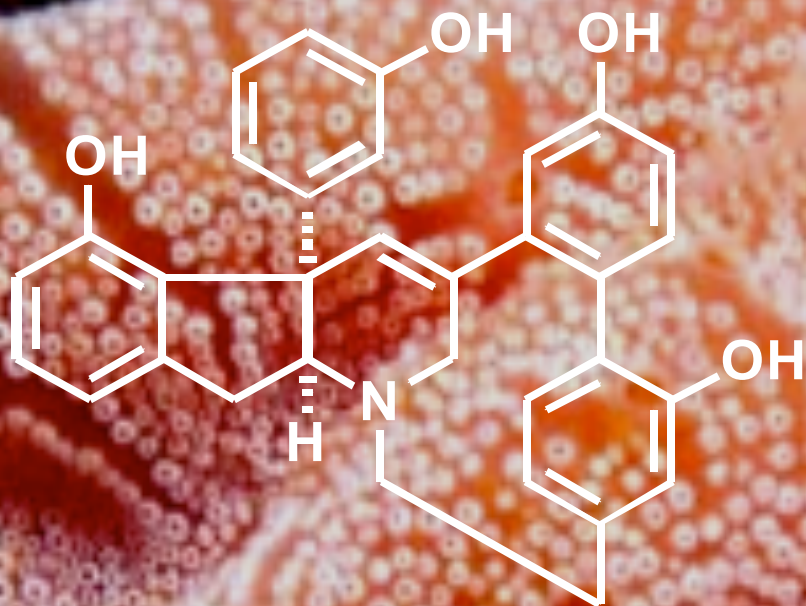


# Progress Toward the Total Synthesis of Haouamine A



Markus Furegati

9/17/2005

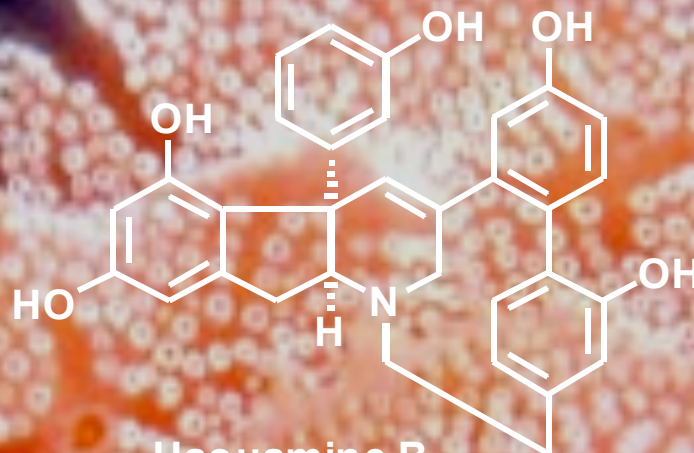
University of Pittsburgh @ Wipf group

Foto © MLSSA 2002





Haouamine A



Haouamine B

- New class of alkaloid isolated from specimen of the tunicate *Aplidium haouarianum* collected off Tarifa Island (Cádiz Spain).
- Haouamine A shows a high and selective activity against the HT-29 human colon carcinoma cell line with  $IC_{50} = 0.1 \mu\text{g/ml}$  (200 nM).
- Structural feature: polyphenol, highly strained 3-aza-[7]-paracyclophane moiety

L. Garrido, E. Zubía, M. J. Ortega, J. Salvá „Haouamines A and B: A New Class of Alkaloids from the Ascidian *Aplidium haouarianum*“, *JOC* **2003**, *68*, 293-299.

Foto © MLSSA 2002

# What's a Tunicate?

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Kingdom	<b>Animalia</b>
Phylum	<b>Chordata</b>
Subphylum	<b><i>Urochordata</i></b>
Class	<b>Ascidiacea</b>
Order	<b>Enterogona</b>
Suborder	<b><i>Aplousobranchia</i></b>
Family	<b>Polyclinidae</b>
Genus	<b>Aplidium</b>
Species	<b>Haouarianum (Pérès 1956)</b>

sometimes known as **tunicata** and commonly called **urochordates**, **tunicates** or **sea squirts**

sac-like marine **filter feeders**, they are characterized by a tough outer "tunic" made of the **polysaccharide** tunicin whilst other **tunicates** are much less robust. Whilst adults are sessile (immobile), larvae resemble **tadpoles** and swim up and down in their marine environment.

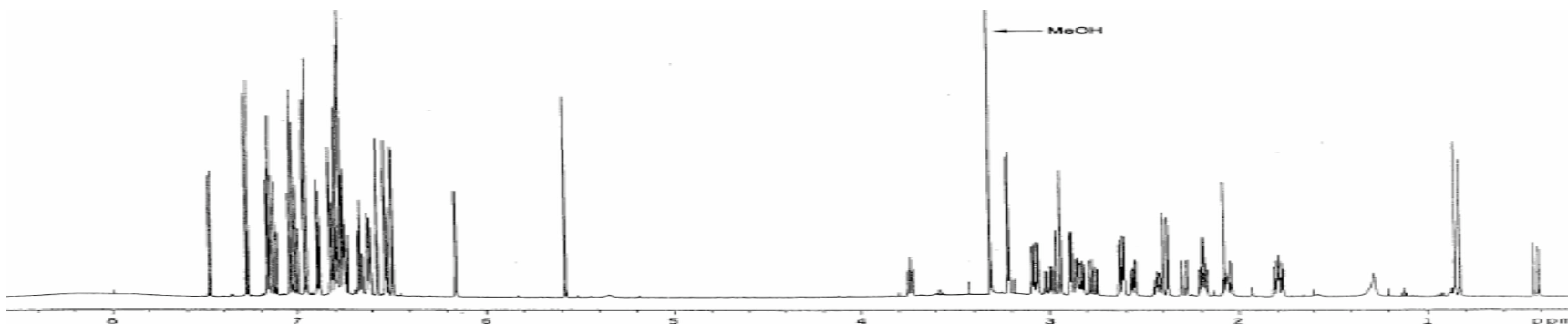


*Aplidium elegans* (Giard, 1872)

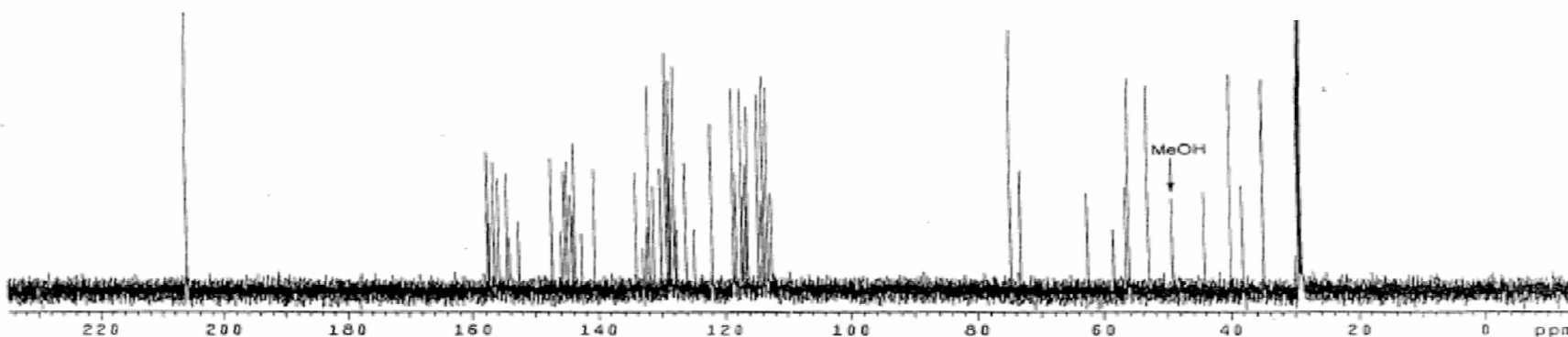
Foto taken from: [www.ascidiacea.com](http://www.ascidiacea.com)

# Characterization of Haouamine A

- white solid, decomposition at 170°C
- $[\alpha]_D^{27} = -52.0$  ( $c = 0.4$ , MeOH)
- $^1\text{H-NMR}$  (600 MHz, acetone- $d_6$ )



- $^{13}\text{C-NMR}$  (125 MHz, acetone- $d_6$ ) -> 2 components with similar structure in a 2:1 ratio (slow pyramidal inversion at the bridgehead amine or atropisomerism)

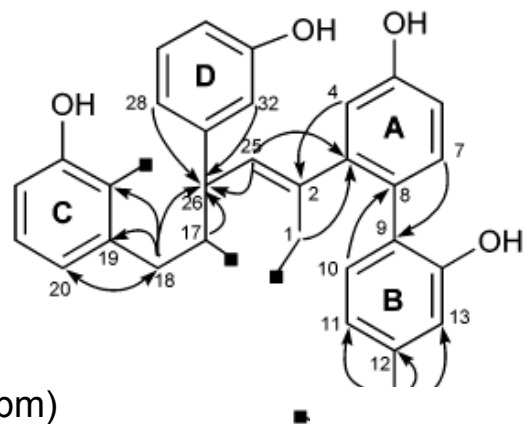


L. Garrido, E. Zubía, M. J. Ortega, J. Salvá „Haouamines A and B: A New Class of Alkaloids from the Ascidian *Aplidium haouarianum*“, *JOC* **2003**, 68, 293-299.

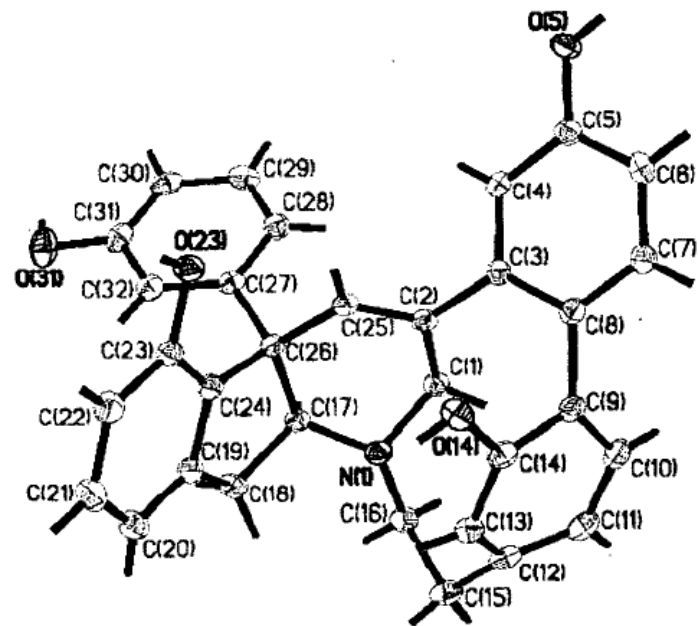
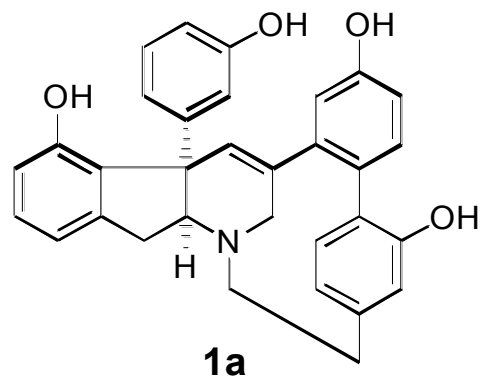


# Characterization of Haouamine A

- $^1\text{H}$ - $^{13}\text{C}$  HMBC correlations:



- HRMS (CI)  $m/z$  489.1909 [ $M^+$ ]  
calcd for  $\text{C}_{32}\text{H}_{27}\text{NO}_4$ , 489.1940 (6 ppm)
- X-ray analysis, Mo- $\text{K}\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ),  
100 K, crystals from MeOH



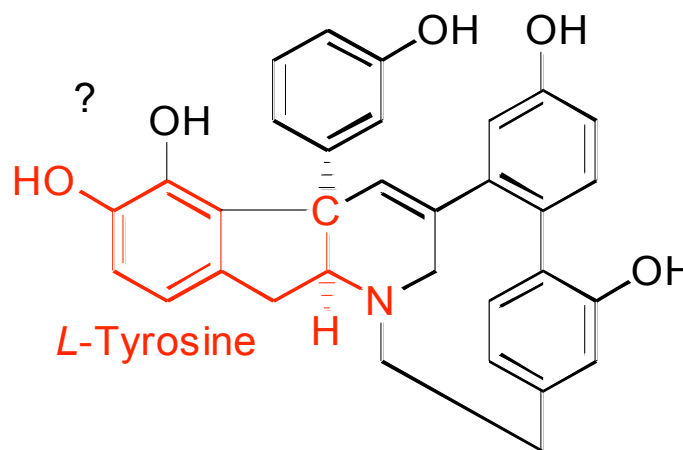
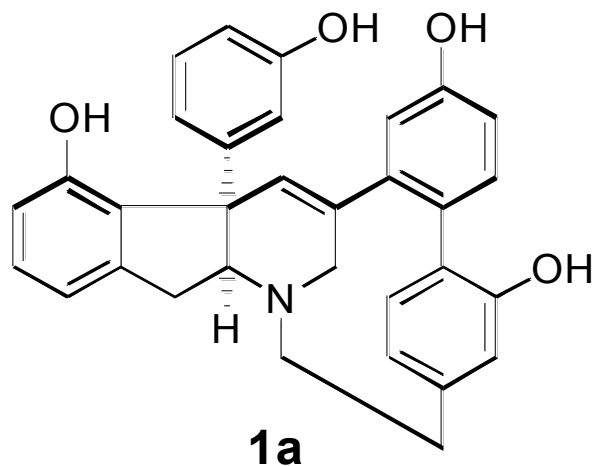
L. Garrido, E. Zubía, M. J. Ortega, J. Salvá „Haouamines A and B: A New Class of Alkaloids from the Ascidian *Aplidium haouarianum*“, *JOC* **2003**, *68*, 293-299.

# Biosynthesis of Haouamine A?

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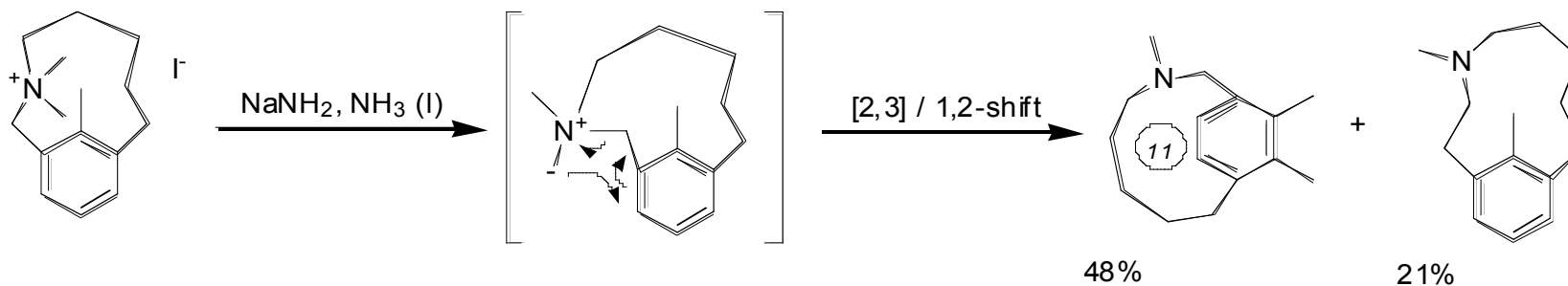
Tyrosine does not match, loss of hydroxyl group? Unknown amino acid precursor?

-> no explanation

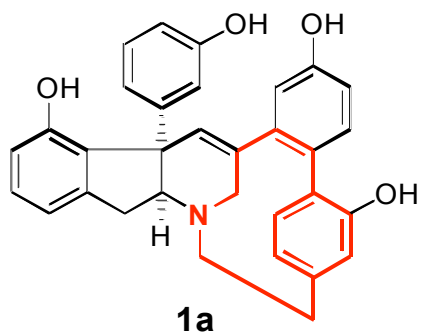


L. Garrido, E. Zubía, M. J. Ortega, J. Salvá „Haouamines A and B: A New Class of Alkaloids from the Ascidian *Aplidium haouarianum*“, *JOC* **2003**, *68*, 293-299.

# Synthesis of 2-Aza-[7]-Paracyclophane

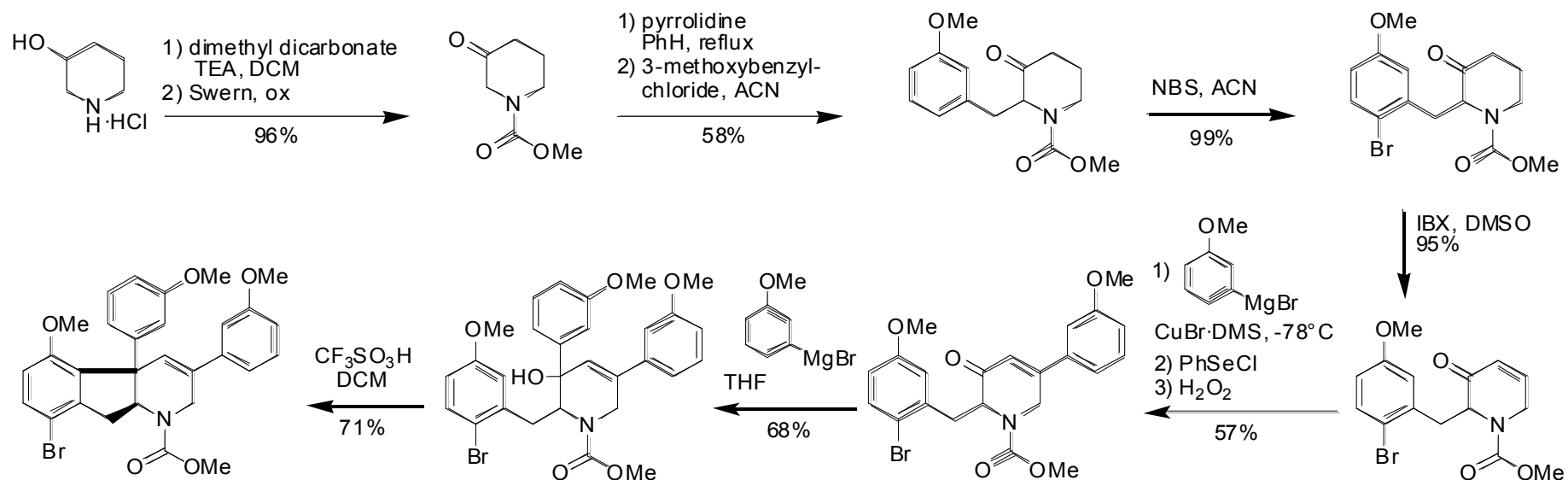
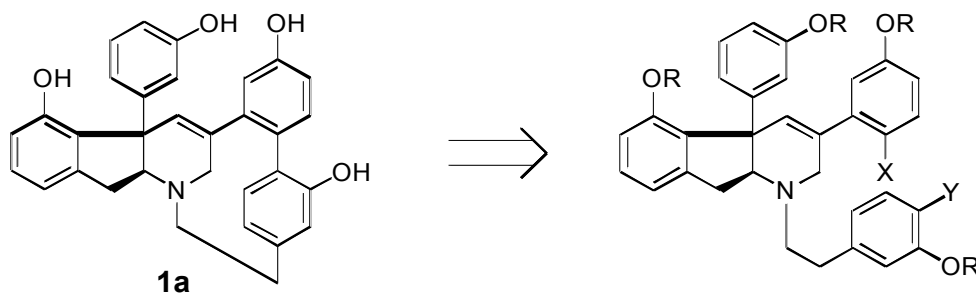


B. Hasiak et al. THL 1990, 31, 5769.



3-aza-[7]-paracyclophane  
-> not applicable

# Published contributions



N. D. Smith, J. Hayashida, V. H. Rawal „Facile Synthesis of the Indeno-Tetrahydropyridine Core of Haouamine A“  
OL ASAP, Web Release Date: August 27, 2005.



# Acknowledgment

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**Prof. Peter Wipf  
Wipf Group Members**



**Members of the NMR, MS, Xray Facilities  
\$ Swiss National Science Foundation \$**