Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A-C

Alejandro Gil,[a,b] Janire Lamariano-Merketegi,[a,b] Adriana Lorente,[a,b,⊥] Fernando Albericio,[b,c,d] and Mercedes Álvarez*[a,b,e]

Abstract: The terminal bromomethoxydiene (BMD) moiety of the polyhydroxylated chain present in phormidolides and oscillariolides has been synthesized for first time. Several strategies for the stereoselective synthesis of the 4-bromo-3-methoxybut-3-en-2-ones are described. Furthermore, a preliminary study to successfully introduce this fragment within the polyol chain and introduction of the fatty acid allowed corroborate the end structure of the polyol.

Oscillariolide[1] and phormidolides A-C[2-3] are members of a family of compounds isolated from marine organisms[4] with interesting structural and biological activities (Figure 1). They have all shown toxicity against different biological targets such as fertilized starfish eggs, brine shrimp and cancer cell lines with an unknown mechanism of action. These natural compounds exhibit characteristic structural similarities such as: a tetrahydrofuran (THF) containing macrolide ring with a different number of unsaturations and a common polyhydroxylated chain containing six stereocenters in a *syn*-relative configuration. This polyol chain ends with a synthetically challenging common bromomethoxydiene moiety (BMD), an (*E*)-3-substituted-1-bromo-2-methoxybuta-1,3-diene. Phormidolides A-C polyhydroxylated chain differs from that of oscillariolide in one fatty acid linked to a polyol via an ester bond with the hydroxyl closest to BMD. Therefore, the importance of this BMD motif relies both on its unprecedented presence in such polyketide macrolides and on its strategic position within the structure of the natural product as its synthesis is crucial to link the polyhydroxy chain to distinct fatty acids.

Several strategies for the synthesis of the macrocyclic core present in Phormidolides B and C have been reported[3],[5] as well as a preliminary study to link the macrocyclic core and the polyol via the formation of the allylic alcohol attached to the THF ring[6] but no publications describing the polyol chain synthesis have been reported yet. To deal with this synthesis, we envisage the formation of the polyol chain BMD moiety by the following reaction sequence: a Mukaiyama aldol addition reaction[7] between 2-bromo-1-methoxyvinyl methyl ketone (BMK) **(*E*)-1** and the corresponding aldehyde, followed by esterification with the appropriate fatty acid and final olefination[8] for the formation of the terminal diene (Figure 2).

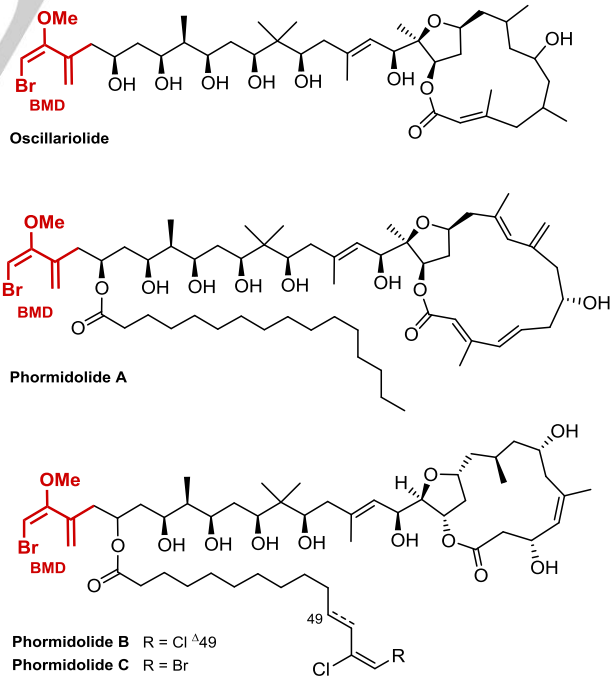

Figure 1. Structures of oscillariolide and phormidolides A-C.

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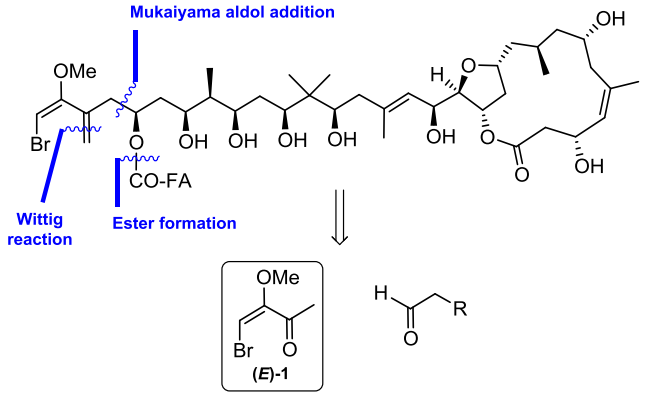
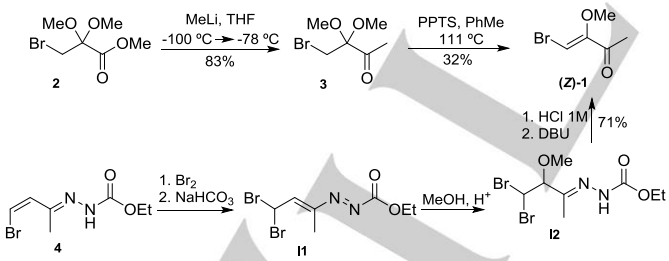


Figure 2. Retrosynthetic analysis for the introduction of key fragment **(*E*)-1**.

For this purpose, the target compound is the (*E*)-4-bromo-3-methoxybut-3-en-2-one **(*E*)-1** used as a single isomer. There are few publications reporting the synthesis of bromoenolether ketones and generally they report the undesired *Z* isomer.[9],[10] Therefore, tremendous efforts have been necessary to develop a suitable strategy that delivers the desired and key compound **(*E*)-1**.

The first attempted methodology used was a three-step procedure based on the transformation of bromopyruvic acid into the dimethyl acetal-methyl esther **2**[11] followed by reaction with MeLi at low temperature to obtain ketone **3**. The final step was the elimination of methanol under acidic conditions to give compound **1** (Scheme 1). After NMR characterization of **1**, NOE 1D studies confirmed the *Z*-stereochemistry for the obtained compound. The lack of NOE correlation between the vinylic proton and the methoxy group was significant.[12] It is worth to mention that photochemical[13] and I_2 promoted isomerization[14] of **(*Z*)-1** to obtain the desired *E* isomer were tested unsuccessfully due to decomposition or unreactivity of **(*Z*)-1**, respectively.

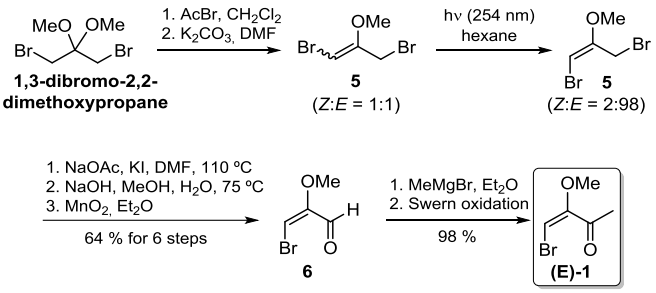


Scheme 1. Different synthetic strategies to obtain **(*Z*)-1**.

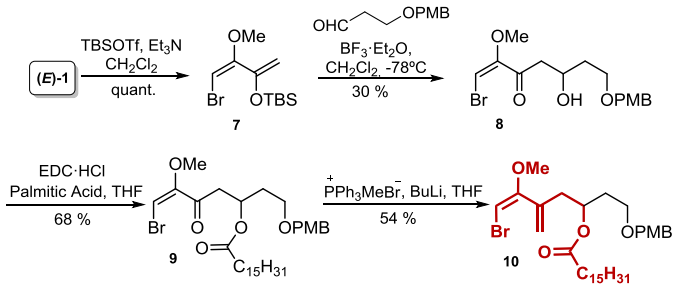
Interestingly, Feuerer and Severin described the synthesis of 3-(benzyloxy)-4-bromo-3-buten-2-one as an isomeric mixture (*E*:*Z* = 10:1). [10] Therefore, their methodology was tested by replacing benzylic alcohol with methanol (Scheme 1). Bromohydrazone **4** was subjected to a one pot – five transformation sequence where the first steps were bromination and elimination leading to the formation of the corresponding intense red ene-azo compound **I1**. Then, methanol addition in acidic media delivered the dibromo-methoxy intermediate **I2**. Finally, hydrolysis and DBU promoted HBr elimination afforded again BMK **(*Z*)-1** in a 71% yield relative to **4**. NMR data matched the previously characterized *Z* isomer.

Finally, the effective methodology to synthesize **(*E*)-1** is depicted in Scheme 2. Dibromo compound **5**[14] as an isomeric mixture (*Z*:*E* = 1:1) was obtained starting from 1,3-dibromo-2,2-dimethoxypropane. This mixture was enriched in the desired *E* isomer by irradiation with UV light at 254 nm in hexane for 8 h. A three-step reaction sequence involving acetylation, hydrolysis and allylic oxidation led to formyl derivative **6**. The overall yield of this six-step sequence was high and no silica purification was needed during the intermediate steps. Finally, alkylation with MeMgBr and a second allylic oxidation delivered **(*E*)-1** as a single isomer.[15] NOE 1D correlation between the vinyl hydrogen and the methoxy group confirmed *E*-stereochemistry.[13] (*E*)-bromomethoxyvinylmethyl ketone **(*E*)-1** was obtained for the first time with an easily scalable procedure.

Once **(*E*)-1** was obtained, a suitable strategy to introduce the BMD moiety into the polyhydroxylated chain was examined (Scheme 3). BMK **(*E*)-1** was converted to the corresponding silylenolether **7** to perform a Mukaiyama aldol addition with 3-((4-methoxybenzyl)oxy)propanal as a model aldehyde to mimic the polyol chain. Interestingly, the use of the *tert*-butyldimethylsilyl enol ether **7** was mandatory due to the reduced stability of the corresponding trimethylsilyl derivative. Both transformations worked well in terms of yield, delivering ketol **8**. Then, palmitic acid, the fatty acid present in phormidolide A, was introduced using carbodiimide as condensation agent. Finally, Wittig olefination resulted in the best method to introduce the methylidene extra carbon with good yield to give diene **10**. The chemical shifts of the key protons in the BMD moiety of compound **10**[16] matched those obtained for the natural products,[1,2,4] thereby demonstrating that this route creates the BMD fragment present in this compound family. This is the first synthetic pathway for the synthetically challenging BMD west fragment of the polyol chain common to oscillariolide and phormidolides and establishes the route for the condensation of the polyhydroxy chain and the fatty acids to complete their total synthesis.



Scheme 2. Synthesis of bromoketone **(*E*)-1**.



Scheme 3. Synthesis of **10**, model of the polyol chain west fragment.

In conclusion, the synthesis of (*E*)- and (*Z*)-4-bromo-3-methoxybut-3-en-2-ones has been described for the first time with good yields and easy procedures. A robust, high yielding, efficient, and scalable methodology for the synthesis of key compound **(*E*)-1** BMK is herein described. It is entirely based in spot to spot reactions from the commercially available 1,3-dibromo-2,2-dimethoxypropane without intermediate purification which only requires a final silica column chromatography to obtain a cleaner sample of **(*E*)-1** with an 63 % overall yield after eight synthetic transformations.

In addition, the Mukaiyama aldol addition-esterification-Wittig olefination strategy was shown to be a nice method to introduce the BMD moiety at the end of the polyhydroxylated chain. This synthesis has given access for the first time to the west fragment of these challenging molecules. These results are of great significance for the synthesis of the polyol chain, common to oscillariolide and phormidolides. The application of this synthetic strategy to the total synthesis of phormidolides is ongoing.

Acknowledgements

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[15] *The chemical shift of the vinylic proton in the two stereoisomers of 1 show an important difference due to the influence of bromide and methoxy groups. They are 6.93 ppm for **(Z)-1** and and 5.64 ppm for **(E)-1**.*

[16] *See **Table 1** in the Supporting information.*

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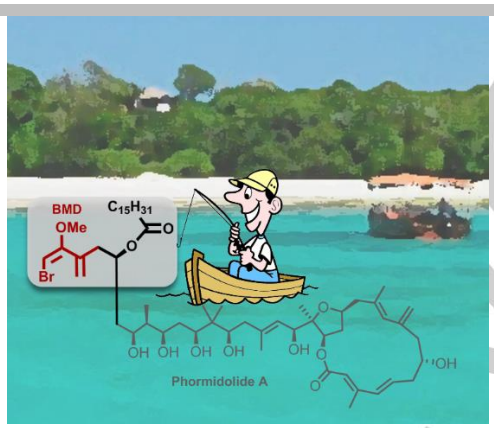
Layout 1:

COMMUNICATION

“Fishing” the difficult BMD moiety



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