Pergamon

Tetrahedron Letters 40 (1999) 2175–2178

TETRAHEDRON LETTERS

# Catalytic Asymmetric Synthesis of Febrifugine and Isofebrifugine

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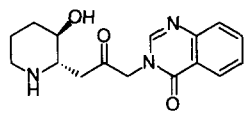
Received 10 December 1998; revised 5 January 1999; accepted 11 January 1999

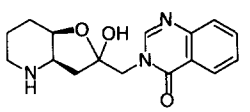
***Abstract:*** *Antimalarial alkaloids, febrifugine (**1**) and isofebrifugine (**2**), were synthesized from simple achiral starting materials using tin(II)-catalyzed catalytic asymmetric aldol reaction and lanthanide-catalyzed aqueous three-component reaction as the key steps. These unambiguous total syntheses revealed that the absolute configurations of febrifugine and isofebrifugine were not (2'S, 3'R) and (2'R, 3'R) as reported previously but (2'R, 3'S) and (2'S, 3'S), respectively.*



Febrifugine (**1**) and isofebrifugine (**2**) (Scheme 1), alkaloids first found in the Chinese plant *Dichroafebrifuga*[1] and later in the common hydrangea,[2] have attracted considerable attention due to their potentially powerful antimalarial activity.[3] Although some synthetic studies have been made,[4] unambiguous asymmetric synthesis of febrifugine and isofebrifugine has never been performed, to the best of our knowledge. In this paper, we describe asymmetric total synthesis of febrifugine and isofebrifugine using catalytic asymmetric reactions as the key steps. We also report here revision of the absolute configurations of febrifugine and isofebrifugine based on the unambiguous total synthesis.[5]



Febrifugine (**1**, reported form)



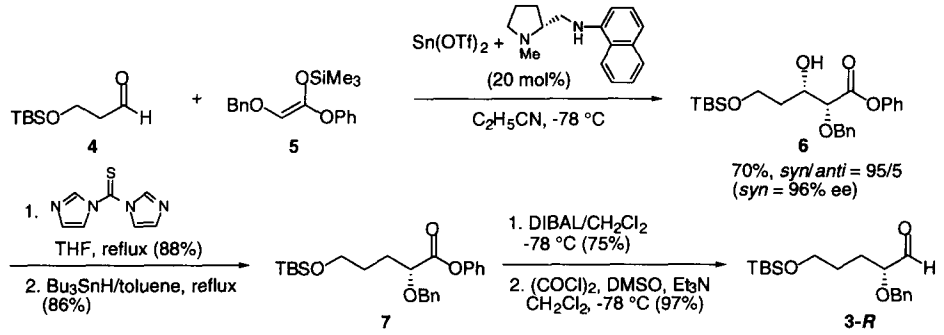
Isofebrifugine (**2**, reported form)

**Scheme 1.** Reported Structure of Febrifugine and Isofebrifugine

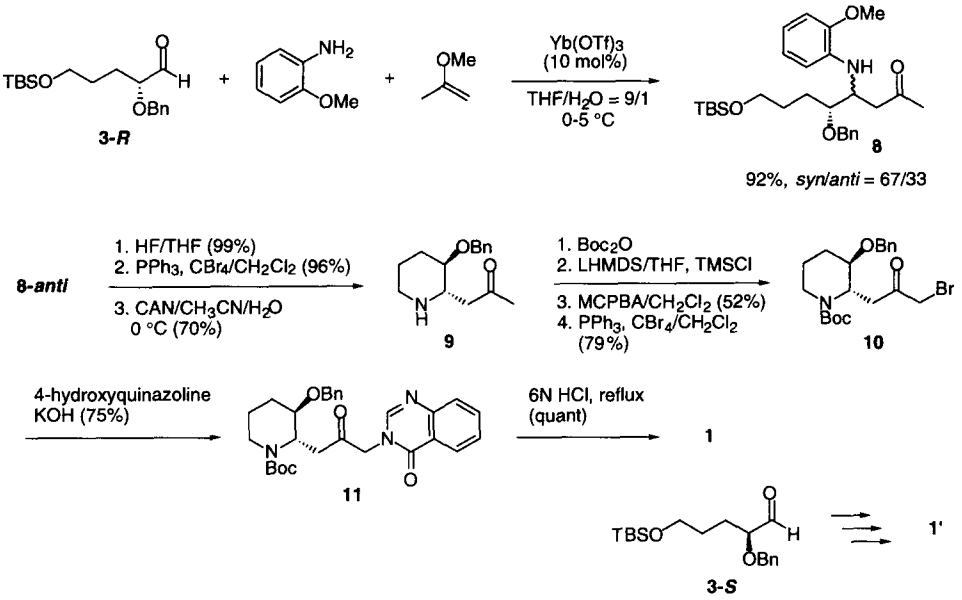
Our synthetic strategy is derived from our own protocol, a lanthanide-catalyzed three-component reaction of aldehyde **3-*R***, 2-methoxyaniline, and 2-methoxypropene, in aqueous media.[6] The aldehyde **3-*R*** was prepared using our protocol, tin(II)-catalyzed asymmetric aldol reaction (Scheme 2).[7] In the presence of a chiral tin(II) Lewis acid (20 mol%) derived from tin(II) triflate and a chiral diamine, 3-*t*-butyldimethysiloxypropanal (**4**)[8] reacted with 2-benzyloxy-1-trimethylsiloxy-1-phenoxyethene (**5**) in propionitrile at -78 °C to afford the corresponding aldol-type adduct (**6**) in 70% yield with excellent diastereo- and enantioselectivities (*syn*/*anti* = 95/5, *syn* = 96% ee). The hydroxyl group at the 3-position was removed

0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)00142-2

via 2 steps,[9] and the resulting phenyl ester (**7**) was reduced to form an alcohol, which was converted to the key aldehyde (**3-*R***) under Swern oxidation conditions.[10,11]




**Scheme 2.** Synthesis of Key Aldehyde **3**

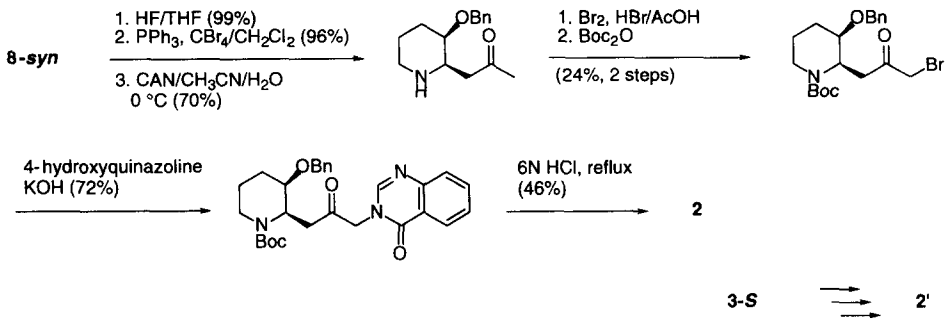



**Scheme 3.** Synthetic Route to Febrifugine

The three-component reaction of aldehyde **3-*R***, 2-methoxyaniline, and 2-methoxypropene was performed in the presence of 10 mol% of ytterbium triflate ($Yb(OTf)_3$) in aqueous media ($THF/H_2O$ = 9/1).[6] The reaction proceeded smoothly at 0-5 °C to afford the desired Mannich-type adduct (**8**) in 92% yield (*syn*/*anti* = 67/33). The diastereomers were separated and the *syn*- and *anti*-adducts (**8-*syn*** and **8-*anti***) were used for the synthesis of isofebrifugine (**2**) and febrifugine (**1**), respectively. The *anti*-adduct (**8-*anti***) was then treated with HF to remove the TBS protecting group, and the following bromination gave a spontaneously cyclized adduct whose *N*-protected group (2-methoxyphenyl group) was removed using cerium ammonium nitrate (CAN)[12,13] to afford **9**. Piperidine **9** was protected as its *N*-Boc group and was treated with

lithiumhexamethyldisilazido (LHMDS) and then trimethylsilyl chloride (TMSCl). The resulting silyl enol ether was oxidized and then brominated to give **10**. The coupling reaction of bromoacetone **10** with 4-hydroxyquinazoline was carried out using potassium hydroxide (KOH)[14] to afford **11**, whose protecting groups were successfully removed using 6N HCl to afford **1**. After recrystallization from ethanol, it was found that its $^{1}H$ and $^{13}C$ NMR specta[15] and melting point were completely consistent with those reported,[16] but the optical rotation of synthetic **1** was negative while the reported optical rotation was positive.[17] This meant that the structure of febrifugine (**1**) shown in Scheme 1 was antipode of the natural product. We then repeated the synthesis according to Scheme 3 using aldehyde **3-*S***. All physical data of the synthetic sample including the optical rotation this time were completely consistent with those reported in the literature.

Similarly, both enantiomers of isofebrifugine (**2**) starting from **8-*syn*** and antipode were prepared (Scheme 4). It was shown that the optical rotation of the synthetic sample from the antipode was consistent with that reported in the literature. It is now concluded that the structures of febrifugine and isofebrifugine were not **1** and **2**, but **1'** and **2'** as shown in Scheme 5.




**Scheme 4.** Synthetic Route to Isofebrifugine

Febrifugine (**1'**, revised form) Isofebrifugine (**2'**, revised form)

**Scheme 5.** Revised Structure of Febrifugine and Isofebrifugine

In summary, catalytic asymmetric synthesis of febrifugine and isofebrifugine was performed using tin(II)-catalyzed asymmetric aldol reaction and lanthanide-catalyzed aqueous three-component reaction as the key steps. These unambiguous total syntheses revised the absolute configurations of febrifugine and isofebrifugine from (2'*S*, 3'*R*) and (2'*R*, 3'*R*) to (2'*R*, 3'*S*) and (2'*S*, 3'*S*), respectively.

**Acknowledgment.** We are grateful to Prof. Y. Oshima and Dr. Y. Takaya (Tohoku University) for providing us with authentic samples of febrifugine and isofebrifugine and spectral data. This work was

partially supported by CREST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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16 138-140 °C (lit. 139-140 °C,[1b] 137-138 °C,[2a] 139-141 °C.[2b]).

17 $[\alpha]_D^{24}$ -28.0 ° (c = 0.24, EtOH) (lit.[1b] $[\alpha]_D^{25}$ +28 ° (c= 0.5, EtOH)).