Synthesis of the C1–C13 Fragment of Biselyngbyaside

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Abstract: An advanced intermediate vinyl iodide corresponding to the C1–C13 fragment of the macrolide biselyngbyaside was prepared by a cross-metathesis reaction between vinyl alcohol and alkene building blocks. The latter fragment, containing two stereocenters, was obtained by employing an asymmetric alkylation, a Wittig reaction, a hydrozirconation, and a Brown allylation as key steps.

Key words: natural products, Brown allylation, cross-metathesis, 1,5-diols, hydrozirconation

Biselyngbyaside (**1**) is a new macrolactone that was isolated from a marine cyanobacterium *Lyngbya* sp. collected in the Okinawa prefecture (Figure 1).[1] The compound was found in the polar methanol extract. The high polarity is likely due to the sugar part, which itself is somewhat unusual because it contains a 3-methoxy group. In preliminary assays, biselyngbyaside (**1**) displayed cytotoxicity against HeLa S3 cells with an IC_{50} of 0.1 μg mL^{-1}. Furthermore, in a panel of 39 cell lines, the average growth inhibition (GI) was 0.6 μM. Cells from the central nervous systems turned out to be particularly sensitive. This assay also led to the conclusion that biselyngbyaside most likely inhibits cell proliferation through a novel mechanism. Accordingly, the total synthesis of this natural product and the synthesis of analogues is very important. Other recently isolated 18-membered macrolides include FD-891[2,3] and the tulearins.[4]

From a structural point of view, the double bonds and the sensitive allylic alcohols (at C3, C7, and C17) make the synthesis very challenging. For example, elimination of the sugar would generate a dienoate subunit. In order to form the macrocycle a ring-closing metathesis approach seems possible. However, the many double bonds in the molecule could complicate the synthesis. Therefore, a classical macrolactonization, either through Yamaguchi or Mitsunobu cyclization, appears a viable option. The lactonization approach generates seco acid **2** as an advanced precursor, however, it was not certain whether the side chain would complicate the lactonization. Alternatively, the side chain could be introduced after macrolactone formation. Disconnection at the C13–C14 bond simplifies the seco acid, resulting in two fragments, vinyl stannane **3** and vinyl iodide **4**. In this paper, we detail the

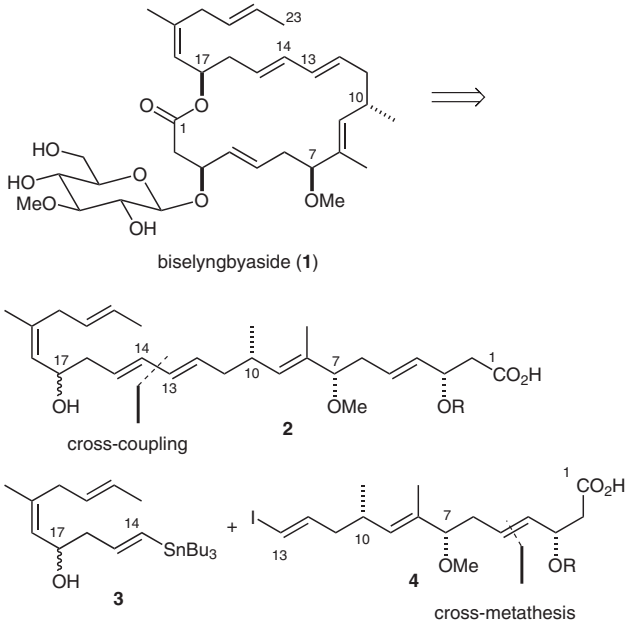

Figure 1 Structure and retrosynthetic analysis of the macrolide biselyngbyaside (**1**)

synthesis of the highly unsaturated fragment **24**, corresponding to acid **4**, using cross-metathesis as the key step.

Fragment **24** (the protected form of **4**) is characterized by three double bonds and three stereocenters. The 1,5-diol subunit with a double bond between is quite common in polyketide-type natural products. One general route to this functional group pattern relies on extension of homoallylic alcohols by cross-metathesis with acrolein followed by asymmetric allylation.[5] Another recent method developed by Friestad et al.[6] extends an α-silyloxy aldehyde in a Julia–Kocienski reaction. In this approach, the sulfone-containing fragment also contains a cyanohydrin function at the γ-position of the sulfone.[7]

With the vinyl iodide present, we realized that it should be possible to use a cross-metathesis reaction to form the C4/C5 double bond since vinyl iodides are essentially inert to cross-metathesis conditions. This has been exploited by Oishi, Murata, and co-workers in the context of the synthesis of the polyol fragment of amphidinol **3**.[8]

Thus, we first prepared the allylic alcohol **10** starting from the racemic 3-hydroxy-4-pentenoate[9] **5** (Scheme 1). A kinetic resolution of racemic **5** with Amano lipase PS in the presence of vinyl acetate in pentane (30 °C, 16 h) led to approximately 50% conversion (assessed by ^1H NMR analysis).[10] After chromatographic separation of the two

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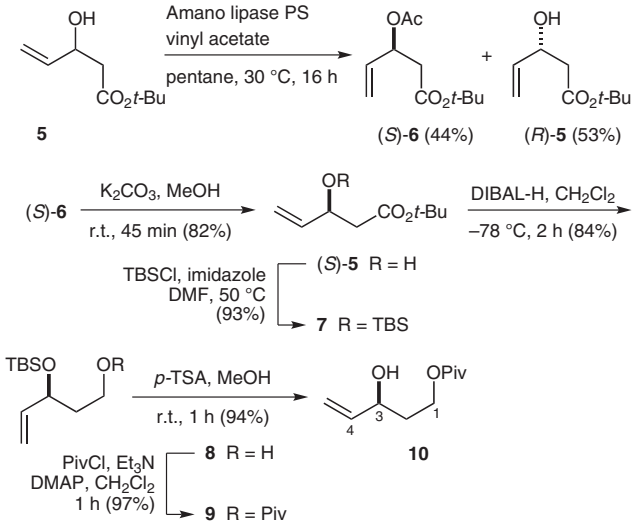
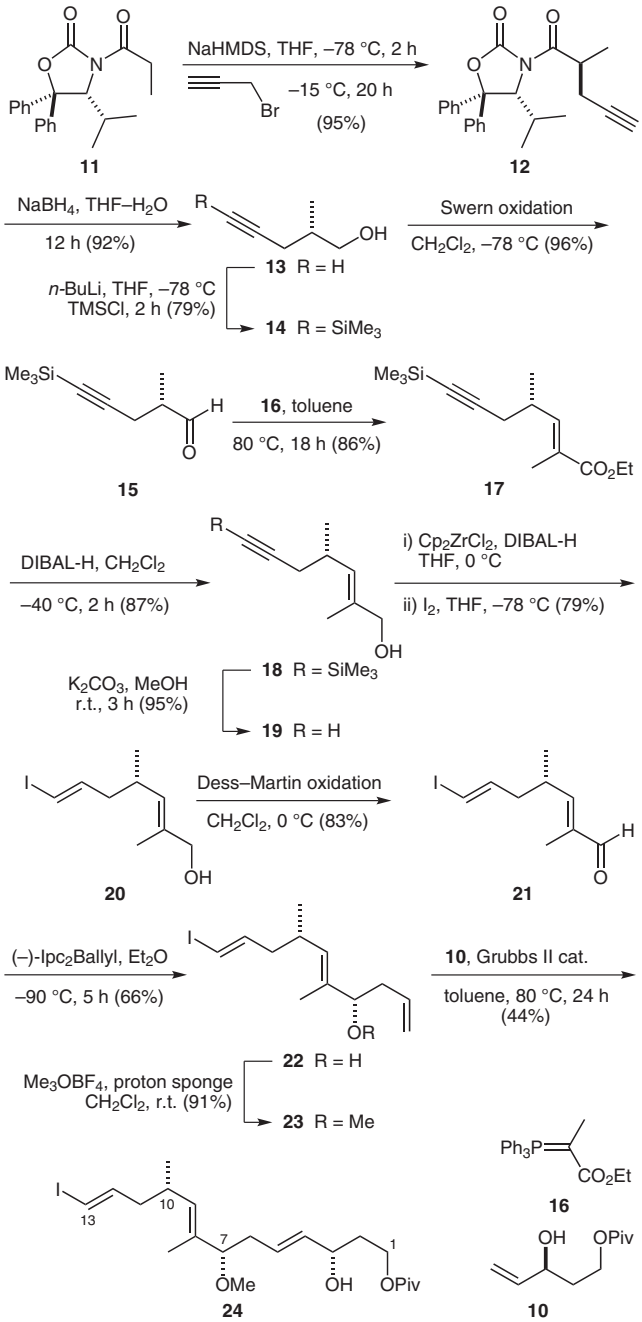
compounds, (*S*)-**6** and (*R*)-**5**, the acetate of (*S*)-**6** was cleaved by stirring in methanol containing K_2CO_3. The enantiomeric excess for the optically pure (*S*)-**5** according to chiral GC was 98.5%. After protection of the hydroxyl group as its silyl ether, the carboxylic function of **7** was reduced with diisobutylaluminum hydride (DIBAL-H) to furnish alcohol **8** in good overall yield. Prior to using this fragment in the cross-metathesis, the primary alcohol was converted into the corresponding pivaloate **9**. Finally, cleavage of the silyl ether by acid-catalyzed transetherification resulted in the release of the C1–C4-fragment **10**.



Scheme 1 Synthesis of the C1–C4 fragment **10** via kinetic resolution of hydroxy ester **5**

Besides the point of chirality at C3, the C1–C13 fragment **24** has two additional stereocenters at C7 and C10. It was planned to introduce one (C10) by asymmetric alkylation and the second (at C7) by Brown allylation. A further feature of the synthetic plan was to use a vinyl iodide at the C12/C13 terminus for later chain extension by cross-coupling reaction.

Accordingly, we started the synthesis with an asymmetric propargylation[11] of the chiral propionyl oxazolidinone **11**, derived from the Seebach auxiliary,[12] which yielded pentynoic acid derivative **12** in high yield and selectivity (Scheme 2). Reductive removal of the auxiliary using $NaBH_4$ in aqueous tetrahydrofuran (THF) furnished pentynol **13**.[13] Silylation of the acetylide function via the corresponding lithium acetylide was followed by Swern oxidation of alcohol[14] **14** to generate aldehyde **15**. One reason for the silylation was to reduce the volatility of the low molecular weight compounds of the synthetic sequence. With aldehyde **15** in hand, chain extension by a Wittig reaction with the stabilized ylide[15] **16** was performed to provide enoate **17** in 86% yield after chromatography. In the next step, the trimethylsilyl group was removed from the alkyne prior to the hydrozirconation, which was performed with Cp_2ZrCl_2 (1.125 equiv) and DIBAL-H (1.125 equiv). The hydrozirconation was performed on the diisobutylalkoxy derivative of **19**, which was generated by combining **19** and DIBAL-H (1.0 equiv).[16,17] The intermediate vinylmetal species was finally quenched with iodine (1.925 equiv), resulting in the formation of vinyl iodide **20** (79% yield). At this point, the alcohol was oxidized to aldehyde **21**, which then was subjected to a Brown allylation reaction.[18] In this way, allyl alcohol **22** was obtained in 66% yield as mixture of diastereoisomers in a ratio of approximately 18:1 as determined by ^1H NMR analysis (integration of 7-CH_3). This result indicates that very little racemization occurred on aldehyde **15** during the Wittig extension to **17**. Continuing with the synthesis, alcohol **22** was converted into the corresponding methyl ether **23** using Meerwein's salt



Scheme 2 Synthesis of the C1–C13 fragment **24** via alkylation, allylation, and cross-metathesis as key steps

(Me_3OBF_4)[19] in the presence of proton sponge.[20,21] The stage was then set for the crucial cross-metathesis reaction.[22] Initially, we attempted the metathesis reaction between homoallylic ether **23** and the silylated vinyl alcohol **9**. However, neither the Hoveyda–Grubbs second-generation, nor the Grubbs second-generation catalyst, nor the Grela catalyst led to formation of the desired product. In contrast, the metathesis reaction with the vinyl alcohol **10** was successfully achieved.[23] Among the various catalysts, the Grubbs second-generation catalyst gave the best results, furnishing the advanced biselyngbyaside fragment **24** in 44% yield.

In summary, a practical pathway to the C1–C13 section of the novel macrolide biselyngbyaside has been outlined. Key features of the strategy include a kinetic resolution to furnish allylic alcohol **10** (C1–C4 fragment). The overall yield for allylic alcohol **10** from the racemic aldol product **5** was 26% (six steps). A second fragment was synthesized by asymmetric propargylation, a Wittig reaction, and a Brown allylation reaction. The triple bond of enynol **19** was converted into the vinyl iodide function, which subsequently allowed for a chemoselective cross-metathesis reaction between the homoallylic ether **23** and the vinyl alcohol **10**. In all, the C1–C13 fragment **24** was prepared in a longest linear sequence of 12 steps, with an overall yield of 8.2%.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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