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Laingolide, a novel 15-Membered Macrolide from *Lyngbya bouillonii* (Cyanophyceae)

Didier Klein, Jean-Claude Braekman, and Désiré Daloze

Laboratory of Bio-organic Chemistry, Faculty of Sciences CP 160/07, University of Brussels, Av. F. D. Roosevelt, 50
B-1050 Brussels, Belgium

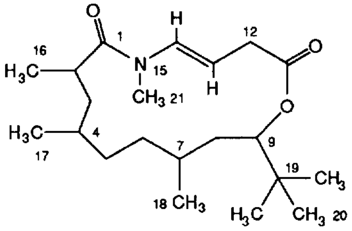
Lucien Hoffmann, and Vincent Demoulin

Laboratory of Algology, Mycology and Experimental Systematics, Department of Botany, University of Liège, Sart Tilman B22,
B-4000 Liège, Belgium.

Abstract: Laingolide (1), a novel 15-membered macrolide containing a lactam group was isolated from the blue-green alga *Lyngbya bouillonii*, collected on Laing Island (Papua-New Guinea). Its structure (without stereochemistry) was established by a detailed high-field 1D and 2D NMR study. Copyright © 1996 Published by Elsevier Science Ltd

Cyanophyceae, or blue-green algae, constitute a rich source of novel bioactive metabolites with unprecedented structures.[1] In the course of a screening program to evaluate blue-green algae as a source of interesting bioactive metabolites, we recently reported the isolation of several hapalindoles from the cultured cyanophyte *Hapalosiphon laingii*.[2] We now have investigated a sample of the recently described *Lyngbya bouillonii*,[3] from Laing Island in Papua-New Guinea, the type locality. A total of 6. 42 g of the dried alga was extracted with CH_2Cl_2, then EtOH, and finally MeOH, affording 0.022 g, 0.305 g, and 1.09 g, respectively. The pooled alcoholic extracts (1.395 g) were desalted, affording 86.2 mg of organic phase-soluble material which was toxic against *Artemia* nauplii. These extracts were thus combined and submitted to a Sephadex LH-20 column eluted with EtOH, affording a toxic fraction (54.6 mg) that was further chromatographied on silica gel (eluent: CH_2Cl_2-MeOH, from 98:2 to pure MeOH), followed by reversed-phase HPLC (C-18, MeCN-H_2O, from 7:3 to pure MeCN), affording 1.2 mg of laingolide (**1**), as an oil.

Laingolide (**1**) (HREIMS: $M^{+\cdot}$ at m/z 351.2761; calc. for $C_{21}H_{37}NO_3$: 351.2773; Δ=1.2 mDa) contained an ester and an enamide moieties (IR: 1732, 1648 and 1676 cm^{-1}; UV (MeOH): λ_{max} 240 nm, ε 10650). The structure of **1** (without stereochemistry) was solved by a combination of one- and two-dimensional NMR methods (^1H, ^{13}C, ^1H-^1H COSY, HMBC, HMQC). The ^1H NMR spectrum of **1** in $CDCl_3$ at 600 MHz (Table 1) exhibited signals for two mutually coupled vinylic methines (δ 5.20 and 6.90), indicating the presence of a



polarized *trans* double bond. The signal at δ 5.20 was coupled to an allylic methylene at δ 2.95 and 3.05, the latter signal being also long-range coupled (^4J) to the δ 6.90 methine. The spectrum also displayed signals for one methine vicinal to an oxygen atom at δ 4.78, an N-CH_3 group at δ 3.08, three methyl doublets at δ 1.18, 0.91 and 0.80 and a 9H singlet corresponding to 3 CH_3 groups at δ 0.88, which was assigned to a *t*-butyl group. The proton-decoupled ^{13}C NMR spectrum, measured at 125.72 MHz with a ^{13}C nanoprobe (Table 1), displayed signals for 21 carbon atoms. The presence of two C=O (δ 176.3 and 171.7), one quaternary C (δ 34.3), two vinyl CH (δ 131.9 and 104.8), four CH, five CH_2 and seven CH_3 (of which three were superimposed at δ 25.6) was deduced from the DEPT and APT spectra. The connectivity pattern of the molecule was inferred from ^1H-^1H COSY, HMQC and HMBC experiments in $CDCl_3$ and C_6D_6. The complete assignments of the ^1H and ^{13}C NMR spectra in $CDCl_3$ are reported in Table 1. Unfortunately, the sample of laingolide (**1**) decomposed during the long acquisition time needed for the measurement of the ^{13}C NMR spectra. Therefore, no information is available up to now on the stereostructure of this molecule.

Laingolide (**1**) appears to be a new type of macrocyclic derivative from blue-green algae, as it is formally derived from 4-*N*-methylaminobut-3-enoic acid linked to a 9-hydroxy-fatty acid. Whereas structural moieties deriving from 4-aminobut-2-enoic acid are frequently encountered in blue-green algae,[4] the 4-aminobut-3-enoic acid moiety present in laingolide seems to be much rarer.

Table 1. NMR data of laingolide (**1**) ($CDCl_3$, δ, *J* in Hz,)

Position	δ_C[a]	δ_H[b]	HMBC (C to H)[c]
1	176.3	-	Me-21, Me-16, H-3a, H-3b, H-4
2	34.5	2.81, 1H, ddd, 6.7, 6.7, 3.5	Me-16, H-4
3a	40.8	1.63, 1H, m	Me-17, Me-16
3b		1.05, 1H, m	
4	31.3	1.58, 1H, m	Me-17, H-2, H-3a
5a	33.7	1.26, 1H, m	Me-17, H-3
5b		1.13, 1H, m	
6a	33.3	1.26, 1H, m	Me-18
6b		1.02, 1H, m	
7	28.5	1.18, 1H, m	Me-18, H-5b[d]
8a	35.4	1.61, 1H, m	Me-18
8b		1.05, 1H, m	
9	79.1	4.79, 1H, dd, 11.4, 1.8	Me-20, H-8a[d]
11	171.7	-	Me-21, H-9[d], H-12a, H-12b
12a	36.3	3.05, 1H, ddd, 13.2, 6.4, 1.5	Me-21[d], H-14
12b		2.95, 1H, dd, 13.2, 9.6	
13	104.8	5.21, 1H, ddd, 13.8, 9.6, 6.4	Me-21, H-12a, H-12b
14	131.9	6.90, 1H, d, 13.8	Me-21, H-12a, H-12b
16	18.5	1.18, 3H, d, 6.7	H-3a, H-3b
17	20.6	0.91, 3H, d, 6.7	H-3a, H-4, H-5b[d]
18	20.6	0.80, 3H, d, 6.4	H-6b[d], H-8a
19	34.3	-	Me-20
20	25.9	0.88, 9H, s	Me-20, H-8b[d], H-9,
21	30.6	3.08, 3H, s	H-2, H-12b, H-14

[a]125.72 MHz, nanoprobe; [b]600 MHz; [c]Optimized for $^nJ_{CH}$ = 5 and 10 Hz; [d]correlations observed in C_6D_6.

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