

Synthesis of Dihydropyran Subunit of (+)-Sorangicin A Using RCM Reaction

Su Ho Park and Hyo Won Lee*

Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea. *E-mail: hwnlee@chungbuk.ac.kr

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The macrolide (+)-sorangicin A (**1**), isolated by Höfle and co-workers¹ from the gliding myxobacterium *Sorangium cellulosum*, has highly effective biological activity against a broad panel of both Gram-positive and Gram-negative bacteria, displaying average MIC values of 10 ng/mL and 10 µg/mL, respectively. The mechanism of action has been shown to be the inhibition of RNA polymerase in both *Escherichia coli* and *Staphylococcus aureus*. In addition, sorangicin A is active *in vitro* against several cancer cell lines.² This fact motivated us to be interested in the synthesis toward sorangicin A. One of key steps in our synthetic plan is the successful preparation of dihydropyran. There have been numerous synthetic efforts reported in the literature.³

In general, dihydropyran units has been elegantly constructed by reactions such as Claisen rearrangement, Ferrier-type reaction, radical, hetero Diels-Alder cyclizations and a few other reactions.⁴ We sought new and concise synthetic methods for this ring. Herein, we describe two new and simple preparations of the dihydropyran moiety based on olefinic ring-closing metathesis (RCM) reaction employing Grubbs catalyst.⁵

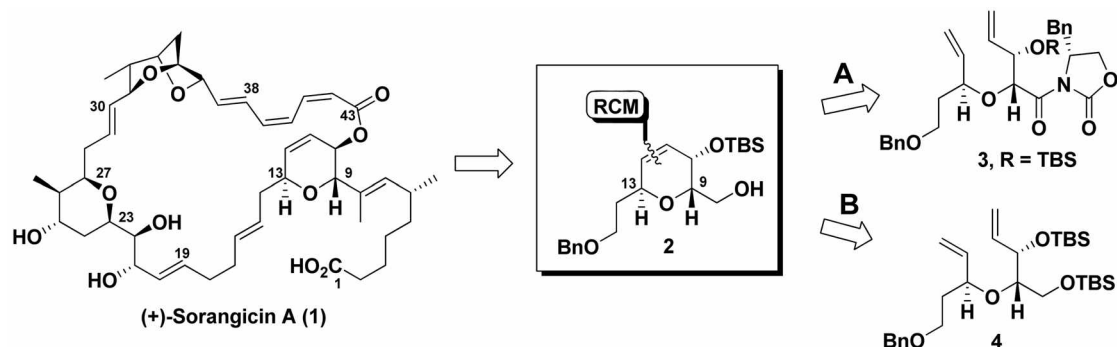
We planned two pathways according to retrosynthetic concept included formation of the C11-C12 double bond by RCM reaction (Scheme 1). First route A is employing oxazolidinone to yield the *syn*-aldol product. This methodology was implemented by Crimmins and She.⁶ The second route B is utilizing enantiospecific rhodium-catalyzed allylic etherification with the copper(I) alkoxide as a nucleophile.⁷

In the first reaction pathway A according to our synthetic plan (Scheme 2), the alcohol **5**^{4k} was reacted with sodium salt of bromoacetic acid in refluxing THF to give glycolic acid, which was converted to its mixed pivalic anhydride and treated with (*R*)-3-lithio-4-benzyl-2-oxazolidinone to

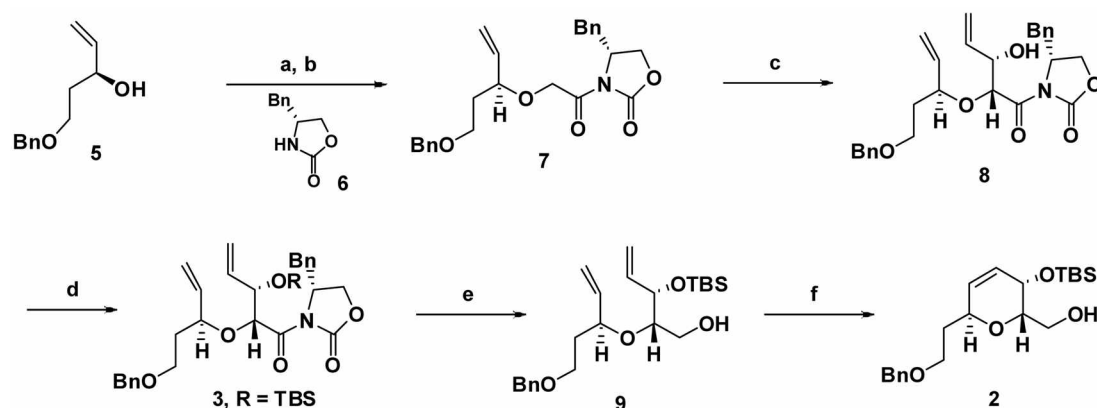
generate the *N*-glycolyloxazolidinone **7** in 81% yield over two steps. The addition reaction of **7** with acrolein furnished hydroxy compound **8** in good yield and high diastereoselectivity (73%, 93:7 dr by ¹H NMR analysis). Protection of the resulting alcohol **8** as its TBS ether **3** and reductive removal of the chiral auxiliary group afforded primary alcohol **9** in 83% yield. The olefinic RCM reaction in the presence of Grubbs' catalyst in CH₂Cl₂ transformed **9** to the desired dihydropyran compound **2**.

In the more convenient second synthetic approach B to dihydropyran **2** (Scheme 3), the stereospecificity in the reaction of rhodium-catalyzed allylic etherification could be maintained by suppressing the rate of isomerization. The copper(I) alkoxide as a nucleophile served to promote the etherification. Thus, this reaction allows for net retention of the absolute configuration through the alkylation of a rhodium-*enyl* complex.⁸

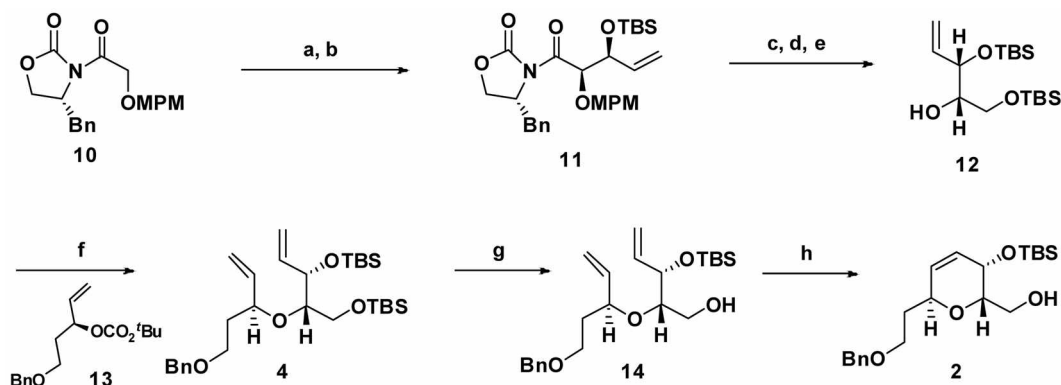
We began the second pathway with an aldol addition of chiral oxazolidinone **10** to acrolein to give *syn*-aldol adduct (84%, 92:8 dr by ¹H NMR analysis). Protection of the resulting secondary hydroxy group as its TBS ether **11** and reductive removal of the chiral auxiliary group afforded an intermediate primary alcohol in 92% yield. Then, silylation of the hydroxy group as the TBS ether and removal of the MPM group yielded the alcohol **12** in 93% yield. Treatment of the allylic carbonate **13** with the trimethylphosphite-modified Wilkinson catalyst and the copper(I) alkoxide derived from the alkenyl alcohol **12**, afforded the diene **4** in 67% yield with excellent diastereoselectivity (98:2 dr by ¹H NMR analysis). The high selectivity observed can be explained using the reported proposed mechanism.^{7,8} Desilylation of the primary hydroxyl group with CSA gave alcohol **14** in 76% isolated yield. Finally, The RCM reaction was



Scheme 1. Retrosynthetic Analysis.



Scheme 2. Reagents and conditions: a) Bromoacetic acid, NaH, THF, reflux, 18 h, 99%; b) Pivaloyl chloride, Et₃N, THF; *n*-BuLi, **6**, -78 °C, 81%, over two steps; c) TiCl₄, Pr₃NEt, acrolein, CH₂Cl₂, -78 °C, 73%; d) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt, 1 h, 96%; e) LiBH₄, cat. H₂O, THF, 0 °C, 2 h, 83%; f) Cl₂(Cy₃P)₂Ru=CHPh, CH₂Cl₂, 86%.



Scheme 3. Reagents and conditions: a) *n*-Bu₂BOTf, Et₃N, acrolein, toluene, -78 °C, 84%; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt, 1 h, 91%; c) LiBH₄, cat. H₂O, THF, 0 °C, 2 h, 92%; d) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt, 1 h, 90%; e) DDQ, wet. CH₂Cl₂, 93%; f) LiHMDS, CuI, P(OMe)₃, [RhCl(PPh₃)₃], THF, 15 h, 67%; g) CSA, CH₂Cl₂:MeOH = 10:1, 76%; h) Cl₂(Cy₃P)₂Ru=CHPh, CH₂Cl₂, 86%.

carried out smoothly in the presence of Grubbs' catalyst to obtain the desired dihydropyran **2**.

In conclusion, we have described a novel and efficient approach to the dihydropyran subunit **2** of sorangicin A. The key steps are Evans aldol reaction, rhodium-catalyzed allylic etherification and RCM reaction. Ongoing efforts toward the completion of sorangicin are currently in progress and will be reported in due course.

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