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The Activity of Dispiro Peroxides Against *Fasciola hepatica*

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Abstract

Dispiro 1,2,4-trioxanes and 1,2,4,5-tetraoxanes had superior efficacy against *Fasciola hepatica* than the corresponding ozonides (1,2,4-trioxolanes). For highest efficacy, spiroadamantane and carboxymethyl substructures were required. Three compounds completely cured *F. hepatica*-infected mice at single oral doses of 50 mg/kg and two were partially curative at single doses of 25 mg/kg.

Keywords

artemisinin; peroxide; *Fasciola hepatica*

The liver flukes *Fasciola hepatica* and *F. gigantica* are pathogenic trematodes infecting an estimated 2.4–17 million people in the Andean countries, Cuba, Western Europe, Egypt and Iran.[1] Moreover, the morbidity and mortality of fascioliasis in cattle and sheep results in considerable economic loss.[2] The benzimidazole triclabendazole (Fig. 1) is the drug of choice used to treat veterinary fascioliasis, but it is registered in only four countries for the treatment of human fascioliasis.[3,4] Evidence of drug resistance to triclabendazole in veterinary medicine[5,6] provides an impetus for the discovery and development of new drugs against fascioliasis.

We have shown that semisynthetic artemisinins (Fig. 1) and synthetic ozonides (Fig. 2) have good efficacy against *F. hepatica*.[7–10] It is postulated[10,11] that such peroxidic compounds possess antiplasmodial[12,13] and flukicidal activities because both plasmodia and *Fasciola* spp. degrade hemoglobin to generate free heme, a likely target[14] of bioactive peroxides. In an effort to identify more effective synthetic peroxides, a structurally diverse ozonide library of OZ78 (*cis*-**1a**) analogues was recently studied.[10] It was found that a spiroadamantane substructure, an acidic functional group (or ester prodrug), and the peroxide bond and non-peroxide oxygen atom of the ozonide heterocycle, were all required for high efficacy against *F. hepatica*.[10] We now report an investigation of the 1,2,4-trioxane and 1,2,4,5-tetraoxane analogs of ozonides (1,2,4-trioxolanes) **1a**–**5a** (Fig. 2).[15] Target peroxide heterocycles **5a**–

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5c were designed on the basis of the superior pharmacokinetic profiles of 8'-aryl ozonides compared to those of 8'-alkyl ozonides.[16]

Griesbaum coozonolysis[17] of oxime ether **6**[18] and ketoester **7** afforded ozonide ester **8** as a 2.5:1 mixture of *cis* and *trans* isomers. Chromatographic separation into the individual isomers followed by hydrolysis of the *cis* isomer afforded **4a** in high yield. Ozonides **1a**–**3a** and **5a** were obtained as previously described.[19–21]

Acid-catalyzed condensation of β–hydroperoxy alcohols **9**–**11** with 2-adamantanone or cyclohexanone afforded trioxane esters **12**–**16** (20–56% yields) (Scheme 2) which were isolated as single trans isomers after crystallization (*vide infra*). Hydrolysis of **12**–**16** afforded trioxane acids **1b**–**5b**. β–Hydroperoxy alcohols **9**–**11** were formed in 52–98% yields by regioselective perhydrolysis[22,23] of the corresponding epoxides, which in turn, were formed predominantly as their cis isomers[24] by treatment of their keto ester precursors[20,21] with the sulfur ylid formed from trimethylsulfoxonium iodide and potassium *tert*-butoxide.[25] Even though β–hydroperoxy alcohols **9**–**11** were formed as mixtures of cis and trans isomers, the trans isomers predominated as demonstrated by the triphenylphosphine reduction of **9** to its corresponding 1,2-diol **19** and NMR analysis of the latter (Scheme 3). Observation of a signal at 66.5 ppm in the ^{13}C NMR spectrum of **19**[26] is consistent with a shielded axial hydroxymethyl group indicating that the hydroperoxide in **9** is equatorial. Similarly, we suggest that the signal at 62.9 ppm in the ^{13}C NMR spectrum of **9** is that of a shielded axial hydroxymethyl group. By way of comparison, Li et al.[23] report hydroxymethyl group ^{13}C NMR signals at 61.6 and 67.2 ppm for the isomers of β–hydroperoxy alcohol **20**. Finally, trioxane acid **1d** was obtained by hydrolysis of trioxane ester **18**; the latter was formed in low yield by acid-catalyzed condensation of β–hydroperoxy alcohol **17**[22] with methyl 2-(4-oxocyclohexyl)acetate.

Tetraoxane acids **2c** and **5c** were obtained by hydrolysis of their respective tetraoxane esters **23** and **24**; the latter were formed in 45 and 75% yields by Re_2O_7 catalyzed condensation[27] of 1,1-dihydroperoxide esters **21** and **22** with 2-adamantanone. 1,1-Dihydroperoxide esters **21** and **22** were obtained in quantitative yields from the corresponding keto esters by treatment with 50% aq. H_2O_2 and I_2 catalyst.[28] Tetraoxane acids **1c**, **3c**, and **4c** were synthesized as previously described.[29,30]

Target compound efficacy data against *F. hepatica* are shown in Tables 1 and 2. At eight to thirteen weeks post-infection, rats were treated with single 25–100 mg/kg oral doses of target compounds prepared as suspensions in 7% (v/v) Tween 80 and 3% (v/v) EtOH. At day 6 post-treatment, rats were sacrificed 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 was calculated using the Kruskal-Wallis test.

Like **1a**, seven compounds were completely curative at 100 mg/kg doses (Table 1). These compounds were then tested at lower doses of 50 and 25 mg/kg (Table 2). Several trends can be seen from the combined efficacy data. First, we suggest that the complete loss of efficacy for 1,2,4-trioxane **1d** compared to its active regioisomer **1b** results from a different iron (II) reaction profile. Previous investigations[22] with the unsubstituted (Y = H) analogs of **1d** and **1b** reveal that although both 1,2,4-trioxanes undergo a preferred attack of iron (II) on the less hindered peroxide oxygen atom, **1d** forms a higher proportion of inactive carbonyl-containing reaction products, and, unlike **1b**, does not form a secondary carbon-centered radical by β-scission of the spiroadamantane substructure. Second, for 1,2,4-trioxolane/1,2,4-trioxane/1,2,4,5-tetraoxane compound sets **1a**–**1c**, **2a**–**2c**, **3a**–**3c**, **4a**–**4c**, and **5a**–**5c**, the trioxanes and tetraoxanes were superior to the trioxolanes. Third, the efficacies of **1a**–**1c**

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compared to **2a**–**2c** show the superiority of an 8'-carboxymethyl vs. 8'-carboxy substituent. Fourth, the efficacies of **1a**–**1c** compared to **3a**–**3c** and **2a**–**2c** compared to **4a**–**4c** show the superiority of a spiroadamantane vs. spirocyclohexane. Fifth, unlike the superior antimalarial efficacies of 8'-aryl vs. 8'-alkyl ozonides,[16] the 8'-aryl **5a**–**5c** were inferior to the corresponding 8'alkyl peroxide heterocycles **1a**–**1c**. Finally, compounds **1b** and **1c** had the highest overall efficacies, but of the two, as previously determined by Kirchhofer et al.,[31] **1c** had the best efficacy against juvenile *F. hepatica* and is easier to synthesize than **1b**. Ongoing investigations will assess if the superior efficacies of the 1,2,4-trioxanes and 1,2,4,5-tetraoxanes vs. the corresponding 1,2,4-trioxolanes are due to pharmacokinetic differences.[32]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

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15. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ 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 77.0 ppm for ^{13}C NMR.*trans*-Adamantane-2-spiro-3'-9'-carboxymethyl-1',2',4'-trioxaspiro[5.5]undecane (**1b**). mp 178–179 °C. ^{1}H NMR δ 0.96–2.20 (m, 21H), 2.29 (d, *J* = 5.0 Hz, 2H), 2.54 (brs, 1H), 2.95 (brs, 1H), 3.74 (s, 2H); ^{13}C NMR δ 27.1, 27.6 (br), 28.6 (br), 29.3 (br), 31.5 (br), 33.4, 36.1 (br), 37.1, 39.7, 62.7, 77.6, 104.4, 177.5. Anal ($C_{19}H_{28}O_5$) C, 67.83; H, 8.39. Found: C, 68.02; H, 8.36.Adamantane-2-spiro-3'-9'-carboxymethyl-1',2',5'-trioxaspiro[5.5]undecane (**1d**). mp 210–211 °C. ^{1}H NMR δ 1.20–2.00(m, 19H), 2.04–2.26 (m, 2H), 2.27 (d, *J* = 6.0 Hz, 2H), 2.73 (brs, 1H), 2.92 (brs, 1H), 3.75 (brs, 1H), 4.07 (brs, 1H), 10.98 (brs, 1H); ^{13}C NMR δ 27.4, 27.5, 28.5 (br), 29.3 (br), 31.9, 33.6, 34.3 (br),

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37.7, 40.5, 63.9, 81.3, 101.4, 178.3. Anal ($C_{19}H_{28}O_5$) C, 67.83; H, 8.39. Found: C, 68.01; H, 8.18.*trans*-Adamantane-2-spiro-3'-9'-carboxy-1',2',4'-trioxaspiro[5.5]undecane (**2b**). mp 180–181 °C. ^{1}H NMR δ 1.20–2.20 (m, 21H), 2.52–2.63 (m, 1H), 2.94 (brs, 1H), 3.62 (brs, 1H), 3.72 (brs, 1H); ^{13}C NMR δ 22.7 (br), 23.8 (br), 27.1, 27.9 (br), 28.5 (br), 30.0 (br), 33.0 (br), 33.3, 36.0 (br), 37.1, 40.5, 64.0, 76.9, 104.4, 181.2. Anal ($C_{18}H_{26}O_5$) C, 67.06; H, 8.13. Found: C, 67.30; H, 8.28.Adamantane-2-spiro-3'-9'-carboxy-1',2',4',5'-tetraoxaspiro[5.5]undecane (**2c**). mp 175–176 °C. ^{1}H NMR δ 1.44–2.12 (m, 20H), 2.42–2.52 (m, 1H), 2.93 (brs, 1H), 3.16 (brs, 1H); ^{13}C NMR δ 23.6 (br), 24.5 (br), 27.0, 28.1 (br), 30.2 (br), 33.1, 34.3 (br), 36.9, 41.2, 107.0, 110.6, 179.8. Anal ($C_{17}H_{24}O_6$) C, 62.95; H, 7.46. Found: C, 62.51; H, 7.50.*trans*-3-Carboxymethyl-7,8,15-trioxadispiro[5.2.5.2]hexadecane (**3b**). mp 196–197 °C. ^{1}H NMR δ 0.96–1.22 (m, 2H), 1.32–2.00 (m, 15H), 2.29 (d, *J* = 6.5 Hz, 2H), 2.18 (brs, 1H), 2.50 (brs, 1H), 3.75 (s, 2H); ^{13}C NMR δ 22.3, 25.5, 28.4 (br), 33.3, 39.8, 63.3, 77.8, 102.3, 177.7. Anal ($C_{15}H_{24}O_5$) C, 63.36; H, 8.51. Found: C, 63.59; H, 8.48.*cis*-3-Carboxy-7,14,15-trioxadispiro[5.1.5.2]pentadecane (**4a**). mp 161–163 °C; ^{1}H NMR δ 1.34–1.99 (m, 18H), 2.35–2.39 (m, 1H); ^{13}C NMR δ 27.7, 24.8, 25.9, 33.1, 34.5, 41.0, 107.7, 109.1, 181.3. Anal ($C_{13}H_{20}O_5$) C, 60.92; H, 7.87. Found: C, 60.74; H, 7.79.*trans*-3-Carboxy-7,8,15-trioxadispiro[5.2.5.2]hexadecane (**4b**). mp 157–158 °C. ^{1}H NMR δ 1.20–2.40 (m, 22H), 2.53–2.64 (m, 1H), 3.61 (brs, 1H), 3.75 (brs, 1H); ^{13}C NMR δ 22.3, 22.7 (br), 25.5, 28.2 (br), 29.9 (br), 34.6 (br), 40.4, 64.6, 102.3, 181.1. Anal ($C_{14}H_{22}O_5$) C, 62.20; H, 8.20. Found: C, 62.26; H, 8.30.*trans*-Adamantane-2-spiro-3'-9'-(4'-carboxyphenyl)-1',2',4'-trioxaspiro[5.5]undecane (**5b**). mp 212–213 °C. ^{1}H NMR δ 1.38–2.20 (m, 20H), 2.64–2.74 (m, 1H), 2.86 (brs, 1H), 2.98 (brs, 1H), 3.76–4.02 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 11.51 (brs, 1H); ^{13}C NMR δ 27.1, 28.8 (br), 33.0 (br), 33.4, 36.4 (br), 37.1, 43.7, 62.3, 77.6, 104.5, 126.9, 127.2, 130.5, 152.2, 171.0. Anal ($C_{24}H_{30}O_5$) C, 72.34; H, 7.59. Found: C, 72.22; H, 7.63.Adamantane-2-spiro-3'-9'-(4'-carboxyphenyl)-1',2',4',5'-tetraoxaspiro[5.5]undecane (**5c**). mp 194–195 °C; ^{1}H NMR δ 1.56–2.14 (m, 20H), 2.66–2.76 (m, 1H), 3.20 (brs, 1H), 3.32 (brs, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 27.0, 29.5 (br), 30.1 (br), 31.8 (br), 33.1, 34.2 (br), 36.9, 43.8, 107.3, 110.6, 127.1, 127.3, 130.5, 152.2, 171.4. Anal ($C_{23}H_{28}O_6$) C, 68.98; H, 7.05. Found: C, 68.90; H, 6.96.

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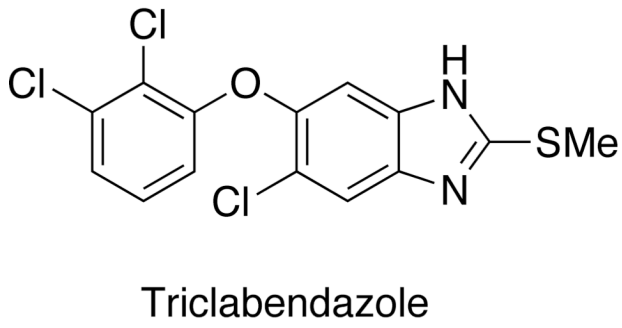

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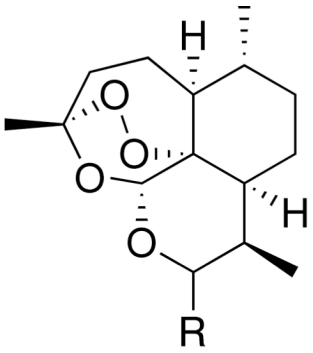

Artemisinin R = =O
Artemether R = ◄OCH3
Artesunate R = ····OCO(CH2)2COOH

Figure 1.

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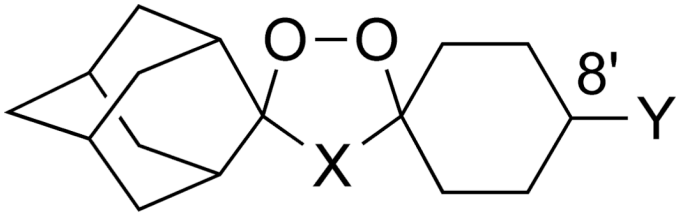
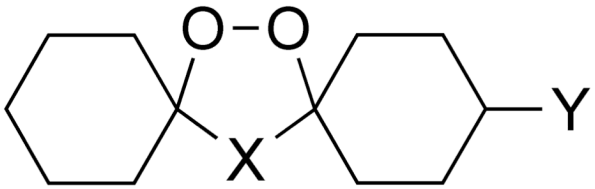
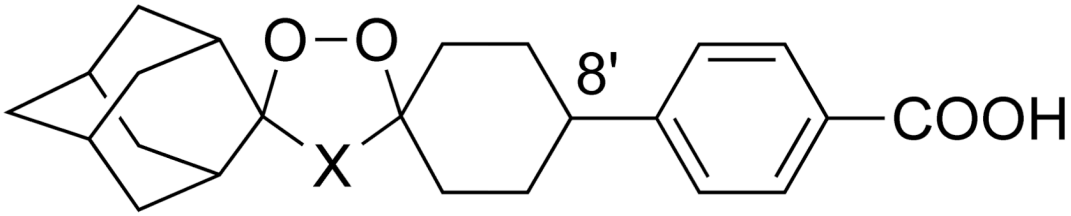




1a–1d, Y = CH_2COOH
2a–2c, Y = COOH

3a–3c, Y = CH_2COOH
4a–4c, Y = COOH



5a–5c

X = O (**a**), OCH_2 (**b**), OO (**c**), CH_2O (**d**)

Figure 2.
Target dispiro peroxides

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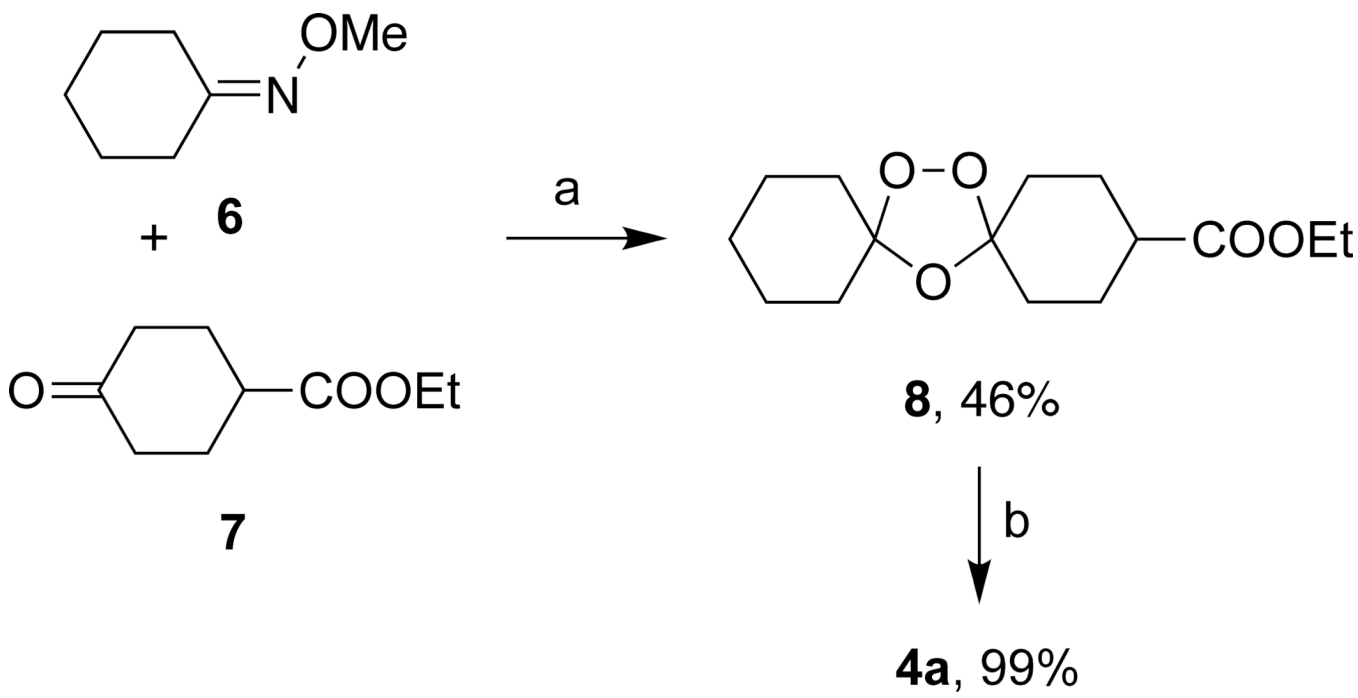
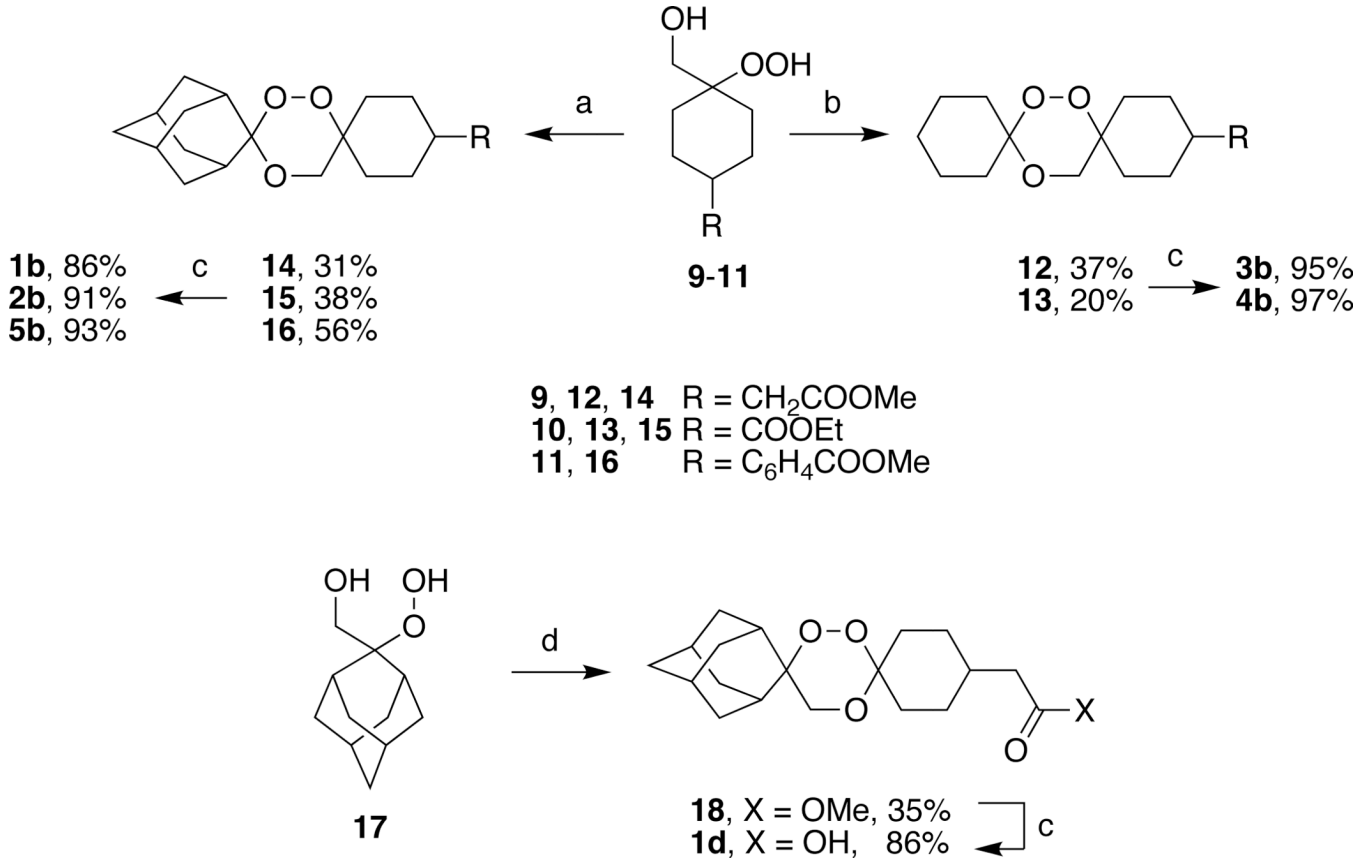


Scheme 1.
Reagents and conditions: (a) O_3, CH_2Cl_2/cyclohexane, 0 °C then sg chromatography; (b) aq. NaOH/EtOH, 60 °C, 4 h, then 1 M HCl, 0 °C.



Scheme 2.

Reagents and conditions: (a) 2-adamantanone, CSA, CH_2Cl_2, rt, 12 h; (b) cyclohexanone, CSA, CH_2Cl_2, rt, 12 h; (c) 15% aq. KOH, EtOH/THF, 50 °C, 4 h, then AcOH; (d) methyl 2-(4-oxocyclohexyl)acetate, CSA, CH_2Cl_2, rt, 12 h.

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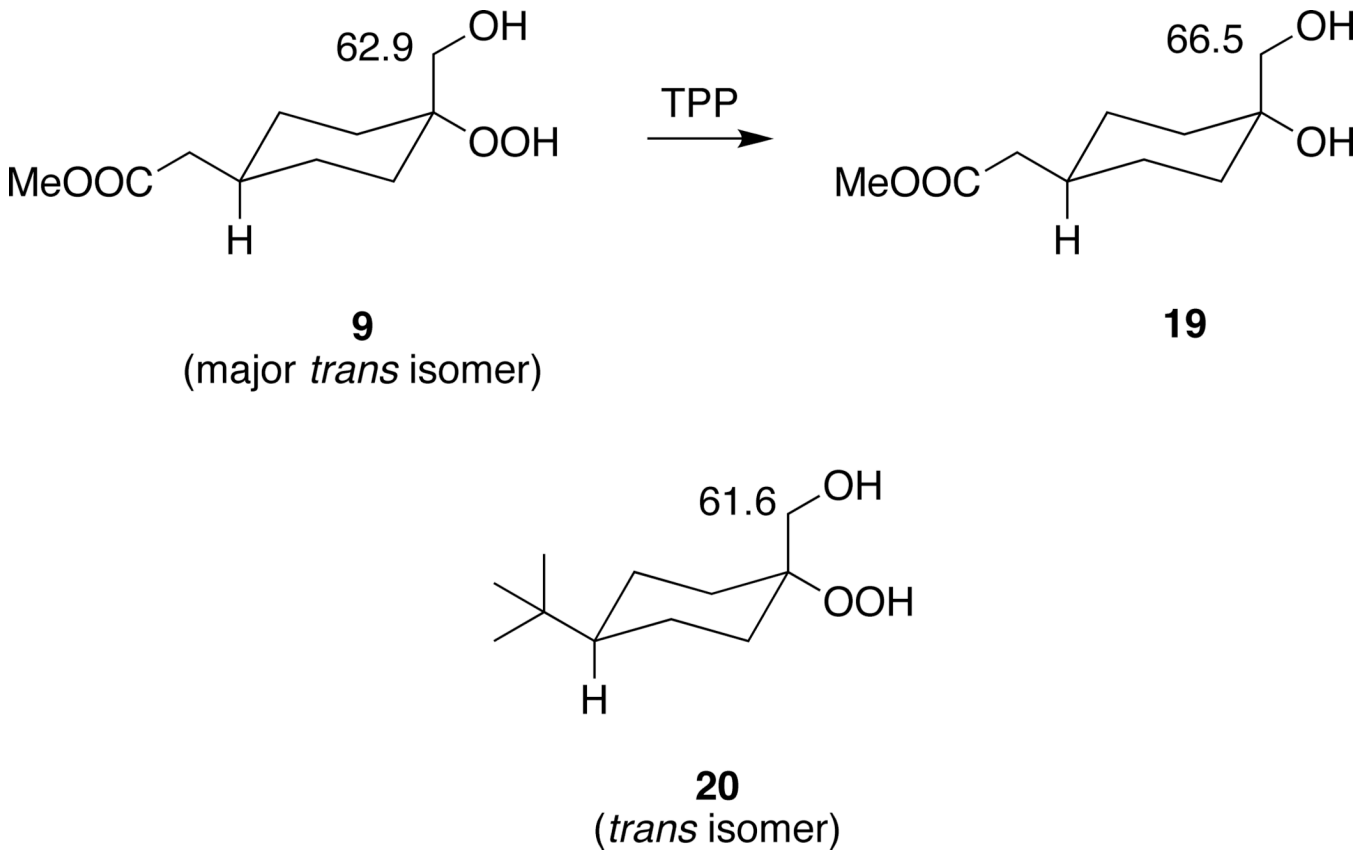
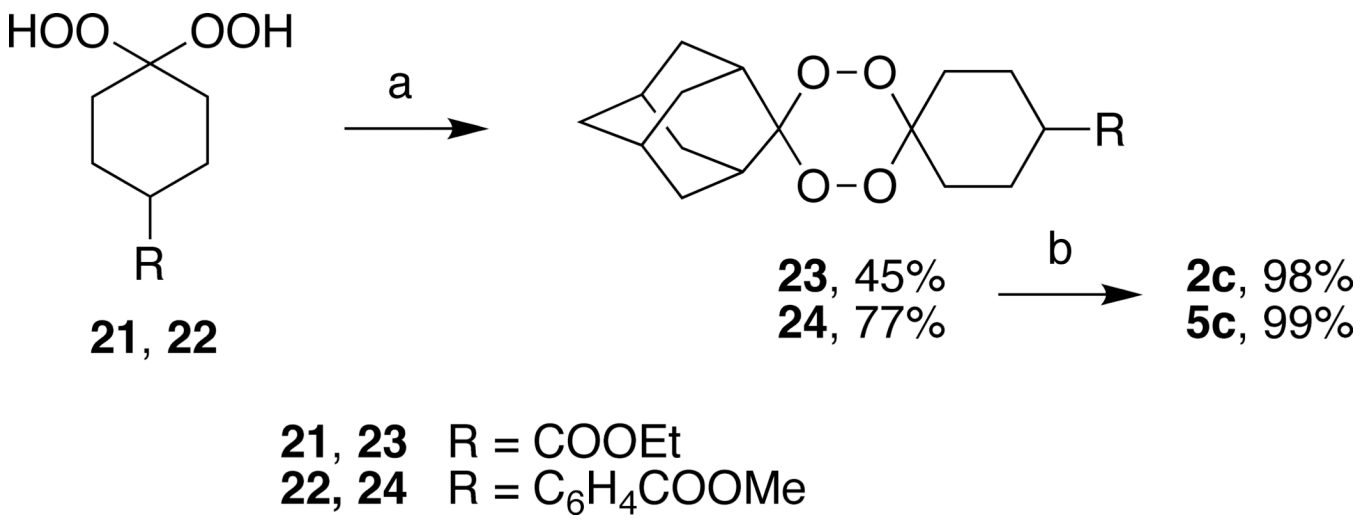


Scheme 3.

β–Hydroperoxy alcohol stereochemistry. Assigned hydroxymethyl group ^{13}C NMR signals are indicated in ppm.



Scheme 4.

Reagents and conditions: (a) 2-adamantanone, Re_2O_7, CH_2Cl_2, rt, 12 h; (b) 15% aq. KOH, EtOH/THF, 50 °C, 4–20 h, then AcOH.

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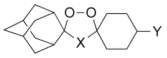
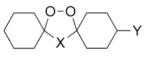
Table 1

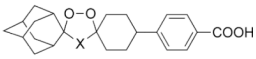
Worm burden reductions in adult *F. hepatica* harbored in rats following the administration of dispiro peroxides at single oral doses of 100 mg/kg.



1a–1d, 2a–2c



3a–3c, 4a–4c



5a–5c

Compd	X	Y	Worm Burden Reduction (%)	Cures[a]
Control	------	------	------	0/12
AS[b]	------	------	30	2/5
1a[c]	O	CH_2COOH	100[e]	10/10
1b	OCH_2	CH_2COOH	100[e]	3/3
1c	OO	CH_2COOH	100[e]	4/4
1d	CH_2O	CH_2COOH	0	0/3
2a	O	COOH	52	0/4
2b	OCH_2	COOH	61[e]	1/3
2c	OO	COOH	100[e]	4/4
3a[d]	O	CH_2COOH	0	0/3
3b	OCH_2	CH_2COOH	95[e]	2/3
3c	OO	CH_2COOH	29	0/3
4a	O	COOH	26	0/3
4b	OCH_2	COOH	100[e]	3/3
4c	OO	COOH	100[e]	3/3
5a	O	------	100[e]	3/3
5b	OCH_2	------	100[e]	3/3
5c	OO	------	92[e]	2/4

[a] cures = number of rats cured/number of rats treated

[b] AS = artesunate

[c] data from Keiser et al.[8]

[d] data from Zhao et al.[10]

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

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Table 2

Worm burden reductions in adult *F. hepatica* harbored in rats following the administration of selected dispiro peroxides at single oral doses of 50 and 25 mg/kg.

Compd	Dose (mg/kg)	Worm Burden Reduction (%)	Cures
Control	------	------	0/12
1a[a]	50	53	2/4
1b[b]	50	100[c]	4/4
1b[b]	25	88[c]	3/4
1c[b]	50	100[c]	4/4
1c[b]	25	71[c]	0/4
2c	50	48	1/4
4b	50	71[c]	0/4
4c[b]	50	61[c]	1/4
5a	50	19	0/4
5b[b]	50	100[c]	3/3
5b[b]	25	0	1/4

[a] data from Zhao et al.[10]

[b] data from Kirchhofer et al.[31]

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