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Stereoselective Total Synthesis of Bioactive Marine Natural Product Biselyngbyolide B

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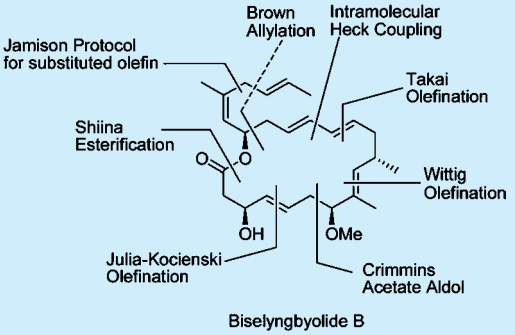
Supporting Information

ABSTRACT: A convergent strategy for the stereoselective total synthesis of biologically active marine natural product biselyngbyolide B has been developed. Key strategies of this synthesis include Jamison protocol of *trans*-hydroalumination/allylation for installation of $C_{18}-C_{23}$ olefin moiety and intramolecular Heck coupling for macrocyclization.



Suenaga and co-workers were the first to discover the bioactive secondary metabolite biselyngbyaside **1** and its congeners biselyngbyolide B **2**, biselyngbyaside B **3**, biselyngbyolide A **4**, biselyngbyaside C **5**, and biselyngbyaside D **6** (Figure 1) during their bioassay-guided fractionation of

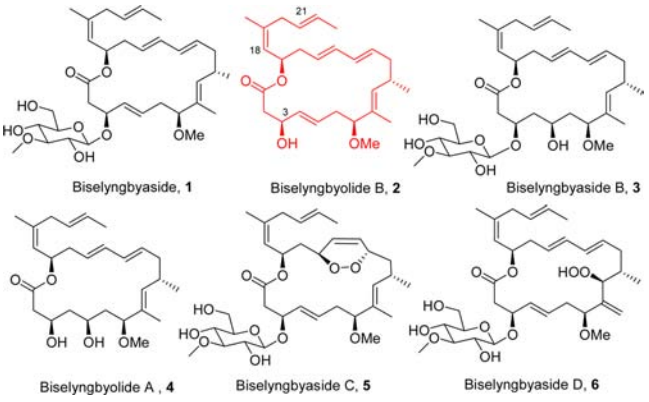
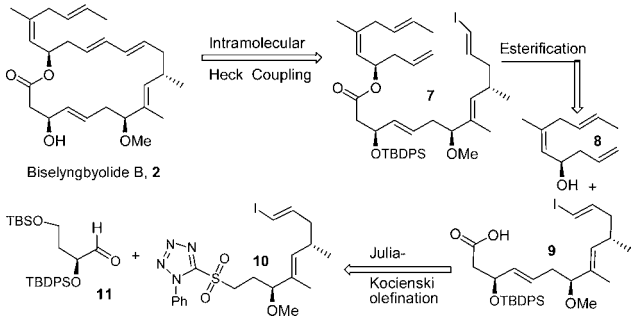


Figure 1. Structure of biselyngbyaside **1** and its congeners **2**–**6**.

methanol extract of marine cyanobacterium *Lyngbya* sp.[1] Biselyngbyaside **1** exhibits inhibitory activity against the growth of human cervical cancer (HeLa) and leukemia (HL60) cells with IC_{50} values of 2.5 and 0.31 μM, respectively.[1c] It also shows a broad-spectrum of cytotoxicity against a series of different human tumor cell lines in submicromolar concentration. Moreover, biselyngbyaside **1** instigates the apoptosis of osteoclasts.[2] Biselyngbyolide B **2**, the aglycon part of biselyngbyaside **1**, shows 30- to 100-fold apoptosis-induction compared to biselyngbyaside **1**. In addition, biselyngbyolide B **2** acts as endoplasmic reticulum stress inducer.[1d] Architecturally it is an 18-membered macrolide embedded with four stereogenic centers. The presence of several double bonds like allylic, skipped, and conjugated olefins made this molecule synthetically challenging. Maier et al.[3] and Chandrasekhar et al.[4] reported the synthesis of the C_1-C_{13} and C_5-C_{23} segments of biselyngbyaside **1**, respectively. Suenaga et al.[5] developed an elegant way to achieve the total synthesis of biselyngbyolide A **4** through an intramolecular Stille coupling based ring closing strategy. The promising bioactivities of biselyngbyolide B **2**, its natural scarcity, its structural uniqueness, and our continued interest[6] in the synthesis of bioactive natural products prompted us to embark on total synthesis of biselyngbyolide B **2**; one of the most active members of biselyngbyaside class of natural products. In this letter, we disclose a highly convergent and flexible stereoselective en route total synthesis of structurally intriguing biselyngbyolide B **2** for the first time.

Retrosynthetic analysis of biselyngbyolide B **2** is summarized in Scheme 1. The targeted molecule **2** could be constructed from

Scheme 1. Retrosynthetic Analysis of Biselynbyolide B 2



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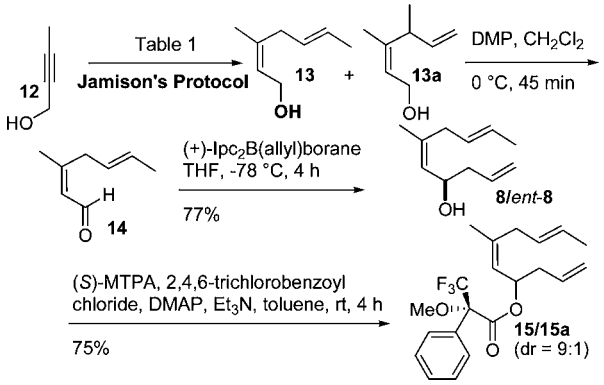
compound **7** by intramolecular macrocyclization using a Heck coupling as one of the key steps.[7] The Heck precursor **7** could be accessed from alcohol **8** and acid **9** by intermolecular esterification. The acid fragment **9** could be assembled from coupling partners **10** and **11** using a Julia–Kocienski olefination[8] as the key step.

The synthesis of intermediate **8** is depicted in Scheme 2. We searched for a protocol that would yield the (C_{18}–C_{23}) olefin

Scheme 2. Synthesis of Intermediate 8



moiety in one pot from readily available starting material. The strategy developed by Jamison et al. where they have shown the synthesis of substituted olefins directly from alkynols by Red-Al assisted *trans*-hydroalumination/allylation sequence in the presence of MeLi and Cu(I) source seemed most judicious.[9] Accordingly we performed the reaction between 2-butyn-1-ol **12** and crotyl bromide **12a** (Table 1, entry 1). The required olefin **13**

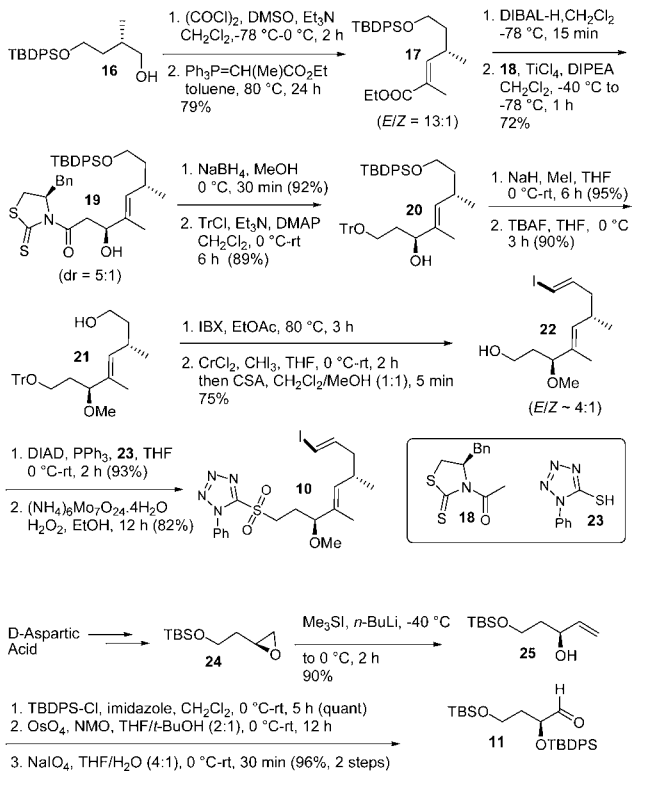
Table 1. Optimization of Reaction between 2-Butyn-1-ol 12 and Crotyl Bromide 12a

entry	conditions	total yield (%)	ratio (**13**/**13a**)
1	Red-Al, 0 °C–rt, 6 h, MeLi, 0 °C, 1.5 h, **12a**, CuCl, THF, 0 °C–rt, 2 h	76	1.3:1
2	Red-Al, 0 °C–rt, 6 h, MeLi, 0 °C, 1.5 h, **12a**, 0 °C–rt, 2 h	60	1:1
3	Red-Al, 0 °C–rt, 6 h, **12a**, CuCl, THF, 0 °C–rt, 2 h	62	1.4:1
4	Red-Al, 0 °C–rt, 6 h, **12a**, 0 °C, 2 h	71	2.3:1
5	Red-Al, 0 °C–rt, 6 h, **12a**, −20 °C, 5 h	60	2.3:1

was obtained along with an inseparable mixture of isomerized compound **13a** in substantial amount (**13**/**13a** = 1.3:1), which stipulates comparable participation of crotyl bromide in both S_N2 and S_N2' type reactions. We have tried different reaction conditions (Table 1) to reduce the formation of unwanted S_N2' product **13a**. Neither the presence of MeLi nor CuCl improved the ratios of olefins **13** and **13a** (Table 1, entries 2 and 3). Activation of either the Alanate species or crotyl bromide or the both, substantially facilitated the S_N2' pathway. We decided to attempt the reaction without any additives. The vinyl alane was generated first from 2-butyn-1-ol **12** by treatment with Red-Al and subsequently quenched with crotyl bromide **12a** at 0 °C (Table 1, entry 4). We were delighted to see that olefin **13** formed along with the isomerized compound **13a** with much improved ratio (**13**/**13a** = 2.3:1) and with an overall yield comparable to Jamison's condition[9] (Table 1, entry 1). We performed this reaction, specially the quenching of vinyl alane species, at a low temperature (−20 °C). However, the formation of unwanted S_N2' product **13a** could not be further reduced (Table 1, entry 5). The required olefin **13** mixed with its inseparable counterpart **13a** was oxidized by Dess–Martin periodinane (DMP) and subsequently the crude reaction mixture was separated by silica gel chromatography to obtain aldehyde **14** in pure form. The aldehyde **14** was then subjected to Brown allylation reaction[10] using (+)-Ipc_2B(allyl)borane to produce **8** in enantiomerically enriched form (*ee* = 80%). The ratio of enantiomers (**8**/*ent*-**8**) was determined unambiguously from the ^1H NMR analysis of the corresponding inseparable mixture of (*S*)-Mosher ester derivatives **15** and **15a** (dr = 9:1). Compound *ent*-**8** was separated at the next stage of synthesis.

The synthesis of the requisite coupling partners **10** and **11** for Julia–Kocienski olefination[8] is described in Scheme 3. We

Scheme 3. Synthesis of Sulfone 10 and Aldehyde 11



started our synthesis from known compound **16**,[11] which was oxidized to the corresponding aldehyde using Swern conditions and concomitantly subjected to Wittig olefination using $Ph_3P{=}C(Me)CO_2Et$ to get α,β-unsaturated ester **17** as the major isomer (*E*/*Z* = 13:1), which was purified by silica gel column chromatography. Careful reduction of ester **17** by DIBAL-H provided the corresponding aldehyde, which, when subsequently subjected to Crimmins acetate aldol[12] using *N*-acetyl thiazolidinethione **18**[12a] in the presence of $TiCl_4$ and Hunig's base, provided **19** as major isomer (dr = 5:1) with overall 72% yield. The major isomer **19** was separated and then reduced to the corresponding diol using $NaBH_4$/MeOH, and the primary alcohol group was selectively protected using TrCl/Et_3N/DMAP to get alcohol **20** in good overall yield (82% in two steps). Next alcohol **20** was reacted with MeI/NaH to get the corresponding *O*-methylated compound and subsequently treated with TBAF to access alcohol **21**. Alcohol **21** was then oxidized to the corresponding aldehyde using IBX and

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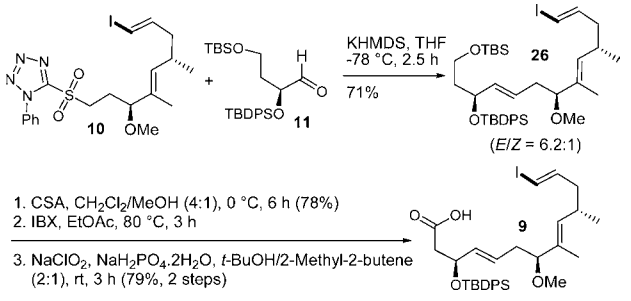
concomitantly subjected to Takai olefination[13] using CHI_3/$CrCl_2$. The crude reaction mixture was further treated with CSA to result in iodoalcohol **22** as a major product ($E/Z \approx 4{:}1$). The minor *Z*-counterpart was found to be inseparable through a few subsequent synthetic steps. The major product **22** was found to be the required 12*E*-isomer as evident from its large coupling constant between H_{12}−H_{13} (J = 14.0 Hz). Alcohol **22**[14] was reacted, first with PTSH **23** in the presence of DIAD/Ph_3P following Mitsunobu conditions[15] to achieve the corresponding sulfide,[14] and then subsequently oxidized to sulfone **10**[14] using $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ in the presence of 30% H_2O_2 with 76% overall yield. However, the known epoxide **24**, prepared from commercially available D-aspartic acid following literature protocol,[16] was treated with Me_3SI/*n*-BuLi[17] to get allylic alcohol **25**, which was then protected as TBDPS ether and finally subjected to oxidative cleavage to get aldehyde **11**.

The synthesis of acid **9** is depicted in Scheme 4. Sulfone **10** and aldehyde **11** were subjected to Julia−Kocienski olefination.[8] A

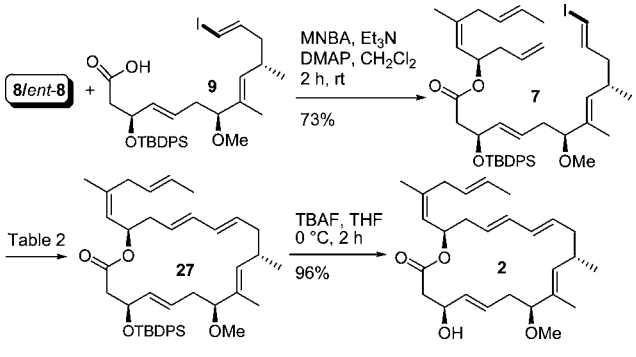
Scheme 4. Synthesis of Acid Fragment 9



number of bases (NaHMDS, KHMDS, LiHMDS, KO*t*-Bu) were screened to optimize the conditions for efficient coupling. KHMDS was found to be optimal with respect to selectivity (E/Z = 6.2:1) and yield (71%). The major *E*-isomer **26**[14] was separated from its minor *Z*-counterpart[14] by silica gel chromatography and subsequently subjected to primary TBS ether cleavage using CSA to get the corresponding primary alcohol[14] in good yield (78%). The alcohol was then oxidized to aldehyde using IBX and subjected to Pinnick oxidation[18] to access the required acid **9**[14] in good overall yield (79%).

The final synthetic endeavor of biselyngbyolide B **2** is illustrated in Scheme 5. The required allylic alcohol **8**, mixed with *ent*-**8**, and acid **9**[14] were subjected to esterification to get the advanced stage intermediate **7**[14] as the major product. We have screened a number of coupling reagents for this condensation. It was observed that Shiina conditions[19] (73%) were more effective

Scheme 5. Completion of Synthesis of Biselyngbyolide B



relative to Yamaguchi[20] (33%) and EDCI[21] conditions (28%). The ester generated from *ent*-**8**, the minor impurity, was not detectable. Ester **7**[14] was finally subjected to a crucial intramolecular macrocyclization using Heck coupling.[7] A number of reagent combinations (Table 2) were tested to

Table 2. Optimization of Intramolecular Heck Cross Coupling for Macrocyclization

entry	reagents	conditions	time (h)	yield (%)
1	$Pd(PPh_3)_4$, Et_3N, MeCN	60 °C	3	decomposition
2	$PdCl_2(MeCN)_2$, Et_3N, HCOOH, MeCN	rt	3	decomposition
3	$PdCl_2(PPh_3)_2$, K_2CO_3, Bu_4NCl, DMF	60 °C	3	trace[a]
4	$Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF	60 °C	1	58[b]

[a]Product identified by mass spectroscopy. [b]Only 12*E*/14*E* isomer was detectable as the sole product.

optimize the yield. We were indeed happy to observe that $Pd(OAc)_2/K_2CO_3/Bu_4NCl$ combination in DMF (Table 2, entry 4) afforded cyclized compound **27** as a sole isolable product (58%). We were not able to detect any cyclized product during this process from the minor ester where the iodoolefin is in *Z*- configuration. A detailed NMR study was carried out to reassure the stereochemistry of the synthesized macrocycle **27**. The large coupling constants between H_{12}−H_{13} and H_{14}−H_{15} are 15.0 and 15.0 Hz, respectively, clearly indicate the *trans*-geometry of the olefins embedded between C_{12}−C_{13} and C_{14}−C_{15} segments. The *transoid* geometry of the conjugated diene was confirmed further from observed NOESY correlations between H_{11}−H_{13} and H_{14}−H_{16} protons. The characteristic COSY, NOESY and HMBC correlations of synthesized macrocycle **27** unambiguously confirmed its structure (please see Supporting Information). Finally the TBDPS ether of compound **27** was removed efficiently using TBAF to produce biselyngbyolide B **2** in 96% yield. The spectral data of the synthesized compound is in good agreement with the literature value reported by Suenaga et al.[1d] (please see Table 1 in Supporting Information). The observed difference in the specific rotation {observed $[\alpha]^{29}_D$ −51.7 (*c* 0.48, $CHCl_3$); reported $[\alpha]^{22}_D$ −240 (*c* 0.058, $CHCl_3$)} could not be reconciled at this point.

In summary, we have demonstrated a convergent and flexible route for the total synthesis of bioactive natural product biselyngbyolide B **2** for the first time from known compound **16**. During this synthetic study, we discovered a new modification of the Jamison protocol of *trans*-hydroalumination/allylation, a crucial step in the synthesis, which was found to be more efficient in preparing the requisite olefin **13** than the original. Finally, the strategic implementation of modified Jamison protocol, Brown allylation, Wittig olefination, Crimmins acetate aldol, Julia−Kocienski olefination, intermolecular Shiina esterification, and intramolecular Heck cyclization protocol render this synthesis efficient.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, spectroscopic data, copies of NMR (^{1}H and ^{13}C) and HRMS of representative compounds, 2D NMR data for compound **27** (PDF)

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Notes

The authors declare no competing financial interest.

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