Total Synthesis of dl-Febrifugine and dl-Isofebrifugine

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Racemic compounds (1 and 2) of the antimalarial agents febrifugine (dl-1) and isofebrifugine (dl-2) were synthesized using an unusual Claisen rearrangement of allyl enol ether (7) and the stereoselective reduction of 2-allyl-3-piperidone (8). This method is widely applicable to the synthesis of derivatives needed to study the structure–activity relationship of febrifugine.

Key words total synthesis; Claisen rearrangement; stereoselective reduction; febrifugine; antimalarial activity

Febrifugine (dl-1) is antimalarial agent that was isolated from Dichroa febrifuga and Hydrangea umbellata with isofebrifugine (dl-2). Errors in the determined structures of dl-1 and dl-2 have caused much confusion in the study of the relationship between the structure and antimalarial activity of febrifugine derivatives. Recently, Kobayashi et al. corrected the absolute structures of dl-1 and dl-2 by achieving the asymmetrical synthesis of all stereoisomers (Fig. 1). Now the definitive study of the structure–activity relationship of febrifugine derivatives can begin. In this paper, we describe a novel synthesis of dl-febrifugine (dl-1) and dl-isofebrifugine (dl-2).

In our planned synthesis leading to 1 and 2, the key intermediate (3) has an allyl group as the required 3-carbon unit on 1 or 2 and a benzoxycarbonyl (Z) group as a protecting group. The intermediate (3) was successfully prepared with complete stereoselectivity (Chart 1). From 3-hydroxypyridine (4), the 3-allyl-N-benzyl derivative (6) was synthesized via pyridinium chloride (5) by improving the reported method. To maintain the stability of the intermediates in the later reactions, the benzyl group was replaced with a Z group by treating 6 with benzyl chloroformate (Z-Cl) to give 7. The unusual Claisen rearrangement of 7 afforded the 3-piperidone derivative (8) with the allyl group at the 2 position. This convenient result shows that the isomerization of the double bond on the piperidine ring of 7 proceeds before the migration of the allyl group in the presence of a Lewis acid. TLC and HPLC data showed that the reduction of 8 gave 3 as the sole product without involving the diastereomeric isomer.

The configuration of 3 was predicted from a semiempirical molecular orbital calculation using 8 (Fig. 2). The PM3 molecular orbital calculation indicated two stable conformers (8a, b). The former, 8a, is the minimized conformer with an allyl group in the axial position, while the latter, 8b, is the optimized conformer with an allyl group in the equatorial position. The significant energy difference (about 4 kcal/mol) between the heats of formation of 8a and 8b showed that 8 exists almost entirely as 8a. We think that hydride attack of the carbonyl group of 8a occurs from the axial direction under the control of chelation or torsional strain.

1 and 2 were successfully prepared from 3 via the cyclic intermediate 9 (Chart 2). The bromoetherification of 3 using N-bromosuccinimide (NBS) afforded octahydrofuro[3,2-b]pyridine (9), which HPLC data indicated was a 3:1 mixture of the diastereomeric isomers, although we could not determine the configuration of the major or minor products. The successive dehydrobromination, bromohydration, and condensation to quinazolinone gave Z-protected dl-isofebrifugine (10). 2 was synthesized by the hydrogenolysis of 10 and 1 was synthesized by the isomerization of 2. The H- and C-NMR data for 1 and 2 agreed with reported values.

We were able to prepare febrifugine derivatives in high...
total yield without using the very expensive, toxic, or dangerous reagents used in other reports. Although it is unreasonable to compare an asymmetric synthetic method with a racemic one directly, our method has higher diastereoselectivity than the reported method. We think that our method is widely applicable to the synthesis of the derivatives needed to study the structure–activity relationship of febrifugine.

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References and Notes
12) dl-Febrifugine: Colorless plates (AcOEt), mp 134—135 °C; dihydrochloride: mp 171—175 °C (dec.). Anal. Calcd for C_{16}H_{19}N_{3}O_{3}: C, 63.77; H, 6.35; N, 13.94. Found: C, 63.67; H, 6.41; N, 13.72. 13C-NMR (125 MHz, CDCl_{3}) (values in parentheses are reported ones 11)) \[\delta: 19.99 (20.1), 26.71 (26.8), 43.24 (43.4), 44.46 (44.6), 49.77 (50.0), 55.62 (55.8), 77.25 (77.0), 105.38 (105.6), 121.82 (122.1), 126.79 (127.1), 127.42 (127.3), 128.26 (128.26), 134.24 (134.6), 147.97 (148.3), 148.14 (148.5), 161.37 (161.8).
13) dl-Isofebrifugine: Colorless plates (EtOH), mp 188—190 °C (lit. 12) 133—134 °C; dihydrochloride mp 202—204 °C (dec.) (lit. 12) 204 °C [dec.]. Anal. Calcd for C_{16}H_{19}N_{3}O_{3}: C, 63.77; H, 6.49; N, 13.94. Found: C, 63.58; H, 6.49; N, 13.95. 13C-NMR (50 MHz, CDCl_{3}) (values in parentheses are reported ones 11)) \[\delta: 25.83 (25.6), 34.26 (34.5), 43.75 (44.0), 45.62 (46.0), 54.70 (55.0), 60.12 (60.2), 70.76 (72.3), 121.39 (122.4), 126.06 (127.0), 127.18 (127.7), 127.26 (127.8), 134.25 (134.8), 148.00 (146.7), 148.11 (148.5), 159.99 (161.3), 203.90 (203.1).