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Total Synthesis of Biselyngbyolide B

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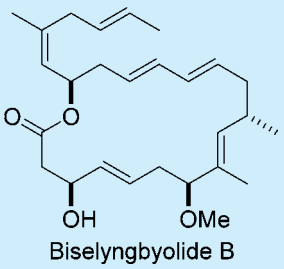
Supporting Information

ABSTRACT: The first total synthesis of biselyngbyolide B, an 18-membered macrolide, was achieved. The 18-membered ring structure was constructed by esterification using the Shiina reagent and an intramolecular Stille coupling reaction.



Biselyngbyaside (**1**, Figure 1), an 18-membered macrolide glycoside, was isolated from the marine cyanobacterium

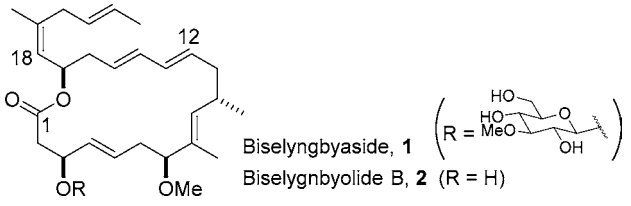


Figure 1. Structure of biselyngbyaside and biselyngbyolide B.

Lyngbya collected at Okinawa. Biselyngbyaside exhibited growth-inhibitory activity against HeLa (0.30 μM) and HL60 (0.31 μM) cells.[1] In a recent study, we clarified that **1** strongly inhibited the ATPase activities of SERCA1a and 2a, and determined the X-ray crystal structure of **1** with SERCA1a.[2] Specifically, the 1,3-diene moiety and the side chain play important roles in the high affinities and unique binding mode, which is supported by the IC50 values of biselyngbyasides C (>10 μM, HeLa) and F (3.1 μM, HeLa).[3]

Synthetic studies of biselyngbyasides have been reported by Maier[4] and Chandrasekhar,[5] and we achieved the total synthesis of biselyngbyolide A (the analog without sugar) in 2014.[6] Herein, we report the first total synthesis of biselyngbyolide B, the aglycone of biselyngbyaside, via a modification of the previous synthetic route.

Our synthetic strategy toward biselyngbyolide B is illustrated in Scheme 1. The 18-membered ring was constructed in the final step using an intramolecular Stille coupling reaction.[7] The precursor was obtained from stannane **3** and vinyl iodide **4** via esterification. The vinyl iodide **4** was synthesized from aldehyde **5**, oxazolidinone **6**,[8] and phosphonate **7**.

The synthesis of stannane **3** began with the Horner–Wadsworth–Emmons reaction for aldehyde **8**[6] (Table 1). In the reaction using normal phosphonate[9] (Table 1, entries 1 and 2), we could not obtain the desired compound and the conversions seemed to be very slow. To achieve good selectivity and a good conversion rate, we used Ando's type phosphonate[10] (Table 1, entry 3). Although the reaction proceeded smoothly, the product was obtained as an undesired 18*Z* compound. As a result, only the reaction using the

Scheme 1. Retrosynthetic Analysis of Biselyngbyolide B

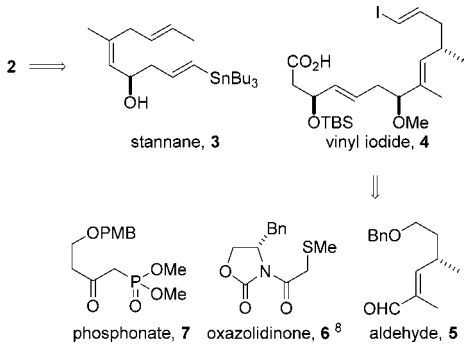
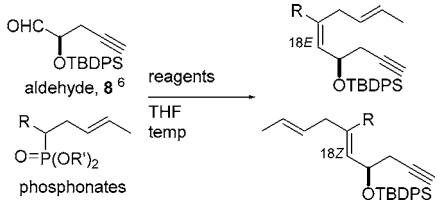


Table 1. Horner–Wadsworth–Emmons Reaction



entry	R	R′	reagents	yield (%) (selectivity)
1	CO_2Et	Et	NaH	27 (only 18Z)
2	CO_2Et	Et	DBU, LiCl	13 (only 18Z)
3	CO_2Et	Ph	NaH	69 (only 18Z)
4	CN	*i*Pr	NaH	87 (18*E*/18*Z* = 4:1)

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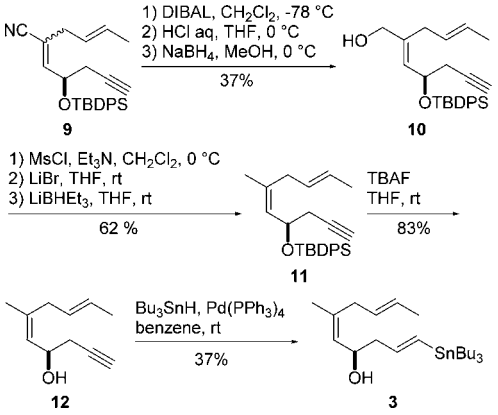
phosphonate with a nitrile group (Table 1, entry 4) gave a good yield and selectivity. The selectivity may be caused by the high reactivity of the phosphonate (kinetic control). While the isomers were not separable at this stage, they were separated in the next step.

The mixture of nitrile **9** was reduced using DIBAL (Scheme 2) and sodium borohydride, and the isomers were then

Scheme 2. Synthesis of Stannane 3



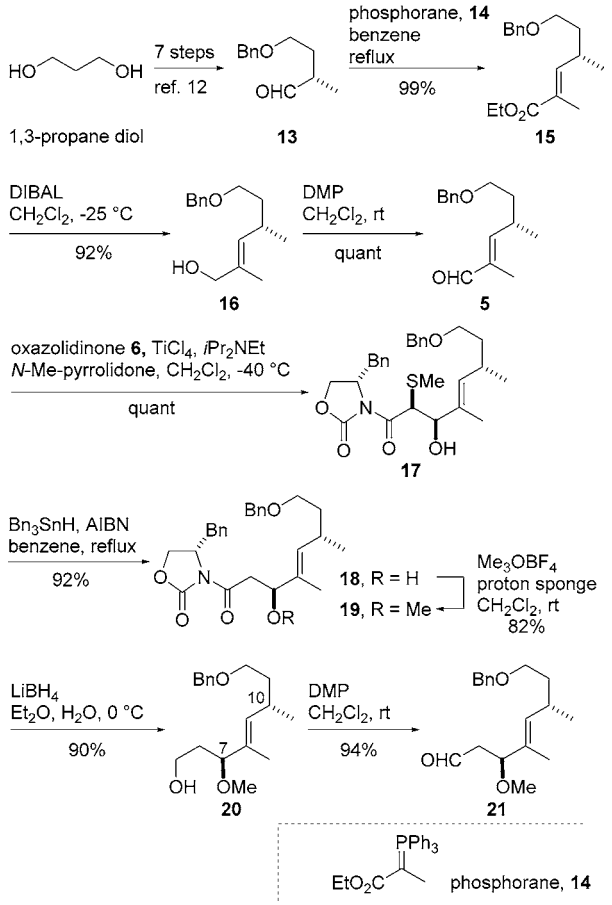
separated by silica gel chromatography to give alcohol **10** (37%) and its isomer (25%). Partial isomerization might occur.[11] The geometry of the trisubstituted double bond was determined by an NOE experiment for alcohol **10** (see the Supporting Information).

Deoxygenation of the alcohol gave good results in the reaction of the corresponding bromide with lithium triethylborohydride (62% in three steps). Finally, the TBDPS group was removed (83%) and the alkyne was converted to stannane **3** using $Pd(PPh_3)_4$ (37%). In the previous study, the stannane was obtained as an inseparable mixture of 18*Z* and *E*. Otherwise, we could investigate the new synthesis of the pure stannane using the Horner−Wadsworth−Emmons reaction and reduction followed by separation of the isomers.

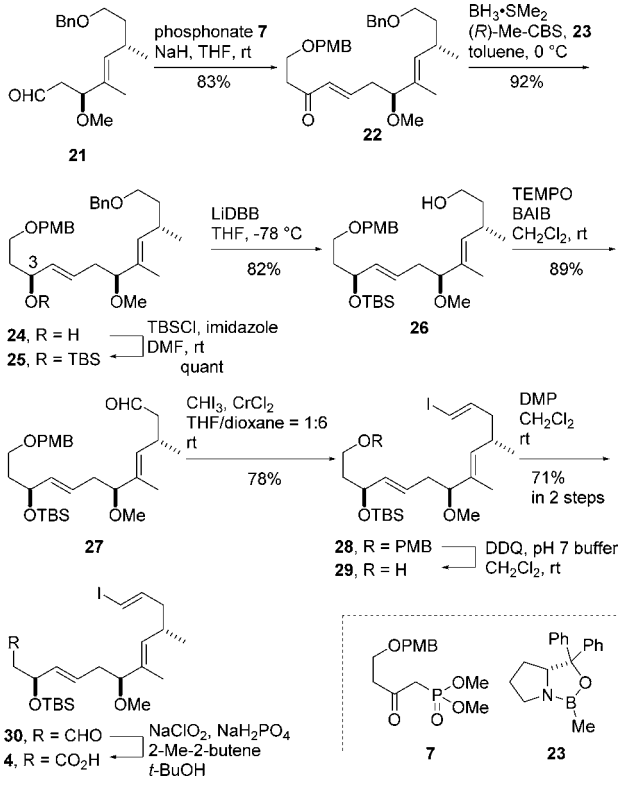
The vinyl iodide **4** was synthesized as follows (Schemes 3 and 4): Enantiopure aldehyde **13**, prepared from 1,3-propane diol in seven steps,[12] was treated with phosphorane **14** to give ester **15** (99%) (Scheme 3). The ester was reduced by DIBAL (92%), and the obtained alcohol **16** was oxidized by Dess-Martin periodinane to give aldehyde **5** (quant). The aldol reaction between aldehyde **5** and oxazolidione **6** provided the desired diastereomer of alcohol **17** (quant). The thiomethyl group was removed by Bu_3SnH and AIBN (92%), and the alcohol **18** was converted to methyl ether using Meerwein reagent (82%). Removal of the chiral auxiliary using $LiBH_4$ gave alcohol **20** (90%). At this stage, the relative configuration between C-7 and C-10 was determined by comparison of the ^1H NMR spectra with reported data[1] (see the Supporting Information). The primary alcohol was oxidized by TEMPO and BAIB to give aldehyde **21** (94%).

The coupling reaction between aldehyde **21** and phosphonate **7**, which was synthesized from 1,3-propane diol in four steps (see the Supporting Information), gave the enone **22** (83%) (Scheme 4). Stereoselective reduction with Corey−Bakshi−Shibata reagent, **23**,[13] delivered alcohol **24** (92%). The stereochemistry of the C-3 hydroxyl group was determined by a modified Mosher method[14] (see the Supporting Information). The hydroxyl group was protected by a TBS group (quant),

Scheme 3. Synthesis of Aldehyde 21



Scheme 4. Synthesis of Carboxylic Acid 4



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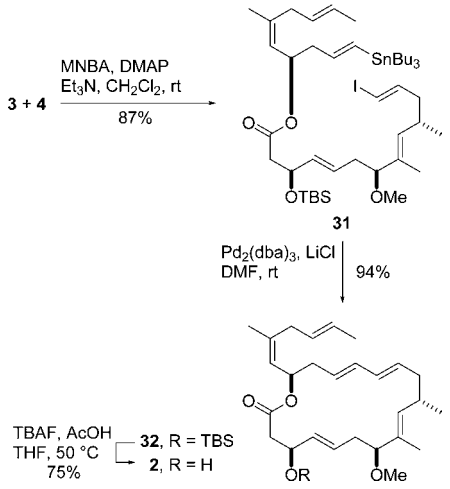
and the benzyl group was selectively removed in the presence of the PMB group with lithium di-*tert*-butylbiphenylide (LiDBB)[15] (82%). Oxidation (89%) of the resulting alcohol **26** followed by the Takai reaction[16] gave vinyl iodide **28** (78%). In the Takai reaction using THF as a solvent, the product was obtained as an inseparable mixture of *E*/*Z* (ca. 4:1) isomers. On the other hand, the use of dioxane gave a low yield, albeit with good selectivity. After an examination of the solvents, the mixed solvent gave vinyl iodide **28** in good yield and selectivity. The PMB group was cleaved by DDQ, and the resulting primary alcohol **29** was oxidized by Dess-Martin periodinane (71% in two steps). Finally, Pinnick oxidation of aldehyde **30** gave carboxylic acid **4**.

With the two segments in hand, we tried to construct the 18-membered ring of biselyngbyolide B. First, we used the Stille coupling reaction between stannane **11** and vinyl iodide **28**. The coupling reaction gave the desired diene, but the diene moiety was too sensitive to deprotection of the PMB and TBDPS groups and gave the corresponding seco acid compound. Thus, we decided to construct the diene moiety in the final stage.

The esterification reaction between alcohol **3** and carboxylic acid **4** using the Shiina reagent gave ester **31** (87%)(Scheme 5),

Scheme 5. Total Synthesis of Biselyngbyolide B



which was cyclized by an intramolecular Stille coupling reaction under high dilution conditions (1.7 mM in DMF)[7] to give protected biselyngbyolide B **32** (94%). The TBS group was removed by tetrabutylammonium fluoride with acetic acid to provide biselyngbyolide B (**1**) (75%). The spectroscopic data (^{1}H and ^{13}C NMR, HRMS, and optical rotation) for the synthetic biselyngbyolide B were fully consistent with those of the natural product.

In summary, we have achieved the first synthesis of biselyngbyolide B, the aglycone of biselyngbyaside (27 linear steps from commercially available 1,3-propane diol and 11% overall yield in 20 steps from aldehyde **13** based on the longest linear sequence).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00660.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Teruya, T.; Sasaki, H.; Kitamura, K.; Nakayama, T.; Suenaga, K. *Org. Lett.* **2009**, *11*, 2421−2424.
(2) Morita, M.; Ogawa, H.; Ohno, O.; Yamori, T.; Suenaga, K.; Toyoshima, C. *FEBS Lett.* **2015**, *589*, 1406−1411.
(3) (a) Morita, M.; Ohno, O.; Suenaga, K. *Chem. Lett.* **2012**, *41*, 165−167. (b) Morita, M.; Ohno, O.; Teruya, T.; Yamori, T.; Inuzuka, T.; Suenaga, K. *Tetrahedron* **2012**, *68*, 5984−5990. (c) Ohno, O.; Watanabe, A.; Morita, M.; Suenaga, K. *Chem. Lett.* **2014**, *43*, 287−289. (d) Watanabe, A.; Ohno, O.; Morita, M.; Inuzuka, T.; Suenaga, K. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1256−1264.
(4) Sawant, P.; Maier, M. E. *Synlett* **2011**, *2011*, 3002−3004.
(5) Chandrasekhar, S.; Rajesh, G.; Naresh, T. *Tetrahedron Lett.* **2013**, *54*, 252−255.
(6) Tanabe, Y.; Sato, E.; Nakajima, N.; Ohkubo, A.; Ohno, O.; Suenaga, K. *Org. Lett.* **2014**, *16*, 2858−2861.
(7) (a) Brodmann, T.; Janssen, D.; Kalesse, M. *J. Am. Chem. Soc.* **2010**, *132*, 13610−13611. For reviews, see: (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (d) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261−268.
(8) Liang, Q.; Zhang, J.; Quan, W.; Sun, Y.; She, X.; Pan, X. *J. Org. Chem.* **2007**, *72*, 2694−2697.
(9) Janecki, T.; Blaszczyk, E. *Tetrahedron Lett.* **2001**, *42*, 2919−2922.
(10) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105−4108. (b) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411−8416. (c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406−8408.
(11) The trisubstituted alkene was partially isomerized during DIBAL reduction followed by acid treatment.
(12) The synthesis of aldehyde **13** was shown in the Supporting Information; also see: (a) Coppi, A.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911−913. (b) Heapy, A. M.; Wagner, T. W.; Brimble, M. M. *Synlett* **2007**, *2007*, 2359−2362. (c) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600−13601. (d) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227−2230.
(13) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.
(14) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.
(15) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930. (b) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899−10905. (c) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941−3944.
(16) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

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