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Stereocontrolled synthesis of a potent antimalarial alkaloid, (+)-febrifugine

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Abstract—A novel and stereocontrolled synthetic path to a potential antimalarial piperidine alkaloid, (+)-febrifugine, was established by employing the reductive deamination and simultaneous recyclization of a proline derivative with samarium diiodide, as a key step.

Febrifugine **1** and isofebrifugine **2**, isolated from the roots of *Dichroa febriguga* Lour. (Chinese name: Cháng Shan),[1] are recognized as active principles against malaria.[2] These alkaloids were approximately 100 times as effective as quinine against *Plasmodia lophurae* in ducks.[1a] It is also known that there is an equilibrium between those alkaloids under acidic conditions.[3] Moreover, isofebrifugine was transformed into febrifugine by heating.[1a] Due to their attractive biological activity, a number of racemic and chiral syntheses of these compounds have been established to date (Fig. 1).[4]

Recently, we have developed a general carbon–nitrogen bond cleavage reaction of α-amino carbonyl compounds by using samarium diiodide as a one-electron reducing agent, as shown in Figure 2.[5] As an extension of our ongoing program utilizing this reaction in the synthesis of biologically active natural products,[6] we are interested in developing an effective and stereocontrolled synthesis of febrifugine starting from readily accessible (+)-4-hydroxyproline.

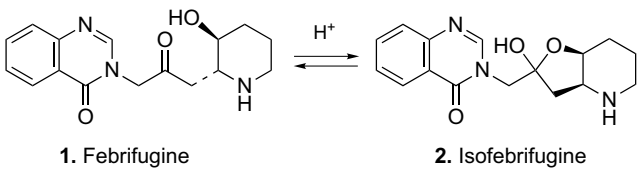

Figure 1. Structures of febrifugine and isofebrifugine.

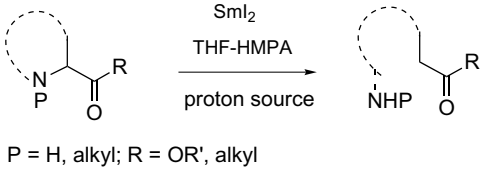

Figure 2. SmI_2-promoted reductive deamination.

N-Boc-(4*S*)-*tert*-butyldimethylsiloxy-L-proline methyl ester **3** was prepared from the commercially available (4*R*)-hydroxy-L-proline according to the literature.[7] The silyl ether **3** was then oxidized with ruthenium tetroxide to give the desired lactam **4**.[7] Although a number of strategies for stereoselective introduction of a side chain at the 5-position have so far been developed,[8] some of them were found to suffer from limitations, in terms of the nucleophile species, conversion yield, reaction conditions, and stereoselectivity. Thus, we attempted to develop an alternative procedure for introduction of an alkyl side chain at the 5-position stereoselectively, and we were able to establish a facile procedure by applying a tandem Horner–Emmons–Michael reaction,[9] for this purpose, as follows.

Reduction of the lactam **4** with lithium triethylborohydride, followed by treatment of the resulting aminal **5** with triethyl phosphonoacetate in the presence of NaH gave the ester **6**, stereoselectively, as the sole product.

Keywords: Febrifugine; Isofebrifugine; Tandem Horner–Emmons–Michael reaction; Samarium diiodide; Antimalarial activity.
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The stereochemistry at the 5-position would be controlled during the Michael addition of the nitrogen to the α,β-unsaturated ester, generated by the Horner–Emmons reaction, where the addition took place from the sterically less hindered side of the substrate (Scheme 1).

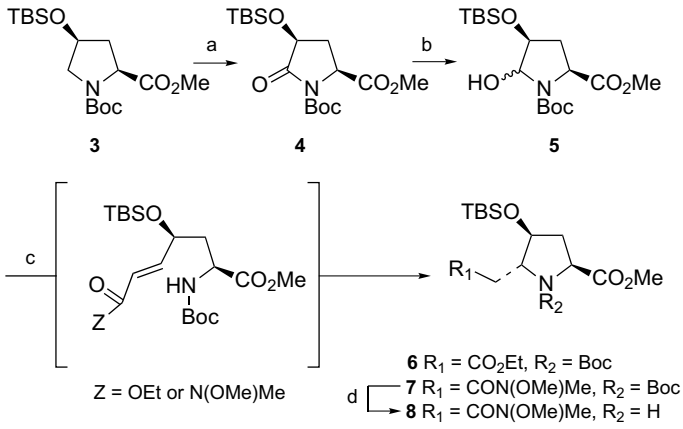
Using diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)-phosphonate under similar reaction conditions, the amide **7** was also obtained, in good yield. The amide **7** seems to be a versatile precursor for further modification of the side chain. The stereochemistry of the amide **7** was unambiguously determined by the X-ray crystallographic analysis of the corresponding NH compound **8** (Scheme 2).[10]

Treatment of the amide **7** with methylmagnesium bromide afforded the methyl ketone **9**, which on methylenation with the Wittig reagent gave the olefin **10**, in 43% yield. The yield of the olefination of the ketone **9** could be improved by using Tebbe's reagent[11] providing **10** in 81% yield.

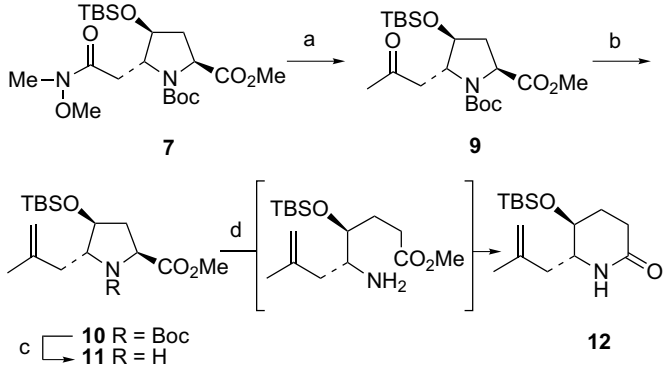
Selective removal of the Boc group of **10** was carried out by using zinc bromide providing the amine **11**, which without further purification was subjected to samarium diiodide-promoted reductive deamination reaction in the presence of MeOH as the proton source to furnish the δ-lactam **12**,[12] where carbon–nitrogen bond cleavage reaction and subsequent recyclization took place simultaneously, as expected (Scheme 3).

Lithium aluminum hydride reduction of the lactam **12** afforded the corresponding hydroxy-amine **13** which, on treatment with CbzCl, gave the desired carbamate **14**. After protection of the secondary hydroxy group as its benzyl ether, the resulting benzyl ether **15** was converted to the methyl ketone **16** by ozonolysis (Scheme 4).

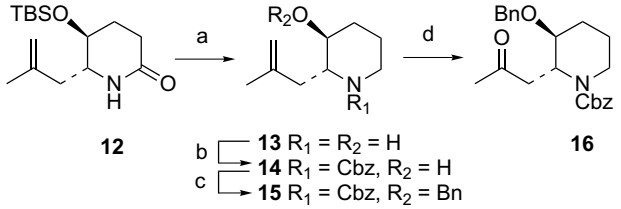
Finally, bromination of **16** by treatment with trimethylsilyl triflate and subsequently with NBS, resulted in the formation of the α-bromoketone which, without purification, was further coupled with 4-hydroxyquinazoline in the presence of potassium hydride to furnish the protected febrifugine **17**. The spectroscopic data of the synthesized compound were identical with those reported, $[\alpha]_D$ −36.0 (*c* 0.51, $CHCl_3$), {lit.[4h] $[\alpha]_D^{31}$ −22.0 (*c* 1.0, $CHCl_3$)}. Deprotection of **17** with 6 N HCl gave febrifugine **1**, mp 139–140 °C; $[\alpha]_D$ +16.0 (*c* 0.4, MeOH) {lit.[1b]



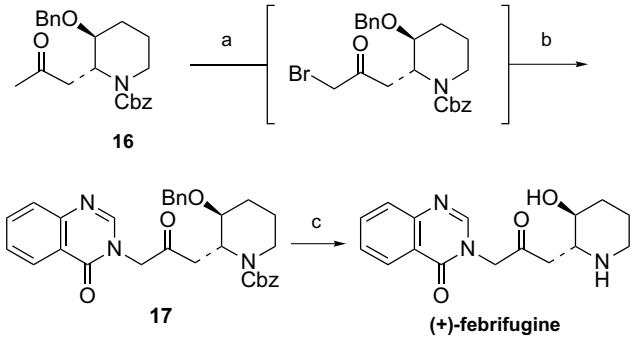
Scheme 1. Reagents and conditions: (a) RuO_2 (cat), $NaIO_4$, AcOEt/H_2O, rt (86%); (b) $LiEt_3BH$, THF, −78 °C; (c) $(EtO)_2P(O)CH_2CO_2Et$ or $(EtO)_2P(O)CH_2CON(Me)OMe$, NaH, THF, rt (**6**: 62% from **4**, **7**: 83% from **4**); (d) TFA, CH_2Cl_2, 0 °C to rt (56%).



Scheme 2. Reagents and conditions: (a) MeMgBr, THF, 0 °C (88%); (b) Tebbe's reagent, THF, −40 °C to rt (81%) (c) $ZnBr_2$, CH_2Cl_2, rt; (d) SmI_2, THF–HMPA, MeOH, 0 °C to rt (90% from **10**).



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF, 65 °C; (b) CbzCl, TEA, DMAP, CH_2Cl_2, rt (95% from **12**); (c) BnBr, NaH, DMF, 0 °C (90%); (d) O_3, MeOH, −78 °C then Me_2S (92%).



Scheme 4. Reagents and conditions: (a) 1. TMSOTf, DIPEA, CH_2Cl_2, rt; 2. NBS, rt; (b) 4-hydroxyquinazoline, KH, DMF, 70 °C (57% from **16**); (c) 6 N HCl, reflux (92%).

mp 139–140 °C; lit.[4b] mp 138–139 °C; lit.[1c] $[\alpha]_D$ +13.0 (*c* 0.65, MeOH)}.

In summary, we were able to establish an alternative stereoselective chiral synthesis of febrifugine **1** by employing reductive deamination of an α-amino carbonyl compound as a key reaction. In this synthesis, we found that the intramolecular Michael addition of the nitrogen to the α,β-unsaturated carbonyl compound proceeded stereoselectively to give the desired product as the sole product. This methodology is obviously applicable for the introduction of a side chain at the 5-position of the substituted pyrrolizidine ring system.

Acknowledgements

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10. Crystal data for **8**: mp 89–91 °C (recrystallized from *n*-hexane). $C_{16}H_{32}N_2O_5Si$, $M=360.52$, monoclinic, space group $P2_1$, $a=6.7052(5)$, $b=7.6518(7)$, $c=20.608(2)$ Å, $\beta=91.043(7)°$, $V=1057.2(2)$ Å^3, $Z=2$, $D_{calcd}=1.129$ g/cm^3. The data were collected at a temperature of 25 ± 1 °C using the ω scan technique to a maximum 2θ values of 136.6°. Of the 5762 reflections that were collected, 2073 were unique ($R_{int}=0.036$); equivalent reflections were merged. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The structure was solved using SIR92. $R=0.045$, $Rw=0.039$.
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12. Selected data for **12**: colorless oil. $[\alpha]_D$ +12.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.72 (3H, s), 1.93–1.99 (1H, m), 1.90 (1H, dd, $J=10.4$, 13.7 Hz), 1.77–1.86 (1H, m), 2.34 (1H, ddd, $J=6.4$, 10.0, 18.0 Hz), 2.47–2.55 (2H, m), 3.26 (1H, ddd, $J=3.0$, 6.9, 10.4 Hz), 3.59 (1H, ddd, $J=3.6$, 6.9, 10.0 Hz), 4.80 (1H, s), 4.93 (1H, s), 5.62 (1H, br s); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.2, 17.9, 21.7, 25.6, 28.7, 28.8, 42.7, 55.9, 69.9, 114.9, 140.8, 170.9; IR (thin film) 3220, 2960, 2960, 2860, 1670, 1090, 840, 770 cm^{-1}; EIMS (*m*/*z*) 283 (M^+); Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.51; H, 10.32, N; 4.97.