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Structures and absolute stereochemistry of nipponallene and neonipponallene, new brominated allenes from the red alga *Laurencia nipponica*

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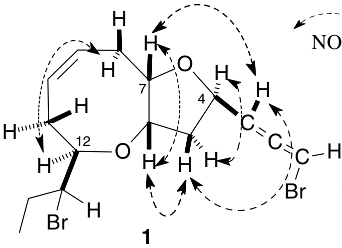
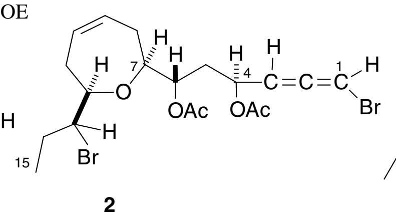
Abstract—Two new natural brominated allenes named as nipponallene **1** and neonipponallene **2** were isolated from the red alga *Laurencia nipponica*, collected near the Russian shore of the Sea of Japan (Troitsa Bay). The structures and absolute stereochemistry of **1** and **2** were elucidated using NMR spectroscopy, chemical transformations, modified Mosher's method and on the basis of biogenetic understanding.

Red algae of the genus *Laurencia* are known to be an unprecedented source of different terpenoid and non-terpenoid secondary metabolites of a C_{15} family, including halogenated cyclic ether enynes and related allenes.[1,2] It is of particular interest that species belonging to this genus, collected from different geographical areas often contain different sets of natural products.[3] In the course of our continuing interest in marine natural products from algae,[4] we studied the secondary metabolites from *Laurencia nipponica* (division Rhodophyta) collected from a depth of about 2–3 m in Troitsa Bay located on the North-Western part of the Sea of Japan in June, 1998. Fresh alga (dry weight 140 g) was extracted with EtOH and $CHCl_3$ and the combined extracts were concentrated to give a dark green oil (2 g) which was separated by column chromatography on silica gel KSK using a stepwise gradient (hexane→EtOAc). Following a combination of HPLC purification on normal and reverse phases, nipponallene[5] **1**, 138 mg (0.1% of dry weight) and neonipponallene[6] **2**, 6 mg (0.004% of dry weight) were isolated.

The molecular formula of **1** and its NMR spectral data (Table 1) showed that this compound is an isomer of the previously known laurallene[7] and pannosallene[8] from *L.* spp. However, the strong negative optical rotation, $[\alpha]_D^{22}$ −144 (*c* 0.1, EtOH) distinguished **1** from other known brominated allenes (for comparison, pannosallene and laurallene showed rotations of +64.3 and +173.6, respectively). Therefore, in contrast to other



1



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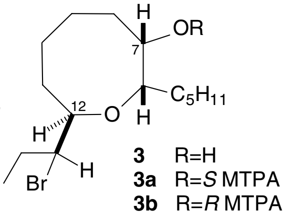

3 R=H
3a R=*S* MTPA
3b R=*R* MTPA

Keywords: Marine natural products; C_{15} nonterpenoids; Algae; *Laurencia*; Absolute stereochemistry; Biogenesis; 1D and 2D NMR spectroscopy.

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Table 1. ^{13}C and ^{1}H NMR data of **1** (125.7 and 500 MHz, respectively, C_6D_6) and **2** (75.5 and 300 MHz, respectively, $CDCl_3$)

	1			**2**[a]		
	δ_C	δ_H (J, Hz)	NOESY	δ_C	δ_H (J, Hz)	NOE
1	74.1 d	5.65 dd (5.6; 1.9)		74.9 d	6.11 dd (5.6; 2.0)	
2	201.1 s			202.0 s		
3	102.9 d	5.17 t (5.6)	H-5β, H-7	100.8 d	5.49 dd (5.6; 5.3)	H-4
4	74.0 d	4.70 dddd (7.2; 7.0; 5.6; 1.9)	H-5α	66.3 d	5.34 dddd (10.6; 2.0; 3.4; 5.3)	H-6, H-5
5	39.3 t	1.80 ddd (13.0; 7.0; 3.4)	H-6	34.5 q	2.14 ddd (14.6; 10.7; 3.4)	
		1.64 ddd (13.0; 6.0; 7.2)			2.01 ddd (14.6; 10.6; 2.8)	
6	73.7 d	3.68 br td (3.5; 6.0)	H-7, H-11α, H-13	71.3 d	5.10 ddd (10.7; 4.1; 2.8)	H-4, H-7
7	83.1 d	3.80 td (3.8; 11.0)	H-3, H-6	80.5 d	3.50 ddd (10.5; 4.1; 1.9)	H-6, H-8α, H-8β
8	29.9 t	2.20 m	H-12	32.7 t	2.33 ddq (16.3; 10.5; 2.1)	
		2.60 m			2.20 ddt (16.3; 6.3; 1.8)	
9	129.9 d[b]	5.55 m		129.0 d[b]	5.78 m	H-8α, H-8β, H-11
10	127.2 d[b]	5.55 m		128.9 d[b]	5.78 m	H-8α, H-8β, H-11
11	30.7 t	2.40 m		34.6 t	2.53 ddt (16.1; 6.9; 1.9)	
		2.52 m			2.42 dddd (16.1; 10.0; 1.8; 2.2)	
12	79.8 d	3.95 ddd (3.1; 6.9; 9.8)	H-8α	83.1 d	3.57 ddd (10.0; 5.6; 1.9)	H-13, H-11
13	58.0 d	3.82 ddd (2.9; 9.8; 8.1)		61.6 d	3.93 ddd (9.3; 5.6; 3.4)	H-12, H-15
14	28.2 t	1.54 qdd (7.3; 15.1; 8.1)		27.2 t	2.00 ddq (14.6; 3.4; 7.3)	
		1.74 dqd (2.8; 7.5; 14.9)			1.87 ddq (14.6; 9.3; 7.3)	
15	11.1 q	0.99 t (7.2)		12.3 q	1.07 t (7.3)	

[a] Acetate groups: ^{13}C 170.6 s; 170.3 s, 21.1 q, 20.9 q; ^{1}H 2.09 s; 2.11 s.

[b] Values can be interchanged.

Table 2. Selected ^{1}H chemical shifts

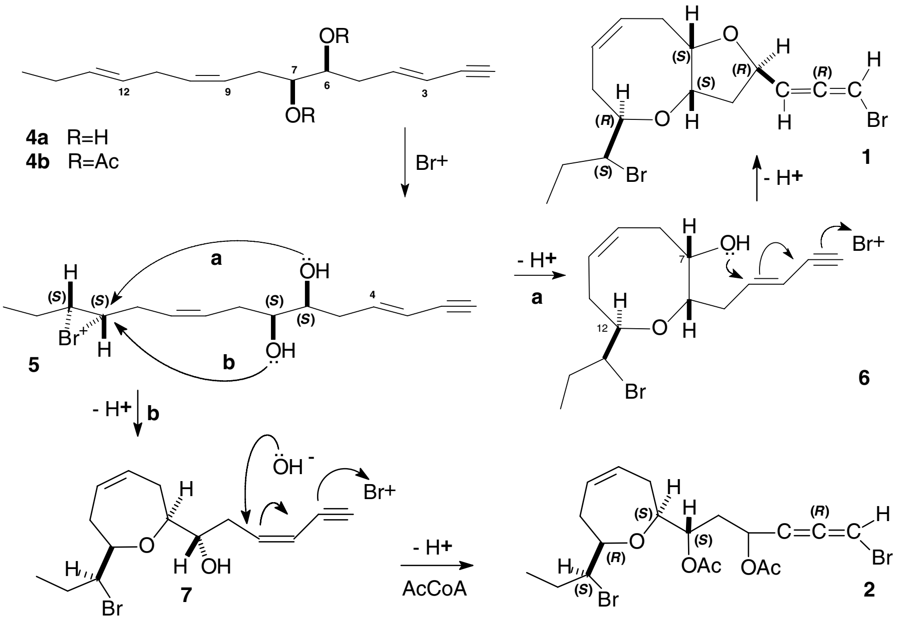
H	**3a**	**3b**	$\Delta\delta$
H-6	3.97	3.94	+0.03
H-7	5.14	5.15	−0.01
H-8	1.73	1.82	−0.09
H′-8	2.00	2.03	−0.03
H-12	3.76	3.75	−0.01
H-13	3.93	3.87	+0.06
H_3-15	1.02	1.00	+0.02

$\Delta\delta(\delta_{(S)\text{-ester}} - \delta_{(R)\text{-ester}})$ for the MTPA esters of **3** (300 MHz, $CDCl_3$).

known stereoisomers the configuration of the bromoallene moiety in **1** would be assigned as *R* by application of Lowe's rule.[9]

The relative configurations in nipponallene, excluding those of the allene moiety and at C-13, were established by NOESY (Table 1) and found to be the same as in laurallene.

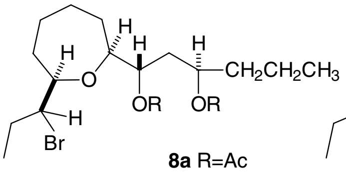
To determine the absolute stereochemistry of the nipponallene core between the possible two (4*R*,6*S*,7*S*,12*R* or 4*S*,6*R*,7*R*,12*S*), we carried out the hydrogenation of **1**



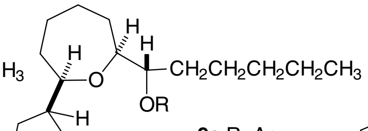
Scheme 1. Biogenesis of allenes **1** and **2**.

over Adams catalyst and obtained the derivative **3**. Its NMR spectra and optical rotation were practically identical to those of the analogous derivative obtained from laurallene which proved to have a*S*,4*R*,6*S*,7*S*,12*R*,13*S* absolute stereochemistry.[10] Next, we obtained (*S*)- and (*R*)-MTPA esters **3a** and **3b** from **3** using Mosher's method.[11] On the basis of the $\Delta(\delta\mathbf{3a} - \delta\mathbf{3b})$ values (Table 2), we established that C-7 in **3** and **1** have the *S*-configuration. As a result, the absolute stereochemistry a*R*,4*R*,6*S*,7*S*,12*R*,13*S* was suggested for nipponallene **1**. This conclusion was confirmed from biogenetic understanding.[12] Along with **1** and **2** we also isolated laurediol diacetate **4b** from our collection of *L. nipponica*. Diacetate **4b** had $[\alpha]_D^{25}$ −33 (*c* 0.070, $CHCl_3$) in contrast with $[\alpha]_D^{25}$ +14.7 (*c* 0.070, $CHCl_3$) for a mixture of laurediol diacetates with a predominance of the (6*R*,7*R*)-isomer found previously from another collection of the same alga.[13] Obviously, **4b** has the (6*S*,7*S*)-stereochemistry. Earlier laurediols were suggested to be biosynthetic precursors of a series of halogenated C_{15} nonterpenoids in red algae, and the formation of oxygen-containing cycles in these natural products (**1**, **2**, and intermediates **6**, **7** should be included in the list) was postulated to take place as a result of attack of the hydroxyl groups on bromonium ions such as **5** (Scheme 1). In the latter process, only transoidal configurations 12*R*,13*S* or 12*S*,13*R* may be realized (reflecting the 12*E*-geometry in **4a**). Taking into consideration that the 12*R* configuration in **1** followed from data obtained on the basis of application of Mosher's method and NOESY, it can be concluded that C-13 in **1** has *S*-configuration. Compound **1** was earlier obtained as a side product (along with laurallene) during bromo-etherification of prelauretin.[14]

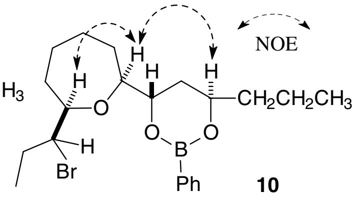
The strong negative optical rotation for **2** $[\alpha]_D^{22}$ −203 (*c* 0.1, EtOH) also suggested that it had the *R*-configuration at the bromoallene moiety.[9] From the same biogenetic considerations (Scheme 1) and NOE (Table 1), the a*R*,6*S*,7*S*,12*R*,13*S* configuration may be suggested for **2**. To confirm this and establish the stereochemistry of C-4, we obtained derivatives **8a** and **9a** after hydrogenation of **2** over Adams catalyst. Treatment of **8a** with MeONa/MeOH followed by reaction with 2,4,6-triphenyl-1,3,5,2,4,6-trioxatriborinane yielded **10**. Its relative stereochemistry was established by NOESY experiments (Table 3).



8a R=Ac
8b R=H



9a R=Ac
9b R=H
9c R=*R* MPA



10

The C-6 absolute configuration in **2** was established by a modified Mosher's method after transformation of **9a** into **9b** with MeONa/MeOH and then obtaining *R*-MPA ester **9c** by reaction with the corresponding acid chloride in CH_2Cl_2 with addition of Et_3N and DMAP.[15] The NMR spectra of **9c** were recorded at different temperatures. As a result, based on the $\Delta\delta(\delta_{T_1} - \delta_{T_2})$ values[16] (Table 4), the 6*S*-configuration was determined for compound **9c** and, therefore, for neonipponallene **2**. All other configurations followed from these data and relative stereochemistries of **2** and **10**. To the best of our knowledge, neonipponallene which proved to have the a*R*,4*S*,6*S*,7*S*,12*R*,13*S* absolute configuration is the first representative of natural halogenated allenes containing an oxepane ring.

Table 3. ^1H NMR data of **10** (500 MHz, C_6D_6)

H	δ_H (*J*, Hz)	NOESY
H_3-1	1.02 t (7.5)	
H-2	1.65 m	
H′-2	1.52 m	
H-3	1.32 m	
H′-3	1.61 m	H-6
H-4	4.26 m	H-7
H-5	1.56 m	
H′-5	1.87 m	
H-6	4.06 dt (8.0; 4.4)	H′-3
H-7	3.42 dt (8.0; 4.8)	H-4, H-12
H-8	1.57 m	
H′-8	1.75 m	
H-11	1.66 m	H-13
H′-11	1.83 m	
H-12	3.56 ddd (4.1; 6.2; 9.3)	H-7, H′-14
H-13	3.84 ddd (2.8; 6.2; 9.4)	H-11
H-14	1.91 m	
H′-14	2.14 m	
H_3-15	1.13 t (7.0)	H-12

Table 4. Selected ^1H chemical shifts

H	**9c** (25 °C)	**9c** (−70 °C)	$\Delta\delta$
H_3-1	0.86	0.87	−0.01
H-4	0.76	0.44	+0.32
H′-4	0.88	0.65	+0.23
H-5	1.39	1.35	+0.04
H-7	3.52	3.52	0.00
H-8	1.51	1.52	−0.01
H′-8	1.67	1.73	−0.06
H-11	1.74	1.78	−0.04
H′-11	1.94	1.94	0.00
H-12	3.64	3.74	−0.10
H-14	1.78	1.76	+0.02
H′-14	2.03	2.05	−0.02
H_3-15	1.06	1.07	−0.01

$\Delta\delta(\delta_{T_1} - \delta_{T_2})$ ($T_1 > T_2$) for the MPA esters of **9b** (500 MHz, $CDCl_3$).

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6. HREIMS, *m/z*: found for $[M^{+}-{}^{79}Br]$ 413.0949, calculated for $C_{19}H_{26}O_5{}^{79}Br$, 413.0934. $[\alpha]_D^{22}$ −203 (*c* 0.1, EtOH). ^{13}C NMR and ^{1}H NMR spectra, see Table 1. EIMS, *m/z* (int.,%): 494 (0.4) $[M]^{+}$, 434 (1) $[M-AcOH]^{+}$, 413 (5), 411 (5) $[M-Br]^{+}$, 374 (1), 353 (4), 355 (4), 311 (12), 313 (12), 293 (12), 295 (12), 275 (2), 263 (7), 245 (6), 247 (6), 231 (4), 217 (8), 219 (8), 213 (10), 203 (9), 185 (10), 173 (8), 161 (17), 143 (44), 128 (29), 109 (80), 93 (35), 79 (58), 67 (100), 55 (35).
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