# Concise Asymmetric Synthesis of Antimalarial Alkaloid (+)-Febrifugine

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**Abstract:** An asymmetric total synthesis of antimalarial alkaloid (+)-febrifugine is accomplished in 23% overall yield over 14 steps from readily available starting materials. The synthesis features a $SmI_2$-mediated reductive cross-coupling of chiral *N*-*tert*-butanesulfinyl imine with aldehyde.

**Key words:** antimalarial, asymmetric synthesis, febrifugine, cross-coupling

(+)-Febrifugine (**1**) and (+)-isofebrifugine (**2**, Figure 1), structurally related quinazolinone alkaloids isolated from the roots of *Dichroa febrifuga* Lour (Chinese name: Cháng Shan) and related *hydrangea* plants, were identified as the principles showing potent antimalarial activity.[1a–c] Structures of these alkaloids had been elusive[1d–f] ever since their isolation in 1947 until being unambiguously elucidated by Kobayashi and co-workers in 1999 via asymmetric total synthesis.[2] Although febrifugine was precluded from being a potential clinical drug owing to its strong liver toxicity and other adverse side effects,[3] renewed efforts have been exerted from synthetic community aiming at developing efficient synthetic pathways which could provide valuable leads for antimalarial drug discoveries.[2,4]

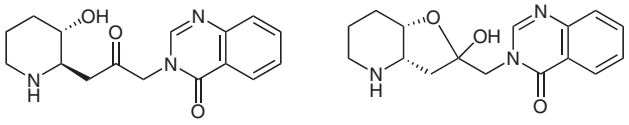
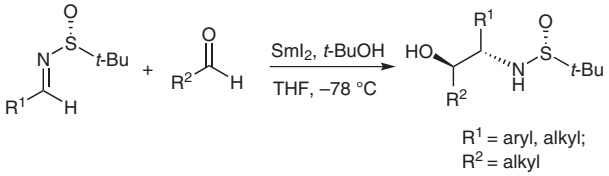


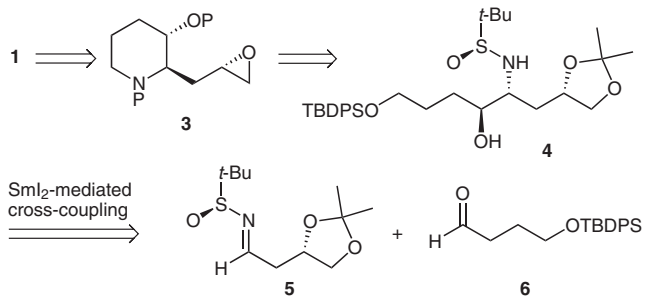

**Figure 1**

Recently, our laboratory developed a highly efficient and practical approach for the synthesis of enantiomerically pure β-amino alcohol by $SmI_2$-mediated reductive cross-coupling of chiral *N*-*tert*-butanesulfinyl imines with aldehydes, with the newly formed hydroxyl group and amido group being in *anti* orientation (Scheme 1).[5] As a part of our continuing program applying this methodology in syntheses of bioactive natural products, herein we present an efficient enantioselective synthesis of (+)-febrifugine (**1**) by taking advantage of this methodology.




**Scheme 1**

As depicted in Scheme 2, retrosynthetically (+)-febrifugine (**1**) could be derived from 4-quinazolone and piperidine epoxide **3**.[4e,g] Containing all the necessary functional groups with defined stereochemistry, the key intermediate β-amido alcohol **4** would be a proper precursor for **3**. Amido alcohol **4** could be derived from *N*-*tert*-butanesulfinyl imine **5** and aldehyde **6** by employing $SmI_2$-mediated reductive cross-coupling. Based on our previous findings, chiral imine **5** with *S*-configuration at the sulfur atom was to be utilized in the cross-coupling reaction in order to generate β-amido alcohol **4** with the desired absolute configurations at the two newly formed carbon centers. It is worth mentioning that the *N*-sulfinyl group as a powerful chiral directing group[5] could be used to dominate over the isolated unsymmetrical acetonide moiety in determining the stereochemical outcome of the reaction.[6]




**Scheme 2** Retrosynthesis of (+)-febrifugine (**1**)

Our synthesis started with the preparation of segment **5** from readily available inexpensive materials (Scheme 3).

Alcohol **7** (prepared from L-malic acid through known procedures)[7]was subjected to oxidation under Swern's conditions[8] to afford crude aldehyde which, without further purification, was treated with Ellman's reagent[9] to afford imine **5** in 85% overall yield. Aldehyde **6** was readily obtained by Swern oxidation of monoprotected butane-

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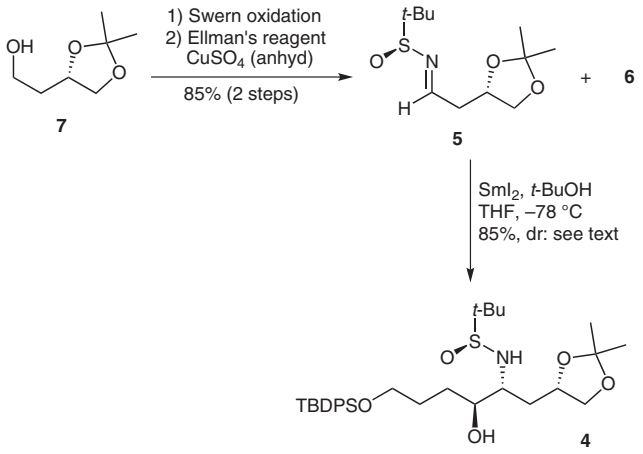
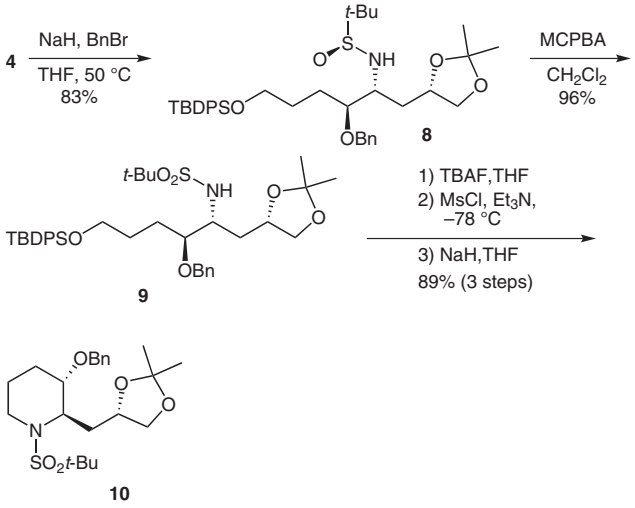



**Scheme 3** Synthesis of amido alcohol **4**




**Scheme 4** Synthesis of sulfonamide **10**

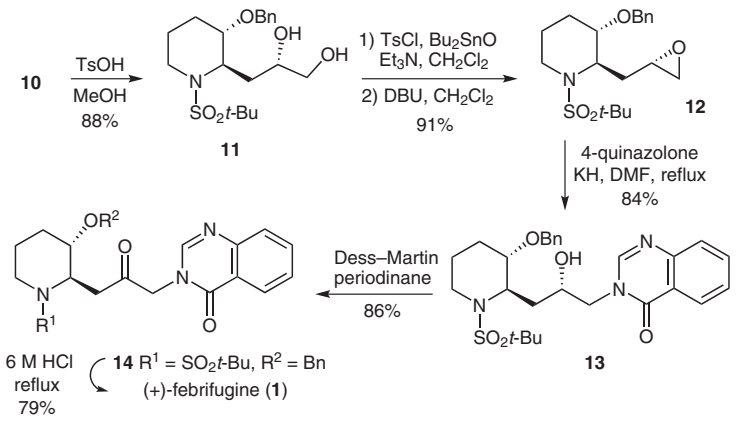
1,4-diol. With imine **5** and aldehyde **6** in hand, we moved on to the crucial $SmI_2$-mediated reductive cross-coupling reaction (Scheme 3). Initial attempts afforded the coupling product amido alcohol **4** in good yield, however, with varying diastereoselectivity as high as 86.0:11.8:2.0:0.2, which was determined by HPLC-MS since $^1$H NMR of the product did not afford differentiable signals belonging to each diastereomers. To our delight, after numerous trials we found that, to obtain consistently high diastereoselectivity, it was crucial to keep the internal low temperature for sufficiently long time. This entailed slow addition of the substrates mixture solution to $SmI_2$ at –78 °C and subsequent maintenance of the reaction mixture at the same temperature for several hours. Furthermore, freshly prepared substrates, compared to the aged ones, were found to give higher diastereoselectivity in the coupling reaction. Eventually, the cross-coupling reaction proceeded to furnish **4** in 85% yield with typical 93.5:4.0:2.0:0.5 diastereoselectivity when the coupling reaction was performed with freshly prepared imine **5** and aldehyde **6** under –78 °C for 7 hours.[15] Thus, the two required stereocenters were established successfully.

The next task was to elaborate amido alcohol **4** into the piperidine derivative. As shown in Scheme 4, the newly formed hydroxyl group in amido alcohol **4** was first converted into benzyl ether **8** in 83% yield by treatment with NaH/BnBr in THF. Surprisingly, additive TBAI was found to be unbeneficial, leading to a less clean reaction and decreased yield. Subsequent exposure of sulfinamide **8** to MCPBA delivered sulfonamide **9** in 96% yield, which was then elaborated into the piperidine derivative **10** by a three-step reaction sequence. Removal of the silyl group with TBAF, mesylation of the resulting free hydroxyl group with $MeSO_2Cl/Et_3N$ followed by treatment with NaH in THF provided *N*-sulfonyl piperidine **10** in 89% yield over 3 steps. Oxidation of **8** to **9** proved necessary since **8**, when subjected to the above identical reaction sequence, failed to undergo a clean mesylation due to the competitive mesylation of the nucleophilic oxygen of the sulfinyl group,[10] which rendered the subsequent base-mediated cyclization complicated.

With compound **10** in hand, efforts were continued toward the total synthesis of (+)-febrifugine (**1**, Scheme 5). Acetonide **10** was then exposed to *p*-toluenesulfonic acid in methanol to give diol **11**, which was converted to epoxide **12** in 91% yield by sequential monotosylation[11] and then base-induced cyclization. An alternative one-step procedure involving *N*-tosylimidazole[12] in the presence of NaH could convert **11** into **12** in 85% yield. Epoxide **12** was then reacted with 4-quinazolone potassium salt[13] to give alcohol **13** in 84% yield, which in turn was treated with Dess–Martin periodinane[14] to furnish **14** in 86% yield. Finally, **14** was subjected to global deprotection in refluxing 6 N hydrochloric acid[4e] to produce (+)-febrifugine (**1**) in 79% yield.[15] The $^1$H NMR, $^{13}$C NMR, melting point, and optical rotation for the synthesized **1** are in well agreement with the reported data.[2b,4g] It's worth mentioning that, thanks to the *anti* orientation of the hydroxyl and the amido group in amido alcohol **4**, and hence the *trans* substitution pattern in piperidine **14**, (+)-febrifugine (**1**) was isolated as the major product in good yield in the deprotection step.[4c,g]

In conclusion, we have accomplished the asymmetric synthesis of (+)-febrifugine in a concise and practical manner from readily available inexpensive starting materials with 23% overall yield. The synthetic route features the $SmI_2$-mediated reductive cross-coupling of chiral *N-tert*-butanesulfinyl imine with aldehyde developed by our group, and can be easily adapted to permit rapid access to various febrifugine analogues by using diversified *N-tert*-butanesulfinyl imines and/or aldehydes and various substituted quinazolone as the reaction substrates. Further endeavors applying this methodology in synthesizing febrifugine analogues and other natural products are currently under way.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.




**Scheme 5** Completion of the synthesis of (+)-febrifugine (**1**)

## Acknowledgment

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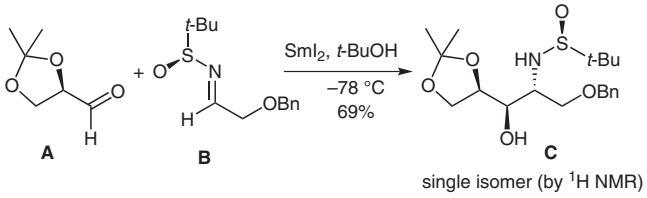
(6) Indeed, a preliminary study, which utilized aldehyde **A** and imine **B** (Scheme 6) as the substrates to investigate the impact of a stereocenter adjacent to the reaction site, has established that the *N*-sulfinyl group determines the stereochemistry of the product **C**, whose structure was confirmed by X-ray crystallography (CCDC deposit no. 724597). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.




**Scheme 6**

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(15) **Selected Experiment and Spectroscopic Data**

**Preparation of Compound 4**

To the solution of $SmI_2$ (4.0 mmol in 20 mL of THF) the solution of imine **5** (480 mg, 1.90 mmol), aldehyde **6** (1.14 g, 3.80 mmol) and *t*-BuOH (380 μL, 4.0 mmol) in 20 mL of THF was dropped in slowly under argon at –78 °C.

The mixture was stirred vigorously for 7 h at the same temperature and then quenched by 10 mL sat. $Na_2S_2O_3$ aq solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed by sat. brine and then dried over anhyd $MgSO_4$, filtered, and concentrated under vacuum. After flash silica gel chromatography, 952 mg (85%) of the pure product **4** was obtained as yellow oil.

Compound **4**: $[\alpha]_D^{28}$ +33.0 (*c* 2.70, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 6.9 Hz, 4 H), 7.45–7.26 (m, 6 H), 4.46 (d, *J* = 4.8 Hz, 1 H), 4.29 (m, 1 H), 4.12 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.74–3.67 (m, 3 H), 3.52 (t, *J* = 7.8 Hz, 1 H), 3.42 (m, 1 H), 3.05 (d, *J* = 4.8 Hz, 1 H), 1.89–1.52 (m, 6 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.24 (s, 9 H), 1.05 (s, 9 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.48, 133.67, 129.55, 127.57, 109.57, 73.65, 72.59, 69.65, 63.79, 57.96, 55.57, 32.16, 29.77, 29.14, 26.83, 26.79, 25.73, 22.62, 19.11. FT-IR (thin film): 3414, 3283, 2983, 2959, 2933, 2860, 1112, 1052 $cm^{-1}$. ESI-MS: *m/z* = 576.3 $[M + H]^+$, 598.3 $[M + Na]^+$. MALDI-HRMS: *m/z* calcd for $C_{31}H_{49}NO_5SSiNa$ $[M + Na]^+$: 598.2993; found: 598.3011.

Compound **14**: $[\alpha]_D^{25}$ +64.6 (*c* 0.60, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.26 (m, 1 H), 7.98 (s, 1 H), 7.81–7.73 (m, 2 H), 7.51 (m, 1 H), 7.32–7.24 (m, 5 H), 4.96 (d, *J* = 17.6 Hz, 1 H), 4.75 (d, *J* = 17.6 Hz, 1 H), 4.63–4.52 (m, 2 H), 4.42 (s, 1 H), 3.62–3.59 (m, 2 H), 3.11–3.03 (m, 2 H), 2.75 (m, 1 H), 2.05–1.92 (m, 2 H), 1.62–1.47 (m, 2 H), 1.38–1.33 (m, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 200.67, 160.95, 148.33, 146.60, 138.18, 134.44, 128.26, 127.70, 127.61, 127.54, 127.29, 126.67, 121.86, 74.29, 70.81, 61.98, 54.80, 54.70, 43.16, 42.05, 24.10, 23.24, 19.62. FT-IR (thin film): 2928, 2870, 1308, 936 $cm^{-1}$. ESI-MS: *m/z* = 512.4 $[M + H]^+$, 534.4 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{27}H_{34}N_3O_5S$ $[M + H]^+$: 512.2214; found: 512.2232.

Compound **1**: mp 137–139 °C; $[\alpha]_D^{26}$ +27.3 (*c* 0.45, EtOH) [lit.[1b] mp 139–140 °C; $[\alpha]_D^{25}$ +28.0 (*c* 0.5, EtOH)]. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.28 (m, 1 H), 7.89 (s, 1 H), 7.77–7.72 (m, 2 H), 7.52 (t, *J* = 6.7 Hz, 1 H), 4.90 (d, *J* = 17.7 Hz, 1 H), 4.81 (d, *J* = 17.7 Hz, 1 H), 3.28 (br s, 1 H), 3.11 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.96 (d, *J* = 11.0 Hz, 1 H), 2.87 (br d, *J* = 3.9 Hz, 1 H), 2.65 (dd, *J* = 15.9, 6.7 Hz, 1 H), 2.58 (m, 1 H), 2.08 (br d, *J* = 10.7 Hz, 1 H), 1.84 (br, 2 H), 1.70 (br d, *J* = 12.4 Hz, 1 H), 1.52 (br d, *J* = 12.8 Hz, 1 H), 1.34 (br d, *J* = 10.1 Hz, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 202.64, 161.01, 148.23, 146.39, 134.54, 127.64, 127.44, 126.80, 121.88, 72.26, 60.18, 54.85, 45.97, 44.04, 34.48, 25.65. FT-IR (thin film): 3304, 3287, 2941, 2931, 2858, 2814, 1722, 1674, 1614, 1475, 1363, 1084, 773, 698 $cm^{-1}$. ESI-MS: *m/z* = 302.2 $[M + H]^+$, 324.2 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{20}N_3O_3$ $[M + H]^+$: 302.1500; found: 302.1499.