Potent Antimalarial Febrifugine Analogues against the *Plasmodium* Malaria Parasite

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Although febrifugine (**1**) and isofebrifugine (**2**), alkaloids isolated from roots of the *Dichroa febrifuga* plant, show powerful antimalarial activity against *Plasmodium falciparum*, strong side effects such as the emetic effect have precluded their clinical use against malaria. However, their antimalarial potency makes them attractive substances as leads for developing new types of chemotherapeutic antimalarial drugs. Thus, we have evaluated the in vitro antimalarial activity of the analogues of febrifugine (**1**) and isofebrifugine (**2**). The activities of the analogues derived from Df-1 (**3**) and Df-2 (**4**), condensation products of **1** and **2** with acetone, respectively, were also obtained. The 3″-keto derivative (**7**, $EC_{50} = 2.0 \times 10^{-8}$ M) of **1** was found to exhibit potential antimalarial activity with high selectivity against *P. falciparum* in vitro. The in vitro activities of the reduction product (**8**, $EC_{50} = 2.0 \times 10^{-8}$ M) of **1** at C-2′ and its cyclic derivatives **9** and **10** ($EC_{50} = 3.7 \times 10^{-9}$ and 8.6×10^{-9} M, respectively) were found to be strongly active and selective. Additionally, the Dess−Martin oxidation product of **3** was found to be strongly active with high selectivity against *P. falciparum*. A structure−activity relationship study (SAR) demonstrates that the essential role played by the 4-quinazolinone ring in the appearance of activity and the presence of a 1″-amino group and C-2′, C-3″ O-functionalities are crucial in the activity of **1**. For **7**, **8**, and **9**, prepared as racemic forms, an in vivo study has also been conducted.

Introduction

Malaria is one of the major parasitic infections in many tropical and subtropical regions. After the introduction of synthetic antimalarial drugs such as chloroquine and mefloquine, use of the *Cinchona* alkaloid quinine declined. However, because of the widespread emergence of chloroquine-resistant and multiple-drug-resistant strains of malarial parasites, its use has become firmly reestablished. Quinine is considered to be the drug of choice for severe, chloroquine-resistant malaria from *Plasmodium falciparum*. In many clinics in the tropics, quinine is the only effective treatment for severe malaria; unfortunately, decreasing sensitivity of *P. falciparum* to quinine has already been reported. This development indicates the increasing importance for discovering new and effective antimalarial drugs.[1]

In China, the roots of *Dichroa febrifuga*, a saxifragaceous plant, have been employed in the treatment of malaria fevers for centuries with no reported parasitic resistance. Febrifugine (**1**) and its stereoisomer, isofebrifugine (**2**), were isolated as the active components against malaria.[2] They have attracted the attention of synthetic organic chemists for their potentially powerful activities, and were recently synthesized independently by the research groups of Kobayashi, Ogasawara, Takeuchi, and Hatakeyama.[3−6] Under protic solvent, **1** is unable to come into equilibrium with **2**, which exhibits in vivo activity approximately 1/211of that of **1** (Table 3). Thus, there is difficulty in handling compound **1**.[7] Many reports have shown that the powerful emetic property associated with **1** has limited its potential usefulness as a chemotherapeutic drug against malaria.[8,9] It is also reported that **1** is precluded as an clinical drug due to liver toxicity.[1] However, the chemical and pharmacological characteristics of **1** encouraged medicinal chemists to pursue suitable lead compounds based on **1** for the development of novel antimalarial drugs. Antimalarial screening demonstrated that febrifugine analogues bearing a modified or unmodified 4-quinazolinone ring are active, while analogues produced through the modification of the side chain attached to the N-3 position of the 4-quinazolinone ring are ineffective.[8−10] Additionally, an enantiomer of **1** prepared synthetically was found to have dramatically decreased activity.[3b,10] We recently proposed new types of febrifugine and isofebrifugine analogues, Df-1 (**3**) and Df-2 (**4**), which exhibit excellent antimalarial activities with high selectivity against the malaria parasite.[7] A detailed study of the structure−activity relationship of compounds **1**−**4** is required in order to develop potent chemotherapeutic drugs from the analogues of **1**.

Chemistry

Febrifugine and Isofebrifugine Analogues. Febrifugine (**1**) was acetylated with Ac_2O and pyridine resulting in 1″,3″-di-*N*,*O*-acetate (**5**). Additionally, **1** was reacted with ethyl chloroformate and K_2CO_3 in acetone

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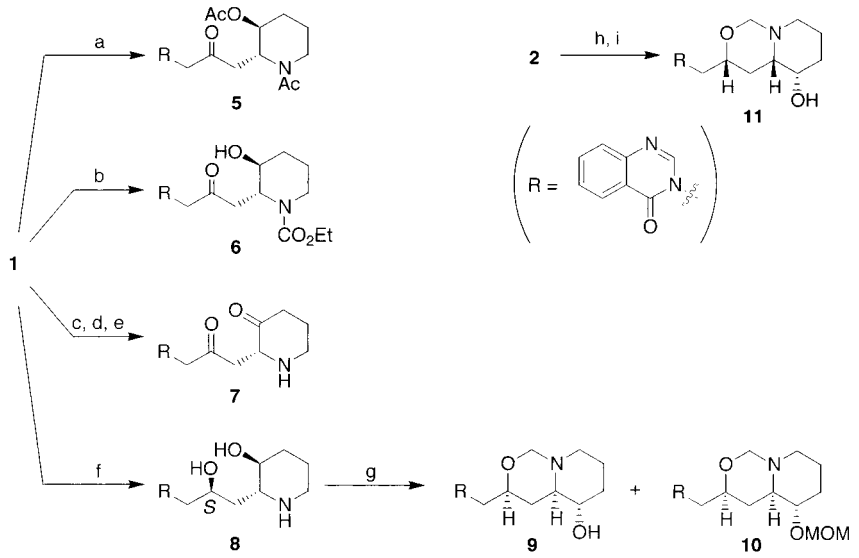
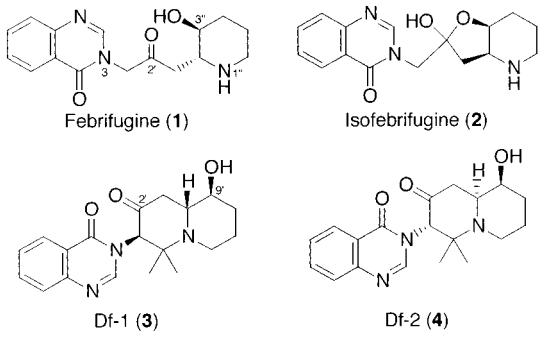
Scheme 1[a]



[a] Reagent and condition: (a) Ac_2O, pyridine, rt, 10 h (100%); (b) ethyl chloroformate, K_2CO_3, acetone, reflux, 2 h (46%); (c) Boc_2O, Et_3N, CH_2Cl_2, 0 °C, 2.5 h; (d) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 2.5 h; (e) HCl, MeOH, rt, 2 h (86% from **1**); (f) $NaBH_4$, MeOH, 0 °C, 0.5 h (86%); (g) dimethoxymethane, TsOH, CH_2Cl_2, rt, 12 h (**9**, 33%; **10**, 10%); (h) $NaBH_4$, MeOH, 0 °C, 0.5 h; (i) dimethoxymethane, TsOH, CH_2Cl_2, rt, 12 h (40% from **2**).

Chart 1. Structures of Febrifugine (**1**), Isofebrifugine (**2**), Df-1 (**3**), and Df-2 (**4**)



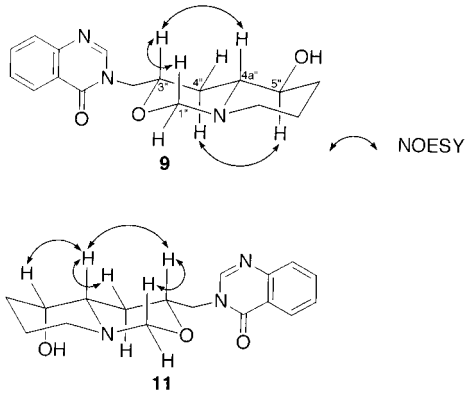
Febrifugine (**1**) Isofebrifugine (**2**)

Df-1 (**3**) Df-2 (**4**)

to yield methyl carbamate (**6**) (Scheme 1). Dess−Martin oxidation of **1** afforded the 3″-keto derivative (**7**). Sodium borohydride reduction of the 2′-carbonyl group of **1** formed the sole product **8**. The product **8** was converted to **9** following cyclization between the C-2′ oxygen and N-1″ atoms by a reaction with dimethoxymethane/TsOH in CH_2Cl_2. Compound **10** was obtained as a byproduct in the transformation of **8** to **9**. The ^{1}H-NMR spectrum of **9** displayed signals for the methylene hydrogens newly formed between the C-2′ oxygen and N-1″ atoms at δ 3.51 and 4.39, respectively (each 1H, d, $J = 8.4$ Hz). The C-3″ carbinyl hydrogen at δ 3.84 exhibited a NOE with the C-1″ axial hydrogen on the methylene carbon at δ 3.51. A NOE was also detected between the C-4″ and C-5″ axial hydrogens (δ 1.42 and 3.42, respectively) (Chart 2). These NMR spectral data unambiguously imply the absolute configuration of **9** at C-3″ is *S*, which fixes the C-2′ stereochemistry of **8** to be *S*. Isofebrifugine (**2**) was also converted to **11** using the same reactions as those performed on **1** (Scheme 1 and Chart 2).

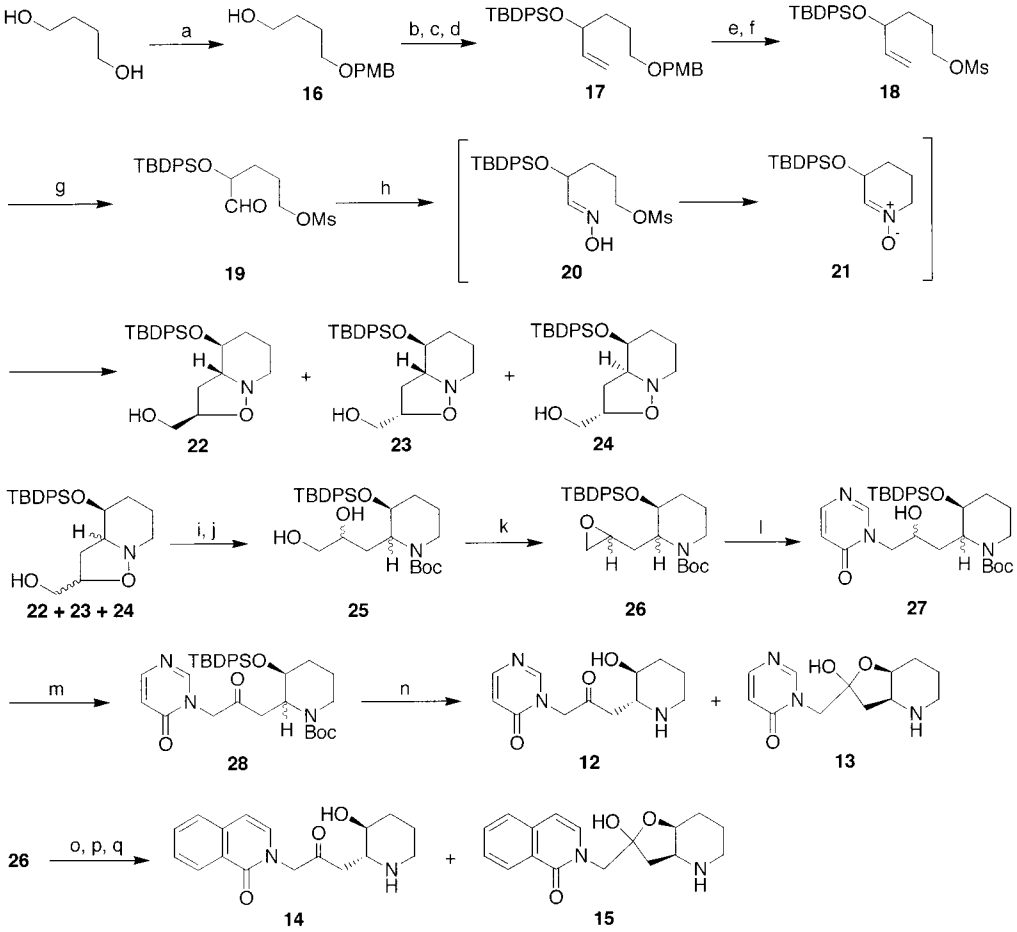
Compounds **12**−**15**, bearing a pyrimidone or isoquinolone ring instead of the quinazolinone ring in **1** and **2**, clearly explain the role of the benzene moiety and nitrogen atom of the quinazolinone ring in the appearance of activity. Racemic **12**−**15** were synthesized employing the synthetic strategy of **1** and **2** which relies

Chart 2. NOEs of **9** and **11**



on the 1,3-dipolar cycloaddition of nitrone to allyl alcohol (Scheme 2).[6] 1,4-Butanediol was reacted with *p*-methoxybenzyl chloride/KOH in DMSO to afford mono-*p*-methoxybenzyl ether **16**. Swern oxidation of **16** followed by a Grignard reaction (vinylmagnesium bromide in THF) and *tert*-butyldiphenyl silylation (TBDPS-Cl) yielded **17**. The *p*-methoxybenzyl group was removed from **17** with DDQ in CH_2Cl_2/H_2O prior to the mesylation of the resulting product with MsCl and Et_3N in CH_2Cl_2, generating mesylate **18**. After ozonolysis of **18**, the resulting aldehyde **19** was directly reacted with hydroxylamine hydrochloride in the presence of Et_3N at room temperature. Therefore, nitrone **21** was generated in situ via oxime **20** which underwent a simultaneous 1,3-dipolar cycloaddition to allyl alcohol to give the diastereomeric mixture of **22**, **23**, and **24**. This mixture was subjected to hydrogenolytic N−O bond fission and *tert*-butoxycarbonylation without separation to give diol **25**. Reaction of **25** with *N*-tosylimidazole in the presence of NaH afforded epoxide **26**; compound **26** was reacted with the potassium salt generated from pyrimidone to produce alcohol **27**. Dess−Martin oxidation of **27** afforded an epimeric mixture of **28**. The epimeric mixture was then subjected to acid hydrolysis in boiling HCl to furnish racemic **12** and **13**. Identical

Scheme 2[a]



[a] Reagent and condition: (a) *p*-methoxybenzyl chloride, KOH, DMSO, 0 °C, 1 h (90%); (b) Swern oxidation, 2 h; (c) vinylmagnesium bromide, THF, −60 °C (60% from **16**); (d) TBDPS-Cl, imidazole, DMF, rt, 12 h (81%); (e) DDQ, CH_2Cl_2·H_2O (10:1), 0 °C, 1.5 h (87%); (f) MsCl, Et_3N, CH_2Cl_2, rt, 1 h (99%); (g) O_3 then Me_2S, $NaHCO_3$, CH_2Cl_2, −78 °C; (h) $HONH_2$·HCl, allyl alcohol, Et_3N, rt, 11 h (**22**+**23**+**24**, 74% from **18**); (i) H_2, $PdCl_2$, MeOH, rt, 12 h; (j) Boc_2O, Et_3N, CH_2Cl_2, rt, 10 h (94% from **22**+**23**+**24**); (k) tosylimidazole, NaH, THF, rt, 12 h (92%); (l) 4(3*H*)-pyrimidone, KH, DMF, 70 °C, 12 h (63%); (m) Dess−Martin periodinane, CH_2Cl_2, rt, 3 h (98%); (n) 6 M HCl, reflux, 4 h (**12**, 58%; **13**, 27%); (o) isocarbostyril, NaH, DMF, 70 °C, 12 h; (p) Dess−Martin periodinane, CH_2Cl_2, rt, 3 h; (q) 6 M HCl, reflux, 4 h (**14**, 18%; **15**, 12% from **26**).

to the synthesis of **12** and **13**, racemic **14** and **15** were obtained by the reaction of **26** with the potassium salt of isocarbostyril followed by oxidation and acid hydrolysis (Scheme 2).

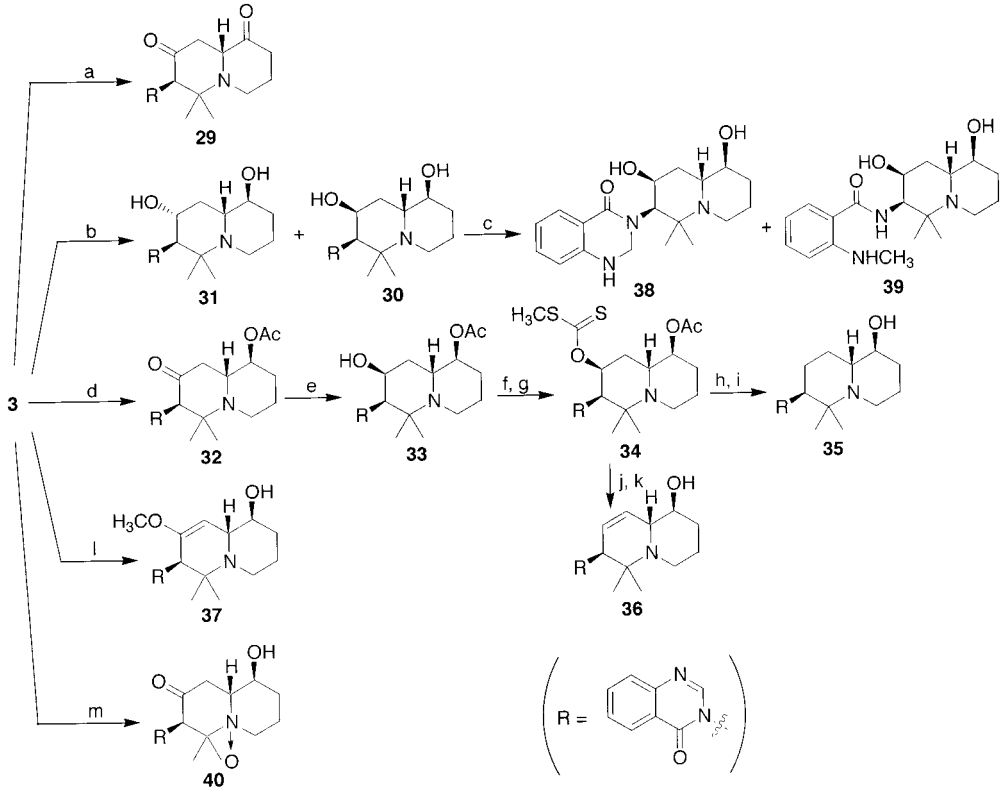
Compounds **7**, **8**, and **9** were also prepared as racemic mixtures from the racemic **1** which was synthesized by the same reactions as in **12** and **14**.

Df-1 and Df-2 Analogues. Dess−Martin oxidation of Df-1 (**3**), the potentially active analogue of **1**, gave the 9′-keto derivative **29** (Scheme 3). Upon the reduction of Df-1 (**3**) with $NaBH_4$ in MeOH, two epimeric alcohols, **30** and **31**, were afforded in a ratio of ca. 5:1. The conversion of the carbonyl group at C-2′ to a methylene group was then performed. Compound **3** was acetylated to give monoacetate **32** which was then treated with K-selectride in THF to generate alcohol **33** as the sole reduction product bearing an axial hydroxyl group at C-2′. A xanthate salt was prepared by treating **33** with CS_2/NaH, and then methylated with CH_3I to form methyl xanthate, **34**. Treatment of **34** with Bu_3SnH/AIBN in toluene followed by alkali hydrolysis with K_2CO_3 in MeOH yielded compound **35**. The Chugaev reaction of **34** followed by alkali hydrolysis afforded **36**. The sodium salt of **3,** prepared with NaH/THF, was treated with CH_3I to generate **37** which occurred in place of the expected transformation in which a methyl group was induced to the C-2′ carbonyl group of **3**. The lithium aluminum hydride reduction of **30** afforded two products, **38** and **39**. *m*-Chloroperbenzoic acid oxidation of **3** afforded *N*-oxide **40**.

As in the case of compound **3**, Df-2 (**4**), the active analogue of **2**, was reduced with $NaBH_4$ to yield two epimeric alcohols, **41** and **42,** bearing axial and equatorial hydroxyl groups at C-2′, respectively. Compound **41** was acetylated to give 9′-*O*-monoacetate (**43**) and 2′,9′-di-*O*-acetate (**44**). Acetylation of **4** afforded monoacetate **45**.

Biological Evaluation. Antimalarial activity against *P. falciparum* (FCR-3 strain) and the cytotoxicity against mouse mammary FM3A cells in vitro[11] were investigated by examining analogues of **1**−**4** whose activities are summarized in Tables 1 and 2. Acetate and ethyl carbamate (**5** and **6**), as analogues of **1** at the N-1″ position, show antimalarial activities of $EC_{50} = 9.1 \times 10^{-7}$ and 4.8×10^{-6} M, respectively, with low therapeutic selectivity against *P. falciparum*. Their potencies decrease considerably compared to that of **1** ($EC_{50} = 7.0 \times 10^{-10}$ M), indicating that the substitution of an electron-withdrawing group with an amino group decreases antimalarial activity. 3″-Keto and 2′-hydroxy

Scheme 3[a]



[a] Reagent and condition: (a) Dess−Martin periodinane, CH_2Cl_2, rt, 3 h (90%); (b) $NaBH_4$, MeOH, 0 °C, 0.5 h (**30**, 66%; **31**, 14%); (c) $LiAlH_4$, THF, reflux, 6 h (**38**, 24%; **39**, 20%); (d) Ac_2O, pyridine, 0 °C, 10 h (93%); (e) K-selectride, THF, 0 °C, 2 h (69%); (f) CS_2, NaH, THF, 0 °C, 1 h; (g) CH_3I, THF, rt, 12 h; (h) Bu_3SnH, AIBN, toluene, reflux, 2 h (81% from **33**); (i) K_2CO_3, MeOH, 0 °C, 2 h (79%); (j) *o*-dichlorobenzene, reflux, 16 h (47% from **33**); (k) K_2CO_3, MeOH, 0 °C, 3 h (43%); (l) CH_3I, NaH, THF, rt, 2 h (100%); (m) *m*-CPBA, K_2CO_3, CH_2Cl_2, −78 °C, 4 h (76%).

Table 1. Antimalarial Activities of Febrifugine (**1**) and Isofebrifugine (**2**) Derivatives in Vitro

compound	EC_{50} (M) antimalarial activity[a]	cytotoxicity[b]	selectivity[c]
1	7.0×10^{-10}	1.7×10^{-7}	243
2	3.4×10^{-9}	1.8×10^{-7}	53
5	9.1×10^{-7}	$>2.9 \times 10^{-5}$	>32
6	4.8×10^{-6}	$>1.7 \times 10^{-5}$	>3.5
7	2.0×10^{-8}	1.0×10^{-5}	500
8	2.0×10^{-8}	1.5×10^{-5}	750
9	3.7×10^{-9}	3.8×10^{-6}	1027
10	8.6×10^{-9}	2.5×10^{-6}	291
11	8.4×10^{-7}	$>2.5 \times 10^{-5}$	>30
12	6.0×10^{-7}	$>1.9 \times 10^{-5}$	>32
13	4.0×10^{-8}	7.0×10^{-6}	175
14	5.0×10^{-7}	$>1.6 \times 10^{-5}$	>32
15	2.1×10^{-6}	$>6.3 \times 10^{-6}$	>3
chloroquine	1.8×10^{-8}	3.2×10^{-5}	1778
artemisinin	1.0×10^{-8}	1.0×10^{-5}	1000

[a] Against *P. falciparum* FCR-3. [b] Against FM3A mouse mammary cells. [c] Cytotoxicity/antimalarial activity.

Table 2. Antimalarial Activities of Df-1 (**3**) and Df-2 (**4**) Derivatives in Vitro

compound	EC_{50} (M) antimalarial activity[a]	cytotoxicity[b]	selectivity[c]
3	1.6×10^{-9}	3.8×10^{-7}	238
4	2.8×10^{-9}	2.4×10^{-6}	857
29	1.9×10^{-9}	5.9×10^{-6}	>3105
30	4.0×10^{-7}	2.8×10^{-6}	70
31	3.0×10^{-7}	8.5×10^{-5}	283
32	3.6×10^{-9}	1.3×10^{-6}	361
35	8.3×10^{-7}	$>2.2 \times 10^{-5}$	>27
36	4.8×10^{-6}	$>3.2 \times 10^{-5}$	>7
37	1.3×10^{-6}	$>6.6 \times 10^{-5}$	>51
38	4.2×10^{-7}	$>1.6 \times 10^{-5}$	>38
39	6.0×10^{-7}	$>1.7 \times 10^{-5}$	>28
40	1.0×10^{-7}	$>2.9 \times 10^{-5}$	>290
41	8.0×10^{-7}	$>2.4 \times 10^{-5}$	>30
42	3.4×10^{-6}	$>1.0 \times 10^{-4}$	>28
43	4.0×10^{-7}	$>1.1 \times 10^{-5}$	>28
44	7.0×10^{-6}	$>2.1 \times 10^{-5}$	>3
45	1.9×10^{-8}	7.0×10^{-6}	368

[a] Against *P. falciparum* FCR-3. [b] Against FM3A mouse mammary cells. [c] Cytotoxicity/antimalarial activity.

analogues (**7** and **8**) of **1** have the same EC_{50} value (2.0×10^{-8} M) for their antimalarial activities with high selectivity. Cyclic compounds **9** and **10** also show powerful antimalarial activities ($EC_{50} = 3.7 \times 10^{-9}$ and 8.6×10^{-9} M, respectively). These results suggest that O-functionality at C-2′ and C-3″ in **1** is crucial to activity; thus, these types of derivatives would make suitable lead compounds for the development of new antimalarial drugs. In contrast, **11,** which was derived from **2,** is found to be less active than **9**. While compounds **3** and **4** derive their stereochemistry from being condensation products of compounds **1** and **2** with acetone, respectively, compounds **9** and **11** are also enantiomers, provided that the stereochemistry of the hydroxyl group is disregarded. The enantiomer of **1** was reported to exhibit reduced antimalarial activity when compared to **1**.[3b,10] Moreover, **3** differs from **4** in the potency of in vivo activity, even though both **3** and **4** exhibited excellent activities with high selectivity in vitro.[7] Data obtained for **9** and **11**, along with reported antimalarial

Table 3. In Vivo Antimalarial Activities of Febrifugine (**1**) Derivatives against Mice Infected with *P. berghei*[a]

compound	ED_{50} (μmol/kg)	ED_{90} (μmol/kg)
1[7]	1.0	5.0
2	211	>267
7	1.3	6.2
8	2.9	22
9	82	>180
chloroquine	4.7	9.4
artemisinin	17.7	46.0

[a] The detail of the experimenal procedure was described in ref 11.

activities,[3b,7,10] imply that analogues of **1** have greater potential than those of **2** in use as powerful antimalarial drugs.

The roles played by the benzene moiety and the N-1 atom of the 4-quinazolinone ring in determining activity were evaluated using synthetic racemates **12**−**15**. They exhibited moderate antimalarial activity ($EC_{50} = 6.0 \times 10^{-7}$, 9.0×10^{-8}, 5.0×10^{-7}, and 2.1×10^{-6} M, respectively) and were not selective against *P. falciparum* (>32, >175, >38, and >3, respectively). This points out the importance of the 4-quinazolinone ring in antimalarial activity and selectivity.

In regards to the analogues of **3** and **4**, the powerful activities of C-9′-keto analogue **29** and acetate **32** ($EC_{50} = 1.9 \times 10^{-9}$ and 3.6×10^{-9} M, respectively) are noteworthy. It should be mentioned that **29** exhibits a surprisingly high selectivity (>3105), especially when compared with those of chloroquine and artemisinin (1778 and 1000, respectively). While other analogues of **3** and **4** showed antimalarial activities, $EC_{50} = 3.0 \times 10^{-7}$ to 4.8×10^{-6} M, they were found to be unselective.

The compounds **7**−**9** chemically transformed from natural **1** were found to be highly effective in vitro (Table 1), and we examined their in vivo antimalarial activity against mice infected with *Plasmodium berghei*.[11] Because a sufficient supply of natural **1** for transformation to **7**−**9** necessary for the test was thought to be difficult to obtain from *D. febrifuga* roots, the racemic **7**−**9** obtained from synthetic **1** were used in the test. The results compiled in Table 3 indicated that febrifugine derivatives **7** and **8** exhibited potent antimalarial activities (ED_{50} = 1.3 and 2.9 mmol/kg, respectively) rather than chloroquine and artemisinin (ED_{50} = 4.7 and 17.7 mmol/kg, respectively). Compound **9** (ED_{50} = 80 mmol/kg) was less effective than **7** and **8**. Furthermore, during administration of **7** and **8** to infected mice by intraperitoneal injection (8.9 mmol/kg/day, 4 days), the survival rate was increased 2 times.

In conclusion, we have described the syntheses and SAR of a new series of febrifugine analogues. We discovered strong antimalarial activities in vitro with high therapeutic selectivity against *P. falciparum* for compounds **7**−**10** which were derived from **1**. In addition, the 4-quinazolinone moiety and C-2′ and C-3″ O-functionalities are found to play an important role in the activity. Compound **29**, the C-9′-keto analogue of **3,** also exhibited good antimalarial activity and very high selectivity. Most importantly, the fact that racemic mixtures of **7** and **8** also exhibited extremely strong in vivo activity against *P. berghei* suggests that they are the leads of a new type of antimalarial agent. As **7**, **8**, and **29** might be metabolites of **1** and **3** in the body, a metabolic study of these compounds will be prudent.

Experimental Section

Analytical TLC was performed on silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} (Merck). Column chromatography was carried out on silica gel 60 (70−230 mesh, Merck), Cosmosil 75C_{18}-OPN (Nacalai Tesque Inc., Kyoto, Japan), and activated alumina (300 mesh, Wako Pure Chemicals Co., Ltd., Osaka, Japan). Chloroquine diphosphate (Sigma) was used as a positive control in the antimalarial assay in vitro and in vivo. Optical rotation were measured using a JASCO DIP-370 digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM GX-500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz) and a Varian Gemini 2000 spectrometer (^{1}H, 300 MHz). Chemical shifts for ^{1}H- and ^{13}C-NMR are given in parts per million (δ) relative to tetramethylsilane (δ_H 0.00) and $CDCl_3$ (δ_C 77.1) as internal standards, respectively, and coupling constants were reported in hertz. High-resolution EI mass spectra were measured on JEOL JMS DX-303 and JMS AX-500 mass spectrometers.

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. The extracts were dried over Na_2SO_4 unless otherwise noted and concentrated by rotary evaporation below 30 °C.

Isolation of Febrifugine (1) and Isofebrifugine (2) from *D. febrifuga* Roots and Preparation of Df-1 (3) and Df-2 (4). Compounds **1** and **2** were isolated from a dried root of *D. febrifuga*, and **3** and **4** were synthesized from **1** and **2**, respectively, following the procedure previously reported.[7]

3-{3-[(2*R*,3*S*)-3-Acetoxy-1-acetyl-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (5). To an ice-cooled solution of **1** (9.9 mg, 0.033 mmol) in pyridine (0.5 mL) was added Ac_2O (0.25 mL), and the mixture was stirred at room temperature for 10 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried, and concentrated. The crude residue was chromatographed over silica gel ($CHCl_3$:MeOH = 98:2) to give **5** (12.7 mg, 100%) as colorless needles.

3-{3-[(2*R*,3*S*)-1-Ethoxycarbonyl-3-hydroxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (6). A mixture of **1** (11.0 mg, 0.040 mmol), K_2CO_3 (100 mg, 0.724 mmol), and ethyl chloroformate (0.10 mL, 1.05 mmol) in acetone (1.0 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature, and the resulting precipitate was filtered. The filtrate was extracted with EtOAc, and the organic layer was washed with brine, dried, and concentrated. Silica gel column chromatography of the crude residue ($CHCl_3$:MeOH = 98:2) afforded **6** (6.3 mg, 46%) as colorless needles.

3-{3-[(2*R*,3*S*)-3-Oxo-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (7). To an ice-cooled solution of **1** (152 mg, 0.506 mmol) in CH_2Cl_2 (6.0 mL) were added triethylamine (78 mL) and di-*tert*-bicarbonate (123 mg, 0.557 mmol), and the mixture was stirred for 2.5 h at 0 °C. The reaction mixture was quenched with aqueous 0.1 M HCl (6.0 mL), and the mixture was extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The crude residue was chromatographed over silica gel ($CHCl_3$:MeOH = 98:2) to give N-Boc derivative (189 mg, 93%) as a colorless oil. N-Boc derivative (20.9 mg, 0.052 mmol) in CH_2Cl_2 (2.0 mL) was treated with Dess−Martin periodinane (88.3 mg, 0.156 mmol) and stirred for 2.5 h at 0 °C. The reaction mixture was quenched with an aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The crude residue was chromatographed over silica gel ($CHCl_3$) to give the 3″-keto compound (20.4 mg, 98%) as a colorless oil. The 3″-keto compound (20.4 mg, 0.051 mmol) was dissolved in 1.25% HCl−MeOH (4.0 mL) at room temperature. After the reaction mixture was stirred for 2 h, it was concentrated and chromatographed over ODS (H_2O:MeOH = 9:1) to yield **7** (16.1 mg, 94%) as colorless needles.

3-{(2*S*)-3-[(2*R*,3*S*)-3-Hydroxy-2-piperidinyl]-2-hydroxypropyl}-4(3*H*)-quinazolinone (8). To an ice-cooled solution

of **1** (10.6 mg, 0.035 mmol) in MeOH (2.0 mL) was added $NaBH_4$ (1.0 mg, 0.026 mmol), and the mixture was stirred at the same temperature for 10 min. The reaction mixture was diluted with MeOH, concentrated, and chromatographed over silica gel ($CHCl_3$:MeOH = 80:20) to yield **8** (9.1 mg, 86%) as colorless needles.

3-{(3*S*,4a*R*,5*S*)-5-Hydroxyhexahydropyrido[1,2-*c*][1,3]-oxazin-3-ylmethyl}-4(3*H*)-quinazolinone (9) and 3-{(3*S*, 4a*R*,5*S*)-5-Methoxymethyloxy-hexahydropyrido[1,2-*c*]-[1,3]oxazin-3-ylmethyl}-4(3*H*)-quinazolinone (10). To a solution of **8** (18.0 mg, 0.059 mmol) in CH_2Cl_2 (1.0 mL) were added dimethoxymethane (10 mL, 0.118 mmol) and *p*TsOH·H_2O (15.0 mg, 0.189 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated. The crude residue was chromatographed over aluminum oxide (*n*-hexane:$CHCl_3$ = 50:50) to give **9** and **10** (4.4 and 1.4 mg, 33 and 10%, respectively) as colorless needles.

3-{(3*S*,4a*R*,5*S*)-5-Hydroxyhexahydropyrido[1,2-*c*][1,3]-oxazin-3-yl-methyl}-4(3*H*)-quinazolinone (11). Compound **11** was synthesized from **2** following the representative procedure described for **9** and **10**, and was obtained as colorless needles in 40% yield.

4-(4-Methoxybenzyloxy)-butan-1-ol (16). To a solution (50 mL) of 1,4-butanediol (25 g, 227 mmol) in DMSO (50 mL) was added KOH (15.5 g, 277 mmol). The mixture was cooled to 0 °C, and *p*-methoxybenzyl chloride (17.5 mL, 0.129 mmol) was added dropwise for 1 h. The reaction mixture was poured into ice-water and extracted with Et_2O. The organic layer was washed with brine, dried, concentrated, and chromatographed over silica gel (*n*-hexanes:EtOAc = 70:30) to yield **16** (24.4 g, 90%) as a colorless oil.

4-(*tert*-Butyldiphenylsilanyloxy)-1-(4-methoxybenzyl-oxy)-5-hexene (17). To a solution of oxalylchloride (20.3 mL, 232 mmol) in CH_2Cl_2 (450 mL) was added dropwise DMSO (33 mL, 465 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To this solution was added dropwise a solution of **16** (24.4 g, 116 mmol) in CH_2Cl_2 (50 mL) at a rate which was sufficient to keep the temperature at −78 °C. After the reaction mixture had been stirred at this temperature for 2 h, Et_3N (81 mL, 581 mmol) was added, and the solution was warmed to room temperature. A saturated aqueous NH_4Cl solution was added, and the organic layer was washed with water and brine, dried, and concentrated to give a crude aldehyde which was used in the following reaction without purification. To a solution of the crude aldehyde in THF (500 mL) was added dropwise a 0.232 M solution of vinylmagnesium bromide in THF (200 mL) at −60 °C, and the mixture was stirred at the same temperature for 18 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated. The crude residue was chromatographed over silica gel (*n*-hexanes:EtOAc = 70:30) to give allyl alcohol (16.5 g, 60%) as a colorless oil: ^{1}H-NMR (300 MHz, $CDCl_3$, δ) 1.56−1.77 (4H, m), 2.46 (1H, d, J = 3.9 Hz), 3.49 (2H, t, J = 5.7 Hz), 3.80 (3H, s), 4.07−4.16 (1H, m), 4.45 (2H, s), 5.09 (1H, dt, J = 10.5, 1.5 Hz), 5.22 (1H, dt, J = 17.4, 1.5 Hz), 5.86 (1H, ddd, J = 17.4, 10.5, 6.0 Hz), 6.88 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 8.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, δ) 25.9, 34.5, 55.4, 70.1, 72.8, 113.9, 114.5, 129.4, 130.4, 141.2.

To a solution of allyl alcohol (3.0 g, 12.7 mmol) in DMF (30 mL) were added imidazole (1.73 g, 25.4 mmol) and *tert*-butyldiphenylsilane chloride (5.23 g, 19.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. A saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with *n*-hexane. The organic layer was washed with brine, dried, and concentrated. Silica gel column chromatography of the crude residue gave **17** (4.9 g, 81%) as a colorless oil.

4-(*tert*-Butyldiphenylsilyl)oxy-5-hexenyl Methanesulfonate (18). A solution of **17** (4.9 g, 10.3 mmol) and DDQ in CH_2Cl_2·H_2O (10:1, 60 mL) was stirred at 0 °C for 1.5 h. A saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated. $NaBH_4$ (189 mg, 5.00 mmol) was added to a solution of the crude residue in MeOH (40 mL) at 0 °C and stirred for 15 min. A saturated aqueous NH_4Cl solution was added, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated to yield a residue which was chromatographed over silica gel (*n*-hexanes:EtOAc = 80:20) to give alcohol (3.07 g, 87%) as a colorless oil: ^{1}H-NMR (300 MHz, $CDCl_3$, δ) 1.07 (9H, s), 1.47−1.56 (5H, m), 3.50 (2H, br t, J = 6.0 Hz), 4.21 (1H, m), 4.97 (1H, ddd, J = 10.5, 2.1, 0.9 Hz), 5.01 (1H, ddd, J = 17.1, 2.1, 1.8 Hz), 5.80 (1H, ddd, J = 17.1, 10.5, 6.6 Hz), 7.32−7.43 (6H, m), 7.64−7.70 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$, δ) 19.4, 27.1, 27.6, 33.8, 62.9, 74.3, 114.7, 127.4, 127.6, 129.6, 129.7, 134.0, 134.3, 135.9, 136.0, 140.4.

To an ice-cooled solution of alcohol (1.80 g, 5.08 mmol) in CH_2Cl_2 (36 mL) were added Et_3N (0.92 mL, 6.60 mmol) and methanesulfonyl chloride (0.43 mL, 5.60 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, a saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted with Et_2O, and the organic layer was washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 80:20) to give **18** (2.17 g, 99%) as a colorless oil.

(2*R,3a*R**,4*S**)-, (2*S**,3a*R**,4*S**)-, and (2*S**,3a*S**,4*S**)-4-(*tert*-Butyldiphenylsilyl)oxy-2-[(hydroxy)methyl]hexahydroisoxazolo[2,3-*a*]pyridine (22, 23, and 24, respectively).** A mixture of **18** (1.87 g, 4.31 mmol) and $NaHCO_3$ (1.87 g, 21.6 mmol) in CH_2Cl_2 (30 mL) was reacted with O_3 at −78 °C for 20 min. After an excess of the O_3 was removed by flushing with argon, Me_2S (0.48 mL, 6.47 mmol) was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2, and the organic layer was washed with brine, dried, and concentrated. To an allyl alcohol solution (20 mL) of the crude aldehyde **19** (1.91 g) obtained were added NH_2OH·HCl (330 mg, 4.75 mmol) and Et_3N (1.32 mL, 9.49 mmol) at room temperature. After the mixture was stirred for 11 h, it was concentrated and chromatographed (*n*-hexane:EtOAc = 65:35) to give a 64:10:26 mixture of **22**, **23**, and **24** (1.31 g, 74%) as a colorless amorphous solid.

***N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)-oxy-2-(2,3-dihydroxypropyl)piperidine (25).** The mixture of **22**, **23**, and **24** (350 mg, 0.85 mmol) was dissolved in MeOH (10 mL) and stirred in the presence of $PdCl_2$ (35 mg, 0.20 mmol) under H_2 at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, filtered through Celite, and concentrated to give crude amino diol (360 mg) as a yellow viscous oil. To a solution of crude amino diol (360 mg) in CH_2Cl_2 (10 mL) were added Et_3N (0.21 mL, 1.53 mmol) and Boc_2O (278 mg, 1.28 mmol) at room temperature. After the mixture was stirred at the same temperature for 10 h, it was diluted with Et_2O, washed with brine, dried, and concentrated. The residue was chromatographed over silica gel (*n*-hexane:EtOAc = 65: 35) to give **25** (410 mg, 94%) as a colorless amorphous solid.

***N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)-oxy-2-[(oxiranyl)methyl]piperidine (26).** To an ice-cooled solution of **25** (400 mg, 0.78 mmol) in THF (10 mL) was added NaH (60% in dispersion oil, 169 mg, 0.86 mmol), and the mixture was stirred at 0 °C for 20 min. Tosylimidazole (190 mg, 0.86 mmol) was added, and the cooling bath was removed. After the mixture was stirred at room temperature for 12 h, it was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried, concentrated, and chromatographed over silica gel (*n*-hexane:EtOAc = 90:10) to give **26** (355 mg, 92%) as a colorless amorphous solid.

3-[3-(3-Hydroxy-piperidin-2-yl)-2-oxopropyl]-3*H*-pyrimidin-4-one (12), 3-(2-Hydroxy-octahydro-furo[3,2-*b*]pyridin-2-ylmethyl)-3*H*-pyrimidin-4-one (13), 2-[3-(3-Hydroxy-piperidin-2-yl)-2-oxopropyl]-2*H*-isoquinolin-1-one (14), and 2-(2-Hydroxy-octahydro-furo[3,2-*b*]pyridin-2-ylmethyl)-2*H*-isoquinolin-1-one (15). To an ice-cooled suspension of KH (24.3 mg, 0.606 mmol) in DMF (1.5 mL) was added

4(3*H*)-pyrimidone (64 mg, 0.667 mmol), and the mixture was stirred at 0 °C for 30 min. A solution of **26** (100 mg, 0.202 mmol) in DMF (1.0 mL) was added, and the mixture was heated at 80 °C for 16 h. The mixture was cooled to room temperature, quenched with a saturated aqueous NH_4Cl solution, and extracted with Et_2O. The organic layer was washed with brine, dried, concentrated, and chromatographed over silica gel (*n*-hexane:EtOAc = 65:35) to give **27** (82 mg, 69%) as an amorphous solid and unreacted **26** (14.4 mg, 14%). To a solution of **27** in CH_2Cl_2 (10 mL) was added Dess−Martin periodinane (533 mg, 1.26 mmol), and the mixture was stirred at room temperature for 17 h. The mixture was diluted with Et_2O, filtered through Celite, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 65:35) to give a mixture of **28** as an 80:20 epimeric mixture (81 mg, 98%). A solution of the mixture in 6 M HCl (10 mL) was refluxed for 12 h. The mixture was cooled in an ice bath, and K_2CO_3 was added and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3, concentrated, and chromatographed over silica gel ($CHCl_3$:MeOH = 90:10) to give **12** and **13** as colorless needles (13 and 9 mg, 38 and 26%, respectively).

Compounds **14** and **15** were synthesized from isocarbostyril and **26** with a 20 and 9% overall yield, respectively, following the representative procedure described for **12** and **13**.

3-[(3*R*,9a*R*)-Octahydro-2,9-dioxo-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (29). Compound **3** (5.0 mg, 0.014 mmol) in CH_2Cl_2 (1.0 mL) was treated with Dess−Martin periodinane (15.8 mg, 0.028 mmol) and stirred for 2.5 h at 0 °C. The reaction mixture was quenched with an aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The crude residue was chromatographed over silica gel ($CHCl_3$) to give **29** (3.7 mg, 79%) as a colorless oil.

3-[(2*S*,3*R*,9*S*,9a*R*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (30) and 3-[(2*R*,3*R*,9*S*,9a*R*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (31). Compounds **30** and **31** were synthesized from **3** following the representative procedure described for **8**, and were obtained as colorless needles (20.8 and 4.4 mg, 66 and 14%, respectively).

3-[(2*S*,3*R*,9*S*,9a*R*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-2,3-dihydroxy-4(1*H*)-quinazolinone (38) and *N*-[(2*S*,3*R*,9*S*,9a*R*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-2-methylaminobenzamide (39). To a solution of **30** (6.1 mg, 0.018 mmol) in THF (2.0 mL) was added $LiAlH_4$ (1.4 mg, 0.037 mmol), and the mixture was refluxed for 6 h. After the mixture was cooled to room temperature, Et_2O (4.0 mL) and 1 N NaOH (1.3 mL) were added, and an excess of $LiAlH_4$ was precipitated. After filtration of the precipitate, the mixture was extracted with EtOAc, washed with brine, dried, and concentrated. Silica gel chromatography of the residue gave **38** and **39** (24 and 20%, respectively) as colorless needles.

3-[(3*R*,9*S*,9a*R*)-Octahydro-9-acetoxy-4,4-dimethyl-2-oxo-2*H*-quinolizin-3-yl]-4-(3*H*)-quinazolinone (32). Compound **32** was synthesized from **3** following the representative procedure described for **5**, and was obtained as colorless needles (93%).

3-[(2*S*,3*R*,9*S*,9a*R*)-Octahydro-9-acetoxy-2-hydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (33). To an ice-cooled solution of **32** (14.3 mg, 0.037 mmol) in THF (1.0 mL) was added K-selectride (1.0 M solution in THF, 0.15 mL), and the mixture was stirred at 0 °C for 2 h. A saturated aqueous NH_4Cl solution (0.4 mL) was added and stirred for 5 min, and the resulting precipitate was filtered. The filtrate was extracted with Et_2O, and the organic layer was washed with brine, dried, concentrated, and chromatographed over aluminum oxide (*n*-hexane:$CHCl_3$ = 80:20) to give **33** (9.9 mg, 69%) as colorless needles.

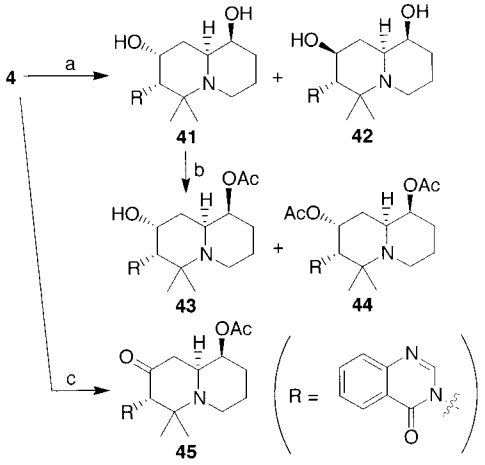
3-[(3*S*,9*S*,9a*R*)-Octahydro-9-hydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (35). To a THF solution (1.0 mL) of NaH (60% in oil, 2.1 mg, 0.053 mmol) was added a THF solution (1.5 mL) of **33** (9.9 mg, 0.026 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. After the mixture was cooled to 0 °C, CS_2 (16 mL, 0.26 mmol) was added. The mixture was warmed to room temperature and stirred for 12 h. The mixture was diluted with EtOAc, washed with brine, dried, and concentrated to give crude **34** (15.1 mg). Without purification, **34** (8.3 mg) in toluene (3 mL) was refluxed with Bu_3SnH (20 mL, 0.075 mmol) and AIBN (1.2 mg, 7.5 mmol) at room temperature for 2 h. After the mixture was cooled to room temperature, it was diluted with *n*-hexane and chromatographed over silica gel (*n*-hexane:$CHCl_3$ = 70:30) to give an acetate of **35** (4.2 mg, 81%). The acetate of **35** in MeOH (1.0 mL) was hydrolyzed with K_2CO_3 (2.4 mg, 0.018 mmol) at 0 °C for 2 h, and then at room temperature for 3 h. The mixture was diluted with EtOAc, washed with brine, dried, concentrated, and chromatographed over aluminum oxide (*n*-hexane:$CHCl_3$ = 70:30) to give **35** (2.3 mg, 79%) as colorless needles.

3-[(3*S*,9*S*,9a*R*)-3,6,7,8,9,9a-Hexahydro-9-hydroxy-4,4-dimethyl-4*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (36). The crude **34** (6.8 mg) was refluxed in *o*-dichlorobenzene (3.0 mL) for 16 h. After the mixture was allowed to cool to room temperature, it was diluted with *n*-hexane and chromatographed over silica gel (*n*-hexane:$CHCl_3$ = 50:50) to give an acetate of **36** (2.0 mg, 47%). The acetate of **36** (26.1 mg, 0.071 mmol) in MeOH (2.0 mL) and K_2CO_3 (25.0 mg, 0.178 mmol) was stirred at room temperature for 3 h. The mixture was diluted with EtOAc, washed with brine, dried, concentrated, and chromatographed over aluminum oxide (*n*-hexane:$CHCl_3$ = 70:30) to give **36** (10.0 mg, 43%) as colorless needles.

3-[(3*R*,9*S*,9a*R*)-3,6,7,8,9,9a-Hexahydro-9-hydroxy-2-methoxy-4,4-dimethyl-4*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (37). To a solution of NaH (60% in oil, 1.0 mg, 0.025 mmol) in THF (1.0 mL) was added dropwise a THF solution (2.0 mL) of **3** (4.1 mg, 0.012 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. After the mixture was cooled to 0 °C, MeI (23 mL, 0.369 mmol) was added, and the mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with EtOAc, washed with brine, dried, and concentrated. Chromatography of the residue over aluminum oxide (*n*-hexane:$CHCl_3$ = 70:30) afforded **37** (4.4 mg, 100%) as colorless needles.

3-[(3*R*,9*S*,9a*R*)-Octahydro-9-hydroxy-4,4-dimethyl-2-oxo-5-oxy-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (40). A mixture of **3** (5.0 mg, 0.014 mmol), *m*-CPBA (3.5 mg, 0.020 mmol), and K_2CO_3 (2.0 mg) in CH_2Cl_2 (200 mL) was stirred at −78 °C for 4 h. The mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with EtOAc, washed with brine, dried, concentrated, and chromatographed over aluminum oxide (*n*-hexane:$CHCl_3$ = 60:40) to give **40** (3.8 mg, 76%) as colorless needles.

Scheme 4[a]



[a] Reagent and condition: (a) $NaBH_4$, MeOH, 0 °C, 0.5 h (**41**, 61%; **42**, 14%); (b) Ac_2O, pyridine, rt, 12 h (**43**, 41%; **44**, 28%); (c) Ac_2O, pyridine, rt, 12 h (62%).

3-[(2*R*,3*S*,9*S*,9a*S*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (41) and 3-[(2*S*,3*S*,9*S*,9a*S*)-Octahydro-2,9-dihydroxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (42). Compounds **41** and **42** were synthesized from **3** following the representative procedure described for **8**, and were obtained as colorless needles (61 and 14%, respectively).

3-[(2*R*,3*S*,9*S*,9a*S*)-Octahydro-9-acetoxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (43) and 3-[(2*R*,3*S*,9*S*,9a*S*)-Octahydro-2,9-diacetoxy-4,4-dimethyl-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (44). Compounds **43** and **44** were synthesized from **41** following the representative procedure described for **5**, and were obtained as colorless needles (41 and 28%, respectively).

3-[(3*S*,9*S*,9a*S*)-Octahydro-9-acetoxy-4,4-dimethyl-2-oxo-2*H*-quinolizin-3-yl]-4(3*H*)-quinazolinone (45). Compound **45** was synthesized from **4** following the representative procedure described for **5**, and was obtained as colorless needles (62%).

Antimalarial assays in Vitro and in Vivo. The antimalarial activities in vitro and in vivo against *P. falciparum* and *P. berghei*, respectively, were investigated as described in ref 11.

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Supporting Information Available: Analytical data and purity criteria for new febrifugine analogues. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) De Smet, P. A. G. M. The Role of Plant-Derived Drugs and Herbal Medicines in Healthcare. *Drugs* **1997**, *54*, 801−840.

(2) (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. An Alkaloid with High Antimalarial Activity from *Dichroa febrifuga*. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. Alkaloids of *Dichroa febrifuga*. I. Isolation and Degradative Studies. *J. Am. Chem. Soc.* **1949**, *71*, 1048−1054.

(3) (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. Catalytic Asymmetric Synthesis of Febrifugine and Isofebrifugine. *Tetrahedron Lett.* **1999**, *40*, 2175−2178. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. Catalytic Asymmetric Synthesis of Antimalarial Alkaloids Febrifugine and Isofebrifugine and Their Biological Activity. *J. Org. Chem.* **1999**, *64*, 6833−6841. (c) Okitsu, O.; Suzuki, R.; Kobayashi, S. Efficient Synthesis of Piperidine Derivatives: Development of Metal Triflate-Catalyzed Diastereoselective Nucleophilic Substitution Reactions of 2-Methoxy- and 2-Acyloxypiperidines. *J. Org. Chem.* **2001**, *66*, 809−823.

(4) Taniguchi, T.; Ogasawara, K. A Diastereocontrolled Synthesis of (+)-Febrifugine: A Potent Antimalarial Piperidine Alkaloid. *Org. Lett.* **2000**, *2*, 3193−3195.

(5) (a) Takeuchi, Y.; Abe, H.; Harayama, T. Total Synthesis of DL-Febrifugine. *Chem. Pharm. Bull.* **1999**, *47*, 905−906. (b) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. Synthesis of D/L-Febrifugine and D/L-Isofebrifugine. *Synthesis* **1999**, 1814−1818. (c) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. Asymmetric Synthesis of Febrifugine and Isofebrifugine Using Yeast Reduction. *Chem. Commun.* **2000**, 1643−1644.

(6) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. A Concise Enantioselective Synthesis of Antimalarial Febrifugine Alkaloids. *Org. Lett.* **2001**, *3*, 953−955.

(7) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.; Kim, H.-S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. New Type of Febrifugine Analogues, Bearing a Quinolizidine Moiety, Show Potent Antimalarial Activity against *Plasmodium* Malaria Parasite. *J. Med. Chem.* **1999**, *42*, 3163−3166.

(8) Fishman, M.; Cruickshank, P. A. Febrifugine Antimalarial Agents. I. Pyridine Analogs of Febrifugine. *J. Med. Chem.* **1970**, *13*, 155−156.

(9) Chien, P.-L.; Cheng, C. C. Structural Modification of Febrifugine. Some Methylenedioxy Analogs. *J. Med. Chem.* **1970**, *13*, 867−870.

(10) Hewitt, R. I.; Wallace, W. S.; Gill, E. R.; Williams, J. H. An Antimalarial Alkaloid from *Hydrangea*. *Am. J. Trop. Med. Hyg.* **1952**, *1*, 768−772.

(11) Kim, H.-S.; Shibata, Y.; Wataya, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M. Synthesis and Antimalarial Activity of Cyclic Peroxides, 1,2,4,5,7-Pentoxocanes and 1,2,4,5-Tetroxanes. *J. Med. Chem.* **1999**, *42*, 2604−2609.

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