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Lissoketal, a Spiroketal from the Palauan Ascidian *Lissoclinum voeltzkowi*

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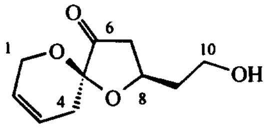
Abstract: Specimens of *Lissoclinum voeltzkowi* from Palau contained lissoketal (**1**), which was identified by analysis of spectral data. Copyright © 1996 Elsevier Science Ltd

Although alkaloids constitute the majority of natural products from ascidians,[1] a small but significant number of acetogenins have been described. These include the didemnenones,[2] the asciatrienolides,[3,4] lissoclinolide,[5] the didemnilactones,[6] and some simple alkyl sulfates.[7] We now report the presence of a new acetogenin, lissoketal (**1**), from specimens of the ascidian *Lissoclinum voeltzkowi*.

The encrusting grey ascidian *Lissoclinum voeltzkowi* (Michaelson, 1920) was collected by hand from sea grass blades in shallow waters in Palau and was kept frozen until it was extracted with methanol to obtain a dark green gum, which showed no bioactivity in simple antimicrobial or brine shrimp toxicity assays. The dichloromethane soluble material from the methanol extract was separated by reversed and regular phase chromatography to obtain a fraction with an interesting ^{1}H NMR spectrum. Purification by HPLC on silica using 4:3 ethyl acetate/hexane as eluant gave lissoketal (**1**, 0.02% dry wt.).



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Lissoketal (**1**), $[\alpha]_D = +2°$ (c 0.14, MeOH), was obtained as a colorless oil. The molecular formula, $C_{10}H_{14}O_4$, was obtained from high resolution mass measurement (*m/z* 199.0966 $[MH]^+$). The infrared spectrum contained bands at 3440 (hydroxyl), 1765 (ketone), 1085 and 1025 (ether) cm^{-1} and the UV spectrum showed only end absorption. The ^{13}C NMR spectrum (Table 1) contained 10 signals that included a ketone signal at δ 209.7, two olefinic methine signals at 126.3 and 122.8, a spiroketal signal at 99.3, an oxymethine signal at 72.6, and two oxymethylene signals at 61.9 and 59.8. The spiroketal must therefore be bicyclic. A COSY analysis of the ^{1}H NMR spectrum (Table 1) revealed two spin systems: a *cis*-olefin flanked by an oxymethylene group and a methylene group and a $-CH_2-CH(OR)-CH_2-CH_2OH$ entity. The 18.5 Hz geminal coupling constant for the H-7 protons (δ 2.76 and 2.25) suggested that the ketone was at C-6 and the IR band at 1765 cm^{-1} required that ketone to be in a 5-membered ring. Thus, there must be an ether ring between C-8 and the spiro center at C-5 and a second ether ring between C-5 and C-1. The HMQC and HMBC experiments confirmed these assignments. The relative stereochemistry was defined by NOESY and NOEDS experiments that showed a significant enhancement of the H-4 signal at δ 1.91 on irradiation of the H-8 signal at 4.55. Insufficient material remained to determine the absolute configuration of lissoketal (**1**).[8]

Table 1. ^{13}C (75 MHz, methanol-d_4) and ^{1}H NMR (300 MHz, methanol-d_4) data for lissoketal (**1**).

C#	δ_C	δ_H	mult., *J* (Hz)	COSY	HMBC
1	61.9	4.34	br d, 15	H-1′, H-4, H-4′	C-2, C-3, C-5
		4.12	br d, 15	H-1, H-2/3, H-4	C-2, C-3, C-5
2	122.8	5.80	br s	H-1′, H-4′	C-1, C-4
3	126.3	5.80	br s	H-1′, H-4′	C-1, C-4
4	29.4	2.57	br d, 18	H-1, H-1′, H-4′	C-5, C-6
		1.91	br d, 18	H-1, H-2/3, H-4	
5	99.3				
6	209.7				
7	41.4	2.76	dd, 18.5, 6	H-7′, H-8	C-5, C-6
		2.25	dd, 18.5, 9	H-7, H-8	C-6, C-8, C-9
8	72.6	4.55	m	H-7, H-7′, H-9	C-10
9	39.6	1.96	m, 2 H	H-8, H-10	C-7, C-8, C-10
10	59.8	3.75	t, 2 H, 6	H-9	C-8, C-92

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8. The ascidian was collected by Larry Sharron and Mary Kay Harper and was identified by Dr. Françoise Monniot (Paris Museum voucher # MNHN: A2 Lis 138). We thank the Coral Reef Research Foundation for providing logistical support in Palau and the Government of Palau for a collecting permit that precludes biological screening by commercial entities. The research was supported by funds from the California Sea Grant College Program (NOAA grant NA36RG0537, project R/MP-60) and a postdoctoral fellowship from Deutsche Forschungsgemeinschaft to C.H.

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