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

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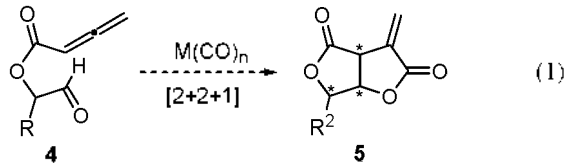
Received January 29, 2009, Accepted February 9, 2009

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

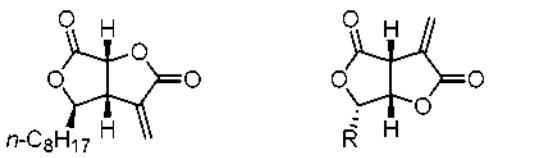
Among a variety of synthetic methodologies for the construction of cyclic compounds, chemical transformations involving the use of transition metal complexes are some of the most attractive methodologies because reactions can directly construct complicate molecules from relatively simple starting materials.[1] As a consequence, many advances in the cyclization mediated by transition metals have been made through a variety of ways in synthetic strategy.[2] Of particular interest is a cyclization strategy between carbonyl and unsaturated bonds to find practical way of chemical routes for the preparation of lactones mainly because the chemical process could dominate over the classical methods in simple trial.[3] 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.[4] Recently, we have disclosed our investigations of direct cyclization methods for the synthesis of avenacilolide **1**,[5] as a part of the allylic transfer strategy utilizing an allene as substrates or intermediates.[6]

Naturally occurring bis-lactones such as avenaciolide **1**, canadensolide **2**, and sporothriolide **3** are secondary metabolites of *Aspergillus, Penicillium canadense*, and *Sporothris sp.* respectively.[7] The biological behaviors such as antifungal, fungicidal, and algicidal activities coupled with their interesting structural features have stimulated considerable synthetic efforts in bislactone moieties.[8]



4 **5** (1)

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.

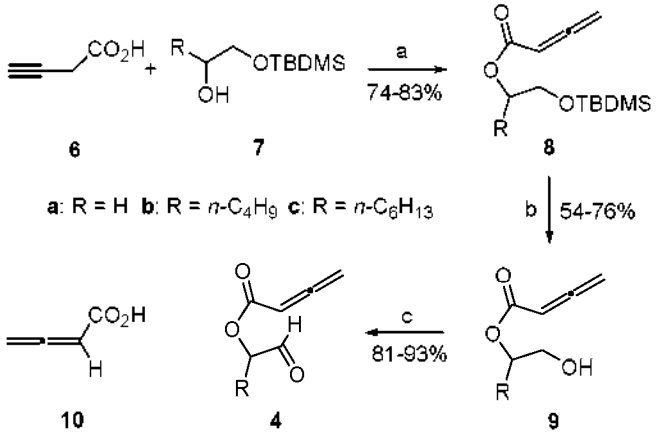


Avenaciolide (1) R = *n*-C_4H_9; Canadensolide (2) R = *n*-C_6H_{13}; Sporothriolide (3)

Figure 1. Naturally occurring bis-lactones.

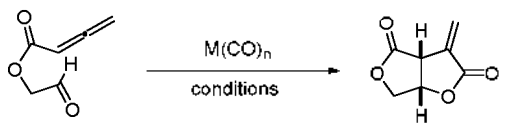
With this issue in mind, several allenoate-aldehydes were prepared as shown in Scheme 1. Attempts to couple of allenic acid **10** with alcohol **7a** under the various conditions using DCC or HATU indicated that the conversion to the corresponding lactone **2a** could not be satisfied. After surveying 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 allenoate during the process. After removal of TBDMS group by amberlyst 15 in MeOH, the Dess-Martin periodane 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 $C_7H_8Mo(CO)_3$, and $Mo(CO)_3(DMF)_3$;[9] ii) the use of 5 equivalents of $Mo(CO)_6$ was needed for optimal yield; iii) the introduction of DMSO



Scheme 1. Reagents and conditions: a. DIAD (1.5 equiv), PPh_3 (1.5 equiv), THF, 0 °C-20 °C, 3 h; b. Amberlyst 15, MeOH, 20 °C, 4 h; c. Dess-Martin periodane (1.3 equiv), CH_2Cl_2, 20 °C, 4 h.

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



4a **5a**

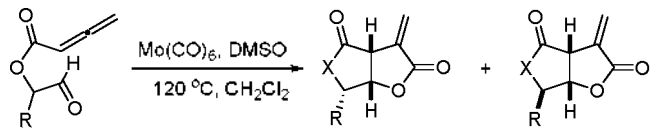
Entry	M	Solvent	T/°C	Time/h	Yield[a]
1	$Mo(CO)_6$[b]	toluene	120	6	18
2	$Mo(CO)_6$[b]	CH_2Cl_2	120	3	22
3	$Mo(CO)_6$[c]	CH_2Cl_2	120	3	63
4	$Mo(CO)_6$[c]	toluene	120	3	28
5	$C_7H_8Mo(CO)_3$[c]	CH_2Cl_2	100	12	NR
6	$Mo(CO)_3(DMF)_3$	CH_2Cl_2	100	12	trace
7	$Ni(CO)_2(PPh_3)_2$	toluene	110	7	decomposed
8	$W(CO)_6$[c]	CH_2Cl_2	120	6	NR
9	$Ru_3(CO)_{12}$, CO[d]	CH_3CN	100	12	NR

[a]refer to isolated product, % [b]1.5 equiv. additive DMSO (10 equiv) [c]5 equiv, additive DMSO (10 equiv) [d]CO (20 atm)

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 CH_2Cl_2 compared to other solvents such as toluene, THF, and CH_3CN in terms of reactivity and chemical yields; v) reaction performed at 120 °C in CH_2Cl_2 resulted in the best chemical yield: vi) other metal carbonyls such as $Ru_3(CO)_{12}$, $Ni(CO)_2(PPh_3)_2$, and $W(CO)_6$ tuned out to be unpromising.

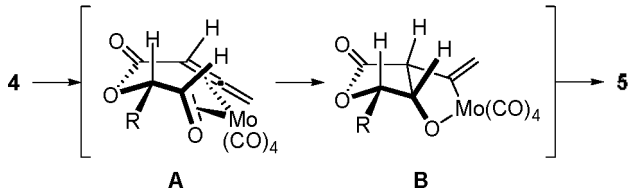
Under optimal conditions (entry 3 in Table 1), the reaction was conducted by an addition of **4a** (1 equiv) and DMSO (10 equiv) in CH_2Cl_2 at 20 °C to a solution of $Mo(CO)_6$ (5 equiv) in CH_2Cl_2 in a seal tube. After stirring at 20 °C for 20 min, the reaction mixture was immediately immersed into a pre-heated oil bath at 120 °C. After 3 h at 120 °C, the reaction mixture was cooled to rt and then filtered through a sintered glass filter containing celite with additional CH_2Cl_2. 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 allenoate-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.



4b (R = *n*-C_4H_9)	67%	**2**	75 : 25	**5a**
4c (R = *n*-C_6H_{13})	54%	**3**	77 : 23	**5b**

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 a allenoate-adehyde **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.

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