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Design, synthesis and in vitro antimalarial activity of spiroperoxides

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Abstract—Several spiroperoxy antimalarial compounds were designed and synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of the H_2O_2 into the organic molecule framework through ketal exchange reaction in the present cases was greatly facilitated by the potential to form a five- or six-membered cyclic hemiketal due to the presence of a hydroxyl group γ or δ to the ketone carbonyl group. When the electron-withdrawing group in the Michael acceptor was a nitro group, the closure of the peroxy ring occurred readily under the hydroxidation conditions. Presence of a benzene ring fused to the peroxy ring effectively reduced the degrees of freedom in the transition state for the ring-closure step and made the otherwise very difficult seven-membered 1,2-dioxepane rather easy to form through the intramolecular Michael addition.
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1. Introduction

Prompted by the excellent activity observed with qinghaosu[1] (artemisinin, **1**) and closely related peroxy compounds in the treatment of malaria including the multi drug-resistant variants, more and more organic chemists around the world are actively engaged in design and synthesis of novel organic peroxides since the late 1980's. Due to lack of generally feasible[2] synthetic methods for forming the O–O bond directly from two separate one oxygen-containing groups, up to now the peroxy bonds in organic peroxides are almost all derived from some species that already contain the O–O bond such as dioxygen[3] (O_2), ozone[4] (O_3), or hydrogen peroxide[5] (H_2O_2). Thus, what is special of synthesis of organic peroxides is that the way and the timing of introducing the fragile O–O bond must be taken into consideration in addition to all other factors encountered in synthesis in general. The limited source of the O–O bond-containing species decides that the span of the reactions that one can choose from is narrow. And the fragile nature of O–O bonds demands circumventing many transformations routinely employed in organic synthesis. Hence, development of new approaches to make facile use of the readily available O–O containing species is critical for synthesis of organic peroxides.

Formation of a carbon–oxygen bond to an inorganic O–O bond-containing reagent through ketalization is one of the most common ways of creating organic peroxy species. In 2001, Kobayashi[5e,f] and co-workers reported a new variant of this methodology, which utilized solid UHP (urea–H_2O_2 complex) instead of liquid H_2O_2 as the source of the peroxy bond. In MeOH with $Sc(OTf)_3$ as catalyst, they obtained MeO/OOH mixed ketals in high yields and successfully closed the peroxy ring by an intramolecular Michael addition catalyzed by $HNEt_2$ in F_3CCH_2OH. Impressed by the convenience of using UHP, we also tried to adopt Kobayashi's methodology in our own work. In the preliminary exploration[6] on the scope and limitation of the UHP protocol, we noticed that the original conditions appeared to be applicable only to synthesis of five- or six-membered peroxy rings in the monocyclic cases. And, the presence of, e.g., an ester group on the ketal carbonyl carbon also led to complete failure in the hydroperoxidation step. These observations, together with the relatively high cost of the essential catalyst $Sc(OTf)_3$, prompted us to turn to new structures with extra rings. Here in this article we wish to detail[7] some of our recent work along this line.

2. Results and discussions

As formation of the hydroperoxy hemiketal is a key step in incorporating H_2O_2 into an organic framework, we chose this as an entry point for this work. The first thing we looked into was whether the hydroperoxidation could be made easier by switching from the open-chain hemiketals to cyclic ones, i.e., to replace the methoxyl group in the monocyclic

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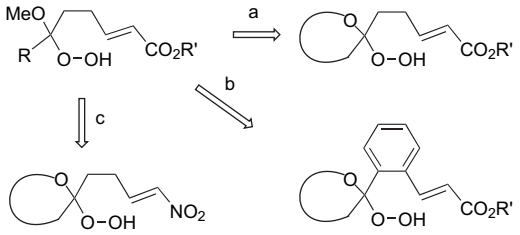


Figure 1. General illustration of the plans for this work: (a) the fundamental idea—switching from the open-chain hemiketal to cyclic hemiketals to facilitate hydroperoxyl group attachment. (b) Introducing UV chromophores to improve molecule-tracing property and facilitate synthesis. (c) Examining other electron-withdrawing groups in place of the ester group in the Michael acceptor.

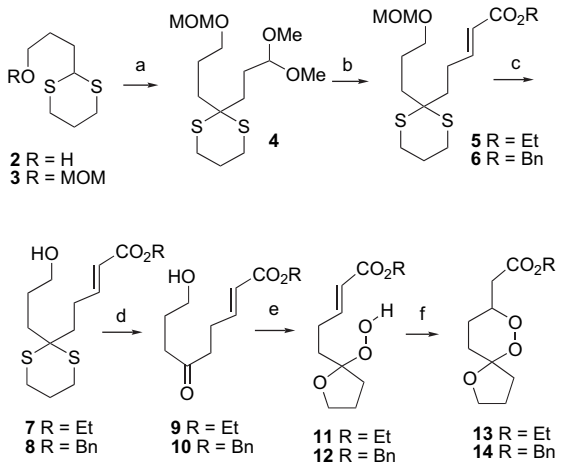
structures with an alkoxyl one that was connected to the ketal carbonyl carbon through a covalent chain (Fig. 1).

To facilitate future mechanistic investigations, it would be also desirable to incorporate some UV chromophore into the molecule. Such chromophore was better directly bonded to the carbon framework so that it would not be lost due to hydrolysis. From synthetic viewpoint, presence of such a chromophore as a benzene ring may also facilitate rapid construction of the molecule because the building blocks could be more readily accessible. Finally, whether the ester group in the Michael acceptor could be replaced by other electron-withdrawing groups was also among what we wished to explore.

Five- or six-membered cyclic hemiketals are generally expected to form easier than the non-cyclic ones. Although according to our experience that the population of the cyclic hemiketal can be rather small in solution (i.e., most of the substrate is present in the open chain form) in some cases, we believe that even very small amount of such cyclic hemiketals would also facilitate the critical exchange of the hemiketal hydroxyl group with the hydroperoxyl group. Once the hydroperoxyl group is introduced into the substrate, it is not so easy to leave as hydroxyl group. Therefore, the hydroperoxidation precursors of all target molecules in this work were designed to carry a hydroxyl group either γ or δ to the ketone carbonyl group.

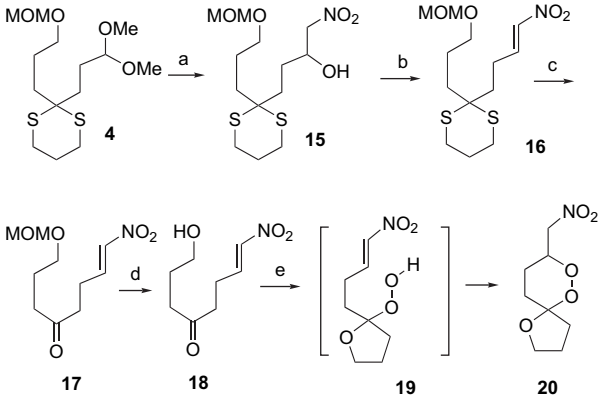
The simplest targets (**13** and **14**) were synthesized using the route shown in Scheme 1. The MOM protected dithiane **3**, which could be readily prepared from the corresponding alcohol (**2**[8]), was alkylated with $I(CH_2)_2CH(OMe)_2$[9] using the standard umpolung technique to give acetal **4**. Selective hydrolysis of the dimethyl acetal with PPTS in aqueous acetone afforded an intermediate aldehyde, which was immediately treated with either $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Bn$ to yield **5** or **6**, respectively. The MOM protecting group was then removed and the resulting hydroxy ketone **9** or **10** was converted into the corresponding hydroperoxyl hemiketal **11** or **12**. The presence of an additional THF ring (cyclic hemiketal) did lead to facile incorporation of the hydroperoxyl group as expected. The expensive catalyst $Sc(OTf)_3$ that was essential in the non-cyclic cases were thus no longer necessary.

Next we examined to replace the ester functionality with a nitro group (Scheme 2). The hydrolysis of the acetal end



Scheme 1. (a) BuLi/HMPA/$I(CH_2)_2CH(OMe)_2$/0 °C/48 h, 88%; (b) i. PPTS/acetone/reflux/12 h; ii. $Ph_3P{=}CHCO_2Et$, 86% for **5** or $Ph_3P{=}CHCO_2Bn/CH_2Cl_2$/rt/12 h, 94% for **6** (yields from **4**); (c) *p*-TsOH/EtOH/reflux, 90% for **7** or 2 N HCl/THF/40–50 °C, 64% for **8**; (d) I_2/acetone/$NaHCO_3$/0 °C/30 min, 83% for **9** or 77% for **10**; (e) UHP/*p*-TsOH/MeOH/rt, 82% for **11** or 75% for **12** and (f) $HNEt_2/CF_3CH_2OH$/rt/24 h, 52% for either **13** or **14**.

of **4** was done as mentioned above. Then, the condensation was realized by using $MeNO_2$ instead of a Wittig reagent. The hydroxyl group was converted to the corresponding mesylate and eliminated immediately, yielding **16**. Up to this stage, the remaining tasks were removing the MOM and dithiane protecting groups. Attempts to hydrolyze the MOM group under similar conditions to those employed in the synthesis of **7/8** completely failed, presumably due to the too high reactivity of the Michael acceptor $–CH{=}CHNO_2$. Although this property turned out to be an advantage in a later stage of the synthesis when an intramolecular Michael addition was needed to construct the 1,2-dioxane ring, at this point we had to switch to an alternative approach—to free the carbonyl group first.

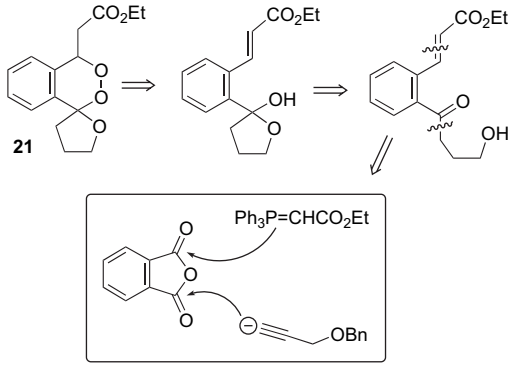


Scheme 2. (a) i. PPTS/acetone/reflux/12 h; ii. CH_3NO_2/DBU/rt/15 h, 94% from **4**; (b) MsCl/NEt_3/rt/24 h, 97%; (c) $I_2/NaHCO_3$/0 °C/30 min, 87%; (d) concd HCl/acetone–H_2O/rt/17 h, 21% and (e) UHP/*p*-TsOH/DME/rt/10.5 h, 35%.

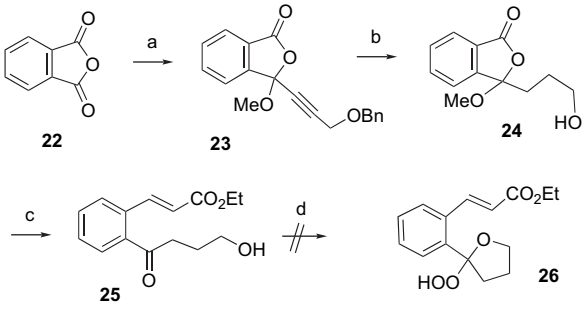
Under the conditions for the similar deprotections of **7** and **8**, the ketone **17** was readily obtained in 87% yield. The subsequent hydrolysis of the MOM group, however, was still very complicated. We managed to isolate the desired **18** in only 21%. Further treatment of **18** with the UHP/*p*-TsOH/DME

($MeO(CH_2)_2OMe$) led to direct formation of the end product **20**. Compound **19** could not be isolated at all. Here the non-alcohol solvent was essential for the hydroperoxidation. Using MeOH as in Kobayashi's original protocol, for instance, led to completely failure.

After completing the syntheses of **13** and **14**, we began to consider the possibility to introduce a benzene ring into the spiro[4,5]decane framework. The first designed structure was **21**, partially because the retrosynthetic analysis (Scheme 3) showed a possible rapid access from three readily available building blocks. Based on this design, we started the synthesis as shown in Scheme 4.



Scheme 3.

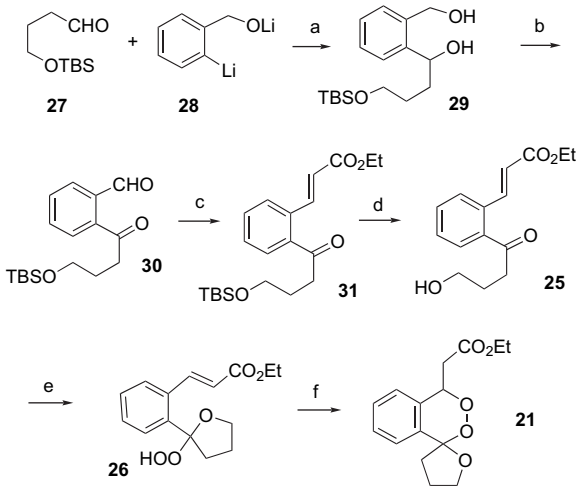


Scheme 4. (a) i. *n*-BuLi/HC≡CCH_2OBn/THF/−25 °C/1.5 h, then **22**/−70 °C/2 h; ii. CH_2N_2/0 °C, 43% from **22**; (b) H_2/Pd–C/MeOH/rt, 38%; (c) i. DIBAL-H/CH_2Cl_2/−75 °C/3 h; ii. MnO_2/$CHCl_3$/rt/4 d; iii. Ph_3P=$CHCO_2Et$/$CHCl_3$/rt/10 h, 47% from **24** and (d) UHP/*p*-TsOH or CSA/MeOH/rt.

Introduction of the three-carbon chain was performed as reported[10] in the literature. The resulting acid was converted to lactone-ketal **23** by treatment with diazomethane. The benzyl protecting group was then removed along with the hydrogenation of the triple bond, leading to **24** in low yield.

Conversion of the lactone **24** into the intermediate aldehyde was achieved by reduction with DIBAL-H to the corresponding triol, followed by a MnO_2 oxidation. A subsequent Wittig reaction with Ph_3P=$CHCO_2Et$ on the aldehyde carbonyl group gave the desired **25** in 47% yield (from **24**). The hydroperoxidation under the conditions for syntheses of **7** and **8**, however, did not lead to any discernible amounts of **26**.

Because the yields along the sequence shown in Scheme 4 were too low, before proceeding we decided to adopt another more practical approach (Scheme 5). Thus, the reaction of aldehyde **27**[11] with lithium species **28** (prepared in situ from the corresponding bromide) gave diol **29**. A Swern oxidation yielded the intermediate dicarbonyl species **30**, which was immediately treated with Ph_3P=$CHCO_2Et$ to afford **31**. The TBS protecting group was then removed and the resulting hydroxy ketone **25** was subjected to the hydroperoxidation.

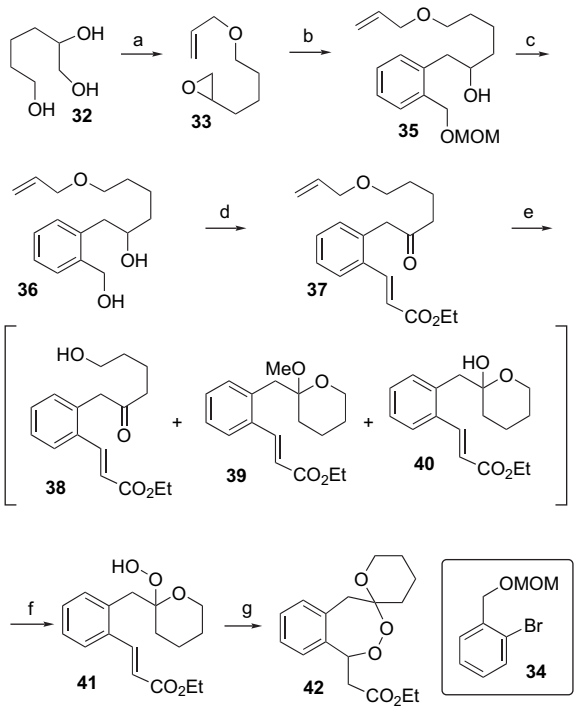


Scheme 5. (a) −78 °C/40min, 61%; (b) $(COCl)_2$/DMSO/CH_2Cl_2/NEt_3; (c) Ph_3P=$CHCO_2Et$/rt/3 h, 74% from **29**; (d) *p*-TsOH/rt/5 h, 96%; (e) UHP/CSA/DME/rt/18 h, 86% and (f) $HNEt_2$/CF_3CH_2OH/rt/2 h, 56% from **26**.

Because as mentioned above we already failed to obtain **26** in MeOH, this time tried to use DME as the solvent. Under such conditions, the desired **26** was formed in 86% yield. Further treatment with $HNEt_2$ in F_3CCH_2OH at the ambient temperature gave the end product **21** as a pair of separable diastereomers. It is interesting to note that this is the only case so far we found, where the diastereomers could be separated on silica gel. Interestingly, the two diastereomers showed different antimalarial activity in the in vitro testing.

Previously, we observed that using the intramolecular Michael addition of the hydroperoxyl group to close a seven-membered ring was impossible if all the bonds involved in the process were σ-bonds without any restrictions on their rotation. In this work, in combination with our intention to incorporate a UV chromophore into the carbon framework, we attempted to fuse a benzene ring to a 1,2-dioxepane ring. Such an additional ring would greatly reduce the degrees of freedom in the transition state for the formation of the seven-membered ring and therefore should increase the possibility to reach the 1,2-dioxepane.

As shown in Scheme 6, from the commercially available inexpensive triol **32** after a five-step sequence, an allyl group protected terminal epoxide **33** was conveniently obtained in 64% overall yield. Ring-opening of the epoxide with a lithium species prepared in situ from known bromide **34** led to alcohol **35**, which on hydrolytic removal of the MOM protecting group and a Swern oxidation followed by treatment with Ph_3P=$CHCO_2Et$ gave the **37**. Cleavage of the allyl protecting group was then achieved using $PdCl_2$/MeOH. The product was a mixture of several interchangeable species, which was therefore all utilized in the next step.

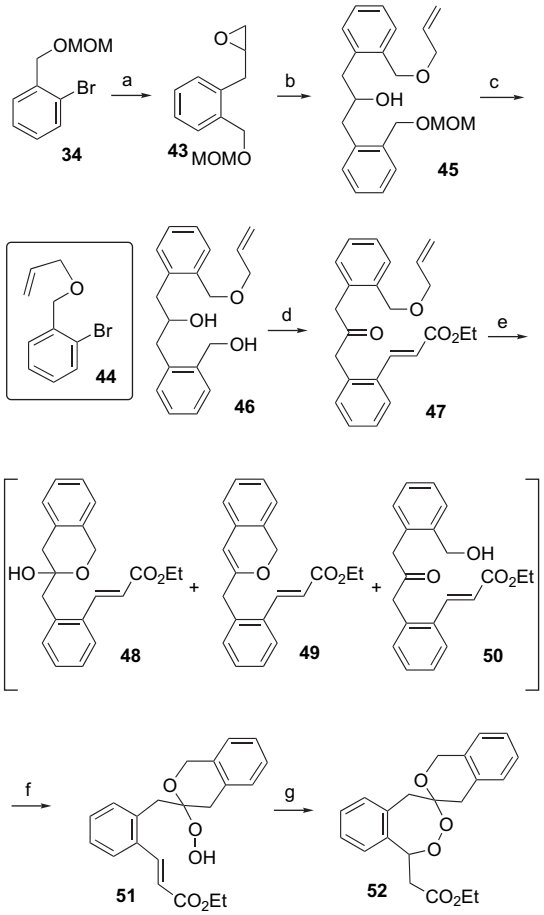


Scheme 6. (a) i. $Me_2C(OMe)_2$/acetone/*p*-TsOH/rt/22 h; ii. NaH/CH_2=$CHCH_2Br$/rt/10 h; iii. 2 N HCl/MeOH/rt/2 h; iv. *p*-TsCl/NEt_3/rt/12 h; v. KOH/Et_2O/rt/5.5 h, 64% from **32**; (b) *n*-BuLi/**34**/−78 °C/1 h, then **33**/$BF_3\cdot OEt_2$/−78 °C/1 h, 80%; (c) concd HCl/MeOH/rt/4 d, 93%; (d) i. $(COCl)_2$/DMSO/NEt_3; ii. Ph_3P=$CHCO_2Et$/rt/12 h, 85% from **36**; (e) $PdCl_2$/MeOH/rt/24 h, then 60 °C/4 h; (f) UHP/*p*-TsOH/DME/rt/22 h, 71% from **37** and (g) $HNEt_2$/CF_3CH_2OH/rt/19 h, 59%.

The hydroperoxidation turned out to be a smooth reaction as we had expected. The starting mixture of **38**, **39**, and **40** led to the hydroperoxy hemiketal **41** in 71% yield. Due to the presence of the additional benzene ring, the intramolecular Michael also proceeded very well, rendering the desired 1,2-dioxepane in 59% yield.

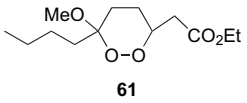
Using a similar strategy we also synthesized **52**, which contained two fused benzene rings. The synthetic sequence is depicted in Scheme 7. The initial steps were rather convenient due to the possibility to use **34**,[12] **44**,[13] and epichlorohydrin. Like in the case of deprotection of **37**, removal of the allyl protecting group in **47** also resulted in a mixture of several closely related species (**48**, **49**, and **50**). Treatment of this mixture with UHP/DME/CSA led to partial conversion of **48** into the anticipated hydroperoxy hemiketal **51**, along with recovered **49** and **50** (which reacted much more slowly than **48**). In order to speed up the reaction, higher doses of UHP (13 equiv) and CSA (5 equiv) were required. Increased amounts of UHP and CSA, however, created solubility problem. Fortunately we found that addition of a carefully controlled amount of EtOH could facilitate dissolution of the reagents without interfering the desired transformation. The presence of an additional benzene ring in **51** also created solubility problem in the final Michael addition step. Unlike **41**, the **51** was not so soluble in F_3CCH_2OH. Some CH_2Cl_2 must be added before the ring closure could proceed to a synthetically useful extent.

Apart from the spirosystems mentioned above, we also attempted to synthesize such bridged peroxides as **60**. As



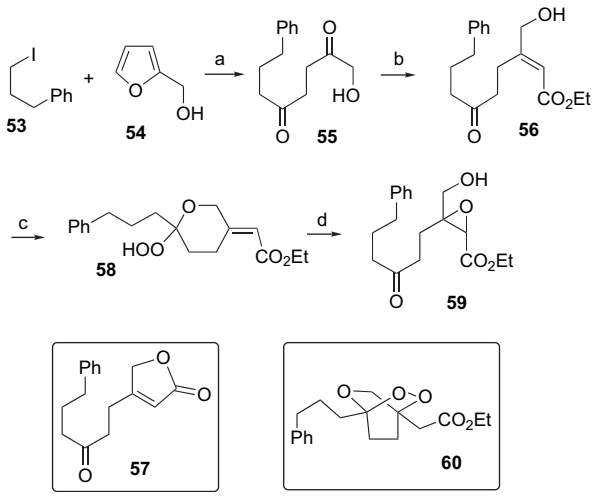
Scheme 7. (a) i. *n*-BuLi/$BF_3\cdot Et_2O$/epichlorohydrin/−78 °C/1 h; ii. NaH/rt/2.5 h, 67% from **34**; (b) *n*-BuLi/**44**/−78 °C/1 h, then **43**/$BF_3\cdot OEt_2$/−78 °C/1 h, 76%; (c) concd HCl/MeOH/rt/3 d, 99%; (d) i. $(COCl)_2$/DMSO/NEt_3; ii. Ph_3P=$CHCO_2Et$/rt/12 h, 77% from **46**; (e) $PdCl_2$/CuCl/DMF–H_2O/air/rt/12 h; (f) UHP/CSA/DME–EtOH/rt/7 d, 33% from **47** and (g) $HNEt_2$/CF_3CH_2OH/rt/21 h, 24%.

shown in Scheme 8, alkylation of furfuryl alcohol with **53** under the conditions similar to those reported[14] in the literature, followed by manipulation of the furan ring by MCPBA oxidation[15] and hydrogenation[16] led to compound **55**.



The hydroxyl group was then masked as an acetate by treatment with Ac_2O before selectively converting the carbonyl group closer to the acetate to an α,β-unsaturated ester. The isomer with ester group cis to the hydroxyl group formed the corresponding lactone **57** easily, which allowed for facile separation of the trans isomer **56** for further transformations. Again, the hydroperoxidation was apparently facilitated by the possibility to form a cyclic hemiketal. The hydroperoxy hemiketal **58** could be obtained in 44% yield. However, no peroxide **60** could be detected at all. Instead, an epoxide (**59**) was formed as the major product and isolated in 58% yield.

The results of the preliminary in vitro tests are shown in Table 1. The EC_{50} values for *Plasmodium falciparum* were



Scheme 8. (a) i. *n*-BuLi/−40 °C/4 h, then **53**/0 °C/43 h, 42%; ii. *m*-CPBA/rt/2 h, 95%; iii. H_2/Pd–C/rt/7 h, 40%; (b) i. Ac_2O/NEt_3/rt/5 h; ii. NaH/$(EtO)_2(O)P{=}CHCO_2Et$/rt/7 h; iii. 2 N HCl/EtOH/rt/2 d, 18% from **55**; (c) UHP/*p*-TsOH/DME/rt/24 h, 44% and (d) $HNEt_2/CF_3CH_2OH$/rt/10 h, 58% for **59**.

Table 1. The results of the preliminary in vitro tests[a]

Entry	Compd	EC_{50}(M)		Ratio[b]
		P. falciparum	FM3A	
1	**13**	8×10^{-6}	$>3.5\times10^{-5}$ (100% growth)	>5
2	**14**	7×10^{-6}	1×10^{-5}	2
3	**20**	$>4.8\times10^{-5}$ (70% growth)	$>4.8\times10^{-5}$ (100% growth)	
4	**21a**[c]	4×10^{-7}	$>2.7\times10^{-5}$ (100% growth)	>63
5	**21b**[d]	6×10^{-6}	1×10^{-5}	2
6	**42**	7×10^{-6}	8×10^{-6}	1
7	**52**	5×10^{-6}	7×10^{-6}	1
8	**61**[e]	6×10^{-7}	7×10^{-6}	12

[a] For detailed information about the biological testing, see the experimental part.
[b] The EC_{50} (*P. falciparum*)/EC_{50} (FM3A).
[c] The less polar diastereomer of **21**.
[d] The more polar diastereomer of **21**.
[e] Published in Ref. 6a (listed here for comparison).

within the range between 10^{-7} to 10^{-6} M, which were more or less the same as those reported[5d,6a] for the monocyclic simple analogues of peroxyplakoric acid. The nitro analogue **20**, however, was apparently less potent than other compounds tested, perhaps because the nitro group somehow interfered the radical reactions after the cleavage of the peroxy bond in the living cell. More work needs to be done before it is possible to give a more plausible explanation. It is also interesting to note that the two diastereomers of **21** showed significantly different activities.

3. Conclusions

Several spiroperoxy antimalarial compounds were designed and synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of the H_2O_2 into the organic molecule framework through ketal exchange reaction was greatly facilitated due to formation of a cyclic hemiketal. When the electron-withdrawing group in the Michael acceptor was a nitro group, the closure of the peroxy ring occurred readily under the hydroxidation conditions. Presence of a benzene ring fused to the peroxy ring effectively reduced the degrees of freedom in the transition state for the ring-closure step and made the otherwise very difficult seven-membered 1,2-dioxepane rather easy to form through the intramolecular Michael addition.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR. 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 a APEX III (7.0 tesla) FTMS mass spectrometer, respectively. 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 CH_2Cl_2 was distilled over CaH_2 and kept over 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.

4.2. MOM protection of 2 (3)

A solution of **2** (14.24 g, 80 mmol) and anhydrous LiBr (1.392 g, 16 mmol) in $CH(OMe)_2$ (160 mL) was stirred at the ambient temperature for 2 d. The mixture was partitioned between brine and Et_2O. The aqueous layer was back-extracted with Et_2O thrice. The combined ethereal phases were concentrated to dryness on a rotary evaporator. The residue was chromatographed on silica gel (20:1 *n*-hexane/EtOAc) to give **3** as a colorless oil (14.448 g, 81% yield). FTIR (film) 2932, 1422, 1276, 1147, 1111, 1041, 919, 771 cm^{-1}; ^1H NMR δ 4.61 (s, 2H), 4.05 (t, J=6.6 Hz, 1H), 3.55 (t, J=6.1 Hz, 2H), 3.36 (s, 3H), 2.89–2.84 (m, 4H), 1.89–1.80 (m, 6H); EIMS *m*/*z* (%) 222 (M^+, 1), 177 ($M^+-CH_2OCH_3$, 26), 103 (49), 45 (100). EIHRMS calcd for $C_9H_{18}O_2S_2$ 222.0748, found 222.0750.

4.3. Alkylation of 3 (4)

With cooling (−78 °C bath) and stirring *n*-BuLi (30.0 mL, 1.6 M) was added dropwise (via a syringe) to a solution of the dithiane **3** (9.033 g, 40.5 mmol) and Ph_3CH (15 mg, as an indicator) in dry THF (120 mL) under argon, followed by HMPA (7 mL, 40.7 mmol) (via a syringe). The bath was allowed to warm to −20 °C and the magenta solution was stirred at that temperature for 4 h, before the iodide (10.295 g, 44.8 mmol) was introduced via a syringe. After further stirring at 0 °C for 48 h, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated

on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **4** (11.654 g, 88%). FTIR (film) 2933, 1451, 1383, 1151, 1128, 1041, 919 cm^{-1}; ^1H NMR δ 4.61 (s, 2H), 4.38 (t, J=5.4 Hz, 1H), 3.54 (t, J=6.0 Hz, 2H), 3.36 (s, 3H), 3.32 (s, 6H), 2.84–2.79 (m, 4H), 1.98–1.92 (m, 6H), 1.81–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 96.3, 67.4, 55.1, 52.7, 52.5, 35.1, 32.8, 27.2, 25.9, 25.3, 24.4; EIMS *m/z* (%) 324 (M^+, 73), 293 (M^+-OCH_3, 22), 75 (100); ESIHRMS calcd for $C_{14}H_{28}O_4S_2Na$ ($[M+Na]^+$) 347.1321, found 347.1326.

4.4. Synthesis of 5

A mixture of **4** (3.202 g, 9.9 mmol) and PPTS (588 mg, 2.4 mmol) in aqueous acetone (100 mL of acetone plus 10 mL water) was heated to reflux with stirring for 12 h, when TLC showed the hydrolysis to be complete. Acetone was removed on a rotary evaporator, and the residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to give aldehyde as a yellowish oil (2.86 g), which was dissolved in CH_2Cl_2 (68 mL) and treated with $Ph_3P{=}CHCO_2Et$ (6.0 g, 18.9 mmol). The mixture was stirred at ambient temperature until TLC showed complete disappearance of the aldehyde. The solvent was removed on a rotary evaporator, and the residue was diluted with Et_2O. The solid–liquid mixture was filtered and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (6:1 *n*-hexane/EtOAc) to give compound **5** as a colorless oil (3.033 g, 86%). FTIR (film) 1717, 1269, 1042, 919 cm^{-1}; ^1H NMR δ 6.99 (dt, J=16, 6.8 Hz, 1H), 5.87(d, J=16 Hz, 1H), 4.63 (s, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.56 (t, J=5.7 Hz, 2H), 3.37 (s, 3H), 2.84–2.81 (m, 4H), 2.43–2.35 (m, 2H), 2.07–1.95 (m, 6H), 1.80–1.73 (m, 2H), 1.30 (t, J=6.9 Hz, 3H); EIMS *m/z* (%) 348 (M^+, 17), 303 ($M^+-OCH_2CH_3$, 4), 45 (100); ESIHRMS calcd for $C_{16}H_{28}O_4S_2Na$ ($[M+Na]^+$) 371.1321, found 371.1312. Anal. calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10. Found: C, 55.26; H, 8.23.

4.5. Removal of the MOM protecting group in 5 (7)

A mixture of **5** (1.946 g, 5.6 mmol) and *p*-TsOH (106 mg, 0.56 mmol) in EtOH (40 mL) was heated to reflux with stirring until TLC showed the hydrolysis to be complete. The mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **7** as a colorless oil (1.52 g, 90%). FTIR (film) 3438, 1713, 1273, 1046, 908 cm^{-1}; ^1H NMR δ 6.99 (dt, J=15, 6.8 Hz, 1H), 5.88 (d, J=15 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.71–3.68 (m, 2H), 2.85–2.81 (m, 4H), 2.43–2.35 (m, 2H), 2.07–1.94 (m, 6H), 1.78–1.69 (m, 2H), 1.30 (t, J=7.1 Hz, 3H); EIMS *m/z* (%) 304 (M^+, 9), 259 (M^+-OEt, 3), 245 (28), 197 (100); EIHRMS calcd for $C_{14}H_{24}O_3S_2Na$ ($[M+Na]^+$) 327.1059, found 327.1063. Anal. calcd for $C_{14}H_{24}O_3S_2$: C, 55.23; H, 7.95. Found: C, 55.39; H, 7.82.

4.6. Hydrolysis of the dithiane protecting group in 7 (9)

$NaHCO_3$ (6.183 g, 73.6 mmol) and I_2 (9.209 g, 36.3 mmol) were added to a solution of **7** (3.34 g, 11.0 mmol) in aqueous acetone (94 mL of acetone plus 17 mL water). The resulting mixture was stirred at 0 °C for 30 min until TLC showed complete disappearance of **7**. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was diluted with Et_2O. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (2:1 *n*-hexane/EtOAc) to give **9** as a yellowish oil (3.892 g, 83%). FTIR (film) 1716, 1655, 1043, 979 cm^{-1}; ^1H NMR δ 6.93 (dt, J=16, 6.9 Hz, 1H), 5.83 (d, J=16 Hz, 1H), 4.18 (q, J=7.4 Hz, 2H), 3.66 (dt, J=10, 5.7 Hz, 2H), 2.65–2.56 (m, 4H), 2.53–2.45 (m, 2H), 1.91–1.82 (m, 2H), 1.28 (t, J=7.2 Hz, 3H); ESIMS *m/z* 232 ($[M+NH_4]^+$); EIHRMS calcd for $C_{11}H_{18}O_4Na$ ($[MNa]^+$) 237.1097, found 237.1089.

4.7. Synthesis of 13

p-TsOH (3.27 g, 17.2 mmol) and UHP (9.927 g, 105.5 mmol) were added to a solution of **9** (2.995 g, 14.0 mmol) in MeOH (280 mL). The resulting mixture was stirred at ambient temperature for 20 h. When TLC showed complete disappearance of **9**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **11** (2.633 g, 82%), which gave the following data: ^1H NMR δ 8.06 (s, 1H), 6.99 (dt, J=16, 6.7 Hz, 1H), 5.85 (dt, J=16, 1.3 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.02–3.97 (m, 2H), 2.27–2.05 (m, 4H), 2.05–1.79 (m, 4H), 1.29 (t, J=7.2 Hz, 3H). The **11** (2.633 g, 11.5 mmol) was then dissolved in CF_3CH_2OH (64 mL) containing $NHEt_2$ (100 μL). The mixture was stirred at the ambient temperature until TLC showed complete disappearance of **11**. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **13** as a colorless oil (1.369 g, 52%). FTIR (film) 1737, 1445, 1370, 1289, 1184, 1032 cm^{-1}; ^1H NMR δ 4.56–4.54 (m, 1H), 4.15 (q, J=7.1 Hz, 2H), 4.08–4.02 (m, 2H), 2.56 (dd, J=7.4, 16 Hz, 1H), 2.39 (dd, J=6.0, 16 Hz, 1H), 2.05–1.74 (m, 8H), 1.25 (t, J=7.1 Hz, 3H); ESIMS *m/z* 248 ($[M+NH_4]^+$). Anal. calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.56; H, 7.87.

4.8. Synthesis of compound 6

Prepared from **4** in 94% yield using the same procedure for the synthesis of **5** described above except that $Ph_3P{=}CHCO_2Bn$ was utilized instead of $Ph_3P{=}CHCO_2Et$. Data for **6** (a colorless oil): FTIR (film) 1720, 1653, 1040, 919 cm^{-1}; ^1H NMR δ 7.39–7.32 (m, 5H), 7.04 (dt, J=16, 6.7 Hz, 1H), 5.92 (d, J=16 Hz, 1H), 5.18 (s, 2H), 3.54 (t, J=6.2 Hz, 2H), 3.34 (s, 3H), 2.81 (t, J=5.7 Hz, 4H), 2.43–2.35 (m, 2H), 2.05–1.93 (m, 6H), 1.78–1.89 (m, 2H); ESIMS

m/z 428 ([M+NH_4]$^+$). ESIHRMS calcd for $C_{21}H_{30}O_4S_2Na$ ([M+Na]+) 433.1478, found 433.1479. Anal. calcd for $C_{21}H_{30}O_4S_2$: C, 61.43; H, 7.36. Found: C, 61.45; H, 7.39.

4.9. Removal of the MOM group in 6 (8)

A solution of **6** (3.941 g, 9.6 mmol) in THF (30 mL) and 2 N HCl (15 mL) was stirred at 40–50 °C until TLC showed complete disappearance of **6**. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **8** (2.246 g, 64%). FTIR (film) 3421, 1717, 1652, 1272, 1163, 1017, 978 cm^{-1}; ^{1}H NMR δ 7.39–7.27 (m, 5H), 7.04 (dt, J=16, 6.7 Hz, 1H), 5.92 (d, J=16 Hz, 1H), 5.18 (s, 2H), 3.67 (t, J=6.1 Hz, 2H), 2.83–2.79 (m, 4H), 2.43–2.35 (m, 2H), 2.06–1.92 (m, 6H), 1.76–1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 148.8, 135.9, 128.4, 128.1, 121.2, 66.0, 62.4, 52.4, 36.2, 36.8, 27.2, 25.8, 25.1; ESIMS *m/z* 384 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{19}H_{27}O_3S_2$ ([M+H]$^+$) 367.1396, found 367.1394.

4.10. Hydrolysis of the dithiane protecting group in 8 (10)

Compound **10** was obtained in 77% yield from **8** using the same procedure described above for the synthesis of **9**. Data for **10** (a colorless oil): FTIR (film) 3420, 1716, 1654, 1267, 1171, 1026, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.27 (m, 5H), 6.98 (dt, J=15, 7.0 Hz, 1H), 5.88 (d, J=15 Hz, 1H), 5.17 (s, 2H), 3.64 (t, J=5.8 Hz, 2H), 2.64–2.45 (m, 6H), 1.89–1.80 (m, 2H); ESIMS *m/z* 294 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{16}H_{20}O_4Na$ ([M+Na]$^+$) 299.1254, found 299.1240.

4.11. Synthesis of compound 14

Using the same procedure described above for converting **9** into **11**, the intermediate hydroperoxide **12** was obtained in 75% from **10**, which showed the following: ^{1}H NMR δ 8.14 (s, 1H), 7.39–7.32 (m, 5H), 7.05 (dt, J=15.3, 6.6 Hz, 1H), 5.91 (d, J=15.6 Hz, 1H), 5.18 (s, 2H), 4.01–3.96 (m, 2H), 2.41–2.15 (m, 3H), 2.08–1.77 (m, 5H). The **12** was then converted into **14** (1:4 mixture of two diastereomers) in 52% yield using the same procedure as described above for the conversion of **11** into **13**. Data for **14** (a colorless oil): FTIR (film) 1724, 1455, 1291,1033 cm^{-1}; ^{1}H NMR δ 7.37–7.31 (m, 5H), 5.14 (s, 2H), 4.63–4.56 (m, 1H), 4.11–4.00 (m, 2H), 2.88 and 2.64 (two doublets in 1:4 ratio, J=16, 7.4 Hz, 1H altogether, part of an AB system), 2.60 and 2.47 (two doublets in 1:4 ratio, J=16, 7.4 Hz, 1H altogether, part of an AB system), 2.06–1.75 (m, 8H); ESIMS *m/z* 310 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{16}H_{20}O_5Na$ ([M+Na]$^+$) 315.1203, found 315.1210. Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.86; H, 6.97.

4.12. Conversion of 4 into 15

A mixture of **4** (6.3582 g, 19.6 mmol) and PPTS (523 mg, 2.0 mmol) in aqueous acetone (178 mL of acetone plus 18 mL of water) was heated to reflux with stirring until TLC showed completion of the hydrolysis (12 h). Acetone was removed on a rotary evaporator. The residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate aldehyde as a yellowish oil (4.92 g), which was dissolved in MeCN (8 mL) and added to a mixture of DBU (0.39 mL, 2.64 mmol), $MeNO_2$ (3.22 g, 26.4 mmol, a commercially available 50% solution in MeOH), and MeCN (40 mL). The mixture was then stirred at the ambient temperature until TLC showed complete disappearance of the aldehyde (ca. 15 h). The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (3:1 *n*-hexane/EtOAc) to give **15** as a colorless oil (5.625 g, 94% overall). FTIR (film) 3425, 2932, 1553, 1383, 1109, 1036 cm^{-1}; ^{1}H NMR δ 4.63 (s, 2H), 4.46–4.42 (m, 2H), 3.56 (t, J=6.0 Hz, 2H), 3.37 (s, 3H), 2.83 (t, J=5.7 Hz, 4H), 2.73 (d, J=5.0 Hz, 1H), 2.25–2.15 (m, 1H), 1.99–1.94 (m, 6H), 1.74–1.70 (m, 4H); EIMS *m/z* (%) 339 (M^+, 4), 294 ($M^+-CH_2OCH_3$), 45 (100); ESIHRMS calcd for $C_{13}H_{25}NO_5S_2Na$ ([M+Na]$^+$) 362.1066, found 362.1075.

4.13. Elimination of the hydroxyl group in 15 (16)

With cooling (0 °C bath) and stirring, MsCl (2.3 mL, 30 mmol) and NEt_3 (5 mL, 36 mmol) were added to a solution of **15** (6.056 g, 17.86 mmol) in CH_2Cl_2 (90 mL). The stirring was continued at the ambient temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (6:1 *n*-hexane/EtOAc) to give **16** as a yellowish colorless oil (5.588 g, 97%). FTIR (film) 2933, 1648, 1524, 1350, 1039 cm^{-1}; ^{1}H NMR δ 7.34–7.27 (m, 1H), 7.04 (d, J= 13 Hz, 1H), 4.63 (s, 2H), 3.55 (t, J=3.1 Hz, 2H), 3.37 (s, 3H), 2.83 (t, J=5.7 Hz, 4H), 2.53–2.45 (m, 2H), 2.10–2.04 (m, 2H), 2.01–1.96 (m, 4H), 1.79–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 139.7, 96.3, 67.3, 55.1, 52.2, 36.1, 35.4, 25.9, 24.9, 24.5, 23.8; EIMS *m/z* (%) 321 (M), 275 (M^+-NO_2, 32), 218 ($M^+-C_2H_6OMOM$, 31), 45 (100); ESIHRMS calcd for $C_{13}H_{23}NO_4S_2Na$ ([M+Na]$^+$) 344.0961, found 344.0966.

4.14. Hydrolysis of the dithiane protecting group in 16 (17)

Compound **17** was obtained in 87% yield from **16** using the same procedure described above for the synthesis of **9**. Data for **17** (a colorless oil): FTIR (film): 1715, 1649, 1525, 1352, 1040 cm^{-1}; ^{1}H NMR δ 7.29–7.20 (m, 1H), 7.01 (d, J=14 Hz, 1H), 4.59 (s, 2H), 3.54 (t, J=6.3 Hz, 2H), 3.35 (s, 3H), 2.68 (t, J=6.7 Hz, 2H), 2.58–2.51 (m, 4H), 1.90 (quint, J=6.6 Hz, 2H); ESIMS *m/z* 254 ([M+Na]$^+$). Anal.

calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.13; H, 7.13; N, 6.06.

4.15. Synthesis of 20

Removal of the MOM group in **17**, utilizing the same procedure described above for transforming **5** into **7**, led to **18** in 21% yield (chromatography on silica gel eluting with 1:1 *n*-hexane/EtOAc). FTIR (film) 3411, 1712, 1650, 1525, 1352, 1058 cm^{-1}; ^1H NMR δ 7.30–7.20 (m, 1H), 7.01 (d, J=14 Hz, 1H), 3.85–3.91 (m, 1H), 3.67 (t, J=5.9 Hz, 2H), 2.72–2.67 (m, 2H), 2.61–2.54 (m, 4H), 1.93–1.85 (m, 2H). The **18** thus obtained (59 mg, 0.32 mmol) was immediately dissolved in DME (3.2 mL). *p*-TsOH (61 mg, 0.32 mmol) and UHP (208 mg, 2.2 mmol) were then added. The mixture was stirred at the ambient temperature until TLC showed complete disappearance of **18** (ca. 10.5 h). The mixture was diluted with Et_2O and washed with water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **20** (23 mg, 35%). FTIR (film) 2960, 1556, 1371, 1041 cm^{-1}; ^1H NMR δ 4.95–4.86 (m, 1H), 4.54 (dd, J=9.1, 14 Hz, 1H), 4.37 (dd, J=3.5, 13.8 Hz, 1H), 4.09–4.03 (m, 2H), 2.08–1.88 (m, 6H), 1.82–1.76 (m, 2H); ESIMS *m/z* 221 ($[M+NH_4]^+$); EIHRMS calcd for $C_8H_{13}NO_5$ (M^+) 203.0806, found 203.0818.

4.16. Synthesis of 23

With cooling (−70 °C bath), *n*-BuLi (13.7 mL, 1.6 M) was added dropwise (via a syringe) to a solution of $HC{\equiv}CCH_2OBn$ (3.193 g, 21.9 mmol) in dry THF (45 mL) stirred under argon. The bath was allowed to warm to −25 °C and kept at that temperature for 1.5 h before being added via a cannula to a solution of **22** (4.855 g, 32.8 mmol) in dry THF (55 mL) stirred at −70 °C under argon. The mixture was stirred at that temperature for 2 h. The reaction was quenched with water and acidified to pH 4 with 2 N HCl. The phases were separated. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate ketone-acid as a yellowish oil (3.906 g), which was dissolved in Et_2O (48 mL) and treated with an excess of CH_2N_2 (an ethereal solution prepared using standard procedure prior to use) at 0 °C. When TLC showed complete disappearance of the ketone-acid, the cooling bath was allowed to warm to the ambient temperature. The stirring was continued for another hour before removal of the solvent by rotary evaporation. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **23** as a yellowish oil (2.103 g, 43%). FTIR (film) 3031, 2951, 2221, 1732, 1650, 1260, 1074, 698 cm^{-1}; ^1H NMR δ 7.94–7.91 (m, 1H), 7.69–7.59 (m, 3H), 7.38–7.27 (m, 5H), 4.65 (s, 2H), 4.41 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 140.2, 139.4, 135.2, 135.1, 133.7, 132.8, 131.7, 131.3, 130.88, 130.86 (2C), 93.4, 87.4, 75.0, 59.8, 55.5; EIMS *m/z* (%) 293 (M^+−Me, 1), 263 (M^+−OEt, 54), 91 (M^+−Bn, 64), 170 (100); MALDIHRMS calcd for $C_{19}H_{16}O_4Na$ ($[M+Na]^+$) 331.0941, found 331.0942.

4.17. Synthesis of compound 24

A mixture of **23** (1.208 g, 3.9 mmol) and 10% palladium on charcoal (500 mg) in MeOH (20 mL) was stirred at the ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **23** (5.5 h). The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **24** as a colorless oil (332 mg, 38%). FTIR (film) 3402, 2932, 1723, 1434, 1264, 1091 cm^{-1}; ^1H NMR δ 7.90 (d, J=7.1 Hz, 1H), 7.46–7.40 (m, 1H), 7.28–7.23 (m, 2H), 3.90 (s, 3H), 3.72 (t, J=5.6 Hz, 2H), 2.97 (t, J=7.7 Hz, 2H), 1.72–1.68 (m, 2H); ESIMS *m/z* 245 ($[M+Na]^+$); ESIHRMS calcd for $C_{12}H_{14}O_4Na$ ($[M+Na]^+$) 245.0784, found 245.0783.

4.18. Synthesis of compound 25 (from 24)

DIBAL-H (1.0 M solution in cyclohexane, 1.8 mL) was added (via a syringe) to a solution of **24** (132 mg, 0.59 mmol) in dry CH_2Cl_2 (3 mL) stirred at −75 °C under N_2. The stirring was continued at that temperature for 3 h. Then the bath was allowed to warm to the ambient temperature before the reaction was quenched with MeOH. The reaction mixture was shaken with aqueous saturated potassium sodium tartrate. The phases were separated. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate triol (160 mg), which was dissolved in $CHCl_3$ (3 mL) and treated with activated MnO_2 (262 mg, 3 mmol). The mixture was stirred at the ambient temperature for 4 d. The solids were filtered off (rinsed with $CHCl_3$) and the combined filtrate/washings were concentrated on a rotary evaporator and added to a solution of $Ph_3P{=}CHCO_2Et$ (150 mg, 0.43 mmol) in $CHCl_3$ (3 mL). The mixture was stirred at the ambient temperature for 10 h. The solvent was removed on a rotary evaporator. The solid residue was triturated with Et_2O. The solids were filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **25** as a colorless oil (73 mg, 47%). FTIR (film) 3417, 2928, 1683, 1634, 1478, 1175, 1036 cm^{-1}; ^1H NMR δ 8.05 (d, J=16 Hz, 1H), 7.72 (d, J=7.7 Hz, 1H), 7.62–7.09 (m, 3H), 6.31 (d, J=16 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 3.76 (t, J=5.8 Hz, 2H), 3.08 (t, J=6.8 Hz, 2H), 2.05–1.98 (m, 2H), 1.69 (br s, 1H), 1.34 (t, J=7.2 Hz, 3H); EIMS *m/z* (%) 245 (M^+−OH, 0.6), 189 (M^+−CO_2Et, 100), 217 (M^+−OEt, 2). Anal. calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.32; H, 6.79.

4.19. Synthesis of compound 29

n-BuLi (50 mL, 1.2 M) was added dropwise (via a syringe) to a solution of *o*-$BrC_6H_4CH_2OH$ (5.578 g, 29.8 mmol) in dry THF (150 mL) stirred at −78 °C under N_2. After the completion of the addition, the stirring was continued at that temperature for 1 h. Then, a solution of **27** (prepared by Swern oxidation from the corresponding alcohol (6.78 g, 33.2 mmol)) in dry THF (20 mL) was added dropwise via a syringe. The mixture was stirred at the same temperature for another 40 min before saturated aqueous NH_4Cl

was introduced to quench the reaction. The mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **29** as a yellowish oil (5.577 g, 61% from **28**). FTIR (film) 3351, 2927, 1463, 1255, 1100 cm^{-1}; ^1H NMR δ 7.43–7.40 (m, 1H), 7.35–7.26 (m, 3H), 4.95 (dd, J=7.9, 5.0 Hz, 1H), 4.72 (s, 2H), 3.79–3.71 (m, 2H), 2.00–1.97 (m, 2H), 2.79–1.74 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H); EIMS *m/z* (%): 292 (M^+-H_2O, 0.9), 195 (M^+-TBS, 1.3), 143 (100); ESIHRMS calcd for $C_{17}H_{30}O_3SiNa$ ($[M+Na]^+$) 333.1856, found 333.1868. Anal. calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.98; H, 9.64.

4.20. Synthesis of compound 31

With cooling (−70 °C bath) and stirring a solution of DMSO (7 mL, 97.4 mmol) was added dropwise (via a syringe) to a solution of $(COCl)_2$ (3.9 mL, 44.3 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at that temperature for 30 min before the alcohol **29** (3.269 g, 10.58 mmol) was introduced via a syringe. The bath was allowed to warm to −60 °C and the stirring was continued at that temperature for 30 min. Then, Et_3N (27 mL, 199.2 mmol) was added to the mixture and the reaction was continued at that temperature for another 30 min. After the reaction was quenched with 2 N HCl (40 mL), the cold bath was removed and the mixture was stirred at ambient temperature for 5 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to give crude ketone–aldehyde **30** as a yellowish oil (3.578 g), which was then converted into α,β-unsaturated ester **31** as a red-orange oil (3.064 g, 74% from **29**) by a similar Wittig reaction as described above for the synthesis of **25**. Data for **31**: FTIR (film) 1716, 1256, 1177 cm^{-1}; ^1H NMR δ 8.02 (d, J=15.9 Hz, 1H), 7.70 (d, J=7.6 Hz, 1H), 7.55 (d, J=7.3 Hz, 1H), 7.49–7.41 (m, 2H), 6.25 (d, J=15.8 Hz, 1H), 4.24 (q, J=7.1 Hz, 2H), 3.66 (t, J=6.1 Hz, 2H), 2.98 (t, J=7.5 Hz, 2H), 1.95–1.85 (m, 2H), 1.29 (t, J=7.1 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ESIMS *m/z*: 377 ($[M+H]^+$). Anal. calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 67.10; H, 8.23.

4.21. Removal of the TBS group in 31 (25)

A mixture of **31** (2.916 g, 7.46 mmol) and *p*-TsOH (380 mg, 2 mmol) in aqueous THF (40 mL of THF plus 10 mL water) was stirred at ambient temperature for 5 h, when TLC showed the hydrolysis to be complete. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, and the phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (2:1 *n*-hexane/EtOAc) to give **25** (1.827 g, 96%). Data for **25** are given above under 'synthesis of **25** (from **24**)'.

4.22. Synthesis of compound 21

A solution of **25** (1.905 g, 7.3 mmol), CSA (5.0 g, 22.0 mmol), and UHP (4.7 g, 51 mmol) in DME (116 mL) was stirred at the ambient temperature until TLC showed complete disappearance of **25** (ca.18 h). The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **26** (1.744 g, 86%), which gave the following data: FTIR (film) 3375, 1712, 1633, 1316, 1183 cm^{-1}; ^1H NMR δ 8.32 (d, J=15.8 Hz, 1H), 8.17 (s, 1H), 7.79–7.76 (m, 1H), 7.59–7.56 (m, 1H), 7.39–7.35 (m, 1H), 6.28 (d, J=15.8 Hz, 1H), 4.31–4.19 (m, 4H altogether, including a quartet at δ 4.26, J=7.1 Hz), 2.52–2.45 (m, 1H), 2.18–2.00 (m, 3H), 1.34 (t, J=7.1 Hz, 3H). The **26** was then transformed into **21a** (the less polar diastereomer, 44.4% yield) and **21b** (the more polar diastereomer, 12.3% yield) using the same procedure described above for converting **9** into **11**. Data for **21a** (the less polar diastereomer): FTIR (film) 1736, 1453, 1374, 1281, 1053 cm^{-1}; ^1H NMR δ 7.37–7.30 (m, 3H), 7.13–7.10 (m, 1H), 5.70 (t, J=6.4 Hz, 1H), 4.26–4.19 (m, 4H), 2.91 (d, J=6.7 Hz, 2H), 2.43–2.36 (m, 4H), 1.29 (t, J=7.1 Hz, 3H); ESIMS *m/z* 296 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{15}H_{18}O_5Na$ ($[M+Na]^+$) 301.1046, found 301.1042. Anal. calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.77; H, 6.52. Data for **21b** (the more polar diastereomer): FTIR (film) 1735, 1454, 1372, 1279, 1050 cm^{-1}; ^1H NMR δ 7.36–7.21 (m, 3H), 7.16–7.13 (m, 1H), 5.50 (dd, J=4.4, 9.0 Hz, 1H), 4.28–4.16 (m, 4H altogether, including a quartet at δ 4.20, J=7.2 Hz), 3.24 (dd, J=8.8, 16 Hz, 1H), 2.80 (dd, J=4.4, 16 Hz, 1H), 2.38–2.35 (m, 1H), 2.23–2.17 (m, 3H), 1.31 (t, J=7.2 Hz, 3H); ESIMS *m/z* 296 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{15}H_{18}O_5Na$ ($[M+Na]^+$) 301.1046, found 301.1042.

4.23. Synthesis of compound 33

A mixture of 1,2,6-hexatriol (14.5 g, 108 mmol), *p*-TsOH (2.05 g, 10.8 mmol), and DMOP (20 mL, 162 mmol) in acetone (300 mL) was stirred at the ambient temperature for 22 h. Aqueous $NaHCO_3$ was added, followed by Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give a yellowish oil. This oil was added to a mixture of NaH (8.4 g, 210 mmol) in DMF (300 mL) stirred at 0 °C. $CH_2{=}CHCH_2Br$ (25.41 g, 210 mmol) was then introduced. The mixture was stirred at the ambient temperature for 10 h before being partitioned between water and Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and concentrated on a rotary evaporator. The residue was dissolved in MeOH (160 mL). HCl 2 N (80 mL) was then added. The mixture was stirred at the ambient temperature for 2 h before the solvent was removed on a rotary evaporator. The residue was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Removal of the solvent on a rotary evaporator left a yellowish

oil, which was dissolved in a mixture of CH_2Cl_2 (422 mL) and NEt_3 (45 mL). The mixture was cooled in a 0 °C bath. *p*-TsCl (23.7 g, 123.5 mmol) was then added. The mixture was stirred at the ambient temperature for 12 h before diluting with CH_2Cl_2, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was added to Et_2O (440 mL), followed by KOH (7.056 g, 126 mmol). The mixture was stirred at the ambient temperature for 5.5 h. Water was added and the phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give **33** as a colorless oil (10.761 g, 69% from 1,2,6-hexatriol). FTIR (film) 2932, 1458, 1360, 1179, 1105 cm^{-1}; ^1H NMR δ 5.92 (ddt, J=17, 10.6, 5.5 Hz, 1H), 5.72 (br d, J=17 Hz, 1H), 5.18 (br d, J=10 Hz, 1H), 3.97 (d, J=5.6 Hz, 2H), 3.45 (t, J=6.2 Hz, 2H), 2.92–2.89 (m, 1H), 2.75 (t, J=4.5 Hz, 1H), 2.48 (dd, J=2.8, 4.9 Hz, 1H), 1.70–1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 116.7, 71.7, 70.0, 52.1, 47.0, 32.2, 29.4, 22.6; EIMS *m/z*: (%) 155 (M^+-H, 6), 99 ($M^+-Oallyl$, 1), 41 (100); EIHRMS calcd for $C_9H_{16}O_2$ (M^+) 156.1103, found 156.1154.

4.24. Synthesis of compound 35

n-BuLi (8.8 mL, 1.6 M) was added dropwise (via a syringe) to a solution of **34** (3.253 g, 14.1 mmol) in dry THF (50 mL) stirred at −70 °C under N_2. After the completion of the addition, the mixture was stirred at −70 °C for 1 h. A solution of epoxide **33** (2.197 g, 14.1 mmol) in dry THF (10 mL) was added, followed by $BF_3\cdot EtO_2$ (2.0 mL, 14.1 mmol). The stirring was continued at the same temperature for another hour. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (7:1 *n*-hexane/EtOAc) to give **35** (3.477 g, 80%). FTIR (film) 3470, 2936, 1453, 1100, 1040 cm^{-1}; ^1H NMR δ 7.36–7.23 (m, 4H), 5.92 (ddt, J=17, 10.2, 5.8 Hz, 1H), 5.27 (br d, J=18 Hz, 1H), 5.18 (br d, J=11 Hz, 1H), 4.71 (s, 4H), 4.67 (d, J=11 Hz, 2H, part of an AB system), 4.60 (d, J=11 Hz, 2H, part of an AB system), 3.97 (dt, J=4.3, 1.4 Hz, 2H), 3.83–3.80 (m, 1H), 3.45 (t, J=6.4 Hz, 2H), 3.42 (s, 3H), 2.91 (dd, J=15, 3.6 Hz, 1H), 2.75 (dd, J=14, 9.0 Hz, 1H), 2.42 (d, J=3.3 Hz, 1H), 1.68–1.58 (m, 6H); EIMS *m/z*: (%) 309 (M^++H, 0.03), 309 (M^+, 0.02), 104 (100); ESIHRMS calcd for $C_{18}H_{28}O_4Na$ ($[M+Na]^+$) 331.1880, found 331.1881. Anal. calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.72; H, 8.78.

4.25. Removal of the MOM group in 35 (36)

Compound **36** was prepared in 93% yield (chromatography on silica gel eluting with 2:1 *n*-hexane/EtOAc) from **35** using the same procedure described above for converting **6** into **8**. Data for **36** (a yellowish oil): FTIR (film) 3331, 2936, 1453, 1100, 1010 cm^{-1}; ^1H NMR δ 7.34–7.20 (m, 4H), 5.92 (ddt, J=17, 10, 5.8 Hz, 1H), 5.27 (br d, J=18 Hz, 1H), 5.18 (br d, J=10 Hz, 1H), 4.76 (d, J=12 Hz, 1H), 4.48 (d, J=12 Hz, 1H), 3.97 (dt, J=5.6, 1.4 Hz, 2H), 3.85–3.77 (m, 1H), 3.46 (t, J=6.4 Hz, 2H), 2.84 (s, 1H), 2.82 (d, J=3.8 Hz, 1H), 1.71–1.46 (m, 8H); EIMS *m/z* (%): 246 (M^+-H_2O, 0.86), 143 (20), 104 (100); ESIHRMS calcd for $C_{16}H_{24}O_3Na$ ($[M+Na]^+$) 287.1618, found 287.1624. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.44; H, 9.36.

4.26. Synthesis of 37

Compound **37** was prepared in 85% yield (chromatography on silica gel eluting with 8:1 *n*-hexane/EtOAc) from compound **36** using the same procedure described above for converting **29** into **31**. Data for **37** (a yellowish oil): FTIR (film) 1713, 1634, 1314, 1178 cm^{-1}; ^1H NMR δ 7.81 (d, J=16 Hz, 1H), 7.61 (d, J=7.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.23 (d, J=7.1 Hz, 1H), 6.36 (d, J=16 Hz, 1H), 5.89 (ddt, J=17, 11, 5.3 Hz, 1H), 5.25 (br d, J=17 Hz, 1H), 5.16 (br d, J=11 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.93 (d, J=5.6 Hz, 2H), 3.86 (s, 2H), 3.40 (t, J=6.2 Hz, 2H), 2.51 (t, J=7.0 Hz, 2H), 1.71–1.51 (m, 4H), 1.33 (t, J=7.2 Hz, 3H); EIMS *m/z* (%): 330 (M^+, 0.97), 273 ($M^+-Oallyl$), 141 (100). Anal. calcd for $C_{20}H_{26}O_4$: C, 72.73; H, 7.88. Found: C, 72.71; H, 8.02.

4.27. Synthesis of compound 42

A mixture of **37** (3.551 g, 10.76 mmol) and $PdCl_2$ (383 mg, 2.15 mmol) in MeOH (54 mL) was stirred at 60 °C until TLC showed the complete disappearance of **37**. The reaction mixture was filtered. The filtrate was concentrated on a rotary evaporator to give an orange oil (a mixture containing **38**, **39**, and **40**, 2.458 g). This crude oil was added to the mixture of UHP (6.9 g, 73.4 mmol) and *p*-TsOH (1.85 g, 9.74 mmol) in DME (110 mL). The mixture was stirred at the ambient temperature until TLC showed disappearance of the starting material. The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **41** as a colorless oil (2.314 g, 71% from **37**), which gave the following data: FTIR (film) 3361, 2943, 1712, 1691, 1632, 1316, 1186 cm^{-1}; ^1H NMR δ 8.23 (s, 1H), 8.20 (d, J=16 Hz, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.40–7.24 (m, 3H), 6.34 (d, J=16 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.88–3.77 (m, 2H), 3.41 (d, J=14 Hz, 1H, part of AB system), 3.13 (d, J=14 Hz, 1H, part of AB system), 1.51–1.03 (m, 6H), 0.88 (t, J=7.1 Hz, 3H). The **41** was then transformed into **42** (a 1:1 mixture of diastereomers) in 51% total yield (chromatography on silica gel eluting with 15:1 *n*-hexane/EtOAc) using the same procedure described above for converting **11** into **13**. Data for **42** (a colorless oil): FTIR (film) 1736, 1445, 1372, 1216, 1180, 1045 cm^{-1}; ^1H NMR δ 7.28–7.07 (m, 4H), 5.93 (dd, J=4.9, 8.4 Hz, 0.5H), 5.88 (dd, J=4.2, 9.1 Hz, 0.5H), 4.29–4.20 (m, 2H, including a quartet at δ 4.17, J=7.1 Hz), 4.15–3.94 (m, 1H), 3.84–3.66 (m, 2H altogether, including a doublet at δ 3.86, J=14 Hz), 3.22 (dd, J=9.1, 16 Hz, 0.5H), 3.01 (dd, J=3.9, 16 Hz, 0.5H), 2.84 (dd, J=8.0, 16 Hz, 0.5H), 2.71 (dd, J=4.9, 16 Hz, 0.5H), 2.59 (d, J=14 Hz, 1H), 1.80–1.40 (m, 6H), 1.31 and 1.25 (two

triplets in 1:1 ratio, J=7.3 Hz, 3H altogether); ESIMS m/z 324 ([M+NH_4]$^+$). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.89; H, 7.37.

4.28. Synthesis of 43

Using the same procedure described above for the synthesis of **35** (except that epichlorohydrin (3.2 g, 41.1 mmol) was utilized as the epoxide instead of **33**) an intermediate alcohol (5.058 g) was obtained from **34** (6.329 g, 27.4 mmol). The crude alcohol–chloride was added to a mixture of NaH (914 mg, 22.8 mmol) in THF (104 mL) stirred at 0 °C. The bath was allowed to warm to ambient temperature and the reaction was continued until TLC showed complete disappearance of the chloride (2.5 h). The reaction was quenched with water and the reaction mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (15:1 *n*-hexane/EtOAc) to give **43** (3.827 g, 67% from **34**). FTIR (film) 2929, 1452, 1212, 1150, 1100 cm^{-1}; ^{1}H NMR δ 6.99–6.95 (m, 1H), 6.90–6.85 (m, 3H), 4.29 (s, 2H), 4.24 (s, 2H), 3.01 (s, 2H), 2.81–2.76 (m, 1H), 2.61 (dd, J=5.5, 15 Hz, 1H), 2.53 (dd, J=5.4, 15 Hz, 1H), 2.39 (t, J=7.4 Hz, 1H), 2.15–2.13 (m, 1H); EIMS m/z (%) 163 ($M^+-CH_2OCH_3$, 14), 133 ($M^+-CH_2OCH_2OCH_3$, 6.7), 91 (Bn, 31), 45 (100); MALDI-HRMS calcd for $C_{12}H_{16}O_3Na$ ([M+Na]$^+$) 231.0992, found 231.0999. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.59.

4.29. Synthesis of 45

Compound **45** was prepared from epoxide **43** and **44** in 76% yield (chromatography on silica gel eluting with 6:1 *n*-hexane/EtOAc) using the same procedure described above for converting **33** into **35** (but with **43** and **44** replacing **33** and **34**, respectively). Data for **45** (a colorless oil): FTIR (film) 3447, 2929, 1452, 1149, 1041 cm^{-1}; ^{1}H NMR δ 7.38–7.21 (m, 8H), 5.93 (ddt, J=17, 11, 5.5 Hz, 1H), 5.31 (br d, J=17 Hz, 1H), 5.22 (br d, J=9.5 Hz, 1H), 4.67 (s, 2H), 4.63 (d, J=2.7 Hz, 1H), 4.55 (d, J=11 Hz, 1H, part of an AB system), 4.60 (d, J=11 Hz, 1H, part of an AB system), 4.06–4.00 (m, 3H altogether, including a doublet at δ 4.01, J=5.4 Hz), 3.40 (s, 3H), 3.05 (d, J=3.8 Hz, 1H), 2.95–2.86 (m, 4H); EIMS m/z (%) 293 (M^+-OCH_2OMe, 1), 119 (−COBn, 7), 104 (100), 91 (Bn, 23). Anal. calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.15; H, 7.85.

4.30. Removal of the MOM group in 45 (46)

Compound **46** was prepared from **45** in 99% yield (chromatography on silica gel eluting with 4:1 *n*-hexane/EtOAc) using the same procedure described above for converting **6** into **8**. Data for **46** (a colorless oil): FTIR (film) 3325, 2923, 1452, 1053 cm^{-1}; ^{1}H NMR δ 7.34–7.19 (m, 8H), 5.85 (ddt, J=17, 10, 6.0 Hz, 1H), 5.27 (br d, J=17 Hz, 1H), 5.22 (br d, J=11 Hz, 1H), 4.72 (d, J=12 Hz, 1H, part of an AB system), 4.55–4.46 (m, 2H), 4.40 (d, J=11 Hz, 1H, part of an AB system), 4.05–3.97 (m, 5H), 3.04–2.85 (m, 4H); EIMS m/z (%) 313 (M^++H, 0.3), 191 (6), 105 (61), 104 (100). Anal. calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.77; H, 8.10.

4.31. Synthesis of 47

Compound **47** was prepared from **46** in 77% yield (chromatography on silica gel eluting with 10:1 *n*-hexane/EtOAc) using the same procedure described above for converting **29** into **31**). Data for **47** (a red-orange oil): FTIR (film) 1711, 1634, 1314, 1178 cm^{-1}; ^{1}H NMR δ 7.79 (d, J=16 Hz, 1H), 7.61–7.58 (m, 1H), 7.34–7.25 (m, 5H), 7.18–7.11 (m, 2H), 6.35 (d, J=16 Hz, 1H), 5.89 (ddt, J=17, 11, 6.0 Hz, 1H), 5.26 (br d, J=18 Hz, 1H), 5.18 (br d, J=12 Hz, 1H), 4.41 (s, 2H), 4.26 (q, J=7.2 Hz, 2H), 3.93–3.86 (m, 6H), 1.34 (t, J=7.1 Hz, 3H); ESIMS m/z 378 ([M+Na]$^+$); ESIHRMS calcd for $C_{24}H_{26}O_4Na$ ([M+Na]$^+$) 401.1723, found 401.1719. Anal. calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 75.97; H, 7.04.

4.32. Synthesis of 52

A mixture of **47** (2.51 g, 6.64 mmol), $PdCl_2$ (1.175 g, 6.64 mmol), and CuCl (657 mg, 6.64 mmol) in DMF–H_2O (50 mL/5 mL) was stirred at the ambient temperature in an open flask (because air was needed in the reaction) until TLC showed completion of the deallylation (ca.12 h). The solids were filtered off. The filtrate was concentrated on a rotary evaporator to give an orange liquid–solid mixture (2.3 g), which was directly added to a mixture of UHP (7.94 g, 84.4 mmol) and CSA (7.83 g, 33.8 mmol) in DME–EtOH (96 mL/22 mL). The resulting mixture was stirred at the ambient temperature until the starting material disappeared on TLC. The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **51** (775 mg, 33% from **47**), which gave the following data: ^{1}H NMR δ 8.70 (s, 1H), 8.20 (d, J=16 Hz, 1H), 7.58 (d, J=7.6 Hz, 1H), 7.41–7.27 (m, 3H), 7.14–7.03 (m, 3H), 6.89 (d, J=6.6 Hz, 1H), 6.34 (d, J=16 Hz, 1H), 5.00 (d, J=14 Hz, 1H, part of an AB system), 4.77 (d, J=15 Hz, 1H, part of an AB system), 4.27 (q, J=7.1 Hz, 2H), 3.64 (d, J=14 Hz, 1H, part of AB system), 3.24 (d, J=15 Hz, 1H, part of AB system), 2.88 (d, J=17 Hz, 1H, part of an AB system), 2.41 (d, J=17 Hz, 1H, part of an AB system), 1.33 (t, J=7.1 Hz, 3H). A solution of **51** (105 mg, 0.28 mmol) and $NHEt_2$ (35 μL) in CF_3CH_2OH–CH_2Cl_2 (1.2 mL/0.6 mL) was stirred at ambient temperature for 21 h. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (16:1 *n*-hexane/EtOAc) to give compound **52** as a colorless oil (46 mg, 24% from **51**). FTIR (film) 1735, 1449, 1372, 1249, 1160, 1027 cm^{-1}; ^{1}H NMR δ 7.31–7.04 (m, 8H), 5.94 (dd, J=4.0, 8.5 Hz, 1H), 5.01 (dd, J=9.1, 15 Hz, 1H), 4.77 (dd, J=12.3, 15 Hz, 1H), 4.25–4.13 (m, 2H, including a quartet at δ 4.21, J=6.9 Hz), 4.03 (d, J=14 Hz, 0.5H), 3.94 (br d, J=14 Hz, 0.5H), 3.22 (dd, J=9.2, 16 Hz, 0.5H), 3.02 (dd, J=4.2, 16 Hz, 1H), 2.95 (d, J=17 Hz, 0.5H), 2.87 (dd, J=8.3, 16 Hz, 0.5H), 2.75 (dd, J=4.2, 16 Hz, 1H), 2.64 (d, J=14 Hz, 1H), 2.48 (d, J=17 Hz, 0.5H), 1.28 and 1.25 (two triplets in 1:1 ratio,

J=7.2 Hz, 3H altogether); ESIMS m/z 372 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{21}H_{22}O_5Na$ ($[M+Na]^+$) 377.1359, found 377.1346. Anal. calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.52; H, 6.54.

4.33. Synthesis of 55

n-BuLi (1.6 M, in hexanes, 6.67 mL, 10 mmol) was added dropwise to a solution of **54** (0.43 mL, 5.0 mmol) in dry THF (22 mL) stirred at −40 °C under N_2. The mixture was stirred at the temperature for 4 h before a soluiton of **53** (2.139 g, 8.15 mmol) in dry THF (2 mL) was introduced. The stirring was continued at 0 °C for another 43 h. The reaction was quenched by addition of water. The mixture was extracted with Et_2O, washed with water, and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give the alkylation product as a yellow-greenish liquid (453 mg, 42% yield). A solution of this compound (300 mg, 1.38 mmol) and *m*-CPBA (261 mg, 1.53 mmol) in CH_2Cl_2 (7 mL) was stirred at the ambient temperature for 3 h. The mixture was partitioned between aqueous Na_2CO_3 and Et_2O. The ethereal layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography of the residue on silica gel (5:1 *n*-hexane/EtOAc) gave the furan ring opened product as a yellowish liquid (306 mg, 95% yield). A solution of this liquid (200 mg, 0.86 mmol) and 10% Pd–C (23 mg) in MeOH (5 mL) was stirred under H_2 (1 atm) for 7 h. The catalyst and the solvent were removed by filtration and rotary evaporation, respectively. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **55** as a yellowish oil (81 mg. 40% yield). FTIR (film) 3426, 2924, 1711, 1406 cm^{-1}; ^1H NMR δ 7.32–7.16 (m, 5H), 4.34 (d, J=5.0 Hz, 2H), 3.00 (t, J=4.8 Hz, 1H), 2.80–2.76 (m, 2H), 2.64–2.59 (m, 4H), 2.47 (t, J=7.3 Hz, 2H), 1.97–1.87 (m, 2H); ESIMS m/z 235 ($[M+H]^+$); ESIHRMS calcd for $C_{14}H_{18}O_3Na$ ($[M+Na]^+$) 257.1148, found 257.1148.

4.34. Wittig reaction of 55 (56 and 57)

A solution of **55** (144 mg, 0.61 mmol) in Ac_2O (2 mL) and NEt_3 (0.3 mL) was stirred at the ambient temperature for 5 h. Aqueous saturated Na_2CO_3 was carefully added. The mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. Removal of the solvent left a yellowish oil (170 mg, ca. 0.6 mmol), which was dissolved in dry THF (0.5 mL) and added to a mixture of $(EtO)_2(O)PCHCO_2Et$ (167 mg, 0.72 mmol) and NaH (33 mg, 0.72 mmol, washed with dry THF three times) in THF (0.5 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the ambient temperature for 7 h. The reaction was quenched by addition of water and the mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. Removal of the solvent left a yellowish oil (245 mg), which was dissolved in EtOH (4 mL) and 2 N HCl (0.5 mL). After stirring at the ambient temperature for 2 d, the mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **56** (34 mg, 18% yield) and **57** (86 mg, 54% yield). Data for compound **56** (a colorless oil): FTIR (film) 3469, 2929, 1709, 1178 cm^{-1}; ^1H NMR δ 7.31–7.15 (m, 5H), 5.95 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 4.17 (d, J=14.0 Hz, 2H), 2.75–2.65 (m, 4H), 2.61 (t, J=7.5 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.34 (t, J=6.1 Hz, 1H), 1.95–1.85 (m, 2H), 1.27 (t, J=7.0 Hz, 3H); ESIMS m/z 305 ($[M+H]^+$); ESIHRMS calcd for $C_{18}H_{24}O_4Na$ ($[M+Na]^+$) 327.1567, found 327.1568. Data for compound **57** (a white solid): mp 69–71 °C. FTIR 1789, 1748, 1638, 1496, 1176 cm^{-1}; ^1H NMR δ 7.33–7.16 (m, 5H), 5.78 (s, 1H), 4.75 (s, 2H), 2.75–2.62 (m, 6H), 2.47 (t, J=7.4 Hz, 2H), 2.00–1.90 (m, 2H); ESIMS m/z 259 ($[M+H]^+$); ESIHRMS calcd for $C_{16}H_{19}O_3Na$ ($[M+H]^+$) 259.1329, found 259.1327.

4.35. Hydroperoxidation of 56 and attempted cyclization (59)

A solution of **56** (26 mg, 0.085 mmol), *p*-TsOH (10 mg, 0.52 mmol), and UHP (30 mg, 0.32 mmol) in DME (1 mL) was stirred at the ambient temperature for 24 h. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **58** as a colorless oil (12 mg, 44% yield), on which the following data were recorded: FTIR (film) 3480, 1747, 1714, 1200 cm^{-1}; ^1H NMR δ 7.65 (s, 1H), 7.30–7.18 (m, 5H), 5.70 (s, 1H), 4.46 (d, J=14 Hz, 1H, part of an AB system), 4.15 (q, J=7.2 Hz, 2H), 3.99 (d, J=14 Hz, 1H, part of an AB system), 3.12–3.05 (m, 1H), 2.84–2.76 (m, 1H), 2.64 (t, J=7.1 Hz, 2H), 2.05–1.63 (m, 6H), 1.25 (t, J=7.2 Hz, 3H). The **58** (12 mg, 0.037 mmol) was dissolved in CF_3CH_2OH (1 mL) and $HNEt_2$ (10 μL). The mixture was stirred at the ambient temperature for 10 h. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **59** as a colorless oil (7 mg, 58% yield). FTIR (film) 3485, 1750, 1713, 1498, 1456, 1282, 1012, 896, 753, 699 cm^{-1}; ^1H NMR δ 7.32–7.15 (m, 5H), 4.28 (q, J=7.1 Hz, 2H), 3.74 (dd, J=13, 5.2 Hz, 1H), 3.63 (s, 1H), 3.61 (dd, J=13, 8.3 Hz, 1H), 2.65–2.55 (m, 4H), 2.44 (t, J=7.3 Hz, 2H), 2.21–2.16 (m, 1H), 2.04–1.86 (m, 4H), 1.30 (t, J=7.2 Hz, 3H); EIMS m/z (%) 292 ($M^+-CH_2{=}CH_2$, 5), 277 ($M^+-C_2H_4CH_3$, 11), 57 (100); MALDI-HRMS calcd for $C_{18}H_{24}O_5Na$ ($[M+Na]^+$) 343.1516, found 343.1523.

4.36. Antimalarial activities of peroxides in vitro

4.36.1. Malaria parasites. *P. falciparum* (ATCC 30932, FCR-3 strain) was used. *P. falciparum* was cultivated by a modification of the method of Trager and Jensen[17] using a 5% hematocrit of type A human red blood cells suspended in RPMI 1640 medium (Gibco, NY) supplemented with heat-inactivated 10% type A human serum. The plates were placed in a CO_2–O_2–N_2 incubator (5% CO_2, 5% O_2, and 90% N_2 atmosphere) at 37 °C, and the medium was changed daily until 5% parasitemia (which means that 5 parasite-infected erythrocytes in every 100 erythrocytes were existing).

4.36.2. Mammalian cells. Mouse mammary tumor FM3A cells (wild-type, subclone F28-7) 16 were supplied by the

Japanese Cancer Research Resources Bank (JCRB). FM3A cells were maintained in suspension culture at 37 °C in a 5% CO_2 atmosphere in plastic bottles containing ES medium (Nissui Pharmaceuticals, Tokyo, Japan) supplemented with 2% heat-inactivated fetal bovine serum (Gibco, NY).

4.36.3. In vitro antimalarial activity of peroxides. The following procedures were used for assay of antimalarial activity.[18,19] Asynchronously cultivated *P. falciparum* were used. Various concentrations of compounds in dimethylsulfoxide were prepared. Five microliters of each solution was added to individual wells of a multidish 24 wells. Erythrocytes with 0.3% parasitemia were added to each well containing 995 μL of culture medium to give a final hematocrit level of 3%. The plates were incubated at 37 °C for 72 h in a CO_2–O_2–N_2 incubator (5% CO_2, 5% O_2, and 90% N_2 atmosphere). To evaluate the antimalarial activity of test compound, we prepared thin blood films from each culture and stained them with Giemsa (E. Merck, Germany). Total 1×104 erythrocytes per one thin blood film were examined under microscopy. All of the test compounds were assayed in duplicate at each concentration. Drug-free control cultures were run simultaneously. All data points represent the mean of three experiments. Parasitemia in control was reaching between 4 and 5% at 72 h. The EC_{50} value refers to the concentration of the compound necessary to inhibit the increase in parasite density at 72 h by 50% of control.

4.36.4. Toxicity against mammalian cell line. FM3A cells grew with a doubling time of about 12 h. Prior to exposure to drugs, cell density was adjusted to 5×104 cells/mL. A cell suspension of 995 μL was dispensed to the test plate, and compound at various concentrations suspended in dimethylsulfoxide (5 μL), were added to individual wells of a multidish 24 wells. The plates were incubated at 37 °C in a 5% CO_2 atmosphere for 48 h. All of the test compounds were assayed in duplicate at each concentration. Cell numbers were measured using a microcell counter CC-130 (Toa Medical Electric Co., Japan). All data points represent the mean of three experiments. The EC_{50} value refers to the concentration of the compound necessary to inhibit the increase in cell density at 48 h by 50% of control. Selectivity refers to the mean of EC_{50} value for FM3A cells per the mean of EC_{50} value for *P. falciparum*.

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