# A Convergent Enantioselective Synthesis of the Anti-Malarial Agent (+)-Febrifugine

Amir Ashoorzadeh, Vittorio Caprio*

Department of Chemistry, University of Auckland, 23 Symonds St., Auckland, New Zealand
Fax +64(9)3737422; E-mail: v.caprio@auckland.ac.nz

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**Abstract:** Chiral pool derived 3-benzyloxy-3,4,5,6-tetrahydropyridine *N*-oxide underwent regio- and diastereoselective 1,3-dipolar cycloaddition with *N*-allylquinazolone to give a cycloadduct that was elaborated to (+)-febrifugine a potent anti-malarial alkaloid.

**Key words:** alkaloids, piperidines, nitrones, cycloadditions, reductive ring-opening

(+)-Febrifugine (**1**) and (+)-isofebrifugine (**2**) are structurally related quinazolinone alkaloids isolated from the roots of *Dichroa febrifugia* and *Hydrangea umbellate* (Figure 1).[1] Febrifugine exhibits potent anti-malarial activity,[2] shown to arise from potentiation of macrophage NO production[3] and, to date, no parasite resistance to **1** has been reported. As such, this compound is an important lead in the search for new anti-malarial drugs and a number of total syntheses of febrifugine in racemic and optically pure form have been published.[4]

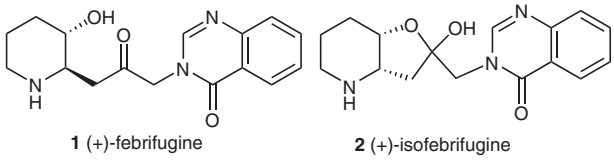
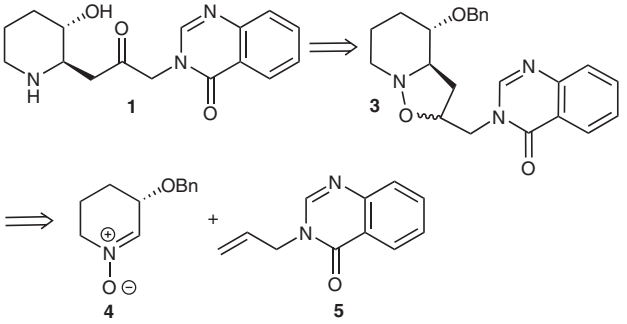



**Figure 1**

We have recently developed a concise synthetic route to chiral, non-racemic 3-hydroxy-3,4,5,6-tetrahydroypyridine *N*-oxides from L-glutamic acid. In an effort to both probe the synthetic utility of these potentially useful chiral building blocks and to develop an efficient synthetic route to febrifugine we have designed an approach to this alkaloid that utilizes nitrone (*S*)-**4** as a key intermediate. Hatakeyama and co-workers have developed a linear synthesis of febrifugine proceeding via the in situ generation of nitrones of type **4**, derived from 1,4-butanediol, in the presence of allyl alcohol.[4o] In contrast, our highly convergent approach centres on the ring-opening of isoxazolidine **3**, formed by stereo- and regioselective 1,3-dipolar cycloaddition of *N*-allylquinazolone **5** to chiral-pool derived nitrone **4** (Scheme 1). Our prediction that isoxazolidine **3** would be the major regioisomer is based on reports that 3,4,5,6-tetrahydropyridine *N*-oxide undergoes highly regioselective 1,3-dipolar addition with a variety of 1-substituted alkenes in favour of the 2-substituted hexahydroisoxazolo[2,3-*a*]pyridine cycloadduct.[5] We also predicted that the incoming dipolarophile would approach nitrone **4** from the face opposite to the benzyloxy substituent to give an isoxazolidine with the desired *trans*-stereochemistry.




**Scheme 1**

Chiral 3-alkoxy- and 3-silyloxy-1-pyrroline *N*-oxides have been widely used as intermediates in alkaloid syntheses.[6] These compounds are synthesised by regioselective oxidation of the corresponding *N*-hydroxypyrrolidines. The *N*-hydroxypyrrolidines, in turn, are conveniently accessed by cyclisation of bis-mesylates, derived from L-malic acid.[6k] We planned to utilize a similar strategy to access the corresponding, hitherto unisolated, tetrahydropyridine *N*-oxide **4** from L-glutamic acid. Thus, our proposed synthetic route to **4** centres on the conversion of L-glutamic acid to a suitably protected 2-hydroxy-1,5-ditosylate followed by cyclisation to give a *N*-hydroxypiperidine that we predict would then undergo oxidation to give a mixture of regioisomeric tetrahydropyridine *N*-oxides. In practice, the requisite bis-tosylate was accessed from L-glutamic acid in 5 steps (Scheme 2). Acid-catalysed ring-opening of lactone acid **6**, derived from L-glutamic acid,[7] followed by protection of the resulting hydroxydiester with benzyl bromide gave benzyl ether **7**. After surveying a number of benzylation conditions it was discovered that optimum yields were obtained using benzyl bromide in the presence of 1.5 equivalents of freshly prepared silver oxide.[8] Reduction of compound **7** using 2 equivalents of LAH followed by di-tosylation of the resulting diol with tosyl chloride in the presence of DMAP at 0 °C gave 1,5-ditosylate **8**. Cyclisation of **8** proceeded in the presence of hydroxylamine hydrochloride in triethylamine under reflux to give *N*-hydroxy-3-benzyloxy-

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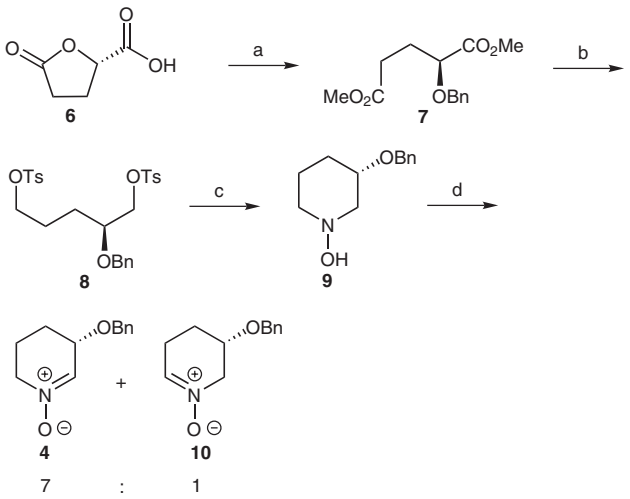
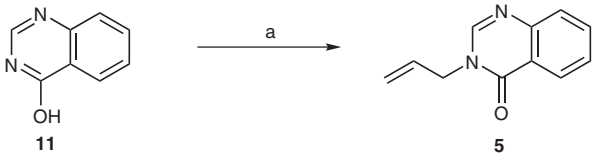
piperidine **9** which was then oxidized, using manganese dioxide in dichloromethane at 0 °C,[9] to give a mixture of readily separable regioisomeric nitrones **4** and **10** in a 7:1 ratio. In contrast to 3,4,5,6-tetrahydropyridine *N*-oxide, which rapidly dimerises,[10] nitrone **4** exhibits no decomposition after storage in a freezer for several weeks.



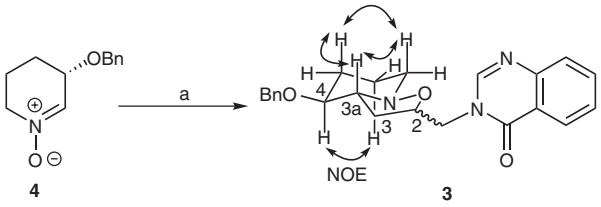

**Scheme 2** *Reagents and conditions*: (a) (i) concd HCl, MeOH, reflux, 12 h, 93%; (ii) BnBr, $Ag_2O$, EtOAc, r.t., 48 h, 79%; (b) (i) $LiAlH_4$, $Et_2O$, 24 h, 88%; (ii) TsCl, DMAP, $Et_3N$, $CH_2Cl_2$, r.t., 12 h, 86%; (c) $NH_2OH{\cdot}HCl$, $Et_3N$, reflux, 4 h, 74%; (d) $MnO_2$, $CH_2Cl_2$, 0 °C, 12 h, 88% overall.

The dipolarophile required in this synthesis, *N*-allylquinazolone **5**, was readily accessed in one step from commercially available 4-hydroxyquinazoline **11**. Stirring a mixture of compound **11** and allyl bromide in freshly prepared sodium methoxide in methanol overnight resulted in N-allylation to give **5** in good yield (Equation 1).[11]



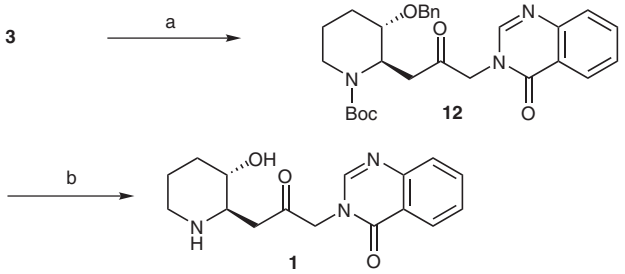

**Equation 1** *Reagents and conditions*: (a) allyl bromide, NaOMe, MeOH, r.t., 12 h, 78%.

The key 1,3-dipolar cycloaddition between nitrone **4** and dipolarophile **5** proceeded to completion in toluene after 24 hours at reflux (Equation 2).[12] The major product isolated was cycloadduct **3**, possessing the desired regiochemistry and *trans*-stereochemistry for the synthesis of the natural product. The presence of a downfield methine proton signal at δ = 4.40 ppm assigned to H-2 confirmed the regiochemistry of addition and NOE data obtained for compound **3** confirmed that addition with the desired stereoselectivity had taken place. While analysis of 2D NOESY spectra recorded in DMSO-$d_6$ at 90 °C did not allow unambiguous assignment of C-2 stereochemistry, the correlations observed were clearly indicative of *trans*-stereochemistry across the C3a-C4 bond.




**Equation 2** *Reagents and conditions*: (a) **5**, PhMe, reflux, 24 h, 48%.

Isoxazolidine **3** was then further elaborated to the target compound according to Scheme 3. The N-O bond of compound **3** was reductively cleaved using zinc/acetic acid and the resulting crude 3-hydroxyamine protected using di-*tert*-butyl dicarbonate. The Boc-protected hydroxyamine was oxidized using Dess–Martin periodinane in the presence of pyridine to give ketone **12**.[13] Finally, deprotection of compound **12** using boiling aqueous 6 M HCl under the conditions developed by Kobayashi and coworkers[4j] proceeded to give (+)-febrifugine (**1**), $[\alpha]_D^{24}$ +26.4 (*c* 0.30, EtOH), mp 139–141 °C {lit.[1b] mp 139–140 °C; $[\alpha]_D^{25}$ +28 (*c* 0.5, EtOH)} in 67% yield.




**Scheme 3** *Reagents and conditions*: (a) (i) Zn, HOAc, reflux; (ii) $BOC_2O$, $Et_3N$, $CH_2Cl_2$; (iii) Dess–Martin periodinane, pyridine, $CH_2Cl_2$, quant.; (b) 6 M HCl, reflux, 67%.

In conclusion a highly convergent and enantioselective synthesis of (+)-febrifugine has been developed proceeding in 12 steps from L-glutamic acid and is highly amenable to scale-up. Furthermore, the key intermediate utilized in this approach – a readily available enantiopure 3-hydroxytetrahydropyridine *N*-oxide has been shown to be a stable chiral building block of much potential. Future work will concentrate on further probing the synthetic utility of nitrone **4** and on incorporating our approach to febrifugine into a programme directed towards the design of new anti-malarial agents.

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(12) Solid *N*-allylquinazolone **5** (0.34 g, 1.83 mmol) was added to a solution of nitrone **4** (0.38 g, 1.85 mmol) in toluene. The mixture was stirred under reflux for 24 h and solvent was then removed under reduced pressure. The crude product was purified by column chromatography on silica gel using $Et_2O$–MeOH 49:1 as eluent to give isoxazolidine **3** as a colourless oil (0.35 g, 48%). $[\alpha]_D^{20}$ –41.4 (*c* 1.0, $CHCl_3$). IR (neat): $\nu_{max}$ = 3062, 2944, 1674, 1610 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$, 90 °C): δ = 1.20–1.32 (m, 1 H), 1.45–1.60 (m, 1 H), 1.64–1.74 (m, 1 H), 2.00 (dddd, 1 H, *J* = 4.0, 4.0, 4,0, 12.7 Hz), 2.12–2.22 (m, 1 H), 2.24–2.31 (m, 1 H), 2.55–2.70 (m, 2 H), 3.12 (ddd, 1 H, *J* = 1.8, 4.0, 4.0 Hz), 3.35–3.45 (m, 1 H), 4.05 (dd, 1 H, *J* = 7.5, 13.9 Hz), 4.22 (dd, 1 H, *J* = 3.9, 13.9 Hz), 4.39 (m, 1 H), 4.48 (d, 1 H, *J* = 12.0 Hz), 4.57 (d, 1 H, *J* = 12.0 Hz), 7.22–7.36 (m, 5 H), 7.54 (ddd, 1 H, *J* = 1.1, 7.1, 8.1 Hz), 7.67 (d, 1 H, *J* = 7.7 Hz), 7.81 (ddd, 1 H, *J* = 1.6, 7.2, 8.5 Hz), 8.20 (dd, 1 H, *J* = 1.4, 8.1 Hz), 8.22 (s, 1 H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$, 90 °C): δ = 19.8, 27.5, 38.6, 48.4, 51.1, 66.3, 69.5, 72.5, 76.0, 121.0, 125.5, 126.21, 126.5, 126.6, 126.8, 127.4, 133.5, 138.3, 147.4, 147.5, 159.6. HRMS (EI): *m/z* calcd for $[C_{23}H_{25}N_3O_3]^+$: 391.1896. Found: 391.1893.

(13) The specific rotation and spectral data of this compound was in agreement with the reported values; see ref.[4j]