Synthesis of C3-C9 Sulfonyl Derivative of Soraphen A†

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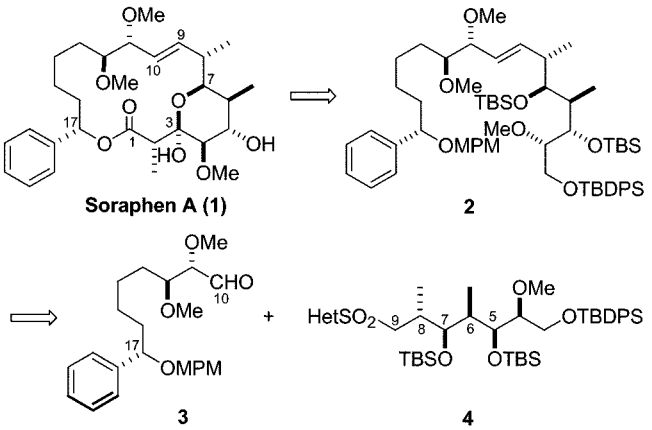
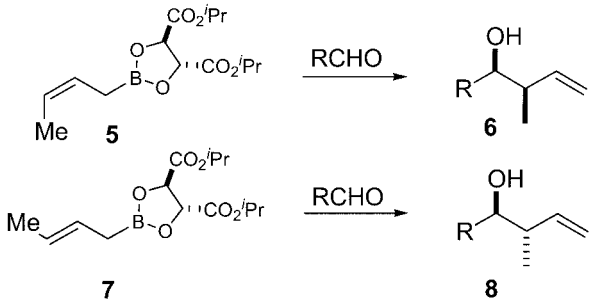
Soraphen A (**1**) is an 18-membered macrolide isolated from myxobacterium *Sorangium Cellulosum*. It displays potent antifungal activity against various pathogenic plant fungi because of its highly efficient and specific inhibitory activity on acetyl CoA carboxylase.[1,2] The structure of soraphen A was well defined by X-ray crystallographic analysis. The presence of an unsubstituted phenyl ring and a hemiketal ring constitutes its structural feature. The first total synthesis of soraphen A was reported by Giese in 1999.[3b] We previously reported our synthetic attempt.[3d,e]

Toward the synthesis of soraphen A, we deliberated the coupling of two fragments **3** and **4** involving Julia olefination and lactonization (Scheme 1). Julia olefination reaction for *trans* C9-C10 double bond requires sulfone **4** with a tetrazole ring. As for this sulfonyl compound we envisioned that the stereochemical *syn-syn-anti* relationship along C5 to C9 could be achieved using the Roush



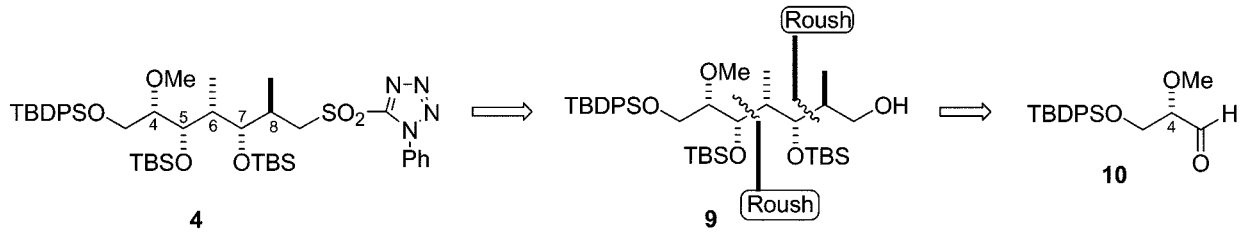
Scheme 1. Retrosynthetic Analysis.



Scheme 2. Roush Crotylation Reaction for *syn*- and *anti*-Homoallylic Alcohols.

crotylation.[4] The reaction of (*R*,*R*)-tartrate ester modified (*Z*)- and (*E*)-crotylboronates **5** and **7** with aldehydes provides *syn*- and *anti*-homoallyl alcohols **6** and **8**, respectively, with required stereochemistry for C5-C9 skeleton (Scheme 2). And the following ozonolysis of the terminal vinyl group of these intermediates would furnish the desired products. The resulting retrosynthetic analysis of the sulfonyl C3-C9 was shown in Scheme 3.

Our synthetic pathway to the C3-C9 sulfonyl derivative according to our retrosynthetic analysis is delineated in Scheme 4. At first, we considered acetonide of L-glyceraldehyde as a substrate for the Roush reaction. But the necessity of methylation at C4 suggests the preparation of glyceraldehyde **10**, which can be easily prepared from L-tartaric acid rather than L-ascorbic acid. In order to prepare glyceraldehyde **10**, (*R*)-1-(*tert*-butyldiphenylsilyloxy)but-3-en-2-ol was prepared from L-tartaric acid by the modification of the procedure reported in the literature.[5] O-Methylation of **11** using methyl iodide and sodium hydride followed by ozonolysis reaction provided aldehyde **10**. The



Scheme 3. Retrosynthetic Analysis of C3-C9 Fragment Using Roush Reaction for the Control of C5-C8 Stereochemistry.

†Dedicated to Professor Yong Hae Kim for his distinguished achievements in organic chemistry.
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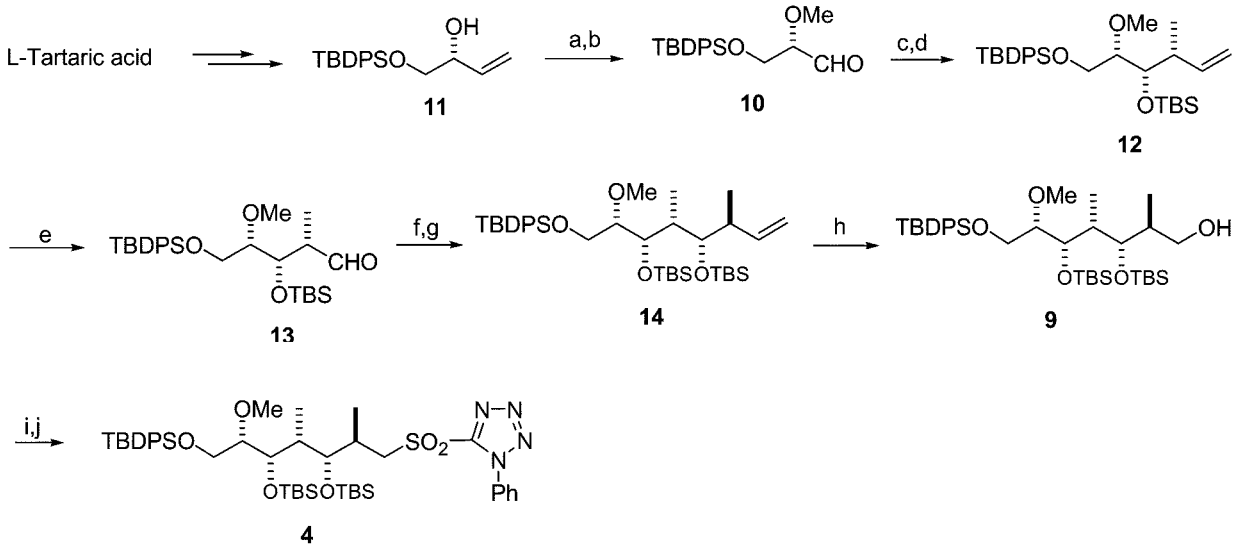

Reagents: (a) MeI, NaH, THF, rt, 3 h, 88%; (b) O_3, MeOH, −78 °C; Me_2S, 80%; (c) **5**, 4A MS, toluene, −78 °C, 3 h, 78%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 93%; (e) O_3, MeOH, −78 °C; Me_2S, 90%; (f) **7**, 4A MS, toluene, −78 °C, 3 h, 72%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 90%; (h) O_3, MeOH, −78 °C; Me_2S, $NaBH_4$, 0 °C, 87%; (i) 1-Phenyl-1H-tetrazole-5-thiol, DIAD, PPh_3, THF, rt, 24 h, 87%; (j) mcpba, $NaHCO_3$, H_2O:CH_2Cl_2 (1 : 2), 0 °C, 80%

Scheme 4. Reaction Pathway to the C3-C9 Fragment.

reaction of the Roush reagent of (*Z*)-crotylboronate **5** gave the desired *syn* stereochemistry (*syn*:*anti* = 95:5). The secondary hydroxy group of the intermediate was converted to *t*-butyldimethylsilyl ether **12** by treatment with *t*-butyldimethylsilyl triflate and 2,6-lutidine in dichloromethane at 0 °C. The ozonolysis on the terminal vinyl group of **12** furnished aldehyde **13**, which was consequently subjected to the Roush reaction using (*E*)-crotylboronate **7** to obtain *anti*-product (*anti*:*syn* = 88:12). This compound was converted to *t*-butyldimethylsilyl ether **14** by treating with *t*-butyldimethylsilyl triflate and 2,6-lutidine. The next step along the sequence was the preparation of alcohol **9**, which is the precursor of the sulfone. Thus the ozonolysis intermediate of **14** was reduced with sodium borohydride to provide alcohol **9**. Preparation of the tetrazole thioether from **9** using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine, and subsequent oxidation with mcpba finally yielded the desired sulfone **4**.

In summary, we have achieved the synthesis of the C3-C9 fragment of soraphen A (**1**) by recurring use of stereoselective Roush crotylation and subsequent ozonolysis as key transformations.

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