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MANOALIDE, AN ANTIBIOTIC SESTERTERPENOID FROM THE MARINE SPONGE LUFFARIELLA VARIABILIS (POLEJAEFF)

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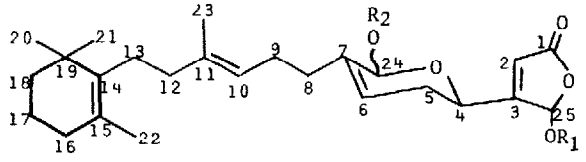
Abstract -- The structure of manoalide (1), a new sesterterpenoid antibiotic isolated from a marine sponge, has been determined by spectral analysis and chemical transformations.

A recent paper from this laboratory described the mokupalides,[2] which are hexaprenoids possessing trimethylcyclohexenyl and γ-hydroxybutenolide end groups that were isolated from a sponge, Megalopastas sp., collected at Enewetak atoll, Marshall Islands.[3] We now wish to report isolation and structure of a pentaprenoid with identical end groups but with one C_5 moiety cyclyzed to an α,β-unsaturated δ-lactol function. The structure of this compound, which we are naming manoalide[4] (1), is based on the following data.



1	$R_1 = R_2 = H$
2a,b	$R_1 = R_2 = Ac$
3a,b	$R_1 = Ac$, $R_2 = H$

The sponge, Luffariella variabilis (Polejaeff), is a dense dark brown animal, which was collected in August 1977 in Palau, Western Carolines, at -20 to -35 m.[5] The methylene chloride extract of the powdered freeze-dried sponge, as did its major constituent (1), showed significant in vitro activity against Streptomyces pyogenes and Staphylococcus aureus. Manoalide was isolated as a colorless amorphous solid (58 mg) from the CH_2Cl_2 extract (3.4 g) by successive chromatographies BioSil A (CH_2Cl_2/EtOAc 3 1), prep TLC (2000 μ silica, CH_2Cl_2/EtOAc 2 1), and LC (Partisil, CH_2Cl_2/EtOAc 2 1), in 0.08% from dried animal. A weak mass spectral peak at m/e 416 coupled with an intense M^+-H_2O at m/e 398 (398.2459; calcd for $C_{25}H_{34}O_4$, 398.2457) suggested

a molecular formula of $C_{25}H_{36}O_5$. The base peak at m/e 137 was reminiscent of the mokupalides[2] and pointed to a $C_{10}H_{17}$ alkylated cyclohexenyl end group. The γ-hydroxybutenolide terminus was secured by uv maxima (MeOH) at 227 (ε 5000) nm and (MeOH/$^-$OH) at 246 (ε 7700) nm, the latter reversible in acid, and by IR (CH_2Cl_2) bands at 3580, 1790 sh, and 1765 cm^{-1}. Close agreement of thirteen ^{13}C NMR resonances of 1 with corresponding signals of hydroxy mokupalide[2] fully confirmed the structure of the two termini (Table 1).

Table 1. Partial ^{13}C NMR (C_6D_6) Data of 1 and of Hydroxymokupalide[6]

	Chemical Shift (δ)	
C	Manoalide (1)	Hydroxymokupalide
1	172.3 (s)	172.1 (s)
2	117.7 (d)	117.1 (d)
3	169.1 (s)	169.9 (s)
25	99.1 (d)	99.3 (d)
14	136.7 (s)	135.7 (s)
15	127.3 (s)*	126.6 (s)
16	33.1 (t)	32.6 (t)
17	20.1 (t)	19.5 (t)
18	40.3 (t)	39.6 (t)
19	35.2 (s)	34.8 (s)
20	28.9 (q)	28.5 (q)
21	28.9 (q)	28.5 (q)
22	20.1 (q)	19.7 (q)

*in acetone-d_6

A C_{25} isoprenoid with the two proven end groups should have a composition of $C_{25}H_{38}O_3$. This differs from the formula of monoalide by two additional oxygen atoms and one ring, ^{13}C NMR data preclude one more double bond. Reaction of 1 with Ac_2O/pyridine furnished C-25 epimeric diacetates (2a,b) thus revealing a second hydroxy group. Manoalide (1) exhibits ^{13}C NMR signals at δ 63.3 (d, C-4) and 91 7 (d, C-24), which show that the second hydroxy group is part of a hemiacetal function. The diacetates (2a,b) were separated by LC (Partisil, hexane/EtOAc 3 1) and fully characterized. Significant ^1H NMR data are shown in Table 2. Decoupling experiments confirmed the assignments. Treatment of 1 with one mole Ac_2O/pyridine yielded C-25 epimeric monoacetates, 3a,b, separable by LC (Partisil, CH_2Cl_2/EtOAc 40 1), which could be converted to the diacetates 2a,b by further Ac_2O/pyridine treatment. Both monoacetates were fully characterized. The more abundant epimer on reaction with pyridinium chlorochromate[7]

Table 2. Partial ^{1}H NMR (C_6D_6) Data of Epimeric Diacetates 2a,b[8]

Compound	Chemical Shifts of H-25	H-2	H-4	H-24	H-6
2a	6.97 d J ∿1	5.97 dd J=2,∿1	4 64 ddd J=10,5,2	6.69 s	5.56 bd J ∿4
2b	7.06 d J ∿1	5.66 dd J=2,∿1	4.44 ddd J=10,4,2	6.56 s	5.56 bd J ∿5

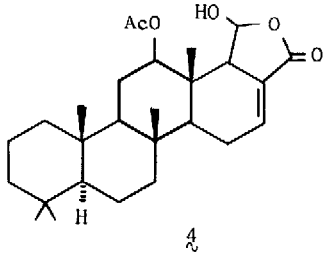
was oxidized to a monoacetate δ-lactone, λ_{max}^{MeOH} 211 nm (11,000), $\nu_{max}^{CH_2Cl_2}$ 1800, 1772, 1730 cm^{-1}, both functions retaining α,β-unsaturation. Significant ^{1}H NMR data ($CDCl_3$): δ 6.97 (d, J < 1, H-25), 6.56 (bt, J = 4, H-6), 6.33 (dd, J ∿ 2, <1, H-2), 5.15 (2 overlapping multiplets, H-4, H-10), 2.58 (bdd, J = 7, 4 H_2-5). Decoupling experiments confirmed these assignments.

Position of the δ-lactol was determined by homonuclear spin decoupling of one of the diacetates (2a). Irradiation of the H-4 signal (δ 4 64) collapsed the H-2 signal to a doublet ≈1 Hz (δ 5.97), while irradiation of the H-2 signal affect the signals for H-4 to a doublet of doublets, J = 10, 5 Hz and H-25 (δ 6.97) to a singlet. Finally, irradiation of the H-25 resonance changed the H-2 signal to a doublet, J = 2 Hz. The axial nature of the H-4 proton can be deduced from its coupling constants to the two C-5 protons, J = 10, 5 Hz.

The mass spectrum of the lactone provided further evidence for its position along the isoprene chain. The molecular ion at m/e 456 first loses acetic acid (m/e 396.2301, calcd 396.2299 for $C_{25}H_{32}O_4$), this fragment in turn loses the $C_{10}H_{17}$ end group (m/e 260 = 398-137 + 1), which is followed by loss of a C_5H_8 group (m/e 192). The δ-lactol, therefore, must be placed as shown in 1.

Trans stereochemistry of the C-10,11 olefin was inferred from the ^{13}C NMR signal at 16.3 (q) ppm assigned to C-23. In (E)-3-methyl-3-hexene the methyl signal is observed at 15.7 ppm in contrast with a δ 22.9 signal for the (Z)-isomer.[9]

Manoalide (1) so far is without close structural analog, but its structure is reminiscent of the tetracarbocyclic sponge sesterterpene scalarin (4).[10]



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REFERENCES AND NOTES

1. East-West Center Grantee, 1977/78. On leave from the University of Sri Lanka, Colombo.

2. M. B. Yunker and P. J. Scheuer, J. Am. Chem. Soc. 100, 307 (1978).

3. Since publication of Ref. 2 the sponge has been identified by Dr. Klaus Reutzler, National Museum of Natural History, Washington, D.C. 20500.

4. Manoa Valley is the location on Oahu, where this work was carried out.

5. The sponge was collected by Dr. Mark Yunker and identified by Professor P. Bergquist, University of New Zealand.

6. Remaining ^{13}C NMR signals of 1 with their assignments are 137.7, 137.3 (s, C-11, C-7), 123.6, 121.1 (d, C-10, C-6), 91.7 (d, C-24), 63.3 (d, C-4), 40.9, 40.3 (t, C-8, C-12), 33.1 (t, C-5), 28.5 (t, C-9), 26.5 (t, C-13), 16.3 (t, C-23).

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8. Comparative ^1H NMR data of 1 ($CDCl_3$), 3a (C_6D_6) and 3b (C_6D_6).

Compound	H-25	H-2	H-4	H-24	H-6
1	6.13 (s)	6.07 (s)	4.85 (dd, J=8,6)	5.32 (s)	5.69 (br t, J≈3)
3a	7.05 (d, J<1)	6.12 (dd, J≈2,<1)	4.83 (ddd, J=10,4,≈2)	5.14 (d, J=4)†	5.45 (overlaps with H-10, m)
3b	7.21 (d, J<1)	5.72 (dd, J≈2,<1)	4.64 (ddd, J=10,4,≈2)	5.20 (d, J=4)†	5.46 (overlaps with H-10, m)

†Coupled to R_2 = H which in 3a resonates at δ 2.72 (d, J=4) and in 3b at δ 3.14 (d, J=4). This (R_2 = H) proton is not observed in the ^1H NMR spectrum of 1.

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