# Total Synthesis of *dl*-Febrifugine and *dl*-Isofebrifugine

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**Racemic compounds (1 and 2) of the antimalarial agents febrifugine (*d*-1) and isofebrifugine (*d*-2) were synthesized using an unusual Claisen rearrangement of allyl enol ether (7) and the stereoselective reduction of 2-allyl-3-piperidone (8). This method is widely applicable to the synthesis of derivatives needed to study the structure–activity relationship of febrifugine.**

**Key words** total synthesis; Claisen rearrangement; stereoselective reduction; febrifugine; antimalarial activity

Febrifugine (*d*-**1**) is antimalarial agent that was isolated from *Dichroa febrifuga* and *Hydrangea umbellata* with isofebrifugine (*d*-**2**).[1a,b] Errors[2a—d] in the determined structures of *d*-**1** and *d*-**2** have caused much confusion in the study of the relationship between the structure and antimalarial activity of febrifugine derivatives. Recently, Kobayashi *et al*. corrected the absolute structures of *d*-**1** and *d*-**2** by achieving the asymmetrical synthesis of all stereoisomers (Fig. 1).[3] Now the definitive study of the structure–activity relationship of febrifugine derivatives can begin. In this paper, we describe a novel synthesis of *dl*-febrifugine (**1**)[4a—d] and *dl*-isofebrifugine (**2**).

In our planned synthesis leading to **1** and **2**, the key intermediate (**3**) has an allyl group as the required 3-carbon unit on **1** or **2** and a benzyloxycarbonyl (Z) group as a protecting group. The intermediate (**3**) was successfully prepared with complete stereoselectivity (Chart 1). From 3-hydroxypyridine (**4**), the 3-allyl-*N*-benzyl derivative (**6**) was synthesized *via* pyridinium chloride (**5**) by improving the reported method.[5] To maintain the stability of the intermediates in the later reactions, the benzyl group was replaced[6] with a Z group by treating **6** with benzyl chloroformate (Z-Cl) to give **7**. The unusual Claisen rearrangement of **7** afforded the 3-piperidone derivative (**8**) with the allyl group at the 2 position. This convenient result shows that the isomerization[7] of the double bond on the piperidine ring of **7** proceeds before the migration[8] of the allyl group in the presence of a Lewis acid. TLC and HPLC data showed that the reduction of **8** gave **3** as the sole product without involving the diastereomeric isomer.

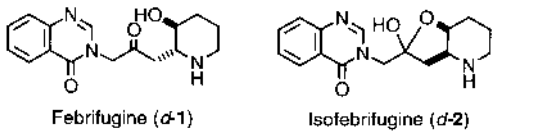
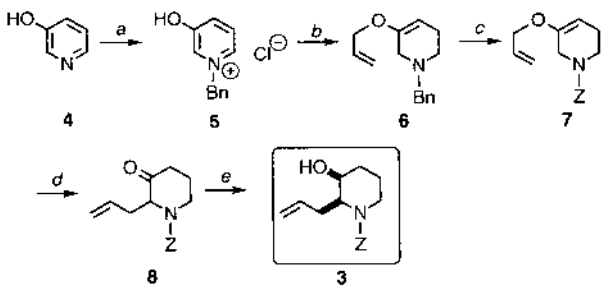



Fig. 1. Revised Structures of Febrifugine and Isofebrifugine




*a*) Benzyl chloride, toluene, reflux, 1 h, 94%; *b*) i) allyl bromide, NaH, MeOH, reflux, 4 h; ii) $NaBH_4$, MeOH, 0°C, 0.5 h, 60%; *c*) benzyl chloroformate, dry THF, r.t., 1 h, 93%; *d*) $BF_3$•$OEt_2$, dry MeCN, r.t., 1.5 h, 74%; *e*) $NaBH_4$, MeOH, 0°C, 0.5 h, 97%.

Chart 1

The configuration of **3** was predicted from a semiempirical molecular orbital calculation using **8** (Fig. 2). The PM3 molecular orbital calculation[9a,b] indicated two stable conformers (**8a**, **b**). The former, **8a**, is the minimized conformer with an allyl group in the axial position, while the latter, **8b**, is the optimized conformer with an allyl group in the equatorial position. The significant energy difference (about 4 kcal/mol) between the heats of formation of **8a** and **8b** showed that **8** exists almost entirely as **8a**. We think that hydride attack of the carbonyl group of **8a** occurs from the axial direction under the control of chelation or torsional strain.

**1** and **2** were successfully prepared from **3** *via* the cyclic intermediate **9** (Chart 2). The bromoetherfication of **3** using *N*-bromosuccinimide (NBS) afforded octahydrofuro[3,2-*b*]pyridine (**9**), which HPLC data indicated was a 3 : 1 mixture of the diastereomeric isomers, although we could not determine the configuration of the major or minor products. The successive dehydrobromination, bromohydration, and condensation to quinazolinone gave Z-protected *dl*-isofebrifugine (**10**). **2** was synthesized by the hydrogenolysis of **10** and **1** was synthesized by the isomerization[10] of **2**. The $^1$H- and $^{13}$C-NMR data for **1** and **2** agreed with reported values.[11]

We were able to prepare febrifugine derivatives in high

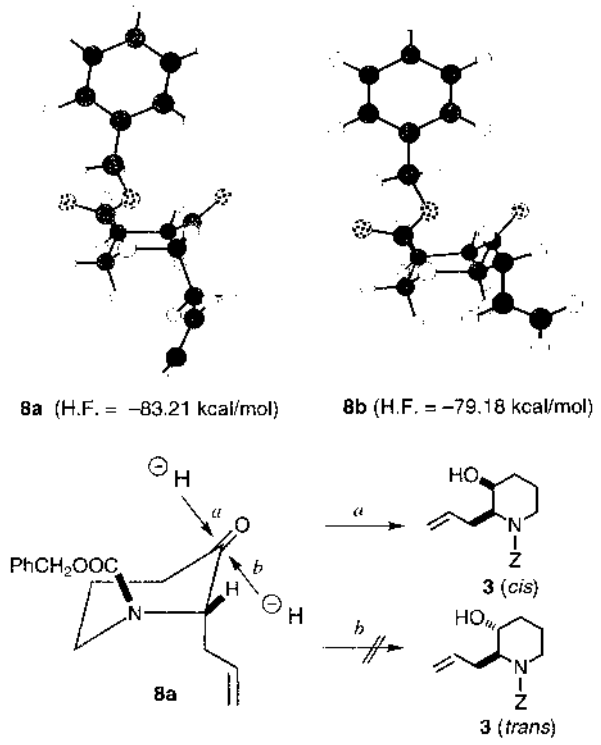



Fig. 2. Stable Conformers of **8**

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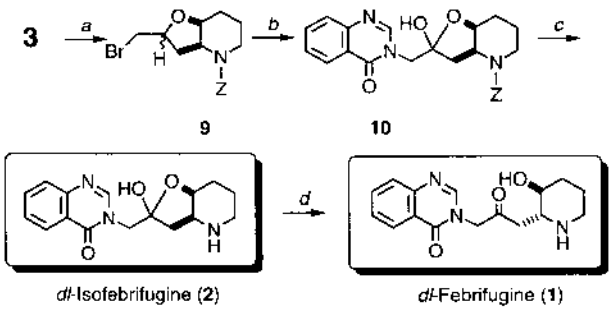


*a*) NBS, dry MeCN, r.t., 0.5 h, 85%; *b*) i) *t*-BuOK, dry THF, reflux, 1h; ii) NBS, $H_2O$, MeCN, r.t., 0.5 h; iii) 4(3*H*)-quinazolinone, $K_2CO_3$, DMF, r.t., 1 h, 40%; *c*) $H_2$, 20%-$Pd(OH)_2$/C, MeOH, r.t., 7 h, 56%[12]; *d*) EtOH, reflux, 2 h, 70%[13]

Chart 2

total yield without using the very expensive, toxic, or dangerous reagents used in other reports.[4a—d] Although it is unreasonable to compare an asymmetric synthetic method with a racemic one directly, our method has higher diastereoselectivity than the reported method.[3] We think that our method is widely applicable to the synthesis of the derivatives needed to study the structure–activity relationship of febrifugine.

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12) *dl*-Isofebrifugine: Colorless plates (AcOEt), mp 134—135 °C; dihydrochloride: mp 171—175 °C (dec.). *Anal*. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.35; N, 13.94. Found: C, 63.67; H, 6.41; N, 13.72. $^{13}$C-NMR (125 MHz, $CDCl_3$) (values in parentheses are reported ones[11]) $\delta$: 19.99 (20.1), 26.71 (26.8), 43.24 (43.4), 44.46 (44.6), 49.77 (50.0), 55.62 (55.8), 77.25 (77.0), 105.38 (105.6), 121.82 (122.1), 126.79 (127.1), 127.42 (127.3), 128.26 (127.7), 134.24 (134.6), 147.97 (148.3), 148.14 (148.5), 161.37 (161.8).
13) *dl*-Febrifugine: Colorless plates (EtOH), mp 188—190 °C (lit.[4b] 133—134 °C); dihydrochloride mp 202—204 °C (dec.) (lit.[4a] 204 °C [dec.]). *Anal*. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.35; N, 13.94. Found: C, 63.58; H, 6.49; N, 13.95. $^{13}$C-NMR (50 MHz, $CDCl_3$) (values in parentheses are reported ones[11]) $\delta$: 25.83 (25.6), 34.26 (34.5), 43.75 (44.0), 45.62 (46.0), 54.70 (55.0), 60.12 (60.2), 70.76 (72.3), 121.39 (122.1), 126.06 (127.0), 127.18 (127.7), 127.26 (127.8), 134.52 (134.8), 148.00 (146.7), 148.11 (148.5), 159.99 (161.3), 203.90 (203.1).