
Synthetic Studies on Soraphen A: Synthesis of the C1-C9 Hemiketal Segment

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Received April 30, 2008

Key Words : Soraphen A, Macrolide, Hemiketal, Aldol reaction, Crotylation

Soraphen A (1) isolated from myxobacterium Sorangium cellulosum exhibits potent antifungal activity against various pathogenic plant fungi. This polyketide has highly efficient inhibitory action on eukaryotic acetyl-coenzyme A carboxylases (ACCs), and specifically their biotin carboxylase (BC) domains of ACCs. ACCs have crucial roles in the metabolism of fatty acids and, therefore, are targets for drug development against obesity, diabetes, and other diseases. This natural product contains an unsaturated 18-membered lactone ring, an unsubstituted phenyl ring, and a hemiketal ring constituting its structural feature. There have been several synthetic studies reported in the literature. The first total synthesis of soraphen A was reported by Giese in 1995. We have reported our synthetic studies. We envisioned that it would be the synthesis of soraphen A via a sequence of the esterification and ring-closing metathesis (RCM) between 2 and 3 segments (Scheme 1).

Herein we disclose our efforts in the construction of the C1-C9 segment. General stereocchemical control of carboxylic acid 3 was devised from the combined application of Evans aldol reaction and Roush asymmetric crotylation (Scheme 1).

As shown in Scheme 2, the synthesis of 3 began with Roush crotylation between (E)-crotylboronate 7 and aldehyde 6, prepared from commercially available (S)-5 to deliver homoallylic alcohol 8 (82%, 97:3 dr). Removal of the TBS group in 8 under mild condition by TBAF followed by exposure to p-methoxybenzaldehyde dimethylacetal 9 and CSA yielded p-methoxyphenyl acetal 10 in good yield. Subsequent regioselective opening of acetal 10 using DIBAL provided the alcohol 11 (90%) and the Swern oxidation upon 11 furnished the intermediate aldehyde. Boron-mediated aldol reaction of the intermediate with oxazolidinone 12 gave the desired aldol adduct 13 (70% over two steps from 11, 93:7 dr) with the requisite stereocchemistry at C4 and C5 of soraphen A. Protection of the hydroxy group of 13 by treatment with TBSOTf and 2,6-lutidine and reductive cleavage of the oxazolidinone moiety of the resulting TBS ether by LiBH4 yielded alcohol 14 in good yield. Similarly, the stereocchemistry at C2 and C3 of soraphen A could be achieved using recurring Evans protocol. Consequently the intermediate aldehyde was obtained quantitatively from Parikh-Doering oxidation upon 14. Other oxidation conditions such as Swern oxidation and Dess-Martin oxidation provided in 43% and 48% yields, respectively. The aldehyde was submitted to the aldol reaction with the chiral oxazolidinone 15. The resultant aldol adduct 4 (72% yield over two steps from 14, a single diastereomer) was transformed into hemiketal 16 by a two-step protocol, oxidation to the secondary alcohol with Dess-Martin periodinane and concomitant cyclization by oxidative cleavage the MPM group of 4 treating with DDQ (79% yield over two steps from 4).

At this stage, the structural configuration of hemiketal 16 was determined on the basis of 2D-NMR spectroscopic data (COSY, HMQC, and HMBC) along with relevant NOE studies (Scheme 2). As we expected, the six-membered ring shows a chair conformation with a methyl, a methoxy, and a hydroxyl groups of the hemiketal ring occupying axial positions, which is concluded that the substituents possess the same orientation as in soraphen A.
With the desired hemiketal 16 in hand, the elaboration to the target acid 3 was required (Scheme 3). The anomic hydroxy group of 16 was converted to intermediate 17 by treatment with HC(OMe)₃ and PPTS (70%). Hydrolysis of 17 by the conventional treatment with LiOH⁶ afforded an epimeric mixture 3a of the desired carboxylic acid (40%). The epimerization at this step was unavoidable under our condition. However, other hydrolysis conditions employing aqueous KOH and NaOH ended up to give us poor conversion. As an alternative measure we performed the reductive cleavage of the chiral auxiliary of intermediate 17 by NaBH₄ to obtain primary alcohol 18 (79%). Thus we expected the oxidation of 18 by Parikh-Doering oxidation would give the intermediate aldehyde, which could be readily oxidized with NaClO₂ to carboxylic acid 3. However, we could not advance in the desired direction. The aldehyde was found to immediately decompose when we carried out oxidation with NaClO₂.

In summary, the C1-C9 segment of soraphen A with C-2 epimer was prepared via 17-step sequence in 4.6% overall yield. Successfully we was introduced the seven stereogenic centers using Evans aldol reaction and Roush asymmetric crotylation and the desired hemiketal ring.

Acknowledgments. This work was supported by the research grant of the Chungbuk National University in 2006.

References