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# Synthesis of the C1−C18 Fragment of Rhizopodin: Late-State Introduction of the Oxazole

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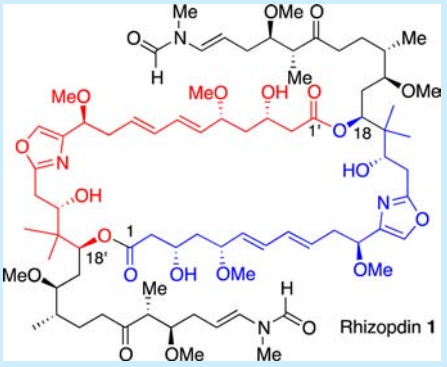
Supporting Information

**ABSTRACT:** The synthesis of the C1−C18 fragment of the myxobacteria metabolite rhizopodin is described. Initial attempts at installing the *E,E*-diene via cross coupling with an oxazole fragment gave poor results. An alternative approach, in which the diene was formed prior and the oxazole introduced by an acylation/*O,N*-shift protocol, gave the C1−C18 fragment **2** of rhizopodin (**1**).

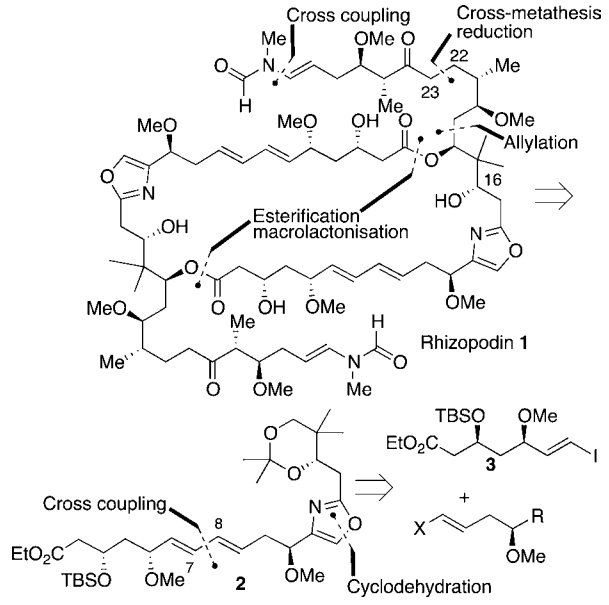



Myxobacteria produce a wide variety of diverse secondary metabolites with a range of biological activities.[1] Höfle and co-workers isolated the novel macrodiolide rhizopodin (**1**) from the extracts of the myxobacterium *Myxoccocus stipitatus* Mx f164.[2] Compound **1** displayed potent cytotoxicity against a number of cancer cell lines, showing an $IC_{50}$ of 30 ng/mL for hamster kidney (GBF), 12 ng/mL for hamster ovarian (DSM ACC 126), and 15 ng/mL L929 mouse fibroblast cell lines.[2] The structure of **1** was originally proposed to be a 19-membered macrolactone, but this was later revised to be the 38 membered $C_2$-symmetric diolide **1** consisting of 18 stereogenic centers, two conjugated diene systems, two 2,4-disubstituted oxazoles, and two enamide side chains.[3] Over the past few years, various groups have published synthetic work toward rhizopodin (**1**) ranging from a number of fragments[4] to a protected monomer[5] as well as macrocyclization studies.[6] Thus far, a total synthesis of monorhizopodin[7] and two total syntheses of rhizopodin (**1**) have been reported.[8,9] In the total synthesis described by Paterson, it was noted that the choice of protecting group at C16/C16′ (TES ether) was pivotal for the successful final deprotection to deliver **1**.[9]

These reported syntheses all install the oxazole at an early stage and then carry out the formation of the *E,E*-diene via cross coupling afterward. We also embarked on a similar strategy but encountered problems. Here we report a synthesis of the C1−C18 fragment of rhizopodin (**1**) in which the 2,4-disubstituted oxazole is installed at a later stage using an acylation/*O,N*-acyl shift/cyclodehydration sequence.[10,11]

An approach to rhizopodin (**1**) is shown in Scheme 1. The macrocycle could be formed by sequential esterification or dimerization followed by Takai homologation[12] and a copper-mediated cross-coupling[13] to install the enamide functionalities.

**Scheme 1. Retrosynthesis of Rhizopodin**




The C22−C23 bond could be constructed via a cross-metathesis followed by an enone reduction and the C18−C19 bond formed via asymmetric allylation. This leads to the C1−C18 fragment **2** in which the C7−C8 linkage could be installed by a suitable cross coupling. Initially, we also investigated formation of this bond by a cross coupling

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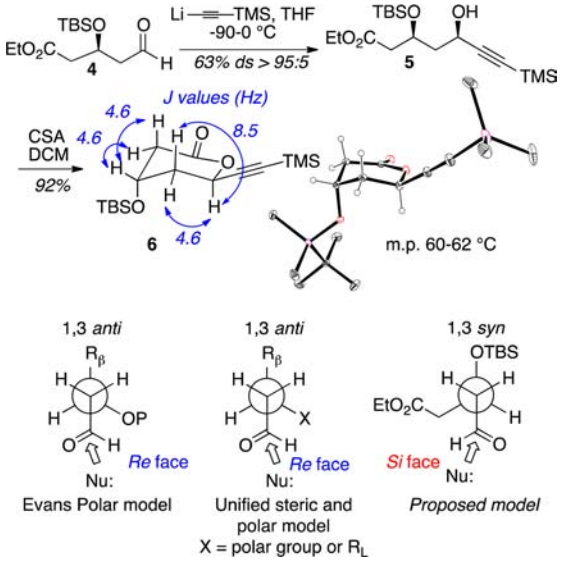
between the vinyl iodide **3** and an appropriately functionalized oxazole coupling partner.

The synthesis of the vinyl iodide fragment began with a stereoselective alkyne addition of lithiated TMS-acetylene to known aldehyde **4** (obtained via a asymmetric enzyme mediated hydrolysis)[14] which afforded alcohol **5** as a single diastereoisomer (Scheme 2). Acid-induced formation of the

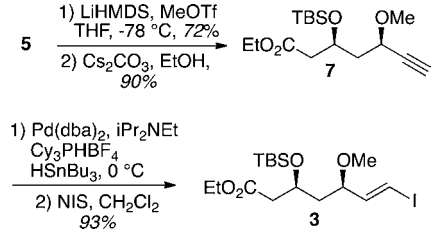
**Scheme 2. Stereoselective Alkyne Addition to Aldehyde 4**




lactone **6** allowed for the relative stereochemistry to be assigned by $^1$H NMR spectroscopy. Analysis of the IR spectrum of lactone **6** indicated a flattened chair conformation (1744 cm$^{-1}$),[15] and $^1$H−$^1$H coupling constant analysis[16] showed the OTBS group was axial and the alkyne equatorial. Fortunately, this compound was crystalline and a single crystal X-ray structure[17] confirmed the relative *syn*-1,3-diol stereochemistry. Thus, acetylide addition had occurred to the *Si* face of the aldehyde via the proposed open transition-state model shown in Scheme 2. This is in contrast to the models for anion addition to *β*-alkoxy aldehydes (Evans polar and unified steric and polar models) which predict *Re* face attack to afford the *anti*-1,3-diol product as the major isomer (Scheme 2).[18] In our proposed model, the ester is the polar group while OTBS group is placed *anti* to the aldehyde and *Si* face attack affords the 1,3-*syn* product.

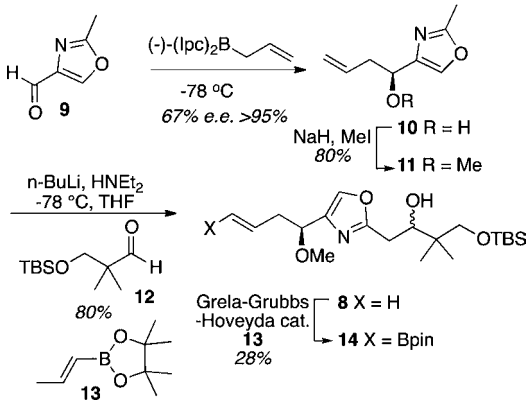
Methylation of **5** with LiHMDS and MeOTf followed by TMS group removal using $Cs_2CO_3$ in EtOH gave alkyne **7** (Scheme 3). Vinyl iodide **3** was then obtained in 93% overall yield by Pd(0)-mediated regioselective hydrostannylation[19] and iodine quench using *N*-iodosuccinimide.

**Scheme 3. Synthesis of Vinyl Iodide 3**




As mentioned, we also investigated a cross coupling of an oxazole fragment with the iodide **3** to install the diene. A truncated oxazole fragment **8** was synthesized as shown in Scheme 4. The known aldehyde **9**[20] was subjected to Brown

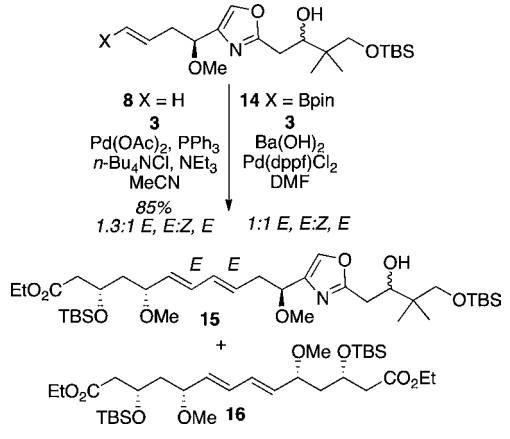
**Scheme 4. Synthesis of Oxazole Boronate 14**




allylation to give the alcohol in good yield and high ee (>95%). Methylation then provided ether **11**. Regioselective deprotonation of the oxazole C2 methyl group using a modification of the Evans protocol[21] followed by addition of the resultant anion to the aldehyde **12** gave oxazole **8** in high yield. Key to success this step was the method for anion generation. We found that preformed $LiNEt_2$ gave mixed results due to its instability. The anion was generated in a reliable manner by the addition of n-BuLi to a solution of the oxazole **11** and $HNEt_2$ in THF at −78 °C. Cross-metathesis between **8** and boronate **13**[22] using Grela modification[23] of the Grubbs−Hoveyda catalyst gave the *E*-vinyl boronate **14** in low yield but as a single geometric isomer.

Initial cross-coupling investigations focused on an intermolecular Heck coupling between alkene **8** and iodide **3** (Scheme 5). The best results were obtained using modified

**Scheme 5. Attempted Cross Couplings with Iodide 3**




Jeffery conditions[24] which gave a good yield but poor *E*:*Z* ratio with a slight preference (1.3:1) for the desired *E*,*E* isomer (**15**) over the undesired *E*,*Z* isomer. The Suzuki coupling approach, which was similar to that reported,[6b,8] also failed to provide good results. In our case, a 1:1 mixture of *E*,*E* and *Z*,*E* isomers was obtained in low yield along with the starting material which could not be separated. In both cases, the dimerization of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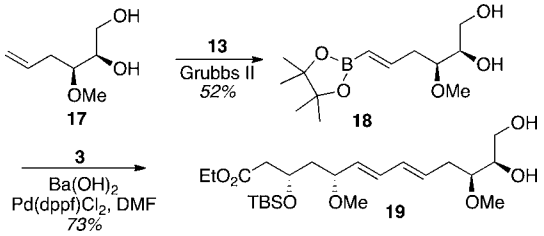
iodide **3** to give diene **16** was a major byproduct. We were also able to affect the dimerization of **3** to form **16** in moderate yield using the same the Heck conditions in the absence of the alkene **8**.

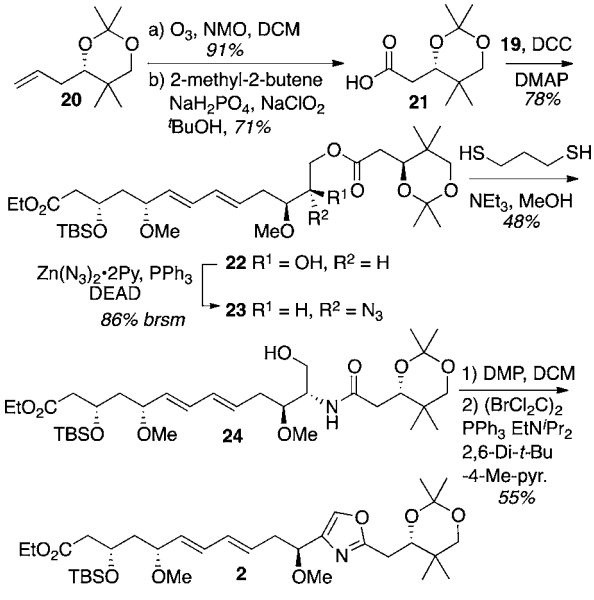
The above results were unexpected considering that the formation of the *E*,*E*-diene by cross coupling in the presence of an oxazole had been successful previous approaches.[5b,c,6−9] We therefore elected to test an alternative strategy whereby construction of the diene would be achieved *prior* to installation of the 2,4-disubstituted oxazole using our modified approach to this heterocyclic system.[10c,d] This began with readily available diol **17**,[25] which was subjected to cross-metathesis[21] with boronate **13** to give vinyl boronate **18** (Scheme 6). Suzuki

**Scheme 6. Synthesis of Diene 19**




coupling with iodide **3** now cleanly afforded diol **19** in 73% yield as a single geometric isomer. Esterification of acid **21** (available in two steps from known alkene **20**[7]) with diol **19** afforded ester **22** (Scheme 7). Treatment of **22** with $Zn(N_3)_2$·

**Scheme 7. Completion of the C1−C18 Fragment 2**




2Py[26] then gave the azide **23**, and reduction with 1,3-propanedithiol in the presence of $NEt_3$ gave hydroxy amide **24** via an *O*,*N*-acyl shift.[10c] Oxidation and Wipf cyclodehydration[11] afforded the desired C1−C18 fragment **2** of rhizopodin (**1**) in 55% over the two steps.

In summary, we have completed the synthesis of the C1−C18 fragment of the diolide rhizopodin in which the oxazole was installed after formation of the *E*,*E*-diene. Highlights of this approach include a stereoselective acetylide addition for the synthesis of the vinyl iodide **3**, an efficient Suzuki coupling to produce diene **19** and an acylation/*O*,*N*-shift/cyclodehydration sequence to form the 2,4-disubstituted oxazole **2**. Application of this approach for the total synthesis of rhizopodin (**1**) is currently underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details as well as characterization data and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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