

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

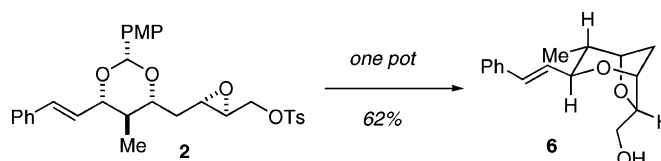
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Received June 1, 2006

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 Reichenbach¹ 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 Smith² and Schinzer³ 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 **6** 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 reasons⁴ and

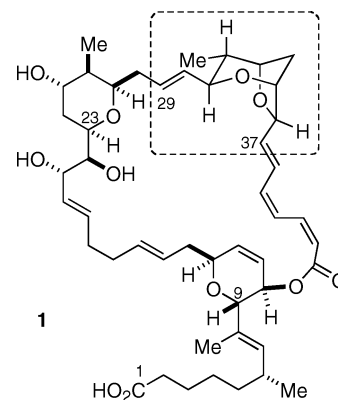


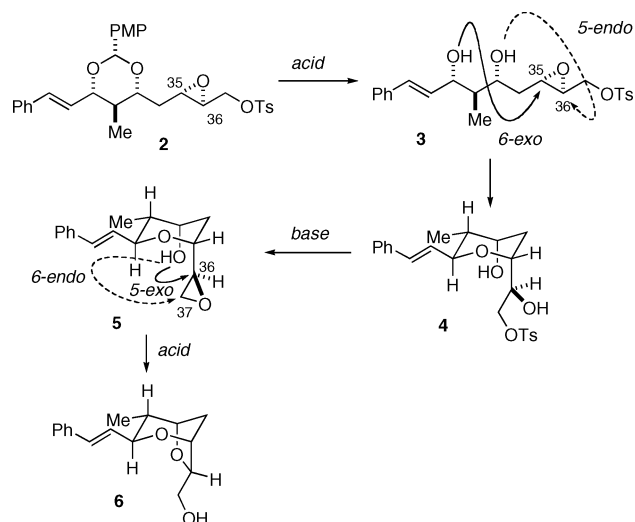
Figure 1. (+)-Sorangicin A.

(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.

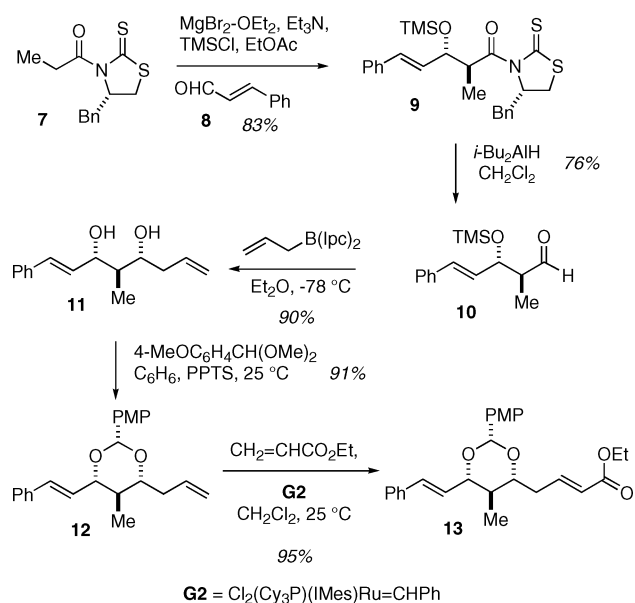
Scheme 1



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.

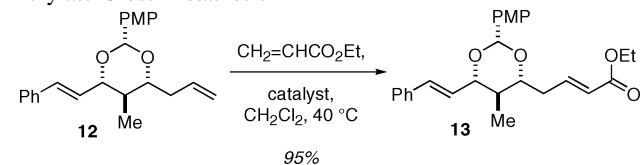
The synthesis of epoxide **2** began with the known Evans anti-aldol reaction between (*E*)-cinnamaldehyde (**8**) and *N*-propionylthiazolidinethione **7**, which delivered the aldol adduct **9** in 83% yield (91:9 dr, Scheme 2).⁵ The chiral auxiliary was reductively removed with *i*-Bu₂AlH,⁶ and the 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 metathesis⁸ were explored. Treatment of terminal alkene **12** and 2 equiv of ethyl acrylate with the Grubbs second generation catalyst [Cl₂(Cy₃P)(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 [Cl₂(Cy₃P)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*-Bu₂AlH (Scheme 3). Allylic alcohol **14** was treated under Sharpless asymmetric epoxidation conditions providing

(4) Baldwin, J. J. *Chem. Soc., Chem. Commun.* **1976**, 734.

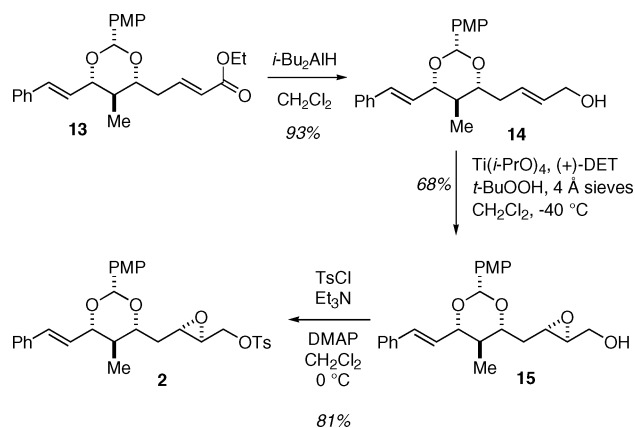
(5) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

(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



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 cyclization¹⁰ to form tetrahydropyran **4** was initially attempted. Exposure of epoxy **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 K₂CO₃ 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.

(9) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, Y. S.; Masamune, H.; Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

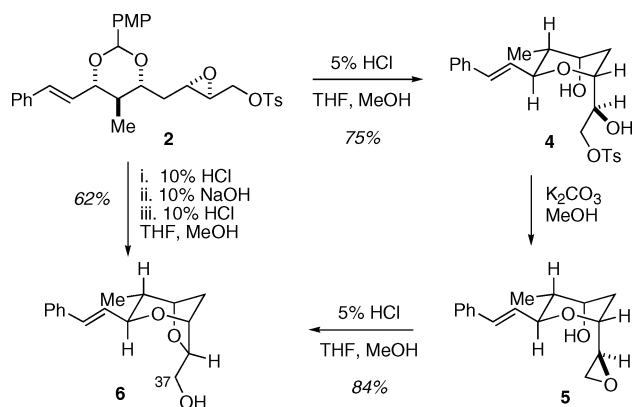
(10) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2741.

(11) A related approach to a similar THP has been reported: Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885.

(12) Lu, W.; Zheng, G.; Gao, D.; Cai, J. *Tetrahedron* **1999**, *55*, 7157.

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

Scheme 4



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.

Acknowledgment. Financial support of this work by the National Institute of General Medical Sciences (GM60567) is acknowledged with thanks. Thanks to Dr. Peter White of UNC-Chapel Hill for X-ray analysis of the *p*-nitrobenzoate of alcohol **6**.

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>.

OL061339E