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Total Synthesis of 13-Demethyllyngbyaloside B

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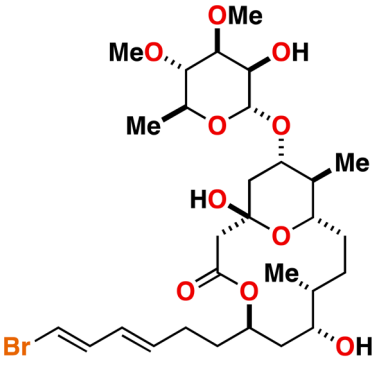
ABSTRACT



(–)-13-demethyllyngbyaloside B

Total synthesis of 13-demethyllyngbyaloside B, an unnatural analogue of a marine macrolide glycoside lyngbyaloside B, has been achieved. The 14-membered macrocyclic backbone was constructed in a convergent manner via esterification and ring-closing metathesis. The bromodiene side chain was introduced by means of a Stille-type reaction and a subsequent bromodesilylation. Finally, the rhamnopyranose unit was stereoselectively introduced by glycosylation under Schmidt conditions.

There is an emerging interest in the secondary metabolites of marine cyanobacteria as a source of novel biologically active compounds with therapeutic potential.[1] Lyngbyaloside B (**1**, Figure 1) was isolated from the marine cyanobacterium *Lyngbya* sp. collected at the Ulong Channel, Palau, by Moore and co-workers.[2] The gross structure and relative stereochemistry of **1** were proposed on the basis of extensive NMR analyses; however, the absolute configuration of **1** remains to be established because of a lack of the authentic sample. Moore et al. reported that **1** exhibited moderate cytotoxicity against KB cells (IC_{50} = 4.3 μM) and LoVo cells (IC_{50} ≈ 15 μM). A structurally related macrolide glycoside, lyngbouilloside (**2**), was identified from the marine cyanobacterium *Lyngbya bouillonii* by the Gerwick group.[3] Recently, Luesch et al. reported the isolation of natural congeners of **1** from *L. bouilloni*.[4] These macrolide glycosides also displayed moderate cytotoxic activity against human cancer cell lines. The intriguing structural aspects of **1** and related natural products have attracted the interest of the synthetic community.[5−8] Herein we report a total synthesis of 13-demethyllyngbyaloside B (**3**), an unnatural analogue of **1**.

(1) For recent reviews, see: (a) Nunnery, J. K.; Mevers, E.; Gerwick, W. H. *Curr. Opin. Biotechnol.* **2010**, *21*, 787–793. (b) Williams, P. G. *Trends Biotechnol.* **2009**, *27*, 45–52. (c) Tan, L. T. *Phytochemistry* **2007**, *68*, 954–979. See also: (d) Gerwick, W. H.; Moore, B. S. *Chem. Biol.* **2012**, *19*, 85–98.

(2) Luesch, H.; Yoshida, W. Y.; Harrigan, G. G.; Doom, J. P.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1945–1948.

(3) Tan, L. T.; Márquez, B. L.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 925–928.

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(5) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9743–9746.

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(7) (a) El Marrouni, A.; Lebeuf, R.; Gebauer, J.; Heras, M.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2012**, *14*, 314–317. (b) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 712–714.

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Hoye,[5] Ley[6] and Cossy[7] have independently reported the synthesis of the 14-membered macrolactone of **1** and **2**, which contains an acylated tertiary alcohol along the backbone. Meanwhile, we chose **3** as an initial target in our ongoing studies toward the total synthesis of **1** and related macrolide glycosides. Our synthesis plan toward **3** is summarized in Scheme 1. We envisioned that the rhamnopyranose unit could be attached to the aglycon **4** by glycosylation[9] with trichloroacetimidate **5**. We planned to construct the bromodiene side chain via a Stille-type reaction[10] using the vinyl stannane **6**. Finally, we considered that the macrolactone domain of **4** would be available from the alcohol **7** and the carboxylic acid **8a** or **8b**. Thus, esterification of **7** and **8a**,**b** followed by ring-closing metathesis (RCM)[11] would forge the macrocyclic framework of **4**.[12]

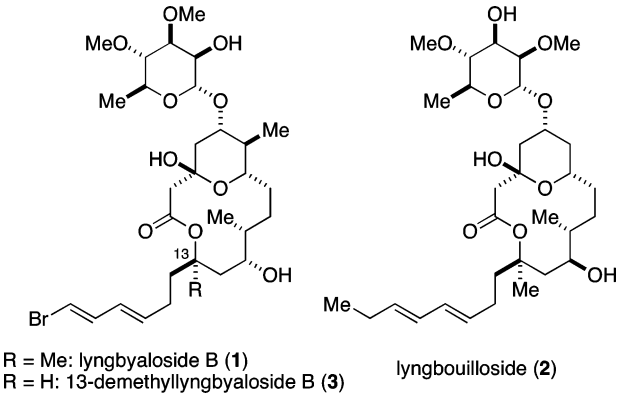
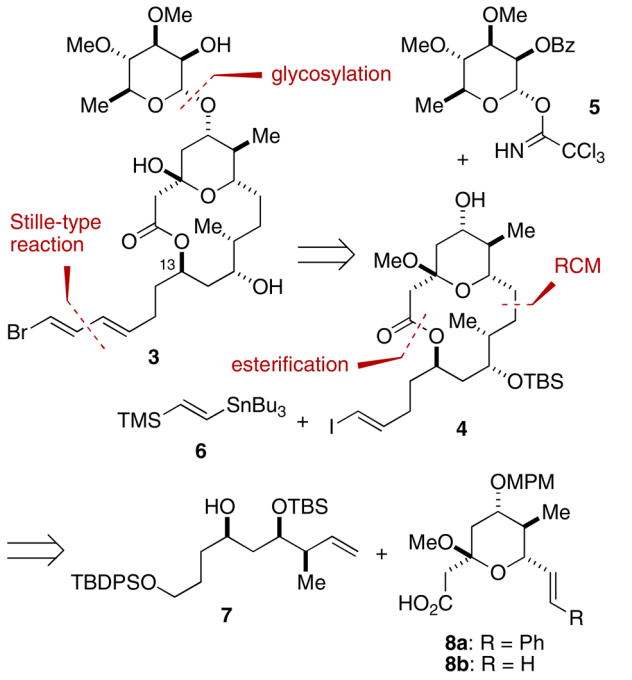


Figure 1. Structures of lyngbyaloside B (**1**), lyngbouilloside (**2**), and 13-demethyllyngbyaloside B (**3**).

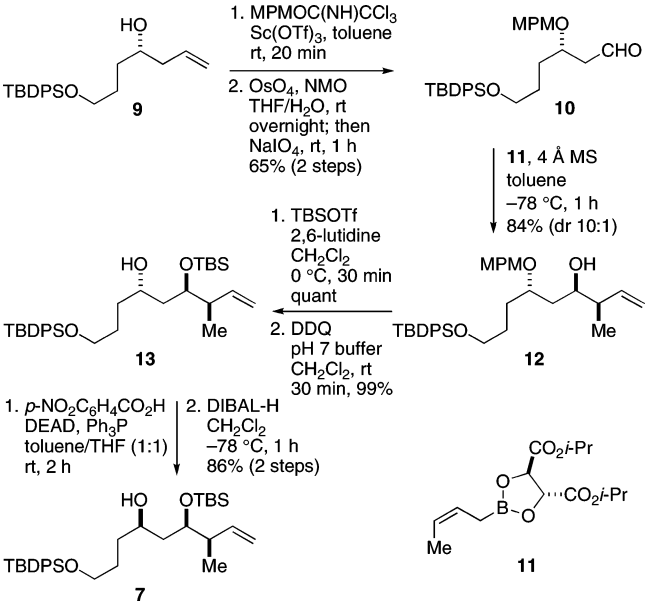
The synthesis of the alcohol **7** started with protection of the known homoallylic alcohol **9**[13] as its *p*-methoxyphenylmethyl (MPM) ether,[14] followed by oxidative cleavage of the double bond, to give the aldehyde **10** (Scheme 2). Roush crotylation[15] of **10** with the crotylboronate **11** under standard conditions (4 Å molecular sieves (MS), toluene, −78 °C) provided the alcohol **12** in 84% yield with 10:1 diastereoselectivity.[16] By contrast, asymmetric crotylation of *ent*-**10** (not shown) using **11** was mismatched and gave

Scheme 1. Synthesis Plan toward **3**



an approximately 1:1 mixture of diastereomers; hence, the homoallylic alcohol **9** was used as the starting material. Silylation of **12** followed by removal of the MPM group gave the alcohol **13**. Mitsunobu reaction[17] of **13** and subsequent reduction of the derived *p*-nitrobenzoate afforded the alcohol **7**.

Scheme 2. Synthesis of Alcohol **7**



The synthesis of the carboxylic acids **8a**,**b** is illustrated in Scheme 3. The known alcohol **14**,[18] readily prepared by

(9) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731–732.
(10) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749. For a review, see: (b) Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276–2286.
(11) For recent reviews, see: (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (b) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.
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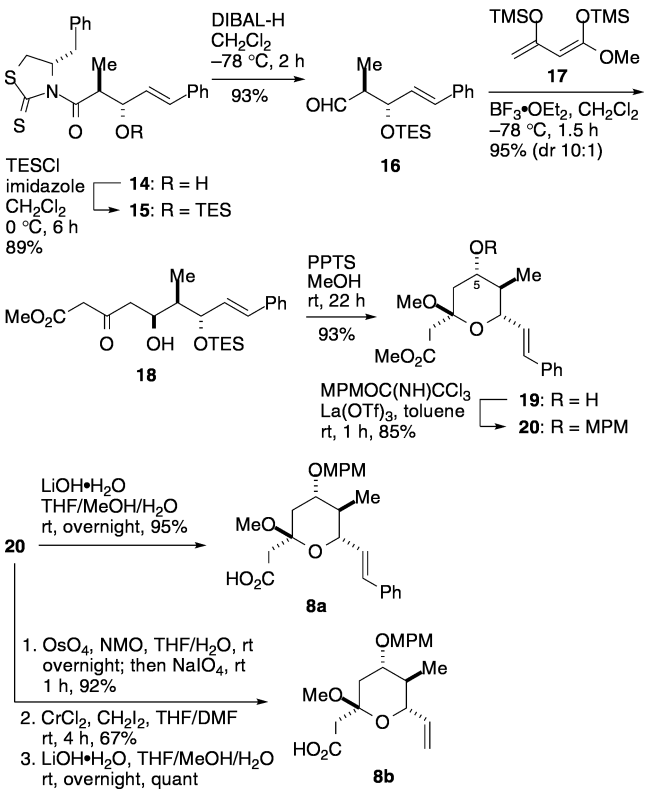
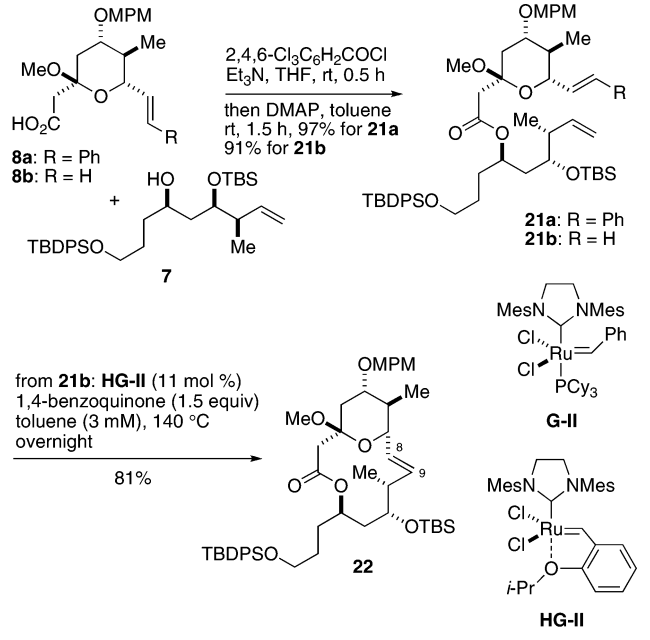
(16) See the Supporting Information for the stereochemical assignment.

Scheme 3. Synthesis of Carboxylic Acids **8a**,**b**



Scheme 4. Construction of the Macrocyclic Backbone



Evans *anti*-aldol reaction[18] of *trans*-cinnamaldehyde, was silylated to give the silyl ether **15**, which was reduced with DIBAL-H to provide the aldehyde **16**. Vinylogous Mukaiyama aldol reaction[19] of **16** with the dienol silyl ether **17**[20] afforded the β-hydroxy ketone **18** in 95% yield with 10:1 diastereoselectivity. Exposure of **18** to pyridinium *p*-toluenesulfonate (PPTS) in MeOH delivered the methyl acetal **19**.[16] At this stage, the minor diastereomer at C5 was removed by flash column chromatography using silica gel. After protection of the C5 hydroxy group as its MPM ether **20**, the ester group was hydrolyzed to afford the carboxylic acid **8a**. Meanwhile, oxidative cleavage of the double bond of **20**, Takai olefination[21] of the derived aldehyde, and subsequent hydrolysis provided the carboxylic acid **8b**.

With the requisite fragments **7** and **8a**,**b** available, we focused our attention on the assembly of the fragments and subsequent RCM (Scheme 4). Esterification of **8** and **9a**,**b** under Yamaguchi conditions[22] proceeded cleanly to afford the dienes **21a**,**b**. We first examined the RCM of **21a** using the second-generation Grubbs (**G-II**)[23] or Hoveyda–Grubbs (**HG-II**)[24] precatalyst under various conditions. However, only traces of the macrolactone **22** were obtained, and the partial degradation of **21a** was observed. We thought that the low reactivity of **21a** toward the RCM could be ascribed to the styryl group. Accordingly, we next investigated the RCM of **21b** and eventually found that **22** could be isolated in 81% yield upon exposure of **21b** to **HG-II** (11 mol %) and 1,4-benzoquinone (1.5 equiv)[25] in toluene (3 mM) at 140 °C. The stereochemistry of the newly generated double bond was determined to be *E* by a large coupling constant, $^3J_{H\text{-}8,H\text{-}9}$ = 15.5 Hz.[26] At this point, the minor diastereomer resulting from the Roush crotylation of **10** was removed by flash column chromatography using silica gel.

Completion of the total synthesis is depicted in Scheme 5. Hydrogenation of **22** followed by selective removal of the TBDPS group[27] gave the alcohol **23**. Oxidation of **23** and Takai olefination[28] of the resultant aldehyde provided,

(17) For reviews, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.

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(22) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

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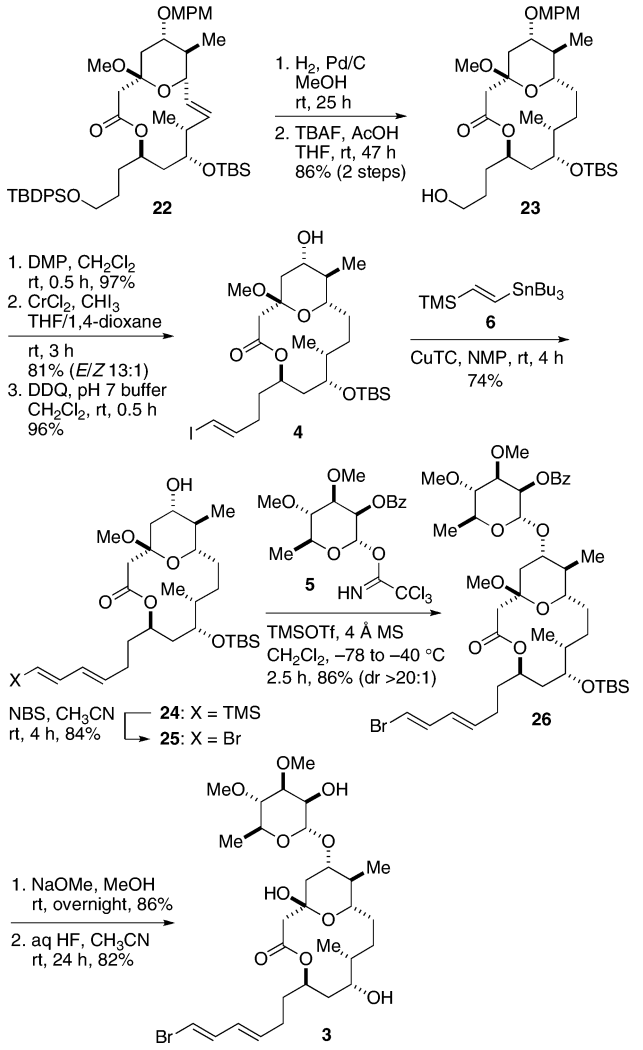
(25) Hong, S. H.; Sanders, H. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(26) The stereoselectivity observed for RCM of **21b** was opposite to that observed in our previous syntheses of structurally related 14-membered macrolides. See: Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Tetrahedron* **2010**, *66*, 7492–7503and ref 12. It appears that the C10 and C11 substituents affected the stereochemical outcome.

(27) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Nakata, M. *Synlett* **2000**, 1306–1308.

(28) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.

Scheme 5. Completion of the Total Synthesis of **3**



after removal of the MPM group, the (*E*)-vinyl iodide **4** (*E*/*Z* = 13:1). The *Z*-isomer was removed by flash column chromatography using silica gel.

Coupling of **4** with the vinyl stannane **6**[29] was best performed by using copper(I) thiophen-2-carboxylate (CuTC)[10] to afford the vinyl silane **24**. The bromodesilylation[30] of **24** led to the aglycon **25**.[31] The stereoselective introduction of the rhamnopyranoside unit to **25** was extensively investigated, and it was eventually found that the glycosylation of **25** with the trichloroacetimidate **5**[32] (TMSOTf, 4 Å MS, CH_2Cl_2, −78 to −40 °C) proceeded cleanly to furnish the α-glycoside **26** in 86% yield (dr > 20:1).[16] Removal of the benzoyl group with NaOMe, followed by cleavage of the silyl ether and methyl acetal, furnished 13-demethyllyngbyaloside B (**3**). The antiproliferative activity of **3** against KB cells was moderate (IC_{50} = 36 μM) according to the WST-8 colorimetric assay.[33]

In conclusion, we completed a total synthesis of 13-demethyllyngbyaloside B (**3**) in 20 steps (longest linear sequence) with an overall yield of 7% from the known homoallylic alcohol **9**. The salient features of our synthesis include (1) a convergent synthesis of the 14-membered macrocyclic framework by exploiting an esterification/RCM strategy; (2) a stereoselective construction of the bromodiene side chain via a CuTC-catalyzed Stille-type reaction; and (3) a highly stereoselective glycosylation to attach the rhamnopyranose unit to the aglycon. Further investigations toward the total synthesis of lyngbyaloside B (**1**) and related compounds are currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedure, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds, and stereochemical confirmation of compounds **12**, **19**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647–8650.
(31) Compound **25** was contaminated with minor impurities ascribable to partial isomerization of the stereochemistry of the diene moiety.[30] The impurities could not be removed until HPLC purification of **3**.
(32) See the Supporting Information for the preparation of **5**.
(33) Tominaga, H.; Ishiyama, M.; Ohseto, F.; Sasamoto, K.; Hamamoto, T.; Suzuki, K.; Watanabe, M. *Anal. Commun.* **1999**, *36*, 47–50.

The authors declare no competing financial interest.