Concise Synthesis of *dl*-Febrifugine

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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 umbellate* 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*-aminoenone[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 planed 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-hydroxypiperidine 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 ^{1}H-NMR. The Michael reaction of *trans*-**5** (*E*-**5**) with $BF_3\cdot OEt_2$ 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 ^{1}H-NMR data (Chart 4).

In the Michael reaction of *E*-**5** with $BF_3\cdot OEt_2$, 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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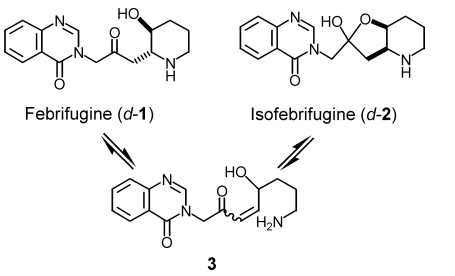


Chart 1

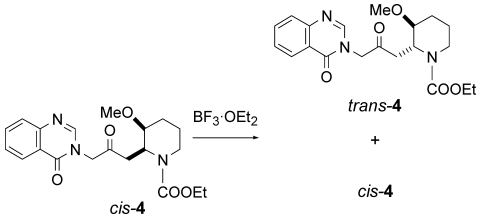


Chart 2

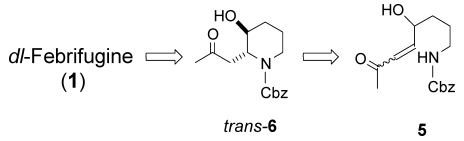
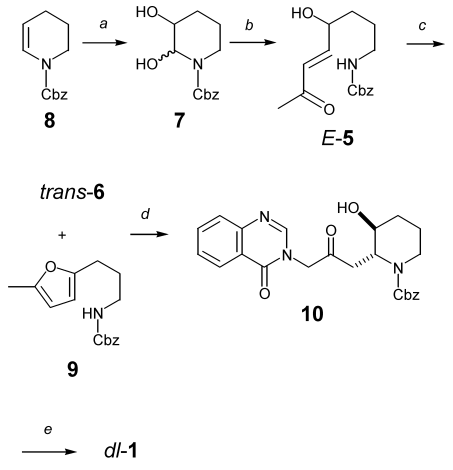


Chart 3



Reagents and Conditions; (a) Oxone®, K_2CO_3, acetone, H_2O, rt, 2 h, 84%; (b) $CH_3COCH{=}PPh_3$, MeCN, reflux, 1 h, 76%; *c*) $BF_3{\bullet}OEt_2$ (0.5 eq.), MeCN,rt, 10 min, 75%; (d) (i) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, rt, 20 min; (ii) NBS, rt, 2 h; (iii) 4(3*H*)-quinazolinone,rt, 4.5 h, 51%; (e) H_2, 20% $Pd(OH)_2$/C, MeOH/THF,rt, 3.5 h, 88%.

Chart 4

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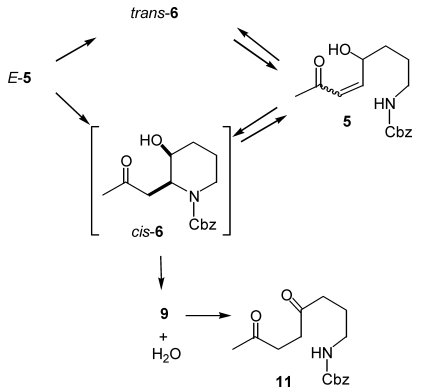
Table 1. Reaction of *E*-**5** with BF_3OEt_2



Entry	Temp. (°C)	Reaction time	Yield (%)		
			trans-**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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