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# Total Synthesis of 2′-*O*-Methylmyxalamide D and (6*E*)-2′-*O*-Methylmyxalamide D

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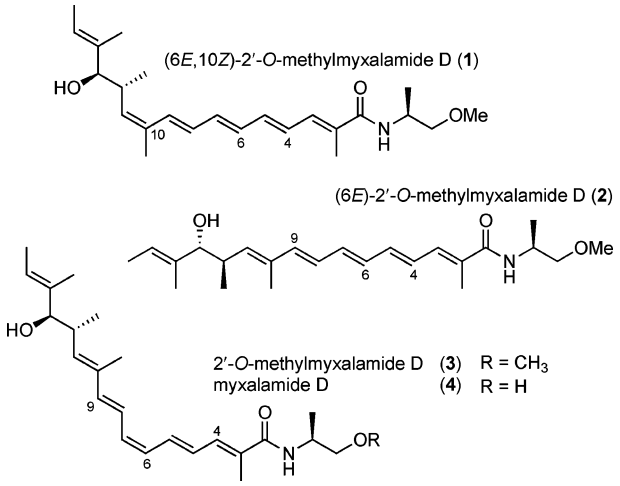
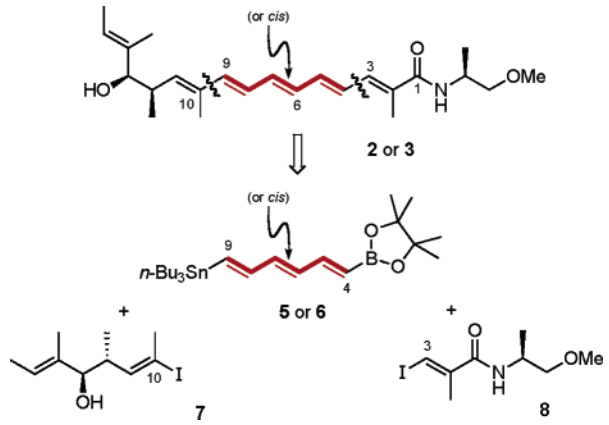
A report by Ojika and co-workers in 2004 described the isolation of three polyene antifungal antibiotic agents (**1**−**3**) from the myxobacterium *Cystobacter fuscus*.[1] These compounds were shown to be O-methylated and geometric isomers of myxalamide D (**4**), which had previously been isolated from *Myxococcus xanthus*.[2] These new myxalamides come from the same species of Gram-negative myxobacteria that produces the antifungal cystothiazoles. The cytotoxicity of these agents results from inhibition of the NADH/ubiquinone oxidoreductase complex. The biosynthetic gene cluster for *O*-methylmyxalamide D was cloned.[3]



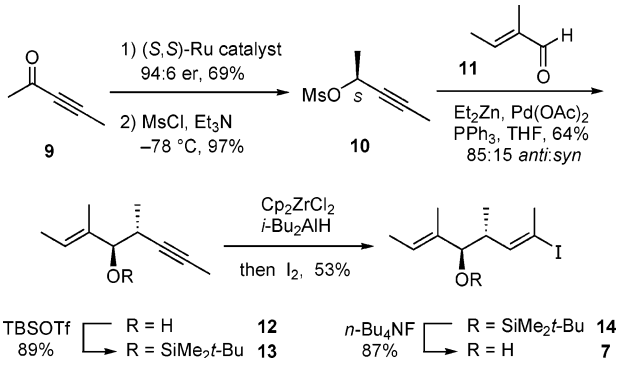

There has been limited synthetic work in this area. Syntheses of myxalamide D,[4] myxalamide A,[5] and the structurally related natural products stipiamide[6] and phenalamide $A_2$[7] have been reported. Although these syntheses were well executed, the long reaction sequences, problematic *cis*/*trans* olefin isomerization, and product purification were always an issue.

Our examination of (6*E*)-2′-*O*-methylmyxalamide D (**2**) and 2′-*O*-methylmyxalamide D (**3**) with a view toward maximal synthetic convergency revealed a central 1,3,5-hexatriene system connecting two more functionalized left and right fragments. Further consideration of the C4−C9 central triene unit as a linchpin revealed the hetero-bis-metalated (1*E*,3*E*,5*E*)-1,3,5-hexatriene **5** or (1*E*,3*Z*,5*E*)-1,3,5-hexatriene **6**. Interpolation of **5** or **6** via palladium-catalyzed $Csp^2-Csp^2$ coupling reactions—in the form of Stille and Suzuki−Miyaura reactions—would bring the left and right vinyl halide-containing fragments **7** and **8** together in a sequential and convergent sequence.

This linchpin strategy was recently used in the total synthesis of the antitumor agent lucilactaene,[8] using a similarly metalated 1,3-butadiene system,[9] and in the total synthesis of the antifungal agent strobilurin B,[10] using an analogous 1,3-pentadiene system. We now report the first total synthesis of 2′-*O*-methylmyxalamide D (**3**) and its (6*E*) isomer (**2**) using this synthetic strategy.




The left-hand vinyl iodide **7** was constructed in a straightforward series of transformations starting with 3-pentynone (**9**).[11] Ruthenium-catalyzed asymmetric reduction[12] afforded the corresponding alcohol, which was determined as a 94:6 ratio of enantiomers by chiral GC. Formation of the methanesulfonate afforded **10**. Palladium-catalyzed addition[13] of **10** to tiglyl aldehyde (**11**) afforded the addition product **12**, which was protected[14] as silyl ether **13**. Hydrozirconation[15] occurred with in situ generation of zirconocene hydrochloride, and reaction of the intermediate vinylzirconium species with iodine afforded **14**, which was deprotected to produce vinyl iodide **7**.[16]




All-*trans* hexatriene **5** was synthesized in four steps from epichlorohydrin and acetylene to initially afford enyne **15**,[17] which, although commercially available, is prohibitively expensive as a starting material. Stannylcupration[18] of **15** afforded the corresponding dienyl stannane, which was subjected to Parikh−Doering oxidation to afford dienal **16**.[19] Boryl−Takai olefination[20] afforded hetero-bis-metalated 1,3,5-hexatriene **5**, exclusively as the *E* isomer at the newly installed double bond.

The triene **5** was interpolated between vinyl iodide **7** and iodide **8**[21] by sequential Stille coupling with **8** to afford tetraenyl boronate **17** as an isolable intermediate, followed by Suzuki-Miyaura



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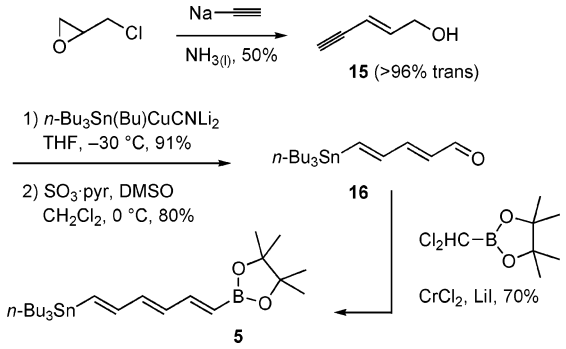
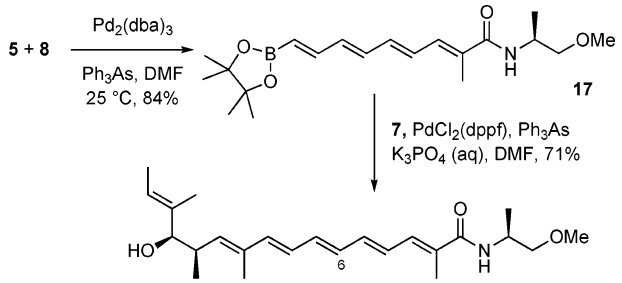
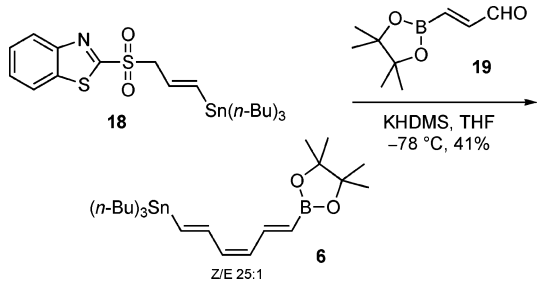


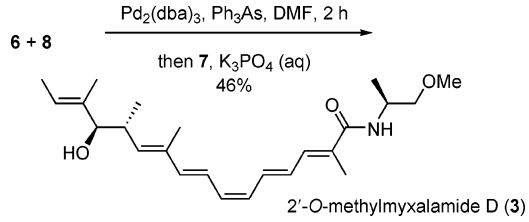

coupling with vinyl iodide **7** to afford directly (6*E*)-*O*-methylmyxalamide (**2**), spectrally identical with the natural product.[1,22]




The (1*E*,3*Z*,5*E*)-hexatriene **6** was obtained directly via a one-pot modified (Sylvestre) Julia olefination between sulfone **18**[23] and pinacol ester of 3-boronoacrolein **19**.[24] Deprotonation of sulfone **18** with K[N(SiMe$_3$)$_2$] in the presence of the aldehyde **19** furnished *Z* isomer **6**, with 25:1 *Z*/*E* selectivity at the newly formed double bond. The high *Z* selectivity of olefination with tributylstannyl-substituted allyl benzothiolyl sulfone has been observed,[23,25] although the mechanism of the selectivity is unclear. The stability of boronate-substituted aldehyde **19** under the basic conditions and the low stability of the triene **6** on the silica gel column were responsible for the modest yield of the reaction.




The completion of the synthesis of **3** now became a straightforward task of sequential cross-coupling reactions, in this instance in a *one-pot fashion*: palladium-promoted Stille coupling between triene **6** and right-hand vinyl iodide **8** followed by the addition of left-hand vinyl iodide **7** and base to promote Suzuki−Miyaura coupling. This procedure directly afforded **3** in good yield for this complex reaction process. Most importantly, the one-pot protocol avoided possible isomerization of an intermediate tetraene species during isolation and purification. Double bond isomerization was not observed during the coupling reaction, or isolation, purification, or characterization, and **3** was obtained as a single stereoisomer. The spectral data of **3** were in excellent agreement with that reported for the natural product.[1,22]




The synthesis of **2** was accomplished in seven linear steps, using a total of 12 synthetic operations from easily accessible chemicals. The synthesis of **3** was completed in 11 total steps using a one-pot Stille/Suzuki−Miyaura reaction sequence as the key step. This convergent one-pot sequence was first developed during methodology studies with aryl iodide substrates,[9] but this is the first time it has been implemented in a natural product synthesis. The total syntheses of **2** and **3** are synthetically efficient, potentially versatile, and exceptionally convergent.

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**Supporting Information Available:** Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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