

Concise Synthesis of *dl*-Febrifugine

Yasuo TAKEUCHI,* Miyo OSHIGE, Kumiko AZUMA,
Hitoshi ABE, and Takashi HARAYAMA*

Faculty of Pharmaceutical Sciences, Okayama University; 1-1-1
Tsushima-naka, Okayama 700-8530, Japan.

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Racemic compound (1) of the antimalarial agents febrifugine (*d*-1) was synthesized using an stereoselective Michael reaction of an ω -amidoenone (5) which was prepared by the Wittig reaction of piperidinediol (7).

Key words total synthesis; stereoselective Michael reaction; Wittig reaction; febrifugine; antimalarial activity

Febrifugine (*d*-1) is an antimalarial agent that has been isolated from *Dichroa febrifuga* and *Hydrangea umbellata* along with isofebrifugine (*d*-2).^{1–4)} It is well known that *d*-1 and *d*-2 are related to each other's isomerization via ω -amidoenone^{5,6)} (3) (Chart 1).

Among reported methods^{7–20)} of *d*-1, we had believed that our method^{10,13)} was widely applicable to the synthesis of the derivatives needed to study the structure–activity relationship of *d*-1. However, we could not successfully prepare some derivatives because our method involved uncontrollable *trans*–*cis* isomerization in the final step. In recent our study, we found that *cis* form of *N*-protected febrifugine derivatives (*cis*-4) also afforded a mixture of *trans*-4 and *cis*-4 form under the presence of acid by the isomerization (Chart 2).²¹⁾

From those findings, we planned a synthetic strategy via an ω -amidoenone (5) as a key intermediate, which would afford *trans* piperidine derivative (*trans*-6) by the intramolecular Michael reaction with the stereoselectivity (Chart 3). In this paper, we describe a novel synthesis of *dl*-febrifugine (*dl*-1).

The synthesis of the key intermediate, ω -amidoenone (5), was achieved to utilize the Wittig reaction of 2-hydroxy-piperidine derivative which we have developed in our synthetic study of deoxyfebrifugine.²²⁾ The Wittig reaction of 2,3-piperidinediol (7), which was easily prepared in 84% yield from tetrahydropyridine (8) by Oxone®-acetone oxidation,²³⁾ afforded (*E*)- ω -amidoenone (*E*-5) in which the double bond had *E* configuration based on the coupling constant (*J* = 16 Hz) of olefinic protons in ¹H-NMR. The Michael reaction of *trans*-5 (*E*-5) with BF₃·OEt₂ afforded the Michael adduct (*trans*-6). *N*-Cbz febrifugine (10) was afforded by successive reactions, silylation of the hydroxy and ketone group, bromination, and coupling with 4(3*H*)-quinazolinone. Hydrogenolysis of 10 gave *dl*-1 which was identical with the reported one by mp or ¹H-NMR data (Chart 4).

In the Michael reaction of *E*-5 with BF₃·OEt₂, we could obtain the furan derivative (9) and 1,4-diketone derivative (11) along with *trans*-6. It is known that 9 and 11 can be transformed from *cis*-6 by acid.²⁴⁾ Decreasing yield of *trans*-6 with the prolongation of the reaction time or heat of reaction mixture suggests that there is an equilibrium relationship via *E*-5 between *trans*-6 and *cis*-6 in the presence of Lewis acid (Table 1).

Herein, we could develop the the synthetic method for *dl*-febrifugine derivatives in high total yield and short steps

without using the very expensive, toxic, or dangerous reagents used in other reports.^{25–30)} We are now progress the asymmetric synthesis using this method.

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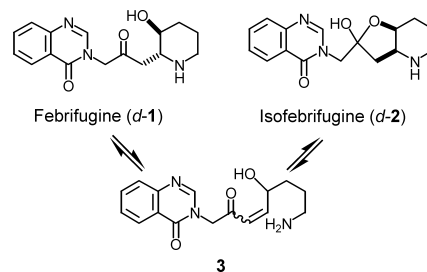


Chart 1

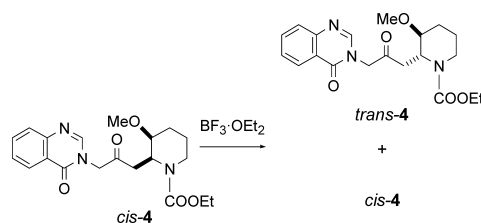


Chart 2

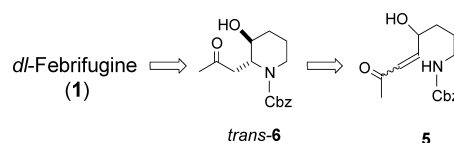
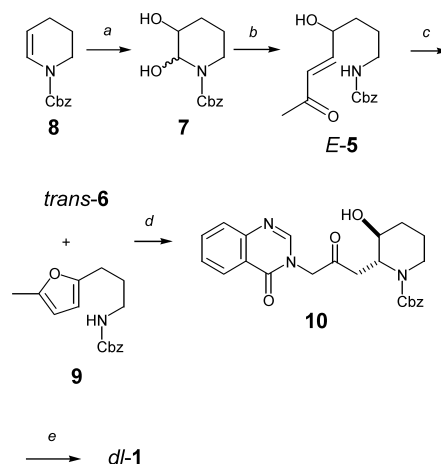


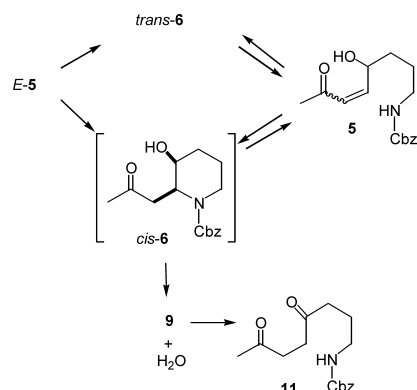
Chart 3



Reagents and Conditions; (a) Oxone®, K₂CO₃, acetone, H₂O, rt, 2 h, 84%; (b) CH₃COCH=PPh₃, MeCN, reflux, 1 h, 76%; (c) BF₃·OEt₂ (0.5 eq.), MeCN, rt, 10 min, 75%; (d) (i) TMSOTf, *i*-Pr₂NEt, CH₂Cl₂, rt, 20 min; (ii) NBS, rt, 2 h; (iii) 4(3*H*)-quinazolinone, rt, 4.5 h, 51%; (e) H₂, 20% Pd(OH)₂/C, MeOH/THF, rt, 3.5 h, 88%.

Chart 4

* To whom correspondence should be addressed. e-mail: take@pharm.okayama-u.ac.jp

Table 1. Reaction of *E*-5 with BF₃·OEt₂

Entry	Temp. (°C)	Reaction time	Yield (%)		
			<i>trans</i> -6	9	11
1	r.t.	10 min	75	11	—
2	r.t.	30 min	72	18	—
3	r.t.	1 h	73	14	3
4	70	10 min	50	35	12
5	70	1 h	23	32	27
6	70	2 h	14	21	30
7	100	10 min	33	32	21
8	100	30 min	28	38	17
9	100	1 h	12	32	9

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