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THE STRUCTURE OF THE SIDE CHAIN OF THE FROG ALKALOID PUMILIOTOXIN B

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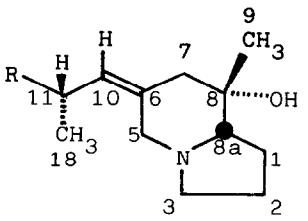
Summary: The E configuration at the double bond and threo relation for diol moiety of the pumiliotoxin B side chain were defined, respectively, through nuclear- Overhauser effects and comparison with model threo- and erythro- diol compounds.

Pumiliotoxins, first isolated from the Panamanian frog Dendrobates pumilio, belong to two structural classes: pumiliotoxin A (1) and B (2) are 8-hydroxy-8-methyl-6-ylidene-1-azabicyclo[4.3.0]nonanes, while pumiliotoxin C is a 2,5-dialkyl-cis-decahydroquinoline[1,2]. A relatively simple member of pumiliotoxin A class was isolated from an Ecuadorian frog, Dendrobates tricolor: X-ray analysis of this alkaloid 251D (3) provided not only its structure and absolute configuration, but the key to the structure of pumiliotoxin-A class of dendrobatid alkaloids[3]. Recently the alkaloid 251D has been synthesized from L-proline[4]. The structures of pumiliotoxin A and B were deduced from magnetic resonance studies to be as in Fig. 1 with R: $-CH_2CH=CCH_3-CHOH-CH_2CH_3$ for pumiliotoxin A and R: $-CH_2CH=CCH_3-CHOH-CHOH-CH_3$ for pumiliotoxin B. The configuration Z or E at the double bond and the configuration of the hydroxy groups in pumiliotoxin A and B remained uncertain. This communication reports on results of the configuration studies on the double bond and relation (threo or erythro) between 15- and 16-hydroxy groups of pumiliotoxin B.

Fig. 1



12 13 19 15 16 17

1 R: $-CH_2-CH=CCH_3-CHOH-CH_2CH_3$

2 R: $-CH_2-CH=CCH_3-CHOH-CHOH-CH_3$

3 R: $-CH_2-CH_2-CH_3$,

4 R: $-CH_2-CH=CCH_3-CHO$

5 R: $-CH_2-CH=CCH_3-COOCH_3$

Definition of the double bond as E configuration was based primarily on nuclear-Overhauser (NOE) effects. Thus, irradiation of the C-15 proton at δ 3.65 resulted in a marked intensity enhancement (14%) in the C-13 olefinic proton at δ 5.39, while irradiation of the C-19 methyl at δ 1.58 resulted in no significant intensity enhancement in the same olefinic proton. Manganese dioxide oxidation of pumiliotoxin B yielded an aldehyde $C_{17}H_{27}NO_2$ (4, m/z 277.2038, δ 9.37 for -CHO, 2,4-dinitrophenylhydrazone m/z 457) through cleavage of the glycol moiety. The aldehyde could be oxidized further to the carboxylic acid methyl ester (m/z 307, δ 3.75 for $-OCH_3$) following the Corey's method[5]. The chemical shifts for the C-13 protons in the aldehyde (δ 6.40) and in the carboxylic acid methyl ester (5, δ 6.67) are compatible with E-configuration of the double bond. Calculated chemical shifts[6,7] for the aldehyde and methyl ester having E-configuration are δ 6.35 and δ 6.53, while for the corresponding compounds having Z-configuration δ 6.61 and δ 5.96 (for further details, see ref. 8).

The hydroxyl groups on C-15 and C-16 of pumiliotoxin B were revealed to be in the threo configuration by comparison with model diol compounds (6, threo and 7, erythro) which were synthesized under stereo control as follows (Fig. 2):

A methyl ketone (8), which was easily obtained from tiglic aldehyde, produced predominantly erythro diol (7) by $LiAlH_4$ or $NaBH_4$ reduction[9] and subsequent debenzylation with $Na-NH_3$ (erythro/threo ratio, 90-95/10-5). The threo diol (6) was obtained from an aldehyde (9) with CH_3MgBr[10] and then $Na-NH_3$ (erythro/threo ratio, 15/85). The stereochemistry of both compounds was confirmed by nuclear-Overhauser effects in experiments in which irradiation at C-5 proton (δ 4.43) on the cyclic phenylboronide (11) of the threo diol resulted in an 11% enhancement in the resonance peak due to the methyl group on carbon-4

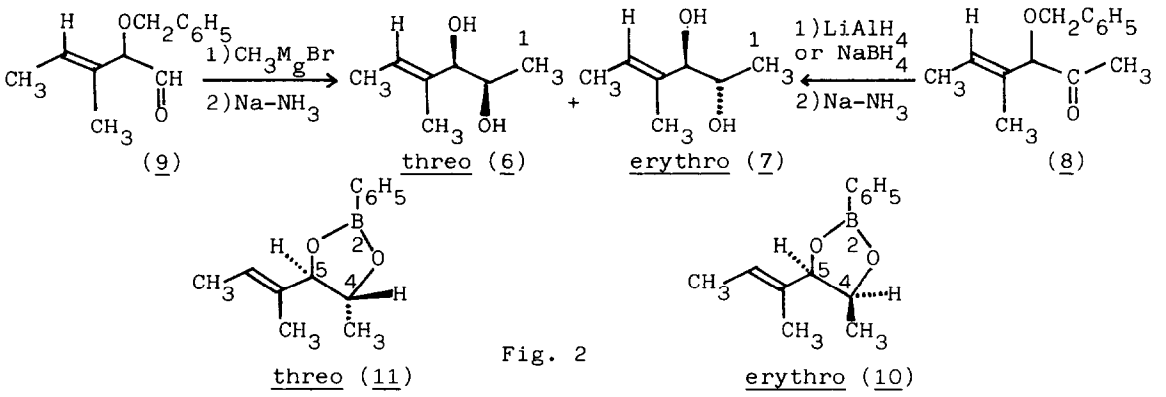


Fig. 2

(δ 1.42) and irradiation at C-4 proton (δ 4.35) resulted in an 8% enhancement in the same methyl group. In the case of the cyclic phenylboronide (10) of the erythro diol, an irradiation at the methyl group on carbon-4 (δ 1.21) resulted in a 7% enhancement in the C-4 proton (δ 4.75) with no significant enhancement in the C-5 proton (δ 4.92). Upon comparison of the model diol's spectra (Table 1), larger differences in the chemical shifts were observed between the cyclic phenylboronides (10, 11) than between the free diols (7, 6). The chemical shifts of C-16 (δ 3.74) and C-15 proton (δ 3.65) of pumiliotoxin B (2) were downfield at 4.29 ppm and 4.37 ppm, respectively, in the phenylboronide derivative. Thus, the chemical shifts of pumiliotoxin B and its phenylboronide are in all respects consonant with those of the model threo diol (6) and its boronide derivative (11).

Table 1. Chemical shifts of pumiliotoxin B, model threo- and erythro- diols and their phenylboronides. Solvent $CDCl_3$.

	Pumiliotoxin B			threo-Diol		erythro-Diol	
	free (2)	Phenyl-boronide		free (6)	Phenyl-boronide (11)	free (7)	Phenyl-boronide (10)
C-15 H	3.65	4.37	C-5 H	3.68	4.43	3.89	4.92
C-16 H	3.74	4.29	C-4 H	3.77	4.35	3.80	4.75
C-17 CH_3	1.09	1.40	CH_3*	1.05	1.42	1.11	1.19

* C-1 CH_3 in (6), (7); CH_3 on C-4 in (10), (11)

In conclusion, the present data allow a definition of the relative configuration of the side chain of pumiliotoxin B with the 13, 14-double bond in the E-configuration and the C-15, 16 diol moiety as the threo configuration[10]. The 13, 14-double bond in pumiliotoxin A and 7-hydroxy derivatives (allopumiliotoxins) of pumiliotoxin A and B also appear to have the E-configuration, and threo diol relation in the side chain of the 7-hydroxy derivatives of pumiliotoxin B are inferred from the similar behavior in nmr of their phenylboronides[8].

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