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Formal Synthesis of (+)-Sorangicin A

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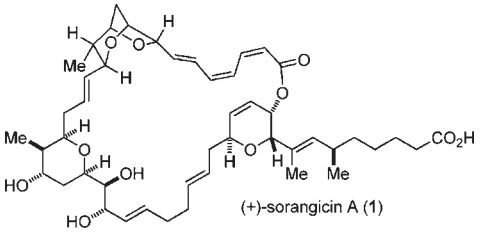
ABSTRACT



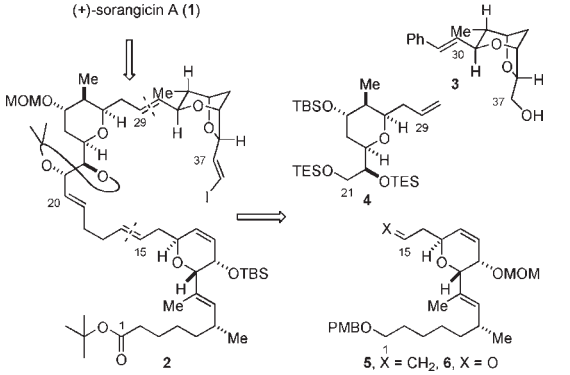
The formal synthesis of (+)-sorangicin A was completed by two independent routes. Both approaches feature a cross metathesis reaction to form the C29−C30 bond to arrive at the bicyclic ether/tetrahydropyran fragment. Formation of the C15−C16 olefin to unite the dihydropyran fragment with the rest of the molecule was achieved by either a cross metathesis reaction or a Julia−Kocienski olefination.

(+)-Sorangicin A (**1**) was isolated in 1985 from the gliding bacterium *Sorangium cellulosum* by Höfle and Reichenbach.[1] It exhibits potent antibiotic activity against both Gram-positive (MIC 0.01−0.1 μg/mL) and Gram-negative bacteria (MIC 3−30 μg/mL) through inhibition of RNA polymerase *in vivo*.[2] Sorangicin A is comprised of several synthetically challenging structural features including the C30−C37 signature bicyclic ether, C21−C29 tetrasubstituted tetrahydropyran, and C1−C15 trisubstituted dihydropyran, all of which are embedded in a 31-membered lactone. Additionally, the macrocyclic skeleton is highly unsaturated featuring a unique and highly sensitive (*Z,Z,E*)-trienoate linkage to which the instability of the natural product toward several reagents has been attributed.[3] The potent antibiotic activity and complex structure of (+)-sorangicin A have prompted several synthetic approaches[4] culminating in a total synthesis by the Smith group.[5]

Herein we describe two approaches toward C1−C38 fragment **2**, an advanced intermediate in Smith's total synthesis of (+)-sorangicin A (**1**). Our synthetic approach involved the preparation of three orthogonally differentiated core fragments: bicyclic ether **3**, tetrahydropyran **4**, and dihydropyran **5** or **6**, which would allow us to investigate a variety of coupling strategies (Scheme 1).

Our initial retrosynthetic plan involved the use of a cross metathesis reaction to form both the C29−C30 and C15−C16 olefins; however, a low yield for the second cross metathesis reaction prompted investigation of a Julia−Kocienski olefination, also used in Smith's synthesis, to form the C15−C16 bond.

Scheme 1. Synthetic Approach toward (+)-Sorangicin A (**1**)



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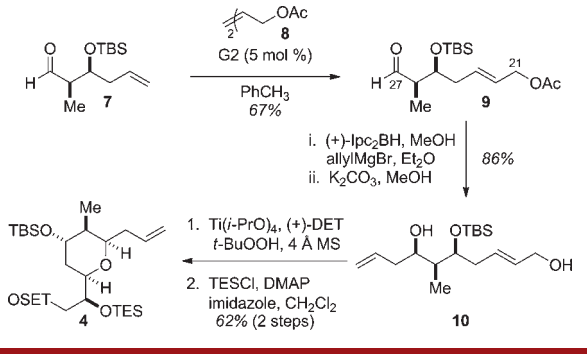
Initial efforts were focused on the synthesis of tetrahydropyran (THP) **4** (Scheme 2). We envisioned that this fragment could be prepared via an acid-catalyzed epoxide-opening cascade, similar to our previously reported route used for the preparation of bicyclic ether **3**.[6] To begin, a cross metathesis reaction[7] between known aldehyde **7**[8] and diacetate **8** was performed with Grubbs' second generation catalyst (G2) to deliver cross metathesis adduct **9** in 67% yield. Subsequent Brown asymmetric allylation[9] of aldehyde **9** with (+)-Ipc_2B-allyl gave rise to diol **10** in 86% yield after basic workup. Allylic alcohol **10** was employed in a Sharpless asymmetric epoxidation reaction,[10] which upon acidic workup of the intermediate epoxy alcohol initiated the epoxide opening/cyclization to arrive at the cyclic ether. Finally, protection of the diol as the bis-triethylsilyl (TES) ether delivered THP **4** in 62% yield over the two-step sequence.

Scheme 2. Synthesis of Tetrahydropyran **4**



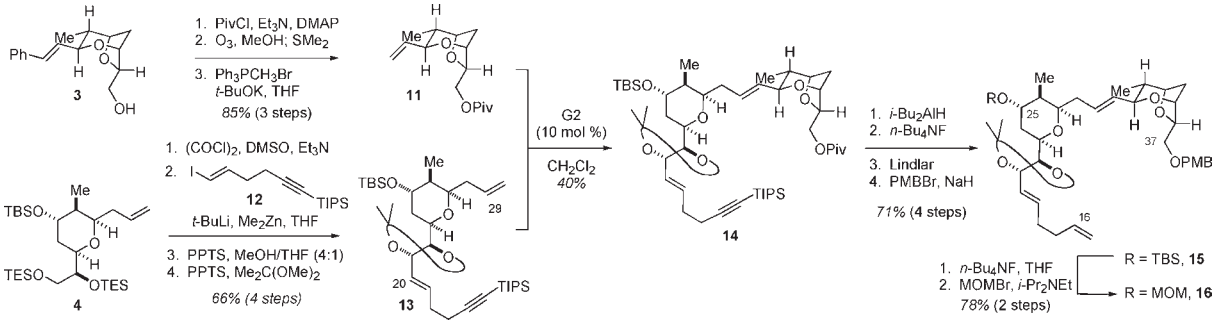
With a route toward both THP **4** and bicyclic ether **3**, cross metathesis to form the C29−C30 bond was explored. The desired cross metathesis substrate, bicyclic ether **11**, was prepared by a three-step sequence of acylation, ozonolysis, and methylenation[11] from previously prepared bicyclic ether **3**[6] in 85% yield (Scheme 3). Elaboration of THP **4** to incorporate the C16−C20 fragment was also carried out prior to the key cross metathesis reaction. Toward this end, selective cleavage and oxidation of the primary TES ether was realized upon subjection of THP **4** to modified Swern conditions.[12] The vinyl zinc species generated *in situ* from C16−C20 vinyl iodide **12** underwent a Felkin−Anh controlled addition to the aldehyde to introduce the C21 stereocenter as an 8:1 mixture of separable diastereomers. Subsequent conversion of the 1,2-diol to the acetonide by a two-step sequence afforded dihydropyran **13** in 66% yield over the four steps.

The cross metathesis reaction between bicyclic ether **11** and THP fragment **13** was accomplished in 40% yield, 69% based on recovered bicyclic ether **11**, upon addition of THP **13** dropwise over several hours to a solution of bicyclic ether **11** and Grubbs' second generation catalyst. Removal of the TIPS protecting group, followed by Lindlar reduction of the alkyne,[13] and subsequent adjustment of the C25 and C37 protecting groups provided terminal olefin **16** in 55% yield over the six-step sequence.

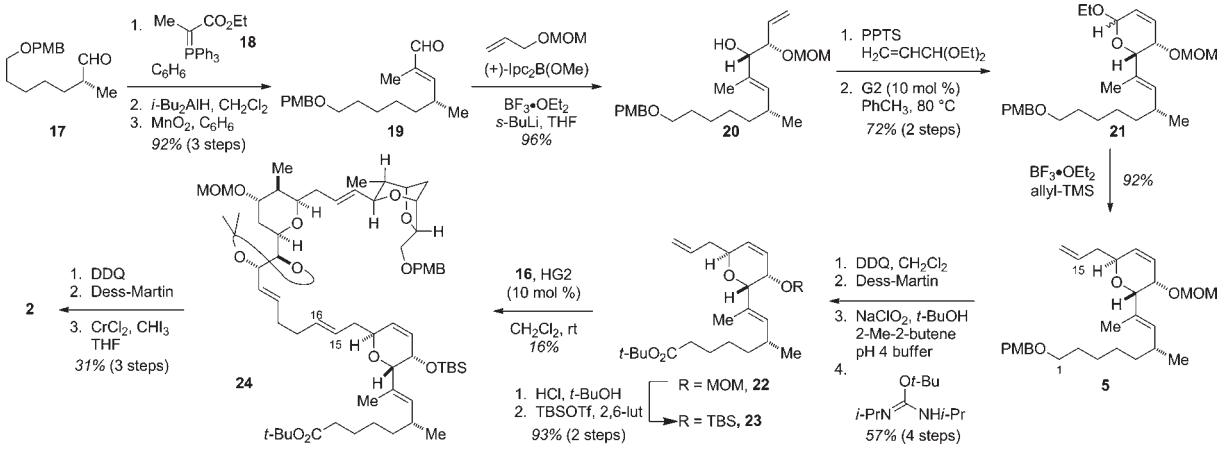
Having developed an efficient route toward bicyclic ether THP/fragment **16**, synthesis and incorporation of the dihydropyran (DHP) fragment was next explored. The synthesis of the dihydropyran fragment commenced with a Wittig, reduction, oxidation sequence of aldehyde **17**,[5c] available in two steps via a Myers alkylation,[14] reduction sequence, to provide trisubstituted olefin **19** in 92% yield over the three steps (Scheme 4). Exposure of aldehyde **19** to a Brown alkyoxy-allylation[15] delivered differentially protected *syn*-1,2-diol **20** in 96% yield. Upon treatment of the allylation adduct with acrolein diethyl acetal,[16] an intermediate diene was obtained, which underwent ring closing metathesis in the presence of Grubbs' second generation catalyst (G2) to generate mixed acetal **21** as an inconsequential 1:1 mixture of diastereomers in 72% yield over two steps.[17] Treatment of the mixed acetal with $BF_3 \cdot OEt_2$ in the presence of allyl-trimethylsilane effected a Sakurai reaction to deliver allylated product **5** in 92% yield as a single diastereomer.[18] Introduction of the desired oxidation state at C1 was achieved by a four-step sequence[5c] involving cleavage of the PMB ether under oxidative conditions, Dess−Martin oxidation,[19] Pinnick oxidation,[20] and finally ester formation[21] to afford C1−C15 dihydropyran **22** in 57% yield. The MOM ether was exchanged for a TBS ether via a two-step sequence to give rise to dihydropyran **23** in 93% yield.

With both cross metathesis partners in hand, bicyclic ether/THP fragment **16** and DHP **23** were exposed to Hoveyda−Grubbs' second generation catalyst (HG2).

Scheme 3. Cross Metathesis To Form Bicyclic Ether/THP Fragment **16**



Scheme 4. Formal Synthesis of C1−C38 Fragment **2** via a Cross Metathesis Approach



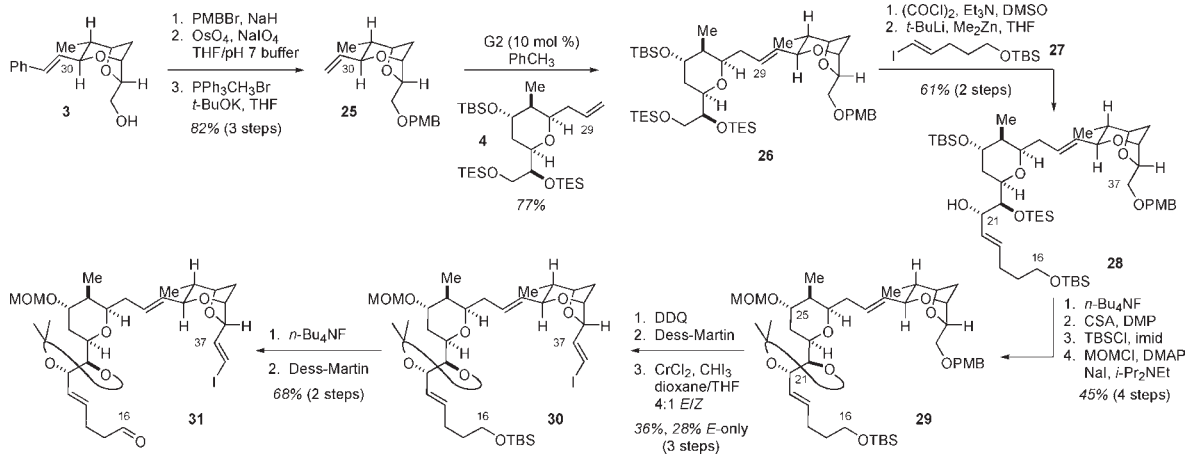
This key bond forming reaction was complicated by the fact that both cross metathesis partners are Type I olefins;[7] thus a statistical mixture of cross metathesis adduct **24** and the C16−C37 fragment **16** and DHP **23** homodimers was expected; however, only a 16% yield of the desired cross metathesis adduct was obtained. Despite the low yield for this key reaction, intermediate **24** was advanced through a three-step sequence to arrive at C1−C38 fragment **2** in 31% yield.[22]

In light of the low yield obtained for the cross metathesis reaction to unite the DHP fragment with the rest of the molecule, we decided to turn our attention toward the Julia−Kocienski olefination used by Smith to form the C15−C16 bond.[5a] To prepare the bicyclic ether/THP and dihydropyran fragments necessary for the Julia olefination, we needed to modify our protecting group strategy and investigate an alternative cross metathesis/vinyl addition sequence.

Attention was first turned toward synthesis of the modified bicyclic ether/THP fragment. Toward this end, previously prepared bicyclic ether **3**[6] was protected as the PMB-ether, which upon oxidative cleavage by the Johnson−Lemieux protocol[23] and methylene Wittig olefination delivered bicyclic ether **25** (Scheme 5). To our delight, upon dropwise addition of THP **4** to a solution of bicyclic ether **25** and Grubbs' second generation catalyst (G2), cross metathesis adduct **26** was obtained in 77% yield as a single detectable *E* isomer. Exposure of TES ether **26** to modified Swern conditions allowed for the selective oxidation of the C21 alcohol to generate an intermediate aldehyde, which, upon treatment with the vinyl zinc species formed from vinyl iodide **27**, afforded bicyclic ether/THP fragment **28** in 64% yield (two steps).

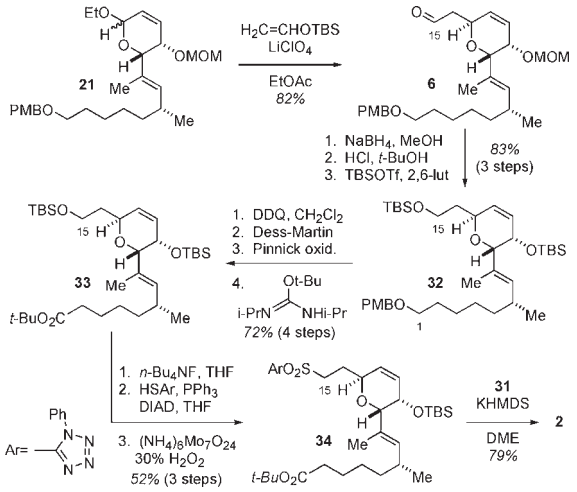
To arrive at C1−C38 fragment **2**, several protecting group manipulations were necessary. Toward this end, all of the silyl protecting groups from vinyl addition product **28** were removed with TBAF to reveal an intermediate tetraol. The tetraol was subjected to CSA in neat dimethoxypropane to effect acetonide formation, whereupon the C16 and C25 alcohols were protected as TBS and

Scheme 5. Cross Metathesis To Form Bicyclic Ether/THP Fragment **31**



MOM ethers respectively,[24] furnishing the fully protected bicyclic ether/THP fragment **29** in 45% yield over the four-step sequence. Introduction of the vinyl iodide moiety was next pursued. Cleavage of the PMB ether was achieved under oxidative conditions with DDQ, and the resultant alcohol was oxidized under Dess–Martin conditions. The resultant intermediate aldehyde was immediately utilized in a Takai olefination[22,25] to give rise to a 4:1 ratio of *E*/*Z*-vinyl iodides. The vinyl iodides were readily separated by flash column chromatography to deliver *E*-vinyl iodide **30** in 28% yield over the three steps. Vinyl iodide **30** was converted to aldehyde **31**, required for the Julia–Kocienski olefination, by a known two-step sequence in 68% yield.[5]

Scheme 6. Julia–Kocienski Olefination Approach to Fragment **2**



With the aldehyde coupling partner in hand, we turned our attention to the synthesis of the C1–C15 sulfone. This was achieved in an efficient manner upon modification of the previously employed route toward dihydropyran **23**. A Lewis acid mediated addition of acetaldehyde silyl ether to mixed acetal **21** delivered aldehyde **6** in 82% yield as a single diastereomer (Scheme 6).[26] Aldehyde **6** was reduced via a sodium borohydride reduction to give rise to the C15 alcohol. The MOM ether was cleaved from the resultant alcohol under acidic conditions to reveal an intermediate diol, which was converted to bis-TBS ether **32** in 83% yield over the three-step sequence. Introduction of the desired oxidation state at C1 was achieved via the previously used sequence,[5c] in which PMB-ether **32** was converted to *tert*-butyl ester **33** in four steps and 72% yield. Ester **33** corresponds to an intermediate from Smith's synthesis; thus a known three-step sequence was carried out to selectively cleave the C15 TBS-ether and convert the resultant alcohol to sulfone **34**.[5a] Finally, sulfone **34** and aldehyde **31** were employed in a Julia–Kocienski olefination,[27] using the conditions described by Smith,[5a] to give rise to C1–C38 fragment **2** in 79% yield. Fragment **2** was spectroscopically identical to that reported by Smith.[5a]

In summary, two routes toward the formal synthesis of the C1–C38 fragment of (+)-sorangicin A (**1**) have been completed. Both routes feature a cross metathesis reaction to unite the bicyclic ether and THP fragments. Our initial approach featured a second cross metathesis to append the DHP fragment; however a low yield for this key reaction prompted us to instead employ a Julia–Kocienski olefination to form the C15–C16 bond.

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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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