Spiro- and Dispiro-1,2-dioxolanes: Contribution of Iron(II)-Mediated One-Electron vs Two-Electron Reduction to the Activity of Antimalarial Peroxides

Xiaofang Wang,[†] Yuxiang Dong,[†] Sergio Wittlin,[‡] Darren Creek,[§] Jacques Chollet,[‡] Susan A. Charman,[§] Josefina Santo Tomas,[‡] Christian Scheurer,[‡] Christopher Snyder,[‡] and Jonathan L. Vennerstrom*[,†]

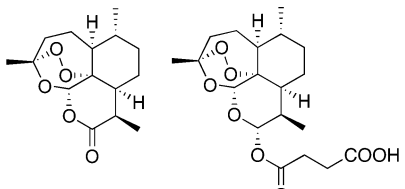
College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, Nebraska, Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland, and Centre for Drug Candidate Optimisation, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

Received June 27, 2007

Fourteen spiro- and dispiro-1,2-dioxolanes were synthesized by peroxycarbenium ion annulations with alkenes in yields ranging from 30% to 94%. Peroxycarbenium ion precursors included triethylsilyldiperoxyketals and -acetals derived from geminal dihydroperoxides and from a new method employing triethylsilylperoxyketals and -acetals derived from ozonolysis of alkenes. The 1,2-dioxolanes were either inactive or orders of magnitude less potent than the corresponding 1,2,4-trioxolanes or artemisinin against *P. falciparum* in vitro and *P. berghei* in vivo. In reactions with iron(II), the predominant reaction course for 1,2-dioxolane **3a** was two-electron reduction. In contrast, the corresponding 1,2,4-trioxolane **1** and the 1,2,4-trioxane artemisinin undergo primarily one-electron iron(II)-mediated reductions. The key structural element in the latter peroxides appears to be an oxygen atom attached to one or both of the peroxide-bearing carbon atoms that permits rapid β-scission reactions (or H shifts) to form primary or secondary carbon-centered radicals rather than further reduction of the initially formed Fe(III) complexed oxy radicals.

Introduction

Without the discovery of quinine from *Cinchona* trees and artemisinin from *Artemisia annua*, it is uncertain how many antimalarial drugs we would have today.[1] Quinine provided the lead for the discovery of a number of synthetic quinoline methanols and 4-aminoquinolines, the most notable of which is chloroquine. A synthetic peroxide antimalarial drug has yet to be identified, although, as exemplified by artesunate, a number of semisynthetic artemisinins are now in wide use.[2] The pharmacophoric peroxide bond in the semisynthetic artemisinins and synthetic peroxides is essential, but not sufficient, for high antimalarial efficacy.[3] Therefore, understanding peroxide bond reactivity is important in elucidating the chemistry that underlies the antimalarial action of peroxide antimalarials and in providing direction in drug design.



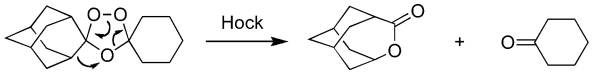
1 **2**

Building on our mechanistic studies of antimalarial 1,2,4-trioxolanes (secondary ozonides) **1** and **2**,[4−6] we synthesized and evaluated the structurally related 1,2-dioxolanes **3**. The structures of the more chemically stable 1,2-dioxolanes preclude the Hock-type fragmentation[7−9] characteristic of 1,2,4-trioxolanes (Scheme 1), leading to a prediction that the former should have better biopharmaceutical properties than the latter.

Chemistry

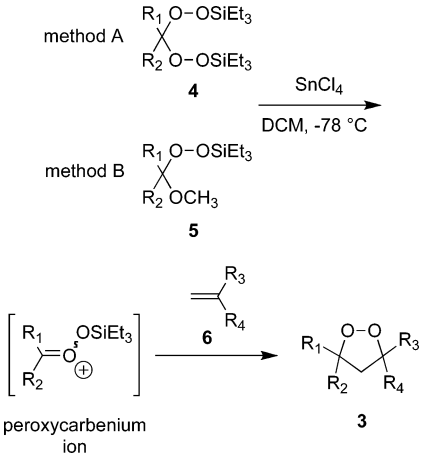
1,2-Dioxolanes have been synthesized by a number of different methods including fragmentation of secondary ozonides[10,11] and hydroperoxyacetals and -ketals[12,13] with various Lewis acids in the presence of alkenes. We employed similar methods to obtain 1,2-dioxolanes **3a**−**l** (Table 1). We used one

Scheme 1. Decomposition of 1,2,4-Trioxolane **1** via a Hock-Type Fragmentation



1

Scheme 2. Synthesis of 1,2-Dioxolanes **3** via Peroxycarbenium Ion Annulations with Alkenes **6**

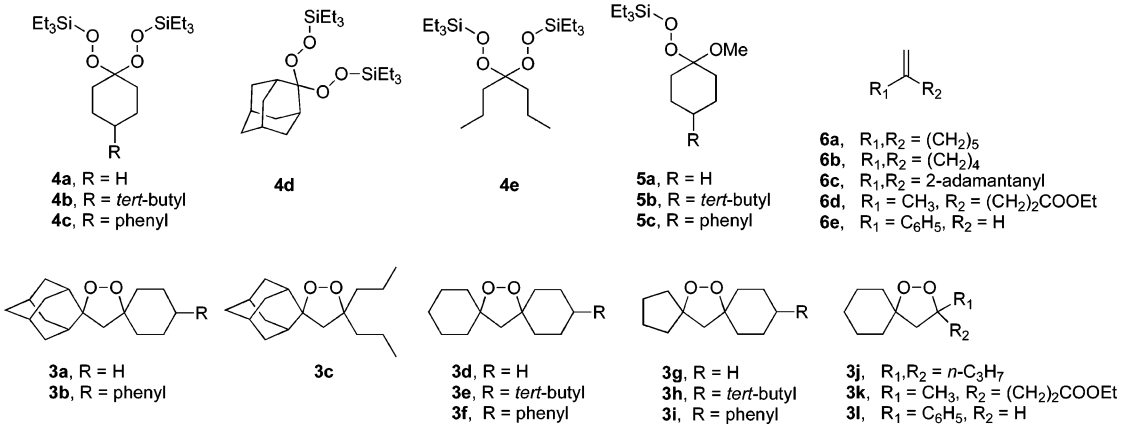


4 **5** **6** **3**

* To whom correspondence should be addressed. Phone: 402.559.5362. Fax: 402.559.9543. E-mail: jvenners@unmc.edu.
[†] University of Nebraska Medical Center.
[‡] Swiss Tropical Institute.
[§] Monash University.

10.1021/jm0707673 CCC: $37.00
Published on Web 10/20/2007

Table 1. Synthesis of 1,2-Dioxolanes **3a**−**l**



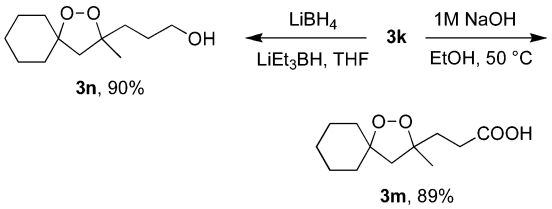
entry	method	peroxycarbenium ion precursor	alkene	1,2-dioxolane product	yield (%)
1	A	**4a**	**6c**	**3a**	74
2	A	**4d**	**6a**	**3a**	35
3	A	**4c**	**6c**	**3b**	68
4	A	**4e**	**6c**	**3c**	48
5	A	**4a**	**6a**	**3d**	86
6	B	**5a**	**6a**	**3d**	83
7	A	**4b**	**6a**	**3e**	94
8	B	**5b**	**6a**	**3e**	94
9	A	**4c**	**6a**	**3f**	88
10	B	**5c**	**6a**	**3f**	88
11	A	**4a**	**6b**	**3g**	90
12	A	**4b**	**6b**	**3h**	77
13	A	**4c**	**6b**	**3i**	73
14	A	**4e**	**6a**	**3j**	56
15	B	**5a**	**6d**	**3k**	30
16	B	**5a**	**6e**	**3l**	55

of two methods (Scheme 2), both of which proceed by way of a common peroxycarbenium ion intermediate. The first (method A) is that of Ramirez and Woerpel[14] whereby triethylsilyldiperoxyketals and -acetals **4** fragment in the presence of $SnCl_4$ to form peroxycarbenium ions that undergo annulation with alkenes **6** to form 1,2-dioxolanes **3**. The second (method B) is a modified procedure of Dussault et al.[12] that differs from method A[14] only in employing different peroxycarbenium ion precursors: triethylsilylperoxyketals and -acetals **5**.

The two 1,2-dioxolane synthetic methods are complementary. Advantages of method B compared to method A are the synthesis of **5** via ozonolysis of alkenes or enol ethers, thereby avoiding the excess hydrogen peroxide required in the synthesis of the geminal dihydroperoxide precursors of **4**, and the presence of one vs two peroxide bonds in **5** vs **4**. On the other hand, advantages of method A compared to method B are use of the more widely available ketones and aldehydes compared to alkenes, and the unambiguous fragmentation of **4** to form peroxycarbenium ion intermediates.

Where investigated, both methods provided 1,2-dioxolanes (**3d**−**f**) in identical or nearly identical yields (entries 5−10). For method B, this implies selective alkoxide complexation of **5** with $SnCl_4$ to effect ionization to the desired peroxycarbenium ion intermediates. Of course, selectivity is not at stake in the fragmentation of **4** to form the peroxycarbenium ion intermediates. The reaction yields for the synthesis of **3** were lower when acyclic precursors **4** (entries 4 and 14) and **6** (entries 15 and 16) were employed. For **3a** (entries 1 and 2), selection of reaction partners was critical to reaction yield. In entry 2, competing Bayer−Villiger reaction of **4e** to adamantane lactone was observed, resulting in a lower reaction yield. 1,2-Dioxolanes **3b** and **3d**−**i** were obtained as single diastereomers, presumed to be in cis configurations based on the stereochemical outcome in similar reactions recorded by Ramirez and Woerpel.[14] 1,2-Dioxolane alcohol **3n** and carboxylic acid **3m** were obtained by reduction and hydrolysis of ester **3k** (Scheme 3).

Scheme 3. Synthesis of 1,2-Dioxolanes **3m** and **3n**



Antimalarial Activity

As previously described,[15] in vitro and in vivo antimalarial activities were measured using the chloroquine-resistant K1 and chloroquine-sensitive NF54 strains of *P. falciparum* and using *P. berghei* infected mice (Table 2). Groups of three *P. berghei* infected mice were treated 1 day after infection with 100 mg/kg oral (po) doses of **3a**−**n** dissolved or suspended in a solubilizing 3% ethanol and 7% Tween-80 vehicle. Antimalarial activity was measured by percent reduction in parasitemia on day 3 after infection compared to an untreated control group.

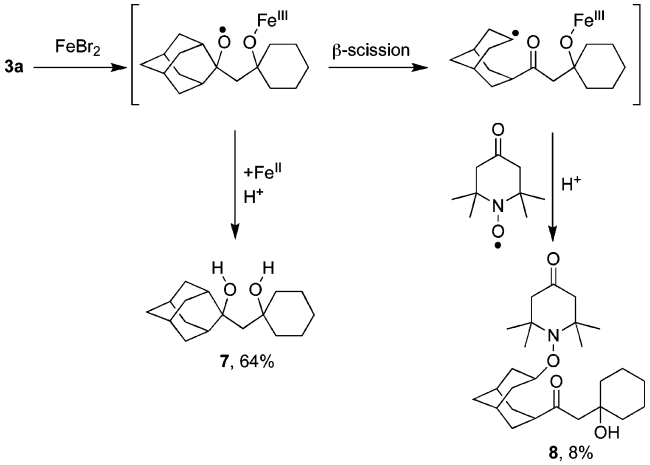
What is immediately evident is that 1,2-dioxolanes **3a**−**n** are either inactive or orders of magnitude less potent than artemisinin or 1,2,4-trioxolane **1** against *P. falciparum*. With the exception of **3f**, **3a**−**n** did not have activities against *P. berghei* that exceeded 50%. Even **3f**, the most active 1,2-dioxolane, is more than 1000-fold less effective than **1** and 5- to 10-fold less effective than its 1,2,4-trioxolane isostere (data not shown). When the sterically bulky spiroadamantane in **3a** and **3b** was replaced with a spirocyclohexane (**3d**, **3f**) or spirocyclopentane

Table 2. Activity of 1,2-Dioxolanes **3a**−**n** and 1,2,4-Trioxolane Isosteres **1** and **2** against *P. falciparum* in Vitro and *P. berghei* in Vivo

compd	IC_{50}, K1/NF54 (ng/mL)[a]	activity (%)[b]
3a	770/660	0
3b	>1000/>1000	0
3c	120/120	6
3d	41/110	0
3e	63/120	30
3f	41/93	84
3g	41/62	0
3h	130/180	45
3i	38/83	49
3j	230/360	0
3k	48/81	18
3l	440/660	0
3m	>1000/>1000	0
3n	50/80	0
1[c]	0.97/1.4	>99.99
2[c]	100/460	0
artemisinin[c]	1.6/2.8	98

[a] Mean of $n = 2-3$ for chloroquine-resistant (K1) and chloroquine-sensitive (NF54) strains of *P. falciparum*. Individual measurements generally differed by less than 50%. [b] Groups of three *P. berghei*-infected NMRI mice were treated (po) 1 day after infection with 1,2-dioxolanes (100 mg/kg) dissolved or suspended in 3% ethanol and 7% Tween-80. Activity was measured as percent reduction in parasitemia on day 3 after infection compared to an untreated control group. Individual measurements generally differed by less than 10%. [c] Data from Dong et al.[4]

Scheme 4. Reaction of **3a** with $FeBr_2$ in the Presence of 4-Oxo-TEMPO



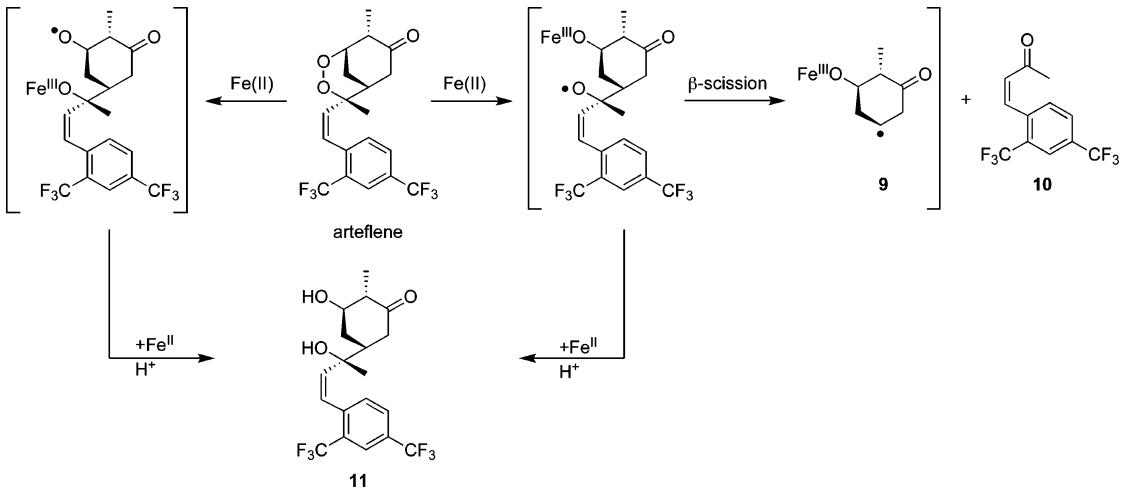
(**3g**, **3i**), potency increased by an order of magnitude. The opposite trend in antimalarial potencies was observed for **1** and **2**,[4] the 1,2,4-trioxolane isosteres of 1,2-dioxolanes **3a** and **3d**. Consistent with what we have observed before for functionalized 1,2,4-trioxolanes[16] and 1,2,4,5-tetraoxanes,[15] carboxylic acid **3m** was much less potent than its corresponding ester **3k** and alcohol **3n**. In summary, these 1,2-dioxolanes were unexpectedly much less potent than the corresponding 1,2,4-trioxolanes, but their weak antimalarial activities were similar to the micromolar IC_{50} values previously recorded for other synthetic[17] and natural product[18] 1,2-dioxolanes.

Interaction of 3a with Iron(II)

The iron activation hypothesis for antimalarial peroxides proposes that the antimalarial activity is mediated by carbon-centered free radicals generated following peroxide bond cleavage by iron within the intraerythrocytic parasite.[19] We investigated the iron(II)-mediated reactivity of **3a**, a representative 1,2-dioxolane and structural analogue of the 1,2,4-trioxolane **1**, and found that **3a** (0.03 mM) had a pseudo-first-order reaction rate constant (k) of 0.14 ± 0.004 h^{-1} with $FeSO_4$ (3 mM) in $MeCN/H_2O$ (1:1) at 37 °C ($n = 3$) under Ar. Under the same conditions, rate constants (k) for **1** and artemisinin were 0.41 ± 0.02 and 0.054 ± 0.006 h^{-1}, respectively.[6,20] Thus, **3a** is intermediate to **1** and artemisinin with respect to its iron(II) reactivity. These small differences in reaction rates with iron(II), however, cannot explain the very low antimalarial activity of **3a** compared to **1** and artemisinin.

In the next experiment, we characterized the reaction products of **3a** with iron(II). Exposure of **3a** to $FeBr_2$ (1.5 equiv) in CH_2Cl_2/MeCN (1:1) at 25 °C in the presence of the stable nitroxide free radical 4-oxo-TEMPO (2 equiv) under Ar afforded a mixture of diol **7** (64%) and 4-oxo-TEMPO adduct **8** (8%) as the major reaction products[21] (Scheme 4). The formation of only one 4-oxo-TEMPO adduct (**8**) resulting from spiroadamantane β-scission indicates regioselective formation of the Fe(III) complexed oxy radical resulting from preferential attack of iron(II) on the less hindered peroxide bond oxygen atom of **3a**. Under comparable reaction conditions, we observed a similar regioselective attack of iron(II) on **1**, but the corresponding 4-oxo-TEMPO adduct was produced in 56% yield with no evidence of any two-electron reduction products.[5] The low yield of 4-oxo-TEMPO adduct **8** (8%) from the reaction of **3a** with iron(II) suggested minimal carbon-centered radical formation, while the predominant reaction product was diol **7**, indicating that the primary reaction course of **3a** was a two-electron

Scheme 5. Reaction of Arteflene with $FeCl_2 \cdot 4H_2O$[24,25]



reduction. Indeed, in a parallel reaction of **3a** with 2 equiv of $FeBr_2$, **8** was not produced, indicating that β-scission is observed only when less than stoichiometric quantitites of iron(II) are used. That **7** was completely without antimalarial activity (*P. falciparum*, $IC_{50} > 1000$ ng/mL) is consistent with the very weak antimalarial activity of **3a**.

As exemplified by arteflene, synthetic 1,2-dioxanes have been relatively well explored,[3] but until this study, very little was known about the antimalarial properties of synthetic 1,2-dioxolanes,[17] their five-membered ring counterparts. The structure of arteflene makes an interesting comparison for 1,2-dioxolanes. First, with an average IC_{50} of 37 ng/mL against five *P. falciparum* isolates,[22] arteflene is only slightly more potent than some of the 1,2-dioxolanes **3** described in this study and is an order of magnitude less potent than artemisinin. Although exposure of arteflene to $FeCl_2 \cdot 4H_2O$ produces secondary carbon-centered radical **9**[23] and enone **10** via β-scission,[24] the predominant reaction product is inactive diol **11**[25] resulting from two-electron reduction (Scheme 5). Similarly, for **3a**, the iron(II)-mediated two-electron reduction pathway (Scheme 4) leading to inactive diol **7** predominates but to an even greater extent, consistent with the 20-fold lower potency of **3a** compared to arteflene.

We suggest that for optimal antimalarial potency, peroxide structures such as artemisinin that permit rapid β-scission reactions (or H shifts) to form primary or secondary carbon-centered radicals, rather than undergoing further reduction of the initially formed Fe(III) complexed oxy radicals, are preferred.[26] The key structural element in these active cyclic peroxides appears to be an oxygen atom attached to one or both of the peroxide-bearing carbon atoms. Indeed, it is observed[5,27] that β-scission reactions arising from oxy radicals at ketal carbon atoms occur much more quickly than competing β-scission reactions arising from oxy radicals at nonketal positions. Thus, 1,2,4-trioxanes and 1,2,4,5-tetraoxanes are more active than the corresponding 1,2-dioxanes,[3] and 1,2,4-trioxolanes[4] are more active than the corresponding 1,2-dioxolanes. We predict that this same trend will also hold true in larger ring cyclic peroxides.[28]

Experimental Section

General. Melting points are uncorrected. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. The alkylidenes 1-*tert*-butyl-4-methylenecyclohexane,[29] 2-methyleneadamantane **6c**,[30] and 1-methylene-4-phenylcyclohexane[31] were prepared according to literature methods.

Adamantane-2-spiro-3′-1′,2′-dioxaspiro[4.5]decane (3a). Method A. To a solution of **4a** (0.68 g, 1.81 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added **6c** (0.55 g, 3.72 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (3.60 mL, 3.60 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (50 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−5% ether in hexane) followed by crystallization from EtOH/H_2O (10:1) afforded **3a** (0.35 g, 74%) as a colorless solid: mp 64−65; °C; ^1H NMR δ 1.32−1.48 (m, 4H), 1.52−1.96 (m, 16H), 1.90−1.94 (m, 2H), 2.08−2.14 (m, 2H), 2.14 (s, 2H); ^{13}C NMR δ 23.6, 25.4, 26.5, 27.1, 33.5, 35.7, 35.8, 36.3, 37.3, 54.3, 85.4, 88.9. Anal. ($C_{17}H_{26}O_2$) C, H.

Alternative Method A. To a solution of **4d** (0.43 g, 1.00 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added **6a** (0.36 mL, 3.02 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.0 mL, 2.0 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−5% ether in hexane) followed by crystallization from EtOH/H_2O (10:1) afforded **3a** (0.09 g, 35%) as a colorless solid.

Adamantane-2-spiro-3′-8′-phenyl-1′,2′-dioxaspiro[4.5]-decane (3b). To a solution of **4c** (0.50 g, 1.10 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added **6c** (0.49 g, 3.31 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.20 mL, 2.20 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−5% ether in hexane) followed by crystallization from EtOH/H_2O (10:1) afforded **3b** (0.25 g, 68%) as a colorless solid: mp 90−92 °C; ^1H NMR δ 1.53−1.88 (m, 16H), 1.95−1.98 (m, 2H), 2.08−2.16 (m, 4H), 2.19 (s, 2H), 2.44−2.52 (m, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR δ 26.5, 27.1, 30.5, 33.5, 35.7, 35.7, 36.3, 37.3, 43.4, 55.7, 84.0, 88.8, 126.0, 126.8, 128.3, 147.0. Anal. ($C_{23}H_{30}O_2$) C, H.

Adamantane-2-spiro-3′-5′,5′-dipropyl-1′,2′-dioxolane (3c). To a solution of **4e** (0.30 g, 0.76 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added **6c** (0.34 g, 2.30 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (1.5 mL, 1.5 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) afforded **3c** (0.10 g, 48%) as a colorless oil. ^1H NMR δ 0.92 (t, $J = 7.5$ Hz, 6H), 1.22−1.94 (m, 20H), 2.07−2.14 (m, 2H), 2.15 (s, 2H); ^{13}C NMR δ 14.6, 17.7, 26.5, 27.1, 33.5, 35.7, 36.3, 37.3, 38.6, 53.3, 88.2, 88.9. Anal. ($C_{18}H_{30}O_2$) C, H.

14,15-Dioxadispiro[5.1.5.2]pentadecane (3d). Method A. To a solution of **4a** (0.40 g, 1.06 mmol) in CH_2Cl_2 (46 mL) at −78 °C was added **6a** (0.31 g, 3.23 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.12 mL, 2.12 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) followed by crystallization from EtOH/H_2O (5:1) afforded **3d** (0.19 g, 86%) as a colorless solid. mp 50−52 °C; ^1H NMR δ 1.32−1.48 (m, 8H), 1.52−1.78 (m, 12H), 2.04 (s, 2H); ^{13}C NMR δ 23.6, 25.3, 35.8, 55.5, 85.1. Anal. ($C_{13}H_{22}O_2$) C, H.

Method B. To a solution of **5a** (0.50 g, 1.92 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added **6a** (0.68 mL, 5.73 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (3.80 mL, 3.80 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (50 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) followed by crystallization from EtOH/H_2O (5:1) afforded **3d** (0.33 g, 83%) as a colorless solid.

3-*tert*-Butyl-14,15-dioxadispiro[5.1.5.2]pentadecane (3e). Method A. To a solution of **4b**[14] (0.30 g, 0.69 mmol) in CH_2Cl_2 (30 mL)

at −78 °C was added **6a** (0.30 mL, 2.50 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (1.38 mL, 1.38 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, hexane) followed by crystallization from EtOH/H_2O (1:1) afforded **3e** (0.17 g, 94%) as a colorless solid: mp 75−76 °C; ^{1}H NMR δ 0.83 (s, 9H), 0.91−1.00 (m, 1H), 1.22−1.78 (m, 16H), 1.98−2.06 (m, 2H), 2.01 (s, 2H); ^{13}C NMR δ 23.6, 23.8, 25.38, 27.58, 32.4, 35.8, 36.0, 47.1, 57.0, 84.0, 84.7. Anal. ($C_{17}H_{30}O_2$) C, H.

Method B. To a solution of **5b** (0.40 g, 1.27 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added **6a** (0.50 mL, 4.17 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.60 mL, 2.60 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (50 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) followed by crystallization from EtOH/H_2O (1:1) afforded **3e** (0.32 g, 94%) as a colorless solid.

3-Phenyl-14,15-dioxadispiro[5.1.5.2]pentadecane (3f). Method A. To a solution of **4c** (0.50 g, 1.10 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added **6a** (0.38 mL, 3.23 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.20 mL, 2.20 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by crystallization from EtOH/H_2O (10:1) afforded **3f** (0.28 g, 88%) as a colorless solid: mp 83−84 °C; ^{1}H NMR δ 1.32−1.50 (m, 4H), 1.55−1.87 (m, 12H), 2.06−2.16 (m, 2H), 2.08 (s, 2H), 2.44−2.52 (m, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR δ 23.6, 25.3, 30.5, 35.75, 35.78, 43.4, 57.0, 83.6, 84.9, 126.0, 126.8, 128.3, 147.0. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.80; H, 8.96.

Method B. To a solution of **5c** (0.32 g, 0.95 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added **6a** (0.34 mL, 2.80 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (1.90 mL, 1.90 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (50 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) followed by crystallization from EtOH/H_2O (10:1) afforded **3f** (0.28 g, 88%) as a colorless solid.

13,14-Dioxadispiro[4.1.5.2]tetradecane (3g). To a solution of **4a** (0.40 g, 1.06 mmol) in CH_2Cl_2 (46 mL) at −78 °C was added **6b** (0.34 mL, 3.16 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.12 mL, 2.12 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) afforded **3g** (0.19 g, 90%) as a colorless oil. ^{1}H NMR δ 1.32−1.48 (m, 4H), 1.54−1.76 (m, 12H), 1.94−2.04 (m, 2H), 2.27 (s, 2H); ^{13}C NMR δ 23.7, 24.3, 25.3, 35.8, 37.0, 54.7, 85.0, 93.8. Anal. ($C_{12}H_{20}O_2$) C, H.

10-*tert*-Butyl-13,14-dioxadispiro[4.1.5.2]tetradecane (3h). To a solution of **4b**[14] (0.30 g, 0.69 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added **6b** (0.22 mL, 2.07 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (1.38 mL, 1.38 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, hexane) followed by crystallization from EtOH/H_2O (3:2) afforded **3h** (0.14 g, 77%) as a colorless solid: mp 68−69 °C; ^{1}H NMR δ 0.84 (s, 9H), 0.91−1.00 (m, 1H), 1.24−1.74 (m, 12H), 1.94−2.06 (m, 4H), 2.24 (s, 2H); ^{13}C NMR δ 23.8, 24.2, 27.5, 32.4, 36.1, 36.9, 47.1, 56.0, 83.9, 93.5. Anal. ($C_{16}H_{28}O_2$) C, H.

10-Phenyl-13,14-dioxadispiro[4.1.5.2]tetradecane (3i). To a solution of **4c** (0.50 g, 1.10 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added **6b** (0.34 mL, 3.17 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.20 mL, 2.20 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0 to 5% ether in hexane) followed by crystallization from EtOH/H_2O (10:1) afforded **3i** (0.22 g, 73%) as a colorless solid: mp 101−102 °C; ^{1}H NMR δ 1.57−1.86 (m, 12H), 1.96−2.06 (m, 2H), 2.08−2.14 (m, 2H), 2.31 (s, 2H), 2.44−2.52 (m, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR δ 24.3, 30.5, 35.8, 36.9, 43.4, 56.1, 83.5, 93.6, 126.0, 126.9, 128.3, 147.0. Anal. ($C_{18}H_{24}O_2$) C, H.

3,3-Dipropyl-1,2-dioxaspiro[4.5]decane (3j). To a solution of **4e** (0.31 g, 0.79 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added **6a** (0.28 mL, 2.40 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (1.6 mL, 1.6 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−5% ether in hexane) afforded **3j** (0.10 g, 56%) as a colorless oil. ^{1}H NMR δ 0.92 (t, J = 7.5 Hz, 6H), 1.21−1.80 (m, 18H), 2.05 (s, 2H); ^{13}C NMR δ 14.6, 17.7, 23.7, 25.3, 35.8, 38.6, 54.6, 85.0, 87.9. Anal. ($C_{14}H_{26}O_2$) C, H.

3-[2-(Ethoxycarbonyl)ethyl]-3-methyl-1,2-dioxaspiro[4.5]-decane (3k). To a solution of **5a** (1.1 g, 4.2 mmol) in CH_2Cl_2 (170 mL) at −78 °C was added **6d** (2.0 mL, 12.6 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (8.0 mL, 8.0 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−10% ether in hexane) afforded **3k** (0.32 g, 30%) as a colorless oil. ^{1}H NMR δ 1.26 (t, J = 7.0 Hz, 3H), 1.30 (s, 3H), 1.32−1.80 (m, 10H), 1.82−1.90 (m, 1H), 2.04−2.18 (m, 3H), 2.32−2.48 (m, 2H), 4.13 (q, J = 7.0 Hz, 2H); ^{13}C NMR δ 14.2, 23.5, 23.6, 23.7, 25.2, 29.5, 34.1, 35.5, 35.8, 55.9, 60.4, 84.5, 85.5, 173.5. Anal. ($C_{14}H_{24}O_4$) C, H.

3-Phenyl-1,2-dioxaspiro[4.5]decane (3l). To a solution of **5a** (0.33 g, 1.3 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added **6e** (0.50 mL, 4.3 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (2.6 mL, 2.6 mmol). The resulting mixture was stirred at −78 °C for 30 min and then kept at −30 °C overnight. The reaction mixture was allowed to warm to −3 °C and quenched with cold (4 °C) water (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography

(silica gel, 0−8% ether in hexane) afforded **3l** (0.15 g, 55%) as a colorless oil. ^{1}H NMR δ 1.36−1.52 (m, 4H), 1.66−1.88 (m, 6H), 2.35 (dd, J = 12.0, 7.5 Hz, 1H), 2.76 (dd, J = 12.0, 7.5 Hz, 1H), 5.27 (t, J = 7.5 Hz, 1H), 7.27−7.71 (m, 5H); ^{13}C NMR δ 23.7, 23.8, 25.3, 35.3, 36.1, 53.2, 82.9, 85.9, 126.6, 128.1, 128.6, 138.9. Anal. ($C_{14}H_{18}O_2$) C, H.

3-(2-Carboxyethyl)-3-methyl-1,2-dioxaspiro[4.5]decane (3m). To a solution of **3k** (0.08 g, 0.31 mmol) in EtOH (30 mL) was added 1 M aqueous NaOH (1 mL). The resulting mixture was stirred at 50 °C for 6 h. After the solvent was removed, the residue was diluted with water (10 mL) and acidified with 1 M aqueous HCl (5 mL). The precipitate was collected by filtration, washed with cold (4 °C) water, and dried in a vacuum oven at 40 °C to afford **3m** (0.063 g, 89%) as a colorless solid: mp 58−59 °C; ^{1}H NMR δ 1.31 (s, 3H), 1.32−1.80 (m, 10H), 1.82−1.90 (m, 1H), 2.07−2.18 (m, 3H), 2.40−2.56 (m, 2H); ^{13}C NMR δ 23.4, 23.5, 23.7, 25.2, 28.9, 33.9, 35.5, 35.9, 56.0, 84.4, 85.7, 177.6. Anal. ($C_{12}H_{20}O_4$) C, H.

3-(3-Hydroxypropyl)-3-methyl-1,2-dioxaspiro[4.5]decane (3n). To a solution of **3k** (0.60 g, 2.3 mmol) in ether (5 mL) and THF (1 mL) was added dropwise 2 M lithium borohydride in THF (1.2 mL, 2.4 mmol) followed by 1 M lithium triethylborohydride in THF (0.24 mL, 0.24 mmol). The resulting mixture was stirred at room temperature overnight, diluted with ether (30 mL), washed with 1 M aqueous NaOH (2 × 5 mL), water (2 × 5 mL), and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (silica gel, 0−20% ether in hexane) afforded **3n** (0.45 g, 90%) as a colorless oil. ^{1}H NMR δ 1.32 (s, 3H), 1.33−1.83 (m, 14H), 2.09 (d, J = 11.7 Hz, 1H), 2.15 (d, J = 11.7 Hz, 1H), 3.67 (q, J = 6.0 Hz, 2H); ^{13}C NMR δ 23.5, 23.6, 23.7, 25.1, 27.6, 35.4, 35.6, 35.7, 55.9, 62.5, 85.4, 85.5. Anal. ($C_{12}H_{22}O_3$) C, H.

1,1-Bis[(triethylsilyl)dioxy]cyclohexane (4a). To a solution of cyclohexanone (3.18 g, 32.40 mmol) in formic acid (18 mL) at 0 °C was added 50% H_2O_2 (30 mL, 521 mmol). After the mixture was stirred at 0 °C for 15 min, it was diluted with CH_2Cl_2 (200 mL) and water (200 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (200 mL) and concentrated to give 1,1-dihydroperoxycyclohexane[32] (1.56 g, 86% purity) that was used in the next step. To a solution of the above unpurified 1,1-dihydroperoxycyclohexane in DMF (40 mL) at 0 °C was added Et_3N (3.03 g, 30 mmol) and DMAP (88 mg, 0.72 mmol) followed by Et_3SiOTf (8.1 mL, 37.5 mmol). The mixture was stirred at 0 °C for 30 min and at room temperature overnight before it was quenched under ice−water cooling with hexane (200 mL) and water (200 mL). After separation of the organic layer, the aqueous layer was extracted with hexane (2 × 50 mL). The combined extracts were washed with water (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (silica gel, 3% ether in hexane) to give **4a** (2.20 g, 18%) as a colorless oil. ^{1}H NMR δ 0.71 (q, J = 7.8 Hz, 12 H), 0.99 (t, J = 7.8 Hz, 18H), 1.35−1.46 (m, 2H), 1.47−1.56 (m, 4H), 1.77 (t, J = 6.1 Hz, 4H). Anal. ($C_{18}H_{40}O_4Si_2$) C, H.

4-Phenyl-1,1-bis[(triethylsilyl)dioxy]cyclohexane (4c). To a solution of 4-phenylcyclohexanone (2.82 g, 16.20 mmol) in CH_2Cl_2 (24 mL) and formic acid (18 mL) at 0 °C was added 50% H_2O_2 (28.8 mL, 480 mmol). After the mixture was stirred at 0 °C for 30 min, it was diluted with CH_2Cl_2 (200 mL) and water (200 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (200 mL) and concentrated to give 1,1-dihydroperoxy-4-phenylcyclohexane (3.95 g, 80% purity) that was used in the next step. To a solution of the above unpurified 1,1-dihydroperoxy-4-phenylcyclohexane in DMF (50 mL) at 0 °C was added 1-methylimidazole (3.30 g, 40 mmol) followed by Et_3SiOTf (7.0 mL, 30.7 mmol). The mixture was stirred at 0 °C for 30 min and at room temperature overnight before it was quenched under ice−water cooling with hexane (200 mL) and water (200 mL). After separation of the organic layer, the aqueous layer was extracted with hexane (2 × 50 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (silica gel, 2% ether in hexane) to give **4c** (3.34 g, 46%) as a colorless oil. ^{1}H NMR δ 0.72 (q, J = 8.3 Hz, 6 H), 0.77 (q, J = 8.3 Hz, 6 H), 1.01 (t, J = 8.3 Hz, 9H), 1.04 (t, J = 8.3 Hz, 9H), 1.42−1.62 (m, 2H), 1.65−1.91 (m, 4H), 2.41 (d, J = 12.7 Hz, 2H), 2.45−2.62 (m, 1H), 7.12−7.39 (m, 5H); ^{13}C NMR δ 3.92, 3.93, 6.80, 6.83, 30.3, 30.4, 43.8, 108.7, 126.0, 126.8, 128.4, 146.7. Anal. ($C_{24}H_{44}O_4Si_2$) C, H.

2,2-Bis[(triethylsilyl)dioxy]adamantane (4d). To a solution of 2-adamantanone (2.43 g, 16.20 mmol) in formic acid (18 mL) at 0 °C was added 50% H_2O_2 (28.8 mL, 480 mmol). After the mixture was stirred at 0 °C for 30 min, the resulting precipitate was filtered, washed with water (50 mL) and hexane (50 mL), and dried at room temperature to give 2,2-dihydroperoxyadamantane[33,34] (2.84 g, 90% purity) that was used in the next step. To a solution of the above unpurified 2,2-dihydroperoxyadamantane in DMF (50 mL) at 0 °C was added 1-methylimidazole (3.30 g, 40 mmol) followed by Et_3SiOTf (7.0 mL, 30.7 mmol). The mixture was stirred at 0 °C for 30 min and at room temperature overnight before it was quenched under ice−water cooling with hexane (200 mL) and water (200 mL). After separation of the organic layer, the aqueous layer was extracted with hexane (2 × 50 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (silica gel, 1.5% ether in hexane) to give **4d** (2.69 g, 39%) as a colorless oil. ^{1}H NMR δ 0.73 (q, J = 8.3 Hz, 12 H), 1.00 (t, J = 8.3 Hz, 18H), 1.60 (d, J = 12.7 Hz, 4H), 1.66 (s, 2H), 1.81 (s, 2H), 1.95 (d, J = 12.2 Hz, 4H), 2.37 (s, 2H); ^{13}C NMR δ 4.0, 6.9, 27.3, 31.6, 34.0, 37.5, 110.7. Anal. ($C_{22}H_{44}O_4Si_2$) C, H.

4,4-Bis[(triethylsilyl)dioxy]heptane (4e). To a solution of I_2 (0.508 g, 2.0 mmol) and 30% H_2O_2 (4.5 mL, 40 mmol) in MeCN (50 mL) was added 4-heptanone (2.8 mL, 20 mmol). After the reaction mixture was stirred at room temperature for 24 h, the solvent was removed. The residue was partitioned between CH_2Cl_2 (30 mL) and water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to afford 4,4-dihydroperoxyheptane as a colorless oil (3.2 g, 80% crude yield), which was used immediately in the next step. ^{1}H NMR δ 0.95 (t, J = 7.5 Hz, 6H), 1.35−1.47 (m, 4H), 1.63−1.72 (m, 4H), 8.38 (brs, 2H). To a solution of the unpurified 4,4-dihydroperoxyheptane (3.2 g) in DMF (100 mL) at 0 °C was added Et_3N (17 mL, 120 mmol) followed by Et_3SiOTf (10.2 mL, 48 mmol). The reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C, and then diluted with hexane (100 mL) and ice−water (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (3 × 100 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (silica gel, hexane) afforded **4e** (2.06 g, 26%) as a colorless oil. ^{1}H NMR δ 0.70 (q, J = 8.0 Hz, 12H), 0.90 (t, J = 7.5 Hz, 6H), 0.98 (t, J = 8.0 Hz, 18H), 1.30−1.40 (m, 4H), 1.65−1.72 (m, 4H); ^{13}C NMR δ 3.9, 6.8, 14.5, 17.3, 33.1, 112.4.

1-Methoxy-1-[(triethylsilyl)dioxy]cyclohexane (5a). A solution of **6a** (0.96 g, 10.0 mmol) in CH_2Cl_2 (25.5 mL) and MeOH (4.5 mL) at −78 °C was treated with ozone. After the ozonolysis, the solution was diluted with CH_2Cl_2 (30 mL) and washed with cold (4 °C) water (2 × 10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to afford 1-methoxycyclohexyl hydroperoxide[35] (1.2 g, 82%) as a colorless oil, which was used immediately in the next step. ^{1}H NMR δ 1.36−1.63 (m, 6H), 1.66−1.82 (m, 4H), 3.31 (s, 3H), 7.48 (brs, 1H). To a solution of the unpurified 1-methoxycyclohexyl hydroperoxide (1.2 g, 8.22 mmol) in DMF (100 mL) at 0 °C was added Et_3N (4.5 mL, 32.4 mmol) followed by Et_3SiOTf (2.54 mL, 12 mmol). The reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C, and then diluted with hexane (100 mL) and cold (4 °C) water (100 mL). After the organic layer was separated, the aqueous layer was extracted with hexane (3 × 100 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (silica gel, 3% ether in hexane) afforded **5a** (1.98 g, 93%) as a colorless oil. ^{1}H NMR δ 0.72 (q, J = 8.0 Hz, 6H), 1.00 (t, J

= 8.0 Hz, 9H), 1.36−1.45 (m, 2H), 1.47−1.56 (m, 4H), 1.67−1.76 (m, 4H), 3.28 (s, 3H); ^{13}C NMR δ 3.8, 6.8, 22.8, 25.6, 31.5, 48.0, 104.8.

4-*tert*-Butyl-1-methoxy-1-[(triethylsilyl)dioxy]cyclohexane (5b). A solution of 1-*tert*-butyl-4-methylenecyclohexane[29] (0.90 g, 5.9 mmol) in CH_2Cl_2 (25.5 mL) and MeOH (4.5 mL) at −78 °C was treated with ozone. After the ozonolysis, the solution was diluted with CH_2Cl_2 (30 mL) and washed with cold (4 °C) water (2 × 10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to afford 4-*tert*-butyl-1-methoxycyclohexyl hydroperoxide[12,33] (0.98 g, 82%) as a colorless solid (2:1 mixture of diastereomers), which was used immediately in the next step: mp 53−56 °C; ^{1}H NMR δ 0.87 (s, 9H), 0.96−1.46 (m, 5H), 1.64−1.74 (m, 2H), 2.06−2.17 (m, 1.33H), 2.18−2.26 (m, 0.67H), 3.29 (s, 2H), 3.32 (s, 1H), 7.47 (s, 0.67H), 7.49 (s, 0.33H). To a solution of the unpurified 4-*tert*-butyl-1-methoxycyclohexyl hydroperoxide (0.98 g, 4.85 mmol) in DMF (50 mL) at 0 °C was added Et_3N (2.10 mL, 14.8 mmol) followed by Et_3SiOTf (1.30 mL, 6.10 mmol). The reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C, and then diluted with hexane (100 mL) and ice−water (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (3 × 100 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (silica gel, 3% ether in hexane) afforded **5b** (0.96 g, 51%) as a colorless oil (5:4 mixture of diastereomers). ^{1}H NMR δ 0.56−0.78 (m, 6H), 0.86 (s, 9H), 0.94−1.06 (m, 9H), 1.10−1.40 (m, 5H), 1.60−1.69 (m, 2H), 2.08−2.16 (m, 1.11H), 2.22−2.30 (m, 0.89H), 3.26 (s, 1.67H), 3.30 (s, 1.33H); ^{13}C NMR δ 3.7, 3.8, 6.8, 23.5, 23.7, 27.6, 27.7, 31.5, 31.8, 32.3, 32.3, 47.3, 47.8, 48.1, 48.3, 104.6, 104.8.

1-Methoxy-4-phenyl-1-[(triethylsilyl)dioxy]cyclohexane (5c). A solution of 1-methylene-4-phenylcyclohexane[31] (3.1 g, 18.0 mmol) in CH_2Cl_2 (85 mL) and MeOH (15 mL) was treated with ozone at −78 °C. After ozonolysis, the solution was diluted with CH_2Cl_2 (30 mL) and washed with cold (4 °C) water (2 × 10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to afford 1-methoxy-4-phenylcyclohexyl hydroperoxide (4.0 g, 100%) as a colorless solid (5:2 mixture of diastereomers), which was used immediately in the next step: mp 66−69 °C; ^{1}H NMR δ 1.44−1.96 (m, 6H), 2.18−2.26 (m, 1.43H), 2.26−2.38 (m, 0.57H), 2.52−2.64 (m, 1H), 3.35 (s, 2.14H), 3.37 (s, 0.86H), 7.16−7.36 (m, 5H), 7.49 (brs, 1H). To a solution of the unpurified 1-methoxy-4-phenylcyclohexyl hydroperoxide (4.0 g, 18.0 mmol) in DMF (100 mL) at 0 °C was added Et_3N (7.5 mL, 54 mmol) followed by Et_3SiOTf (4.7 mL, 22 mmol). The reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C, and then diluted with ice-cold hexane (100 mL) and ice−water (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (3 × 100 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (silica gel, 3% ether in hexane) afforded **5c** (5.2 g, 86%) as a colorless liquid (5:3 mixture of diastereomers). ^{1}H NMR δ 0.62−0.84 (m, 6H), 0.90−1.14 (m, 9H), 1.40−1.88 (m, 6H), 2.18−2.28 (m, 1.25H), 2.32−2.42 (m, 0.75), 2.46−2.60 (m, 1H), 3.34 (s, 1.88H), 3.36 (s, 1.12H), 7.18−7.40 (m, 5H); ^{13}C NMR δ 3.8, 6.76, 6.79, 30.2, 30.5, 31.4, 31.8, 43.6, 43.8, 48.2, 48.4, 104.3, 104.4, 126.1, 126.8, 126.9, 128.3, 128.4, 146.5, 146.7.

Reaction of 3a with $FeBr_2$ and 4-Oxo-TEMPO. To a solution of **3a** (95 mg, 0.36 mmol), 4-oxo-TEMPO (130 mg, 0.76 mmol) in CH_2Cl_2 (10 mL), and CH_3CN (10 mL) was added $FeBr_2$ (120 mg, 0.56 mmol). The resulting mixture was stirred at room temperature under N_2 for 24 h before being quenched with water (50 mL) and acetic acid (3 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 10−50% ether in hexane) to afford 2-[(1-hydroxycyclohexyl)methyl]-2-adamantanol (**7**) as colorless solid (61 mg, 64%), 3-[2-(1-hydroxycyclohexyl)-1-oxoethyl]-7-[(2,2,6,6-tetramethyl-4-oxo-1-piperidinyl)oxy]bicyclo[3.3.1]-nonane (**8**) as a colorless solid (12 mg, 8%), and a mixture of unidentified unsaturated alcohol dehydration products of **7** (5 mg, 6%). For **7**: mp 128−129 °C; ^{1}H NMR δ 1.23−1.33 (m, 1H), 1.42−1.84 (m, 17H), 1.84−1.92 (m, 4H), 1.89 (s, 2H), 2.17−2.24 (m, 2H), 3.19 (br s, 1H), 3.59 (br s, 1H); ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.23−1.33 (m, 1H), 1.42−1.65 (m, 9H), 1.66−1.84 (m, 8H), 1.84−1.92 (m, 4H), 1.89 (s, 2H), 2.17−2.24 (m, 2H); ^{13}C NMR δ 22.3, 25.6, 26.9, 27.2, 32.8, 34.7, 38.3, 39.0, 39.9, 46.5, 73.6, 77.0; ^{1}H NMR (DMSO-d_6) δ 1.18−1.28 (m, 1H), 1.29−1.70 (m, 17H), 1.71−1.79 (m, 2H), 1.74 (s, 2H), 1.80−1.88 (m, 2H), 2.20−2.27 (m, 2H), 5.17 (br s, 1H), 5.35 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.1, 25.5, 26.8, 27.0, 32.5, 34.3, 38.2, 38.8, 39.6, 46.2, 72.6, 75.4; HRMS-FAB for $C_{17}H_{28}O_2$ $[M + H]^+$. For **8**: mp 109−110 °C; ^{1}H NMR δ 1.13 (s, 6H), 1.18−1.74 (m, 16H), 1.29 (s, 6H), 2.00−2.12 (m, 4H), 2.15−2.32 (m, 4H), 2.46−2.62 (m, 1H), 2.58 (s, 4H), 3.89 (s, 1H), 3.98−4.08 (m, 1H); ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.13 (s, 6H), 1.18−1.74 (m, 16H), 1.29 (s, 6H), 2.00−2.12 (m, 4H), 2.15−2.32 (m, 4H), 2.46−2.62 (m, 1H), 2.58 (s, 4H), 3.98−4.08 (m, 1H); ^{13}C NMR δ 21.9, 22.7, 25.7, 25.8, 28.3, 28.5, 34.0, 37.7, 39.7, 44.2, 50.8, 53.6, 62.7, 70.7, 75.9, 208.6, 216.7. HRMS-FAB for $C_{26}H_{43}NO_4$ $[M + H]^+$.

Pseudo-First-Order Reaction Rate Constant of 3a with Ferrous Sulfate. 1,2-Dioxolane **3a** (0.03 mM) was added to a solution of $FeSO_4$ (3 mM) in MeCN/H_2O (1:1, 1.5 mL) and kept at 37 °C under argon for automated kinetic analysis over 6 h as previously described.[20] 1,2-Dioxolane **3a** concentrations were monitored by HPLC/APCI-MS (Waters 2795 HPLC/Waters Micromass ZQ single quadrupole mass spectrometer, Waters Corp., Milford, MA) using the assay previously described for analysis of neutral 1,2,4-trioxolanes[6] with the quasi-molecular ion (*m*/*z* 263.3) monitored at cone voltage 15 V and corona current 15 μA. Concentrations of **3a** were determined from a linear calibration curve, and pseudo-first-order degradation rate constants were calculated from three independent reactions. The stability of **3a** in MeCN/H_2O (1:1) at 37 °C was also confirmed, with no significant degradation observed in iron-free controls over the time course of these reactions.

Antimalarial Screens. In vitro and in vivo antimalarial data were obtained as previously described.[15]

Acknowledgment. This investigation received financial support from the Medicines for Malaria Venture (MMV).

Supporting Information Available: Elemental analysis results and HRMS data for **3a**−**n**, **4a**,**c**,**d**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Bray, P. G.; Ward, S. A.; O'Neill, P. M. Quinolines and Artemisinin: Chemistry, Biology and History. *Curr. Top. Microbiol. Immunol.* **2005**, *295*, 3−38.
(2) Winstanley, P.; Ward, S. Malaria Chemotherapy. *Adv. Parasitol.* **2006**, *61*, 47−76.
(3) Tang, Y.; Dong, Y.; Vennerstrom, J. L. Synthetic Peroxides as Antimalarials. *Med. Res. Rev.* **2004**, *24*, 425−448.
(4) Dong, Y.; Chollet, J.; Matile, H.; Charman, S. A.; Chiu, F. C. K.; Charman, W. N.; Scorneaux, B.; Urwyler, H.; Santo, Tomas, J.; Scheurer, C.; Snyder, C.; Dorn, A.; Wang, X.; Karle, J. M.; Tang, Y.; Wittlin, S.; Brun, R.; Vennerstrom, J. L. Spiro and Dispiro-1,2,4-Trioxolanes as Antimalarial Peroxides: Charting a Workable SAR Using Simple Prototypes. *J. Med. Chem.* **2005**, *48*, 4953−4961.
(5) Tang, Y.; Dong, Y.; Wang, X.; Sriraghavan, K.; Wood, J. K.; Vennerstrom, J. L. Dispiro-1,2,4-trioxane Analogs of a Prototype Dispiro-1,2,4-trioxolane: Mechanistic Comparators for Artemisinin in the Context of Reaction Pathways with Iron(II). *J. Org. Chem.* **2005**, *70*, 5103−5110.
(6) Creek, D. J.; Charman, W. N.; Chiu, F. C. K.; Prankerd, R. J.; McCullough, K. J.; Dong, Y.; Vennerstrom, J. L.; Charman, S. A. Iron Mediated Degradation Kinetics of Substituted Dispiro-1,2,4-Trioxolane Antimalarials. *J. Pharm. Sci.* **2007**, *96*, 2945−2956.
(7) Griesbaum, K.; Krieger-Beck, P.; Beck, J. Dispiro-1,2,4-trioxlane durch Ozonolyse von Cycloalkylidencycloalkanen auf Polyethylen (Dispiro-1,2,4-trioxolane by Ozonolysis of Cycloalkylidenecycloalkanes on Polyethylene). *Chem. Ber.* **1991**, *124*, 391−396.

(8) Perry, C. S.; Charman, S. A.; Prankerd, R. J.; Chiu, F. C. K.; Dong, Y.; Vennerstrom, J. L.; Charman, W. N. Chemical Kinetics and Aqueous Degradation Pathways of a New Class of Synthetic Ozonide Antimalarials. *J. Pharm. Sci.* **2006**, *95*, 737−747.
(9) Tang, Y.; Dong, Y.; Karle, J. M.; DiTusa, C. A.; Vennerstrom, J. L. Synthesis of Tetrasubstituted Ozonides by the Griesbaum Coozonolysis Reaction: Diastereoselectivity and Functional Group Transformations by Post-Ozonolysis Reactions. *J. Org. Chem.* **2004**, *69*, 6470−6473.
(10) Yoshida, M.; Miura, M.; Nojima, M.; Kusabayashi, S. Synthesis and Decomposition of *E*- and *Z*-3,3,5-Trisubstituted 1,2-Dioxolanes. *J. Am. Chem. Soc.* **1983**, *105*, 6279−6285.
(11) Dussault, P. H.; Lee, H.-J.; Liu, X. Selectivity in Lewis Acid-Mediated Fragmentations of Peroxides and Ozonides: Application to the Synthesis of Alkenes, Homoallyl Ethers, and 1,2-Dioxolanes. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3006−3013.
(12) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Lee, R. L.; Niu, Q. J.; Schultz, J. A.; Zope U. R. Peroxycarbenium-Mediated C−C Bond Formation: Applications to the Synthesis of Hydroperoxides and Peroxides. *J. Org. Chem.* **2000**, *65*, 8407−8414.
(13) Dussault, P. H.; Zope, U. Hydroperoxide-Mediated C−C Bond Formation: Synthesis of 1,2-Dioxolanes from Alkoxyhydroperoxides in the Presence of Lewis Acids. *Tetrahedron Lett.* **1995**, *36*, 3655−3658.
(14) Ramirez, A.; Woerpel, K. A. Synthesis of 1,2-Dioxolanes by Annulation Reactions of Peroxycarbenium Ions with Alkenes. *Org. Lett.* **2005**, *7*, 4617−4620.
(15) Dong, Y.; Matile, H.; Chollet, J.; Kaminsky, R.; Wood, J. K.; Vennerstrom, J. L. Synthesis and Antimalarial Activity of Eleven Dispiro-1,2,4,5-tetraoxane Analogs of WR 148999. 7,8,15,16-Tetraoxadispiro[5.2.5.2]hexadecanes Substituted at the 1 and 10 Positions with Unsaturated and Polar Functional Groups. *J. Med. Chem.* **1999**, *42*, 1477−1480.
(16) (a) Dong, Y.; Tang, T.; Chollet, J.; Matile, H.; Wittlin, S.; Charman, S. A.; Charman, W. N.; Santo Tomas, J.; Scheurer, C.; Snyder, C.; Scorneaux, B.; Bajpai, S.; Alexander, S. A.; Wang, X.; Padmanilayam, M.; Rao, C. S.; Brun, R.; Vennerstrom, J. L. Effect of Functional Group Polarity on the Antimalarial Activity of Spiro and Dispiro-1,2,4-Trioxolanes. *Bioorg. Med. Chem.* **2006**, *14*, 6368−6382. (b) Padmanilayam, M.; Scorneaux, B.; Dong, Y.; Chollet, J.; Matile, H.; Charman, S. A.; Creek, D. J.; Charman, W. N.; Santo Tomas, J.; Scheurer, C.; Wittlin, S.; Brun, R.; Vennerstrom, J. L. Antimalarial Activity of *N*-Alkyl Amine, Carboxamide, Sulfonamide, and Urea Derivatives of a Dispiro-1,2,4-trioxolane Piperidine. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5542−5545.
(17) Helesbeux, J. J.; Peyronnet, D.; Labaied, M.; Grellier, P.; Frappier, F.; Seraphin, D.; Richomme, P.; Duval, O. Synthesis and Antimalarial Activity of Some New 1,2-Dioxolane Derivatives. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 431−437.
(18) Rücker, G.; Walter, R. D.; Manns, D.; Mayer, R. Antimalarial Activity of Some Natural Peroxides. *Planta Med.* **1991**, *57*, 295−296.
(19) (a) Jefford, C. W. Why Artemisinin and Certain Synthetic Peroxides Are Potent Antimalarials. Implications for the Mode of Action. *Curr. Med. Chem.* **2001**, *8*, 1803−1826. (b) Wu, Y. How Might Qinghaosu (Artemisinin) and Related Compounds Kill the Intraerythrocytic Malaria Parasite? A Chemist's View. *Acc. Chem. Res.* **2002**, *35*, 255−259. (c) Dong, Y.; Vennerstrom, J. L. Mechanisms of in Situ Activation for Peroxidic Antimalarials. *Redox Rep.* **2003**, *8*, 284−288. (d) O'Neill, P. M.; Posner, G. H. A Medicinal Chemistry Perspective on Artemisinin and Related Endoperoxides. *J. Med. Chem.* **2004**, *47*, 2945−2964. (e) Posner, G. H.; O'Neill, P. H. Knowledge of the Proposed Chemical Mechanism of Action and Cytochrome P450 Metabolism of Antimalarial Trioxanes Like Artemisinin Allows Rational Design of New Antimalarial Peroxides. *Acc. Chem. Res.* **2004**, *37*, 397−404. (f) Jefford, C. W. New Developments in Synthetic Peroxidic Drugs as Artemisinin Mimics. *Drug Discovery Today* **2007**, *12*, 487−495.
(20) Creek, D. J.; Chiu, F. C. K.; Prankerd, R. J.; Charman, S. A.; Charman, W. N. Kinetics of Iron-Mediated Artemisinin Degradation: Effect of Solvent Composition and Iron Salt. *J. Pharm. Sci.* **2005**, *94*, 1820−1829.
(21) We also isolated a 6% yield of an inseparable mixture of olefinic dehydration products of diol **7** as evidenced by a broad peak at δ 5.5 in the proton NMR.
(22) Jaquet, C.; Stohler, H. R.; Chollet, J.; Peters. W. Antimalarial Activity of the Bicyclic Peroxide Ro 42-1611 (Arteflene) in Experimental Models. *Trop. Med. Parasitol.* **1994**, *45*, 266−271.
(23) Cazelles, J.; Robert, A.; Meunier, B. Characterization of the Main Radical and Products Resulting from a Reductive Activation of the Antimalarial Arteflene (Ro 42-1611). *J. Org. Chem.* **1999**, *64*, 6776−6781. In this study, reaction of arteflene with manganese(II)-tetraphenylporphyrin in the presence of the stable nitroxide 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) formed an adduct between **9** and TEMPO in 6% yield.
(24) O'Neill, P. M.; Bishop, L. P. D.; Searle, N. L.; Maggs, J. L.; Storr, R. C.; Ward, S. A.; Park. B. K.; Mabbs, F. Biomimetic Fe(II)-Mediated Degradation of Arteflene (Ro-42-1611). The First EPR Spin-Trapping Evidence for the Previously Postulated Secondary Carbon-Centered Cyclohexyl Radical. *J. Org. Chem.* **2000**, *65*, 1578−1582.
(25) O'Neill, P. M.; Bishop, L. P.; Searle, N. L.; Maggs, J. L.; Ward, S. A.; Bray, P. G.; Storr, R. C.; Park, B. K. The Biomimetic Iron-Mediated Degradation of Arteflene (Ro-42-1611), an Endoperoxide Antimalarial: Implications for the Mechanism of Antimalarial Activity. *Tetrahedron Lett.* **1997**, *38*, 4263−4266.
(26) (a) Bloodworth, A. J.; Shah, A. Iron(II)-Mediated Rearrangement of 1,2,4-Trioxanes into 1,2-Diol Monoesters via l,5-Hydrogen Transfer. *Tetrahedron Lett.* **1995**, *36*, 7551−7554. (b) Bloodworth, A. J.; Hagen, T.; Johnson, K. A.; LeNoir, I.; Moussy, C. Versatility of the Cyclo-oxymercuriation Route to 1,2,4-Trioxanes. *Tetrahedron Lett.* **1997**, *38*, 635−638. In certain cases, reactions of 1,2,4-trioxanes with iron(II) can lead to 1,5-hydrogen atom transfer with the concomitant formation of ketyl radicals which lose iron(II) to form stable carbonyl reaction products devoid of antimalarial activity. Such 1,2,4-trioxanes have weak antimalarial activities.
(27) (a) Haq, A.; Kerr, B.; McCullough, K. J. A Rapid Route to Medium to Large Ring Lactones via the Thermoloysis of Dispiro-1,2,4-trioxane Derivatives. *J. Chem. Soc., Chem. Commun.* **1993**, 1076−1078. (b) Kerr, B.; McCullough, K. J. Dispiro-1,2,4-trioxanes as Precursors of Medium Ring Lactones: Thermolysis of Indan-2-spiro-3′-(1′,2′,4′-trioxane)-6′-spiro-1″-cyclohexane. *J. Chem. Soc., Chem. Commun.* **1985**, 590−592.
(28) McCullough, K. J.; Nojima, M. Recent Advances in the Chemistry of Cyclic Peroxides. *Curr. Org. Chem.* **2001**, *5*, 601−636.
(29) Sekiguchi, A.; Ando, W. Direct Synthesis of Terminal Olefins from Ketones. Application of (Chloromethyl)trimethylsilane to a Wittig Reaction. *J. Org. Chem.* **1979**, *44*, 413−415.
(30) Hughes, L.; Ingold, K. U.; Walton, J. C. Cycloalkylmethyl Radicals. 6. The Unexpectedly High Barrier to the Rotation of Axial CH_2• Groups in Cyclohexylmethyl Radicals. *J. Am. Chem. Soc*. **1988**, *110*, 7494−7499.
(31) Barrett, A. G. M.; Betts, M. J.; Fenwick, A. Acyl and Sulfonyl Isocyanates in β-Lactam Synthesis. *J. Org. Chem.* **1985**, *50*, 169−175.
(32) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. A New Method for the Synthesis of Bishydroperoxides Based on a Reaction of Ketals with Hydrogen Peroxide Catalyzed by Boron Trifluoride Complexes. *Tetrahedron Lett.* **2003**, *44*, 7359−7363.
(33) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. Iodine as a Catalyst for Efficient Conversion of Ketones to *gem*-Dihydroperoxides by Aqueous Hydrogen Peroxide. *Org. Lett.* **2006**, *8*, 2491−2494.
(34) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. Synthesis and Antimalarial Activity of Novel Medium-Sized 1,2,4,5-Tetraoxacycloalkanes. *J. Med. Chem.* **2001**, *44*, 2357−2361.
(35) Griesbaum, K.; Kim, W.-S.; Nakamura, N.; Mori, M.; Nojima, M.; Kusabayashi, S. Ozonolysis of Vinyl Ethers in Solution and on Polyethylene. *J. Org. Chem.* **1990**, *55*, 6153−6161.

JM0707673