Tetrahedron Letters Vol. 21, pp 2787 - 2790 0040-4039/80/0715-2787$02.00/0

PALISADINS A,B AND RELATED MONOCYCLOFARNESOL-DERIVED SESQUITERPENOIDS FROM THE RED MARINE ALGA LAURENCIA cf. PALISADA

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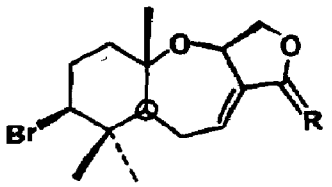
Summary: Five new monocyclofarnesol-derived sesquiterpenoids, along with the previously report lactone aplysistatin, have been isolated from the tropical red alga Laurencia cf. palisada. The structures of these new compounds were defined by spectral and chemical analyses, including their partial interconversion with aplysistatin.

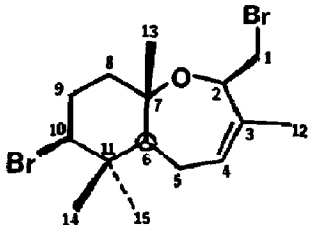
As part of our long-term interest in defining the scope and diversity of terpenoid biosynthe in the red algal genus Laurencia[1], we have extended our initial studies in more temperate regions to tropical species of the Indo-Pacific. Herein we wish to report the structures of five new ses quiterpenoids from Laurencia cf. palisada Yamada, which are derived by simple transformations fro a monocyclofarnesol precursor. Along with these compounds, we have also isolated small amounts o the cytotoxic lactone, aplysistatin (1), reported earlier as a component of the Australian sea ha Aplysia angasi[2]. Aplysistatin appears to be a minor metabolite of L. palisada, but it is also slowly produced when the major metabolite, palisadin A, is exposed to air.

Chloroform-methanol(2/1) extraction of the fresh alga[3], collected in Palau, May 1979, (Weste Caroline Islands), followed by silica gel chromatography(open-column and HPLC) yielded five new compounds assigned as structures 2-6, and a very small amount (ca. 3 mg) of aplysistatin (1). Th lactone we obtained was identical (including optical rotation at the sodium-D line) to an authen sample of aplysistatin kindly provided by Professor Pettit[2].

The major metabolite (2% extract) palisadin A (2), an oil, showed $[\alpha]_D 19.5^\circ$ (c 1.5, $CHCl_3$), analysed for $C_{15}H_{23}O_2Br$ by elemental analysis and by low resolution mass spectrometry (M^+ m/e = 31 316). Infrared absorptions at 1450, 1375, 1150, 1100 and 1070 cm^{-1} suggested 2 contained gem-di- methyl and ether functionalities. Based upon ^1H and ^{13}C NMR data (Tables 1 and 2), the 4 degrees of unsaturation could readily be assigned to one trisubstituted olefinic bond, two cyclic ethers, and to one carbocyclic ring. Jones' oxidation, or exposure to air in benzene overnight, yielded 10% conversion of 2 to aplysistatin. Based on the interconversion with 1, palisadin A is assigne including absolute stereochemistry, as the bis-ether 2.



1, R = O
2, R = H_2



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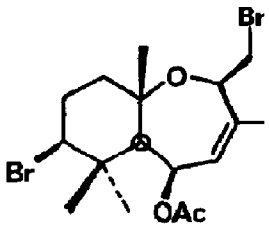
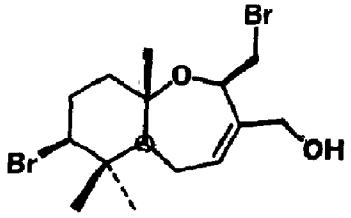
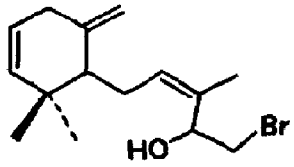


4



5



6

Palisadin B (3), an oil, $[\alpha]_D$ 8.8° (c 1.3, $CHCl_3$), analysed for $C_{15}H_{24}OBr_2$ by mass spectrometry (M^+ m/e 378/380/382), and showed $M^+ - CH_2Br$ fragmentation. In the carbon-13 NMR spectrum of 3 a triplet at 36.2 ppm, with residual coupling of 22.4Hz (corresponding to proton chemical shift of ca. 3.5 ppm) confirmed a primary bromide. The spectral comparison with 1 and 2, and decouplin studies at 220 MHz, firmly established structure 3 and allowed the unambiguous assignments in Tables 1 and 2[6].

5-Acetoxypalisadin B (4), an oil, $[\alpha]_D$-131.7° (c 0.6, $CHCl_3$), analysed for $C_{17}H_{26}O_3Br_2$ by mass spectrometry (M^+ m/e 436/438/440), and showed acetate ester features in its infrared spectrum (ν_{CO} = 1724 cm^{-1}), and ^1H and ^{13}C NMR spectra(see Tables). Complete spin-decoupling studies fixed the acetate group at C-5 in the "up" or trans position to the C-6 bridgehead proton. A 0 H coupling constant between these two protons was born out by a ca. 90° dihedral angle in the molec lar model. As with 3, the total structure analysis was reinforced by interpretation of ^{13}C NMR data, including methyl group assignments based upon calculations of predicted γ-shielding effects Further, a qualitative $Eu(fod)_3$-induced shift measurement of ^1H NMR signals yielded qualitative support for structure 4, and the Δδ values obtained are listed in Table 1.

12-Hydroxypalisadin B (5), isolated as 0.2% of the extract, showed $[\alpha]_D$ 19.7° (c 0.4, $CHCl_3$) and analysed for $C_{15}H_{24}O_2Br_2$ by both ^{13}C NMR and mass spectrometry (M^+-Br only, m/e 315/317). Acetylation (Ac_2O/py) yielded a monoacetate ($\gamma_{C=O}$ 1740 cm^{-1}), and treatment with 5% KOH in MeOH gave a smooth conversion of 5 to palisadin A, thus establishing the absolute structure and stereochemistry of this metabolite. A shift of the C-12 AB pattern at δ4.22/4.02 in the ^1H NMR spectrum of 5 to δ 4.52/4.40 in the corresponding acetate confirmed the C-12 placement of hydroxyl.

Palisol (6) was, along with aplysistatin, isolated as a very minor metabolite of the extract of L. palisada (0.01%). Palisol showed a hindered hydroxyl stretching frequency absorption in its

Table 1, ^{1}H NMR Data for Compounds 2-6[a], Recorded at 220 MHz (couplings in Hz)

C#	2	3	4	(Δδ)	5	6
1	4.10 dd(8,8) 3.95 dd(8,8)	3.73 dd(11,3) 3.41 dd(11,7)	3.72 dd(11,3) 3.45 dd(11,8)	(0.5) (0.4)	3.93 m 3.54 dd(12,10)	3.50 dd(9,9) 3.39 dd(9,5)
2	4.95 bs	4.54 bs	4.53 d(10)	(0.5)	4.68 bs	4.77 ddd(9,5,1)
4	5.63 bs	5.63 d(8)	5.73 d(8)	(4.5)	5.90 d(8)	5.30 m
5	2.40 m	2.05 m	5.81 d(8)		2.27 m	2.00 m
6	2.40 m	2.05 m	2.27 m	(0.5)	1.86 m	2.32 m
8	1.85 m 1.55 m	1.77 m	2.00 m	(0.5)	1.86 m 1.68 m	2.60 m
9	2.25 m	2.25 m	2.27 m	(0.5)	2.27 m	5.52 ddd(10,4,4)
10	3.95 dd(12,5)	3.95 dd(12,5)	3.90 dd(12,4)	(0.4)	3.93 m	5.36 ddd(10,1,1)
12	4.45 bs	1.27 s	1.80 s	(0.2)	4.22 d(11) 4.02 d(11)	1.70 s
13	1.37 s	1.36 s	1.68 s	(1.0)	1.33 s	4.70 s, 4.10 s
14	1.00 s	0.95 s	1.10 s	(1.1)	0.93 s	1.02 s
15	1.25 s	1.15 s	1.25 s	(0.7)	1.13 s	0.95 s
OAc	-	-	2.11 s		-	-

Table 2, ^{13}C NMR Data for Compounds 2-6[a], Recorded at 20 MHz.

C#	2	3	4	5[d]	6[d]
1	75.4t[b]	36.2t	34.9t	35.8[b]	37.8
2	71.0d	70.7d	70.1d	66.1	70.4
3	141.9s	136.1s	142.6s	133.2	133.2
4	121.1d	129.4d	127.1d	120.7	123.1
5	26.3t	25.9t	69.7d	25.9	32.5[c]
6	51.8d	52.8d	53.8d	52.4	52.9
7	78.3s	77.5s	77.9s	77.6	145.4
8	37.5t[c]	36.7t	39.4t	36.7[b]	30.4[c]
9	32.7t[c]	32.9t	32.9t	32.9	129.9
10	66.3d	66.3d	66.2d	66.1[c]	137.0
11	40.9s	40.8s	41.4s	40.8	37.2
12	72.0t[b]	21.0q	21.3q	69.6[c]	17.5
13	21.9q	22.0q	21.6q	22.0	110.1
14ax	18.0q	17.9q	18.8q	18.0	25.0
15eq	30.8q	30.7q	30.9q	30.7	25.2
OAc	-	-	(25.4q,170.4s)	-	-

[a] Recorded in $CDCl_3$ solution with internal TMS as standard. Assignments aided in 2-4 by residual coupling constant analysis.

[b,c] Assignments may be reversed.

[d] Multiplicities were not recorded and assignments are tentative.

infrared spectrum (γ_{OH} 3640 cm^{-1}), and acetylation (Ac_2O/py) yielded a monoacetate, $[\alpha]_D$ -0.6° (c 0.51, $CHCl_3$). Proton NMR analysis of 6, and its acetate, allowed the assignment of bromine C-1 and hydroxyl at C-2, as well as illustrated the C-4 through C-6 and C-8 through C-10 isolat spin systems (Table 1). Analysis of the ^{13}C NMR spectrum from this alcohol, particularly consi ing the C-12 methyl at 17.5 ppm and the C-5 methylene at 30-35 ppm, suggested the assignment of Z stereochemistry at the C-3 - C-4 olefin, based upon model compounds[8].

Acknowledgements

We wish to thank Dr. Jim Norris, Smithsonian Institution, Washington, D. C., for his close taxonomic guidance, and Professor G. R. Pettit for an authentic sample of aplysistatin. This research is a result of financial support from the National Science Foundation, Oceanography Section, for both laboratory research in La Jolla, and for our use of R/V ALPHA HELIX in Palau.

References and Notes

1. B. M. Howard and W. Fenical, Progress in Phytochemistry, Volume 7, 1980. in press.
2. G. R. Pettit, C. L. Herald, M. S. Allen, R. B. VonDreele, L. D. Vanelle, J. P. Y. Kao, and W. Blake, J. Am. Chem. Soc., 99, 262 (1977).
3. This alga has been tentatively assigned as L. palisada by comparison with the literature description of this plant from Taiwan as described by Yamada[4]. Voucher # US-071231 has be assigned to this specimen, and it has been placed on deposit in the National Herbarium in the Smithsonian Institution, Washington, D. C.
4. Y. Yamada, Univ. Calif. Publ. Botany, 16, 185 (1931).
5. According to the nomenclature proposed by Pettit, et al.[2], compound 2 would be 3S-bromo-5S 12R,14S-aplysist-7,8-ene. Trivial names have been assigned here for these metabolites sin 3-6 cannot be named using the ether-based ring system aplysistane. It should be pointed o that 1-6 are closely related to the snyderols from L. snyderae; see B. M. Howard and W. Fe Tetrahedron Lett.41 (1976).
6. Only relative stereochemistry is suggested for compounds 3 and 4.
7. P. Crews and E. Kho-Wiseman, Tetrahedron Lett. 2483 (1978).
8. P. Crews and E. Kho-Wiseman, J. Org. Chem., 42, 2812 (1977).

(Received in USA 26 February 1980)