Synthesis of D/L-Febrifugine and D/L-Isofebrifugine

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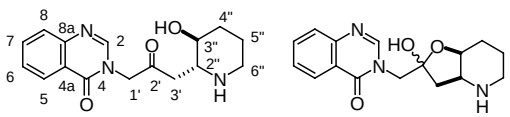
Abstract: Racemic compounds (**1** and **2**) of the antimalarial agents febrifugine (D-**1**) and isofebrifugine (D-**2**) were synthesized using an unusual Claisen rearrangement of allyl enol ether **6** and the stereoselective reduction of 2-allylpiperid-3-one **8**. This method is widely applicable to the synthesis of febirifugine derivatives.

Key words: Claisen rearrangement, stereoselective reduction, febrifugine, isofebrifugine, antimalarial agent

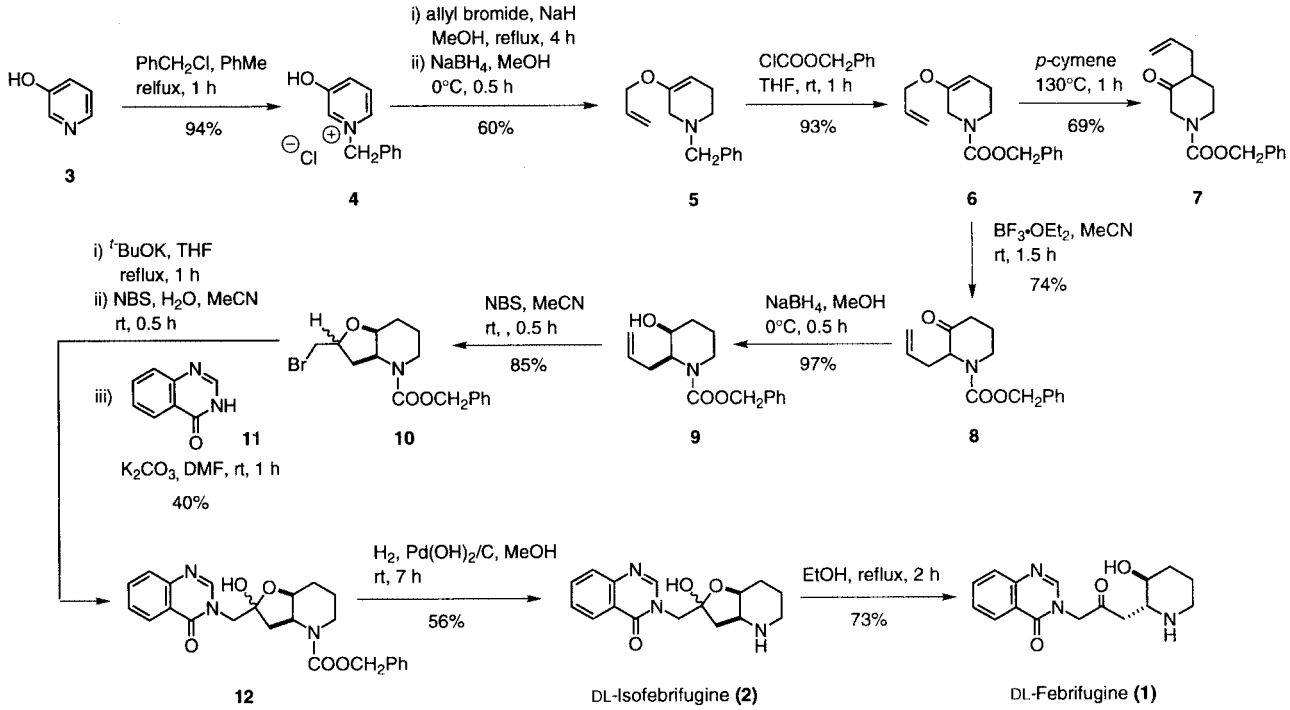
Febrifugine (D-**1**) is an antimalarial agent that was isolated from *Dichroa febrifuga* and *Hydrangea umbellata* along with isofebrifugine (D-**2**).[1a,b] After the first proposal of the plane structure of D-**1** and D-**2** in 1952,[2a] the relative[2b] and absolute[2c] structure were proposed on the basis of the Baker's synthetic work.[3a-c] However, relative configuration was corrected in 1972[2d] and then Kobayashi et al. corrected the absolute structures of D-**1** and D-**2** by achieving the asymmetrical synthesis of all stereoisomers in 1999[2e] (Figure 1). The overall synthetic yield of the racemate (**1**) of D-**1** in the reported methods[3a-d] is low and the synthetic method of the racemate (**2**) of D-**2** is not known. In this paper, we describe a novel and widely applicable synthetic method of **1**, **2**, and those derivatives.



Febrifugine (D-**1**) Isofebrifugine (D-**2**)

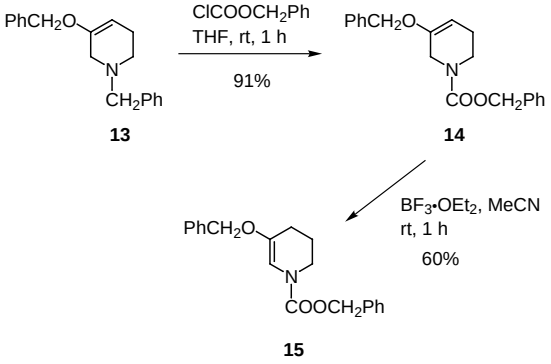
Figure 1

The key intermediate **8** was successfully prepared with complete stereoselectivity (Scheme 1). The *O*-allylation and reduction[4] of the pyridinium chloride **4**, which was prepared from 3-hydroxypyridine (**3**) and benzyl chloride in 94% yield, afforded 3-allyl-*N*-benzyl derivative **5** in 60% yield. The benzyl group was replaced[5] to a benzyloxycarbonyl *(Z)* group by treating **5** with benzyl chloroformate in tetrahydrofuran (THF) to give **6** in 93% yield.



Scheme 1

The Claisen rearrangement of **6** at 130 °C in cymene smoothly proceeded to give 4-allylpiperidin-3 one derivative **7** in 69% yield. On the other hand, in the presence of boron trifluoride-diethyl ether complex (BF_3·OEt_2) at room temperature, the unusual Claisen rearrangement of **6** afforded the piperidin-3-one derivative **8** with the allyl group at the 2 position in 74% yield. This convenient result shows that the isomerization[6] of the double bond on the piperidine ring of **6** proceeds before the migration[7] of the allyl group in the presence of a Lewis acid. The proof of the isomerization of the double bond was suppported by the result that $\Delta^{3,4}$ piperidine derivatives **14** prepared from *N*-benzyl derivative **13** gave $\Delta^{2,3}$ piperidine derivatives **15** in 60% yield under the same conditions as in the reaction of **6** (Scheme 2).



Scheme 2

Reduction of **8** with sodium borohydride ($NaBH_4$) at room temperature gave **9** in 97% yield as the sole product without involving the diastereomeric isomer. The PM3 calculation[8a,b] of **8** indicated two stable conformers (**8a**,**b**) based on the anti and gauche conformations between the Z and allyl groups (Figure 2). One is minimized conformer **8a** having the allyl group at the axial position and the other is optimized conformer **8b** having the allyl group at the equatorial position. The unexpected energy difference (about 4 kcal/mol) of heat of formation of **8a** and **8b** showed that **8** almost exists in the form of **8a** and that hydride attack toward carbonyl group of **8a** would occur from the axial direction under the control of the torsional strain to give **9**.

D/L-Febrifugine (**1**) and D/L-isofebrifugine (**2**) were successfully prepared from **9** via the cyclic intermediate **10**. The bromoetherfication of **8** using *N*-bromosuccinimide (NBS) afforded benzyl 2-(bromomethyl)hexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (**10**) in 85% yield, of which HPLC data indicated was a 3:1 mixture of the diastereomeric isomers, although we could not determine the configuration of products. The reaction of 3 successive steps, which is dehydrobromination using potassium *tert*-butoxide, bromohydration using NBS and water, and coupling reaction with quinazolinone (**11**), afforded *Z*-protected D/L-isofebrifugine (**12**) in 40% yield from **10**. The

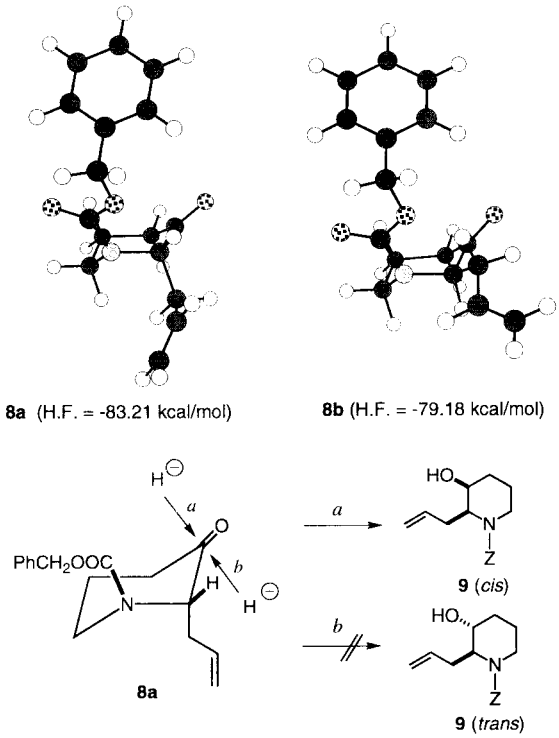


Figure 2

hydrogenolysis of **12** gave D/L-isofebrifugine (**2**) in 56%, which isomerized[9] to give D/L-febrifugine (**1**) in 70% yield. The ^1H and ^{13}C NMR data for **1** and **2** agreed with reported values[10] of D-**1** and D-**2**, respectively (Table).

We were able to prepare febrifugine derivatives in the highest overall yield (5.2% from **3**) without using the very expensive, toxic, or dangerous reagents used in other reports.[2a-d] We think that our method is widely applicable to the synthesis of the derivatives needed to study the structure-activity relationship of febrifugine.

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ^1H and ^{13}C NMR spectra were run on a Hitachi R-1500 or a Varian VXR-500 spectrometer. Analytical HPLC was performed on Chemcosorb 5Si-U (Chemco). Merck silica gel 60 (230–400 mesh) was employed for column chromatography. Extracts were dried using anhyd $MgSO_4$.

1-Benzyl-3-hydroxypyridinium Chloride

To a suspended solution of **1** (25.5 g, 26.8 mmol) in toluene (200 mL) (chloromethyl)benzene (31 mL, 26.9 mmol) was added. The mixture was heated at reflux for 1 h. The precipitates were filtered off and washed with EtOAc and Et_2O. Recrystallization of the residue from $CHCl_3$ gave **4** (55.6 g, 94%) as colorless needles, mp 159–160 °C.

IR (KBr): ν = 3380, 3020, 1580, 1500, 1320, 740 cm^{-1}.

^1H NMR (60 MHz, CD_3OD): δ = 5.79 (2 H, s), 7.49 (5 H, s), 7.80–8.10 (2 H, m), 8.40–8.70 (1 H, m), 8.57 (1 H, s).

Table ^{13}C- and ^{1}H NMR of Febrifugine (D-**1**, DL-**1**) and Isofebrifugine (D-**2**, DL-**2**)

Position[a]	Febrifugine				Isofebrifugine			
	^{13}C NMR		^{1}H NMR		^{13}C NMR		^{1}H NMR	
	D-**1**[b]	DL-**1**[c]	D-**1**[d]	DL-**1**[e]	D-**2**[b]	DL-**2**[f]	D-**2**[d]	DL-**2**[g]
2	146.7	148.0	7.93 (s)	8.20 (s)	148.5	148.1	8.31 (s)	8.29 (s)
4	161.3	160.0			161.8	161.4		
4a	122.1	121.4			122.1	121.8		
5	127.8	127.3	8.26 (dd)	8.14 (br d)	127.7	128.3	8.35 (ddd)	8.28 (br d)
6	127.7	127.2	7.50 (ddd)	7.57 (br t)	127.3	127.4	7.50 (ddd)	7.47 (br t)
7	134.8	134.5	7.77 (ddd)	7.86 (br t)	134.6	134.2	7.76 (ddd)	7.73 (br t)
8	127.0	126.1	7.72 (ddd)	7.71 (br d)	127.1	126.8	7.71 (ddd)	7.68 (br d)
8a	148.5	148.1			148.3	148.0		
1'	55.0	54.7	4.84 (d), 4.92 (d)	4.99 (d), 5.03 (d)	50.0	49.8	4.15 (d), 4.45 (d)	4.13 (d), 4.30 (d)
2'	203.1	203.9			105.6	105.4		
3'	46.0	45.6	2.63 (dd), 3.12 (dd)	2.75 (dt), 3.07 (br t)	44.6	43.2	1.88 (d), 2.08 (d)	1.86 (d), 2.03–2.12
2"	60.2	60.1	2.86 (ddd)	2.85 (br d)	55.8	55.6	3.30 (dd)	3.27 (br t)
3"	72.3	70.8	3.28 (ddd)	–	77.0	77.3	3.89 (ddd)	3.86 (br d)
4"	44.0	34.3	1.36 (ddt), 2.06 (ddd)	1.25–1.42, 1.91 (br d)	43.4	26.7	1.57 (ddd), 2.12 (ddd)	1.50–1.55, 2.03–2.12
5"	25.6	25.8	1.51 (dt), 1.72 (dt)	1.36-1.44, 1.61 (br t)	20.1	20.0	1.50 (m), 1.78 (m)	1.50–1.55, 1.78–1.82
6"	34.5	43.8	2.55 (dt), 2.95 (dd)	2.45 (dt), 3.02 (dd)	26.8	44.5	2.54 (dt), 3.00 (dd)	2.53 (br t), 2.97 (br d)

[a] See Figure 1
[b] $CDCl_3$, 75.5 MHz (Lit. 10)
[c] $CDCl_3$, 125 MHz
[d] $CDCl_3$, 300 MHz (Lit. 10)
[e] $CDCl_3$, 500 MHz
[f] DMSO-d_6, 125 MHz
[g] DMSO-d_6, 500 MHz

Anal. calcd for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.32. Found: C, 64.94; H, 5.51, N, 6.36.

5-(Allyloxy)-1-benzyl-1,2,3,6-tetrahydropyridine (5)

To a solution of **4** (22.17 g, 0.10 mol) and allyl bromide (9.6 mL, 0.11 mol) in anhyd MeOH (50 mL) NaH (4.40 g, 0.11 mol as 60% dispersion in mineral oil) was added portionwise. After reflux for 4 h, the mixture was cooled and $NaBH_4$ (3.78 g, 0.10 mol) was added portionwise at 0 °C. The mixture was stirred at r.t. for 0.5 h, acidified with 10% HCl and basified with sat. $KHCO_3$. The mixture was poured into H_2O (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL) and the solvent was removed. The residue purified by column chromatography (silica gel, hexane: EtOAc = 15:1) to give **5** (13.86 g, 60%) as colorless oil.

IR ($CHCl_3$): ν = 2900, 1670, 1180, 1020, 920 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.00–2.30 (2 H, m), 2.40–2.70 (2 H, m), 2.95 (2 H, br d, *J* = 1.4 Hz), 3.59 (2 H, s), 4.20 (2 H, br d, *J* = 5.0 Hz), 4.66 (1 H, br, *J* = 3.5 Hz), 5.00–5.50 (2 H, m), 5.60–6.40 (1 H, m), 7.31 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{15}H_{20}NO(MH^+)$230.1545; found 230.1573.

Benzyl 5-(Allyloxy)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (6)

To a solution of **1** (0.46 g, 2.0 mmol) in anhyd THF (2 mL) benzyl chloroformate (benzyl chloridocarbonate) (0.86 mL, 6.0 mmol) was added dropwise at 0 °C. The mixture was stirred at r.t. for 1 h, poured into sat. $KHCO_3$ (50 mL), and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried, filtered and concentrated. The residue was purified by column chromatography (silica gel, EtOAc:hexane = 1:15) to give **6** (0.51 g, 93%) as colorless oil.

IR ($CHCl_3$): ν = 2900, 1680, 1430, 1220, 1110, 1000 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 2.00–2.40 (2 H, m), 3.53 (2 H, br t, *J* = 5.7 Hz), 3.93 (2 H, br d, *J* = 1.4 Hz), 4.23 (2 H, br d, *J* = 5.0 Hz), 4.60–4.90 (1 H, m), 5.10–5.50 (2 H, m), 5.15 (2 H, s), 5.60–6.20 (1 H, m), 7.35 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{16}H_{20}NO_3(MH^+)$ 274.1443; found 274.1444.

Benzyl 4-Allyl-3-oxo-1-piperidinecarboxylate (7)

A solution of **6** (0.55 g, 2.0 mmol) in *p*-cymene (3 mL) was heated at 130 °C for 1 h. The residue was purified by column chromatography (silica gel, EtOAc:hexane = 1:3) to give **7** (0.38 g, 69%) as colorless oil.

IR (neat): ν = 3400, 2930, 1700, 1420 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$, rotomers): δ = 1.00–3.00 (5 H, m), 3.20–4.00 (2 H, m), 4.07 (2 H, br, *J* = 1.7 Hz), 4.30–6.20 (3 H, m) 5.14 (2 H, s), 7.34 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{16}H_{19}NO_3$ 273.1365; found 273.1326.

Benzyl 2-allyl-3-oxo-1-piperidinecarboxylate (8)

To a solution of **6** (10.93 g, 40.0 mmol) in anhyd MeCN (40 mL) $BF_3{\cdot}OEt_2$ (5.1 mL, 40.2 mmol) was added dropwise. The mixture was stirred at r.t. for 1.5 h under Ar, poured into sat. $KHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated. The residue was subjected to column chromatography (silica gel; hexane: EtOAc = 3:1) to give **8** (8.09 g, 74%) as colorless oil.

IR ($CHCl_3$): ν = 2950, 1680, 1420, 1310, 1220 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$, rotomers): δ = 1.60–2.20 (2 H, m), 2.20–2.80 (4 H, m), 2.80–3.50 (1 H, m), 3.90–4.40 (1 H, m), 4.50–6.20 (4 H, m), 5.14 (2 H, s), 7.35 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{16}H_{20}NO_3$ (MH^+) 274.1443; found 274.1463.

(2*S, 3*S**)-Benzyl 2-Allyl-3-hydroxy-1-piperidinecarboxylate (9)**

To a solution of **8** (7.42 g, 27.1 mmol) in MeOH (30 mL) $NaBH_4$ (0.51 g, 13.5 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 1 h, poured into 10% HCl (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated to give **9** (7.26 g, 97%) as colorless oil.

IR ($CHCl_3$): ν = 3400, 2950, 1670, 1420, 1240 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$, rotomers): δ = 1.40–1.90 (4 H, m), 2.07 (1 H, s), 2.20–3.00 (3 H, m), 3.10–5.30 (5 H, m), 5.11 (2 H, s), 5.30–6.20 (1 H, m), 7.33 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{16}H_{22}NO_3$ (MH^+) 276.1600; found 276.1571.

(3a*S, 7a*S**)-Benzyl 2-(Bromomethyl)hexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (10)**

To a solution of **9** (7.26 g, 26.4 mmol) in MeCN (50 mL) NBS (5.16 g, 29.0 mmol) was added. The mixture was stirred at r.t. for 0.5 h, poured into 10% $Na_2S_2O_3$ (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with sat. $KHCO_3$ (100 mL) and brine (100 mL), dried, filtered and concentrated. The residue was subjected to column chromatography (silica gel; hexane: EtOAc = 3:1) to give **10** (7.98 g, 85%) as light yellow oil.

HPLC: column, Chemcosorb 5Si-U; column temperature, r.t.; eluent, hexane: EtOAc = 3:1; flow rate = 1.0 mL/min; wavelength, 254 nm; t_R = 10.0 and 11.0 min (75:25).

IR (neat): ν = 2950, 1700, 1420, 1260 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$, rotomers): δ = 1.30–2.50 (6 H, m), 2.60–3.30 (1 H, m), 3.30–3.50 (2 H, m), 3.60–5.00 (4 H, m), 5.15 (2 H, s), 7.35 (5 H, s).

HRMS (FAB): *m/z* calcd for $C_{16}H_{21}BrNO_3$ (MH^+) 354.0705, found 354.0733.

(3a*S, 7a*S**)-Benzyl 2-Hydroxy-2-[(4-oxo-3(4*H*)-quinazolinyl)methyl]hexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (12)**

To a solution of **10** (1.78 g, 5.0 mmol) in anhyd THF (5 mL) potassium *tert*-butoxide (0.74 g, 6.0 mmol) was added. The mixture was heated at reflux for 1 h. After cooling, the mixture was added to a solution of NBS (1.07 g, 6.0 mmol) in MeCN (5 mL) and H_2O (5 mL). The mixture was stirred at r.t. for 0.5 h, poured into 10% $Na_2S_2O_3$ (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with sat. $KHCO_3$ (100 mL) and brine (100 mL), dried, filtered and concentrated. A mixture of the residue, 4(3*H*)-quinazolinone (11, 0.88 g, 6.0 mmol), anhyd K_2CO_3 (0.83 g, 6.0 mmol) in anhyd DMF (10 mL) was stirred at r.t. for 1 h. The mixture was poured into brine (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried, filtered and concentrated. The residue was subjected to column chromatography (Al_2O_3; EtOAc:*i*-PrOH = 2:1) to give **12** (0.87 g, 40%) as amorphous solid.

IR (neat): ν = 3380, 1680, 1430, 1260 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, rotomers): δ = 1.34–1.44 (4/3 H, m), 1.53–1.58 (2/3 H, m), 1.70–1.73 (1/3 H, m), 1.77–1.85 (4/3 H, m), 1.89–1.93 (1/3 H, m), 2.10 (2/3 H, dd, *J* = 13.0, 10.0 Hz), 2.24 (1/3 H, dd, *J* = 13.5, 10.0 Hz), 2.30 (2/3 H, dd, *J* = 13.5, 8.0 Hz), 2.45 (1/3 H, dd, *J* = 13.5, 8.0 Hz), 2.86–2.90 (2/3 H, m), 2.97 (1/3 H, td, *J* = 12.5, 3.0 Hz), 3.76 (2/3 H, br d, *J* = 12.5 Hz), 3.88 (1/3 H, dt, *J* = 13.0, 4.0 Hz), 4.02–4.08 (2/3 H, m), 4.25–4.40 (7/3 H, m), 4.58 (1/3 H, br q, *J* = 8.0 Hz), 4.95 (2/3 H, br q, *J* = 7.5 Hz), 5.06–5.13 (2 H, m), 7.26–7.37 (5 H, m), 7.50 (1 H, br t, *J* = 7.0 Hz), 7.69–7.78 (2 H, m), 8.10 (1/3 H, s), 8.18 (2/3 H, s), 8.28 (1 H, br, *J* = 8.0 Hz).

HRMS (FAB): *m/z* calcd for $C_{24}H_{26}N_3O_5$ (MH^+) 436.1872, found 436.1928. *m/z* calcd for $C_{24}H_{24}N_3O_4$ ($MH\text{-}H_2O$) 418.1769; found 418.1779.

D/L-**Isofebrifugine (2)**

A mixture of **11** (0.44 g, 1.0 mmol), 20% $Pd(OH)_2/C$ (0.05 g) in anhyd MeOH (5 mL) was stirred at r.t. for 7 h under H_2. After filtration, the solvent was removed. The residure was recrystallized from EtOAc to give **2** (0.17 g, 56%) as colorless needles, mp 134–135 °C; dihydrochloride: mp 171–175 °C (dec.).

IR ($CHCl_3$): ν = 3300, 1660 cm^{-1}.

The ^1H and ^{13}C NMR data are included in the Table.

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.

D/L-**Febrifugine (1)**

A solution of **2** (108.5 mg, 0.36 mmol) in EtOH (0.5 mL) was heated at reflux for 2 h. The precipitate was filtered off and recrystallized from EtOAc to give **1** (79.3 mg, 73%) as colorless needles, mp 188–190 °C (lit.[3b] 133–134 °C); dihydrochloride mp 202–204 °C (dec.) (lit.[3a] 204 °C (dec.))

IR ($CHCl_3$): ν = 3320, 3030, 1730, 1670 cm^{-1}.

The ^1H and ^{13}C NMR data are included in the Table.

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.

Benzyl 3-(Benzyloxy)-1-piperidinecarboxylate (14)

To a solution of **13**[4] (1.40 g, 5.0 mmol) in anhyd THF (5 mL) benzyl chloridocarbonate (2.2 mL, 15.4 mmol) was added dropwise at 0 °C. The mixture was stirred at r.t. for 1 h, and the solvent was removed. The residue was purified by column chromatography (silica gel, EtOAc:hexane = 1:15) to give **14** (1.48 g, 91%) as colorless oil.

IR (neat): ν = 2900, 1700, 1670, 1440, 1230, 1100 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 2.00–2.40 (2 H, m), 3.53 (2 H, t, *J* = 5.5 Hz), 3.97 (2 H, br d, *J* = 1.7 Hz), 4.74, (2 H, s), 4.60–5.00 (1 H, m), 5.14 (2 H, s), 7.33 (10 H, s).

HRMS (FAB): *m/z* calcd for $C_{20}H_{22}NO_3$ (MH^+) 324.1600, found:324.1646.

Benzyl 5-(Benzyloxy)-3,4-dihydro-1(2*H*)-pyridinecarboxylate (15)

To a solution of **14** (0.65 g, 2.0 mmol) in anhyd MeCN (3 mL) $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise. The mixture was stirred at r.t. for 1 h under Ar, poured into H_2O (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. $KHCO_3$ (50 mL) and brine (100 mL), dried, filtered and concentrated. The residue was subjected to column chromatographiy (silica gel; hexane:EtOAc = 15:1) to give **15** (0.39 g, 60%) as colorless oil.

IR ($CHCl_3$): ν = 2950, 1700, 1410 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$, rotomers): δ = 1.60–2.40 (4 H, m), 3.40–3.70 (2 H, m), 4.74 (2 H, s), 5.18 (2 H, s), 6.30–6.60 (1 H, m), 7.35 (10 H, s).

MS (FAB): *m/z* = 324 (MH^+), 323 (M^+).

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