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Asymmetric synthesis of febrifugine and isofebrifugine using yeast reduction

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The antimalarial agents febrifugine ((+)-1) and isofebrifugine ((+)-2) were asymmetrically synthesized from chiral piperidin-3-ol ((+)-4), which was prepared by the reductive dynamic optical resolution of the 3-piperidone derivatives ((±)-3) using baker's yeast.

Febrifugine ((+)-**1**) is an antimalarial agent that was isolated from *Dichroa febrifuga* and *Hydrangea umbellata* along with isofebrifugine ((+)-**2**).[1a–c] The plane structure[2a] of (+)-**1** and (+)-**2** was first proposed in 1950. Subsequently, the relative[2b] and absolute[2c] structures were proposed on the basis of Baker's synthetic work.[3a–c] The relative configuration[2d] of (+)-**1** was corrected in 1973 and then the absolute structures[2e,f] of (+)-**1** and (+)-**2** were corrected in 1999 (Fig. 1). We previously synthesized the racemates of (+)-**1** and (+)-**2** *via* the unusual Claisen rearrangement and highly diastereoselective reduction.[4a,b] In this paper, we describe the asymmetric synthesis of (+)-**1** and (+)-**2** based on our synthetic method.

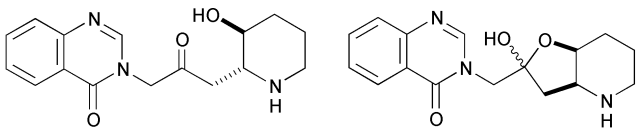
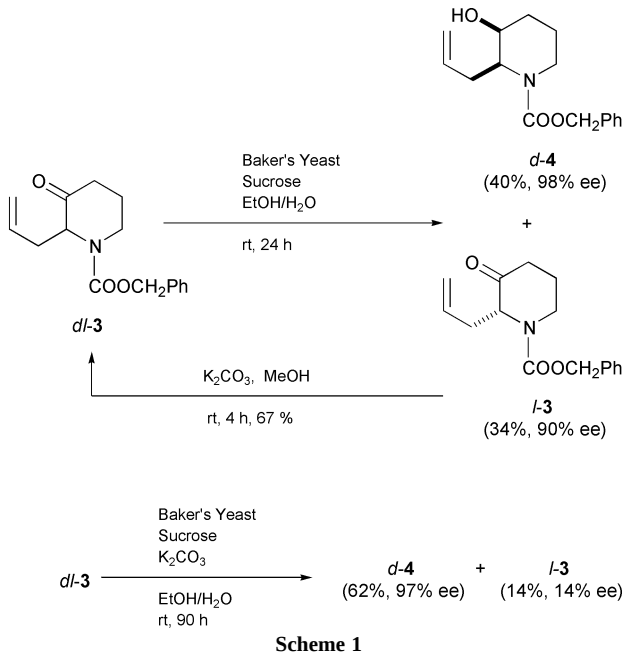


Fig. 1 Structures of febrifugine and isofebrifugine

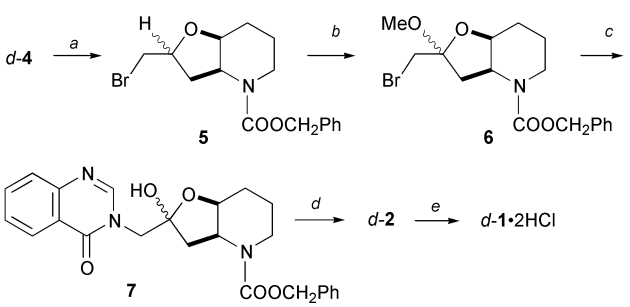
As a key asymmetric reaction, we selected the yeast reduction of 3-piperidone derivatives ((±)-**3**)[4a,b] protected by a benzyloxycarbonyl (*Z*) group (Scheme 1). The reaction of (±)-**3** with baker's yeast and sucrose in EtOH and water at rt for 24 h afforded chiral piperidin-3-ol ((±)-**4**), for which the ^{1}H-NMR data agreed with reported values[4b] for (±)**4**, in high yield (40%) and enantiomeric purity (98% ee).[5] The remaining piperidone ((−)-**3**, 34%) also had high enantiomeric purity (90% ee). Since epimerization of (−)-**3** with K_2CO_3 for 4 h gave (±)-**3** in 67% yield, we could be sure of the possibility of reductive dynamic optical resolution. Epimerization that maintained the reductive activity of the yeast was examined under a variety of concentrations of K_2CO_3 and EtOH in water. Stirring a mixture of (±)-**3**, baker's yeast, sucrose, and K_2CO_3 in EtOH and water at rt for 90 h afforded (+)-**4** in 62% yield (97% ee) along with (−)-**3** in 14% yield (14% ee).[6]



Scheme 1

Isofebrifugine ((+)-**2**) was prepared by improving our previous method (Scheme 2). The intramolecular bromoetherification of (+)-**4** using NBS afforded octahydrofuro[3,2-*b*]-pyridine (**5**) in 87% yield. The HPLC data indicated that this was a 3:1 mixture of the diastereomeric isomers. To improve the yield and reproductivity of preparing *Z*-protected isofebrifugine (**7**) from **5**, we designed a 2-methoxy derivative **6**. The new intermediate **6** could be prepared by a 2-step reaction in high yield (90%) as a 4 : 1 mixture of the diastereomeric isomers. The steps were dehydrobromination using potassium *tert*-butoxide and bromoetherification using NBS and MeOH. Deacetalization of **6** followed by a coupling reaction with 4(3*H*)-quinazolinone afforded **7** in 69% yield. The hydrogenolysis of **7** gave isofebrifugine ((+)-**2**) in 62% yield as a crystalline solid. The melting point,[1b] ^{1}H-NMR data,[7a,b] and optical rotation[1b] for (+)-**2** agreed with reported values for the natural product.[8] It was clear that the yeast reduction of (±)-**3** followed the Prelog rule[9] with high enantio- and diastereoselectivity to give (+)-**4** having the absolute configuration of 2*S*,3*S*.

In our previous method for synthesizing (±)-febrifugine ((±)-**1**), the large differences[4b] in the melting point and solubility of (±)-**1** and (±)-**2** played a convenient role for the isolation of (±)-**1**. However, we could not isolate pure (+)-**1** by refluxing (+)-**2** in EtOH. Although it is known that isomerization of the congeners of (+)-**2** run under the reversible Michael reactions,[7a,10] there are no reports of (+)-**2** itself. We examined the isomerization of (+)-**2** to (+)-**1** in various solvents, including toluene, DMF, pyridine, EtOH, water, and 10% HCl aq. Heating (+)-**2** at 80 °C for 30 min in water resulted in the largest ratio (2 : 1) of (+)-**1** to (+)-**2** among these solvents. On the other hand, the epimerization of (+)-**2** in 10% HCl aq. was not observed under the same conditions. Based on these results, we isolated pure (+)-**1**[11] as the hydrochloride salt and its physicochemical



Scheme 2 *Reagents and conditions*: *a*, NBS, MeCN, rt, 0.5 h, 87%; *b*, (i) ^{t}BuOK, THF, 0 °C, 0.5 h; (ii) NBS, MeOH, rt, 1 h, 90%; *c*, (i) H^+, MeCN, rt, 1 h; (ii) 4(3*H*)-quinazolinone, K_2CO_3, DMF, rt, 2 h, 69%; *d*, H_2, 20%-Pd(OH)$_2$/C, MeOH, rt, 3.5 h, 62%; *e*, (i) H_2O, 80 °C, 15 min; (ii) H^+, 73%.

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properties[1c] and spectral data[7a,b] were identical with those reported for the natural product.

We were able to prepare febrifugine ((+)-**1**) in 15.2% yield and 6 isolated steps from (±)-**3** without using compounds that were very expensive, toxic, or dangerous. 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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Notes and references

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5 **Yeast Reduction (Method A)**; A mixture of (±)-**3** (3.00 g), baker's yeast (30 g), and sucrose (30 g) in EtOH (30 ml) and water (300 ml) was stirred at rt for 24 h. AcOEt (900 ml) was added to the mixture and stirred at rt for 10 min. The AcOEt layer separated by centrifugation (×1000 *g*, 10 min) was dried, filtered, and concentrated. MeCN was added to the residue and the precipitates were filtered through a membrane filter (0.5 μm). The filtrate was concentrated and the residue was subjected to column chromatography (silica gel). The first eluant (AcOEt–hexane, 1:7) gave (−)-**3** (1.02 g, 90% ee based on HPLC with a chiral column) as a colorless oil, $[\alpha]_D^{29}$ −45.5 (*c* 1.00, EtOH). HPLC conditions: column, Chiralcel OJ (Daicel); column temperature, rt; eluant, hexane–IPA, 37:3; flow rate = 1.5 ml min^{-1}; wavelength, 254 nm; t_R = 8.54 and 11.17 min. The second eluant (AcOEt–hexane, 1:3) gave (+)-**4** (1.20 g, 98% ee based on HPLC with a chiral column) as a viscous colorless oil. HPLC conditions: column, Chiralcel OJ (Daicel); column temperature, rt; eluent, hexane–IPA, 37:3; flow rate = 1.5 ml min^{-1}; wavelength, 254 nm; t_R = 6.43 and 7.51 min.

6 **Yeast Reduction (Method B)**; A mixture of (±)-**3** (1.00 g), K_2CO_3 (1.00 g), baker's yeast (10 g), and sucrose (30 g) in EtOH (30 ml) and water (300 ml) was stirred at rt for 90 h. The reaction mixture was treated in the same way as described above. The eluant (AcOEt–hexane, 1:7) gave (−)-**3** (0.14 g, 14% ee based on HPLC with a chiral column) as a colorless oil. The second eluant (AcOEt–hexane, 1:3) gave (+)-**4** (0.62 g, 97% ee based on HPLC with a chiral column) as a viscous colorless oil, $[\alpha]_D^{24}$ +76.2 (*c* 1.00, EtOH).

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8 **Isofebrifugine**; mp 130–131 °C (lit.[1b] 129–130 °C). $[\alpha]_D^{22}$ +124.3 (*c* 0.50, $CHCl_3$) {lit.[1b] $[\alpha]_D^{25}$ +131 (*c* 0.35, $CHCl_3$)}. The ^1H NMR spectrum agreed with that reported in the literature.[7a,b]

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11 **Febrifugine dihydrochloride**; Isofebrifugine ((+)-**2**, 0.34 g) in water (10 ml) was heated at 80 °C for 15 min. To the mixture, 10% HCl aq. (2 ml) was added and the solvent was evaporated off. The residue was washed with hot EtOH to give almost pure febrifugine dihydrochloride ((+)-**1**•2HCl, 0.31 g, 73%), which was recrystallized from a mixture of EtOH and water (9:1), mp 218–219 °C (decomp.) (lit.[1c] 223–225 °C (decomp.)). $[\alpha]_D^{29}$ +13.3 (*c* 1.01, H_2O) {lit.[1c] $[\alpha]_D^{31}$ +12.8 (*c* 0.85, H_2O)}. The ^1H NMR spectrum of free base ((+)-**1**) agreed with that reported in the literature.[7a,b]