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Labiatamides A, B, and other Eunicellan Diterpenoids from the Senegalese Gorgonian *Eunicella labiata*

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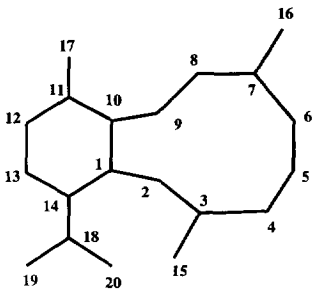
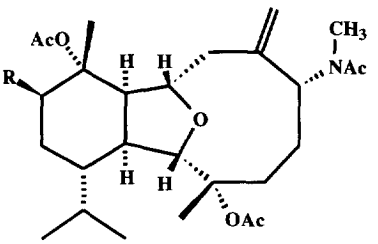
Abstract: Five new diterpenoids of the eunicellan class, labiatamides A-B (**1, 2**) and labiatins A-C (**3-5**) have been isolated from the organic extract of the Senegalese gorgonian *Eunicella labiata*. A unique feature of labiatamides A and B (**1, 2**) is the *N* -methyl acetamide group, an uncommon functionality in soft coral metabolites. Labiatin A (**3**), possesses an unprecedented ether linkage between C-2 and C-6. The structure elucidations of the new secondary metabolites were provided by comprehensive spectroscopic analyses. Labiatin B exhibited cytotoxic activity against human colon cancer cells (HCT-116) with ED_{50} = 0.85 μg/ml.

As part of our overall interest in the chemistry of gorgonian octocorals, we have had the opportunity to investigate several species found off the coasts of Senegal.[3] Few studies have been performed with any marine organism from this relatively remote area of Western Africa, and this is especially true for the gorgonian octocorals which are found in abundance in this region of the eastern Atlantic Ocean.[4] In this paper, we report the structures of five new eunicellan diterpenoids from *Eunicella labiata*, a relatively deep water gorgonian collected near Dakar, Senegal. Gorgonians of the genus *Eunicella*, from various geographical locales, have been a rich resource of unique, mainly diterpenoid metabolites. Eunicellin, the first example of the bicyclo [8.4.0] tetradecane "eunicellan" diterpenoid carbon skeleton, was reported by the Tursch and Djerassi groups in 1968 from the Mediterranean gorgonian *Eunicella stricta*.[5] Since this pioneering study, numerous eunicellan (also known as cladiellan) diterpenoids have been isolated from taxonomically diverse marine octocorals.[6-19] In this report, we describe the structure determination of labiatamides A and B (**1, 2**) and labiatins A, B and C (**3 -5**) from *E. labiata*. Labiatamides A and B are unusual amino diterpenoids with *N* -methyl acetamide functionalities. Labiatin A (**3**) is a eunicellan

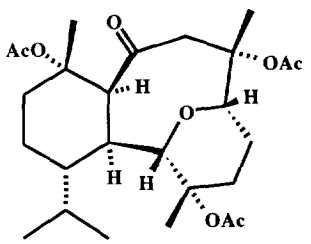


eunicellan

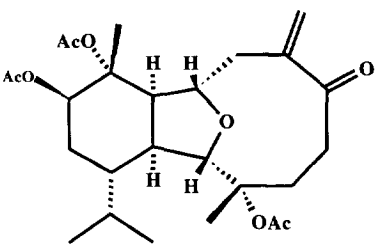


1, R = OAc, Labiatamide A

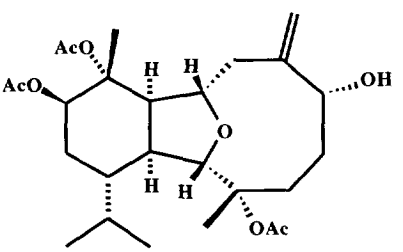
2, R = H, Labiatamide B



3, Labiatin A



4, Labiatin B



5, Labiatin C

diterpenoid with an unprecedented ether linkage between the C-2 and C-6 positions. Labiatins B and C (**4, 5**) possess the more common C-2 - C-9 ether linkage characteristic of this class of diterpenoids.

After collection, colonies of *E. labiata* were briefly air dried and immediately extracted twice with a mixture of $CHCl_3$ / MeOH (9/1). The combined organic extracts were reduced *in vacuo* to a brown oily residue which was then fractionated by vacuum flash chromatography using TLC grade silica gel and mixtures of isooctane / ethyl acetate. The medium polarity fractions were further purified by silica normal phase HPLC using the same solvents. Final purification yielded compounds **1-5**, which in total comprised slightly less than 3% of the organic extract. A common NMR characteristic of compounds **1-5** was the large number of acetyl methyl signals and five skeletal methyl equivalents, suggesting that the compounds were related polyacetylated diterpenoids.

A major component of the extract, labiatamide A (**1**), was isolated as a colorless oil which analyzed for $C_{29}H_{45}NO_8$ by combined mass spectrometric and ^{13}C NMR methods (see Table 1.). The most striking feature of the proton NMR spectrum of **1** (Table 2.) was the large number of methyl signals observed, consisting of four acetyl methyl singlets at δ 2.13, 2.09, 2.06, and 1.99, and two methyl singlets at δ 1.62 and 1.63 which were assumed to be vinyl methyls or methyls on oxygenated quaternary carbons. The presence of an isopropyl group in the molecule was also clearly illustrated by two doublets (integrating for 3H each) at δ 0.79 and 0.92 which were coupled to the same methine proton. Two one-proton singlets at δ 5.47 and 5.38 were assigned to a terminal olefinic methylene. Most interesting of all was the unusual methyl singlet at δ 2.72, which by its low field chemical shift was assumed to be attached to the lone nitrogen atom in **1**. The ^{13}C NMR spectrum of labiatamide A illustrated 29 carbon resonances, confirming the presence of four acetyl groups (δ 169.8, 169.7, 167.5, 169.4) and one terminal olefinic methylene (δ 141.9 -C, 120.1 $-CH_2$). The absence of any other double bonds indicated that the two methyls at δ 1.62 and 1.63 had to be attached to oxygenated carbons. Analysis of HMQC data allowed all protonated carbons to be correlated to their respective ^1H NMR signals (Table 2.).

On the basis of HRMS and ^{13}C NMR data, the molecule was concluded to possess eight degrees of unsaturation which indicated a tricyclic structure. The mass spectrum also showed an efficient loss of a C_3H_6NO fragment (*m/z* = 463; base peak) which indicated that labiatamide A possessed an *N*-methyl acetamide functionality. Consideration of the elemental composition and unsaturation data above illustrated that labiatamide A also contained an ether linkage. Given the source of these compounds, and the overwhelming similarity of the spectral data obtained in comparison with eunicellin, labiatamide A was concluded to be a closely related eunicellan diterpenoid. The connectivities and assignments of the carbon and proton resonances for labiatamide A were then subsequently made by interpretation of homonuclear and heteronuclear direct and long range 2D NMR experiments. The stereochemistry illustrated is based on interpretation of coupling constants in comparison with related eunicellan diterpenoids, and upon NOE experiments (see Figure at left). A long-range W coupling was observed between the protons at C-10 and C-12, thus allowing their assignment in 1,3-diequatorial positions within a rigid chair cyclohexane ring. X-ray experiments with related eunicellan derivatives have shown that the 6-membered ring adopts this conformation.[13] A typical ax - eq coupling constant between protons at C-1 and C-10 (4.1 Hz), and a typical ax - ax coupling constant (12.2 Hz) found between protons at C-1 and C-14 established the ring juncture as *cis* and placed an equatorial isopropyl functionality at C-14. The equatorial orientation of the isopropyl group was also confirmed by NOE measurements when irradiation of the isopropyl methyl groups produced intense enhancements of the protons at C-1 and C-2. Irradiation of those protons, in the reverse experiment, produced identical correlations.

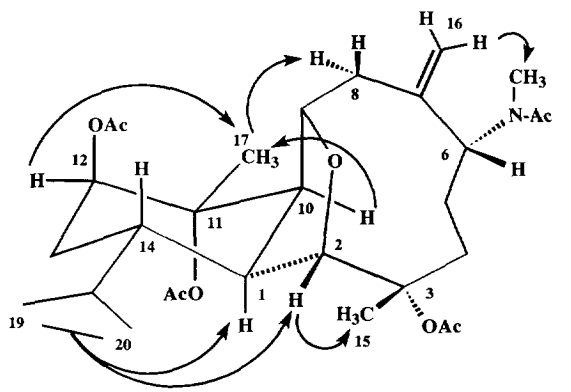


Figure. Proposed Three-Dimensional Structure of Labiatamide A. NOE results are indicated by arrows.

Table 1. ^{13}C NMR Data for Labiatamides A, B (**1, 2**) and for Labiatins A - C (**3 -5**)*

C#	**1**	**2**	**3**	**4**	**5**
1.	40.6 CH	41.7 CH	48.5 CH	42.2 CH	41.0 CH
2.	89.8 CH	91.1 CH	78.1 CH	89.5 CH	89.4 CH
3.	84.8 C	84.7 C	83.7 C	84.3 C	84.7 C
4.	29.5 CH_2	30.2 CH_2	27.5 CH_2	33.5 CH_2	29.9 CH_2
5.	29.5 CH_2	30.2 CH_2	19.5 CH_2	35.2 CH_2	29.9 CH_2
6.	70.9 CH	71.4 CH	78.0 CH	205.4 C	87.4 CH
7.	141.9 C	143.9 C	92.7 C	148.2 C	145.1 C
8.	42.6 CH_2	43.1 CH_2	44.2 CH_2	41.4 CH_2	41.7 CH_2
9.	78.8 CH	79.4 CH	204.6 C	77.8 CH	78.1 CH
10.	43.8 CH	43.8 CH	55.4 CH	47.3 CH	43.9 CH
11.	80.8 C	82.1 C	80.5 C	80.3 C	80.8 C
12.	73.2 CH	32.1 CH_2	32.1 CH_2	73.3 CH	73.4 CH
13.	22.6 CH_2	18.4 CH_2	19.8 CH_2	22.8 CH_2	22.8 CH_2
14.	36.5 CH	43.8 CH	36.5 CH	34.7 CH	35.9 CH
15.	22.2 CH_3	22.1 CH_3	23.6 CH_3	21.4 CH_3	21.7 CH_3
16.	120.1 CH_2	119.6 CH_2	19.6 CH3	119.4 CH_2	118.5 CH_2
17.	21.6 CH_3	22.4 CH_3	24.5 CH_3	22.6 CH_3	22.7 CH_3
18.	26.9 CH	27.7 CH	27.2 CH	27.5 CH	26.9 CH
19.	15.0 CH_3	15.4 CH_3	14.6 CH_3	14.8 CH_3	15.0 CH_3
20.	21.5 CH_3	21.9 CH_3	21.6 CH_3	21.3 CH_3	21.5 CH_3
Ac	169.8 C	169.4 C	170.9 C	170.1 C	170.3 C
(CO)	169.7 C	169.1 C	169.8 C	169.7 C	169.9 C
	169.5 C	169.0 C	169.1 C	169.6 C	169.7 C
	169.4 C	---	---	---	---
(Me)	22.6 CH_3	25.5 CH_3	22.1 CH_3	22.1 CH_3	22.5 CH_3
	22.5 CH_3	22.4 CH_3	21.9 CH_3	22.5 CH_3	22.3 CH_3
	21.2 CH_3	19.3 CH_3	21.9 CH_3	21.3 CH_3	21.2 CH_3
	19.6 CH_3	---	---	---	---
NMe	43.8 CH_3	46.5 CH_3	---	---	---

*Spectra recorded in $CDCl_3$ at 50 MHz. Assignments were facilitated by HMQC and HMBC experiments. Attached protons were determined by DEPT sequence experiments.

Table 2. ^{1}H NMR Data for Labiatamides A, B (**1, 2**) and Labiatins A - C (**3 - 5**)*

C#	1[a]	2[a]	3[b]	4[a]	5[a]
1.	2.21 dd (12.2, 4.2)	2.27 dd (11.6, 7.4)	2.41 dd (12.2, 4.4)	2.18 m	2.20 m
2.	3.64 s	3.58 s	3.71 s	3.58 s	3.62 s
4.	1.70 m	1.70 m	2.83 ddd (13.3, 4.0, 2.1)	2.18 m	1.50 m
		0.95 dt (13.3, 3.4)			
5.	2.20 m	2.05 m	1.05 m	2.75 m	2.10 m
6.	3.57 brd (10.9)	3.56 m	3.83 dd (10.9, 6.9)		4.61 dd (10.2, 2.9)
8.	2.49 d (13.6)	2.48 d (13.7)	3.39 d (12.7)	2.98 dd (13.7, 5.0)	2.55 d (13.7)
	2.66 dd (13.6, 4.5)	2.66 dd (13.7, 4.5)	2.47 d (12.7)	2.67 d (13.7)	2.83 dd (13.7, 5.2)
9.	4.59 dd (4.5, 10.5)	4.12 dd (4.5, 10.3)		4.31 ddd (9.8, 7.2, 5.1)	4.54 dd (10.4, 5.2)
10.	3.42 dd (10.5, 4.2)	3.15 dd (8.2, 10.3)	4.22 dd (4.4, 1.8)	3.65 dd (9.5, 7.2)	3.44 dd (10.4, 7.5)
12.	5.21 brs	nr	2.72 dt (12.3, 4.6)	5.04 brs	5.13 brs
			2.21 dt (12.3, 3.0)		
13.	1.76 m	nr	1.59 m	1.68 m	1.70 m
			1.33 m		
14.	1.45 m	1.45 m	2.17 m	1.47 m	1.50 m
15.	1.62 s	1.43 s	1.37 s	1.41 s	1.60 s
16.	5.47 s	5.46 s	1.28 s	5.58 s	5.47 s
	5.38 s	5.32 s		5.24 s	5.39 s
17.	1.63 s	1.39 s	1.55 s	1.58 s	1.53 s
18.	2.00 m	1.90 m	1.76 dh (6.9, 2.5)	1.78 m	1.95 m
19.	0.79 d (6.8)	0.79 d (6.8)	0.63 d (6.8)	0.78 d (6.8)	0.78 d (6.8)
20.	0.92 d (6.8)	0.95 d (6.8)	0.81 d (6.8)	0.90 d (6.8)	0.92 d (6.8)
Ac	2.13 s	2.03 s	2.04 s	2.04 s	2.09 s
	2.09 s	2.02 s	2.03 s	2.06 s	2.03 s
	2.06 s	1.94 s	1.62 s	2.10 s	1.96 s
	1.99 s				
NMe	2.72 s	2.72 s			

* Spectra were recorded in the solvent indicated at 360 MHz. a = $CDCl_3$, b = C_6D_6. Numbers in parentheses are *J* values in Hertz. Assignments were assisted by COSY experiments and by HMQC and HMBC heteronuclear correlation methods. nr = signals not resolved.

Analysis of dihedral angles between protons at C-1 and C-2 showed an almost 90° relationship, which was supported by the absence of coupling between these protons. Enhancement of the C-15 methyl resonance was observed upon irradiation of the C-2 proton, thus indicating the methyl group to be positioned in the "up" or β configuration. The *N* -methylacetamide functionality was placed in the "down" or α position on the basis of a significant enhancement of the *syn* C-16 olefinic proton upon irradiation of the *N* -methyl group. The equatorial orientation of the C-17 methyl group was deduced by similar NOE measurements which showed enhancements of the protons at C-10, C-12 and C-8 (the α proton only) upon irradiation. On the basis of COSY experiments and chemical shift arguments, the acetoxyl functionalities were located at C-3, C-11, and C-12 with the stereochemistries shown. Based upon these data, labiatamide A is proposed to possess the following relative stereochemistry: C-1 **S***, C-2 **S***, C-3 **S***, C-6 **R***, C-9 **S***, C-10 **R***, C-11 **R***, C-12 **R***, C-14 **S***.

Labiatamide B (**2**) was isolated in slightly smaller quantities. By HRMS and ^{13}C NMR methods, labiatamide B analyzed for $C_{27}H_{43}NO_6$, a molecular formula 58 mass units less than labiatamide A. From these data, and from the ^{1}H NMR characteristics of this compound, the molecule was concluded to be identical to labiatamide A except that it lacked one of the acetoxyl groups. The position of the missing acetoxyl was determined to be C-12 by comparison of spectral data. NOE measurements and analyses of coupling constants showed that **2** possessed the same relative stereochemistry as **1**.

Labiatin A (**3**), a major metabolite, was isolated as a viscous oil which analyzed for $C_{26}H_{40}O_8$ by HRMS and ^{13}C NMR methods. Although the molecule lacked the C-6 nitrogen atom, the spectral data were very similar to those derived from **1** and **2**. In the ^{1}H NMR spectrum of **3**, a new AB spin system at δ 3.39 and 2.47 was observed, and the chemical shift of the C-10 proton was significantly shifted to low field. These observations, in conjunction with a ^{13}C NMR band at δ 204.6, suggested that C-9 was the location of a new ketone carbonyl, and that the ether linkage had been rearranged within the molecule. Spectral studies, and in particular, COSY ^{1}H NMR, and HMQC and HMBC experiments, showed that the ether linkage was between the C-2 and C-6 positions. Irradiation of the C-16 methyl group enhanced the proton at C-6 and one of the C-8 protons, suggesting a *cis* relationship. Coupling constant analysis of the 6-membered ring ether showed it existed in a chair configuration (see Table 2.). Finally, as in **1** and **2**, evidence to assign the relative stereochemistry as C-1 **S***, C-2 **S***,C-3 **S***, C-6 **S***, C-7 **S***, C-10 **R***, C-11 **R***, C-14 **S*** was acquired by ^{1}H NMR and NOE studies.

Labiatin B (**4**) analyzed for $C_{26}H_{38}O_8$ by HRMS and ^{13}C NMR methods. Instead of the C-7 methyl and acetoxyl groups observed in **3**, labiatin B possessed an exocyclic methylene. Allylic coupling between the C-16 olefinic protons and the C-8 methylene protons supported this assignment. The upfield shift of the C-10 proton, replacement of the C-8 AB pattern with and ABX system, and relevant IR data, showed that the C-9 ketone had been replaced by an alcohol.or an ether. Based on the HMBC correlations observed between the C-9 C-2 protons and carbons, the ether linkage was assigned at this position. The presence of a ketone carbonyl and the absence of the C-6 methylene protons suggested that C-6 was the location of the carbonyl group. In labiatin B, the third acetoxyl group was positioned β at C-12 on the basis of the cyclohexane ring NMR data which were similar to labiatamide A. All other proton shifts and couplings indicated that **4** possessed the same C-1 **S***, C-2 **S***, C-3 **S***, C-6 **S***, C-9 **S***, C-10 **R***, C-11 **R***, C-12 **R***, C-14 **S*** relative stereochemistry.

Labiatin C (**5**) analyzed for $C_{26}H_{40}O_8$ by HRMS and ^{13}C NMR methods. Although isomeric with

labiatin A, the spectral data showed significant modifications had taken place. The 2D long range heteronuclear correlations suggested the same ring system as in labiatin B (**4**). From the ^{1}H and ^{13}C NMR spectra it was evident that the C-6 carbonyl had been reduced to a hydroxyl group. Irradiation of the C-6 proton, observed at δ 4.61, enhanced the C-15 methyl group indicating the alcohol is down or α. NOE measurements and analyses of coupling constants showed that labiatin C (**5**) possessed the same relative stereochemistry as labiatin B (**4**).

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EXPERIMENTAL

General. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer. Ultraviolet spectra were obtained in methanol using a Beckman Acta XIV spectrophotometer. Proton NMR spectra were recorded in deuteriochloroform or deuteriobenzene at 360 MHz, using a spectrometer constructed from an Oxford magnet and Nicolet-1180E Fourier transform data system, at the UCSD NMR Facility. Samples were prepared for NOEDS measurements by first degassing with nitrogen. Carbon-13 NMR spectra were recorded using an IBM WP-200SY spectrometer. HMBC and HMQC spectra were obtained using a Varian Unity 500 MHz spectrometer. High resolution mass spectral data were provided from the University of Iowa Mass Spectrometry Laboratory. Optical rotations were measured using a Perkin-Elmer model 141 polarimeter and a 10 cm microcell. All solvents were dried and distilled from glass.

Collection, Extraction and Isolation of Compounds **1-5**. Specimens of *Eunicella labiata* (450 gm wet wt.) were collected by hand using SCUBA at Konakhe, Senegal, at a depth of 40 meters, in the summers of 1988 and 1993. After collection and maceration, the colonies were soaked in a mixture of $CHCl_3$/MeOH (9/1). The organic extract was dried over sodium sulfate and reduced *in vacuo* to a brown oily residue. The residue (2.5 g) was chromatographed, by vacuum flash methods, over TLC grade (250-300 mesh) silica gel. Fractions eluted with 40% - 60% ethyl acetate in isooctane were further purified by silica HPLC using the same solvent mixtures. Labiatamide A (**1**), 10 mg (0.02 % wet wt.), eluted with 60% EtOAc in isooctane, labiatamide B (**2**), 10 mg (0.02 % wet wt.), eluted with 50% EtOAc in isooctane and labiatins A, B and C (**3 - 5**), 16 (0.04 % wet wt.) and 2.5 (0.005 % wet wt.) and 5 mg (0.01 % wet wt.), respectively, eluted with 35% EtOAc in isooctane. The new compounds were judged as pure on the basis of clean, "one spot" TLC results using several solvents, and on the basis of ^{1}H NMR and mass spectral results.

Labiatamide A (**1**): $[\alpha]_D$ = +12.8°, (c 0.60, $CHCl_3$); IR (film) 2964, 1750, 1735, 1685, 1370, 1230 cm^{-1}; EI HRMS: $[M\text{-}Ac]^+$*m/z* obsd 492.2937 $C_{27}H_{42}NO_7$ requires 492.2962.

Labiatamide B (**2**): $[\alpha]_D$ -6°, (c 0.20, $CHCl_3$); IR (film) 2940, 1760, 1685, 1370, 1244 cm^{-1}; EI HRMS [M-Ac]$^+$*m/z*- obsd 434.2882 $C_{25}H_{40}NO_5$ requires 434.2908.

Labiatin A (**3**): $[\alpha]_D$ +17.3°, (c 0.80, $CHCl_3$); IR (film) 3440, 2940, 1738, 1440, 1370, 1230 cm^{-1}; FAB HRMS [M+H]$^+$*m/z* obsd 481.2801 $C_{26}H_{41}O_8$ requires 481.2802.

Labiatin B (**4**): $[\alpha]_D$ +22.5° (c 0.30, $CHCl_3$); IR (film) 2940, 1734, 1685, 1440, 1370, 1235 cm^{-1}; EI HRMS [M-HOAc]$^+$ *m/z* obsd 418.2345 $C_{24}H_{34}O_6$ requires 418.2356; UV (MeOH): λ_{max} 219 nm (ε 15800).

Labiatin C (**5**): $[\alpha]_D$ -6° (c 0.40, $CHCl_3$); IR (film) 2948, 1734, 1691, 1450, 1372, 1251 cm^{-1}; FAB HRMS [M]$^+$*m/z* obsd 480.2723 $C_{26}H_{40}O_8$ requires 480.2724.

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