# An Efficient Synthesis of C3-C9 Segment of Soraphen A[§]

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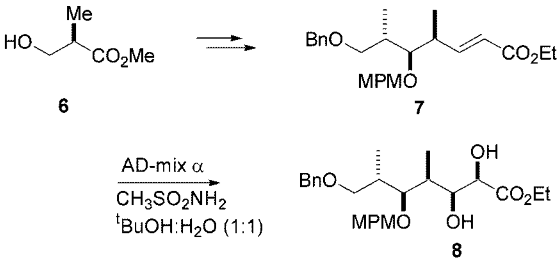
*Received June 7, 2002*

**Key Words :** Soraphen A, Myxobacterium, Antifungal, Asymmetric dihydroxylation.

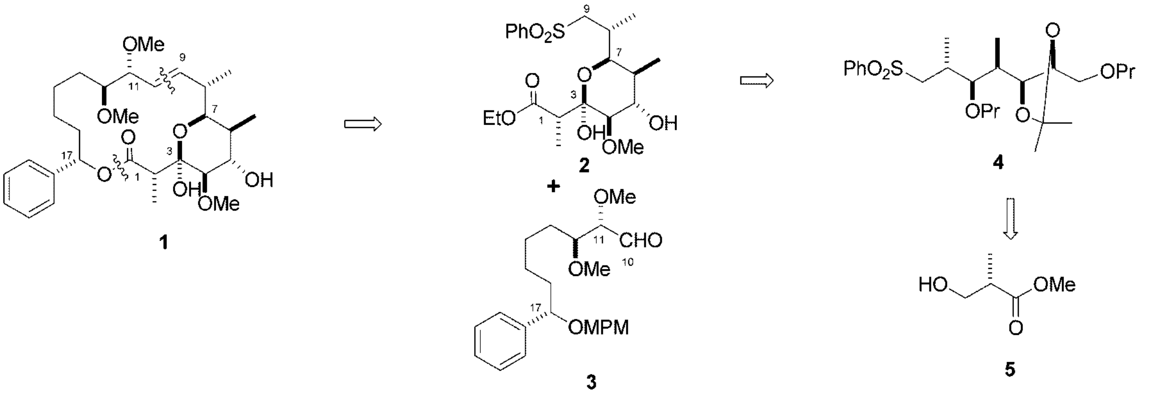
Macrolide soraphen A (**1**) isolated from myxobacterium *Sorangium cellulosum* exhibits potent antifungal activity against various pathogenic plant fungi.[1,2] Soraphen A has highly efficient and specific inhibitory action on acetyl CoA carboxylase. The structure was well defined by X-ray crystallographic study. This 18-membered macrolide with an unsubstituted phenyl ring has received considerable attention as synthetic target. Numerous synthetic studies have been reported.[3] The first total synthesis of soraphen A was reported by Giese in 1999.[3b] As a part of on-going project toward the total synthesis of soraphen A, we reported the synthesis of C10-C17 fragment **2** of soraphen A in 1996. Here we describe the efficient synthesis of the C3-C9 moiety of soraphen A.

Our synthetic strategy is focused on the cleavages at C9-C10 and lactonic bonds. Thus soraphen A can be divided into two synthetic units, **2** and **3**. Fragment **2** can be further disconnected to (*S*)-3-hydroxy-2-methylpropanoate (**5**). As for the C3-C9 segment of soraphen A, Gurjar *et al*. reported synthesis of **8** from methyl (*R*)-hydroxy-2-methylpropanoate (**6**) as shown in Eq. (1).[3c] The key reaction of their synthesis lies in the use of asymmetric dihydroxylation using AD-mix $\alpha$ to get the corresponding stereochemisty at C4 and C5 positions. We used similar approach to prepare compound **15** using methyl (*S*)-3-hydroxy-2-methylpropanoate (**5**) as a starting material (Scheme 1).



(1)

First of all, ester **5** was transformed to compound **9**, which was converted to compound **10** by the *Z*-selective Horner-Wadsworth-Emmons reaction with a reagent of ethyl (diphenyl-phosphono)acetate.[4] The following reduction with DIBAL and epoxidation with mcpba provided epoxyallyl alcohol **11**. The opening of epoxide ring of **11** with dimethylcuprate provided 1,3-diol **12** with introduction of a methyl group. The protection of the secondary hydroxyl group was performed by consecutive manipulations of protection involving conversion of the primary hydroxyl group as TBS ether and benzylation of the secondary hydroxyl group followed by removal of TBS group to obtain compound **13**. The aldehyhde intermediate obtained by Sworn oxidation of **13** was transformed to $\alpha,\beta$-unsaturated ester **14** by Horner-Wadsworth-Emmons reaction. When compound **15** was subjected to asymmetric dihydroxylation with AD-mix $\alpha$, we could not obtain good stereoselectivity as we expected. The ratio of the desired product **15** to its diastereomer was 6 : 4. We had to circumvent this poor selectivity of asymmetric dihydroxylation. Simple molecular mechanics calculation reveals that the benzyl group is located over the plane of double bond, impeding the approach of the osmium



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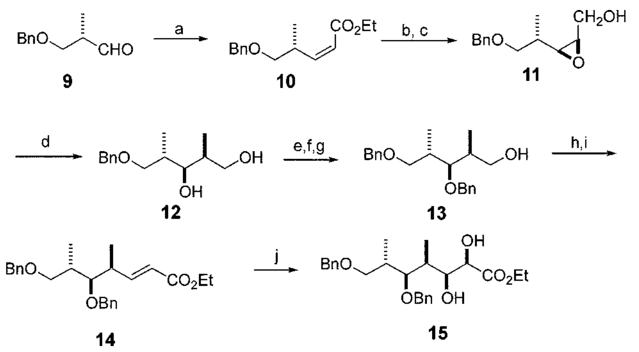
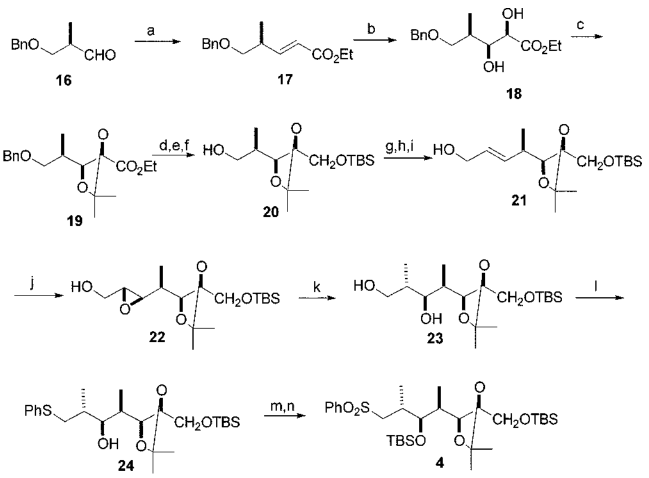
[§] This paper is dedicated to the late Professor Sang Chul Shim.



**Scheme 1**. *Reagents*: a. $(PhO)_2POCH_2CO_2Et$, *t*-BuOK, THF, -78 °C, 92%; b. DIBAL, THF, -78 °C, 89%; c. mcpba, $CH_2Cl_2$, 90%, d. $Me_2CuLi$, $Et_2O$, -40 °C, 81%; e. TBSCl, imidazole, DMF, 89%; f. BnBr, *t*-BuOK, $Bu_4NI$, THF, 87%; g. TBAF, THF, 92%; h. Swern ox., 97%; i. $(EtO)_2POCH_2CO_2Et$, *t*-BuOK, THF, -78 °C, 94%; j. AD-mix $\alpha$, $CH_3SO_2NH_2$, *t*BuOH : $H_2O$ (1 : 1), 60%.

complex reagent.

Apart from the above synthetic route, we had to use an alternative and efficient approach including the utilization of asymmetric dihydroxylation at the early stage of synthesis (Scheme 2). The preparation of this dihydroxy compound **18** from methyl (*R*)-3-hydroxy-2-methylpropanoate (**6**) was reported in the literature.$^5$ We converted **18** to diacetonide **19** as usual. The ester group of this compound was reduced to alcohol by treatment with DIBAL and the resulting primary hydroxyl group was protected as TBS ether. The release of benzyl group of this intermediate by hydrogenolysis provided compound **20**, which was subsequently transformed by Horner-Wadsworth-Emmons reaction to obtain $\alpha,\beta$-unsaturated ester, which was converted to allylic alcohol **21** by reduction with DIBAL. The Sharpless reaction of **21** furnished epoxide **22** and stereoselective opening reaction of the epoxide ring of **22** with dimethylcuprate furnished compound **23**. The subjection of **23** to Hata reaction yielded phenyl sulfide **24** and protection of the secondary hydroxy group of **24** to TBS ether followed by oxidation of sulfide with mcpba finally provided sulfonyl **4** of C3-C9 fragment with desired stereochemistry.



**Scheme 2**. *Reagents*: a. $(EtO)_2POCH_2CO_2Et$, NaH, THF, -78 °C, 89%; b. AD-mix $\alpha$ $CH_3SO_2NH_2$, *t*BuOH : $H_2O$ (1 : 1), 76%; c. $(CH_3)_2C(OCH_3)_2$, CSA, $CH_2Cl_2$, 92%; d. DIBAL, THF, -78 °C, 93%; e. TBSCI, imidazole, THF, 97%; f. Pd/C, $H_2$, EtOH, 94%; g. Swern ox., 93%; h. $(EtO)_2POCH_2CO_2Et$, NaH, THF, -78 °C, 86%; i. DIBAL, THF, -78 °C, 90%; j. D-DET, $Ti(OiPr)_4$, 4A MS, TBHP, $CH_2Cl_2$, 88%; k. $Me_2CuLi$, $Et_2O$, -40 °C, 92%; I. $(PhS)_2$, *n*-$Bu_3P$, THF, 82%; m. TBSOTf, 2,6-Lutidine, $CH_2Cl_2$, 81%; n. mcpba, $NaHCO_3$, $CH_2Cl_2$; $Na_2SO_3$, 80%.

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