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A Concise Enantioselective Synthesis of Antimalarial Febrifugine Alkaloids

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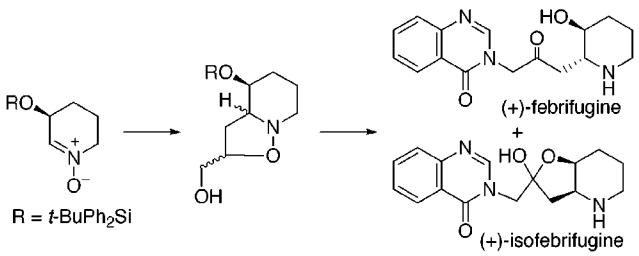
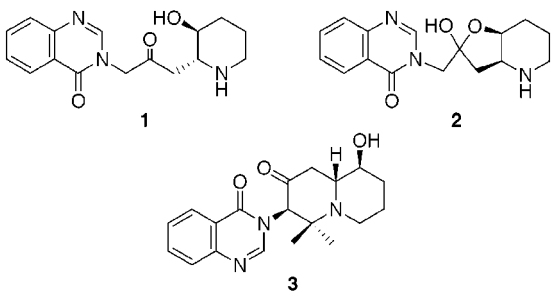
ABSTRACT



Reaction of (*S*)-2-(*tert*-butyldiphenylsilyloxy)-5-(mesyloxy)pentanal with hydroxylamine in allyl alcohol brought about simultaneous 1,3-dipolar cycloaddition of the resulting nitrone to allyl alcohol to give three diastereoisomeric adducts, from which (+)-febrifugine and (+)-isofebrifugine, potent antimalarial alkaloids, were synthesized.

Febrifugine (**1**) and isofebrifugine (**2**) are active principals against malaria, occurring in the roots of *Dichroa febrifuga* (Chinese name: Cháng Shan)[1] and related hydrangea plants.[2] The absolute structures of these alkaloids were elucidated by the asymmetric total synthesis achieved by Kobayashi and co-workers.[3] Recently, Oshima and co-workers reported[4] that analogue **3**, prepared by Mannich reaction of **1** with



acetone, exhibits potent antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* with good therapeutic selectivity as well as comparable activity in vivo to that of chloroquine. This finding as well as its low availability from natural sources has spurred much research on the synthesis of febrifugine and its analogues with the aim of developing a new antimalarial drug.[3,5]

We now wish to report an efficient synthesis of (+)-febrifugine (**1**) and (+)-isofebrifugine (**2**) in naturally occurring forms based on a new strategy, which relies on 1,3-dipolar cycloaddition[6] of nitrone **4** to allyl alcohol.

(1) (a) Koepeli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc*. **1947**, *69*, 1837. (b) Koepeli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc*. **1949**, *71*, 1048.

(2) (a) Ablondi, F.; Gordon, S.; Morton, J.; II.; Williams, J. H. *J. Org. Chem*. **1952**, *17*, 14. (b) Kato, M.; Inaba, M.; Itahana, H.; Ohara, E.; Nakamura, K.; Uesato, S.; Inouye, H.; Fujita, T. *Shoyakugaku Zasshi* **1990**, *44*, 288.

(3) (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett*. **1999**, *40*, 2175. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem*. **1999**, *64*, 6833.

(4) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.; Kim, H.-S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. *J. Med. Chem*. **1999**, *42*, 3163.

(5) (a) Takeuchi, Y.; Abe, H.; Harayama, T. *Chem. Pharm. Bull*. **1999**, *47*, 905. (b) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814. (c) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989. (d) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. *J. Chem. Soc., Chem. Commun*. **2000**, 1643. (e) Taniguchi, T.; Ogasawara, K. *Org. Lett*. **2000**, *2*, 3193.

(6) For a review on asymmetric 1,3-dipolar cycloaddition reactions, see: Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863.

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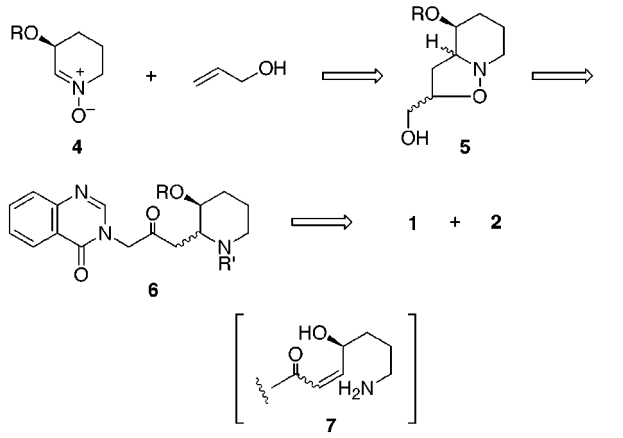
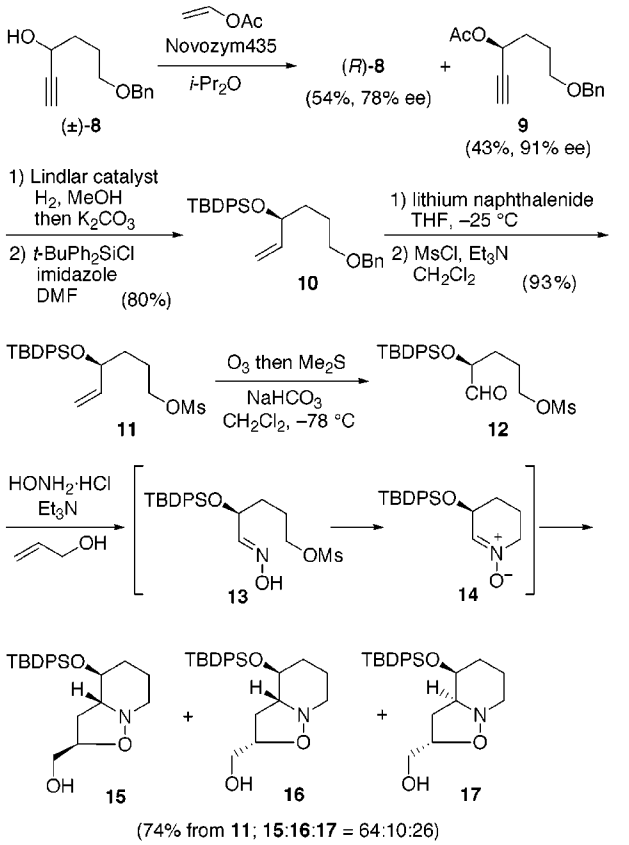
Tufariello and co-worker[7] reported that 1,3-dipolar cycloaddition of 2,3,4,5-trahydropyridine-1-oxide to allyl alcohol took place with perfect regioselectivity and high exo-selectivity to produce the corresponding cycloadduct in excellent yield. This report prompted us to envisage the synthesis of febrifugine alkaloids by employing a 1,3-dipolar cycloaddition reaction of chiral nitrone **4** with allyl alcohol as a key reaction despite uncertainty of the regio- and stereoselectivity (Scheme 1).[8] In this approach, the stereoselectivity of the key cycloaddition is not a serious problem because, as long as the regioselectivity is perfect, all stereoisomers of **5** would be converted to either febrifugine (**1**) or isofebrifugine (**2**) via **6** and isofebrifugine (**2**) can be isomerized to febrifugine (**1**) through equilibration via **7**.[4,5d]

Scheme 1



Our synthesis started with kinetic resolution of racemic propargylic alcohol **8**[9] by lipase-mediated acetylation (Scheme 2). Thus, reaction[10] of **8** with vinyl acetate in the presence of Novozym 435 in *tert*-butyl methyl ether at room temperature gave (*S*)-acetate **9** (91% ee)[11] and (*R*)-**8** (78% ee) in 43% and 54% yields, respectively. Lindlar semi-hydrogenation followed by in situ methanolysis and silylation converted **9** into olefin **10** in 80% yield. Upon reductive removal of the benzyl ether using lithium naphthalenide[12] and mesylation, **10** gave mesylate **11** in 93% yield. After ozonolysis of **11**, the resulting aldehyde **12** was directly reacted[13] with hydroxylamine hydrochloride in the presence of triethylamine in allyl alcohol at room temperature. As a result, nitrone **14** was generated in situ via oxime **13** which underwent simultaneous 1,3-dipolar cycloaddition to allyl alcohol to give **15**, **16**, and **17** in a ratio of 64:10:26 in 74% yield from **11**. The stereostructures of these diastereomers were determined by NOE experiments of the corresponding acetates. The optical purity (>90% ee) of the acetates[11] allowed us to conclude that no racemization occurred during formation of the nitrone and the cycloaddition. Interestingly, 1,3-dipolar cycloaddition of **14** to allyl acetate also occurred at room temperature with perfect regioselectivity, and the acetates of **15**, **16**, and **17** were quantitatively produced in exactly the same ratio as observed in the reaction of **14** with allyl alcohol. These results tell us that both cycloadditions occurred with 90:10 exo/endo-selectivity, 74:26 diastereofacial selectivity, and perfect regioselectivity.

Scheme 2



Although the above-mentioned 1,3-dipolar cycloadducts were separable by silica gel column chromatography, the following reactions were carried out without separation. The diastereoisomeric mixture of adducts was subjected to hydrogenolytic N−O bond fission and *tert*-butoxycarbonylation to give diol **18** in 94% yield. Reaction of **18** with *N*-tosylimidazole[14] in the presence of NaH afforded epoxide **19**, which was then reacted[5e] with the potassium salt

(7) Tufariello, J. J.; Ali, A. A. *Tetrahedron Lett*. **1978**, 4647.

(8) Goti et al. reported that reaction of 3-(*tert*-butyldimethylsilyl)oxy-1-pyrroline-1-oxide, a five-membered ring nitrone, with allyl alcohol occurred with perfect regioselectivity but poor stereoselectivity: Goti, A.; Cicci, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem*. **1997**, *62*, 3119.

(9) Prepared from 1,4-butanediol in 70% yield by a three-step sequence involving benzylation ($PhCH_2Br$, NaH, DMF), Swern oxidation, and addition of acetylene (C_2HMgBr, THF, 0 °C).

(10) For lipase-catalyzed resolution of racemic propargylic alcohols, see: (a) Ohtani, T.; Kikuchi, K.; Kamezawa, M.; Hamatani, H.; Tachibana, H.; Totani, T.; Naoshima, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 961. (b) Ohtani, T.; Nakatsukasa, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal. B.: Enzym*. **1998**, *4*, 53. (c) Morishita, K.; Kamezawa, M.; Ohtani, T.; Tachibana, H.; Kawase, M.; Kishimoto, M.; Naoshima, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 513.

(11) Determined by HPLC analysis using a chiral column (Chiralcel OD).

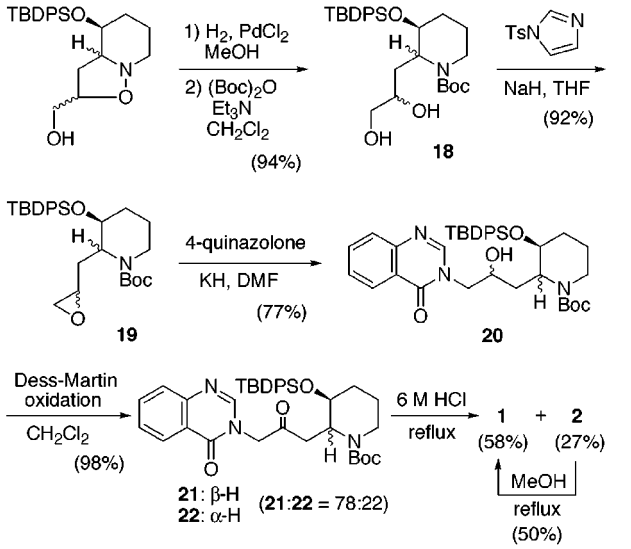
(12) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253.

(13) Obtained via modification of the procedure for substituted pyrroline-1-oxides: see ref 8 and Closa, M.; Wightman, R. H. *Synth. Commun*. **1998**, *28*, 3443.

(14) Cink, R. D.; Forsyth, C. J. *J. Org. Chem*. **1995**, *60*, 8122.

generated from 4-quinazolone to give alcohol **20** in 71% overall yield (Scheme 3). Dess−Martin oxidation[15] of **20**

Scheme 3



afforded a 78:22 separable mixture of **21** and **22** in almost quantitative yield. Finally, this epimeric mixture was subjected to acid hydrolysis in boiling hydrochloric acid to furnish (+)-febrifugine (**1**), $[\alpha]_D^{24}$ +28.0° (*c* 0.30, EtOH), mp 152−154 °C [lit.[5e] mp 152−153 °C, $[\alpha]_D^{31}$ +27.5° (*c* 0.30, EtOH)], and (+)-isofebrifugine (**2**), $[\alpha]_D^{22}$ +130.0° (*c* 0.30, $CHCl_3$), mp 152−154 °C [lit.[1] mp 129−130 °C, $[\alpha]_D^{23}$ +131° (*c* 0.35, $CHCl_3$)], in 58% and 27% yields, respectively. The synthetic **1** and **2** were identical with the corresponding natural specimens by spectroscopic and chromatographic comparisons. The ratio of **1** and **2** (67:33) produced tells us that isomerization between these alkaloids occurred through a reversible Michael reaction process under the above-mentioned acidic hydrolysis conditions (reflux, 4 h). Prolonged reaction times (reflux, 12 h) led to a 62:38 mixture of **1** and **2**. Furthermore, after separation, **21** and **22** were subjected to acidic hydrolysis under the exact conditions as used above, respectively. As a result, it was found that **21** provided a 84:16 mixture of **1** and **2** while **22** gave only **2**. These results suggest that, under acidic conditions, febrifugine (**1**) can undergo this isomerization but isofebrifugine (**2**) cannot.[16] Isofebrifugine (**2**) thus obtained was converted to febrifugine (**1**) in 50% yield by isomerization under neutral conditions (MeOH, reflux) as reported by Oshima and co-workers.[4]

In conclusion, (+)-febrifugine (**1**) and (+)-isofebrifugine (**2**) were synthesized from easily available chiral building block **9** in 12 steps in 21% and 10% overall yields, respectively. The convergent route established herein should enable us to synthesize a variety of interesting analogues.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015655Z

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

(16) Takeuchi and co-workers also reported that isofebrifugine (**2**) did not isomerize under acidic conditions; see ref 5d.