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Synthesis of the C29–C37 Bicyclic Ether Core of (+)-Sorangicin A

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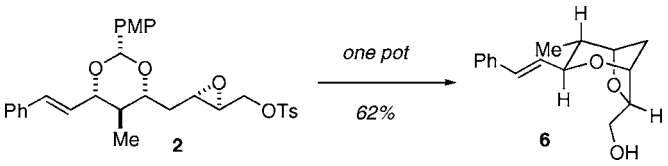
ABSTRACT



Construction of the unique bicyclic bis-ether core of the macrolide (+)-sorangicin A has been achieved. This fragment was prepared by utilizing a one-pot cascade of three bond forming events. An epoxide opening of the epoxy tosylate 2 led to the formation of the tetrahydropyran and subsequently to a second epoxide. Finally, a second epoxide opening closed the tetrahydrofuran ring. The bicyclic fragment was synthesized in just nine steps from (*E*)-cinnamaldehyde.

Sorangicin A (**1**) was isolated in 1985 by Höfle and Reichenbach[1] from the gliding bacterium *Sorangium cellulosum*. It is highly active against a spectrum of both Gram-positive (MIC 0.01−0.3 μg/mL) and Gram-negative bacteria (MIC 3−25 μg/mL). Sorangicin A hinders bacterial growth (e.g., *Escherichia coli* and *Staphylococcus aureus*) in vivo by inhibiting RNA polymerase.[1]

The unique 31-membered lactone features a tetrasubstituted tetrahydropyran, a trisubstituted dihydropyran, a (*Z*,*Z*,*E*)-trienoate, and the signature C29−C37 bicyclic ether moiety, which in combination presents a formidable challenge for chemical synthesis. The Smith[2] and Schinzer[3] laboratories have both reported efforts toward the synthesis of (+)-sorangicin A, including syntheses of bicyclic ether fragments similar to bis-ether **6** (Scheme 1). Herein we disclose our initial efforts toward the synthesis of (+)-sorangicin A (Figure 1) by way of construction of the C29−C37 bicyclic ether fragment.

We envisioned construction of the C29−C37 bicyclic ether utilizing the epoxy tosylate **2** (Scheme 1). The approach was designed around a three-step sequence of epoxide opening, epoxide formation, and a second epoxide opening (Scheme 1) to fashion the bicyclic fragment **6** from epoxide **2**. It was anticipated that exposure of epoxide **2** to acid would effect hydrolysis of the acetal to form diol **3** as well as catalyze the opening of the epoxide (Scheme 1). In the epoxide cleavage, formation of the six-membered tetrahydropyran (attack at C35) relative to the tetrahydrofuran (attack at C36) was expected to be favored for both geometric reasons[4] and

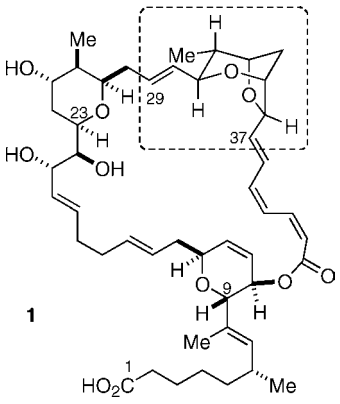


Figure 1. (+)-Sorangicin A.

(1) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Hofle, G. *Tetrahedron Lett.* **1985**, *26*, 6031.
(2) (a)Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477. (b) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099.
(3) Schinzer, D.; Schulz, C.; Krug, O. *Synlett* **2004**, *15*, 2689.

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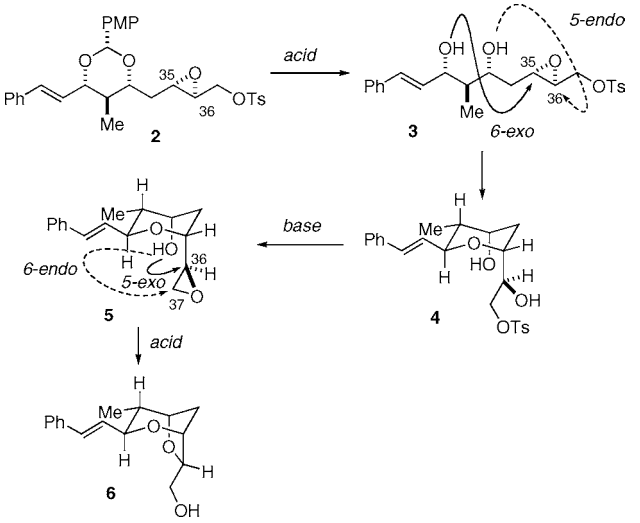
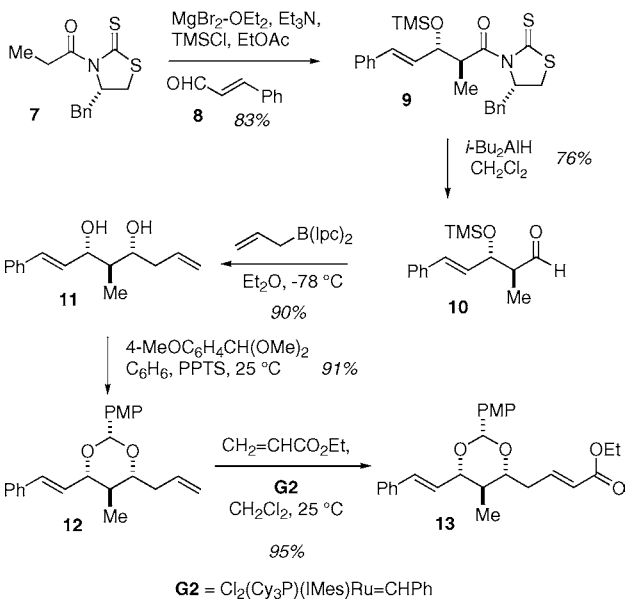
Scheme 1



the superior ability of C35 (relative to C36) to stabilize the developing positive charge in the transition state. Treating the resulting diol **4** with base was expected to produce epoxide **5** via a displacement of the tosylate. Upon acidification, epoxide **5** was projected to cyclize to the desired bridged bicyclic diether **6**, again based on the better trajectory for attack and the greater positive charge stabilization at C36 relative to C37.

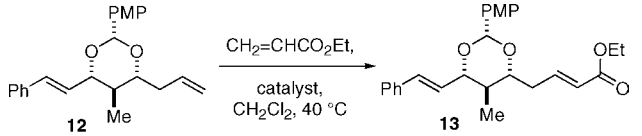
The synthesis of epoxide **2** began with the known Evans anti-aldol reaction between (*E*)-cinnamaldehyde (**8**) and *N*-propionylthiazolidinethione **7**, which delivered the aldol adduct **9** in 83% yield (91:9 dr, Scheme 2).[5] The chiral auxiliary was reductively removed with *i*-Bu_2AlH,[6] and the resultant aldehyde **10** was immediately subjected to Brown's asymmetric allylation protocol (>95:5 dr).[7] Diol **11** was

Scheme 2



protected as its *p*-methoxyphenyl acetal **12** by exposure to PPTS and 4-methoxybenzaldehyde dimethylacetal. The carbon chain was next elongated via a cross metathesis reaction with ethyl acrylate (Table 1). The cyclic acetal was

Table 1. Optimization of the Terminal Olefin **12**/Ethyl Acrylate Cross Metathesis[a]



entry	catalyst	temperature	ethyl acrylate (equiv)	yield (%)
1	G2	rt	2	61
2[b]	G2	40 °C	2	37
3[c]	G2	rt	2	53
4[d,e]	G1	40 °C	5	20
5	G1	40 °C	4	0
6	G2	rt	10	71
7	G2	rt	20	95

[a] Reactions run in degassed methylene chloride (0.1 M) for 14 h using 5 mol % catalyst. [b] Reaction was run for 3 h. [c] 7.5 mol % catalyst was used. [d] Reaction was run for 4 h. [e] 10 mol % catalyst was used.

chosen as the diol protecting group since the six-membered acetal orients the two alkenyl substituents in equatorial positions strongly disfavoring ring-closing metathesis to give a six-membered bridged bicyclic structure.

Several conditions for the cross metathesis[8] were explored. Treatment of terminal alkene **12** and 2 equiv of ethyl acrylate with the Grubbs second generation catalyst [$Cl_2(Cy_3P)$(IMes)-Ru=CHPh] at room temperature for 14 h produced unsaturated ester **13** in 61% yield (Table 1). In addition to ester **13**, other metathesis byproducts (15%) as well as alkene **12** (7%) were recovered. Increasing temperature or catalyst loading had no favorable effect on the yield (entries 2 and 3, respectively). The Grubbs first generation catalyst [$Cl_2(Cy_3P)_2$-Ru=CHPh] produced mostly the dimer of **12**. The best results were realized when olefin **12** and 20 equiv of ethyl acrylate were treated with 5 mol % of the Grubbs second generation catalyst (entry 7). The desired enoate **13** was isolated in 95% yield after 14 h at room temperature.

Ester **13** was converted to the desired epoxide **2**, as illustrated in Scheme 3. Reduction of ester **13** to allylic alcohol **14** was accomplished in 93% yield by exposure to *i*-Bu_2AlH (Scheme 3). Allylic alcohol **14** was treated under Sharpless asymmetric epoxidation conditions providing

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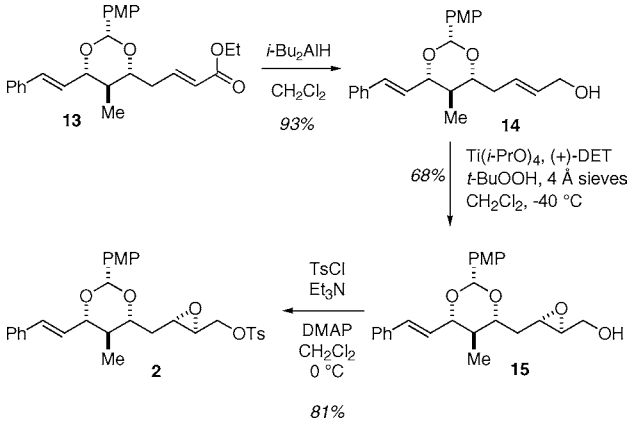
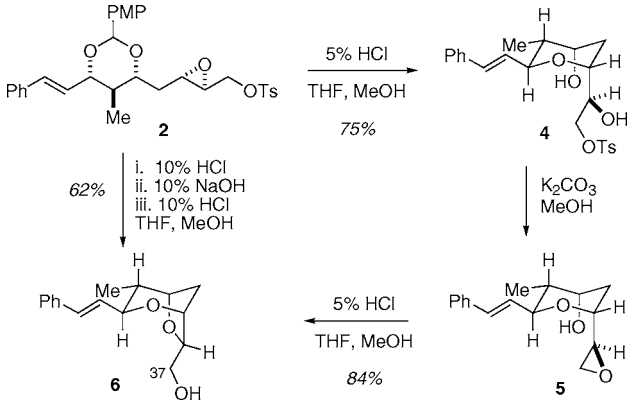
(5) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.
(6) (a) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
(7) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
(8) Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

Scheme 3



Scheme 4



epoxide **15** (>98:2 dr).[9] Epoxy alcohol **15** was treated with base and tosyl chloride to yield tosylate **2**.

With the epoxy tosylate **2** in hand, the investigation of its conversion to the bicyclic diether was undertaken. Acid-catalyzed cyclization[10] to form tetrahydropyran **4** was initially attempted. Exposure of epoxide **2** to 5% aqueous HCl in THF−MeOH (Scheme 4) produced the tetrahydropyran **4** in 75% yield after 14 h at 25 °C.[11] Tosylate **4** was rapidly converted to epoxide **5** upon treating with K_2CO_3 in MeOH.[12] Epoxide **5** was somewhat unstable and decomposed during attempted purification. Alternatively, epoxy alcohol **5** was subjected, without purification, to 5% aqueous HCl in THF−MeOH.[13] The bicyclic ether **6** was obtained in 84% yield over the final two steps. The structure of bicyclic ether **6** was confirmed by X-ray analysis of the C37 *p*-nitrobenzoate derivative.

In an attempt to further streamline the sequence, the final three steps were combined in a one-pot three-step sequence (Scheme 4). To this end, tosylate **3** was treated with 10% aqueous HCl in THF−MeOH and allowed to stir for 18 h. A solution of 10% aqueous NaOH was added to the mixture until the reaction mixture became basic. Under these conditions, the epoxide formation was complete in less than 2 min. Finally, the solution was acidified with 10% aqueous HCl, and the reaction was quenched after 4 h. The more convenient one-pot sequence provided the bicyclic ether **6** in essentially the same overall yield (62%) as the stepwise process.

In summary, an efficient route to the C29−C37 bicyclic fragment **6** of (+)-sorangicin A has been developed. The synthesis requires only nine steps and proceeds in good overall yield. This synthetic strategy relies upon a cross metathesis to complete the construction of the carbon backbone and a three-step one-pot sequence to regioselectively close both rings of the bridged bicyclic ether. Further efforts toward the completion of (+)-sorangicin A (**1**) are currently underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a related cyclization, see: Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.