Catalytic Asymmetric Synthesis of Antimalarial Alkaloids Febrifugine and Isofebrifugine and Their Biological Activity

Shū Kobayashi,*,† Masaharu Ueno,† Ritsu Suzuki,† Haruro Ishitani,† Hye-Sook Kim,‡ and Yusuke Wataya‡

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka, Okayama 700-8530, Japan

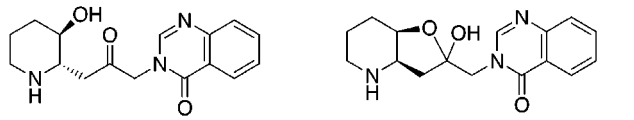
Received June 1, 1999

Antimalarial alkaloids febrifugine (**1**) and isofebrifugine (**2**) were efficiently synthesized from simple achiral starting materials on the basis of the catalytic asymmetric synthesis. The first key reaction was performed using the tin(II)-mediated catalytic asymmetric aldol protocol to afford chiral aldehyde **3** in high yield with high diastereo- and enantioselectivities. The second key step, a Mannich-type reaction, did not give satisfactory results according to the conventional methods. We then developed a novel aqueous Mannich-type three-component reaction of an aldehyde, an amine, and a vinyl ether using a Lewis acid−surfactant combined catalyst (LASC), and the key intermediates **16** and **17** were obtained in high yields. The final coupling reactions of bromoacetone **14** with 4-hydroxyquinazoline were carried out using basic conditions, and successive deprotection gave **1** and **2**, respectively, without any isomerization. These unambiguous total asymmetric syntheses revealed that the absolute configurations of febrifugine and isofebrifugine were not (2′*S*,3′*R*) and (2′*R*,3′*R*) as reported previously but (2′*R*,3′*S*) and (2′*S*,3′*S*), respectively (**1′** and **2′**). Finally, antimalarial activities of the synthesized febrifugine and isofebrifugine, and their antipodes, were examined. It was revealed that the activities and selectivities of natural febrifugine and isofebrifugine were much higher than those of the antipodes.

Introduction

Febrifugine (**1**) and isofebrifugine (**2**) (Chart 1), alkaloids first found in the Chinese plant *Dichroafebrifuga*[1] and later in the common hydrangea,[2] have attracted considerable attention due to their potentially powerful antimalarial activity.[3] Since natural sources are rather limited, there has been strong demand on chemical synthesis, especially asymmetric synthesis of naturally occurring **1** and **2**. Baker et al. performed the first racemic synthesis in 1952,[4] and in 1953, his group reported enantiomer synthesis using a chiral intermediate that was obtained by optical resolution.[5] Despite these efforts, some obscurity regarding the structures of **1** and **2** including absolute configurations still remained. In 1962, Hill et al. reported the absolute configuration of **1** on the basis of a Baker's synthetic intermediate;[6] however, this was corrected by Barringer et al. in 1973 using ^{1}H NMR techniques.[7] This meant that the structure proposed by Hill and previous researchers was erroneous. Since then, although some unclear aspects, which were mainly due to instability of **1** and **2**,[4−8] still remained, the structure proposed by Barringer et al. has been widely accepted and it was also used for the structure determination of febrifugine- and isofebrifugine-related compounds.[8]

Chart 1. Reported Structure of Febrifugine and Isofebrifugine



Febrifugine (**1**, reported form) Isofebrifugine (**2**, reported form)

Our purpose is to show an unambiguous and efficient asymmetric synthetic route to **1** and **2**. In this paper, we describe the asymmetric total synthesis of **1** and **2** using catalytic enantioselective reactions as the key steps. We also report here revision of the absolute configurations of febrifugine and isofebrifugine, on the basis of the unambiguous total synthesis, and the antimalarial activities of **1** and **2** and their enantiomers (**1′** and **2′**).[9]

† The University of Tokyo.
‡ Okayama University.

(1) (a) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1948**, *70*, 1048.

(2) (a) Ablondi, F.; Gordon, S.; Morton, J., II; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 14. (b) Kato, M.; Inaba, M.; Itahana, H.; Ohara, E.; Nakamura, K.; Uesato, S.; Inouye, H.; Fujita, T. *Shoyakugaku Zasshi* **1990**, *44*, 288.

(3) (a) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. *Science* **1946**, *103*, 59. (b) Chou, T.-Q.; Fu, F. Y.; Kao, Y. S. *J. Am. Chem. Soc.* **1948**, *70*, 1765. (c) Frederick, Jr., A. K.; Spencer, C. F.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 2091. See also refs 1, 2, and 25.

(4) Baker B. R.; Schaub, R. E.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 132.

(5) (a) Baker B. R.; McEvoy, F. J.; Schaub, R. E.; Joseph, J. P.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 178. See also: (b) Baker B. R.; Schaub, R. E.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 153. (c) Baker B. R.; McEvoy, F. J. *J. Org. Chem.* **1955**, *20*, 136.

(6) Hill, R. K.; Edwards, A. G. *Chem. Ind.* **1962**, 858.

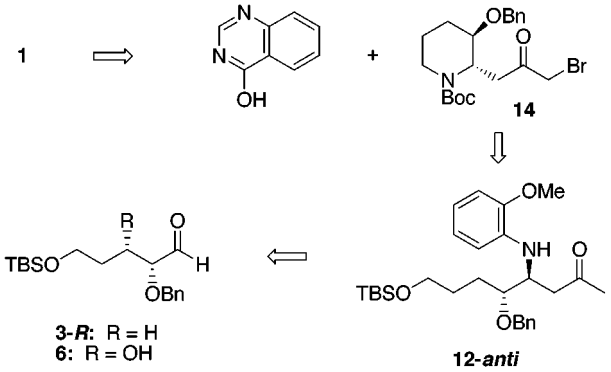
(7) Barringer, D. F., Jr.; Beakelhammer, G. B.; Wayne, R. S. *J. Org. Chem.* **1973**, *38*, 1937.

(8) (a) Uesato, S.; Kuroda, Y.; Kato, M.; Fujiwara, Y.; Hase, Y.; Fujita, T. *Chem. Pharm. Bull.* **1998**, *46*, 1. (b) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255.

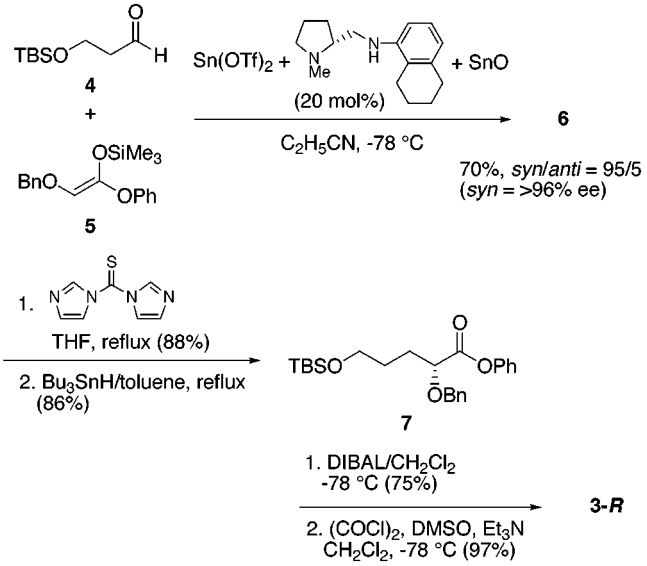
(9) A preliminary communication on the synthesis of febrifugine and isofebrifugine: Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.

10.1021/jo990877k CCC: $18.00
Published on Web 08/19/1999

Scheme 1. Retrosynthetic Analysis of 1



Scheme 2. Synthesis of Key Aldehyde 3

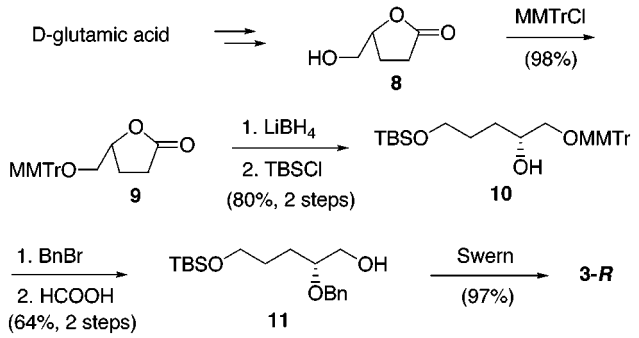


Results and Discussion

Synthetic Plan. Our retrosynthetic analysis is shown in Scheme 1. The final stage is coupling of 4-hydroxyquinazoline with bromoketone **14**, which could be cyclized from acyclic compound **12**. Amino ketone **12** could be prepared via the Mannich-type reaction using chiral aldehyde **3-*R***. The chiral tin(II)-catalyzed asymmetric aldol protocol could be convenient for the synthesis of **3-*R***.

Synthesis of Chiral Aldehyde 3-*R*. The aldehyde **3-*R*** was prepared using the tin(II)-catalyzed asymmetric aldol reaction (Scheme 2).[10] In the presence of a chiral tin(II) Lewis acid (20 mol %) derived from tin(II) triflate, a chiral diamine, and tin(II) oxide, 3-(*tert*-butyldimethysiloxy)propanal (**4**)[11] reacted with 2-(benzyloxy)-1-(trimethylsiloxy)-1-phenoxyethene (**5**) in propionitrile at −78 °C to afford the corresponding aldol-type adduct (**6**) in 70% yield with excellent diastereo- and enantioselectivities (*syn*/*anti* = 95/5, *syn* ≥ 96% ee). The hydroxyl group at the 3-position was removed via 2 steps,[12] and the resulting phenyl ester (**7**) was reduced to form an alcohol, which was converted to the key aldehyde (**3-*R***) under Swern oxidation conditions.[13]

Scheme 3. Alternative Synthesis of Aldehyde 3



To confirm the absolute configuration of **3-*R***, we also prepared **3-*R*** from D-glutamic acid according to Scheme 3. Lactone **8** was prepared from D-glutamic acid according to the literature,[14] and the hydroxyl group of **8** was protected as its mono-*p*-methoxytrityl (MMTr) group.[15] Reduction of **9** using $LiBH_4$ to afford diol **10**, whose primary hydroxyl group was protected as its *tert*-butyldimethylsilyl (TBS) ether, and then the secondary hydroxyl group was protected as its benzyl ether, respectively. Deprotection of the MMTr group and successive Swern oxidation gave chiral aldehyde **3-*R***. Its optical rotation was consistent with that of **3-*R*** prepared via the catalytic asymmetric aldol reaction.

Synthesis of Bromo Ketone 14 (Method 1). The next key step is a Mannich-type reaction for the synthesis of **12**. The Mannich and related reactions provide a fundamental and useful methodology for the synthesis of β-amino ketones and esters.[16] Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have improved the process.[17] Some of these materials are, however, unstable and difficult to isolate, and deamination of the products that occurs under the reaction conditions still remains as a problem. The direct synthesis of β-amino ketones from aldehydes, amines, and third carbonyl compounds under mild conditions is desirable from a synthetic point of view. On the basis of this consideration, we have recently developed lanthanide-catalyzed three-component reactions of aldehydes, amines, and vinyl ethers in aqueous media,[18] and this protocol was successfully applied to the synthesis of **12** (Scheme 4). In the presence of 10 mol % of ytterbium triflate ($Yb(OTf)_3$), the three-component reaction of **3-*R***, 2-methoxyaniline, and 2-methoxypropene was performed in aqueous media (THF/H_2O = 9/1). The reaction proceeded smoothly at 0−5 °C to afford the desired Mannich-type adduct (**12**) in 92% yield (*syn*/*anti* = 67/33). The diastereomers were separated and the *syn*- and *anti*-adducts

(10) (a) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911. (b) Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* **1994**, 217. (c) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. (d) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805. (e) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098. (f) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472.

(11) The aldehyde was prepared via 2 steps from propane-1,3-diol.

(12) Rasmussen, J. R.; Slinnger. C. J.; Kordish. R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.

(13) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

(14) (a) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron Lett.* **1974**, *30*, 3547. (b) Ravid, U.; Silverstein, R.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.

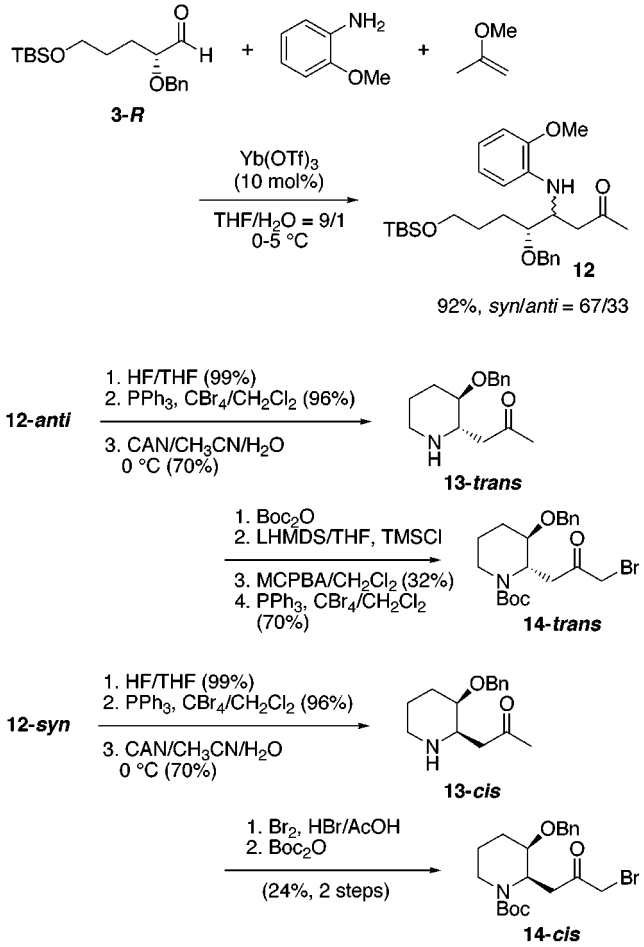
(15) (a) Khorana, H. G. *Pure Appl. Chem.* **1968**, *17*, 349. (b) Smith, M.; Rammler, D. H.; Goldgerg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430.

(16) Blicke, F. F. *Org. React.* **1942**, *1*, 303.

(17) (a) Kleimman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Chapter 2.3, Vol. 2. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044.

(18) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.

Scheme 4. Synthesis of Bromo Ketone 14



(**12-*syn*** and **12-*anti***) were used for the synthesis of isofebrifugine (**2**) and febrifugine (**1**), respectively. The anti-adduct (**12-*anti***) was then treated with HF to remove the TBS protecting group, and the following bromination gave a spontaneously cyclized adduct whose *N*-protected group (2-methoxyphenyl group) was removed using cerium ammonium nitrate (CAN)[19,20] to afford **13-*trans***. Several trials to perform direct bromination of **13** failed. Alternatively, piperidine **13-*trans*** was protected as its *N*-Boc group and was treated with lithium hexamethyldisilazido (LHMDS) followed by trimethylsilyl chloride (TMSCl). The resulting silyl enol ether was oxidized and then brominated to give bromo ketone **14-*trans***. On the other hand, **12-*syn*** was similarly converted to piperidine **13-*cis*** in a good yield. In this case, direct bromination proceeded in a low yield to afford bromo ketone **14-*cis***.[5c] Although the desired bromo ketones **14-*trans*** and **14-*cis*** were prepared according to this scheme, the yields were not satisfactory. Despite examination of several reaction conditions in these schemes, the yields were not improved and we decided to change the routes to bromo ketone **14**.

Synthesis of Bromo Ketone 14 (Method 2). Since the bromination of ketone **13** was found to be unexpectedly difficult, our next plan was to introduce bromine at an earlier stage. We devised a new key three-component

Scheme 5. A New Three-Component Reaction

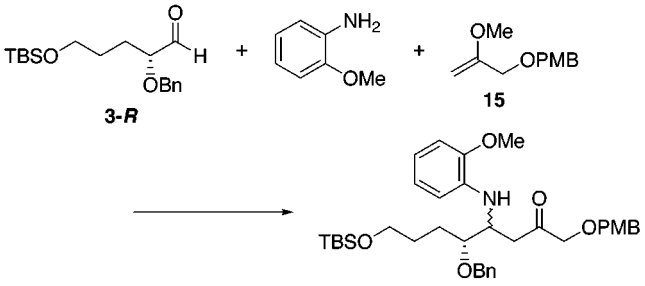
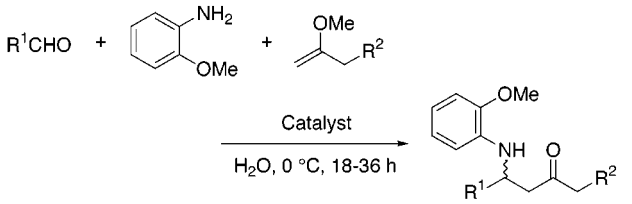
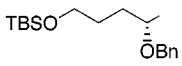


Table 1. Three-Component Reactions in Water



R^1	R^2	Catalyst	Yield (%)
Ph	H	$Cu(DS)_2$	65
c-C_6H_{11}	H	$Cu(DS)_2$	86
c-C_6H_{11}	H	$Yb(DS)_3$	78
	H	$Cu(DS)_2$	82
Ph	OPMB	$Cu(DS)_2$	62
	OPMB	$Cu(DS)_2$	73
	OPMB	$Yb(DS)_3$	91

reaction of **3-*R***, methoxyaniline, and 2-methoxy-3-(*p*-methoxybenzyloxy)-1-propene (**15**) as shown in Scheme 5. The reaction was first tried in the presence of a catalytic amount of $Yb(OTf)_3$ in aqueous media (THF/H_2O = 9/1);[18] however, only a trace amount of the desired adduct was obtained.

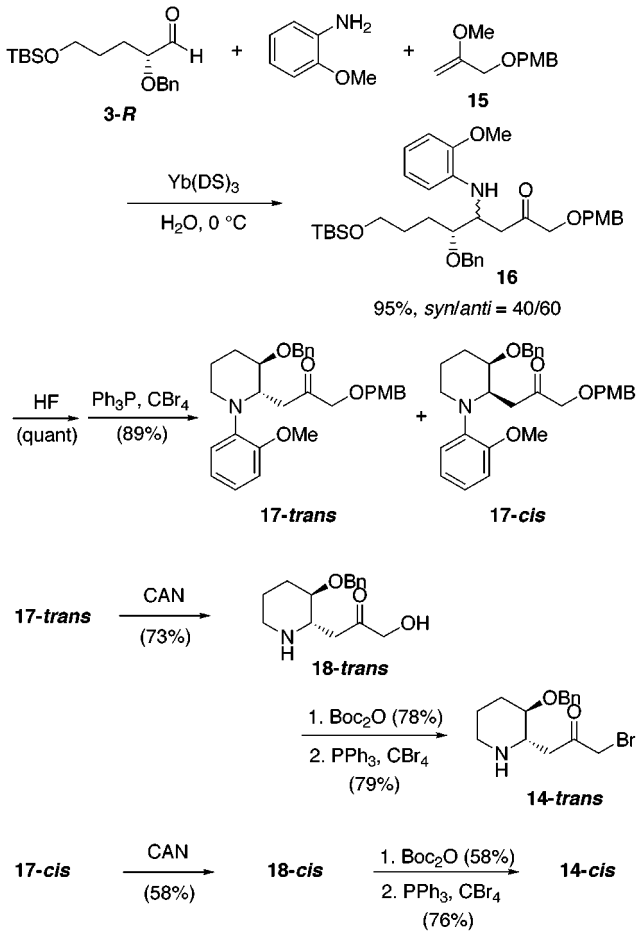
At this stage, we were required to develop a novel Mannich-type reaction. We have recently developed a Lewis acid−surfactant-combined catalyst (LASC) that forms efficient hydrophobic reaction fields and works efficiently as a catalyst in water.[21] It was found that a new type of a three-component Mannich reaction of aldehydes, amines, and vinyl ethers proceeded smoothly in the presence of ytterbium(III) dodecyl sulfate ($Yb(DS)_3$) or copper(II) dodecyl sulfate ($Cu(DS)_2$) in water. Several examples are shown in Table 1. In all cases, the reactions proceeded cleanly and the corresponding β-amino ketones were obtained in good to high yields. When the same combinations were performed in organic solvents, tetrahydroquinolines were produced as the main adducts. Considerable amounts of deamination adducts were isolated, when silyl enol ethers were used instead of vinyl ethers in organic solvents. It is noted that the reactions were successfully performed not in organic solvents or water−organic solvents but in pure water and that use of LASC and water as a catalyst and a solvent, respectively, is crucial to obtain the desired products.

(19) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(20) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(21) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389.

Scheme 6. Synthesis of Bromo Ketone 14 (Method 2)



As the newly developed aqueous Mannich-type reactions were developed, we continued the synthesis of the alkaloids. In the presence of 10 mol % of $Yb(DS)_3$, the three-component reaction of **3-*R***, *o*-methoxyaniline, and **15** proceeded smoothly at 0 °C to afford the desired *β*-amino ketone (**16**) in 95% yield. The TBSO group of **16** was then removed and brominated to give piperidine **17** (Scheme 6). The two diastereomers were separated at this stage (**17-*cis*** and **17-*trans***). After the *p*-methoxybenzyl (PMB) group and the *N*-protecting *o*-methoxyphenyl group of **17** were removed, *tert*-butoxycarbonyl (BOC) protection of the secondary amine was performed selectively, and the successive substitution to a bromo group from the hydroxy group gave the desired bromo ketone (**14**) in good yields (**14-*trans*** and **14-*cis***).

Coupling with 4-Hydroxyquinazoline. The coupling reaction of bromoacetone **14** with 4-hydroxyquinazoline was carried out using potassium hydroxide (KOH)[22] to afford **19**, whose protecting groups were successfully removed using 6N HCl to afford **1** (Scheme 7). After recrystallization from ethanol, it was found that its ^1H and ^{13}C NMR spectra[8a] and melting point were completely consistent with those reported (mp 138-140 °C (lit. mp 139−140,[1b] 137−138,[2a] 139−141 °C[2b])), but the optical rotation of synthetic **1** was negative while the reported optical rotation was positive ($[\alpha]^{24}_D$ −28.0 (*c* = 0.24, EtOH), lit.[1b] $[\alpha]^{25}_D$ +28 (*c* = 0.5, EtOH)). This meant that

(22) Ranganathan, D.; Farrooqui, F. *Tetrahedron Lett.* **1984**, *25*, 5701.

Scheme 7. Coupling with 4-Hydroxyquinazoline

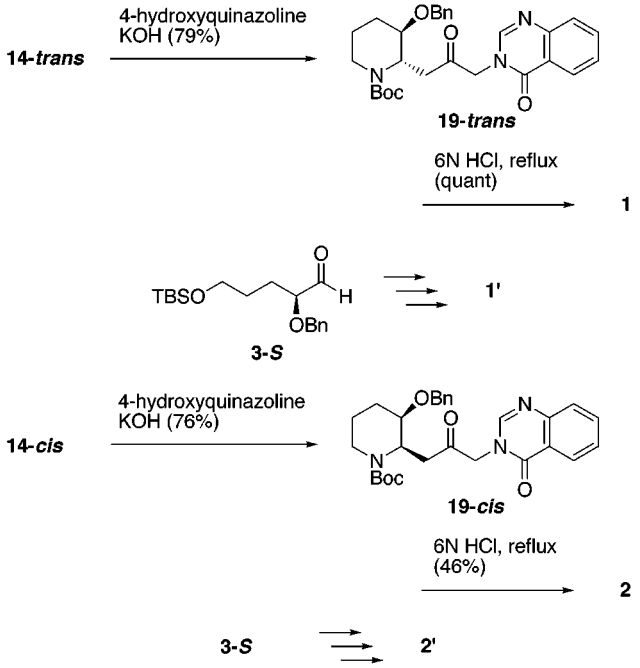
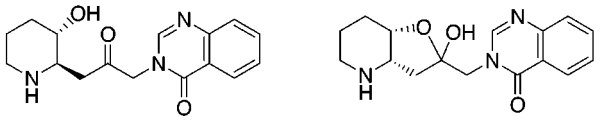


Chart 2. Revised Structure of Febrifugine and Isofebrifugine



Febrifugine (**1'**, revised form) Isofebrifugine (**2'**, revised form)

Table 2. Antimalarial Activity against *P. falciparum* in Vitro and Cytotoxicities against FM3A Cells

	EC_{50} (M)		
compd	*P. falciparum*[a]	FM3A cell[b]	selectivity[c]
1	$(2.0 \pm 0.3) \times 10^{-7}$	$(2.1 \pm 0.1) \times 10^{-5}$	105
1′	$(7.6 \pm 0.4) \times 10^{-11}$	$(2.1 \pm 0.1) \times 10^{-7}$	2763
2	$(1.6 \pm 0.2) \times 10^{-7}$	$(1.9 \pm 0.1) \times 10^{-5}$	119
2′	$(2.9 \pm 0.3) \times 10^{-10}$	$(7.3 \pm 1.4) \times 10^{-7}$	2517

[a] Chloroquine sensitive strain (FCR-3). [b] Mouse mammary tumor FM3A cells representing a model of host. [c] Selectivity = mean of EC_{50} value for FM3A cells/mean of EC_{50} for *P. falciparum*. The data shown are the mean values ±SD of the EC_{50} values from independent triplicate measurements.

the structure of febrifugine (**1**) shown in Chart 1 was an antipode of the natural product. We then repeated the synthesis according to Scheme 6 using aldehyde **3-*S***. All physical data of the synthetic sample, including the optical rotation this time, were completely consistent with those reported in the literature.

Similarly, both enantiomers of isofebrifugine (**2**) starting from **17-*cis*** and antipode were prepared (Schemes 6 and 7). It was shown that the optical rotation of the synthetic sample from the antipode was consistent with that reported in the literature. It is now concluded that the structures of febrifugine and isofebrifugine were not **1** and **2** but **1′** and **2′** as shown in Chart 2.

Biological Activity. Antimalarial activities of synthetic febrifugine, isofebrifugine, and their antipodes were examined (Table 2). The EC_{50} values of synthetic febrifugine **1′** and its antipode **1** against *Plasmodium falciparum* are 7.6×10^{-11} and 2.0×10^{-7} M, and the

EC_{50} values for **1′** was $^1/_{2632}$ of that of enantiomer **1**. Moreover, the value for synthetic isofebrifugine **2′** and its antipode **2** were 2.9×10^{-10} and 1.6×10^{-7} M, and the EC_{50} values for **2′** was $^1/_{552}$ of that of enantiomer **2**. Excellent selectivities of the natural form **1′** and **2′** were shown. Natural febrifugine and isofebrifugine obtained from *Dichroa febrifuga* were reported as potent antimalarial agents[1b,23] and the EC_{50} values of the compounds for *P. falciparum in vitro* were approximately 10^{-10} and 10^{-9} M, respectively.[24] These results also support that the synthetic **1′** and **2′** correspond to natural febrifugine and isofebrifugine. It is surprising to note that **1′** and **2′**, in contrast with their antipode **1** and **2**, have potent antimalarial activities, suggesting that the differences in stereoisomeric structures play an important role for development of a new antimalarial drug.

Conclusion and Perspective

In summary, catalytic asymmetric synthesis of febrifugine and isofebrifugine was performed using the tin(II)-catalyzed asymmetric aldol reaction and lanthanide-catalyzed aqueous Mannich-type three-component reaction as the key steps. The novel Mannich-type reactions have been developed using LASC (Lewis acid−surfactant-combined catalyst) in water. These unambiguous total syntheses revised the absolute configurations of febrifugine and isofebrifugine from (2′*S*,3′*R*) and (2′*R*,3′*R*) to (2′*R*,3′*S*) and (2′*S*,3′*S*), respectively. In addition, antimalarial activities and selectivities of the synthesized febrifugine and isofebrifugine were proved to be much higher than those of the antipodes. Malaria is the most prevalent disease in the world, and some 1.5−2.7 million people die of malaria each year. Malaria risk of varying degrees exists in 100 countries and territories, and it is noted that over 40% of the world population live in areas with malaria risk. The synthetic method reported here would be applied to the preparation of many febrifugine and isofebrifugine derivatives including combinatorial synthetic techniques,[25] and further investigations to develop truly efficient antimalarial drugs are now in progress in our laboratories.

Experimental Section

General Methods. Melting points were uncorrected. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dichloromethane and acetonitrile were distilled from P_2O_5 and then from CaH_2 and dried over MS 4A. Toluene was distilled and dried over MS 4A. Sn(II) triflate[26] and Yb(III) triflate[27] were prepared on the basis of reported procedures. All silyl enol ethers were prepared according to the modified House procedure.[28] All chemical compounds were purified on the basis of standard procedures; especially, aldehydes, amines, and vinyl ether were purified by distillation before use. (*R*)-γ-(Hydroxymethyl)-γ-butyrolactone (**8**) was prepared from D-glutamic acid according to the known protocol.[14]

Plasmodium falciparum (ATCC 30932, FCR-3 strain) was used in our study. *P. falciparum* was cultivated by a modification of the method of Trager and Jensen[29] using a 5% hematocrit of type A human red blood cells suspended in RPMI 1640 medium (Gibco, NY) supplemented with inactivated 10% type A. 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. Mouse mammary tumor FM3A cells (wild-type, subclone F28-7) 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).[30]

(2*R*,3*S*)-Phenyl 2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-3-hydroxypentanoate (6). To a solution of tin(II) triflate (0.16 mmol) and tin(II) oxide (0.16 mmol) in propionitrile (2.0 mL) was added a solution of (*R*)-1-methyl-2-(5,6,7,8-tetrahydro-1-naphthylaminomethyl)pyrrolidine (0.19 mmol) in propionitrile (2.0 mL). The mixture was cooled to −78 °C, and **4** (0.77 mmol) in propionitrile (1.0 mL) and **5** (0.93 mmol) in propionitrile (1.0 mL) were slowly added to the catalyst over 4 h. The reaction mixture was further stirred for 2 h at the same temperature and then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product was treated with THF−1 N HCl (20:1) at 0 °C. After the usual workup, the crude aldol was chromatographed on silica gel to afford **6** in 70% yield. The diastereomer ratio was determined by ^{1}H NMR analysis (*syn*/*anti* = 95/5). The enantiomeric excess of the *syn* adduct was determined to be >96% ee by HPLC analysis using Daicel Chiralcel AD (hexane/*i*-PrOH, 9:1, flow rate 1.0 mL/min, t_R = 8.2 min (2*S*, 3*R*), 15.6 min (2*R*,3*S*)). **6-*syn*:** $[\alpha]^{25}_D$ +58.0 (*c* = 2.0, $CHCl_3$); IR (neat) 3478, 2928, 1771, 1594, 1493, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 1.65−1.95 (m, 2H), 2.96 (d, 1H, *J* = 5.6 Hz), 3.66−3.85 (m, 2H), 4.09 (d, 1H, *J* = 3.96 Hz), 4.26 (m, 1H), 4.52 (d, 1H, *J* = 11.6 Hz), 4.85 (d, 1H, *J* = 11.6 Hz), 7.04−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −5.5, 18.2, 25.8, 35.4, 60.8, 71.3, 72.9, 80.6, 121.3, 121.4, 126.0, 128.2, 128.3, 128.4, 128.5, 129.4, 136.9, 150.4, 169.6; HRMS calcd for $C_{24}H_{34}O_5Si$ (M^+) 430.2176, found 430.2169.

(*R*)-Phenyl 2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-pentanoate (7). Solid *N*,*N*′-thiocarbonyldiimidazole (8.1 mmol) was added to a solution of **6** (2.7 mmol) in dry THF (18.0 mL). The reaction mixture was heated under gentle refluxing conditions for 1.5 h. After cooling, the solution was concentrated under reduced pressure and the product was purified by flush chromatography on silica gel to afford the corresponding thiocarbonate in 88% yield. The thiocarbonate (2.9 mmol) in dry toluene (250 mL) was then added dropwise over 30 min to a refluxing toluene solution (40.0 mL) of Bu_3SnH (8.6 mmol). The reaction mixture was heated under reflux for 6 h and then cooled to room temperature. The mixture was concentrated under reduced pressure and was chromatographed on silica gel to afford **7** in 86% yield: $[\alpha]^{24}_D$ +14.3 (*c* = 0.9, $CHCl_3$); IR (neat) 2954, 1739, 1593, 1493, 1254, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.71 (m, 2H), 1.96 (m, 2H), 3.57−3.62 (m, 3H), 4.16 (m, 1H), 4.49 (d, 1H, *J* = 11.6 Hz), 4.83 (d, 1H, *J* = 11.6 Hz), 7.03−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.2, 25.9, 28.4, 29.5, 62.4, 72.4, 77.7, 121.3, 121.5, 125.9, 128.0, 128.1, 128.4, 129.4, 137.3, 150.3, 171.3; HRMS calcd for $C_{24}H_{34}O_4Si$ (M^+) 414.2226, found 414.2230.

(*R*)-2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)pentanal (3-*R*). A solution of **7** (0.97 mmol) in dichloromethane (5.0 mL) was cooled to −78 °C, and to this solution was added

(23) Wataya, Y.; Kim, H.-S. Unpublished data.
(24) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1.
(25) Kuehl, F. A., Jr.; Spencer, C. F.; Folkers, K. *J. Am. Chem. Soc.* **1949**, *71*, 1048.
(26) (a) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.
(27) (a) Thom, K. F. U.S. Patent 3615169 1971; *Chem. Abstr.* **1972**, *76*, 5436a. (b) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017.
(28) House, H. O.; Cuzba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(29) Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673.
(30) Yoshioka, A.; Tannaka, S.; Hiraoka, O.; Koyama, Y.; Hirota, Y.; Ayusawa, D.; Seno, T.; Garrett, C.; Wataya, Y. *J. Biol. Chem.* **1987**, *262*, 8235.

DIBAL (0.98 M hexane solution, 3.0 mL) over 5 min. After being stirred for 1 h, the reaction mixture was quenched with MeOH at the same temperature. The resulting mixture was warmed to room temperature, and 30% aqueous potassium sodium tertarate solution was added to the mixture. After being stirred for 1 h, the mixture was filtered through a Cerite pad, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the corresponding alcohol in 75% yield. A dichloromethane solution (1.0 mL) of oxalyl chloride (0.21 mmol) and DMSO (0.46 mmol) was cooled to −78 °C, and to this solution was added the alcohol (0.096 mmol) in dichloromethane (0.50 mL); the mixture was then stirred for 30 min. To this reaction mixture was added a dichloromethane solution (0.50 mL) of triethylamine (0.48 mmol), and the mixture was stirred at the same temperature for 5 min. The mixture was then warmed to room temperature and further stirred for 30 min. Water was added to the mixture, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the corresponding aldehyde (**3**) in 97% yield. **3-*R*:** $[\alpha]^{26}_D$ +42.5 (c = 1.0, $CHCl_3$); IR (neat) 1735, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.57−1.78 (m, 4H), 3.57 (t, 2H, J = 6.2 Hz), 3.77 (m, 1H), 4.51 (d, 1H, J = 11.6 Hz), 4.65 (d, 1H, J = 11.6 Hz), 7.28 (m, 5H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.3, 25.9, 26.4, 27.9, 62.4, 72.4, 83.2, 128.0, 128.0, 128.5, 137.3, 203.6. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.86; H, 9.34. **3-*S*:** $[\alpha]^{26}_D$ −43.9 (c = 1.2, $CHCl_3$)

(*R*)-γ-(Monomethoxytrityloxymethyl)-γ-butyrolactone (9). The trytyl-type protected lactone ((*R*)-**9**) was obtained from **8** quantitatively by the standard procedure:[14] $[\alpha]^{26}_D$ −15.5 (c = 1.0, $CHCl_3$); IR (KBr) 1768, 1606, 1511, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99−2.07 (m, 1H), 2.18−2.28 (m, 1H), 2.45−2.54 (m, 1H), 2.63−2.72 (m, 1H), 3.14 (dd, J = 4.3, 10.4 Hz), 3.41 (dd, J = 3.3, 10.4 Hz), 3.79 (s, 3H), 4.64 (m, 1H), 6.84 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.24−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 24.2, 28.4, 55.2, 65.2, 79.1, 86.6, 113.2, 127.0, 127.9, 128.3, 130.3, 135.1 143.9, 144.0, 158.6, 177.5. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.03; H, 6.23. Found: C, 76.76; H, 6.19.

(*R*)-5-(*tert*-Butyldimethylsiloxy)-1-(monomethoxytrityloxy)-2-pentanol (10). Lithium borohydride (67.0 mmol) was suspended in dry THF (40.0 mL). A solution of **9** (22.3 mmol) in dry THF (20.0 mL) was added gently dropwise to a suspension of lithium borohydride. Dry methanol (3.0 mL) was then slowly added to complete the reaction, and after the addition of methanol, the reaction mixture was cooled to 0 °C and excess methanol was added to quench the reaction. Ether and water were then added, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure, and the resulting almost pure diol was treated with (TBS)Cl and imidazole according to a usual method. The crude product was purified by silica gel column chromatography to afford 5-(*tert*-butyldimethylsiloxy)-1-(monomethoxytrityloxy)-2-pentanol ((*R*)-**10**) in 80% yield: $[\alpha]_D^{27}$ −1.5 (c = 1.1, $CHCl_3$); IR (neat) 3432, 2926, 1210, 1252, 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.84 (s, 9H), 1.42−1.59 (m, 4H), 2.76 (s, 1H), 3.02−3.11 (m, 2H), 3.57 (t, 2H, J = 5.6 Hz), 3.75 (br s, 4H), 6.79 (d, 2H, J = 8.8 Hz), 7.16−7.29 (m, 8H), 7.40 (d, 4H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ −5.4, 13.3, 25.9, 28.8, 30.4, 55.2, 63.3, 67.5, 70.7, 86.2, 113.1, 126.9, 127.8, 128.4, 130.3, 135.6, 144.4, 158.5. Anal. Calcd for $C_{31}H_{42}O_4Si$: C, 73.47; H, 8.35. Found: C, 73.38; H, 8.19.

(*R*)-2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)pentanol (11). To a suspension of NaH (60% dispersion in mineral oil, 53.5 mmol) in dry THF (20.0 mL) was added a THF solution (10.0 mL) of **10** dropwise at room temperature. After the mixture was stirred for 30 min, benzyl bromide (3.0 mL) was added at 0 °C. The reaction mixture was stirred at room temperature until the reaction complete. After the usual work up, the crude mixture was dissolved in ether (20.0 mL) and the solution cooled to 0 °C. Concentrated formic acid was then added in portionwise to the ether solution. The reaction was monitored carefully, and as soon as the reaction was completed, water and ether were added to the acidic mixture. The organic layer was separated and washed with water, saturated aqueous $NaHCO_3$, and brine. The crude product was purified by silica gel column chromatography to afford (*R*)-**11** in 64% yield. **(*R*)-11:** $[\alpha]_D^{27}$ −14.0 (c = 1.2, $CHCl_3$); IR (neat) 3435, 2938, 2856, 1471, 1254, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.45−1.65 (m, 4H), 2.04 (s, 1H), 3.51 (m, 2H), 3.57 (m, 2H), 3.64 (m, 1H), 4.50 (d, 1H, J = 11.6 Hz), 4.57 (d, 1H, J = 11.6 Hz), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.3, 18.3, 25.9, 27.0, 28.4, 63.0, 64.2, 71.4, 79.5, 127.7, 127.8, 128.4, 138.4. Anal. Calcd for $C_{18}H_{22}O_3S$: C, 66.62; H, 9.94. Found: C, 66.42; H, 10.15. **(*S*)-11:** $[\alpha]^{26}_D$ +14.4 (c = 1.2, $CHCl_3$).

(*R*)-2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)pentanal (3-*R*). A dichloromethane solution (30.0 mL) of oxalyl chloride (23.7 mmol) and DMSO (51.6 mmol) was cooled to −78 °C. To this solution was added **11** (10.8 mmol) in dichloromethane (12.0 mL), and the mixture was stirred for 30 min. Triethylamine (12.0 mL) was added to the reaction mixture, and the mixture was stirred at the same temperature for 5 min. The mixture was then warmed to room temperature and further stirred for 30 min. After the usual workup, the pure aldehyde was isolated by silica gel column chromatography in 97% yield: $[\alpha]^{26}_D$ +43.2 (c = 1.0, $CHCl_3$).

(4*R*,5*R*)-5-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)-4-((2′-methoxyphenyl)amino)-2-octanone (12-*syn*) and (4*S*, 5*R*)-5-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)-4-((2′-methoxyphenyl)amino)-2-octanone (12-*anti*). To a solution of aldehyde **3-*R*** and *o*-anisidine (3.0 mmol, respectively) in 2.5 mL of aqueous THF (9:1 THF/H_2O) were added $Yb(OTf)_3$ (0.30 mmol) and an aqueous THF solution (0.5 mL) of 2-methoxypropene (15 mmol) successively at 0 °C. After the solution was stirred for 45 h, saturated aqueous $NaHCO_3$ was added to quench the reaction. After the usual workup, the crude product was purified by silica gel column chromatography to afford **12** as a diastereomer mixture in 92% yield (*syn*/*anti* = 67/33). **12-*syn*:** $[\alpha]^{26}_D$ −2.0 (c = 0.9, $CHCl_3$); IR (neat) 2952, 1712, 1601, 1514, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.86 (s, 9H), 1.49−1.70 (m, 4H), 1.95 (s, 3H), 2.69 (d, 2H, J = 6.6 Hz), 3.53 (m, 3H), 3.76 (s, 3H), 4.05 (s, 1H), 4.43 (d, 1H, J = 11.6 Hz), 4.46 (d, 1H, J = 11.6 Hz), 6.55−6.79 (m, 4H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.3, 18.3, 25.9, 26.4, 27.9, 44.6, 50.1, 55.3, 62.8, 71.7, 79.2, 109.7, 116.3, 121.3, 128.0, 128.0, 128.5, 137.3, 138.4, 147.1, 208.1; HRMS calcd for $C_{28}H_{43}NO_4Si$ (M^+) 485.2961, found 485.2964. **12-*anti*:** $[\alpha]^{27}_D$ −9.8 (c = 0.7, $CHCl_3$); IR (neat) 2952, 1714, 1602, 1512, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.49−1.71 (m, 4H), 2.08 (s, 3H), 2.68 (d, 2H, J = 5.7 Hz), 3.54−3.61 (m, 3H), 3.76 (s, 3H), 4.02−4.04 (m, 1H), 4.41 (d, 1H, J = 11.2 Hz), 4.55 (d, 1H, J = 11.2 Hz), 6.60−6.84 (m, 4H), 7.27−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.3, 18.3, 25.9, 27.4, 28.7, 30.7, 43.7, 52.0, 55.3, 62.9, 72.6, 80.3, 109.7, 110.9, 116.8, 121.3, 127.6, 127.8, 128.3, 136.7, 138.5, 147.2, 207.9; HRMS calcd for $C_{28}H_{43}NO_4Si$ (M^+) 485.2961, found 485.2976.

(2′*S*,3′*R*)-1-[2′-(3′-Benzyloxy)piperidino]-2-propanone (13-*trans*) and (2′*R*,3′*R*)-1-[2′-(3′-Benzyloxy)piperidino]-2-propanone (13-*cis*). To a THF solution (10.0 mL) of Mannich base **12-*anti*** (2.76 mmol) was added 48% aqueous HF. As soon as the reaction was completed, the reaction was quenched with saturated aqueous $NaHCO_3$, and the organic layer was extracted with dichloromethane. The pure alcohol was obtained by column chromatography on silica gel in quantitative yield. The alcohol (2.7 mmol) was dissolved in dichloromethane (15.0 mL), and to this solution were added tetrabromomethane (5.3 mmol) and triphenylphosphine (5.3 mmol) in dichloromethane (10.0 mL) successively. After a few minutes, water and dichloromethane were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The pure *N*-protected piperidine derivative was obtained after column chromatography on silica gel in 96%

yield. To a solution of the piperidine derivative (2.6 mmol) in 20.0 mL of aqueous acetonitrile (4:1 acetonitrile/water) was added cerium(IV) ammonium nitrate (13.1 mmol) at 0 °C. After the solution was stirried for 2 h, water and ethyl acetate were added, and the aqueous layer was basified with potassium carbonate. The insoluble materials were filtered through a Cerite pad, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (1:10 methanol/chloroform as an elutant) to afford **13-*trans*** in 70% yield: $[\alpha]^{26}_D$ −79.3 (c = 1.3, $CHCl_3$); IR (neat) 2933, 1709, 1455, 1357, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23−1.36 (m, 1H), 1.44−1.56 (m, 1H), 2.07−2.28 (m, 1H), 2.11 (s, 3H), 2.45 (dd, 1H, J = 17.6, 8.8 Hz), 2.61 (dt, 1H, J = 2.7 12.0 Hz), 2.89−2.97 (m, 1H), 3.06 (dd, 1H, J = 3.1, 17.9 Hz), 3.12 (m, 1H), 3.50 (br, 1H), 4.39 (d, 1H, J = 11.5 Hz), 4.63 (d, 1H, J = 11.5 Hz), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.6, 29.8, 30.4, 45.6, 45.8, 57.3, 70.5, 77.9, 127.6, 127.7, 128.3, 138.3, 208.9; HRMS calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1572, found 247.1572.

Similarly, **13-*cis*** was prepared from **12-*syn*** in 70% yield: $[\alpha]^{26}_D$ −49.0 (c = 0.4, $CHCl_3$); IR (neat) 2930, 1713, 1602, 1455, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37−1.55 (m, 2H), 1.65−1.80 (m, 1H), 1.94 (br, 1H), 2.08 (s, 3H), 2.51−2.71 (m, 3H), 2.99 (d, 1H, J = 12.7 Hz), 3.13−3.18 (m, 1H), 3.40 (t, 1H, J = 2.0 Hz), 4.34 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H. J = 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 26.9, 30.6, 45.7, 55.0, 70.3, 73.5, 127.5, 127.8, 128.2, 138.6, 208.1; HRMS calcd for $C_{15}H_{21}NO_2$ (M^+) 274.1572, found 247.1572.

(2′*S*,3′*R*)-1-[2′-(3′-(Benzyloxy)-1′-(*tert*-butoxycarbonyl)-piperidino)]-3-bromo-2-propanone (14-*trans*). 13-*trans* (0.076 mmol) was treated with $(Boc)_2O$ in dichloromethane at 0 °C for 3 h. After the usual workup, the *N*-Boc piperidine derivative was obtained. A solution of lithium hexamethyldisilazide (0.23 mmol) in dry THF (2.0 mL) was cooled to −78 °C, and to this solution was added the Boc-protected piperidine derivative in THF (1.0 mL) slowly. After 1 h, (TMS)Cl (0.40 mmol) was added to the mixture, which was further stirred for 1 h. The reaction mixture was diluted with 20.0 mL of hexane at −78 °C and washed quickly with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude silyl enol ether was dissolved in dichloromethane (2.0 mL), and to this solution was added MCPBA (0.15 mmol) in dichloromethane (1.0 mL) at −78 °C. The reaction mixture was warmed gradually to room temperature and quenched with 5% aqueous sodium sulfite. The crude mixture was then treated with THF−1 N HCl (20:1) at 0 °C for 1 h. After the usual workup, the α-hydroxy ketone was obtained in 32% yield, and the starting material (the Boc-protected piperidine derivative) was recovered (39%, 52% conversion).

The α-hydroxy ketone (0.024 mmol) was dissolved in dichloromethane (0.50 mL), and to this solution were added tetrabromomethane (0.050 mmol) and triphenylphosphine (0.050 mmol) in dichloromethane (0.50 mL) successively. After a few minutes, water and dichloromethane were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The pure α-bromo ketone was obtained after silica gel column chromatography in 70% yield: $[\alpha]_D^{26}$ +28.4 (c = 0.2, $CHCl_3$); IR (neat) 2930, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26−1.65 (m, 4H), 1.43 (s, 9H), 1.86−1.91 (m, 2H), 2.81−2.86 (m, 3H), 3.43 (br, 1H), 4.01 (br, 1H), 4.52 (d, 1H, J = 11.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.98 (br, 1H), 7.25−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.5, 24.7, 34.1, 39.8, 49.6, 70.1, 73.5, 76.8, 80.0, 127.4, 127.5, 128.3, 138.5, 155.3, 199.7; HRMS calcd for $C_{20}H_{28}NO_4Br$ (M^+) 425.1202, found 425.1195.

(2′*R*,3′*S*)-1-[2′-(3′-(Benzyloxy)-1′-(*tert*-butoxycarbonyl)-piperidino)]-3-bromo-2-propanone (14-*cis*). 13-*cis* (0.29 mmol) was treated with 0.20 mL of acetic acid and 0.20 mL of 30% HBr−AcOH. To the reaction mixture was added 15% bromine in acetic acid (0.15 mL), and the resulting mixture was stirred for 1 h. The excess reagents were removed under the reduced pressure, and the residue was dissolved in chloroform (2.0 mL). To this chloroform solution were added saturated aqueous $NaHCO_3$ (1.0 mL) and $(Boc)_2O$ (0.86 mmol) at 0 °C. After being stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The crude product was purified by silica gel column chromatography to afford the corresponding bromo ketone in 24% yield (2 steps): $[\alpha]_D^{25}$ +22.5 (c = 0.3, $CHCl_3$); IR (neat) 2929, 1731, 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6, 50 °C) δ 1.05−1.43 (m, 4H), 1.31 (s, 9H), 1.55−1.61 (m, 1H), 1.74−1.80 (m, 1H), 2.66 (dt, 1H, J = 2.5, 13.2 Hz), 2.85 (dd, 1H, J = 8.4, 16.0 Hz), 3.09 (dd, 1H, J = 5.0, 16.0 Hz), 3.39 (m, 1H), 3.71 (dd, 1H, J = 3.7, 13.2 Hz), 4.42 (d, 1H, J = 12.1 Hz), 4.48 (d, 1H, J = 12.1 Hz), 4.87 (m, 1H), 7.19−7.28 (m, 5H); ^{13}C NMR (DMSO-d_6, 50 °C) δ 23.9, 25.5, 28.4, 32.5, 46.4, 50.9, 70.1, 75.3, 79.6, 126.8, 127.9, 128.7, 138.8, 154.2, 194.3; HRMS calcd for $C_{20}H_{28}NO_4Br$ (M^+) 425.1202, found 425.1204.

LASC-Catalyzed Mannich-Type Reaction in Water. General Procedure. To a solution of 0.030 mmol of LASC (Yb(III) dodecyl sulfate or Cu(II) dodecyl sulfate) in water (1.8 mL) were added an aldehyde (0.30 mmol), an aniline derivative (0.30 mmol), and a vinyl ether (0.45−0.90 mmol) at 0 °C. After the reaction mixture was stirred for 18 h, saturated aqueous $NaHCO_3$ was added to quench the reaction. The aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding β-amino ketone.

2-Methoxy-3-(*p*-methoxybenzyloxy)-1-propene (**15**) was prepared from allyl alcohol according to standard procedures (*p*-methoxybenzyl protection, bromomethoxylation, and elimination): IR (neat) 2939, 2841, 1667, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 3H), 3.79 (s, 3H), 3.92 (s, 2H), 4.10 (d, 1H, J = 12.2 Hz), 4.19 (d, 1H, J = 12.2 Hz), 4.48 (s, 2H), 6.87 (d, 1H, J = 8.4 Hz), 7.28 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3, 67.4, 70.2, 71.9, 83.4, 99.6, 129.5, 129.9, 159.2, 160.1; HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1104.

4-((2-Methoxyphenyl)amino)-4-phenyl-2-butanone: IR (neat) 3412, 2834, 1715, 1603, 1511, 1240, 1223 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.90 (dd, 1H, J = 6.0, 15.0 Hz), 2.96 (dd, 1H, J = 7.0, 15.0 Hz), 3.78−3.83 (m, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 4.87 (dd, 1H. J = 6.0, 7.0 Hz), 3.85 (s, 3H), 4.87 (dd, 1H, J = 6.0, 7.0 Hz), 6.42−7.39 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 30.6, 51.7, 54.1, 55.5, 109.5, 111.3, 117.0, 121.1, 126.3, 127.3, 128.7, 136.6, 142.7, 147.0, 206.7; HRMS calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1416, found 269.1404.

4-Cyclohexyl-4-((2-methoxyphenyl)amino)-2-butanone: IR (neat) 3413, 1716, 1602, 1253, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94−1.29 (m, 6H), 1.51−1.85 (m, 7H), 2.12 (s, 3H), 2.58 (m, 1H), 2.54−2.66 (m, 2H), 3.74−3.80 (m, 1H), 3.82 (s, 3H), 4.25 (br, 1H), 6.58−6.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.5, 29.2, 29.4, 30.6, 42.0, 46.0, 53.9, 55.4, 109.6, 110.1, 116.0, 121.3, 137.4, 146.7, 208.2; HRMS calcd for $C_{17}H_{25}NO_2$ (M^+) 275.1885, found 275.1866.

(*S*)-5-(Benzyloxy)-4-((2-methoxyphenyl)amino)-2-hexanone: IR (neat) 3411, 1711, 1602, 1248, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19−1.24 (m, 3H), 2.01−2.10 (s, 3H), 2.55−2.82 (m, 2H), 3.67−3.77 (m, 1H), 3.81 (s, 3H), 3.92−4.00 (m, 1H), 4.35−4.69 (m, 2H), 4.37−4.59 (br, 1H), 6.55−6.80 (m, 4H), 7.22−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.7, 16.8, 30.6, 30.8, 43.7, 44.7, 52.6, 54.1, 55.4, 70.7, 71.2, 74.5, 109.7, 109.9, 111.0, 116.3, 116.8, 121.3, 127.6, 127.7, 127.9, 128.3, 128.4, 136.9, 137.0, 138.6, 149.6, 208.3; HRMS calcd for $C_{20}H_{25}NO_3$ (M^+) 327.1834, found 327.1820.

1-(4-Methoxybenzyloxy)-4-((2-methoxyphenyl)amino)-4-phenyl-2-butanone: IR (neat) 3374, 1724, 1606, 1514, 1251, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08−1.35 (m, 3H), 2.63−2.79 (m, 2H), 3.64−3.73 (m, 1H), 3.77−3.83 (m, 6H), 3.89−3.95 (m, 2H), 4.06 (br, 1H), 4.40−4.41 (m, 2H), 4.44−4.73 (m, 3H), 6.65−7.35 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 14.2, 15.7, 16.9, 39.4, 40.5, 52.7, 54.3, 55.2, 55.4, 60.4, 70.7, 71.2, 72.8, 72.9, 74.8, 75.1, 109.7, 109.8, 110.1, 111.2, 113.7, 113.8, 116.4, 116.9, 121.3, 127.6, 127.7, 127.8, 128.3, 128.4, 129.3, 129.4, 129.6, 136.8, 137.0, 138.5, 146.9, 159.4, 208.1, 208.2; HRMS calcd for $C_{25}H_{27}NO_4$ (M^+) 405.1940, found 405.1916.

(*S*)-5-(Benzyloxy)-1-((4-methoxybenzyl)oxy)-4-(2-methoxyphenyl)amino-2-hexanone: IR (neat) 3401, 1722, 1605, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.94 (dd, 1H, J = 6.0, 15.2 Hz),

3.14 (dd, 1H, J = 7.6, 15.2 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 3.91 (s, 2H), 4.41 (d, 1H. J = 11.6 Hz), 4.48 (d, 1H. J = 11.6 Hz) 4.40 (dd, 1H, J = 6.0, 7.6 Hz) 5.01 (br, 1H), 6.59−7.40 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 47.0, 54.0, 55.3, 55.5, 72.9, 75.1, 109.4, 111.4, 113.9, 117.0, 121.1, 126.3, 127.3, 128.5, 128.7, 129.0, 129.6, 142.5, 146.9, 159.5, 207.2; HRMS calcd for $C_{28}H_{33}NO_5$ (M^+) 463.2359, found 463.2352.

(*R*)-5-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)-1-((4-methoxybenzyl)oxy)-4-(2-methoxyphenyl)amino-2-octanone (16): IR (neat) 3411, 1713, 1601, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (m, 6H), 0.84−0.89 (m, 9H), 1.55−1.60 (m, 4H), 2.59−2.77 (m, 2H), 3.55 (m, 3H), 3.74−3.80 (m, 6H), 3.95 (s, 1H), 4.41−4.65 (m, 2H), 6.55−6.89 (m, 6H), 7.16−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.2, 25.9, 26.1, 27.3, 28.5, 29.1, 39.3, 40.4, 50.1, 52.2, 55.1, 55.2, 55.3, 62.8, 71.7, 72.5, 72.7, 72.8, 79.3, 80.2, 109.6, 109.7, 118.3, 121.0, 121.3, 127.5, 127.6, 128.0, 128.2, 128.3, 129.2, 129.5, 136.6, 136.7, 138.4, 146.8, 147.1, 159.3, 208.1; HRMS calcd for $C_{36}H_{51}NO_6Si$ (M^+) 621.3486, found 621.3485.

(2′*S*,3′*R*)-1-[2′-(3′-Benzyloxy)piperidino]-3-((4-methoxybenzyl)oxy)-2-propanone (17-*trans*) and (2′*R*,3′*R*)-1-[2′-(3′-Benzyloxy)piperidino]-3-((4-methoxybenzyl)oxy)-2-propanone (17-*cis*). To a THF solution (4.0 mL) of the Mannich base **16** (0.50 mmol) was added 48% aqueous HF. After the reaction was completed, the reaction was quenched with saturated aqueous $NaHCO_3$, and the organic layer was extracted with dichloromethane. The pure alcohol was obtained by column chromatography on silica gel in quantitative yield. The alcohol (0.50 mmol) was dissolved in dichloromethane (1.5 mL), and to this solution were added tetrabromomethane (1.0 mmol) and triphenylphosphine (1.0 mmol) in dichloromethane (2.0 mL) successively. After a few minutes, water and dichloromethane were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The each diastereomer of the pure *N*-protected piperidine derivative was obtained after column chromatography on silica gel in 36% (cis) and 53% (trans) yield, respectively. **17-*trans*:** $[\alpha]_D^{25}$ −45.3 (c = 1.9, $CHCl_3$); IR (neat) 2937, 1724, 1612, 1514, 1499, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52−1.98 (m, 4H), 2.50 (m, 2H), 2.83 (m, 1H), 3.11 (m, 1H), 3.40 (br, 1H), 3.69 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.89 (m, 1H), 4.24 (m. 2H), 4.26 (d, 1H, J = 11.5 Hz), 4.29 (d, 1H, J = 11.5 Hz), 4.62 (m, 1H), 6.80−7.35 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 22.4, 27.0, 31.9, 38.8, 44.1, 49.5, 55.3, 56.5, 70.3, 72.8, 74.7, 111.6, 113.8, 120.7, 123.2, 124.2, 127.3, 127.7, 128.3, 129.5, 138.9, 139.8, 152.5, 154.2, 159.4, 207.2; HRMS calcd for $C_{30}H_{35}NO_5$ (M^+) 489.2515, found 489.2508. **17-*cis*:** $[\alpha]_D^{25}$ +59.2 (c = 1.6, $CHCl_3$); IR (neat) 2936, 1725, 1612, 1513, 1455, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48−1.94 (m, 6H), 2.25−2.32 (m, 1H), 2.75−2.83 (m, 1H), 2.87−3.03 (m, 2H), 3.70−3.88 (m, 1H), 3.79 (s, 3H), 3.90 (s, 3H), 4.28 (m. 2H), 4.47 (d, 1H, J = 11.9 Hz), 4.57 (d, 1H, J = 11.9 Hz), 4.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0, 25.6, 31.8, 44.1, 55.0, 55.3, 55.6, 70.4, 72.7, 75.0, 75.9, 111.7, 113.8, 120.2, 123.1, 127.5, 127.9, 128.3, 129.5, 129.6, 138.6, 139.7, 152.4, 159.3, 207.6; HRMS calcd for $C_{30}H_{35}NO_5$ (M^+) 489.2515, found 489.2513.

(2′*S*,3′*R*)-1-[2′-(3′-Benzyloxy)piperidino]-3-hydroxy-2-propanone (18-*trans*) and (2′*R*,3′*R*)-1-[2′-(3′-Benzyloxy)-piperidino]-3-hydroxy-2-propanone (18-*cis*). To a solution of **17-*trans*** (0.20 mmol) in 4.0 mL of aqueous acetonitrile (4:1 acetonitrile/water) was added cerium(IV) ammonium nitrate (1.4 mmol) at 0 °C. After the solution was stirred for 4 h, water and ethyl acetate were added, and the aqueous layer was basified with potassium carbonate. The insoluble materials were filtered through a Cerite pad, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (1:10 methanol/chloroform as an elutant) to afford ***18-trans*** in 73% yield: $[\alpha]_D^{26}$ −41.4 (c = 0.8, $CHCl_3$); IR (neat) 3413, 2934, 1719, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20−1.77 (m, 4H), 2.24−2.63 (m, 2H), 2.88−2.98 (m, 2H), 3.14 (br, 1H), 3.90 (s, 1H), 4.06−4.23 (m, 2H), 4.11−4.18 (m, 2H), 4.36 (d, 1H, J = 11.7 Hz), 4.63 (d, 1H, J = 11.7 Hz), 7.23−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.1, 29.8, 41.4, 45.8, 57.6, 68.5, 70.4, 78.3, 112.5, 127.8, 128.5, 138.2, 209.7; HRMS calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1542.

Similarly, **18-*cis*** was prepared from **17-*cis*** in 58% yield: $[\alpha]_D^{27}$ −21.5 (c = 0.7, $CHCl_3$); IR (neat) 3399, 2926, 1721, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25−1.79 (m, 4H), 2.02 (s, 1H), 2.17−2.48 (m, 4H), 2.58−2.67 (m, 1H), 2.96−3.13 (m, 3H), 4.12−4.25 (m, 1H), 4.38 (d, 1H, J = 11.5 Hz), 4.64 (d, 1H, J = 11.5 Hz), 7.23−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.1, 29.8, 41.4, 45.8, 87.6, 68.7, 70.4, 78.4, 112.5, 127.8, 128.5, 138.2, 209.6; HRMS calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1525.

(2′*S*,3′*R*)-1-[2′-(3′-(Benzyloxy)-1′-(*tert*-butoxycarbonyl)-piperidino)]-3-bromo-2-propanone (14-*trans*) and (2′*R*,3′*R*)-1-[2′-(3′-(Benzyloxy)-1′-(*tert*-butoxycarbonyl)piperidino)]-3-bromo-2-propanone (14-*cis*). 18-*trans* (0.26 mmol) was treated with $(Boc)_2O$ in dichloromethane at 0 °C for 3 h. After the usual workup, the *N*-Boc piperidine derivative was obtained in 78% yield. The *N*-Boc piperidine derivative (0.20 mmol) was dissolved in dichloromethane (0.50 mL), and to this solution were added tetrabromomethane (0.40 mmol) and triphenylphosphine (0.40 mmol) in dichloromethane (2.0 mL) successively. After a few minutes, water and dichloromethane were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The pure α-bromo ketone (**14-*trans***) was obtained after column chromatography on silica gel in 79% yield.

Similarly, **14-*cis*** was prepared from **18-*cis*** (58%, 76% yields, respectively).

N*-,*O*-Protected febrifugine (19-*trans*, 19-*cis*).** To an ethanol solution (0.50 mL) of **14-*trans (0.15 mmol) were added an ethanol solution (0.10 mL) of 4-hydroxyquinazoline (0.15 mmol) and potassium hydroxide (0.15 mmol) at room temperature. The reaction mixture was stirred for 2 h and was quenched with saturated aqueous NH_4Cl. After the usual workup, the crude product was purified by column chromatography on silica gel (1:19 methanol/chloroform as an elutant) to afford **19-*trans*** in 79% yield: $[\alpha]_D^{27}$ +38.7 (c = 0.3, $CHCl_3$); IR (neat) 2930, 1732, 1681, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39−1.48 (m, 1H), 1.45 (s, 9H), 1.57−1.72 (m, 1H), 1.87−1.95 (m, 2H), 2.72 (dd, 1H, J = 5.5, 14.3 Hz), 2.84 (dd, 1H, J = 4.6, 14.2 Hz), 2.90 (br s, 1H), 3.49 (s, 1H), 3.98 (br s, 1H), 4.53 (d, 1H, J = 12.2 Hz), 4.68 (d, 1H, J = 12.2 Hz), 4.94 (br s, 1H), 4.98 (t, J = 6.7 Hz), 7.25−7.36 (m, 5H), 7.50 (dd, 1H, J = 1.5, 7.5 Hz), 7.73−7.79 (m, 2H), 7.93 (s, 1H), 8.26−8.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.4, 24.5, 28.4, 41.0, 50.1, 53.8, 60.3, 70.3, 73.9, 80.2, 121.9, 126.7, 127.3, 127.5, 127.5, 127.6, 128.3, 134.4., 138.4, 146.6, 148.3, 155.7, 160.9, 200.0; HRMS calcd for $C_{28}H_{33}N_3O_5$ (M^+) 491.2420, found 491.2413.

Similarly, **19-*cis*** was prepared from **14-*cis*** in 76% yield: $[\alpha]_D^{27}$ −37.6 (c = 1.2, $CHCl_3$); IR (neat) 2934, 1732, 1680, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6, 50 °C) δ 1.35−1.52 (m, 3H), 1.42 (s, 9H), 1.54−1.59 (m, 1H), 1.70 (d, 1H, J = 13.4 Hz), 1.89−1.93 (m, 1H), 3.07 (dd, 1H, J = 5.5, 15.8 Hz), 3.47−3.50 (m, 1H), 3.82 (d, 1H, J = 11.9 Hz), 4.54−4.58 (m, 2H), 5.03−5.05 (m, 3H), 7.34−7.41 (m, 5H), 7.62 (dd, 1H, J = 1.2, 7.6 Hz), 7.75 (d, 1H, J = 8.2 Hz), 7.90 (dd, 1H, J = 1.5, 7.8 Hz), 8.03 (s 1H), 8.19 (dd, 1H, J = 1.5, 7.8 Hz); ^{13}C NMR (DMSO-d_6, 50 °C) δ 23.99, 24.03, 25.4, 28.4, 36.2, 36.3, 54.6, 70.0, 75.2, 79.7, 121.8, 126.5, 127.7, 127.9, 128.7, 135.0, 138.8, 148.3, 148.4, 154.6, 160.4, 202.1; HRMS calcd for $C_{28}H_{33}N_3O_5$ (M^+) 491.2420, found 491.2406.

Febrifugine (1). 19-*trans* (0.026 mmol) was treated with 6 N HCl (1.0 mL), and the resulting mixture was heated under reflux for 35 min. Aqueous Na_2CO_3 (20%) was added carefully until the pH of the media changed to 9. The resulting mixture was extracted with chloroform and dried over Na_2SO_4 and Na_2CO_3. The crude product was purified by column chromatography (silica gel) to afford febrifugine quantitaively: Mp 138−140 °C (lit. mp 139−140,[1b] 137−138,[2a] 139−141 °C[2b]); $[\alpha]_D^{25}$ −28.0 (c = 0.1, EtOH) (lit.[1b] $[\alpha]^{25}{}_D$ +28 (c = 0.5, EtOH)); IR (KBr) 2929, 2853, 1725, 1678, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30−1.38 (m, 1H), 1.48−1.57 (m, 1H), 1.72−1.74 (m, 1H), 2.07−2.10 (m, 1H), 2.58 (dt, 1H, J = 2.4, 12.2 Hz), 2.65 (dd, 1H, J = 7.3, 15.8 Hz), 2.88 (dd, 1H, J = 4.6, 7.7 Hz), 2.97 (d, 1H, J = 12.2 Hz), 3.12 (dd, 1H, J = 4.8, 15.8 Hz), 3.29 (m, 1H), 4.83 (d, 1H, J = 17.4 Hz), 4.89 (d, 1H, J = 17.4 Hz), 7.51

(dt, 1H, J = 1.2, 8.1 Hz), 7.73 (d, 1H, J = 7.6 Hz), 7.78 (dt, 1H, J = 1.2, 8.1 Hz), 7.90 (s, 1H), 8.28 (dd, 1H, J = 0.9, 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 25.6, 35.4, 44.0, 45.9, 54.8, 60.1, 72.2, 121.9, 126.8, 127.4, 127.6, 134.5, 146.3, 148.2, 161.0, 202.6; HRMS calcd for $C_{16}H_{19}N_3O_3$ (M^+) 301.1426, found 301.1422. **1′:** $[\alpha]_D^{27}$ +26.6 (c = 0.1, EtOH)

Isofebrifugine was also obtained from **19-*cis*** by the same procedure in 46% yield. **Isofebrifugine (2):** $[\alpha]_D^{26}$ −115.6 (c = 0.2, $CHCl_3$) (lit.[1b] $[\alpha]^{25}_D$ +131 (c = 0.35, $CHCl_3$)); IR (neat) 2923, 2853, 1670, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44−1.51 (m, 2H), 1.74−1.82 (m, 1H), 1.80 (d, 1H, J = 13.2 Hz), 1.99−2.08 (m, 1H), 2.01 (d, 1H, J = 13.2 Hz), 2.46 (dt, 1H, J = 1.7, 11.8 Hz), 2.92 (dd, 1H, J = 2.7, 11.2 Hz), 3.22 (t, 1H, J = 3.3 Hz), 3.81 (d, 1H, J = 2.9 Hz), 4.08 (d, 1H, J = 13.9 Hz), 4.40 (d, 1H, J = 13.9 Hz), 7.41−7.45 (m, 1H), 7.63−7.72 (m, 2H), 8.23−8.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.1, 26.8, 43.3, 44.5, 49.8, 55.7, 77.2, 105.4, 121.9, 126.9, 127.1, 127.5, 134.3, 148.0, 148.2, 161.4; HRMS calcd for $C_{16}H_{19}N_3O_3$ (M^+) 301.1426, found 301.1418. **2′:** $[\alpha]_D^{25}$ +129.3 (c = 0.2, $CHCl_3$)

Antimalarial Assay: In vitro Antimalarial Activity of Febrifugine, Isofebrifugine, and Their Enantiomers: The following procedures were used for assay of antimalarial activity.[31] Various concentrations of compounds in ethanol were prepared. A 5 μL amount of each solution was added to individual wells of a multidish 24 wells arrangement. 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 a compound, we prepared thin blood films from each culture and stained them with Giemsa (E. Merck, Darmstadt, Germany). A total of 10 000 erythrocytes per one thin blood film were examined by 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. 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.

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 5×10^4 cells/mL. A cell suspension of 995 μL was dispensed to the test plate, and compounds at various concentrations suspended in ethanol (5.0 μL) were added to individual wells of a multidish 24 well arrangement. The plates were incubated at 37 °C in 5% CO_2 atmosphere for 48 h. All the test compounds were assayed in duplicate at each concentration. Cell numbers were measured using a microcell counter CC-130 (Toa Medical Electric Co., Kobe, 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% control.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

JO990877K

(31) Kim, H.-S., Miyake, H.; Arai, M.; Wataya, Y. *Parasitol. Int.* **1998**, *47*, 59.