Synthesis of C10-C17 Fragment of Soraphen A

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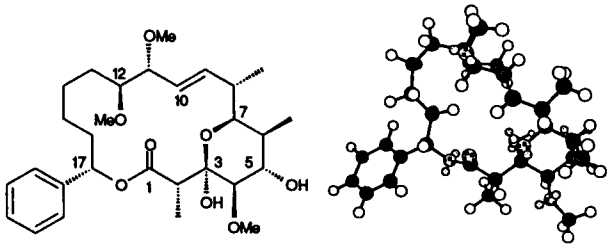
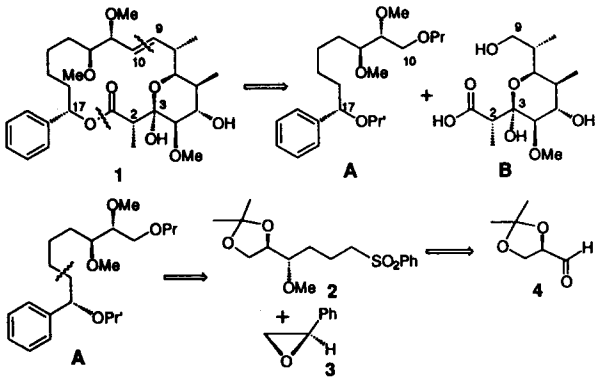
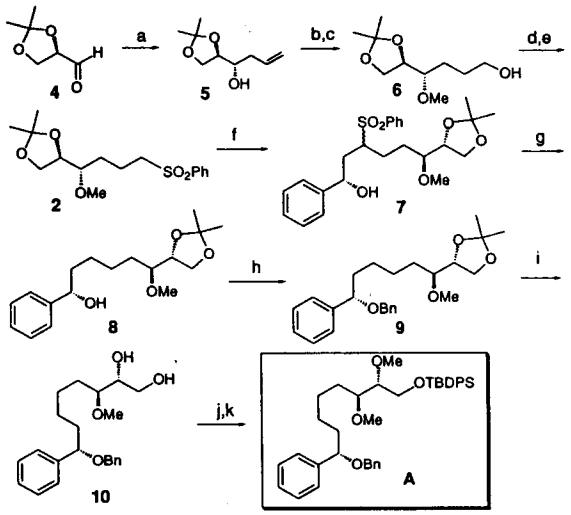
Soraphen A (**1**) is a macrolide isolated from the myxobacterium *Sorangium cellulosum.*[1] Soraphen A has potent fungicidal activity against various plant pathogenic fungi. So far the synthesis of soraphen A reported in the literature has been mainly about the fragment of C1-C9.[2] Herewith we would like to report synthesis of C10-C17 fragment of soraphen A.



Retrosynthetic analysis of soraphen A straightforwardly reveals two major fragments A and B, resulted from the disconnection at a pair of bonds at C9-C10 and C-O of lactone (Scheme 1). Further retrosynthetic analysis of fragment A suggests use of (*R*)-glyceraldehyde (**4**) as a starting material to introduce the stereochemistry at C11 and C12. Accordingly in our synthetic route toward the fragment A, reaction of (*R*)-glyceraldehyde with organometallic allylic reagent was carried out in the first place (Scheme 2). In general, reaction between organometallic allylic compound and (*R*)-glyceraldehyde usually gives a mixture of product. In our case, the desired product is chelated Cram's product **5**. Although reactions of glyceraldehyde with allylic boronic esters with chiral auxiliary such as one derived from *L*-(+)-diisopropyl tartrate have been reported to give predominantly **5**,[3] we have found the utilization of an allylindium reagent to be more advantageous not only because of its simplicity but also because of its appropriateness for large scale reactions.[4] After the chromatographic separation, **5** was subjected to methylation with NaH and CH_3I and subsequent hydroboration with $BH_3 \cdot Me_2S$ to obtain **6** in 82% yield for two steps. The treatment of hydroxyl group of **6** with diphenyl disulfide and tributyl phosphine provided a phenyl sulfide derivative[5] and following oxidation of the sulfide with mcpba and $NaHCO_3$ gave **2** in 92% yield. The next step along the sequence was the coupling of sulfone with epoxide to provide the necessary stereogenic hydroxyl group at C-17. The reaction of dicarbanion of **2**, generated by two equivalents of *n*-BuLi, with commercially available (*R*)-styrene oxide (**3**) gave coupled sulfonyl products **7** as a diastereoisomeric mixture in 86% yield. ^1H NMR spectrum of this mixture showed two distinctive peaks of CH_3O^- at δ 3.23 and δ 3.33. Without separation of isomers, reductive removal of sulfonyl group of **7** was performed by employing sodium amalgam in a buffered methanolic solution to furnish **8** in 82% yield. ^1H NMR spectrum of **8** exhibited only one singlet peak at δ 3.37. Furthermore, (*R*)-MTPA ester derivative of **8** showed the presence of single isomeric product. Consequently we achieved all the required stereochemistry for fragment **A**. The hydroxyl group of **8** was transformed to benzyl ether by treatment with NaH and benzyl bromide in DMF to obtain **9** in 93% yield. The acidic treatment of acetonide group of **9** in 70% aqueous acetic acid afforded diol **10** in 98% yield. The methylation of the secondary hydroxyl group of **10** needs the protection of a primary hydroxyl group. Compound **10** was selectively protected as TBDPS ether at a primary hydroxyl group by treating with TBDPSCl and imidazole in the presence of catalytic amount of dimethylaminopyridine. The consecutive methylation at the remaining secondary hydroxyl group of **10** provided the desired product A in 65% for two steps and thus this formally completed the synthesis of C10-C17 moiety of soraphen A.



Scheme 1.



Scheme 2.

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