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BRIEF ARTICLE

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Synthesis and Antiplasmodial Activity of Bicyclic Dioxanes as Simplified Dihydroplakortin Analogues

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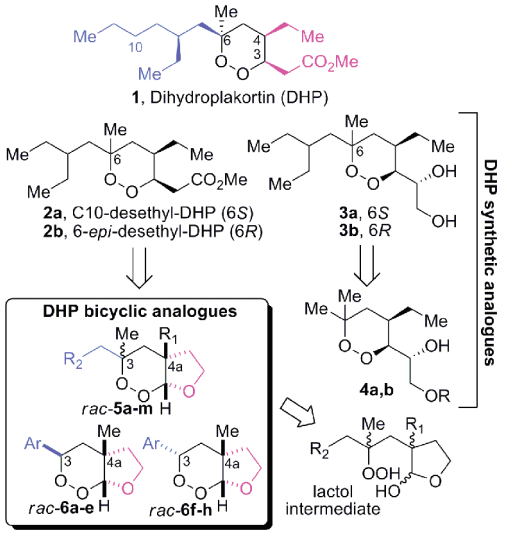
Supporting Information

ABSTRACT: Here we report the synthesis and evaluation of antiplasmodial activity of a novel series of bicyclic peroxides inspired by the marine natural compound dihydroplakortin. We developed a synthetic strategy leading to the dihydroplakortin-related peroxides in only a few steps. The in vitro antiplasmodial potency of the peroxides was similar to, or greater than, that of the reference natural compound, and structure−activity relationship studies revealed several key structural requirements for activity and potency.

INTRODUCTION

Organic compounds from terrestrial and marine organisms are important sources of new drugs and are good templates for synthetic elaboration during drug development. Natural products have profoundly influenced the history of malaria chemotherapy,[1] a plague that kills millions of people worldwide, especially in the poorest countries where it is endemic. Quinine was the first drug to be used against malaria and has been exploited as a template for the development of chloroquine (CQ),[2] one of the most potent and effective chemotherapeutics currently known. Despite the initial efficacy of CQ and structurally related quinoline derivatives, the emergence of *Plasmodium falciparum* (*Pf*) strains resistant to CQ, the failure of vector control programs, and the lack of progress in the development of vaccines have caused recrudescence of the disease and is leading to a worldwide catastrophe in terms of number of victims and socioeconomic costs. The discovery of the endoperoxide-containing sesquiterpene lactone artemisinin has been a major breakthrough in the fight against multidrug resistant parasites. Artemisinin and its semisynthetic derivatives possess exceedingly potent and broad-spectrum antimalarial activity. However, the complex molecular architecture of artemisinin makes extraction from the medicinal plant *Artemisia annua* the only available source of the drug and poses a formidable economic barrier to its widespread distribution to the poorest malaria-endemic countries.[3−5] Moreover, because of reports of delayed parasite clearance in patients receiving artemisinin combination therapy (ACT), the identification of structurally distinct classes of peroxides that are easy to synthesize by low-cost synthetic strategies and are structurally unrelated to the parent natural compound is an urgent task.[6,7] As a part of our ongoing work in the field of antimalarial drug discovery, we were interested in identifying simpler endoperoxide-containing molecular scaffolds as lead compounds for drug development and found inspiration from nature in the form of the endoperoxide 9,10-dihydroplakortin (DHP, **1**, Chart 1), isolated from the Caribbean sponge *Plakortis simplex*,[8] which shows interesting antimalarial properties and has a remarkably simpler skeleton

Chart 1. Reference and Title Compounds, Retrosynthetic Analysis[a]



[a]R_1, R_2, and Ar are as defined in Schemes 1 and 2. Unwedged bold and dashed lines indicate relative configuration.

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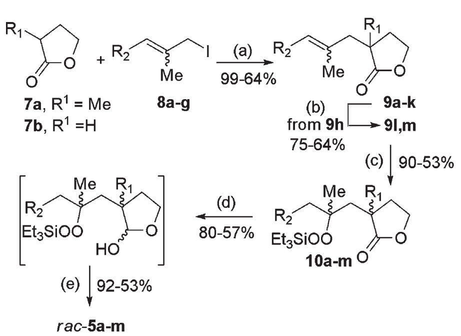
than artemisinin.[9] Consequently, we chose DHP as a lead compound for developing synthetically affordable antiplasmodials. In our previous work, we had already synthesized some semisynthetic analogues of DHP and related peroxides and identified some of the structural requirements necessary for achieving antiplasmodial activity.[10] On the basis of the original structure−activity relationships (SARs) for semisynthetic DHP and plakortin analogues, the endoperoxide moiety was deemed to be crucial for antiplasmodial activity, as well as the "western" chain at C6 of the 1,2-dioxane scaffold (depicted in violet in Chart 1). Regarding the "eastern" groups (depicted in magenta in Chart 1), the ester moiety was not viewed to be essential for potency. Although it has been intensely debated in the literature,[11−13] the mechanism of action of peroxide-containing compounds seems to be related to their ability to react with iron(II) to form radical species that are harmful for the parasite, and formation of radical species is similarly involved in the mechanism of action of plakortin and DHP.[14] Indeed, upon in vitro reaction with iron(II) chloride, the peroxide system of DHP forms an O-centered radical that undergoes an intramolecular 1,5-H shift to form a C-centered radical in the western lateral chain, in agreement with the previously observed SARs. We recently described the first synthetic strategy leading to DHP and used it to prepare the first DHP synthetic analogues **2a,b**, **3a,b**, and **4a,b** (Chart 1) with simplified western side chains.[15,16] As an extension of this work, we directed our efforts to modifications of the 1,2-dioxane skeleton of DHP in order to further simplify the synthesis while maintaining or improving the antiplasmodial potency of the natural compound. For this purpose, we merged the eastern groups of DHP (C3 and C4, Chart 1) by creating a condensed tetrahydrofuran ring (*rac*-**5a**−**m**). The resulting tetrahydrofuro[2,3-*c*]-[1,2]dioxane system was chosen since (i) it gave access to a synthetic strategy based on the well-known acid-catalyzed dehydrative cyclization of lactols (Chart 1) and (ii) it partially recapitulated the peroxyacetal system of artemisinin. Here we report the synthesis and the investigation of the SARs of the novel DHP bicyclic analogues *rac*-**5a**−**m** and *rac*-**6a**−**h** and the antiplasmodial activity of DHP synthetic analogues **2a,b**, **3a,b**, and **4a,b**.

■ RESULTS AND DISCUSSION

Chemistry. The synthetic strategy for the construction of the tetrahydrofuro[2,3-*c*][1,2]dioxane bicyclic system is described in Scheme 1 for *rac*-**5a**−**m**. The key intermediates for the synthesis of the bicyclic scaffold are **9a**−**m**, embodying an olefin moiety, necessary to introduce the peroxide functionality through the Mukaiyama protocol, and a lactone functionality that can serve as the precursor to the lactol intermediate (Chart 1 and Scheme 1). The olefin was introduced by α-alkylation of butyrolactones **7a,b** with the appropriate allyl iodides **8a**−**g**. Intermediates **9l,m** were prepared from **9h** by alkylation with ethyl iodide and isobutyl iodide, respectively. Starting from **9a**−**m**, the hydroperoxysilylation reaction was accomplished by using cobalt(II) bis[2,2,6,6-tetramehtyl-heptane-3,5-dienoate] as the catalyst, in the presence of oxygen and triethylsilane.[17] The resulting intermediates **10a**−**m** were regioselectively obtained as a mixture of diasteroisomers. In the next steps, diisobutylaluminum hydride (DIBAL) promoted reduction of lactones **10a**−**m** furnished the corresponding lactols in quantitative yields. These latter intermediates were finally treated with an excess of trimethylsilyl triflate in DCM at −78 °C, resulting in simultaneous deprotection of the silyl peroxide moiety and cyclization to afford the desired products *rac*-**5a**−**m**. Compounds *rac*-**5a,h,l,m**, containing only two chiral centers, were obtained as mixtures of enantiomers with cis-fused 1,2-dioxane and furan rings, while *rac*-**5b**−**g**,**i**−**k**, with an additional chiral center at C3, were obtained as inseparable mixtures of diasteroisomers. *rac*-**5g** was resolved in the corresponding enantiomers via semipreparative chiral HPLC (see Figures 1 and 2 of Supporting Information for further details).

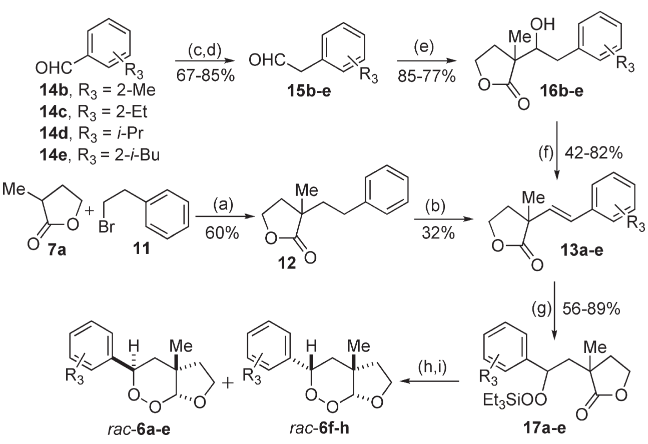
Scheme 1. Synthesis of C3-Aliphatic Derivatives *rac*-5a−m[a]



	R_1	R_2
a	Me	H
b	Me	*n*-Pr
c	Me	*n*-Bu
d	Me	3-pentyl
e	Me	cyclopentyl
f	Me	cyclohexyl
g	Me	2-adamantyl
h	H	H
i	H	*n*-Pr
j	H	*n*-Bu
k	H	3-pentyl
l	Et	H
m	*i*-Bu	H

[a] Reagents and conditions: (a) (i) **7a,b**, LiHMDS, THF, −78 °C, 30 min; (ii) **8a**−**g**, −78 °C, 10 min, then 25 °C, 2 h; (b) (i) **9h**, LiHMDS, THF, −78 °C, 30 min; (ii) EtI for **9l**, *i*-BuI for **9m**, THF, −78 °C, 10 min, then 25 °C, 2 h; (c) Co(thd)$_2$, Et_3SiH, O_2, *t*-BuOOH (5 M in nonane), 1,2-DCE, 25 °C, 4 h; (d) DIBAL, DCM, −78 °C, 1.5 h; (e) TMSOTf, DCM, −78 °C, 5 min.

Scheme 2. Synthesis of Endoperoxides *rac*-6a−h[a]



[a] Reagents and conditions: (a) (i) **7a**, LiHMDS, THF, −78 °C, 30 min; (ii) **11**, −78 °C, 10 min, then 25 °C, 16 h; (b) for **13a**, (i) NBS, AIBN, CCl_4, reflux, 4 h; (ii) DBU, sealed tube, 70 °C, 20 min; (c) (i) $(MeOCH_2)PPh_3^+Cl^-$, NaHMDS, THF, 0 °C, 30 min; (ii) **14b**−**e**, −78 °C, 30 min, then 25 °C, 1.5 h; (d) 6 N HCl, acetone, 25 °C, 16 h; (e) **7a**, LiHMDS, THF, −78 °C, 30 min, then **15b**−**e**, −78 °C → 25 °C, 2 h; (f) (i) Tf_2O, pyridine, DCM, from −78 °C to 0 °C, 1 h; (ii) DBU, 25 °C, 1 h; (g) Co(acac)$_2$, Et_3SiH, O_2, *t*-BuOOH (5 M in nonane), 1,2-DCE, 25 °C, 3 h; (h) DIBAL, DCM, −78 °C, 1.5 h; (i) TMSOTf, DCM, −78 °C, 5 min. Bold and dashed lines indicate relative configuration.

The synthesis of noncommercially available allyl iodides **8b**−**g** is reported in Scheme 1 of the Supporting Information. The synthesis of C3-aryl-substituted analogues *rac*-**6a**−**h** was realized as described in Scheme 2, and the relative configuration at C3 of *rac*-**6a** and *rac*-**6f** was assigned by NOESY experiments (see Supporting Information for further details).

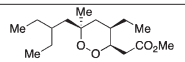
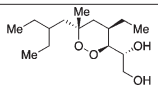
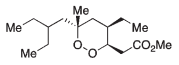
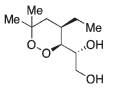
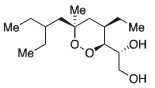
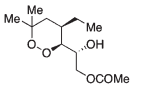
Antiplasmodial Activity and Structure−Activity Relationships. All synthesized compounds were tested in vitro against two *Pf* strains, namely, the CQ-sensitive (CQ-S) D10 and the CQ-resistant

(CQ-R) W2. The antiplasmodial activity (IC_{50}, μM) was quantified as inhibition of parasite growth measured with a standardized parasite lactate dehydrogenase assay (Tables 1−3).

*DHP Synthetic Analogues **2a,b**, **3a,b**, and **4a,b***. We previously synthesized the C10-desethyl analogue of DHP (**2a**), its epimer at C6 (**2b**), and the corresponding diols **3a,b**. Compounds **4a,b**, lacking the western lateral chain, were also previously prepared. Here we report for the first time their in vitro antimalarial activities (Table 1). Compound **2a** displayed an antiplasmodial potency against D10 and W2 strains similar to that of the natural compound DHP, while the epimeric derivative **2b** displayed a decreased potency against the CQ-R *Pf* strain (**2b** vs **2a**) and slightly greater potency against the CQ-S *Pf* strain. Diols **3a** and **3b** proved to be less potent than the corresponding ester analogues **2a** and **2b** when tested against CQ-S and CQ-R *Pf* strains. Finally, **4a,b**, lacking the western lateral chain, were not active against either of the *Pf* strains at concentrations up to 10 μM. The antipalsmodial data reported here confirm the previous SARs for western side chain analogues and provide further information regarding the role of stereochemistry at the C6 stereogenic center of the dioxane ring, i.e., that this seems to have only a minor influence, especially against CQ-R strain.

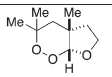
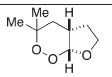
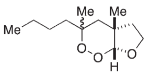
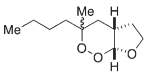
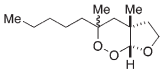
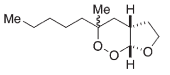
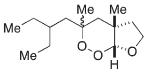
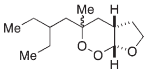
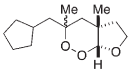
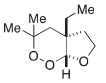
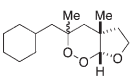
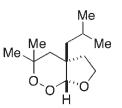
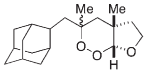
*C3-Alkyl Substituted DHP Bicyclic Analogues rac-**5a**−**m***. Because of the importance of the western side chain in modulating antiplasmodial activity and potency in DHP synthetic analogues, we examined this as well in the novel series of DHP bicyclic analogues (*rac*-**5a**−**g**) that were tested as a diasteroisomer mixtures. As expected, *rac*-**5a**, with a methyl group on the western side chain, displayed no activity up to 10 μM. On the other hand, introduction of linear alkyl chains as in *rac*-**5b** (*n*-butyl) and *rac*-**5c** (*n*-pentyl) resulted in compounds endowed with single digit micromolar potencies and higher potency against CQ-R *Pf* strain than the CQ-S strain. Branching of the alkyl chain at C3 resulted in compounds with better activities (*rac*-**5d**−**g**). Thus, *rac*-**5d**, bearing the same western side chains as DHP synthetic analogue **2a**, was 4 times more potent than the unbranched analogue *rac*-**5b**. Introduction of cyclohexylmethyl or cyclopentylmethyl side chains as in *rac*-**5e** or *rac*-**5f**, respectively, had only a marginal effect on the antiplasmodial potency relative to *rac*-**5d**. Introduction of an adamantyl-2-methylene moiety (*rac*-**5g**) resulted in the most potent analogue of the series, being twice as potent as the natural compound DHP. Compounds *rac*-**5i**−**m**, lacking the methyl group

Table 1. Antiplasmodial Activity of 2a,b, 3a,b, 4a,b, and Reference Compounds DHP (1) and CQ

Cpd	Structure	D10	W2	Cpd	Structure	D10	W2
		IC_{50} (μM)[a]				IC_{50} (μM)[a]	
2a[b]		0.89	0.64	**3b**[b]		2.4	1.3
2b[b]		2.4	0.87	**4a**[c]		>10	>10
3a[b]		1.2	0.84	**4b**[c]		>10	>10
1[d]	-	0.86	0.44	CQ	-	0.02	0.28

[a] IC_{50} values are the mean of at least three determinations. Standard errors were all within 10% of the mean. [b] Synthesis reported in ref 15. [c] Synthesis reported in ref 16. [d] IC_{50} value from ref 10.

Table 2. Antiplasmodial Activity of *rac*-5a−m and Reference Compounds DHP (1) and CQ

Cpd	Structure[a]	D10	W2	Cpd	Structure[a]	D10	W2
		IC_{50} (μM)[b]				IC_{50} (μM)[b]	
rac-**5a**		>10	>10	*rac*-**5h**		>10	>10
rac-**5b**		2.9	1.4	*rac*-**5i**		>10	>10
rac-**5c**		2.9	1.5	*rac*-**5j**		>10	>10
rac-**5d**		0.76	0.39	*rac*-**5k**		>10	8.6
rac-**5e**		0.55	0.34	*rac*-**5l**		>10	>10
rac-**5f**		0.49	0.36	*rac*-**5m**		>10	>10
rac-**5g**		0.23	0.15	DHP (**1**)[c]	-	0.86	0.44
				CQ	-	0.02	0.28

[a] Unwedged bold and dashed lines indicate relative configuration. [b] IC_{50} values are the mean of at least three determinations. Standard errors were all within 10% of the mean. [c] IC_{50} value from ref 10.

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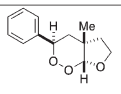
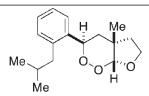
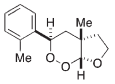
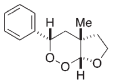
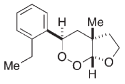
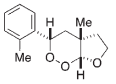
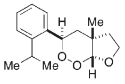
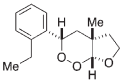
Table 3. Antiplasmodial Activity of *rac*-6a−h and Reference Compounds DHP (1) and CQ

Cpd	Structure[a]	D10 IC$_{50}$ (μM)[b]	W2 IC$_{50}$ (μM)[b]	Cpd	Structure[a]	D10 IC$_{50}$ (μM)[b]	W2 IC$_{50}$ (μM)[b]
rac-**6a**		>20	>20	*rac*-**6e**		13	5.7
rac-**6b**		>20	11	*rac*-**6f**		>20	>20
rac-**6c**		15	7.7	*rac*-**6g**		>20	>20
rac-**6d**		8.3	4.6	*rac*-**6h**		>20	>20
DHP (**1**)[c]	-	0.86	0.44	CQ	-	0.02	0.28

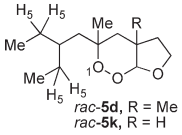
[a] Bold and dashed lines indicate relative configuration. [b] IC$_{50}$ values are the mean of at least three determinations. Standard errors were all within 10% of the mean. [c] IC$_{50}$ value from ref 10.

at C4a, did not show activity at the concentration tested, suggesting that this group is important for activity (*rac*-**5i,j,k** vs *rac*-**5b,c,d**). On the other hand, elongation of the alkyl chain at C4a as in *rac*-**5l,m** gave inactive compounds, presumably because of the lack of an appropriate alkyl substituent at C3. To determine whether diasteroisomers at C3 had different antiplasmodial activities, the most potent compound of the series, *rac*-**5g**, was resolved into single enantiomers by semipreparative chiral HPLC (see Supporting Information for details). Two well-resolved peaks, eluting at 10.6 and 11.4 min, respectively, and identified by NMR as C-3 diasteroisomers, were tested for antiplasmodial activity (data not shown) and were found to have potencies similar to that of *rac*-**5g**, suggesting that in this series of compounds stereochemistry of the substituents on the dioxane ring is not critical for activity.

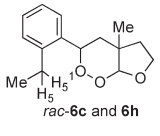
*C3-Aryl Substituted DHP Bicyclic Analogues rac-**6a**−**h***. We also tested *rac*-**6a**−**h** bearing an aromatic substituent at C3 (Table 3). The C3 diasteroisomers in this series were easily separated by column chromatography and were tested independently. Compounds *rac*-**6a** and *rac*-**6f**, bearing an unsubstituted phenyl ring, displayed no activity up to 20 μM. Because of the importance of the C3 side chain that was noted in the previous series, a set of *o*-alkylaryl derivatives was prepared, and a slight improvement of activity over *rac*-**6a** was observed for *rac*-**6c**−**e**. Although potency improved slightly upon modifcation of the alkyl chain at the ortho position, this set of compounds considered as a group showed an antiplasmodial potency 30−50 times lower than was observed in the alkyl series.

Conformational Analysis. The key role played by the side chain at C3 for antiplasmodial potency observed for *rac*-**5a**−**g** led us to hypothesize that this series of compounds could react with iron(II) heme following a mechanism similar to the one described for DHP,[14] probably by forming an initial O1-centered radical (Table 4) that can subsequently undergo an intramolecular 1,5-H shift to form a C-centered radical. Analysis of predicted conformational energies (see Supporting Information for further details) of the four enantiomers of *rac*-**5d** revealed that 55.3% of conformers within 20 kJ/mol should have a distance of

Table 4. Percentage of Conformers Displaying a Distance O1···H5 ≤ 3 Å



rac-**5d**, R = Me
rac-**5k**, R = H



rac-**6c** and **6h**

compd	% of conformers with O1···H5 ≤ 3 Å
rac-**5d**	55.3
rac-**5k**	39.9
rac-**6c**	50.0
rac-**6h**	36.8

<3 Å between O1 and H5 (Table 4, cf. ref 14). Compound *rac*-**5k**, differing from *rac*-**5d** by the lack of a methyl group at C4a, showed a lower percentage (39.9%) of conformers with a calculated O1···H5 distance of <3 Å (putative bioactive conformers), which presumably explains its lower potency. Moreover, the two diasteroisomers of *rac*-**5d** showed a similar percentage of putatively bioactive conformers. In contrast, the same conformational analysis performed on the two C3-aryl substituted diasteroisomers *rac*-**6c** and *rac*-**6h** revealed a higher percentage of putatively bioactive conformers predicted for *rac*-**6c** than for *rac*-**6h** (50.0% and 36.8%, respectively). Moreover, C3-aryl derivatives were less effective than the corresponding C3-alkyl analogues *rac*-**5a**−**g**, presumably because of the different spatial requirements of the resulting C-centered radicals.

CONCLUSIONS

In summary, we present herein the synthesis and antiplasmodial evaluation of a novel series of structurally simplified endoperoxide-containing compounds related to the natural product DHP. Several of the newly synthesized bicyclic endoperoxides (*rac*-**5d**−**g**) exhibit in vitro potencies similar to that of DHP based on standard in vitro assays of lactate dehydrogenase activity. More importantly, the bicyclic scaffold of these compounds is accessible via a high-yielding, four-step procedure starting from readily available starting materials. By contrast, the preparation of DHP synthetic analogues such as **2a** requires a longer and more expensive 11-step procedure. SAR analysis of these simplified compounds allowed definition of some of the structural requirements necessary for potency.

EXPERIMENTAL SECTION

General Methods. Starting materials and solvents were purchased from commercial suppliers and used without further purification. Reaction progress was monitored by TLC using silica gel 60 F254 (0.040−0.063 mm) with detection by UV. Silica gel 60 (0.040−0.063 mm) was used for column chromatography. Yields refer to purified materials and are not optimized. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz or a Bruker 400 MHz spectrometer using the residual signal of the deuterated solvent as internal standard. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), and broad (br); chemical shifts (δ) are given in ppm and coupling constants (*J*) in hertz (Hz). Mass spectra were recorded utilizing electrospray ionization (ESI). All moisture-sensitive reactions were performed under argon atmosphere using oven-dried glassware and anhydrous solvents. All compounds that were tested in

the biological assays were analyzed by combustion analysis (CHN) to confirm the purity, ≥95%. *R** and *S** indicate relative configurations.

(3*R,4a*S**,7a*R**)-3-(Adamantan-2-ylmethyl)-3,4a-dimethyltetrahydrofuro[2,3-*c*][1,2]dioxane and (3*S**,4a*S**,7a*R**)-3-(Adamantan-2-ylmethyl)-3,4a-dimethyltetrahydrofuro[2,3-*c*][1,2]dioxane (5g).** The title compound was prepared as described for the synthesis of **5a**. The mixture of four enantiomers was separated by semipreparative chiral HPLC (10% isopropanol in *n*-hexane) and two out of four enantiomers were obtained in pure form. t_R = 10.6 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H, H-7a), 4.26−4.16 (m, 1H, H-6), 3.98 (dd, *J* = 15.4, 7.6 Hz, 1H, H-6), 2.40−2.24 (m, 1H, H-5), 1.93 (d, *J* = 14.1 Hz, 1H, H-4), 1.88−1.68 (m, 11H, Ada), 1.65−1.46 (m, 8H, Ada/H-5/H-4), 1.30 (s, 3H, 3-Me), 1.14 (s, 3H, 4a-Me); t_R = 11.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.30−4.19 (m, 1H), 4.04−3.91 (m, 1H), 2.42−2.28 (m, 1H), 1.94 (d, *J* = 14.1 Hz, 1H), 1.88−1.69 (m, 11H), 1.65−1.51 (m, 10H), 1.42 (dd, *J* = 14.3, 4.0 Hz, 1H), 1.25 (s, 3H); MS (ESI) *m*/*z* 324 $(M + Na)^+$, 345 $(M + K)^+$, 635 $(2M + Na)^+$. Anal. ($C_{19}H_{30}O_3$) C, H, N.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

CQ, chloroquine; *Pf*, *Plasmodium falciparum*; ACT, artemisinin combination therapy; DHP, dihydroplakortin; DIBAL, diisobutylaluminum hydride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; CQ-S, chloroquine-sensitive; CQ-R, chloroquine-resistant

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