A Concise Enantioselective Synthesis of Antimalarial Febrifugine Alkaloids

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Supporting Information

General Procedure. Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. The extracts were dried over $MgSO_4$ unless otherwise noted and concentrated by rotary evaporation below 30 °C at ca. 25 Torr. Analytical and preparative thin-layer chromatography were performed with Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230-400 mesh ASTM, Merk).
Materials. Commercial reagents and solvents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine, and *N*,*N*-dimethyformamide (DMF) were distilled from calcium hydride. 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was purified by kugelrohr distillation after washing with 10% NaOH just prior to use.
Instrumentation. All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. Infrared spectra were measured on a JASCO FT/IR-230 spectrometer. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 300 or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in hertz. TMS was defined as 0 ppm for ^1H NMR spectra and the center line of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. High resolution Mass spectra were measured on a JEOL JMS-DX303.

Lipase-catalyzed acetylation of racemic alcohol 8 giving (*S*)-9 and (*R*)-8.

(*R*)-**8**   **9**

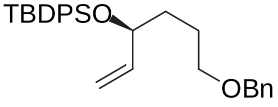
A mixture of racemic **8** (500 mg, 2.45 mmol), vinyl acetate (0.23 ml, 2.50 mmol), and Novozym 435 (250 mg) in *t*-BuOMe (25 ml) was stirred at room temperature for 40 min. The reaction mixture was filtered through Celite, concentrated, and chromatographed (hexane:EtOAc = 10:1) to give (*S*)-**9** (260 mg, 44%) and (*R*)-**8** (270 mg, 54%).

(*S*)-Acetate **9**: a colorless oil, $[\alpha]_D^{16}$ –50.6° (*c* 1.80, $CHCl_3$) (91% ee); FT-IR (neat) 3286, 1741, 1369, 1232, 1099, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73-1.83 (m, 2H), 1.85-1.94

(m, 2H), 2.08 (s, 3H), 2.45 (d, *J* = 2.1 Hz, 1H), 3.51 (t, *J* = 6.0 Hz, 2H), 4.51 (s, 2H), 5.38 (dt, *J* = 2.1, 6.3 Hz, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 25.3, 31.5, 63.5, 69.5, 73.0, 73.6, 81.1, 127.7, 128.4, 138.4, 169.9; HRMS (EI) calcd for $C_{15}H_{18}O_3$ (M^+): 240.1256, found: 240.1254.

(*R*)-Alcohol **8**: a colorless oil, $[\alpha]_D^{20}$ +10.7° (*c* 0.86, $CHCl_3$) (78% ee); FT-IR (neat) 3396, 3288, 1450, 1363, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74-1.92 (m, 4H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.91 (br d, *J* = 3.6 Hz, 1H), 3.50-3.56 (m, 2H), 4.42 (m, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 35.0, 61.8, 70.0, 72.8, 73.0, 85.0, 127.7, 127.8, 128.4, 138.0; HRMS (EI) calcd for $C_{13}H_{16}O_3$ (M^+): 204.1150, found: 204.1140.

(*S*)-6-Benzyloxy-3-(*tert*-butyldiphenylsilyl)oxy-1-hexene (10).

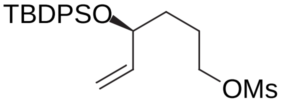


10

Compound **9** (3.00 g, 12.5 mmol) was hydrogenated in MeOH (150 ml) using Lindlar catalyst (Pd on $CaCO_3$, poisoned with lead, 300 mg) under hydrogen atomosphere at room temperature for 5h. K_2CO_3 (1.00 g, 7.24 mmol) was added and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite, diluted with Et_2O, washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give (*S*)-6-benzyloxy-1-hexen-3-ol (2.23 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ +5.3° (*c* 0.99, $CHCl_3$); FT-IR (neat) 3404, 1448, 1363, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54-1.77 (m, 4H), 2.45 (br s, 1H), 3.51 (t, *J* = 6.0 Hz, 2H), 4.12 (br q, *J* = 5.7 Hz, 1H), 4.51 (s, 2H), 5.09 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.22 (dt, *J* = 16.8, 1.5 Hz, 1H), 5.86 (ddd, *J* = 6.0, 10.5, 16.8 Hz, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 34.3, 70.4, 72.8, 73.1, 114.5, 127.7, 127.8, 128.5, 138.2, 141.1; HRMS (EI) calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307, found: 206.1313.

To an ice-cooled solution of (*S*)-6-benzyloxy-1-hexen-3-ol (2.0 g, 9.71 mmol) in DMF (30 ml) were added imidazole (4.58 g, 17.5 mmol) and *tert*-butyldiphenylsilyl chloride (4.0 g, 14.6 mmol). After being stirred at room temperature for 12 h, the reaction mixture was diluted with hexane, washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 30:1) to give **10** (3.90 g, 90%) as a colorless oil: $[\alpha]_D^{19}$ +24.3° (*c* 1.02, $CHCl_3$); FT-IR (neat) 1462, 1427, 1362, 1105, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.48-1.64 (m, 4H), 3.32 (br t, *J* = 6.3 Hz, 2H), 4.18 (br q, *J* = 5.1 Hz, 1H), 4.42 (s, 2H), 4.96 (dd, *J*= 10.4, 1.8 Hz, 1H), 4.98 (dd, *J* = 16.9., 0.9 Hz, 1H), 5.78 (ddd, *J* = 6.3, 10.4, 16.9 Hz, 1H), 7.29-7.42 (m, 11H), 7.66 (br t, *J* = 7.8 Hz, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.5, 24.7, 27.1, 34.1, 70.4, 72.8, 74.4, 114.6, 127.4, 127.5, 127.5, 127.6, 128.4, 129.5, 129.6, 134.3, 134.5, 135.6, 135.9, 136.0, 138.7, 140.6; HRMS (EI) calcd for $C_{25}H_{27}O_2Si$ ($M^+ – C_4H_9$): 387.1780, found: 387.1767.

(*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-5-hexenyl Methanesulfonate (11).

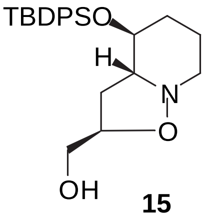


11

To a stirred solution of naphthalene (2.60 g, 20 mmol) at room temperature was added Li (110 mg, 16 mmol) and the mixture was stirred at room temperature for 3h. The resulting deep green solution was cooled to –25 °C and a solution of **10** (2.40 g, 5.4 mmol) was added. After being stirred at –25 °C for 20 min, the reaction mixture was allowed to warm to 0 °C, quenched with saturated NH_4Cl, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) to give (*S*)-4-(*tert*-butyldiphenylsilyl)oxy-5-hexen-1-ol (1.81 g, 95%) as a colorless oil; $[\alpha]_D^{21}$ +15.8° (*c* 1.03, $CHCl_3$); FT-IR (neat) 3344, 1468, 1427, 1109, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.47-1.56 (m, 5H), 3.50 (br t, *J* = 6.0 Hz, 2H), 4.21 (m, 1H), 4.97 (ddd, *J* = 10.5, 2.1, 0.9 Hz, 1H), 5.01 (ddd, *J* = 17.1, 1.8, 1.2 Hz, 1H), 5.80 (ddd, *J* = 6.6, 10.5, 17.1 Hz, 1H), 7.32-7.43 (m, 6H), 7.64-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 27.1, 27.6, 33.8, 62.9, 74.3, 114.7, 127.4, 127.6, 129.6, 129.7, 134.0, 134.3, 135.9, 136.0, 140.4; HRMS (EI) calcd for $C_{18}H_{21}O_2Si$ (M^+–C_4H_9) 297.1311, found: 297.1289.

To an ice-cooled solution of (*S*)-4-(*tert*-butyldiphenylsilyl)oxy-5-hexen-1-ol (1.81 g, 5.1 mmol) and triethylamine (0.92 ml, 6.6 mmol) was added methanesulfonyl chloride (0.43 ml, 5.6 mmol) and the mixture was allowed to warm to room temperature. After 1h, the reaction mixture was diluted with with Et_2O, washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give **11** (2.17 g, 98%) as a colorless oil; $[\alpha]_D^{21}$ +20.5° (*c* 1.02, $CHCl_3$); FT-IR (neat) 1354, 1176, 1107, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.47-1.53 (m, 2H), 1.58-1.85 (m, 2H), 2.92 (s, 3H), 4.06 (dt, *J* = 9.6, 6.6 Hz, 1H), 4.11 (dt, *J* = 9.6, 6.6 Hz, 1H), 4.23 (br q, *J* = 5.7 Hz, 1H), 5.02 (ddd, *J* = 10.5, 1.5, 1.2 Hz, 1H), 5.05 (ddd, *J* = 16.8, 1.8, 1.5 Hz, 1H), 5.77 (ddd, *J* = 6.6, 10.5, 16.8 Hz, 1H), 7.33-7.46 (m, 5H), 7.61-7.69 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.3, 24.0, 27.1, 33.0, 37.2, 70.1, 73.5, 115.0, 127.5, 127.6, 129.6, 129.7, 133.8, 134.1, 135.8, 135.9, 140.0; HRMS (EI) calcd for $C_{19}H_{23}O_4SSi$ (M^+–C_4H_9): 375.1086, found: 375.1069.

(2*R*,3a*R*,4*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-2-[(hydroxy)methyl]hexahydroisoxazolo[2,3-*a*]pyridine (15), (2*S*,3a*R*,4*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-2-[(hydroxy)methyl]hexahydroisoxazolo[2,3-*a*]pyridine (16), and (2*S*,3a*S*,4*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-2-[(hydroxy)methyl]hexahydroisoxazolo[2,3-*a*]pyridine (17).



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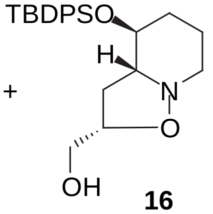

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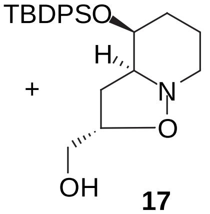


17

A mixture of **11** (1.87 g, 4.31 mmol) and $NaHCO_3$ (1.87 g, 21.6 mmol) in CH_2Cl_2 (30 ml) was reacted with O_3 at –78 °C for 20 min. After removal of an excess of the O_3 by flushing argon, dimethyl sulfide (0.48 ml, 6.47 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with brine, dried, and concentrated to give crude aldehyde **12** (1.91 g) as a pale yellow oil.

To a stirred solution of crude **12** (1.91 g) in allyl alcohol (20 ml) at room temperature were added hydroxylamine hydrochloride (330 mg, 4.75 mmol) and triethylamine (1.32 ml, 9.49 mmol). After being stirred at room temperature for 11 h, the reaction mixture was concentrated and chromatographed (hexane:EtOAc = 2:1) to give a 64:10:26 mixture of **15**, **16**, and **17** (1.31 g, 74%)

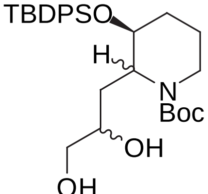
as a colorless amorphous solid. These compounds were characterized as the corresponding acetates after separation.

The acetate of **15**; FT-IR (neat) 1741, 1236, 1107 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.35 (2H), 1.68 (1H), 1.77 (1H), 1.93 (1H), 2.05 (1H), 2.10 (s, 3H), 2.30 (1H), 2.40 (1H), 3.29 (1H), 3.60 (1H), 3.99 (dd, *J* = 7.0, 10.5, 1H), 4.20 (2H), 7.35-7.39 (m, 4H), 7.41-7.47 (m, 2H), 7.64-7.70 (m, 4H), the peaks showing just integration value were too broadening to read the splitting pattern; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.9, 21.0, 21.9, 26.9, 27.0, 33.8, 35.9, 54.0, 65.8, 72.2, 73.2, 73.7, 127.6, 127.7, 129.8, 129.9, 133.6, 134.1, 135.9, 170.9; HRMS (EI) calcd for $C_{26}H_{35}NO_4Si$ (M^+): 453.2335, found 453.2336.

The acetate of **16**; FT-IR (neat) 1741, 1236, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.31 (2H), 1.67 (1H), 1.78 (1H), 2.05 (s, 3H), 2.08 (1H), 2.10 (br d, *J* = 11.5Hz, 1H), 2.32 (2H), 2.47 (1H), 3.27 (br d, *J* = 8.0 Hz, 1H), 3.55 (dt, *J* = 4.5, 9.5 Hz, 1H), 3.87 (br d, *J* = 11.5 Hz, 1H), 3.94 (dd, *J* = 3.0, 11.5Hz, 1H), 4.19 (1H), 7.33-7.48 (m, 6H), 7.62-7.70 (m, 4H), the peaks showing just integration value were too broadening to read the splitting pattern; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.1, 21.9, 27.0, 27.1, 33.8, 36.1, 53.9, 66.8, 72.6, 73.2, 74.0, 127.6, 127.8, 129.8, 130.0, 133.6, 134.2, 140.0, 171.0.

The acetate of **17**; FT-IR (neat) 1743, 1429, 1365, 1236, 1109, 1039 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.22 (1H), 1.43 (br dt, *J* = 10.0, 11.5 Hz, 1H), 1.96 (1H), 2.07 (s, 3H), 2.46 (br t, *J* = 10.8 Hz, 1H), 2.55 (br dt, *J* = 10.5, 12.0 Hz, 1H), 2.98 (br d, *J* = 10.2 Hz, 1H), 3.59 (br dt, *J* = 11.0, 6.5 Hz, 1H), 4.01 (dd, *J* = 6.0, 11.5 Hz, 1H), 4.17 (dd, *J* = 11.0, 3.0 Hz, 1H), 4.19 (dd, *J* = 11.0, 5.0 Hz, 1H), 4.62 (1H), 7.35-7.46 (m, 6H), 7.64 (d, *J* = 7.2 Hz, 4H), the peaks showing just integration value were too broadening to read the splitting pattern; ^{13}C NMR (75MHz, $CDCl_3$) δ 19.3, 20.7, 20.9, 21.0, 27.0, 27.6, 29.6, 49.3, 65.8, 66.0, 69.1, 74.2, 127.7, 127.8, 129.8, 130.0, 133.5, 134.0, 135.7, 171.0.

***N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)oxy-2-(2,3-dihydroxypropyl)piperidine (18).**



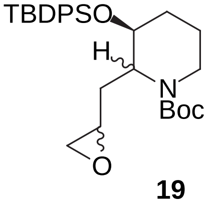
18

The diastereoisomeric mixture of **15**, **16**, and **17** (350 mg, 0.85 mmol) was dissolved in MeOH (10 ml) and stirred in the presence of $PdCl_2$ (35 mg, 0.20 mmol) under a hydrogen atmosphere at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, filtered through Celite, and concentrated to give crude amino diol (360 mg) as a yellow viscous oil.

To a stirred solution of crude amino diol (360 mg) in CH_2Cl_2 (10 ml) at room temperature were added triethylamine (0.21 ml, 1.53 mmol) and Boc_2O (278 mg, 1.28 mmol). After being stirred at room temperature for 10 h, the reaction mixture was diluted with Et_2O, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give **18** (410 mg, 94%) as a colorless amorphous solid; FT-IR (neat) 3425, 1660, 1471, 1425, 1367, 1267, 1169, 1107, 1036 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.06 and 1.07 (2 x s, 9H), 1.41 (s, 0.3 x 9H), 1.49 (s, 0.7 x 9H), 1.58-1.74 (m, 4H), 1.89 (tt, *J* = 3.6, 10.5 Hz, 0.3H), 1.98-2.22 (m, 1.4H), 2.33 (t, *J* = 6.0 Hz, 0.1H), 2.50-2.72 (m, 1.2H), 3.34-3.50 (m, 2H), 3.61 (dd, *J* = 5.4, 6.6 Hz, 1H), 3.72-3.81 (m, 2H), 4.02 (br d, *J* = 12.3 Hz, 0.7H) 4.12-4.44 (m, 2H), 4.48-

4.55 (m, 0.3H), 7.34-7.45 (m, 6H), 7.63-7.67 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.2, 19.3, 23.8, 26.8, 26.9, 28.3, 28.4, 31.8, 38.4, 39.2, 51.3, 53.5, 66.2, 66.8, 67.9, 69.2, 69.3, 70.2, 79.8, 80.1, 80.5, 127.6, 127.7, 129.6, 129.7, 133.2, 133.5, 134.2, 135.6, 135.7, 135.8, 156.4, 157.0; HRMS (EI) calcd for $C_{25}H_{34}NO_5Si$ ($M^+–C_4H_9$): 456.2206, found 456.2208.

***N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)oxy-2-[(oxiranyl)methyl]piperidine (19).**



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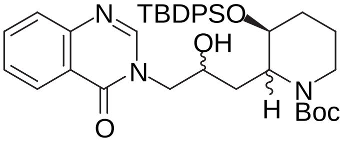
To an ice-cooled solution of **18** (400 mg, 0.78 mmol) in THF (10 ml) was added NaH (60% in dispersion oil, 169 mg, 0.86 mmol) and the mixture was stirred at 0 °C for 20 min. Tosylimidazole (190 mg, 0.86 mmol) was added and the cooling bath was removed. After being stirred at room temperature for 12h, the reaction mixture was quenched with water and extracted with Et_2O. The extract was washed with brine, dried, concentrated, and chromatographed (hexane:EtOAc = 10:1) to give **19** (355 mg, 92%) as a colorless amorphous solid; FT-IR (neat) 1689, 1419, 1259, 1369, 1169, 1144, 1101 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.07 (s, 6H), 1.09 (s, 3H), 1.38 (s, 6H), 1.40 (s, 3H), 1.40-1.64 (m, 3.9H), 1.97-2.28 (m, 1.6H), 2.30 (dd, *J* = 3.0, 4.5 Hz, 0.7H), 2.45 (dd, *J* = 2.7, 5.1Hz, 0.3H), 2.40-2.68 (m, 1H), 2.73 (q, *J* = 4.5 Hz, 1H), 2.90 (m, 0.3H), 3.09 (m, 0.1H), 3.66-3.86 (m, 1.3H), 3.93 (dd, *J* = 4.2, 13.8 Hz, 0.3H), 4.10-4.32 (1H), 4.36-4.46 (0.3H), 4.62 (0.1H), 7.34-7.42 (m, 6H), 7.64-7.71 (m, 4H), the peaks showing just integration value were too broadening to read the splitting pattern; ^{13}C NMR (75MHz, $CDCl_3$) δ 19.4, 23.9, 24.1, 26.7, 27.0, 28.3, 28.4, 28.5, 29.8, 32.7, 36.8, 38.0, 46.9, 47.5, 49.8, 50.4, 51.0, 52.4, 53.8, 55.7, 68.6, 70.3, 79.6, 79.8, 127.6, 127.7, 129.8, 133.7, 133.9, 134.1, 134.2, 135.8, 135.9, 154.8, 155.5; HRMS (EI) calcd for $C_{28}H_{38}NO_4Si$ ($M–CH_3$): 480.2570, found 480.2545.

***N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)oxy-2-[2-hydroxy-3-(4-oxo-4*H*-quinazolin-3-yl)propyl]piperidine (20).**

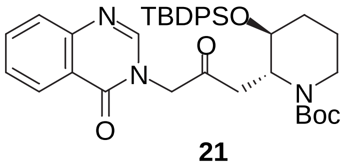


20

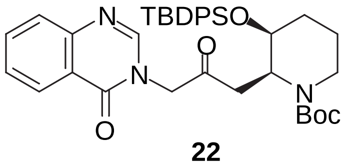
To an ice-cooled suspension of KH (41 mg, 1.03 mmol) in DMF (3 ml) was added 4-hydroxyquinazoline (184 mg, 1.26 mmol) and the mixture was stirred at 0 °C for 30 min. A solution of **19** (250 mg, 0.51 mmol) in DMF (2 ml) was added and the mixture was heated at 70 °C for 40 h. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl, and extracted with Et_2O. The extract was washed with brine, dried, concentrated, and chromatographed (hexane:EtOAc = 10:1~1:1) to give **20** (250 mg, 77%, 88% based on recovered **19**) and **19** (30 mg, 12%) each as a colorless amorphous solid; FT-IR (neat) 3388, 1678, 1610, 1473, 1425, 1369, 1155, 1109, 1084 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.05 (s, 6H), 1.33 (s, 3H), 1.43 (s, 6H), 1.45-1.80 (m, 2.6H), 1.88-1.93 (m, 0.4H), 1.96-2.14 (m, 1H), 2.42-2.90 (m, 1H), 3.56-3.77 (m, 3H), 3.99 (br d, *J* = 10.5 Hz, 1H), 4.99-4.34 (m, 2H), 4.38-4.43 (m, 0.4H), 4.53 (br s, 0.6H), 7.29-7.42

(m, 6H), 7.47-7.51 (m, 2H), 7.61-7.65 (m, 4H), 7.74 (s, 2H), 8.18 (s, 0.8H), 8.28(t, *J* = 8.1 Hz, 1.2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.2, 19.3, 23.9, 27.0, 28.3, 28.4, 33.5, 38.7, 39.5, 51.1, 53.6, 65.7, 66.6, 69.3, 69.4, 70.1, 80.4, 80.7, 122.1, 126.7, 127.0, 127.6, 127.7, 127.8, 129.7, 129.9, 133.3, 133.5, 134.2, 135.7, 135.8, 135.9, 148.2, 156.5, 157.1, 161.5; HRMS (EI) calcd for $C_{33}H_{38}N_3O_5Si$ (M–C_4H_9): 584.2581, found 584.2585.

(2*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)oxy-2-[2-oxo-3-(4-oxo-4*H*-quinazolin-3-yl)propyl]piperidine (21) and (2*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyl)oxy-2-[2-oxo-3-(4-oxo-4*H*-quinazolin-3-yl)propyl]piperidine (22).



21



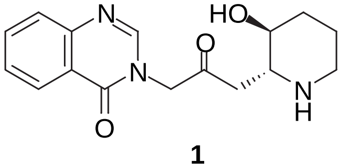
22

To a stirred solution of **20** (120 mg, 0.19 mmol) in CH_2Cl_2 (10 ml) was added Dess-Martin periodinane (198 mg, 1.36 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O, filtered through Celite, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give a 78:22 mixture of **21** and **22** (117 mg, 98%) as a colorless amorphous solid. This epimeric mixture was used for the next reaction without separation. The following spectral data of **22** and **23** were collected after separation by preparative TLC (hexane:EtOAc = 3:2).

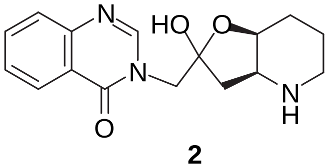
21: colorless needles (recrystallized from EtOH), mp 156-158 °C, $[\alpha]_D^{21}$ –110.8° (*c* 1.68, $CHCl_3$); FT-IR (neat) 1731, 1680, 1612, 1471, 1419, 1365, 1263, 1146, 1099, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.46 (s, 9H), 1.77 (m, 2H), 2.07 (br d, *J* = 12.3 Hz, 1H), 2.16 (br d, *J* = 11.4 Hz, 1H), 2.54 (br t, *J* = 12.0 Hz, 1H), 2.86 (br t, *J* = 12.9 Hz, 1H), 3.82 (br s, 1H), 3.96 (br d, *J* = 12.0 Hz, 1H), 4.40-4.80 (m, 3H), 7.420 (m, 7H), 7.60-7.84 (m, 6H), 7.93 (br s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.2, 27.0, 28.5, 39.2, 41.0, 52.9, 53.9, 68.9, 80.0, 122.0, 126.8, 127.1, 127.7, 127.8, 127.9, 129.9, 130.1, 133.8, 134.0, 134.3, 135.7, 136.3, 147.1, 148.4, 199.7; HRMS (EI) calcd for $C_{33}H_{36}N_3O_5Si$ (M^+–C_4H_9): 582.2424, found 582.2406.

22: a colorless viscous oil, $[\alpha]_D^{21}$ +13.7 (*c* 0.38, $CHCl_3$); FT-IR (neat) 1730, 1682, 1612, 1469, 1414, 1363, 1259, 1155, 1105 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.18-1.32 (m, 2H), 1.37 (s, 9H), 1.42-1.66 (m, 2H), 2.72 (br t, *J* = 12.6 Hz, 1H), 2.81 (br t, *J* = 12.9 Hz, 1H), 3.15 (dd, *J* = 3.0, 12.9 Hz, 1H), 3.72 (br d, *J* = 10.8 Hz, 1H), 3.89-3.94 (m, 1H), 4.68-4.80 (m, 1H) 4.70 (br d, *J* = 17.1 Hz, 1H), 5.12 (br d, *J* = 17.1 Hz, 1H), 7.40-7.45 (m, 7H), 7.65 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.74-7.78 (m, 4H), 8.02 (br s, 1H), 8.34 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.2, 23.7, 27.1, 28.3, 28.4, 36.2, 38.4, 53.0, 70.2, 80.5, 122.1, 126.9, 127.1, 127.6, 127.8, 128.1, 130.0, 130.2, 133.5, 133.8, 134.3, 135.8, 135.9, 147.3, 148.4, 201.6; HRMS (EI) calcd for $C_{33}H_{36}N_3O_5Si$ (M^+–C_4H_9): 582.2424, found 582.2416.

(+)-Febrifugine (1) and (+)-Isofeburifugine (2).



1



2

A solution of the above-mentioned epimeric mixture of **21** and **22** (130 mg, 0.20 mmol) in 6 M HCl (15 ml) was refluxed for 4 h. The reaction mixture was cooled in an ice bath, basified to pH 9 by the addition of K_2CO_3, and extracted with $CHCl_3$. The extract was dried over K_2CO_3, concentrated, and chromatographed (hexane:EtOAc = 10:1~1:1) to give febrifugine (**1**) (35 mg, 58%) and isofebrifugine (**19**) (16 mg, 27%).

Febrifugine (**1**): colorless needles (recrystallized from EtOH), mp 156-158 °C, $[\alpha]_D^{23}$ +28.0° (*c* 0.10, EtOH) [lit.[1] mp 152-153 °C, $[\alpha]_D^{23}$ +27.5° (*c* 0.10, EtOH)]; FT-IR (neat) 3288, 1726, 1674, 1612, 1473, 1365, 1325 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.26-1.40 (m, 1H), 1.46-1.58 (m, 1H), 1.73 (br d, *J* = 13.8 Hz, 1H), 1.98-2.10 (m, 3H), 2.58 (dt, *J* = 3.0, 11.7 Hz, 1H), 2.65 (dd, *J* = 7.5, 16.2 Hz, 1H), 2.82-2.87 (m, 1H), 2.96 (d, *J* = 11.4 Hz, 1H), 3.11 (dd, *J* = 4.2, 16.2 Hz, 1H), 3.28 (ddd, *J* = 4.5, 9.3, 11.4 Hz, 1H), 4.82 (d, *J* = 17.7 Hz, 1H), 4.90 (d, *J* = 17.7 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.12-7.81 (m, 2H), 7.90 (s, 1H), 8.28 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 25.7, 34.6, 44.1, 46.1, 54.9, 60.3, 72.3, 121.9, 126.9, 127.5, 127.7, 134.6, 146.5, 148.3, 161.1, 202.7; HRMS (EI) calcd for $C_{16}H_{19}N_3O_5$ (M^+): 301.1426, found 301.1399.

Isofebrifugine (**2**): colorless chunky prisms (recrystallized from MeOH), mp 134-137 °C, $[\alpha]_D^{22}$ +130° (*c* 0.30, $CHCl_3$) [lit.[2] mp 129-130 °C, $[\alpha]_D^{23}$ +131° (*c* 0.35, $CHCl_3$)]; FT-IR (neat) 3309, 1676, 1610, 1471, 1369, 1323, 1103 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.50-1.61 (m, 2H), 1.75-1.84 (m, 1H), 1.87 (d, *J* = 13.2Hz, 1H), 2.08 (dd, *J* = 3.9, 13.2 Hz, 1H), 2.14 (br s, 1H), 2.53 (dt, *J* = 1.8, 11.1 Hz, 1H), 2.99 (dd, *J* = 3.0, 11.4 Hz, 1H), 3.29 (t, *J* = 3.0 Hz, 1H), 3.89 (br d, *J* = 2.7 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 4.46 (d, *J* = 13.8 Hz, 1H), 7.50 (ddd, *J* = 1.5, 6.6, 8.1 Hz, 1H), 7.69-7.79 (m, 2H), 8.31 (s, 1H), 8.31 (dd, *J* = 1.2, 7.2 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.2, 26.9, 43.5, 44.7, 45.0, 55.8, 77.3, 77.9, 105.6, 127.0, 127.0, 127.6, 135.4, 148.3; HRMS (EI) calcd for $C_{16}H_{19}N_3O_5$ (M^+): 301.1426, found 301.1414.

References

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(2) (a) Koepeli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Koepeli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1048.