Dispiro-1,2,4-trioxane Analogues of a Prototype Dispiro-1,2,4-trioxolane: Mechanistic Comparators for Artemisinin in the Context of Reaction Pathways with Iron(II)

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Dispiro-1,2,4-trioxane Analogues of a Prototype
Dispiro-1,2,4-trioxolane: Mechanistic Comparators for Artemisinin in the Context of Reaction Pathways with Iron(II)

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Introduction

Artemisinin and Iron(II). The discovery of artemisinin (1, qinghaosu) and its semisynthetic derivatives provided a new class of antimalarial drugs. As summarized by Klayman, early work demonstrated that the pharmacophoric peroxide bond in the 1,2,4-trioxane heterocycle of 1 is essential for activity. Considerable evidence suggests that the peroxide bond in 1 undergoes reductive activation by heme released by parasite hemoglobin digestion. This irreversible redox reaction produces carbon-centered free radicals or carbocations that may convey the parasiticidal effects and unique antimalarial specificity of the artemisinins by alkylation of heme or proteins, including the putative target SERCA PfATP6.

The two major pathways (Scheme 1) for reductive cleavage of 1 are initiated by delivery of an electron from ferrous bromide and 4-oxo-TEMPO. Our results suggest a small preference for attack of Fe(II) on the nonketal peroxide oxygen atom of 1. For 4, but not for 5 and 6, there was a strong preference for attack of Fe(II) on the less hindered peroxide bond oxygen atom. The steric hindrance afforded by a spiroadamantane in a five-membered trioxolane is evidently much greater than that for a corresponding six-membered trioxane. Unlike 1, 5–7 fragment by entropically favored β-scission pathways forming relatively stable α-oxa carbon-centered radicals. These data suggest that formation of either primary or secondary carbon-centered radicals is a necessary but insufficient criterion for antimalarial activity of 1 and synthetic peroxides.

Single electron reduction of the 1,2,4-trioxane heterocycle of artemisinin (1) forms primary and secondary carbon-centered radicals. The complex structure of 1 does not lend itself to a satisfactory dissection of the electronic and steric effects that influence the formation and subsequent reaction of these carbon-centered free radicals. To help demarcate these effects, we characterized the reactions of achiral dispiro-1,2,4-trioxolane 4 and dispiro-1,2,4-trioxanes 5–7 with ferrous bromide and 4-oxo-TEMPO. Our results suggest a small preference for attack of Fe(II) on the nonketal peroxide oxygen atom of 1. For 4, but not for 5 and 6, there was a strong preference for attack of Fe(II) on the less hindered peroxide bond oxygen atom. The steric hindrance afforded by a spiroadamantane in a five-membered trioxolane is evidently much greater than that for a corresponding six-membered trioxane. Unlike 1, 5–7 fragment by entropically favored β-scission pathways forming relatively stable α-oxa carbon-centered radicals. These data suggest that formation of either primary or secondary carbon-centered radicals is a necessary but insufficient criterion for antimalarial activity of 1 and synthetic peroxides.

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Fe(II) to the antibonding σ* orbital of the peroxide bond to form a pair of oxy radicals. The first involves the attack of Fe(II) on O1 of the peroxide bond, producing an O2 free radical. This oxygen free radical is short-lived and rearranges via β-scission to a C4-centered primary radical thermodynamically facilitated by concomitant formation of an ester functionality; apparently, no methyl radical is produced by the alternate β-scission pathway. In the second, initial attack of Fe(II) on O2 of the peroxide linkage results in formation of an O1 free radical. Rather than fragment by any of the three possible β-scission pathways a–c, the O1 free radical undergoes a 1,5 H-shift, giving rise to a C4-centered secondary radical. Both artemisinin-derived C4-centered radicals are irreversibly formed kinetic intermediates that self-quench in intramolecular reactions to produce 2 and 3, both of which are devoid of antimalarial activity. In summary, available evidence suggests that electron transfer leading to formation of carbon-centered radicals may constitute the required activation step of the artemisinins and other peroxidic antimalarials.

Whether the primary or secondary carbon-centered radicals or a combination of the two contribute to the antimalarial activity of 1 has been a subject of debate. The difficulty lies in the fact that both carbon-centered radicals can be observed in iron(II) models, largely depending on the particular reaction conditions, including solvents and counterions as discussed in detail by Wu et al. The complex structure of 1 does not lend itself to satisfactory dissection of the electronic and steric effects that influence the formation and subsequent reaction of these carbon-centered free radicals. On the basis of the achiral prototype dispiro-1,2,4-trioxolane 4, we envisioned that achiral dispiro-1,2,4-trioxanes 5–7 could provide tools to help demarcate these effects.

Results and Discussion

Trioxane Synthesis. Preparation of target trioxanes 5–7 (Scheme 2) required precursor β-hydroperoxy alcohols 10 and 11. Although β-hydroperoxy alcohols have been prepared by treatment of epoxides with anhydrous H2O2 with or without an acid catalyst, we elected to use the commercially available 50% aqueous H2O2 as a safer alternative. Hydroperoxidation of spiro epoxide 815 with 50% aqueous H2O2 (10 equiv) pretreated with anhydrous MgSO4 (ca. 1 g of anhydrous MgSO4 per 1 mL of 50% H2O2 in 15 mL of ether) and molybdenyl acetylaceonate (5%)16 as catalyst afforded 1012 in modest yield.


SCHEME 1

SCHEME 2. Synthesis of 5–7


Use of alternative solvents and catalysts such as THF and sulfuric acid, respectively, led to decreased ratios of 10 and diol 12\textsuperscript{19} and lower reaction yields. Under nearly identical conditions, hydperoxidation of spiro epoxide 9\textsuperscript{18} afforded 11 in low yield accompanied by nearly equal quantities of diol 13.\textsuperscript{19} Little or no conversion of 9 to 11 took place using other solvents (ether, acetonitrile, 2-propanol) or catalysts.

In the presence of catalytic p-toluenesulfonic acid (PTSA), target trioxanes 5 and 7\textsuperscript{20,21} were readily formed by reaction of 10 with 2adamantanone and cyclohexanone, respectively. Similarly, reaction of 11 with cyclohexanone in the presence of catalytic camphorsulfonic acid (CSA) afforded target trioxane 6. Trioxane 5 was also obtained (77% yield) using the triethylsilylperoxy derivative of 10, although the latter was obtained in yields of less than 30% from 1-cyclohexene-1-methanol using the method of O’Neill et al.\textsuperscript{21} (data not shown).

**Antimalarial Activity.** The antimalarial properties of 5–7 compared to that of 1 and 4 were measured against *P. falciparum* in vitro and *P. berghei* in vivo.\textsuperscript{22} The results were unexpected in that 5 and 7 with IC\textsubscript{50}'s of 49 and 120 ng/mL were an order of magnitude less active than 30% from 1-cyclohexene-1-methanol using the method of O’Neill et al.\textsuperscript{21} (data not shown).

**Reactions with Iron(II).** Next, we turned our attention to investigating the reaction pathways of 4–7 with FeBr\textsubscript{2} (1 equiv) in THF\textsuperscript{20} not only to shed further light on the mechanism of action of 1 but also to understand the striking loss of antimalarial activity of 5 and 6 compared to that of 1 and 4.

Reaction of 4 with iron(II) produced lactone 14, bromoacid 15 and unsaturated acid 16\textsuperscript{23} in a combined isolated yield of 72% along with a 3% yield of 6-bromo-hexanoic acid 17\textsuperscript{24} (Scheme 3). This result was confirmed by the 22:1 ratio of cyclohexanone and 2-adamantanone trapped as their oxide ethers\textsuperscript{25} by post-reaction treatment with O-benzylhydroxylamine and pyridine and quantitated by ¹H NMR.\textsuperscript{26} The 22–24:1 ratio of reaction products resulting from ⁴-sciision of the spiroadamantane and spirocyclohexanone, respectively, indicates regioselective formation of the oxy radical resulting from preferential attack of Fe(II) on the less hindered peroxide bond oxygen atom (O¹) of 4. Similar regioselective iron-mediated decompositions of other unsymmetrical trioxolanes due to steric hindrance were noted by Abe et al.\textsuperscript{27}

Reaction of 5 with iron(II) produced bromoeister carbinols 18 and 19, unsaturated ester carbinol 20, 2-adamantanone, cyclohexanone, and formaldehyde (Scheme 4). A 2:1 ratio of the O¹-O₂ pathways was evident in the 2:1:1:0.43 ratio of (18 + 20)/2-adamantanone/cyclohexanone/formaldehyde, the latter three of which were quantitated\textsuperscript{26} as their O-benzyl oximes.\textsuperscript{25,28} The less than theoretical quantity of formaldehyde observed was probably due to the loss of formaldehyde during the reaction and of its O-benzyl oxime during the reaction workup.\textsuperscript{29} Bromoester carbinol 18 was initially formed as a 2:1 mixture of two isomers that isomerized both in the crude reaction mixture and in CDCl\textsubscript{3} solution to form a mixture of four isomers. These four 3,7-disubstituted bicyclo[3.3.1]nonane isomers could be purified to 80–95% by RP-HPLC, but their exo/endo stereochemistry was not


\textsuperscript{22} In vitro activity was measured against the chloroquine-sensitive NF54 (airport, unknown origin) and chloroquine-resistant K1 (Thai-land) strains of *Plasmodium falciparum*. The IC\textsubscript{50}'s are average values (n = 2 to 3) against the NF54 and K1 strains in vivo activity was measured against *P. berghei* as previously described (ref 11). Against the K1 strain, O’Neill et al. (ref 21) report an IC\textsubscript{50} of 33 ng/mL for 7; our measured IC\textsubscript{50} of 130 ng/mL for 7 was 4-fold higher.


\textsuperscript{24} McGrady, J.; Laughlin, R. G. Synthesis 1984, 426–428.


\textsuperscript{26} Because of the volatility of 2-adamantanone, cyclohexanone, and formaldehyde, their less volatile O-benzyl oximes (refs 25 and 28) were independently prepared to identify diagnostic ¹H NMR signals appropriate for quantitation: δ 5.57 (s), 2.20 (t), and 7.08 (d), respectively.


\textsuperscript{29} For 5–7, we also observed small quantities of benzaldehyde O-benzyl oxime (δ 8.14) (ref 25) that may have arisen from Fe(III) oxidation of O-benzylhydroxylamine to form benzaldehyde that subsequently reacted with O-benzylhydroxylamine.
defined\textsuperscript{30} because of difficulty in calculating coupling constants, although exo 7-bromo and 3-ester substituents in one (18d) of the isomers were deduced by a strong correlation between H-3 (2.82–2.91 ppm) and H-7 (4.68–4.76 ppm) in the NOESY spectrum. The only way we could account for the formation of bromoester carbinol 19 (vide infra; Scheme 6) was via iron(II) decomposition of trioxane 7 formed from cyclohexanone and \( \beta \)-hydroperoxy alcohol 10 liberated during the course of the reaction of 5 with iron(II). An analogous Lewis acid catalyzed heterolytic fragmentation of the 1,2,4-trioxane ring of artemisinin has been previously proposed.\textsuperscript{31}

This 2:1 proportion of reaction products indicates a modest preference for attack of Fe(II) on the less hindered peroxide bond oxygen atom (O\( ^{1} \)) of 5. Interestingly, attack of Fe(II) on the more hindered peroxide bond oxygen atom (O\( ^{2} \)) generates an Fe(III)-complexed oxy radical that can undergo two \( \beta \)-scission pathways, only one of which is observed. In this pathway, an \( \alpha \)-oxa primary carbon-centered radical and cyclohexanone are initially formed, and the former then unravels to 2-adamantanone and formaldehyde. We observed no \( \alpha \)-hydroxy ketone reaction product that would have arisen from the \( \beta \)-scission pathway to form the primary carbon-centered radical.

Reaction of 6 with iron(II) produced bromoester carbinol 21, 2-adamantanone, cyclohexanone, and formaldehyde (Scheme 5). A 1:3 ratio of the O\( ^{1}:O\( ^{2} \) pathways was evident in the 1:3.1:3.3:1.5 ratio of 21/2-adamantanone/cyclohexanone/formaldehyde, the latter three of which were quantitated\textsuperscript{25,28} as their \( O \)-benzyl oximes.\textsuperscript{25,28} As was the case for 5, the less than theoretical quantity of formaldehyde observed was probably due to the loss of formaldehyde during the reaction and of its \( O \)-benzyl oxime during the reaction workup. This 1:3 proportion of reaction products indicates a modest preference for attack of Fe(II) on the less hindered peroxide bond oxygen atom (O\( ^{2} \)) of 6. Attack of Fe(II) on O\( ^{2} \) generates an Fe(III) complexed oxy radical that can undergo two \( \beta \)-scission pathways, only one of which is observed. In this pathway, 2-adamantanone and an \( \alpha \)-oxa primary carbon-centered radical are initially formed, and the latter then unravels.
to cyclohexanone and formaldehyde. Similar to 5, we observed no \( \alpha \)-hydroxy ketone reaction product that would have arisen from the \( \beta \)-scission pathway to form the secondary carbon-centered radical.

For 4–6, confirmation of the proposed carbon-centered free radical intermediates was provided by spin-trapping experiments with the nitroxide free radical, 4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxy (4-oxo-TEMPO). Treatment of 4 with 1.5 equiv each of FeBr\(_2\) and 4-oxo-TEMPO in THF did form the expected aminoxy acid 22 in 7% yield, but the major product was 14 (70%) accompanied by 15 (8%), 16 (3%), and 17 (6%). However, using conditions (1.5 equiv of Fe(OAc)\(_2\) and 2 equiv of 4-oxo-TEMPO in 1:1 CH\(_2\)Cl\(_2\)/CH\(_3\)CN) that we had used earlier in a similar experiment\(^{11}\) with a trioxolane ketone, we were produced in 56% yield along with 14 (28%) and 16 (6%). For 5 and 6, reactions were conducted with 2.5 equiv each of FeBr\(_2\) and 4-oxo-TEMPO in THF. Trioxane 5 formed aminoxy ester alcohol 23 (57%), 2-adamantanone (3%), and unsaturated ester carbinol 24 (4%). Trioxane 6 formed aminoxy ester alcohol 24 (22%) and 2-adamantanone (39%). Aminoxy reaction products 22–24 correspond to the proposed carbon-centered free radical intermediates invoked to account for the observed reaction products in Schemes 3–5. However, this does not necessarily imply that bromoacids 15 and 17, bromoester carbinols 18, 19 (Scheme 6; vide infra), and 21, the unsaturated acid 16 and ester carbinol 20 were formed exclusively by carbon-centered radical pathways. For example, an alternative mechanism to account for the formation of 15–21 is intra- or intermolecular electron transfer between Fe(III) and the carbon-centered radicals to simultaneously regenerate Fe(II) and produce the corresponding carbenions,\(^{20,b}\) the latter of which could react with bromide or undergo elimination.

Reaction of 7 with iron(II) produced bromoester carbinol 19, cyclohexanone, and formaldehyde (Scheme 6). A 1:1.4 ratio of 19:cyclohexanone was observed; the latter was quantitated\(^{26}\) as its \( O \)-benzyl oxime.\(^{25}\) Since the \( O \)\(^2\) pathway produces 2 equiv of cyclohexanone, this result indicates a 3:2 ratio of the \( O^1:O^2 \) pathways. Since steric effects do not play a role in reaction of 7 with iron(II), this proportion of reaction products indicates a small preference for attack of Fe(II) on the nonketal peroxide oxygen atom \( (O^1) \) of the peroxide bond. In this pathway, subsequent \( \beta \)-scission simultaneously forms a primary carbon-centered radical and ester. Attack of Fe(II) on \( O^2 \) generates an Fe(III) complexed oxy radical that can undergo two \( \beta \)-scission pathways, only one of which is observed. In this pathway, cyclohexanone and an \( \alpha \)-oxa primary carbon-centered radical are initially formed, and the latter then unravels to formaldehyde and a second molecule of cyclohexanone. As was observed for 5 and 6, such entropically favored \( O^2 \) \( \beta \)-scission reaction pathways that form relatively stable\(^{32}\) \( \alpha \)-oxa primary carbon-centered radicals are apparently much too rapid to observe the competing \( \beta \)-scission pathways\(^{33}\) leading to the unobserved \( \alpha \)-hydroxy ketone reaction products. Similar \( \alpha \)-oxa carbon-centered radicals may be invoked to account for the carbonyl end products produced from single-electron reductions of other synthetic trioxanes.\(^{34}\)

**Discussion.** We suggest that the observed reaction product distributions in the reactions of 4–7 with Fe(II)

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\[ \text{SCHEME 6} \]
are determined by regioselective formation of one of two possible oxy radicals generated by delivery of an electron from Fe(II) to the peroxide bond antibonding \( \sigma^* \) orbitals\(^{27} \) rather than the relative stability of the two oxy radical species per se. As is observed for \( 1^{2b} \), the ensuing conversions of the oxy radicals to the more stable\(^{28} \) carbon-centered radical intermediates by \( \beta \)-scission pathways\(^{35} \) are irreversible and strongly exothermic. For \( 5-7 \), the observed reaction products also confirm\(^{12,20} \) that ring-opening \( \beta \)-scissions arising from oxy radicals at ketal (O\(^2\)) positions occur much faster than competing ring-opening \( \beta \)-scissions arising from oxy radicals at nonketal (O\(^1\)) positions.

In consideration of the small preference for attack of Fe(II) on the nonketal peroxide oxygen atom (O\(^1\)) of the peroxide bond in \( 7 \), we observed a less than expected 2:1 preference for attack of Fe(II) on the nonketal and sterically less-hindered oxygen atom (O\(^1\)) of the peroxide bond in \( 5 \) keeping in mind the 3:1 preference for attack of Fe(II) on the ketal and sterically less-hindered oxygen atom (O\(^2\)) of the peroxide bond in \( 6 \). For \( 4 \) on the other hand, there is a strong preference for attack of Fe(II) on the less hindered peroxide bond oxygen atom (O\(^1\)). Since there is little difference in the electronic character of the peroxide oxygen atoms in \( 4 \), apparently steric hindrance to attack of Fe(II) on the more hindered peroxide bond oxygen atom (O\(^2\)) determines the observed regioselectivity. In the subsequent reaction pathways, both \( \beta \)-scission pathways are equally facilitated by concomitant ester formation. The regioselectivity of attack of Fe(II) on the peroxide bond afforded by the spiro adamantane in the five-membered 1,2,4-trioxolane \( 4 \) is evidently much greater than that for the six-membered 1,2,4-trioxanes \( 5 \) and \( 6 \). This is illustrated by the greater steric crowding on the adamantane side of the peroxide bond antibonding \( \sigma^* \) orbital in \( 4 \) vs \( 5 \) and \( 6 \) (Figure 1).

Although conformers of \( 4-6^{36} \) with the axial peroxide are more stable (\( \Delta E = E_{eq} - E_{ax} \) = 0.280, 1.45, and 0.145 kcal/mol for \( 4 \), \( 5 \), and \( 6 \)), conformers with the equatorial peroxide (depicted in Figure 1) provide less steric hindrance to the peroxide antibonding \( \sigma^* \) orbital. As viewed down the axis of the O–O bond of \( 4 \), the \( \sigma^* \) (LUMO) is not visible to the incoming Fe(II) from the adamantane side but is clearly visible and presumably readily accessible to the incoming Fe(II) from the cyclohexane side. For \( 5 \) and \( 6 \), the LUMO is not as accessible from either direction as it is from the cyclohexane side of \( 4 \). The reduced accessibility of the LUMO in \( 5 \) and \( 6 \) is due to the additional methylene group of the trioxane heterocycle increasing the steric hindrance of the peroxide bond by both ring systems. This increased steric effect is manifested by a decrease in the angle between the adamantane and cyclohexane rings as measured through the axis of the peroxide bond. By defining planes of the spiro and vicinal carbon atoms, the angle between the

![FIGURE 1. LUMO (blue) mapped on isodensity surfaces of 4, 5, and 6 viewed down the axis of the equatorial peroxide bond from the adamantane (a) and cyclohexane (b) sides.](image)

planes of the adamantane and cyclohexane rings can be calculated; for \( 4 \) it is 214°, whereas for \( 5 \) and \( 6 \) it is 167°.

The less exposed and presumably more biologically stable peroxide bonds in \( 5 \) and \( 6 \) vs \( 1 \) and \( 4 \) (Figures 1 and 2) may explain why the two trioxanes are so much less active than \( 1 \) or their trioxolane chemical cousin \( 4 \), although the release of ring strain with peroxide bond cleavage in the six-membered 1,2,4-trioxolane \( 1 \) is less than that for the five-membered 1,2,4-trioxolane \( 4 \). Another contributing factor could be that \( 5 \) and \( 6 \), unlike \( 1 \) and \( 4 \), undergo reaction pathways to form relatively stable \( \alpha \)-oxa primary carbon-centered radicals that unravel to carbonyl-containing end products. The latter, unlike carbon-centered radicals, presumably contribute little to their antimalarial properties. In this regard, it is notable that \( 6 \), the trioxane completely devoid of antimalarial activity, also produced the largest proportion of carbonyl-containing end products and the lowest proportion of carbon-centered radicals. Consistent with this, \( 1 \) does not undergo \( \beta \)-scission pathway c (Scheme 1) that would form the stabilized \( \alpha \)-dioxa (methylene dioxy) carbon-centered radical, as evidenced by the absence of the expected diketo acid end product \( 25 \) (Scheme 7). A complementary example is provided by synthetic trioxane \( 26^{37} \) that undergoes exclusive \( \beta \)-scission to form an \( \alpha \)-oxa primary
carbon-centered radical; as predicted, this trioxane is inactive. The foregoing, however, does not provide a satisfactory explanation for the 4-fold greater potency of deoxoartemisinin (27) vs that of 1,38 as the major iron(II) reaction product of the former is diketo formate ester 2839 produced by a putative β-scission pathway92b that we suggest proceeds by way of an α-dioxo (methylene dioxy) carbon-centered radical.40 Derivatives of 27 seem to fragment by this same pathway to afford carbonyl-containing end products.41

Although this study did not provide definitive answers to whether the primary or secondary carbon-centered radicals or a combination of the two contribute to the antimalarial activity of 1, the results did suggest a small preference for attack of Fe(II) on the nonketo peroxide oxygen atom (O1) of 1.42 In addition, the iron(II) fragmentation of 4 clearly demonstrates that a peroxide need not fragment to form a primary carbon-centered radical to be active. Nevertheless, 1 alkylates free heme3 or hemoglobin heme43 by way of the primary carbon-centered radical (O1 pathay), possibly the only malaria-parasite relevant fully characterized alkylation reactions so far reported for 1.

**Experimental Section**

Adamantane-2-spiro-3′,1′,2′,4′-trioxaspiro[5.5]undecane (5). p-Toluenesulfonic acid monohydrate (40 mg, 0.2 mmol) was added to a mixture of 1040 (280 mg, 1.9 mmol), 2-adamantanone (450 mg, 3 mmol), CH$_2$Cl$_2$ (10 mL) and 1,2-dichloroethane (10 mL). The reaction mixture was stirred at room temperature overnight, washed with saturated NaHCO$_3$ (15 mL), water (15 mL) and brine (15 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (sg, 2–4% ether in hexane) to afford 5 as a colorless solid (760 mg, 76%). Mp 85–87 °C (80% aqueous ethanol); 1H NMR in 48 °C (ethanol/H$_2$O 2:1); 13C NMR δ 21.4, 25.9, 27.1, 27.2, 28.5, 30.2, 32.3, 33.3, 33.9, 34.2, 36.2, 37.2, 65.3, 77.3, 104.2. Anal. Calcd for C$_{17}$H$_{26}$O$_3$: C, 73.34; H, 9.41. Found: C, 73.50; H, 9.21.

Adamantane-2-spiro-3′,1′,2′,5′-trioxaspiro[5.5]undecane (6). 10-Camphorsulfonic acid (80 mg, 0.35 mmol) was added to a mixture of 11 (680 mg, 3.5 mmol), cyclohexanone (686 mg, 7.0 mmol) and CH$_2$Cl$_2$ (30 mL). The reaction mixture was stirred at room temperature overnight, washed with saturated NaHCO$_3$ (30 mL), water (30 mL) and brine (30 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was crystallized from 80% aqueous ethanol to afford 6 as a colorless solid (740 mg, 76%). Mp 85–87 °C (80% aqueous ethanol); 1H NMR δ 1.40–2.36 (m, 23H), 2.73 (brs, 1H), 3.71 (brs, 1H), 4.05 (brs, 1H), 13C NMR δ 2.24, 25.6, 27.4, 28.5, 30.2, 32.3, 33.3, 33.9, 34.2, 36.2, 37.2, 65.3, 77.3, 104.2. Anal. Calcd for C$_{17}$H$_{26}$O$_3$: C, 73.34; H, 9.41. Found: C, 73.50; H, 9.21.

7-(4-Oxo-2,2,6,6-tetramethyl-1-piperidinyloxy)bicyclo-[3.3.1]nonane-3-carboxylic acid (22). To a solution of 4 (264 mg, 1.0 mmol), 4-oxo-TEMPO (340 mg, 2.0 mmol) in CH$_2$Cl$_2$ (10 mL) and CH$_3$CN (10 mL) was added Fe(OAc)$_2$ (261 mg, 1.5 mmol). The resulting mixture was stirred under N$_2$ and 35 °C 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$_2$Cl$_2$ (2 × 20 mL). The combined extracts were washed with brine (2 × 30 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (sg,
(1-Hydroxycyclohexyl)methyl 7-(4-Oxo-2,2,6,6-tetramethyl-1-piperidinyloxy)-bicyclo[3.3.1]nonane-3-carboxylate (23). A mixture of 5 (240 mg, 0.86 mmol), FeBr2 (370 mg, 1.72 mmol), 4-oxo-TEMPO (294 mg, 1.72 mmol) and THF (10 mL) was stirred at ambient temperature under a N2 atmosphere for 16 h and concentrated. The crude product was dissolved in EtOAc, washed with water and brine, dried over MgSO4, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (sg, 10–50% EtOAc in hexane) to give 2-adamantanone (50 mg, 39%) and 24 (85 mg, 22%) as a colorless oil. 1H NMR δ 1.15 (s, 6H), 1.10–1.18 (m, 1H), 1.28 (s, 6H), 1.40–1.46 (m, 2H), 1.52–1.68 (m, 16H), 2.05 (brs, 1H, OH), 2.39 (t, J = 7.4 Hz, 2H), 2.50 (d, J = 12.7 Hz, 2H), 3.82 (t, J = 6.4 Hz, 2H), 4.29 (s, 2H); 13C NMR δ 21.5, 25.1, 26.0, 27.0, 27.4, 28.3, 32.4, 32.5, 34.2, 34.4, 34.6, 38.0, 53.5, 62.9, 68.9, 74.0, 76.7, 173.8, 208.3. HRMS-FAB for C26H44NO5 [M + H]+: calcd 450.3219, found 450.3221.

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Supporting Information Available: Alternate synthesis of 5 and synthesis and characterization data for 7–21, O-benzyl oxime synthesis and quantitation, antimalarial assays, computational chemistry methods, 13C NMR spectra for compounds 18a–d and 19–24, and total energies and atomic coordinates to support the M.M. and M.O. calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050385+

10–90% EtOAc in hexane) to give 2-adamantanone (8 mg, 5%), 14 (46 mg, 28%), 16 (10 mg, 6%), and 22 (190 mg, 56%) as a colorless solid. For 22: mp 179–180 °C (ether/hexane 1:3); 1H NMR δ 1.14 (s, 6H), 1.14–1.18 (m, 1H), 1.24–1.35 (m, 3H), 1.30 (s, 6H), 1.50–1.61 (m, 3H), 2.08–2.30 (m, 7H), 2.48–2.62 (m, 3H), 4.04–4.13 (m, 1H); 13C NMR δ 22.7, 26.0, 28.7, 29.2, 33.8, 35.4, 39.5, 53.5, 62.8, 76.1, 181.7, 208.6. HRMS-FAB for C19H31NO4 [M + H]+: calcd 338.2253, found 338.2321.

(2-Hydroxy-2-adamantyl)methyl 6-(4-Oxo-2,2,6,6-tetramethyl-1-piperidinyloxy)hexanoate (24). A mixture of 6 (240 mg, 0.86 mmol), FeBr2 (370 mg, 1.72 mmol), 4-oxo-TEMPO (294 mg, 1.72 mmol) and THF (10 mL) was stirred at ambient temperature under a N2 atmosphere for 30 h and concentrated. The crude product was dissolved in EtOAc, washed with water and brine, dried over MgSO4, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (sg, 10–50% EtOAc in hexane) to give 2-adamantanone (50 mg, 39%) and 24 (85 mg, 22%) as a colorless oil. 1H NMR δ 1.15 (s, 6H), 1.10–1.18 (m, 1H), 1.28 (s, 6H), 1.40–1.46 (m, 2H), 1.52–1.68 (m, 16H), 2.05 (brs, 1H, OH), 2.39 (t, J = 7.4 Hz, 2H), 2.50 (d, J = 12.7 Hz, 2H), 3.82 (t, J = 6.4 Hz, 2H), 4.29 (s, 2H); 13C NMR δ 21.5, 22.6, 25.6, 25.9, 28.4, 29.4, 33.9, 34.3, 35.6, 39.5, 53.5, 62.6, 70.5, 71.3, 76.1, 176.5, 208.6. HRMS-FAB for C26H44NO5 [M + H]+: calcd 450.3219, found 450.3221.