Stereoselective Cyclization of Allenoates Containing Carbonyl Functionalities Mediated Mo(CO)$_6$: Synthesis of Canadensolide and Sporothriolide

Jisook Kwon, Suyeon Gong, Seok-Hoon Woo, and Chan-Mo Yu

Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea. *E-mail: cmyu@chem.skku.ac.kr

Received January 29, 2009, Accepted February 9, 2009

Key Words: Allenoate, Cyclocarbonylation, Diastereoselectivity, Lactone, Molybdenum

Among a variety of synthetic methodologies for the construction of cyclic compounds, chemical transformations involving the use of transition metal complexes are some of the most attractive methodologies because reactions can directly construct complex molecules from relatively simple starting materials. As a consequence, many advances in the cyclization mediated by transition metals have been made through a variety of ways in synthetic strategy. Of particular interest is a cyclization strategy between carbonyl and unsaturated bonds to find practical way of chemical processes could dominate over the classical methods in simple trial. In this regard, an allene has been proven to be an useful substrate for a variety of transition metal catalytic reactions, particularly for the cyclizations in the construction of carbo- and heterocycles. Recently, we have disclosed our investigations of direct cyclization methods for the synthesis of avenaciolide 1, 5 as a part of the allylic transfer strategy utilizing an allene as substrates or intermediates.

Naturally occurring bis-lactones such as avenaciolide 1, canadensolide 2, and sporothriolide 3 are secondary metabolites of Aspergillus, Penicillium canadense, and Sporothris sp. respectively. The biological behaviors such as antifungal, fungicidal, and algicidal activities coupled with their interesting structural features have stimulated considerable synthetic efforts in bislactone moieties.

\[
\begin{align*}
4 & \quad \text{M(CO)$_6$} \\
\text{[2+2+1]} & \quad \rightarrow \\
5 & \quad \text{R}^2 \\
\end{align*}
\]

Structural difference between avenaciolide 1 and canadensolide 2 is a constitution of the bis-lactone system. As a consequence, we became quite interested in carrying out investigation with substituted allenoate-aldehydes 4 to construct a bislactone unit for canadensolide 2 and sporothriolide as shown in eq 1. This research led to the discovery of the cyclization of electronically deficient allene-aldehyde.

With this issue in mind, several allenoate-aldehydes were prepared as shown in Scheme 1. Attempts to couple of allenic acid 10 with alcohol 7a under the various conditions using DCC or HATU indicated that the conversion to the corresponding lactone 2a could not be satisfied. After surveying numerous conditions, we were delighted to find that the Mitsunobu conditions for the conversion of but-3-ynoic acid (6) with 7 to the corresponding 8 turned out to be only possible method. Fortunately, a propargyl moiety was isomerized to an allene during the process. After removal of TBDMS group by amberlyst 15 in MeOH, the Dess-Martin periodide was effective for the synthesis of the allenoate-aldehyde 4 in good yield.

As a starting point, the allenoate-aldehyde 4a was selected as a model substrate for orienting experiments. Initial attempts to cyclocarbonylation of 4a under the previous conditions employed for an unsubstituted allene-aldehyde 6a indicated that the conversion to the corresponding lactone 5a could not be satisfied in terms of chemical conversion (Table 1, entry 1). After intensive investigations for orienting experiments as summarized in Table 1, several key findings are emerged as follows: i) the use of Mo(CO)$_6$ was superior to other molybdenum carbonyls such as C$_7$H$_8$Mo(CO)$_3$ and Mo(CO)$_3$(DMF)$_3$; ii) the use of 5 equivalents of Mo(CO)$_6$ was needed for optimal yield; iii) the introduction of DMSO

![Figure 1](image_url)

Figure 1. Naturally occurring bis-lactones.
as an additive proved to be most effective in comparison with other sulfoxides such as tetramethylene sulfoxide and methyl phenyl sulfoxide; iv) dramatic solvent effect was observed by introducing CH2Cl2 compared to other solvents such as toluene, THF, and CH3CN in terms of reactivity and chemical yields; v) reaction performed at 120 °C in CH2Cl2 resulted in the best chemical yield; vi) other metal carbonyls such as Ru3(CO)12, Ni(CO)2(PPh3)2, and W(CO)6 tuned out to be unpromising.

Under optimal conditions (entry 3 in Table 1), the reaction was conducted by an addition of 4a (1 equiv) and DMSO (10 equiv) in CH2Cl2 at 20 °C to a solution of Mo(CO)6 (5 equiv) in CH2Cl2 in a seal tube. After stirring at 20 °C for 20 min, the reaction mixture was cooled to rt and then filtered through a sintered glass filter containing celite with additional CH2Cl2. After removal volatile materials under reduced pressure, final purification was effected by column chromatography to yield 5a in 63% yield.

In the light of the above results for the carbocyclization with the allenolate-aldehyde 4a, we next turned our attention to extend the strategy with substituted 4b and 4c for the synthesis of canadensolide 2 and sporothriolide 3. Unfortunately, the reaction of 4b under the same conditions as described in Table 1 gave the two separable diastereomers 2 and 5a in 67% yield as a 75:25 mixture. Reaction of 4c was shown to produce 3 and 5b in 54% yield with 77:23 ratio as illustrated in Scheme 2.

**Table 1. Selected preliminary investigations with 4a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Solvent</th>
<th>T/°C</th>
<th>Time/h</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mo(CO)6</td>
<td>toluene</td>
<td>120</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Mo(CO)6</td>
<td>CH2Cl2</td>
<td>120</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Mo(CO)6</td>
<td>CH2Cl2</td>
<td>120</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>Mo(CO)6</td>
<td>toluene</td>
<td>120</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>C7H6Mo(CO)4</td>
<td>CH2Cl2</td>
<td>100</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Mo(CO)6(DMF)3</td>
<td>CH2Cl2</td>
<td>120</td>
<td>12</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Ni(CO)2(PPh3)2</td>
<td>toluene</td>
<td>110</td>
<td>7</td>
<td>decomposed</td>
</tr>
<tr>
<td>8</td>
<td>W(CO)6</td>
<td>CH2Cl2</td>
<td>120</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Ru3(CO)12, CO</td>
<td>CH2CN</td>
<td>100</td>
<td>12</td>
<td>NR</td>
</tr>
</tbody>
</table>

*refer to isolated product, % *1.5 equiv, additive DMSO (10 equiv) *2 equiv, additive DMSO (10 equiv) *3 CO (20 atm)

**Scheme 2. Synthesis of canadensolide 2 and sporothriolide 3.**

**Scheme 3. Stereochemical route.**

The stereochemical outcome for the transformations can be explained by the analysis of stereochemical model as depicted in Scheme 3. The stereochemical course of this process from 4 to 5 is likely to be due to a geometrical preference for A with optimal steric repulsion.

In summary, this communication describes a diastereoselective synthetic route to canadensolide 2 and sporothriolide 3 from an allenote-aldehyde 4 via the cyclocarbonylation process mediated by Mo(CO)6. Studies are in progress to incorporate with chiral environment into an enantioselective synthesis of biologically interesting natural product.

**Acknowledgments.** Generous financial support from the Korea Research Foundation (KRF-2006-312-C00234; KRF-2005-005-J11901) and the Korea Science & Engineering Foundation (R01-2007-000-20315-0) is gratefully acknowledged.

**References and Notes**