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Synthetic studies toward biselides. Part 2: synthesis of the macrolactone part of biselides A and B using allylic oxidation

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ABSTRACT

Synthesis of the macrolactone part of biselides A (**1**) and B (**2**), marine cytotoxic polyketides, was achieved by using regioselective allylic oxidation as a key step.

Introduction

Biselides A (**1**) and B (**2**) are cytotoxic macrolides isolated from Okinawan ascidian Didemnidae sp. by our group (Fig. 1), and are analogues of haterumalides.[1,2] In the preceding paper,[3] we reported synthesis of the C-1–C-15 segment of biselides A (**1**) and B (**2**) by using Stille coupling and regioselective oxidative cleavage of an olefin bond as key steps (Scheme 1). However, the yield and regioselectivity of dihydroxylation at the terminal olefin in **8** were low. Therefore, we planned to develop another method for synthesizing biselides A (**1**) and B (**2**). We describe here the synthesis of the macrolactone part of biselides A and B by using allylic oxidation as a key step.

We planned to synthesize biselides by the introduction of a hydroxy group at C-20 in the synthetic intermediate of haterumalides, **12**, and our strategies are shown in Scheme 2. Thus, the C-20 hydroxy group would be introduced into **13** by using allylic oxidation. Synthesis of a precursor for allylic oxidation, **13**, started from the α,β-unsaturated ester **12**, the intermediate in our total synthesis of haterumalides. Allylic alcohol **14** could be transformed into macrolactone **15** by the strategy of our total synthesis of haterumalides.[4]

The investigation of regioselective allylic oxidation by using model compounds **17a–f**[5] is summarized in Table 1. First, the allylic oxidation of TBDPS ether **17a** with SeO_2[6] gave only the undesired aldehyde **19**, but the desired allylic alcohol **18a** could not be obtained (entry 1). The undesired aldehyde **19** was thought to be produced by oxidation at the C-3 oxymethylene group (Scheme 3). We considered that the electron density of the allylic position is important for the regioselectivity of this allylic oxidation and that reducing the electron density of the C-3 oxymethylene group would improve the regioselectivity. Therefore, the optimization of precursors with an electron-withdrawing group at C-3 for this allylic oxidation was investigated (entries 2–6). The reaction of acetate **17b** gave the desired alcohol **18b**, but the yield was low (entry 2). Furthermore, a considerable degree of migration of the acetyl group occurred under these reaction conditions. We next investigated the substituent effect on benzoate derivatives (entries 3–6). The results showed that the allylic oxidation at C-20 of *p*-nitrobenzoate **17f** gave the best result (40% yield,

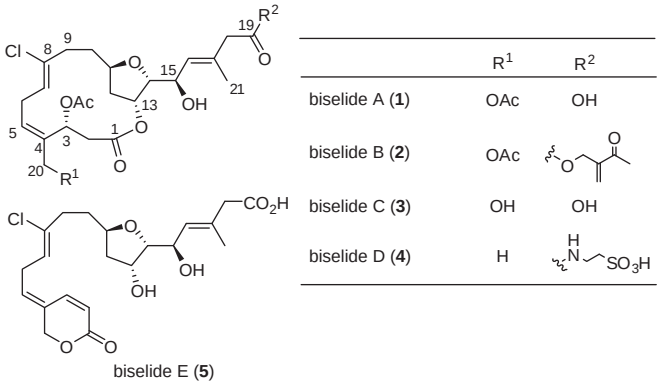

Figure 1. Structures of biselides.

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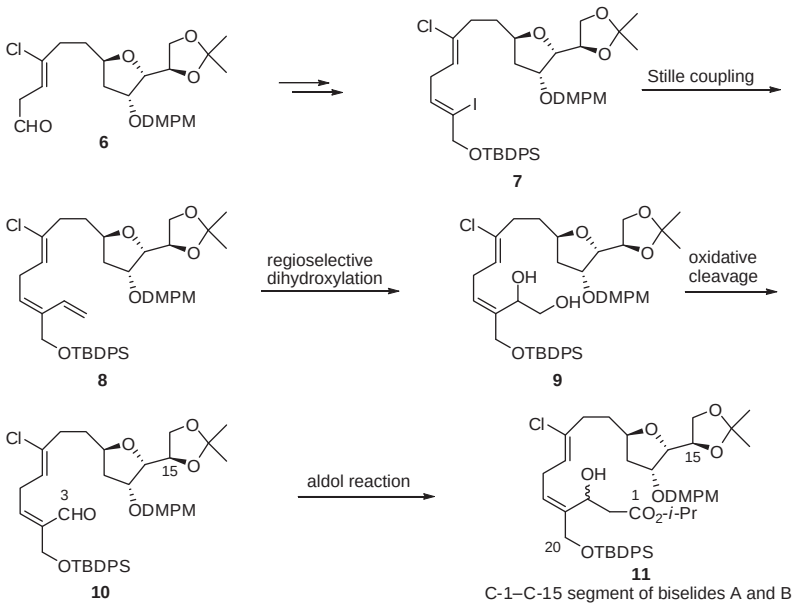
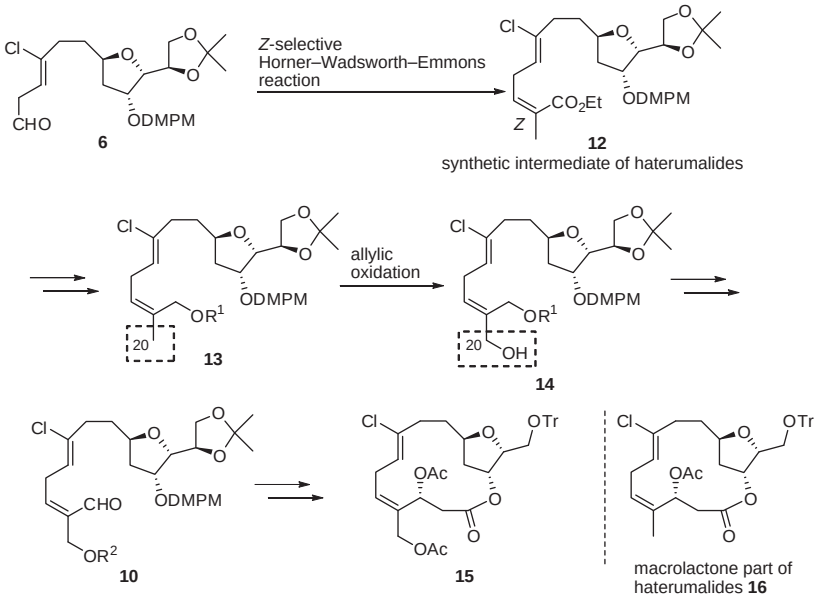


Scheme 1. Synthesis of the C-1–C-15 segment of biselides A (**1**) and B (**2**) using regioselective oxidative cleavage by our group.



Scheme 2. Synthetic plan of the macrolactone part of biselides A (**1**) and B (**2**).

entry 6). These results indicated that the acyl group at C-3 is an important factor in the yield and regioselectivity of this allylic oxidation, which was supported by the Hammett rule.

We applied this regioselective allylic oxidation for the synthesis of biselides A (**1**) and B (**2**) (Scheme 4). *p*-Nitrobenzoate **24**, a precursor of regioselective allylic oxidation, was synthesized from our previous synthetic intermediate **23** by acylation.[4b,c] We attempted the regioselective allylic oxidation of *p*-nitrobenzoate **24** with SeO_2 to afford the desired allylic alcohol **25** (35% yield) and the undesired aldehyde **26** (20% yield).

Protection of the allylic hydroxy group in **25** as a TBDPS ether, and removal of the *p*-nitrobenzoyl group afforded allylic alcohol **27** (Scheme 5). Dess–Martin oxidation of the primary alcohol of **27** gave aldehyde **10**, which was converted into β-hydroxy ester **11** as a 1:1 diastereomeric mixture of hydroxy group at C-3. Separation of the diastereomers was effected at the later stage. To convert **11** into macrolactone **15**, we followed our previous total synthesis of haterumalides. Thus, protection of the secondary hydroxy group of **11** as a TBS ether and subsequent removal of the acetonide group gave a diol compound. Oxidative cleavage of the diol group with $NaIO_4$ followed by reductive workup with $NaBH_4$ and protection of the resultant hydroxy group as a trityl group afforded compound **28**. Removal of the DMPM group of **28** and hydrolysis of the isopropyl ester gave seco acid **29**. The macrolactonization of seco acid **29** under the conditions described by Yamaguchi and co-workers[7] gave lactone **30**. Next, selective