ALTERNATIVE CHIRAL PREPARATIONS OF A SWAMINATHAN KETONE VIA ASYMMETRIC ALDOL REACTIONS MEDIATED BY CHIRAL AMINES BEARING A PYRROLIDINE

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Abstract – We established a novel chiral route to provide a Swaminathan ketone (3) bearing a 7-membered ring via intramolecular aldol reaction of trione (7) mediated by chiral pyrrolidinylmethylamine derivatives. Despite the moderate enantioselectivity of 3, we succeeded in increasing optical purities by using a lipase-mediated asymmetric esterification of an alcohol (16) at a later synthetic stage. The absolute configuration was determined by Mosher’s ester method, and relations between absolute configurations and optical rotations of 3 were clarified.

Hajos-Parrish (1) and Wieland-Miescher (2) ketones, which include carbobicyclic enediones, are highly useful synthons in the total synthesis of many natural products and pharmaceutically important compounds (Figure 1).1-5

Figure 1

These useful enediones can be easily prepared by proline-mediated asymmetric intramolecular aldol reactions.6 This asymmetric aldol reaction was first reported by Hajos et al. and is widely recognized to involve an enamine-based mechanism.7-9 However, few reports regarding the preparation of 3 bearing a
7-membered ring have been published.\textsuperscript{10-12} Since many pharmaceutically important natural products containing 7-membered carbocycles have been published,\textsuperscript{13} enedione (3) is an attractive potential chiral synthon to be used to achieve total synthesis of these important products. The pioneering studies for obtaining 3 were reported by Swaminathan et al.,\textsuperscript{10} synthesizing 3 as a racemic material via a pyrrolidine-mediated aldol reaction of trione (7) in the presence of acetic acid (AcOH). The authors also reported that similar reactions mediated by (S)-proline (5) did not yield the expected optically active 3 (Scheme 1).\textsuperscript{10b}

![Scheme 1](image)

Uwai et al. first reported the lipase-mediated aldol reactions of 7 to afford (S)-(+)\textsuperscript{-}3 with a low enantioselectivity (8\% ee) and retention times for both enantiomers of 3 on an HPLC instrument equipped with a chiral stationary phase column (Chiralcel OB). However, the authors did not provide any evidence for the determination of an absolute configuration of 3.\textsuperscript{12a} Although Pericàs et al. reported catalytic asymmetric aldol reactions of 7 mediated by a polymer-supported chiral amine, affording (R)-3 with 53\% ee, they did not discuss the details of its absolute configuration and optical rotation.\textsuperscript{12b} Recently, Xu et al. reported the practical chiral preparation of (R)-3 (70\% ee) using aldol reactions of 7 mediated by (S)-prolinamide (8), elegantly achieving the total synthesis of (−)-himalensine A (9) starting from (R)-3.\textsuperscript{12c} The authors determined an absolute configuration from single crystal X-ray analysis of (R)-3 which was alternatively derived from commercially available (R)-2 (> 98\% ee). In their total synthesis, a chiral center at C-9a in (R)-3 was directly reflected to natural (−)-himalensine A (9). This study indicated that the absolute configuration of (R)-3 can be unambiguously identified (Scheme 2). However, both optical rotations and retention times of (R)- and (S)-3 on the HPLC instrument equipped with a chiral stationary phase column have not been reported. Therefore, a method to determine the absolute configuration of 3 remains to be developed. Additionally, according to Xu’s method, (R)-prolinamide (\textit{ent}-8), which is derived from unnatural (R)-proline (\textit{ent}-5), is necessary to form (S)-3. From these
reasons, novel and alternative chiral routes for 3 to clarify the relations among absolute configurations, optical rotations, and behaviors using HPLC of (R)- and (S)-3 are required.

We previously reported the asymmetric intramolecular aldol reaction of 6 mediated by chiral diamines (10) or (11) in the presence of trifluoroacetic acid (TFA). These reactions afforded (R)-2 in high yield and enantioselectivity (Scheme 3). According to this method, we attempted to use these chiral amines in the aldol reactions of 7. Herein, we report the details of these reactions, chiral properties of (R)- and (S)-3 including optical rotations and HPLC behaviors, and methods to increase optical purities through lipase-mediated asymmetric esterifications for 3 derived compounds.

First, we studied the aldol reactions of 7 mediated by a stoichiometric amount of 10 or 11 in the presence of a Brønsted acid, and the results are summarized in Table 1. According to Xu’s method, the reactions were performed in dichloromethane (DCM) at room temperature in the presence of AcOH or TFA. The reactions proceeded very slowly to afford 3 in low yields and low enantioselectivities (entries 1-4). Under
these conditions, the reactions did not proceed to completion. The reactions were then performed according to our previously developed method. A similar reaction in dimethyl sulfoxide (DMSO) at room temperature slightly improved the yield of 3 accompanied with a high enantioselectivity (entry 5). However, the reaction did not proceed to completion even after 93 h. The same reaction as entry 5 at 50 °C completed after a short time and greatly improved the yield of (S)-3 with an acceptable enantioselectivity (entry 6). Details of the procedure used to determine the absolute configuration of 3 are described later (vide infra). The reaction conditions described in entry 6 were used for further studies.

Table 1. The aldol reaction of 7 mediated by 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid (equiv.)</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yieldb,c (%)</th>
<th>Ee d (%)</th>
<th>Absolute configuration of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>TFA (1.0)</td>
<td>rt</td>
<td>44</td>
<td>trace</td>
<td>ND e</td>
<td>ND e</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>AcOH (1.0)</td>
<td>rt</td>
<td>44</td>
<td>15</td>
<td>14</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>TFA (0.5)</td>
<td>rt</td>
<td>90</td>
<td>9 (19)</td>
<td>2.9</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>AcOH (0.5)</td>
<td>rt</td>
<td>90</td>
<td>18 (31)</td>
<td>6.5</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>TFA (1.5)</td>
<td>rt</td>
<td>93</td>
<td>47 (63)</td>
<td>64</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>TFA (1.5)</td>
<td>50 °C</td>
<td>26</td>
<td>92</td>
<td>55</td>
<td>S</td>
</tr>
</tbody>
</table>

a 100 mg of 7 was used for all reactions.
b Isolated yield.
c Yields based on a recovery of starting 7 were shown in parentheses.
d Determined by HPLC equipped with a chiral stationary phase column.
e Not determined.

The reactions were studied in the presence of other chiral amines bearing a pyrrolidine and the obtained results are summarized in Table 2. The reaction mediated by (S)-proline (5) proceeded to afford (R)-3 in a moderate yield and low enantioselectivity (entry 1). The reaction mediated by 8 was also performed to compare the Xu’s method. However, lower yield and enantioselectivity were observed than the results reported in Ref. 12c (entry 2). The mediator (11),1b which exhibited high enantioselectivity in the aldol reaction of 6, was unsuccessful in this reaction (entry 3), because of the lower yield and enantioselectivity compared to the reaction mediated by 10. Although enantioselectivities under each conditions were not satisfactory, we planned to use enzymatic reactions focusing on two oxygen functionalities at C-1 and C-7 in (S)-3 to increase the obtained optical purities.
Table 2. The aldol reaction of 7 mediated by chiral pyrrolidines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mediator</th>
<th>Time (h)</th>
<th>Yield(^b,c) (%)</th>
<th>Ee(^d) (%)</th>
<th>Absolute configuration of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>17.5</td>
<td>54</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>398(^e)</td>
<td>36 (54)</td>
<td>56</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>48</td>
<td>27</td>
<td>33</td>
<td>S</td>
</tr>
</tbody>
</table>

\(^a\) 100 mg of 7 was used for all reactions.

\(^b\) Isolated yield.

\(^c\) Yields based on a recovery of starting 7 were shown in parentheses.

\(^d\) Determined by HPLC equipped with a chiral stationary phase column.

\(^e\) The reaction was performed at rt.

The reduction of both carbonyl groups in (S)-3 with diisobutylaluminum hydride (DIBALH) and following allylic oxidation in the presence of MnO\(_2\) afforded known alcohols (12) and (13\(^b\)) with 82:18 diastereoselectivity. The major alcohol (12) was converted to acetate (14) using a common method. Unfortunately, both lipase-mediated asymmetric esterification\(^c\) of 12 and asymmetric hydrolysis of 14 hardly proceeded to yield the expected alcohol (12) or acetate (14) with higher ee than the starting materials. In all cases, the starting 12 or 14 was completely recovered. These results indicated that 12 and 14 exist in the cis-orientation between the hydroxy group at C-1 and methyl group at C-9a and were unsuitable substrates for the lipases (Scheme 4).

We next focused on the oxygen functionality at C-7. The optical purities were determined using HPLC, so a benzoyl group was introduced to the major alcohol (12) as a UV chromophore. Sodium borohydride reduction of 15 in methanol afforded a diastereomeric mixture of 16 and 17 in a 75:25 ratio, which were readily separated by silica gel column chromatography. Acetylations of the obtained alcohols (16) and (17) using a typical method yielded the corresponding acetates (18) and (19), respectively (Scheme 5). NOE correlations of 19, shown in Figure 2, indicated that the angular methyl at C-9a and the acetoxy group at C-7 existed in a trans-orientation. Therefore, the other diastereomeric acetate (18) must exist in the cis-configuration.
The absolute configuration of 16 was determined using Mosher’s ester method. Mosher’s esters (20a) and (20b) were synthesized from 16 using (R)- or (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride. The difference values ($\delta = \delta^{20a} - \delta^{20b}$) of the chemical shifts in the $^1$H-NMR spectra are shown in Scheme 6. We observed high field shifts of the protons on C-8 and C-9 and low field shifts...
of the protons on C-5 and C-6. These results strongly indicated that the absolute configuration at C-7 was S. Because the relative configuration between the hydroxy group at C-7 and angular methyl at C-9a was cis (vide supra), the absolute configuration at C-9a must be S. This indicated that the aldol reaction of entry 6 in Table 1 afforded (S)-3.

Scheme 6

The lipase-mediated asymmetric esterification of 16 was subsequently examined to increase the obtained optical purities. All reactions were performed in tert-butyl methyl ether (tBuOMe) in the presence of 2.0 equiv. of vinyl acetate, and the obtained results are summarized in Table 3. All reactions afforded the acetate (18) with higher ee than the starting 16. Especially, lipase AS was effective for increasing the optical purity and affording 18 with high ee (entry 4). In all reactions, the major enantiomer of the unreacted 16 remained in the same 7S configuration as the starting 16, but with a lower ee. This indicated that enantioselectivity of lipase at C-7 was not high. However, these results revealed that the obtained (S)-3 can be used as a chiral synthon despite of its moderate ee, because it was possible to increase optical purity at a later synthetic stage.

Finally, we clarified the relationship between the absolute configurations, optical rotations, and HPLC retention times of both enantiomers of 3 and the obtained results are summarized in Table 4. It was observed that (S)-3, prepared from entry 6 in Table 1, exhibited similar optical rotations (dextrorotatory), and similar HPLC retention times on a OB-H column (entry 2) as entry 1, which was reported in Ref. 12a. However, the retention times of (R)- and (S)-3 on the HPLC equipped with AS-H were different from those reported in Ref. 12b (entry 4 vs 5). Thus, we observed short retention time for (R)-3 and long retention time for (S)-3, opposite to that of entry 5. Because the optical rotation data for (R)-3 was not reported in Ref. 12b or 12c, we prepared (R)-3 according to Xu’s method. The obtained (R)-3, which exhibited slightly lower ee than that previously reported, exhibited similar retention times for (R)- and (S)-3 as entry 4 (entry 6). Additionally, (R)-3 was levorotatory and the absolute values of [α]D between
(R)- and (S)-3 were similar. Therefore, the behaviors of (R)- and (S)-3 on HPLC with AS-H (entries 4 and 6), were reliable and it was clear that (S)-(+-)3 was obtained from the asymmetric aldol reactions.

Table 3. Lipase-mediated asymmetric esterifications of 16

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lipase&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>18 Yield&lt;sup&gt;g&lt;/sup&gt;</th>
<th>E&lt;sub&gt;e&lt;/sub&gt;&lt;sup&gt;h,i&lt;/sup&gt;</th>
<th>16 Yield&lt;sup&gt;g&lt;/sup&gt;</th>
<th>E&lt;sub&gt;e&lt;/sub&gt;&lt;sup&gt;h,i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AK&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61.5</td>
<td>19</td>
<td>75 (7S)</td>
<td>76</td>
<td>50 (7S)</td>
</tr>
<tr>
<td>2</td>
<td>PS-D&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7</td>
<td>53</td>
<td>73 (7S)</td>
<td>42</td>
<td>52 (7S)</td>
</tr>
<tr>
<td>3</td>
<td>AYS&lt;sup&gt;e&lt;/sup&gt;</td>
<td>22.5</td>
<td>33</td>
<td>82 (7S)</td>
<td>54</td>
<td>39 (7S)</td>
</tr>
<tr>
<td>4</td>
<td>AS&lt;sup&gt;f&lt;/sup&gt;</td>
<td>68</td>
<td>23</td>
<td>88 (7S)</td>
<td>76</td>
<td>45 (7S)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 50 mg of 16 was used for all reactions.
<sup>b</sup> All lipases were commercially available from Amano Pharmaceutical Co., LTD.
<sup>c</sup> Pseudomonas fluorescens.
<sup>d</sup> Pseudomonas cepacia (immobilized on ceramic).
<sup>e</sup> Candida rugosa.
<sup>f</sup> Aspergillus niger.
<sup>g</sup> Isolated yield.
<sup>h</sup> Determined using an HPLC equipped with a chiral stationary phase column.
<sup>i</sup> Absolute configuration at C-7 of the major enantiomer was shown in parentheses.

Table 4. The relations of (R)- and (S)-3 among absolute configurations, optical rotations, and HPLC retention times

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound (ee)</th>
<th>[α]&lt;sub&gt;D&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt; (in CHCl&lt;sub&gt;3&lt;/sub&gt;)</th>
<th>Column&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Eluent (v/v)</th>
<th>Rt&lt;sup&gt;c&lt;/sup&gt; (R, min)</th>
<th>Rt&lt;sup&gt;c&lt;/sup&gt; (S, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-3 (8)</td>
<td>+7.9</td>
<td>OB</td>
<td>hexane: 2-propanol = 96:4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>27.7</td>
<td>23.7</td>
</tr>
<tr>
<td>2</td>
<td>(S)-3&lt;sup&gt;e&lt;/sup&gt; (55)</td>
<td>+49.7</td>
<td>OB-H</td>
<td>hexane: 2-propanol = 96:4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40.7</td>
<td>27.8</td>
</tr>
<tr>
<td>3</td>
<td>(S)-3&lt;sup&gt;e&lt;/sup&gt; (55)</td>
<td>+49.7</td>
<td>OJ-H</td>
<td>hexane: 2-propanol = 9:1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>15.2</td>
<td>17.3</td>
</tr>
<tr>
<td>4</td>
<td>(R)-3 (53)</td>
<td>NR&lt;sup&gt;g&lt;/sup&gt;</td>
<td>AS-H</td>
<td>hexane: ethanol = 9:1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>37.0</td>
<td>42.5</td>
</tr>
<tr>
<td>5</td>
<td>(R)-3&lt;sup&gt;e&lt;/sup&gt; (51)</td>
<td>-47.2</td>
<td>AS-H</td>
<td>hexane: ethanol = 9:1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>37.0</td>
<td>44.4</td>
</tr>
</tbody>
</table>

<sup>a</sup> The observed [α]<sub>D</sub> accompanied with the corresponding enantiomeric excess.
<sup>b</sup> All of chiral stationary phase columns were commercially available as CHIRALCEL<sup>®</sup> or
In conclusion, we established a novel chiral route to provide a Swaminathan ketone (3) bearing a 7-membered ring via intramolecular aldol reaction of trione (7) mediated by chiral amines bearing a pyrroolidine. Although the enantioselectivity of 3 was moderate, we successfully increased the optical purities by using a lipase-mediated asymmetric esterification of alcohol (16) at a later synthetic stage. The absolute configuration was determined by Mosher’s ester method, and the relationship between absolute configuration and optical rotation of 3 was determined. Further studies regarding the detailed reaction mechanism and development of a more efficient mediator for the reactions is currently in progress.

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