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Total Synthesis of (+)-Sorangicin A

Amos B. Smith, III,* Shuzhi Dong, Jehrod B. Brenneman, and Richard J. Fox

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

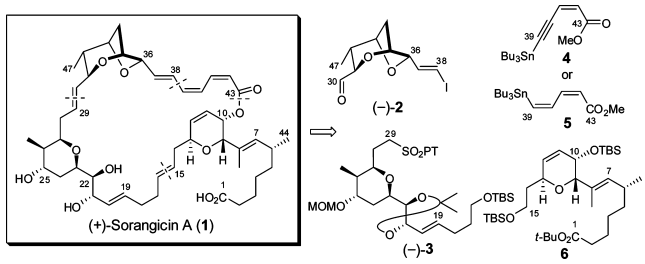
Received July 22, 2009; E-mail: smithab@sas.upenn.edu

Myxobacteria *Sorangium cellulosum* is a rich source of secondary metabolites possessing important biological profiles. Perhaps most notable, the epothilone class of natural products, analogues of which are currently in clinical use for the treatment of solid tumors resistant to alternative treatments (i.e., Taxol), were isolated by Höfle and co-workers in 1996 from the *S. cellulosum* strain So ce 90.[1] Earlier (1985), the same research group reported the isolation of members of another family of architecturally complex macrolides from the strain So ce 12, termed the sorangicins.[2] Importantly, (+)-sorangicin A (**1**), the most potent and prevalent congener, demonstrated remarkable antibiotic activity against a broad spectrum of both Gram-positive [minimum inhibitory concentration (MIC) 0.01−0.3 μg/mL] and Gram-negative bacteria (MIC 3−25 μg/mL). The mechanism of action was subsequently determined to entail inhibition of RNA polymerase in both *Escherichia coli* and *Staphylococcus aureus* without affecting eukaryotic cells.[3] Elegant cross-resistance studies by the Jansen and Darst groups on (+)-sorangicin A and rifampicin, the latter a clinically used ansamycin antibiotic, also revealed that although both bind the same β-subunit pocket of RNA polymerase, (+)-sorangicin A displays an advantageous profile against rifampicin-resistant microbial mutants, a result proposed to arise from increased conformational flexibility, leading to better adaption to mutational changes in the binding pocket.[4]

The structure of (+)-sorangicin A (**1**, Scheme 1)[5] comprises a signature dioxabicyclo[3.2.1]octane skeleton in conjunction with a rare (*Z*,*Z*,*E*)-trienoate linkage, both inscribed within a highly unsaturated 31-membered macrolactone ring. The initial structural assignment was based on extensive one- and two-dimensional NMR experiments along with high-resolution mass spectrometry.[2] Confirmation of both the connectivity and absolute configurations of the 15 stereogenic centers was subsequently secured by X-ray analysis.[6] The structural features, in particular the (*Z*,*Z*,*E*)-trienoate linkage affixed to the bicyclic ether core, provide the major source of the reported instability of the natural product toward a variety of reagents (e.g., fluoride ion, DDQ, and the dissolving metal sodium amalgam),[7] thus presenting a serious challenge to the current state of the art in organic synthesis. In addition, two polar structural elements, the C(1) carboxyl group and the C(21, 22, 25)-triol moiety of (+)-sorangicin A associate via a hydrogen bond to generate a hydrophilic region of this amphiphilic natural product. This interaction is particularly sensitive to the solvent and pH environments, thereby leading to a significant dependence of the ^{1}H and ^{13}C NMR spectra on the exact experimental variants.[6]

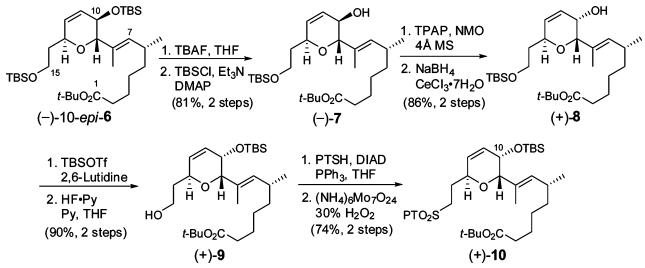
Not surprisingly, the intricate architecture of **1**, in conjunction with the important biological properties, has stimulated considerable interest within the synthetic community. Indeed, significant progress has been registered by the Schinzer,[8] Crimmins,[9] and Lee[10] laboratories in addition to ours.[11] Although successful preparations of mono- and bicyclic subtargets have been described, assembly of the highly sensitive (*Z*,*Z*,*E*)-trienoate linkage has been reported only in a simple model system.[11c] The total synthesis of **1** has thus remained an elusive goal. Herein, we describe the development of chemistry that addresses the synthetic challenges associated with **1**, that in turn has led to the first total synthesis of this intriguing natural product.

Scheme 1



Although scalable routes to access bicyclic aldehyde (−)-**2**,[11a,c] tetrahydropyran (−)-**3**,[11b,12] and dihydropyran (−)-10-*epi*-**6**[11b,13] had been developed by our research group, the stereogenicity at C(10) in (−)-10-*epi*-**6** required revision because of some confusion relating to this stereogenic center.[5] Toward this end, we outline in Scheme 2 the requisite inversion of the C(10) stereogenic center. Global desilylation of (−)-10-*epi*-**6** followed by chemoselective silylation[14] furnished allylic alcohol (−)-**7**. Initial attempts to invert the C(10) center with Mitsunobu methods failed because of the predominance of an S_N2' pathway, which is favored by the steric nature of the C(1)−C(8) side chain. Recourse was thus made to a Ley oxidation[15]/Luche reduction[16] sequence, which generated the desired allylic alcohol (+)-**8** as a single diastereomer. The high selectivity can be attributed to the same bulky side chain. Formal transposition of the TBS group followed by standard protocols to introduce the sulfone unit furnished fragment (+)-**10** in good yield (46% over eight steps).

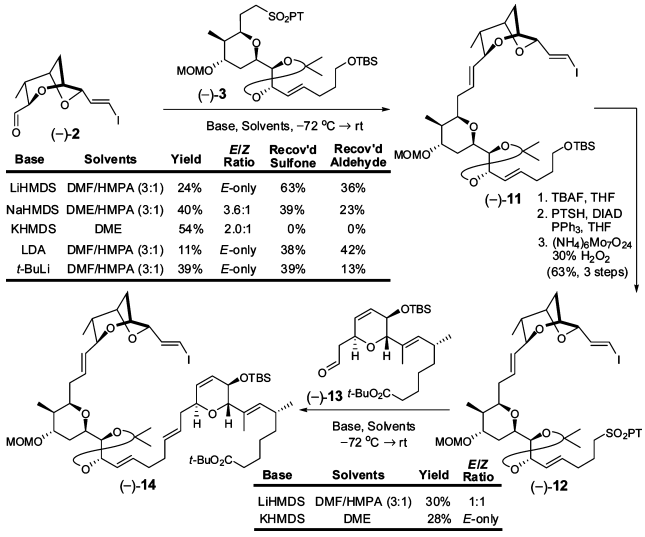
Scheme 2



With all of the major subtargets in hand, we were set to achieve their union. Toward this end, we envisaged construction of both the C(29)−C(30) and C(15)−C(16) trans double bonds via Julia−Kociénski olefinations, followed in turn by Stille union of **4** and macrolactonization to complete the overall carbon skeleton.

However, the first Julia−Kociénski olefination raised an unexpected challenge. Through the use of conditions developed by the Jacobsen group (LiHMDS in DMF/HMPA),[17] *E*-olefin (−)-**11** was obtained, albeit in low yield (24%), along with substantial recovery of the two coupling partners (−)-**2** (36%) and (−)-**3** (63%, Scheme 3). Switching the base counterion to Na^+ increased the yield (40%), but the *E*/*Z* selectivity (3.6:1) decreased. Use of the traditional *E*-selective conditions (KHMDS in DME)[18] provided the highest yield (54%) but the lowest *E*/*Z* selectivity (2.0:1). Neither Barbier conditions[19] nor the corresponding benzothiazole sulfone (BT-sulfone) improved the situation. In the end, the most reliable conditions proved to be use of *t*-BuLi in aprotic polar solvents (DMF/HMPA), which on a 300 mg scale furnished the *E*-configured product in 39% yield. Several recycles permitted the advance of material to (−)-**11** in upward of 65% yield.

Scheme 3



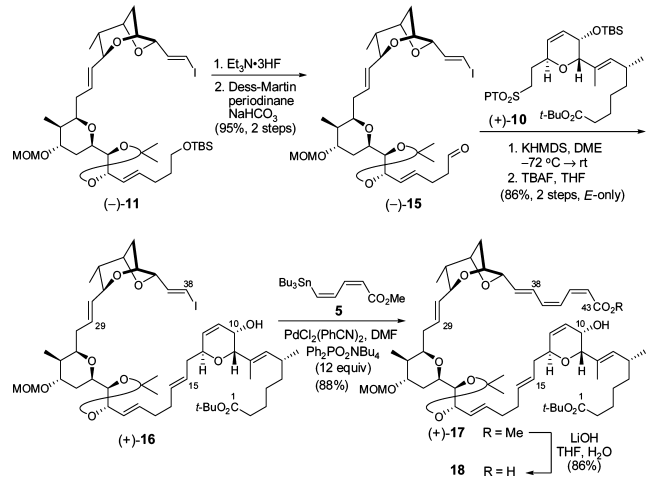
Base	Solvents	Yield	*E*/*Z* Ratio	Recov'd Sulfone	Recov'd Aldehyde
LiHMDS	DMF/HMPA (3:1)	24%	*E*-only	63%	36%
NaHMDS	DME/HMPA (3:1)	40%	3.6:1	39%	23%
KHMDS	DME	54%	2.0:1	0%	0%
LDA	DMF/HMPA (3:1)	11%	*E*-only	38%	42%
t-BuLi	DMF/HMPA (3:1)	39%	*E*-only	39%	13%

Base	Solvents	Yield	*E*/*Z* Ratio
LiHMDS	DMF/HMPA (3:1)	30%	1:1
KHMDS	DME	28%	*E*-only

The second Julia−Kociénski olefination involving sulfone (−)-**12** [obtained from (−)-**11**] and aldehyde (−)-**13** [derived from (−)-10-*epi*-**6**] also proved problematic. In this case, the *E*/*Z*-selectivity trend was reversed, with the best selectivity obtained employing KHMDS in DME. Interestingly, no selectivity was observed with LiHMDS in DMF/HMPA (Scheme 3). In addition, both sets of conditions suffered from low conversion. At this point, we surmised that the low efficiency in both olefinations might arise from the nature of the sulfone fragments [i.e., (−)-**3** and (−)-**12**)], that is, from difficulty with the initial deprotonation and/or intramolecular coordination of the resulting metalated species. To test these ideas, we reversed the coupling partners, preparing aldehyde (−)-**15** from (−)-**11** in two steps (Scheme 4) and sulfone (+)-**10** as outlined in Scheme 2. Gratifyingly, under the conditions of KHMDS in DME, the union proceeded with both complete conversion and excellent stereocontrol to provide *E*-olefin (+)-**16** in 86% yield after desilylation,[20] with this product having the correct stereogenicity at C(10).[21]

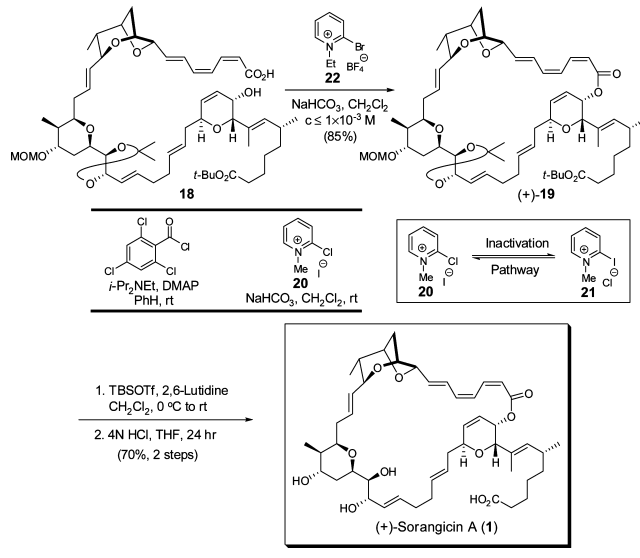
Having installed both the C(29)−C(30) and C(15)−C(16) trans olefins with high stereoprecision, all that remained to complete the synthesis of **1** was construction of the C(38)−C(39) and C(43)−O σ bonds followed by global deprotection. Initially, we envisioned that the labile (*Z*,*Z*,*E*)-trienoate moiety could be introduced in a protected form comprising a dienyne that would mask the C(39)−C(40) *Z*-olefin as an alkyne. Although the dienyne moiety could be introduced into a simple model bicyclic vinyl iodide by employing known alkynyl stannane **4**,[22] subsequent semihydrogenation suffered extensive *E*/*Z* isomerization upon purification. A solution to this issue entailed the use of an alternative linker, stannyl dienoate **5**,[23] which proved to be surprisingly stable under standard laboratory conditions. Again in a model system, we demonstrated the effective use of **5** in a Stille union employing excess $Ph_2PO_2NBu_4$ (6 equiv) to suppress the *E*/*Z* isomerization.[11c] With (+)-**16**, however, an even larger excess of $Ph_2PO_2NBu_4$ (12 equiv) was required for delivery of geometrically pure (*Z*,*Z*,*E*)-trienoate (+)-**17** in good yield (88%). Equally important, the subsequent hydrolysis of trienoate (+)-**17** with LiOH in aqueous THF furnished the corresponding trienoacid **18** without noticeable geometric isomerism (Scheme 4). However, acid **18** did prove to be extremely unstable and was therefore employed in the next step without full characterization.

Scheme 4



In the transformations leading up to the critical macrocyclization, we fully anticipated the possibility of significant isomerization during activation of the trienoacid. This indeed proved to be the case! However, a careful survey revealed two sets of mild conditions that delivered the desired (*Z*,*Z*,*E*)-configured macrolactone (+)-**19** as the major product (Scheme 5): (1) the Yonemitsu modification of the Yamaguchi conditions[24] involving direct introduction at room temperature of DMAP at the outset without preformation of the mixed anhydride and (2) the Evans-modified Mukaiyama protocol[25]

Scheme 5



employing $NaHCO_3$ and **20** at room temperature. Notwithstanding our initial success in solving the challenging macrolactonization, (+)-**19** was contaminated with minor amounts of other geometric isomers, which proved difficult to separate. The problem appears to lie with the reversibility of a Michael addition of DMAP or iodide to the activated trienoacid during the lactonization process. Another issue associated with Mukaiyama reagent **20** is halogen exchange to give **21**, which is known to be nonreactive as an activating agent for carboxylic acid coupling.[26] To address these issues, we adopted the modified Mukaiyama reagent **22**,[27] which possesses a non-nucleophilic counterion (i.e., tetrafluoroborate), thus mitigating the undesired Michael addition as well as the inactivation pathway. Pleasingly, reagent **22** delivered macrolide (+)-**19** in 85% yield with minimum isomerization (ca. <4%).

Clearly aware that our late-stage intermediates were exceedingly prone to isomerization and/or decomposition because of the delicate (*Z*,*Z*,*E*)-trienoate moiety, we were now compelled to identify conditions that were mild but still sufficiently potent to remove the MOM, acetonide, and *tert*-butyl protecting groups. This task proved to be nontrivial! We first took the lead of the Höfle group, who had employed TFA in aqueous THF at 85 °C to remove the acetonide group in their synthesis of an extensive library of sorangicin analogues.[28] The product yields, however, were highly substrate-dependent, varying from 20 to 70%. Application of these conditions to the fully protected macrolide (+)-**19** led only to decomposition. We therefore initiated an extensive series of deprotection studies on available individual fragments, which in the end led to the observation that although the MOM and acetonide groups could be removed under aqueous protic acidic conditions (at 85 and 45 °C, respectively), hydrolysis of the *tert*-butyl ester was far from efficient (only 50% conversion at 85 °C for 3 h). A more efficient protocol for removing the *tert*-butyl group had to be devised. Use of TFA in anhydrous CH_2Cl_2 led to destruction of the trienoate moiety. In regard to Lewis acids, *B*-bromocatecholborane[29] rapidly removed both the MOM and acetonide groups, but removal of the *tert*-butyl group was quite slow. Initially, TMSOTf was able to remove the MOM and *tert*-butyl moieties efficiently on individual fragments, but with the fully protected macrolide (+)-**19**, only decomposition occurred. Clearly TMSOTf was too reactive. Eventually we learned that employing the milder TBSOTf reagent (buffered with 2,6-lutidine) allowed the *tert*-butyl ester to be cleanly transformed into the TBS ester without compromising the delicate (*Z*,*Z*,*E*)-trienoate linkage. Without further purification, the TBS ester was then treated with 4 N HCl in THF at room temperature for 24 h to produce (+)-sorangicin A (**1**) in 70% yield for the two steps (Scheme 5). The totally synthetic **1** was identical in all respects (e,g., ^1H, ^{13}C, HRMS, and HPLC−LRMS) to an authentic natural sample provided by Dr. Jansen,[30] including chiroptic properties {$[\alpha]_D^{19}$: +56 (*c* 0.06, MeOH); lit.[6] $[\alpha]_D^{22}$ +60.9 (*c* 0.7, MeOH)}.

In summary, the first total synthesis of the structurally complex macrolide (+)-sorangicin A (**1**) has been achieved in a highly convergent fashion. Late stages of the synthetic venture featured the use of two Julia−Kociénski olefinations to unite three complex advanced fragments with high *E*-stereoselectivity. The final steps of the synthesis then involved a modified Stille union and Mukaiyama macrolactonization as well as Lewis and protic acid-promoted deprotections employing carefully defined conditions required to suppress *E*/*Z* isomerization and/or destruction of the sensitive (*Z*,*Z*,*E*)-trienoate linkage.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all transformations and new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The stereocenter at C(10) in **1**, as confirmed by Dr. R. Jansen (Helmholtz Center for Infection Research, Braunschweig, Germany) is *S* (as originally reported in ref 6) and not *R* (as depicted in ref 7). We thank Dr. Jansen for this clarification.
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(19) Under Barbier conditions, LiHMDS was added to a mixture of sulfone (−)-**3** and aldehyde (−)-**2** in 3:1 DMF/HMPA, leading to a <24% yield of (−)-**11** along with recovery of starting materials.
(20) For the first Julia−Kociénski olefination, we envisioned that reversal of the coupling partners might be not without risk because of the proclivity of β-elimination from the bicyclic sulfone derived from (−)-**2**.
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(30) The NMR spectra of both the natural and synthetic samples are sensitive to NMR experimental conditions. More specifically, in the ^1H NMR spectra, the resonances for protons of the C(1)−C(8) side chain depend on the pH and solvent environments, most apparently for H(2), H(7), and H(44). In the ^{13}C NMR spectra, the chemical shifts and intensities for both C(1) and C(2) vary significantly in different solvent and pH environments.

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