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SPONGIOLACTONE, AN UNUSUAL ß-LACTONE DITERPENE ISOVALERATE BASED ON A NEW REARRANGED SPONGIANE SKELETON FROM SPONGIONELLA GRACILIS.

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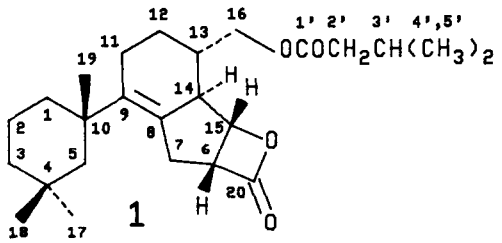
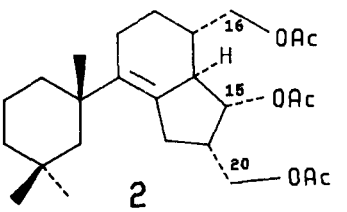
Abstract. - From a further investigation of the extractives of the mediterranean sponge Spongionella gracilis a new diterpene isovalerate, spongiolactone (1), was isolated and its stereostructure elucidated on the basis of chemical and physicochemical evidence.

Our investigation of the secondary metabolites of the mediterranean sponge Spongionella gracilis has resulted in the isolation and identification of a series of unusual nor- and bis-nor-diterpenes[1-4]. As for the former class of isolated compounds, a common origin from a spongiane precursor was hypothesized and a plausible biogenetic scheme was proposed[4].

In the course of reisolating quantities of these compounds for biological assays, we encountered a diterpene isovalerate, spongiolactone (1), whose structural features somewhat resemble those of the previously isolated metabolites from S. gracilis, thus suggesting it is also derived from a similar precursor but through a different biogenetic pathway.



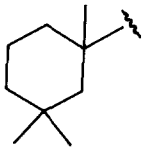


This new diterpene was isolated as an optically active colourless oil ($[\alpha]_D$ +67.6, c 1.7, $CHCl_3$) from the chloroform-methanol (1:1) extract of the fresh tissues of Spongionella gracilis, collected in the Bay of Naples in the Summer 1986, through flash chromatography on silica gel, followed by reverse phase HPLC on a µ-Bondapak C_{18} column (eluent: CH_3CN-H_2O, 85:15). The molecular formula, $C_{25}H_{38}O_4$, was deduced by HRMS in combination with ^{13}C-NMR data (Table). The IR spectrum showed two carbonyl absorptions at 1830 cm^{-1}, typical of a ß-lactone, and 1730 cm^{-1} attributed to an ester derivative of isovaleric acid on the basis of the mass spectrum, which diplayed an intense ion at m/z 300 indicating the facile loss of $C_5H_{10}O_2$, and

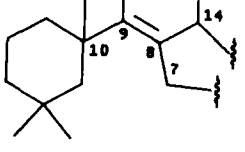
both the ^{1}H- and ^{13}C-NMR spectra (Table), which contained all the signals pertinent to an isovaleric acid unit. The mass spectrum also corroborated the presence of a lactone showing an intense ion at m/z 256 (M^{+}-isovaleric acid-CO_2).

The ^{13}C-NMR spectrum showed only two resonances attributable to fully substituted olefinic carbons (δ 133.7 and 139.4), in addition to the two carbonyl signals at δ 171.8 and 172.9, in the sp^2 region. Thus, from a consideration of the molecular formula the diterpene moiety must incorporate three carbocyclic rings, the last degree of unsaturation being due to the ß-lactone functionality. The formulation of a complete and rational gross structure for the compound under investigation along with the total assignment of both the ^{1}H- and ^{13}C-NMR spectra was accomplished through extensive decoupling work and the use of ^{13}C-^{1}H shift correlation 2D-spectroscopy via ^{1}J and long range[5,6]. The ^{1}H-NMR spectrum showed the presence of three Me singlets at δ 0.77, 0.84 and 0.96. Considering that only two sp^3 quaternary carbon atoms are indicated by the ^{13}C-NMR spectrum (δ 31.4 and 39.4), at least two methyls must be linked to the same carbon. Furthermore, the two fully substituted carbon atoms are separated by an isolated methylene carbon since two geminal protons appeared as doublets at δ 1.93 and 1.02 (the former signal was further split into triplets with J= 1.2 Hz by long range couplings). A set of signals (centered at δ 0.98, 1.10, 1.25, 1.47 and 1.90) accounted for six protons altogether, and, on the basis of ^{13}C- ^{1}H-NMR correlations via ^{1}J, these must belong to three methylenes. Although the values of all the coupling constants could not be determined owing to the complexity of the six-spin system and/or partial overlapping with other signals, homonuclear decoupling experiments provided evidence that the methylenes in question are contiguous and not coupled with the rest of the hydrogens, apart from long range couplings of the signals at δ 1.90 and 1.25 with the above doublet at δ 1.93. These results allowed us to recognise the presence of the same cyclohexane system (partial structure A) already encountered in other metabolites isolated from S. gracilis. This is further supported by the above mentioned long range couplings among the protons resonating at δ 1.93, 1.90 and 1.25 typically observed in cyclohexane rings in the chair conformation, and by the mass spectrum of 1 where the base peak at m/z 125 is attributable to the fragment deriving from the scission of C9-C10 bond[2].

The disposition of the tetrasubstituted double bond was established as follows. The ^{1}H-NMR spectrum of 1 displayed signals relative to five allylic protons which, on the basis of ^{13}C-^{1}H-2D correlation, belong to one methyne and two methylene carbons, δ 2.42 (14-H), 2.29 and



A



B

Table. ^{1}H- and ^{13}C-NMR data for spongiolactone 1[a]

Position	δ_C	δ_H (J)	H/C long-range correlation
		Hax 0.98 ddd (12.0,12.0,5.0)	
1	38.3		Me-19
		Heq 1.90 m	
2	20.9	1.47 m	
		Hax 1.10 ddd (12.0,12.0,5.0)	
3	39.7		Me-17, Me-18
		Heq 1.25 m	
4	31.4		Hax-5,Heq-5,Me-17,Me-18
		Hax 1.02 d (14.0)	
5	49.9		Me-17, Me-18, Me-19
		Heq 1.93 dt (14.0, 1.2)	
6	54.3	3.90 ddd (11.0,6.0,6.0)	Ha-7
		Ha 3.04 bdd (16.0,11.0)	
7	30.5		
		Hb 2.66 bdd (16.0,6.0)	
8	133.7		H-6
9	139.4		Ha-7, Me-19
10	39.4		Hax-5, Heq-5, Me-19
		Ha 2.29 m	
11	26.3		
		Hb 1.99 m	
		Ha 1.83 m	
12	26.8		
		Hb 1.28 m	
13	36.8	1.66 m	
14	50.2	2.42 bdd (12.0,4.4)	
15	79.9	4.73 dd (6.0,4.4)	Ha-7
		Ha 4.14 dd (11.0,6.6)	
16	67.6		
		Hb 4.04 dd (11.0,6.6)	
17	26.5[b]	0.77[c] s	Me-18
18	32.7[b]	0.84[c] s	Me-17
19	30.3	0.96 s	
20	171.8		Ha-7
1'	172.9		H-2'
2'	43.3	2.19 d (6.6)	H-4', H-5'
3'	25.6	2.07 m	H-4', H-5'
4'	22.4	0.94 d (6.6)	H-2'
5'	22.4	0.94 d (6.6)	H-2'

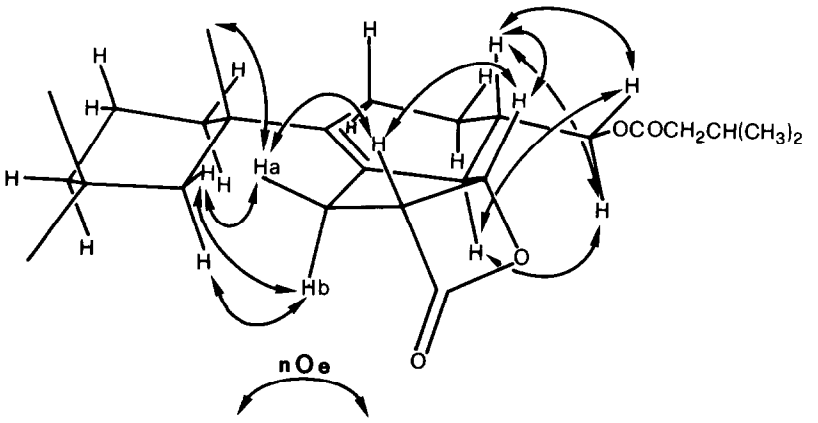
a δ values ($CDCl_3$) are in ppm from TMS. Assignments are based on ^{13}C-^{1}H shift correlated 2D-NMR spectroscopy via ^{1}J and long range (COLOC). These experiments were performed adjusting the fixed delays to give maximum polarization transfer for J_{C-H} = 135.0 and 6.25 Hz, respectively.

b-c Values with identical superscript within each column may be interchanged.

1.99 (11-H_2), 3.04 and 2.66 (7-H_2), respectively. The latter methylene and the methyne must be linked to the same carbon (C8) since the pertinent protons are homoallylically coupled with 11-H_2. The fourth substituent of the olefinic system (C10) was deduced by a COLOC experiment

which showed correlation from 19-H_3 to C9. The above NMR data allowed the extension of partial structure A to B.

Figure



The completion of the gross structure was straightforward and based on extensive spin decoupling experiments which showed the connectivities C7-C6-C15-C14-C13-(C16)-C12-C11.

The COLOC experiment revealed a set of three- and two-bond couplings which fully agree with the proposed structure (see Table).

Additional evidence for the structure was furnished by LAH reduction of 1 followed by acetylation which afforded the expected triacetate 2, whose structure was assigned on consideration of its spectral data. Compound 2, $[\alpha]_D$ = -10.3 (c 0.4, $CHCl_3$), m/z 328 (M^+-2AcOH), 313 (M^+-2AcOH-CH_3), 268 (M^+-3AcOH), 253 (M^+-3AcOH-CH_3), ν_{max} ($CHCl_3$) 1740 and 1235 cm^{-1}, ^1H NMR: δ 4.90 (1H, dd, J= 8.0 and 8.0 Hz, 15-H), 4.13 (1H, dd, J= 11.0 and 4.4 Hz, 16-Ha), 4.04 (2H, d, J= 6.6 Hz, 20-H_2), 3.98 (1H, dd, J= 11.0 and 6.2 Hz, 16-Hb), 2.80 (1H, bdd, J= 16.5 and 8.4 Hz, 7-Ha), 2.51 (1H, m, 6-H), 2.29 (2H, m, 7-Hb and 14-H), 2.03 (6H, s, acetates), 2.02 (3H, s, acetate), 0.96 (3H, s, 10-Me), 0.85 and 0.80 (3H each, s's, 4-Me's). ^{13}C-NMR: δ 171.0 (s), 170.9 (s), 170.4 (s), 138.3 (s), 129.1 (s), 78.2 (d), 67.3 (t), 64.1 (t), 49.3 (t), 48.2 (d), 40.1 (t), 39. (s), 38.9 (d), 38.4 (t), 37.9 (d), 33.4 (t), 32.8 (q), 30.2 (q), 31.5 (s), 27.1 (t), 26.7 (q), 26.4 (t), 22.7 (t), 20.9 (q), 20.9 (q) and 20.8 (q).

The overall relative stereochemistry of 1 was accomplished by nOed's data depicted in Figure.

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