

Complementary chemoenzymatic routes to both enantiomers of febrifugine†

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Two complementary strategies for the synthesis of febrifugine are detailed based on previously developed chemoenzymatic approaches to the 3-hydroxypiperidine skeleton. The introduction of the quinazalone-containing side chain in both strategies was based on an *N*-acyliminium ion-mediated coupling reaction.

Introduction

Febrifugine (**1**) (Fig. 1) was first isolated in 1946 from *Dichroa febrifuga*¹ and later also from the more common *Hydrangea umbellata*.² Due to facile epimerization of febrifugine into isomeric isofebrifugine (**2**), the relative and absolute stereochemistry were corrected on several occasions.^{3–5} In 1999, Kobayashi and co-workers published the first asymmetric synthesis thereby also establishing the absolute stereochemistry.⁶ The latter result has spurred renewed synthetic and medicinal interest in febrifugine and derivatives.⁷ The interest mainly stems from the fact that febrifugine shows powerful antimalarial activity—it is more potent than chloroquine⁸—although severe side effects have precluded clinical use so far. In recent years, we have developed complementary chemoenzymatic approaches for the rapid construction of 3-hydroxypiperidine scaffolds, either starting from the amino acid allysine ethylene acetal,⁹ or from an enantiopure cyanohydrin.¹⁰ It was envisaged that these pathways would also be well suited for the synthesis of febrifugine and potentially useful derivatives. In this contribution, we detail two chemoenzymatic strategies which have resulted in enantioselective syntheses of either enantiomer of febrifugine.

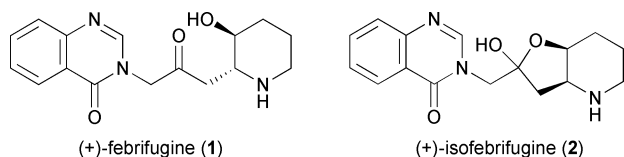
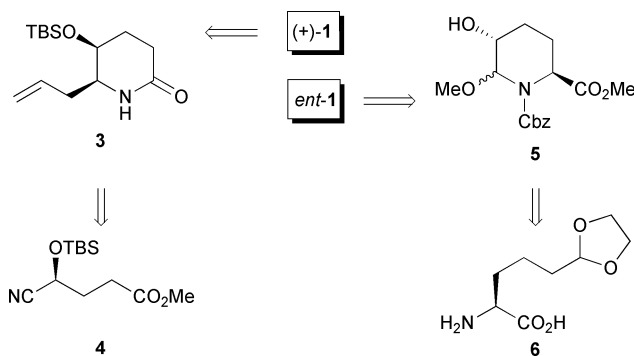


Fig. 1 Febrifugine and isofebrifugine.

A retrosynthesis of the first approach is shown in Scheme 1, where it was anticipated that the allyl function of lactam **3** could be converted in a number of steps into the desired quinazalone moiety



Scheme 1 Retrosynthesis.

of febrifugine. It was shown previously in our group,^{10b} that lactam **3** can be readily obtained from the chemoenzymatically generated cyanohydrin **4** using *N*-acyliminium ion chemistry.

The second approach, in this case leading to *ent*-**1** was thought to proceed *via* the known hydroxypiperidic acid **5**,^{9a} involving introduction of the quinazalone-containing side chain and removal of the ester function. The latter compound in turn can be readily obtained from L-allysine ethylene acetal **6**.

Results

Our studies commenced with reductive cyclization of cyanohydrin **4** (Scheme 2), followed by conversion of the resulting *N,N*-acetal into the *N,O*-acetal **7** *via* diazotation.^{10b} In initial approaches, we focused on introducing the side chain as a whole *via* the corresponding stannyl enol ether **9** (M = SnOTf) as previously described by Kobayashi *et al.* for exocyclic *N*-acyliminium ions.^{7d} However, this strategy appeared unsuccessful in our hands using the endocyclic *N*-acyliminium precursor **7** despite trying a variety of conditions and Lewis acids, also in combination with the corresponding silyl enol ether (M = TMS).

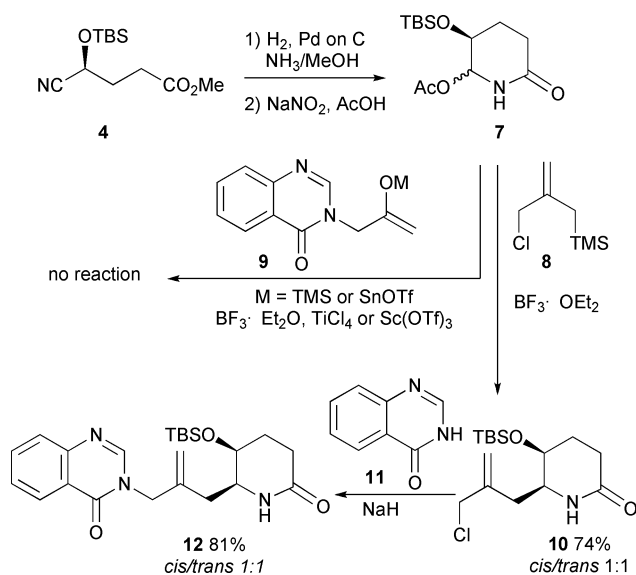
Due to these unsuccessful results, we anticipated that the side chain could be built up in two steps, first by introducing a 2-(chloromethyl)allyl moiety, followed by nucleophilic displacement of the chloride by a quinazalone nucleophile. Thus, *N*-acyliminium ion precursor **7** was reacted with allylsilane **8** under the influence of BF₃·OEt₂ to give the corresponding adduct **10** in good yield (74%) as a 1:1 mixture of *cis/trans*-isomers. Both isomers could be successfully reacted with quinazalone

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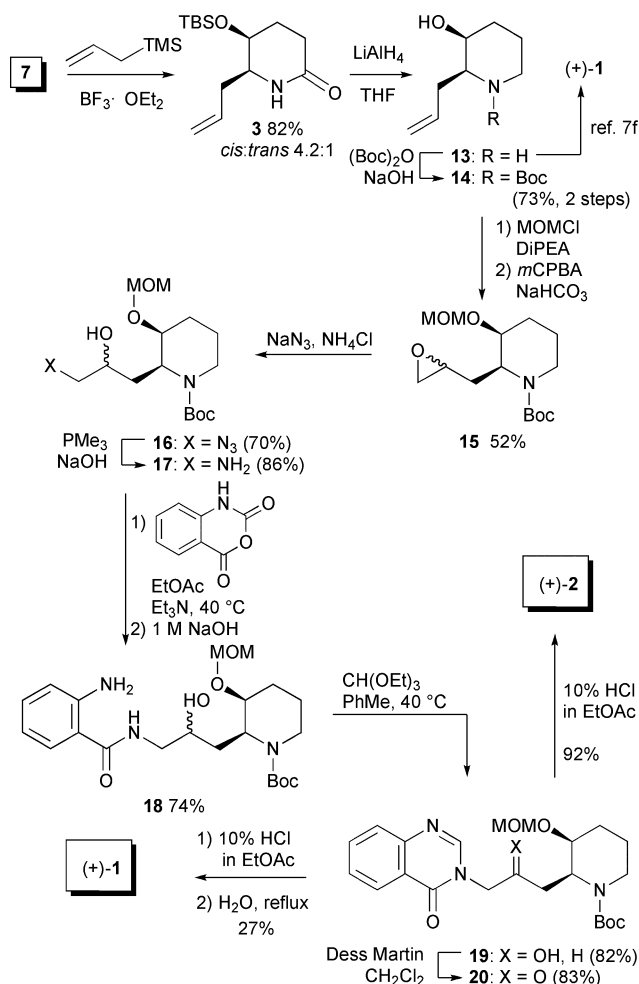
† Electronic supplementary information (ESI) available: Experimental procedures of compounds **4**, **16–20**, **22** and ¹H and ¹³C spectra of all new compounds. See DOI: 10.1039/b901670h



Scheme 2 Initial approaches to febrifugine.

11 in the presence of NaH to give the substitution product **12** in 81% yield. At this stage, selective reduction of the lactam carbonyl was in order, which was attempted in a variety of ways. However, none of our approaches (*e.g.* Boc-protection followed by reduction, Boc-protection followed by enol triflate formation and subsequent reduction, selective thionolactam formation followed by reduction) led to successful selective reduction to the corresponding piperidine system, so this pathway was also abandoned.

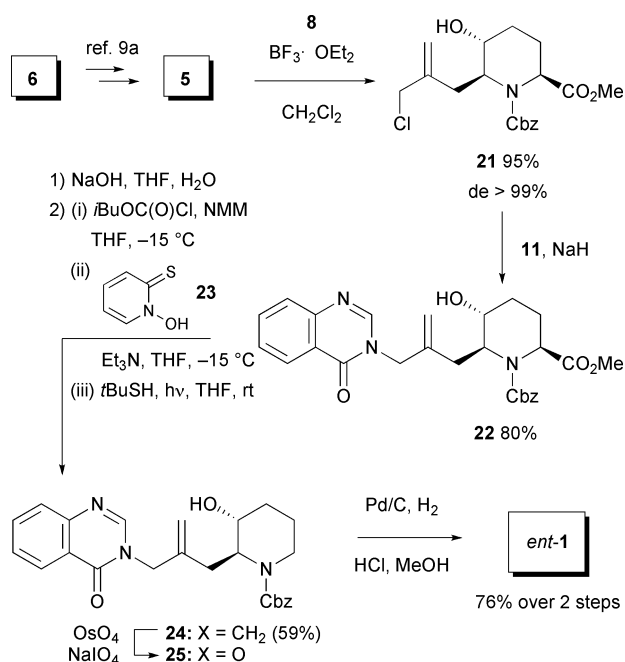
We then chose to build-up the side chain more gradually, which we anticipated would also be advantageous for preparing derivatives of febrifugine. In this case, precursor **7** was reacted with allyltrimethylsilane and $\text{BF}_3 \cdot \text{OEt}_2$ to give lactam **3** as a 4.2:1 mixture of *cis/trans*-isomers (Scheme 3).^{10b} After chromatographic separation of both diastereoisomers, we continued with the *cis*-isomer. Reduction with LiAlH_4 resulted in the formation of **13** in good yield, which at this stage represents a formal synthesis of febrifugine, since literature describes its further conversion into the natural product.^{7f} However, we chose to develop a synthetically more versatile route offering opportunities to synthesize analogues at a later stage. To this end, the amine and hydroxyl were protected with a Boc and a MOM group, respectively. Subsequent *m*CPBA-mediated epoxidation afforded **15** as a 2.5:1 mixture of diastereoisomers in 52% yield over two steps. The epoxide was then regioselectively opened with sodium azide to give **16** (70%), followed by Staudinger reduction to form amine **17** in 86% yield. The amine function was intended to serve as a handle for introduction of the aromatic part. Thus, treatment with isoic anhydride (Et_3N , EtOAc , 40°C) led to introduction of anthranilic acid at the amine and hydroxy function. Subsequent hydrolysis of the ester then afforded the desired amide **18** in a satisfactory 74% yield. The quinazolinone moiety was then formed *via* condensation under the influence of triethyl orthoformate in toluene at elevated temperatures, providing **19** in 82% yield. The final steps involved Dess Martin periodinane oxidation to give ketone **20** (83%), followed by protecting group removal with HCl in EtOAc to afford isofebrifugine (**2**), which was isomerized



Scheme 3 Synthesis of (+)-febrifugine.

in refluxing water into (+)-febrifugine (**1**). Analytical data of both natural products were in accordance with those reported in literature.⁶

The second approach commenced with the earlier reported strategy to convert allylsine ethylene acetal **6** into the corresponding *N,O*-acetal **5** in a four step sequence.⁹ At this stage, we also attempted to introduce the side chain as a whole applying similar conditions as mentioned before, but we did not observe any product formation either. Then, we switched to the two-step sequence described in Scheme 4. This pathway proceeded *via* the introduction of the (chloromethyl)allyl moiety by reacting *N,O*-acetal **5** with 2-(chloromethyl)allylsilane **8** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ yielding **21** in 95% yield as sole diastereoisomer. Next, the skeleton of febrifugine was completed *via* a successful reaction of **21** with the deprotonated quinazolinone **11** to afford **22** in 80% yield. Subsequent quantitative ester saponification (NaOH , $\text{THF}/\text{H}_2\text{O}$), followed by a Barton decarboxylation, involving mixed anhydride formation, coupling with thiolactam **23** and *t*BuSH-mediated radical removal of the carboxylate, provided **24** in a satisfactory yield of 59%. Finally, *ent*-febrifugine was obtained in 76% yield *via* oxidative cleavage of the allylic double bond with osmium tetroxide and sodium periodate, followed by hydrogenolysis of the Cbz-protection group.

Scheme 4 Synthesis of *ent*-febrifugine.

Conclusions

We successfully applied our previously developed strategies for the synthesis of 3-hydroxypiperidines to the total synthesis of febrifugine, providing access to both enantiomers. The first approach proceeds in 15 steps with an overall yield of 2.5% starting from cheap materials and offering various possibilities for the synthesis of analogues. Using the second strategy, febrifugine is obtained in 10 steps with 32% overall yield. One of the reasons for the higher efficiency is the higher selectivity in the *N*-acyliminium ion reaction, which renders the epimerization of isofebrifugine into febrifugine superfluous. Access to the starting material is somewhat more limited, however, and there are also fewer possibilities for the synthesis of analogues as compared to the first route. The synthesis of series of analogues and their biological evaluation are currently under investigation in our laboratory.

Experimental section

(2*S*,3*S*)-2-(3-Azido-2-hydroxypropyl)-3-methoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (16)

Epoxide **15** (20 mg, 0.066 mmol) was dissolved in a mixture of methanol (4 mL) and H₂O (0.5 mL), and sodium azide (22 mg, 0.33 mmol) and ammonium chloride (11 mg, 0.2 mmol) were added. The reaction mixture was stirred overnight at 70 °C and then quenched with saturated aqueous NaHCO₃ (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. Flash chromatography (1:5 EtOAc:heptane) afforded the two pure diastereoisomers **16**_{major} (11 mg, 0.032 mmol, 50%) and **16**_{minor} (4 mg, 0.012 mmol, 20%) as colorless oils.

Major-16: [α]_D²⁰ −15.7 (c 0.31, CH₂Cl₂). IR (film) 3434, 2967, 2933, 2881, 2094, 1679, 1649, 1419, 1161, 1031 cm^{−1}. ¹H-NMR (400 MHz, CDCl₃, rotamers) δ 4.69–4.690 (m, 3H), 4.35–4.34 (m, 1H), 3.90–3.86 (m, 1H), 3.73 (m, 1H), 3.57–3.56 (m, 1H), 3.38–3.35 (m, 3H), 3.23–3.19 (m, 2H), 2.65–2.59 (m, 2H), 1.87–1.86 (m, 2H), 1.71 (m, 3H), 1.69 (m, 9H). ¹³C-NMR (75 MHz, CHCl₃) δ 156.5, 95.0, 80.9, 73.4, 66.8, 56.1, 55.6, 49.4, 38.6, 28.6, 28.3, 25.7, 24.0. HRMS (ESI⁺): calcd for C₁₅H₂₈N₄NaO₅ (*M*+Na⁺): 367.1957, found: 367.1944.

Minor-16: [α]_D²⁰ +25.3 (c 0.20, CH₂Cl₂). IR (film) 3438, 2933, 2872, 2107, 1684, 1666, 1416, 1148, 1040 cm^{−1}. ¹H-NMR (400 MHz, CDCl₃, rotamers) δ 4.67 (m, 2H), 4.44–4.39 (m, 1H), 3.89 (m, 2H), 3.62 (m, 2H), 3.37–3.32 (m, 5H), 2.77–2.70 (m, 1H), 1.94–1.91 (m, 3H), 1.62 (m, 2H), 1.46 (m, 10H). ¹³C-NMR (75 MHz, CHCl₃) δ 155.9, 95.2, 80.6, 74.5, 70.4, 56.3, 55.6, 51.7, 38.8, 29.8, 28.4, 25.7, 24.0. HRMS (ESI⁺): calcd for C₁₅H₂₈N₄NaO₅ (*M*+Na⁺): 367.1957, found: 367.1932.

(2*S*,3*S*)-2-[3-(2-Aminobenzoylamine)-2-hydroxypropyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (18)

To a solution of **17**_{major} (239 mg, 0.75 mmol) in dry EtOAc (70 mL) were added isatoic anhydride (429 mg, 2.63 mmol) and triethyl amine (151 μ L, 1.125 mmol) and the mixture was stirred overnight at 40 °C. The reaction was quenched by the addition of saturated aqueous NaHCO₃ (50 mL) and extracted with EtOAc (4 × 75 mL). The combined organic layers were washed with brine (150 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. The crude product was dissolved in a mixture of THF (20 mL), methanol (20 mL) and aqueous 1 M NaOH (20 mL). After stirring for 2 h, the reaction was quenched by adding saturated aqueous NaHCO₃ (70 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. Flash chromatography (1:2–3:1 EtOAc:heptane) afforded product **18**_{major} (222 mg, 0.51 mmol, 67%) as a colorless oil. [α]_D²⁰ +8.8 (c 0.19, CH₂Cl₂). IR (film) 3443, 3339, 2971, 2928, 2889, 1649, 1416, 1152, 1031 cm^{−1}. ¹H-NMR (400 MHz, CDCl₃, rotamers) δ 7.35–7.50 (m, 1H), 7.33 (m, 1H), 6.71–6.63 (m, 3H), 5.50 (m, 2H), 4.67–4.66 (m, 2H), 4.65–4.59 (m, 1H), 3.88–3.81 (m, 2H), 3.76–3.70 (m, 1H), 3.55–3.54 (m, 1H), 3.38 (m, 3H), 3.20–3.14 (m, 1H), 1.88–1.68 (m, 5H), 1.60–1.45 (m, 12H). ¹³C-NMR (75 MHz, CHCl₃) δ 169.2, 156.6, 148.6, 132.1, 127.3, 117.1, 116.6, 116.3, 95.0, 80.8, 73.6, 66.4, 55.6, 49.6, 44.6, 38.7, 28.7, 28.3, 25.7, 24.0. HRMS (ESI⁺): calcd for C₂₂H₃₅N₃NaO₆ (*M*+Na⁺): 460.2424, found: 460.2381.

(2*S*,3*S*)-2-[2-Hydroxy-3-(4-oxo-4*H*-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (19)

To a solution of **18**_{major} (232 mg, 0.52 mmol) in toluene (10 mL) were added *p*-TsOH (20 mg, 0.11 mmol) and triethyl orthoformate (260 mg, 1.56 mmol) and the mixture was stirred overnight at 40 °C. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. Flash chromatography (1:2–2:1 EtOAc:heptane) afforded product **19**_{major} (197 mg, 0.44 mmol, 85%) as a colorless oil. [α]_D²⁰ +59.8 (c 0.28,

CH₂Cl₂). IR (film) 2971, 2941, 2876, 2353, 2340, 1684, 1645, 1558, 1152, 1035 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃, rotamers) δ 8.29–8.22 (m, 2H), 7.73 (m, 2H), 7.48 (m, 1H), 4.68 (m, 3H), 4.48–4.38 (m, 2H), 3.86 (m, 1H), 3.73 (m, 2H), 3.60–3.57 (m, 1H), 3.37 (m, 3H), 2.70 (m, 1H), 1.88 (m, 2H), 1.70 (m, 2H), 1.53–1.41 (m, 2H), 1.37 (m, 9H). ¹³C-NMR (75 MHz, CHCl₃) δ 161.3, 156.5, 148.3, 148.0, 134.1, 127.5, 126.8, 126.5, 122.0, 95.0, 80.9, 73.4, 65.3, 55.6, 51.8, 49.5, 38.7, 28.7, 28.2, 25.7, 24.0. HRMS (ESI⁺): calcd for C₂₃H₃₃N₃NaO₆ (M+Na⁺): 470.2267, found: 470.2267.

(2*S*,3*S*)-2-[2-Oxo-3-(4-oxo-4*H*-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (20)

Both diastereoisomers of **19** (14 mg, 0.035 mmol) were dissolved in CH₂Cl₂ (5 mL) and Dess-Martin periodinane (39 mg, 0.091 mmol) was added. After stirring overnight, the reaction was quenched with saturated aqueous NaHCO₃ (5 mL) and extracted with dichloromethane (4 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtrated and the solvent was removed under reduced pressure. Flash chromatography (1:2–2:1 EtOAc:heptane) afforded product **20** (10 mg, 0.022 mmol, 83%). [α]_D²⁰ +41.3 (c 0.20, CH₂Cl₂). IR (film) 2976, 2937, 2885, 1675, 1606, 1351, 1148, 1031 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃, rotamers) δ 8.29–8.27 (m, 1H), 8.04 (m, 1H), 7.76–7.71 (m, 2H), 7.51–7.47 (m, 1H), 5.24–5.20 (m, 1H), 5.00–4.98 (m, 2H), 4.69 (m, 2H), 3.86–3.84 (m, 1H), 3.75–3.73 (m, 1H), 3.40 (m, 3H), 3.07–04 (m, 1H), 2.85–2.65 (m, 2H), 2.07–2.04 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.44 (m, 10H). ¹³C-NMR (75 MHz, CHCl₃) δ 201.1, 160.9, 155.3, 148.2, 146.9, 134.2, 127.5, 127.1, 126.6, 121.8, 95.5, 80.5, 74.1, 55.7, 53.4, 51.2, 38.4, 36.5, 28.3, 25.4, 23.7. HRMS (ESI⁺): calcd for C₂₃H₃₁N₃NaO₆ (M+Na⁺): 468.2111, found: 468.2148.

(+)-Febrifugine-2HCl (1)

A solution of **20** (76 mg, 0.17 mmol) in methanol (10 mL) and concentrated HCl (1 mL) was stirred for 2 h and then concentrated *in vacuo* to yield isofebrifugine-2HCl (**2**, 59 mg, 0.16 mmol, 92%). Isofebrifugine-2HCl (59 mg, 0.16 mmol) was dissolved in 1M NaOH (2 mL) and EtOAc (2 mL) and after stirring for 10 min extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtrated and concentrated *in vacuo*. The free amine was dissolved in H₂O (20 mL) and heated to 80 °C for 20 min. Concentrated HCl (4 mL) was added and the solvent was removed under reduced pressure. Crystallization from ethanol afforded (+)-febrifugine-2HCl (**1**). mp = 209 °C. [α]_D²⁰ +13.2 (c 0.07, D₂O). ¹H-NMR (400 MHz, CD₃OD) δ 8.79 (s, 1H), 8.29–8.27 (m, 1H), 7.98–7.95 (m, 1H), 7.78–7.76 (m, 1H), 7.72–7.68 (m, 1H), 5.23–5.12 (m, 2H), 3.64–3.60 (m, 1H), 3.45–3.40 (m, 2H), 3.35–3.37 (m, 1H), 3.10–2.88 (m, 2H), 2.10–1.99 (m, 2H), 1.78–1.74 (m, 1H), 1.60–1.57 (m, 1H). ¹³C-NMR (75 MHz, CD₃OD) δ 201.5, 160.6, 151.3, 143.4, 137.3, 130.3, 128.4, 124.4, 121.9, 68.3, 58.1, 56.3, 45.0, 40.1, 31.7, 21.5. HRMS (ESI⁺): calcd for C₁₆H₂₀N₃O₃ (M+H⁺): 302.1504, found: 302.1505. Analytical data of both natural products were in accordance with those reported in literature.⁶

(2*S*,5*R*,6*S*)-6-(2-Chloromethylallyl)-5-hydroxypiperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (21)

To a solution of **5** (400 mg, 1.24 mmol) in CH₂Cl₂ (10 mL) were added 2-chloromethylallyltrimethylsilane (720 μL, 3.96 mmol) and BF₃·OEt₂ (462 μL, 2.46 mmol) at –30 °C. The reaction was warmed to rt, stirred for 3 h and quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (2:1–5:1 EtOAc:heptane) afforded product **21** as a colorless oil (449 mg, 1.18 mmol, 95%). [α]_D²⁰ –40 (c 1.19, CH₂Cl₂). IR (film) 3444, 2949, 1753, 1694, 1408, 1292, 1207, 1011 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃, rotamers) δ 7.31–7.29 (m, 5H), 5.18–4.81 (m, 5H), 4.34–4.26 (m, 2H), 3.86–3.80 (m, 2H), 3.68–3.65 (m, 3H), 2.60–2.51 (m, 2H), 2.23–2.13 (m, 2H), 1.75–1.61 (m, 2H). No clear ¹³C-NMR due to rotamers. HRMS (ESI⁺): calcd for C₁₉H₂₄ClNNaO₅ (M+Na⁺): 404.1241, found: 404.1241.

(2*S*,5*R*,6*S*)-5-Hydroxy-6-[2-(4-oxo-4*H*-quinazolin-3-ylmethyl)-allyl]piperidine-1-carboxylic acid benzyl ester (24)

To a solution of **22** (123 mg, 0.25 mmol) in THF (1 mL) was added 1 M aqueous NaOH (1.84 mL) in 4 portions over 3 h. The solution was neutralized with 1 M aqueous HCl to pH = 7, concentrated *in vacuo* and acidified to pH = 2 with 1M aqueous HCl. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic phases are dried over Na₂SO₄ and concentrated *in vacuo*. The crude acid (120 mg, 0.25 mmol) was dissolved in THF (4 mL) and cooled to –15 °C. Isobutyl chloroformate (34 μL, 0.25 mmol) and *N*-methylmorpholine (28 μL, 0.25 mmol) were added subsequently and the mixture was stirred for 5 minutes, followed by the addition of a solution of 2-mercaptopyridine *N*-oxide (40 mg, 0.30 mmol) and Et₃N (44 μL, 0.30 mmol) in THF (8 mL). The reaction mixture was stirred for 1 h with the exclusion of light, where after 2-methyl-2-propanethiol (86 μL, 0.75 mmol) was added and the mixture was exposed to a sunlamp for 3 h. The reaction was quenched with H₂O (20 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (100:0–95:5 EtOAc:MeOH) afforded product **24** as a colorless oil (64 mg, 0.148 mmol, 59%). [α]_D²⁰ +64 (c 0.19, CH₂Cl₂). IR (film) 3417, 1674, 1609, 1255, 774, 733, 696 cm⁻¹. ¹H-NMR (200 MHz, CDCl₃, rotamers) δ 8.39–8.28 + 8.11 (2 x m, 2H), 7.77–7.70 (m, 2H), 7.55–7.47 (m, 1H), 7.32–7.30 (m, 5H), 5.14 (m, 2H), 4.93 (m, 1H), 4.63 (m, 3H), 4.14 (m, 1H), 3.88 (m, 1H), 2.97–2.85 (m, 1H), 2.22–2.05 (m, 3H), 1.97–1.71 (m, 3H), 1.49–1.37 (m, 1H). No clear ¹³C-NMR due to rotamers. HRMS (ESI⁺): calcd for C₂₅H₂₇N₃NaO₄ (M+Na⁺): 456.1893, found: 456.1899.

(5*R*,6*S*)-3-[3-(3-Hydroxy-piperidin-2-yl)-2-oxo-propyl]-3*H*-quinolizin-4-one-2HCl (*ent*-febrifugine-2HCl) ((–)-1)

To a solution of **24** (59 mg, 0.14 mmol) in a mixture of THF (0.9 mL) and H₂O (1.7 mL) were added OsO₄ (2 mol%, 17 μL of a solution of 4 wt% in H₂O) and NaIO₄ (73 mg, 0.34 mmol). After stirring for 2 h, the reaction was quenched with saturated aqueous NaHCO₃ (4 mL), and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo* and dissolved in methanol. Pd/C (7.5 mg, 0.07 mmol)

and 1M aqueous HCl (154 μ L) were added and the solution was stirred under H₂ (1 atm) for 2 h. The reaction mixture was filtered over Celite and the solvent was evaporated under reduced pressure to afford product (–)-1·2HCl (32 mg, 0.11 mmol, 76%). [α]_D²⁰ –11 (c 0.31, H₂O). ¹H-NMR (400 MHz, CD₃OD) δ 8.92 (s, 1H), 8.31–8.29 (m, 1H), 7.99–7.97 (m, 1H), 7.79–7.77 (m, 1H), 7.74–7.71 (m, 1H), 5.25–5.14 (m, 2H), 3.67–3.62 (m, 1H), 3.49–3.40 (m, 2H), 3.35–3.37 (m, 1H), 3.11–2.97 (m, 2H), 2.10–1.99 (m, 2H), 1.78–1.74 (m, 1H), 1.60–1.57 (m, 1H). ¹³C-NMR (75 MHz, D₂O) δ 202.4, 161.7, 149.3, 143.5, 136.9, 129.7, 127.2, 124.5, 120.6, 67.8, 56.7, 56.0, 44.4, 39.3, 30.5, 20.5 Spectral data are in accordance with (+)-febrifugine (1).⁶

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Notes and references

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