Communications

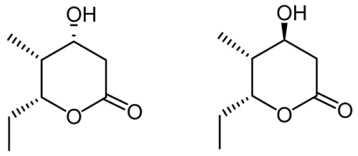
Improved Synthesis of Triketide δ-Lactones from the Pikromycin Biosynthetic Pathway

Hae-Heon Yang, Eung-Soo Kim,[†] Yeo Joon Yoon,[‡] and Han-Young Kang[*]

Department of Chemistry and Institute of Basic Sciences, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea
[*]E-mail: hykang@chungbuk.ac.kr
[†]School of Chemical Engineering and Biotechnology, Inha University, Incheon 402-751, Korea
[‡]Division of Nano Sciences and Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
Received January 30, 2006

Key Words : Polyketide biosynthesis, Stereoselective synthesis, Lactones, Allylations, Pikromycin biosynthesis

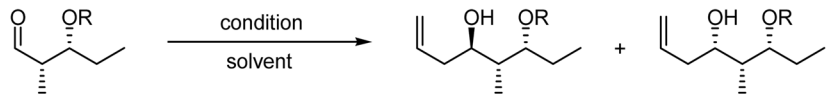
In connection with the generation of hybrid polyketide synthases (PKSs) derived from the pikromycin PKS system,[1] we have been interested in δ-lactones **1** and **2**. We reported a synthesis of both lactones by the routes based on the asymmetric aldol and the Reformatsky reaction as key steps.[2] Although the desired δ-lactones **1** and **2** were prepared successfully, the synthesis did have limitations. While the δ-lactone **2** was efficiently synthesized by the reported route, the lactone **1** having an epimeric stereochemistry on C-3 could not be prepared efficiently due to the low diastereomeric selectivity in the asymmetric Reformatsky reaction step. Also, the origin of the stereoselectivity was based on the Evans chiral oxazolidinone auxiliary. It is, therefore, desirable to eliminate the use of rather expensive Evans chiral auxiliary to prepare the lactone **1** more practically. Herein, we wish to report modified synthetic routes to the δ-lactones, focusing especially on more efficient and more practical synthesis of the lactone **1**.



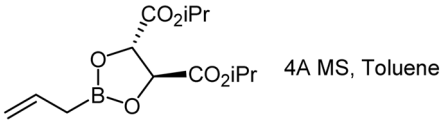
1 **2**

After we reported a chemical synthesis of both lactones, another synthesis of δ-lactone **1** appeared in the literature, which exploited the intramolecular Claisen condensation reaction.[3] It is well known to use the allylation (or

Table 1. Allylation of aldehyde **3**



3 **4** (1,3-anti) **5** (1,3-syn)

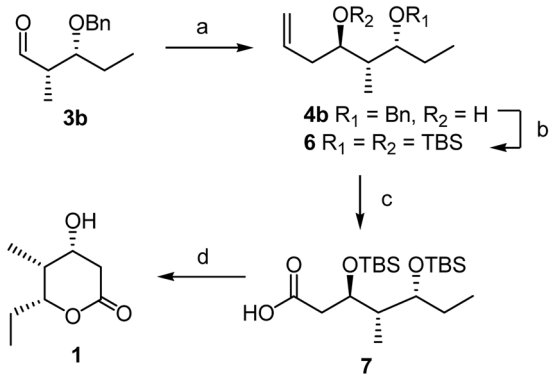
Entry	R	Reagents/Solvents	Temp.	Yield (%)	4/5 (*Anti/Syn*)
1	TBS (**3a**)	In, allyl bromide / THF : H_2O = 1 : 1	RT	85	1/1.2
2	Bn (**3b**)	In, allyl bromide / THF : H_2O = 1 : 1	RT	87	1/1.3
3	PMB(**3c**)	In, allyl bromide / THF : H_2O = 1 : 1	RT	70	1/1.5
4	TBS (**3a**)	SmI_2, allyl iodide / THF	RT	90	1/2
5	TBS (**3a**)	(S)-BINOL, allyltributyltin, $Ti(OiPr)_4$, $B(OMe)_3$, CH_2Cl_2	RT	10	Only syn
6	TBS (**3a**)	 4A MS, Toluene	RT	69	1/4.2
7	H(**3c**)	In, allyl bromide / THF : H_2O = 1 : 1	RT	Not measured	1/1
8	Bn (**3b**)	Allylbutyltin, $SnCl_4$, CH_2Cl_2	RT	82	1/3
9	TBS (**3a**)	Allyltributyltin, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2	RT	86	3.4/1
10	Bn (**3b**)	Allyltributyltin, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2	RT	91	Anti only

crotylation) to carbonyl groups as an alternative for aldol reactions. We, therefore, intended to study the allylation of aldehyde **3** to produce the relevant intermediate which can act as the precursor for the lactone **1**. The critical aspect is to find the condition for stereoselective allylation to produce the homoallylic alcohol **4**. We searched for various conditions for achieving stereoselective allylation, especially producing **4** exclusively. The results are shown in Table 1.

Indium-mediated allylation in THF/water (1 : 1) provide the alcohol with no selectivity [**4**(1,3-*anti*) : **5**(1,3-*syn*) = 1 : 1.2] (Table 1, entry 1).[4] Indium-mediated allylation of aldehyde having different protecting groups (**3a**-**3c**) with allyl bromide provided the corressponding homoallylic alcohols (**4a**-**4c** and **5a**-**5c**) in relatively similar *anti*/*syn* ratios (The *syn* product was slightly favored.) (entries 1-3). Samarium(II) iodide-mediated allylation also proceeded in the presence of allyl iodide to give 1 : 2 ratio of *anti*/*syn* product (entry 4). A catalytic method using allyltributyltin in the presence of (*S*)-BINOL has also been investigated. The *syn* product was obtained only (entry 5) albeit in low yield. The Roush's protocol also provided the *syn* alcohol as a major product (entry 6). We observed that indium-mediated allylation of **3c** was not selective giving only 1 : 1 ratio of the 1,3-*anti*/*syn*-diol which is in contrast to the *anti*-selective allylation reported by Paquette group with the similar aldehyde (entry 7).[5] Keck reported the allylation to aldehyde with allyltributyltin in the presence of a Lewis acid provided the *anti*-diol as the major product.[6] However, allylation of aldehyde **3b** with allyltributyltin in the presence of $SnCl_4$ as a Lewis acid provided the homoallyl alcohol with moderate *syn*-selectivity (*anti*:*syn* = 1 : 3) (entry 8).

Lee reported that in their total synthesis of pamamycin-607 allylation with allyltributyltin in the presence of $MgBr_2{\cdot}OEt_2$ provided the product with the 1,3-*anti* diol relationship exclusively.[7] We were pleased to find that under this condition the desired homoallylic alcohol **4** with 1,3-*anti*-diol relationship was successfully produced. Allylation of aldehyde **3a** (R=TBS) provided the 1,3-*anti* product **4a** as a major product (entry 9). Aldehyde **3b** in which the hydroxyl group was protected with benzyl group provided the desired 1,3-*anti* product **4b** exclusively in excellent yield (entry 10).

With the desired *anti*-product **4b** in hand we were able to complete the synthesis of the triketide lactone **1**, the route of which was summarized in Scheme 1. The aldehyde **3b** was prepared with the straightforward manner using the Evans aldol methodology. After the stereoselective allylation of **3b**, the resulting homoallylic alcohol **4b** was debenzylated under the reductive condition and the resulting diol was protected



Scheme 1. (a) Allyltributyltin, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, RT (91%) (b) (i) Li, di-*tert*-butylbiphenyl, THF, −78 °C (ii) TBSOTf, 2,6-lutidine (54% in two steps) (c) (i) O_3, Me_2S (77%) (ii) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH : H_2O : THF = 5 : 2 : 10 (98%) (d) 1 M HCl : THF = 5 : 1, 40 °C (70%)

with *t*-butyldimethylsilyl group to provide **6**. Ozonolysis produced the corressponding aldehyde which was subsequently oxidized to a carboxylic acid **7**. Lactonization under the acidic condition provided the desired triketide lactone **1**. Starting from the homoallylic alcohol **5a**, the epimeric triketide lactone **2** was also efficiently prepared in a similar manner.

In conclusion, we have successfully achieved the efficient synthesis of δ-lactone **1** and **2** based on the stereoselective allylation of **3b**. This demonstrates the efficiency of the *anti*-selective allylation method with allyltributyltin in the presence of $MgBr_2{\cdot}EtO_2$ which would be used for the synthesis of similar polyketide derivatives.

Acknowledgement. This work is supported by the Korea Research Foundation Grant (KRF-2004-015-C00267).

References

1. Xue, Y.; Sherman, D. H. *Nature* **2000**, *403*, 571.
2. Kim, S.-J.; Kang, H.-Y.; Sherman, D. H. *Synthesis* **2001**, 1790.
3. Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001**, *42*, 8463.
4. (a) Kang, H.-Y.; Yu, Y.-K. *Bull. Korean Chem. Soc.* **2004**, *25*, 1627. (b) Cha, J. H.; Cho, Y. S.; Koh, H. Y.; Lee, E.; Kim, Y.-T.; Yang, H.-H.; Kang, H.-Y. *ibid* **2004**, *25*, 1123.
5. Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.
6. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.
7. (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131. (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655.