Journal of Medicinal Chemistry
Article

J. Med. Chem. **2010,** *53,* 4223–4233 **4223**
DOI: 10.1021/jm100226t

Structure−Activity Relationship of an Ozonide Carboxylic Acid (OZ78) against *Fasciola hepatica*

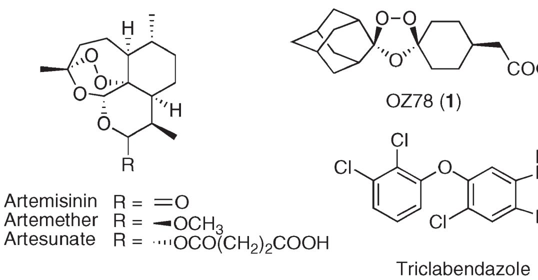
Qingjie Zhao,[†] Mireille Vargas,[‡,§] Yuxiang Dong,[†] Lin Zhou,[†] Xiaofang Wang,[†] Kamaraj Sriraghavan,[†] Jennifer Keiser,[‡,§] and Jonathan L. Vennerstrom*[,†]

[†]*College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, Nebraska,* [‡]*Swiss Tropical and Public Health Institute, Socinstrasse 57, CH-4002 Basel, Switzerland, and* [§]*University of Basel, Petersplatz 1, CH-4003 Basel, Switzerland*

Received February 20, 2010

In this paper, we describe the SAR of ozonide carboxylic acid OZ78 (**1**) as the first part of our search for a trematocidal synthetic peroxide drug development candidate. We found that relatively small structural changes to **1** resulted most commonly in loss of activity against *Fasciola hepatica* in vivo. A spiroadamantane substructure and acidic functional group (or ester prodrug) were required for activity. Of 26 new compounds administered at single 100 mg/kg oral doses to *F. hepatica* infected rats, 8 had statistically significant worm burden reductions, 7 were partially curative, and 1 (acylsulfonamide **6**) was completely curative and comparable to **1** in flukicidal efficacy. This study also showed that the activity of **1** is peroxide-bond-dependent, suggesting that its flukicidal efficacy depends upon hemoglobin digestion in *F. hepatica*.

Some 250 million people are infected with parasitic trematode worms. Of these, the most widespread are blood flukes of the genus *Schistosoma*.[1] However, the liver flukes *Fasciola hepatica* and *F. gigantica* are also important pathogenic trematodes infecting an estimated 2.4−17 million people.[2] Fascioliasis is of considerable public health and great veterinary significance and occurs worldwide, with the highest number of infected people in the Andean countries, Cuba, Western Europe, Egypt, and Iran.[2,3] Triclabendazole, which has been routinely used since the early 1980s in veterinary medicine, is currently the sole drug used to treat human fascioliasis and is registered in only four countries.[4] Evidence of drug resistance to triclabendazole in veterinary medicine[5] provides an impetus for the discovery and development of new drugs against fascioliasis. In this respect, data from a recent clinical trial in Vietnam[6] demonstrated that artesunate, a semisynthetic artemisinin derivative, had good efficacy in the treatment of human fascioliasis, although it was less effective than triclabendazole.



Although the semisynthetic artemisinins are best known for their powerful antimalarial properties, it is not surprising that they, as well as other peroxidic compounds, possess both antiplasmodial and trematocidal[7−9] activities, since both plasmodia and several trematodes including *Fasciola* spp. degrade hemoglobin to generate free heme, a possible target[10] for bioactive peroxides. That the artemisinins and ozonide OZ78 (**1**) are so much less effective against the nonhemoglobin-degrading intestinal fluke *Echinostoma caproni* than against hemoglobin-degrading flukes *F. hepatica*, *Clonorchis sinensis*, and various schistosome species[9,11−13] supports this hypothesis.[14] Thus, the artemisinins and synthetic peroxides offer excellent starting points[15,16] for the discovery of broad-spectrum, orally active trematocidal agents that would minimize drug resistance and lead to superior treatment and control options. In this paper, we describe the SAR of ozonide **1** as the first part of our search for a flukicidal synthetic peroxide drug development candidate.

Chemistry

Following the method of Tsandi et al.,[17] acylsulfonamide **6** (Scheme 1) was prepared by reaction of **1** with methanesulfonamide in the presence of DMAP and DCC.[a] Hydrazide **10** was readily prepared by reaction of the corresponding methyl ester **2** with hydrazine. Ozonides **7** and **8**, the glycine and taurine conjugates of **1**, were synthesized by reaction of HOBt active ester **28**[18] with glycine ethyl ester (subsequent ester hydrolysis) and taurine, respectively.

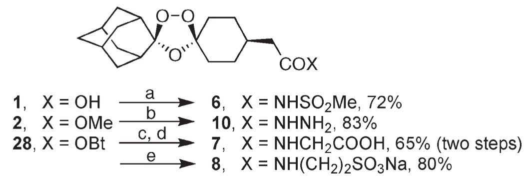
Ozonide dicarboxylic acid **14** was synthesized in a five-step sequence (Scheme 2) starting from **29**,[19] the Knoevenagel condensation product of 1,4-cyclohexanedione monoethylene ketal and isopropylidene malonate (Meldrum's acid).[20]

*To whom correspondence should be addressed. Phone: 402-559-5362. Fax: 402-559-9543. E-mail: jvenners@unmc.edu.

[a] Abbreviations: AS, artesunate; DIPEA, diisopropylethylamine; DMAP, dimethylaminopyridine; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; *p*-TSA, *p*-toluenesulfonic acid; sg, silica gel.

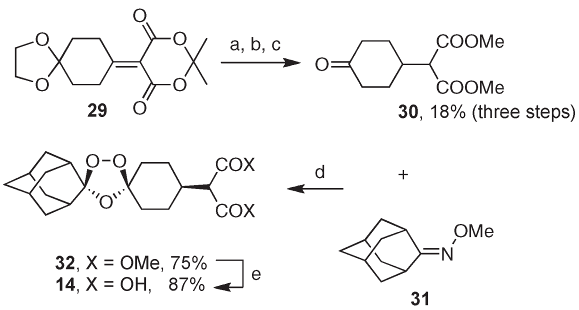
Published on Web 04/27/2010

Scheme 1[a]



[a] Reagents and conditions: (a) $MeSO_2NH_2$, DMAP, DCC, CH_2Cl_2, room temp, 24 h, then 1 M HCl; (b) hydrazine hydrate, MeOH/THF, 60 °C, 24 h; (c) glycine ethyl ester HCl, DIPEA, CH_2Cl_2, room temp, 24 h; (d) aqueous NaOH, EtOH, then 1 M HCl to pH 5; (e) taurine, THF/aqueous NaOH.

Scheme 2[a]

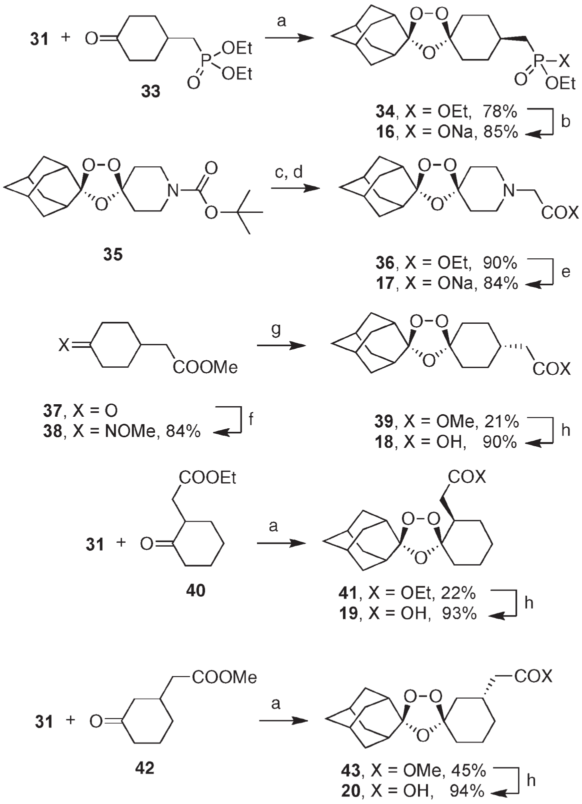


[a] Reagents and conditions: (a) 4 Å molecular sieves, pyridine, room temp, 2 days; (b) H_2, 10% Pd−C, CH_2Cl_2, room temp, 24 h; (c) MeOH/Et_2O, H_2SO_4, reflux, 12 h; (d) O_3, CH_2Cl_2/cyclohexane, 0 °C, solid $NaHCO_3$, 2 h; (e) 1 N KOH/THF, room temp, 12 h, then 1 M HCl.

Reduction (99%), deketalization (27%), and esterification (37%) afforded diester ketone **30** which underwent Griesbaum coozonolysis[21] with oxime ether **31**[22] to afford diester ozonide **32** in 75% yield. The latter was hydrolyzed to afford **14** in high yield.

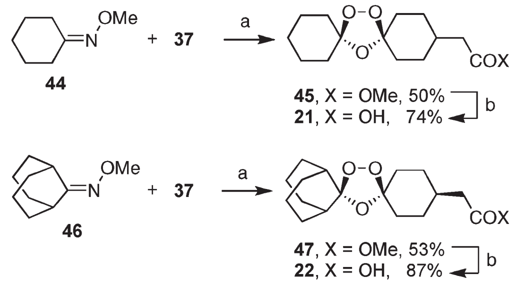
The synthesis of ozonide **16**, the monoethylphosphonic acid isostere of **1**, began with the synthesis of ketophosphonate diester **33** (26% yield) (Scheme 3) from 4-(bromomethyl)-cyclohexanone in an Arbuzov reaction following the method of Yamagishi et al.[23] 4-(Bromomethyl)cyclohexanone, in turn, was obtained by HCl deprotection of the corresponding ethylene ketal[24] in 74% yield. Ozonide diethyl phosphonate **34**, obtained in good yield by Griesbaum coozonolysis[21] between oxime ether **31**[22] and **33**, was treated with potassium trimethylsilanolate[25] to afford **16**. Ozonide piperidine carboxylate **17** was obtained by hydrolysis of its corresponding ester **36** in 84% yield; the latter was obtained by deprotection of BOC ozonide **35**[26] with methanesulfonic acid followed by alkylation with ethyl bromoacetate in 90% overall yield. Ozonide ester **39**, the precursor of ozonide carboxylic acid **18**, the trans isomer of **1**, was obtained in 21% yield by Griesbaum coozonolysis[21] of oxime ether **38** and 2-adamantanone. With this combination of reaction partners, cis (**2**) and trans (**39**) ester ozonides were produced in a ratio of 1:2.5 and **39** was purified by flash column chromatography. In contrast, **2** is the major reaction product in a Griesbaum coozonolysis of oxime ether **31** and keto ester **37**.[27] Ozonide carboxylic acids **19** and **20**, regioisomers of **1**, were both obtained in a straightforward two-step Griesbaum coozonolysis/ester hydrolysis sequence starting from oxime ether **31** and the corresponding keto esters **40** and **42**. Unexpectedly, both **41** and **43** were formed with high diastereoselectivity and were isolated as single isomers. Assuming the peroxide bond is axial and the alkyl ester substituent is equatorial,[18,27−29] we

Scheme 3[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2/cyclohexane, 0 °C; (b) Me_3SiOK, THF, 50 °C, 4 h; (c) MSA, CH_3CN, room temp, 24 h; (d) $BrCH_2COOEt$, aqueous K_2CO_3/THF, room temp, 6 h; (e) aqueous NaOH/EtOH, room temp, 2 h; (f) $MeONH_2 \cdot HCl$, EtOH, pyridine, room temp, 2−6 h; (g) 2-adamantanone, O_3, CH_2Cl_2/cyclohexane, 0 °C; (h) 1 N NaOH, aqueous EtOH, 25−60 °C, 3 h, then 1 M HCl, 0 °C.

Scheme 4[a]



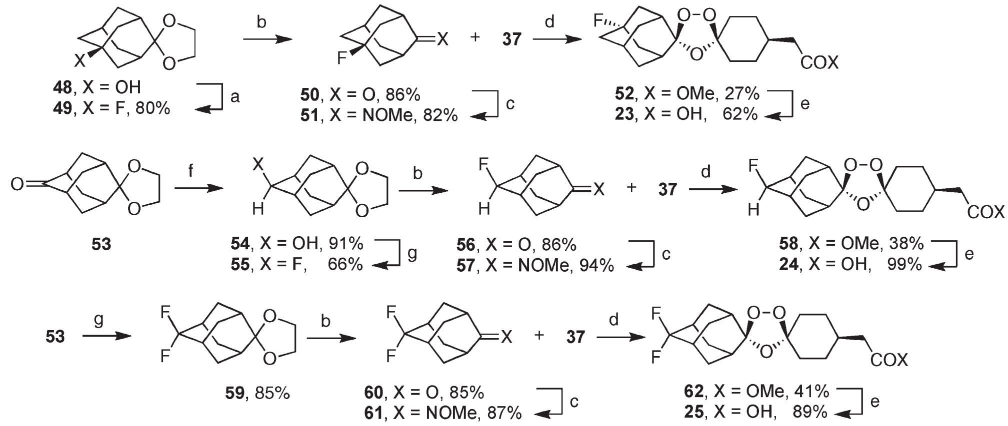
[a] Reagents and conditions: (a) O_3, CH_2Cl_2/cyclohexane, 0 °C; (b) 1 N NaOH, aqueous EtOH, 25−60 °C, 3 h, then 1 M HCl, 0 °C.

assigned structures for **19** and **20** as indicated in Scheme 3, although X-ray crystallographic analysis would be required to substantiate this.

Ozonide acids **21** (2.3:1 mixture of isomers) and **22** (single isomer) (Scheme 4) were obtained by hydrolysis of ozonide esters **45** (4:1 mixture of isomers) and **47** (9:1 mixture of isomers), which in turn were obtained by Greisbaum coozonolysis[21] of keto ester **37**[18] and oxime ethers **44**[30] and **46**,[28] respectively. On the basis of the axial peroxide bonds and equatorial cyclohexyl substituents in ozonide products from similar coozonolysis reactions,[18,27−29] we assigned the structures for **47** and **22** as indicated in Scheme 4.

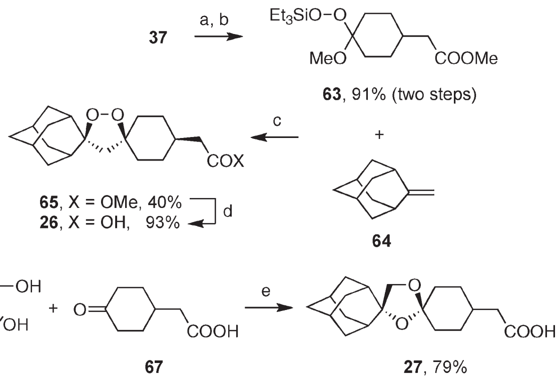
Fluorinated ozonide acids **23**−**25** (Scheme 5) were obtained in parallel five- to six-step sequences for which the key reaction

Scheme 5[a]



[a] Reagents and conditions: (a) bis(2-methoxyethyl)aminosulfur trifluoride, CH_2Cl_2, 0 °C, 1 h; (b) concentrated HCl, aqueous acetone, room temp, 1 h; (c) $MeONH_2 \cdot HCl$, EtOH, pyridine, room temp, 2−6 h; (d) O_3, CH_2Cl_2/cyclohexane, 0 °C; (e) 2-adamantanone, O_3, CH_2Cl_2/cyclohexane, 0 °C; (f) $NaBH_4$, MeOH, 0−10 °C to room temp, 24 h; (g) bis(2-methoxyethyl)aminosulfur trifluoride, CH_2Cl_2, room temp, 24 h.

Scheme 6[a]

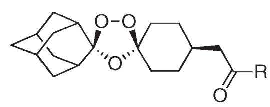


[a] Reagents and conditions: (a) 50% H_2O_2, I_2, MeOH, room temp, 24 h; (b) Et_3SiOTf, Et_3N, DMF, 0 °C to room temp, 24 h; (c) 1 N $SnCl_4$, CH_2Cl_2, −78 to −30 °C, 12 h; (d) 15% aqueous KOH, 60 °C, 20 h; (e) *p*-TSA, CH_2Cl_2, room temp, 4 h.

was a Griesbaum coozonolysis[21] between fluorinated oxime ethers **51**, **57**, and **61** and keto ester **37**[18] to form the corresponding ozonide esters **52**, **58**, and **62** in low to moderate yields; hydrolysis of the latter yielded **23**−**25** (62−99%). Ozonide esters **58** and **62** were obtained as single diastereomers and were assigned as cis based on the previously observed[27] diastereoselectivity of the Griesbaum coozonolysis reaction. Ozonide ester **52** was obtained as a 3:1 ratio of diastereomers; as depicted in Scheme 5, the major isomer was assigned as trans, cis based on the diastereoselectivity of similar coozonolysis reactions with other 5-substituted-2-adamantanones.[31] The fluorinated oxime ethers **51**, **57**, and **61** were obtained in high overall yields by successive treatment of 5-hydroxy-2-adamantanone ethylene ketal (**48**),[32] 6-hydroxy-2-adamantanone ethylene ketal (**54**), and 2,6-adamantanedione monoethylene ketal (**53**)[33] with bis(2-methoxyethyl)aminosulfur trifluoride followed by deprotection and condensation with methoxylamine.

Triethylsilylperoxyketal ester **63**, the key intermediate in the synthesis of 1,2-dioxolane **26**, was obtained in a two-step sequence[34] from keto ester **37** (Scheme 6). Formation of the peroxycarbenium intermediate[35] by treatment of **63** with $SnCl_4$ in the presence of 2-methyleneadamantane afforded 1,2-dioxolane ester **65** (40%) that was hydrolyzed to form **26** (93%).

Table 1. Worm Burden Reductions in Adult *F. hepatica* Harbored in Rats after the Administration of Ozonides **1**−**11** at Single Oral Doses of 100 mg/kg



compd	R	worm burden reduction (%)	cures
control			0/12
AS[a,b]		30	2/5
1[c]	OH	100[e]	10/10
2	OMe	99[e]	2/3
3[d]	OEt	36	2/4
4	NHOH	34	0/3
5	NHC=NH(NH$_2$)	0	0/4
6	NHSO$_2$CH$_3$	100[e]	4/4
7	NHCH$_2$COOH	86[e]	2/4
8	NH(CH$_2$)$_2$SO$_3$Na	0	0/4
9	NH$_2$	7	0/3
10	NHNH$_2$	12	0/3
11	N(CH$_2$CH$_2$)$_2$NH	0	0/4

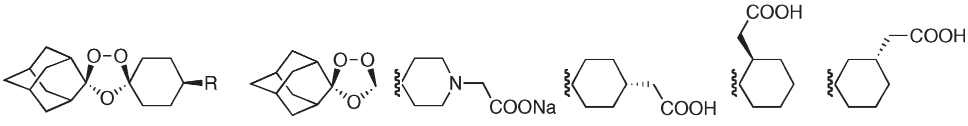
[a] AS = artesunate. [b] Data from Keiser et al.[13] [c] Data from Keiser et al.[12] [d] Tested at 50 mg/kg. [e] $p < 0.05$ from the Kruskal−Wallis test comparing the median values of the responses between the treatment and control groups.

1,2-Dioxolane ester **65** was obtained as a single diastereomer and was assigned a cis configuration based on the stereochemistry observed in similar reactions.[36] Ketal **27**, the nonperoxidic isostere of **1**, was obtained in 79% yield as a 1.3:1 mixture of isomers by *p*-TSA catalyzed condensation[14] of 2-hydroxymethyl-2-adamantanol (**66**)[37] and 2-(4-oxocyclohexyl)acetic acid (**67**). Ozonides **1**−**5**, **9**, **11**−**13**, and **15** were obtained as previously described.[18,27,38]

Activity against *F. hepatica*

Efficacy data for the target compounds administered at oral doses of 100 mg/kg to *F. hepatica* infected rats[39] are shown in Tables 1−3. At 8 weeks postinfection, rats were treated with single 50−100 mg/kg oral doses of target compounds prepared as suspensions in 7% (v/v) Tween-80 and 3% (v/v) EtOH. At day 6 after treatment, rats were sacrificed and adult flukes were recovered from the bile ducts and livers. Target compound efficacies were evaluated by comparing the mean

Table 2. Worm Burden Reductions in Adult *F. hepatica* Harbored in Rats after the Administration of Ozonides **12–20** at Single Oral Doses of 100 mg/kg



12-16 **17** **18** **19** **20**

compd	R	worm burden reduction (%)	cures
12	COOH	52[a]	1/4
13	CH_2CH_2COOH	14	0/5
14	$CH(COOH)_2$	0	0/4
15	$CH_2NHCOCOOH$	14	0/3
16	$CH_2PO(OEt)OK$	16	0/3
17		0	0/3
18		95[a]	2/3
19		46	0/3
20		90[a]	2/3

[a] $p < 0.05$ from the Kruskal–Wallis test comparing the median values of the responses between the treatment and control groups.

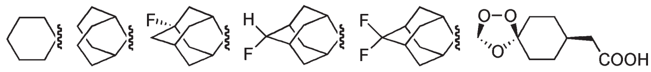
total worm burdens of treated and untreated control rats. Statistical significance was calculated using the Kruskal–Wallis test.

Table 1 shows efficacy data for a range of acidic, neutral, and weak base amide derivatives of **1**. Of these compounds, the only one with efficacy equal to **1** was acylsulfonamide **6**, although methyl ester **2** and glycine conjugate **7** achieved statistically significant worm burden reductions and partial cures; a 50 mg/kg dose of ethyl ester **3** also produced partial cures. The presence of an acidic functional group was no guarantee of good activity for these ozonides. For example, hydroxamic acid **4**, amphoteric acylguanidine **5**, and taurine conjugate **8** either were completely inactive or produced marginal decreases in total worm burdens and cured no infected animals. Unlike **2** and **3**, the alkyl ester prodrugs of **1**, the primary amide (**9**), hydrazide (**10**), and piperazinamide (**11**) derivatives were inactive or only weakly active and cured no infected rats.

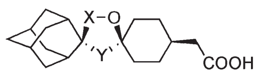
Table 2 shows efficacy data for compounds that probe the effect of changing the position (**12**, **13**, **19**, **20**) and stereochemistry (**18**) of the carboxylic acid functional group of **1**. The position and stereochemistry of the carboxylic acid functional group in **1** seem to be optimal, since removing (**12**) or extending (**13**) the connecting alkyl link reduced efficacy, as did changing the stereochemistry from cis (**1**) to trans (**18**) and changing the position of attachment of the carboxymethyl substituent on the cyclohexyl substructure (**19**, **20**). Even though the preceding five compounds were less effective than **1**, ozonides **12**, **18**, and **20** were partially curative and achieved statistically significant worm burden reductions. In addition, the effects of an additional carboxylic acid functional group (**14**), replacement of the carboxylic acid with a monoethylphosphonic acid (**16**) or carboxyoxamide (**15**), and substitution of the spirocyclohexyl substructure of **1** with a spiropiperidinyl in **17** were examined. Not one of compounds **14–17** significantly reduced worm burden reductions nor were they curative; the lack of efficacy of **17** is consistent with SAR trends of antimalarial ozonides.[26]

Table 3 shows efficacy data for compounds that probe the effect of replacing the spiroadamantyl substructure of **1** with a spirocyclohexyl (**21**) or bicyclo[3.3.1]nonane (**22**) or of fluorine substitution (**23–25**) of the spiroadamantyl substructure of **1**. The nonexistent to low efficacies for **21** and **22** is an outcome consistent with SAR trends for antimalarial ozonides.[28] Target ozonides **23–25** were designed to slow or block potentially

Table 3. Worm Burden Reductions in Adult *F. hepatica* Harbored in Rats after the Administration of Ozonides **21–27** at Single Oral Doses of 100 mg/kg



21 **22** **23** **24** **25**



26, X = O, Y = CH_2
27, X = CH_2, Y = O

compd	worm burden reduction (%)	cures
21	0	0/3
22	51	0/3
23	80[a]	2/3
24	76[b]	1/3
25	80[a]	0/3
26	7	0/3
27	0	0/3

[a] $p < 0.05$ from the Kruskal–Wallis test comparing the median values of the responses between the treatment and control groups. [b] $p = 0.051$.

inactivating CYP450 metabolism of the distal bridgehead carbon atoms of **1** based on the known inactive CYP450 metabolites[31] of arterolane (OZ277).[40] Although **23–25** had moderate efficacies against *F. hepatica*, none was more active than **1**.

The complete loss of efficacy for **27** (Table 3), the nonperoxidic isostere of **1**, shows that the activity of **1** is peroxide-bond-dependent. The lack of efficacy for the peroxidic 1,2-dioxolane **26**, consistent with our previous data[35] showing that 1,2-dioxolanes have very low to no antimalarial activity, provides additional mechanistic insight. 1,2-Dioxolanes react with Fe(II) primarily by two-electron vs one-electron reduction to form inactive diol reaction products rather than carbon-centered radicals,[35] the latter of which are formed by β-scission reactions of the initially formed Fe(III) complexed oxy radicals. These β-scission reactions are accelerated by the adjacent oxygen atom[41] present in ozonides (1,2,4-trioxolanes) but absent in 1,2-dioxolanes.

Of 26 new compounds tested (Tables 1–3), 8 had statistically significant worm burden reductions, 7 were partially curative, and 1 (**6**) was completely curative. Compounds that were more effective in reducing worm burdens in the *F. hepatica* infected rats also tended to result in partial cures, although ozonide ester **3** (36% worm burden reduction at 50 mg/kg, 2/4 cures) and artesunate (30% worm burden reduction, 2/5 cures) were exceptions. Given that acylsulfonamide **6** was the only compound with efficacy equal to that of **1** at the 100 mg/kg dose, it was tested at the lower dose of 50 mg/kg and compared to existing data[12] for **1**. At 50 mg/kg, **1** and **6** reduced worm burdens by 53% and 17%, respectively, but only **1** cured (2/4) the infected rats. Interestingly, previous SAR[18,26,29,42] reveals that acidic ozonides have relatively weak antimalarial activities so that it may be possible to identify an ozonide with selectivity for inhibition of *F. hepatica*. However, **1** and **6** are clearly less effective than triclabendazole; at 10 mg/kg, triclabendazole reduced burden reduction by 95% and cured 3/4 infected rats.[16]

Summary

These data indicate that relatively small structural changes to **1** led, in most cases, to substantial, if not complete, loss of activity against *F. hepatica* in vivo. A peroxide bond, spiroadamantane substructure, and acidic functional group (or prodrug) were required for activity. Although **1** seems to be an "optimized" ozonide structure for efficacy against *F. hepatica*, its peroxide-dependent activity suggests that, like antimalarial peroxides,[14] its efficacy depends upon hemoglobin digestion in *F. hepatica*. The mechanistic basis for the superior efficacy of ozonide acids is unclear, but it may be derived from a favorable distribution of the un-ionized forms to the low pH mileau[43] of the trematode gut, the site of hemoglobin digestion. Indeed, in an electron microscopy study[44] of ex vivo *F. hepatica*, **1** caused extensive damage to the gut. Investigation of the flukicidal properties of other peroxy heterocycles is in progress.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm), or DMSO-d_6 (39.7 ppm) for ^{13}C NMR. Combustion analysis confirmed that all target compounds possessed purities of ≥95%.

***cis*-Adamantane-2-spiro-3′-8′-[[[(methylsulfonyl)amino]carbonyl]-methyl]-1′,2′,4′-trioxaspiro[4.5]decane (6).** Ozonide **6** was synthesized following the method of Tsandi et al.[17] To a solution of **1** (1.61 g, 5.0 mmol), methanesulfonamide (951 mg, 10.0 mmol), and DMAP (611 mg, 5.0 mmol) in CH_2Cl_2 (40 mL) was added DCC (1.14 g, 5.5 mmol). After 24 h, the reaction mixture was filtered and 1 M aqueous HCl was added to the filtrate. After the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), the combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to produce a residue that was purified by chromatography (sg, 10:1 CH_2Cl_2/MeOH) to afford **6** (1.05 g, 72%) as a white solid. Mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 1.26−1.30 (m, 3H), 1.68−1.96 (m, 20H), 2.22 (d, J = 6.4 Hz, 2H), 3.32 (s, 3H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.40, 26.79, 29.78, 32.82, 33.77, 34.74, 36.32, 36.72, 41.63, 42.88, 108.16, 111.50, 170.96. Anal. ($C_{19}H_{29}NO_6S$) C, H, N.

***cis*-Adamantane-2-spiro-3′-8′-[[[(carboxymethyl)amino]carbonyl]-methyl]-1′,2′,4′-trioxaspiro[4.5]decane (7). Step 1.** To a solution of *cis*-adamantane-2-spiro-3′-8′-[[(1′*H*-benzotriazol-1′-yloxy)-carbonyl]methyl]-1′,2′,4′-trioxaspiro[4.5]decane (**28**)[18] (2.00 g, 4.6 mmol) and glycine ethyl ester hydrochloride (762 mg, 5.4 mmol) in CH_2Cl_2 (60 mL) was added DIPEA (1.29 g, 10 mmol). The resulting mixture was stirred at room temperature for 2 h before quenching with water (30 mL). After separation of the water layer, the organic layer was washed with water (4×30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from 1:5 EtOH/H_2O to afford *cis*-adamantane-2-spiro-3′-8′-[[[(ethoxycarbonylmethyl)amino]carbonyl]methyl]-1′,2′,4′-trioxaspiro[4.5]decane (1.50 g, 81%) as a white solid. Mp 157−159 °C; ^{1}H NMR ($CDCl_3$) δ 1.23−1.30 (m, 5H), 1.68−1.99 (m, 21H), 2.13 (d, J = 6.8 Hz, 2H), 4.03 (d, J = 4.9 Hz, 2H), 4.22 (q, J = 7.3 Hz, 2H), 5.97 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.10, 26.42, 26.79, 29.94, 33.47, 33.92, 34.73, 36.31, 36.74, 41.29, 43.10, 61.53, 108.50, 111.30, 169.95, 172.11.

Step 2. To a solution of *cis*-adamantane-2-spiro-3′-8′-[[[(ethoxycarbonylmethyl)amino]carbonyl]methyl]-1′,2′,4′-trioxaspiro[4.5]decane (1.01 g, 2.5 mmol) in EtOH (80 mL) was added a solution of NaOH (198 mg, 5.0 mmol) in water (15 mL). The mixture was stirred for 16 h at room temperature, evaporated to give an oil, and acidified with 1 M aqueous HCl to pH 5. After the aqueous phase was extracted with ethyl acetate (4 × 50 mL), the EtOAc extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give an oil that was crystallized from $CHCl_3$ to afford **7** (752 mg, 80%) as a white solid. Mp 146−148 °C; ^{1}H NMR (DMSO-d_6) δ 1.04−1.12 (m, 2H), 1.62−1.89 (m, 21H), 2.02 (d, J = 6.8 Hz, 2H), 3.71 (d, J = 5.9 Hz, 2H), 8.15 (t, J = 5.9 Hz, 1H), 12.44 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 26.00, 26.41, 29.65, 33.07, 33.64, 34.45, 35.94, 36.28, 40.72, 41.82, 108.62, 110.66, 171.60, 171.79. Anal. ($C_{20}H_{29}NO_6$) C, H, N.

***cis*-Adamantane-2-spiro-3′-8′-[[[(2′-sulfoethyl)amino]carbonyl]-methyl]-1′,2′,4′-trioxaspiro[4.5]decane Sodium Salt (8).** To a solution of **28**[18] (1.50 g, 3.4 mmol) and taurine (387 mg, 3.1 mmol) in THF (200 mL) was added a solution of NaOH (247 mg, 6.2 mmol) in water (15 mL). After the mixture was stirred for 24 h at room temperature, an additional portion of **28** (44 mg, 0.1 mmol) was added. After the mixture was further stirred for 24 h at room temperature, the solvents were removed in vacuo to produce an oil that was purified by reverse phase chromatography (C18, 1:1 MeOH/H_2O) to afford **8** (1.23 g, 80%) as a white solid. Mp 154−156 °C; ^{1}H NMR (DMSO-d_6) δ 1.02−1.10 (m, 2H), 1.61−1.93 (m, 23H), 2.53 (t, J = 7.9 Hz, 2H), 3.28 (td, J = 7.9, 6.9 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.02, 26.42, 29.71, 33.02, 33.66, 34.46, 35.64, 35.95, 36.30, 42.38, 50.88, 108.63, 110.63, 170.91. Anal. ($C_{20}H_{30}NNaO_7S$) C, H, N.

***cis*-Adamantane-2-spiro-3′-8′-(2′-oxo-2′-hydrazinoethyl)-1′,2′,4′-trioxaspiro[4.5]decane (10).** To a stirred solution of **2** (0.68 g, 2 mmol) in MeOH (10 mL) and THF (5 mL) was added hydrazine monohydrate (3.0 g, 60 mmol). The resulting mixture was heated at 50−60 °C for 24 h, then cooled to room temperature and concentrated. The residue was dissolved in EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered. After removal of the solvent, the crude product was purified by crystallization from 5:1 CH_2Cl_2/EtOH to afford **10** (0.56 g, 83%) as a colorless solid. Mp 124−126 °C; ^{1}H NMR ($CDCl_3$) δ 1.15−1.35 (m, 2H), 1.61−2.02 (m, 21H), 2.03 (d, J = 6.8 Hz, 2H), 3.55−4.09 (m, 2H), 6.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.46, 26.85, 29.99, 33.36, 33.91, 34.77, 36.37, 36.77, 41.23, 108.43, 111.40, 172.77. Anal. ($C_{18}H_{28}N_2O_4$) C, H, N.

***cis*-Adamantane-2-spiro-3′-8′-dicarboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (14). Step 1.** A mixture of 1,4-cyclohexanedione monoethylene ketal (31.2 g, 200 mmol), isopropylidene malonate (32.4 g, 220 mmol), molecular sieves, 4 Å (9 g), and pyridine (300 mL) was stirred at room temperature for 2 days under Ar. The reaction suspension was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 1 M HCl (2×150 mL) and water (3× 150 mL). The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated in vacuo to give 5-(1,4-dioxaspiro[4.5]dec-8-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**29**)[19] (39.1 g, 69%) as a red powder. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 6H), 1.91 (t, J = 6.6 Hz, 4H), 3.15 (t, J = 6.6 Hz, 4H), 4.00 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 26.9, 30.5, 35.4, 64.6, 103.8, 106.9, 115.2, 160.8, 178.6.

Step 2. A solution of crude **29** (39.1 g, 138.5 mmol) and 10% Pd−C (1.0 g) in CH_2Cl_2 (450 mL) was hydrogenated at 500 psi at room temperature for 1 day. After filtration, the filtrate was concentrated in vacuo to give crude 5-(1,4-dioxaspiro[4.5]dec-8-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (38.8 g, 99%) which was used for the next step. An analytical sample was obtained by flash chromatography (sg, 50% ether in hexane) as a yellow powder. Mp 145−148 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.55−1.65 (m, 4H), 1.75 (s, 3H), 1.77 (s, 3H), 1.80 (s, 1H), 1.82 (s, 1H), 1.97−2.05 (m, 2H), 2.41−2.46 (m, 1H), 3.45 (d, J = 2.9 Hz, 1H), 3.95 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 26.4, 27.4, 28.2, 34.7, 37.6, 50.2, 64.2, 64.3, 104.8, 107.8, 164.8.

Step 3. A solution of 5-(1,4-dioxaspiro[4.5]dec-8-yl)-2,2-dimethyl 1,3-dioxane-4,6-dione (38.8 g, 136.6 mmol) and pyridinium *p*-toluenesulfonate (5.0 g, 20 mmol) in acetone (400 mL) was refluxed for 20 h. The reaction solution was concentrated and then dissolved in CH_2Cl_2 (300 mL), washed with water (3× 100 mL), dried over $MgSO_4$, and evaporated to dryness. Because of the poor yield of the deprotection and the difficulty of separation, the above process was repeated four times to produce crude 5-(4-oxocyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.0 g, 27%) which was used for the next step. An analytical sample was obtained by flash chromatography (sg, 60% ether in hexane) as a white powder. Mp 152−154 °C dec.; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 1.81 (s, 3H), 1.94−1.99 (m, 2H), 2.18−2.27 (m, 2H), 2.37−2.48 (m, 4H), 2.88−2.95 (m, 1H), 3.61 (d, J = 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.0, 28.1, 28.2, 36.2, 40.7, 49.8, 105.0, 164.3, and 209.9.

Step 4. A solution of 5-(4-oxocyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.0 g, 37.5 mmol), MeOH (300 mL), Et_2O (300 mL), and concentrated H_2SO_4 (2.0 mL, 37.6 mmol) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with water (3×100 mL). The CH_2Cl_2 layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash chromatography (sg, 50% ether in hexane) to give 4-[bis(methoxycarbonyl)methyl]-cyclohexanone (**30**) (3.2 g, 37%) as a white solid. Mp 59−60 °C; ^{1}H NMR ($CDCl_3$) δ 1.53−1.61 (m, 2H), 2.06−2.09 (m, 2H), 2.39−2.42 (m, 4H), 2.54−2.60 (m, 1H), 3.33 (d, J = 8.8 Hz,1H), 3.76 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 29.9, 35.8, 40.1, 52.4, 56.1, 168.4, 210.2.

Step 5. A suspension of **30** (3.2 g, 14 mmol), *O*-methyl 2-adamantanone oxime (**31**)[22] (5.0 g, 28 mmol), $NaHCO_3$ (no product was formed without the addition of solid $NaHCO_3$) (1.7 g, 20 mmol) in CH_2Cl_2 (80 mL), and cyclohexane (240 mL) was treated with ozone at 0 °C for 2 h. The reaction solution was concentrated and the residue was purified by flash chromatography (sg, 6% ether in hexane) to give *cis*-adamantane-2-spiro-3′-8′-[bis(methoxycarbonyl)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (**32**) (4.2 g, 75%) as colorless crystals. Mp 94−95 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 1.29−1.37 (m, 2H), 1.68−1.99 (m, 20H), 2.09−2.16 (m, 1H), 3.19 (d, J = 8.8 Hz, 1H), 3.73 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.8, 27.7, 33.7, 34.7, 36.2, 36.3, 36.7, 52.4, 56.9, 108.0, 111.4, and 168.9.

Step 6. To a solution of **32** (1.0 g, 2.5 mmol) in THF (50 mL) was added a solution of KOH (1.12 g, 20 mmol) in H_2O (3.0 mL). After being stirred at room temperature for 12 h, the reaction solution was concentrated. The residue was dissolved in EtOAc (100 mL) and H_2O (50 mL) and acidified with 1 M HCl to pH 2. The EtOAc layer was separated, washed with H_2O (3 × 50 mL), dried over $MgSO_4$, and evaporated in vacuo to give **14** (0.81 g, 87%) as a white powder. Mp 152−153 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.16−1.25 (m, 2H), 1.65−1.93 (m, 21H), 3.02 (d, J = 8.8 Hz, 1H), 12.7 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 26.0, 26.5, 27.5, 33.6, 34.5, 35.3, 36.0, 36.3, 57.1, 108.4, 110.8, 170.2. Anal. ($C_{19}H_{26}O_7$) C, H.

***cis*-Adamantane-2-spiro-3′-8′-[[(ethoxy)hydroxyphosphinyl]-methyl]-1′,2′,4′-trioxaspiro[4.5]decane Potassium Salt (16). Step 1.** A solution of 8-(bromomethyl)-1,4-dioxaspiro[4.5]decane[24] (10 g, 42.5 mmol) in EtOH (70 mL) and 6 M aqueous HCl (15 mL, 90 mmol) was stirred overnight at room temperature. After addition of saturated aqueous $NaHCO_3$ to bring the pH to 8, most of the solvent was removed in vacuo and water (100 mL) and ether (100 mL) were added. After separation of the ether layer, the aqueous phase was extracted with ether (3×100 mL). The combined organic phases were dried and evaporated to give an oil that was purified by sg chromatography (sg, 10% EtOAc in hexane) to afford 4-(bromomethyl)cyclohexanone (6.0 g, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.51−1.59 (m, 2H), 2.11−2.18 (m, 1H), 2.20−2.24 (m, 3H), 2.34−2.45 (m, 4H), 3.39 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.00, 37.83, 38.29, 40.02, 210.74.

Step 2. According to the method of Yamagishi et al.,[23] a mixture of 4-(bromomethyl)cyclohexanone (3.0 g, 15.7 mmol) and triethyl phosphite (10.4 g, 62.8 mmol) was heated to 170 °C for 8 h. After the mixture was cooled, saturated aqueous $NaHCO_3$ was added to raise the pH to 8. The aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated to give an oil that was purified with chromatography (sg, 50% EtOAc and hexane to 100% EtOAc) to afford diethyl [(4-oxocyclohexyl)-methyl]phosphonate (**33**) (1.0 g, 26%). ^{1}H NMR ($CDCl_3$) δ 1.33−1.36 (t, J = 7.3 Hz, 6H), 1.52−1.56 (m, 2H), 1.75−1.80 (dd, J = 18.6, 7.4 Hz, 1H), 2.23−2.26 (m, 3H), 2.37−2.40 (m, 4H), 4.08−4.16 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.46 (d, J = 5.8 Hz), 31.21 (d, J = 3.8 Hz), 31.54 (d, J = 140.6 Hz), 33.79 (d, J = 11.0 Hz), 40.54, 61.51 (d, J = 6.7 Hz).

Step 3. A solution of **31**[22] (11.06 g, 61.7 mmol) and **33** (7.0 g, 41.1 mmol) in cyclohexane (200 mL) and CH_2Cl_2 (40 mL) was treated with ozone following the method of Dong et al.[28] After removal of solvents in vacuo, the crude product was purified by chromatography (sg, 50% EtOAc in hexane) to afford *cis*-adamantane-2-spiro-3′-8′-[(diethoxyphosphinyl)-methyl]-1′,2′,4′-trioxaspiro[4.5]decane (**34**) (10.83 g, 78%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.29−1.34 (m, 8H), 1.65−1.99 (m, 23H), 4.04−4.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.44 (d, J = 5.0 Hz), 26.47, 26.86, 31.15, 31.36 (d, J = 11.4 Hz), 32.10 (d, J = 133.2 Hz), 33.96, 34.77, 36.37, 36.79, 61.37 (d, J = 6.4 Hz), 108.27, 111.35.

Step 4. According to the method of Dziemidowicz et al.,[25] a mixture of **34** (333 mg, 0.8 mmol) and potassium trimethylsilanolate (412 mg, 3.2 mmol) in anhydrous THF (12 mL) was stirred at 50 °C for 4 h. Removal of the solvent gave a residue that was purified by reverse phase chromatography (C18, 1:1 CH_3OH/H_2O) to afford **16** (264 mg, 85%) as a white solid. Mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 1.21−1.23 (m, 5H), 1.44−1.48 (m, 2H), 1.61−1.99 (m, 21H), 3.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.66 (d, J = 6.7 Hz), 26.45, 26.84, 31.49 (d, J = 9.6 Hz), 32.10 (d, J = 2.2 Hz), 33.00 (d, J = 130.0 Hz), 34.10, 34.73, 36.35, 36.77, 60.28 (d, J = 4.6 Hz), 108.60, 111.11. Anal. ($C_{19}H_{30}KO_6P$) C, H.

Adamantane-2-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxa-8′-azaspiro[4.5]decane Sodium Salt (17). Step 1. To a suspension of adamantane-2-spiro-3′-8′-*tert*-butoxycarbonyl-1′,2′,4′-trioxa-8′-azaspiro[4.5]decane (**35**)[26] (1.462 g, 4.0 mmol) in THF (10 mL) was added dropwise a solution of methanesulfonic acid (1.54 g, 16.0 mmol) in CH_3CN (2 mL) at room temperature, and the mixture was stirred at room temperature for 24 h. A solution of K_2CO_3 (2.211 g, 16.0 mmol) in H_2O (6 mL) and a solution of ethyl bromoacetate (802 mg, 4.8 mmol) in THF (12 mL) were added. After the mixture was stirred for 6 h, the solvents were removed and the residue was diluted with EtOAc (40 mL) and H_2O (30 mL). After phase separation, the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by sg chromatography (sg, 20% EtOAc in hexane) to afford adamantane-2-spiro-3′-8′-ethoxycarbonylmethyl-1′,2′,4′-trioxa-8′-azaspiro[4.5]decane (**36**) (1.26 g, 90%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 6.8 Hz, 3H), 1.67−2.03 (m, 18H), 2.58−2.62 (m, 2H), 2.71−2.75 (m, 2H), 3.23 (s, 2H), 4.19 (q, $J = 6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.07, 26.26, 26.66, 34.08, 34.54, 34.60, 36.17, 36.56, 50.96, 58.94, 60.43, 106.44, 111.47, 170.21.

Step 2. To a solution of **36** (517 mg, 1.47 mmol) in EtOH (50 mL) was added a solution of NaOH (117 mg, 2.94 mmol) in water (10 mL). After the mixture was stirred at room temperature for 2 h, the resulting precipitate was collected by filtration, washed with H_2O (5 mL), and dried in vacuo at 40 °C to give **17** (305 mg, 84%) as a white solid. Mp 140−142 °C; ^{1}H NMR (CD_3OD) δ 1.71−2.05 (m, 18H), 2.56 (m, 2H), 2.67 (m, 2H), 2.98 (s, 2H); ^{13}C NMR (CD_3OD) δ 27.96, 28.36, 35.06, 35.75, 35.83, 37.81, 37.83, 52.38, 63.29, 108.06, 112.57, 177.62. Anal. ($C_{17}H_{24}NNaO_5$) C, H, N.

***trans*-Adamantane-2-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (18). Step 1.** To a solution of methyl 2-(4-oxocyclohexyl)acetate (**37**) (5.106 g, 30 mmol) in EtOH (100 mL) was added pyridine (3.559 g, 45 mmol) followed by methoxylamine hydrochloride (2.756 g, 33 mmol). The reaction mixture was stirred at room temperature for 4.5 h, concentrated in vacuo, and diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 1 M HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL) and dried over $MgSO_4$. Removal of the solvents in vacuo afforded methyl 2-[4-(methoxyimino)cyclohexyl]acetate (**38**) (5.02 g, 84%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.12−1.28 (m, 2H), 1.68−2.20 (m, 6H), 2.26 (d, $J = 7.3$ Hz, 2H), 2.37−2.41 (m, 1H), 3.16−3.21 (m, 1H), 3.68 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 23.96, 31.09, 31.35, 32.58, 33.85, 40.50, 51.47, 60.96, 158.88, 172.92.

Step 2. A solution of 2-adamantanone (2.25 g, 14.4 mmol) and **38** (1.91 g, 9.59 mmol) in cyclohexane (50 mL) and CH_2Cl_2 (10 mL) was treated with ozone according to the method of Dong et al.[28] After removal of the solvents in vacuo, the crude product was purified by flash chromatography (sg, 100:1 hexane/ethyl acetate) to afford *trans*-adamantane-2-spiro-3′-8′-methoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**39**) (680 mg, 21%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.35−1.43 (m, 2H), 1.58−2.03 (m, 21H), 2.27 (d, $J = 6.8$ Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.38, 26.81, 29.65, 33.27, 33.61, 34.64, 34.83, 36.28, 36.70, 40.41, 51.43, 108.35, 111.51, 173.19.

Step 3. To a solution of **39** (402 mg, 1.2 mmol) in EtOH (10 mL) was added a solution of NaOH (143 mg, 3.6 mmol) in water (3 mL). The mixture was stirred at 60 °C for 3 h and evaporated to give an oil. The residue was cooled to 0 °C and treated with 1 M HCl to pH 3. The resulting solid was filtered, washed with water, and dried in vacuo to afford **18** (346 mg, 90%) as a white solid. Mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.38−1.45 (m, 2H), 1.60−2.03 (m, 21H), 2.31 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.43, 26.85, 29.66, 33.10, 33.65, 34.70, 34.88, 36.32, 36.74, 40.31, 108.33, 111.65, 178.66. Anal. ($C_{18}H_{26}O_5$) C, H.

***cis*-Adamantane-2-spiro-3′-6′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (19). Step 1.** A solution of *O*-methyl 2-adamantanone oxime (**31**)[22] (896 mg, 5.0 mmol) and ethyl 2-(2-oxocyclohexyl)acetate (**40**) (1.38 g, 7.5 mmol) in cyclohexane (30 mL) and CH_2Cl_2 (6 mL) was treated with ozone according to the method of Dong et al.[28] After removal of the solvents in vacuo, the crude product was purified by flash chromatography (sg, 40:1 hexane/ethyl acetate) to afford *cis*-adamantane-2-spiro-3′-6′-ethoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**41**) (380 mg, 22%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.25−1.31 (m, 5H), 1.40−2.40 (m, 23H), 2.76 (dd, $J = 15.6$, 2.4 Hz, 1H), 4.12−4.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.50, 26.18, 26.59, 27.27, 33.80, 33.94, 34.57, 35.16, 35.65, 36.10, 36.52, 36.73, 39.07, 39.26, 46.77, 60.18, 109.58, 111.26, 172.98.

Step 2. To a solution of **41** (350 mg, 1.0 mmol) in EtOH (8 mL) was added a solution of NaOH (120 mg, 3.0 mmol) in water (3 mL). The mixture was stirred at room temperature for 3 h and concentrated in vacuo to afford an oil that was cooled to 0 °C and treated with 1 M HCl to pH 3. The resulting solid was filtered, washed with water, and dried in vacuo to afford **19** (320 mg, 93%) as a white solid. Mp 66−69 °C; ^{1}H NMR ($CDCl_3$) δ 1.29−1.39 (m, 2H), 1.44−2.37 (m, 23H), 2.84 (dd, $J = 6.1$, 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.61, 24.30, 26.29, 26.72, 29.66, 33.80, 34.07, 34.72, 34.90, 35.34, 35.83, 36.63, 36.89, 39.24, 109.65, 111.62, 178.90. Anal. ($C_{18}H_{26}O_5$) C, H.

***trans*-Adamantane-2-spiro-3′-7′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (20). Step 1.** A solution of **31**[22] (1.44 g, 8.0 mmol) and methyl 2-(3-oxocyclohexyl)acetate (**42**)[45] (1.14 g, 6.7 mmol) in cyclohexane (30 mL) and CH_2Cl_2 (10 mL) was treated with ozone according to the method of Dong et al.[28] After removal of the solvents in vacuo, the crude product was purified by column chromatography (sg, 50:1 hexane/ethyl acetate) to afford *trans*-adamantane-2-spiro-3′-7′-methoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**43**) (998 mg, 45%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.93−1.00 (m, 1H), 1.40−2.09 (m, 22H), 2.20−2.29 (m, 2H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 22.44, 26.30, 26.70, 30.76, 32.32, 34.02, 34.56, 34.59, 36.20, 36.58, 40.38, 40.70, 51.16, 108.44, 110.99, 172.39.

Step 2. To a solution of **43** (627 mg, 1.8 mmol) in EtOH (16 mL) was added a solution of NaOH (224 mg, 5.6 mmol) in water (4 mL), and the mixture was stirred at 60 °C for 3 h. Removal of the solvents afforded an oil that was cooled to 0 °C and treated with 1 M HCl to pH 3. The resulting solid was filtered, washed with water, and dried in vacuo to afford **20** (567 mg, 94%) as a white solid. Mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 0.95−1.02 (m, 1H), 1.42−2.08 (m, 22H), 2.22−2.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.61, 26.44, 26.83, 30.86, 32.29, 34.18, 34.76, 34.78, 36.35, 36.76, 40.53, 40.96, 108.65, 111.35, 178.46. Anal. ($C_{18}H_{26}O_5$) C, H.

3-Carboxymethyl-7,14,15-trioxadispiro[5.1.5.2]pentadecane (21). Step 1. A solution of *O*-methylcyclohexanone oxime (**44**)[30] (2.16 g, 17 mmol) and **37** (3.47 g, 20.4 mmol) in cyclohexane (120 mL) and CH_2Cl_2 (30 mL) was treated with ozone following the method of Dong et al.[28] After removal of solvents in vacuo, the crude product was purified by chromatography (sg, 4% EtOAc in hexane) followed by crystallization from cold MeOH to afford 3-methoxycarbonylmethyl-7,14,15-trioxadispiro[5.1.5.2]pentadecane (**45**) (2.4 g, 50%, 4:1 mixture of two isomers based on the ^{1}H NMR doublets at 2.22 and 2.26) as a white solid. Mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 2H), 1.36 (m, 1H), 1.43 (m, 1H), 1.56−1.82 (m, 13H), 1.94 (d, $J = 15.6$ Hz, 2H), 2.22 (d, $J = 7.5$ Hz, 1.6H), 2.26 (d, $J = 7.0$ Hz, 0.4H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 22.46, 22.58, 23.72, 23.77, 24.82, 29.55, 29.84, 33.08, 33.22, 33.50, 33.76, 34.54, 40.36, 40.59, 51.46, 108.32, 108.86, 109.24, 171.11, 173.21.

Step 2. To a solution of 45 (678 mg, 2.24 mmol) in EtOH (50 mL) was added a solution of NaOH (180 mg, 4.48 mmol) in water (10 mL). The mixture was stirred at room temperature for 12 h, cooled to 0 °C, and treated with 1 M aqueous HCl (5 mL) and H_2O (50 mL). The precipitate was collected by filtration, washed with 50% aqueous EtOH (10 mL), and dried in vacuo at 40 °C to give **21** (450 mg, 74%, 2.3:1 mixture of two isomers based on the ^{1}H NMR doublets at 2.27 and 2.30) as a colorless solid. Mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−1.47 (m, 4H), 1.54−1.95 (m, 15H), 2.27 (d, $J = 6.8$ Hz, 1.4H), 2.30 (d, $J = 6.8$ Hz, 0.6H); ^{13}C NMR ($CDCl_3$) δ 23.74, 23.79, 24.84, 24.87, 29.52, 29.80, 32.88, 33.01, 33.51, 33.76, 34.56, 40.28, 40.41, 40.51, 108.27, 108.28, 108.96, 109.33, 178.76. Anal. ($C_{14}H_{22}O_5$) C, H.

Bicyclo[3.3.1]nonane-9-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (22). Step 1. A solution of *O*-methyl bicyclo[3.3.1]nonan-9-one oxime (**46**)[28] (792 mg, 4.7 mmol) and **37** (1.21 g, 7.1 mmol) in cyclohexane (30 mL) and CH_2Cl_2 (50 mL) was treated with ozone following the method of Dong et al.[28] After removal of the solvents, the crude product was purified by column chromatography (sg, 50:1 hexane/ethyl acetate) to afford bicyclo[3.3.1]nonane-9-spiro-3′-8′-methoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**47**) (807 mg, 53%) as a white solid. Mp 82−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−2.06 (m, 23H), 2.22 (d, $J = 7.3$ Hz, 2H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.41, 20.82, 29.33, 29.52, 29.87, 33.10, 33.94, 36.20, 40.60, 51.40, 108.27, 111.22, 173.15.

Step 2. To a solution of **47** (785 mg, 2.4 mmol) in EtOH (20 mL) was added a solution of NaOH (290 mg, 7.3 mmol) in water (3 mL). The mixture was stirred at 60 °C for 3 h, evaporated to give an oil, cooled to 0 °C, and treated with 1 M HCl to pH 3. The resulting solid was filtered, washed with water, and dried in vacuo to afford **22** (651 mg, 87%) as a white solid. Mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.33 (m, 2H), 1.44−1.52 (m, 2H), 1.64−2.07 (m, 19H), 2.27 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.44, 20.84, 29.36, 29.54, 29.84, 32.91, 33.95, 36.21, 40.55, 108.24, 111.35, 178.79. Anal. ($C_{17}H_{26}O_5$) C, H.

***trans,cis*-5-Fluoroadamantane-2-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (23). Step 1.** To a stirred solution of 5-hydroxy-2-adamantanone ethylene ketal (**48**)[32] (100 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added bis(2-methoxyethyl)aminosulfur trifluoride (158 mg, 0.7 mmol). After 1 h of stirring, the reaction was quenched with water (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to afford a residue that was purified by crystallization from 1:1 MeOH/H_2O to afford 5-fluoro-2-adamantanone ethylene ketal (**49**) (81 mg, 80%) as a white solid. Mp 44−46 °C; ^{1}H NMR ($CDCl_3$) δ 1.55−1.57 (d, 2H), 1.73−1.75 (m, 2H), 1.89−1.92 (m, 4H), 2.01 (s, 2H), 2.18−2.22 (m, 3H), 3.92−3.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 29.80 (d, J = 10.1 Hz), 33.23 (d, J = 1.9 Hz), 38.76 (d, J = 10.6 Hz), 39.39 (d, J = 19.2 Hz), 42.30 (d, J = 16.8 Hz), 64.32, 64.48, 91.56 (d, J = 183.8 Hz), 109.74.

Step 2. To a solution of **49** in 2:1 acetone/water (12 mL) was added concentrated HCl (4 mL), and the reaction mixture was stirred for 1 h at room temperature before removal of the solvents in vacuo. CH_2Cl_2 (6 mL) and water (6 mL) were added, and the two phases were separated followed by extraction of the aqueous phase with CH_2Cl_2 (2 × 4 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo to afford 5-fluoro-2-adamantanone (**50**) (55 mg, 86%) as a colorless solid. Mp 269−271 °C; ^{1}H NMR ($CDCl_3$) δ 1.66−2.44 (m, 11H), 2.68 (s, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 30.43 (d, J = 10.1 Hz), 37.94 (d, J = 2.4 Hz), 41.55 (d, J = 17.8 Hz), 42.05 (d, J = 20.2 Hz), 47.05 (d, J = 10.1 Hz), 90.18 (d, J = 185.7 Hz), 214.92 (d, J = 1.9 Hz).

Step 3. To a solution of **50** (800 mg, 4.8 mmol) in EtOH (40 mL) was added pyridine (564 mg, 7.1 mmol) followed by methoxylamine hydrochloride (477 mg, 5.7 mmol). The reaction mixture was stirred at room temperature for 2 h, concentrated in vacuo, and diluted with water (10 mL). After filtration, *O*-methyl-5-fluoro-2-adamantanone oxime (**51**) was obtained as a white solid (773 mg, 82%). Mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 1.70−2.06 (m, 10H), 2.37 (d, J = 2.0 Hz, 1H), 2.78 (s, 1H), 3.69 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 30.78 (d, J = 10.0 Hz), 30.96 (d, J = 9.6 Hz), 36.08 (d, J = 2.4 Hz), 37.50 (d, J = 1.9 Hz), 37.90 (d, J = 10.6 Hz), 41.45 (d, J = 18.7 Hz), 41.74 (d, J = 17.3 Hz), 42.69 (d, J = 18.7 Hz), 61.12, 91.23 (d, J = 185.2 Hz), 162.81 (d, J = 2.4 Hz).

Step 4. A solution of **51** (918 mg, 4.66 mmol) and **37** (1.19 g, 6.99 mmol) in cyclohexane (40 mL) and CH_2Cl_2 (20 mL) was treated with ozone according to the method of Dong et al.[28] After removal of solvents, the crude product was purified by crystallization from EtOH to afford *trans,cis*-5-fluoroadamantane-2-spiro-3′-8′-methoxycarbonylmethyl- 1′,2′,4′-trioxaspiro-[4.5]decane (**52**) (450 mg, 27%, 3:1 mixture of diastereomers) as a white solid. Mp 126−128 °C; ^{1}H NMR ($CDCl_3$) δ 1.23−1.28 (m, 2H), 1.55−1.95 (m, 15H), 2.18−2.23 (m, 7H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 29.40 (d, J = 10.1 Hz), 29.80, 32.99, 33.14 (d, J = 1.9 Hz), 33.75, 38.76 (d, J = 11.4 Hz), 39.20 (d, J = 19.7 Hz), 40.54, 41.97 (d, J = 17.3 Hz), 51.49, 91.20 (d, J = 184.3 Hz), 109.01, 109.46, 173.12.

Step 5. To a solution of **52** (450 mg, 1.27 mmol) in EtOH (10 mL) was added a solution of NaOH (152 mg, 3.81 mmol) in water (4 mL). The mixture was stirred for 4 h at 55 °C and evaporated to give an oil. The residue was cooled to 0 °C and treated with 1 M aqueous HCl (4 mL) and CH_2Cl_2 (30 mL). After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and evaporated to give **23** (266 mg, 62%, 5:1 mixture of diastereomers) as a white solid. Mp 147−149 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−1.32 (m, 2H), 1.55−1.93 (m, 15H), 2.19−2.28 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 29.40 (d, J = 9.6 Hz), 29.74, 32.78, 33.15 (d, J = 1.9 Hz), 33.73, 38.77 (d, J = 10.6 Hz), 39.21 (d, J = 19.7 Hz), 40.47, 41.97 (d, J = 17.3 Hz), 91.23 (d, J = 184.7 Hz), 108.93, 109.53, 178.80. Anal. ($C_{18}H_{25}FO_5$) C, H.

***cis*-6-Fluoroadamantane-2-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (24). Step 1.** Sodium borohydride (1.11 g, 29.2 mmol) was added portionwise to a ice-cold solution of 2,6-adamantandione monoethylene ketal (**53**)[33] (1.74 g, 8.35 mmol) in MeOH (100 mL) at such a rate as to keep the internal temperature below 10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. After the reaction was quenched with water (10 mL), the solvents were removed in vacuo and the residue was partitioned between CH_2Cl_2 (80 mL) and water (60 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 6-hydroxy-2-adamantanone monoethylene ketal (**54**) (1.6 g, 91%) as a white solid. Mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−2.08 (m, 13H), 3.80 (s, 1H), 3.95 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 28.21, 33.29, 33.39, 35.24, 35.83, 64.19, 73.55, 110.95.

Step 2. To a solution of **54** (808 mg, 3.8 mmol) in CH_2Cl_2 (40 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (850 mg, 3.8 mmol), and the reaction mixture was stirred at room temperature for 24 h before quenching with water (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2× 30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to afford crude 6-fluoro-2-adamantanone monoethylene ketal (**55**) (540 mg, 66%) as a white solid. Mp 45−47 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, J = 12.7 Hz, 2H), 1.74 (s, 2H), 1.79 (d, J = 12.7 Hz, 2H), 2.01−2.11 (m, 6H), 3.94 (s, 4H), 4.59 (d, J = 50.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.40 (J = 1.0 Hz), 31.34 (J = 18.2 Hz), 32.37 (J = 8.7 Hz), 34.92 (J = 1.4 Hz), 35.45, 64.11, 94.17 (J = 179.5 Hz), 110.29.

Step 3. To a solution of **55** in 2:1 acetone/water (12 mL) was added concentrated HCl (4 mL), and the reaction mixture was stirred at 70 °C for 1 h. After removal of the solvents in vacuo, CH_2Cl_2 (6 mL) and water (6 mL) were added. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 4 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to afford 6-fluoro-2-adamantanone (**56**) (55 mg, 86%) as a white solid. Mp 230−232 °C; ^{1}H NMR ($CDCl_3$) δ 1.81−2.49 (m, 12H), 4.85 (dt, J = 49.8, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.73 (J = 18.7 Hz), 32.68 (J = 1.4 Hz), 36.42 (J = 8.6 Hz), 44.67 (J = 1.9 Hz), 45.48, 92.72 (J = 180.9 Hz), 215.95.

Step 4. To a solution of **56** (336 mg, 2.0 mmol) in EtOH (25 mL) was added pyridine (316 mg, 3.0 mmol) followed by methoxylamine hydrochloride (200 mg, 2.4 mmol). The reaction mixture was stirred at room temperature for 6 h, concentrated in vacuo, and diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. Removal of the solvents in vacuo afforded *O*-methyl-6-fluoro-2-adamantanone oxime (**57**) (370 mg, 94%, 1:1 mixture of diastereomers) as a white solid. Mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 1.61−2.49 (m, 11H), 3.41−3.44 (m, 1H), 3.81 (s, 1.5H), 3.82 (s, 1.5H), 4.71−4.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.24 (J = 1.0 Hz), 32.30 (J = 18.2 Hz), 32.36 (J = 18.2 Hz), 34.36, 35.00, 35.28 (J = 8.6 Hz), 36.53 (J = 8.6 Hz), 60.96, 44.67 (J = 1.9 Hz), 45.48, 92.72 (J = 180.9 Hz), 215.95.

Step 5. A solution of **57** (370 mg, 1.9 mmol) and **37** (479 mg, 2.8 mmol) in cyclohexane (30 mL) and CH_2Cl_2 (60 mL) was treated with ozone according to the method of Dong et al.[28] After removal of solvents in vacuo, the crude product was purified by crystallization from cold EtOH to afford *cis*-6-fluoroadamantane-2-spiro-3′-8′-methoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**58**) (250 mg, 38%) as a white solid. Mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 1.23−1.30 (m, 2H), 1.58−2.13 (m, 19H), 2.22 (d, J = 7.3 Hz, 1H), 3.67 (s, 3H), 4.59 (d, J = 50.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.51 (J = 1.0 Hz), 28.57, 29.84 (J = 3.8 Hz), 31.02 (J = 18.2 Hz), 31.43 (J = 18.2 Hz), 32.38 (J = 4.3 Hz), 32.45 (J = 4.3 Hz), 33.07, 33.83 (J = 2.9 Hz), 34.86 (J = 1.4 Hz), 35.43, 40.57, 51.46, 93.90 (J = 179.5 Hz), 108.74, 110.32, 173.15.

Step 6. To a solution of **58** (250 mg, 0.7 mmol) in EtOH (12 mL) was added a solution of NaOH (85 mg, 2.1 mmol) in water (3 mL). The mixture was stirred at 60 °C for 3 h and concentrated in vacuo. The residue was cooled to 0 °C and treated with 1 M aqueous HCl (5 mL) and H_2O (10 mL). The precipitate was collected by filtration and dried in vacuo at 40 °C to afford **24** (237 mg, 99%) as a white solid. Mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−1.32 (m, 2H), 1.59−2.10 (m, 19H), 2.27 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 50.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.52, 28.57, 29.78 (J = 3.4 Hz), 30.99 (J = 18.2 Hz), 31.41 (J = 18.2 Hz), 32.37 (J = 3.8 Hz), 32.44 (J = 3.8 Hz), 32.85, 33.80 (J = 2.9 Hz), 34.83, 35.40, 40.44, 93.93 (J = 179.0 Hz), 108.66, 110.39, 178.46. Anal. ($C_{18}H_{25}FO_5$) C, H.

***cis*-6,6-Difluoroadamantane-2-spiro-3′-8′-carboxymethyl-1′,2′,4′-trioxaspiro[4.5]decane (25). Step 1.** To a solution of 2,6-adamantanedione monoethylene ketal (**53**)[33] (1.17 g, 5.6 mmol) in CH_2Cl_2 (85 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (2.27 g, 10.3 mmol), and the reaction mixture was stirred at room temperature for 24 h before quenching with water (50 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2×40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue that was purified by flash chromatography (sg, 40:1 hexane/ethyl acetate) to afford 6,6-difluoro-2-adamantanone monoethylene ketal (**59**) (1.10 g, 85%) as a colorless solid. Mp 76−78 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 2H), 1.87−1.90 (d, J = 12.7 Hz, 4H), 2.00−2.02 (d, J = 12.2 Hz, 4H), 2.11 (s, 2H), 3.95 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 30.76 (J = 3.8 Hz), 34.58 (J = 21.6 Hz), 34.87, 64.37, 109.31, 124.43 (J = 246.6 Hz).

Step 2. To a solution of **59** (1.1 g, 4.78 mmol) in 5:1 acetone/water (96 mL) was added concentrated HCl (40 mL), and the reaction mixture was heated to 70 °C gradually. After the disappearance of the starting material as determined by GC−MS (0.5 h), the mixture was cooled to 0 °C and $NaHCO_3$ was added to adjust the pH to 7. After CH_2Cl_2 (80 mL) was added to the mixture, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 6,6-difluoro-2-adamantanone (**60**) as a white solid (760 mg, 85%). Mp 252−255 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (d, J = 12.7 Hz, 4H), 2.29 (d, J = 12.7 Hz, 4H), 2.35 (s, 2H), 2.53 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 34.86 (J = 3.8 Hz), 35.06 (J = 22.1 Hz), 44.47, 123.15 (J = 247.6 Hz), 214.28.

Step 3. To a solution of **60** (760 mg, 4.1 mmol) in EtOH (50 mL) was added pyridine (483 mg, 6.1 mmol) followed by methoxylamine hydrochloride (409 mg, 4.9 mmol). The reaction mixture was stirred at room temperature for 6 h, concentrated in vacuo, and diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The combined organic phases were washed with 1 M HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), and dried over $MgSO_4$. Removal of the solvent in vacuo afforded *O*-methyl-6,6-difluoro-2-adamantanone oxime (**61**) (760 mg, 87%) as a white solid. Mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 1.80−1.89 (m, 4H), 2.09−2.18 (m, 4H), 2.30 (s, 1H), 2.52 (s, 1H), 3.46 (s, 1H), 3.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.22, 33.59 (J = 3.4 Hz), 34.06, 34.87 (J = 3.4 Hz), 35.53 (J = 3.4 Hz), 61.10, 123.90 (J = 247.1 Hz), 162.97.

Step 4. A solution of **61** (460 mg, 2.1 mmol) and **37** (546 mg, 3.2 mmol) in cyclohexane (30 mL) and CH_2Cl_2 (6 mL) was treated with ozone according to the method of Dong et al.[28] After removal of solvents in vacuo, the crude product was purified by crystallization from cold EtOH to afford *cis*-6,6-difluoroadamantane-2-spiro-3′-8′- methoxycarbonylmethyl-1′,2′,4′-trioxaspiro[4.5]decane (**62**) (322 mg, 41%) as a white solid. Mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−1.29 (m, 2H), 1.69−2.14 (m, 19H), 2.23 (d, J = 6.8 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 30.65 (J = 3.8 Hz), 30.68 (J = 3.4 Hz), 32.99, 34.11 (J = 21.6 Hz), 34.52 (J = 21.6 Hz), 34.57, 40.49, 51.47, 108.94, 109.08, 123.94 (J = 247.1 Hz), 173.11.

Step 5. To a solution of **62** (322 mg, 0.87 mmol) in EtOH (8 mL) was added a solution of NaOH (104 mg, 2.6 mmol) in water (3 mL). The mixture was stirred at room temperature for 4 h and evaporated to give an oil. After the residue was treated with 1 M HCl to lower the pH to 3, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated to afford **25** (277 mg, 89%) as a white solid. Mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 1.29−1.37 (m, 2H), 1.75−2.20 (m, 19H), 2.23 (d, J = 6.8 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 29.72, 30.67 (J = 3.8 Hz), 30.70 (J = 3.8 Hz), 32.79, 33.73, 34.12 (J = 21.6 Hz), 34.54 (J = 21.6 Hz), 34.58, 40.53, 108.87, 109.16, 123.96 (J = 247.1 Hz), 179.20. Anal. ($C_{18}H_{24}F_2O_5$) C, H.

Adamantane-2-spiro-3′-8′-carboxymethyl-1′,2′-dioxaspiro[4.5]-decane (26). Step 1. To a solution of I_2 (0.254 g, 1.0 mmol) and 50% H_2O_2 (4.5 mL, 40 mmol) in MeOH (50 mL) was added **37** (1.70 g, 10 mmol). After the mixture was stirred at room temperature for 24 h, it was concentrated in vacuo and 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, brine, dried over $MgSO_4$, filtered, and concentrated to afford methyl 2-(4-hydroperoxy-4-methoxycyclohexyl)acetate as a 1:1 mixture of diastereomers (2.15 g, 99%) which was used immediately in the next step. ^{1}H NMR ($CDCl_3$) δ 0.92−2.46 (m, 11H), 3.30 (s, 1.5H), 3.34 (s, 1.5H), 3.70 (s, 3H), 7.42 (s, 0.5H), 7.52 (s, 0.5H).

Step 2. To a solution of the unpurified methyl 2-(4-hydroperoxy-4-methoxycyclohexyl)acetate (2.15 g, 9.86 mmol) in DMF (100 mL) at 0 °C was added Et_3N (4.5 mL, 32 mmol) followed by Et_3SiOTf (2.54 mL, 12 mmol). The reaction mixture was stirred at room temperature for 24 h 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 organic extracts were combined, dried over $MgSO_4$, and concentrated to afford methyl 2-[4-methoxy-4-(triethylsilylperoxy)cyclohexyl]acetate (**63**) as a 1:1 mixture of diastereomers (3.02 g, 92%) which was used immediately in the next step. ^{1}H NMR ($CDCl_3$) δ 0.68−0.80 (m, 6H), 0.94−1.08 (m, 9H), 0.84−2.44 (m, 11H), 3.26 (s, 1.5H), 3.29 (s, 1.5H), 3.67 (s, 3H).

Step 3. To a solution of **63** (3.02 g, 9.10 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added 2-methyleneadamantane[46] (**64**) (0.67 g, 4.53 mmol) followed by 1 M $SnCl_4$ in CH_2Cl_2 (10 mL, 10 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 ice−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 in vacuo. Purification by chromatography (sg, 0−10% ether in hexane) afforded adamantane-2-spiro-3′-8′-methoxycarbonylmethyl-1′,2′-dioxaspiro-[4.5]decane (**65**) as a colorless solid (0.60 g, 40%). Mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−1.36 (m, 2H), 1.44−1.96 (m, 17H), 1.95−2.02 (m, 2H), 2.06−2.14 (m, 2H), 2.13 (s, 2H), 2.20 (d, J = 7.5 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 26.44, 26.99, 29.07, 33.45, 34.93, 35.64, 36.24, 37.21, 41.17, 51.42, 55.47, 84.02, 88.71, 173.47.

Step 4. To a solution of **65** (0.45 g, 1.35 mmol) in EtOH (20 mL) was added 15% aqueous KOH (2 mL), and the resulting mixture was stirred at 60 °C for 20 h. The solution was concentrated to ~5 mL, and the residue was diluted with water (10 mL) and acidified with acetic acid (5 mL). The precipitate was collected by filtration, washed with cold water, and dried in vacuo at 40 °C to afford **26** as a colorless solid (0.40 g, 93%). Mp 184−185 °C; ^{1}H NMR ($CDCl_3$) δ 1.27−1.40 (m, 2H), 1.42−1.96 (m, 17H), 1.95−2.04 (m, 2H), 2.06−2.14 (m, 2H), 2.13 (s, 2H), 2.24 (d, $J = 7.5$ Hz, 2H), 11.14 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 26.44, 26.99, 29.00, 33.26, 33.45, 34.90, 35.64, 36.24, 37.20, 41.04, 55.46, 83.98, 88.75, 178.74. Anal. ($C_{19}H_{28}O_4$) C, H.

Adamantane-2-spiro-2′-8′-carboxymethyl-1′,4′-dioxaspiro[4.5]-decane (27). *p*-Toluenesulfonic acid monohydrate (260 mg, 1.37 mmol) was added to a solution of 2-hydroxymethyl-2-adamantanol (**66**)[37] (1.22 g, 6.69 mmol) and 2-(4-oxocyclohexyl)-acetic acid (**67**) (1.14 g, 7.29 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature for 4 h, washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by crystallization from aqueous MeOH to afford **27** as a white solid (1.69 g, 79%, 1.3:1 mixture of isomers based on the ^{1}H NMR singlets at 3.84 and 3.88). Mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.85 (m, 21H), 2.18 (q, 2H), 2.26 (d, $J = 6.8$ Hz, 0.78H), 2.29 (d, $J = 6.8$ Hz, 1.11H), 3.84 (s, 0.87H), 3.88 (s, 1.13H); ^{13}C NMR ($CDCl_3$) δ 26.67, 26.70, 26.79, 26.93, 30.01, 30.05, 33.08, 33.46, 33.64, 35.82, 35.91, 35.96, 36.33, 37.25, 37.34, 37.41, 40.66, 40.74, 72.14, 72.32, 84.33, 84.48, 108.35, 108.46, 178.79, 178.89. Anal. ($C_{19}H_{28}O_4$) C, H.

Evaluation of Activity against *F. hepatica*. All animal studies[39] were approved by regulatory authorities following Swiss National regulations. Metacercariae of *F. hepatica* were purchased from Baldwin Aquatics (Monmouth, OR). Female Wistar rats (weight, ~100 g) were purchased from Harlan (Horst, The Netherlands). Animals were kept in groups of four in Makrolon cages in environmentally controlled conditions (temperature, ~25 °C; humidity, ~70%; 12 h light/dark cycle) and acclimatized for 1 week. Rats were infected with ~20 metacercariae each. They had free access to water and rodent diet. At 8 weeks after infection, rats were treated with single 50−100 mg/kg oral doses of target compounds prepared as suspensions in 7% (v/v) Tween-80 and 3% (v/v) EtOH. At day 6 after treatment, rats were sacrificed by CO_2 and adult flukes were recovered from the bile ducts and livers. Target compound efficacies were evaluated by comparing the mean total worm burdens of treated and untreated control rats. Statistical significance (at a significance level of 5%) was calculated using the Kruskal−Wallis test (Statsdirect, version 2.4.5; Cheshire, U.K.).

Acknowledgment. This investigation received financial support from NIH (Grant R21AI076783), the Nebraska Research Initiative, the Swiss National Science Foundation (Project No. PPOOA-114941), and the Medicines for Malaria Venture.

Supporting Information Available: Elemental analysis results for **6**−**8**, **10**, **14**, and **16**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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