ORGANIC LETTERS

2000
Vol. 2, No. 20
3193−3195

# A Diastereocontrolled Synthesis of (+)-Febrifugine: A Potent Antimalarial Piperidine Alkaloid

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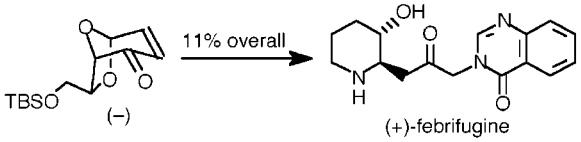
**Received July 26, 2000**

## ABSTRACT




**A diastereocontrolled synthesis of (+)-febrifugine, a potent antimalarial piperidine alkaloid, has been achieved using a chiral block having a bicyclo[3.2.1]octane framework which exhibits inherent convex-face selectivity.**

Although (+)-febrifugine **1** and (+)-isofebrifugine **2**, constituents of the Chinese medicinal plant *Dichroa febrifuga* Lour. (Chinese name: Chang Shan), were isolated more than a half century ago as active principles against malaria,[1] their absolute structures have just been determined quite recently as shown[2] (Figure 1). Their antimalarial activity as well as

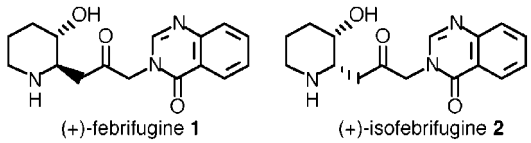



**Figure 1.**

their chemistry was reinvestigated which revealed their high activity against *Plasmodium* Malaria parasite. In particular, (+)-febrifugine **1** exhibits comparable activity in vivo to the clinically used drug chloroqine.[1f,2b,3] Since its racemate and natural (+)-isofebrifugine **2** as well as the enantiomers of the natural products were found to exhibit much less activity than natural (+)-febrifugine **1** and since febrifugine **1** could be epimerized to isofebrifugine **2**, development of efficient enantio- and diastereocontrolled preparation of natural (+)-febrifugine **1** is most important for extensive biological investigation. If we look at (+)-febrifugine **1** retrosynthetically, presuming the construction of its piperidine moiety by a ring-closing metathesis (RCM) reaction,[4] we can reach to the 4-allylamino-3-heptene-3,7-diol **4** which in turn can be connected to the chiral building block[5,6] (−)-**5** having a dioxabicyclo[3.2.1]octane framework. This building block was readily prepared either by catalytically[5] or enzymatically[6] from frufural in enantiomerically pure forms and utilized for

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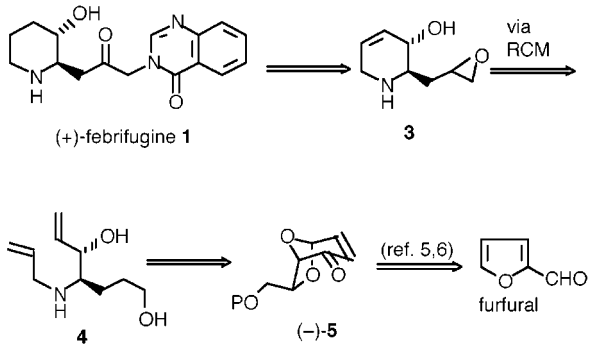
10.1021/ol006384f CCC: $19.00 
**Published on Web 09/07/2000**

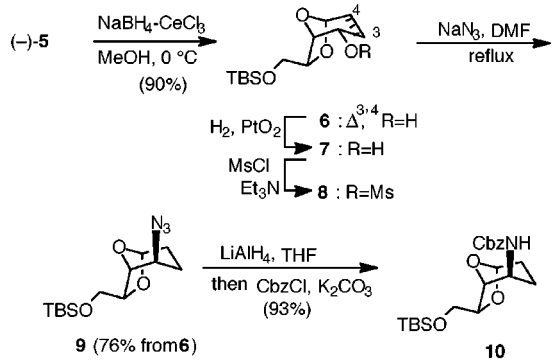
the diastereocontrolled construction of aldohexoses[5,7] and other natural products[8] on the basis of its inherent convex-face selectivity and high functionality. In this paper, we report its utilization for a diastereocontrolled synthesis of (+)-febrifugine **1** on the retrosynthetic analysis shown (Scheme 1).

**Scheme 1**



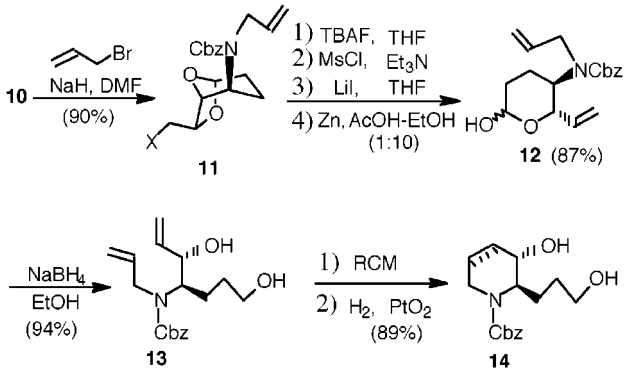

Enantiopure enone (−)-**5** was first converted diastereoselectively into the *endo*-allyl alcohol **6**, $[\alpha]^{26}_D$ +2.8 (*c* 1.1, $CHCl_3$), by convex-face selective 1,2-reduction,[9] which was hydrogenated to give the saturated alcohol **7**, $[\alpha]^{28}_D$ +17.2 (*c* 1.1, $CHCl_3$). Replacement of the hydroxy functionality of **7** by an azide was carried out in an acceptable overall yield through the mesylate **8** which afforded the *exo*-azide **9**, $[\alpha]^{26}_D$ +11.8 (*c* 2.1, $CHCl_3$), on reflux with sodium azide in DMF. Having installed the nitrogen functionality with the requisite stereochemistry, the azide **9** was next transformed into the carbamate **10**, $[\alpha]^{30}_D$ +17.3 (*c* 1.0, $CHCl_3$), by one-pot reduction and carbamoylation. Overall yield of **10** from the chiral block (−)-**5** was 63% in six steps (Scheme 2).

**Scheme 2**




To construct the piperidine moiety of (+)-febrifugine **1**, the secondary carbamate **10** was first *N*-allylated to give the tertiary carbamate **11** (X = OTBS), $[\alpha]^{28}_D$ +37.6 (*c* 1.1, $CHCl_3$), whose siloxy functionality was replaced by iodine via the primary alcohol **11** (X = OH), $[\alpha]^{28}_D$ +77.5 (*c* 1.0, $CHCl_3$), by a sequence of reactions involving desilylation, mesylation, and substitution. The iodide **11** (X = I), $[\alpha]^{26}_D$ +33.9 (*c* 1.1, $CHCl_3$), thus obtained was then treated with zinc to give the hemiacetal **12** which was further reduced to afford the dihydroxydiene **13**, $[\alpha]^{27}_D$ +13.1 (*c* 1.0, $CHCl_3$). Upon RCM reaction in the presence of Grubbs' catalyst[10] (5 mol %), **13** furnished the dedihydropiperidine **14** (4,5-dehydro) in 89% yield, which was hydrogenated to give the piperidinediol **14**, $[\alpha]^{30}_D$ −31.3 (*c* 1.4, $CHCl_3$), corresponding to the retron **4** (Scheme 3).

**Scheme 3**




To connect the quinazoline moiety required for (+)-febrifugine **1**, the diol **14** was transformed regioselectively into the primary sulfide **15** (R = H), $[\alpha]^{29}_D$ −19.5 (*c* 1.0, $CHCl_3$), on reaction with diphenyl disulfide in pyridine in the presence of tributylphosphine.[11,12] A similar reaction using *o*-nitrophenyl selenocyanate[13] in place of diphenyl disulfide proceeded in nonregioselective way. After benzylation of the secondary hydroxy functionality, the benzyl ether **15** (R = Bn), $[\alpha]^{27}_D$ −29.1 (*c* 1.1, $CHCl_3$), obtained was converted into the sulfoxide which was refluxed in diphenyl ether in the presence of calcium carbonate[14] to furnish the terminal olefin **16**, $[\alpha]^{28}_D$ −45.1 (*c* 1.0, $CHCl_3$), in acceptable overall yield. Since direct epoxidation with a

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(8) Utilization of the chiral building block for enantiocontrolled synthesis of other natural products, see: (a) (+)-noviose: Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2609. (b) FK-506 fragment: Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **2000**, *11*, 1601. (c) (−)-Shikimic acid: Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, 1375. (d) (−)-Physostigmine and (−)-physovenine: ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757.

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(10) Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride was purchased from Strem Chemicals and used without further purification.

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(14) Trost, B. M.; Saltzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.

(15) Diastereomeric ratio could not be determined by spectroscopically ($^1$H NMR).

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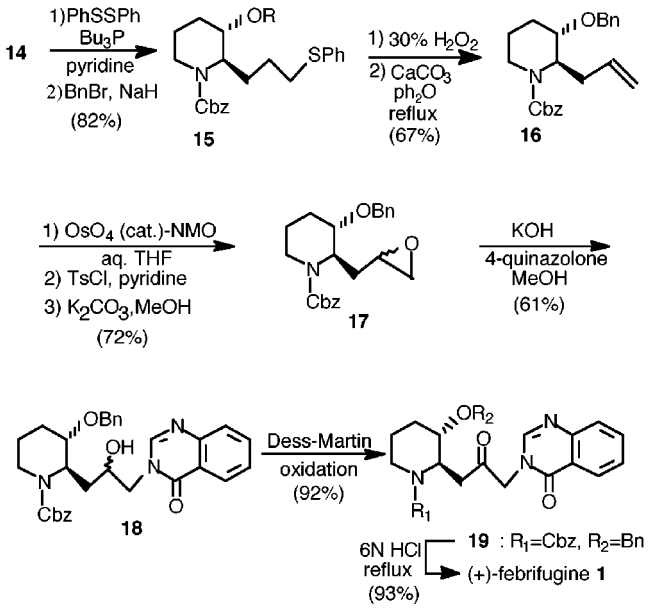
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

**Scheme 4**




peracid proceeded very slowly, **16** was converted sequentially into the epoxide **17** corresponding to the retron **3**, as an inseparable mixture of two diastereomers,[15] by sequential dihydroxylation, monotosylation, and base-induced cyclization. The mixture was then reacted with the potassium salt[16] generated from 4-quinazolone to furnish the secondary alcohol **18** as an inseparable mixture of two diastereomers,[15] which was oxidized with the Dess−Martin reagent[17] to give the protected febrifugine **19**, $[\alpha]^{31}_{D}$ −22.0 (*c* 1.0, $CHCl_3$), as a single product. Finally **19** was refluxed with 6 N hydrochloric acid to afford (+)-febrifugine **1**, mp 152−153 °C, $[\alpha]^{31}_{D}$ +27.5 (*c* 0.3, EtOH) [natural[1b]: mp 139−140 °C; $[\alpha]^{25}_{D}$ +28 (*c* 0.5, EtOH)], after basic workup, by concurrent removal of the nitrogen and the oxygen protecting groups. Overall yield of (+)-febrifugine **1** from the chiral building block **5** was 11% in 24 steps (Scheme 4).

In conclusion, we have demonstrated an alternative utilization of the chiral building block which is developed for the construction of the aldohexoses by a diastereocontrolled synthesis of (+)-febrifugine.

**Acknowledgment.** We thank Professor Yoshiteru Oshima, Pharmaceutical Institute, Tohoku University, for kindly providing us with natural (+)-febrifugine for comparison and helpful discussions.

OL006384F