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A concise enantioselective synthesis of (+)-febrifugine

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ABSTRACT

A short enantioselective synthesis of (+)-febrifugine, a potent antimalarial alkaloid, has been described based on the regioselective asymmetric dihydroxylation of a 1,4-dienic ester as the key step. The strategy also involves chemoselective [3,3]-sigmatropic rearrangement of 1,5-hexadiene-3-ol and intramolecular lactamization of azidolactone for the construction of piperidine core.

1. Introduction

(+)-Febrifugine **1** and its stereoisomer (+)-isofebrifugine **2** are quinazolinone-type antimalarial alkaloids that have been identified as the active constituents of the Chinese medicinal herb Chang Shan (*Dichroa febrifuga* Lour) and related *Hydrangea* plants (Fig. 1).[1] Due to their potentially powerful antimalarial activity, several new analogues and derivatives of febrifugine have been synthesized in recent years.[2] Since natural (+)-febrifugine **1** has been found to exhibit much more activity[3] than its isomer **2** and the fact that both are epimerizable under acidic conditions,[4] the development of efficient methods for the preparation of **1** assumes importance for extensive biological investigations. Due to their attractive biological activity, a number of total syntheses of these compounds in racemic and optically active forms have been established.[5] However, many of the reported methods either make use of chiral building blocks[5h] or involve longer reaction sequences; often accompanying low product selectivity. In continuation of our ongoing programme aimed at the development of general approaches to bioactive molecules,[6] we herein report a short enantioselective synthesis of (+)-febrifugine **1** based upon regioselective asymmetric dihydroxylation (ADH) of 1,4-dienic ester **5** as the key asymmetry inducing reaction.

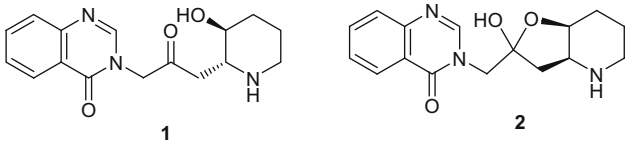

Figure 1.

2. Results and discussion

The retrosynthetic analysis of (+)-febrifugine **1** is outlined in Scheme 1, wherein 2-allyl-3-hydroxypiperidine **3** was visualized as the key intermediate. We further thought that the piperidine moiety in **3** could be constructed by the reductive *N*-to *O*-ring expansion of azidolactone **4**, which in turn may be obtained by the regioselective ADH of 1,4-dienic ester **5** (Scheme 1).

The asymmetric synthesis of (+)-febrifugine **1** was carried out starting from the commercially available 1,5-hexadien-3-ol **6**. Alcohol **6**, upon Claisen–Johnson rearrangement[7] (trimethyl orthoacetate, catalytic amount of propanoic acid, xylene, 135 °C) produced (*E*)-1,4-dienic ester **5**, exclusively, in 86% yield. It should be noted that 5-hexenal, an oxy-Cope product, was not formed during the rearrangement. The Os-catalyzed regioselective ADH of 1,4-dienic ester **5** was achieved using $(DHQ)_2$-PHAL as the chiral ligand to provide hydroxy lactone **7** in 73% yield and 82% ee [determined from its Mosher's ester] when the reaction was conducted for a short period of time (2 h).[8] However, if conducted for a longer period of time, both double bonds in **5** were dihydroxylated to a large extent; the same trend was observed, even at 0 °C, when OsO_4 was replaced with potassium osmate. The hydroxyl group in **7** was protected as its mesylate followed by its S_N2 displacement with NaN_3 to give the azidolactone **4** in 82% yield over two steps with complete inversion $\{[\alpha]_D^{25} = -21$ (c 0.5, $CHCl_3$)$\}$. Reductive cyclization of azide **4** under Staudinger condition (PPh_3, H_2O, heat)[9] proceeded smoothly to afford the ring expanded hydroxy lactam **9** in excellent yield.[10] The lactam carbonyl in **9** was then reduced ($LiAlH_4$, THF) to give 2-allylpiperidin-3-ol **10** in 85% yield; $\{[\alpha]_D^{25} = -46$ (c 1, MeOH) (recrystallized from $CHCl_3$)$\}$. The amine group in compound **10** was then protected as its benzyl carbamate to give **11** in 85% ee (determined by chiral HPLC).[11] The protection of the hydroxyl group as its benzyl ether was subsequently

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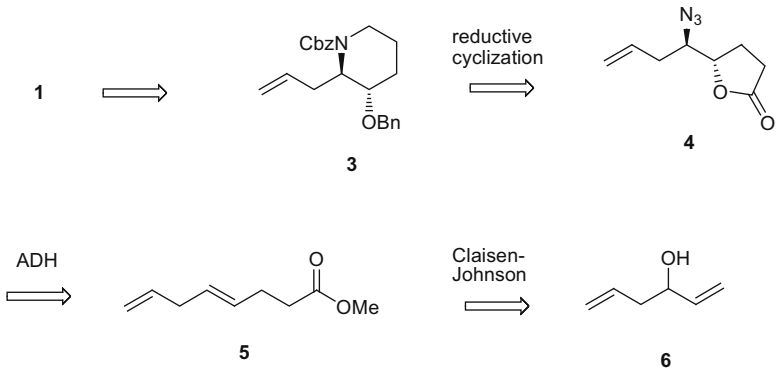
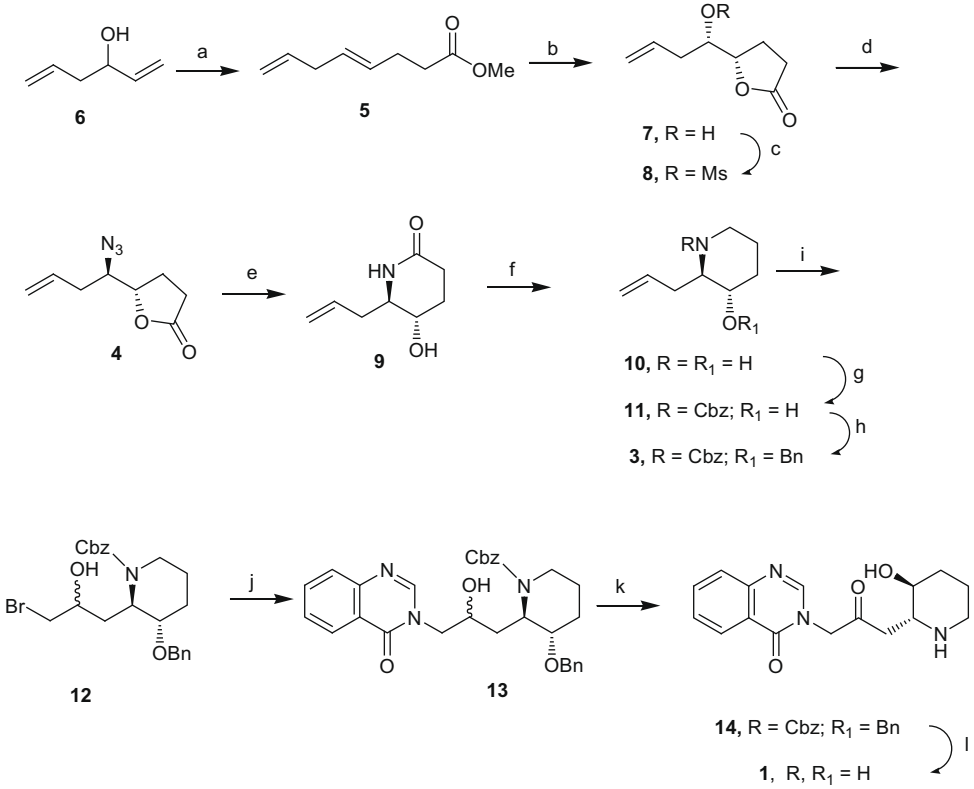


Scheme 1. Retrosynthetic analysis of (+)- febrifugine **1**.



Scheme 2. Reagents and conditions: (a) $CH_3C(OMe)_3$, cat. propanoic acid, xylene, 135 °C, 88%; (b) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH/H_2O (1:1), 73%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 80 °C, 82% over two steps; (e) PPh_3, THF, 25 °C then H_2O reflux; 93%; (f) $LiAlH_4$, THF, reflux; 85%; (g) CbzCl, K_2CO_3, THF/H_2O (1:1); (h) BnBr, NaH, DMF, 0 °C; 84% over two steps; (i) NBS, CH_3CN/H_2O (2:1), 88%; (j) 4-quinazolinone, KOH (2 equiv), MeOH, 25 °C; (k) Dess–Martin periodinane, CH_2Cl_2, 78% over two steps; (l) 6 M HCl, reflux, 63%.

achieved to give the key intermediate **3** in 72% yield over three steps {$[\alpha]_D^{25} = -37$ (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]_D^{25} = -45$ (*c* 1.55, $CHCl_3$)} (Scheme 2).

With olefin **3** in hand, we began bromohydroxylation (NBS, CH_3CN/H_2O), which took place regioselectively to give the diastereomers of terminal halide **12** (dr = 1.5:1, from ^1H NMR) along with the corresponding dibromo compound (9%). Without purification, the diastereomers of halohydrin **12** were coupled with 4-hydroxyquinazoline in the presence of KOH. The free alcohol group in **13** was subsequently oxidized using a Dess–Martin periodinane[12] to furnish the protected febrifugine {$[\alpha]_D^{25} = -25.0$ (*c* 0.5, $CHCl_3$); lit.[5h] $[\alpha]_D^{25} = -22.0$ (*c* 1.0, $CHCl_3$)}. Finally, removal of the protecting groups under acidic conditions (6 M HCl) produced (+)-febrifugine **1**, whose ^1H and ^{13}C NMR spectra and melting point are in complete agreement with the reported values.

3. Conclusion

In conclusion, an alternative, concise enantioselective synthesis of (+)-febrifugine **1** has been achieved based on the asymmetric dihydroxylation of 1,4 dienic ester. The reductive ring expansion of azidolactone was employed as one of the key steps for the construction of the piperidine moiety. It is a practical route that seems applicable for the synthesis of several substituted hydroxyl piperidines.

4. Experimental

4.1. General experimental

All melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were re-

corded on Bruker AV200 MHz digital NMR spectrometer in $CDCl_3$ or CD_3OD. The solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used for column chromatography. Optical rotations were measured using a sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer. Enantiomeric excesses of the products were determined by Mosher's ester analysis or comparing the specific rotation of the known compounds. All evaporations were performed under reduced pressure. For column chromatography, silica gel (60–120 mesh) was employed.

4.2. (*E*)-Methyl octa-4,7-dienoate 5

An oven-dried 500 mL round-bottomed flask was charged with **6** (9.8 g, 100 mmol), propanoic acid (390 mg, 5 mol %), trimethyl orthoacetate (72.0 g, 600 mmol) and xylene (300 mL). The mixture was refluxed at 135 °C for 18 h. After completion of the reaction as monitored by TLC, it was cooled to room temperature, and the excess trimethyl orthoacetate and xylene were removed under reduced pressure. It was then extracted with ethyl acetate (3 × 25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give crude ester **5** as a colourless oil, which was purified by column chromatography using petroleum ether/ethyl acetate (9:1). Yield: 88% (13.55 g); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (m, 6H), 2.73 (dt, J = 4.8, 1.2 Hz, 2H), 3.67 (s, 3H), 4.95 (t, J = 1.5 Hz, 1H), 5.02 (m, 1H), 5.46 (m, 2H), 579 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 33.9, 36.6, 51.4, 115.1, 129.0, 129.3, 136.8, 173.3; IR (neat, cm^{-1}): 2936, 2861, 2355, 2332, 1735, 1520, 1442, 1251, 1176, 956, 852. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.21.

4.3. (*S*)-Dihydro-5-((*S*)-1-hydroxybut-3-enyl)furan-2(3*H*)-one 7

A 500 mL two-necked round-bottomed flask was charged with potassium ferricyanide (8.39 g, 120 mmol), potassium carbonate (39.48 g, 120 mmol), $(DHQ)_2$-PHAL (311 mg, 1 mol %) and *t*-BuOH/H_2O (1:1, 300 mL). The reaction mixture was cooled to 0 °C on an ice bath, and OsO_4 (10.8 mg in toluene, 0.22 mL, 0.5 mol %) was added via syringe. After 10 min of stirring at 0 °C diene **5** (6.16 g, 40 mmol) was added drop-wise and was allowed to stir for 2 h at 0 °C. After the completion of the reaction as monitored by TLC, it was quenched with saturated sodium sulfite and extracted with ethyl acetate (3 × 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude lactone **7**, which was purified by column chromatography using petroleum ether/ethyl acetate (1:1) to give **7** as a viscous gum. Yield: 73% (4.55 g); $[\alpha]_D^{25} = +42$ (c 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13–2.42 (m, 5H), 2.5–2.65 (m, 2H), 3.61–3.69 (ddd, J = 10.3, 6.7, 3.5 Hz, 1H), 4.43–4.52 (ddd, J = 10.9, 7.3, 3.7 Hz, 1H), 5.14 (dd, J = 2.3, 1.2 Hz, 1H), 5.17–5.23 (m, 1H), 5.75–5.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 28.6, 37.8, 72.6, 82.2, 118.5, 133.7, 178.0; IR ($CHCl_3$, cm^{-1}): 3445, 2936, 2866, 1769, 1519, 1247, 1185, 1035, 963. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.61; H, 7.79.

4.4. (*S*)-1-((*S*)-Tetrahydro-5-oxofuran-2-yl)but-3-enyl methanesulfonate 8

To a stirred solution of alcohol **7** (4 g, 25.6 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (3.87 g, 38 mmol) at 0 °C. After 5 min, methanesulfonyl chloride (3.5 g, 30.7 mmol) was added drop-wise. The reaction mixture was then stirred for another 1 h at 0 °C and brought to room temperature. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 × 50 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain crude mesylate **8**, which was purified by column chromatography using petroleum ether/ethyl acetate (1:1) to give pure mesylate **8** as a viscous liquid. Yield: 94% (5.63 g); $[\alpha]_D^{25} = +28$ (c 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29–2.40 (m, 4H), 2.45–2.65 (m, 2H), 3.07 (s, 3H), 4.16–4.37 (m, 1H), 4.61–4.78 (m, 1H), 5.20 (dd, J = 2.1, 1.0 Hz, 1H), 5.22–5.29 (m, 1H), 5.57–5.87 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.9, 27.9, 35.8, 39.1, 78.9, 82.0, 118.0, 133.1, 176.1; IR ($CHCl_3$, cm^{-1}): 2939, 2868, 1775, 1735, 1512, 1355, 1250, 1185, 1011, 815. Anal. Calcd for $C_9H_{14}O_5S$: C, 46.14; H, 6.02; S, 13.69. Found: C, 46.19; H, 6.14.

4.5. (*S*)-5-((*R*)-1-Azidobut-3-enyl)-dihydrofuran-2(3*H*)-one 4

To a stirred mixture of crude methanesulfonate ester **8** (5.95 g) in DMF (30 mL) was added sodium azide (87 g, 475 mmol), and the reaction mixture was heated at 80 °C for 7 h. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 × 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone **4,** which was purified by column chromatography using petroleum ether/ethyl acetate (7:3). Yield: 87% (3.8 g); $[\alpha]_D^{25} = -21$ (c 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.1–2.43 (m, 4H), 2.51–2.63 (m, 2H), 3.70–3.80 (ddd, J = 11.2, 6.3, 5.1 Hz, 1H), 4.42–4.51 (ddd, J = 11.8, 7.4, 5.0 Hz, 1H), 5.18 (dd, J = 2.1, 1.0 Hz, 1H), 5.21–5.29 (m, 1H), 5.73–5.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.7, 28.1, 35.2, 63.8, 80.1, 119.4, 132.4, 176.1; IR ($CHCl_3$, cm^{-1}): 2935, 2865, 2110, 1775, 1514, 1247, 1031, 819. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.10; H, 6.18; N, 23.24.

4.6. (5*S*,6*R*)-6-Allyl-5-hydroxypiperidin-2-one 9

To a stirred solution of azidolactone **4** (3.5 g, 19.3 mmol) in dry THF (50 mL) was added triphenyl phosphine (5.06 g, 21.23 mmol) at room temperature. The reaction mixture was stirred at room temperature until the evaluation of nitrogen gas ceased. Water (720 mg, 40 mmol) was added, and the reaction mixture was refluxed for 3 h. After the completion of the reaction, solvent and trace amounts of water were removed under reduced pressure to give the crude lactam **9**, which was purified by column chromatography using petroleum ether/ethyl acetate (1:1) to provide the pure lactam **9**. Yield: 93% (2.8 g); $[\alpha]_D^{25} = +10$ (c 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79–2.28 (m, 4H), 2.40–2.63 (m, 2H), 3.25 (m, 1H), 3.67 (m, 1H), 5.13–5.17 (dd, J = 8.5, 1.1 Hz, 1H), 5.22 (m, 1H), 5.64–5.84 (m, 1H), 6.08 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.4, 38.5, 57.7, 67.5, 119.4, 133.4, 172.0, 122.2, 138.9; IR ($CHCl_3$, cm^{-1}): 3445, 2939, 2895, 1657, 1132, 965. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.41; N, 9.11.

4.7. (2*R*,3*S*)-2-Allylpiperidin-3-ol 10

An oven-dried two-necked round-bottomed flask was charged with lithium aluminium hydride (648 mg, 24 mmol) and dry THF (50 mL) was added via syringe. The suspension was cooled to 0 °C and a solution of amide **9** (2.5 g, 16 mmol) in THF (20 mL) was added drop-wise while maintaining the temperature of the reaction mixture below 10 °C. After the addition was complete, the reaction mixture was stirred at the same temperature for 1 h and was then refluxed for 5 h to ensure the completion of the reaction. It was then quenched with ethyl acetate and filtered through Celite. The filtrate was washed with water, brine and dried over

anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude amino alcohol **10,** which was purified by column chromatography using petroleum ether/ethyl acetate (1:1) to give amino alcohol **10** as a colourless solid. Yield: 85% (2.1 g); mp: 112–114 °C (recrystallized from $CHCl_3$); $[\alpha]_D^{25} = -46$ (*c* 1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21–1.35 (m, 1H), 1.45–1.57 (m, 1H), 1.63–1.74 (m, 1H), 1.98–2.14 (m, 2H), 2.11 (br s, 2H), 2.30–2.41 (dt, *J* = 9.6, 3.1 Hz, 1H), 2.46–2.59 (dt, *J* = 12.0, 3.8 Hz, 1H), 2.62–2.75 (m, 1H), 2.92–3.02 (m, 1H), 3.21–3.33 (ddd, *J* = 13.9, 9.68, 4.18 Hz, 1H), 5.10 (t, *J* = 1.0 Hz, 1H), 5.13–5.24 (m, 1H), 5.71–5.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.6, 37.5, 40.2, 49.5, 65.5, 74.7, 122.2, 138.9; IR (KBr, cm^{-1}): 3412, 2942, 2893, 1672, 1395. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.09; H, 10.65; N, 9.85.

4.8. (2*R*,3*S*)-Benzyl 2-allyl-3-hydroxypiperidine-1-carboxylate 11

To a mixture of amino alcohol **10** (1.9 g, 13.5 mmol) in THF/H_2O (20 mL, 1:1) was added K_2CO_3 (3.73 g, 27 mmol) followed by benzyl chloroformate (2.754 g, 16.2 mmol) drop-wise at 0 °C. After stirring for 5 h, the reaction mixture was extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude N-protected amino alcohol **11**, which was purified by column chromatography using petroleum ether/ethyl acetate (8:2) to give **11** as a viscous brown oil. $[\alpha]_D^{25} = -37$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39–1.50 (m, 1H), 1.65–2.05 (m, 4H), 2.17–2.46 (m, 2H), 2.85 (dt, *J* = 10.24, 2.33 Hz, 1H), 3.83 (br s, 1H), 4.03–4.12 (m, 1H), 4.30–4.38 (m, 1H), 4.98–5.02 (m, 2H), 5.13 (s, 2H), 5.59–5.79 (m, 1H), 7.33 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0, 25.8, 33.8, 38.9, 57.1, 66.7, 72.8, 117.3, 127.8, 127.9, 128.5, 134.4, 136.8, 156.7; IR (neat, cm^{-1}): 3412, 2935, 2889, 1723, 1685, 1352, 1163, 1025, 982. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.98; H, 7.58; N, 5.11.

4.9. (2*R*,3*S*)-Benzyl 2-allyl-3-(benzyloxy)piperidine-1-carboxylate 3

To a stirred solution of crude amino alcohol **11** (3.5 g) in DMF (40 mL) was added 60% sodium hydride (550 mg, 16.2 mmol) dispersed in mineral oil at 0 °C. After 5 min of stirring, benzyl bromide (2.6 g, 15 mmol) was added drop-wise via syringe and allowed to stir for another 4 h. After completion of the reaction as monitored by TLC, it was quenched with satd NH_4Cl solution. It was then extracted with ethyl acetate (3 × 200 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give crude product **3**, which was purified by column chromatography using petroleum ether/ethyl acetate (4:1) to afford **3** as colourless liquid. Yield: 84% (4.14 g, two steps); $[\alpha]_D^{25} = -37$ (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]_D^{25} = -45$ (*c* 1.55, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36–1.43 (m, 1H), 1.61–1.95 (m, 3H), 2.11–2.25 (m, 1H), 2.31–2.46 (m, 1H), 2.82–2.93 (dt, *J* = 13.4, 2.4 Hz, 1H), 3.44 (br s, 1H), 3.99–4.17 (m, 1H), 4.4–4.67 (m, 3H), 4.97–5.18 (m, 4H), 5.59–5.73 (m, 1H), 7.21–7.29 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 24.1, 33.9, 38.8, 52.3, 66.9, 70.0, 73.3, 117.4, 127.4, 127.7, 127.8, 128.3, 128.4, 134.5, 137.0, 138.7, 156.1; IR (neat, cm^{-1}): 2939, 2887, 1727, 1680, 1625, 1352, 1163. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.63; H, 7.52; N, 3.92.

4.10. Diastereomers of halohydrin 12

To a stirred solution of **3** (2 g, 5.48 mmol) in CH_3CN/H_2O (2:1, 20 mL) was added *N*-bromosuccinimide (1.67 g, 6 mmol) at room temperature. After completion of the reaction, it was quenched with sodium thiosulfate solution and extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude halohydrin **12**, which was purified by column chromatography using petroleum ether/ethyl acetate (4:1) to give **12** as a gum. Yield: 87% (2.2 g); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39– 1.44 (d, *J* = 8.60 Hz, 1H), 1.53–1.72 (m, 3H), 1.82–1.98 (m, 2H), 2.25 (1H), 2.67–2.74 and 2.80–2.93 (t, *J* = 13 Hz, 1H), 3.33 and 3.4 (s, 1H), 3.52–3.64 (m, 1H), 3.70–3.90 (m, 1H), 3.99–4.21 (m, 2H), 4.44 and 4.50 (s, 2H), 5.11 and 5.15 (s, 2H), 7.21–7.35 (m, 10H); IR ($CHCl_3$, cm^{-1}): 3456, 2912, 2872, 1728, 1683, 1031, 819.

4.11. *O*-Benzyl-*N*-benzyloxycarbonyl febrifugine 14

To a stirred solution of **12** (668 mg, 1.8 mmol) in dry methanol (10 mL) was added KOH (0.5 g, 3.6 mmol) and 4-hydroxyquinazoline (263 mg, 1.8 mmol) and the mixture was stirred at the room temperature for 24 h. Next the solvent was removed under reduced pressure and the residue extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give inseparable mixture of **13** as a viscous liquid, which was subjected to oxidation as described below. To a stirred solution of **13** in dry CH_2Cl_2 was added Dess–Martin periodinane (848 mg, 2 mmol) at room temperature. After the completion of the reaction, it was quenched with water. The precipitate formed was filtered through a sintered funnel and the filtrate was concentrated and subjected to column chromatographic purification to give the protected febrifugine **14** as a pale yellow oil. Yield 78%; $[\alpha]_D^{25} = -25.0$ (*c* 0.5, $CHCl_3$); lit.[5h] $[\alpha]_D^{25} = -22.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (d, *J* = 10.5 Hz, 1H), 1.60–1.66 (m, 1H), 1.86–1.93 (m, 2H), 2.74–2.95 (m, 3H), 3.50 (s, 1H), 4.05 (br, 1H), 4.50–5.25 (m, 7H), 7.24–7.31 (m, 10H), 7.46–7.49 (m, 1H), 7.70–7.90 (m, 4H), 8.24–8.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 24.1, 39.4, 40.7, 50.5, 50.6, 53.8, 67.2, 70.3, 73.5, 121.7, 126.5, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.4, 134.3, 136.4, 138.2, 146.4, 148.1, 160.8, 200.0; IR (neat) 2932, 2895, 1730, 1680, 1620, 1352, 1163 cm^{-1}; Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.63; H, 7.52; N, 3.92.

4.12. Febrifugine 1

A mixture of **14** (116 mg, 0.30 mmol) and 6 M aqueous HCl solution was heated at reflux for 4 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. The residue was subjected to column chromatographic purification (neutral Al_2O_3; ethyl acetate/petroleum ether 2:1) to give **1** as colourless needles. Yield: 63% (57 mg); mp: 138–140 °C (lit.[5m] mp 139–140 °C); $[\alpha]_D^{25} = +25.0$ (*c* 0.1, EtOH) {lit.[5j] $[\alpha]_D^{25} = +28$ (*c* 0.5, EtOH)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30–1.38 (m, 1H), 1.48–1.57 (m, 1H), 1.72–1.74 (m, 1H), 2.07–2.10 (m, 1H), 2.58 (dt, *J* = 2.4, 12.2 Hz, 1H), 2.65 (dd, *J* = 7.3, 15.8 Hz, 1H), 2.88 (dd, *J* = 4.6, 7.7 Hz, 1H), 2.97 (d, *J* = 12.2 Hz, 1H), 3.12 (dd, *J* = 4.8, 15.8 Hz, 1H), 3.29 (m, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 4.89 (d, *J* = 17.4 Hz, 1H), 7.51 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.78 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.90 (s, 1H), 8.28 (dd, *J* = 0.9, 7.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.7, 35.3, 44.0, 45.9, 54.7, 60.1, 72.2, 121.9, 126.8, 127.4, 127.6, 134.5, 146.4, 148.2, 161.0, 202.7; IR (KBr, cm^{-1}) 2928, 2856, 1722, 1675, 1616. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.79; H, 6.39; N, 13.96.

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11. HPLC, Chiracel OD-H column (2-propanol/*n*-hexane = 1:9, flow rate 0.5 mL/min, λ = 304 nm). Retention time (min): 84.31 (minor) and 85.62 (major). It may be noted that an increase of 3% ee in its enantiomeric purity is probably attributed to repeated recrystallization of compound **10**.
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