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

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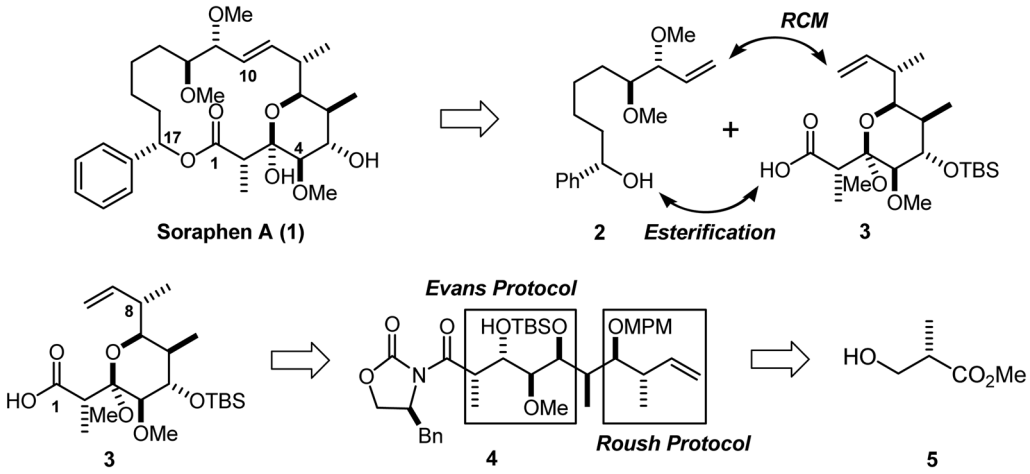
Soraphen A (**1**) isolated from myxobacterium *Sorangium cellulosum* exhibits potent antifungal activity against various pathogenic plant fungi.[1] This polyketide has highly efficient inhibitory action on eukaryotic acetyl-coenzyme A carboxylases (ACCs), and specifically their biotin carboxylase (BC)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

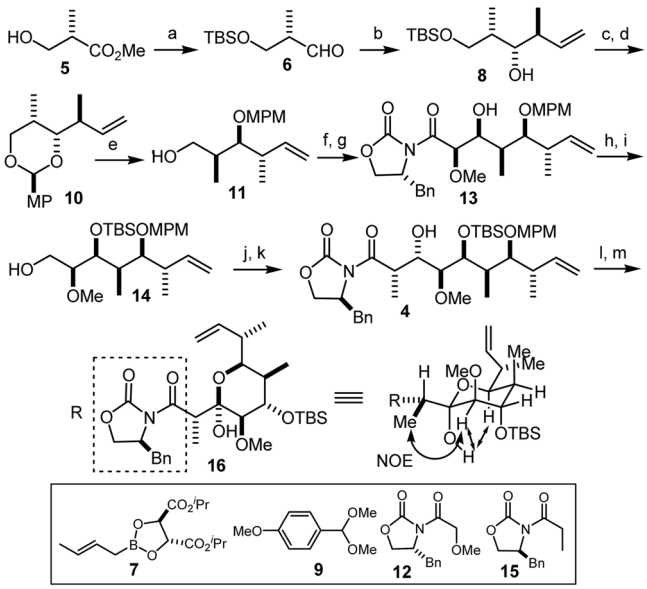
We envisioned that it would be the synthesis of soraphen A *via* a sequence of the esterification and ring-closing metathesis (RCM) between **2**[3e] and **3** segments (Scheme 1). Herein we disclose our efforts in the construction of the C1-C9 segment. General stereochemical control of carboxylic acid **3** was devised from the combined application of Evans aldol reaction[4] and Roush asymmeric crotylation[5] (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**,[6] to deliver homoallylic alcohol **8** (82%, 97:3 dr).[5] 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**[4] gave the desired aldol adduct **13** (70% over two steps from **11**, 93:7 dr) with the requisite stereochemistry 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 $LiBH_4$ yielded alcohol **14** in good yield. Similarly, the stereochemistry 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[7] 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**.[4] 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-Matin periodinane and concomitant cyclization by oxidative cleavage the MPM group of **4** treating with DDQ (79% yield over two steps from **4**).

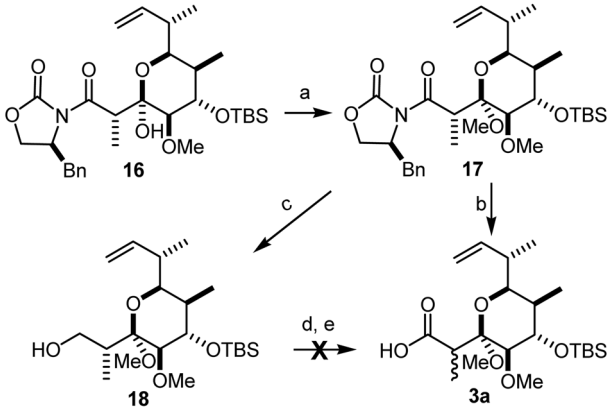
At this stage, the structural configuration of hemiketal **16** was determined on the basis of 2D-NMR spectroscopic data (COSY, HMQC, and HMBC) along with relevant NOE studies (Scheme 2). As we expected, the six-membered ring shows a chair conformation with a methyl, a methoxy, and a hydroxyl groups of the hemiketal ring occupying axial positions, which is concluded that the substituents possess the same orientation as in soraphen A.[1a,3l]



Scheme 1. Retrosynthetic Analysis.



Scheme 2. Reaction Pathway to the Hemiketal **16**. (a) Ref. 6. (b) **7**, 4A MS, MePh, −78 °C, 3 h, 82%. (c) TBAF, THF, rt, 1 h, 92%. (d) **9**, CSA, CH_2Cl_2, 0 °C, 30 min, 88%. (e) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 90%. (f) $(CICO)_2$, DMSO, Et_3N, CH_2Cl_2, 1 h. (g) **12**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 3 h, 70% over two steps from **11**. (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h, 90%. (i) $LiBH_4$, H_2O, THF, 0 °C, 3 h. 85%. (j) SO_3·py, Et_3N, DMSO:CH_2Cl_2 (1:1), 0 °C, 1 h. (k) **15**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 3 h, 72% over two steps from **14**. (l) DMP, CH_2Cl_2, rt, 1 h, 92%. (m) DDQ, CH_2Cl_2, H_2O, rt, 2 h, 86%.



Scheme 3. Approach to the Desired Acid **3**. (a) $HC(OMe)_3$: CH_2Cl_2 (2:1), PPTS, rt, 48 h, 70%. (b) LiOH·H_2O, H_2O_2, THF, H_2O, 0 °C, 3 h, 40%. (c) $NaBH_4$, THF:H_2O (5:1), 0 °C, 3 h, 79%; (d) SO_3·py, Et_3N, DMSO:CH_2Cl_2 (1:1), 0 °C, 1 h; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF:^{t}BuOH:H_2O (3:3:1), 0 °C, 30 min, decomposed.

With the desired hemiketal **16** in hand, the elaboration to the target acid **3** was required (Scheme 3). The anomeric 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 LiOOH[8] 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 $NaBH_4$ 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 $NaClO_2$ 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 $NaClO_2$.

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 asymmeric crotylation and the desired hemiketal ring.

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References

1. (a) Bedorf, N.; Schomburg, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 1017-1021. (b) Gerth, K.; Reichenbach, H.; Bedorf, N.; Irschik, H.; Höfle, G. *J. Antibiotics* **1994**, *47*, 23-31. (c) GBF mbH and Ciba-Geigy *AG*, EP 0282455 A3.
2. Shen, Y.; Volrath, S. L.; Weatherly, S. C.; Elich, T. D.; Tong, L. *Molecular Cell* **2004**, *16*(6), 881-891.
3. (a) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2466-2468. (b) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* **1999**, 188-197. (c) Vincent, G.; Mansfield, D. J.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett.* **2006**, *11*, 2791-2794. (d) Diaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 8130-8139. (e) Lee, H. W.; Kim, Y. J. *Bull. Korean Chem. Soc.* **1996**, *17*, 1107-1108. (f) Lee, H. W.; Lee, I.-C.; Kim, Y.-S.; Park, S.-U. *Bull. Korean Chem. Soc.* **2002**, *23*, 1197-1198. (g) Park, S. H.; Lee, H. W.; Park, S.-U. *Bull. Korean Chem. Soc.* **2004**, *25*, 1613-1614. (h) Gurjar, M. K.; Mainkar, A. S.; Srinivas, P. *Tetrahedron Lett.* **1995**, *36*, 5967-5968. (i) Cao, Y.; Eweas, A. F.; Donaldson, W. A. *Tetrahedron Lett.* **2002**, *43*, 7831-7834. (j) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Helv. Chim. Acta* **1995**, *78*, 122-128. (k) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549-3558. (l) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *J. Org. Chem.* **1995**, *60*, 953-959.
4. (a) Gage, J.; Evans, D. A. *Org. Symth.* **1990**, *68*, 83-91. (b) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129. (b) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173-181. (c) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513. (d) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060-5063. (e) Hwang, J. M.; Yeom, S. H.; Jung, K. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 821-826.
5. (a) Roush, W. R.; Ando, K.; Power, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348. (b) Roush, W. R.; Ando, K.; Power, D. B.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117-4126. (d) Yang, H.-H.; Kim, E.-S.; Yoon, Y. J.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 473-474.
6. (a) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998-3017. (b) Paik, S. *Bull. Korean Chem. Soc.* **1999**, *20*, 217-219.
7. (a) Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507. (b) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1997**, *62*, 8290-8291.
8. (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83-91. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.