Concise Synthesis of dl-Febrifugine

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Racemic compound (1) of the antimalarial agents febrifugine (d-1) was synthesized using a stereoselective Michael reaction of an ω-amidoenone (5) which was prepared by the Wittig reaction of piperidinediol (7).

Key words total synthesis; stereoselective Michael reaction; Wittig reaction; febrifugine; antimalarial activity

Febrifugine (d-1) is an antimalarial agent that has been isolated from Dichroa febrifuga and Hydrangea umbellate along with isofebrifugine (d-2).1—4) It is well known that d-1 and d-2 are related to each other’s isomerization via ω-aminoenone5,6) (Chart 1).

Among reported methods7—20) of d-1, we had believed that our method10,13) was widely applicable to the synthesis of the derivatives needed to study the structure–activity relationship of d-1. However, we could not successfully prepare some derivatives because our method involved uncontrollable trans–cis isomerization in the final step. In recent our study, we found that cis form of N-protected febrifugine derivatives (cis-4) also afforded a mixture of trans-4 and cis-4 form under the presence of acid by the isomerization (Chart 2).21)

From those findings, we planned a synthetic strategy via an ω-amidoenone (5) as a key intermediate, which would afford trans piperidine derivative (trans-6) by the intramolecular Michael reaction with the stereoselectivity (Chart 3). In this paper, we describe a novel synthesis of dl-Febrifugine (dl-1).

The synthesis of the key intermediate, ω-amidoenone (5), was achieved to utilize the Wittig reaction of 2-hydroxy-piperidine derivative which we have developed in our synthetic study of deoxyfebrifugine.22) The Wittig reaction of 2,3-piperidinediol (7), which was easily prepared in 84% yield from tetrahydropyridine (8) by Oxone®-acetone oxidation,23) afforded (E)-ω-aminoenone (E-5) in which the double bond had E configuration based on the coupling constant (J=16 Hz) of olefinic protons in 1H-NMR. The Michael reaction of trans-5 (E-5) with BF3·OEt2 afforded the Michael adduct (trans-6). N-Cbz febrifugine (10) was afforded by successive reactions, silylation of the hydroxy and ketone group, bromination, and coupling with 4(3H)-quinazolinone. Hydrogenolysis of 10 gave dl-1 which was identical with the reported one by mp or 1H-NMR data (Chart 4).

In the Michael reaction of E-5 with BF3·OEt2, we could obtain the furan derivative (9) and 1,4-diketone derivative (11) along with trans-6. It is known that 9 and 11 can be transformed from cis-6 by acid.24) Decreasing yield of trans-6 with the prolongation of the reaction time or heat of reaction mixture suggests that there is an equilibrium relationship via E-5 between trans-6 and cis-6 in the presence of Lewis acid (Table 1).

Herein, we could develop the the synthetic method for dl-febrifugine derivatives in high total yield and short steps without using the very expensive, toxic, or dangerous reagents used in other reports.25—30) We are now progress the asymmetric synthesis using this method.

Acknowledgments We are grateful to the SC-NMR Laboratory of Okayama University for the use of the facilities.

Chart 1

Chart 2

Chart 3

Chart 4

Reagents and Conditions: (a) Oxone®, K2CO3, acetone, H2O, rt, 2 h, 84%. (b) CH3COCH=PPPh3, MeCN, reflux, 1 h, 76%. c) BF3·OEt2 (0.5 eq.), MeCN/r.t, 10 min, 75%. d) (i) TMSOTf, i-Pr2NEt, CH2Cl2, rt, 20 min; (ii) NBS, rt, 2 h; (iii) 4(3H)-quinazolinone/r.t, 4.5 h, 51%. (e) H2, 20% Pd(OH)2/C, MeOH/THF/r.t, 3.5 h, 88%.
Table 1. Reaction of E-5 with BF$_3$OEt$_2$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Reaction time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans-6</td>
</tr>
<tr>
<td>1</td>
<td>r.t.</td>
<td>10 min</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>r.t.</td>
<td>30 min</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>r.t.</td>
<td>1 h</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>10 min</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1 h</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>2 h</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>10 min</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>30 min</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>1 h</td>
<td>12</td>
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References