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Enantioselective Synthesis of the Polyhydroxylated Chain of Oscillariolide and Phormidolides A−C

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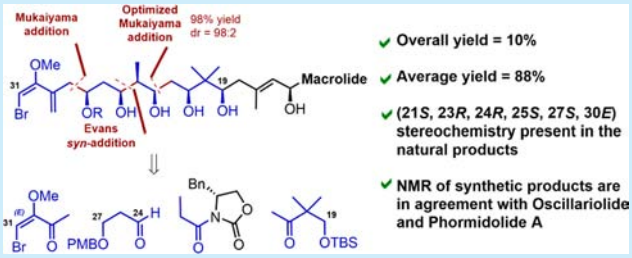
Supporting Information

ABSTRACT: The first enantioselective synthesis of the polyhydroxylated chain common to marine natural products oscillariolide and phormidolides A−C is described herein. This chain represents a synthetic challenge that needs to be solved before the total synthesis of this family of natural products can be approached. It contains seven stereocenters, six of them having a *syn*-hydroxylated functionality, and a tricky terminal (*E*)-bromomethoxydiene (BMD). The described effective enantioselective strategy affords the polyketide chain and represents an important breakthrough to complete the total synthesis of these marine compounds.



Natural products isolated from marine sources have a huge impact on the antitumor drug discovery scenario of the present day.[1] During the past few years, the isolation of polyketide macrolides with the occurrence of oxygen-containing heterocycles has opened a challenging field in structure determination as well as in chemical synthesis of these potent compounds.[2] The complex polyketides oscillariolide,[3] phormidolide A,[4] and phormidolides B and C[5] exhibit similar structures based on a macrocyclic core bonded to a common polyhydroxylated chain. The phormidolides present an extra fatty acid linked by an ester bond to the hydroxyl next to the BMD motif. In phormidolide A, the polyhydroxy chain is linked to palmitic acid, and in phormidolides B and C it is linked to two different halogenated unsaturated fatty acids.

Our group is focused on the total synthesis of phormidolides B and C and has developed approaches for the stereoselective synthesis of their macrocyclic core[5,6] and a model-based study to find the best conditions to link this macrocyclic core to the polyhydroxy chain.[7] Additionally, the first chemical strategy to synthesize the complex BMD moiety present at the end of the polyhydroxylated chain has been recently reported.[8] The retrosynthetic analysis of phormidolides B and C proposed in the previous work[7] (Figure 1) was based on two main disconnections to give three molecular fragments: polyol **A** containing the C19−C31 chain functionalized as an aldehyde at C19, propargylic organometallic **B**, and macrocyclic lactone **C**[6] with C15 functionalized as an aldehyde. From now on, the numeration of carbon in the polyhydroxylated chain will be the same as the one reported in the isolation of phormidolides B and C.[5]

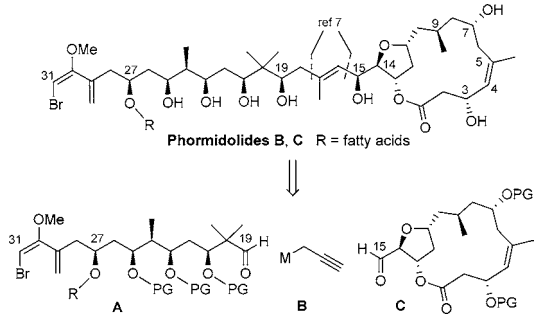


Figure 1. Retrosynthetic plan for phormidolides B and C.

The first enantioselective synthesis of the C19−C31 fragment of the polyol chain present in oscillariolide (**1**) and phormidolide A (**2**) is reported in this paper. Palmitic acid, which is the fatty acid present in phormidolide A, was used in the present work to show the viability of our strategy. The retrosynthetic analysis (Figure 2) starts with the esterification of **1** with the corresponding fatty acid to access the phormidolide chain **2**. The introduction of the terminal

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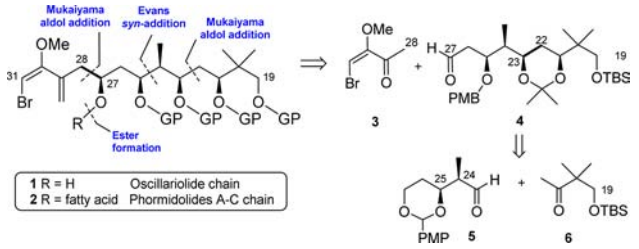


Figure 2. Retrosynthetic analysis of the polyhydroxy chain C19−C31.

bromodiene by means of a Mukaiyama aldol addition[9] of ketone **3**[8] to aldehyde **4** followed by olefination will be used for the synthesis of **1**. The formation of the C22−C23 bond was envisioned through an asymmetric aldol addition between aldehyde **5** and known ketone **6**.[10] It is important to mention that the selection of the protecting groups is a critical part of this project. The possibility of installing the BMD moiety at C27 and the propargyl unit at C19 orthogonally depending on the synthetic requirements is vital for the success of this strategy.

The synthesis of the protected C19−C27 core **11** (Scheme 1) started with the protection of the two hydroxyl groups of aldol **7**[11] by oxidation of the *O*-*p*-methoxybenzyl (PMB) moiety with DDQ to give the *p*-methoxyphenyl (PMP) acetal **8** in high yield. Removal of the oxazolidinone asymmetric inductor and subsequent Dess−Martin periodinane (DMP) oxidation rendered aldehyde **5** in 74% yield for the two steps. Silyl enol ether **9**[12] reacted with aldehyde **5** in an exceptional 98% yield with complete stereocontrol toward our desired 23,24,25-*syn* aldol **10**. Optimization of the conditions[13] was critical to modulate the yield and stereochemical outcome[14] of this key transformation. The 1,3-*syn* reduction using DIBAL-H[15] as the reducing agent instead of catecholborane[16] gave a higher yield[17] (73%, *dr* = 86:14) and simplified the purification. Final protection of the resulting 1,3-diol by acetal formation with 2-methoxypropene under acidic conditions afforded **11** in quantitative yield.

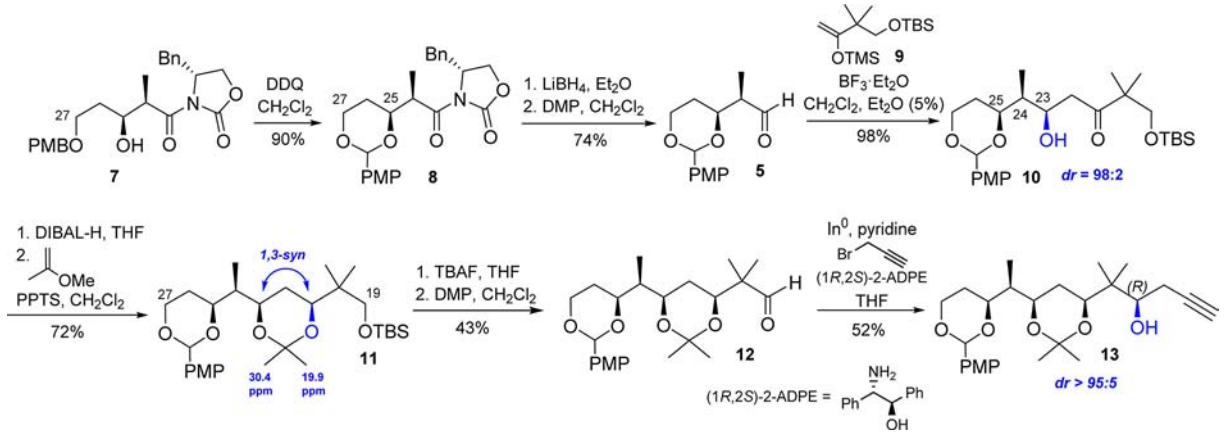
The C21−C23-*syn* relative configuration of **11** was confirmed by ^{13}C NMR analysis of the corresponding acetonide.[18] The orthogonality of the protecting groups has given us the possibility to propargylate C19, transforming compound **11** to **13** in three steps. Thus, chemoselective removal of the TBS protecting group of **11** and oxidation gave aldehyde **12**. The final stereoselective addition using propargylindium following the Singaram procedure[19] afforded compound **13** with an excellent *dr* in 52% yield.[14]

Next, a valid route to install the BMD motif at C27 was investigated. It started with the transformation of compound **11** into aldehyde **4** by chemoselective reduction of the PMP acetal and oxidation of the resulting primary alcohol **14** (Scheme 2). Our strategy takes advantage of an usual consecutive PMB−PMP−PMB manipulation (oxidation−reduction), which allowed efficient transformations **7** → **8** and **11** → **14**. Afterward, (*E*)-bromoketone **3**[8] was converted quantitatively into its corresponding silyl enol ether **15**, and the crude material was reacted directly with aldehyde **4** to render ketol **16** in 62% yield (*dr* > 95:5). Formation of 25,27-*anti* diol **16** was expected[20] and confirmed by NOE analysis of the cyclic acetal obtained by oxidation of **16**.[21]

In order to make the synthesis of the target C19−C31 chain with minimum protection steps, inversion and olefination over unprotected the C27-OH of **16** were tested unsuccessfully.[22] Therefore, a very efficient three-step procedure including TES protection, Tebbe olefination, and deprotection was developed. The methylene was inserted to obtain diene **17** in 88% yield. It is worth mentioning that the Tebbe reagent was not reactive enough at rt and the reaction mixture had to be heated to 50 °C for 2 h. This unreactivity was most likely a result of the steric hindrance caused by the bromine and the triethylsilyl protecting group surrounding the ketone. Finally, the configuration of C27 of **17** was inverted using the widely used Mitsunobu hydrolysis protocol in good yield to give alcohol **1**, the protected C19−C31 fragment of the polyhydroxylated chain of oscillariolide. Alcohol **1** was esterified with palmitic acid under standard conditions to reach ester **2**, the polyhydroxylated chain present in phormidolide A.

In conclusion, we have developed an enantioselective strategy toward the protected polyhydroxylated chains of oscillariolide (**1**) and phormidolide A (**2**) from cheap and accessible starting materials. The longest linear sequence to obtain **1** is 17 steps long with an average yield of 88% and a 10% overall yield. This first method for the synthesis of the polyhydroxylated chain common to oscillariolide and phormidolides A−C is an important requirement to approach their total synthesis. The configurations of all of the stereocenters present in the chain have been determined using different NMR methods, and the (21*S*,23*R*,24*R*,25*S*,27*S*,30*E*) stereochemistry present in the natural products has been confirmed.

Scheme 1. Synthesis of the C19−C27 Protected Fragment (13) and Incorporation of the Propargyl Residue



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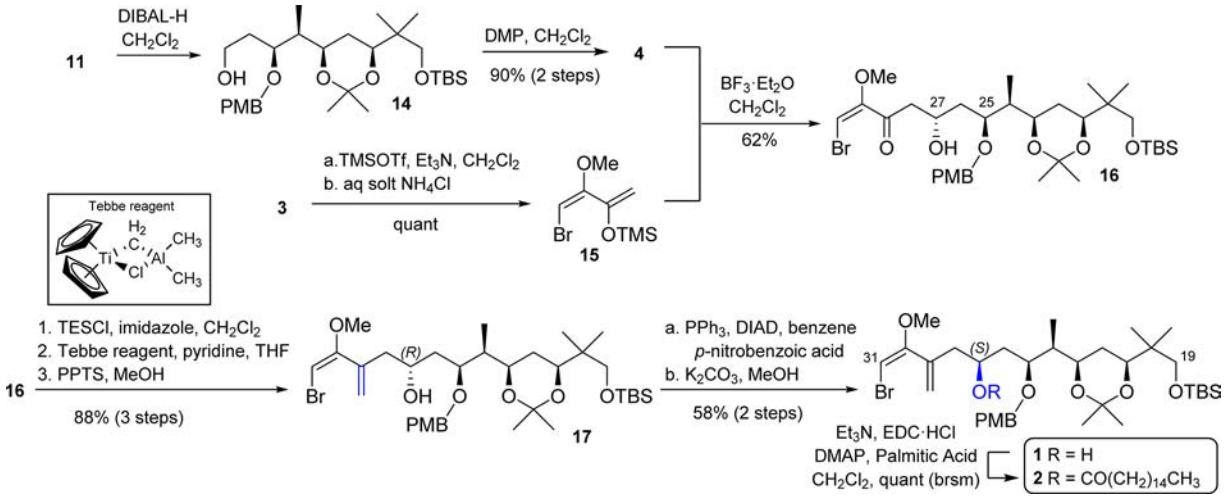
Scheme 2. Synthesis of the C19−C31 Chain of Oscillariolide (1) and Phormidolide A (2)



Furthermore, the NMR signals of **1** and **2** are in agreement with those reported for the natural products.[3,4,23] Remarkable features in the route are the polyvalence and atom economy afforded using the PMB−PMP protecting group moving around different chain positions, the optimization of Mukaiyama addition to obtain compound **10** in excellent yield (98%) and stereoselectivity, and finally, the efficient stereoselective preparation of compound **16** by addition of the C28−C31 fragment **15** over a complex and highly functionalized precursor. This synthetic procedure should pave the way for the total synthesis of this family of intriguing molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02014.

Experimental procedures and characterization of the described compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) A table with the detailed data (yield, *dr*, solvents tested) from this optimization is available in the Supporting Information.

(14) The absolute configuration of the new hydroxyl was determined using Mosher's derivatization method. See the Supporting Information.

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(21) 1D NOE experiments on the cyclic acetal of **16** are available in the Supporting Information.

(22) Mitsunobu conditions for inversion led to the elimination product, and all of the tested olefination conditions (Wittig, Petasis, Lombardo, etc.) led to decomposition of the starting material.

(23) A comparison of the key NMR signals in **1** and **2** with those of oscillariolide and phormidolide A is available in the Supporting Information.

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