Lyngbyaloside B, a New Glycoside Macrolide from a Palauan Marine Cyanobacterium, *Lyngbya* sp.[1]

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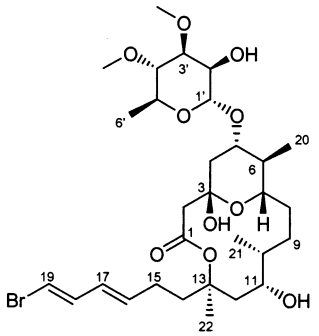
A Palauan collection of the marine cyanobacterium *Lyngbya* sp., which had already afforded diverse peptide-based cytotoxins, also yielded a new glycoside macrolide exhibiting slight cytotoxicity. The compound was termed lyngbyaloside B (**1**) due to its structural analogy to the previously isolated lyngbyaloside (**2**). Lyngbyaloside B (**1**) appears to be only the third glycoside macrolide and second brominated compound of its kind from a marine cyanobacterium. Its gross structure was determined by a combination of NMR spectroscopy and mass spectrometric techniques. The relative stereochemistry for the 12 stereocenters is proposed on the basis of proton−proton spin-coupling constants and ROESY data.

Cyanobacteria have drawn attention for their ability to produce an immense number and variety of bioactive secondary metabolites, ranging from notorious toxins[2] to potential therapeutic agents.[3] Most of the compounds isolated are nitrogenous,[4] which might be linked to the diazotrophic property of many cyanobacteria.[5] In our search for novel antitumor compounds from marine cyanobacterial sources, we have encountered a particularly prolific producer of secondary metabolites, closely resembling *Lyngbya bouillonii* Hoffmann et Demoulin (Oscillatoriaceae) morphologically as well as in its general habitat.[6] Chemical investigations of populations of this extraordinary organism collected at Guam and Palau yielded diverse cytotoxins and other metabolites, all of which are alkaloids, viz., peptides, depsipeptides, and thiazole-containing macrolides.[7] One extract from Palau (Ulong Channel) afforded a weak cytotoxin, compound **1**, belonging to a different structural class than all the other metabolites isolated so far from this intriguing cyanobacterium. Compound **1** is a non-nitrogenous, brominated glycoside macrolide and has been termed lyngbyaloside B since it closely resembles a known cyanobacterial metabolite, lyngbyaloside (**2**).[8] Lyngbyaloside B (**1**) is also a structural analogue of the more recently reported lyngbouilloside (**3**).[9] The isolation and structure determination of lyngbyaloside B (**1**) is described in the present report.



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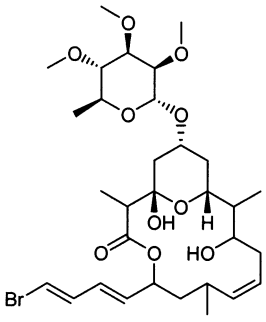

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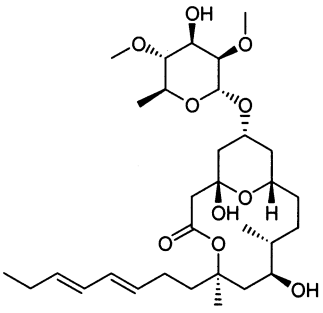

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Solvent partitioning of the lipophilic extract of the lyophilized cyanobacterial collection followed by silica gel chromatography and reversed-phase HPLC afforded compound **1** (see Experimental Section). Accurate mass measurements (ESI) for **1** of *m*/*z* 666.2804, corresponding to $[M + NH_4]^+$, and an isotope pattern typical for a brominated compound indicated a molecular formula of $C_{30}H_{49}BrO_{10}$. The molecular formula together with ^1H and ^{13}C NMR spectra in $CDCl_3$ revealed that compound **1** was not a peptide, in contrast to all previously identified secondary metabolites from this extract.[7c,d] The NMR spectra lacked

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Table 1. NMR Spectral Data for Lyngbyaloside B (**1**) at 500 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$

C/H no.[a]	δ_H (J in Hz)	δ_C[b]	HMBC[c]	ROESY[d]
1		172.5, s	H_2-2	
2a	2.39, d (−12.4)	46.8, t		3-OH, H-4b
2b	2.50, d (−12.4)			H-4a
3		96.1, s	H_2-2, 3-OH, H-4b	
3-OH	4.67, d (2.4)			H-2a, H-7
4a	1.42, ddd (−12.0, 12.0, 2.4)	42.1, t	3-OH	H-2b
4b	2.21, dd (−12.0, 4.8)			H-2a, H-5
5	3.61, td (12.0, 4.8)	79.1, d	H-4b, H_3-20, H-1′	H-4b, H-7, H_3-20, H-1′
6	1.30, m	41.5, d	H-4b	H_3−20
7	3.45, ddd (10, 8, 2)	75.6, d	H_3-20	3-OH, H-5, H_3-20
8a	1.51, m	28.1, t		
8b	1.73, dq (−14.6, ∼2)			H_3-20
9a	1.28, m	32.8, t	H_3-21	H_3-21
9b	1.49, m			
10	1.49, m	36.9, d	H-12b, H_3-21	H_3-21
11	4.26, br m	65.7, d	H-12a, H_3-21	H-12b, H-14a, H-14b
11-OH	not observed			
12a	1.45, dd (−15.5, 6.0)	44.1, t	H_3-22	
12b	2.78, d (−15.5)			H-11, H_3-21, H_3-22
13		86.4, s	H-12b, H-14b, H_3-22	
14a	1.64, m	38.6, t	H-12b, H_2−15, H_3-22	H-11
14b	1.98, m			H-11, H-15, H_3-22
15	2.18, m	26.7, t		H-14b, H-16, H_3-22
16	5.76, dt (15.2, 6.8)	135.6, d	H_2-15	H-15
17	6.01, dd (15.2, 10.7)	127.7, d	H_2-15, H-19	
18	6.67, dd (13.5, 10.7)	137.5, d	H-16, H-19	
19	6.19, d (13.5)	106.5, d		
20	0.93, d (6.4)	13.6, q		H-5, H-6, H-7, H-8b, H-1′, H-2′
21	0.81, d (5.9)	13.6, q		H-9a, H-10, H-12b
22	1.52, s	23.4, q		H-12b, H-14b, H-15
1′	4.88, d (1.4)	101.1, d	H-5	H-5, H_3-20, H-2′
2′	4.03, br t (∼1)	67.9, d		H_3-20, H-1′, H-3′, 3′-*O*-CH_3
2′-OH	not observed			
3′	3.41, dd (9.3, 3.3)	81.2, d	H-1′, 3′-*O*-CH_3, H-4′	H-2′, H-5′
3′-*O*-CH_3	3.49, s	57.4, q	H-3′	H-2′
4′	3.05, t (9.3)	81.8, d	4′-*O*-CH_3, H_3-6′	H-6′
4′-*O*-CH_3	3.54, s	61.0, q	H-4′	
5′	3.64, (9.3, 6.2)	67.4, d	H-1′, H-4′, H_3-6′	H-3′, H-6′
6′	1.26, d (6.2)	17.6, q	H-4′	H-4′, H-5′

[a] Numbering system for lyngbyaloside (**2**) adopted.[8] [b] Multiplicity deduced from DEPT and HSQC experiments. [c] Protons showing long-range correlation with indicated carbon. [d] Selected correlations listed.

the typical peptide resonances. The ^{13}C NMR spectrum displayed only one carbonyl carbon signal (C-1, δ 172.5) and disclosed that **1** was highly oxygenated. DEPT and HSQC spectra enabled one to infer the multiplicity of the carbons. The only other two quaternary carbons (δ_{C-3} 96.1, δ_{C-13} 86.4) were both oxygenated. One of them (C-3) belonged to a hemiketal function, supported by the low-field ^{13}C NMR chemical shift and an HMBC correlation to an exchangeable proton (δ 4.67). Eight of the 14 methines were oxygenated, one of which was apparently part of an acetal function ($\delta_{C-1'}$ 101.1). Four other methines were olefinic. The structure also incorporated seven methylenes and six methyls, two of the latter being oxygenated as well. These data already suggested a mixed glycoside-polyketide structure.

^{1}H−^{1}H COSY and HMBC data revealed the hexopyranoside structure for **1** and that the two oxygenated methyl groups were located at C-3′ and C-4′ (Table 1). Although there was no direct evidence of an OH group at C-2′ by ^{1}H NMR, C-2′ was clearly oxygenated (δ 67.9) and expectedly shifted upfield, compared with the other oxygenated carbons in the sugar moiety, due to the absence of an alkyl group at the C-2′ oxygen. Furthermore, the ^{13}C NMR spectrum taken in a MeOH-d_3/d_4 solvent mixture (1:1) displayed a split C-2′ carbon signal, proving the presence of a hydroxyl group. The 9.3 Hz triplet at δ 3.05 for H-4′ established that H-3′, H-4′, and H-5′ are in axial positions and hence ascertained the relative stereochemistry of those hydrogens. H-2′ had to be equatorial since it coupled only weakly ($J \approx 1$ Hz) to both vicinal methine protons. ROESY

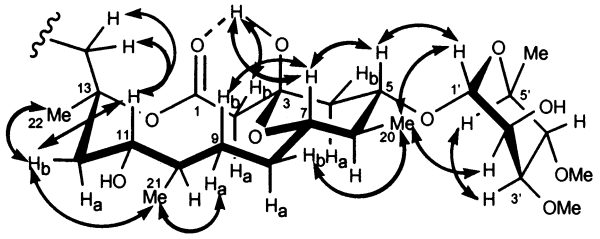


Figure 1. Proposed stereostructure of lyngbyaloside B (**1**) in $CDCl_3$ and selected ROESY correlations.

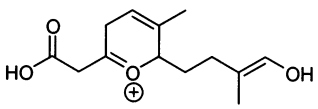
data (Table 1) clarified that the relative stereochemistry was as indicated and that **1** was a rhamnopyranoside existing in the α-form (Figure 1). The anomeric proton at δ 4.88 (H-1′) did not show NOEs arising from 1,3-diaxial interactions in the sugar moiety and therefore had to be in equatorial orientation. This partial structure is identical with the glycoside portion of **2**, except that **2** bore a methoxy group at C-2′ instead of the OH.

HMBC and 1D TOCSY/^{1}H−^{1}H COSY analysis permitted the elucidation of the polyketide part of **1**. The planar assembly of C-1 to C-7 and the attachment of a methyl group (C-20) at C-6 were straightforward using 2D NMR data (Table 1). The connection to the glycoside portion of the molecule via C-5 was made due to HMBC correlations between H-5 and C-1′ as well as H-1′ and C-5. Although there was no HMBC correlation of H-7 with the hemiketal carbon, the linkage of C-7 to C-3 via an oxygen atom was evident from the coupling constants and ROESY data in

that system. The data (Table 1) suggested the presence of a rigid, chairlike six-membered ring and enabled the assignment of the relative stereochemistry. The hemiketal OH showed a NOE to H-7, indicating their 1,3-diaxial positioning. H-5 possessed two large vicinal coupling constants (12.0 Hz) to H-4a and H-6. Therefore, H-5 was axial as well, and the methyl substituent (C-20) at C-6 had to be equatorial. Other ROESY data support the relative stereochemistry in that moiety (Figure 1). In addition, the large ^4J coupling ($J = 2.4$ Hz) from H-4a (axial) to 3-OH is noteworthy. This long-range coupling is likely on account of a fixed W-arrangement, presumably assisted by the carbonyl oxygen in β-position (C-1) that permits hydrogen bonding and keeps the exchangeable proton in place. The same postulate had been made for compounds **2** and **3**.[8,9]

HMBC analysis unambiguously established the sequence of C-9 to C-19 and the location of methyl substituents at C-10 and C-13 (Table 1). Although C-8 lacked any HMBC correlation, the placement of a methylene group between C-7 and C-9 was supported by 1D TOCSY analysis, which then accounted for all observed signals in the ^{1}H and ^{13}C NMR spectra. No direct evidence arose from HMBC experiments to determine whether C-1 was an ester carbonyl carbon and was then linked to either C-11 or C-13. Of these two oxygenated carbons in that portion of the molecule, the methine carbon (C-11) bore a hydroxyl group. Even though the OH proton was not observed in the ^{1}H NMR spectrum, the characteristic chemical shift (δ_{H-11} 4.26) and the broadness of the H-11 signal suggested that assignment and discounted the possibility of its being an acyloxy methine. This conclusion was supported by a TOCSY correlation of H-11 with the H_2O signal in $CDCl_3$ and by the sharpening of the H-11 signal after deuterium exchange. Since C-13 was quaternary, the ester linkage to C-1 could not be deduced from an HMBC experiment or predicted by ^{1}H NMR shifts. However, the fact that the ^{13}C NMR signal for C-13 did not double in a mixture of MeOH-d_3/d_4 (1:1) was suggestive of an acyloxy group at C-13 and overall consistent with the macrolide structure **1**.

The ^{13}C NMR chemical shift for C-19 (δ 106.5) was consistent with the presence of bromine as established by MS and by comparison with literature data.[8,10] The $^3J_{H,H}$ coupling constants for H-16/H-17 (15.2 Hz) and H-18/H-19 (13.5 Hz) were consistent with the *E* configuration of a bromine-containing conjugated diene, all of which are features of compound **2** as well. A fragment ion observed in the HRESIM spectrum of **1** at *m*/*z* 439.1445 ($C_{22}H_{32}{}^{79}BrO_4$) and in the CIDM spectra of *m*/*z* 666 along with an isotope peak of equal intensity at *m*/*z* 441 is consistent with the molecular formula for the aglycone moiety of lyngbyaloside B (**1**). For comparison, ions at *m*/*z* 437/439 were recorded in the positive ion FABM spectrum of lyngbyaloside (**2**), whose aglycone's elementary composition is 2 H less.[8] Furthermore, an ion at *m*/*z* 177.14 in the CIDM spectrum (high-energy collision) is consistent with the molecular formula of the glycone, while the ion at *m*/*z* 239.13 could be attributable to the ion **4** shown.



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Compound **1** contains two carbons less than **2** in its macrocyclic structure, and thus less conformational flexibility was expected for **1**. The macrolide size including the substitution pattern corresponds to that of lyngbouilloside (**3**), a compound that, however, does not contain bromine. Predominantly ROESY data allowed us to tentatively assign the relative stereochemistry of C-10, C-11, and C-13 in relation to the six-membered hemiketal portion. Out of the eight possible diastereomers, we have found one isomer that fits the experimental NMR data best. The conformation depicted in Figure 1 accounts for observed ROESY correlations, is in agreement with the approximate magnitude of $^3J_{H,H}$ coupling constants, constitutes the preferred orientation adapted by esters, allows hydrogen bonding of the hemiketal OH and the carbonyl oxygen discussed above, and is also consistent with our molecular modeling studies. Key ROESY correlations between both H_2-14 protons and H-11 could be rationalized by a pseudoaxial arrangement of the diene-containing substituent and H-11. ROESY correlations between H-12b (lowfield) and H_3-22, and between H-12b and H_3-21, hinted at their position on the same side of the macrocycle. The lack of NOE contact between H_3-21 and H-11 combined with the weak coupling of H-10 and H-11 suggested an approximate *anti* relationship of the methyl substituent at C-10 (CH_3-21) and H-11, corresponding to a *threo* configuration in our model (Figure 1). CH_3-21 shows a weak ROESY correlation to H-9a, placing them on the same side. The cross-peak in the ROESY spectrum between H-7 (δ 3.45) and a signal at δ 1.49 cannot be attributed unambiguously to H-9b or H-10 due to their identical chemical shift, but likely to H-9b according to our model. Therefore, we tentatively propose a 3*S**,5*S**,6*S**,7*S**,10*R**,11*R**,13*R** stereochemistry for the polyketide portion of **1**.[11] Lack of sufficient material, however, precluded the measurements of carbon−proton coupling constants and, therefore, a *J*-based configuration analysis for that portion.[12]

Similar to what has been described for **2**,[8] the glycoside portion of **1** could be related to the hemiketal portion on the basis of ROESY data (Figure 1), in particular due to correlations H_3-20/H-1′, H_3-20/H-2′, and H-5/H-1′. Establishment of the absolute stereochemistry by Mosher's analysis failed due to problems in identifying and isolating a suitable MTPA derivative, starting with only minute amounts of material that were available. However, structure **1** depicts the more likely absolute stereochemistry based on the configuration of the commonly occurring L-rhamnose, also present in related glycoside macrolides, aurisides A and B.[13]

Lyngbyaloside B (**1**) was weakly cytotoxic against KB cells with an IC_{50} value of 4.3 μM and exhibited a considerably smaller effect on LoVo cells ($IC_{50} \approx 15$ μM). Following the isolation of lyngbyaloside (**2**)[8] and lyngbouilloside (**3**),[9] compound **1** appears to be the third glycoside macrolide from a marine cyanobacterium. As mentioned above, compounds **1**−**3** structurally closely resemble aurisides A and B, cytotoxins isolated from the sea hare *Dolabella auricularia*.[13] However, most certainly those sea hare isolates are of cyanobacterial, dietary origin, as is the case for the dolastatins.[14] Other structurally related compounds are callipeltosides A−C, isolated from a marine lithistid sponge and postulated to be of microbial origin.[15] These compounds were also weakly cytotoxic, and studies on their mode of action have been initiated.[15a] Other marine glycoside macrolides are polycavernoside A and a number of congeners from the red alga *Polycavernosa tsudai*, which were responsible for fatal human intoxication resulting from ingestion of the red alga.[16]

Experimental Section

General Experimental Procedures. All NMR experiments were run on a Varian Unity Inova 500 spectrometer.

^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using residual solvent signals as internal references. The HSQC experiment was optimized for $^1J_{CH} = 140$ Hz, and the HMBC experiment for $^nJ_{CH} = 7$ Hz. HRESIMS data were acquired in positive ion mode on a Mariner electrospray time-of-flight biospectrometry workstation (PerSeptive Biosystems). The sample was dissolved in a 10 mM methanolic NH_4OAc solution and analyzed in flow injection mode. The mobile phase was MeOH−H_2O−MeCN (1:1:1) at 50 μL/min. Spectra were recorded over the *m*/*z* range 100−1000 at a scanning rate of 3 s. Lock mass calibration was at *m*/*z* 609 (reserpine). MS/MS was performed using electrospray ionization in positive ion mode on an Ultima QTOF spectrometer (Micromass). The sample, dissolved in a 10 mM methanolic NH_4OAc solution, was infused at 0.4 μL/min by a Harvard syringe pump. Fragmentation of the parent ion was recorded at a collision energy of 0 V (fragmentation by ionization alone) and at a collision energy of 10 V (fragmentation by applying an acceleration voltage of 10 V to the ions to push them through the high-pressure region).

Biological Material. The cyanobacterium *Lyngbya* sp. NIH309 was collected on April 18, 2000, at Ulong Channel, Palau. The organism is consistent with the description of *L. bouillonii*.[6] In addition to the known compounds lyngbyabellin A[17] and apratoxins A[7a] and C,[7b] the collection has already afforded the novel metabolites ulongamides B−F[7c] and lyngbyapeptins B and C.[7d] A specimen is deposited at the University of Hawaii at Manoa.

Extraction and Isolation. Extraction of the organism and fractionation of the lipophilic extract has been described previously.[7c] After solvent partition and silica gel chromatography, the fraction eluting with 5% *i*-PrOH in CH_2Cl_2 contained compound **1**, ulongamide F, and lyngbyapeptins B and C. The concentrated fraction was subjected to semipreparative reversed-phase HPLC (Ultracarb, 5 ODS 30, 250 × 10 mm, 3.0 mL/min, 65% aqueous MeCN; UV detection at 220 nm), accomplishing the separation of these compounds and their final purification. Compound **1** eluted at t_R 33.0 min (0.6 mg).

Lyngbyaloside B (1): colorless, amorphous solid; $[\alpha]^{25}_D$ −20° (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 233 (3.66), 240 (3.66), 246 (sh) (3.55) nm; ^{1}H NMR, ^{13}C NMR, HMBC, and ROESY data, see Table 1; HRESIMS *m*/*z* $[M + NH_4]^+$ 666.2804 (calcd for $C_{30}H_{49}{}^{79}BrO_{10} + NH_4$, 666.2847), *m*/*z* $[M + Na]^+$ 671.2375 (calcd for $C_{30}H_{49}{}^{79}BrO_{10} + Na$, 671.2407), *m*/*z* 439.1445 (6) (calcd for $C_{22}H_{32}{}^{79}BrO_4$, 439.1484); CIDMS with collision energy = 0 V on *m*/*z* 666, *m*/*z* 666/668 (100), 648/650 (7), 439/441 (68), 239 (5); CIDMS with collision energy = 10 V on *m*/*z* 666, *m*/*z* 439/441 (25), 421/423 (12), 359 (4), 341 (5), 323 (4), 230 (100), 221 (20), 195 (15), 177 (8).

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Supporting Information Available: Spectra of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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