentially with 1 N HCl (20 mL), sat. aq. $NaHCO_3$ (40 mL), and brine (40 mL). The combined organic layers were subjected to standard drying and purification with 5 % EA/hex to afford citronellyl benzoate (3.1784 g, 89%) as a yellow oil. R_f (10% EA/hex) = 0.74. ^{1}H NMR (300 MHz): 8.05 (d, J = 7.5, 2H), 7.62-7.39 (3H), 5.16-5.05 (1H), 4.37 (m, 2H), 2.14-0.91 (16H). ^{13}C (75 MHz): 166.8, 133.0, 131.6, 130.7, 129.7, 128.5, 124.7, 63.6, 37.1, 35.7, 29.7, 25.9, 25.6, 19.7, 17.8.



3-Methyl-6-oxohexyl benzoate (33):

To an oven-dried RBF containing citronellyl benzoate (762.6 mg, 2.93 mmol) in acetone (20 mL) was added H_2O (1 mL, 56 mmol) and Sudan Red III (trace). The solution was cooled to 0^oC and O_3/O_2 was passed through the flask until the red color dissipated. H_2O (25 mL) was added and the suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were subjected to standard drying and purification with 30% Et_2O/hex to afford **33** (515.5 mg, 75%) as a yellow oil. R_f (30% Et_2O/pentane): 0.72. ^1H (300 MHz): 9.74 (t, J = 1.7, 1H), 8.05-7.92 (2H), 7.58-7.33 (2H), 4.41-4.26 (2H), 2.54-2.34 (2H), 1.88-0.76 (8H). The NMR spectra matched those previously reported.[43]

Section 3

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Chapter 2

3-Alkoxy-1,2-dioxolanes as potential antimalarials

This chapter will discuss the disease malaria and current treatments using both synthetic and natural peroxides. There is also an in depth discussion of 3-alkoxy-1,2-dioxlanes as a new class of peroxides for the treatment of malaria.

Section 1: Malaria and current antimalarial treatments

Section 2: Previous synthesizes and reactivity of 3-alkoxy-1,2,-dioxolane

Section 3: "First Generation" 3-alkoxy-1,2-dioxolanes

Section 4: "Second Generation" 3-alkoxy-1,2-dioxolanes

Section 5: "Third Generation" 3-alkoxy-1,2,-dioxolanes

Section 6: Experimentals

Section 7: References

Section 1

Section 1.1: Malaria

Section 1.2: Antimalarial Treatments

Section 1.3: Artemisinin as a treatment for malaria

Section 1.4: Mechanism of Fe-mediated artemisinin degradation

Section 1.5: Artemisinin mechanism of action against malaria

Section 1.6: Vennerstrom's ozonides

Section 1.7: Rationale for 3-alkoxy-1,2-dioxolanes

Section 1.1

Malaria

Malaria is a global health epidemic affecting 300-500 million people and causing 1-2 million deaths annually, predominately in children.[1] Malaria infection occurs primarily in Africa and Southeast Asia. There are five strains of malaria that infect humans; the most deadly strain of malaria is P. *falciparum*.[1]

The following is a very brief overview to provide a perspective on the challenges in treating this disease. An excellent review on malaria infection was published by Miller in 2002.[2] The life cycle of malaria is complex and occurs in both the transmitting mosquito and the infected host. The multiplication of malaria in the infected mosquito occurs in the midgut and takes approximately 10 days for the salivary glands to become infected.[3] Humans are infected by a bite from an infected mosquito. Within one hour the transferred sporozites infect the cells of the liver.[3] Over the next 5-15 days the infection

develops into exoerythrocytic shizonts that contain tens of thousands of merozoites.[3] Release of these merozoites into the blood stream leads to rapid infection of red blood cells. The eventual rupture of the infected red blood cells leads to further infection.[3] The presence of multiple stages makes treating malaria difficult.

Section 1.2

Antimalarial treatments

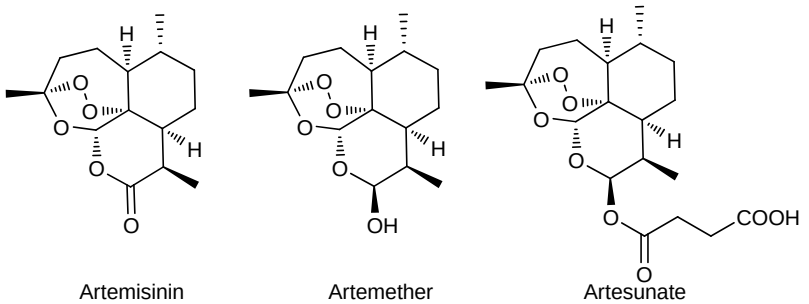
The ultimate goal for the treatment of malaria is the development of a vaccine; however, this goal has proved elusive.[4] As such, a continued need exists for the development of novel chemotherapeutics. Several reviews have been published on chemotherapeutic treatments of malaria.[3,5-11]

Malaria can be treated by non-peroxide means (quinine,[6] chloroquine,[6] mefloqquine,[6] ferrocene conjugates,[12-14] peptides[15-17]). Several classes of peroxide-containing compounds have demonstrated activity against malaria: 1,2-dioxanes,[18] 1,2,4-trioxepanes,[18-20] 1,2,4-trioxanes,[21-24] tetraoxanes,[25-27] artemisinin dimers,[28-30] and artemisinin derivatives.[31,32] However, only a few of these have demonstrated efficacy in humans. Artemisinin combination therapy (ACT) is currently the prescribed treatment for malaria, but the development of artemisinin resistant malaria in Cambodia has spurned the interest in chemotherapeutics.[33] This introduction will discuss artemisinin, along with 1,2,4-trixolanes (ozonides); several molecules of the later class are in clinical trials against malaria.

Section 1.3

Artemisinin as treatment for malaria

Artemisinin (**1**) is a naturally occurring endoperoxide isolated from the Chinese wormwood.[34] Isolation continues to be the primary source of artemisinin but synthetic approaches have been reported.[5] The total synthesis of artemisinin was first reported by Schimd and Hofheinz in 1983.[35] Semi-synthesis of artemisinin based upon biosynthesis of artemisinic acid has been reported by Keasling.[36,37] Currently, artemisinin (**1**) is not used directly for treatment due to rapid metabolism. Instead, the closely related artemether (**2**)[38] and artesunate (**3**)[38] are given as part of a combination therapy.[39] Artemisinin and analogs **2** and **3** demonstrate long shelf life[40] as well as stability to many chemical transformations.[41] However, artemisinin is degraded by Pd-catalyzed hydrogenation and treatment with strong acid or base.[34]

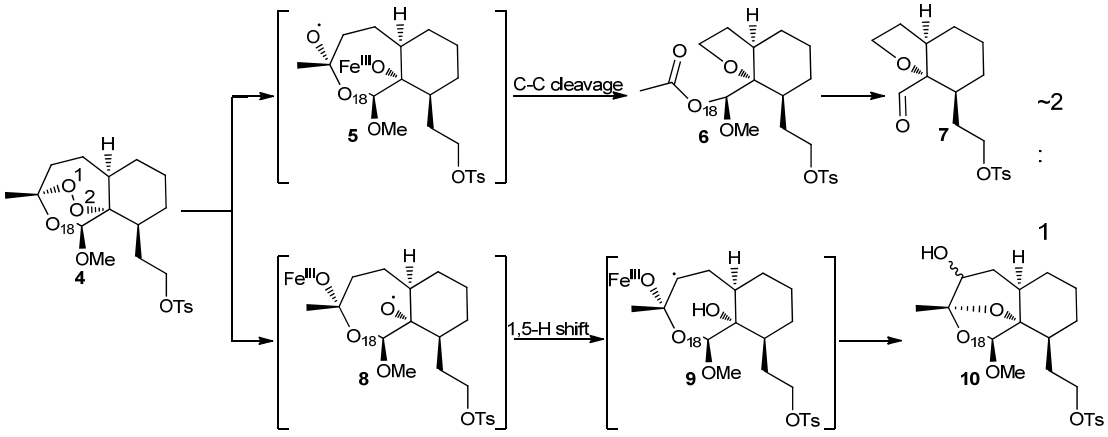


Section 1.4

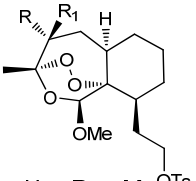
Mechanism of Fe-mediated artemisinin degradation

In 1992, Posner undertook a study of an ^{18}O-labeled artemisinin analog to elucidate a mechanism for the Fe (II)-mediated degradation of the endoperoxide. The degradation can proceed by two pathways. The first is by radical scission to provide

intermediate **5** with the alkoxy radical on O^1. This intermediate can undergo C-C cleavage via β-scission to generate the mixed acetal **6**, which undergoes hydrolysis to provide aldehyde **7**. Alternatively, if the initial cleavage occurs to create an alkoxy radical on O^2, intermediate **8** is obtained. A subsequent 1,5-H shift provides intermediate **9**, which can undergo cyclization with loss of Fe(II) to furnish epoxide **10**. A later paper supports the transformation of **9** to **10** through the generation of a hydroxyl-epoxide and Fe(IV)=O.[42] The combined yields of **7** and **10** (~2:1) were 60 – 70%, demonstrating that these are major pathways.



With a preliminary mechanism proposed, Posner explored the 1,5-H shift involved in the conversion of alkoxy radical **8** to carbon radical **9**. The hypothesis was that if the hydrogen was not in the correct spatial alignment to undergo a shift there would be no activity.[43] Peroxides **11** and **12** were synthesized and activity against P. *falciparum* was measured test this hypothesis. When no H is available to perform a shift (**12**), no activity is observed. Likewise, when the H is in the wrong spatial alignment (**11**) to allow hydrogen abstraction, the peroxide is devoid of activity. In contrast, control peroxide **4**, which is similar to artemisinin in stereochemistry at the methyl-bearing center, possessed high activity.



4 R = H, R_1 = Me
11 R = Me, R_1 = H
12 R = Me, R_1 = Me

Section 1.5

Artemisinin mechanism of action against malaria

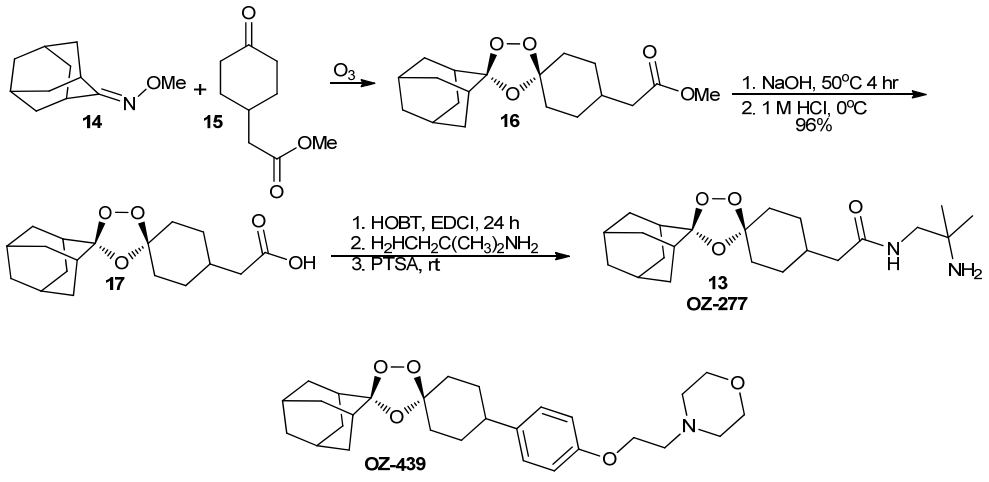
Several reviews have been published on the mechanism of action (MOA) of artemisinin.[44-46]

In 1991, Meshnick reported the alkylation of heme by artemisinin.[47] However, Meshnick and subsequent researchers have struggled to understand the role that the alkylated heme plays in antimalarial activity. More recently proposed MOAs have included artemisinin blocking PfATP6 (Plasmodium *falciparum* Ca^{2+} ATPase)[48,49] and artemisinin causing parasite membrane damage.[50] Although a MOA based upon Fe(II)-mediated generation of reactive radicals is the most widely accepted. A minority of research papers support the idea that activity is not derived from the formation of carbon centered radicals, but rather a result of reactive intermediates derived from an ionic opening of the peroxide.[51-53] None of these MOAs are without debate and thus far no consensus is present in the literature. Arguably, until the MOA of endoperoxide containing drugs is confirmed no truly rationale design of a potential treatment can be undertaken.

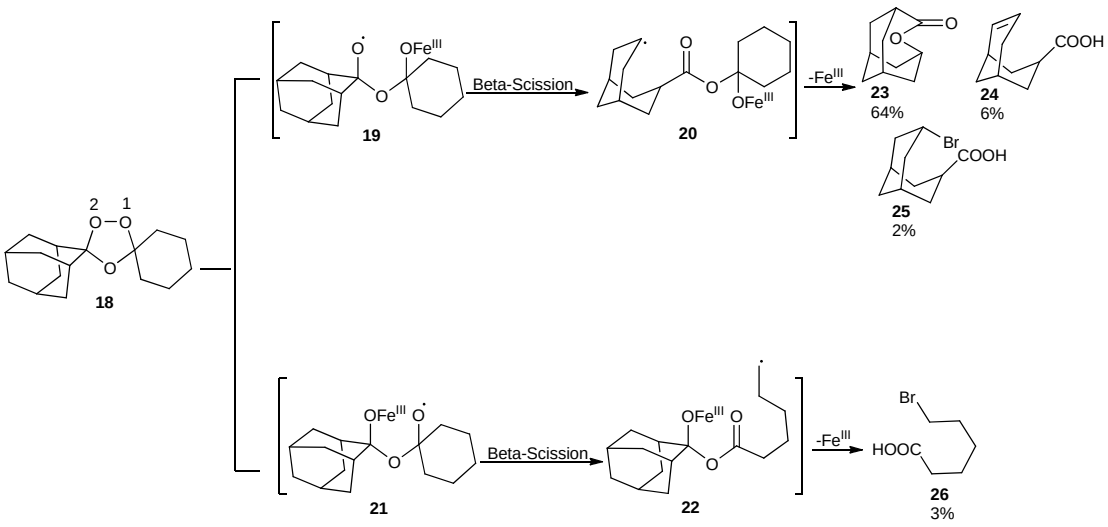
Section 1.6

Vennerstrom's ozonides

In 2004, Vennerstrom and coworkers reported the first example of a 1,2,4-trioxolane (ozonide) as a potential treatment for malaria.[54] Ozonide **13** was synthesized utilizing a Griesbaum co-ozonolysis of oxime **14** and ketone **15** to afford ozonide **16**.[55] Saponification of ester **16** to the corresponding acid **17** followed by amine coupling produced arterolane (OZ-277), **13**. Arterolane exhibits high activity against both chloroquine sensitive (NF54) and chloroquine resistant (K1) strains of P. *falciparum in vitro* (2.5 nM). Excellent activity is also observed *in vivo* with P. *berghei* infected mice (100% cure); this system is typically used as the standard mammalian model for malaria. Arterolane is now in phase III trials.[56] Further structural optimizations led to the discovery of OZ-439, which is currently in a Phase I clinical trial.[57,58] In an attempt to determine the MOA of arterolane, Vennerstrom investigated the reactivity of 1,2,4-trioxolanes towards heme. Vennerstrom reported that synthetic 1,2,4-trioxolanes can alkylate free heme,[59] but not the protein bound heme that is abundant in healthy cells.[60]

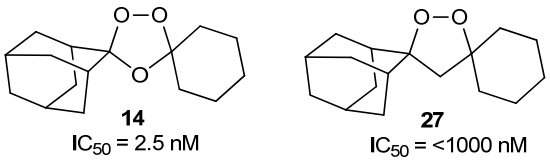


The postulated antimalarial activity of arterolane is derived from the formation of carbon centered free radicals. (A discussion of this mechanism in the context of 1,2,4-trioxolanes, 1,2,4-trioxanes, and 1,2,4-trioxpenaes will be discussed in section 5.) To test this hypothesis, model ozonide **18** was treated with $FeBr_2$ where iron can attack either O^1 or O^2 of the peroxide bond. [23] Experimentally, it was found that attack on O^1 is preferred and was rationalized by O^1 being more accessible then O^2. The resulting alkoxy radical **19** undergoes β-scission to afford carbon radical **20**. Intramolecular attack of the radical on the ester carbonyl and loss of Fe(II) forms products **23**-**25**, with lactone **23** being the predominant product. If iron attacks O^2, the resulting alkoxy radical (**21**) would be expected to undergo β-scission to provide carbon radical **22**. The only isolated product related to **22** is bromo acid **26** which is formed in very low yield.



It was unclear if the 1,2,4-trioxolane (ozonide) functionality was necessary or if the same level of antimalarial activity could be accomplished with a 1,2-dioxolane, a class of peroxide expected to have much greater stability.[61] However, only limited investigations of 1,2-dioxolanes as antimalarials have been reported.[62] To test the relative activity of 1,2-dioxolanes and 1,2,4-trioxolanes, Vennerstrom prepared and

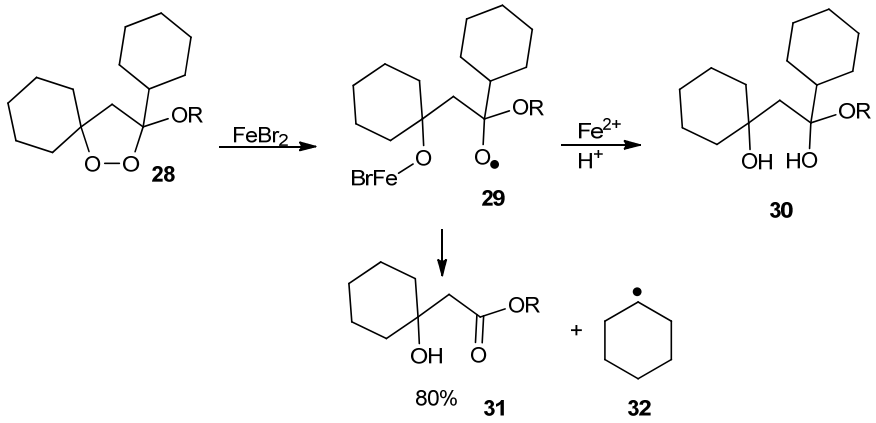
screened 1,2-dioxolane **27** for *in vitro* activity against P. *falciparum*.[63] The results reveal that 1,2-dioxolane **27** possesses virtually no activity when compared to ozonide **14**. Reaction of 1,2-dioxolane **27** with $FeBr_2$ did not lead to formation of carbon centered radicals through β-scission, as determined by trapping with 4-oxo TEMPO.[63] This suggests that the fate of the intermediate alkoxy radicals may be a crucial factor in the antimalarial activities of ozonides.



Section 1.7

Rationale for 3-alkoxy-1,2-dioxolanes

We became interested in 3-alkoxy-1,2-dioxolanes as potential antimalarials because they are isosteric to ozonides and should possess similar activity. The oxygen alpha to the peroxide bond should facilitate β-scission of one of the derived 3-alkoxy-1,2-dioxolane radicals, enhancing generation of a carbon centered radical. This hypothesis is supported by theoretical and experimental work reported by Erhardt on a related system.[22] Our hypothesis is illustrated for 3-alkoxy-1,2-dioxolane **28.** We postulated that 3-alkoxy-1,2-dioxolane **28** would undergo β-scission to provide radical intermediate **29**. This intermediate could either undergo quenching to afford **30** or β-scission to provide the desired free radical **32**. As can be seen, the alkoxydioxolanes undergoes reaction with $FeBr_2$ to predominantly furnish the expected products from formation and scission of an α-alkoxy radical.



The potential advantage of 3-alkoxy-1,2-dioxolanes relative to ozonides is their increased stability and the safety of their synthesis. By design ozonides, such as arterolane, require the use of ozone which can lead to the buildup of unstable intermediates. Although no stability issues have been reported by Vennerstrom, ozonides such as arterolane are high energy species that can undergo exothermic decomposistion.[64] In contrast, the synthesis of 3-alkoxy-1,2-dioxolanes can be done in the absence of ozone. Though the synthesises that follow do utilize some potentially hazardous reagents, the peroxide bond is always installed with molecular oxygen and not ozone. As a class, 1,2-dioxolanes exhibit increased stability over 1,2,4-trioxolanes, potentially making them a platform for development of drugs which are more field stable.[61]

Section 2

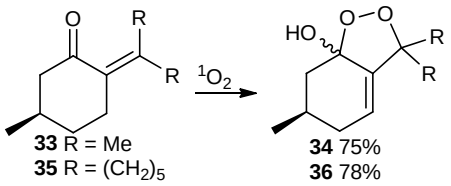
Section 2.1

Synthesis of 3-alkoxydioxolanes and 1,2-dioxolan-3-ols

This section describes investigations of the synthesis and reactivity of 3-alkoxy-1,2-dioxolanes and related species. A review of the synthesis of cyclic peroxides has been written by Bachi.[65]

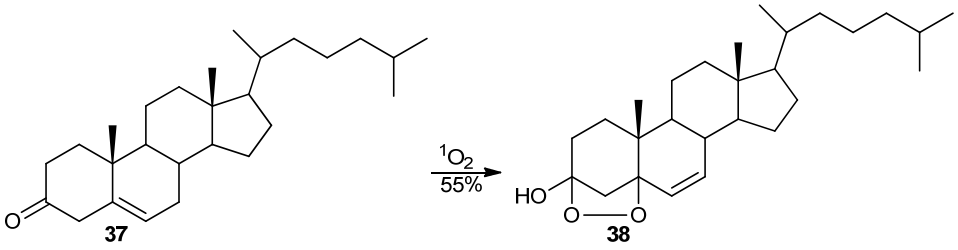
Singlet oxygen

In 1980, Ensley studied the addition of $^1O_2$ to α-β-unsaturated ketones and lactones.[66] In the course of this work, he reported the reaction of $^1O_2$ and (*R*)-(+)-pulegone, **33**, to form the 1,2-dioxolan-3-ol **34** in 75% yield. The oxygenation of more sterically hindered cyclohexylidine analog **35** produced 1,2-dioxolan-3-ol **36** as the major product in comparable yield.

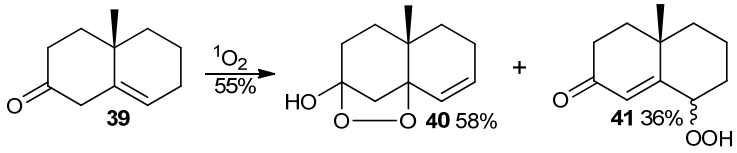


Several groups have investigated the reaction of cholest-5-en-3-one, **37**, with $^1O_2$ and reported the isolation of alcohols, after a reductive workup.[67-70] Note that in the example as well as an additional example below, $^1O_2$ is generated via dye-sensitized excitation of $^3O_2$ in the presence of substrate. From the location of the alcohols the authors extrapolated that they had been hydroperoxides before reduction. Based upon the work below, we can suggest the precursors of the alcohols were in fact 1,2-dioxolan-3-ols. In 1990, Schiesser studied the reaction of $^1O_2$ on cholest-5-en-3-one, **37**, and reported the first isolation of a 1,2-dioxolan-3-ol.[71] Schiesser reported that reaction of **37**

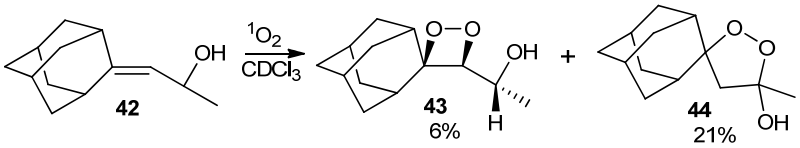
with $^1O_2$ in the absence of a reductive workup resulted in isolation of 1,2-dioxolan-3-ol **38** after chromatography.



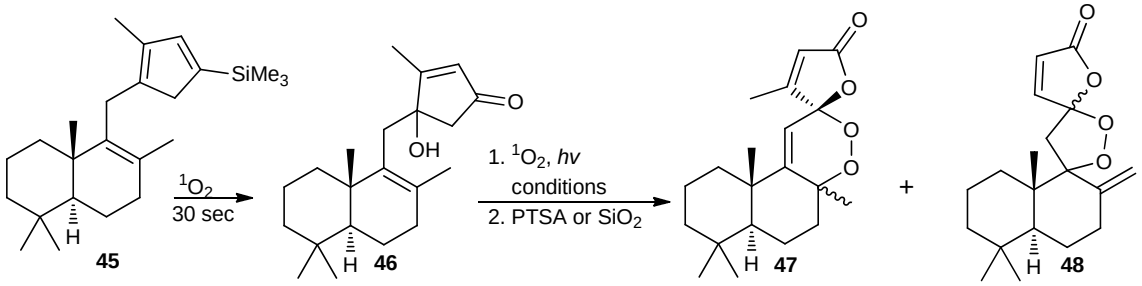
In the same report Schiesser disclosed that this reaction is not specific to cholest-5-en-3-one, but is also successful on a much simpler system. The treatment of octahydronaphthalenone **39** with $^1O_2$ afforded 1,2-dioxolan-3-ol **40** as the major product and hydroperoxide **41** as a minor product.



In 1999, Adam explored the reaction of $^1O_2$ and adamantylidene alcohol **42**.[72] The treatment of **42** with $^1O_2$ led to formation of **43** and **44** in approximately equal amounts as judged by ^1H NMR. However, **44** was the major isolated product. Dioxetane **43** was isolated almost exclusively as the *threo* isomer (shown), a result rationalized on the basis of hydroxyl-directed addition of $^1O_2$ to a single major conformer, which is favored by allylic 1,2-strain present in other conformations. 1,2-Dioxolan-3-ol **44** is presumably formed *in situ* cyclization of the initially generated hydroperoxide in the ene product. When the oxygenation was performed in a polar protic solvent such as methanol, dioxetane **43** was formed almost exclusively.



In the course of efforts directed towards the synthesis of (+)-Premnalane A Vassilikogiamakis and coworkers investigated the oxygenation of **45**. The desired spiroendoperoxide **47** was formed but as a minor product with the spiroalkoxydioxolane **48** formed as the major product.[73] The synthesis of **45** was accomplished in six steps from commercially available (+)-sclareolide. The authors found that **46** needs to be preformed via a oxygenation/fragmentation of the silylcyclopentadiene **45**. Subsequent addition of $^1O_2$ to **46** leads to a mixture of **47** and **48**. The authors screened several conditions for this reaction and determined that 3-alkoxy-1,2-dioxolane **48** was the preferred product under all conditions. Though desired product **47** was not formed exclusively, this route shows the power of $^1O_2$ to quickly form very complex peroxide containing systems.

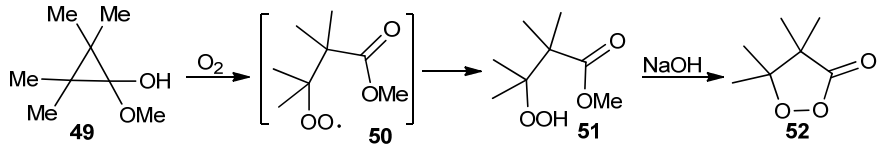


Conditions	47:48	Yield
$CDCl_3$, MB, 8°C	1:2	73%
MeOH, MB, 8°C	1:4	NR
Toluene, TPP, 8°C	1:1.3	NR
Toluene, TPP, 65°C	1:1.2	NR

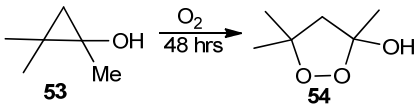
DePuy ring expansion

In 1969, DePuy reported the oxidative expansion of cyclopropanols under O_2 as a synthetic route to 1,2-dioxolan-3-ols.[74] Cyclopropanol **49** underwent ring expansion to hydroperoxyalkenoate **51** presumably through intermediate **50**. The cyclization of **51**

was accomplished under basic conditions to afford perlactone **52**, but no yield was reported.

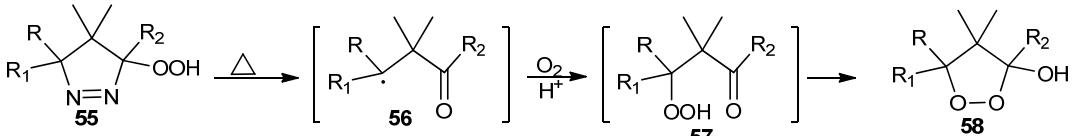


With this methodology established, DePuy showed that 1,2-dioxolan-3-ols can be synthesized via a similar approach. The expansion of **53** was reported to give the desired 1,2-dioxolan-3-ol **54**; however, no yield was reported.



Thermolysis

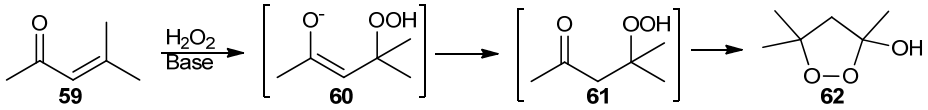
In 1992, Baumstark reported the thermolysis of azahydroperoxide **55** to generate 1,2,-dioxolane-3-ol **58**.[75] He postulated that the reaction proceeded through radical intermediate **56**, which rapidly trapped O_2 forming hydroperoxide **57**. *In situ* cyclization of hydroperoxide **57** affords the desired 1,2-dioxolan-3-ol **58**. The reaction worked well with a variety of substitution patterns in **55**, but the limiting factor in this methodology is the synthesis of the precursors, **55**. The reported synthesis of the azohydroperoxides is not general enough to make this a widely applicable reaction.[76]



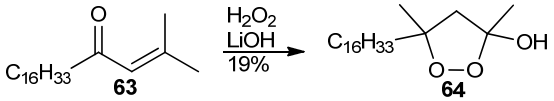
R	R_1	R_2	Yield
Ph	Ph	Ph	52%
Ph	Me	Ph	48%
Me	Me	Ph	36%
Ph	Me	Me	38%
Me	Me	Me	49%

Conjugate addition to α-β-unsaturated carbonyls

In 1958, Payne reported the first example of the addition of basic hydrogen peroxide to an enone, mesityl oxide.[77] The reaction was further explored by Rieche in 1960.[78] Early work used alkaline bases but more recent work has used hydrotalcite[79,80] or natural phosphate[81]. In all of these systems the reaction proceeds through conjugate addition of hydroperoxy anion to the enone generate an enolate, which protonates to generate hydroperoxy ketone **61**. Subsequent cyclization affords 1,2-dioxolan-3-ol **62**. However, the intermediate hydroperoxyenolate **60** can easily undergo a 3-*exo* cyclization to form an epoxide, which can often become the major product.

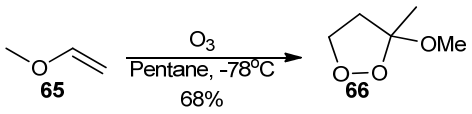


Attempts to use this methodology on more hydrophobic substrates have proved problematic. Dussault reported that the conversion of **63** to **64** can be accomplished, but required highly optimized conditions to obtain even modest yields.[82]



Ozonolysis of enol ethers

In 1984, Kuczkowski reported the first synthesis of 3-alkoxy-1,2-dioxolanes through ozonolysis.[83] In this initial report, the ozonolysis of methyl vinyl ether, **65**, in pentane afforded the desired 3-alkoxy-1,2-dioxolane **66**. The use of methyl formate or ethyl acetate as solvent led to lower yields, while the use of methanol resulted in the isolation of hydroperoxyacetal as the only product.

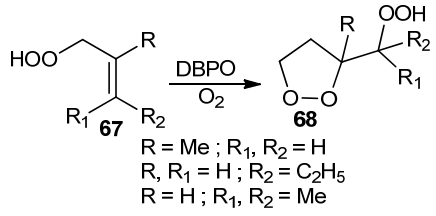


In subsequent work, Kuczkowski expanded this reaction to methoxy and ethoxyethene,[84] 1- ethoxypropene,[85] and 1,2-dimethoxyethene.[86] This synthetic approach is limited to unsubstituted 3-alkoxy-1,2-dioxolanes as decreased yield occurs with aliphatic substitution at C5 in **65**. In addition, the substituents cannot contain ozone reactive groups (for example, alkenes) other than the enol ether.

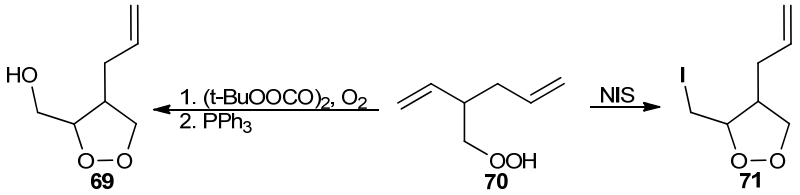
Radical cyclization

The 6-*exo* cyclization of a peroxyl radical onto an alkene for the synthesis of 1,2-dioxanes has been established and will not be discussed in detail.[87-90] To the best of my knowledge a radical cyclization has not been used for the synthesis of 3-alkoxy-1,2-dioxolanes or 1,2-dioxolan-3-ols, but I will discuss radical cyclization in the synthesis of 1,2-dioxolanes.

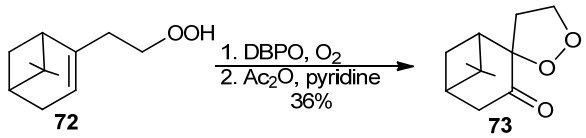
In 1976, Porter reported the synthesis of 1,2-dioxolanes through radical cyclization as part of a program towards the synthesis of prostaglandins.[88] Porter reported that reaction of hydroperoxy alkenes **67** in the presence of a radical initiator, di-tert-butyl-peroxyoxalate (DBPO), and O_2 resulted in cyclization to afford 1,2-dioxolanes **68**. No yields were reported other than to say that analytically pure samples were obtained.



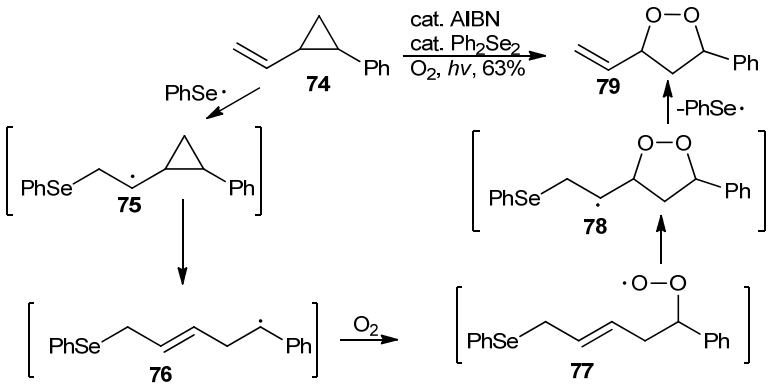
In 1989, Bloodworth undertook a study to determine the relative rate of 1,2-dioxolane vs. 1,2-dioxane formation via free radical cyclization.[91] Bloodworth found that radical cyclization of hydroperoxydiene **70** led to 1,2-dioxolane exclusively. The reaction was completed successfully under two different sets of conditions to afford either **69** or **71** as the final 1,2-dioxolane products, though no yields were reported.



In 2002, Mayrargue undertook a study of peroxyl radical cyclizations in an effort to develop 7-*exo*-trig cyclization.[87] A 7-*exo* cyclization (not shown) was unsuccessful, but the 5-*exo*-trig cyclization of hydroperoxyalkene **72** proceeded in low yield.



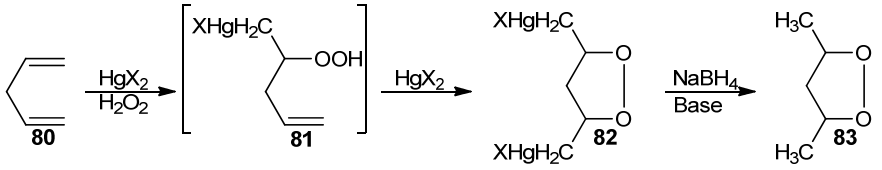
The ring opening of vinylcyclopropanes via a free radical process has been explored heavily in the literature[92-95] and has formed the core of an approach towards plakortide E.[96] The general mechanism is outlined below. Addition of phenylselenide radical to alkene **74** forms an unstable cyclopropylcarbinal radical, **75**. The homoallyl radical derived from opening of **76** is rapidly trapped by O_2, providing peroxide radical **77**, which after cyclization and loss of phenylselenyl radical affords the desired 1,2-dioxolane **79**.



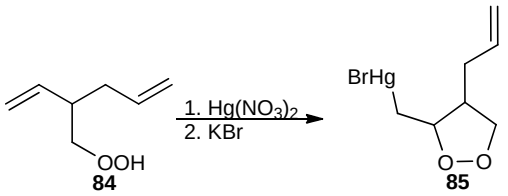
Electrophilic cyclization

To the best of my knowledge, the use of electrophilic cyclization with iodine or mercury to afford 3-alkoxy-1,2-dioxolanes has not been previously reported. The following section will discuss the synthesis of 1,2-dioxolanes via electrophilic cyclization.

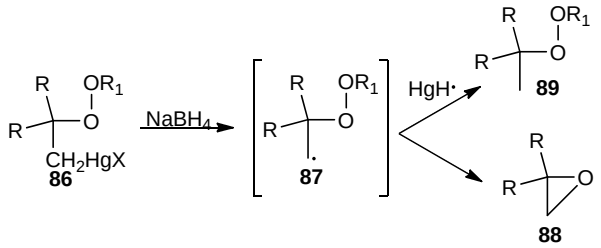
In 1978, Bloodworth reported the synthesis of 1,2-dioxolanes through peroxymercuration.[97] Diene **80** was first subjected to intermolecular hydroperoxymercuration to afford hydroperoxide **81** as a transient intermediate that undergoes an intramolecular electrophilic peroxymercuration to the 1,2-dioxolane. Demercuration was accomplished with $NaBH_4$ affording the desired 1,2-dioxolane **83**. A further study of this type of cyclization was reported by Bloodworth in 1980.[98]



Bloodworth later reported the relative rates of electrophilic cyclizations to form 1,2-dioxolanes and 1,2-dioxanes.[91] The major products of peroxymercuration were 1,2-dioxanes, but 1,2-dioxolanes were isolated as the minor product. The cyclization of hydroperoxide **84** was accomplished using $Hg(NO_3)_2$ to form 1,2-dioxolane **85**.

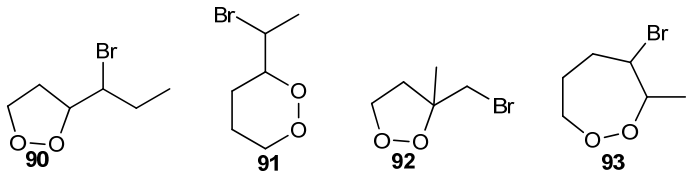


The problem that has plagued the formation of 1,2-dioxolanes using electrophilic cyclization has been the final demercuration or dehalogenation. As early as 1970 Bloodworth reported that decomposition of the peroxide occurred when transforming a β-peroxyorganomercurial to a halide.[99] In 1972, Bloodworth reported an investigation of the demercuration of β-peroxyorganomercurial with $NaBH_4$.[100] Radical scission of the peroxide bond leads to epoxide **88** while trapping of the radical leads to peroxide **89**. Bloodworth reported that this side reaction can be decreased through reduction at lower temperature, but cannot be eliminated. In subsequent work, Bloodworth reported that increased substitution of the peroxide R = Me increases the rate of the scission.[101]



In 1978, Porter undertook a study of the S_H scission reaction and concluded that the dihedral angle of the peroxide bond and the radical must be 180° for maximum reactivity.[102] When bromides **90-93** were treated with Bu_3SnH it was found that each of the bromides gave a different ratio of reduction (peroxide) vs. scission (epoxide). Bromide **91** is easily able to adopt the proper dihedral angle in a low-energy chair conformation and as a result undergoes predominantly scission. For the bromoalkyl dioxolanes **90** and **92**, the conformation allowing overlap of the radical with the backside

of the peroxide is disfavored, and reduction of the radical becomes the dominant reaction. In the case of a 4-bromo-1,2-dioxepane (**93**), the intermediate radical is unable to interact with the backside of the O-O and only reduction is observed.



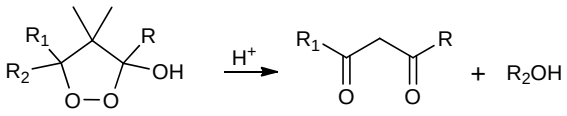
Compound	Peroxide (%)	Expoxide (%)
90	82	18
91	17	83
92	92	8
93	100	0

Section 2.2

Reactions of 1,2-dioxolan-3-ols and 3-alkoxy-1,2-dioxolanes

Acid-Mediated etherification

In 1994, Baumstark undertook an investigation of the etherification of 1,2-dioxolan-3-ols under acidic conditions.[103] Subjecting 1,2-dioxolan-3-ols **94-96** to acidic conditions led to decomposition at varying rates to the corresponding diketone. Qualitatively the order of decomposition was found to be **94**>**95**>**96**. Baumstark postulated the 1,2-dioxolan-3-ols underwent a Criegee-like decomposition with C-O migration to afford the diketone and a molecule of alcohol or phenol.



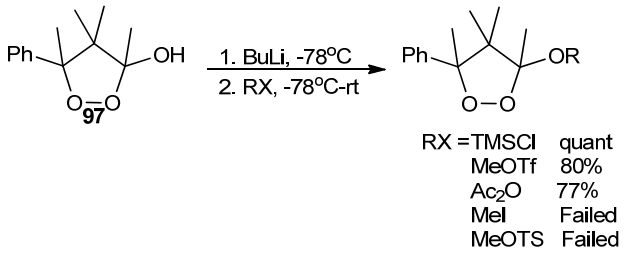
94 R=R_1=R_2=Ph
95 R=R_1=Me; R_2=Ph
96 R=Ph; R_1=R_2=Me

As **96** underwent decomposition the slowest, it was resubjected to the same conditions in the presence of methanol as a nucleophile. The result was the synthesis of

the 3-methoxy-1,2-dioxolane in good yield. This represented a new synthetic strategy that was later exploited by Dussault in his synthesis of 3-alkoxy-1,2-dioxolanes.[82]

Base-Mediated etherification

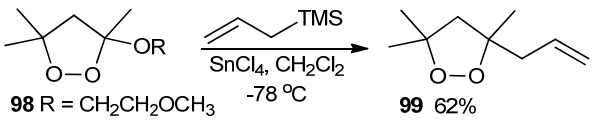
In 1994, Baumstark reported a base mediated etherification of 1,2-dioxolan-3-ols.[103] Pentasubstituted 1,2-dioxolan-3-ol, **97**, successfully underwent base mediated silylation (TMSCl), alkylation (MeOTf), and esterification (Ac_2O) in good yield. Attempts to use less active electrophiles such as MeI and MeOTs were unsuccessful. This reaction was only reported for pentasubstituted 1,2-dioxolan-3-ols.



Allylation of 3-alkoxy-1,2-dioxolanes

The allylation of either hydroperoxyacetals[104-106] or silyl peroxyketals[107] that result in the formation of 1,2-dioxolanes has been reported and will not be discussed in depth.

In 1999, Dussault reported the allylation of 3-alkoxy-1,2-dioxolanes to form 1,2-dioxolanes. The reaction of **98** with allyltrimethylsilane and $SnCl_4$ proceeded in good yield to afford 1,2-dioxolanes **99**. The authors suggested that the reaction involved ionization to a peroxide-stabilized carbenium anion. The best yield was obtained when $SnCl_4$ was used as opposed to $TiCl_4$ as the Lewis acid. A variety of silyl enol ethers were also successfully applied as nucleophiles under similar the reaction conditions (Not shown).



98 R = $CH_2CH_2OCH_3$ **99** 62%

Section 3

This section describes the synthesis of first generation 3-alkoxy-1,2-dioxolanes and evaluation of their antimalarial activity.

A portion of this work has been previously published.[108]

Section 3.1: Early work

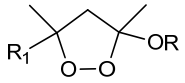
Section 3.2: Synthesis of 3-alkoxy-1,2p-dioxolanes

Section 3.3 Antimalarial results

Section 3.1

Early work on 3-alkoxy-1,2-dioxolanes

Previous work in the Dussault lab by Dr. Liu led to a new method for the synthesis of 3-alkoxy-1,2-dioxolanes.[82] Six of these 3-alkoxy-1,2-dioxolanes, **100-105**, were later tested against P. *falciparum* and showed promising *in vitro* activity (Table 2.1).[109-111] Inhibition was determined by measuring the uptake and incorporation of [^{3}H]hypoxanthine by the parasite compared to the control. Initial analysis of quantitative structure activity relationship (QSAR) data suggested the following: R should not be an aliphatic hydrocarbon (compare **100** and **105**); and, that the molecule as a whole not be too polar (compare **103** vs. **104)**. Two of the initial compounds with the best activity, **101** and **102**, share the common structural feature of an aromatic ring in the alkoxy side chain.



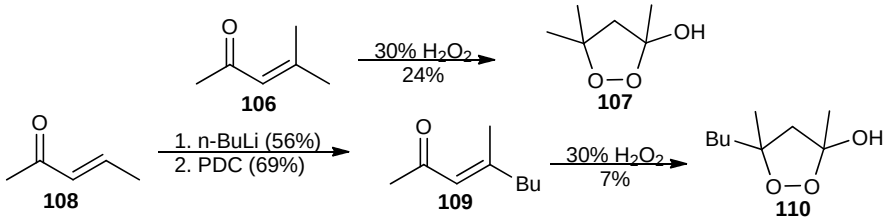
Compound	R_1	R	IC_{50} (nM)
100	Me	Heptyl	>1000
101	Me	Bn	472
102	Me	2-phenylethyl	415
103	Me	2-methoxyethyl	>1000
104	Bu	2-methoxyethyl	392
105	Bu	propyl	>1000

Table 2.1 Initial Screen of 3-alkoxy-1,2-dioxolanes

Section 3.2

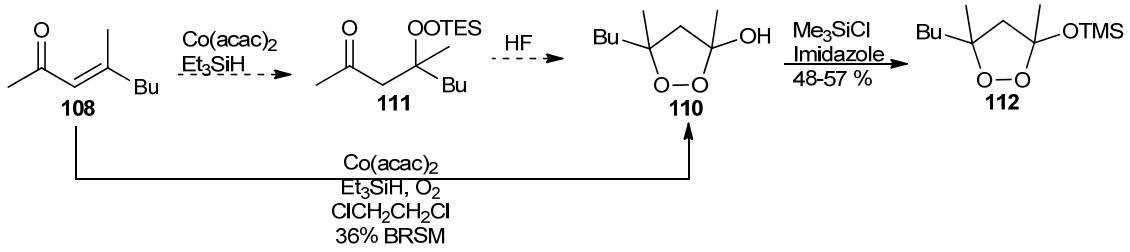
Synthesis of additional "first generation" 3-alkoxy-1,2-dioxolanes

These early results encouraged further exploration of the QSAR of 3-alkoxy-1,2-dioxolanes to gain more insight into which features affect activity. At this stage, I mainly focused on varying only the substitution on the alkoxy sidechain. The synthesis of **107** utilized addition of basic H_2O_2 to mesityl oxide, **106**.[77] The low yield was tolerated as mesityl oxide is both cheap and commercially available. The synthesis of **110** began with commercially available enone **108** which underwent a nucleophilic addition and oxidative rearrangement to afford enone **109** in moderate yield. However, conjugate addition of basic H_2O_2 to this more hydrophobic enone led primarily to the epoxide and gave the desired 1,2-dioxolan-3-ol, **110**, in low yield.



Since a route to ketone **109** was established, I decided to investigate Mukaiyama cobalt-mediated peroxidation for the insertion of the peroxide bond.[112] It was envisioned that the crude product of oxygenation, **111**, would cyclize in the presence of acid to form

the desired 1,2-dioxolan-3-ol, **110**. However, upon performing the oxygenation under standard conditions, analysis of the reaction by TLC found that only starting ketone **109** and 1,2-dioxolan-3-ol **110** were present in appreciable amounts. A faint spot that might have been **111** was present, but all attempts to isolate this spot were unsuccessful. The attractiveness of this route is the formation of **110** in a one-pot fashion. In addition, unreacted **109** can be recovered and resubmitted to the reaction conditions.

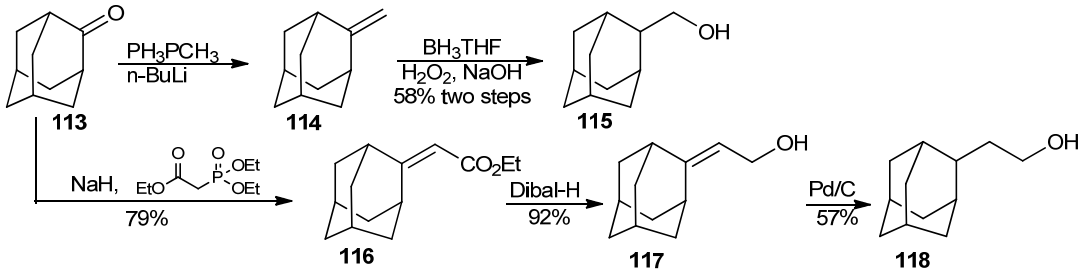


The Co-mediated oxygenation, while an improvement over the conjugate addition of H_2O_2, does have a couple of drawbacks. When the recovered ketone is resubmitted to the reaction conditions, the reaction does not always initiate. This issue can be circumvented by utilizing Isayama's protocol of adding a catalytic amount of t-BuOOH.[113] In addition, purification of 1,2-dioxolan-3-ol (**110**) is hampered by the co-elution of a species whose exact identity was never determined but was assumed to be a Co^{III} species based upon the green color. One solution to this problem is the use of a larger ratio of silica gel to compound. Another solution is to transform **110** into the trimethylsilyl ether **112**, which is easily purified.

With the synthetic route to the precursors established, it became necessary to decide which alkoxy sidechains would be employed. The best results in the initial screen were observed for substituents which contained an aromatic ring (Table 2.1). To determine if the beneficial effect of the aromatic ring was related to steric bulk, we became interested in the potential of an adamantane ring. In addition to allowing the

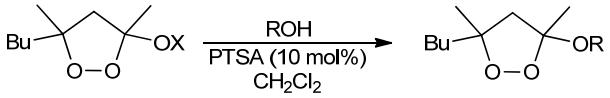
investigation of steric bulk, the adamantane ring allows investigation of isomeric modes of connectivity (1 vs. 2-adamantyl) to the alkoxide sidechain.

2-Adamantanemethanol (**115**) and 2-adamantaneethanol (**116**) were not commercially available and needed to be synthesized. Two different approaches were employed. The synthesis of **115** began with Wittig olefination of 2-adamantanone to afford alkene **114** which, without purification, was subjected to hydroboration/oxidation to provide 2-adamantanemethanol, **115**. A Horner-Wadsworth-Emmons olefination of 2-adamantanone afforded ester **116** which upon reduction with Dibal-H provided allylic alcohol **117**. Hydrogenation of **117** was accomplished over a Pd/C catalyst, but under these conditions the deoxygenated product was also isolated. This problem can be circumvented by hydrogenation over Pt/C. Regardless of which catalyst is used, 2-adamantaneethanol, **118** is isolated in moderate yield.



Acid catalyzed etherification of the 1,2-dioxolan-3-ols with a variety of alcohols proceeded in low yield and required long reaction times. It was thought that the corresponding OTMS ether **112** might be a more effective electrophile that would react to generate the same carbocation as the 1,2-dioxolan-3-ol but would not liberate water. This approach worked better than expected, providing improved yields of 3-alkoxy-1,2-dioxolane, **119**, after much shorter reaction times as compared with the free alcohol. The

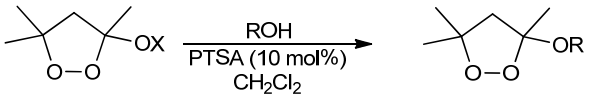
superiority of the trimethylsiloxydioxolanes as electrophiles for transetherification was also observed for other backbones as can be seen in Table 2.2.



Compound	X	R	t (h)	Yield (%)
119	H	Bn	>12	60
119	TMS	"	0.3	60
120	TMS	Cyclohexanemethyl	2	86
121	H	CH_2CH_2Ph	>12	30
121	TMS	"	1	80
122	TMS	Cyclohexaneethyl	2	82
123	TMS	$CH_2CH_2CH_2Ph$	3	92
124	H	1-adamantanemethyl	48	26
124	TMS	"	1	62
125	H	2-adamantanemethyl	72	34
125	TMS	"	1	57
126	H	1-adamantaneethanol	72	43
126	TMS	"	1	72
127	H	2-adamantaneethanol	12	23
127	TMS	"	1	60
128	H	Butyl	48	56

Table 2.2 C5-Bu/C5'-Me series

With the 5,5'-butyl/methyl series complete, I undertook the synthesis of the 5-methyl/methyl series. The same strategy as described above was employed for this series as well. As expected, utilization of the trimethylsiloxydioxolane led to improved yields and shorter reaction times compared with the use of 1,2-dioxolan-3-ol.



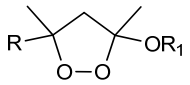
Compound	X	R	t (h)	Yield (%)
129	H	Bn	3	66
129	TMS	"	<0.1	74
130	TMS	Cyclohexanemethyl	2	84
131	H	CH_2CH_2Ph	5	73
132	TMS	Cyclohexaneethyl	2	71
133	H	$CH_2CH_2CH_2Ph$	2	71
134	H	1-adamantanemethyl	12	33
134	TMS	"	3	65
135	H	2-adamantanemethyl	48	75
135	TMS	"	2	62
136	H	1-adamantaneethyl	12	16
136	TMS	"	1	76
137	H	2-adamantanethyl	12	59
138	H	Butyl	3	56
138	TMS	Butyl	1	51

Table 2.3 C5 /C5' Me series

Section 3.3

Antimalarial results and discussion

The results of *in vitro* antimalarial screening for 3-alkoxy-1,2-dioxolanes **119-138** are shown in Table 2.4.[109-111]



Compound	R	R_1	IC_{50} nM
119	Bu	Bn	140
120	Bu	Cyclohexanemethyl	69
121	Bu	CH_2CH_2Ph	76
122	Bu	Cyclohexaneethyl	91
123	Bu	$CH_2CH_2CH_2Ph$	27
124	Bu	1-adamantanemethyl	136
125	Bu	2-adamantanemethyl	118
126	Bu	1-adamantaneethyl	155
127	Bu	2-adamantaneethyl	169
128	Bu	Butyl	1400
129	Me	Bn	472
130	Me	Cyclohexanemethyl	83
131	Me	CH_2CH_2Ph	415
132	Me	Cyclohexaneethyl	132
133	Me	$CH_2CH_2CH_2Ph$	46
134	Me	1-adamantanemethyl	289
135	Me	2-adamantanemethyl	257
136	Me	1-adamantaneethyl	252
137	Me	2-adamantaneethyl	218
138	Me	Butyl	>10000

Table 2.4 Antimalarial results

I was excited to see several of the molecules with IC_{50} values <100 nM. When analyzing the QSAR data the most obvious trend is the importance of the substitution at C5: dioxolanes with R = Bu are significantly more active than those with R = Me. Only the trends within the R = Bu series will be discussed in detail; the same trends also hold in R = Me series. The most active compounds **123** and **133** were synthesized at a later date. They are included in this table as they are structurally most closely related to the

"first generation" shown here. Of the originally synthesized compounds, **131** was the most active and demonstrates that the length of the alkoxy sidechain is important, for example **119** vs. **121**. The use of a cyclohexane ring in the sidechain instead of the aromatic ring leads to a slight decrease in activity, as can be seen for **120** and **122**. When a bulkier adamantyl group is present in the alkoxy side chain (**124**-**127**) there is a decrease in activity, regardless of connectivity. Taken together, these results suggest that the most active compound will have a bulky group at C5 and an alkoxy sidechain that is phenylethyl.

These results show that the 3-alkoxy-1,2-dioxolanes are a promising scaffold for potential antimalarials and support further exploration of this framework is needed. Given that there was limited rational design to the molecules that were initially synthesized, it is reasonable to believe that even higher activities are attainable. These early results give the impression that higher activities can be obtained by placing a bulkier group or aromatic ring here or there, but subsequent work will reveal that identification of optimal attributes within this system is more complicated.

Section 4

Second generation alkoxydioxolanes: design and synthesis

Portions of the work described in this section have been previously published.[108]

This chapter has been organized in the following sections:

Section 4.1: Rationale

Section 4.2: Incorporation of spirocycle at C5/C5'

Section 4.3: Effect of ring size at C5/C5'

Section 4.4: Investigation of the nature of the radical leaving group at C3

Section 4.5: Spirocyclic alkoxydioxolanes

Section 4.6: Future directions

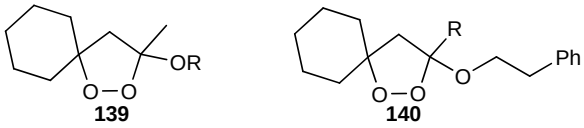
Section 4.7: Experimentals

Section 4.1

Rationale for new series

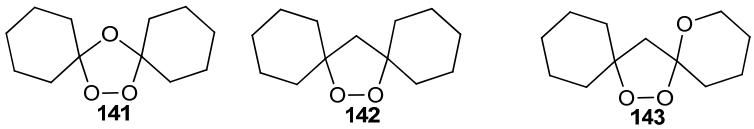
With the knowledge that even simple 3-alkoxy-1,2-dioxolanes possessed significant antimalarial activity, I set about optimizing the structures to maximize activity. I approached this optimization from three different angles. The first was incorporating cyclic restraint in the form of a spirocyclohexane at the C5 position forming a family of spirocycles exemplified by **139**. The second approach is related to our hypothesis, which was that the postulated activity of 3-alkoxy-1,2-dioxolanes is related to a carbon centered radical generated at the C3 position. We therefore predicted

that changing the proposed radical leaving group to a better leaving group should lead to increased activity (**140**).



139 **140**

The third approach was to synthesize a molecule that more closely resembled Vennerstrom's ozonides enabling a direct comparison.[63] As described in the introduction, Vennerstrom reported that 1,2-dioxolanes such as **142** had essentially zero antimalarial activity even though analogous ozonides (**141**) were very potent. We hypothesized that this difference reflected a lower rate of β-fragmentation of the intermediate alkoxy radical compared with the α-alkoxy alkoxy radical derived from the ozonides. We hypothesized that the faster rate of fragmentation would be restored in 3-alkoxy-1,2-dioxolanes such as **143**. Like the ozonides, the alkoxydioxolanes place an oxygen on the peroxide-bearing carbon. Support for this approach comes from McCullough's work demonstrating that 1,2,4-trioxanes undergo rapid β -scission forming a carbon centered radical.[22]



141 **142** **143**

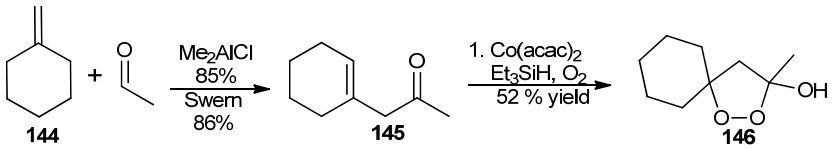
IC_{50} = 1900 nM IC_{50} = >4000 nM

Section 4.2

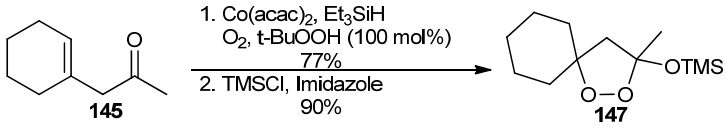
Incorporation of a spirocycle at C5/5'

I began with the synthesis of the spirocyclic series represented by **139**. I envisioned a Mukaiyama cobalt peroxidation of an unsaturated ketone as the key step to insert the peroxide. A Prins[114] reaction of **144** with acetaldehyde furnished the homoallylic alcohol which underwent Swern oxidation to afford ketone **145**. However,

peroxidation of ketone **145** under Mukaiyama conditions proceeded in moderate yield with starting material being recovered (~30%).[112]

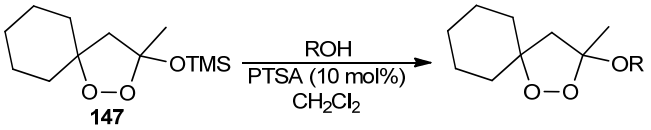


Isayama reported that the use of catalytic *t*-BuOOH led to decreased reaction times and increased yields in the Mukaiyama cobalt-mediated peroxidation.[113] Serendipitously, I discovered that the use of 100 mol % of *t*-BuOOH as an additive leads to both rapid initiation and increased yield of **146**. This protocol, while more efficient in terms of reactivity, still requires optimization as 1,2-dioxolan-3-ol **146** is not produced as the sole product. A TLC of the reaction appears to show some uncyclized intermediate (hydroperoxy ketone), but all attempts to force the cyclization with the use of TsOH led to decomposition. The more significant problem with this approach is the formation of an alkene impurity that is not present in reactions conducted in the absence of *t*-BuOOH or in the presence of catalytic amounts of *t*-BuOOH. The impurity can be removed by ozonolysis, creating a tradeoff of increased yield versus an additional purification step.



The transetherification of **147** was undertaken with a variety of primary alcohols. Both aromatic and non-aromatic containing alkoxy sidechains were introduced in this manner. In all cases the transetherification proceeded in good yield to afford compounds **148-155**. It was subsequently discovered that 3-alkoxy-1,2-dioxolanes derived from 2-phenylethanol (**148**) was contaminated with less than 5% of the acetal formed from 2-phenylethanol and bis-2-phenylethylacetal of 2-phenylacetaldehyde. Although I could

detect very little of the aldehyde as an impurity in the 2-phenylethanol used as a reagent, the problem was solved by using a fresh supply of reagent.



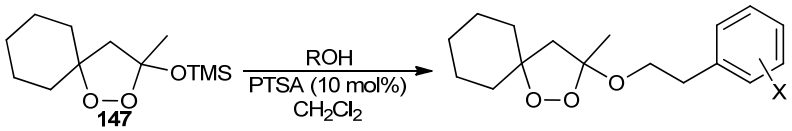
Compound	R	t (h)	Yield (%)	IC_{50} (nM) NF54
148	2-phenylethyl	2	86	9
149	Bn	1	57	19
150	3-phenylpropyl	2	88	19
151	4-phenylbutyl	3	72	17
152	2-cyclohexylethyl	2	81	41
153	Cyclohexylmethyl	2	84	30
154	1-adamantylethyl	24	70	29
155	1-adamantylmethyl	2	89	35

Table 2.5 spirocycle at C5/5'

The screening of this set of molecules provided some important QSAR data that helped guide subsequent synthesis. All of the different ethers **148**-**155** demonstrate good or better activity then the "first generation" ether (Section 3), suggesting the most important design element is the C5/C5' spirocycle group. The most active molecule in this series, **148**, contains a phenylethyl side chain. The two carbon spacer between the oxygen and the arene was optimal, but the chain could either be shortened or lengthened, **149**-**151**, with only slight decrease in activity. As was found in the earlier series, there was a loss of activity when the non-aromatic analogs were employed (**148** vs. **152**, **149** vs. **153**), though again this decrease was minor. Finally, incorporation of adamantane as a bulky non-aromatic group in the alkoxy sidechain is effective, but led to a lower IC_{50} than the aromatic analog.

Since the best activity in 3-alkoxy-1,2-dioxolanes was observed in substrates containing an aromatic ring in the ether sidechain, Dr. Vennerstrom suggested that I

complete a Topliss scheme. The Topliss scheme, developed by John Topliss provides a pathway for modifying the substitution around an aromatic ring to most rapidly identify the derivatives with the best activity.[115,116] Due to the time delay between synthesis and biological testing, I did not follow the Topliss scheme literally. Instead, I synthesized several "Topliss" generations of 3-alkoxy-1,2-dioxolanes which were submitted for biological testing. The alkene impurity formed as a byproduct in the *t*-BuOOH mediated synthesis of **147** complicated the purification of this series. Initially, I hoped it would be possible to adequately purify the compounds by HPLC, but this was not the case. It became necessary to ozonize 3-alkoxy-1,2-dioxolanes **156-163** in a separate step prior to chromatography. The majority of the compounds were not affected, but electron rich substrates such as **157** and **165** underwent significant decomposition.



Compound	X	t (h)	Yield (%)	IC_{50} (nM) NF54	IC_{50} (nM) K1
148	H	-	-	9	ND
156	4-Cl	3	61	18	13
157	4-OMe	24	39	15	14
158	4-Me	2	65	18	15
159	3,4-Cl	3	22	18	20
160	3-Cl	3	37	19	17
161	4-F	3	71	15	14
162	4-tBu	3	65	23	19
163	4-OH	4	62	11	11
164	2-Cl	3	57	18	16
165	4-Br	3	47	29	30

Table 2.6 Topliss results

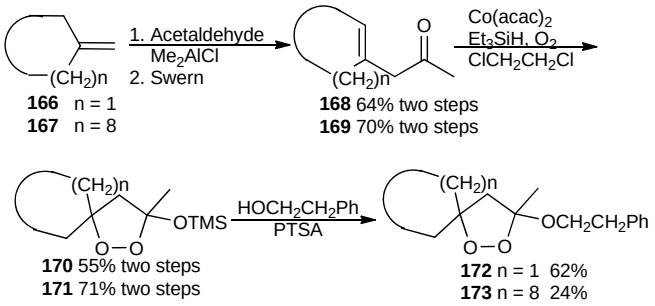
Compounds **156-165** were tested *in vitro* against both chloroquine-sensitive (NF54) and chloroquine-resistant (K1) strains of P. *falciparum* and all exhibited excellent activity.[109-111] Moreover, in almost all cases **156-165** exhibit as good if not better activity

against chloroquine-resistant malaria as against chloroquine-sensitive malaria. Analyses of the results from a Topliss perspective show they do not follow the expected activity trends. Since p-chlorophenol derivative **156** was less active than unsubstituted arene **148**, it was expected that p-methoxyphenol derivative **157** would be more active, however, this is not the case. These results suggest that the sterics or electronics of the substituents of the aromatic ring are not a major factor in activity. The fact that the substitution of the aromatic ring does not significantly affect activity suggests the ring may provide a synthetic handle to synthesize a more diverse set of compounds.

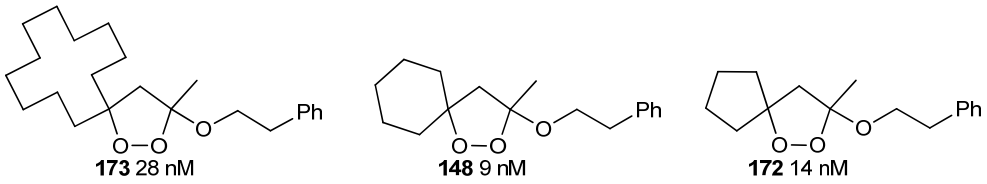
Section 4.3

Effect of ring size at C5/C5'

O'Neill reported that the antimalarial activity of 1,2,4,5-tetraoxanes could be modified by altering the attached ring in the following sequence: cyclohexane < cyclodecane < adamantyl.[25] This report prompted me to briefly explore the effect ring size at the C5 position in 3-alkoxy-1,2-dioxolanes to see if it follows the trend reported by O'Neill. I prepared the C5,5' spirocyclopentane (5-membered) and the spirocyclodecyl (12-membered) rings following a similar strategy to that used for the synthesis of **148**. The synthesis began with alkenes **166/167**, which readily underwent Prins[114] addition and Swern oxidation to afford ketones **168/169**. As expected, the cobalt-mediated peroxidation followed by silylation afforded the trimethylsiloxy alkoxydioxolanes **170/171**. Finally, transetherification with 2-phenylethanol under acidic conditions afforded the desired 3-alkoxy-1,2-dioxolanes **172/173**. Both of the final compounds were accompanied by an alkene impurity, which could be removed by ozonation followed by HPLC purification.



In vitro testing against P. *falciparum* revealed a decrease in activity as the ring size either increased or decreased.[109-111] This does not follow the trend extrapolated from O'Neill's work. Though **172/173** are less active then **148**, they possess good activity and show how robust the system is to changes away from the 3-alkoxy-1,2-dioxolane core. If, for example, activity of **148** was related to binding the spirocyclohexyl into a cleft or pocket, it would be expected that **173** would have virtually no activity as the larger molecule would not be able to fit in the same pocket as **148**. These results appear to indicate that the size of the ring at C5 is important but not critical to activity.

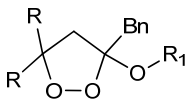


Section 4.4

Improved leaving group

Based upon the hypothesis that the antimalarial activity is related to ejection of a carbon radical from the intermediate α-alkoxyl radical, I wanted to investigate alterations of the putative leaving group. To test this hypothesis I prepared compounds **174-176**. I postulated that activity would increase with the ability of the leaving group to stabilize a developing radical, and should follow the trend **174**>**175**>**176**. The synthesis of **176** (phenylethyl leaving group) as a negative control was undertaken for two reasons. The

first is that it should behave in a similar manner to methyl in terms of radical stabilization while possessing steric bulk more similar to benzyl, enabling a more direct measure of the effect the leaving group has on activity. Synthesis of both the C5 Me/Me and spirocyclohexyl series was undertaken as it was not known if substitution at that position would have an effect on activity.



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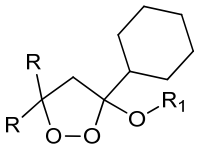

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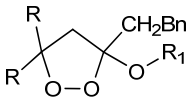
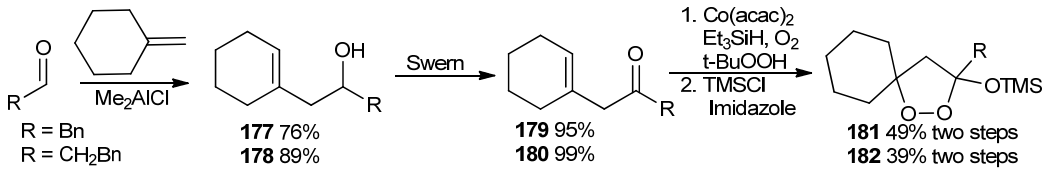


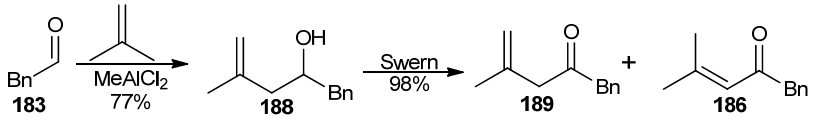
176

The synthesis of **181** and **182** began with the Prins[114] reaction of the appropriate aldehyde to afford homoallylic alcohols **177** and **178.** The alcohols underwent Swern oxidation to afford ketones **179** and **180**. Subsequent Mukaiyama cobalt-mediated peroxidation with the *t*-BuOOH modification was followed by silylation to afford siloxydioxolanes **181** and **182**.

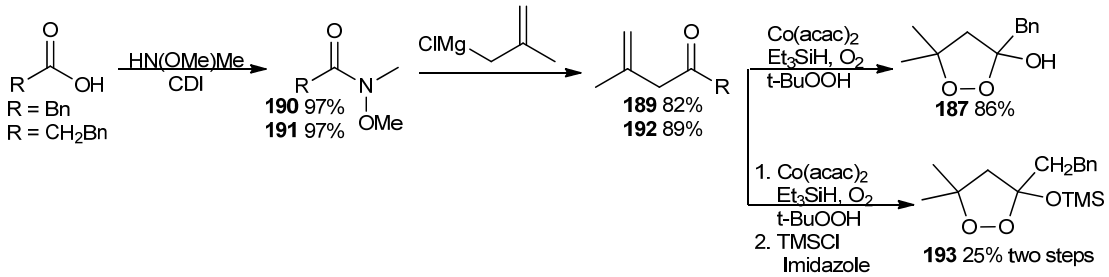


The synthesis of **187** began with the addition of Grignard **184** to aldehyde **183** to provide alcohol **185**. Oxidation of the alcohol with PDC afforded ketone **186.** Cobalt-mediated peroxidation under Isayama conditions[113] provided 1,2-dioxolan-3-ol **187**. The yield for this reaction is low, in line with my previous experiences for enones. This low yield, in conjunction with the low yields of the previous steps, made this route not viable.

I had observed that cobalt-mediated peroxidation of deconjugated systems often proceed in higher yields. I therefore was interested in preparing β-γ-unsaturated ketone **258**. I decided to utilize a Prins reaction of **183** with isobutylene to afford **188**. However, the Swern oxidation of **188** was accompanied by isomerization of the alkene leading to isomers **189** and **186**.

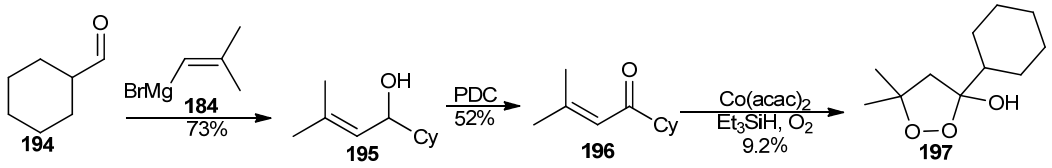


Use of a Weinreb amide would allow the formation of the ketone without having to perform any oxidation. Formation of the Weinreb amides, **190** and **191**, from the corresponding acids was accomplished in excellent yield. Addition of methylallylmagnesium chloride proceeded in good yield to afford **189** and **192**. However, if excess 2N HCl was used during workup, isomerization of the alkene does become a problem. The synthesis of dioxolanes **187** and **193** was completed by cobalt-mediated peroxidation and silylation.

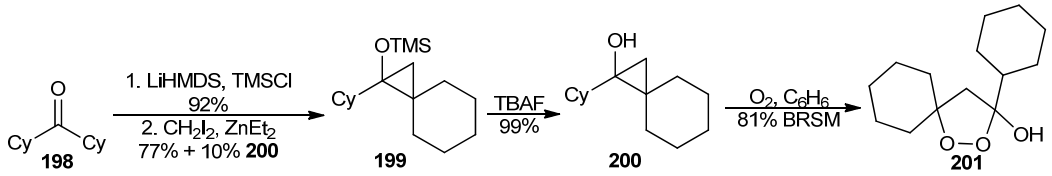


The final molecules in this class that I wished to synthesize would incorporate a cyclohexane at C3. The addition of Grignard **184** to aldehyde **194** afforded alcohol **195** in moderate yield. The oxidation of **195** proceeded to complete conversion only with PDC; the use of MnO_2 or Swern oxidation either led to incomplete oxidation or a mixture of products. Unfortunately, the cobalt-mediated peroxidation proceeded in very low

yield to give 1,2-dioxolan-3-ol **197**. This route was deemed impractical due to the series of low yielding steps and the difficulty in obtaining the cyclohexylidene analog of **184**.

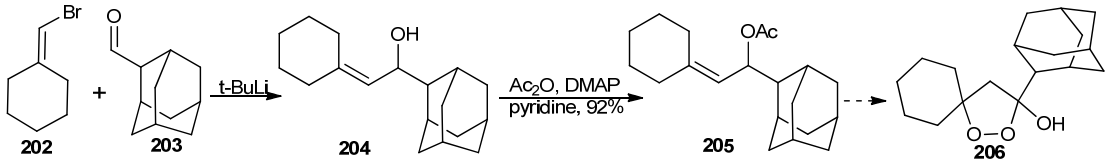


This setback encouraged me to employ a DePuy ring expansion to install the peroxide moiety.[74] The attractiveness of the DePuy expansion in this system was the ease of setup and the mildness of the conditions. The synthesis began with commercially available dicyclohexyl ketone **198** which was converted to the silyl enol ether. Simmons-Smith reaction formed cyclopropane **199**. The workup of the Simmons-Smith reaction led to formation of 10% of the deprotected product **200**. If I was to perform this synthesis again, I would perform an acidic workup and isolate only cyclopropanol **200**. Deprotection of **199** was accomplished with TBAF to afford cyclopropanol **200** in excellent yield. Finally, DePuy oxidative ring expansion proceeded in good yield to afford desired 1,2-dioxolan-3-ol **201**. In the course of scaling the reaction up, I found this process to be less efficient at larger scale. In addition, the use of distilled benzene was found to be vital as the use of benzene from the bottle did not work even with the addition of triethylborane.



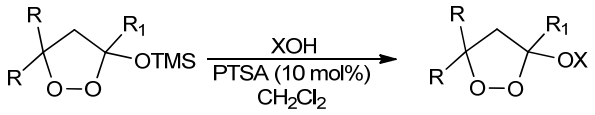
I attempted to extend this methodology to the 3-adamantyl analog of **206**, but this endeavor turned out to be more challenging than anticipated. Initially, a route that utilized the Mukaiyama cobalt-mediated peroxidation was planned on the ketone derived

from **204**. However, the synthesis of the precursor allylic alcohol (**204**) proved more difficult then anticipated. The synthesis of **202** was uneventful. However, preparation of **203** by oxidation of the corresponding alcohol was plagued by formation of the formate as a major byproduct. At this point it was decided that it was more important to know if the planned cobalt peroxidation would work, so the synthesis continued with impure **203**. Reaction of the alkenyl lithium of **202**, generated *in situ*, and aldehyde **203** afforded **204**. The oxidation of **204** could not be accomplished with a variety of oxidants including Swern, PCC, MnO_2, or Dess-Martin. Undeterred by this set back, I converted alcohol **204** to acetate **205**. Unfortunately, the acetate also failed to undergo Mukaiyama cobalt-mediated peroxidation.



With most of the desired 1,2-dioxolan-3-ol precursors in hand, I performed a series of acid catalyzed transetherifications yielding 3-alkoxy-1,2-dioxolanes **207-213**. The resulting 3-alkoxy-1,2-dioxolanes were tested *in vitro* against P. *falciparum* (NF54).[109-111] As predicted from the previous generations, the molecules containing a spirocyclohexyl at C5 led to increased activity over those with C5/5' dimethyl. According to the leaving group hypothesis, benzyl **210** should be the most active molecule of the series **210-213**; instead it was the least active. In contrast, **213** which was predicted to be middle of the road, was very active. The negative controls **211** and **212** were also very active. Closer examination of the screening data reveals that none of the modifications were able to increase activity above the level of **148**, which features a C3 Me as the putative leaving group. Sterically, **148** and **211** are almost identical and have

virtually the same activity. The inhibition data on **212** suggests that having too much steric bulk leads to decreased activity. The only constant in these results is that the activity is not greatly improved by having a better radical leaving group at C5, as evidenced by the lower activity of **207** and **210**.



Compound	R	R_1	X	t (h)	Yield (%)	IC_{50} (nM) NF54
207[A]	Me	Bn	Me	72	73	968
208	Me	CH_2Bn	Me	>12	99	23
209	Me	CH_2Bn	CH_2Bn	5	61	30
210	$(CH_2)_5$	Bn	Me	>12	93	335
211	$(CH_2)_5$	CH_2Bn	Me	5	66	8.6
212	$(CH_2)_5$	CH_2Bn	CH_2Bn	6	66	21
213 [A]	$(CH_2)_5$	C_6H_{10}	Me	>12	90	9.2
148	$(CH_2)_5$	Me	CH_2Bn	2	86	9

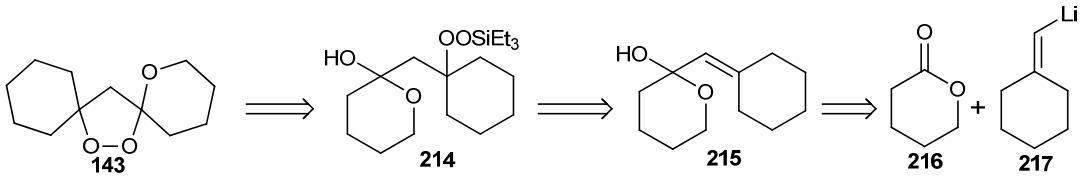
Table 2.7 [A]Free 1,2-dioxolan-3-ol was employed

Section 4.5

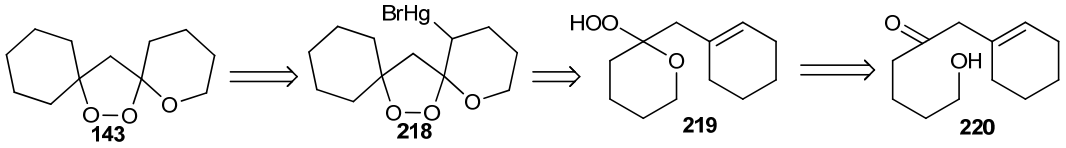
Spirocyclic 3-alkoxy-1,2-dioxolanes

The final target in this series was **143**, which would be a close structural mimic for one of Vennerstrom's ozonides and would therefore allow comparison of the 3-alkoxy-1,2-dioxolanes and the ozonides. Retrosynthetically, I envisioned **143** being formed via an acid catalyzed ring closure of **214**, with the key step in this synthesis being a Mukaiyama cobalt-mediated peroxidation of alkenyl hemiacetal **215**. It was hoped that **214** could be quickly assembled via addition of alkenyl lithium **217** to lactone **216**. A test reaction showed that n-BuLi could be added successfully to **216**. However, when this reaction was repeated with alkenyl lithium **217** the desired lactol **216** was either not

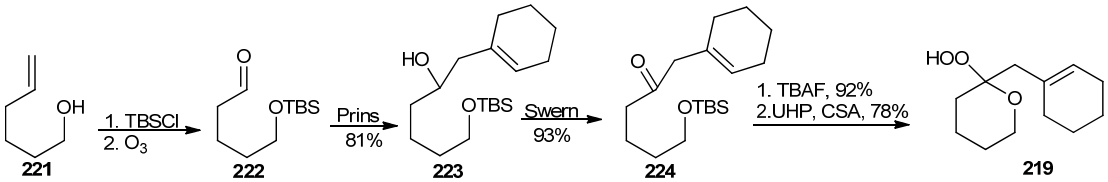
formed or formed in very low yield as part of a mixture.



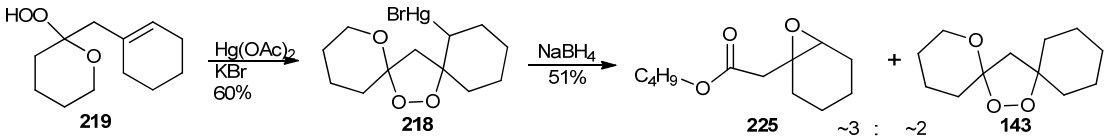
Ultimately, I decided upon a route that would establish the 1,2-dioxolane via electrophilic cyclization. Hydroxyalkenone **220** would be treated with acidic hydrogen peroxide to form hydroperoxyacetal **219**. Cyclization with Hg (II) would provide organomercurial **218**, which upon demercuration would afford the target 3-alkoxy-1,2-dioxolane **143**.



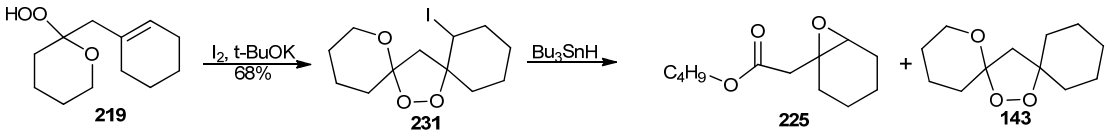
The synthesis of the cyclization precursor **219** began from commercially available 5-hexen-1-ol, **221**. The alcohol was protected as the OTBS ether and the alkene was subjected to ozonolysis, affording aldehyde **222**. Prins reaction of **222** with methylenecyclohexane, followed by a Swern oxidation of the resulting alcohol afforded ketone **224**. Treatment of **224** with TBAF resulted in deprotection to the free alcohol. Some isomerization of the alkene occurred during the desilylation. This was of no concern as a treatment of the mixture under acidic conditions with urea hydrogen peroxide afforded solely **219**. [117]



Unsaturated hydroperoxide **219** underwent electrophilic cyclization with $Hg(OAc)_2$ to afford organomercurial **218**, as a mixture of isomers. Demercuration with $NaBH_4$ led to a mixture of epoxide **225** and 3-alkoxy-1,2-dioxolane **143**. The epoxide arises through a S_Hi reaction of the intermediate radical. Demercuration with $HsnBu_3$, a method reported by Bloodworth, was unsuccessful on this system.[118]

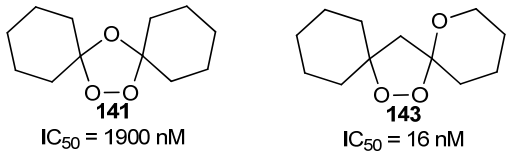


I therefore pursued the corresponding peroxyiodination assuming that dehalogenation of an iodide would be more easily accomplished. Peroxyiodination of **219** furnished dioxolane **231** in moderate yield. Initially, reduction of the iodide was performed with a dilute solution of $HsnBu_3$ in benzene, but the S_Hi product dominated. Increasing the concentration of Bu_3SnH resulted in the desired peroxide **143** becoming the major product. The use of neat Bu_3SnH leads to almost complete suppression of **225** formation. Separation of **225** and **143** could only be accomplished by HPLC, so the crude mixture was treated with a hydride reagent to selectively reduce **225** to the more polar alcohol. Dibal-H did not lead to complete consumption of ester **225**, but $LiAlH_4$ was employed successfully. Since an alkyl tin was used in the final stages of this synthesis, there was concern that residual tin might be present in **143**. ICPMS revealed that tin was present, but only in ppb concentration.



Conc. of $HSnBu_3$			
0.02 M benzene (41% overall)	7	:	2
Neat (41% **143** after LAH)	1	:	19

When **143** was tested against P. *falciparum in vitro* the reported activity was 16 nM.[109-111] This result is in line with the other 3-alkoxy-1,2-dioxolanes that have tested, but is a significant improvement compared with the corresponding Vennerstrom ozonide **141**.[119] An explanation for this difference in activity is not known, but suggests the need for further exploration of these dispiro systems.



Section 4.6

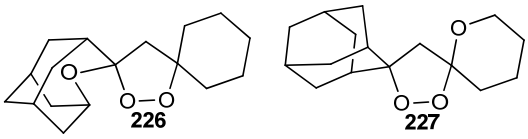
Future directions

The following discussions suggest potentially profitable future research directions related to the results described within this section.

For the cyclohexyl 3-alkoxy-1,2-dioxolanes (sec. 2.1), future work needs to focus on the incorporation of amine containing sidechains. Throughout this work the presence of an aromatic ring has led to increased activity and the Topliss work has shown the robustness of this system. By robust I mean that the 3-alkoxy-1,2-dioxolanes do not appear to lose significant efficacy despite changes made around the 1,2-dioxolane core. It would have been expected that as changes were made to the aromatic ring there would have been an increase or decrease in activity, but, instead it remained fairly constant. The next step in the development of this class of compounds would be the incorporation of an amine into the alkoxy sidechain to facilitate solubility and drug delivery.

I do not believe that further investigations into a better radical leaving group are warranted (Sec 4.4). The nature of the leaving group appears to have no effect on activity and thus the one that is simplest to incorporate synthetically should be employed. This

anomaly can be further explored if the mechanism of action is ever studied. It would be interesting to determine if the better radical leaving groups are less active because the radicals are insufficiently reactive with the yet unknown target. Or does the radical binding require a sterically small radical like a methyl or phenylethyl? Based upon the most widely accepted MOA the major radical formed from artemisinin is in essence an ethyl radical (see section 1) **226** needs to be synthesized. Out of all the compounds synthesized, I believe that this molecule has the highest potential for further success as it is a direct analog of the ozonide series, some of the most active synthetic peroxide antimalarials. The higher activity of **143** to **141** suggests that **226** should have even higher activity. Likewise **227** would provide the other Vennerstrom mimic and should be synthesized as well.



226 **227**

Section 5

"Third generation" 3-alkoxy-1,2-dioxolanes"

This section describes investigations of 3-alkoxy-1,2-dioxolanes bearing additional functionalization beyond that contained in the frameworks explored in Section 2. All but one of the compounds in this section features the C5/5' dimethyl substitution. While the spirocyclohexyl analogs are always more active than the dimethyl analogs, the same trends hold in the two lines. Therefore, since the dimethyl is both quicker and cheaper to synthesize it was used as the initial screen to find potential hits.

This section contains:

Section 5.1: Esters

Section 5.2: Alcohols

Section 5.3: Derivatized alcohols

Section 5.4: Other Functional groups

Section 5.5: Animal studies

Section 5.6: Comments on stability

Section 5.7: Future directions

Section 5.1

Esters

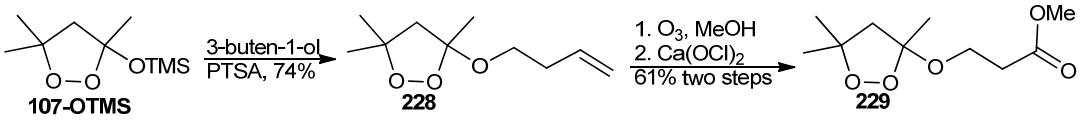
Rationale

The synthesis of 3-alkoxy-1,2-dioxolanes containing esters in the alkoxy sidechain was driven by the desire to create more polar 3-alkoxy-1,2-dioxolanes and to add a synthetic handle for further functionalization. For example, saponification of the ester would provide an acid that could be used to install a more biologically relevant

amide. Up to this point, all of the 3-alkoxy-1,2-dioxolanes have been hydrophobic with Log P values 1.5 to 6.73, as computed by ChemDraw. Though the majority of previously synthesized 3-alkoxy-1,2-dioxolanes fall within Lipinski's guidelines for Log P,[120] most are at the higher end of the Log P limit. Therefore, I wanted to synthesize a small library of compounds with Log P values ranging from 1.47 to 4.26.

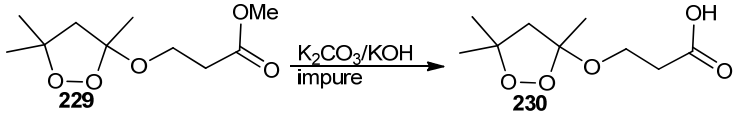
Synthesis

The key step in the synthesis of the esters would utilize the $Ca(OCl)_2$-mediated decomposition of hydroperoxyacetals, a reaction that was recently reported in our lab.[121] Peroxide **107-OTMS** underwent acid-catalyzed transetherification with 3-buten-1-ol to afford 3-alkoxy-1,2-dioxolane **228**. Ozonolysis of the alkene in the presence of methanol afforded the hydroperoxyacetal, which was subsequently treated with $Ca(OCl)_2$ in the same reaction flask to provide ester **229** in moderate yield.



107-OTMS 228 229

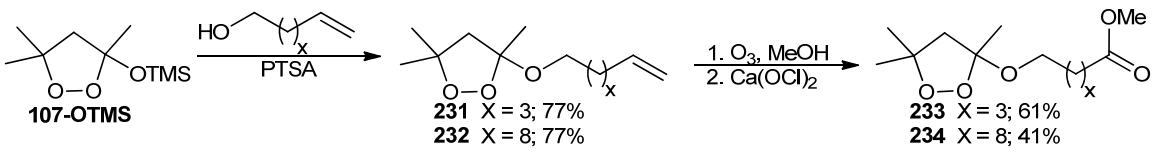
Saponification of ester **229** was attempted with K_2CO_3, but no reaction was observed. The addition of KOH pellets and heating of the reaction led to consumption of the starting ester. By TLC the reaction appeared to be complete and the crude acid **230** was subjected to column chromatography. However, by NMR the resulting acid was impure. An acid/base extraction provided a product that appeared by TLC to be pure, but remained impure by NMR, suggesting that the impurity was also an acidic species.



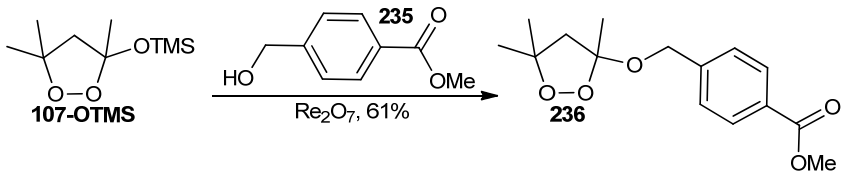
229 230

Failure of the saponification led to the exploration of other routes to acid **303**. The oxidative cleavage of alkenes to the corresponding acid is well established and I decided to explore this route. The use of $NaIO_4$ and $KmnO_4$ or OsO4 and oxone[122] led to complete conversion of the starting material, but the acid could not be purified. The use of Jones reagent to oxidize the alcohol was not employed as there were concerns that the acidic conditions might lead to the hydrolysis of the 3-alkoxy-1,2-dioxolane to produce the 1,2-dioxolan-3-ol. In hindsight, the formation of the benzyl ester followed by hydrogenation should lead to the desired acid and should have been explored.

With a route established for the synthesis of the esters, I set about preparing two additional targets. The synthesis began with transetherification of **107-OTMS** using 5-hexen-1-ol or 10-undecen-1-ol to afford 3-alkoxy-1,2-dioxolane **231** and **232** respectively. Formation of the hydroperoxyacetal and subsequent treatment with $Ca(OCl)_2$ provided the desired esters **233** and **234**.

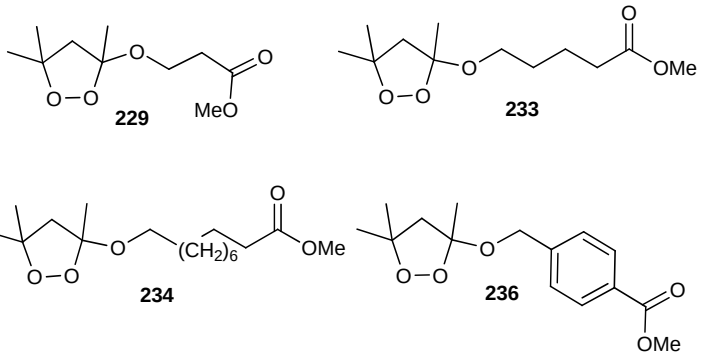


The synthesis of a 3-alkoxy-1,2-dioxolane that contained both an ester and aromatic ring was also undertaken. Transetherification of **107-OTMS** with alcohol **235** to afford 3-alkoxy-1,2-dioxolane **236** was accomplished using Re_2O_7. The use of Re_2O_7 as a catalyst for this reaction will be discussed in chapter 4.



Antimalarial results and analysis

The ester-substituted 3-alkoxy-1,2-dioxolanes were tested for antimalarial activity, as described previously (section 1.3).[109-111] What is most striking about this class of substrates is that all of the activities are higher for the K1 (chloroquine resistant) strain of P. *falciparum* compared with the chloroquine sensitive NF54 strain. Out of this series, ester **236** is the most active possibly due to the presence of an aromatic ring in the alkoxy sidechain. The other esters all exhibited similar in their activity against NF54 (chloroquine sensitive). I would have expected a greater change in activity as either the Log P or the length of the alkoxy sidechain changed. In future generations of this class, it would be interesting to alter the ester group to determine what effect this has on activity. For example, would the benzyl or phenylethyl ester lead to higher activity or would it lead to a drop off in activity?



Compound	Log P	IC_{50} (nM) NF54	IC_{50} (nM) K1
229	1.47	159	93
233	2.17	130	60
234	4.26	174	141
236	3.2	56	34

Table 2.8 Esters in alkoxy side chain

Section 5.2

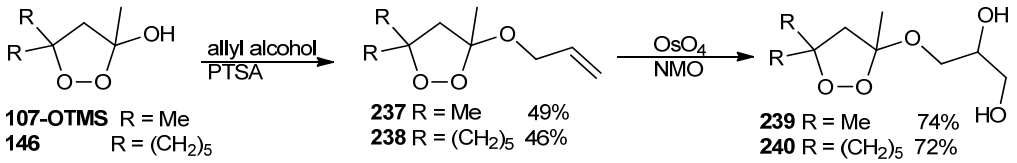
Alcohols

Rationale

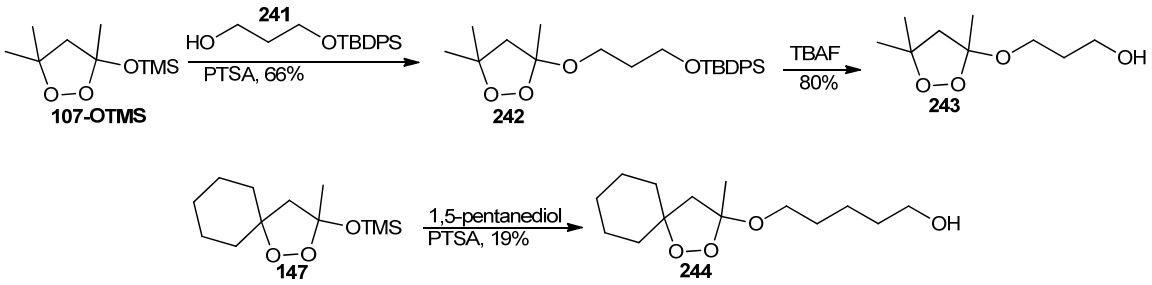
The synthesis of 3-alkoxy-1,2-dioxolanes featuring a free alcohol in the C3-alkoxide was undertaken. The alcohols would provide polarity, a functional handle for subsequent modification, and an opportunity to test the stability of 3-alkoxy-1,2-dioxolanes under a variety of reaction conditions. The synthesis of sidechain diols was also undertaken because of a 2007 report from Agre demonstrating the importance of the glycerol channel to malaria infection in the mouse model.[123] If the glycerol channel was knocked out, then malaria resistance was imparted onto the mice. De Kimpe[124] and Flitsch[125] reported small molecules that they claim were able to block the glycerol channel. With this knowledge, it was thought that 3-alkoxy-1,2-dioxolanes possessing a diol sidechain could either block the glycerol channel or else hijack this channel for transport of the 3-alkoxy-1,2-dioxolanes.

Synthesis

The synthesis of diols **239** and **240** was straightforward and began with the synthesis of 3-alkoxy-1,2-dioxolanes **237** and **238**. These were then subjected to dihydroxylation with OsO_4 to afford diols **239** and **240** in good yield. After diol **240** had already been submitted for *in vitro* screening it was found to be contaminated with a small amount of alkene impurity that appeared to have formed during the synthesis of **146**.



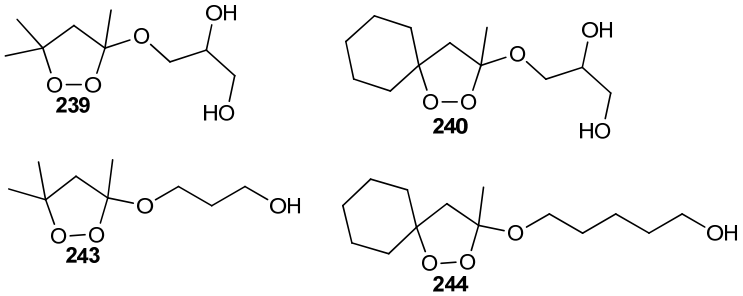
The synthesis of alcohol **243** began with the transetherification of **107-OTMS** with alcohol **241** to afford 3-alkoxy-1,2-dioxolane **242**. Diol monoether **241** was used instead of 1,3-propanediol because of a desire to avoid dimer formation. The dimer side reaction could also have been suppressed by the use of a gross excess of 1,3-propanediol, but this would have complicated purification. TBAF deprotection of **242** afforded the desired 3-alkoxy-1,2-dioxolane **243** in good yield. The pentanediol derivative **244** was obtained as a byproduct of the attempted synthesis of the dimer, was also isolated and tested.



Antimalarial results and analysis

The analysis of the *in vitro* screening data shows diols **239** and **240** to exhibit low to moderate activity against P. *falciparum*.[109-111] Though **240** does possess moderate activity it is not clear if the activity results from blocking the glycerol channel or through the hypothesized formation of a carbon radical upon Fe (II)-mediated scission of the 3-alkoxy-1,2-dioxolane. One way to determine which of the pathways is operative would be to prepare an analog lacking the peroxide group.

The activity of the alcohols suggests there is not a direct correlation between Log P and activity. Compound **243** has low activity, but the slightly less polar **244** possesses remarkable activity. Up to this point the hypothesis has been that there was a correlation between high activity and a bulky group in the alkoxy sidechain. However, 3-alkoxy-1,2-dioxolane **244** does not possess a bulky sidechain, yet has an activity rivaling that of the most active compounds described in section 4. If a Log P argument is applied there is also no direct correlation as **148**, phenylethyl sidechain, has a Log P of 4.55.



Compound	Log P	IC_{50} (nM) NF54	IC_{50} (nM) K1
239	0.6	1318	ND
240	1.49	63	ND
243	1.24	278	180
244	3	20	13
148	4.55	9	ND

Table 2.9 Alcohols and Diols

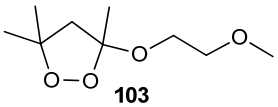
Section 5.3

Derivatized alcohol

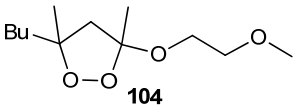
Rationale

When analyzing the data from the first generation 3-alkoxy-1,2-dioxolanes (Section 1.3) I became interested in the activity, of substrates featuring a methoxyethyl sidechain. As the Log P of the compound increased the activity also increased, for example **103** vs. **104**. Previous results have demonstrated that having an aromatic ring in

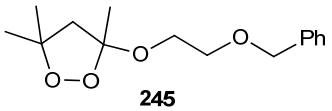
the alkoxy sidechain increases activity. Therefore, I thought that combining these two factors in compound **245** would provide a compound that was destined to have good activity.



103
IC_{50} = >1000 nM
Log P : 1.5



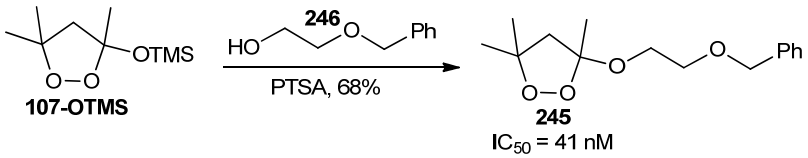
104
IC_{50} = 392 nM
Log P: 2.82



245
Log P: 3.23

Synthesis and antimalarial results

The synthesis of **245** was accomplished through an acid mediated transetherification of **107-OTMS** with alcohol **246**. As predicted, 3-alkoxy-1,2-dioxolane **245** exhibited very good activity against P. *falciparum* (NF54) *in vitro*, 41 nM.[109-111] This represents a promising lead that should be followed up with a cyclohexane analog to investigate the role of the aromatic ring.



107-OTMS **246** PTSA, 68% **245**
IC_{50} = 41 nM

Section 5.4

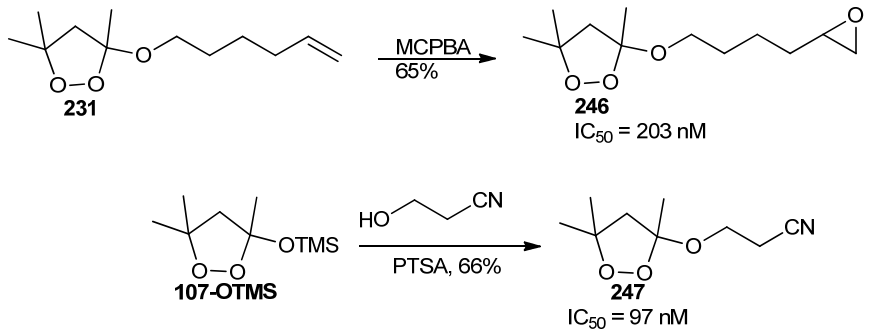
Other functional groups

Rationale

The synthesis of several compounds with polar alkoxy sidechains was undertaken to test the limits of what functionality could be tolerated in this position. The choice of substrates did not reflect any systematic search, but rather was intended to rapidly test the boundaries of the influences of polar functional groups on the activity of 3-alkoxy-1,2-dioxolanes.

Synthesis and antimalarial results

The synthesis of **246** began with previously synthesized 3-alkoxy-1,2-dioxolane **231**. Reaction with *m*CPBA afforded epoxide **246**. Nitrile **247** was prepared by acid-catalyzed transetherification of peroxide **107-OTMS**. Neither epoxide **246** nor nitrile **247** possessed notable antimalarial activity.



IC_{50} values are *in vitro* against P. *falciparum* (NF54)

Section 5.5

Animal studies

Having indentified several 3-alkoxy-1,2-dioxolanes that possessed very good *in vitro* activity, I was interested in pursuing *in vivo* studies against P. *berghei*. The molecules chosen as candidates possess good *in vitro* activity and have a polar functional group. However, no therapeutic effect was observed; all of the mice needed to be euthanized on day three. It is unclear as to why the 3-alkoxy-1,2-dioxolanes had no therapeutic effect *in vivo* and further investigation needs to be undertaken.[110]

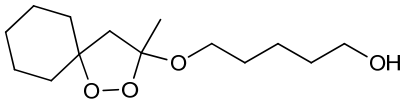
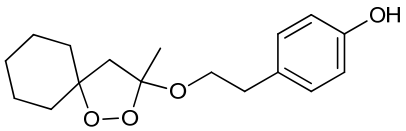
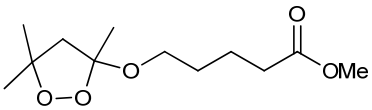
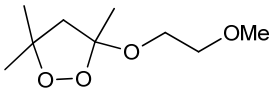
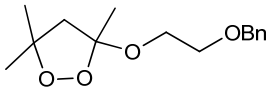
	3-alkoxy-1,2-dioxolane	Parasitized RBC over 100	% control
244		15.94	92.59
163		17.23	100.06
233		19.71	114.46
103		16.06	93.28
245		18.50	107.41
NA	Control	17.22	NA

Table 2.10 *In vivo* testing against P. *berghei*. Method of administration was subcutaneous injection and values are an average over three days.

Section 5.6

Stability of 3-alkoxy-1,2-dioxolanes

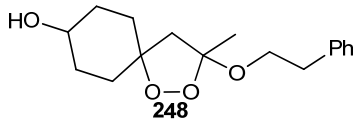
Throughout this work a variety of 3-alkoxy-1,2-dioxolanes have been subjected to conditions that would lead to decomposition of many peroxides. The tetrasubstituted 3-alkoxy-3,5,5-trialkyl-1,2-dioxolanes proved stable to reducing agents ($LiAlH_4$, Dibal-H, and PPh_3), base (TBAF, KOH), oxidants (*m*CPBA, O_3), and heat (60^{o}C for 3 days). Decomposition of 3-alkoxy-1,2-dioxolanes was only accomplished with $FeBr_2$. This stability provides an excellent platform on which to explore SAR.

Section 5.7

Future work

My research has shown that 3-alkoxy-1,2-dioxolanes possess a remarkable robustness in terms of maintaining antimalarial activity across a range of structures, as

long as the 3-alkoxy-1,2-dioxolane core is kept intact. Changes to the substitution at either C3 or C5 do lead to changes in activity but as a whole, do not lead a dramatic change in activity. However, *in vivo* studies found little activity for these relatively hydrophobic 3-alkoxy-1,2-dioxolanes. This makes the most obvious future direction to synthesize molecules that are more drug-like and determine if that increases their *in vivo* efficacy. One of the ways, I envision this can be done is by changing the substitution at C5. The optimal alkoxy sidechain for C3 is the phenylethyl and the best substitution thus far at C3 has been a spirocyclohexyl. I propose changing the cyclohexane by making a compound similar to **248**. In this system the 4-position of the cyclohexane can undergo further derivatization to give the molecule more drug-like properties.



248

A more ambitious goal is to determine the mechanism of action (MOA) of 3-alkoxy-1,2-dioxolanes. Currently, the MOA of peroxide antimalarials is of debate and most synthetic peroxide antimalarials have been developed based upon the hypothesis of the generation of a carbon centered free radical upon reductive cleavage of the peroxide bond. The exact MOA of 3-alkoxy-1,2-dioxolanes has not been determined as they are a new class of peroxide antimalarials. Determination of the MOA might allow more rationale design of a small molecule.

I do not have a comprehensive plan to determine the MOA of 3-alkoxy-1,2-dioxolanes, but do have several experiments that would be beneficial in that pursuit. A degradation study was done with $FeBr_2$, but was never done in the presence of heme to determine if the radical formed from the Fe (II)-mediated peroxide decomposition is able

to alkylate the heme. If alkylation of heme was noted, the alkylated product can be tested in a manner similar to that reported by Meshnick[47] to determine if the alkylated compound is the source of activity. This experiment is beneficial because if a lack of alkylation would indicate that 3-alkoxy-1,2-dioxolanes utilize a novel MOA from the other reported synthetic peroxides.

The synthesis of the non-peroxide analog of a 3-alkoxy-1,2-dioxolane should be undertaken to determine if antimalarial activity is from the decomposition of the peroxide bond. The possibility that 3-alkoxy-1,2-dioxolanes block a channel has not been excluded and the synthesis of a non-peroxide analog would quickly show if this was a component of activity.

Though outside of my field of expertise, utilization of either radio labeled or flourophore tagged 3-alkoxy-1,2-dioxolanes can be used to determine if there is uptake of the 3-alkoxy-1,2-dioxolane into the infected cell. I believe that the peroxide is being uptaken by the cell, but without experimental evidence it is impossible to rule out some surface binding effect.

Since all of these experiments have been conducted with either artemisinin or a synthetic peroxide, they will in their own right not prove the answer, but will instead provide a roadmap. Determination of the MOA of 3-alkoxy-1,2-dioxolanes would require significant collaboration across several disciplines. In the end, the MOA of this class of compounds may never be discovered, but even attempts would provide much needed information to guide future synthesis.

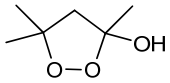
Section 6

Experimentals

Abbreviations: THF (tetrahydrofuran); DMF (*N*,*N*-dimethylformamide); TsOH (*p*-toluenesulfonic acid, monohydrate); EA/hex (ethyl acetate/hexane); DMSO (dimethylsulfoxide); RBF (round-bottom flask); rt (room temperature); TLC (thin-layer chromatography),

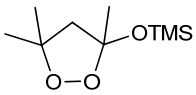
General Experimental Conditions: All reagents were used as received from commercial vendors, with the exception of CH_2Cl_2, which was distilled from calcium hydride, and THF, which was distilled from sodium/benzophenone. All reactions were conducted under an atmosphere of N_2 except where noted. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized with a hand-held UV lamp or by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% *N,N'*-dimethyl-*p*-phenylenediamine solution in 1:20:100 acetic acid/water/methanol (specific for peroxides);[126] 1% aq. $KMnO_4$ (for unsaturated compounds); 3% vanillin in 3% H_2SO_4 in ethanol (general stain after charring). "Standard drying and purification" refers to drying of organic extracts over $MgSO_4$, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. ^1H /^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise indicated; peaks are reported as: chemical shift (multiplicity, J couplings in Hz, number of protons). Infrared spectra were recorded as neat films (ZnSe, ATR mode) with selected absorbances reported in wavenumbers (cm^{-1}). Melting points

were collected using a melting point apparatus and all values are uncorrected unless otherwise noted.



3,5,5-Trimethyl-1,2-dioxolan-3-ol (107):

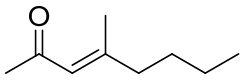
Mesityl oxide (5.2924 g, 53.9 mmol) was stirred with aq. KOH (1.0 mL, 7.1 mmol, 7.1 M) in a RBF for 5 min at -5 ºC, after which aq. H_2O_2 (11 mL, ~97 mmol, 30%) was added. The resulting solution was stirred at 0 ºC for 3 h and then allowed to warm to rt and held at that temperature for 1 h. The reaction mixture was then extracted with Et_2O (30 mL) and the organic layer washed with brine (2 x 30 mL). The combined organic layers were dried with $MgSO_4$ and chromatographed twice with 30% ether/hexanes to afford **107** as a colorless oil (1.5647 g, 24%). R_f (30% ether/hexanes): 0.22. ^{1}H NMR (300 MHz): 3.15 (s, 1H), 2.51 (d, J = 12.8, 1H), 2.42 (d, J = 12.8, 1H), 1.55 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H). ^{13}C (75 MHz): 106.3, 84.2, 58.7, 27.4, 25.0, 23.5. IR: 3292, 2899, 2847. HRMS (ESI): calc for $C_6H_{12}O_3Na$: 155.0684; found: 155.0686 (1.3 ppm).



3-Trimethylsilyloxy-3,5,5-trimethyl-1,2-dioxolane (107-OTMS):

A solution of **107** (142.1 mg, 1.07 mmol) in CH_2Cl_2 (7.5 mL) in a flame-dried RBF was treated sequentially with imidazole (257.7 mg, 2.8 mmol) and chlorotrimethylsilane (0.3 mL, 2 mmol). After 10 min, the reaction was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography with 5% EA/hex to afford **107-OTMS**, as a colorless oil (129 mg, 57%). R_f (5% EA/hex): 0.68. ^{1}H NMR (400 MHz): 2.56 (d, J = 12.4, 1H), 2.40 (d, J = 12.4, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.34 (s,

3H), 0.18 (s, 9H). ^{13}C (100 MHz): 107.4, 83.7, 61.3, 27.4, 25.3, 24.8, 1.5. HRMS (ESI): calc for $C_9H_{20}NaO_3Si$: 227.1079; found: 227.1052 (11.0 ppm).

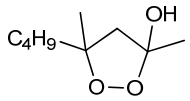


(3*E*,3*Z*)-4-methyl-3-octen-2-one (109):

To a -78 °C solution of 4-penten-2-one (9.7962 g, 117 mmol) in ether (238 mL) in a flame-dried RBF was added n-BuLi (119 mL, 298 mmol, 2.5 M in hexanes). The reaction was stirred for 30 min at -78ºC and at rt for 14 hr. The reaction was quenched with H_2O (60 mL) and filtered through a pad of Celite. The combined Et_2O extracts (3 x 100 mL) were subjected to standard drying and purification with 15% EA/hex and a subsequent column with 10% EA/hex to afford *E*-4-methyl-3-octen-2-ol as a yellow oil (6.5554 g, 56%). R_f (15% EA/hex): 0.57. ^{1}H NMR (400 MHz): 5.68-5.48 (2H), 1.7 (dd, J = 6, 1.1, 3H), 1.5 (m, 2H), 1.38 (s, 1H), 1.36-1.21 (7H), 0.91 (overlapping triplets, J = 7, 3H). ^{13}C (100 MHz): 138.4, 122.7, 73.0, 42.8, 28.0, 26.4, 23.3, 17.9, 14.3. IR: 3381, 2958, 2932, 2861. HRMS (CI): calc for $C_9H_{19}O$: 143.1436; found: 143.1435 (0.6 ppm).

To a 0 °C solution of pyridinium dichromate (3.047 g, 8 mmol) in DMF (12.6 mL) was added *E*-4-methyl-2-octen-4-ol (871.0 mg, 6.1 mmol) as a solution in DMF (1 mL). The reaction was stirred for 4 h at 0 ºC and rt for 3 hr, and then diluted with H_2O (100 mL). The combined Et_2O extracts (3 x 30 mL) were washed with brine (30 mL) and subjected to standard drying and purification with 15% EA/hex to afford **109** as a colorless oil and as an E/Z mixture (68:22) (352.9 mg, 41%). R_f (10% EA/hex): 0.42. ^{1}H NMR: 6.05 (m, 1H), 2.55 (m, 0.5H), 2.25-2.06 (5.5H), 1.87 (d, J = 1.3, 1H), 1.50-1.21 (4H), 0.91 (t, J = 7.4, 3H). ^{13}C NMR (75 MHz): 199.0, 159.7, 159.1, 124.0, 123.4, 41.0,

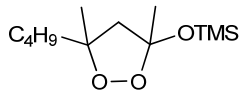
33.4, 31.8, 30.3, 29.7, 25.4, 22.9, 22.4, 19.3, 14.0, 13.9. IR: 2957, 2931, 2862, 1687, 1614. HRMS (CI): calc for $C_9H_{16}ONa$: 163.1099; found: 163.1094 (3.1 ppm).



(3,5-*cis*)(3,5-*trans*)-5-Butyl-3,5-dimethyl-1,2-dioxolan-3-ol (110):

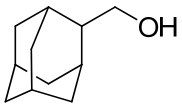
H_2O_2 method: To a RBF containing **109** (1.2125, 8.5 mmol) in THF (8.5 mL) was added aq. KOH (0.15 mL, 1.1 mmol, 7.1 M). The solution was cooled to 0 ºC, after which aq. H_2O_2 (1 mL, ~5 mmol, 30%) was added. The resulting solution was allowed to warm to rt and was stirred for 2 days. The reaction mixture was then diluted with H_2O (10 mL) and extracted with Et_2O (2 x 20 mL) and the combined organic layers washed with brine (2 x 30 mL) and subjected to standard drying and purification with 20% EA/hex to afford a 1:1 *cis*/*trans* mixture of **110** as a colorless oil (105.5 mg, 7%). R_f (10% EA/hex): 0.25. ^{1}H NMR (100 MHz): 3.45 (s, 1H), 2.53 (d, J = 12.9, 0.5H), 2.45 (d, J = 12.8, 0.5H), 2.41 (d, J = 12.8, 0.5H), 2.31 (d, J = 12.9, 0.5H), 1.73-1.44 (5H), 1.42-1.16 (7H), 0.90 (apparent triplet, J = 6.5, 3H). ^{13}C (100 MHz): 106.1, 105.9, 86.7, 86.3, 57.6, 57.3, 39.7, 37.9, 27.2, 26.6, 25.1, 23.5, 23.3, 23.2, 23.1, 22.4, 14.1, 14.0. IR: 3448, 2957, 2935, 2870. HRMS (ESI): calc for 197.1154; found: 197.1149 (2.5 ppm).

Cobalt method: To a RBF containing cobalt (II) acetylacetone (490 mg, 1.9 mmol) in 1,2-dichloroethane (170 mL) was added sequentially 4-methyl-3-octen-2-one (2.7228g, 19 mmol) in 1,2-dichloroethane (20 mL) and triethylsilane (6.1 mL, 38 mmol). The mixture was placed under an O_2 balloon and stirred overnight. The reaction was diluted with sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford a 1:1 *cis*/*trans* mixture of **110** as a colorless oil (395.7 mg, 36% BRSM)



(3,5-*cis*)(3,5-*trans*)-3-Trimethylsilyloxy-5-butyl-3,5-dimethyl-1,2-dioxolane (112):

A solution of **110** (129.9 mg, 0.92 mmol) in CH_2Cl_2 (9.2 mL) in a flame-dried RBF was treated sequentially with imidazole (195mg, 2.7 mmol) and chlorotrimethylsilane (302 mg, 2.8 mmol). After 2 h, the reaction was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was was subjected to standard drying and purification with 5% EA/hex to afford a 1:1 *cis*/*trans* mixture of **112** as a colorless oil (129 mg, 57%). R_f (5% EA/hex): 0.69. ^{1}H NMR (300 MHz): 2.58 (d, J = 12.5, 0.5H), 2.50 (d, J = 12.4, 0.5H), 2.40 (d, J = 12.4, 0.5H), 2.30 (d, J = 12.5, 0.5H), 1.76-1.6 (2.5H), 1.6-1.48 (3.5H), 1.44-1.2 (7H), 0.91 (overlapping triplets, J = 6.8, 3H), 0.20 (overlapping singlets, 9H). ^{13}C (75 MHz): 107.4, 107.3, 86.4, 86.0, 60.4, 60.0, 40.2, 37.9, 27.3, 26.8, 25.6, 25.5, 25.2, 23.4, 23.3, 22.6, 14.2, 14.2, 1.7. HRMS (ESI): cal for $C_{12}H_{26}O_3SiNa$: 269.1549; found: 269.1547 (0.7 ppm).

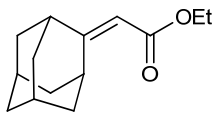


2-adamantanemethanol (115):

In a flame-dried three neck RBF a solution of methyltriphenylphosphine bromide (16.84 g, 47 mmol) in THF (32 mL) was cooled to 0ºC. A solution of n- BuLi (26.4 mL, 66 mmol, 2.5M in hexanes) was added and the solution was brought to rt and stirred for 1 hr. A solution of 2-adamantanone (5.2883g, 35.5 mmol) in THF (35 mL) was added dropwise from an addition funnel. The reaction was heated at reflux for 7 hrs, and then cooled to 0ºC. The reaction was quenched with H_2O (100 mL), and extracted with Et_2O (2 x 100 mL). The combined organic layers were dried with $MgSO_4$, and filtered through

a silica plug. The 2-methyleneadamantane obtained was used without further purification.

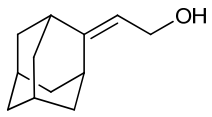
The 2-methyleneadamantane (nominally 4.3g, 29 mmol) was dissolved in THF (58mL) in a flame-dried RBF and the solution cooled to 0ºC. A solution of BH_3-THF (20.6 mL, 20.6 mmol, 1M in THF) was added drop wise. The reaction was stirred for 30 min, after which H_2O (3 mL, 167 mmol) was added. The reaction was heated to 45ºC and treated sequentially with aq. NaOH (3 M, 15 mL, 46 mmol), and H_2O_2 (8.2 mL, 65 mmol, 30% in H_2O). After 1 hr, the reaction was diluted with H_2O (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 10% EA acetate/hex): 0.29. Melting point: 90-91ºC. ^{1}H NMR (400 MHz): 3.74 (d, J = 7.06, 2H), 1.04-1.72 (13H), 1.56 (d, J = 11.92, 2H), 1.26 (s, 1H). ^{13}C NMR (100 MHz): 65.1, 47.1, 38.9, 38.2, 31.9, 29.2, 28.4, 28.0. IR: 3247, 2900, 2848. HRMS (CI): calc for $C_{11}H_{18}O$: 166.1358; found: 166.1361.



Adamantan-2-ylidene-acetic acid ethyl ester (116):

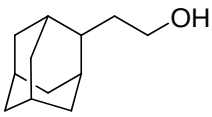
In a flame-dried RBF sodium hydride (1.3g, 32 mmol) in THF (45 mL) was slurried. Triethyl phosphonoacetate (8.1g, 36 mmol) was added drop wise, and the resulting solution was stirred for 1 hr. A solution of 2-adamantanone (4.1g, 27 mmol) in THF (20 mL) was added and the reaction stirred overnight. The reaction was quenched with sat. NH_4Cl (80 mL) and extracted with Et_2O (3 x 80 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **116** as a colorless oil (4.7267 g, 79%). R_f (10% EA/hex): 0.6. ^{1}H NMR (400 MHz): 5.6 (s,

1H), 4.15 (q, J = 7, 2H), 4.08 (s, 1H), 2.45 (s, 1H), 2.06-1.93 (6H), 1.92-1.80 (6H), 1.29 (t, J = 7, 3H). ^{13}C (100 MHz): 172.3, 167.1, 108.6, 59.4, 41.4, 40.1, 39.1, 36.8, 32.9, 27.9, 14.3. IR: 2902, 2850, 1709, 1644. HRMS (FAB): calc for $C_{14}H_{20}O_2Li$: 227.1623; found: 227.1627.



2-Adamantylideneethanol (117):

A solution of enoate **116** (1.0083 g, 4.5 mmol) in THF (15 mL) was added to a flame-dried RBF and cooled to -40ºC. DIBAL-H (1.5 M in toluene, 6.7mL, 10 mmol) was added and the reaction stirred at -40ºC for 2 hrs. The reaction was warmed to rt and quenched with a solution of sat. aq. Rochelles salt (20 mL). The resulting mixture was treated sequentially with glycol (1 mL) and ethyl acetate (10 mL). After 2 hrs, the mixture was extracted with Et_2O (25 mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford **117** as a colorless oil (748.6 mg, 92%). R_f (30% EA/hex): 0.57. ^{1}H NMR (400 MHz): 5.35 (t, J = 7.1, 1H), 4.15 (d, J = 7.1, 2H), 2.90 (s, 1H), 2.40 (s, 1H), 2.08-1.68 (12H), 1.18 (s, 1H). ^{13}C (100 MHz): 152.8, 115.4, 58.2, 40.4, 39.7, 39.1, 37.1, 32.4, 28.4. IR: 3207, 2897, 2846. HRMS (FAB): calc for $C_{12}H_{18}OLi$: 185.1518; found: 185.1514.



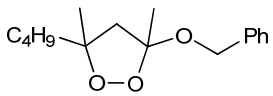
2-Adamantaneethanol (118):

A RBF was charged with 10% Pd/C (2.46 g, 0.23 mmol) and evacuated under vacuum. The flask was placed under an atmosphere of H_2 (balloon) and a solution of **117**

(2.0311 g, 11.4 mmol) in EA (110 mL) was added and the reaction was allowed to stir overnight. The flask was purged with N_2 and the supernatant filtered through celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography with 30% EA/hex to afford **118** as a white solid (1.18 g, 57%). R_f (10% EA/hex): 0.21. Melting point: 60-62ºC. ^{1}H NMR (400 MHz): 3.69 (t, J = 6.9, 2H), 1.92-1.66 (14H), 1.55 (m, 3H), 1.22 (s, 1H). ^{13}C NMR (100 MHz): 61.7, 40.7, 39.1, 38.4, 35.9, 32.0, 31.7, 28.2, 28.0. IR: 3292, 2899, 2847. HRMS (FAB): calc for $C_{12}H_{20}OLi$: 187.1674; found: 187.1668.

Method A: From the corresponding 1,2-dioxolan-3-ol

Method B: From the corresponding 3-trimethylsiloxy-1,2-dioxolane



(3,5-*cis*)(3,5-*trans*)-3-(1-Phenyl)methoxy-5-butyl-3,5-dimethyl-1,2-dioxolane (119):

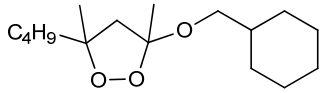
Method A:

To a vial containing **110** (197.6 mg, 1.1 mmol) was added sequentially benzyl alcohol (15.5, 143 mmol) and TsOH (37.2 mg, 0.2 mmol) and the reaction was stirred overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **119** as a yellow oil (180.7 mg, 60%).

Method B:

To a vial containing **112** (126.7 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) was added sequentially benzyl alcohol (175 mg, 1.62 mmol) and TsOH (9.2 mg, 0.05mmol). After 20 min, the reaction was treated with sat. $NaHCO_3$ (5 mL) and H_2O (10 mL) and

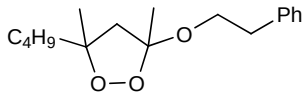
extracted with CH_2Cl_2 (20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **119** as a yellow oil (83.4 mg, 60%). R_f (10% EA/hex):0.45. ^{1}H NMR (400 MHz): 7.48-7.24 (5H), 4.78 (d, J = 11.2, 1H), 4.52 (d, J = 11.2, 1H), 2.71 (d, J = 12.5, 0.5H), 2.62 (d, J = 12.5, 0.5H), 2.45 (d, J = 12.5, 0.5H), 2.35 (d, J = 12.5, 0.5H), 1.83-1.55 (5H), 1.52-1.28 (7H), 0.95 (overlapping triplets, J = 6.9, 3H). ^{13}C (100 MHz): 138.8, 128.3, 128.2, 127.8, 127.7, 127.3, 108.4, 108.3, 86.4, 86.0, 64.0, 63.9, 57.8, 57.4, 40.1, 37.6, 27.2, 26.6, 25.5, 23.2, 22.3, 20.2, 19.6, 14.1, 14.0. HRMS (CI): calc for $C_{16}H_{24}O_3$: 264.1725; found: 264.1727.



(3,5-*cis*)(3,5-*trans*)-3-Butyl-5-(cyclohexylmethoxy)-3,5-dimethyl-1,2-dioxolane (120)

Method B:

To a vial containing **112** (196.5 mg, 0.80 mmol) in CH_2Cl_2 (8 mL) was added sequentially cyclohexanemethanol (0.5 mL, 4.05 mmol) and TsOH (15 mg, 0.08 mmol). After 2 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 10% ethyl acetate/hexanes to afford **120** as a yellow oil (185.8 mg, 86%). R_f (10% /hex): 0.61. ^{1}H NMR (600 MHz): 3.40 (m, 1H), 3.21 (m, 1H), 2.56 (d, J = 12.5, 0.5H), 2.46 (d, J = 12.5, 0.5H), 2.33 (d, J = 12.5, 0.5H), 2.22 (d, J = 12.5, 0.5H), 1.83-1.49 (8H), 1.45 (d, J = 12.5, 3H), 1.40-1.11 (10H), 1.0-0.86 (5H). ^{13}C (150 MHz):108.1, 108.0, 86.3, 85.9, 67.43, 67.41, 58.0, 57.5, 40.3, 38.33, 38.31, 37.8, 30.3, 30.28, 30.25, 27.3, 26.9, 26.8, 26.1, 26.0, 25.7, 23.4, 23.3, 22.5, 20.1, 19.6, 14.2, 14.1. HRMS (ESI): calc for $C_{16}H_{30}O_3Na$: 293.2093; found: 293.2088 (2 ppm).



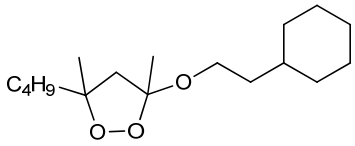
(3,5-*cis*)(3,5-*trans*)-3-Butyl-3,5-dimethyl-5-(2-phenyl)ethoxy-1,2-dioxolane (121):

Method A:

To a vial containing **110** (62 mg, 0.35 mmol) was added sequentially 2-phenylethanol (5.4186g, 44 mmol) and TsOH (7.2 mg, 0.04 mmol) and the solution stirred overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **121** as a yellow oil (32.6 mg, 30%).

Method B:

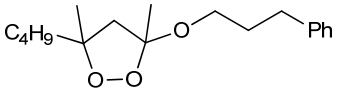
To a vial containing **112** (74.0 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added sequentially 2-phenylethanol (102 mg, 0.84 mmol) and TsOH (6.7 mg, 0.04mmol). After 1 hr, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **121** as a yellow oil (66.6 mg, 80%). R_f (10% EA/hex):0.5. ^{1}H NMR (400 MHz): 7.4-7.2 (5H), 3.88 (m, 1H), 3.66 (m, 1H), 2.9 (m, 2H), 2.58 (d, J = 12.5, 0.5H), 2.50 (d, J = 12.5, 0.5H), 2.37 (d, J = 12.5, 0.5H), 2.25 (d, J = 12.5, 0.5H), 1.78-1.5 (2H), 1.47 (d, J = 9, 3H), 1.44-1.24 (7H), 0.93 (overlapping triplets, J = 6.9, 3H). ^{13}C (100 MHz): 139.2, 129.0, 128.2, 126.1, 108.1, 108.0, 85.9, 62.6, 62.5, 57.8, 57.3, 40.1, 37.6, 36.7, 27.2, 26.6, 25.4, 23.2, 22.2, 20.0, 19.5, 14.1, 14.0. HRMS (FAB): calc for $C_{17}H_{26}O_3Li$: 285.2042; found: 285.2053.



(3,5-*cis*)(3,5-*trans*)-3-Butyl-5-(2-cyclohexylethoxy)-3,5-dimethyl-1,2-dioxolane (122)

Method B:

To a vial containing **112** (133.5 mg, 0.54 mmol) in CH_2Cl_2 (6 mL) was added sequentially 2-cyclohexylethanol (0.38 mL, 2.7 mmol) and TsOH (10 mg, 0.05 mmol). After 2 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **122** as a yellow oil (126.1 mg, 82%). R_f (10% EA/hex): 0.55. ^{1}H NMR (600 MHz): 3.64 (m, 1H), 3.44 (m, 1H), 2.55 (d, J = 12.6, 0.5H), 2.47 (d, J = 12.6, 0.5H), 2.33 (d, J = 12.6, 0.5H), 2.22 (d, J = 12.6, 0.5H), 1.80-1.10 (23H), 0.96-0.84 (5H). ^{13}C (150 MHz):108.1, 108.0, 86.3, 86.0, 59.62, 59.60, 57.9, 57.5, 40.3, 37.8, 37.6, 34.8, 34.7, 33.74, 33.71, 33.24, 33.21, 27.3, 26.9, 26.8, 26.6, 26.5, 25.7, 23.4, 23.3, 22.5, 20.1, 19.6, 14.2, 14.1. HRMS (ESI): calc for $C_{17}H_{32}O_3Na$: 307.2249; found: 307.2243 (2 ppm).

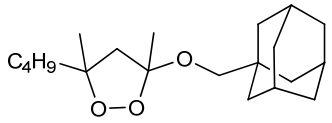


(3,5-*cis*)(3,5-*trans*)-3-butyl-3,5-dimethyl-5-(3-phenylpropoxy)-1,2-dioxolane (123)

Method B:

To a vial containing **112** (211.3 mg, 0.86 mmol) in CH_2Cl_2 (8 mL) was added sequentially 3-phenyl-1-propanol (0.55 mL, 4.1 mmol) and TsOH (15 mg, 0.08 mmol). After 3 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard

drying and purification with 10% EA/hex to afford **123** as a yellow oil (211.3 mg, 92%). R_f (10% EA/hex): 0.41. ^{1}H NMR (600 MHz): 7.29 (5H), 3.63 (m, 1H), 3.44 (m, 1H), 2.71 (m, 2H), 2.58 (d, J = 12.5, 0.5H), 2.48 (d, J = 12.5, 0.5H), 2.35 (d, J = 12.5, 0.5H), 2.23 (d, J = 12.5, 0.5H), 1.88 m, 2H, 1.72-1.48 (2H), 1.44 (d, J = 13.2, 3H), 1.40-1.23 (7H), 0.88 (m, 3H). ^{13}C (150 MHz): 142.5, 128.73, 128.71, 128.4, 125.8, 108.2, 108.1, 86.4, 86.0, 61.0, 60.9, 58.0, 57.5, 40.3, 37.8, 32.6, 32.6, 32.0, 31.9, 27.3, 26.8, 25.6, 23.4, 23.3, 22.5, 20.2, 19.6, 14.2, 14.1. HRMS (ESI): calc for $C_{18}H_{28}O_3Na$: 315.1936; found: 315.1936 (<1 ppm).



(3,5-*cis*)(3,5-*trans*)-3-(1-(1-Adamantyl)methoxy)-5-butyl-3,5-dimethyl-1,2-dioxolane (124):

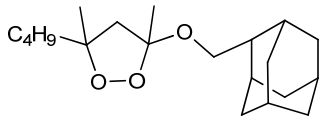
Method A:

To a vial containing **110** (161.9 mg, 0.93 mmol) in CH_2Cl_2 (10 mL) was added sequentially 1-adamantanemethanol (754.1 mg, 4.54 mmol) and TsOH (42.2 mg, 0.22 mmol). After 48 hrs, the reaction was treated with sat. aq $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10mL). The combined organic layers were subjected to standard drying and purification with 2.5% EA/hex to afford **124** as a yellow oil (78.4 mg, 26%).

Method B:

To a vial containing **112** (74.5 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added sequentially 1-adamantanemethanol (176.9 mg, 1.1 mmol) and TsOH (5 mg, 0.03mmol). After 1 hr, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted

with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **124** as a yellow oil (60.4 mg, 62%). R_f (5% EA/hex): 0.31. ^{1}H NMR (400 MHz): 3.19 (d, J = 3.7, 0.5H), 3.17 (d, J = 3.7, 0.5H), 2.96 (dd, J = 0.7, 8.8, 1H), 2.58 (d, J = 12.4, 0.5H), 2.48 (d, J = 12.4, 0.5H), 2.34 (d, J = 12.2, 0.5H), 2.22 (d, J = 12.2, 0.5H), 2.04-1.93 (3H), 1.76-1.48 (14H), 1.44 (d, J = 8.2, 3H), 1.41-1.24 (7H), 0.92 (t, J = 7.1, 3H). ^{13}C (100 MHz): 107.8, 107.7, 85.9, 85.6, 72.0, 71.9, 57.8, 57.1, 40.3, 39.7, 37.7, 37.3, 33.3, 33.2, 28.3, 27.1, 26.6, 26.0, 23.2, 23.1, 22.5, 19.6, 19.1, 14.1, 14.0. HRMS (FAB): calc for $C_{20}H_{35}O_3$: 323.2586; found: 323.2594.



((3,5-*cis*)(3,5-*trans*)-3-(1-(2-Adamantyl)methoxy)-5-butyl-3,5-dimethyl-1,2-dioxolane (125):

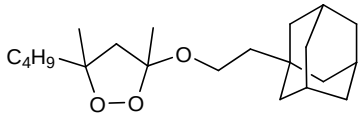
Method A:

To a vial containing **110** (198.3 mg, 1.14 mmol) in CH_2Cl_2 (11 mL) was added sequentially 2-adamantanemethanol (755.2 mg, 4.5 mmol) and TsOH (22.4 mg, 0.12 mmol). After 72 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and 5 mL H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **125** as a yellow oil (145.8 mg, 34%).

Method B:

To a vial containing **112** (72.9 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was added sequentially 2-adamantanemethanol (176.9 mg, 1.1 mmol) and TsOH (5 mg, 0.03mmol). After 1 hr, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted

with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **125** as a yellow oil (54.9 mg, 57%). R_f (5% EA/hex): 0.41. ^{1}H NMR (300 MHz): 3.72 (m, 1H), 3.45 (ddd, J = 2.1, 6.6, 9.2, 1H), 2.56 (d, J = 12.5, 0.5H), 2.46 (d, J = 12.4, 0.5H), 2.33, 2.33 (d, J = 12.4, 0.5H), 2.27 (d, J = 12.4, 0.5H), 2.05-1.67 (13H), 1.67-1.49 (4H), 1.46 (d, J = 6.3, 3H), 1.42-1.20 (7H), 0.91 (overlapping triplet, J = 7.1, 3H). ^{13}C (75 MHz): 107.9, 107.8, 86.0, 85.7, 63.6, 57.7, 57.2, 44.2, 44.1, 40.2, 39.0, 38.9, 38.8, 38.3, 37.6, 32.1, 31.8, 29.7, 29.2, 28.5, 28.0, 27.0, 26.6, 25.6, 23.2, 23.1, 22.3, 19.9, 19.4, 14.0, 13.96. HRMS (FAB): calc for $C_{20}H_{35}O_3$: 323.2586; found: 323.2675.



(3,5-*cis*)(3,5-*trans*)-3-(2-(1-Adamantyl)ethoxy)-5-butyl-3,5-dimethyl-1,2-dioxolane (126):

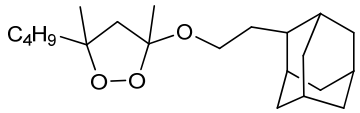
Method A:

To a vial containing **110** (54.4 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was added sequentially 1-adamantaneethanol (223.2 mg, 1.24 mmol) and TsOH (15.3 mg, 0.08 mmol). After 3 days, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **126** as a yellow oil (191 mg, 43%).

Method B:

To a vial containing **112** (76.5 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added sequentially 1-adamantaneethanol (153 mg, 0.85 mmol) and TsOH (10.1 mg, 0.05mmol). After 1 hr,

the reaction was treated with sat. aq. $NaHCO_3$ (3 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **126** as a yellow oil (75.5 mg, 72%). R_f (10% EA/hex):0.7. ^1H NMR (300 MHz): 3.67 (m, 1H), 3.46 (m, 1H), 2.54 (d, J = 12.4, 0.5H), 2.46 (d, J = 12.4, 0.5H), 2.34 (d, J = 12.4, 0.5H), 2.23 (d, J = 12.4, 0.5H), 2-1.87 (3H), 1.78-1.58 (7H), 1.58-1.5 (5H), 1.47 (d, J = 6.4, 3H), 1.43-1.2 (9H), 0.92 (overlapping triplets, J = 7.1, 3H). ^{13}C (75 MHz): 108.1, 108, 86.2, 85.8, 57.9, 57.59, 57.55, 57.5, 44, 43.9, 42.7, 40, 37.6, 37.2, 31.8, 28.7, 27.2, 26.6, 25.3, 23.2, 23.1, 22.2, 20.1, 19.6, 14, 13.9. HRMS (FAB): calc for $C_{21}H_{36}LiO_3$: 343.2824; found: 343.2839.



(3,5-*cis*)(3,5-*trans*)-3-(2-(2-Adamantyl)ethoxy)-5-butyl-3,5-dimethyl-1,2-dioxolane (127):

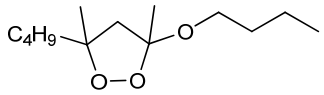
Method A:

To a vial containing **110** (220.3 mg, 1.27 mmol) in CH_2Cl_2 (5 mL) was added sequentially 2-adamantaneethanol (614.3 mg, 3.4 mmol) and TsOH (30.6 mg, 0.16 mmol). After 12 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **127** as a yellow oil (99.1 mg, 23%).

Method B:

To a vial containing **112** (52.2 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) was added sequentially 2-adamantaneethanol (128.3 mg, 0.71 mmol) and TsOH (7.1 mg, 0.04mmol). After 1 hr,

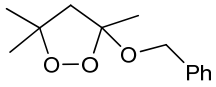
the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **127** as a yellow oil (42.6 mg, 60%). R_f (10% EA/hex): 0.37. ^1H NMR (400 MHz): 3.62 (m, 1H), 3.44 (m, 1H), 2.54 (d, J = 12.6, 0.5), 2.45 (d, J = 12.4, 0.5H), 2.34 (d, J = 12.6, 0.5H), 2.22 (d, J = 12.6, 0.5H), 1.97-1.57 (16H), 1.57-1.43 (5H), 1.41-1.22 (7H), 0.91 (overlapping triplets, J = 6.8, 3H). ^{13}C (100 MHz): 108.1, 108.0, 86.3, 86.0, 60.4, 60.3, 57.9, 57.5, 41.1, 41.0, 40.3, 39.4, 39.3, 38.6, 37.8, 33.1, 33.0, 32.4, 32.0, 31.8, 31.5, 28.5, 28.3, 27.3, 26.8, 25.6, 23.4, 23.3, 22.4, 20.1, 19.6, 14.3, 14.2. HRMS (FAB): calc for $C_{21}H_{36}LiO_3$: 343.2824; found: 343.2830.



(3,5-*cis*)(3,5-*trans*)-3-Butoxy-5-butyl-3,5-dimethyl-1,2-dioxolane (128):

Method A:

To a vial containing **110** (71 mg, 0.41 mmol) was added sequentially 1-butanol (3.25g, 44 mmol) and TsOH (7.1 mg, 0.04 mmol). After 2 days, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **128** as a yellow oil (162 mg, 56%). R_f (5% EA/hex): 0.41. ^1H NMR (400 MHz): 3.62 (m, 1H), 3.44 (m, 1H), 2.57 (d, J = 12.6, 0.5H), 2.47 (d, J = 12.4, 0.5H), 2.35 (d, J = 12.4, 0.5H), 2.24 (d, J = 12.6, 0.5H), 1.76-1.53 (4H), 1.47 (d, J = 8.6, 3H), 1.44-1.24 (9H), 0.93 (m, 3H). ^{13}C (100 MHz): 108.0, 107.8, 86.1, 85.8, 61.3, 57.8, 57.3, 40.1, 37.6, 32.13, 32.11, 27.1, 26.6, 25.4, 23.2, 23.1, 22.2, 20.0, 19.5, 19.4, 19.3, 14.1, 14.0, 13.9, 13.8. HRMS (EI): calc for $C_{13}H_{26}O_3$: 230.1882; found: 230.1883.



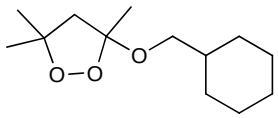
3-(1-Phenylmethoxy)-3,5,5-trimethyl-1,2-dioxolane (129):

Method A:

To a vial containing **107** (203.7 mg, 1.5 mmol) was added sequentially benzyl alcohol (19.376 g, 108 mmol) and TsOH (28.53 mg, 0.15 mmol). After 3 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (20 mL) and extracted with Et_2O (30 mL). The combined organic layers were washed with brine (30 mL) and subjected to standard drying and purification with 10% EA/hex to afford **129** as a yellow oil (226.4 mg, 66%).

Method B:

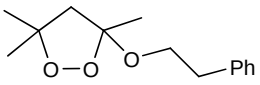
To a vial containing **107-OTMS** (110.7 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) was added sequentially benzyl alcohol (158 mg, 1.46 mmol) and TsOH (10 mg, 0.05mmol). After 5 min, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **129** as a yellow oil (89.2 mg, 74%). R_f (10% EA/hex): 0.62. ^1H NMR (500 MHz): 7.36 (m, 5H), 4.78 (d, J = 11.3, 1H), 4.54 (d, J = 11.3, 1H), 2.69 (d, J = 12.6, 1H), 2.42 (d, J = 12.6, 1H), 1.60 (s, 3H), 1.44 (s, 6H). ^{13}C (125 MHz): 138.8, 12.3, 127.7, 127.4, 108.7, 83.9, 64.1, 58.8, 27.7, 24.7, 20.1. LRMS (ESI): calc for $C_{13}H_{18}O_3Na$: 245.1; found: 245.1. HRMS (EI M-CH_3): calc for $C_{12}H_{15}O_3$: 207.1021; found: 207.1012 (4.4 ppm).



3-(Cyclohexylmethoxy)-3,5,5-trimethyl-1,2-dioxolane (130)

Method B:

To a vial containing **107-OTMS** (202.8 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) was added sequentially cyclohexanemethanol (0.60 mL, 4.9 mmol) and TsOH (19 mg, 0.1mmol). After 2 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and 5 mL H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **130** as a yellow oil (180 mg, 79%). R_f (10% EA/hex): 0.52. ^{1}H NMR (400 MHz): 3.39 (m, 1H), 3.22 (m, 1H), 2.53 (d, J = 12.4, 1H), 2.31 (d, J = 12.4, 1H), 1.84-1.59 (5H), 1.58-1.47 (1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.31-1.08 (3H), 1.0-0.86 (2H). ^{13}C (100 MHz): 108.3, 83.7, 76.9, 67.5, 58.8, 38.3, 30.3, 30.2, 27.8, 26.8, 26.1, 26.0, 24.8, 20.0. HRMS (ESI): calc for $C_{13}H_{24}O_3Na$: 251.1623; found: 251.1622 (1 ppm).

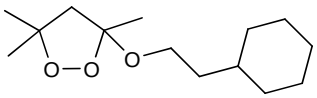


3-(2-phenylethoxy)-3,5,5-Trimethyl-1,2-dioxolane (131):

Method A:

To a vial containing **107** (190.9 mg, 1.44 mmol) was added sequentially 1-phenylethanol (22 mL, 183 mmol) and TsOH (26.3 mg, 0.14 mmol). After 5 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with Et_2O (25 mL). The combined organic layers were washed with brine (25 mL) and subjected to standard drying and purification with 5% EA/hex to afford **131** as a yellow oil (234 mg, 73%). R_f (5% EA/hex): 0.46. ^{1}H NMR (500 MHz): 7.17 (m, 5H), 3.89 (m, 1H), 3.67 (m, 1H), 2.92

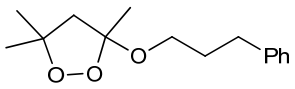
(m, 2H), 2.55 (d, J = 12.4, 1H), 2.34 (d, J = 12.4, 1H), 1.47 (s, 3H), 1.39 (d, J = 6.2, 6H). ^{13}C (125 MHz): 139.2, 129.0, 128.3, 126.1, 108.4, 83.8, 62.7, 58.7, 36.7, 27.6, 24.6, 19.9. HRMS (ESI): calc for $C_{14}H_{21}O_3$: 237.1491; found: 237.1499 (0.8 ppm)



3-(2-Cyclohexylethoxy)-3,5,5-trimethyl-1,2-dioxolane (132)

Method B:

To a vial containing **107-OTMS** (202.1 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-cyclohexylethanol (0.69 mL, 4.9 mmol) and TsOH (19 mg, 0.1mmol). After 2 hrs, the reaction was treated sequentially with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **132** as a yellow oil (180 mg, 79%). R_f (10% EA/hex): 0.48. ^{1}H NMR (400 MHz): 3.64 (m, 1H), 3.45 (m, 1H), 2.53 (d, J = 12.4, 1H), 2.32 (d, J = 12.4, 1H), 1.81-1.59 (5H), 1.54-1.33 (12H), 1.30-1.08 (3H), 0.98-0.82 (2H). ^{13}C (100 MHz): 108.4, 83.8, 59.8, 58.9, 34.7, 33.7, 33.2, 27.8, 26.8, 26.6, 26.5, 24.8, 20.1. HRMS (ESI): calc for $C_{14}H_{26}O_3Na$: 265.1779; found: 265.1176 (1 ppm).

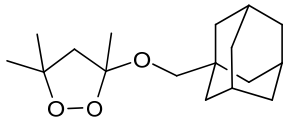


3-(3-phenylpropoxy)-3,5,5-Trimethyl-1,2-dioxolane (133)

Method A:

To a vial containing **107** (203.5 mg, 1.54 mmol) in CH_2Cl_2 (15 mL) was added sequentially 3-phenyl-1-propanol (1 mL, 7.5 mmol) and TsOH (27 mg, 0.14 mmol). After 2 hrs, the reaction was treated sequentially with sat. aq. $NaHCO_3$ (5 mL) and H_2O

(5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **133** as a yellow oil (272.2 mg, 71%). R_f (10% EA/hex): 0.5. ^{1}H NMR (400 MHz): 7.34-7.17 (5H), 3.67 (m, 1H), 3.51 (m, 1H), 2.82-2.70 (2H), 2.59 (d, J = 12.5, 1H), 2.38 (d, J = 12.5, 1H), 2.0-1.89 (2H), 1.20 9s, 3H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C (100 MHz): 142.4, 128.7, 128.4, 125.8, 108.4, 83.8, 61.0, 58.9, 32.5, 31.9, 27.8, 24.8, 20.1. HRMS (ESI): calc for $C_{15}H_{22}O_3Na$: 273.14687; found: 273.1468 (<1 ppm).



3-(1-(1-Adamantyl)methoxy)-3,5,5-trimethyl-1,2-dioxolane (134):

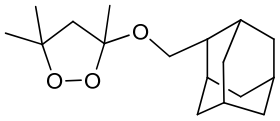
Method A:

To a vial containing **107** (236.8 mg, 1.8 mmol) in dichloromethane (15 mL) was added sequentially 1-adamantanemethanol (1.1228 g, 6.8 mmol) and TsOH (32 mg, 0.17 mmol). After 12 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine (30 mL) and subjected to standard drying and purification with 5% EA/hex to afford **134** as a yellow oil (164 mg, 33%).

Method B:

To a vial containing **107-OTMS** (81.2 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was added sequentially 1-adamantanemethanol (171 mg, 1.02 mmol) and TsOH (6.46 mg, 0.034mmol). After 3 hrs, the reaction was treated sequentially with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **134**

as a yellow oil (77.6 mg, 65%). R_f(5% EA/hex): 0.38. ^{1}H NMR (400 MHz): 3.19 (d, J = 8.9, 1H), 2.99 (d, J = 8.9, 1H), 2.55 (d, J = 12.3, 1H), 2.56 (d, J = 12.3, 1H), 2.01-1.94 (3H), 1.78-1.63 (6H), 1.63-1.52 (7H), 1.45 (s, 3H), 1.38 (d, J = 5.6, 6H). ^{13}C (100 MHz): 108.1, 83.4, 72.0, 58.7, 39.7, 37.3, 33.3, 28.3, 27.7, 24.9, 19.6. HRMS (FAB): calc for $C_{17}H_{28}O_3Li$: 280.2030; found: 280.2038.



3-(1-(2-adamantyl)methoxy)-3,5,5-trimethyl-1,2-dioxolane (135):

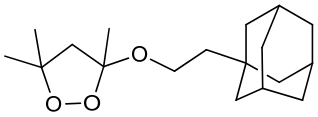
Method A:

To a vial containing **107** (213 mg, 1.61 mmol) in CH_2Cl_2 (15 mL) was added sequentially 2-adamantanemethanol (1.2134 g, 7.3 mmol) and TsOH (20 mg, 0.11 mmol). After 2 days, the reaction was treated with sat. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **135** as a yellow oil (340.7 mg, 75%).

Method B:

To a vial containing **107-OTMS** (81.2 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) was added sequentially 1-adamantanemethanol (171 mg, 1.03 mmol) and TsOH (6.4 mg, 0.03mmol). After 2 hrs, the reaction was treated with sat. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 10mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **135** as a yellow oil (60.4 mg, 62%). R_f(10% EA/hex): 0.7. ^{1}H NMR (500 MHz): 3.7 (apparent triplet, J = 8.4, 1H), 3.46 (m, 1H), 2.51 (d, J = 12.4, 1H), 2.3 (d, J = 12.4, 1H), 2.08-1.64 (13H), 1.54 (d, J = 12.6, 2H), 1.45 (s, 3H), 1.34 (m, 6H). ^{13}C (100 MHz): 108.1, 83.4, 63.7, 58.6, 44.1, 39.0,

38.8, 38.3, 32.1, 31.7, 29.6, 29.2, 28.4, 28.0, 27.6, 24.6, 19.8. HRMS (FAB): calc for $C_{17}H_{29}O_3$: 281.2117; found: 281.2206.



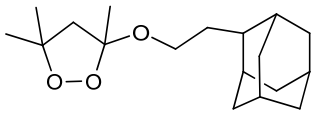
3-(2-(1-Adamantyl)ethoxy)- 3,5,5-trimethyl-1,2-dioxolane (136):

Method A:

To a vial containing **107** (262.2 mg, 1.99 mmol) in CH_2Cl_2 (15 mL) was added sequentially 1-adamantaneethanol (837.2 mg, 4.7 mmol) and TsOH (31 mg, 0.16 mmol). After 12 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were and washed with brine (30 mL) and subjected to standard drying and purification with 10% EA/hex to afford **136** as a yellow oil (93 mg, 16%).

Method B:

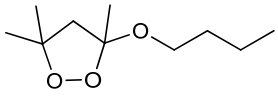
To a vial containing **107-OTMS** (76.2 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was added sequentially 1-adamantaneethanol (184.6 mg, 1.02 mmol) and TsOH (5.4 mg, 0.03mmol). After 1 hr, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **136** as a yellow oil (83.1 mg, 76%). R_f (5% EA/hex): 0.38. ^{1}H NMR (400 MHz): 3.60 (OT, J = 9.0, 1H), 3.51 (overlapping triplets, J = 9.0, 1H), 2.54 (d, J = 12.4, 1H), 2.34 (d, J = 12.4, 1H), 2-1.91 (3H), 1.75-1.63 (6H), 1.58-1.52 (6H), 1.49 (s, 3H), 1.46-1.30 (8H). ^{13}C (100 MHz): 108.3, 83.7, 58.8, 57.7, 44.0, 42.7, 37.1, 31.8, 28.7, 27.5, 24.6, 20.1. HRMS (EI): calc for $C_{18}H_{30}O_3$: 294.2195; found: 294.2196.



3-(2-(2-Adamantyl)ethoxy)- 3,5,5-trimethyl-1,2-dioxolane (137):

Method A:

To a vial containing **107** (123.6 mg, 0.96 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-adamantaneethanol (540 mg, 3.0 mmol) and TsOH (20.8 mg, 0.11 mmol). After 12 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and extracted Et_2O (30 mL). The combined organic layers were and washed with brine (30 mL) and subjected to standard drying and purification with 5% EA/hex to afford **137** as a yellow oil (161.9 mg, 59%). R_f (5% EA/hex): 0.37. ^1H (400 MHz): 3.63 (m, 1H), 3.45 (m, 1H), 2.51 (d, J = 12.4, 1H), 2.3 (d, J = 12.4, 1H), 1.93-1.60 (15H), 1.53-1.43 (5H), 1.36 (d, J = 3.1, 6H). ^{13}C (100 MHz): 108.2, 83.5, 60.3, 58.7, 41.0, 39.2, 39.1, 38.4, 32.8, 32.2, 31.8, 31.6, 31.4, 28.3, 28.0, 27.6, 24.6, 19.8. HRMS (FAB): calc for $C_{18}H_{31}O_3$: 295.2273; found: 295.2270.



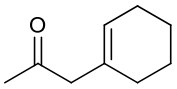
3-Butoxy-3,5,5-trimethyl-1,2-dioxolane (138):

Method A:

To a vial containing **107** (201.4 mg, 1.53 mmol) was added sequentially 1-butanol (13.2764 g, 179.1 mmol) and TsOH (46.6 mg, 0.25 mmol). After 3 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL) and subjected to standard drying and purification with 2.5% EA/hex to afford **138** as a yellow oil (162 mg, 56%).

Method B:

To a solution of **107-OTMS** (70.4 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) in a vial was added sequentially 1-butanol (75 mg, 1.02 mmol) and TsOH (6.3 mg, 0.03 mmol). After 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **138** as a yellow oil (33 mg, 51%). R_f (5% EA/hex): 0.23. ^1H NMR (300 MHz): 3.6 (overlapping triplets, J = 6.5, 1H), 3.45 (overlapping triplets, J = 6.3, 1H), 2.54 (d, J = 12.4, 1H), 2.84 (d, J = 12.4, 1H), 1.56 (m, 2H), 1.48 (s, 3H), 1.70-1.34 (8H), 0.94 (t, J = 7.3, 3H). ^{13}C (75 MHz): 108.4, 83.8, 61.6, 58.8, 32.3, 27.8, 24.8, 20.1, 19.5, 14.0. HRMS (CI): calc for $C_{10}H_{21}O_3$: 189.1491; found: 189.1498 (3.9 ppm).

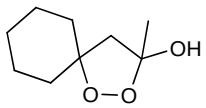


1-(Cyclohex-1-en-1-yl)propan-2-one (145):

To a 0 °C solution of methylene cyclohexane (5 g, 100 mmol) and acetaldehyde (3.8 mL, 68 mmol) in CH_2Cl_2 (174 mL) in a flame-dried RBF was added Me_2AlCl (68 mL, 68 mmol, nominally 1M in hexanes). The reaction was allowed to stir at 0 °C for 2 hr and then brought to rt. After two more hours of stirring, the reaction was treated with sat. aq. Na_2HPO_4 (20 mL) and aq. 2N HCl (10 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 20 % EA/hex to afford 1-cyclohexenyl-2-propanol as a yellow oil (6.619g, 90%). R_f (20% EA/hex): 0.30. ^1H NMR: 5.54 (s, 1H), 3.87 (m, 1H), 2.14-1.83 (4H), 1.76 (d, J = 2.2, 1H), 1.70-1.50 (6H), 1.19 (d, J = 6.3, 3H). ^{13}C: 135.0, 125.1, 65.0, 48.5, 28.5, 25.4, 23.0,

22.9, 22.5. HRMS (ESI): calc for $C_9H_{16}NaO$: 163.1099; found: 163.1098 (0.6 ppm). The NMR spectra matched those previously reported.[114]

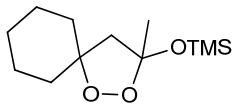
To a -78 °C solution of oxalyl chloride (0.96 mL, 12 mmol) in CH_2Cl_2 (72 mL) in a flame-dried RBF containing was added DMSO (1.3 mL, 19 mmol) in CH_2Cl_2 (20 mL) drop wise via an addition funnel and allowed to stir for 20 min. 1-cyclohexenyl-2-propanol (1.35 g, 9.6 mmol) in CH_2Cl_2 (20 mL) was added drop wise via an addition funnel and the reaction allowed to stir at -78°C for 1 hr. Et_3N (7 mL, 48 mmol) was next added and the reaction stirred at -78°C for 30 min and rt for 1 hr. The reaction was then treated with H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **145** as a yellow oil (1.0833g, 81%). R_f (10% EA/hex): 0.27. ^1H NMR (300 MHz): 5.61-5.53 (1H), 3.00 (s, 2H), 2.09-2.00 (2H), 1.96-1.87 (2H), 1.70-1.51 (4H). ^{13}C (75 MHz): 208.1, 131.9, 126.5, 53.6, 29.2, 28.8, 25.6, 22.9, 22.2. IR: 2925, 2836, 1710, 1437, 1354. HRMS (CI): calc for $C_9H_{15}O$: 139.1123; found: 139.1123 (0.1 ppm).



3-Methyl-1,2-dioxaspiro[4.5]decan-3-ol (146):

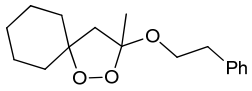
In a RBF containing cobalt (II) acetylacetonate (77.4 mg, 0.30 mmol) in 1,2-dichloroethane (29 mL) was added **145** (404.2 mg, 2.93 mmol) and triethylsilane (0.96 mL, 5.8 mmol) and the solution placed under an atmosphere of O_2 (balloon). The reaction was stirred overnight and treated with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 40% Et_2O/pent to afford **146** as a colorless oil (262.9 mg, 52 %). R_f (30% EA/hex): 0.30. ^1H NMR (600 MHz): 3.32 (s, 1H), 2.4 (d, J = 12.8, 1H), 2.36 (d, J

= 12.8, 1H), 1.80-1.53 (6H), 1.52 (s, 3H), 1.44-1.31 (4H). ^{13}C (150 MHz): 105.7, 86.0, 57.1, 36.0, 34.9, 25.2, 24.2, 23.4, 23.2. IR: 3452, 2933, 2858, 1447, 1256. HRMS (ESI): calc for $C_9H_{16}NaO_3$: 195.0997; found: 195.0990 (3.5 ppm).



3-Methyl-3-trimethylsiloxy-1,2-dioxaspiro[4.5]decane (147):

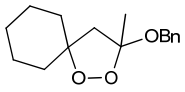
To a flame-dried RBF containing **146** (960.7 mg, 5.6 mmol) in CH_2Cl_2 (56 mL) was added imidazole (1.1 g, 17 mmol) and chlorotrimethylsilane (1.1 mL, 8.4 mmol) and the reaction was stirred at rt for 1 hr. The reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 5 % EA/hex to afford **147** as a yellow oil (1.2255 g, 90%). R_f (5% EA/hex): 0.48. ^{1}H NMR (600 MHz): (2.46 (d, J = 12.3, 1H), 2.34 (d, J = 12.3, 1H), 1.80-1.53 (6H), 1.51 (s, 3H), 1.44-1.43 (4H), 0.19 (9H). ^{13}C (75 MHz): 107.0, 85.7, 59.8, 36.5, 35.0, 25.5, 25.4, 24.4, 23.4, 1.7. HRMS (ESI): calc for $C_{12}H_{24}NaO_3Si$: 267.1392; found: 267.1398 (2.2 ppm).



3-Methyl-3-(1-phenylethoxy)-1,2-dioxaspiro[4.5]decane (148):

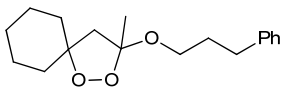
To a vial containing a solution of **147** (102.6 mg, 0.42 mmol) in CH_2Cl_2 (8 mL) was added sequentially 2-phenylethanol (250 mg, 2.0 mmol) and TsOH (8.0 mg, 0.04 mmol) and the solution stirred for 2 hr. The reaction was then treated with sat. aq. $NaHCO_3$ (8 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **148** as a yellow oil (99.3 mg, 86%). R_f (5% EA/hex): 0.43. ^{1}H NMR (300 MHz): 7.36-7.12 (5H), 3.92

(dt, J = 9.2, 7.2, 1H), 3.69 (dt, J = 9.2, 7.2), 3.04 (2H), 2.49 (d, J = 12.5, 1H), 2.31 (d, J = 12.5, 1H), 1.90-1.30 (13H). ^{13}C (75 MHz): 139.3, 129.1, 128.3, 126.2, 107.9, 85.6, 62.7, 57.3, 36.8, 36.4, 34.6, 25.3, 24.3, 23.3, 20.0. HRMS (ESI): calc for $C_{17}H_{24}NaO_3$: 299.1623; found: 299.1615 (2.6 ppm).



3-Methyl-3-(1-phenylmethoxy)-1,2-dioxaspiro[4.5]decane (149):

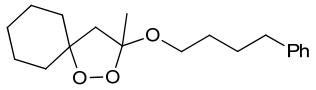
To a vial containing a solution of **147** (202.9mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially benzyl alcohol (0.42 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 1 hr. After which the reaction was treated with sat. aq. $NaHCO_3$ (8 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were concentrated *in vacuo*, and the residue was purified via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography with 10% EA/hex to afford **149** (123.6 mg, 57%). R_f (5% EA/hex): 0.54. ^1H NMR (300 MHz): 7.48-7.25 (5H), 4.77 (d, J = 11.4, 1H), 4.51 (d, J = 11.4, 1H), 2.59 (d, J = 12.5, 1H), 2.37 (d, J = 12.5, 1H), 1.91-1.54 (9H), 1.50-1.33 (4H). ^{13}C (75 MHz): 139.0, 128.5, 127.9, 127.5, 108.2, 85.8, 64.1, 57.3, 36.6, 34.7, 25.4, 24.4, 23.4, 20.2. HRMS (ESI): calc for $C_{16}H_{22}O_3Na$: 285.1467; found: 285.1466 (0.4 ppm).



3-Methyl-3-(1-phenylpropoxy)-1,2-dioxaspiro[4.5]decane (150):

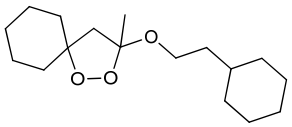
To a vial containing a solution of **147** (201.2 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added sequentially 3-phenyl-1-propanol (0.55 mL, 4.1 mmol) and TsOH (11.5 mg, 0.06

mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification 10% EA/hex to afford **150** as a yellow oil (209.7 mg, 88%). R_f (10% EA/hex): 0.48. ^1H NMR (400 MHz): 7.33-7.17 (5H), 3.67 (m, 1H), 3.48 (m, 1H), 2.75 (m, 2H), 2.50 (d, J = 12.5, 1H), 2.33 (d, J = 12.5, 1H), 1.99-1.55 (8H), 1.51-1.35 (7H). ^{13}C (100 MHz): 142.5, 128.7, 128.4, 125.8, 107.9, 85.6, 61.0, 57.3, 36.5, 34.7, 32.6, 31.9, 25.4, 24.4, 23.4, 20.0. HRMS (ESI): calc for $C_{18}H_{26}O_3Na$: 313.1780; found: 313.1770 (3 ppm).



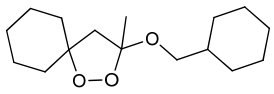
3-Methyl-3-(1-phenylbutoxy)-1,2-dioxaspiro[4.5]decane (151):

To a vial containing **147** (202.3 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-phenyl-1-butanol (0.63 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. After which the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with column chromatography, ozonolysis, column chromatography and HPLC with 10% EA/hex to afford **151** as a yellow oil (188.9 mg, 72%). R_f (10% EA/hex): 0.59. ^1H NMR (600 MHz): 7.28-7.14 (5H), 3.62 (m, 1H), 3.45 (m, 1H), 2.64 (m, 2H), 2.42 (d, J = 12.4, 1H), 2.27 (d, J = 12.4, 1H), 1.81-1.50 (10 H), 1.46-1.32 (7H). ^{13}C (150 MHz): 142.9, 128.6, 128.4, 125.8, 107.8, 85.6, 61.5, 57.3, 36.5, 35.8, 34.7, 29.8, 28.2, 25.4, 24.4, 23.4, 20.1. HRMS (ESI): calc for $C_{19}H_{28}O_3Na$: 327.1936; found: 327.1926.



3-(2-Cyclohexylethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (152):

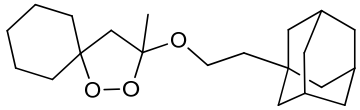
To a vial containing a solution of **147** (198.9 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added sequentially 2-cyclohexaneethanol (0.57 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **152** as a yellow oil (185.8 mg, 81%). R_f (10% EA/hex): 0.56. ^{1}H NMR (400 MHz): 3.39 (dd, J = 9.0, 6.8, 1H), 3.21 (dd, J = 9.0, 6.8, 1H), 2.43 (d, J = 12.4, 1H), 2.26 (d, J = 12.4, 1H), 1.84-0.82 (26H).. ^{13}C (100 MHz): 107.8, 85.5, 59.6, 57.3, 37.6, 36.6, 34.72, 34.70, 33.72, 33.2, 26.8, 26.6, 26.5, 25.4, 24.4, 23.4, 20.0. HRMS (ESI): calc for $C_{17}H_{30}O_3Na$: 305.2093; found 305.2091 (1 ppm).



3-(2-Cyclohexylmethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (153):

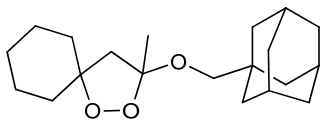
To a vial containing a solution of **147** (195.9 mg, 0.80 mmol) in CH_2Cl_2 (8 mL) was added sequentially 2-cyclohexanemethanol (0.5 mL, 4 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **153** as a yellow oil (181.5 mg, 84%). R_f (10% EA/hex): 0.6. ^{1}H NMR (600 MHz): 3.7 (m, 1H), 3.47 (m, 1H), 2.44 (d, J = 12.5, 1H), 2.27 (d, J = 12.5, 1H), 1.84-0.81 (24H). ^{13}C (100 MHz): 107.8, 85.6, 67.5, 57.3, 38.3, 36.6, 34.7, 30.3, 30.2, 26.9, 26.1, 26.0, 25.4,

24.4, 23.4, 20.0. HRMS (ESI): calc for $C_{16}H_{28}O_3Na$: 291.1936; found 291.1922 (4.8 ppm).



3-(1-(1-Adamantyl)ethoxy))-3-methyl-1,2-dioxaspiro[4.5]decane (154):

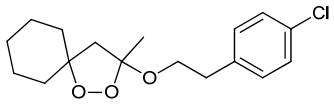
To a vial containing a solution of **147** (202.1 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially 1-adamantaneethanol (735.8 mg, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 24 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were subjected to standard drying and the residue was purified via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 5% EA/hex to afford **154** as a yellow oil (185.8 mg, 81%). R_f (5% EA/hex): 0.4. ^1H NMR (600 MHz): 3.67 (m, 1H), 3.49 (m, 1H), 2.42 (d, J = 12.5, 1H), 2.29 (d, J = 12.5, 1H), 1.63 (s, 3H), 1.84-1.28 (27H). ^{13}C (150 MHz): 107.9, 85.6, 57.8, 57.4, 44.2, 42.9, 37.3, 36.5, 34.7, 32.0, 28.9, 25.4, 24.4, 23.4, 20.2. HRMS (ESI): calc for $C_{21}H_{34}O_3Na$: 357.2406; found: 357.2399 (2.0 ppm).



3-(1-(1-Adamantyl)methoxy))-3-methyl-1,2-dioxaspiro[4.5]decane (155):

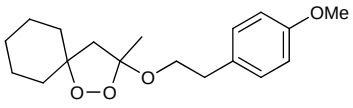
To a vial containing a solution of **147** (101.5mg, 0.42 mmol) in CH_2Cl_2 was added sequentially 1-adamantanemethanol (350.8 mg, 2.11 mmol) and TsOH (11.3 mg, 0.06 mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$

(8 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **155** as a white solid (116.7 mg, 89%). R_f (5% EA/hex): 0.21. MP = 36-38 ^oC. ^1H NMR (300 MHz): 3.17 (d, J = 8.9, 1H), 2.95 (d, J = 8.9, 1H), 2.44 (d, J = 12.4, 1H), 2.24 (d, J = 12.4, 1H), 2.0-1.90 (3H), 1.80-1.45 (17H), 1.45-1.30 (6H). ^{13}C (75 MHz): 107.6, 85.4, 72.1, 57.3, 39.8, 37.5, 36.7, 34.8, 33.4, 28.5, 25.4, 24.4, 23.4, 19.7. HRMS (ESI): calc for $C_{20}H_{32}NaO_3$: 343.2249; found: 343.2255 (2 ppm).



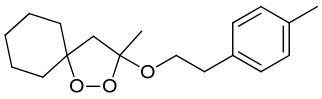
3-(4-Chlorophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (156):

To a vial containing a solution of **147** (197.7 mg, 0.81 mmol) in CH_2Cl_2 (10 mL) was added sequentially 4-chlorophenethyl alcohol (0.51 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification and was purified via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **156** as a yellow oil (152.6 mg, 61%). R_f (10% EA/hex): 0.56. ^1H NMR (400 MHz): 7.30-7.18 (4H), 3.87 (dt, J = 9.3, 7.0, 1H), 3.63 (dt, J = 9.3, 7.0, 2.94-2.82 (2H), 2.43 (d, J = 12.5, 1H), 2.28 (d, J = 12.5, 1H), 1.89-1.31 (13H). ^{13}C (100 MHz): 138.0, 132.0, 130.5, 128.5, 107.9, 85.7, 62.3, 36.5, 36.0, 34.7, 25.4, 24.3, 23.4, 19.9. HRMS (ESI): calc for $C_{17}H_{23}O_3NaCl$: 333.1233; found: 333.1218 (4.5 ppm).



3-(4-Methoxyphenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (157):

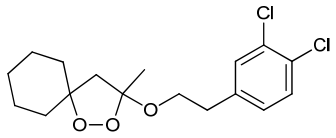
To a vial containing a solution of **147** (201.7 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-methoxyphenethyl alcohol (663.5 mg, 4.4 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 24 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification and was purified via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **157** as a yellow oil (98.2 mg, 39%). R_f (10% EA/hex): 0.47. ^{1}H NMR (600 MHz): 7.18 (d, J = 8.7, 2H), 6.84 (d, J = 8.7, 2H), 3.84 (m, 1H), 3.79 (s, 3H), 3.61(m, 1H), 2.84 (m, 2H), 2.44 (d, J = 12.6, 1H), 2.28 (d, J = 12.6, 1H), 1.81-1.51 (6H), 1.45-1.33 (7H). ^{13}C (150 MHz): 158.2, 131.4, 130.0, 113.8, 107.9, 85.7, 63.0, 57.3, 55.4, 36.5, 35.9, 34.6, 25.4, 24.4, 23.4, 20.1. HRMS (ESI): calc for $C_{18}H_{26}O_4Na$: 329.1729; found 329.1721 (2.4 ppm).



3-Methyl-3-(4-methylphenethoxy)-1,2-dioxaspiro[4.5]decane (158):

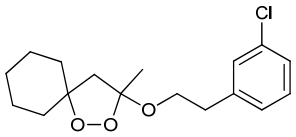
To a vial containing a solution of **147** (197 mg, 0.81 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-methylphenethyl alcohol (0.57 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification and was purified via column

chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography with 5% EA/hex to afford **158** (155.7 mg, 65%). R_f (10% EA/hex): 0.43. ^{1}H NMR (600 MHz): 7.19-7.05 (4H), 3.85 (m, 1H), 3.62 (m, 1H), 2.87 (m, 2H). 2.45 (d, J = 12.4, 1H), 2.35-2.25 (4H), 1.84-1.49 (6H), 1.48-1.29 (7H). ^{13}C (150 MHz): 136.2, 135.7, 129.1, 129.0, 107.9, 85.7, 63.0, 57.3, 36.5, 36.4, 34.6, 25.4, 24.4, 23.4, 21.2, 20.1. HRMS (ESI): calc for $C_{18}H_{26}O_3Na$: 313.1780; found: 313.1766 (4.47 ppm).



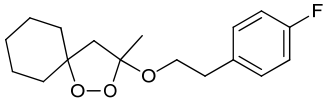
3-(3,4-Dichlorophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (159):

To a vial containing a solution of **147** (203 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially 3,4-dichlorophenethyl alcohol (0.59 mL, 4.1 mmol) and TsOH (17.1 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification and was purified via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC (x2) with 5% EA/hex to afford **159** (63.7 mg, 22%). R_f (10% EA/hex): 0.3. ^{1}H NMR (600 MHz): 7.39 (d, J = 1.9, 1H), 7.34 (d, J = 8.3, 1H), 7.10 (dd, J = 8.3, 1.8, 1H), 3.86 (m, 1H), 3.62 (m, 1H), 2.84 (t, J = 6.8, 2H), 2.4 (d, J = 12.5, 1H), 2.27 (d, J = 12.5, 1H), 1.80-1.50 (6H), 1.40-1.32 (7H). ^{13}C (150 MHz): 140.0, 132.2, 131.2, 130.2, 130.1, 128.7, 107.9, 85.7, 61.8, 57.4, 36.5, 35.7, 34.7, 25.3, 24.3, 23.3, 19.8. HRMS (ESI): calc for $C_{17}H_{22}O_3NaCl_2$: 367.0344; found: 367.0843 (3.0 ppm).



3-(3-Chlorophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (160):

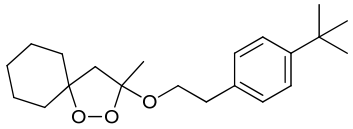
To a vial containing a solution of **147** (249.1 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) was added sequentially 3-chlorophenethyl alcohol (0.66 mL, 5 mmol) and TsOH (19 mg, 0.1 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 5% EA/hex and HPLC with 2.5% EA/hex to afford **160** (117.2 mg, 37%). R_f (10% EA/hex): 0.56. ^{1}H NMR (600 MHz): 7.30-7.09 (5H), 3.86 (m, 1H), 3.63 (m, 1H), 2.87 (m, 2H), 2.42 (d, J = 12.5, 1H), 2.27 (d, J = 12.5, 1H), 1.81-1.50 (6H), 1.45-1.30 (7H). ^{13}C (150 MHz): 141.6, 134.1, 129.6, 129.4, 127.4, 126.4, 107.9, 85.7, 62.2, 57.4, 36.5, 36.4, 34.6, 25.4, 24.4, 23.4, 19.9. HRMS (ESI): calc for $C_{17}H_{23}O_3NaCl$: 333.1233; found: 333.1223 (3.0 ppm).



3-(4-Fluorophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (161):

To a vial containing a solution of **147** (200 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-fluorophenethyl alcohol (0.51 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic

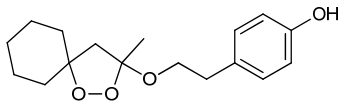
layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **161** (144.5 mg, 71%). R_f (10% EA/hex): 0.55. ^{1}H NMR (600 MHz): 7.24-7.19 (2H), 7.0-6.94 (2H), 3.85 (m, 1H), 3.61 (m, 1H), 2.42 (d, J = 12.5, 1H), 2.28 (d, J = 12.5, 1H), 1.82-1.51 (6H), 1.47-1.33 (7H). ^{13}C (150 MHz): 162.5, 160.9, 135.1, 135.1, 130.6, 130.5, 115.2, 115.0, 107.9, 85.7, 62.6, 57.4, 57.3, 36.5, 35.9, 24.7, 25.4, 24.4, 23.4, 20.0. ^{19}F (376 MHz): -117.52, -117.53, -117.54, -117.56, -117.57, -117.58, -117.6. HRMS (ESI): calc for $C_{17}H_{23}O_3NaF$: 317.1529; found: 317.1521 (2.5 ppm).



3-(4-(tert-Butyl)phenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (162):

To a vial containing a solution of **147** (204.2 mg, 0.84 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-t-butylphenethyl alcohol (0.75 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography with 5% EA/hex to afford **162** (176.3 mg, 65%). R_f (10% EA/hex): 0.35. ^{1}H NMR (300 MHz): 7.36-7.3 (2H), 7.24-7.17 (2H), 3.87 (m, 1H), 3.65 (m, 1H), 3.65 (m, 1H), 2.80 (m, 2H), 2.46 (d, J = 12.5, 1H), 2.30 (d, J = 12.5, 1H), 1.86-1.51 (6H),

1.50-1.27 (16H). ^{13}C (75 MHz): 149.0, 136.2, 128.8, 125.3, 107.9, 85.7, 62.9, 57.3, 36.5, 36.5, 36.2, 34.6, 34.5, 31.6, 25.4, 24.4, 23.3, 20.1. HRMS (ESI): calc for $C_{21}H_{32}O_3Na$: 355.2249; found: 355.2253 (1.1 ppm).

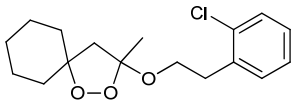


3-(4-Hydroxyphenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (163):

To a flame-dried RBF containing a solution of **147** (1.2513 g, 5.1 mmol) in CH_2Cl_2 (51 mL) was added sequentially 2-[4-(tert-butyldimethylsilanyloxy)phenyl]ethanol (3.8872 g, 15.4 mmol) and TsOH (97 mg, 0.51 mmol) and the solution stirred for 2 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (8 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford 3-((tert-butyldimethyl(phenoxy)silane)ethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (1.2919 g, 62%). R_f (10% EA/hex): 0.62. ^1H NMR (400 MHz): 7.12-7.08 (2H), 6.78-6.72 (2H), 3.82 (m, 1H), 3.6 (m, 1H), 2.82 (m, 2H), 2.44 (d, J = 12.6, 1H), 2.27 (d, J = 12.6, 1H), 1.83-1.50 (6H), 1.46-1.32 (7H), 0.99 (s, 9H), 0.19 (s, 6H). ^{13}C (100 MHz): 154.1, 133.0, 130.0, 120.0, 108.0, 85.7, 63.0, 57.3, 36.5, 36.0, 34.7, 25.9, 25.4, 24.4, 23.4, 20.1, 18.4, -4.2. HRMS (ESI):; calc for $C_{23}H_{38}O_4NaSi$: 429.2437; found: 429.2427 (2.3ppm).

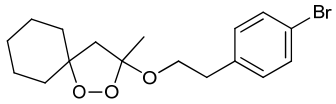
To a flame-dried vial containing a solution of 3-((tert-butyldimethyl(phenoxy)silane)ethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (1.1509 g, 2.8 mmol) in THF (15 mL) was added TBAF (3.4 mL, 3.4 mmol, 1M in THF). After 30 min the reaction was treated with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were subjected to standard drying and purified twice by column chromatography with 30% EA/hex to afford **163** (790.5 mg, 96%). R_f (30%

EA/hex): 0.48. ^{1}H NMR (400 MHz): 7.11 (d, J = 8.5, 2H), 6.76 (m, 2H), 4.85 (s, 1H), 3.82 (m, 1H), 3.60 (m, 1H), 2.82 (m, 2H), 2.45 (d, J = 12.5, 1H), 2.29 (d, J = 12.5, 1H), 1.82-1.52 (7H), 1.47-1.32 (6H). ^{13}C (100 MHz): 154.1, 131.5, 130.2, 115.3, 108.0, 85.8, 63.1, 57.3, 36.5, 35.9, 34.6, 25.4, 24.4, 23.4, 20.1. HRMS (ESI): calc for $C_{17}H_{24}O_3Na$: 315.1572; found: 315.1562 (3.2 ppm).



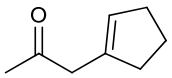
3-(2-Chlorophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (164):

To a vial containing a solution of **147** (200.1 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added sequentially 2-chlorophenethyl alcohol (0.54 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **164** (146 mg, 57%). R_f (10% EA/hex): 0.50. ^{1}H NMR (600 MHz): 7.37-7.32 (2H), 7.21-7.12 (2H), 3.88 (m, 1H), 3.71 (m, 1H), 3.03 (m, 2H), 2.43 (d, J = 12.5, 1H), 2.28 (d, J = 12.5, 1H), 1.82-1.52 (6H), 1.48-1.32 (7H). ^{13}C (150 MHz): 136.8, 134.2, 131.3, 129.3, 127.6, 126.6, 107.9, 85.5, 60.8, 57.1, 36.3, 34.5, 34.3, 25.2, 24.2, 23.2, 19.9. HRMS (ESI): calc for $C_{17}H_{23}O_3NaCl$: 333.1233; found: 333.1231 (0.6 ppm).



3-(4-Bromophenethoxy)-3-methyl-1,2-dioxaspiro[4.5]decane (165):

To a vial containing a solution of **147** (203.5 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added sequentially 4-bromophenethyl alcohol (0.57 mL, 4.1 mmol) and TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **165** (140.1 mg, 47%). R_f (10% EA/hex): 0.52. ^{1}H NMR (600 MHz): 7.40 (d, J = 8.3, 2H), 7.14 (d, J = 8.3, 2H), 3.85 (m, 1H), 3.61 (m, 1H), 2.85 (m, 1H), 2.40 (d, j = 12.5, 1H), 2.32 (d, J = 12.5, 1H), 1.81-1.51 (6H), 1.44-1.32 (7H). ^{13}C (150 MHz): 138.5, 131.4, 131.0, 120.0, 107.9, 85.7, 62.2, 57.4, 36.5, 36.1, 34.6, 25.4, 24.3, 23.4, 19.9. HRMS (ESI): calc for $C_{17}H_{23}O_3NaBr$: 377.0728; found: 377.0715 (3.0 ppm).

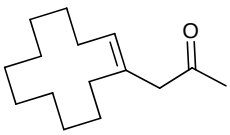


1-(Cyclopent-1-en-1-yl)propan-2-one (168):

To a flame-dried RBF containing a 0 °C solution of acetaldehyde (1.7 mL, 29 mmol) and methylene cyclopentane (2.3 mL, 22 mmol) in CH_2Cl_2 (106 mL) was added Me_2AlCl (28 mL, 28 mmol, nominally 1M in hexanes). The resulting solution was stirred at 0 °C for 2 hrs and allowed to warm to rt. After stirring an additional 3 hrs, the reaction was treated with sat. aq. NaH_2PO_4 (20 mL) and aq. 2N HCl until clear. The resulting suspension was

extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford 1-(cyclopent-1-en-1-yl)propan-2-ol (2.15 g, 78%). R_f (30% EA/hex): 0.53. ^{1}H NMR (400 MHz): 5.51-5.48 (1H), 3.97-3.88 (1H), 2.37-2.15 (6H), 1.88 (m, 2H), 1.70 (s, 1H), 1.20 (d, J = 6.1, 3H). ^{13}C (100 MHz): 141.5, 127.3, 65.7, 41.5, 35.3, 32.7, 23.6, 23.1.

To a flame-dried RBF containing a -78^{o}C solution of oxalyl chloride (1.5 mL, 18 mmol) in CH_2Cl_2 (90 mL) was added a solution of DMSO (2.2 mL, 30 mmol) in CH_2Cl_2 (30 mL) via an addition funnel. The resulting solution was stirred at -78 ^{o}C for 30 min, after which 1-(cyclopent-1-en-1-yl)propan-2-ol (1.89 g, 15 mmol) in CH_2Cl_2 (30 mL) was added via an addition funnel. The reaction was stirred for 1 hr, after which Et_3N (11 mL, 75 mmol) was added. The reaction was stirred at -78 °C for 30 min and then allowed to warm to rt. After 30 min, the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x50 mL). The combined organic layers were subjected to standard drying and purification with 20% Et_2O/pent to 30% Et_2O/pent to afford **168** (1.48 g, 82%). R_f (20% EA/hex): 0.61. ^{1}H NMR (300 MHz): 5.53 (s, 3H), 3.20 (s, 2H), 2.39-2.21 (4H), 2.15 (s, 3H), 1.96-1.89 (1H). ^{13}C (75 MHz): 207.3, 137.3, 128.9, 46.7, 35.4, 32.8, 29.5, 23.7. IR: 2925, 2836, 1710. HRMS (CI): calc for $C_8H_{13}O$: 125.0966; found: 125.0967 (0.5 ppm).

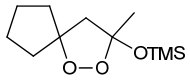


1-(Cyclododec-1-en-1-yl)propan-2-one (169):

To a flame-dried RBF containing a 0 °C solution of acetaldehyde (0.47 mL, 8.4 mmol) and 1-methylidenecyclododecane (1.1642g, 6.5 mmol) in CH_2Cl_2 (33 mL) was added

Me_2AlCl (8.4 mL, 8.4 mmol, nominally 1M in hexanes). The resulting solution was stirred at 0 °C for 2 hrs and allowed to warm to rt. After stirring an additional 3hrs, the reaction was treated with sat. aq. NaH_2PO_4 (20 mL) and aq. 2N HCl until clear. The resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford 1-(cyclododec-1-en-1-yl)propan-2-ol (1.15 g, 79%). R_f (20% EA/hex): 0.44. ^{1}H NMR (300 MHz): 5.57-5.46 (1H), 3.88 (m, 1H), 2.44-1.88 (6H), 1.71 (s, 1H), 1.65-1.11 (18H). ^{13}C (75 MHz): 134.7, 131.8, 66.3, 38.8, 36.0, 27.7, 26.7, 26.6, 26.0, 25.5, 25.0, 24.7, 24.66, 24.63, 24.0, 23.1. HRMS (ESI): calc for $C_{15}H_{28}ONa$: 247.2038; found: 247.2037 (0.4 ppm).

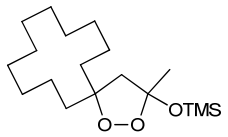
To a flame-dried RBF containing a -78^{o}C solution of oxalyl chloride (0.45 mL, 5.4 mmol) in CH_2Cl_2 (30 mL) was added a solution of DMSO (0.64 mL, 9 mmol) in CH_2Cl_2 (10 mL) via an addition funnel. The resulting solution was stirred at -78 ^{o}C for 30 min, after which 1-(cyclododec-1-en-1-yl)propan-2-ol (930 mg, 4.2 mmol) in CH_2Cl_2 (10 mL) was added via an addition funnel. The reaction was stirred for 1 hr, after which Et_3N (3.1 mL, 23 mmol) was added. The reaction was stirred at -78 °C for 30 min and then allowed to warm to rt. After 30 min, the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **169** (789.7 mg, 86%). R_f (5% EA/hex): 0.48. ^{1}H NMR (600 MHz): 5.56 (t, J = 7.7, 1H), 3.15 (s, 2H), 2.18-2.02 (7H), 1.56-1.13 (16H). ^{13}C (75 MHz): 207.2, 132.1, 131.1, 44.8, 36.5, 29.3, 28.1, 27.0, 26.4, 26.1, 25.4, 25.0, 24.5, 24.2, 24.1. IR: 2924, 2855, 1708 HRMS (ESI): calc for $C_{15}H_{26}ONa$: 245.1881; found: 245.1873 (3.3 ppm).



3-Methyl-3-trimethylsiloxy-1,2-dioxaspiro[4.4]-nonane (170):

To a RBF containing a solution of cobalt (II) acetylacetonate (247 mg, 0.96 mmol) in 1,2-dichloroethane (96 mL) was added sequentially **168** (1.1936 g, 9.6 mmol), triethylsilane (3.1 mL, 19.2 mmol), and *t*-BuOOH (1.75 mL, 9.6 mmol, 5.5M in decane). The resulting solution was stirred under an atmosphere of O_2 (balloon). After 24 hrs the reaction was diluted with NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford 3-methyl-1,2-dioxaspiro[4.4]nonan-3-ol (979.4 mg, 65%). ^{1}H NMR (300 MHz): 3.01 (s, 1H), 2.69 (d, J = 13.0, 1H), 2.57 (d, J = 13.0, 1H), 2.26 (1H), 1.94-1.37 (10H). ^{13}C (75 MHz): 105.9, 94.6, 56.7, 38.7, 34.9, 24.5, 24.4, 23.4. HRMS (ESI): calc for $C_8H_{14}O_3Na$: 181.0841; found: 181.0839 (1.1 ppm).

To a flame-dried RBF containing a solution of 3-methyl-1,2-dioxaspiro[4.4]nonan-3-ol (853.6 mg, 5.4 mmol) in CH_2Cl_2 (23 mL) was added sequentially imidazole (1.1 g, 16 mmol) and chlorotrimethylsilane (1.0 mL, 8.1 mmol) and the reaction was allowed to stir for 1 hr. The reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with column chromatography with 5% EA/hex to afford **170** (1.0401 g, 89%). R_f (5% EA/hex): 0.38. ^{1}H NMR (400 MHz): 2.73 (d, J = 12.6, 1H), 2.54 (d, J = 12.6, 1H), 2.22-2.13 (1H), 1.92-1.85 (2H), 1.77-1.39 98H), 0.20 (s, 9H). ^{13}C (100 MHz): 107.3, 94.5, 59.3, 38.5, 34.7, 25.8, 24.6, 24.3, 1.7. HRMS (ESI): calc for $C_1H_{22}O_3Na$: 253.1236; found: 253.1240 (1.6 ppm).

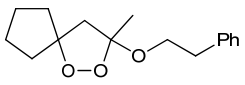


3-Methyl-3-trimethylsiloxy-1,2-dioxaspiro[4.4]-hexadecane (171):

To a RBF containing a solution of cobalt (II) acetylacetonate (85 mg, 0.32 mmol) in 1,2-dichloroethane (32 mL) was added sequentially **169** (720.7 mg, 3.2 mmol), triethylsilane (1.1 mL, 6.4 mmol), and *t*-BuOOH (0.6 mL, 3.2 mmol, 5.5M in decane). The resulting solution was stirred under an atmosphere of O_2. After 24 hrs the reaction was diluted with NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford 3-methyl-1,2-dioxaspiro[4.11]hexadecan-3-ol (645.1 mg, 78%). ^{1}H NMR (400 MHz): 3.00 (s, 1H), 2.47 (d, J = 12.9, 1H), 2.37 (d, J = 12.9, 1H), 1.86-1.74 (2H), 1.62-1.27 (24H). ^{13}C (100 MHz): 105.8, 100.2, 89.4, 57.2, 32.1, 31.6, 26.6, 26.4, 26.1, 23.5, 22.7, 22.6, 22.4, 22.2, 20.7, 19.7. HRMS (ESI): calc for $C_{15}H_{28}O_3Na$: 279.1936; found: 279.1927 (3.2 ppm).

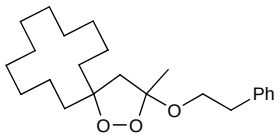
To a flame-dried RBF containing a solution of 3-Methyl-1,2-dioxaspiro[4.11]hexadecan-3-ol (587.3 mg, 2.3 mmol) in CH_2Cl_2 (23 mL) was treated sequentially with imidazole (0.80 g, 12 mmol) and chlorotrimethylsilane (0.9 mL, 7 mmol) and was allowed to stir for 1 hr. After which the reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with column chromatography twice with 5% EA/hex to afford **171** (688.3 mg, 91%). R_f (10% EA/hex): 0.57. ^{1}H NMR (400 MHz): 2.50 (d, J = 12.4, 1H), 2.31 (d, J = 12.4, 1H), 1.88-138 (1H), 1.63-1.22 (24H), 0.18 (s, 9H). ^{13}C (100 MHz): 107.1, 89.1, 59.9, 32.4, 31.3, 26.7, 26.4, 26.1, 25.6, 22.7,

22.6, 22.4, 22.2, 20.8, 19.7, 1.7. HRMS (ESI): calc for $C_{18}H_{36}O_3NaSi$: 351.2331; found: 351.2328 (0.85 ppm).



3-Methyl-3-phenethoxy-1,2-dioxaspiro[4.4]nonane (172):

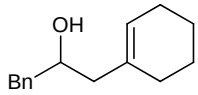
To a vial containing a solution of **170** (202 mg, 1.5 mmol) in CH_2Cl_2 (9 mL) was added sequentially 2-phenethanol (0.73 mL, 4.4 mmol) and TsOH (17 mg, 0.09 mmol) and the solution stirred for 3 hrs. The reaction was then treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography (5% EA/hex) and HPLC (x3 with 5% EA/hex) to afford **172** (141.8 mg, 62%). R_f (5% EA/hex): 0.40. ^1H NMR (400 MHz): 7.36-7.18 (5H), 3.87 (m, 1H), 3.70 (m, 1H), 2.93 (m, 2H), 2.74 9d, J = 12.4, 1H), 2.48 (d, J = 12.4, 1H), 2.24-2.15 (1h), 1.94-1.43 (10H). ^{13}C (100 MHz): 138.3, 129.2, 128.4, 126.3, 108.2, 94.4, 63.2, 56.4, 38.7, 36.9, 34.7, 24.6, 24.3, 20.4. HRMS (ESI): calc for $C_{16}H_{22}O_3Na$: 285.1467; found: 285.1472 (1.8 ppm).



3-Methyl-3-phenethoxy-1,2-dioxaspiro[4.11]hexadecane (173):

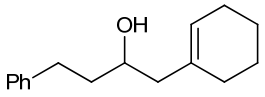
To a vial containing a solution of **171** (501.2 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) was added sequentially 2-phenethanol (0.90 mL, 7.5 mmol) and TsOH (29 mg, 0.15 mmol) and the solution stirred overnight. After which the reaction was treated with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers

were subjected to standard drying and purification via column chromatography. The semi purified product was dissolved in CH_2Cl_2 and treated with O_3 (O_3/O_2). The residue obtained upon concentration was purified by column chromatography and HPLC with 10% EA/hex to afford **173** (132.8 mg, 24%). R_f (10% EA/hex): 0.46. ^{1}H NMR (600 MHz): 7.34-7.16 (5H), 3.87 (m, 1H), 3.65 (m, 1H), 2.91 (m, 2H), 2.48 (d, J = 12.5, 1H), 2.26 (d, J = 12.5, 1H), 1.83-1.70 (2H), 1.59-1.24 (23H). ^{13}C (150 MHz): 139.4, 129.2, 128.4, 126.3, 108.1, 89.2, 62.8, 57.2, 36.9, 32.5, 31.0, 26.7, 26.4, 26.1, 22.7, 22.6, 22.5, 22.3, 20.8, 20.1, 19.7. HRMS (ESI): calc for $C_{23}H_{36}O_3Na$: 383.2562; found: 383.2574 (3.1 ppm).



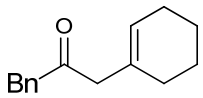
1-(Cyclohex-1-en-1-yl)-3-phenylpropan-2-ol (177):

To a flame-dried RBF containing a 0 °C solution of phenylacetaldehyde (1.2443 g, 10.3 mmol) and methylenecyclohexane (1.0873 g, 11.3 mmol) in CH_2Cl_2 (30 mL) was added Me_2AlCl (13 mL, 13 mmol, nominally 1M in hexanes). The resulting solution was stirred at 0 °C for 2 hrs and then allowed to warm to rt. After stirring an additional 1 hr, the reaction was treated with sat. aq. NaH_2PO_4 (10 mL) and aq. 2N HCl (5 mL) and extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford **177** as a yellow oil (1.7025 g, 76%). R_f (20% EA/hex): 0.44. ^{1}H NMR (300 MHz): 7.40-7.20 (5H), 5.58 (s, 1H), 3.96 (m, 1H), 2.80 (s, 1H), 2.77 (s, 1H), 2.26-1.78 (7H), 1.70-1.52 (4H). ^{13}C (75 MHz): 139.0, 134.8, 129.6, 128.6, 126.5, 125.2, 70.0, 46.1, 43.7, 28.6, 25.6, 25.5, 23.0, 22.5. IR: 3424, 2922, 2855, 2833, 1495. HRMS (CI): calc for $C_{15}H_{19}O$: 215.1436; found: 215.1437 (0.5ppm).



1-(Cyclohex-1-en-1-yl)-4-phenylbutan-2-ol (178):

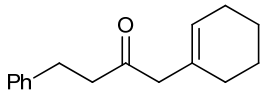
To a flame-dried RBF containing a 0 °C solution of 3-phenyl-1-propanal (1.4592 g, 10.9 mmol) and methylenecyclohexane (1.0562 g, 11 mmol) in CH_2Cl_2 (30 mL) was added Me_2AlCl (13 mL, 13 mmol, nominally 1M in hexanes). The resulting solution was stirred at 0 °C for 2 hrs and allowed to warm to rt. After stirring an additional hour, the reaction was treated with sat. aq. NaH_2PO_4 (10 mL) and aq. 2N HCl (5 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford **178** (2.0325 g, 89%). R_f (20% EA/hex): 0.48. ^{1}H NMR (400 MHz): 7.34-7.14 (5H), 5.55 (s, 1H), 3.76-3.65 (1H), 2.89-2.63 (2H), 2.22-1.47 (13H). ^{13}C (100 MHz): 142.3, 134.6, 128.4, 128.3, 125.7, 125.2, 67.9, 46.6, 38.7, 32.2, 28.4, 25.3, 22.9, 22.3. HRMS (FAB): calc for $C_{16}H_{22}ONa$: 253.1568; found: 253.1566 (0.7 ppm).



1-(Cyclohex-1-en-1-yl)-3-phenylpropan-2-one (179):

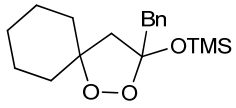
To a flame-dried RBF containing a -78^{o}C solution of oxalyl chloride (0.76 mL, 9 mmol) in CH_2Cl_2 (36 mL) was added a solution of DMSO (1.1 mL, 15 mmol) in CH_2Cl_2 (15 mL) via an addition funnel. The resulting solution was stirred at -78 ^{o}C for 30 min, after which **177** (1.6192g, 7.5 mmol) in CH_2Cl_2 (15 mL) was added via an addition funnel. The reaction was stirred for 1h, after which Et_3N (5.3 mL, 37 mmol) was added. The reaction was stirred at -78 °C for 30 min and then allowed to warm to rt. After 30 min, the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x5 0 mL).

The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **179** as a yellow oil (1.5189 g, 95%). R_f (20% EA/hex): 0.64. ^{1}H NMR (600 MHz): 7.36-7.30 (2H), 7.27 (m, 1H), 7.23-7.19 (2H), 5.55 (s, 1H), 3.72 (s, 2H), 3.06 (s, 2H), 2.07-2.01 (2H), 1.89-1.83 (2H), 1.63-1.53 (4H). ^{13}C (150 MHz): 207.0, 134.5, 131.7, 129.7, 128.8, 127.1, 126.8, 51.9, 48.9, 28.7, 25.6, 22.9, 22.2. IR: 2942, 2856, 2834, 1711, 1495. HRMS (CI): calc for $C_{15}H_{19}O$: 215.1436; found: 215.1441 (2.4 ppm).



1-(Cyclohex-1-en-1-yl)-4-phenylbutan-2-one (180):

To a flame-dried RBF containing a -78 ^{o}C solution of oxalyl chloride (0.84 mL, 10 mmol) in CH_2Cl_2 (40 mL) was added a solution of DMSO (1.2 mL, 16.6 mmol) in CH_2Cl_2 (17 mL) via an addition funnel. The resulting solution was stirred at -78 ^{o}C for 30 min, after which **178** (1.909 g, 8.3 mmol) in CH_2Cl_2 (17 mL) was added via an addition funnel. The reaction was stirred for 1 hr, after which Et_3N (6 mL, 42 mmol) was added. The reaction was stirred at -78 °C for 30 min and then allowed to warm to rt. After 30 min, the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **180** (1.8667 g, 99%). R_f (10% EA/hex): 0.54. ^{1}H NMR (600 MHz): 7.32-7.13 (5H), 5.54 (s, 1H), 3.00 (s, 2H), 2.92-2.88 (2H), 2.81-2.76 (2H), 2.05-2.00 (2H), 1.91-1.86 (2H), 1.66-1.53 (4H). ^{13}C (150 MHz): 208.7, 141.2, 131.6, 128.4, 128.3, 126.4, 126.1, 52.8, 43.1, 29.8, 28.6, 25.4, 22.7, 22.0. IR: 2924, 2857, 1710. HRMS (FAB): calc for $C_{16}H_{21}O$: 229.1592; found: 229.1589 (1.5 ppm).

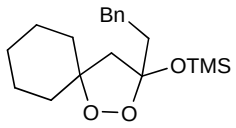


3-Benzyl-3-trimethylsiloxy-1,2-dioxaspiro[4.5]decane (181):

To a RBF containing a solution of cobalt (II) acetylacetonate (179 mg, 0.7 mmol) in 1,2-dichloroethane (70 mL) were added sequentially **179** (1.4915 g, 7 mmol) and triethylsilane (2.3 mL, 14 mmol). The solution was stirred under an atmosphere of O_2 (balloon). After 2 hrs it was noticed that the reaction had not begun so *t*-BuOOH (1.3 mL, 7 mmol, 5.5M in decane) was added and the reaction allowed to stir overnight. The reaction was quenched with NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford 3-benzyl-1,2-dioxaspiro[4.5]decan-3-ol as a light green solid (1.0111 g, 58%). The green color is presumably due to some residual cobalt and the sample contains an alkene impurity <5% which could not be separated by column chromatography. R_f (20% EA/hex): 0.32. ^{1}H NMR (400 MHz): 7.36-7.25 (5H), 3.14 (d, J = 14, 1H), 3.09 (d, J = 14, 1H), 2.88 (bs, 1H), 2.44 (d, J = 12.6, 1H), 2.35 (d, J = 12.6, 1H), 1.78-1.56 (5H), 1.45 -1.22 (5H). ^{13}C (100 MHz): 135.1, 130.7, 128.6, 127.4, 106.7, 85.7, 55.2, 43.2, 35.9, 35.0, 25.3, 24.3, 23.3. IR: 3471, 2987, 2926, 1394, 1111. HRMS (ESI): calc for $C_{15}H_{20}NaO_3$: 271.1310; found: 271.1297 (4.7 ppm).

To a flame-dried RBF containing a solution of 3-benzyl-1,2-dioxaspiro[4.5]decan-3-ol (393.6 mg, 1.59 mmol) in CH_2Cl_2 (16 mL) was treated sequentially with imidazole (129 mg, 1.9 mmol) and chlorotrimethylsilane (0.25 mL, 1.9 mmol) and was allowed to stir for 1 hr. The reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **181** as a white solid (423.8 mg, 84%). R_f (5% EA/hex): 0.42. MP: 58-

59 °C. ^{1}H NMR (300 MHz): 7.34-7.20 (5H), 3.01 (s, 2H), 2.45 (d, J = 12.5, 1H), 2.25 (d, J = 12.5, 1H), 1.72-1.12 (10H), 0.18 (s, 9H). ^{13}C (75 MHz): 136.5, 130.8, 128.2, 126.9, 108.7, 85.6, 56.9, 44.7, 35.9, 35.0, 25.3, 24.4, 23.3, 1.8. HRMS (ESI): calc for $C_{18}H_{28}NaO_3Si$: 343.1705; found: 343.1712 (2.0 ppm).

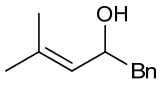


3-Phenethyl-3-trimethylsiloxy-1,2-dioxaspiro[4.5]decane (182):

To a RBF containing a solution of cobalt (II) acetylacetonate (205 mg, 0.8 mmol) in 1,2-dichloroethane (80 mL) were added sequentially **180** (1.821 g, 8 mmol), triethylsilane (2.7 mL, 16 mmol) and *t*-BuOOH (5.5M in decane, 1.45 mL, 8 mmol). The solution was placed under an atmosphere of O_2 (balloon) and the reaction allowed to stir overnight. The reaction was quenched with NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 50mL). The combined organic layers were subjected to standard drying and purification with 15% EA/hex to afford 3-phenethyl-1,2-dioxaspiro[4.5]decan-3-ol (1.5071 g, 72%) that was carried through to the next reaction.

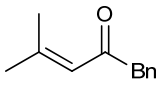
To a flame-dried RBF containing a solution of 3-phenethyl-1,2-dioxaspiro[4.5]decan-3-ol (767.5 mg, 2.92 mmol) in CH_2Cl_2 (30 mL) was treated sequentially with imidazole (0.6 g, 9 mmol) and chlorotrimethylsilane (1.1 mL, 9 mmol) and was allowed to stir for 30 min. The reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with column chromatography twice with 5% EA/hex to afford **182** (530.3 mg, 54%). R_f (5% EA/hex): 0.34. ^{1}H NMR (300 MHz): 7.36-7.17 (5H), 2.77 (m, 1H), 2.38 (s, 2H), 2.17-1.21 912h), 0.22 (s, 9H). ^{13}C (75 MHz): 141.7,

128.6, 128.5, 126.2, 108.6, 85.5, 57.9, 40.3, 36.5, 35.0, 21.8, 31.7, 25.4, 24.4, 23.4, 1.8. HRMS (ESI): calc for $C_{19}H_{30}O_3SiNa$ 357.1862, found 357.1877 (4 ppm).



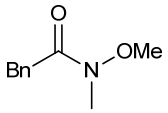
4-Methyl-1-phenylpent-3-en-2-ol (185):

To a flask containing a 0°C solution of 3-phenyl-1-propanal (606.2 mg, 5 mmol) in THF (25 mL) was added 2-methyl-1-propenylmagnesium bromide (12 mL, 6 mmol, 0.5 M in THF). The reaction was stirred for 7 hrs and then treated with sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were subjected to standard drying and purification with column chromatography with 30% EA/hex to afford **185** (609 mg, 69%). R_f (30% EA/hex): 0.45. ^{1}H NMR (600 MHz): 7.39-7.19 (5H), 5.27-5.23 (1H), 4.60-4.55 (1H), 2.81 (m, 2H), 1.71 (s, 3H), 1.60 (s, 3H), 1.49 (d, J = 3.3, 1H).



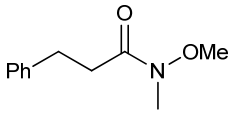
4-Methyl-1-phenylpent-3-en-2-one (186):

To a flame-dried RBF containing a solution of **185** (557.7 mg, 3.1 mmol) in DMF (15 mL) was added PDC (1.4 g, 3.8 mmol) and was stirred overnight. The reaction was treated with H_2O (20 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (20 mL) and subjected to standard drying and purification with column chromatography with 10% EA/hex to afford **186** (277.8, 50%). R_f (10% EA/hex): 0.44. ^{1}H NMR (400 MHz): 7.40-7.20 (5H), 6.13 (s, 1H), 3.71 (s, 2H), 2.17 (s, 3H), 1.88 (s, 3H). The NMR spectra matched that previously reported.[127]



***N*-Methoxy-*N*-methylbenzeneacetamide (190):**

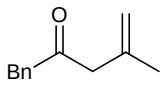
In a flame-dried RBF containing a solution of phenylacetic acid (2.7 g, 20 mmol) in CH_2Cl_2 (50 mL) was added 1,1'-carbonyldiimidazole (4.3 g, 26.5 mmol) portion wise and stirred for 1 hr. *N*,*O*-Dimethylhydroxylamine hydrochloride (3.8 g, 40 mmol) was added and stirred overnight. The reaction flask was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 50% EA/hex to afford **190** as a colorless oil (3.4345 g, 97%). R_f (50% EA/hex): 0.36. ^{1}H NMR (400 MHz): 7.36-7.21 (5H), 3.78 (s,2H), 3.61 (s, 3H), 3.2 (s, 3H). ^{13}C (75 MHz): 172.5, 135.1, 129.4, 128.6, 126.9, 61.4, 39.5, 32.3. HRMS (CI): calc for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1019 (3.1 ppm).



***N*-Methoxy-N-methyl-3-phenylpropanamide (191):**

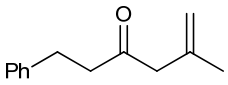
In a flame-dried RBF containing a solution of 3-phenylpropanoic acid (3.03 g, 20 mmol) in CH_2Cl_2 (54 mL) was added 1,1'-carbonyldiimidazole (3.8g, 24 mmol) in small portions. The reaction was stirred for 1 hr and *N*,*O*-Dimethylhydroxylamine hydrochloride (3.8g, 40 mmol) was added and stirred overnight. The reaction flask was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 50% EA/hex to afford **191** (3.7778 g, 97%). R_f (50% EA/hex): 0.50. ^{1}H NMR (400 MHz): 7.37-7.18

(5H), 3.62 (s, 3H), 3.20 (s, 3H), 3.01-2.95 (2H), 2.82-2.71 (2H). The NMR spectra matched those previously reported.[128]



4-Methyl-1-phenyl-4-penten-2-one (189):

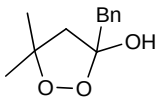
A solution of **190** (1.0056 g, 5.6 mmol) in THF (56 mL) in a flame-dried RBF was cooled to 0 ^{o}C and 2-methylallylmagnesium chloride (13.5 mL, 6.8 mmol, 0.5M in 2-methylTHF) was added. The reaction was stirred at 0 ^{o}C for 30 min and rt for 1 hr. The reaction was quenched with H_2O (20 mL) and aq. 2N HCl (2 mL) and extracted with ether (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **189** as a yellow oil (797.1 mg, 82%). R_f (10% EA/hex): 0.48. ^{1}H NMR: 7.37-7.17 (5H), 4.97 (m, 1H), 4.82 (m, 1H), 3.74 (s, 2H), 3.16 (s, 2H), 1.73 (s, 3H). ^{13}C: 206.2, 139.2, 134.3, 129.7, 128.9, 127.2, 115.4, 51.4, 49.2, 22.8. IR: 1709, 890, 657. HRMS (CI): calc for $C_{12}H_{15}O$: 175.1123; found: 175.1115 (4.5 ppm).



5-Methyl-1-phenylhex-5-en-3-one (192):

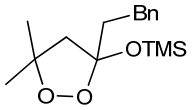
A solution of **191** (970.4g, 5 mmol) in THF (25 mL) in a flame-dried RBF was cooled to 0 ^{o}C and 2-methylallylmagnesium chloride (12 mL, 6 mmol, 0.5 M in 2-methylTHF) was added and stirred at 0 ^{o}C for 30 min and rt for 1 hr. The reaction was quenched with H_2O (20 mL) and aq. 2N HCl (10 mL) and extracted with Et_2O (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **192** (844.2 mg, 89%). R_f (10% EA/hex): 0.48. ^{1}H NMR (400): 2.33-2.27 (2H),

7.29-7.19 (3H), 4.95 (m, 1H), 4.82-4.80 (1H), 3.11 (s, 2H), 2.92 (m, 2H), 2.81 (m, 2H), 1.79 (s, 3H). ^{13}C (100 MHz): 208.0, 141.2, 139.3, 128.5, 126.3, 115.2, 52.6, 43.5, 29.9, 22.8. HRMS (FAB): calc for $C_{13}H_{17}O$: 189.1279; found: 189.1274 (2.85 ppm).



3-Benzyl-5,5-dimethyl-1,2-dioxolan-3-ol (187):

To a RBF containing a solution of cobalt (II) acetylacetonate (103 mg, 0.40 mmol) in 1,2-dichloroethane (40 mL) was added sequentially **189** (697.1 mg, 4 mmol), triethylsilane (1.3 mL, 8 mmol), and *t*-BuOOH (0.73 mL, 4 mmol, 5.5 M in decane). The resulting solution was placed under an atmosphere of O_2 (balloon). After 24 hrs the reaction was diluted with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford **187** as a golden oil (715.3 mg, 86%). R_f (10% EA/hex): 0.43. ^{1}H NMR (300 MHz): 7.43-7.22 (5H), 3.12 (m, 2H), 2.98 (s, 1H), 2.47 (m, 2H), 1.39 (s, 3H), 1.20 (s, 3H). ^{13}C (75 MHz): 135.0, 130.7, 128.6, 127.4, 107.3, 83.9, 56.9, 43.2, 27.2, 25.0. IR: 3443, 3031, 2975, 1604, 1367. HRMS (ESI): calc for $C_{12}H_{16}NaO_3$: 231.0997; found: 231.0989 (3.0 ppm).

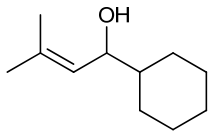


5,5-Dimethyl-3-phenethyl-3-trimethylsiloxy-1,2-dioxolane (193):

To a RBF containing a solution of cobalt (II) acetylacetonate (101.3 mg, 0.40 mmol) in 1,2-dichloroethane (40 mL) was added sequentially **192** (751.3 mg, 4 mmol), triethylsilane (1.3 mL, 8 mmol), and *t*-BuOOH (0.72 mL, 4 mmol, 5.5 M in decane). The resulting solution was placed under an atmosphere of O_2 (balloon). After 24 hrs the

reaction was diluted with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 30% EA/hex to afford 5,5-dimethyl-3-phenethyl-1,2-dioxolan-3-ol (435.4 mg, 49%).

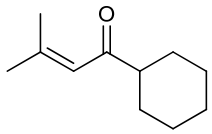
To a flame-dried RBF containing a solution of 5,5-dimethyl-3-phenethyl-1,2-dioxolan-3-ol (388.7 mg, 1.75 mmol) in CH_2Cl_2 (18 mL) was added imidazole (174.4 mg, 2.6 mmol) and chlorotrimethylsilane (0.33 mL, 2.6 mmol). The reaction was allowed to stir for 1 hr. The reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with column chromatography twice with 10% EA/hex to afford **193** (261 mg, 51%). R_f (10% EA/hex): 0.57. ^{1}H NMR (400 MHz): 7.44-7.07 (5H), 2.82 (m, 1H), 2.71 (m, 1H), 2.47 (d, J = 12.5, 1H), 2.42 (d, J = 1H), 2.10 (m, 1H), 1.87 (m, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 0.23 (s, 9H). ^{13}C (100 MHz): 141.7, 128.7, 128.5, 126.2, 109.3, 83.7, 59.7, 40.3, 31.8, 27.7, 25.0, 17.8. HRMS (ESI); calc for $C_{16}H_{26}O_3SiNa$: 317.1549; found: 317.1547 (1 ppm).



1-Cyclohexyl-3-methylbut-2-en-1-ol (195):

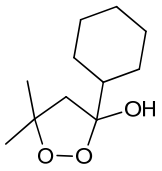
To a flask containing a -78^{o}C solution of cyclohexanecarboxaldehyde (553.6 mg, 4.9 mmol) in THF (25 mL) was added 2-methyl-1-propenylmagnesium bromide (12 mL, 6 mmol, 0.5M in THF). After stirring for 3 hrs the reaction was treated with H_2O (100 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (20 mL) and subjected to standard drying and purification with column chromatography with 20% EA/hex to afford **195** (608.2 mg, 73%). R_f (20% EA/hex):

0.43. ^{1}H NMR (500 MHz): 5.18 (d, J = 9.1, 1H), 4.06 (t, J = 8.2, 1H), 1.97-1.89 (1H), 1.82-1.61 (10H), 1.40-0.85 (6H).



1-Cyclohexyl-3-methylbut-2-en-1-one (196):

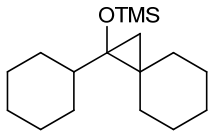
To a flame-dried RBF containing a solution of **195** (390.1 mg, 2.3 mmol) in DMF (10 mL) was added PDC (1.09g mg, 2.9 mmol). After stirring overnight the reaction was treated with H_2O (50 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (20 mL) and subjected to standard drying and purification with column chromatography with 5% EA/hex to afford **196** (196.5 mg, 51%). R_f (5% EA/hex): 0.53. ^{1}H NMR (400 MHz): 6.04-6.01 (1H), 2.25-2.16 91H), 2.04 (s, 3H), 2.04 (s, 3H), 1.76-1.51 (6H), 1.78-1.02 (6H). ^{13}C (100 MHz): 203.9, 155.1, 122.9, 51.5, 28.5, 27.6, 25.9, 25.7, 20.6.



3-Cyclohexyl-5,5-dimethyl-1,2-dioxolan-3-ol (197):

To a RBF containing a suspension of cobalt (II) acetylacetonate (110.3 mg, 0.43 mmol) in 1,2-dichloroethane (41 mL) was added sequentially **196** (688.3 mg, 4.1 mmol) and triethylsilane (1.4 mL, 8 mmol). The resulting solution was placed under an atmosphere of O_2 (balloon). After 24 hrs the reaction was diluted with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford **197** (75.2 mg, 9%). R_f (20%

EA/hex): 0.25. ^{1}H NMR (400 MHz): 2.73 (s, 1H), 2.45 (d, J = 12.8, 1H), 2.34 (d, J = 12.8, 1H), 1.93-1.59 (6H), 1.42 (s, 3H), 1.36 (s, 3H), 1.32-1.05 (5H). ^{13}C (100 MHz): 109.7, 100.2, 83.4, 55.8, 44.7, 28.3, 27.7, 27.5, 26.3, 26.2, 26.1, 25.4.

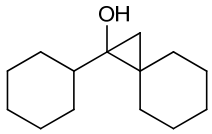


1-Cyclohexyl-1-trimethylsiloxyspiro[2.5]octane (199):

In a flame-dried RBF dicyclohexylketone (5g, 25.7 mmol) was dissolved in THF (100 mL). LiHMDS (39 mL, 39 mmol, 1M in THF) was added and the reaction was allowed to stir for 30 min before chlorotrimethylsilane (3.9 mL, 31 mmol) was added. After 30 min the reaction was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were subjected to standard drying and purification with 2.5% EA/hex to afford 1-cyclohexyl-1-trimethylsiloxy-methylenecyclohexane as a colorless oil (6.2954g, 92%). R_f (2.5% EA/hex): 0.38. ^{1}H NMR (400 MHz): 2.46 (m, 1H), 2.17-2.05 (4H), 1.82-1.04 (16H), 0.21 (s, 9H). ^{13}C (75 MHz): 146.4, 116.5, 39.6, 30.9, 29.5, 28.5, 28.4, 27.6, 27.2, 26.8, 26.4, 1.3. HRMS (EI): calc for $C_{16}H_{30}OSi$: 266.2066; found: 266.2058 (3.0 ppm).

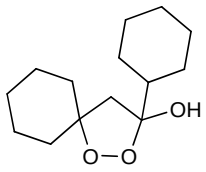
In a flame-dried RBF, 1-cyclohexyl-1-trimethylsiloxy-methylenecyclohexane (6 g, 23 mmol) was dissolved in CH_2Cl_2 (225 mL) and the solution was cooled to 0 ^{o}C. To the flask via an addition funnel was added drop wise $ZnEt_2$ (45 mL, 45 mmol, 1M in hexanes) followed by addition of CH_2I_2 (5.4 mL, 67.5 mmol) in one portion and stirred at 0 ^{o}C for 1 hr and rt for 1 hr. After which the reaction was treated with H_2O (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were subjected to standard drying and purification with 2.5% - 10% EA/hex to afford **199** as a white solid

(4.8426 g, 77%). R_f (5% EA/hex): 0.75. MP: 29-30 ^oC. ^1H NMR (400 MHz): 2.46 (m, 1H), 2.28-2.03 (4H), 1.81-1.05 (16H), 0.22 (s, 9H). ^{13}C (100 MHz): 69.0, 43.0, 32.2, 31.3, 30.2, 29.7, 28.5, 27.2, 27.0, 26.8, 26.7, 25.9, 25.6, 23.9, 2.24. HRMS (ESI): calc for $C_{17}H_{32}NaOSi$ 303.2120, found 303.2112 (0.1 ppm). Also isolated from the reaction was 1-cyclohexylspiro[2.5]octan-1-ol, **270**, (481.4 mg, 10%).



1-Cyclohexylspiro[2.5]octan-1-ol (200)

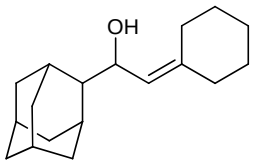
To a flame-dried RBF containing a solution of **199** (4.0 g, 14 mmol) in THF (70 mL) was added TBAF (17.2 mL, 17.2 mmol, 1 M in THF) and stirred for 2 hrs. The reaction was treated with H_2O (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were subjected to standard drying and purification to afford **200** as a colorless oil (2.9354 g, 99%). R_f (10% EA/hex): 0.47. ^1H NMR (400 MHz): 1.88-1.01 (22H), 0.37 (d, J = 5.3, 1H), 0.18 (d, J = 5.3, 1H). ^{13}C (100 MHz): 66.3, 42.1, 31.8, 30.7, 30.2, 29.1, 28.8, 27.0, 26.9, 26.7, 26.6, 26.0, 25.7, 24.1. IR: 3369, 2922, 2848, 1444, 1243. HRMS (FAB): calc for $C_{14}H_{23}O_2$: 223.1698; found: 223.1692 (2.8 ppm).



3-Cyclohexyl-1,2-dioxaspiro[4.5]decan-3-ol (201):

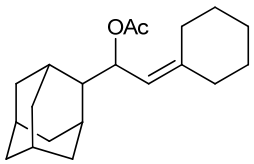
A vial containing a solution of **200** (493.2 mg, 2.4 mmol) in benzene (10 mL) was placed under an atmosphere of O_2 (balloon) and stirred for 3 days. After which the solvent was removed *in vacuo* and was purified via column chromatography with 20% EA/hex to

afford **201** as a yellow oil that slowly crystallizes to a white solid (360 mg, 81% BRSM). R_f (40% EA/hex): 0.5. MP: 61-32 ^oC. ^1H NMR (300 MHz): 2.82 (s, 1H), 2.37 (d, J = 12.8, 1H), 2.23 (d, J = 12.8, 1H), 1.93-1.03 (23H). ^{13}C (75 MHz): 109.0, 85.1, 54.0, 44.6, 36.3, 35.3, 28.2, 27.5, 26.3, 26.2, 26.1, 25.3, 24.4, 23.3. IR: 3453, 2930, 2854, 1448, 1168. HRMS (ESI): calc for $C_{14}H_{24}NaO_3$: 263.1623; found: 263.1636 (4.9 ppm).



1-adamantan-2-yl-2-cyclohexylideneethanol (204):

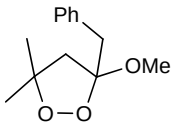
To a flame-dried RBF containing a -78^{o}C solution of bromomethylene cyclohexane (1.0655 g, 6 mmol) in THF (65 mL) was added t-BuLi (3.9 mL, 6.2 mmol, 1.6 M in pentane). After the solution had stirred for 1 hr 2-adamantanecarboxaldehyde (953 mg, 5.7 mmol, impure) was added in THF (5 mL) and allowed to warm to rt and stirred for 3 hrs. The reaction was treated with sat. aq. NH_4Cl (20 mL) and the resulting suspension was extracted with Et_2O (3 x 20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **204** (450.3 mg, 30%). R_f (10% EA/hex): 0.29. ^1H NMR (400 MHz): 5.05-5.01 (1H), 4.65 (t, J = 9.8, 1H), 2.33-1.35 (25H).



1-adamantan-2-yl-2-cyclohexylideneethyl acetate (205):

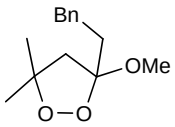
To a flame-dried RBF containing a solution of **204** (450.3 mg, 1.73 mmol) in pyridine (10 mL) was added sequentially Ac_2O (353 mg, 3.46 mmol) and DMAP (21 mg, 0.2

mmol). After 3 hrs the reaction was treated with 2N HCl (20 mL) and the resulting suspension was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and subjected to standard drying and purification with 5% EA/hex to afford **205** (483.1 mg, 92%). Rf (10% EA/hex): 0.74. ^{1}H NMR (400 MHz): 5.90 (t, J = 10.3, 1H), 4.93 (d, J = 9.7, 1H), 2.41-1.42 (28H). ^{13}C (100 MHz): 170.4, 145.8, 120.0, 70.9, 47.9, 39.0, 28.6, 38.1, 37.2, 32.2, 31.9, 29.9, 29.0, 28.7, 28.03, 28.01, 28.0, 27.6, 26.7, 21.3.



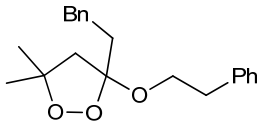
3-Benzyl-3-methoxy-5,5-dimethyl-1,2-dioxolane (207):

In a vial containing a solution of **187** (190 mg, 0.91 mmol) in CH_2Cl_2 (5 mL) and methanol (5 ml) was added TsOH (16 mg, 0.08 mmol) and the solution stirred for 3 days. After which the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **207** as a yellow oil (147.7 mg, 73%). R_f (10% EA/hex): 0.50. ^{1}H NMR (300 MHz): 7.37-7.20 (5H), 3.45 (s, 3H), 3.07 (2H), 2.42 (d, J = 12.8, 1H), 2.34 (d, J = 12.8, 1H), 1.34 (s, 3H), 1.06 (s, 3H). ^{13}C (75 MHz): 136.1, 130.5, 128.5, 127.0, 110.4, 83.8, 55.4, 49.5, 38.1, 27.2, 24.8. HRMS (ESI): calc for $C_{13}H_{18}NaO_3$: 245.1154; found: 245.1144 (4 ppm).



3-Methoxy-5,5-dimethyl-3-phenethyl-1,2-dioxolane (208):

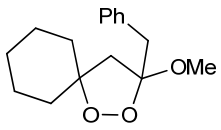
In a vial containing a solution of **193** (130.2 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) and methanol (4 ml) was added TsOH (10 mg, 0.05 mmol) and the solution stirred overnight. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **208** (103.1 mg, 99%). R_f (10% EA/hex): 0.44. ^1H NMR (500 MHz): 7.34-7.30 (2H), 7.25-7.20 (3h), 3.37 (s, 3H), 2.77 (m, 1H), 2.67 (m, 1H), 2.48 (d, J = 12.6, 1H), 2.39 (d, J = 12.6, 1H), 2.25 (m, 1H), 1.89 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H). ^{13}C (125 MHz): 141.2, 128.6, 128.4, 126.3, 110.2, 83.7, 56.5, 49.2, 33.9, 31.2, 27.8, 24.7. HRMS (ESI): calc for $C_{14}H_{20}O_3Na$: 259.1310; found: 259.1307 (1.5 ppm).



3,3-Dimethyl-5-phenethoxy-5-phenethyl-1,2-dioxolane (209):

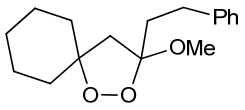
In a vial containing a solution of **193** (101.1 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) was sequentially 2-phenylethanol (0.2 mL, 1.7 mmol) and TsOH (6 mg, 0.03 mmol). After the reaction had stirred for 5 hrs, it was treated with sat. aq. $NaHCO_3$ (8 mL) and H_2O (8 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **209** (60 mg, 55%). R_f (10% EA/hex): 0.57. ^1H NMR (400 MHz): .7.38-7.11 (10H), 3.96 (m, 1H), 3.70 (m, 1H), 2.98 (m, 1H), 2.65 (m, 1H), 2.49 (d, J = 12.5, 1H), 2.36 (d, J = 12.5, 1H),

2.22 (m, 1H), 1.90 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C (100 MHz): 141.4, 139.5, 129.2, 128.6, 128.4, 126.3, 126.2, 110.1, 83.7, 62.5, 56.8, 36.8, 34.7, 31.2, 27.9, 24.8. HRMS (ESI): calc for $C_{21}H_{26}O_3Na$: 349.1780; found: 349.1785 (0 ppm).



3-Benzyl-3-methoxy-1,2-dioxaspiro[4.5]decane (210):

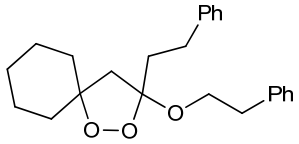
To a vial containing a solution of **181** (105.1 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) was added sequentially methanol (3.1 mL) and TsOH (12.6 mg, 0.07 mmol) and the reaction was stirred overnight. The reaction was treated with sat. aq. $NaHCO_3$ (8 mL) and H_2O (8 mL) and extracted with CH_2Cl_2 (2 x 8 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **210** as a yellow oil (89.5 mg, 93%). R_f (10% EA/hex): 0.38. ^{1}H NMR (500 MHz): 7.40-7.23 (5H), 3.64 (s, 3H), 3.1 (d, J = 12.5, 1H), 3.04 (d, J = 12.5, 1H), 2.39 (d, J = 12.6, 1H), 2.25 (d, J = 12.6, 1H), 1.74-1.12 (10H). ^{13}C (125 MHz): 136.1, 130.4, 128.4, 126.9, 109.7, 85.6, 53.4, 49.4, 38.0, 35.8, 34.6, 25.2, 24.4, 23.2. HRMS (ESI): calc for $C_{16}H_{22}NaO_3$: 285.1467; found: 285.1463 (2 ppm).



3-Methoxy-3-phenethyl-1,2-dioxaspiro[4.5]decane (211):

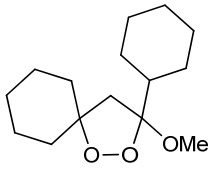
To a vial containing a solution of **182** (205.9 mg, 0.61 mmol) in CH_2Cl_2 (2 mL) was added sequentially methanol (6 mL) and TsOH (10.1 mg, 0.05 mmol) and was stirred for 5 hrs. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were subjected to

standard drying and purification with 10% EA/hex to afford **211** (111.4 mg, 66%). R_f (10% EA/hex): 0.37. ^{1}H NMR (300 MHz): 7.35-7.12 (5H), 3.36 (s, 3H), 2.71 (m, 2H), 2.39 (d, J = 12.7, 1H), 2.33 (d, J = 12.7, 1H), 2.22 (m, 1H), 1.91-1.25 (11H). ^{13}C (75 MHz): 141.3, 128.7, 128.4, 126.3, 109.6, 85.6, 55.0, 49.2, 36.5, 34.7, 33.9, 31.3, 25.4, 24.4, 23.3. HRMS (ESI): calc for $C_{17}H_{24}O_3Na$: 299.1623; found: 299.1629 (2 ppm).



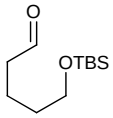
3-Phenethoxy-3-phenethyl-1,2-dioxaspiro[4.5]decane (212):

To a vial containing a solution of **182** (209.5 mg, 0.6 mmol) in CH_2Cl_2 (6 mL) was added sequentially 2-phenylethanol (0.36 mL, 3 mmol) and TsOH (10.4 mg, 0.06 mmol). After stirring for 6 hrs, the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (8 mL) was added and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **212** (151.4 mg, 66%). Less than 5% of uncharacterized impurities were present by ^{1}H NMR and the sample was submitted for *in vitro* testing. A pure sample can be obtained by subjecting **212** to ozonolysis and re-purification prior to the etherification, R_f (10% EA/hex): 0.48. ^{1}H NMR (500 MHz): 7.34-7.10 (10H), 3.92 (m, 1H), 3.64 (m, 1H), 2.92 (m, 1H), 2.61 (m, 1H), 2.37 (d, J = 12.5, 1H), 2.27 (d, J = 12.5, 1H), 2.21-2.14 (1H), 1.87-1.32 (11H). ^{13}C (100 MHz): 141.4, 139.5, 129.2, 128.6, 128.4, 126.3, 126.2, 109.5, 85.5, 62.5, 55.2, 36.7, 34.7, 34.6, 31.3, 25.4, 24.4, 23.4. HRMS (ESI): calc for $C_{24}H_{30}O_3Na$: 389.2093; found: 289.2074 (<5 ppm).



3-Cyclohexyl-3-methoxy-1,2-dioxaspiro[4.5]decane (213):

To a vial containing a solution of **201** (360 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) and methanol (10 mL) was added TsOH (29.5 mg, 0.16 mmol) and was stirred overnight. The reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **213** as a white solid (344.8 mg, 90%). R_f (10% EA/hex): 0.57. MP: 44 ^oC. ^1H NMR (400 MHz): 3.28 (s, 3H), 2.39 (d, J = 12.7, 1H), 2.16 (d, J = 12.7, 1H), 1.90-0.85 (21H). ^{13}C (100MHz): 111.8, 85.0, 51.5, 48.7, 38.8, 36.3, 34.9, 28.6, 28.2, 26.5, 26.4, 26.1, 25.4, 24.5, 23.4. HRMS (ESI): calc for $C_{15}H_{26}NaO_3$: 277.1779; found: 277.1774 (1 ppm).

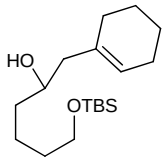


5-(tert-Butyldimethylsilanyloxy)pentanal (222):

To a flame-dried RBF containing a solution of 5-hexen-1-ol (1.9878 g, 20 mmol) in THF (40 mL) was added sequentially imidazole (3.22 g, 47 mmol) and TBSCl (3.72 g, 25 mmol) in THF (10 mL) and stirred overnight. The reaction was treated with H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were subjected to standard drying and purification with 2.5% EA/hex to afford 6-tert-butyldimethylsiloxy)hex-1-ene (3.8385 g, 90%). R_f (2.5% EA/hex): 0.42. ^1H NMR (400 MHz): 5.02 (ddt, J = 17.0, 10.1, 6.9, 1H). 5.07-4.90 (2H), 3.62 (t, J = 6.4, 2H), 2.07

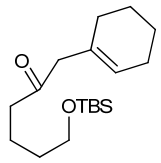
(m, 2H), 1.68-1.37 (4H), 0.90 (s, 9H), 0.06 (s, 6H). The NMR spectra matched those previously reported.[129]

To a flame-dried RBF containing a 0°C solution of 6-tert-butyldimethylsiloxy)hex-1-ene (3.7776 g, 17.6 mmol) in acetone (120 mL) and Sudan Red (trace) was passed O_3 until disappearance of the red color. The flask was purged with O_2 for 2 min. The contents of the flask were concentrated *in vacuo* and the residue obtained upon concerntation was purified via column chromatography with 10% EA/hex to afford **222** (2.859 g, 75%). R_f (10% EA/hex): 0.41. ^{1}H NMR (400 MHz): 9.78 (t, J = 1.8, 1H), 3.64 (t, J = 6.2, 2H), 2.47 (dt, J = 1.8, 6.8, 2H), 1.75-1.65 (2H), 1.62-1.51 (2H), 0.90 (s, 9H), 0.05 (s, 6H). The NMR spectra matched those previously reported.[130]



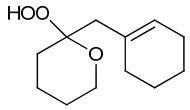
6-((tert-Butyldimethylsilyl)oxy)-1-(cyclohex-1-en-1-yl)hexan-2-ol (223):

To a flame-dried RBF containing a 0°C solution of methylene cyclohexane (2.5 mL, 20 mmol) and **222** (3.68 g, 17 mmol) was added Me_2AlCl (22 mL, 22 mmol, 1 M in hexanes) and stirred for 3 hrs. The reaction was treated with sat. aq. NaH_2PO_4 (20 mL) and 2 N HCl was added until the solution became clear and was extracted with Et_2O (3 x 50 mL). The combined organic layers were subjected to standard drying and purification with 20 % EA/hex to afford **223** (4.2695 g, 81%). R_f (20% EA/hex): 0.38. (400 MHz): 5.55-5.50 (1H), 3.71-3.59 (3H), 2.17-1.30 (17H), 0.090 (s, 9H), 0.05 (s, 6H). ^{13}C (100 MHz): 135.0, 125.2, 68.7, 63.4, 46.7, 37.0, 33.0, 28.5, 26.2, 25.5, 23.1, 22.5, 22.2, 18.6, -5.1. IR: 3399, 2927, 2856. HRMS (FAB): calc for $C_{18}H_{36}O_2SiLi$: 319.2645; found: 319.2654 (2.9 ppm).



6-((tert-Butyldimethylsilyl)oxy)-1-(cyclohex-1-en-1-yl)hexan-2-one (224):

To a flame-dried RBF containing a -78 °C solution of oxalyl chloride (1.024 g, 8 mmol) in CH_2Cl_2 (30 mL) was added DMSO (0.9 mL, 12.8 mmol) in CH_2Cl_2 (13 mL) dropwise via an addition funnel and allowed to stir for 20 min. After which **223** (1.35g, 9.6 mmol) in CH_2Cl_2 (13 mL) was added dropwise via an addition funnel and allowed to stir at -78 ^oC for 1 hr and Et_3N (4.4 mL, 32 mmol) was added and stirred at -78^oC for 30 min and rt for 1 hr. The reaction was treated with H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford 2**24** a yellow oil (1.8971 g, 93%). R_f (10% EA/hex): 0.317. ^1H NMR (400 MHz): 5.54 (bs, 1H), 3.61 (t, J = 6.1, 2H), 3.00 (s, 2H), 2.46 (t, J = 7.3, 2H), 2.07-2.00 (2H), 1.94-1.88 (2H), 1.67-1.46 (8H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C (100 MHz): 209.8131.8, 126.1, 62.9, 52.5, 41.5, 32.2, 28.6, 26.0, 25.4, 22.8, 22.0, 20.3, 18.3, -5.3. IR: 2927, 2856, 1713. HRMS (FAB): calc for $C_{18}H_{34}O_2SiLi$: 317.2488; found: 317.2500 (3.9 ppm).

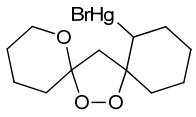


2-(Cyclohex-1-en-1-ylmethyl)-2-hydroperoxytetrahydro-2H-pyran (219):

To a flame-dried RBF containing a solution of **224** (3.672 g, 11.8 mmol) in THF (118 mL) was cooled to 0^oC and TBAF (13 mL, 13 mmol, 1 M in THF) was added. After 4 hrs the reaction was treated with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic layers were subjected to standard drying and purified twice

by column chromatography with 50% EA/hex to afford 2-(cyclohex-1-en-1-ylmethyl)tetrahydro-2H-pyran-2-ol (2.0815 mg, 90%).

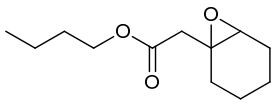
To a flame-dried RBF containing a solution of 2-(cyclohex-1-en-1-ylmethyl)tetrahydro-2H-pyran-2-ol (567 mg, 2.9 mmol) in THF (50 mL) was added sequentially urea hydrogen peroxide (1.9 g, 20 mmol) and camphor sulfonic acid (2 g, 9 mmol) and stirred for 24 hrs. The reaction was diluted with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL). The combined organic layers were dried with Na_2SO_4 and the residue obtained upon concentration *in vacuo* was purified by column chromatography with 30 % EA/hex to afford **219** (472.3 mg, 78%). R_f (50 % EA/hex): 0.74. ^{1}H NMR (300 MHz): 7.56 (s, 1H), 5.51 (bs, 1H), 3.90-3.69 (2H), 2.60 (d, J = 14.0, 1H), 1.72 (d, J = 14.0, 1H), 1.77-1.47 (10H). ^{13}C (75 MHz): 133.4, 126.1, 104.5, 61.9, 44.8, 29.8, 29.2, 25.6, 24.8, 23.1, 22.3, 18.7. IR: 3296, 2925, 2854, 2831. HRMS (ESI): calc for $C_{12}H_{20}O_3Na$: 235.1310; found: 235.1319 (3.8 ppm).



8-bromomercurial-1,2,4-trioxaspiro[5.4.5]pentadecane (218):

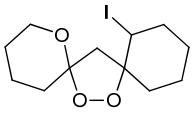
To a flame-dried RBF containing a solution of **219** (326 mg, 1.6 mmol) in CH_2Cl_2 (60 mL) was added $Hg(OAc)_2$ (542, 1.7) and stirred for 3 days. The reaction was treated with H_2O (50 mL) and KBr (200 mg, 1.7 mmol) and strirred for 2 hrs. The suspension was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford **218** (464.3 mg, 60%). R_f

(20% EA/hex): 0.45. ^{1}H NMR (400 MHz): 4.04-3.91 (1H), 3.75-3.65 (1H), 2.73-2.63 (1H), 2.48 (d, J = 13.2, 1H), 2.39-1.15 (15H). ^{13}C (100 MHz): 106.8, 88.7, 66.1, 62.5, 57.7, 37.2, 31.2, 30.8, 28.0, 25.0, 24.5, 20.4. HRMS (ESI); calc for $C_{12}H_{19}O_3NaHgBr$: 513.0091; found: 513.0089 (0.1 ppm).



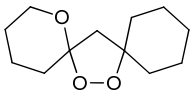
Epoxide byproduct (225):

Isolated via HPLC with 10 % EA/hex from the $HSnBu_3$ reduction of **218**. ^{1}H NMR (400 MHz): 4.14-4.04 (2H): 3.09-3.06 (1H), 2.71 (d, J = 15.4, 1H), 2.36 (d, J = 15.4, 1H), 1.99-1.17 (12H), 0.92 (t, J = 7.4, 3H). ^{13}C (100 MHz): 170.7, 64.7, 58.7, 57.2, 43.8, 30.8, 28.4, 24.7, 20.2, 19.3, 19.2, 13.8.



8-iodo-1,2,4-trioxaspiro[5.4.5]pentadecane (231):

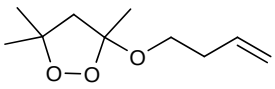
To a flame-dried RBF containing a solution of **219** (221.0 mg, 1 mmol) in CH_2Cl_2 (30 mL) was added sequentially I_2 (280, 1.1 mmol) and potassium tert-butoxide (128 mg, 1 mmol). After 10 min the reaction was treated with sat. aq. $Na_2S_2O_3$ (20 mL). The resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with H_2O (20 mL) and subjected to standard drying and purification with 20% EA/hex to afford **231** (239.5 mg, 68%). R_f (30% EA/hex): 0.80. ^{1}H NMR (500 MHz): 4.636-4.56 (1H), 4.00-3.89 (1H), 3.76-3.65 (1H), 2.82-2.63 (1H), 2.42-2.09 (3H), 1.96-1.93 (12H). ^{13}C (150 MHz): 106.8, 106.3, 86.2, 62.6, 62.5, 41.0, 34.4, 32.01, 32.00, 31.8, 30.9, 24.7, 24.6, 23.0, 22.1, 20.4, 20.3. HRMS (ESI); calc for $C_{12}H_{19}O_3INa$: 361.0277; found: 361.0263 (3.8 ppm).



One-Pot Procedure:

1,2,4-trioxaspiro[5.4.5]pentadecane (143):

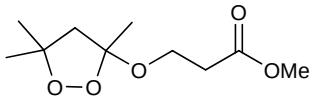
To a flame-dried RBF containing a solution of **219** (206.6 mg, 1 mmol) in CH_2Cl_2 (30 mL) was added sequentially I_2 (289.2 mg, 1.1) and potassium tert-butoxide (138.8 mg, 1.1 mmol). After 30 min. the reaction was treated with sat. aq. $Na_2S_2O_3$ (30 mL). The resulting suspension was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with H_2O (20 mL), dried with $MgSO_4$, and filtered through a silica plug. The residue obtained upon concentration *in vacuo* was dissolved in $HSnBu_3$ (1.8 mL, 10 mmol) and stirred overnight. The contents of the reaction were purified directly via column chromatography twice with 1 x 10% EA/hex and 1 x 20% EA/hex. The isolated product was dissolved in THF (5 mL) in a vial and $LiAlH_4$ (21.8mg) was added and stirred overnight. H_2O (10 mL) was added and the resulting suspension was extracted with Et_2O (2 x 10 mL) and subjected to standard drying and purification with 20% EA/hex to afford **143** (85.2 mg, 41%). ^{1}H NMR (400 MHz): 4.01-3.90 (1H), 3.72-3.62 (1H), 2.30 (d, 12.6, 1H), 2.17 (d, 12.6, 1H), 1.91-1.26 (16H). ^{13}C (100 MHz): 106.3, 84.9, 62.6, 57.4, 36.2, 34.7, 32.1, 25.3, 24.8, 24.2, 23.2, 20.5. HRMS (FAB): calc for $C_{12}H_{21}O_3$: 213.1491; found: 213.1490 (0.2 ppm).



3-(But-3-en-1-yloxy)-3,5,5-trimethyl-1,2-dioxolane (228):

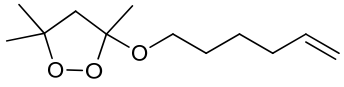
To a flame-dried vial containing a solution of **107-OTMS** (3.3724g, 16.5 mmol) in CH_2Cl_2 (160 mL) was added sequentially 3-buten-1-ol (4.2 mL, 48 mmol) and TsOH

(313 mg, 1.65 mmol). After 3 hrs the reaction was treated with sat. aq. $NaHCO_3$ (40 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **228** (2.2212 g, 74%). R_f (10% EA/hex): 0.48. ^{1}H NMR (300 MHz): 5.86 (ddt, J = 17.1, 10.3, 6.8, 1H), 5.07 (m, 2H), 3.68 (m, 1H), 3.49 (m, 1H), 2.55 (d, J = 12.5, 1H), 2.40-2.28 (3H) 1.47 (s, 3H), 1.37 (s, 6H). ^{13}C (75 MHz): 135.7, 116.3, 108.5, 83.9, 61.3, 58.9, 34.7, 27.8, 24.8, 20.1. HRMS (ESI): calc for $C_{10}H_{18}O_3Na$: 209.1154; found: 209.1163 (4 ppm).



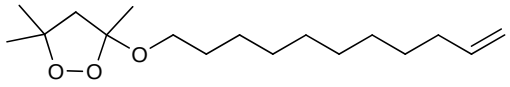
Methyl 3-((3,5,5-trimethyl-1,2-dioxolan-3-yl)oxy)propanoate (229):

A flame-dried RBF containing a solution of **228** (503.7 mg, 2.7 mg) in MeOH (0.6 mL) and CH_2Cl_2 (20mL) was cooled to -78^{o}C. A nominally 1% solution of O_3/O_2 was bubbled into the reaction flask solution until the solution was blue in color. The reaction mixture was purged with O_2 for 2 min and allowed to warm to rt. To the flask was added sequentially acetonitrile (11 mL) and $Ca(OCl)_2$ (0.76g, 5.4 mmol). After 20 min the reaction was filtered through a pad of silica, concentrated *in vacuo*, and purified by flash chromatography twice with 30% EA/hex to afford **229** as a yellow oil (359.6 mg, 61%). R_f (30% EA/hex): 0.5. ^{1}H NMR (300 MHz): 3.84 (m, 2H), 3.70 (s, 3H), 2.61 (m, 2H), 2.55 (d, J = 12.7, 1H), 2.32 (d, J = 12.7, 1H), 1.48 (s, 3H), 1.36 (s, 6H). ^{13}C (75 MHz): 108.6, 83.9, 58.7, 57.7, 51.8, 35.5, 27.8, 24.7, 19.9. IR: 2976, 1736. HRMS (ESI): calc for $C_{10}H_{18}O_5Na$: 241.1052; found: 241.1045 (3 ppm).



3-(Hex-5-en-1-yloxy)-3,5,5-trimethyl-1,2-dioxolane (231)

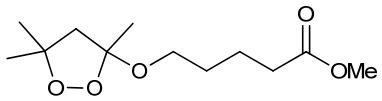
To a flame-dried vial containing a solution of **107-OTMS** (2.67 g, 13.1 mmol) in CH_2Cl_2 (130 mL) was added sequentially 5-hexen-1-ol (4.7 mL, 39.3 mmol) and TsOH (247 mg, 1.3 mmol). After 3 hrs the reaction was treated with sat. aq. $NaHCO_3$ (40 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **231** (2.1497 g, 77%). R_f (10% EA/hex): 0.50. ^{1}H NMR (300 MHz): 5.82 (ddt, J = 16.9, 10.2, 6.8), 5.0 (m, 2H), 3.61 (m, 1H), 3.45 (m, 1H), 2.54 (d, J = 12.5, 1H), 2.41 (d, J = 12.5, 1H), 2.15-2.02 (2H), 1.70-1.44 (7H), 1.37 (s, 6H). ^{13}C (75 MHz): 139.1, 114.6, 108.4, 83.8, 61.7, 58.9, 33.7, 29.6, 27.8, 25.7, 24.8, 20.1. HRMS (ESI): calc for $C_{12}H_{22}O_3Na$: 237.1467; found: 237.1474 (3 ppm).



3,3,5-Trimethyl-5-(undec-10-en-1-yloxy)-1,2-dioxolane (232):

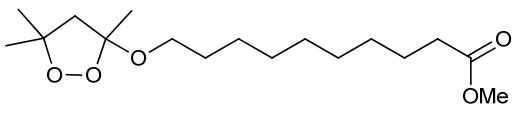
To a flame-dried vial containing a solution of **107-OTMS** (2.5713 g, 12.6 mmol) in CH_2Cl_2 (126 mL) was added sequentially 10-undecen-1-ol (7.6 mL, 37.8 mmol) and TsOH (247 mg, 1.3 mmol). After 4 hrs the reaction was treated with sat. aq. $NaHCO_3$ (40 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford **232** (2.7486 g, 77%). R_f (5% EA/hex): 0.34. ^{1}H NMR (400 MHz): 5.78 (ddt, J = 17.0, 10.0, 6.9, 1H), 4.97 (m, 2H), 3.59 (m, 1H), 3.43 (m, 1H), 2.53 (d, J = 12.5, 1H), 2.32 (d, J = 12.5, 1H), 2.05 (m, 2H), 1.58 (2H), 1.47 (s, 3H), 1.42-1.24 (12H), 1.37 (d, J = 2.5, 6H). ^{13}C (100 MHz): 139.5, 114.2, 108.4, 83.8, 62.0, 58.8, 34.0, 30.2, 29.7,

29.6, 29.5, 29.3, 29.1, 27.8, 26.3, 24.8, 20.2. HRMS (ESI): calc for $C_{17}H_{32}O_3Na$: 307.2249; found: 307.2250 (0.3 ppm).



methyl 5-((3,5,5-trimethyl-1,2-dioxolan-3-yl)oxy)pentanoate (233):

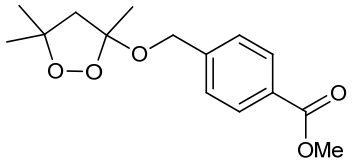
A solution of **231** (501.8 mg, 2.3 mmol) in MeOH (0.5 mL, 12 mmol) and CH_2Cl_2 (15mL) was cooled to -78°C in a flame-dried RBF. A 1% solution of O_3/O_2 was bubbled into the reaction flask until the solution was blue in color. At this time the reaction mixture was purged with O_2 for 2 min and allowed to warm to rt. The contents of the flask were concentrated *in vacuo* and purified by flash chromatography with 40% EA/hex. A solution of the isolated hydroperoxyacetal (473.6 mg, 1.8 mmol) in MeCN (7.2 mL) in a RBF was added $Ca(OCl)_2$ (511 mg, 3.6 mmol). After 20 min the reaction was filtered through a pad of silica, concentrated *in vacuo*, and the residue purified via flash chromatography with 20% EA/hex to afford **233** (349.8 mg, 61%). R_f (20% EA/hex): 0.45. ^{1}H NMR (400 MHz): 3.63 (s, 3H), 3.58 (m, 1H), 3.42 (m, 1H), 2.49 (d, J = 12.6, 1H), 2.33 (at, J = 7.4, 2H), 2.29 (d, J = 12.6, 1H), 1.70 (m, 2H), 1.58 (m, 2H), 1.43 (s, 3H), 1.33 (s, 6H). ^{13}C (100 MHz):174.3, 108.3, 83.8, 61.1, 58.7, 51.5, 33.8, 29.4, 27.7, 24.7, 21.8, 20.0. HRMS (ESI): calc for $C_{12}H_{22}O_5Na$: 269.1365; found: 269.1353 (4.5 ppm).



Methyl 10-((3,5,5-trimethyl-1,2-dioxolan-3-yl)oxy)decanoate (234):

A flame-dried RBF containing a solution of **232** (599.2 mg, 2.1 mmol) in MeOH (0.43 mL, 10.6 mmol) and CH_2Cl_2 (14 mL) was cooled to -78°C. A 1% solution of O_3/O_2 was

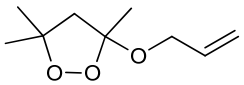
bubbled into the reaction flask until the solution was blue in color. At this time the reaction mixture was purged with O_2 for 2 min and allowed to warm to rt. The contents of the flask were concentrated *in vacuo* and the residue was purified by flash chromatography with 30% EA/hex. To a RBF containing a solution of the isolated hydroperoxyacetal (398.9 mg, 1.2 mmol) in MeCN (10 mL) was added $Ca(OCl)_2$ (340 mg, 2.4 mmol). After 20 min the reaction was filtered through a pad of silica, concentrated *in vacuo*, and the residue purified by flash chromatography with 20% EA/hex and with 10% EA/hex to afford **233** (273.5 mg, 41%). R_f (10% EA/hex): 0.25. ^{1}H NMR (600 MHz): 3.67 (s, 3H), 3.59 (m, 1H), 3.44 (m, 1H), 2.53 (d, J = 12.4, 1H), 2.35-2.27 (3H), 1.66-1.51 (4H), 1.47 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.39-1.25 (10). ^{13}C (150 MHz): 174.5, 108.4, 83.8, 61.9, 58.9, 51.6, 34.3, 30.2, 29.6, 29.5, 29.4, 29.3, 27.8, 26.3, 25.1, 24.8, 20.2. HRMS (ESI): calc for $C_{17}H_{32}O_5Na$: 339.2147; found: 339.2140 (2 ppm).



3,5,5-trimethyl-3-(4-acetyl-phenylmethoxy)-1,2-dioxolane (236):

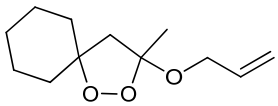
To a flame-dried vial containing a suspension of Re_2O_7 (8.1 mg, 0.02 mmol) in CH_2Cl_2 (10 mL) was added sequentially **107-OTMS** (206.6 mg, 1.0 mmol) and methyl 4-(hydroxymethyl)benzoate (837 mg, 5.0 mmol). After 5 hrs the reaction was concentrated *in vacuo* and the residue purified sequentially by flash chromatography and HPLC with 20% EA/hex to afford **236** (174.8 g, 61%). R_f (20% EA/hex): 0.40. ^{1}H NMR (400 MHz):8.01 (d, J = 8.3, 2H), 7.46 (d, J = 8.3, 2H), 4.79 (d, J = 12.5, 1H), 4.56 (d, J = 12.5, 1H), 3.91 (s, 3H), 2.66 (d, 12.6, 1H), 2.41 (d, J = 12.6, 1H), 1.57 (s, 3H), 1.41 (s, 6H). ^{13}C

(100 MHz): 167.2, 144.4, 129.8, 129.2, 127.4, 108.9, 84.1, 63.7, 58.9, 52.2, 27.9, 24.8, 20.2. HRMS (ESI): calc for $C_{15}H_{20}O_5Na$: 303.1203; found: 303.1219 (3.6 ppm).



3-(Allyloxy)-3,5,5-trimethyl-1,2-dioxolane (237):

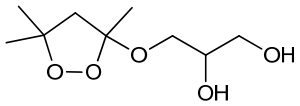
To a RBF containing a solution of **107** (189.0 mg, 1.43 mmol) in CH_2Cl_2 (15 mL) was added sequentially allyl alcohol (0.52 mL, 7.6 mmol) and TsOH (28.5 mg, 0.15 mmol). After 24 hrs the reaction was treated with sat. $NaHCO_3$ (5 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **237** (127.5 mg, 49%). R_f (5% EA/hex): 0.34. ^{1}H NMR (500 MHz): 5.95 (m, 1H), 5.30 (apparent doublet of quartets, J = 17.2, 1.7, 1H), 5.15 (apparent doublet of quartets, J = 10.4, 1.7, 1H), 4.18 (m, 1H), 4.01 (m, 1H), 2.60 (d, J = 12.6, 1H), 2.37 (d, J = 12.6, 1H), 1.50 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H). ^{13}C (MHz): 135.5, 116.3, 108.7, 83.4, 63.3, 58.9, 27.7, 24.7, 20.3. HRMS (ESI): calc for $C_9H_{16}O_3Na$: 195.0997; found: 195.1003 (2 ppm).



3-(Allyloxy)-3-methyl-1,2-dioxaspiro[4.5]decane (238):

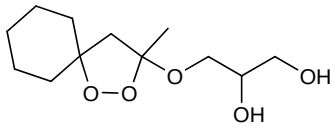
To a flame-dried RBF containing a solution of **146** (661 mg, 3.8 mmol) in CH_2Cl_2 (385 mL) was added sequentially allyl alcohol (1.3 mL, 19 mmol) and TsOH (72 mg, 0.38 mmol). After 17 hrs the reaction was treated with sat. aq. $NaHCO_3$ (20 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **238** (374 mg, 46%). R_f (10% EA/hex): 0.44. ^{1}H NMR (300 MHz): 5.98 (m, 1H), 5.3 (m, 1H),

5.15 (m, 1H), 4.19 (m, 1H), 4.01 (m, 1H), 2.51 (d, J = 12.6, 1H), 2.32 (d, J = 12.6, 1H), 1.87-1.28 (13H). ^{13}C (75 MHz): 135.5, 116.2, 108.1, 85.7, 63.2, 57.3, 36.5, 34.6, 25.4, 24.4, 23.4, 20.3. HRMS (ESI): calc for $C_{12}H_{20}O_3Na$: 235.1310; found: 235.1304 (3 ppm).



3-((3,5,5-Trimethyl-1,2-dioxolan-3-yl)oxy)propane-1,2-diol (239):

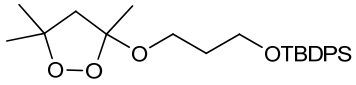
To a flame-dried RBF containing a solution of **237** (200.1 mg, 1.2 mmol) and NMO (168 mg, 1.44 mmol) in acetone (60 mL) was added OsO_4 (0.16M in H_2O, 0.15 mL, 0.024 mmol). After 24 hrs the reaction was treated with sat. $NaHSO_3$ (20 mL) and stirred for 30 min. The solution was diluted with sat. aq. NH_4Cl (50 mL) and the resulting suspension was extracted with CH_2Cl_2 (10 x 100 mL). The combined organic layers were subjected to standard drying and purification with 100% EA to afford **239** (176.6 mg, 74%). R_f(100% EA): 0.32. ^1H NMR (400 MHz): 3.89-3.54 (5H), 3.10 (s, 0.5H), 2.85 (ad, J = 6.3, 0.5H), 2.56 (dd, J = 12.6, 5.8, 1H), 2.44 (bs, 0.5H), 2.36 (d, J = 12.6, 1H), 2.28 (bs, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H). ^{13}C (100 MHz):108.9, 108.8, 84.4, 84.3, 70.8, 70.7, 64.3, 64.1, 63.8, 63.0, 58.7, 58.7, 28.0, 27.9, 24.9, 24.8, 19.3, 19.1. HRMS (ESI): calc for $C_9H_{18}O_5Na$: 229.1052; found: 229.1042 (4 ppm).



3-((3-methyl-1,2-dioxaspiro[4.5]decan-3-yl)oxy)propane-1,2-diol (240):

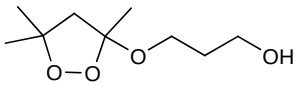
To a flame-dried RBF containing a solution of **238** (197.4 mg, 0.9 mmol) and NMO (132 mg, 1.1 mmol) in acetone (47 mL) was added OsO_4 (0.16 M in H_2O, 0.12 mL, 0.028

mmol). After 24 hrs the reaction was treated with sat. $NaHSO_3$ (20 mL) and stirred for 30 min. The solution was diluted with sat. aq. NH_4Cl (50 mL) and the resulting suspension was extracted with CH_2Cl_2 (10 x 100 mL). The combined organic layers were subjected to standard drying and purification with 100% EA to afford **240** (164.1 mg, 72%). R_f (100% EA): 0.31. ^1H NMR (400 MHz): 3.88-3.48 (5H), 3.20 (s, 0.5H), 2.93 (s, 0.5H), 2.57-2.24 (3H), 1.86-1.32 (13H). ^{13}C (150 MHz): 108.29, 108.27, 86.3, 26.2, 70.8, 70.7, 64.3, 64.1, 63.8, 63.0, 57.1, 36.7, 36.6, 34.8, 25.2, 25.1, 24.3, 23.3, 19.2,, 19.0. HRMS (ESI): calc for $C_{12}H_{22}O_5Na$: 285.1104; found: 285.1115 (3 ppm).



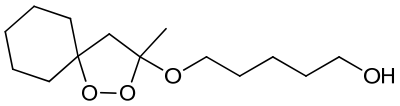
3,5,5-Trimethyl-3- (3-t-butyl-diphenylsilyloxy-propoxy1,2-dioxolane (242):

To a flame-dried vial containing a solution of **107-OTMS** (508.2 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) was added sequentially 3-[(tert-butyldiphenylsilyl)oxy]-1-propanol (3 g, 7.3 mmol) and TsOH (48 mg, 0.25 mmol). After 2 hrs the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (20 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **242** (704.7 mg, 66%). R_f (10% EA/hex): 0.60. ^1H NMR (400 MHz): 7.73-7.66 (4H), 7.46-7.35 (6H), 3.85-3.61 (4H), 2.52 (d, J = 12.4, 1H), 2.32 (d, J = 12.4, 1H), 1.85 (quintet, J = 6.3, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.06 (9H). ^{13}C (100 MHz):135.8, 134.25, 134.21, 129.7, 127.8, 127.7, 108.5, 83.8, 61.1, 58.7, 33.2, 27.7, 27.0, 24.7, 20.2, 19.4. HRMS (ESI): calc for $C_{25}H_{36}O_4NaSi$: 451.2281; found: 451.2273 (1.8 ppm).



3-((3,5,5-Trimethyl-1,2-dioxolan-3-yl)oxy)propan-1-ol (243):

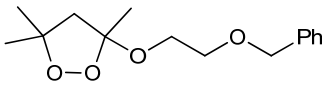
To a flame-dried vial containing a solution of **242** (669.8 mg, 1.6 mmol) in THF (16 mL) was added TBAF (1M in THF, 1.8 mL, 1.8 mmol). After 3 hrs the reaction was treated with H_2O (50 mL) and the resulting suspension was extracted with Et_2O (3 x 50 mL). The combined organic layers were subjected to standard drying and purification with 50% EA/hex to afford **243** (242.2 mg, 80%). R_f (50% EA/hex): 0.47. ^{1}H NMR (400 MHz): 3.87-3.69 (3H), 3.62 (m, 3H), 2.59 (bs, 1H), 2.52 (d, J = 12.6, 1H), 2.34 (d, J = 12.6, 1H), 1.89-1.70 (2H), 1.48 (s, 3H), 1.37 (s, 6H). ^{13}C (75 MHz): 108.6, 84.2, 61.2, 60.0, 58.9, 32.0, 27.9, 24.8, 19.4. IR: 3430, 2940, 2880, 1447. HRMS (ESI): calc for $C_9H_{18}O_4Na$: 213.1103; found: 213.1100 (1.4 ppm).



5-((3-Methyl-1,2-dioxaspiro[4.5]decan-3-yl)oxy)pentan-1-ol (244):

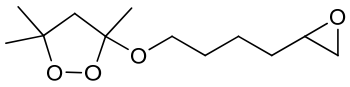
To a flame-dried vial containing a solution of **147** (504.1 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added sequentially 1,5-pentanediol (0.09 mL, 0.87 mmol) and TsOH (16 mg, 0.087 mmol). After 2 hrs the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (20 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification sequentially with flash chromatography and HPLC with 30% EA/hex to afford **244** (95 mg, 19%). R_f (20% EA/hex): 0.08. ^{1}H NMR (400 MHz): 3.72-3.56 (3H), 3.50 (m, 1H), 2.43 (d, J = 12.5, 1H), 2.28 (d, J = 12.5, 1H), 1.83-1.30 (20H). ^{13}C (75 MHz):107.8, 85.7, 63.1, 61.5,

57.3, 36.5, 34.6, 32.5, 29.7, 25.4, 24.4, 23.3, 22.4, 20.0. IR: 3374, 2933, 2859, 1446. HRMS (ESI): calc for $C_{14}H_{26}O_4Na$: 281.1729; found: 281.1725 (1.4 ppm).



3-(2-(Benzyloxy)ethoxy)-3,5,5-trimethyl-1,2-dioxolane (245):

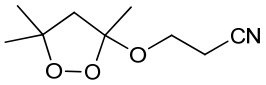
To a flame-dried vial containing a solution of **107-OTMS** (200 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-(Benzyloxy)ethanol (0.76 mL, 5 mmol) and TsOH (19 mg, 0.1 mmol). After 2 hrs the reaction was treated with sat. $NaHCO_3$ (20 mL) and H_2O (5 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford **245** (157.2 mg, 68%). R_f (20% EA/hex): 0.55. ^{1}H NMR (400 MHz): 7.3 (m, 5H), 4.62 (dd, J = 18.1,12.2, 2H), 3.86-3.61 (4H), 2.64 (d, J = 12.5, 1H), 2.35 (d, J = 12.5, 1H), 1.51 (s, 3H), 1.40 (d, J = 1.7, 6H). ^{13}C (100 MHz): 138.6, 128.5, 127.9, 127.7, 102.7, 84.0, 73.3, 69.7, 61.5, 58.7, 27.7, 24.7, 20.2. HRMS (ESI): calc for $C_{15}H_{22}O_4Na$: 289.1416; found: 289.1415 (0.3 ppm).



3,3,5-trimethyl-5-(4-(oxiran-2-yl)butoxy)-1,2-dioxolane (246):

To a flame-dried vial containing a solution of **231** (501.6 mg, 2.3 mmol) in CH_2Cl_2 (23 mL) was added sequentially $NaHCO_3$ (252 mg, 3 mmol) and mCPBA (739.2 mg, 3 mmol)). After 24 hrs the reaction was treated with H_2O (50 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with sat. aq. $NaHSO_3$ (50 mL) and subjected to standard drying and purification with 20% EA/hex to afford **246** (346.7 mg, 65%). R_f (20% EA/hex): 0.50. ^{1}H NMR (300

MHz): 3.62 (m, 1H), 3.46 (m, 1H), 2.98-2.88 (1H), 2.75 (dd, J = 4.8, 4.3, 1H), 2.53 (d, J = 12.5, 1H), 2.48 (m, 1H), 2.33, (d, J = 12.5, 1H), 1.71- 1.50 (6H), 1.47 (s, 3H), 1.37 (s, 6H). ^{13}C (75 MHz): 108.4, 83.8, 61.6, 61.4, 58.9, 58.8, 52.5, 52.4, 47.3, 47.2, 32.4, 32.3, 29.9, 29.8, 27.8, 24.81, 24.8, 22.8, 22.7, 20.1, 20.0. HRMS (ESI): calc for $C_{12}H_{22}O_4Na$: 253.1416; found: 253.1409 (2.7 ppm).



3-((3,5,5-Trimethyl-1,2-dioxolan-3-yl)oxy)propanenitrile (247):

To a flame-dried vial containing a solution of **107-OTMS** (202.3 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-cyanoethanol and TsOH (19 mg, 0.1 mmol). After 1 hr the reaction was treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **247** (121.9 mg, 66%). R_f (30% EA/hex):0.28. ^{1}H NMR (400 MHz): 3.79 (m, 1H), 3.65 (m, 1H), 2.65 (m, 2H), 2.55 (d, J = 12.6, 1H), 2.33 (d, J = 12.6, 1H), 1.40 (s, 3H), 1.34 (d, J = 5.9, 6H). ^{13}C (75 MHz): 118.2, 108.7, 84.1, 58.6, 57.0, 27.7, 24.6, 19.6, 19.5. HRMS (ESI): calc for $C_9H_{15}O_3Na$: 208.0950; found: 208.0942 (3 ppm).

Section 7

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Chapter 3

1,2,4-Trioxepanes as potential antimalarials

This chapter details my synthesis of 1,2,4-trioxepanes and their investigation as potential antimalarials.

Section 1: Previous synthesises

Section 2: Rationale

Section 3: Results and Discussion

Section 4: Antimalarial results

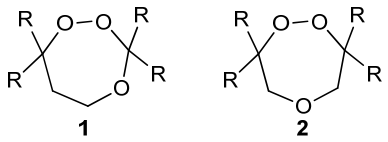
Section 5: Experimentals

Section 6: References

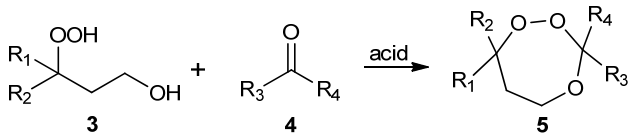
Section 1

Previous synthesis

When discussing trioxepanes it is important to first understand the nomenclature that is used. There are two isomeric forms of trioxepane peroxides that can exist depending on the relative positions of the oxygens in the ring. The first is a 1,2,4-trioxepane exemplified by **1**. The second is 1,2,5-trioxepane which is represented by **2**.



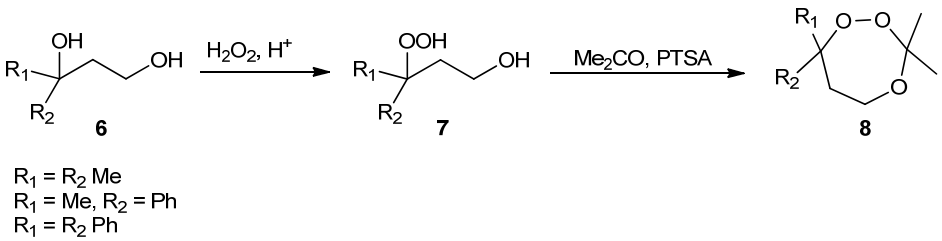
The synthesis of 1,2,4-trioxepanes is well established in the literature. All of the methods rely upon a similar acid catalyzed ketalization to close the trioxepane ring. The key intermediate employed by all the routes proceed through is typified by 3-hydroperoxyalkanol **3**, which undergoes an acid catalyzed ketalization with ketone **4** to afford trioxepane **5**. The difference in individual routes reflects the strategy employed for the synthesis of hydroperoxide intermediate **3.**



Acid displacement

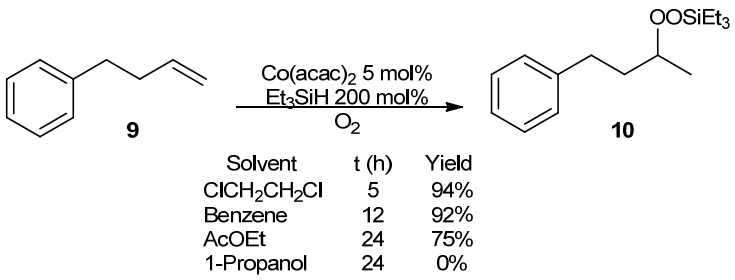
The first synthesis of 1,2,4-trioxepanes was described by Adam and Duran in 1972.[1] The diol precursor **6** was formed via a Reformatsky reaction, on the corresponding ketone, which is followed by a $LiAlH_4$ reduction on the resulting ester. Selective substitution of the tertiary alcohol of **6** with ethereal H_2O_2 under acidic conditions afforded the desired hydroperoxide intermediate **7**, which readily undergoes

acid catalyzed ketalization to afford **8**. In the course of this study Adam and Durran also conducted some initial stability studies on **7** and **8**, finding that H_2 and Pd/C reduced both hydroperoxide **7** and trioxepane **8** to diol **6**.



Cobalt-mediated peroxidation

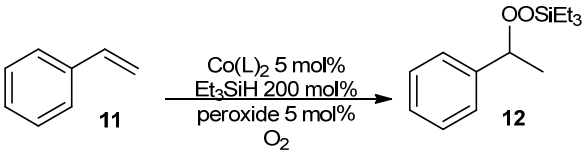
To appreciate the usefulness of this approach, it is first necessary to understand what makes cobalt peroxidation so different from other methodologies. The use of cobalt for the synthesis of hydroperoxides from alkenes was first reported by Mukaiyama in 1989.[2] In this seminal work Mukaiyama showed that alkene **9** was readily converted to peroxide **10** in a variety of solvents in good yield. Although the reaction is shown here only for $Co(acac)_2$ and a terminal alkene the reaction was shown to work with a variety of cobalt (II) sources and alkenes.



Solvent	t (h)	Yield
$ClCH_2CH_2Cl$	5	94%
Benzene	12	92%
AcOEt	24	75%
1-Propanol	24	0%

In 1990, Isayama was exploring this reaction on styrene and found that the reaction required a long initiation time, and proceeded with low conversion.[3] He reported that the initiation time can be decreased and yield increased with the use a peroxide initiator. This effect was most dramatic for cobalt (II) acetylacetone, $Co(acac)_2$. Though

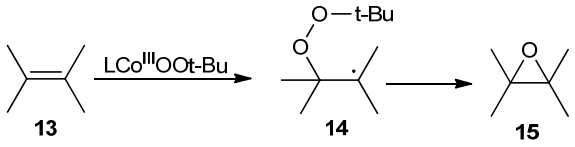
Isayama did not give a rationale for this peroxide effect, he postulated that the peroxide most likely speeds up the initiation reaction.



CoL_2	t (h)	Peroxide	Yield
$Co(acac)_2$	24	-	30%
$Co(acac)_2$	5	t-BuOOH	85%
$Co(acac)_2$	5	CHP	82%
$Co(tfa)_2$	12	-	73%
$Co(tfa)_2$	5	t-BuOOH	85%

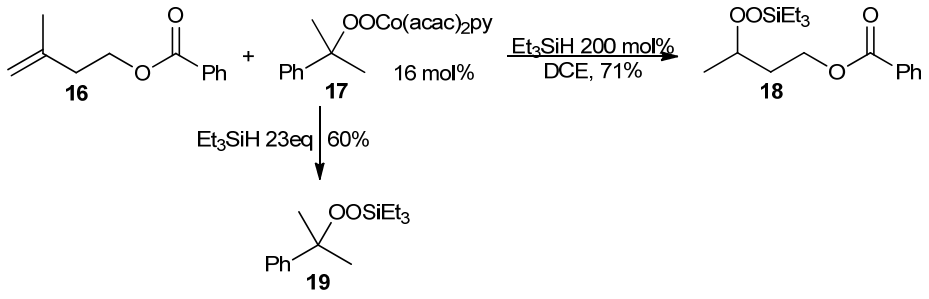
CHP = Cumyl hydroperoxide

An initial investigation of cobalt peroxide complexes was reported by Weiss in 1985.[4] Weiss drew upon the work of Kochi who had studied cobalt-mediated epoxidation of alkenes.[5] Weiss found that cyclohexene and ethylbenzene gave large amounts of the alkyl peroxides while styrene and norbornene gave the epoxide. Weiss postulated that a radical addition of *t*-butyl peroxy radical to alkene **13** afforded intermediate **14**. As there is no effective hydrogen atom donor, the newly formed radical, undergoes S_H substitution to generate epoxide **15**.

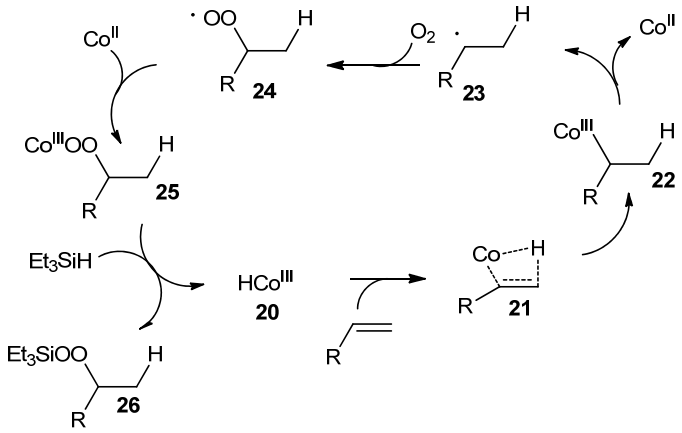


A 2002 mechanistic study by Nojima postulated a mechanism, building upon the work of Weiss.[6] Nojima initially postulated that there was a cobalt peroxide complex present in the reaction. The support for this came from the work of Isayama demonstrating the importance of the peroxide formed, and Weiss's observation of the ability of cobalt peroxide complexes to perform the proposed reaction. Nojima synthesized peroxide complex **17** and reacted it with an excess of alkene **16** under standard peroxidation conditions. Observing that peroxide **18** was formed in very good

yield. In contrast, if **17** was treated with triethylsilane under argon with no alkene present, silylperoxide **19** was isolated in high yield, suggesting the intermediacy of a cobalt triethylsilane complex.

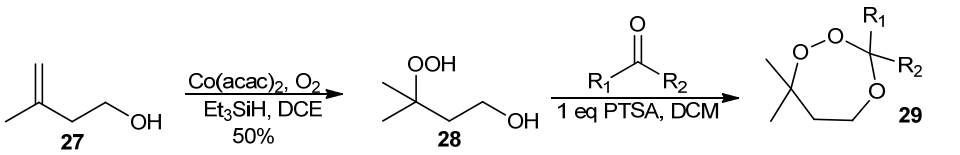


With this information Nojima proposed a complete mechanism. The postulated key intermediate a hydrido cobalt (II) species (**20**), which complexes to the alkene and delivers a hydride to provide intermediate **22**. Loss of Co^{II} generates radical **23** which readily traps O_2 to form **25**. Finally, displacement with triethylsilane affords the product **26** and regenerates **20**, restarting the cycle. O'Neill later provided further support for the intermediacy of a carbon radical by performing the reaction with a chiral cobalt catalyst.[7] The lack of asymmetric induction suggests that O_2 attacks an achiral intermediate, such as **23**, after loss of a chiral cobalt catalyst.



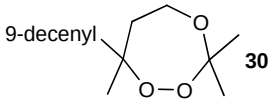
In 2004, Dussault reported the use of cobalt peroxidation on homoallyl alcohols as a different method to synthesize 1,2,4-trioxepanes.[8] This work built upon work by Oh

who, isolated the triethylsilyl peroxide of **28**.[9] Unlike what would be expected under these conditions, Dussault found that the free hydroperoxide **28** was formed as the major product instead of the triethylsilyl analog. Though this peroxidation was performed only on alcohol **27**, this strategy could be applied to any number of homoallyl alcohols as a approach to 1,2,4-trioxepanes. Dussault found that the ketones with varying electronics can be ketalized with **28** to afford trioxepanes **29**.



R_1 = 4-MeO_2CPh	R_2 = H	90%
R_1 = 4-EtO_2Ph	R_2 = Me	91%
R_1 = Bu	R_2 = Bu	>95%
R_1 = 9-decenyl	R_2 = H	86%
R_1 = $MeO_2C(CH_2)_2$	R_2 = hexyl	>90%
R_1 = 4-t-butylcyclohexyl		89%
R_1 = PhChCH	R_2 = H	83%

Dussault became interested in trioxepanes as potential protecting groups for carbonyl compounds. Thus, trioxepane **30** was tested against a variety of reaction conditions to determine its stability. Peroxides are often quite reactive and therefore would not be expected to make a good protecting group. However, Dussault found that **30** exhibited remarkable stability to various reducing agents. The exception was n-BuLi which caused decomposition even at -78^{o}C. Dussault reported that deprotection to the carbonyl was achieved with a dissolving metal reduction by either Zn/HOAc or Mg/MeOH.



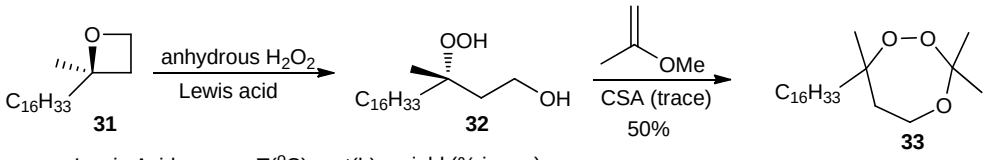
30

Reagent	$t_1/_2$
PPh_3	>24h
$NaBH_4$	>24h
H_2CrO_4	>24h
DDQ	>24h
Et_3N	>24h
10% NaOH/MeOH	>24h
TsOH/MeOH	>24h
n-BuLi (3 eq) -78^o	0.25h

Oxetane opening

In 2002, Dussault reported the synthesis of enantiomerically enriched 1,2,4-trioxepanes that were derived from chiral oxetanes.[10] It was found that the oxetane could be opened with ethereal H_2O_2 and a variety of Lewis acids. The choice of Lewis acid was found to be important in that $BF_3{\cdot}OEt_2$, $ZnCl_2$, and $MgCl_2$ produced no reaction, but the use of TMSOTf, $Yb(OTf)_3$, and $Sc(OTf)_3$ afforded the desired hydroperoxide, **32**, in varying yields. The main issue that was encountered in the opening was the extent of inversion of the stereocenter. The final ketalization step proceeded in moderate yield to afford **33**.

The solvation of the H_2O_2 was also found to be important to the course of the reaction. When H_2O_2 in CH_2Cl_2 was formed by iterative addition and evaporation from ethereal H_2O_2, the inversion product was formed exclusively, even at -78^oC. In contrast, the use of H_2O_2 in CH_2Cl_2 obtained from direct extraction of H_2O_2 with CH_2Cl_2 led to elimination giving the homoallyl alcohol. Dilution of the CH_2Cl_2-extracted H_2O_2 with an equal volume of ether leads the suppression of inversion.

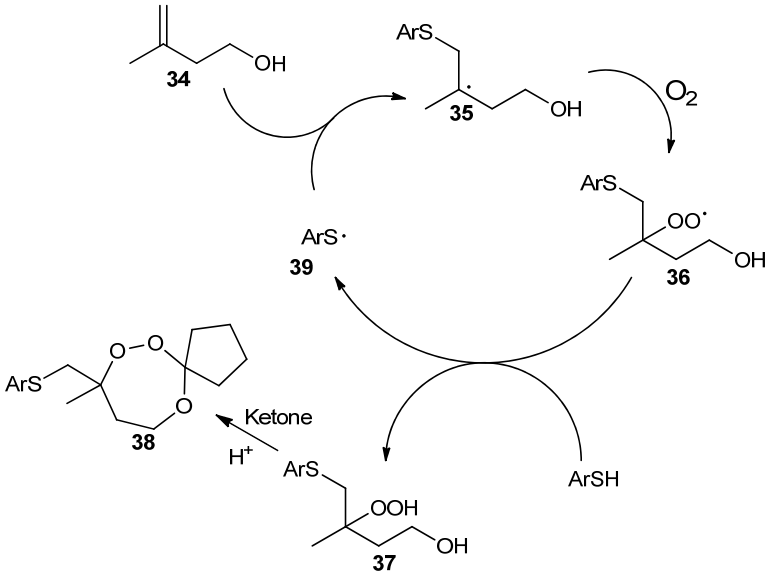


31 **32** **33**

Lewis Acid	eq	T(°C)	t(h)	yield (% inver.)
TMSOTf	0.4	-25 - 0	0.5	48% (>90)
$Yb(OTf)_3$	0.1	-25 - 0	2	60%
$Sc(OTf)_3$	0.1	-25 - 0	3	50%

Thiol-Olefin Co-Oxygenation

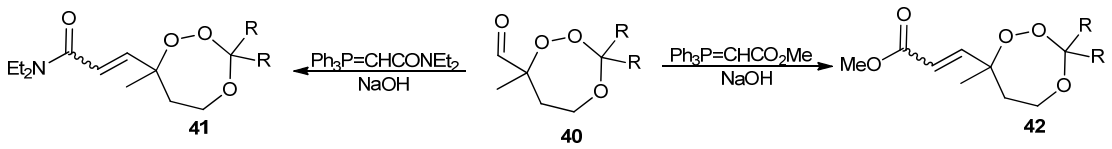
The use of thiol-olefin co-oxygenation to synthesize trioxepanes was reported by O'Neill in 2006.[11] The mechanism for this reaction is reliant upon the generation of a thiyl radical. The reaction is typically initiated by an agent such as AIBN. The synthesis of the 1,2,4-trioxepane was then readily accomplished by ketalization with a variety of ketones to afford 1,2,4-trioxepane **38**.



34 **35** **36** **39** **38** **37**

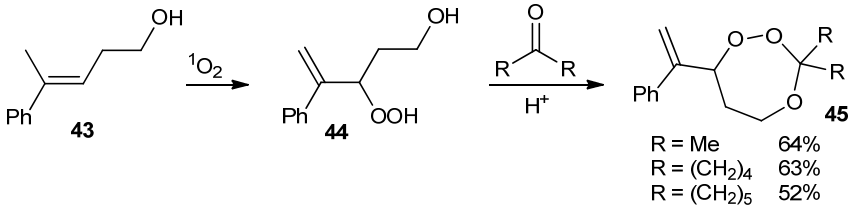
In attempts to make more water soluble 1,2,4-trioxepanes a variety of manipulations were successfully carried on trioxepane **38**. The oxidation of sulfide **38** to the corresponding sulfone and sulfoxide was readily accomplished with *m*CPBA. Treatment of the sulfoxide under Pummerer conditions afforded aldehyde **40**. Aldehyde

40 successfully underwent Wittig olefination to afford amide **41** and ester **42**. A reductive amination of aldehyde **40** with morpholine was attempted, but led to peroxide decomposition.



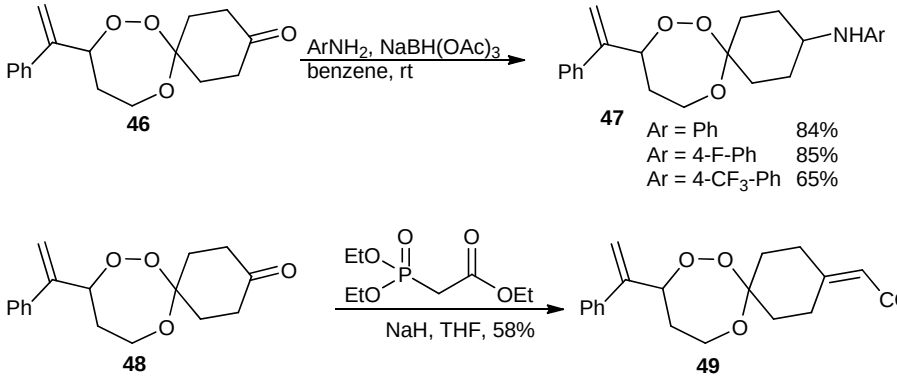
Singlet oxygen

In 2006, Singh reported that singlet oxygenation of homoallylic alcohols is an effective method for the generation of a 3-hydroperoxy-4-alken-1-ol **44.**[12] This route starts with alcohol **43**, that is readily synthesized in two steps from commercial starting materials. The formation of the final 1,2,4-trioxepanes was accomplished by ketalization of **44** with either acetone, cyclopentanone, or cyclohexanone.



In 2008, Singh synthesized a new series of 1,2,4-trioxepanes in the pursuit of a potentially new antimalarial treatment.[13] In the course of this work he furthered the knowledge of 1,2,4-trioxepanes by performing reactions that are typically not compatible with peroxides. Singh reported successful a reductive amination with a variety of aryl amines to form substituted 1,2,4-trioxepanes represented by **47**. This result was unexpected given the issues that had been reported by O'Neill on a similar substrate.[11] Though not discussed, the success of this reaction could be due to the use of the less active $NaBH(OAc)_3$. Trioxepane **48** was also stable towards Horner-Wadsworth-Emmons (HWE) homologation conditions to afford **49**. The low yield for the HWE

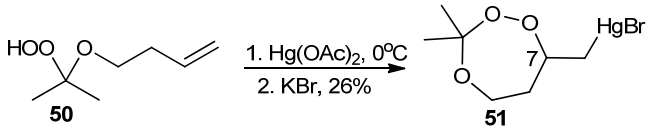
reaction was not discussed by Singh and it is unclear if the lower yield is inherent to the olefination of a ketone or if peroxide decomposition occurred.



Electrophilic cyclization

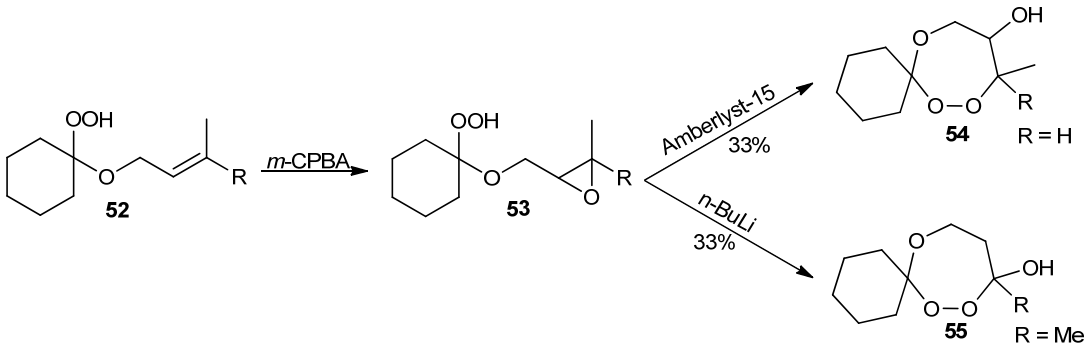
Electrophilic cyclization was discussed in full in Chapter 2 Section 2.1. A brief discussion relevant to 1,2,4-trioxepanes follows.

In 1996, Dussault reported that it was possible to use electrophilic cyclization of a hydroperoxide onto an alkene to afford 1,2,4-trioxepanes.[14] The peroxymercuration of **50** with $Hg(OAc)_2$ was successful, while the corresponding peroxyiodination was not. Dussault reported that trioxepane **51** lacked stability, though no explanation was given. This lack of stability is possibly due to the hydrogen present in the **7** and the potential for E_1CB decomposition. Nojima reported that cyclization of hydroperoxy acetal similar to **50** with NIS resulted in a low yield and complex mixture of isomers.[15]

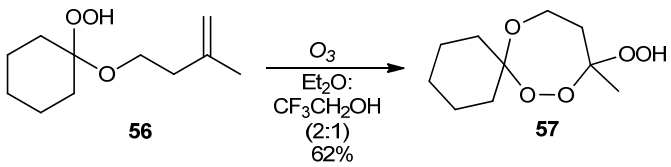


Ozonolysis

In 1997, Nojima reported that the closure of a hydroperoxy acetal onto an epoxide could be used to synthesize 1,2,4-trioxepanes.[16] Hydroperoxide acetal **52**, which was formed through ozonolysis, was subjected to epoxidation conditions to yield **53**. As would be expected acidic treatment of **53** resulted in cyclization at the more hindered site to give **54**. If **53** was subjected to basic conditions, then cyclization occurred at the less hindered site to afford **55**.



Nojima reported in 1997 that the ozonolysis of an alkene in the presence of a hydroperoxy acetal would result in intramolecular trapping to give a 7-hydroperoxy-1,2,4-trioxepane.[17] When hydroperoxy acetal **56** is subjected to ozonolysis, hydroperoxytrioxepane **57** was produced in good yield. Nojima found that the choice of solvent was important for this reaction. A 2: 1 mixture of ether/trifluoroethanol gave optimal yields, while the use of ether alone resulted in the ozonide of **56** forming as a major byproduct. The use of trifluoroethanol as a solvent resulted in only **57** forming, but in decreased yield.

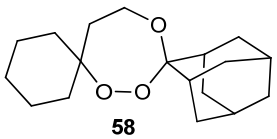


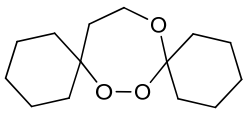
Section 2

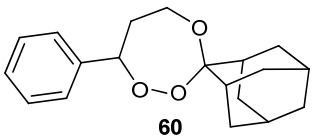
Rationale

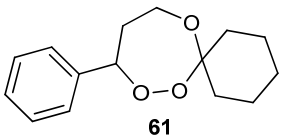
The following work has largely been published.[18]

Given the high activity of selected 1,2,4-trioxolanes against P. *falciparum* in situ and as potential antimalarial drugs, we became interested in determining the effect that ring size has on activity. This work was done in collaboration of the Vennerstrom group at the University of Nebraska Medical Center. It was decided that I would synthesize four 1,2,4-trioxepanes (**58 - 61**) and their activity against P. *falciparum* would be determined. The Vennerstrom group would synthesize the corresponding 1,2,4-trioxolanes and 1,2,4-trioxanes. The hypothesis is that as the ring size increased the peroxide bond would be less accessible and antimalarial activity would diminish. Nonetheless it was necessary to synthesize this series to determine if that theory was valid.


58

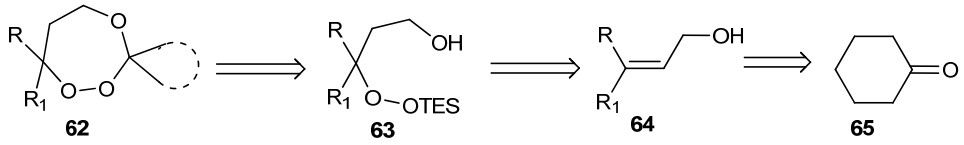

59


60


61

Retro-synthetically it was envisioned that a parallel synthesis would be employed, using a common hydroperoxyalkanol as a common intermediate and that final differentiation between **58/59** and **60/61** would occur at the ketalization step. Given the work that has been done previously, I envisioned that hydroperoxide **63** would be formed via a Mukaiyama cobalt peroxidation from an allyl alcohol **64**. In the case of the cyclohexyl derivative, is available via a Horner-Wadsworth-Emmons olefination of

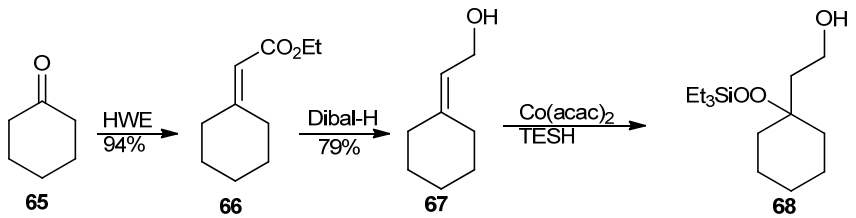
cyclohexanone. While in the case of the phenyl propanol derivative, hydroperoxide **63**, the precursor of 1,2,4-trioxepanes **60** and **61**, would be formed from cinnamyl alcohol.



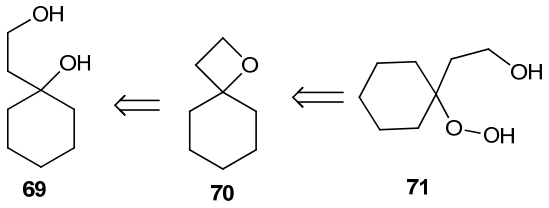
Section 3

Results and discussion

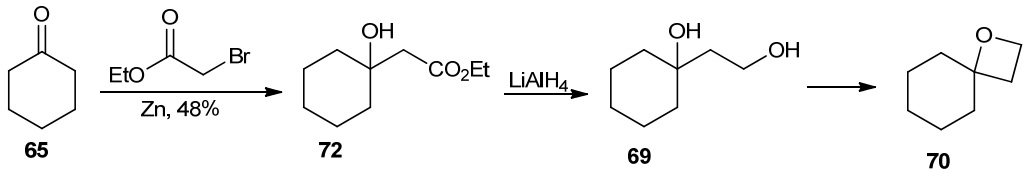
Although the olefination of cyclohexanone to form ester **66** was uneventful, the subsequent reduction was found to be problematic. Initially, $LiAlH_4$ was employed as the reducing agent however this led to an inseparable mixture of saturated and unsaturated **67**. [19] It was found that this issue was readily circumvented by reduction with Dibal-H. Allyl alcohol **67** was then subjected to Mukaiyama cobalt-mediated peroxidation using several solvents (1,2-dichloroethane, EtOH) and cobalt complexes ($Co(acac)_2$ and Cobalt(II) (2,2,6,6-tetramethyl-3,5-heptanedionate ($Co(THD)_2$). However, it was found that all tested conditions gave a poor yield to the desired peroxide and always as part of an inseparable mixture. This outcome is not entirely surprising when the earlier Dussault work is considered.[8] Alcohol **67** is expected to be a problematic substrate which will react to mainly furnish the free hydroperoxide and not the triethylsilyl peroxide. Therefore, it would have been prudent to perform a model reaction on a known substrate as a model, but this was not done.



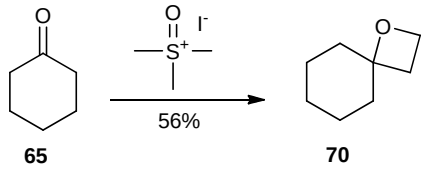
Given these synthetic issues I decided that the use of an oxetane as the peroxide precursor might be a more successful strategy. Our lab has previously reported the opening of oxetanes similar to **70** with hydrogen peroxide as a route to hydroperoxides **71**.[20] It was envisioned that the desired oxetane (**70)** could be formed by a intramolecular nucleophilic displacement of the primary tosylate formed from diol **69**.



The synthesis of oxetane **70** began with a Reformatsky reaction of cyclohexanone to afford ester **72** which underwent $LiAlH_4$ reduction to provide diol **69**. Closure of the oxetane could be accomplished by formation of the primary tosylate followed by an intramolecular displacement. This approach, however, provided the desired oxetane **70** in poor yield and this route was abandoned.

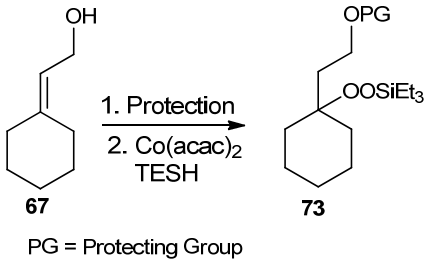


At this point, I decided that it would be beneficial to employ a modified version of the Corey-Chaukovski reaction to obtain the oxetane in one-step from the ketone. I investigated the oxetane in one-step formation of oxetane as reported by Okuma.[21] Though the yield for this reaction is not exemplary, it provided the desired product in a one-pot one step procedure.



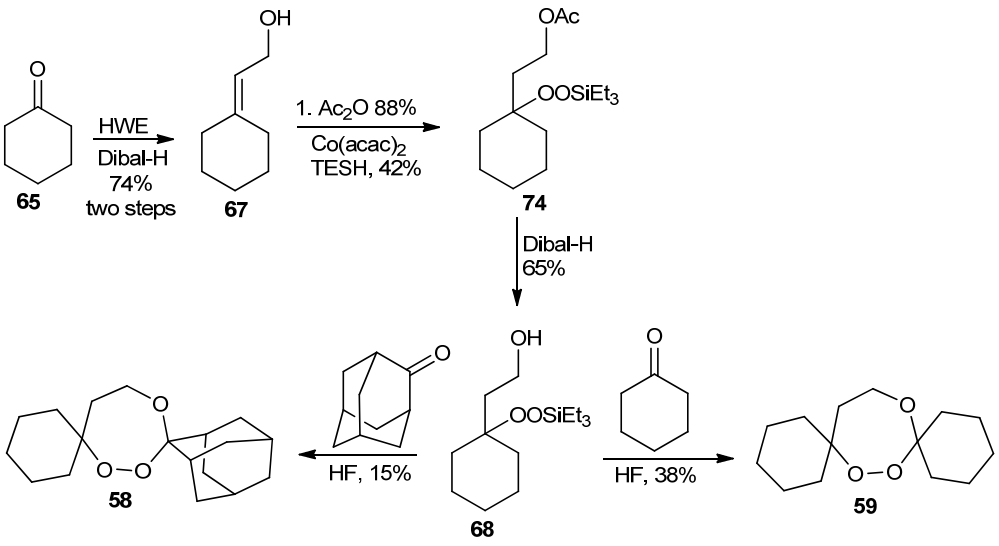
With the oxetane in hand, I attempted to perform the opening with hydrogen peroxide as was previously reported by Dussault.[20] However, when I attempted the opening I ran into significant trouble with every condition attempted. The reason for this failure is unclear although most of the earlier examples are in acyclic substrates.

With these troubles I returned to investigations of the Mukaiyama cobalt-mediated peroxidation. I thought that the use of a protecting group on the alcohol might improve the outcome of the cobalt-mediated dioxygenation. Initially, it was planned that the TMS or TES ether would be employed, as deprotection and ketalization could be accomplished in one-step. Attempts to form the OTMS ether were unsuccessful, but the OTES ether was successfully prepared. Unfortunately cobalt peroxidation was unsuccessful. In hindsight, the use of the bulkier OTBS ether would have been more prudent as it would be less likely to undergo deprotection during the cobalt peroxidation.

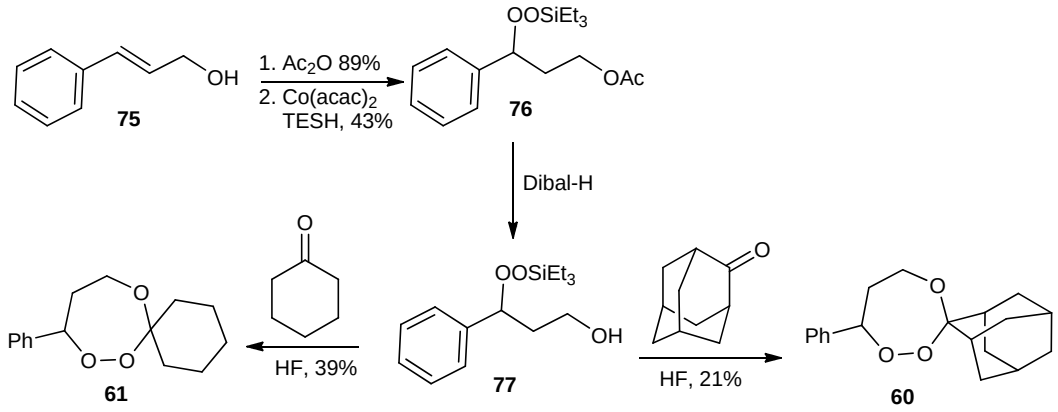


I thought that this strategy merited further investigation using a protecting group that would not be labile under cobalt-mediated peroxidation conditions. A paper by Wu reporting the selective reduction of esters in the presence of a dialkyl peroxide encouraged me to utilize a ester protecting group.[22] To my delight, the acetate derived

from alcohol **67** underwent cobalt-mediated peroxidation to yield silyl peroxide **74**, which underwent Dibal-H reduction to afford the long sought after peroxyalkanol **68**. Finally, ketalization with either 2-adamantanone or cyclohexanone proceeded in moderate yield to afford the desired 1,2,4-trioxepanes **58** and **59** respectively.



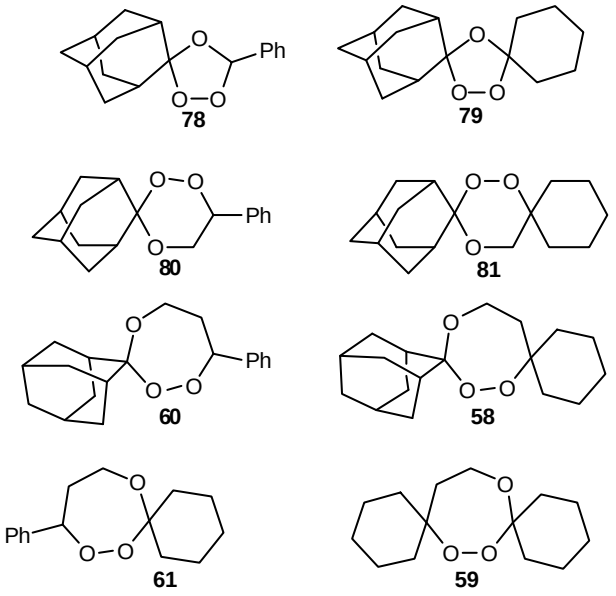
The same chemistry was used to prepare the cinnamyl analog (**77**), the 3-peroxy-3-phenylpropanol in good yield. Ketalization of **77** with 2-adamantanone or cyclohexanone afforded trioxepanes **60** or **61**, respectively in moderate yield.



Section 4

Antimalarial results

The desired 1,2,4-trioxepanes were subjected to in vitro testing against P. *falciparum* and were compared against structural analogs 1,2,4-trioxolanes and 1,2,4-trioxoanes (Table 3.1).[23,24] There was a decrease in activity as the peroxide ring size increased, 5>6>7. The trioxepanes that I synthesized showed no activity. Although we had expected little activity, we had not expected a complete absence of activity. Previous work showed that the difference in Fe (II) reactivity between **79** and **80** could be correlated with the accessibility of the peroxide bond to Fe^{II}.[25] I believe that this same rationale can be extended to the lack of activity for the 1,2,4-trioxepanes. Our collaborators investigated the degradation of trioxepane **58** by soluble Fe(II) and found no reaction after 24 hrs, conditions that would have resulted in complete degradation of a 1,2,4-trioxolane or a 1,2,4-trioxane. The results show there is a tradeoff between stability and activity.



Compound	IC_{50} (nM)
78	>1000
79	5.3
80	66
81	158
58	>1000
59	>1000
60	>1000
61	>1000

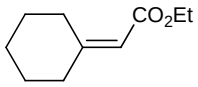
Table 3.1

Section 5

Experimentals

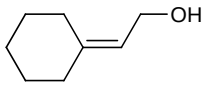
All reagents were used as received from commercial vendors, with the exception of CH_2Cl_2, which was distilled from calcium hydride, and THF, which was distilled from sodium/benzophenone. All reactions were conducted under an atmosphere of N_2 except where noted; "RBF" indicates round-bottom flask. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized with a hand-held UV lamp or by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% *N,N'*-dimethyl-*p*-

phenylenediamine solution in 1:20:100 acetic acid/water/methanol (specific for peroxides);[26] 1% aq. $KMnO_4$ (for unsaturated compounds). "Standard drying and purification" refers to drying of organic extracts over Na_2SO_4, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. $^1H/^{13}C$ NMR spectra were obtained in $CDCl_3$ unless otherwise indicated; peaks are reported as: chemical shift (multiplicity, J couplings in Hz, number of protons). Infrared spectra were recorded as neat ATR films with selected absorbances reported in wavenumbers (cm^{-1}).



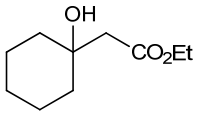
Ethyl 2-cyclohexylideneacetate (66):

A suspension containing sodium hydride (2.3g, 57 mmol, 60% in mineral oil) in a flame-dried RBF was washed with pentane (2 x 20 mL). The residue was suspended in THF (90 mL) and the suspension cooled to 0^oC. Following the drop wise addition of triethylphosphonoacetate (13.72 g, 61 mmol), the reaction was allowed to warm to rt and stirred at this temperature for 90 min. Cyclohexanone (5g, 51 mmol) was then added drop wise and the reaction allowed to stir overnight. The reaction was diluted with H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried with Na_2SO_4. The residue obtained upon concentration *in vacuo* was purified by chromatography with 10% EA/hex to afford **66** (8.0992g, 94 %) as a colorless oil. R_f (10% EA/hex) = 0.68. ^1H NMR (300 MHz): 5.60 (s, 1H), 4.15 (q, 2H, J=7), 2.83 (apparent t, 2H, J=6), 2.20 (apparent t, 2H, J=6), 1.72-1.54 (6H), 1.28 (t, 3H, J=7.12). The NMR spectra matched those previously reported.[27]



2-Cyclohexylideneethanol (67)

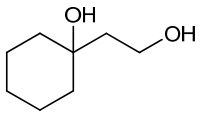
In a flame-dried RBF containing a 0^{o}C solution of **5** (7.62 g, 45 mmol) in Et_2O (150 mL) was added Dibal-H (91 mL, 91 mmol, 1 M). The reaction was stirred for 2 hrs and then was treated with sat. aq. Rochelle's salt (30 mL) followed by H_2O (500 mL). The resulting suspension was extracted with Et_2O (2 x 500 mL) and the combined organic layers were washed with brine (500 mL) and dried with Na_2SO_4. The residue obtained upon concentration *in vacuo* was purified via column chromatography with 30% Et_2O/pent to afford **67** (4.4458 g, 79%) as a colorless oil. ^{1}H (300 MHz): 5.36 (m, 1H), 4.15 (m, 2H), 2.2-2.03 (4H), 1.62-1.45 (6H), 1.25 (s, 1H). The NMR spectra matched those previously reported.[27]



1-Carboethoxymethyl-1-cyclohexanol (72):

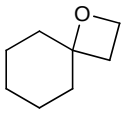
Cyclohexanone (5 g, 51 mmol) and ethyl bromoacetate (8.52g, 51 mmol) were dissolved in a mixture of benzene (60 mL) and toluene (50 mL) in a RBF. To a separate flame-dried RBF were added sequentially Zn dust (3.31g, 51 mmol) and 25 mL of the solution from the other RB. The reaction was heated to reflux at which point the remainder of the first solution was added. The reaction was held at reflux for 2 hrs after which dilute H_2SO_4 (50 mL) was added and the resulting suspension filtered. The organic layer was washed with brine (2 x 15 mL) and dried with Na_2SO_4. The residue obtained upon concentration *in vacuo* was purified by column chromatography with 10% EA/hex to afford **72** (4.683 g, 48%). R_f (10 % EA/hex): 0.43. ^{1}H (300 MHz): 4.13(q, J =

7.1, 2H), 3.40 (s, 1H), 2.42 (s, 2H), 1.72-1.33 (10H), 1.23 (t, J = 7.1, 3H). The NMR spectra matched those previously reported.[28]



1-(2-Hydroxyethyl)cyclohexanol (69):

A suspension of $LiAlH_4$ (306 mg, 38 mmol) in Et_2O was cooled to 0°C in a flame-dried RBF. To the suspension was added **72** (500 mg, 2.68 mmol) in Et_2O (10 mL). The reaction was stirred for 30 min and then quenched by sequential addition of H_2O (0.3 mL), 10% aq. NaOH (0.3 mL) and H_2O (0.9 mL). The suspension was filtered and the aq. layer extracted with Et_2O (3 x 15 mL). The combined organic layers were dried with Na_2SO_4 and the residue obtained upon concentration *in vacuo* was purified via column chromatography with 30% Et_2O/hex. As the subsequent oxetane closure proceeded in very low yield, this route was not pursued further.

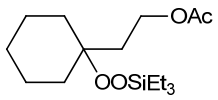


1-Oxaspiro[3.5]nonane (70):

(Corey-Chaukovski method)[21]

To a flame-dried RBF was added sequentianlly trimethylsulfoxonium iodide (8.8 g, 40 mmol), potassium *t*-butoxide (4.75 g, 40 mmol), and *t*-butanol (40 mL). The slurry was allowed to stir at 50°C for 30 min. A solution of cyclohexanone (1g, 10 mmol) in *t*-butanol (10 mL) was added and the reaction was allowed to stir at 50°C for 3 days. The reaction was then treated with H_2O (100 mL) and the suspension was extracted with pentane (3 x 60 mL). The combined organic layers were washed with brine (2 x 80 mL)

and subjected to standard drying and purification with 7.5% Et_2O/pent to afford **70** (706.1 mg, 56%). ^1H NMR (300 MHz): 4.49 (t, J = 7.8, 2H), 2.33 (t, J = 7.8, 2H), 1.90-1.75 (10H). The NMR contained approximately 10% Et_2O but otherwise matched those previously reported.[21]

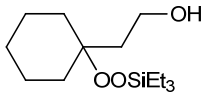


2-(1-((Triethylsilyl)peroxy)cyclohexyl)ethyl acetate (74):

To a flame-dried RBF was added sequentially **67** (4.4458 g, 35 mmol), pyridine (50 mL), Ac_2O (3.88 mL, 52 mmol), and DMAP (437.8 mg, 3.5 mmol). The reaction was stirred for 2 hrs and then quenched by addition of 2N aq. HCl (75 mL). The suspension was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed sequentially with 2N HCl (75 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried with Na_2SO_4 and the residue upon concentration *in vacuo* was purified via column chromatography with 10 % EA/hex to afford 2-cyclohexylideneethyl acetate (5.1477 g, 88%). R_f (10% EA/hex) = 0.62. ^1H NMR (300 MHz): 5.28 (dt, J = 7.3, 1.1, 1H), 4.57 (d, J = 7.3, 2H), 2.24-2.06 (4H), 2.04 (s, 3H), 1.61-1.44 (6H). The NMR spectra matched those previously reported.[29]

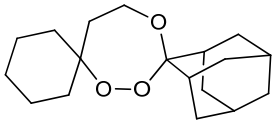
To a flame-dried RBF containing $Co(acac)_2$ (437 mg, 1.7 mmol) was added 2-cyclohexylideneethyl acetate (2.9883 g, 17 mmol) in EtOH (60 mL) and Et_3SiH (3.9 g, 34 mmol). The reaction was placed under an atmosphere of O_2 (balloon) and allowed to stir overnight. The reaction was then concentrated *in vacuo* and the residue subjected to column chromatography with 5 % EA/hex to afford **74** (2.2596 g, 42%). Rf (5% EA/hex): 0.44. ^1H NMR (300 MHz): 4.19 (t, J = 7.3, 0.8H), 4.1 (t, J = 6.9, 1.2H), 3.69

(q, J = 7.0, 1H), 2.03 (d, J = 3.1, 3H), 1.93 (t, J = 1.96, 1H), 1.83-1.08 (13H), 1.06-0.83 (8H), 0.75-0.53 (4H).



2-(1-((Triethylsilyl)peroxy)cyclohexyl)ethanol (68):

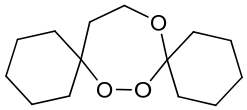
A flame-dried RBF containing **74** (2.25 g, 6.9 mmol) in CH_2Cl_2 (60 mL) was cooled to -78^oC and Dibal-H (13.9 mL, 13.9 mmol, 1M) was added. The reaction was allowed to stir for 3 hrs after which the reaction was treated with sat. Rochelle's salt (60 mL). The suspension was extracted with Et_2O (3 x 40 mL) and the combined organic fractions were washed with brine (2 x 100 mL) and dried over Na_2SO_4. The residue obtained upon concentration *in vacuo* was purified via column chromatography with 30 % Et_2O/pent to afford **68** (1.2355g, 65%). R_f (30% Et_2O/pent): 0.52. ^1H (300 MHz): 3.78-3.61 (3H), 1.90 (t, J = 6.9, 1H), 1.83-1.09 (14H), 1.04-0.83 (8H), 0.78-0.54 (4H). ^{13}C (75 MHz): 83.8, 61.0, 58.6, 58.5, 40.6, 39.2, 34.4, 33.54, 33.52, 26.7, 26.4, 22.3, 18.8, 6.9, 6.8, 4.6, 4.0.



Adamantane-2-spiro-3'-7'-cyclohexyl-1',2',4'-trioxepane (58)

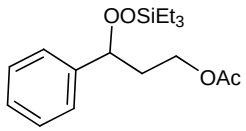
To a flame-dried RBF containing **68** (509.9 mg, 1.83 mmol) in CH_2Cl_2 (2 mL) was added sequentially 2-adamantanone (301 mg, 2 mmol) and HF (48% in H_2O, 1 mL). After stirring for 1 hr the reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (2 x 20 mL) and dried with Na_2SO_4. The residue

obtained upon concentration *in vacuo* was purified via column chromatography with 10 % EA/hex. Subsequent purification through HPLC with 10 % EA/hex afforded the desired product **58** (79.5 mg, 15 %). R_f (5% EA/hex):0.28. ^{1}H NMR (400 MHz): 3.90 (apparent pentet (probably dt), J = 6.2, 12.2 1H), 3.69 (dt, J = 3.7, 12.4, 1H), 2.40 (br, s, 1H), 2.15-2.02 (m, 2H), 2.02-1.9 (m, 3H), 1.86-1.30 (20H). ^{13}C NMR (100 MHz, $CDCl_3$): 107.5, 81.7, 58.1, 42.3, 37.5, 35.7, 34.6, 34.2, 33.8, 33.8, 33.7, 33.6, 32.9, 27.3, 26.0, 22.4, 22.0. HRMS (FAB); calc for $C_{18}H_{29}O_3$: 293.2117; found: 293.2103.



Cyclohexane-2-spiro-3'-7'-cyclohexyl-1',2',4'-trioxepane (59)

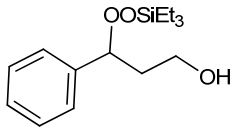
To a flame-dried RBF containing **68** (267 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added sequentially cyclohexanone (139 mg, 1.4 mmol) and HF (48% in H_2O, 2 mL). The reaction was stirred for 1 hr after which sat. aq. $NaHCO_3$ (30 mL) was added. The suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (2 x 20 mL) and dried with Na_2SO_4. The residue obtained upon concentration in vacuo was purified via column chromatography with 5 % EA/hex. Subsequent purification through HPLC with 5 % EA/hex afforded the desired product **59** (92 mg, 39 %). R_f (5% EA/hex): 0.48. ^{1}H NMR (400 MHz): 3.60 (m, 1H), 3.66 (m, 1H), 2.15-2.04 (1H), 1.95-1.72 (21H). ^{13}C NMR (100 MHz): 105.9, 82.0, 58.5, 42.8, 35.9, 33.4, 32.8, 32.2, 26.0, 25.7, 23.3, 22.9, 22.4, 22.0. HRMS (EI); calc for$C_{14}H_{24}O_3$: 240.1725; found: 240.1723.



3-Phenyl-3-(triethylsilylperoxy)propyl acetate (76):

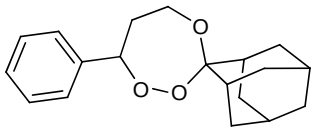
To a flame-dried RBF containing cinnamyl alcohol (2.46 g, 18.4 mmol) in pyridine (30 mL) was added sequentially Ac_2O (2 mL, 23.6 mmol) and DMAP (226 mg, 1.84 mmol). The reaction was allowed to stir for 1 hr after which 2N aq. HCl (40 mL) was added. The suspension was extracted with Et_2O (3 x 30 mL) and washed with sat. aq. $NaHCO_3$ (2 x 40 mL). The combined organic layers were dried with Na_2SO_4 and the residue obtained upon concentration *in vacuo* purified via column chromatography with 5% EA/Hex to afford cinnamyl acetate (2.8754 g, 89%) as a yellow oil. ^{1}H NMR (300 MHz): 7.75-7.24 (5H), 6.68 (d, J = 16.4, 1H), 6.30 (dt, J = 15.9, 6.5, 1H), 4.78 (apparent doublet, J = 6.4, 2H), 2.12 (s, 3H). ^{13}C (75 MHz): 170.9, 136.3, 134.3, 128.7, 128.2, 126.7, 123.3, 65.2, 21.1.

To a flame-dried RBF containing $Co(acac)_2$ (146 mg, 0.57 mmol) was added a solution of cinnamyl acetate (1.03 g, 5.7 mmol) in EtOH (20 mL) and Et_3SiH (1.32 g, 11.3 mmol). The reaction was placed under an atmosphere of O_2 (balloon) and allowed to stir overnight. The reaction was then concentrated *in vacuo* and the residue obtained was purified via column chromatography with 5 % EA/hex to afford **76** (815.7 mg, 43%). R_f (5% EA/hex): 0.43. ^{1}H NMR (300 MHz): 7.41-7.24 (5H), 4.97 (t, J = 6.8, 1H), 4.24-3.98 (2H), 2.30 (m, 1H), 2.01 (m, 1H), 2.02 (s, 3H), 0.94 (t, J = 7.6, 9H), 0.64 (aq, 6H).



3-Phenyl-3-(triethylsilylperoxy)propan-1-ol (77):

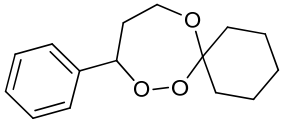
A flame-dried RBF containing **76** (815.7 mg, 2.5 mmol) in CH_2Cl_2 (20 mL) was cooled to -78^oC and Dibal-H (5 mL, 5 mmol, 1M) was added. The reaction was stirred for 3 hrs and then treated with sat. aq. Rochelle's salt (30 mL). The resulting suspension was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The residue obtained upon concentration (672.4 mg, 95%) was used in the subsequent reactions without purification.



Adamantane-2-spiro-3'-7'-phenyl-1',2',4'-trioxepane (60)

To a flame-dried RBF containing **77** (320.2 mg, 1.13 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-adamantanone (165 mg, 1.1 mmol) and HF (48% in H_2O, 2 mL). After stirring for 1 hr the reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (2 x 20 mL) and dried with Na_2SO_4. The residue obtained upon concentration in vacuo was purified via column chromatography with 7.5 % Et_2O/pent. Subsequent purification through HPLC with 10 % EA/hex afforded the desired product **60** (70 mg, 21 %). R_f (55% EA/Hex):0.65. ^1H NMR (400 MHz):7.40-7.29 (m, 5H), 5.14 (dd, J = 11.5, 3.5, 1H), 4.13 (app t, J = 11.3, 1H), 3.85 (dt, J = 3.4, 12.2, 1H), 2.4-2.2 (m, 2H), 2.14-1.9 (m, 6H), 1.86-1.79 (m, 2H), 1.75-1.6 (m, 6H). ^{13}C NMR (75.5 MHz):138.5, 128.5, 128.4, 127.3, 108.6, 86.1, 76.6, 60.0, 39.4, 37.5, 35.0,

34.7, 34.1, 33.9, 33.6, 33.1, 27.2, 27.1. HRMS (FAB); calc for $C_{19}H_{25}O_3$: 301.1804; found: 301.1809.



Cyclohexane-2-spiro-3'-7'-phenyl-1',2',4'-trioxepane (61):

To a flame-dried RBF containing **77** (285.0 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added sequentially cyclohexanone (0.11 g, 1.1 mmol) and HF (48% in H_2O, 2 mL). After stirring for 1 hr the reaction was treated with sat. aq. $NaHCO_3$ (30 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (2 x 20 mL) and dried with Na_2SO_4. The residue obtained upon concentration in vacuo was purified via column chromatography with 10 % EA/hex. Subsequent purification through HPLC with 10 % EA/hex afforded the desired product **61** (95.5 mg, 39 %). ^{1}H NMR (400 MHz)7.41-7.29 (5H), 5.14 (dd, J = 11.4, 5.15, 1H), 4.20-4.08 (1H), 3.84 (dt, J = 12.5, 3.4, 1H), 2.37-1.20 (12H). ^{13}C (75 MHz): 138.5, 128.7, 128.6, 127.5, 106.9, 86.3, 60.5, 39.4, 34.2, 31.9, 25.6, 23.3, 22.9. HRMS (FAB): calc for $C_{15}H_{21}O_3$: 249.1492; found: 249.1489.

Section 6

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Chapter 4

Re (VII) oxide as a catalyst for the generation of stabilized carbocations

This chapter describes my investigation of Re(VII) as a catalyst for the formation of stabilized carbocations that are utilized in various displacement of activated alcohols.

Section 1: Previous work

Section 2: Hypothesis

Section 3: Etherification/acetalization of 3-alkoxy-1,2-dioxolanes

Section 4: Etherification of lactols

Section 5: Allylation

Section 6: Stabilized carbocations

Section 7: Conclusions

Section 8: Experimentals

Section 9: References

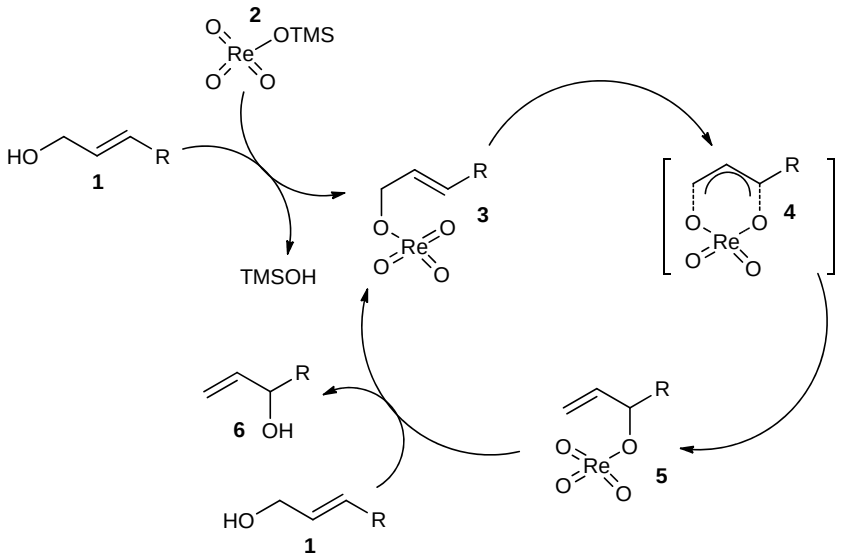
Chapter 4 includes a description of my application of Re(VII) to the transetherification (transacetalisation) of 1,2-dioxolan-3-ols to the corresponding 3-alkoxy-1,2-dioxolanes. This chapter will discuss in detail my investigations of the ability of Re_2O_7 to catalyze reactions involving *in situ* generation of carbocations from alcohols. Several reviews on the chemistry of rhenium have been published.[1,2]

Section 1

Previous work

Isomerization of allylic alcohols by rhenium

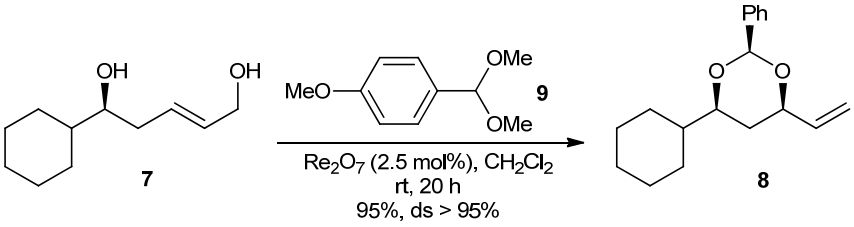
In 1997, Osborn first reported that $ReO_3(OSiMe_3)$ or $ReO_3(OSiPh_3)$ was able to catalyze the isomerization of allyl alcohols.[3] Osborn's proposed mechanism (below) begins with insertion of rhenium into the C-O bond of **1**. This type of insertion is supported by an analogous insertion reported by Wilkinson.[4] Complex **3** rearranges to the isomerized complex (**5**) via transition state **4**, a pathway supported by the analogous work of Chabardes.[5] Finally, the catalytic cycle in the presence of **1** and produces isomerized alcohol **6**.



In 2000, Osborn built upon his earlier work by showing that this allylic rearrangement also works for trimethylsilyl ether of **1**.[6] Osborn also reported that Re_2O_7 was able to catalyze this reaction in MeCN, THF, and CH_2Cl_2. There is a solvent effect on the reaction with a twenty-fold decrease in turnover observed for MeCN or THF compared to CH_2Cl_2. This was attributed to coordination to the $ReO_3(OSiMe_3)$ catalyst. The rate of the reaction with Re_2O_7 could not be determined due to the insolubility in CH_2Cl_2.

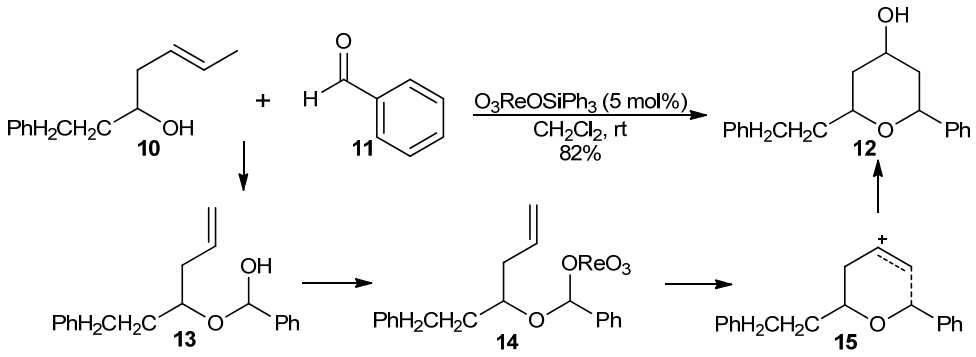
In 2010, Zakarian developed a method to control the regioselectivity of Re_2O_7-promoted isomerization of enediols,[7] providing one solution to the lack of regioselectivity typically encountered in the reactions of simple allyl alcohols.[8-10] Transformation of **7** to the diol of **8** in the absence of an acetal (**9**) led to poor conversion (60%) and low diastereoselectivity. The addition of **9** was found to significantly increase both the yield of the isomerized product and the diastereoselectivity of the reaction. The authors hypothesized that perrhenic acid catalyzed the conversion of the product regioisomer into the benzylidene acetal, which also provided a bias for formation of the

thermodynamically preferred 1,3-*syn* isomer. A variety of solvents were screened and CH_2Cl_2 was found to be optimal: Re_2O_7 was shown to be an effective rhenium source. This methodology was successfully applied to a variety of substrates. However, it was noted that acid labile groups such as t-butyldiphenylsilyl ethers (TBDPS) and p-methoxybenzyl ethers (PMB) underwent deprotection upon prolonged exposure (20 hrs) but deprotection can be circumvented with the use of a different acetal.



Utilization in Prins cyclization

In 2008, Rychnovsky reported using rhenium to catalyze an intramolecular Prins reaction.[11] The reaction of alcohol **10** and benzaldehyde, **11**, afforded tetrahydropyran **12** utilizing $O_3ReOSiPh_3$ as a catalyst. Rychnovsky postulates that **10** and **11** react to form hemiacetal **13**, which is then able to undergo rearrangement to give **15**. Exchange with Ph_3SiOH, formed in the reaction, gives product **12**. Rychnovsky found that this reaction works for a variety of alkenes and benzaldehydes. The reaction was successfully performed in several solvent systems but CH_2Cl_2 was the best. In 2009, Rychnovsky built upon this work by successfully applying this reaction to a more complicated system to achieve an intramolecular macrolactonization.[12]

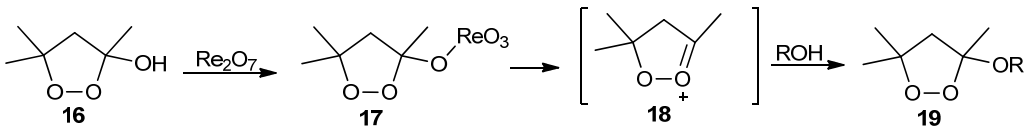


Section 2

Hypothesis

The work of Rychnovsky led me to believe that Re (VII) should act as a mild catalyst for the acetalization/transetherification of 1,2-dioxolan-3-ols and/or the corresponding trimethylsilyl ethers.

The etherification of **16** under strongly acidic conditions (*p*-toluene sulfonic acid) is likely to involve the formation of cationic intermediate **18** that undergoes trapping by an alcohol. Given the previous work, we anticipated that Re_2O_7 should be able to insert in C-OH bond of **16** to afford an intermediate (**17**) that could fragment to the same carbocation (**18**), with the difference being that the ionization might occur under much milder conditions.

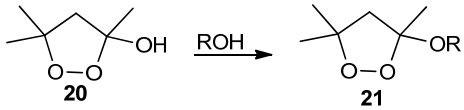


Section 3

Etherification/acetalization of 3-alkoxy-1,2-dioxolanes

To test our hypothesis, I compared the transformation of **20** and **21** in the presence of Re_2O_7 vs. sulfonic acid. (below). When Re_2O_7 (10 mol%) was used it was

found the yield of 2-phenylethanol was unchanged relative to sulfonic acid (10 mol%). In contrast, the yield for etherification with 1-adamantanemethanol increased dramatically with Re_2O_7. Both of these etherifications proceeded in slightly higher yield using only 1 mol% of Re_2O_7. The use of less than 1 mol% Re_2O_7 was not investigated, but I believe that the reaction could proceed at even lower catalyst loading. As expected the etherification of sterically hindered 1-adamantanol was unsuccessful for either catalyst system.

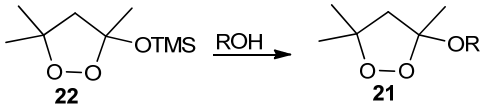


20 **21**

Alcohol	PTSA	Re_2O_7 10 mol%	Re_2O_7 1 mol%
2-phenylethanol	73% (3h)	75 % (1h)	83% (1h)
1-adamantanemethanol	28% (>12h)	74 % (1h)	78% (2h)
1-adamantanol	Failed	Failed	Failed

Table 4.1

I had prepared the dioxolane trimethylsilylether (**22**) to assist with purification, and became interested if the 3-trimethyl-1,2-silyloxydioxolane would be a useful substrate for the transetherification. Gratifyingly the reaction did proceed to afford **21** in comparable yield relative to the transetherification on the free alcohol. The yield of the 1-adamantylmethyl acetal was slightly depressed compared with the reaction from the free alcohol. The ability to employ trimethylsilyl ethers represents a useful expansion of the methodology.



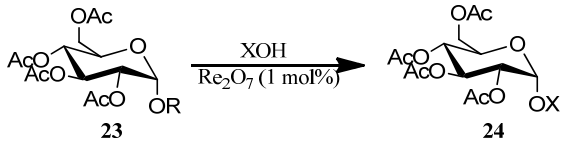
Alcohol	Re_2O_7 (1 mol%)
2-phenylethanol	81% (2h)
1-adamantanemethanol	65% (>12h)
1-adamantanol	Failed

Table 4.2

Given the successful application of Re_2O_7 to catalyze the etherification of anomerically-activated 1,2-dioxolan-3-ols, I became interested in the potential of this reagent to catalyze the corresponding etherification (glycosylation) of sugars. This approach was unsuccessful with a variety of glucose pentaacetate derivatives, **23**. Only when methanol was employed did any noticeable reaction occur.

Section 4

Etherification of lactols

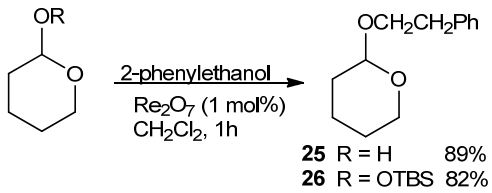


R	X	Yield **24**
H	CH_2CH_2Ph	Failed
OAc	CH_2CH_2Ph	Failed
TBS	CH_2CH_2Ph	Failed
H	Me	4%

Table 4.3

The failure to achieve Re_2O_7-promoted etherification of sugars could result from the presence of strongly electron-withdrawing C-O linkages on the carbons adjacent to the hemiacetal. I therefore decided to screen lactols. As was expected from earlier work with peroxyhemiacetal **20** this reaction proceeded in good yield on the free hemiacetal (**25**). Unexpectedly, transetherification also proceeded in good yield on the t-

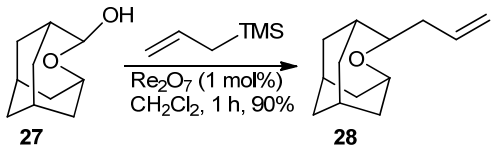
butyldimethylsilyl (TBS) acetal, **26**. This result was unexpected as the bulkier TBS ethers were not expected to undergo insertion of Re(VII) into the C-O bond as had been observed for the corresponding trimethylsilyl ethers. This result broadens the potential application of this methodology as the TBS ether is a more widely used protecting group.



Section 5

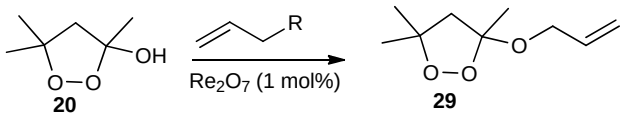
Allylation

As we postulated that a carbocation intermediate, or something with comparable reactivity, was formed in the etherification reaction the next logical step was to explore the possibility of achieving C-C bond formation under these conditions. The allylation of **25** with allyl trimethylsilane appeared to cleanly furnish one major product (TLC) but resulted in low yield (37%) presumably because of volatility. Therefore, I utilized lactol **27** which was readily synthesized in two steps from 2-adamantanone. As was expected the allylation of **27** proceeded in excellent yield to afford **28**.



These allylation results made me wonder if it was possible to also perform an allylation of 1.2-dioxolan-3-ol using Re_2O_7. Previous reports from our group had demonstrated successful addition of allylsilane and silyl ketene acetal nucleophiles to 3-alkoxy-1,2-dioxolanes, however, these reactions were achieved using very powerful Lewis acids. [13] I initially investigated the use of allyltrimethylsilane as a nucleophile;

however, no reaction was observed. I therefore investigated the use of more nucleophilic allyltributyltin. The use of the tin compound led to no reaction and a change in reaction color, possibly indicating a reaction with Re_2O_7.



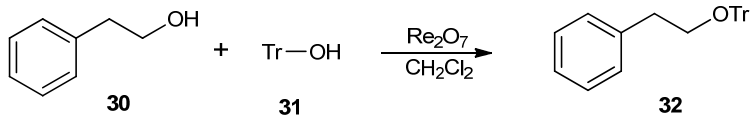
The etherifications of **20** to **21** have shown that a carbocation intermediate is formed, but does not indicate if it is a fully dissociated carbocation. The failure to observe allylation led me to conclude that Re_2O_7 is not able to convert a 1,2-dioxolan-3-ol to a carbocation intermediate possessing sufficient reactivity to capture an alkene nucleophile.

Section 6

Stabilized carbocations

I next conducted a brief investigation of the ability of Re_2O_7 to catalyze other reactions involving a stabilized carbocation intermediate. As an initial target, I chose triphenylmethanol, **31**, as a substrate capable of forming a relatively stable trityl cation as an intermediate. With the first set of conditions the use of excess nucleophile (5 eq). I found that the reaction was in fact successful, though not in synthetically useful yields (Entry 1). Interestingly, the amount of Re_2O_7 catalyst and the reaction time could be decreased without loss of efficacy (Entry 2). This led to me rethinking how I approached this investigation. As the trityl group is traditionally used as a protecting group I decided to use **31** in excess under more standard conditions. This change led to a significant improvement in the yield (Entry 3). Alternatively, adding activated 3Å molecular sieves in the reaction allowed me to obtain comparable yields in the presence of two equivalents

of **31** (Entry 4). A comparison of entries 4 and 5 demonstrate that the use of Re_2O_7 catalysis provides yields comparable to those obtained with a strong acid catalyst.

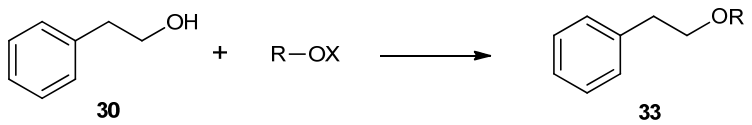


Entry	**30** (eq)	**31** (eq)	Re_2O_7 (mol%)	t (h)	Sieves (3Å)	Yield **32** (%)
1	5	1	10	5	No	48
2	5	1	1	3	No	59
3	1	5	1	3	No	81
4	1	2	1	3	Yes	84
5	1	2	PTSA (10)	3	Yes	87

Table 4.4

These results encouraged me to investigate the Re_2O_7-mediated activation of alcohols as a potentially mild method for the synthesis of ethers. The first alcohol that was chosen was 3,4-dimethoxy benzyl alcohol (3,4-DMB) (Entries 1-4). I found that under previously known conditions (Entry 1) the reaction with 2-phenylethanol proceeded in moderate yield, but when MeCN, which is able to solubilize both water and Re_2O_7, was used the reaction did not proceed. It is unknown if the Re_2O_7 forms a complex with MeCN that renders it inactive. Under more protecting group like conditions, an excess of the protecting agent, with the reaction proceeded, but in depressed yield (Entry 3). I decided to use the OTBS analog of 3,4-DMB as I had previously demonstrated that Re_2O_7 was capable of catalyzing the insertion into C-OSiR_3 linkages. I found that the reaction proceeded in synthetically useful yield (Entry 4). The use of less electron rich 4-methoxybenzyl alcohol (PMB) was successful (Entry 5) and proceeded in similar yield to that of 3,4-DMB (Entry 3). However, when the OTBS analog of PMB was employed the reaction was unsuccessful (Entry 6). The protection of cumyl alcohol (cumyl) with 2-phenylethanol also proceeded in moderate yield under the

reaction conditions (Entry 7). As the alcohol became less electron rich and sterically hindered formation of the dimer became a serious problem. For example benzhydrol gave predominantly dimer with a very low yield of the desired product.



30 **33**

Entry	**30** (eq)	R (eq)	X	Re_2O_7 mol%	t (h)	Sieves (3Å)	Yield (%)
1	5	3,4-DMB (1)	H	10	5	Yes	58
2[a]	5	3,4-DMB (1)	H	10	1	Yes	NR
3	1	3,4-DMB (2)	H	1	3	Yes	38
4	5	3,4-DMB (1)	TBS	10	1	No	71
5	1	PMB (2)	H	1	3	Yes	40
6	1	PMB (2)	TBS	1	1	No	NR
7	1	Cumyl (2)	H	1	3	Yes	46

Table 4.5 [a]MeCN used as solvent

Section 7

Conclusions

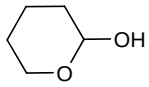
Through this work I have shown that Re_2O_7 is capable of catalyzing a variety of reactions. The first is the synthesis of 3-alkoxy-1,2-dioxolanes from 1,2-dioxolan-3-ols in good yield. Re_2O_7 is also able to catalyze the etherification and allylation of a lactol and its OTBS analog in excellent yield.

I have also shown that Re_2O_7 is able to catalyze the formation of stabilized carbocations, potentially providing a new method for the introduction of several alcohol protecting groups. This approach is most successful for the introduction of the trityl group, but also showed promise with the 3,4-DMB group. If this work is to be expanded to other ether protecting groups further optimization must be done.

Section 8

Experimentals

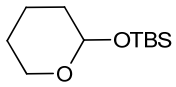
All reagents were used as received from commercial vendors, with the exception of CH_2Cl_2, which was distilled from calcium hydride, and THF, which was distilled from sodium/benzophenone. All reactions were conducted under an atmosphere of N_2 except where noted; "RBF" indicates round-bottom flask. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized with a hand-held UV lamp or by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% *N,N'*-dimethyl-*p*-phenylenediamine solution in 1:20:100 acetic acid/water/methanol (specific for peroxides);[14] 1% aq. $KMnO_4$ (for unsaturated compounds); 3% vanillin in 3% H_2SO_4 in ethanol (general stain after charring). "Standard drying and purification" refers to drying of organic extracts over $MgSO_4$, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. ^1H /^{13}C NMR spectra were obtained in $CDCl_3$ unless otherwise indicated; peaks are reported as: chemical shift (multiplicity, J couplings in Hz, number of protons). Infrared spectra were recorded as neat ATR films with selected absorbances reported in wavenumbers (cm^{-1}).



Tetrahydro-2H-pyran-2-ol (25):

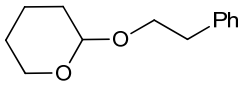
To a RBF containing 3,4-dihydro-2*H*-pyran (3.4204g, 40.7 mmol) neat cooled to 0°C was added aq. HCl (8.3 mL, 41.5mmol, 0.2 M). The reaction was stirred overnight and then diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (25 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (25 mL) and subjected to standard drying

and purification with 40% EA/hex to **25** (2.297g, 55%). R_f (50% EA/hex): 0.45. ^{1}H NMR (600 MHz): 4.60 (m, 1H), 4.02 (m, 1H), 3.54 (m, 1H), 3.45 (d, J = 4.64, 1H), 1.91-1.76 (2H), 1.57-1.46 (4H). The NMR spectra matched those previously reported.[15]



tert-Butyldimethyl((tetrahydro-2H-pyran-2-yl)oxy)silane (26):

To a flame-dried RBF containing **25** (501.4 mg, 4.9 mmol) in THF (49 mL) was added imidazole (0.4g, 5.9 mmol) and TBSCl (0.9g, 5.9 mmol) as a solution in THF (5 mL). The reaction was stirred for 36 hrs, after which it was treated with H_2O (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford **26** (322.9 mg, 31%). R_f (10% EA/hex): 0.52. ^{1}H NMR (300 MHz): 4.93 (m, 1H), 3.97 (m, 1H), 3.49 (m, 1H), 1.94-1.43 (6H), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C (75 MHz): 94.3, 63.0, 33.6, 26.0, 25.7, 19.9, 18.3, -4.1, -5.2.



2-Phenethoxytetrahydro-2H-pyran

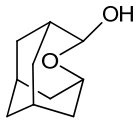
Via etherification of alcohol

To a flame-dried vial containing **25** (153.1 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) was added sequentially 2-phenylethanol (0.9 mL, 7.5 mmol) and Re_2O_7 (7.26 mg, 0.015 mmol). After stirring for 1 hr, the reaction was concentrated *in vacuo* and the residue obtained was purified via column chromatography with 10% EA/hex to afford 2-phenethoxytetrahydro-2H-pyran (275.5 mg, 89%). R_f (10% EA/hex): 0.41. ^{1}H (400 MHz): 7.36 (m, 5H), 4.63 (t, J = 4.6, 1H), 3.98 (m, 1h), 3.79 (m, 1H), 3.65 (m, 1H), 3.48

(m, 1H), 2.95 (t, J = 7.2, 2H), 1.90-1.65 (6H). ^{13}C (100 MHz): 139.3, 129.2, 128.4, 126.3, 98.9, 68.5, 62.4, 36.6, 30.9, 25.6, 19.7. The NMR spectra matched those previously reported.[16]

Via etherification of silyl ether

To a flame-dried vial containing a solution of **26** (216 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added sequentially 2-phenylethanol (0.6 mL, 5 mmol) and Re_2O_7 (4.8 mg, 0.01 mmol). After stirring for 1 hr, the reaction was concentrated *in vacuo* and the residue obtained was purified via column chromatography with 10% EA/hex to afford 2-phenethoxytetrahydro-2H-pyran (168.5 mg, 82%).

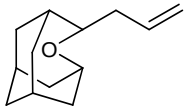


4-Oxatricyclo[4.3.1.1^{3,8}]undecan-5-ol (27):

To a flame-dried RBF containing a solution of 2-adamantanone (3.0 g, 20 mmol) in CH_2Cl_2 (100 mL) was added sequentially *m*-chloroperoxybenzoic acid (7.15 g, 25 mmol) and aq. $NaHCO_3$ (40 mL, 20 mmol, 6.5 M in H_2O). After stirring for 24 hrs, the reaction was quenched with Na_2SO_3 (1g) and washed sequentially with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic layers were dried with $MgSO_4$, and the residue obtained upon concentration *in vacuo* was purified via column chromatography with 60% EA/hex to afford 4-oxatricyclo[4.3.1.1^{3,8}]undecan-5-one (2.8522g, 86%) as a white solid. R_f (60% EA/hex):0.48. ^1H (400 MHz): 4.46 (m, 1H), 3.07 (m, 1H), 2.15-1.68 (12H). The NMR spectra matched those previously reported.[17]

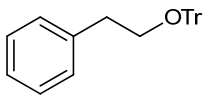
To a flame-dried RBF containing a -78^oC solution of 4-oxatricyclo[4.3.1.1^{3,8}]undecan-5-one (2.0 g, 11 mmol) in CH_2Cl_2 (60 mL) was added

Dibal-H (8.3 mL, 12.5 mmol, 1.5M in toluene) dropwise. The reaction was stirred at -78^{o}C for 1 hr and quenched with MeOH (0.5 mL). The reaction was warmed to rt and stirred for 45 min. Sat. aq. Rochelle's salt (30 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with H_2O (40 mL), and subjected to standard drying a purification with 40 % EA/hex to afford hemiacetal **27** (1.9104g, quant). R_f (40 % EA/hex): 0.43. ^{1}H NMR (400 MHz): 5.29 (d, J = 3.0, 1H), 4.27-4.12 (1H), 2.98 (bs, 1H), 2.35-1.28 (13H). ^{13}C (100 MHz): 100.2, 72.4, 38.5, 38.3, 37.4, 25.8, 33.0, 29.4, 26.8, 26.7. The NMR spectra matched those previously reported.[18]



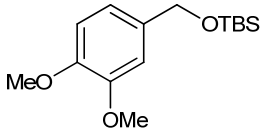
(1R,8S)-5-Allyl-4-oxatricyclo[4.3.1.^{13,8}]undecane (28):

To a flame-dried vial containing a solution of **27** (168.4 mg, 1 mmol) and Re_2O_7 (4.8mg, 0.01 mmol) in CH_2Cl_2 (10 mL) was added allyltrimethylsilane (0.8 mL, 5 mmol). The reaction was stirred for 1 hr and then treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried with Na_2SO_4. The residue obtained upon concentration *in vacuo* was subjected to column chromatography with EA/hex (1 x 10% EA/hex, 1 x 5% EA/hex) to afford **28** (166.5 mg, 90%). R_f (10% EA/hex): 0.6. ^{1}H NMR (400 MHz): 5.83 (m, 1H), 5.10-5.00 (2H), 4.18 (m, 1H), 3.81 (t, J = 6.8, 1H), 2.37 (m, 1H), 2.18 (m, 1H), 2.00 – 1.64 (10H), 1.61 -1.49 (3H). ^{13}C (100 MHz): 136.6, 116.5, 81.9, 71.8, 41.5, 40.9, 40.0, 26.1, 36.0, 34.6, 30.0, 26.9, 26.4.



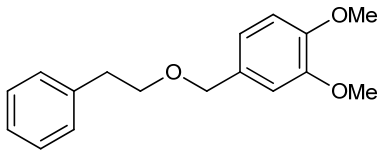
Phenylethyl triphenylethyl (trityl) ether (32):

To a flame-dried RBF containing a solution of trityl alcohol (3.9g, 15 mmol) in CH_2Cl_2 (30 mL) was added sequentially Re_2O_7 (15 mg, 0.03 mmol) and 2-phenylethanol (0.36 mL, 3 mmol). The reaction was stirred for 3 hrs, and then treated with sat. aq. $NaHCO_3$ (10 mL) and H_2O (20 mL). The combined CH_2Cl_2 (3 x 20) extracts were subjected to standard drying and purification with 10% EA/hex to afford **112** (879.4 mg, 81%) as a white solid. R_f (10% EA/hex):0.64. ^{1}H NMR (400 MHz): 7.46-7.39 (5H), 7.35-7.20 (14H), 3.34 (t, J = 7.0, 2H), 2.93 (t, J = 7.0, 2H). ^{13}C (100 MHz): 144.4, 139.5, 129.4, 128.8, 128.4, 127.9, 127.0, 126.3, 86.8, 65.2, 36.9.



***tert*-Butyl-(3,4-dimethoxybenzyloxy)-dimethylsilane:**

To a flame-dried RBF containing a solution of imidazole (1.0 g, 15 mmol) and 3,4-dimethoxybenzyl alcohol (0.73 mL, 5 mmol) in DMF (50 mL) was added TBSCl (1.1 g, 7.5 mmol). The reaction was stirred for 20 hrs and then treated with H_2O (100 mL). The resulting suspension was extracted with Et_2O (3 x 100 mL). The combined organic layers were subjected to standard drying and purification with (1 x 25% EA/hex and 1 x 10% EA/hex) to afford *tert*-butyl-(3,4-dimethoxy-benzyloxy)-dimethyl-silane (1.3845 g, 98%). R_f (5% EA/hex):0.46. ^{1}H NMR (300 MHz): 6.91 (s, 1H), 6.84 (s, 2H), 4.69 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 0.95, 9H), 0.10 (s, 6H). ^{13}C (75 MHz): 149.1, 148.2, 134.3, 118.4, 111.1, 109.8, 65.0, 56.1, 55.9, 26.1, 18.6, -5.0.

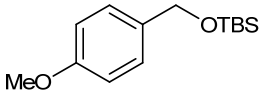


1,2-dimethoxy-4-(phenethoxymethyl)benzene

To a flame-dried RBF containing a suspension of Re_2O_7 (48 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added sequentially 3,4-dimethoxybenzyl alcohol (0.15 mL, 1 mmol) and 2-phenylethanol (0.6 mL, 5 mmol). The reaction was allowed to stir for 1 hr and then treated with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20). The combined organic layers were dried with Na_2SO_4, and the residue obtained upon concentration *in vacuo* was purified via column chromatography with 20% EA/hex to afford 1,2-dimethoxy-4-(phenethoxymethyl)benzene (192 mg, 71%).

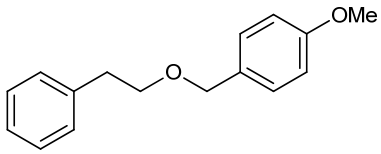
Procedure with TBS analog

To a flame-dried RBF containing a suspension of Re_2O_7 (47.5 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added sequentially *tert*-butyl-(3,4-dimethoxy-benzyloxy)-dimethyl-silane (280.4 mg, 0.99 mmol), 2-phenylethanol (0.6 mL, 5 mmol), and 3A sieves. The reaction was allowed to stir for 5 hrs and was treated with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10). The combined organic layers were subjected to standard drying and purification with 20% EA/hex to afford 1,2-dimethoxy-4-(phenethoxymethyl)benzene (158.9 mg, 58%). R_f (5% EA/hex):0.42. ^1H (300 MHz): 7.35-7.19 (5H), 6.90 – 6.81 (3H), 4.5 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.72 (t, J = 7.0, 2H), 2.96 (t, J = 7.0, 2H). ^{13}C (75 MHz): 149.2, 148.7, 139.2, 131.1, 129.1, 128.5, 126.3, 120.2, 111.1, 111.0, 73.0, 71.1, 56.1, 71.1, 56.1, 55.9, 36.5.



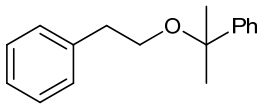
_t_-Butyl-(4-methoxybenzyloxy)-dimethylsilane

To a flame-dried RBF containing imidazole (2 g, 30 mmol) and 4-methoxybenzyl alcohol (1.4g, 10 mmol) in DMF (100 mL) was added TBSCl (2.3 g, 15 mmol). After 12 hrs the reaction was treated with H_2O (100 mL) and extracted with Et_2O (3 x 75 mL). The combined organic layers were subjected to standard drying and purification with 5% EA/hex to afford _t_-butyl-(4-methoxybenzyloxy)-dimethylsilane (2.4148 g, 96%). R_f (5% EA/hex):0.67. ^1H (400 MHz): 7.25 (m, 2H), 6.85 (m, 2H), 4.68 (s, 3H), 3.81 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H). The NMR spectra matched those previously reported.[19]



4-Methoxybenzyl phenethyl ether

To a flame-dried RBF containing a suspension of Re_2O_7 (15.2 mg, 0.03 mmol) in CH_2Cl_2 (30 mL) was added sequentially 4-methoxybenzyl alcohol (824 mg, 6 mmol), 2-phenylethanol (0.36 mL, 3 mmol), and 3A sieves. After 3 hrs the reaction was treated with sat. aq. $NaHCO_3$ (10 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford 4-methoxybenzyl phenethyl ether (291.5 mg, 40%). R_f (10% EA/hex):0.56. ^1H (300 MHz): 7.39-7.21 (7H), 7.0-6.89 (2H), 4.52 (s, 2H), 3.85 (s, 3H), 3.72 (t, J = 7.1, 2H), 2.98 (t, J = 7.1, 2H). The NMR spectra matched those previously reported.[20]



1-Methyl-1-phenylethyl phenethyl ether

To a flame-dried RBF containing a suspension of Re_2O_7 (16.6 mg, 0.03 mmol) in CH_2Cl_2 (30 mL) was added sequentially cumyl alcohol (816 mg, 6 mmol), 2-phenylethanol (0.36 mL, 3 mmol), and 3A sieves. After 3 hrs the reaction was treated with sat. aq. $NaHCO_3$ (10 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20). The combined organic layers were subjected to standard drying and purification with 10% EA/hex to afford 1-methyl-1-phenylethyl phenethyl ether (334.4 mg, 46%). R_f (10% EA/hex):0.55. ^1H (400 MHz): 7.39-7.16 (10H), 3.41 (t, J = 7.5, 2H), 2.89 (t, J = 7.3, 2H), 1.55 (s, 6H). The NMR spectra matched those previously reported.[20]

Section 9

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