CYTOTOXIC BISPYRONES FROM *ONCHIDIUM* SP.: ABSOLUTE STEREOCHEMISTRY OF ONCHITRIOLS I AND II

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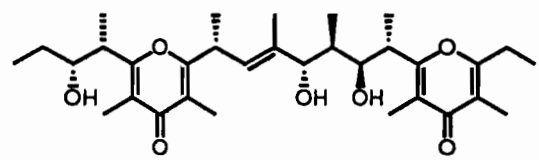
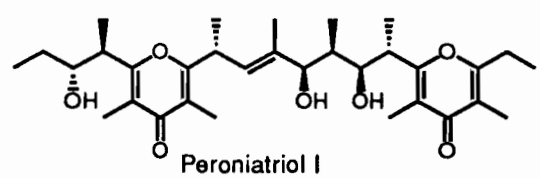
Recently, Ireland and coworkers reported the structure of Peroniatriol I and II isolated from the saponified extracts of *Peronia peronii* (1).These polypropionates present a bispyrone structure similar to that of Ilikonapyrone isolated from *Onchidium verruculatum* (2). Although an X-ray crystallographic analysis of the acetonide of Ilikonapyrone, proved the general structure and the relative stereochemistry, the absolute stereochemistry could not be deduced from that study.

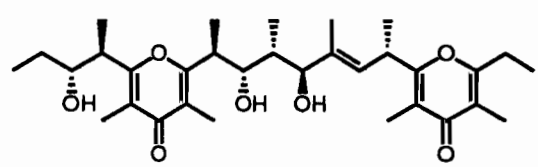
A successful synthetic process (3) of optically active left wing segments of these compounds has been recently published but still, the absolute stereochemistry remain unknown.



Peroniatriol I



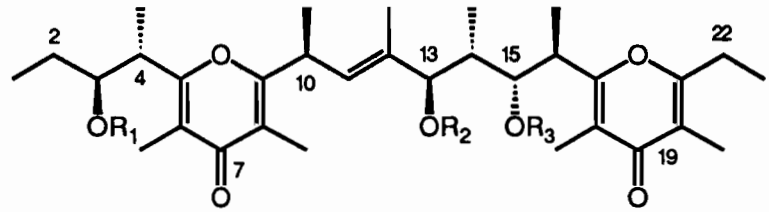
Peroniatriol I



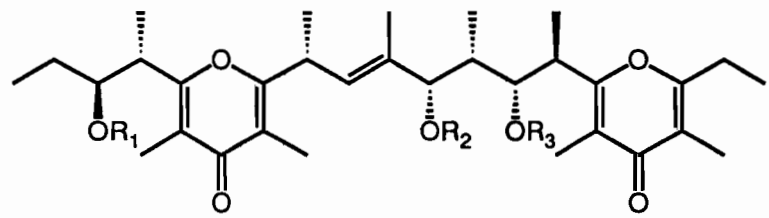
Ilikonapyrone

In the course of an study on the cytotoxic components of New Caledonia marine organisms, we isolated from *Onchidium sp*., a pulmonate mollusc, a serie of eight acetates and propionates (**1-4, 6-9**) that were separated by hplc and saponified to give two new bis-pyrone polypropionate triols named Onchitriol I (**10**) and Onchitriol II (**10**).

We report here the structure and absolute stereochemistry of **5** and **10**, obtained by use of the Mosher's nmr method.

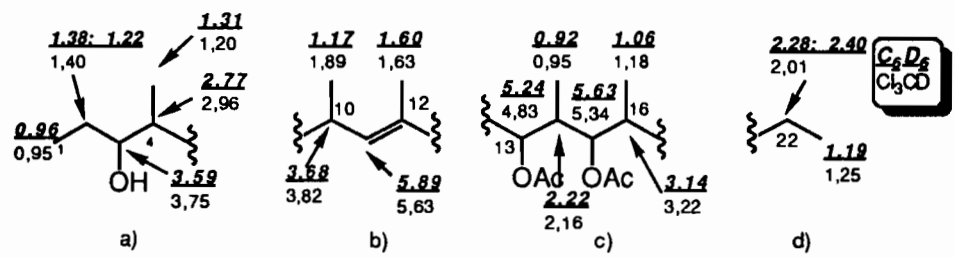


1 R_1=H, R_2=R_3=Ac
2 R_1=H, R_2=Ac, R_3=Pr
3 R_1=H, R_2=Pr, R_3=Ac
4 R_1=Ac, R_2=R_3=Pr
5 R_1=R_2=R_3=H

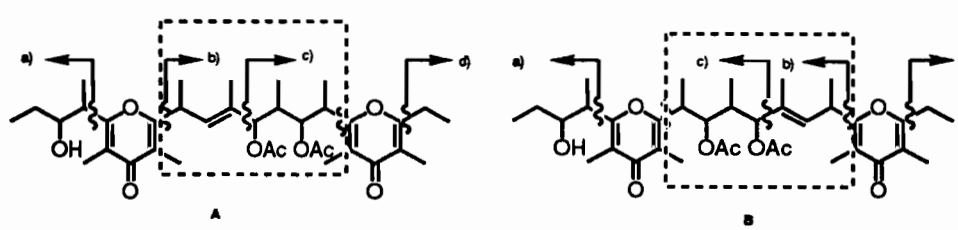


6 R_1=H, R_2=H, R_3=Ac
7 R_1=H, R_2=H, R_3=Pr
8 R_1=R_3=Ac, R_2=H
9 R_1=R_2=R_3=Ac
10 R_1=R_2=R_3=H

The skeleton and position of the functional groups were deduced by extensive NMR studies. COSY and C-H correlated spectra showed, in addition to the two pyrone rings, the presence of the four relevant spin systems, a-d shown and that could be arranged in two different ways, forming either an Ilikonapyrone-like structure (a-c-b-d) or a Peroniatriol-type one (a-b-c-d).



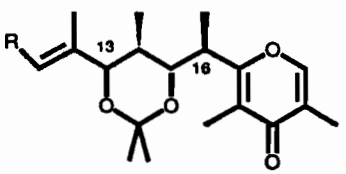
The exact arrangement (structure A) could be deduced from the presence in the EI mass spectra of **5** and **10** of a peak at m/z=365.2333 due to the loss of the pyrone ring bonded to fragments c and d, by clevage of the C16-C17 bond. No such fragment could possibly be obtained from the a-c-b-d arrangement shown in structure B.



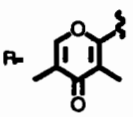
The precise position of the hydroxyle, acetate and propionate groups was inferred from NOESY experiments and mass spectra. Under EI MS, the loss of hydroxyle (M-17), acetate (M-59), and propionate (M-73), from both the molecular ion and the McLafferty rearrangement ion, is prominent due to the formation of an allylic ion, when those groups are in position 13 .

The relative stereochemistry of **5** and **10** was obtained by nmr analysis, M.M. calculations and comparison of these data with those of Peroniatriols and Ilikonapyrone. Thus, the C10-C16 molecular fragment of Onchitriol I (**5**) presents chemical shifts and vicinal J values coincident with those for Peroniatriol I. In the same way, the C3-C4 fragment in both Onchitriols **5** and **10**, have the same relative stereochemistry reported for Peroniatriol II and analogous characteristics are found in the C13-C16 fragment of Onchitriol II (**10**) with respect to Peroniatriol II .

Proton nmr analysis on the acetonides of **5** and **10**, and M.M calculations on the model compounds shown, corroborate the relative stereochemistry of the C13-C16 fragment.

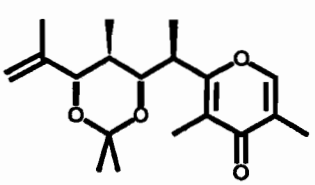


Coupling constants (J)
and calculated dihedral angles (φ)

		$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$	E. (Kcal. mol^{-1})
Calc	R= H	10,2 (152°)	4,3 (57°)	9,8 (152°)	26,4
	R= 	10,4 (152°)	4,1 (57°)	9,7 (152°)	18,2

Onchitriol I dioxolane

	$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$
Exp	7,0 (147°)	4,0 (57°)	9,6 (152°)



	$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$
Calc	1,8 (54°)	3,8 (58°)	9,8 (152°)

Energy 36,6 Kcal. mol^{-1}

Onchitriol II dioxolane

	$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$
Exp	2,3 (53°)	4,6 (57°)	9,6 (152°)

The absolute stereochemistry of **5** and **10** was obtained by measuring the ^{1}H NMR spectra of the corresponding R and S-methoxyphenylacetic esters.

This methodology is based on Mosher's concept that the *O*-methoxymandelates behave in nmr as if the conformation in which the carbinyl proton, the C=O carbonyl bond and the methoxy group are in the same plane (4), were the most relevant. In this way, the (R/S) configuration on C-3, C-13 and C-15 could be directly obtained from the nmr of the mandelates of **5** and **10** while that of the the remaining assymetric centers, could be deduced by use of the relative stereochemistry. The applicability of this method to a 1, 3-diol system was previously checked on 2R,4R (-)Pentanediol.

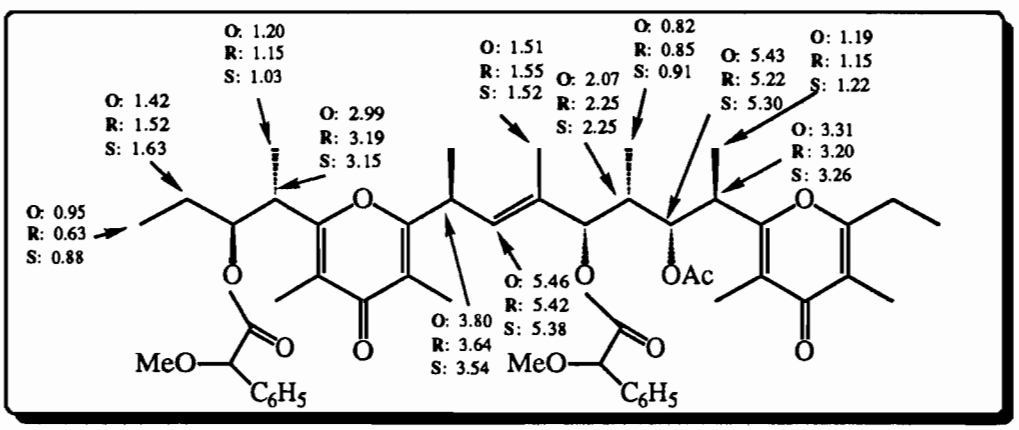


Figure 1. Proton chemicsl shifts of : O: compound 6; S and R :quiral bimandelates of 6.

Thus, a comparison of the H-nmr signals of the (R) and the (S)-trimandelates of Onchitriol I **5**, shows that the C-1 methyl group, is at lower field in the (S) ester than in the (R), while signals for H-13 and H-15, are in the (S) at higher field than in the (R) trimandelate.The absolute configuration is 3S, 13R and 15R ; the other centers can be work up just by knowing their relative spatial distribution.

In a similar way, the (R) and (S) Dimandelates of the 15-acetate of Onchitriol II, (**6**) gave chemical shifts (see figure 1) indicating that Onchitriol II (**10**) has the following configurations: 3S, 4S,10R, 13S, 14R, 15R and 16R.

Onchitriol I and II showed antitumor activity (IC_{50} 10 and 20µg/ml respectively) when tested *in vitro* against P388, A-549 and HT-29 cell lines. Both compounds were also found moderately active as antiviral (HSV-1 and VSV cell lines) at 20µg/ml.

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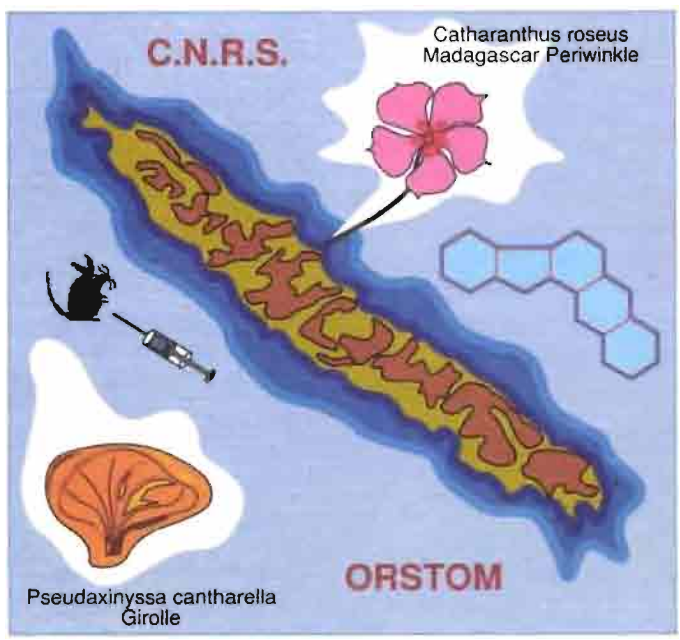

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