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Natural Products

Total Synthesis and Structural Reassignment of Lyngbyaloside C Highlighted by Intermolecular Ketene Esterification

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Abstract: Lyngbyaloside C, a classic macrolide, isolated from Lyngbya bouilloni, has shown moderate anticancer activity against several cancer cell lines. Here, we report the first total synthesis and stereochemical configuration reassignment of lyngbyaloside C. The synthesis highlights a one-pot intermolecular ketene esterification reaction to form the crucial tertiary ester and tetrahydropyran. In addition, a novel and concise synthetic pathway towards the 1,3-*syn* secondary, tertiary diol fragment is described using a regio- and stereospecific electrophilic ether transfer reaction.

Naturally occurring, biologically active molecules that have evolved structurally over centuries, have long served as useful therapeutics agents.[1] Polyketides, a unique class of natural products, possess a broad range of privileged scaffolds, structural diversity, and biological activities. Since 2007, a series of polyketide natural products have been isolated from the marine cyanobacteria,[2] *Lyngbya bouilloni*, including lyngbyaloside C (*Z/E*) **1**, lyngbouilloside, and lyngbyaloside B (Figure 1).[3]

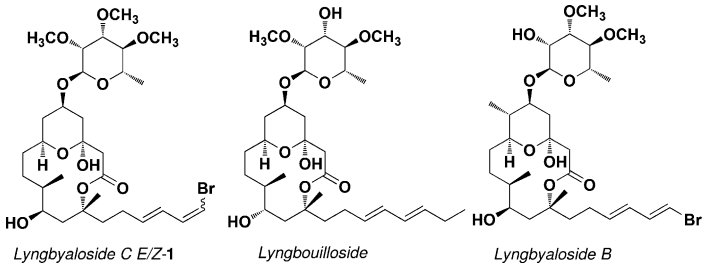

Figure 1. Proposed structures of polyketide natural products isolated from *Lyngbya bouilloni*.

These structures are characterized as 14-membered glycosylated macrolides, embedded with a 2,6-*cis* tetrahydropyran ring and an appended diene side chain. Notably, the tertiary ester moiety is not only interesting from a biosynthetic standpoint, but it also poses a unique synthetic challenge. Preliminary biological studies show that the lyngbyalosides exhibit moderate cytotoxicity against several cancer cell lines.[3] As a result, the lyngbyalosides have garnered recent interest from the synthetic community.[4] These efforts culminated in the first total synthesis of lyngbyaloside B by Fuwa et al. in 2014, in which the stereochemical configuration of lyngbyaloside B was reassigned.[4f] However, previous synthetic endeavors all focused on the lyngbyalosides which possess the (*E,E*) diene appendage (lyngbouilloside and lyngbyaloside B). Lyngbyaloside B also contains an additional methyl stereogenic center at C6. With that in mind, we also envisioned an intermolecular ketene esterification reaction that could generate the challenging tertiary ester from readily accessible fragments. Accordingly, lyngbyaloside C is the perfect target for the development of a general pathway to both isomers via intermolecular ketene esterification. Furthermore, the total synthesis of lyngbyaloside C would allow the confirmation of its stereochemical configuration assignment. Herein, we report the first total synthesis of lyngbyaloside C which warrants a structural revision, while providing a significant amount of material including two diastereoisomers, for more thorough biological investigation.

Our synthetic plan is outlined in Figure 2. We conceived that selective glycosylation of the C5 hydroxyl would allow late-stage installation of the sugar moiety. The precursory aglycone would be constructed via a highly convergent, sequential ketene esterification and ring-closing metathesis (RCM). Accordingly, the aglycone was broken into tertiary alcohol and ketene precursor fragments. Yadav et al. recently reported a similar strategy towards the synthesis of lyngbyaloside B.[4d] For preparation of the tertiary alcohol, we envisioned the installation of the 1,3-*syn* diol through utilization of an electrophilic-induced ether transfer methodology recently developed in our labs.[5] The alkene required for the subsequent RCM step provided us with an opportunity to explore a unique ether transfer substrate which contains potentially competing 1,1-disubstituted and terminal alkenes.

Synthesis of the ether transfer substrate commenced with the application of a Leighton crotylation[6] of known aldehyde **2** (Scheme 1). Sequential protection of the resulting alcohol followed by a Wittig olefination furnished homoallylic alkoxy ether **6**. Gratifyingly, the ether transfer reaction, carried out using iodine monchloride (ICl, −95 °C), produced the desired

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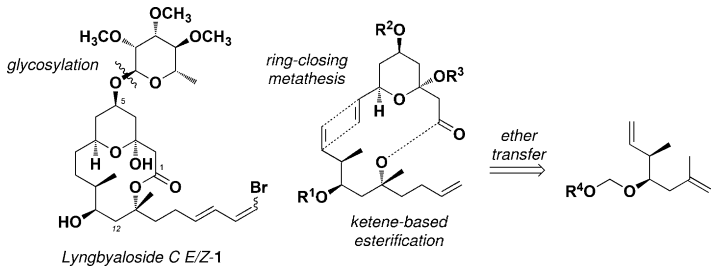
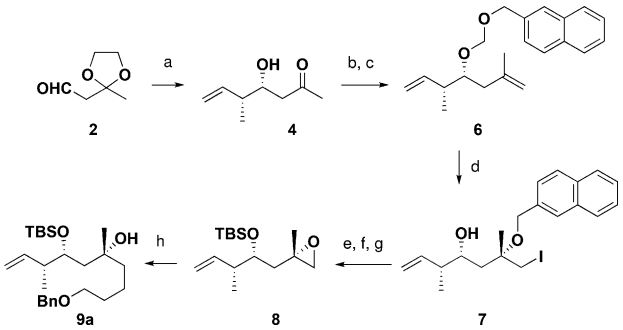


Figure 2. Retrosynthetic analysis of lynbyaloside C.



Scheme 1. Synthesis of tertiary alcohol **9a** by electrophilic ether transfer reaction. Reagents and conditions: a) Z-crotyl-trichlorosilane, Leighton catalyst (*R,R*)-**3**, DBU, CH_2Cl_2, 0 °C, 1 h; TBAF, HCl, 93%, 99% *ee*; b) chloromethyl-2-naphthylmethyl ether **5**, DIPEA, TBAI, CH_2Cl_2, 40 °C, 12 h, 70%; c) CH_3PPh_3Br, *n*BuLi, THF, 0 °C to RT, overnight, 71%; d) ICl, $PhCH_3$, −95 °C, 1 min; DIPA/H_2O, 3 h, 76%, d.r. = 10:1; e) TBSOTf, 2,6-lut., CH_2Cl_2, 0 °C, 30 min, 95%; f) DDQ, CH_2Cl_2, pH 7 phosphate buffer, RT, 1 h, 93%; g) NaH, THF, 0 °C to RT, overnight, 86%; h) 3-benzoxylpropyl magnesium bromide, CuI, THF, −78 to −15 °C, 2 h, 65%. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAI: tetrabutylammonium iodide; DIPA: diisopropylamine; TBSOTf: trimethylsilyl trifluoromethanesulfonate; 2,6-lut.: 2,6-lutidine; DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; RT: room temperature.

1,3-*syn* diol monoether **7** in 76% yield with reasonable diastereoselectivity (10:1 *syn:anti)*. Interestingly, no reactivity was observed at the monosubstituted olefin, representing the first report of a regioselective ether transfer in the presence of two reactive olefins. The resulting diol monoether **7** was then converted to epoxide **8** via the three-step functional group manipulation, followed by ring opening with the corresponding Grignard reagent in the presence of copper(I) iodide to afford tertiary alcohol **9a**.

With tertiary alcohol **9a** in hand, we then turned our focus towards the synthesis of the ketene precursor fragment. The application of ketene chemistry for the synthesis of sterically encumbered esters has been investigated.[7] On the basis of these prior studies, several ketene precursors, such as carboxylic acid **I**,[7a–f] acid halides **II**, and alkynyl ether **IV**[7g–l] were explored (Figure 3). Unfortunately, none of these ketene precursors proved to be efficient for generating the desired tertiary ester moiety. We believe that this is the result of the instability of the ketene intermediates and a preference for degradative over productive pathways. However, β-keto esters **V** have been shown to generate stabilized β-keto ketenes in the context of macrolactonization reactions.[4d] In our preliminary investigation of these precursors, low yields were obtained when we tried to scale up (~100 mg), which was presumably caused by the competing ketene polymerization.[7g] To address this issue, we explored the use of a thioester substrate **VI** activated by a thiophilic metal salt,[8] allowing the corresponding ketene to be generated under comparatively mild conditions.

Synthesis of β-keto ester fragment **16** started from the Mukaiyama aldol reaction of dienol ether **10** with acrolein,[9] followed by Sharpless kinetic resolution,[10] to afford chiral, non-racemic allylic alcohol **12**. Desired ester **13** was accessed by trapping the acetylketene intermediate of **12** with methanol. Utilization of intramolecular hydride delivery[11] provided the 1,3-*anti* diol, which was subsequently silylated to afford ester **14**. Reduction of the aforementioned ester with DiBALH gave the corresponding aldehyde, which was then treated with *tert*-butylthiol diazoacetate **15**[12] in the presence of tin(II) chloride to successfully afford β-keto-thioester **16** (Scheme 2).

With the two requisite building blocks of **1** in hand, we turned our attention to developing a robust and scalable ketene esterification reaction. After screening numerous conditions, silver trifluoroacetate was found to affect gram-scale one-pot intermolecular ketene esterification in which the tertiary ester and pyran are formed consecutively to afford **17** (Scheme 3). The formation of the methyl ketal was achieved by refluxing with dry MeOH in the presence of citric acid, and subsequent protection of the secondary alcohol provided diene **18a**. The ensuing RCM proceeded smoothly upon treatment with Hoveyda–Grubbs 2nd generation catalyst[13] in the presence of benzoquinone[14] to yield **19a** exclusively as the *E* isomer. Regioselective hydrogenation of the disubstituted olefin and deprotection of the benzyl ether was accomplished by using activated Raney nickel, which was followed by Grieco olefination conditions[15] to provide **20a**. At this point, we attempted to prepare the diene side chain through the method of Fuwa et al.[4f] Alkene **20a** was converted to the aldehyde via two-step oxidation cleavage. Unfortunately, Takai olefination[16] conditions yielded vinyl iodide **21** but also resulted in an unexpected double elimination, a problem that could not be resolved.

The unexpected elimination process was successfully circumvented by use of a cross-metathesis homologation and

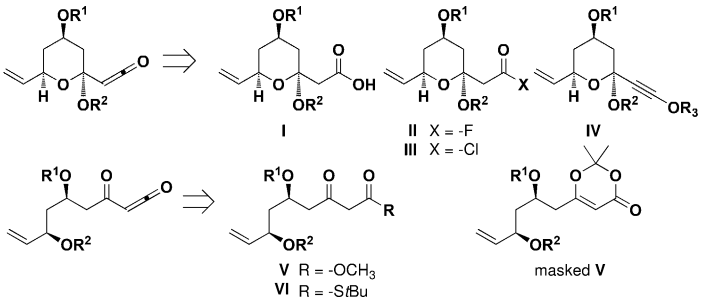
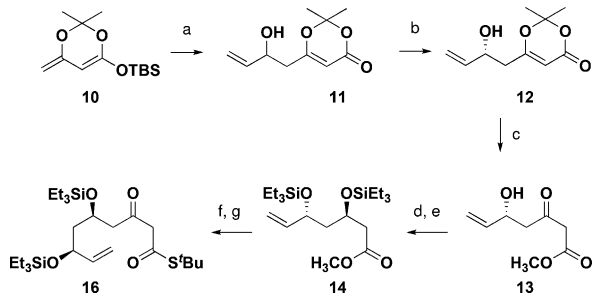
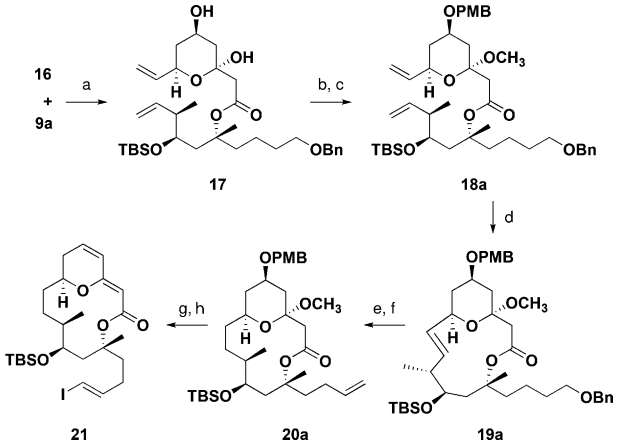


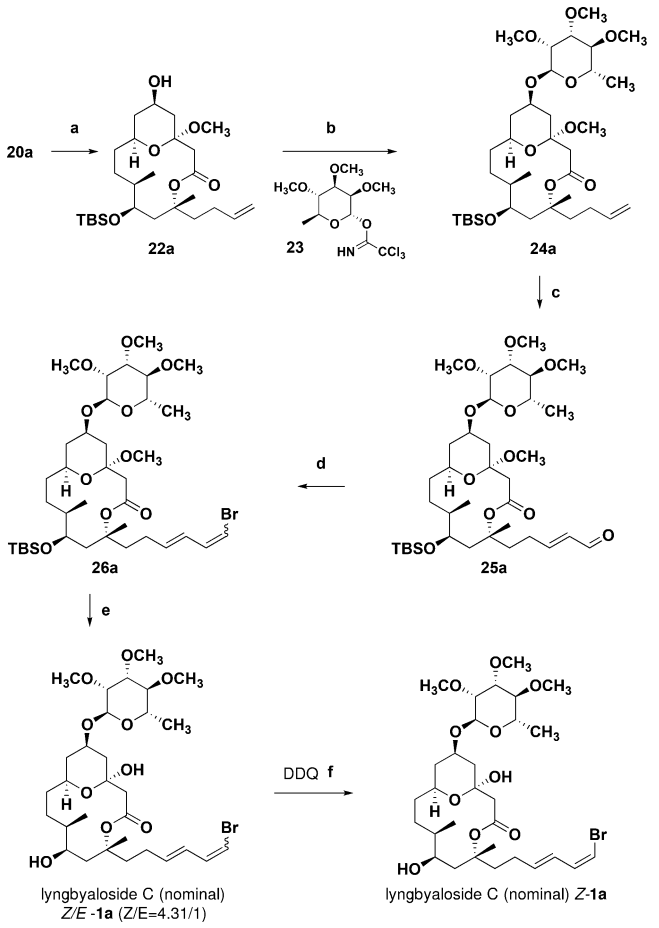
Figure 3. Ketene precursor fragments for esterification reaction.



Scheme 2. Synthesis of β-keto thioester **16**. Reagents and conditions: a) acrolein, $SiCl_4$, CH_2Cl_2, −78 °C, overnight, 80%; b) TBHP, L-(+)-DIPT, $Ti(OiPr)_4$, MS 4 Å, CH_2Cl_2, −20 °C, 40 h, 90%, 99% *ee*; c) CH_3OH, $PhCH_3$, refluxing, 2 h, 90%; d) $Me_4NBH(OAc)_3$, AcOH/CH_3CN, −35 °C, 60 h, 92%; e) Et_3SiOTf, 2,6-lut., CH_2Cl_2, 0 °C, 2 h to RT, 87%; f) DiBALH, CH_2Cl_2, −76 °C, 30 min, 93%; g) *tert*-butylthiol diazoacetate **15**, $SnCl_2$, CH_2Cl_2, RT, 4 h, 80%. TBHP: *tert*-butylhydrogenperoxide; DiBALH: diisobutylaluminum hydride.



Scheme 3. Synthesis of macrocyclic core **20a**. Reagents and conditions: a) AgTFA, Et_2O (0.08 M), RT, 10 min, 73%; b) citric acid, MeOH, 70 °C, overnight, 90%; c) $PMBONHCCl_3$, $La(OTf)_3$, $PhCH_3$, RT, 30 min, 80%; d) Hoyveda–Grubbs II, benzoquinone, CH_3Ph (0.003 M), refluxing, overnight, 80%; e) H_2 (1 atm), Raney Ni, MeOH, RT, overnight, 99%; f) 2-nitrophenyl seleocyanate, PBu_3, THF, RT, 15 min; H_2O_2, $NaHCO_3$, THF, 55 °C, 40 min, 85%; g) OsO_4, NMO, CH_2Cl_2, RT, overnight; $NaIO_4$, 0 °C, 1 h, 78%; h) $CrCl_2$, CHI_3, 1,4-dioxane/THF, 0 °C to RT, 72%. AgTFA: silver(I) trifluoroacetate; PMB: *p*-methoxylbenzyl; NMO: *N*-methylmorpholine-*N*-oxide.



Scheme 4. Total synthesis of nominal lyngbyaloside C. Reagents and conditions: a) DDQ, CH_2Cl_2, pH 7 phosphate buffer, RT, 1 h, 95%; b) **23**, $La(OTf)_3$, $PhCH_3$, RT, 15 min, 81%; c) crotonaldehyde, Hoveyda–Grubbs II, CH_2Cl_2, refluxing, 90%; d) Ph_3PCH_2BrBr, NaHMDS, HMPA, THF, RT to −78 °C, 15 min, 84%, *Z*/*E* = 4.3/1; e) HF, CH_3CN, RT, 4 h 77%; f) DDQ, CH_2Cl_2, pH 7 phosphate buffer, RT, 10 min, 70%. NaHMDS: sodium bis(trimethylsilyl)amide; HMPA: hexamethylphosphoramide.

a Wittig olefination. Deprotection of the PMB ether followed by treatment of the resultant free alcohol with the corresponding glycosylated trichloroimidate **23**, in the presence of catalytic $La(OTf)_3$[17] yielded the desired glycosylated macrolide **24a** as a single β-isomer. Cross-metathesis of the terminal alkene with crotonaldehyde afforded **25a** as a single *E* isomer. The installation of bromodiene was completed by using Menche's optimized Wittig reaction conditions, which successfully inhibited the formation of the dibromide side product.[18] Finally, global deprotection with hydrogen fluoride furnished nominal lyngbyaloside C *Z*/*E*-**1a** (*Z*/*E* 4.3/1) (Scheme 4). During preliminary studies on compounds earlier in the sequence, we found that *Z*/*E* mixtures of related bromodienes could be converted to exclusively *Z* by exposure to catalytic quantities of DDQ. Much to our delight, DDQ treatment of a *Z*/*E* mixture of **1a** provided isomerically pure *Z*-**1a** in 70% yield. At this point, the mechanism of the reaction remains unclear and the reaction may, in fact, involve selective degradation of the *E*-bromodiene.

Comparing the ^1H and ^{13}C NMR data for the synthetic nominal compound **1a** to those in the literature for natural lyngbyaloside C, we found there were appreciable disparities between them (Figure 4). In the ^1H spectrum, the doublet at $\delta =$ 2.80 ppm and the singlet at $\delta = 4.57$ ppm are missing in the synthetic compound. In addition, several signals in both ^1H and ^{13}C show broadening or are absent.[19] These substantial disparities indicate one or more of the stereochemical configurations of natural lyngbyaloside C and nominal structure **1a** are different. During our studies, Fuwa et al. reported the synthesis of nominal lyngbyaloside B, which resulted in the structural configuration reassignment at three stereogenic centers (C_{10}, C_{11}, C_{13}).[4f] Therefore, we surmised the spectral disagreements in the current effort resulted from a misassignment of lyngbyaloside C at these same positions.

Based on NOE studies of the natural product, we considered two potential diastereomers as the likely stereochemical configuration for natural lyngbyaloside C. To access both tertiary

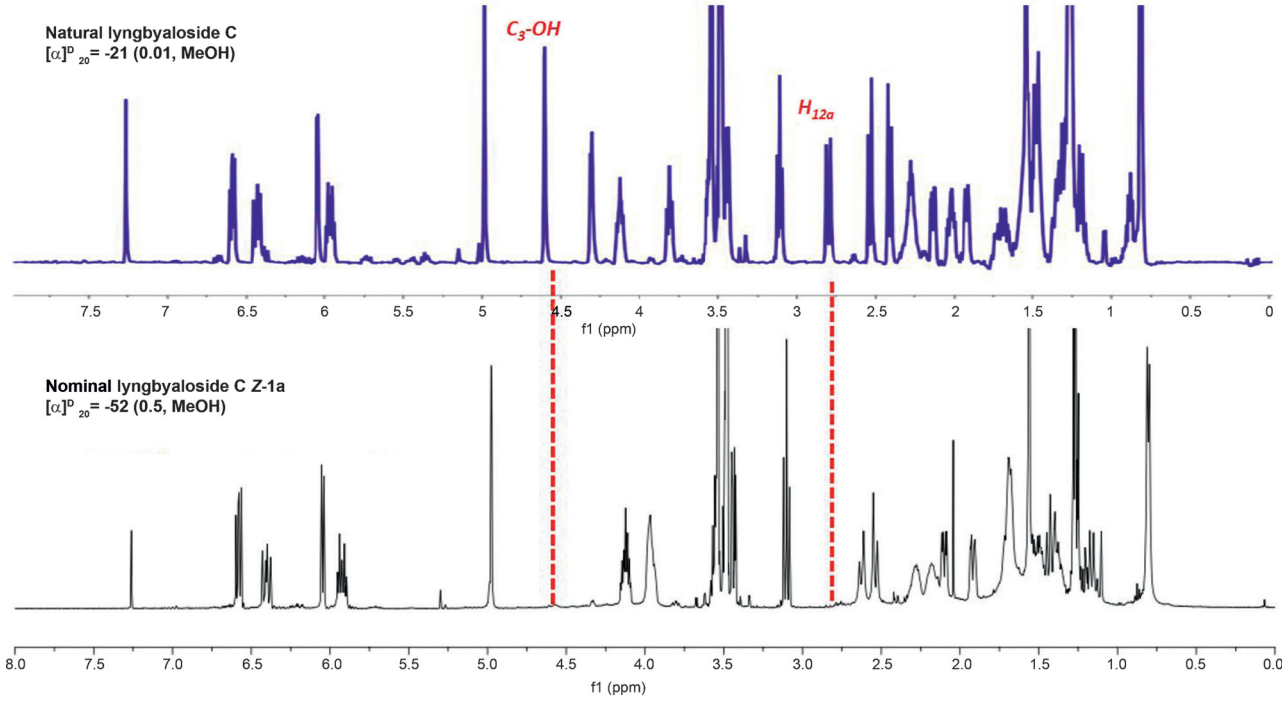
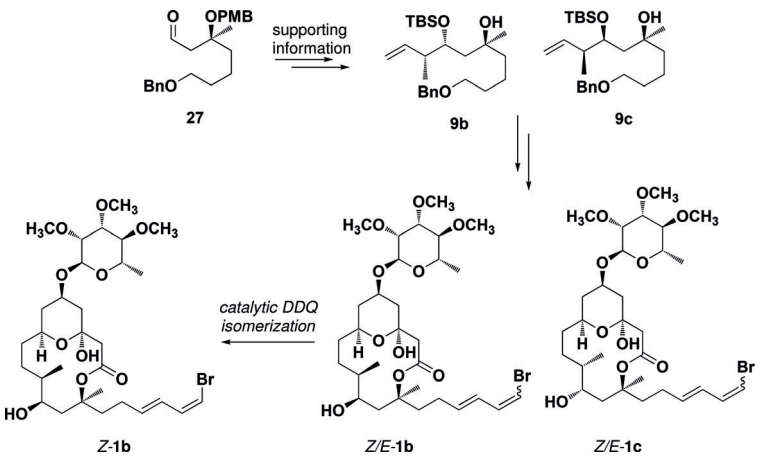


Figure 4. ^{1}H NMR ($CDCl_3$) comparison between natural lyngbyaloside C(*Z*)[3c] and *Z*-**1a** (nominal).

alcohol fragments **9b** and **9c**, divergent routes from a common intermediate were developed highlighted by stereochemically complementary Ti-mediated aldol reactions (Scheme 5).[20,21] Gratifyingly, fully diastereomeric targets *Z/E*-**1b** and *Z/E*-**1c** were then generated efficiently via the optimized synthetic pathway developed for the synthesis of *Z/E*-**1a** through ketene fragment **16**.[22] Upon a comparison of NMR data, **1b** encountered similar irregularities with the originally proposed structure **1a**. In contrast, characterization data for **1c** was consistent with those of the natural product, indicating the stereochemical configuration of lyngbyaloside C is unambiguously assigned as structure **1c** (Figure 5).[23] Furthermore, lyngbyaloside C shares the same absolute stereochemistry with lyngbyaloside B, and we propose that lyngbouilloside can be reassigned accordingly.

In summary, we have completed the first total synthesis of lyngbyaloisde C **1c**, which has confirmed the need for reassignment of the stereochemical configuration of the natural product. Our synthetic pathway featured an intermolecular thioester transesterification through a ketene intermediate. In addition, we also developed a concise approach toward key tertiary alcohol **12a** by a regio-and-stereoselective electrophilic ether transfer reaction on a unique substrate. Lastly, in synthesizing the diene bromide appendage, we determined that a catalytic DDQ-mediated isomerization could be successfully applied at a late-stage to access exclusively the *Z*-bromodiene for each of the three stereoisomeric compounds. The mechanism of this potentially useful methodology along with the biological evaluation of the isomeric macrolides are currently topics of investigation in our laboratory.



Scheme 5. Total synthesis of diastereomers **1b** and **1c** and completion of the total synthesis of lyngbyaloside C.

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Keywords: electrophilic ether transfer · ketene · lyngbyaloside C · natural products · polyketides · total synthesis

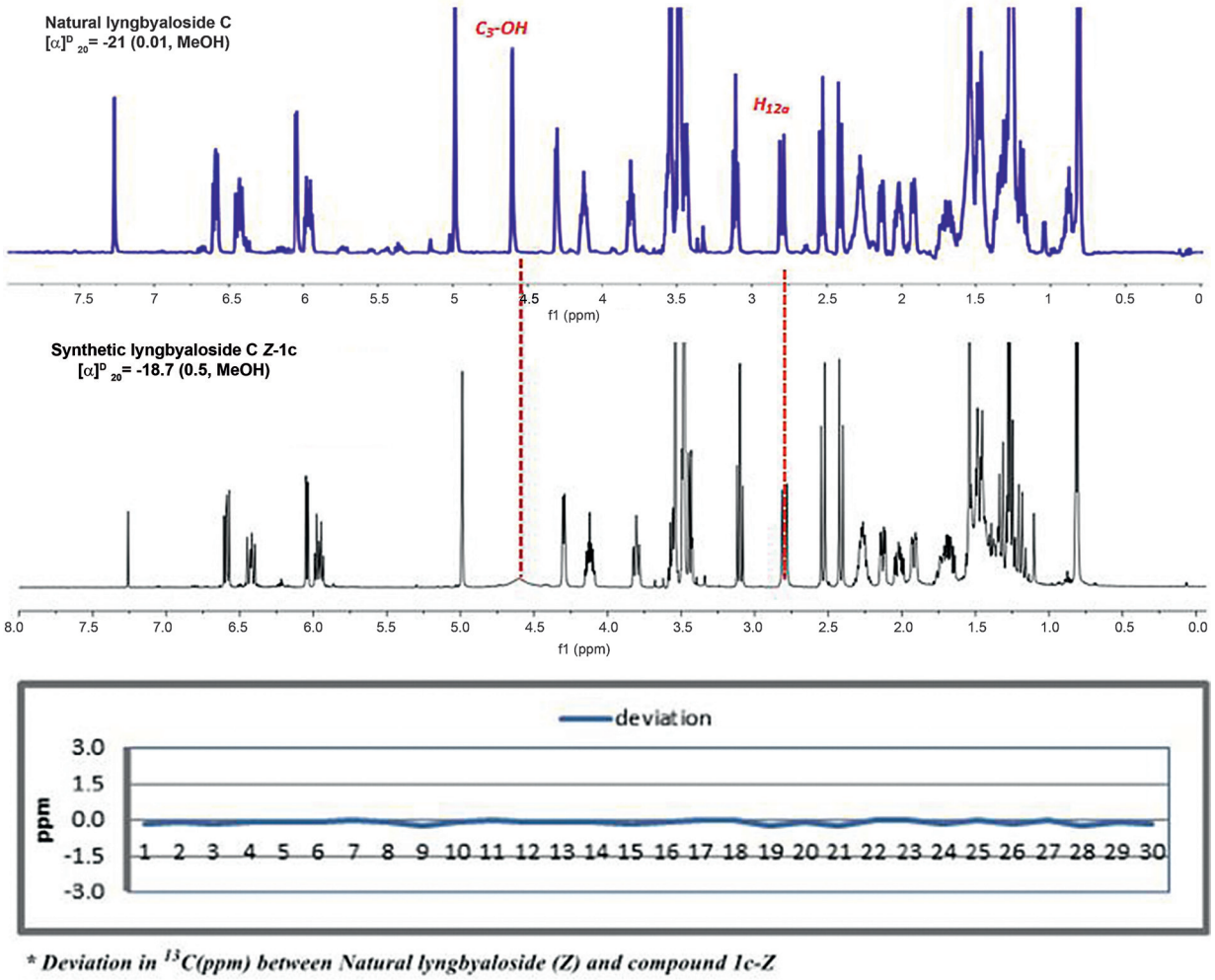

Figure 5. ^{1}H NMR ($CDCl_3$) and ^{13}C NMR comparison between natural lyngbyaloside C(*Z*)[3c] and *Z*-**1 c**.

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