

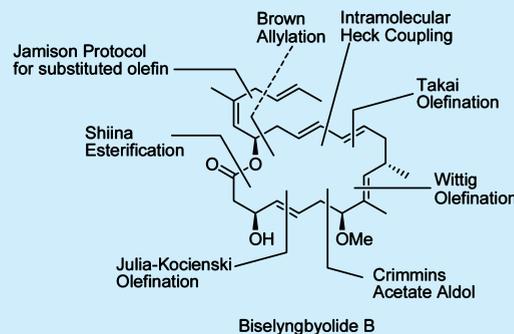
Stereoselective Total Synthesis of Bioactive Marine Natural Product Biselyngbyolide B

Sayantana Das, Debobrata Paul, and Rajib Kumar Goswami*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata-700032, India

S 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 C₁₈–C₂₃ 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

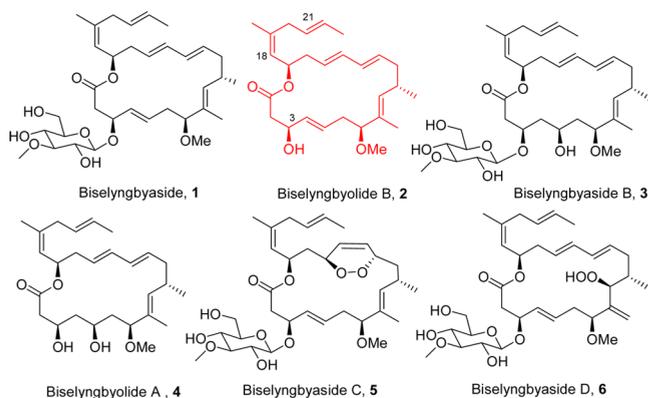


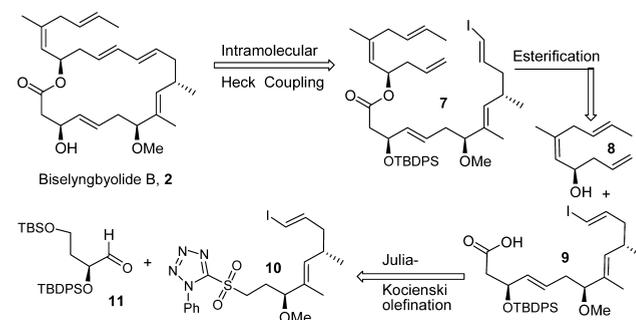
Figure 1. Structure of biselyngbyaside 1 and its congeners 2–6.

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 IC₅₀ 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 C₁–C₁₃ and C₅–C₂₃ 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 interest⁶ 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 Biselyngbyolide B 2

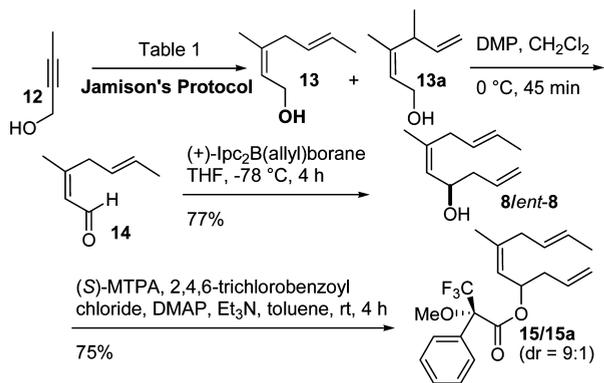


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compound **7** by intramolecular macrocyclization using a Heck coupling as one of the key steps.⁷ The Heck precursor **7** could be accessed from alcohol **8** and acid **9** by intermolecular esterification. The acid fragment **9** could be assembled from coupling partners **10** and **11** using a Julia–Kocienski olefination⁸ as the key step.

The synthesis of intermediate **8** is depicted in Scheme 2. We searched for a protocol that would yield the (C₁₈–C₂₃) 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-butyne-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****

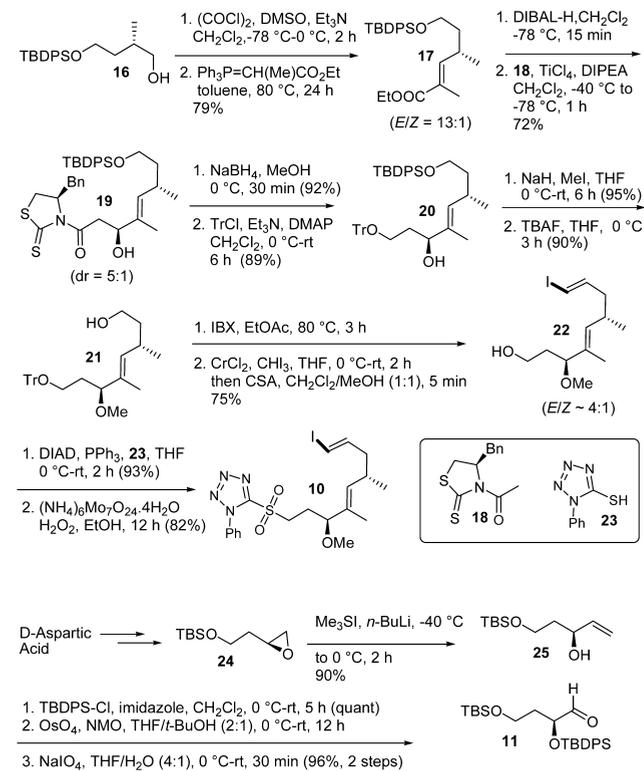
entry	conditions	total yield (%)	ratio (13/13a)
1	Red-Al, 0 °C–rt, 6 h, MeLi, 0 °C, 1.5 h, 12a , CuCl, THF, 0 °C–rt, 2 h	76	1.3:1
2	Red-Al, 0 °C–rt, 6 h, MeLi, 0 °C, 1.5 h, 12a , 0 °C–rt, 2 h	60	1:1
3	Red-Al, 0 °C–rt, 6 h, 12a , CuCl, THF, 0 °C–rt, 2 h	62	1.4:1
4	Red-Al, 0 °C–rt, 6 h, 12a , 0 °C, 2 h	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 ane was generated first from 2-butyne-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 condition⁹ (Table 1, entry 1). We performed this reaction, specially the quenching of vinyl ane

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 reaction¹⁰ using (+)-Ipc₂B(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 olefination⁸ is described in Scheme 3. We

Scheme 3. Synthesis of Sulfone **10** and Aldehyde **11**

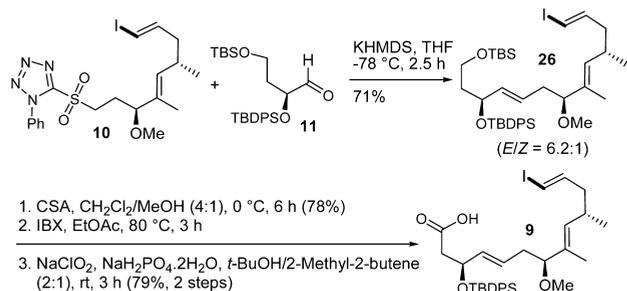


started our synthesis from known compound **16**,¹¹ which was oxidized to the corresponding aldehyde using Swern conditions and concomitantly subjected to Wittig olefination using Ph₃P=C(Me)CO₂Et to get α,β -unsaturated ester **17** as the major isomer (*E/Z* = 13:1), which was purified by silica gel column chromatography. Careful reduction of ester **17** by DIBAL-H provided the corresponding aldehyde, which, when subsequently subjected to Crimmins acetate aldol¹² using *N*-acetyl thiazolidinethione **18**^{12a} in the presence of TiCl₄ 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 NaBH₄/MeOH, and the primary alcohol group was selectively protected using TrCl/Et₃N/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

concomitantly subjected to Takai olefination¹³ using $\text{CHI}_3/\text{CrCl}_2$. 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 $12E$ -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 conditions¹⁵ to achieve the corresponding sulfide,¹⁴ and then subsequently oxidized to sulfone **10**¹⁴ using $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ 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 $\text{Me}_3\text{Si}/n\text{-BuLi}$ 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

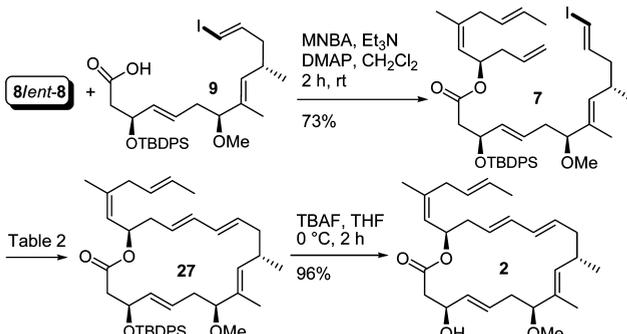
Scheme 4. Synthesis of Acid Fragment 9



number of bases (NaHMDS , KHMDS , LiHMDS , $\text{KO}t\text{-Bu}$) 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 -counterpart¹⁴ by silica gel chromatography and subsequently subjected to primary TBS ether cleavage using CSA to get the corresponding primary alcohol¹⁴ in good yield (78%). The alcohol was then oxidized to aldehyde using IBX and subjected to Pinnick oxidation¹⁸ 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 $ent\text{-8}$, 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 conditions¹⁹ (73%) were more effective

Scheme 5. Completion of Synthesis of Biselyngbyolide B



relative to Yamaguchi²⁰ (33%) and EDCI²¹ conditions (28%). The ester generated from $ent\text{-8}$, 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	$\text{Pd}(\text{PPh}_3)_4$, Et_3N , MeCN	60 °C	3	decomposition
2	$\text{PdCl}_2(\text{MeCN})_2$, Et_3N , HCOOH, MeCN	rt	3	decomposition
3	$\text{PdCl}_2(\text{PPh}_3)_2$, K_2CO_3 , Bu_4NCl , DMF	60 °C	3	trace ^a
4	$\text{Pd}(\text{OAc})_2$, K_2CO_3 , Bu_4NCl , DMF	60 °C	1	58 ^b

^aProduct identified by mass spectroscopy. ^bOnly $12E/14E$ isomer was detectable as the sole product.

optimize the yield. We were indeed happy to observe that $\text{Pd}(\text{OAc})_2/\text{K}_2\text{CO}_3/\text{Bu}_4\text{NCl}$ 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 $[\alpha]_D^{29} - 51.7$ (c 0.48, CHCl_3); reported $[\alpha]_D^{29} - 240$ (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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00713.

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

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AUTHOR INFORMATION

Corresponding Author

*E-mail: ocrkg@iacs.res.in.

Notes

The authors declare no competing financial interest.

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