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Simplified analogues of qinghaosu (artemisinin)

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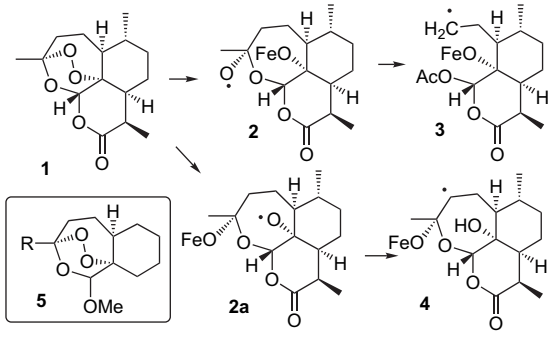
Abstract—Three new simplified analogues of qinghaosu have been designed and synthesized through simple routes without recourse to the commonly employed photosensitized oxidation. The peroxy bonds in the target molecules were taken from UHP with the first peroxy–carbon bond formed through a hemiketal exchange reaction and the second by either an intramolecular Michael addition or a Hg(II)-mediated ring-closure reaction. All three peroxides possess a seven-membered peroxy ring fused to an all-carbon six-membered ring, a structural motif required for generating the carbon-centered substituted ethyl radicals.

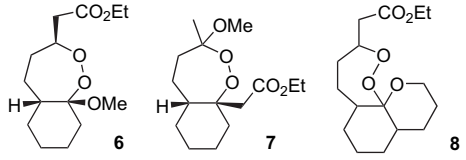
1. Introduction

Discovery of qinghaosu[1] (**1**, artemisinin) by Chinese scientists in the 1970s not only ushered in a new era for chemotherapy of malaria, but also greatly stimulated the studies on organic peroxides. Since then, design and synthesis of organic peroxides have gradually developed into a highly active area of organic chemistry.

It was known[1e,g] long time ago that the peroxy bond is the essential functionality for qinghaosu's antimalarial activity. However, the antimalarial potency of organic peroxides does vary tremendously with the molecular structure, indicating that the carbon framework also plays an important role. Although up to now no definite conclusion on the mode of antimalarial action is available, it is broadly accepted that the transient carbon-centered radicals generated after cleavage of the peroxy bond may be the lethal species.[2] In particular, the primary radical **3** (Scheme 1), which is able to alkylate heme[3] and sulfur ligand[4] of cysteine–iron chelates, has drawn considerable attention.



Scheme 1.



A seven-membered peroxy ring is a pre-requisite for generating such substituted ethyl radicals as in **3**. It thus appears that those peroxides able to generate similar radicals may also be potent antimalarials. Several analogues of general structure **5** indeed have been proven to be highly effective.[5]

We have also been working on design and synthesis of organic peroxides, with a preference for using ground-state reagents as the source of the peroxy bonds.[6] Herein we wish to report on three new simplified analogues (**6**, **7**, and **8**) of qinghaosu, all of which contain a seven-membered peroxy ring fused to an all-carbon six-membered ring, a structural motif required for generating the carbon-centered substituted ethyl radicals similar to **3**.

2. Results and discussions

The UHP/$Sc(OTf)_3$–Et_2NH/F_3CCH_2OH protocol developed by Kobayashi and co-workers[7] is a convenient way to incorporate the peroxy bond into the substrate molecular framework. However, this method completely failed in our previous attempt[6e] to synthesize a seven-membered

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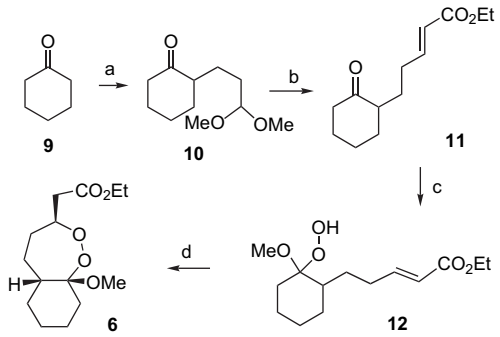
monocyclic peroxy ring. In the present work, we thought that the degrees of freedom in the transition state for the final ring-closure step could be significantly reduced and therefore still deserved a further try.

The synthesis of **6** is outlined in Scheme 2. Alkylation of the enolate of cyclohexanone with $I(CH_2)_2CH(OCH_3)_2$[8] in the presence of HMPA gave the known[9] **10**. Hydrolysis of the dimethyl acetal in acetone–H_2O catalyzed by pyridium *p*-toluenesulfonate (PPTS) led to the intermediate aldehyde, which on treatment with $Ph_3P{=}CHCO_2Et$ resulted in the known[10] α,β-unsaturated ester **11**. The hydroperoxyl group was then introduced using UHP/$Sc(OTf)_3\cdot xH_2O$ to yield the peroxy hemiketal **12** smoothly as a 1:1 mixture of two diastereomers.



Scheme 2. (a) (i) LDA/−78 °C/1 h; (ii) HMPA/$I(CH_2)_2CH(OCH_3)_2$/−78 °C to rt/17 h, 56%; (b) (i) PPTS/acetone–H_2O/40 °C, (ii) $Ph_3P{=}CHCO_2Et$/rt/12 h, 83% from **10**; (c) UHP/$Sc(OTf)_3\cdot xH_2O$/MeOH/rt/1 d, 86%; and (d) cf. Table 1 and the text.

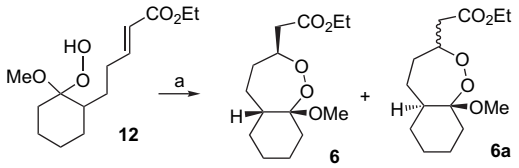
The final ring-closure was first attempted under the Et_2NH/F_3CCH_2OH conditions of Kobayashi. However, stirring at the ambient temperature for 15 h led to no reaction at all. At slightly elevated temperature (40 °C) after 17 h, only traces of **6** could be detected on TLC (Table 1). The main components in the reaction mixture were the ketone **11** and the hemiketal similar to **12**, but with the MeO– group replaced by a F_3CCH_2O– (from the solvent). Using other organic bases such as Et_3N, *i*-Pr_2NEt, DBU, TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), pyridine, piperidine, and DMAP to replace Et_2NH did not lead to any improvements. Inorganic bases such as K_2CO_3 or Cs_2CO_3 appeared to be better (entries 9–11). With K_2CO_3 as the base and F_3CCH_2OH as the solvent compound **6** was obtained in 33% yield. The relative configuration of **6** shown in Scheme 2 was established by 2D NMR spectroscopy (vide infra).

Table 1. Intramolecular Michael addition of **12** under different conditions

Entry	Conditions[a]	Yield of **6** (%)
1	$HNEt_2/CF_3CH_2OH$	Traces
2	NEt_3/CF_3CH_2OH	—[b]
3	*i*-Pr_2EtN/CF_3CH_2OH	—[b]
4	DBU/CF_3CH_2OH	—[b]
5	TBD/CF_3CH_2OH	—[b]
6	$Pyridine/CF_3CH_2OH$	Traces
7	$Piperidine/CF_3CH_2OH$	Traces
8	$DMAP/CF_3CH_2OH$	—[b]
9	K_2CO_3/CF_3CH_2OH[c]	33
10	Cs_2CO_3/CF_3CH_2OH	18
11	K_2CO_3/MeOH	8

[a] In all runs the substrate concentration was 0.016 M, with the quantity of the added base being 0.32 M equiv with respect to the substrate. The reaction mixtures were stirred at ambient temperature for the first 15 h and at 40 °C for the subsequent 17 h.
[b] No **6** (and/or **6a** as well as **6b**) could be detected on TLC.
[c] The mixture was stirred at 40 °C for 3 d.

Apart from the intramolecular Michael addition, we also tried a Hg(II)-induced addition of the hydroperoxyl group to the C–C double bond at the final ring-closure step. As shown in Scheme 3, treatment of **12** with $Hg(OAc)_2$ in CH_2Cl_2 at ambient temperature for 15 h led to complete disappearance of starting compound **12**. The intermediate organomercury compounds were not isolated, but directly treated with a solution of $NaBH_4$ in 3 M aqueous NaOH at 0 °C for 1 h to give the end products in a 63% total yield. Interestingly, under such conditions apart from **6** another two diastereomers **6a** and **6b** were also formed (which were absent in the Michael addition).



Scheme 3. (a) (i) $Hg(OAc)_2/CH_2Cl_2$/rt/15 h; (ii) $NaBH_4$ in 3 M NaOH aq/CH_2Cl_2/0 °C/1 h, 63% from **12** (dr **6**/**6a**=1.8:1).

Careful ^1H NMR analyses revealed that **6** should have the relative configuration as shown in Figure 1 and Scheme 2. In the NOSEY spectrum, an NOE was observed between the methoxy protons and the methine proton H-4 (arbitrary numbering), ensuring a cis relationship at the ring juncture.

In the COSY spectrum, only H-5a (Fig. 1) is coupled with the H-4, suggesting a dihedral angle of nearly 90 degrees between the H-4 and the H-5b. An NOE signal was also observed between the H-7 and one (H-5a) of the two protons at position 5. Close inspection of molecular model reveals that only the relative configurations drawn in Figure 1 can explain these observations.

The other diastereomers **6a** and **6b** formed in the Hg(II)-mediated ring-closure demercuration, which were obtained in 1:3 ratio as an inseparable mixture of the C-7 (arbitrary numbering, Fig. 2) epimers, did not show any NOE signal between the H-4 and the methoxy protons. Therefore, the ring conjuncture must be trans as depicted in Figure 2.

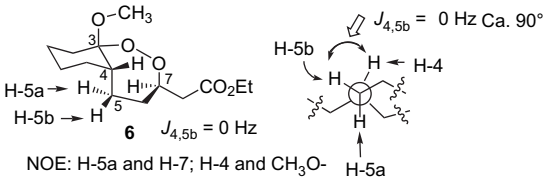


Figure 1. The relative configuration of compound **6**.

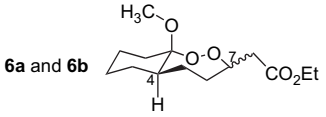
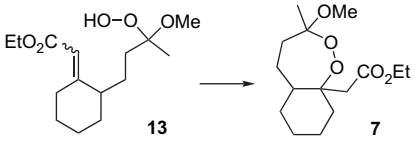


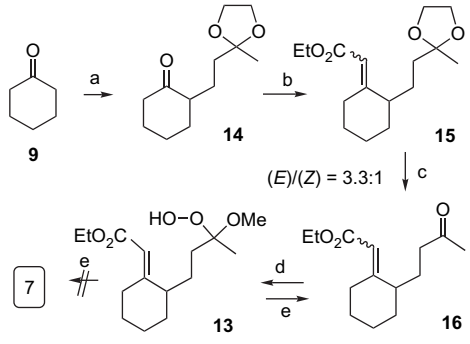
Figure 2. The relative configuration of **6a** and **6b**.

The second target molecule (**7**) mimics qinghaosu even better than **6**, because the methyl ketal partial structure is completely retained and the both terminals of the peroxy bond are connected to quaternary carbons. Using the same strategy of introducing the peroxy bond adopted above to reach such a structural motif requires an adjustment in the ring-closure precursor—moving the peroxy hemiketal to the side chain and putting the Michael acceptor at the cyclohexane ring (Scheme 4). Such changes are expected to lead to increased difficulty in the final ring-closure reaction, because the C–C double bond (Michael acceptor) here is tri-substituted—more hindered than those di-substituted ones in all previously known successful cases. However, these changes also make this system a good scenario for examining the scope and limitations of the methodology.



Scheme 4.

The precursor **13** was synthesized using the route shown in Scheme 5. Alkylation of cyclohexanone was achieved in a fashion similar to that employed in the synthesis of **10**, through reaction of the intermediate enolate with the known[11] halide $I(CH_2)_2CMe(OCH_2)_2$ in the presence of HMPA. The resultant **14**[12] was treated with the anion of $(EtO)_2POCH_2CO_2Et$ in THF at refluxing temperature for 6 h to give the α,β-unsaturated ester **15** as a 3.3:1 mixture of the (*E*)- and (*Z*)-isomers as determined by ^1H NMR. These isomers were very difficult to separate from each other. Therefore in the preparative runs, the mixture of the two isomers was used in the next step.



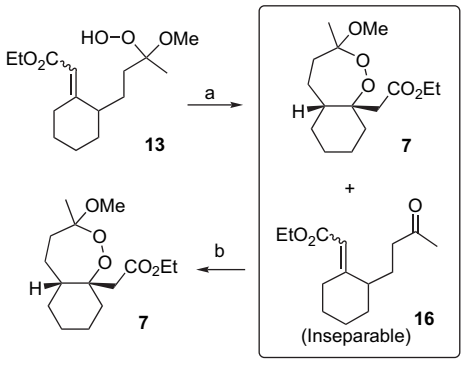
Scheme 5. (a) (i) LDA/−78 °C/1 h; (ii) HMPA/$I(CH_2)_2CMe(OCH_2)_2$/−78 °C to rt/17 h, 58%; (b) NaH/$(EtO)_2POCH_2CO_2Et$/THF/reflux/6 h, 81% ((*E*)/(*Z*)=3.3:1); (c) DDQ/CH_3CN–H_2O/0 °C/30 min, 90%; (d) UHP/$Sc(OTf)_3\cdot xH_2O$/MeOH/rt/3 d, 56%; and (e) K_2CO_3/CF_3CH_2OH/rt/1 d then 35 °C/2 d, 66% of **16** (from **13**).

The ketal functionality was then hydrolyzed by reaction with DDQ[13] to obtain the ketone **16**. The C–C double bond isomers were readily separated here. The (*E*)-isomer was smoothly converted into hydroperoxyl hemiketal **13** under the conditions of Kobayashi (Scheme 5).

The critical ring-closure was first attempted under the K_2CO_3/CF_3CH_2OH conditions, which was proved to be most satisfactory in the synthesis of **6** (Table 1, entry 9). In sharp contrast to the facile addition with **12**, no reaction took place after 24 h at ambient temperature although the ring-size and the degrees of freedom of the transition state should be essentially the same as those for the transition state in the reaction of **12**. Further reaction at slightly elevated temperature (35 °C) for 2 d led to **16** in 66% yield. However, no **7** could be detected.

The unfruitful efforts with the simple base-catalyzed intramolecular Michael addition prompted us to adopt the Hg(II)-mediated ring-closure protocol again, because it worked so well for **12**. However, this time the reaction was rather sluggish. Stirring at ambient temperature for 15 h did not result in dissolution as observed in reaction with **12**. No products could be detected on TLC.

The mixture was then stirred at 35 °C for 5 d, when most of the starting **13** disappeared (Scheme 6). The intermediate organomercury compounds were then treated with freshly prepared solution of $NaBH_4$ in aq 3 M NaOH at 0 °C for 1 h to give the demercurated product(s).



Scheme 6. (a) (i) $Hg(OAc)_2/CH_2Cl_2$/35 °C/5 d; (ii) $NaBH_4$ in 3 M NaOH aq/CH_2Cl_2/0 °C/1 h and (b) O_3/CH_2Cl_2 26% from **13**.

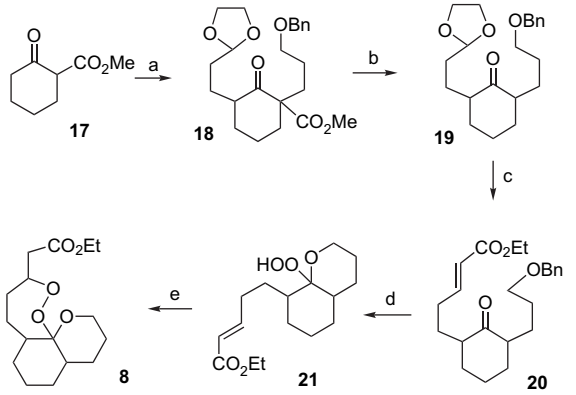
The demercurated product was readily isolated by chromatography. However, spectroscopic analyses clearly revealed co-existence of **16**. As the polarity of the two substances is almost the same and thus practically inseparable by chromatography on silica gel, we decided to try chemical means to remove **16**.

One of the reactions that may selectively occur with **16** but not **7** appears to be ozonolysis. Therefore, we tried it immediately. To our gratification, passing ozone into the mixture of **7** and **16** in CH_2Cl_2 at −78 °C indeed eliminated **16** completely, affording pure **7** after simple chromatographic separation.

The relative configuration at the ring juncture of **7** was determined to be cis, on the basis of an observed NOE between the methine H(CH) and those protons at the carbon α to the ester carbonyl group. However, the configuration of the ketal carbon remained unclear, because of lack of usable signals in 1D and 2D NMR.

Synthesis of **8** is outlined in Scheme 7. The commercially available ketone-ester **17** was converted to its dianion by sequential treatment with NaH and *n*-BuLi. The dianion was then alkylated with $I(CH_2)_2CH(OCH_2)_2$[8] to obtain an

intermediate, which on further alkylation with $I(CH_2)_3OBn$ yielded **18** as a 1:5.7 mixture of two diastereomers as shown by ^1H NMR.



Scheme 7. (a) (i) NaH/0 °C/30 min; (ii) *n*-BuLi/$I(CH_2)_2CH(OCH_2)_2$/THF/−78 °C to rt/15 h; (iii) NaH/DMF–THF/0 °C/30 min; (iv) $I(CH_2)_3OBn$, reflux/2 h, 75% from **17** (dr=5.7:1); (b) $MgCl_2$/DMSO/reflux, 78%; (c) (i) 1 M HCl/THF/60 °C/2 h; (ii) $Ph_3P{=}CHCO_2Et/CH_2Cl_2$, 83% from **19** (dr=1.5:1); (d) (i) BCl_3/−78 °C/4 h; (ii) UHP/*p*-TsOH·H_2O/DME/rt/3 d, 75% and (e) (i) $Hg(OAc)_2$/cat. $HClO_4/CH_2Cl_2$; (ii) $NaBH_4$ in 3 M NaOH/CH_2Cl_2/0 °C/1 h, 35% from **21**.

Removal of the ester functionality was then achieved by heating **18** in DMSO in the presence[14] of $MgCl_2$. The acetal in the side chain was hydrolyzed. The resultant aldehyde was treated with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 to give **20** as a 1:1.5 mixture of two diastereomers differing only at the configurations at the two carbons α to the ketone carbonyl group. The two isomers were separated by column chromatography and the major component was utilized in the next step.

Cleavage of the benzyl protecting group was first attempted using the DDQ[15] conditions. The reaction was very slow and the reaction mixture became increasingly sticky with time. Using BCl_3[16] as the reagent led to a much faster reaction, yielding a multi-component mixture presumably consisting of the expected open-chain ketone-alcohol, cyclic hemiketal, and its dehydration product(s). Because these interchangeable components were rather difficult to be separated from each other while they all might serve well in the next step of reaction, we used the mixture directly in the following hydroperoxidation. Indeed, exposure of the this mixture to UHP/*p*-TsOH·H_2O[6f,g] in $MeO(CH_2)_2OMe$ (DME) afforded the expected **21**[17]in 75% yield.

The Hg(II)-mediated ring closure proceeded extremely slow at either ambient temperature or 35 °C. Essentially no products could be detected on TLC after stirring for 1 d. However, addition of 0.05 equiv of $HClO_4$ dramatically speeded up the reaction.[18] The starting **21** disappeared (TLC monitoring) rapidly after addition of $HClO_4$, yielding a rather complex mixture. Direct treatment of this mixture with $NaBH_4$ followed by careful chromatographic separation afforded the desired end product **8** in 35% yield.[19]

3. Conclusions

Three new simplified analogues of qinghaosu were designed and synthesized through simple routes without invoking the traditional photooxidation commonly employed in the synthesis of closely related compounds. All the three compounds have a seven-membered peroxy ring fused to an all-carbon six-membered ring, a structural feature that is required for generating the substituted ethyl radical and broadly believed to contribute to qinghaosu and its derivatives and/or analogues' potent antimalarial activity.

4. Experimental

4.1. General

Unless otherwise stated, the ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruker Avance 300 (operating at 300 MHz for proton) or a Bruker Avance 400 instrument (operating at 400 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR spectrometer. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 T) FTMS mass spectrometer, respectively. MALDIHRMS were recorded on an IonSpec 4.7 Tesla FTMS instrument. Elemental analyses were performed on an Elementar VarioEL III instrument. The melting point was uncorrected. Dry THF was distilled from Na/Ph_2CO under N_2. Dry HMPA, *i*-Pr_2NH, and DMF were stirred with CaH_2 at ambient temperature under N_2 for 4 d before being distilled under reduced pressure and kept under N_2 over activated 4 Å molecular sieves. Dry CH_2Cl_2 was distilled over CaH_2 and kept over activated 4 Å molecular sieves. UHP was purchased from Acros. All other solvents and reagents were commercially available and used as received without any further purification. PE stands for petroleum ether (bp 60–90 °C).

4.1.1. Alkylation of cyclohexanone leading to 10. *n*-BuLi (1.60 M in hexanes, 5.2 mL, 8.28 mmol) was added to a solution of dry *i*-Pr_2NH (1.54 mL, 8.97 mmol) in dry THF (8 mL) stirred at 0 °C under N_2. The stirring was continued for 30 min before the bath temperature was lowered to −78 °C. A solution of cyclohexanone (**9**, 0.86 mL, 8.28 mmol) in dry THF (10 mL) was added very slowly. After completion of the addition, the mixture was stirred at the same temperature for 1 h. Dry HMPA (1 mL) was introduced, followed by $I(CH_2)_2CH(OMe)_2$ (1.586 g, 6.90 mmol). The bath temperature was allowed to rise naturally to ambient temperature. The stirring was continued at ambient temperature for 17 h, before addition of satd aq NH_4Cl (5 mL). The mixture was diluted with Et_2O, washed with aq $KHSO_4$ (to pH 7), and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **10**[9] as a yellowish liquid (773 mg, 3.86 mmol, 56% yield). ^1H NMR (300 MHz, $CHCl_3$) δ 4.37 (t, J=6.8 Hz, 1H), 3.24 (s, 3H), 3.22 (s, 3H), 2.25–2.21 (m, 1H), 2.04–1.04 (m, 12H).

4.1.2. Synthesis of ester 11 from acetal 10. A solution of **10** (334 mg, 1.67 mmol) in acetone (14 mL) and water (2 mL) containing PPTS (88 mg, 0.33 mmol) was heated to 40 °C with stirring for 3 h. Most of the solvent was removed by rotary evaporation. The residue was diluted with Et_2O, washed

with water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue (the crude aldehyde, 234 mg, 1.52 mmol) was dissolved in CH_2Cl_2 (8 mL) and stirred with $Ph_3P{=}CHCO_2Et$ (640 mg, 1.84 mmol) at ambient temperature overnight. The solvent was removed by rotary evaporation. The residue was diluted with Et_2O. The solids were filtered off. The filtrate was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **11**[10] as a yellowish liquid (310 mg, 1.38 mmol, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dt, J=15.8, 6.8 Hz, 1H), 5.80 (d, J=15.8 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 2.36–1.65 (m, 10H), 1.40–1.25 (m, 6H); ESIMS m/z 247.2 ([M+Na]$^+$).

4.1.3. Hydroperoxidation of 11. A solution of **11** (1.277 g, 5.70 mmol), UHP (4.019 g, 42.76 mmol), and $Sc(OTf)_3\cdot xH_2O$ (345 mg, 0.70 mmol) in MeOH (114 mL) was stirred at ambient temperature overnight. The mixture was diluted with CH_2Cl_2 (100 mL) and allowed to stand at ambient temperature for 1 h. The solids were filtered off. The filtrate was passed through a short pad of neutral Al_2O_3. The filtrate was chromatographed on silica gel (6:1 PE/EtOAc) to afford **12** as a colorless oil (1:1 mixture of the two diastereomers, 1.333 g, 4.90 mmol, 86% yield, not very stable and should be used as soon as possible). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 0.5H), 7.73 (s, 0.5H), 6.78 (dt, J=6.1, 15.3 Hz, 1H), 6.05 (d, J=15.4 Hz, 1H), 4.21 (q, J=6.9 Hz, 2H), 3.30 (s, 1.5H), 3.29 (s, 1.5H), 1.82–1.36 (m, 13H), 1.28 (t, J=7.2 Hz, 3H).

4.1.4. Synthesis of bicyclic peroxides 6 and 6a/6b. Method A (K_2CO_3/CF_3CH_2OH conditions). A solution of **12** (24 mg, 0.088 mmol) and K_2CO_3 (4 mg, 0.028 mmol) in CF_3CH_2OH (5.5 mL) was stirred at 40 °C for 3 d. The solvent was removed by rotary evaporation. The residue was chromatographed (10:1 PE/EtOAc) on silica gel to give **6** as colorless oil (8.0 mg, 0.029 mmol, 33% yield).

Method B ($Hg(OAc)_2/NaBH_4$ conditions). $Hg(OAc)_2$ (32 mg, 0.1 mmol) was added to a solution of **12** (27 mg, 0.099 mmol) in CH_2Cl_2 (1 mL) stirred at ambient temperature. The stirring was continued overnight until the starting **12** disappeared on TLC. With cooling (ice-water bath) a freshly prepared solution of $NaBH_4$ (12 mg) in 3 M aq NaOH (0.1 mL) was added. The mixture was stirred at 0 °C for 1 h. The precipitated Hg black was filtered off. The filtrate was diluted with Et_2O, washed with water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **6** (11 mg, 0.0040 mmol) and an inseparable mixture of **6a/6b** (6.0 mg, 0.022 mmol). Total yield: 63%.

Data for compound **6** (the more polar component, a colorless oil): FTIR (film) 1736, 1560, 1459, 1170, 1090, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62–4.53 (m, 1H), 4.15 (q, J=7.0 Hz, 2H), 3.28 (s, 3H), 2.50 (dd, J=7.6, 15.7 Hz, 1H), 2.33 (dd, J=5.8, 15.9 Hz, 1H), 2.28–2.23 (m, 1H), 1.93–1.86 (m, 2H), 1.78–1.72 (m, 2H), 1.63–1.40 (m, 5H), 1.36–1.19 (m, 3H), 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 108.2, 82.1, 60.7, 48.3, 42.8, 38.8, 36.1, 31.1, 29.3, 25.2, 22.5, 21.3, 14.2; ESIMS m/z 294.9 ([M+Na]$^+$); MALDIHRMS calcd for $C_{14}H_{24}O_5Na$ ([M+Na]$^+$) 295.1516, found 295.1527.

Data for compound **6a/6b** (a 1:3 inseparable mixture of the two components, less polar than **6**, a colorless oil): FTIR (film) 1738, 1451, 1372, 1087, 1009, 925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81–4.78 (m, 0.75H), 4.44–4.39 (m, 0.25H), 4.15 (q, J=7.0 Hz, 2H), 3.29 (s, 0.75H), 3.26 (s, 2.25H), 2.56 (dd, J=8.0, 15.7 Hz, 1H), 2.37 (dd, J=6.2, 15.7 Hz, 1H), 2.19–2.15 (m, 1H), 1.95–1.86 (m, 2H), 1.96–1.62 (m, 4H), 1.51–1.06 (m, 6H), 1.26 (t, J=7.2 Hz, 3H); ESIMS m/z 295.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{14}H_{24}O_5Na$ ([M+Na]$^+$) 295.1516, found 295.1519.

4.1.5. Alkylation of cyclohexanone leading to 14. n-BuLi (1.60 M in hexanes, 2.7 mL, 4.30 mmol) was added to a solution of dry i-Pr_2NH (0.60 mL, 4.30 mmol) in dry THF (5 mL) stirred at 0 °C under N_2. The stirring was continued for 30 min before the bath temperature was lowered to −78 °C. A solution of cyclohexanone (**9**, 0.44 mL, 4.30 mmol) in dry THF (10 mL) was added very slowly. After completion of the addition, the mixture was stirred at the same temperature for 1 h. Dry HMPA (0.75 mL) was introduced, followed by $I(CH_2)_2CMe(OCH_2)_2$ (1.67 g, 6.9 mmol). The bath temperature was allowed to rise naturally to ambient temperature. The stirring was continued at ambient temperature for 17 h, before addition of satd aq NH_4Cl (5 mL). The mixture was diluted with Et_2O, washed with aq $KHSO_4$ (to pH 7), and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **14**[12] as a yellowish liquid (529 mg, 2.50 mmol, 58% yield). ^{1}H NMR (300 MHz, $CHCl_3$) δ 3.96–3.91 (m, 4H), 2.37–2.26 (m, 2H), 2.08–1.82 (m, 4H), 1.70–1.60 (m, 4H), 1.36–1.26 (m, 3H), 1.32 (s, 3H).

4.1.6. Wittig reaction of 14 leading to 15. NaH (60% in mineral oil, 32 mg, 0.8 mmol) was placed in a flask and washed with hexane twice. Dry THF (4 mL) was added. With cooling (0 °C bath) and stirring, $(EtO)_2POCH_2CO_2Et$ (0.16 mL, 0.80 mmol) was added dropwise. After completion of the addition, the mixture was stirred at ambient temperature for 1 h. With cooling (0 °C bath) and stirring, a solution of **14** (140 mg, 0.66 mmol) in dry THF (2.6 mL) was added. The mixture was then heated to reflux (80 °C bath) with stirring for 6 h. The mixture was cooled down to ambient temperature, diluted with Et_2O, washed with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **15** as a colorless oil (a 1:3.3 mixture of the (*Z*)- and (*E*)-diastereomers, 150 mg, 0.53 mmol, 81% yield).

Repeated chromatography of the above mentioned mixture afforded a small sample of pure (*E*)-**15**, from which the following data were acquired: FTIR (film) 1714, 1642, 1448, 1379, 1162, 1041, 861 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.41 (q, J=7.3 Hz, 2H), 3.96–2.91 (m, 4H), 2.93–2.71 (m, 2H), 2.10–2.08 (m, 1H), 1.80–1.42 (m, 10H), 1.32 (s, 3H), 1.28 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 166.0, 112.6, 110.0, 44.6, 59.5, 45.8, 37.0, 34.1, 28.4, 27.7, 26.2, 23.8, 23.2, 14.3; ESIMS m/z 305.2 ([M+Na]$^+$); EIHRMS calcd for $C_{16}H_{26}O_4$ (M$^+$) 282.1831, found 282.1844.

4.1.7. Hydrolysis of ketal 15 leading to ketone 16. DDQ (50 mg, 0.22 mmol) was added to a solution of (*Z*)- and (*E*)-isomers of **15** (260 mg, 0.92 mmol) in MeCN (9 mL) and H_2O (1 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the same temperature for 30 min before being diluted with Et_2O, washed with water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave (*Z*)-**16** (45 mg, 0.19 mmol) and (*E*)-**16** (152 mg, 0.64 mmol). Total yield: 90%.

Data for compound (*E*)-**16** (the more polar component, a colorless oil): FTIR (film) 1714, 1642, 1447, 1366, 1214, 1161, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 2.96–2.89 (m, 1H), 2.73–2.68 (m, 1H), 2.40 (t, J=7.3 Hz, 2H), 2.14 (s, 3H), 1.96–1.48 (m, 9H), 0.95 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 166.7, 165.3, 112.9, 59.6, 44.9, 41.4, 34.0, 30.0, 28.2, 27.4, 25.5, 22.9, 14.2; ESIMS *m*/*z* 261.1 ([M+Na]$^+$). Anal. calcd for $C_{14}H_{22}O_3$ C 70.56, H 9.30, found C 70.54, H 9.67.

Data for compound (*Z*)-**16** (the less polar component, a colorless oil): FTIR (film) 1713, 1640, 1448, 1382, 1366, 1266, 1162, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.88–3.96 (m, 1H), 2.53 (ddd, J=17.7, 9.8, 6.3 Hz, 1H), 2.41–2.28 (m, 2H), 2.12 (s, 3H), 2.06–1.33 (m, 9H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 166.6, 165.5, 114.8, 59.5, 41.5, 35.6, 33.3, 32.0, 30.0, 28.5, 25.9, 20.6, 14.3; ESIMS *m*/*z* 261.1 ([M+Na]$^+$); EIHRMS calcd for $C_{14}H_{22}O_3$ (M^+) 238.1869, found 238.1566.

4.1.8. Hydroperoxidation of 16 giving hemiketal 13. A solution of (*E*)-**16** (583 mg, 2.45 mmol), UHP (1.727 g, 18.38 mmol), and $Sc(OTf)_3 \cdot xH_2O$ (296 mg, 0.60 mmol) in MeOH (49 mL) was stirred at ambient temperature for 3 d. The mixture was diluted with CH_2Cl_2 (50 mL) and allowed to stand for 1 h. The solids were filtered off. The filtrate was passed through a short pad of neutral Al_2O_3 to remove the acidic catalyst. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (6:1 PE/EtOAc) to afford **13** as a colorless oil (392 mg, 1.37 mmol, 56% yield, not very stable and should be used as soon as possible). ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 5.60 (s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.30 (s, 3H), 2.91–2.72 (m, 2H), 2.10 (br s, 1H), 1.81–1.39 (m, 10H), 1.34 (s, 3H), 1.28 (t, J=7.1 Hz, 3H).

4.1.9. Synthesis of the bicyclic peroxide 7. $Hg(OAc)_2$ (48 mg, 0.15 mmol) was added to a solution of **13** (43 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) stirred at ambient temperature. The stirring was continued at 35 °C for 5 d. With cooling (ice-water bath) a freshly prepared solution of $NaBH_4$ (23 mg) in 3 M aq NaOH (0.2 mL) was added. The mixture was stirred at 0 °C for 1 h. The precipitated Hg black was filtered off. The filtrate was diluted with Et_2O, washed with water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave a mixture of **7** and (*E*)-**16**, which was dissolved in CH_2Cl_2 (5 mL) and treated with O_3 at −78 °C until the solution turned blue. The excess O_3 was expelled by bubbling N_2 into the solution. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **7** as a colorless oil (11 mg, 0.038 mmol, 26% from **13**): FTIR (film) 2931, 2862, 1732, 1462, 1370, 1185, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, J=7.2 Hz, 2H), 3.33 (s, 3H), 2.69 (d, J=14.0 Hz, 1H), 2.55 (d, J=14.0 Hz, 1H), 2.25 (br s, 1H), 2.05–1.88 (m, 4H), 1.79–1.76 (m, 2H), 1.59 (br s, 2H), 1.41–1.24 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 107.4, 86.3, 60.3, 49.1, 45.5, 41.6, 39.1, 31.6, 27.7, 26.4, 23.7, 20.8, 19.7, 14.2; ESIMS *m*/*z* 309.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{15}H_{26}O_5Na$ ([M+Na]$^+$) 309.1672, found 309.1676.

4.1.10. Alkylation of 17 leading to 18. NaH (60% in mineral oil, 220 mg, 5.5 mmol) was placed in a flask and washed with hexane twice. Under argon (balloon) dry THF (20 mL) was added. With cooling (0 °C bath) and stirring, a solution of **17** (780 mg, 5 mmol) in dry THF (5 mL) was added dropwise. After completion of the addition, the mixture was stirred at 0 °C for 30 min. With cooling (0 °C bath) and stirring, *n*-BuLi (1.6 M in hexanes, 3.1 mL, 5 mmol) was added dropwise. The mixture was stirred at the same temperature for 10 min before a solution of $I(CH_2)_2CH(OCH_2)_2$ (1.14 g, 5.0 mmol) in dry THF (5 mL) was introduced. The mixture was stirred at ambient temperature overnight before being diluted with Et_2O, washed in turn with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent left a residue (1.244 g, 4.86 mmol), which was dissolved in dry THF (5 mL) and added to a suspension of NaH (60% in mineral oil, 220 mg, 5.5 mmol, washed with hexane as mentioned above) in dry DMF (3 mL) and THF (20 mL) stirred at 0 °C. The mixture was stirred at the same temperature for 30 min before a solution of $I(CH_2)_3OBn$ (1.38 g, 5.0 mmol) in dry THF (5 mL) was introduced. The mixture was heated to reflux for 2 h. After being cooled to ambient temperature, the reaction was quenched with satd aq NH_4Cl. The mixture was diluted with Et_2O, washed in turn with 1 M HCl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (5:1 PE/EtOAc) gave **18** as a colorless oil (1:5.7 mixture of two diastereomers, 1.520 g, 3.76 mmol, 75% over two steps): FTIR (film) 1741, 1712, 1453, 1202, 1132, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 5.02 (t, J=4.9 Hz, 0.15H), 4.85 (t, J=4.1 Hz, 0.85H), 4.83 (s, 2H), 3.98–3.93 (m, 2H), 3.85–3.81 (m, 2H), 3.72 (s, 0.45H), 3.77 (s, 2.55H), 3.46 (t, J=6.4 Hz, 2H), 2.57–2.52 (m, 0.85H), 2.39 (dt, J=5.7, 12.7 Hz, 1H), 2.29–2.27 (m, 0.15H), 2.07–1.96 (m, 2H), 1.89–1.22 (m, 11H); ESIMS *m*/*z* 427.3 ([M+Na]$^+$). Anal. calcd for $C_{23}H_{32}O_6$ C 68.29, H 7.97, found C 68.21, H 8.21.

4.1.11. Demethoxycarbonylation of 18 leading to 19. A solution of **18** (434 mg, 1.07 mmol) and $MgCl_2$ (508 mg, 5.35 mmol) in DMSO (10 mL) was heated to reflux for 6 h. After being cooled down to ambient temperature, the mixture was partitioned between Et_2O (30 mL) and water (10 mL). The phases were separated. The aqueous layer was extracted with Et_2O (20 mL×3). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (5:1 PE/EtOAc) afforded **19** as a colorless oil (291 mg, 0.84 mmol, 78% yield): FTIR

(film) 3458, 1707, 1453, 1098, 1027, 946, 847, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 4.84 (t, J=4.7 Hz, 2H), 4.49 (s, 2H), 3.98–3.81 (m, 4H), 3.46 (t, J=6.2 Hz, 2H), 2.35–2.26 (m, 2H), 2.17–2.11 (m, 2H), 1.89–1.54 (m, 6H), 1.37–1.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 138.7, 128.3, 127.6, 127.4, 104.7, 72.8, 70.6, 64.8, 50.9, 50.8, 35.6, 31.5, 29.7, 27.5, 25.9, 25.6, 23.7; ESIMS *m/z* 369.3 ([M+Na]$^+$); EIHRMS calcd for $C_{21}H_{30}O_4$ (M^+) 346.2144, found 346.2146.

4.1.12. Conversion of 19 into 20. Aq HCl (1 M) was added to a solution of **19** (280 mg, 0.81 mmol) in THF (10 mL). The mixture was heated in a 60 °C bath for 2 h. After being cooled to ambient temperature the mixture was diluted with Et_2O, washed with satd aq $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent left a residue, which was dissolved in CH_2Cl_2 (5 mL). $Ph_3P{=}CHCO_2Et$ (425 mg, 1.22 mmol) was added. The mixture was stirred at ambient temperature overnight. The solvent was removed by rotary evaporation. The residue was diluted with Et_2O. The solids were filtered off. The filtrate was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (5:1 PE/EtOAc) gave **20** as two isomers (the less polar one 149 mg, 0.40 mmol, and the more polar one 100 mg, 0.27 mmol). Total yield: 83%.

Data for the less polar isomer of **20** (colorless oil): FTIR (film) 1713, 1652, 1452, 1367, 1207, 1160, 1100, 736, 698 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 7.33–7.25 (m, 5H), 6.90 (dt, J=15.6, 6.9 Hz, 1H), 5.80 (d, J=15.6 Hz, 1H), 4.47 (s, 2H), 4.12 (q, J=7.3 Hz, 2H), 3.45 (t, J=6.4 Hz, 2H), 2.40–2.37 (m, 2H), 2.22–2.12 (m, 4H), 1.90–1.76 (m, 4H), 1.61–1.55 (m, 2H), 1.30–1.20 (m, 4H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 212.9, 166.5, 149.7, 140.1, 129.0, 128.2, 128.0, 122.1, 73.1, 71.1, 60.4, 51.3, 50.8, 36.3, 36.2, 30.4, 28.6, 28.2, 26.9, 26.2, 14.6; EIMS *m/z* (%) 372 (M^+, 0.38), 91 (100); EIHRMS calcd for $C_{23}H_{32}O_4$ (M^+) 372.2301, found 372.2295.

Data for the more polar isomer of **20** (colorless oil): FTIR (film) 1717, 1654, 1453, 1367, 1270, 1182, 1101, 1043, 737, 698 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 7.33–7.25 (m, 5H), 6.90 (dt, J=15.6, 6.9 Hz, 1H), 5.81 (d, J=15.6 Hz, 1H), 4.47 (s, 2H), 4.12 (q, J=7.3 Hz, 2H), 3.64 (t, J=6.2 Hz, 2H), 2.47–2.40 (m, 2H), 2.20–2.14 (m, 2H), 1.96–1.74 (m, 6H), 1.62–1.42 (m, 6H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 214.8, 166.5, 149.2, 140.1, 129.0, 128.2, 128.0, 122.4, 73.1, 70.7, 60.4, 49.5, 48.5, 33.9, 33.8, 30.5, 29.4, 28.3, 27.9, 21.3, 14.6; EIMS *m/z* (%) 372 (M^+, 0.26), 327 (M^+-OEt, 0.53), 91(100); EIHRMS calcd for $C_{23}H_{32}O_4$ (M^+) 372.2301, found 372.2297.

4.1.13. Synthesis of hydroxy hemiketal 21 from 20. BCl_3 (1 M in CH_2Cl_2, 2.4 mL, 2.4 mmol) was added dropwise to a solution of the major (less polar) isomer of **20** obtained above (219 mg, 0.59 mmol) in dry THF (15 mL) stirred at −78 °C under argon. The stirring was continued at the same temperature for 4 h. The reaction was quenched by addition of water (5 mL). The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent left a residue, which was dissolved in DME (10 mL). UHP (416 mg, 4.43 mmol) and p-TsOH·H_2O (135 mg, 0.71 mmol) were added. The mixture was stirred at ambient temperature for 3 d before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography on silica gel (4:1 PE/EtOAc) afforded **21** as a colorless oil (132 mg, 0.44 mmol, 75% from **20**, not very stable and should be used as soon as possible). ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 0.71H), 7.29 (s, 0.12H), 7.00 (dt, J=15.4, 7.0 Hz, 1H), 5.85 (d, J=15.7 Hz, 1H), 4.18 (q, J=7.0 Hz, 2H), 3.98–3.67 (m, 2H), 2.32–2.25 (m, 1H), 2.18–1.73 (m, 8H), 1.50–1.15 (m, 10H).

4.1.14. Synthesis of the tricyclic peroxide 8. $Hg(OAc)_2$ (64 mg, 0.20 mmol) and $HClO_4$ (0.61 μL, 0.01 mmol) were added to a solution of **21** (60 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) stirred at ambient temperature. The stirring was continued at ambient temperature for 1 h. With cooling (ice-water bath) a freshly prepared solution of $NaBH_4$ (23 mg) in 3 M aq NaOH (0.2 mL) was added. The mixture was stirred at 0 °C for 1 h. The precipitated Hg black was filtered off. The filtrate was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (10:1 PE/EtOAc) gave **8** as a colorless oil (21 mg, 0.070 mmol, 35% yield from **21**): FTIR (film) 2956, 2782, 1739, 1465, 1372, 1284, 1195, 1165, 1070, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48–4.40 (m, 1H), 4.16 (q, J=7.1 Hz, 2H), 5.35 (dt, J=12.3, 3.2 Hz, 1H), 3.74 (dd, J=11.2, 5.8 Hz, 1H), 2.86 (dd, J=7.1, 15.2 Hz, 1H), 2.56 (dd, J=15.3, 9.4 Hz, 1H), 2.21–2.09 (m, 2H), 2.02–1.84 (m, 3H), 1.72–1.69 (m, 1H), 1.54–1.19 (s, 10H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 104.3, 79.6, 62.1, 60.4, 53.0, 40.8, 36.6, 35.9, 31.1, 28.1, 26.1, 26.0, 23.6, 19.7, 14.2; ESIMS *m/z* 321.3 ([M+Na]$^+$); EIHRMS calcd for $C_{16}H_{26}O_5$ (M^+) 298.1780, found 298.1791.

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References and notes

1. See: e.g., (a) Liu, J.-M.; Ni, M.-Y.; Fan, J.-F.; Tu, Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Chou, W.-S. *Acta Chim. Sin.* **1979**, *37*, 129; (*Chem. Abstr.* **1980**, *92*, 94594w); (b) Li, Y.; Wu, Y.-L. *Curr. Med. Chem.* **2003**, *10*, 2197–2230; (c) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73–79; (d) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945–2964; (e) Robert, A.; Dechy-Cabaret, O.; Cazalles, J. M.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167–174; (f) Klayman, D. L. *Science* **1985**, *228*, 1049–1055; (g) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448; (h) Gu, H.-M.; Lu, B.-F.; Qu, Z.-X. *Acta Pharmacol. Sin.* **1980**, *1*, 48–50.
2. (a) Wu, Y.-K. *Acc. Chem. Res.* **2002**, *35*, 255–259; (b) Olliaro, P. L.; Haynes, R. K.; Meunier, B.; Yuthavong, Y. *Trends Parasitol.* **2001**, *17*, 122–126; (c) Robert, A.; Meunier, B.

Chem. Soc. Rev. **1998**, *27*, 273–279; (d) Bloodworth, A. J.; Shah, A. *Tetrahedron Lett.* **1995**, *36*, 7551–7554; (e) Jefford, C. W.; Vicente, M. G. H.; Jacquier, Y.; Favarger, F.; Mareda, J.; Millasson-Schmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta* **1996**, *79*, 1475–1487; (f) Eckstein-Ludwig, U.; Webb, R. J.; Van Goethem, I. D.; Lee, A. G.; Kimura, M.; O'Neill, P. M.; Bray, P. G.; Ward, S. A.; Krishna, S. *Nature* **2003**, *424*, 957–961; (g) Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 5885–5886; (h) Posner, G. H.; Wang, D.-S.; Cumming, J. N.; Oh, C. H.; French, A. N.; Bodley, A. L.; Shapiro, T. A. *J. Med. Chem.* **1995**, *38*, 2273–2275; (i) Posner, G. H.; Park, S. B.; Gonzalez, L.; Wang, D.-S.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A.; Balci, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 3537–3538; (j) Posner, G. H.; Wang, D.-S.; Gonzalez, L.; Tao, X.-L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 815–818; (k) Posner, G. H.; Gonzalez, L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron* **1997**, *53*, 37–50; (l) Posner, G. H.; Oh, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8328–8329; (m) Posner, G. H.; Oh, C. H.; Wang, D.; Gerena, L.; Milhous, W. K.; Meshnick, S.; Asawamahasadka, W. *J. Med. Chem.* **1994**, *37*, 1256–1258; (n) Avery, M. A.; Fan, P.-C.; Karle, J. M.; Bonk, J. D.; Miller, R.; Goins, D. K. *J. Med. Chem.* **1996**, *39*, 1885–1897; (o) Avery, M. A.; Mehrotra, S.; Bonk, J. D.; Vroman, J. A.; Goins, D. K.; Miller, R. *J. Med. Chem.* **1996**, *39*, 2900–2906; (p) Avery, M. A.; Mehrotra, S.; Johnson, T. L.; Bonk, J. D.; Vroman, J. A.; Miller, R. *J. Med. Chem.* **1996**, *39*, 4149–4155; (q) Haynes, R. K.; Vonwiller, S. C. *Tetrahedron Lett.* **1996**, *37*, 253–256; (r) Haynes, R. K.; Vonwiller, S. C. *Tetrahedron Lett.* **1996**, *37*, 257–260; (s) O'Neill, P. M.; Bishop, L. P.; Searle, N. L.; Maggs, J. L.; Ward, S. A.; Bray, P. G.; Storr, R. C.; Park, B. K. *Tetrahedron Lett.* **1997**, *38*, 4263–4266; (t) Wu, W.-M.; Wu, Y.-K.; Wu, Y.-L.; Yao, Z.-J.; Zhou, C.-M.; Li, Y.; Shan, F. *J. Am. Chem. Soc.* **1998**, *120*, 3316–3325; (u) Kapetanaki, S.; Varotsis, C. *J. Med. Chem.* **2001**, *44*, 3150–3156.

3. (a) Robert, A.; Coppel, Y.; Meunier, B. *Chem. Commun.* **2002**, 414–415; (b) Robert, A.; Cazelles, J.; Meunier, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1954–1957; (c) Robert, A.; Cazelles, J.; Meunier, B. *J. Am. Chem. Soc.* **1997**, *119*, 5968–5969.
4. (a) Wu, Y.-K.; Yue, Z.-Y.; Wu, Y.-L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2580–2582; (b) Wu, Y.-K.; Liu, H.-H. *Chem. Res. Toxicol.* **2003**, *16*, 1202–1206; (c) Wu, Y.-K.; Liu, H.-H. *Helv. Chim. Acta* **2003**, *86*, 3074–3080; (d) Wu, Y.-K.; Yue, Z.-Y.; Liu, H.-H. *Helv. Chim. Acta* **2001**, *84*, 928–932.
5. (a) O'Neill, P. M.; Miller, A.; Bickley, J. F.; Scheinmann, F.; Oh, C. H.; Posner, G. H. *Tetrahedron Lett.* **1999**, *40*, 9133–9136; (b) Posner, G. H.; Oh, C. H.; Miller, W. K. *Tetrahedron Lett.* **1991**, *32*, 4235–4238; (c) Ref. 2i; (d) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459–2467; (e) Haraldson, C. A.; Karle, J. M.; Freeman, S. G.; Duvadie, R. K.; Avaery, M. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2357–2362.
6. (a) Jin, H.-X.; Zhang, Q.; Kim, S.-H.; Wataya, Y.; Liu, H.-H.; Wu, Y.-K. *Tetrahedron* **2006**, *62*, 7699–7711; (b) Liu, H.-H.; Zhang, Q.; Jin, H.-X.; Shen, X.; Wu, Y.-K. *Chin. J. Chem.* **2006**, *24*, 1180–1189; (c) Zhang, Q.; Jin, H.-X.; Liu, H.-H.; Wu, Y.-K. *Chin. J. Chem.* **2006**, *24*, 1190–1195; (d) Zhang, Q.; Jin, H.-X.; Wu, Y.-K. *Tetrahedron* **2006**, *62*, 11627–11634; (e) Liu, H.-H.; Jin, H.-X.; Zhang, Q.; Wu, Y.-K.; Kim, H.-S.; Wataya, Y. *Chin. J. Chem.* **2005**, *23*, 1469–1473; (f) Jin, H.-X.; Wu, Y.-K. *Tetrahedron Lett.* **2005**, *46*, 6801–6803; (g) Jin, H.-X.; Liu, H.-H.; Zhang, Q.; Wu, Y.-K. *Tetrahedron Lett.* **2005**, *46*, 5767–5769.
7. (a) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281–7285; (b) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 69–72; (c) Kawanishi, M.; Kotoku, N.; Itagaki, S.; Horiib, T.; Kobayashi, M. *Bioorg. Med. Chem.* **2004**, *12*, 5297–5307.
8. Clive, D. L. J.; Paul, C. C.; Wang, Z. R. *J. Org. Chem.* **1981**, *14*, 2981–2983.
9. (a) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379–6387; (b) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927–8940.
10. Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Org. Chem.* **1997**, *62*, 5966–5973.
11. Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3333–3340.
12. Meoller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033–1041.
13. Tanemura, T.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 979–980.
14. Krapcho, A. P.; Grenon, B. J. *Tetrahedron Lett.* **1967**, 215–217.
15. Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8791–8796.
16. Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663–664.
17. It appeared to be ca. 6:1 mixture of two diastereomers as suggested by the presence of two –OOH signals at δ 7.55 and 7.29 in ^{1}H NMR (cf. Section 4).
18. Use of $HClO_4$ in peroxymercuration mediated by $Hg(OAc)_2$ was previously known, presumably to facilitate the reaction via partial formation of more reactive $Hg(ClO_4)_2$. See, e.g.: (a) Bloodworth, A. J.; Bunce, R. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2787–2792; However, addition of $HClO_4$ does not always lead to better yields. See, e.g.: (b) Zhang, Q.; Li, Y.; Wu, Y.-K. *Chin. J. Chem.* **2007**, *25*, 1304–1308.
19. The ^{1}H NMR of **8** was very clean, suggesting presence of only one diastereomer. However, the information in 1D and 2D NMR did not allow for assignment of the relative configuration. Note that there have been reports that the antimalarial potency of peroxide antimalarial is not affected by stereochemistry. See, e.g.: O'Neill, P. M.; Rawe, S. L.; Borstnik, K.; Miller, A.; Ward, S. A.; Bray, P. G.; Davies, J.; Oh, C. H.; Gary, H.; Posner, G. H. *ChemBioChem* **2005**, *6*, 2048–2054.