Natural Products

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Total Synthesis, Stereochemical Reassignment, and Biological Evaluation of (−)-Lyngbyaloside B**

Haruhiko Fuwa, Yuta Okuaki, Naoya Yamagata, and Makoto Sasaki*

Abstract: *(−)-Lyngbyaloside B is a 14-membered macrolide glycoside isolated from the marine cyanobacterium Lyngbya sp. as a cytotoxic substance by Moore and co-workers. The first total synthesis of (−)-lyngbyaloside B and the reassignment of its stereostructure is described. The synthesis features an Abiko–Masamune aldol reaction, a vinylogous Mukaiyama aldol reaction, and a macrocyclization involving an acyl ketene intermediate for the construction of the macrocyclic backbone, which contains an acylated tertiary alcohol. The antiproliferative activity of selected compounds against a small panel of human cancer cell lines is also reported.*

Marine cyanobacteria are recognized to be a rich source of novel biologically active secondary metabolites.[1] Marine macrolide glycosides constitute a growing family of structurally and biologically intriguing natural products that are supposed to be of cyanobaterial origin[2] and continue to attract intense attention from the synthetic community. (−)-Lyngbyaloside B (proposed structure **1**, Figure 1) is a tetrahydropyran-containing 14-membered macrolide glycoside that was isolated from the marine cyanobacterium *Lyngbya* sp. collected at Palau by the Moore group.[3] The gross structure was established by extensive 2D-NMR analyses and the relative configuration proposed on the basis of ROESY correlations and $^{3}J_{H,H}$ values. However, the absolute configuration remains undetermined because of its scarce availability from natural sources. Moore et al. reported that (−)-lyngbyaloside B displayed cytotoxicity against the human epidermoid carcinoma KB cell line and the human colon adenocarcinoma LoVo cell line in low micromolar concentrations. Luesch et al. recently reported the isolation and characterization of several natural congeners of (−)-lyngbyaloside B as moderately cytotoxic secondary metabolites of the marine cyanobacterium *Lyngbya bouillonii*.[4] Meanwhile, Gerwick and co-workers have reported the isolation of a closely related cytotoxic macrolide glycoside, (−)-lyngbouilloside (proposed structure **2**), from *L. bouillonii*.[5] The highly complex, synthetically challenging structure of **1** and **2**, characterized by a 14-membered macrolactone with an unusual backbone that contains an acylated tertiary alcohol, has heightened the interest of synthetic organic chemists.[6] Moreover, previous synthetic work has raised questions about the originally proposed structure **2** of (−)-lyngbouilloside.[6c,d] Ley and co-workers observed that the spectroscopic properties of their synthetic aglycon model of **2** significantly differ from those of the corresponding part of natural (−)-lyngbouilloside.[6c] Cossy et al. have suggested on the basis of their synthetic and spectroscopic studies on the aglycon of **2** that the relative configuration of the C10/C11 stereogenic centers of **2** should be same as that of **1**.[6d] However, the structures of these natural products have not been established by means of total synthesis. Herein, we describe the first total synthesis, stereochemical reassignment, and biological evaluation of (−)-lyngbyaloside B.

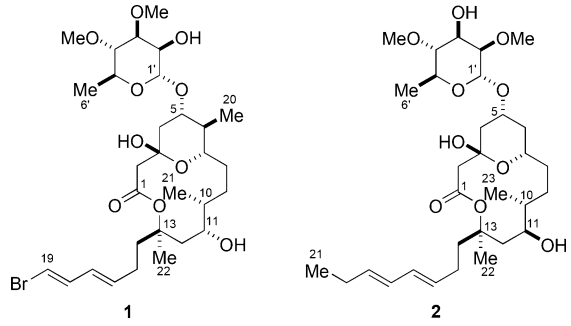

Figure 1. Proposed structures of (−)-lyngbyaloside B (**1**) and (−)-lyngbouilloside (**2**).

Our synthesis plan for **1** is summarized in Scheme 1. We planned to introduce the 3,4-di-*O*-methyl-L-rhamnopyranoside and the bromodiene side chain to aglycon **3** via a stereoselective glycosylation[7] and a Stille-type reaction,[8] respectively.[6f] The macrocyclic backbone of **3** would be constructed by means of a macrocyclization involving an acyl ketene intermediate[9] generated from dioxinone **5**.[6b,d] Notably, in our hands, acylation of the C13 tertiary alcohol was impractical by any other means. We planned to assemble **5** from three readily available building blocks; aldehyde **6**, ester **7**, and the known silyl dienol ether **8**;[10] in a convergent manner by exploiting an Abiko–Masamune *anti*-aldol reaction[11] and a vinylogous Mukaiyama aldol reaction.[12]

The synthesis of building block **6** was performed in eight steps from ester **9**[13] (Scheme 2). Reduction of **9**, silylation of the derived alcohol, and removal of the MPM group gave allylic alcohol **10**. Sharpless asymmetric epoxidation of **10** provided a 2,3-epoxy alcohol (e.r. 96:4),[14] which was

[*] Prof. Dr. H. Fuwa, Y. Okuaki, N. Yamagata, Prof. Dr. M. Sasaki
Graduate School of Life Sciences, Tohoku University
2-1-1 Katahira, Aoba-ku, Sendai 980-8577 (Japan)
E-mail: hfuwa@m.tohoku.ac.jp

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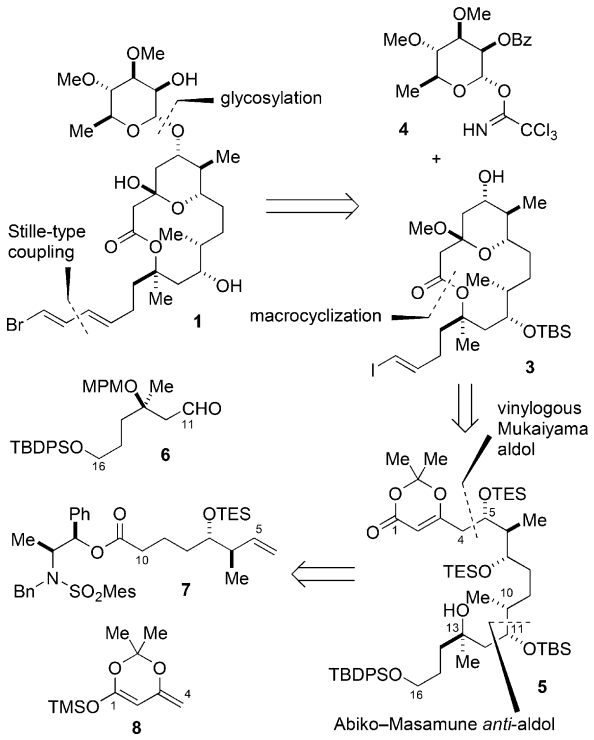
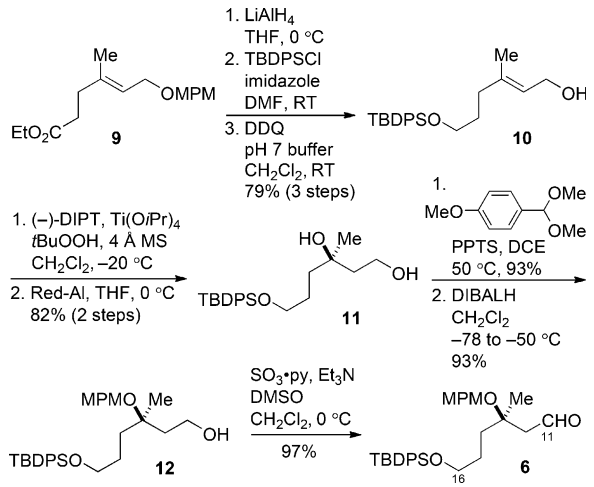


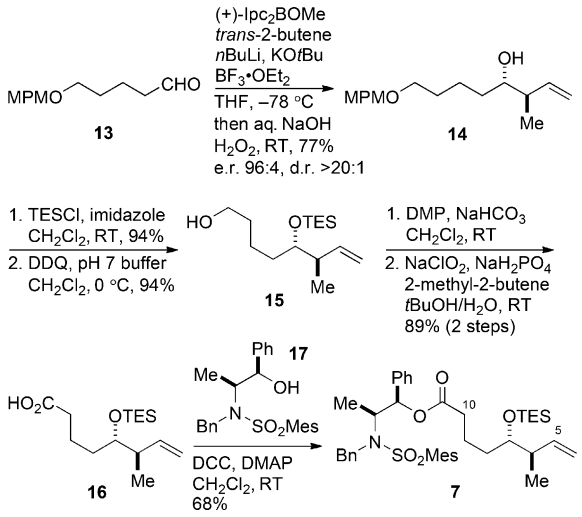
Scheme 1. Planned synthetic approach to **1**. Bn = benzyl, Bz = benzoyl, TBS = *tert*-butyldimethylsilyl, Mes = 2,4,6-trimethylbenzenesulfonyl, MPM = *p*-methoxyphenylmethyl, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.



Scheme 2. Synthesis of aldehyde **6**. DCE = 1,2-dichloroethane, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DIBALH = diisobutylaluminum hydride, DIPT = diisopropyl tartrate, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, MS = molecular sieves, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, THF = tetrahydrofuran.

regioselectively reduced[15] to deliver 1,3-diol **11**. Protection of **11** as its *p*-methoxybenzylidene acetal and DIBALH reduction[16] led to alcohol **12**, which was oxidized[17] to give aldehyde **6**.

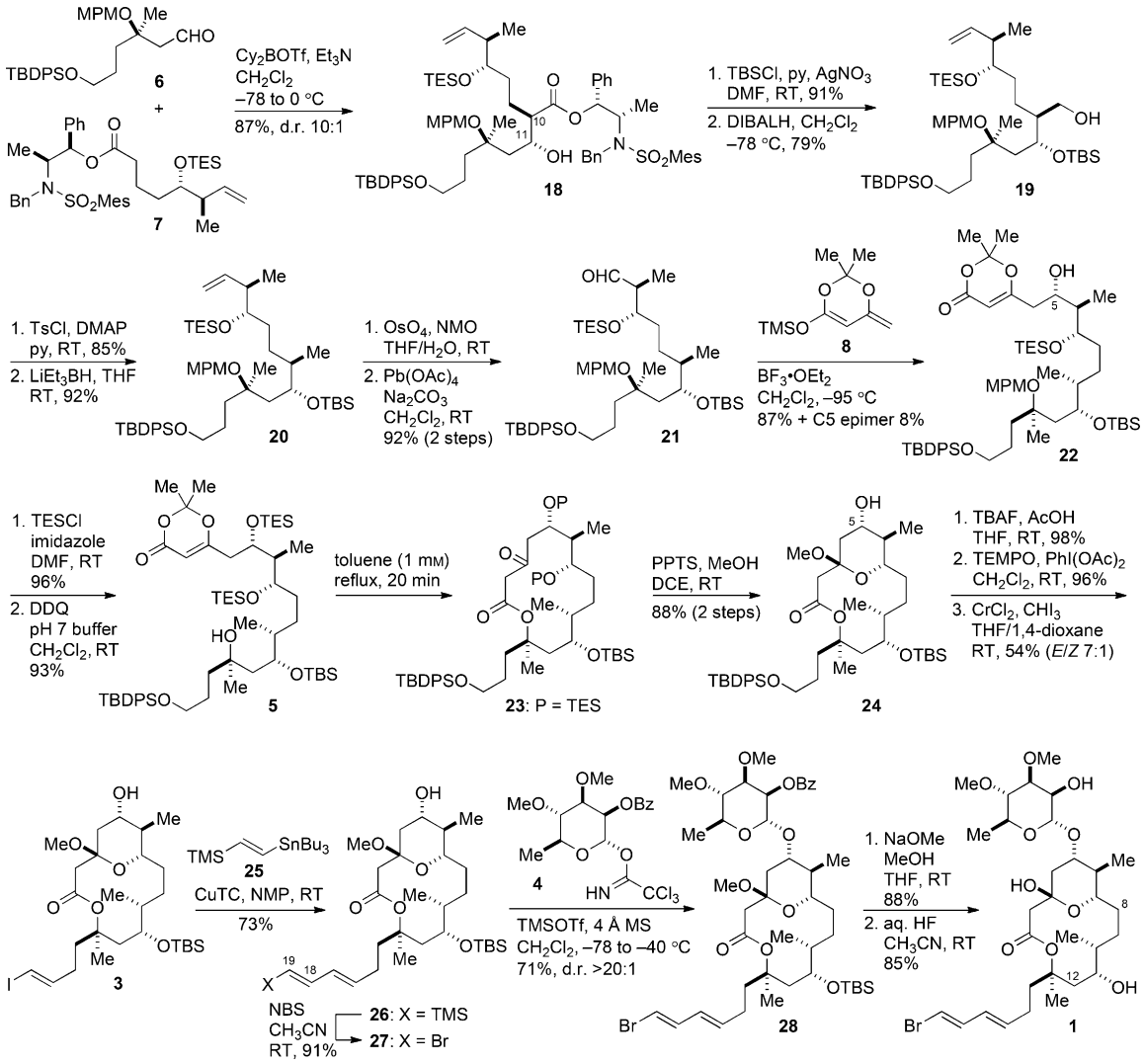
Building block **7** was synthesized from aldehyde **13**[18] in six steps (Scheme 3). Brown asymmetric crotylation[19] of **13**



Scheme 3. Synthesis of ester **7**. aq. = aqueous, DCC = *N*,*N*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, Ipc = isopinocampheyl.

(77%, e.r. 96:4, d.r. > 20:1),[14] silylation of the derived alcohol **14**, and subsequent removal of the MPM group gave alcohol **15**. Oxidation[20,21] of **15** to carboxylic acid **16** followed by condensation with alcohol **17**[11] afforded ester **7**.

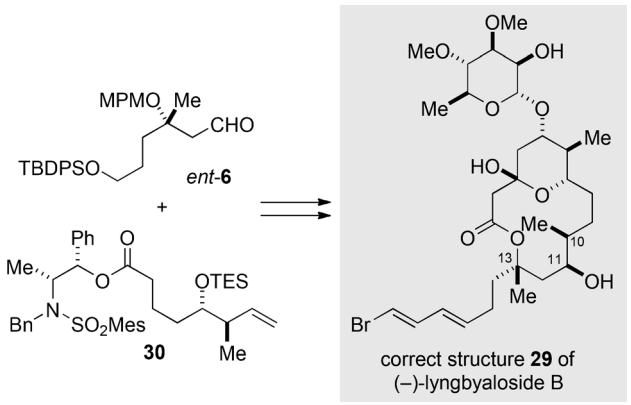
With the requisite building blocks available, we proceeded to elaborate the macrocyclization precursor **5** and completed the synthesis of **1** (Scheme 4). Abiko–Masamune *anti*-aldol reaction[11] of the boron enolate derived from **7** with aldehyde **6** under standard conditions (Cy_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C) afforded alcohol **18** in 87% yield (d.r. 10:1).[22,23] Stereochemical assignment of the C10 and C11 stereogenic centers of **18** was made through NMR experiments on suitable derivatives.[24] Silylation[25] of **18** followed by reduction of the ester moiety gave alcohol **19**, which was tosylated and then reduced with $LiEt_3BH$ to furnish olefin **20**. Oxidative cleavage of **20** provided aldehyde **21** (92%, two steps), and subsequent vinylogous Mukaiyama aldol reaction[12] with silyl dienol ether **8**[10] ($BF_3{\cdot}OEt_2$, CH_2Cl_2, −95 °C) gave dioxinone **22** in 87% yield, along with its C5 epimer in 8% yield, and the two epimers were separable by flash column chromatography over silica gel. Silylation of **22** and removal of the MPM group afforded the macrocyclization precursor **5**. Thermolysis of **5** in refluxing toluene (1 mM) for 20 min most effectively realized the macrocyclization via an acyl ketene intermediate to deliver macrolactone **23**.[26] Exposure of **23** to mild acidic methanol effected cleavage of the TES groups and concomitant cyclization of the tetrahydropyran ring to afford methyl acetal **24** (88%, two steps).[27] At this point, the absolute configuration of the C5 stereogenic center was established by NOE experiments.[24] Selective removal of the TBDPS group[28] of **24** (98%), followed by selective oxidation[29] of the liberated primary alcohol (96%), and ensuing Takai iodoolefination[30] provided vinyl iodide **3** (54%) as an inseparable 7:1 mixture of *E*/*Z* isomers.[22] Stille-type reaction[8] of **3** with vinylstannane **25**[31] led to vinylsilane **26** (73%), which was treated with NBS to afford bromodiene **27** (91%).[32,33] Stereoselective glycosylation[7] of **27** with



Scheme 4. Synthesis of cyclization precursor **5** and completion of the total synthesis of **1**. Ac = acetyl, Cy = cyclohexyl, NBS = *N*-bromosuccinimide, NMO = *N*-methylmorpholine *N*-oxide, NMP = *N*-methylpyrrolidin-2-one, TBAF = tetra-*n*-butylammonium fluoride, TC = thiophene-2-carboxylate, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

trichloroacetimidate **4**[6f] in the presence of a catalytic amount of TMSOTf (4 Å molecular sieves, CH_2Cl_2, −78 to −40 °C) delivered the glycosylated product **28** (71 %, d.r. > 20:1).[22] Finally, methanolysis of the benzoyl ester and treatment with aqueous hydrofluoric acid completed the first total synthesis of **1**. However, there were significant discrepancies between the ^{1}H and ^{13}C NMR spectroscopic data for our synthetic material and those reported for the isolated natural product.[3]

In contrast to the ^{1}H and ^{13}C NMR spectra of the authentic natural product, we observed significant line broadening of the signals correspond to the C8–C12 region in the ^{1}H NMR spectrum of **1** recorded in $CDCl_3$ at room temperature.[24] Furthermore, we could not observe any clear signals for the C8–C12 region in the ^{13}C NMR spectrum of **1** under the same conditions. These observations could be attributed to slow interconversion of two or more conformers of **1** within the NMR time scale. Accordingly, the structure of **1** was investigated in greater detail by measuring its ^{1}H and ^{13}C NMR spectra in CD_3CN at room temperature.[24] The planar structure of **1** was ascertained through extensive 2D NMR analyses, and the relative configuration of the stereogenic centers within **1** has already been confirmed by stereochemical analyses of synthetic intermediates and their derivatives. The original stereochemical assignment of the natural product thus needed to be reconsidered. Our spectroscopic consideration of the natural product based on the ROESY correlations and the characteristic long-range "W coupling" between the C3-OH proton and the H-4 axial proton, combined with molecular mechanics calculations on possible stereoisomers, suggested that diastereomer **29** (Scheme 5) is the most likely candidate for the correct structure of the natural product.[24] Accordingly, we synthesized **29** from *ent*-**6** and **30** in a similar manner as that described for **1**,[24] and demonstrated that synthetic **29** was spectroscopically indistinguishable from the natural product. Moreover, the specific rotation value of **29** ($[\alpha]_D^{25}$ −16.9 (*c* 0.20, $CHCl_3$)) was in agreement with that of the authentic material ($[\alpha]_D^{25}$ −20 (*c* 0.10, $CHCl_3$)).[3] We have thus unambiguously established the complete stereostructure of (−)-lyngbyaloside B to be that of compound **29**.



Scheme 5. Synthesis of the correct structure **29** of (−)-lyngbyaloside B.

Finally, we evaluated the antiproliferative activity of **1**, **29**, and **31**,[34] along with our previously synthesized 13-demethyl analogue **32**,[6f] against human oral epidermoid carcinoma KB cells, human non-small cell lung adenocarcinoma A549 cells, and human promyelocytic leukemia HL-60 cells, by performing WST-8 assays (Figure 2 and Figure 3).[35] The results have some important implications for understanding the structure–activity relationships of (−)-lyngbyaloside B. First, the 3,4-di-

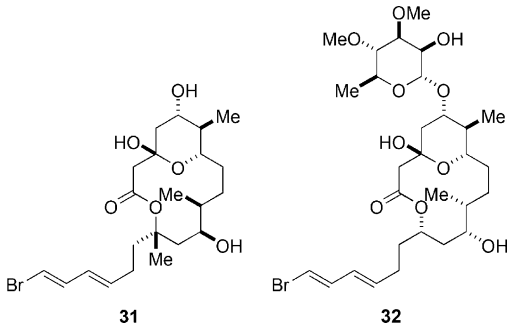


Figure 2. Structures of **31** and **32**.

O-methyl-L-rhamnopyranoside moiety is important for the antiproliferative activity against the tested cells. Second, we found, by comparing **1** and **29**, that the stereochemistry of the macrocyclic backbone mostly does not affect the antiproliferative activity, although it certainly has a significant impact on the conformation in solution. Third, the 13-demethyl analogue **32** was more potent than **1** and **29** against all of the tested cell lines. This finding is important because omission of the C13 methyl group significantly simplifies the synthesis (32 steps for **1** versus 22 steps for **32**).

In conclusion, we have accomplished the first total synthesis of the proposed and correct structures of (−)-lyngbyaloside B (**1** and **29**, respectively). The most salient feature of our synthesis is the use of an Abiko–Masamune *anti*-aldol reaction and a vinylogous Mukaiyama aldol reaction for the stereocontrolled, convergent assembly of readily available building blocks. Significantly, our synthesis represents one of the most complex applications of the Abiko–

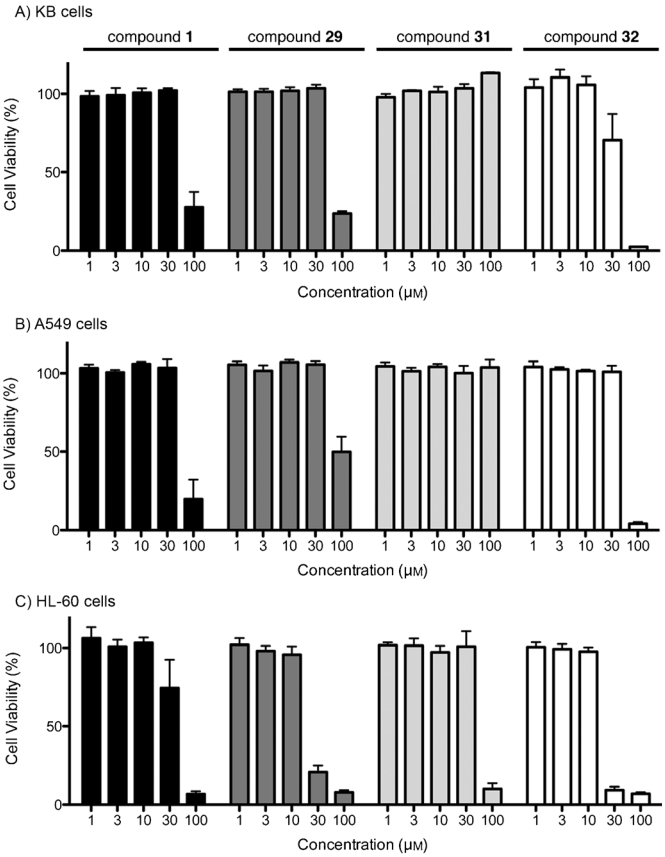


Figure 3. Antiproliferative activity of **1**, **29**, **31**, and **32** against human cancer cell lines. Cell viability (relative to control) was determined after 48 h of compound treatment by WST-8 assay. Data are expressed as the mean ± SD for three independent experiments ($n = 3$), except for **31** against KB and A549 cells ($n = 2$). Each experiment was performed in triplicate. WST-8 = 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium, SD = standard deviation.

Masamune *anti*-aldol reaction to date,[36] thus further expanding its synthetic utility. The 14-membered macrocyclic backbone was forged by means of a macrocyclization involving an acyl ketene as a reactive intermediate. It was found that the ^{1}H and ^{13}C NMR spectroscopic properties of the originally assigned structure **1** were significantly different to those of the natural product. However, our synthetic, spectroscopic, and molecular modeling studies culminated in an unequivocal determination of the complete stereostructure of (−)-lyngbyaloside B, which was shown to be that of compound **29**.[37,38] The structures of (−)-lyngbouilloside and the natural congeners of (−)-lyngbyaloside B may also be reconsidered accordingly. Our biological evaluation of **1**, **29**, **31**, and **32** against a small panel of human cancer cell lines demonstrated that **29** and **32** inhibit the proliferation of HL-60 cells with good potencies and that deleting the C13 methyl group is favorable for simplifying the synthesis and potentiating the antiproliferative activity.[39]

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