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Total Synthesis of Biselyngbyolide A

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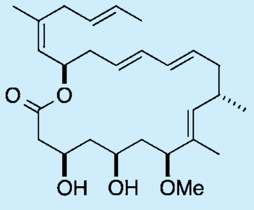
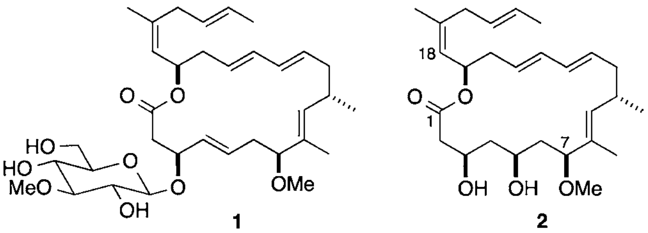
Supporting Information

ABSTRACT: Biselyngbyolide A is an 18-membered macrolide that exhibits significant biological activities such as growth-inhibitory activity and apoptosis inducing activity against cancer cells. In this study, the first total synthesis of biselyngbyolide A by using an intramolecular Stille coupling reaction as a key step is achieved.



Biselyngbyolide A

In 2009, we elucidated the structure of biselyngbyaside (**1**) isolated from the marine cyanobacterium *Lyngbya* sp. collected at Okinawa (Figure 1).[1] Biselyngbyaside (**1**) exhibited growth-inhibitory activity against cancer cells with IC_{50} values of 2.5 μM (HeLa S_3) and 0.31 μM (HL60). In addition, **1** was shown to inhibit osteoclastogenesis and induce the apoptosis of osteoclast, and thus may be useful for the prevention of bone lytic diseases.[2] We recently found five biselyngbyaside congeners including biselyngbyolide A.[3−5] Biselyngbyasides also induced apoptosis of cancer cells and increased the cytosolic Ca^{2+} concentration in HeLa S_3 cells.[4] Biselyngbyolide A, an aglycone of biselyngbyaside B, showed much more potent activity against cancer cells with IC_{50} values of 0.039 μM (HeLa S_3) and 0.012 μM (HL60) than biselyngbyaside.



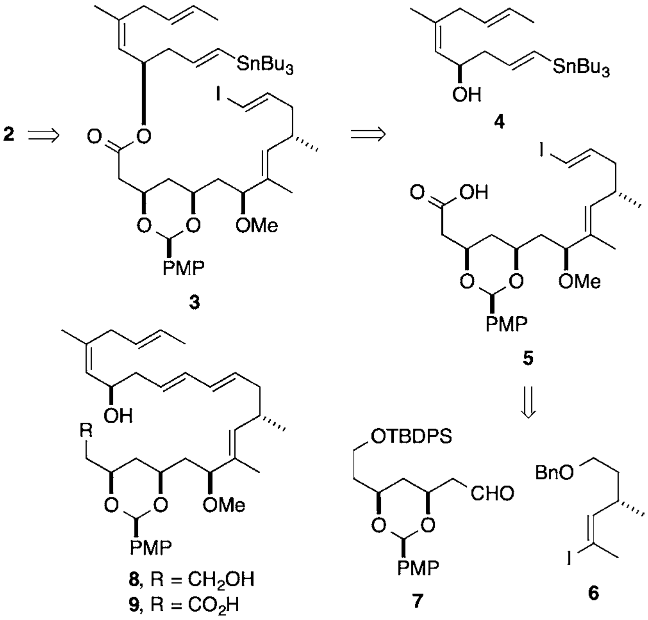
1 **2**

Figure 1. Structures of biselyngbyaside and biselyngbyolide A.

These biological activities and its novel 18-membered macrolide structure prompted us to synthesize biselyngbyolide A (**2**). Synthetic studies of biselyngbyaside have been reported by Maier[6] and Chandrasekhar.[7] We describe here the first total synthesis of biselyngbyolide A (**2**).

Scheme 1 outlines our strategy for synthesizing biselyngbyolide A (**2**). We planned to construct its 18-membered cyclic structure by an intramolecular Stille coupling reaction[8] of ester **3**, which could be synthesized by condensation between alcohol **4** and carboxylic acid **5**. Carboxylic acid **5** might be obtained from the Nozaki−Hiyama−Kishi (NHK) reaction[9] between vinyl iodide **6** and aldehyde **7**. Initially, we planned to construct the macrolide ring by macrolactonization of hydroxyl carboxylic acid **9**. However, we could not obtain **9** from alcohol **8** in good yield, because the conjugated diene moiety in **8** was unstable under the oxidation reaction conditions. Therefore, we decided to construct the conjugated diene in the last stage of the synthesis.

Scheme 1. Retrosynthetic Analysis of Biselyngbyolide A



The synthesis of alcohol **4** began with the ring-opening reaction of trityl glycidyl ether (**10**) with lithium acetylide. Protection of the resultant hydroxyl group with TBDPS (Scheme 2, 99% in two steps) followed by removal of the trityl protecting group led to alcohol **11** (85%). Oxidation of alcohol **11** with Dess-Martin periodinane gave aldehyde (96%),

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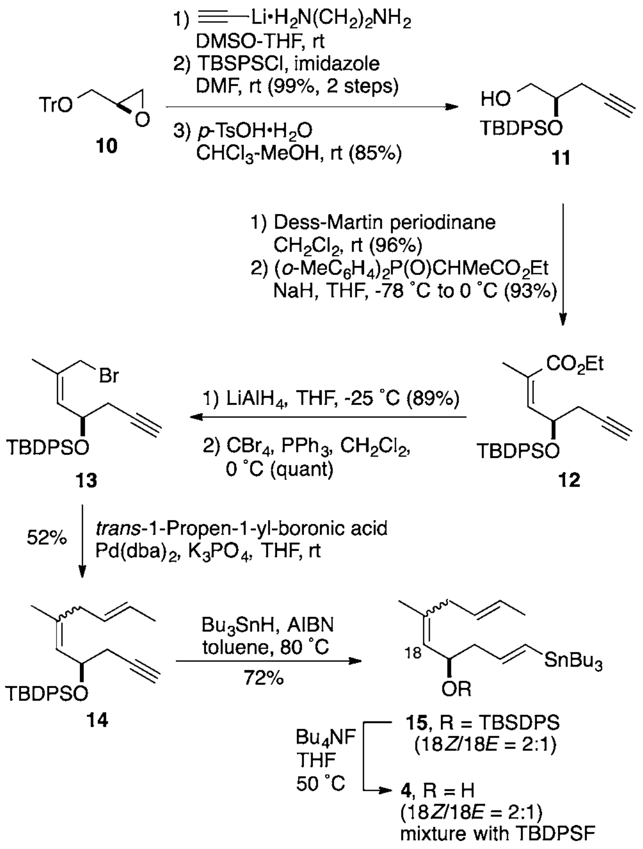
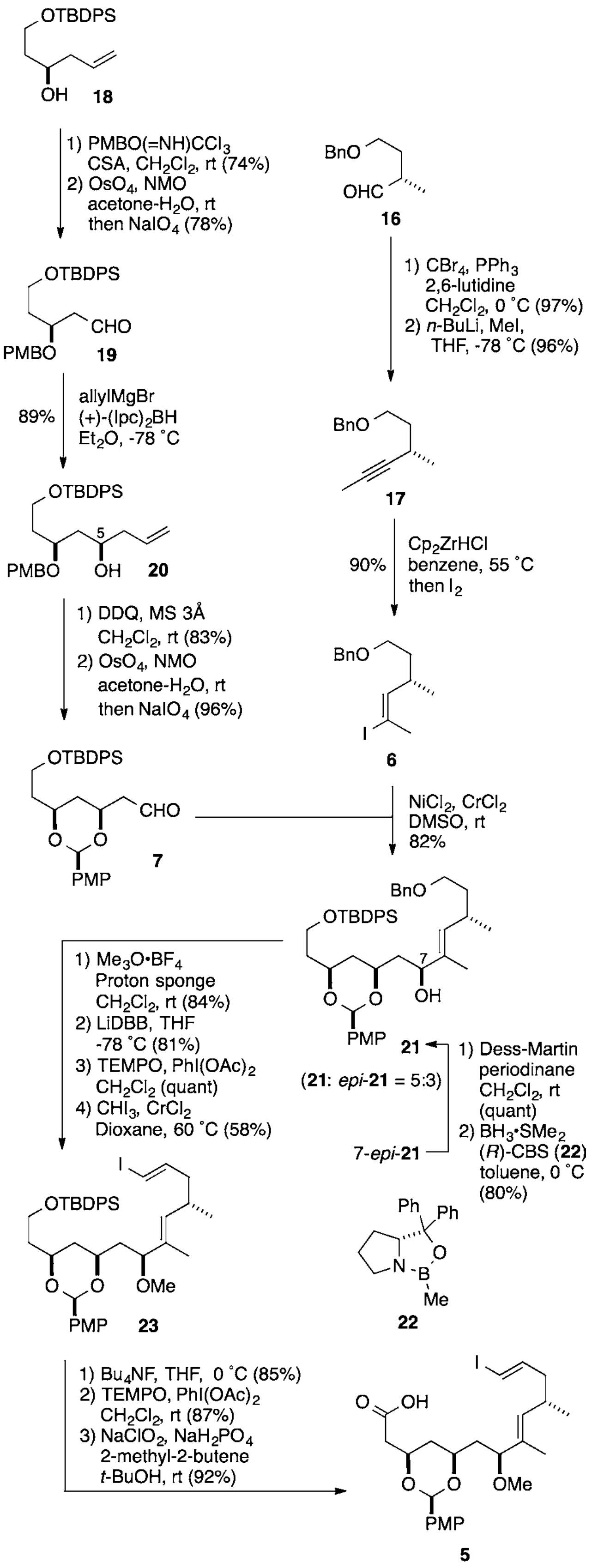
Scheme 2. Synthesis of Alcohol 4



the Horner–Wadsworth–Emmons reaction of which with Ando's reagent[10] afforded conjugated ester **12** (93%). Reduction of **12** provided the corresponding allylic alcohol (89%), which was converted into allylic bromide **13** (quant). The Suzuki–Miyaura coupling reaction[11] of **13** with *trans*-1-propen-1-yl-boronic acid gave diene **14** (52%) as an inseparable ca. 2:1 mixture of 18*Z* and 18*E* isomers.[12] We tried various conditions for Suzuki–Miyaura coupling, boronate esters, a variety of bases, and Pd catalysts such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, and $Pd(dppf)Cl_2$, but the yield and *Z*/*E* selectivity were not improved. The 18*E* isomer could be separated at a later stage in the synthesis, i.e., after macrocyclization of ester **3**. Diene **14** was transformed into vinylstannane **15** with tributylstannane and AIBN (72%). Removal of the TBDPS group in **15** gave alcohol **4** as a mixture with TBDPS fluoride.

Two small segments, vinyl iodide **6** and aldehyde **7**, were prepared as follows (Scheme 3). Vinyl iodide **6** was prepared from known aldehyde **16**.[13] Aldehyde **16** was converted into the corresponding dibromoolefin (97%), which was treated with a base followed by methylation providing alkyne **17** (96%). Hydrozirconation of **17** followed by iodination gave vinyl iodide **6** (90%). Aldehyde **7** was synthesized from known alcohol **18**,[14] with subsequent protection of the hydroxyl group (74%) followed by oxidative cleavage of the olefin providing aldehyde **19** (78%). Stereoselective allylation with (+)-isopinocampheylborane[15] delivered alcohol **20** (89%). The stereochemistry of the C5 hydroxyl group was determined on the basis of NOE experiments for the derived cyclic PMP acetal (see the Supporting Information). Treatment of **20** with DDQ (83%) followed by oxidative cleavage of the olefin afforded aldehyde **7** (96%).

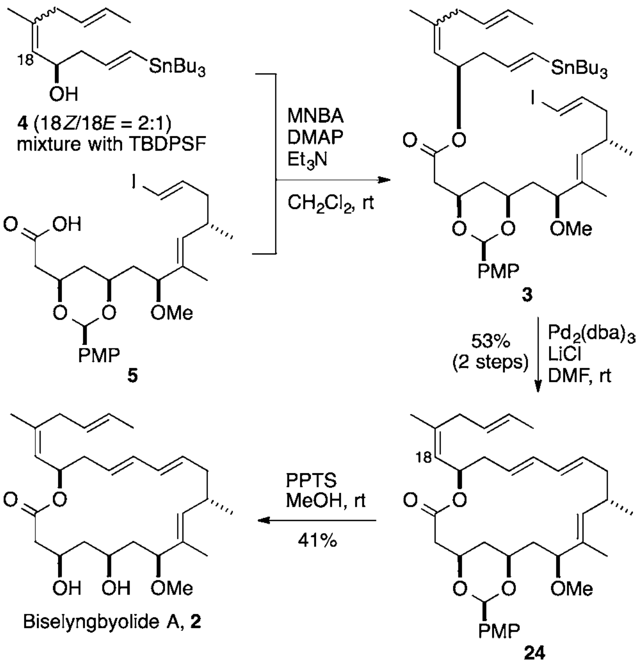
Scheme 3. Synthesis of Carboxylic Acid 5



The NHK coupling reaction between vinyl iodide **6** and aldehyde **7** provided diastereomeric alcohols **21** and *epi*-**21** (82%), which could be separated by chromatography. The stereochemistry of each was determined by a modified Mosher method[16] (see the Supporting Information). Undesired *epi*-**21** was transformed into alcohol **21** by oxidation (quant) followed by stereoselective reduction with Corey−Bakshi−Shibata (CBS) reagent (*R*)-**22** (80%);[17] desired alcohol **21** was obtained from aldehyde **7** in 76% yield, including the conversion of *epi*-**21** into **21**. The secondary hydroxyl group of **21** was methylated (84%), and the benzyl group was selectively removed in the presence of the PMP acetal with lithium di-*tert*-butylbiphenylide (LiDBB) (81%).[18] Oxidation of the resulting primary alcohol (quant) followed by the Takai olefination reaction[19] gave vinyl iodide **23** (58%). Removal of the TBDPS group in **23** (85%) followed by catalytic TEMPO oxidation afforded the corresponding aldehyde (87%), which was further oxidized with sodium chlorite to carboxylic acid **5** (92%).

The stage was set for the task of connecting alcohol **4** and carboxylic acid **5** (Scheme 4). Esterification between **4** and **5** with 2-methyl-6-nitrobenzoic anhydride (MNBA)/DMAP under the Shiina conditions[20] afforded ester **3** which was cyclized by the intramolecular Stille coupling reaction under high dilution conditions (3.6 mM in DMF) to give protected biselyngbyolide A **24** as a single 18*Z* isomer (53% in two steps).[21] The PMP acetal of **24** was removed under acidic conditions to provide biselyngbyolide A (**2**) (41%).[22] Synthetic biselyngbyolide A (**2**) was found to correspond uniquely to natural **2** based on a comparison of their spectroscopic and chromatographic properties and cytotoxicity [IC_{50} values of synthetic **2**: 0.050 μM (HeLa S_3) and 0.019 μM (HL60)].

Scheme 4. Synthesis of Biselyngbyolide A



In conclusion, we have achieved the first total synthesis of biselyngbyolide A (**2**) (2.1% overall yield in 16 steps from **16** based on the longest linear sequence), which confirmed the absolute stereostructure and biological activity of **2**. Synthetic studies on other biselyngbyasides are currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) We could not get any products derived from the 18*E* isomer of **3**. They might decompose during esterification and macrocyclization.

(22) Under the conditions for deprotection of the PMP acetal with DDQ, the substrate was oxidatively decomposed.