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RESEARCH ARTICLE

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Enantioselective Total Synthesis of the Putative Biosynthetic Intermediate Ambruticin J

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Abstract: The family of anti-fungal natural products known as the ambruticins are structurally distinguished by a pair of pyran rings adorning a divinylcyclopropane core. Previous characterization of their biosynthesis, including the expression of a genetically modified producing organism, revealed that the polyketide synthase pathway proceeds through a diol intermediate, known as ambruticin J. Here we report the first enantioselective total synthesis of the putative PKS product, ambruticin J, via a triply-convergent synthetic route featuring a Suzuki-Miyaura cross-coupling and a Julia-Kocienski olefination for fragment assembly. This synthesis takes advantage of synthetic methodology, previously developed by our laboratory, for the stereoselective generation of the trisubstituted cyclopropyl linchpin.

Introduction

The ambruticin family of polyketide natural products, first isolated from the myxobacterium *Sorangium cellulosum* in 1977, display potentially useful biological properties, including significant antifungal activity.[1–8] Studies of the mechanism of action of these compounds suggest that the ambruticins interfere with fungal osmoregulation by targeting the Hik1 kinase.[9,10] A recent study of the effect of ambruticin VS3 on soil myxobacteria confirms an impact on a group III hybrid histidine kinase (HHK) and provides an environmental advantage by affecting the development of competitive myxobacterial species.[11] Several studies using ambruticins and their derivatives, in both *in vitro* and *in vivo* plant and murine models of fungal infection, have shown therapeutic properties including low toxicity and promising activity against fungal infections including histoplasmosis and coccidiomycosis both intravenously and orally administered.[2,9,10,12–14] Structurally, the ambruticins consist of a trisubstituted divinylcyclopropane ring core appended with two pyrans (**Figure 1**). Ambruticin congeners vary in the C5 position, but it is the atypical trisubstituted cyclopropane core and promising biological activity that have made these molecules popular synthetic targets. The first total synthesis of ambruticin S was completed in 1993 and several additional successful strategies have been completed to date.[15–20] No other congener has been targeted by total or semi-synthesis.

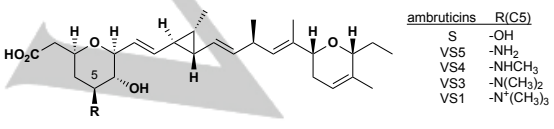


Figure 1. The Structures of Natural Ambruticins.

The biosynthesis of these polyketides has been characterized by Reeves et. al. *via* gene sequencing and knockout experiments using wild-type and mutant *S. cellulosum*.[21] Fermentation of an *AmbJ*$^{--}$ mutant allowed isolation of an intermediate C3,C5 diol, characterized as ambruticin J, **1** (**Figure 2**) and no other ambruticins were observed. The enzyme AmbJ, a flavin-dependent monooxygenase, was proposed to be responsible for conversion of ambruticin J to a second putative intermediate, ambruticin F, **2**, in which the stereochemical configuration at C5 is epimeric to isolated ambruticins. Thus, further post-PKS modifications includes oxidation of C5 followed by divergent functionalization to provide the known ambruticins. As AmbJ is a flavin-dependent monooxygenase homologous to epoxidases associated with polyether biosynthesis, including MonCI and NanO, it is likely that the transformation of ambruticin J to ambruticin F proceeds through epoxidation of the C6-C7 alkene followed by 6-*endo*-tet ring formation *via* epoxide ring opening by the C3 alcohol.[20–23] The mechanism of this cyclization step is unclear and because the putative epoxide intermediate consists of two three-membered rings in conjugation, degradative pathways appear plausible which include cyclopropane fragmentation. While the cyclization is likely spontaneous, it is unknown if AmbJ plays any role in ensuring a productive pathway towards the isolated ambruticins. Moreover, the role of the C5-hydroxyl stereochemical configuration in the epoxidation and cyclization steps as well as ambruticin's biological activity is unknown.

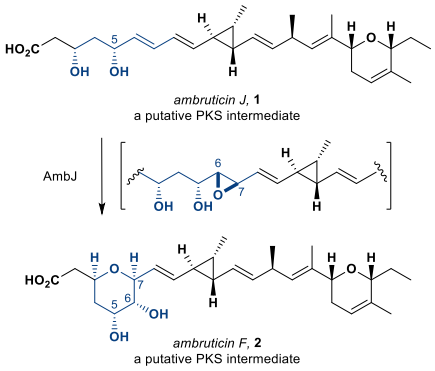


Figure 2. Post-PKS Epoxidation/Cyclization Mediated by AmbJ.

A number of natural products contain substituted tetrahydropyran rings, including lasonolide A, the phorboxazoles, cyanolide A, centrolobine, neopeltolide, zampanolide, and dactylolide.[22] In addition, pyrans are among the most common ring systems found in small molecule drugs.[23] Therefore, strategies to efficiently and stereoselectively construct pyran rings are of great synthetic interest and have the potential to

prove very useful in both natural product and medicinal chemistry. Enzyme-catalyzed reactions may be especially desirable, as they often provide the desired regio- and stereoselectivity under relatively mild reaction conditions.[24–26].Previous work by the Hahn lab has identified the enzyme responsible for the biosynthetic formation of the dihydropyran ring on the eastern side of the ambruticins. Exploration of the dehydratase enzyme, AmbDH3, which catalyzed a dehydration-oxa-Michael reaction, indicated a significant degree of substrate flexibility.[27] However, no similar investigation has been conducted into the possible scope and applications of the flavin-dependent monooxygenase AmbJ. Therefore, to enable exploration of this interesting post-PKS oxidation-cyclization and the biocatalytic potential of AmbJ, we have developed a synthetic route to the putative biosynthetic intermediate ambruticin J.

Results and Discussion

A desire for a convergent synthetic strategy for ambruticin J inspires construction from three structural fragments such as vinyl iodide **3**, sulfone **4**, and vinylcyclopropane linchpin **5** (**Figure 3**). This route also allows us to highlight synthetic methodology previously developed in our lab which enables the stereoselective and efficient creation of enantiomerically and diastereomerically pure trisubstituted cyclopropanes from readily available homoallylic alcohol precursors.[28–32] The vinyl iodide and cyclopropane fragments would be coupled *via* a Suzuki-Miyaura cross coupling.[33–35] and the final fragment would be adjoined with a Julia-Kocienski olefination.[36]

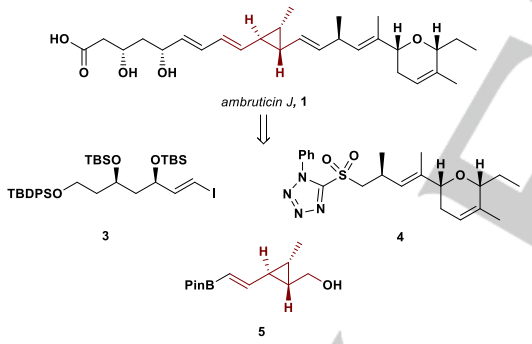
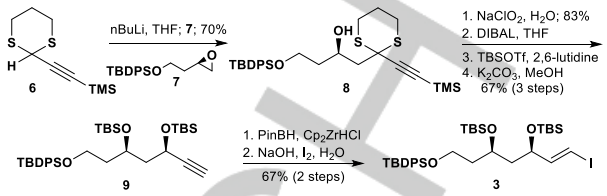


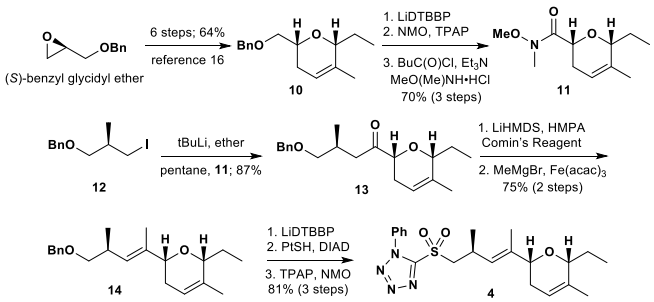
Figure 3. Cyclopropyl Linchpin Strategy for the Total Synthesis of Ambruticin J.

Our total synthesis effort began with known dithiane **6**, which was prepared on a multi-gram scale in three steps from propargyl alcohol (**Scheme 1**).[37] The lithiated dithiane was then condensed with epoxide **7**, which was also available on a multi-gram scale in three steps from *L*-aspartic acid as previously reported.[38] Application of this Corey-Seebach reaction yielded dithiane **8** in 70% yield.[39] The dithiane group was hydrolyzed to give the corresponding ketoalcohol in 83% yield using Nakata's conditions.[40] Stereoselective reduction with diisobutylaluminum hydride generated the *syn*-diol in 81% yield with >20:1 diastereoselectivity. The relative stereochemistry of the diol was confirmed by NMR analysis of an acetonide derivative, which showed ^{13}C NMR shifts characteristic of an acetal derived from a syn diol.[41,42] The diol was protected with *t*-butyldimethylsilyl triflate followed by selective removal of the trimethylsilyl group with basic methanol to give terminal alkyne **9** in 83% yield over two steps. Unfortunately, conversion of the alkyne to the *E*-iodo-alkene proved more difficult than anticipated, with attempts at using Schwartz reagent and *N*-iodosuccinimide proving unsuccessful. However, exploitation of an intermediate vinyl boronic acid provided the desired vinyl iodide **3** in 67% yield from alkyne **9** despite necessitating an additional step.



Scheme 1. Preparation of Vinyl Iodide **3**.

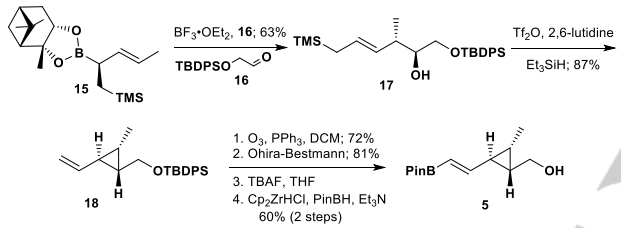
The C13-C24 divinyl pyran fragment of ambruticin J is identical to that found in the isolated ambruticins and jerangolides[43] due to duplication within their PKS gene clusters.[21] Our optimized route to this fragment is unique but borrows significantly from previous independent efforts reported by Hanessian and Lee (**Scheme 2**).[16,19] Dihydropyran **10** was prepared using Hanessian's route in 64% overall yield from (*S*)-benzyl-glycidyl ether and highlighted by an electrophilic cyclization. We then applied the strategy used by Lee to stereoselectively generate the trisubstituted olefin, allowing us to exploit the most advantageous portions of both Lee's and Hanessian's routes. Specifically, benzyl deprotection with lithium di-*tert*-butylbiphenyl complex afforded the desired free alcohol, which then underwent Stark oxidation to give the carboxylic acid.[44] The Weinreb amide **11** was then formed by amidation and condensed with the organolithium generated from iodide **12**, to provide ketone **13** in 87% yield. Conversion of the ketone to a vinyl triflate was carried out using Comins' reagent, which yielded exclusively the *E*-olefin.[45] The vinyl triflate then underwent iron-mediated methylation using the conditions developed by Fürstner to produce the desired tri-substituted olefin **14** in 75% yield over two steps.[46,47] Benzyl deprotection using identical conditions as before yielded unprotected alcohol, which was then converted to the desired phenyl tetrazole sulfone **4** in two steps using a Mitsonobu reaction followed by oxidation with tetrapropylammonium perruthenate (TPAP). Molybdenum-mediated oxidation conditions were also explored but were found to be significantly lower yielding, potentially due to the low solubility of the starting material. Characterization data for both the unprotected alcohol and phenyl tetrazole sulfone **4** demonstrated excellent agreement with previous literature characterizations of this compound.[16,48]



Scheme 2. Preparation of Pyran Fragment 4.

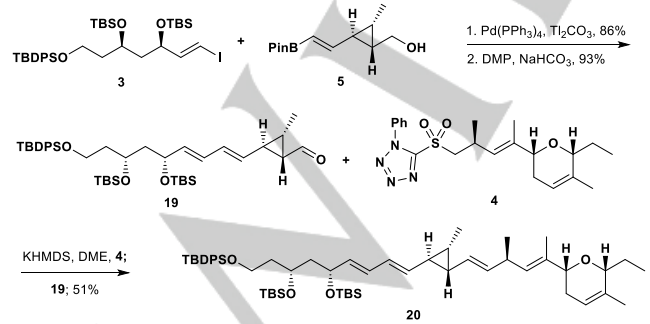
Synthesis of the vinylcyclopropane linchpin was highlighted by application of methodology previously developed in our laboratory. Our efforts combined well-established asymmetric, aldehyde allylation reactions with subsequent olefin metathesis chemistry to access allylsilane homoallylic alcohols as

cyclization substrates. In the current application, we eliminated one step by taking advantage of Hall's "double allylation" reagent (**Scheme 3**) which was shown to condense with aldehydes with up to 99:1 enantiomeric ratios. Allylboronate **15** was synthesized in four steps from commercially available starting materials according to literature precedent.[49] This reagent was then used for the allylation of aldehyde **16**, which was synthesized in 92% yield by ozonolysis from the corresponding symmetrical alkene. The homoallylic alcohol **17** was obtained in 63% yield as a single diastereomer. Crucially, this reaction was found to scale well, allowing multi-gram scale reactions to be conducted without notable loss of yield. The homoallylic alcohol was then treated with our standard conditions, triflic anhydride, triethylsilane, and 2,6-lutidine to give cyclopropane **18** in 87% yield.[30] As we noted previously, only a single stereoisomeric cyclopropane was observed. This reaction was also carried out at large scale and maintained both yield and selectivity, enabling large scale production of the cyclopropyl linchpin of our convergent strategy. Ozonolysis of the vinylcyclopropane gave the intermediate aldehyde in 72% yield, and reaction with Ohira-Bestmann reagent produced the alkyne in 81% yield.[50–52] Removal of the silyl ether protecting group with tetrabutylammonium fluoride (TBAF) gave unprotected alcohol in quantitative yield. This cyclopropylalkyne then underwent conversion to the pinacol boronic ester with Schwartz reagent, freshly distilled pinacolborane, and triethylamine to provide the linchpin **5** in 60% yield for the desired *E*-alkene.[53]



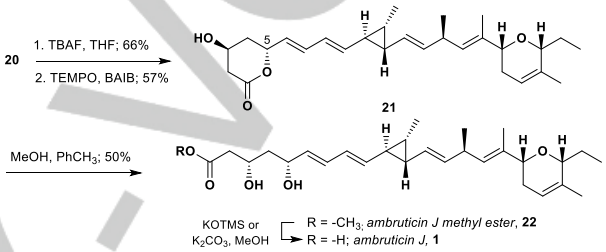
Scheme 3. Preparation of Tri-Substituted Cyclopropyl Linchpin **5**.

With all three fragments in hand, we proceeded with the sequential fragment coupling reactions (**Scheme 4**). Vinyl iodide **3** and vinyl pinacol boronic ester **5** were combined under Suzuki coupling conditions using thallium carbonate as a base, providing desired (*E,E*)-diene in 86% yield. The resultant primary alcohol was then oxidized to an aldehyde using Dess-Martin periodinane, providing aldehyde **19** in excellent yield. Finally, Julia-Kocienski olefination was performed to add the final fragment, yielding the desired *E*-olefin and providing the linear skeleton of ambruticin J, **20**.



Scheme 4. Preparation of Protected *syn*-3,5-Diol Fragment **20**.

Completion of the synthesis of ambruticin J required only desilylation and terminal oxidation. Global deprotection of the silyl groups using TBAF yielded the expected triol intermediate. Previous characterization of the target had suggested that the divinylcyclopropane is potentially unstable and may be especially sensitive to acidic conditions, leading to some concern over the final oxidation step. Therefore, we took advantage of the 1,3,5-triol intermediate and generated lactone **21** directly using TEMPO/BAIB with sodium bicarbonate as a buffer (**Scheme 5**). This allowed for selective oxidation of the primary alcohol under mild conditions and avoided issues related to selectivity of the oxidation and instability of the compound to harsher conditions. Methanolysis of the resulting lactone gave the methyl ester in 50% yield (with 37% of the lactone starting material being recovered and the remaining 13% being lost to degradation pathways). While ester saponification under a number of conditions provided an intermediate carboxylate, the acidification necessary to isolate ambruticin J was accompanied by degradation. We were eventually able to isolate characterizable quantities of ambruticin J using either potassium trimethylsilanoate or potassium carbonate in aqueous methanol.

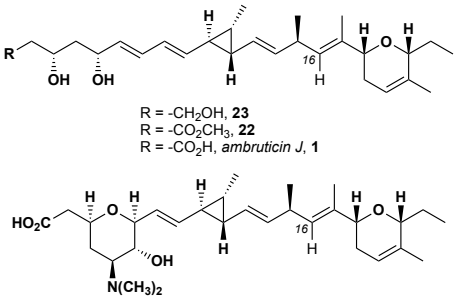


Scheme 5. Completion of the Total Synthesis of Ambruticin J, **1**

Unfortunately, an authentic sample of ambruticin J was not available as a comparative standard. Comparison of the carbon and proton NMR data of our synthetic ambruticin J to the data reported by Reeves et al. was further complicated because the literature data was limited to an NMR peak list.[21] However, spectral data shows excellent agreement with that reported with a single exception. Agreement between the proton NMR data is excellent, with deviations of 0.04 ppm or less, with the exception of a single proton with a deviation of 0.1 ppm. This deviation is almost certainly due to issues assigning overlapping complex resonances; the peak with the deviation of 0.1 ppm (belonging to proton 4b), overlaps with H4a, H23b, and H27. The overlapping signals also made determination of coupling constants difficult in some instances, leading to minor variations in reported *J*-values. Reeves also reported difficulty in obtaining a pure sample of ambruticin J, so overlapping impurity peaks may have also confounded *J*-value assignments. We speculate that this may have also confounded ^{13}C NMR assignments, as discussed below.

The carbon NMR data shows deviations of 0.1 ppm or less for all peaks with the exception of the peak belonging to C16, which shows a deviation of 6.6 ppm. In an effort to alleviate this ambiguity, we obtained one- and two-dimensional NMR data for for the triol **23** and methyl ester **22** (**Figure 4**). Reeves reported that the C16 ^{13}C resonance for isolated ambruticin J was found at 124.3 ppm. However, synthetic ambruticin J carboxylic acid **1**, synthetic ambruticin J methyl ester **22**, and synthetic triol intermediate **23** all have no peak in this region and instead have a peak at 130.9 ppm. The proton NMR signals were assigned using COSY data obtained for the triol and methyl ester intermediates, confirming Reeves' assignments of all proton peaks, including the peak at 5.25 ppm which belongs to H16. HSQC data for the triol showed a strong correlation between the proton peak at 5.25 ppm and the carbon peak at 130.9 ppm, confirming our assignment for C16 in ambruticin J. The HSQC data for the ambruticin J methyl ester also identified four other carbon peaks which were incorrectly assigned in the literature data. While COSY data supports the assignments of all

protons, HSQC indicates that the C3 and C5 carbon signals were previously interchanged in Reeves' assignments, as well as the C4 and C12 carbon resonances. Seeking further evidence for our assignment of the signal at 130.9 ppm as C16, we also found literature proton and carbon data obtained for the natural product ambruticin VS3[54]. Assignments in this data set closely matched the eastern half of our synthetic ambruticin J and identified C16 at 130.7 ppm. The sum of this analysis confirms our assignment of the carbon NMR data for ambruticin J and the total synthesis of this putative biosynthetic intermediate.



ambruticin VS3

Natural and synthetic ambruticin structures	^{1}H-16 (ppm)	^{13}C-16 (ppm)
isolated *ambruticin J*, **1**	5.25	124.3
synthetic *ambruticin J*, **1**	5.26	130.9
intermediate triol, **23**	5.25	130.9
ambruticin J methyl ester, **22**	5.25	130.9
isolated ambruticin VS3	5.30	130.7

Figure 4. NMR Correlation between Ambruticin Structures.

Conclusion

In summary, we have completed the first total synthesis of ambruticin J, a putative biosynthetic intermediate in the biosynthesis of the ambruticin family of natural products. We synthesized this compound *via* a triply convergent synthetic route relying on a Suzuki-Miyaura coupling and a Julia-Kocienski olefination for fragment assembly to a vinylcyclopropane core. The synthesis of this strategic linchpin was highlighted by application of our cyclopropanation methodology. Through total synthesis we have confirmed the structural assignment of ambruticin J and corrected an assignment within the existing literature NMR data for this compound. This synthesis also provides access to ambruticin J and congeners and sets the stage for biochemical studies of the enzyme AmbJ and its role in the epoxidation and cyclization process that eventually leads to the isolated ambruticins.

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Keywords: cyclopropane • biosynthesis • myxobacteria • total synthesis • natural product

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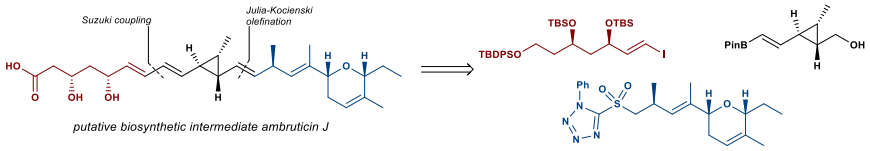

The first total synthesis of a putative intermediate in the biosynthesis of the ambruticins has been prepared by a convergent synthetic route that takes advantage of a trisubstituted cyclopropyl linchpin. The stereochemical assignment has been confirmed while previously reported, incorrect spectral data, has been updated. Access to this material will enable studies of the post-PKS processing that leads to isolated ambruticin structures and garner greater understanding of the evolution of their structures and potent anti-fungal activity.

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