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Simple Analogues of Qinghaosu (Artemisinin)

Yun Li,[a] Hong-Dong Hao,[a] Sergio Wittlin,[b, c] and Yikang Wu*[a]

Abstract: A series of 1,2,4-trioxanes were synthesized in which the key peroxy bonds were installed through a molybdenum-catalyzed perhydrolysis of the epoxy rings. A core structure was identified that may serve as a promising lead structure for further investigations because of its high antimalarial activity (comparable to that of artesunate and chloroquine), apparent potential for scale-up and derivatization, and facile monitoring/tracing by using UV light.

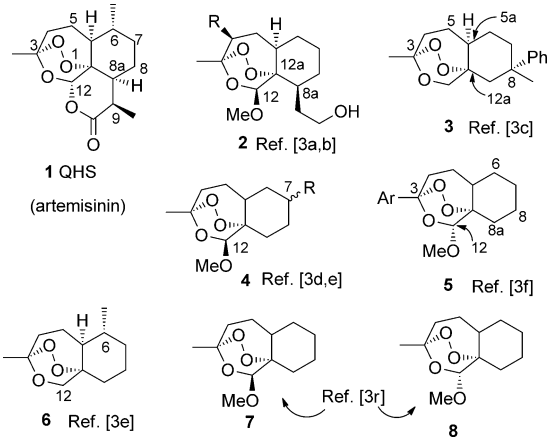
Keywords: cyclization · epoxides · peroxides · ring-opening · terpenoids

Introduction

The sesquiterpenoid qinghaosu[1] (QHS, artemisinin, **1**; Scheme 1), which was first isolated in the 1970s from the Chinese herb qinghao (*Artemisia annuua* L.), was a milestone[2] compound in the chemotherapy of malaria. This organic peroxide does not contain any nitrogen atoms or aromatic rings in its structure and hence its potent antimalarial activity cannot be explained by previous theories, thereby strongly suggesting a new mode of action. At a time when cases of multi-drug-resistant malaria were increasing at an alarming rate and began to create a global panic, the appearance of QHS and its derivatives as antimalarial drugs that were highly effective against even the "drug-resistant strains" naturally raised enormous interest in the scientific community around the world.

In most cases, synthetic studies on QHS have been directed towards developing new bioactive derivatives and analogues. Pioneering efforts in this area have led to the appearance of many synthetic organic peroxides with potent antimalarial activity,[3] including simple 1,2,4-trioxanes that were closely related to QHS (**2**–**8**).

In a continuation of our long-standing interest in the synthesis of organic peroxides, we recently developed a novel route to QHS,[4] which did not involve singlet oxygen or ozone during the installation of the key peroxy bond, as in all previous approaches. Herein, we prepared a range of simplified QHS analogues from their corresponding epoxy precursors by using the same perhydrolysis-based methodology. Some of these products were particularly interesting because of their facile accessibility and high antimalarial activity, which was comparable to that of chloroquine and artesunate.



Scheme 1. Structures of QHS (**1**) and several (synthetic) simplified analogues (**2**–**8**) that have been reported to have significant in vitro antimalarial activity. For the sake of comparison, the atom numbering of QHS was also used in the analogues when appropriate.

Results and Discussion

The QHS analogues that were investigated herein all contained a bicyclic core structure that was similar to that in compounds **2**–**8**, but with fewer substituents attached onto the fused-ring framework. To explore the scope and limitations of molybdenum complex **9**, which was formed from the reaction of Na_2MoO_4 and glycine,[4] the catalyzed-perhydrolysis and subsequent trioxane-formation procedure that

[a] Dr. Y. Li, Dr. H.-D. Hao, Prof. Dr. Y. Wu
State Key Laboratory of Bioorganic and
Natural Products Chemistry
Shanghai Institution of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
E-mail: yikangwu@sioc.ac.cn

[b] Dr. S. Wittlin
Swiss Tropical and Public Health Institute,
Socinstrasse 57, CH-4002 Basel (Switzerland)

[c] Dr. S. Wittlin
University of Basel
CH-4051 Basel (Switzerland)

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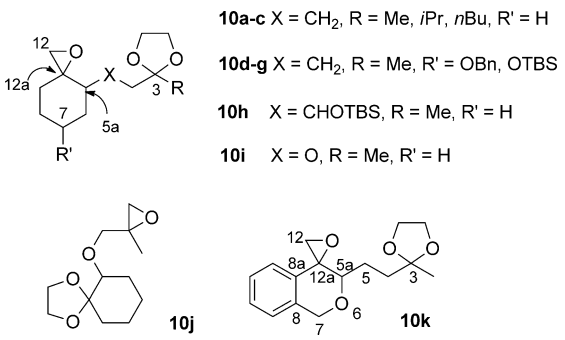
was recently developed in our laboratories, and to examine the effects of structural variation on antimalarial activity, we performed several structural changes that included: 1) changing the alkyl group at the C-3 position; 2) introducing a hydroxy group at the C-5 or C-7 positions; 3) replacing the C-5 CH_2 group with an oxygen atom; and 4) switching the positions of the C-12 and O-13 moieties (see below). Because of the convenience of our synthetic procedure and because of the potential advantages in biomedical studies that are associated with the introduction of a UV chromophore onto the trioxane structure, a substrate that contained a benzene ring was also investigated, which turned out to be the most promising drug candidate (see below).

The starting epoxy substrates (**10a–10k**) are shown in Scheme 2. O'Neill, Posner, and co-workers[3h] have shown that the absolute configuration of the organic peroxides did not significantly affect their antimalarial activity; therefore, to speed up the synthesis, racemic epoxy substrates were used (except for compound **10h**[5]).



Scheme 2. Starting epoxides for the perhydrolysis reaction; for the sake of comparison, the atom numbering of QHS (see Scheme 1) was also used.

The perhydrolysis of **10a–10k** was performed under the same conditions as in our synthesis of QHS ($9/H_2O_2/Et_2O$). Because the epoxy groups were installed through a Corey–Chaykovsky[6] reaction of the corresponding ketones without much diastereoselectivity, only a percentage of the epoxy substrates were of the correct relative configuration for perhydrolysis. Therefore, the yields of the resulting β-hydroxy hydroperoxides (Table 1)[7] were typically lower than those of the corresponding conversion in the synthesis of QHS (74%).[4]

The conversion of compounds **11a–11k** into compounds **12a–12k** proceeded rather smoothly, although their yields were heavily dependent on the structure. In many cases, the isolated trioxanes were enriched in, or predominated by, one diastereomer, but the configuration of the C-12a position (where H_2O_2 opened the epoxy ring) with respect to the ring conjuncture could not be established experimentally. Nevertheless, judging from the striking structural similarity, the relative configurations in these cases were likely to be the same as that in QHS (Table 1).

The relative configuration of the C-7 atom with respect to the C-5a atom in compounds **12d–12g** was confirmed by NOESY experiments on the precursors. In the case of compound (−)-**12h**, the selectivity of the well-established aldol reaction and the Mosher method allowed us to establish the configurations at the C-5 and C-5a positions. In the case of compound **12i**, two diastereomers were isolated, but their relative configurations were not identified.

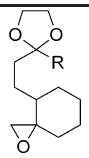
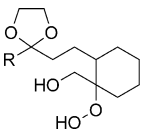
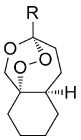
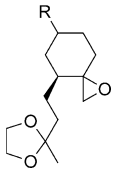
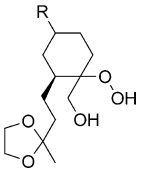
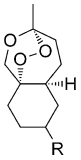
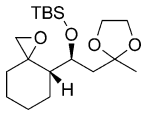
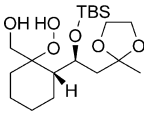
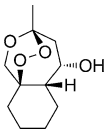
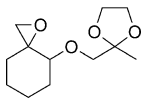
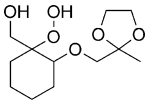
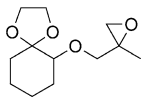
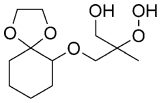
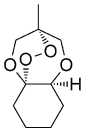
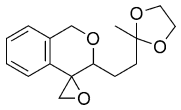
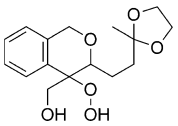
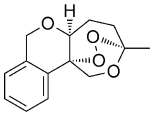
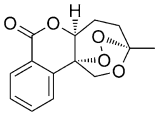
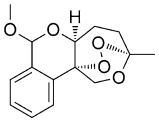
Because of its high antimalarial potency, the synthesis of compound **12k** appeared to merit particular attention. As shown in Scheme 3, alkylation of alcohol **13**[8] with bromide **14**[9] under NaH/THF/HMPA[10] conditions afforded benzyl ether **15**. Then, the Heck reaction of compound **15** with $Pd(OAc)_2$ in MeCN at 80°C for 36 hours in the presence of Ph_3P/K_2CO_3[10] afforded the desired alkene (**16**). Higher reaction temperatures (>110°C) did not afford any improvements but rather caused an undesired partial migration of the C–C double bond and hydrolysis of the ketal protecting group. Notably, if the reaction was performed in *N*,*N*-dimethylformamide (DMF) instead of MeCN, the yield of compound **16** was dramatically reduced (41%).

The C–C double bond was then converted into the corresponding epoxide, thereby setting a stage for the key transformation step: the incorporation of a hydroperoxy group into the carbon framework. The perhydrolysis[11] of compound **10k** proceeded smoothly under our previously reported conditions for the synthesis of QHS.[4] Intermediate compound **11k** readily underwent acid-catalyzed cyclization, thereby delivering compound **12k** in 75% yield.

Inspired by the conversion[12] of deoxo-QHS into QHS and by the literature synthesis of artemether,[13] we also performed similar transformations on compound **12k**. The oxidation of compound **12k** was realized by using a more recently reported procedure ($KMnO_4/FeCl_3$).[14] The resulting lactone (**12l**) was then reduced with DIBAL-H into a hemiacetal intermediate, which, on exposure to *p*-TsOH/MeOH, yielded acetal **12m** as an inseparable mixture of two epimers.

The in vitro antimalarial activity of the synthesized trioxanes are given in Table 1. From the simplest compounds considered herein (**12a–12c**), a larger alkyl group at the C-3 position was beneficial (Table 1, entries 1–3). The introduction of an OBn group at the C-7 position (**12d** and **12e**) led to an enhancement in activity that was comparable to that caused by the replacement of the C-3 methyl group with an *n*-butyl or *iso*-propyl group (Table 1, entries 4 and 5). This result, together with the observation that the stereochemistry at the C-7 position that was associated with the attachment of a substituent did not seem to make much difference in terms of antimalarial activity, revealed that this position could be potentially useful for further structural modification. In contrast, an unprotected hydroxy group at the C-7 position (**12f** and **12g**) decreased the antimalarial activity significantly (Table 1, entries 6 and 7). Perhaps the presence of a free hydroxy group made the substrate more sensitive towards oxidation and other reactions that lead to decomposition of these molecules. Indeed, the attachment of a hy-

Table 1. Conversion of the epoxides into trioxanes and the IC_{50} values of the products.[a]

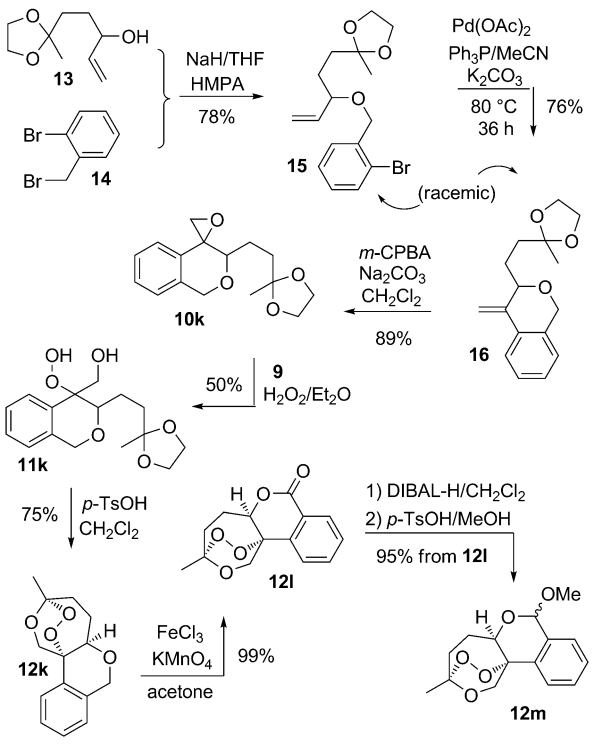
Entry	Epoxide **10**	R	β-Hydroxy perhydroxide **11**	Yield [%]	Trioxane **12**	Yield [%]	IC_{50} [ng mL^{-1}][b]
1	 **10a**	Me	 **11a**	61	 **12a**	74	1.8×10^2
2	**10b**	*i*Pr	**11b**	68	**12b**	74	5.3×10
3	**10c**	*i*Bu	**11c**	61	**12c**	78	4.8×10
4	 **10d**	α-OBn	 **11d**	42	 **12d**	78	4.8×10
5	**10e**	ß-OBn	**11e**	49	**12e**	58	4.9×10
6	**10f**	α-OTBS	**11f**	59	**12f**	62	7.0×10^2
7	**10g**	ß-OTBS	**11g**	52	**12g**	68	4.8×10^2
8	 **10h**		 **11h**	53	 **12h**	92	2.1×10^3[c] (6.4×10^2)[d]
9	 **10i**		 **11i**	54	 **12i** **12i'**	20 20	3.7×10^2[e] 5.3×10^2[f]
10	 **10j**		 **11j**	71	 **12j**	30	1.6×10^3
11	 **10k**		 **11k**	50	 **12k**	75	3.9
12	**10l**		**11l**		 **12l**		5.7
13	**10m**		**11m**		 **12m**		5.0
14					artesunate		1.2
15					chloroquine diphosphate		6.7

[a] All of the compounds were racemic except for compounds (−)-**12h** and its precursors; the relative configurations (see text) are shown when major diastereomers were observed. [b] Tested on *P. falciparum* (strain NF45); these data are the averages of 2–3 independent experiments (for further details of the procedure, see Ref. [7]). [c] For compound (±)-**12h**. [d] For compound (−)-**12h**. [e] The less-polar diastereomer. [f] The more-polar diastereomer.

droxy group at the C-5 position (**12h**) also showed similar adverse effects (Table 1, entry 8).

Substitution of the C-5 CH_2 group with an oxygen atom greatly facilitated the reaction (**12i** and **12i'**). However, unfortunately, this change in what was seemingly a non-functional unit resulted in substantially reduced antimalarial activity compared to that of compound **12a** (Table 1, entry 9). If the C-5 oxy substituent was accompanied by a switch of the C-12 CH_2 group and the C-13 oxygen atom (**12j**), even poorer activity was observed (Table 1, entry 10). Thus, structural variation along this line was not pursued further.

The trioxanes that contained a fused benzene ring (**12k**–**12m**) were significantly dissimilar to QHS than the other trioxanes considered herein. Nevertheless, these three peroxides all showed much higher potency (Table 1, entries 12–14) than those that were expected to be the most active because of their stronger structural resemblance to QHS. These results, together with the potential advantages of their facile synthesis and UV-detectable nature owing to the presence of a benzene ring, strongly suggested that the core structure that was shared by compounds **12k**–**12m** may be a promising lead structure for further studies.



Scheme 3. Synthesis of compounds **12k**–**12m**. HMPA = hexamethyl-phosphoramide, *p*-TsOH = *para*-toluenesulfonic acid, DIBAL-H = diisobutylaluminum hydride, *m*-CPBA = *meta*-chloroperbenzoic acid.

Conclusions

A series of simplified QHS analogues were synthesized with remarkable ease by using hydrogen peroxide in the key formation of the peroxy bonds. The incorporation of the inorganic peroxy unit into the organic frameworks was achieved through perhydrolysis of the epoxy rings under very mild conditions that were recently developed in our laboratories. Apart from demonstrating the distinct potential of this procedure in the synthesis of other organic peroxides, these newly accessed trioxanes also helped to unveil some previously unknown facets of the structure–activity relationship (SAR) of QHS-related antimalarial compounds, thereby contributing to the existing knowledge of SAR of organic peroxy antimalarial compounds. A new core structure that was remarkably dissimilar to QHS compared with the other trioxanes studied herein was identified, which might serve as a promising lead compound for further investigation because of its unexpectedly high antimalarial activity (comparable to that of artesunate and chloroquine), apparent potential for scale-up and derivatization, and facile monitoring/tracing by using UV light.

Experimental Section

General

THF and Et_2O (for the moisture-sensitive reactions) were distilled over Na/benzophenone under an argon atmosphere prior to use. CH_2Cl_2 and MeCN were distilled over CaH_2 prior to use. HMPA and DMSO were stirred with CaH_2 at ambient temperature for several days (in a sealed flask with a flat balloon to collect the H_2 gas evolved), distilled under a vacuum, and kept over activated 4 Å molecular sieves under an argon atmosphere. Ethereal H_2O_2[15] and molybdenum catalyst **9**[4] were prepared according to literature procedures.

*Alkylation of Compound **13** with Compound **14** to Afford Compound **15***

A solution of alcohol **13** (103 mg, 0.60 mmol) in dry THF (2 mL) was added to NaH (60% in mineral oil, 77 mg, 1.92 mmol, washed 3×petroleum ether). The mixture was stirred at ambient temperature for 1 h. Dry HMPA (0.24 mL, 1.2 mmol) was added, followed by a solution of bromide **14** (300 mg, 1.2 mmol) in dry THF (1 mL). The orange–yellow mixture was stirred at ambient temperature overnight. The mixture was portioned between Et_2O (10 mL) and saturated aqueous NH_4Cl (5 mL). The phases were separated and the aqueous layer was back-extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (2×15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (EtOAc/petroleum ether, 1:50) gave ether **15** as a colorless oil (160 mg, 0.47 mmol, 78% from compound **13**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (t, J = 7.0 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 5.70–5.82 (m, 1H), 5.27 (d, J = 6.4 Hz, 1H), 5.23 (s, 1H), 4.61 (d, J = 13 Hz, 1H), 4.43 (d, J = 13 Hz, 1H), 3.90–3.95 (m, 4H), 3.80 (dd, J = 5.3, 7.5 Hz, 1H), 1.74–1.88 (m, 2H), 1.62–1.74 (m, 2H), 1.32 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 138.1, 132.4, 129.1, 128.7, 127.3, 122.6, 117.5, 109.9, 81.1, 69.5, 64.6, 34.7, 29.8, 23.9 ppm; FTIR (film): $\tilde{\nu}$ = 2981, 2876, 1568, 1470, 1441, 1376, 1207, 1066, 927, 750 cm^{-1}; MS (ESI): *m/z*: 363.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{16}H_{21}O_3Br$: C 56.32, H 6.20; found: C 56.49, H 66.20.

*Cyclization of Compound **15** to Afford Compound **16***

PPh_3 (60 mg, 0.23 mmol), K_2CO_3 (480 mg, 3.50 mmol), and $Pd(OAc)_2$ (26 mg, 0.12 mmol) were added sequentially to a solution of compound **15** (200 mg, 0.58 mmol) in degassed MeCN (12 mL). The red–orange mixture was frozen in liquid N_2, evacuated with an oil pump, and warmed to ambient temperature after releasing the vacuum with argon gas (repeated three times). The mixture was then stirred at 80 °C under an argon atmosphere for 36 h. After cooling to ambient temperature, Et_2O (50 mL) was added, followed by water (20 mL). The phases were separated and the aqueous layer was back-extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (2×15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (EtOAc/petroleum ether, 1:20) gave ether **16** as a yellowish oil (114 mg, 0.44 mmol, 76% from **15**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.65 (m, 1H), 7.20–7.26 (m, 2H), 7.00–7.03 (m, 1H), 5.64 (s, 1H), 5.08 (s, 1H), 4.87 (d, J = 15.2 Hz, 1H), 4.75 (d, J = 15.3 Hz, 1H), 4.33 (t, J = 6.2 Hz, 1H), 3.89–3.98 (m, 4H), 1.72–2.06 (m, 4H), 1.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 134.3, 131.4, 127.7, 126.9, 124.3, 123.8, 109.9, 107.0, 65.6, 64.6, 34.8, 26.9, 23.9 ppm; FTIR (film): $\tilde{\nu}$ = 2980, 2880, 1635, 1485, 1449, 1375, 1255, 1065, 891, 776 cm^{-1}; MS (EI): *m/z*: 260 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{16}H_{20}O_3$: 260.1412 $[M]^+$; found: 260.1425.

*Epoxidation of Alkene **16** into Epoxide **10k***

Na_2CO_3 (8.0 mg, 0.07 mmol) and *m*-CPBA (75%, 34 mg, 0.15 mmol) were added to a stirring solution of alkene **16** (35 mg, 0.13 mmol) in dry CH_2Cl_2 (2 mL) in an ice-water bath. The mixture was then stirred at ambient temperature until TLC showed the complete consumption of the alkene. Saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (15 mL) and brine (2×20 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (EtOAc/petroleum ether, 1:10) gave epoxide **10k** as a colorless sticky oil (32 mg, 0.12 mmol, 89% from compound **16**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.31 (m, 2H), 7.13 (t, J = 3.8 Hz, 1H), 7.03 (t, J = 3.7 Hz, 1H), 4.92 (s, 2H), 3.82–4.03 (m, 5H), 3.31 (d, J = 4.4 Hz, 1H), 2.92 (d, J = 4.7 Hz,

1H), 1.94–2.08 (m, 1H), 1.55–1.78 (m, 2H), 1.39–1.54 (m, 1H), 1.34 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 133.6, 127.7, 127.1, 123.5, 123.2, 109.8, 68.1, 64.7, 64.6, 55.9, 54.0, 35.1, 23.9, 23.7 ppm; FTIR (film): $\tilde{\nu}$ = 2979, 2878, 1696, 1494, 1447, 1375, 1256, 1207, 1062, 869, 757 cm^{-1}; MS (EI): *m/z*: 276 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{16}H_{20}O_4$: 276.1362 $[M]^+$; found: 276.1358.

*Perhydrolysis of Compound **10k** to Afford Compound **11k***

Catalyst **7** (4 mg, 0.009 mmol) was added to a stirring solution of epoxide **10k** (37 mg, 0.13 mmol) in ethereal H_2O_2 (1 M, 1.5 mL) at ambient temperature. The mixture was stirred at ambient temperature for 4 h then water (5 mL) was added to the reaction mixture. The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator and column chromatography on silica gel (petroleum ether/EtOAc, 1:1) gave compound **11k** as a colorless oil (20 mg, 0.063 mmol, 50% from compound **10k**) along with recovered compound **10k** (10 mg, 0.035 mmol, 27%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.27–7.39 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 4.85 (s, 2H), 4.15 (dd, *J* = 2.3, 9.9 Hz, 1H), 3.90–4.04 (m, 5H), 3.83 (dd, *J* = 8.3, 11.2 Hz, 1H), 1.99–2.19 (m, 3H), 1.67–1.89 (m, 2H), 1.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.1, 134.2, 127.7, 127.1, 126.4, 123.6, 109.9, 82.3, 67.6, 64.5, 64.0, 40.6, 35.7, 23.8, 22.9 ppm; FTIR (film): $\tilde{\nu}$ = 3360, 2927, 1455, 1377, 1211, 1099, 1060, 762, 728 cm^{-1}; MS (ESI): *m/z*: 333.2 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_6$: 333.13086 $[M+Na]^+$; found: 333.12989.

*Cyclization of Compound **11k** to Afford Trioxane **12k***

p-TsOH (4 mg, 0.02 mmol) was added into a solution of **11k** (12 mg, 0.038 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at ambient temperature overnight until TLC showed complete consumption of the starting compound **11k**. Saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, the filtrate was concentrated on a rotary evaporator, and column chromatography on silica gel (EtOAc/petroleum ether, 1:20) gave trioxane **12k** as a white solid (7 mg, 0.028 mmol, 75%). M.p.: 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 6.8 Hz, 1H), 7.23–7.38 (m, 2H), 6.98 (d, *J* = 6.4 Hz, 1H), 4.81 (s, 2H), 4.27 (d, *J* = 11.7 Hz, 1H), 4.21 (dd, *J* = 11.6, 1.7 Hz, 1H), 3.69–3.90 (m, 1H), 2.31–2.52 (m, 1H), 1.84–2.19 (m, 3H), 1.43 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.0, 134.1, 128.6, 127.8, 127.2, 123.5, 103.7, 78.5, 73.4, 68.1, 65.2, 35.8, 34.4, 25.9, 25.4 ppm; FTIR (KBr): $\tilde{\nu}$ = 2927, 2853, 1490, 1448, 1372, 1255, 1215, 1147, 1104, 1078, 756 cm^{-1}; MS (EI): *m/z*: 248 (0.5) $[M]^+$, 216 (18), 204 (21); HRMS (EI): *m/z* calcd for $C_{14}H_{16}O_4$: 248.1049 $[M]^+$; found: 248.1042.

*Oxidation of Compound **12k** to Afford Lactone **12l***

$FeCl_3$ (77 mg, 0.48 mmol) and $KMnO_4$ (122 mg, 0.77 mmol) were added to a stirring solution of compound **12k** (21 mg, 0.077 mmol) in acetone (6 mL) at −78 °C. The bath was allowed to warm to ambient temperature and stirring was continued for 12 h before Et_2O (10 mL) and water (5 mL) were added. The phases were separated and the aqueous layer was back-extracted with Et_2O (3×15 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a crude residue, which was purified by column chromatography on silica gel (EtOAc/petroleum ether, 1:10) to afford compound **12l** as a colorless oil (20 mg, 0.076 mmol, 99% from compound **12k**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–8.14 (m, 1H), 7.64–7.82 (m, 2H), 7.47–7.58 (m, 1H), 4.56–4.67 (m, 1H), 4.50 (d, *J* = 7.9 Hz, 0.3H), 4.14–4.26 (m, 1.3H), 3.52 (d, *J* = 7.9 Hz, 0.3H), 2.25–2.55 (m, 2H), 2.11–2.53 (m, 1.3H), 1.84–2.06 (m, 0.7H), 1.63 (s, 2H), 1.46 ppm (s, 1H); FTIR (film): $\tilde{\nu}$ = 2935, 1736, 1603, 1458, 1275, 1150, 1136, 1076, 1039, 845, 757 cm^{-1}; MS (EI): *m/z* (%): 267 (2) $[M]^+$, 230 (28), 189 (55), 104 (100), 76 (57); HRMS (EI): *m/z* calcd for $C_{14}H_{14}O_5$: 262.0841 $[M]^+$; found: 262.0838.

*Conversion of Lactone **12l** into Acetal **12m***

DIBAL-H (1 M, in cyclohexane, 0.13 mL, 0.13 mmol) was added to a stirring solution of lactone **12l** (15 mg, 0.057 mmol) in dry CH_2Cl_2 (2 mL) at −78 °C under N_2. The mixture was stirred at −78 °C until TLC showed complete consumption of the lactone. MeOH (1 mL) was carefully added to quench the excess hydride, followed by saturated aqueous potassium sodium tartrate (5 mL) and Et_2O (5 mL). Stirring was continued at ambient temperature until the mixture became transparent. The mixture was extracted with Et_2O (3×15 mL) and the combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. The crude material was dissolved in anhydrous MeOH (4 mL) that contained *p*-TsOH (2 mg, 0.01 mmol) and the solution was stirred at ambient temperature for 2 h, after which time TLC analysis showed that the reaction had gone to completion. Saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (EtOAc/petroleum ether, 1:50) gave compound **12m** as a colorless oil (15 mg, 0.054 mmol, 95% from compound **12l**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.6 Hz, 0.7H), 7.57 (d, *J* = 7.6 Hz, 0.3H), 7.43–7.29 (m, 2H), 7.25–7.17 (m, 1H), 5.45 (s, 0.3H), 5.43 (s, 0.7H), 4.42 (d, *J* = 7.6 Hz, 0.3H), 4.34–4.14 (m, 2.4H), 3.56 (s, 3H), 3.53 (d, *J* = 7.6 Hz, 0.3H), 2.53–2.39 (m, 1H), 2.20–2.04 (m, 2H), 2.01–1.82 (m, 1H), 1.59 (s, 1H), 1.44 ppm (s, 2H); FTIR (film): $\tilde{\nu}$ = 2934, 2887, 1453, 1271, 1257, 1149, 1094, 1053, 1039, 1013, 759 cm^{-1}; MS (EI): *m/z* (%): 278 (2) $[M]^+$, 262 (16), 246 (3), 149 (48), 43 (100); HRMS (EI): *m/z* calcd for $C_{15}H_{18}O_5$: 278.1154 $[M]^+$; found: 278.1158.

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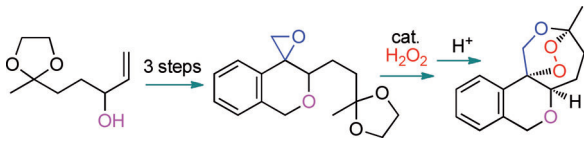

The temple of artemisinin: The key peroxy bonds in a series of 1,2,4-trioxanes were installed by molybdenum-catalyzed perhydrolysis of the epoxy rings. A novel core structure with potent antimalarial activity was identified.

Terpenoids

*Yun Li, Hong-Dong Hao, Sergio Wittlin, Yikang Wu** - ▮▮▮▮–▮▮▮▮

Simple Analogues of Qinghaosu (Artemisinin)