Pergamon

Tetrahedron Letters 40 (1999) 5519–5522

TETRAHEDRON LETTERS

Synthesis of The Marine Carbinolamine (+/-) Longamide Control of N-1 and C-3 Bromopyrrole Nucleophilicity

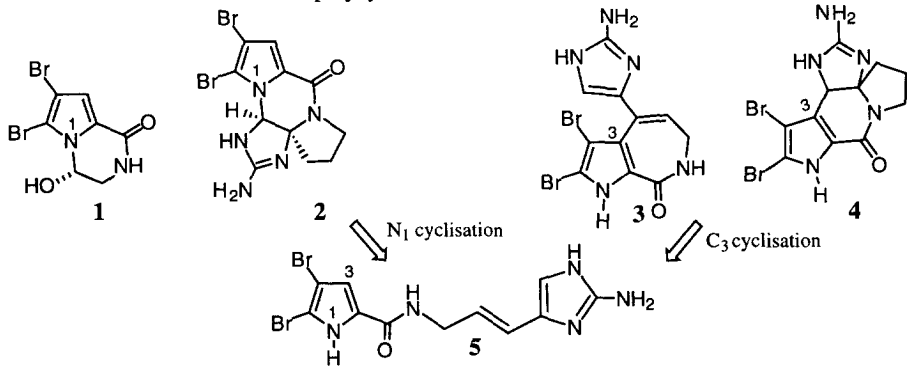
S. Marchais, A. Al Mourabit*, A. Ahond, C. Poupat and P. Potier

Institut de Chimie des Substances Naturelles du C.N.R.S.,
BP 1, 91190 Gif-sur-Yvette , France

Received 8 April 1999; accepted 1 June 1999

Abstract : A short synthesis of (+/-) longamide **1** using a probable biomimetic cyclisation of **12** is described. The separation of its enantiomeric forms and their racemisation are examined. The ring-chain tautomerism involving a potential nucleophilicity of N_1/C_3 of bromopyrrole compounds has been examined. The behaviour of **7** in protic mild or in vigorous acidic conditions provides an entry to regioselective synthesis of marine polycycle alkaloids such as **2**, **3**, and **4**. A biogenetic pathway is proposed for polycyclic 2-aminoimidazolopyrrole marine metabolites.

Several polycyclic bioactive metabolites possessing a bromopyrrole moiety (*Scheme* 1) have been isolated from marine Sponges. Among these are longamide **1**[1], dibromophakelline **2**[2,3], odiline **3**[4,5] and dibromocantharelline **4**[4]. Structure analysis of **2**, **3** and **4** shows their close chemical relationship with the "linear" oroidin **5**[6,7] (*Scheme* 1), first isolated from *Agelas oroides* in 1971[6] , and then from various Sponges [8-16] . The presence of oroidin as a central precursor in all these species suggests that these similar cyclized compounds ($C_{11}N_5$) are biogenetically related. Kitagawa et al.[17] and Braekman et al.[18] reported chemotaxonomic considerations and postulated that ornithine and proline may be precursors of a hypothetical "linear" pyrroloimidazolone from which the other polycyclic derivatives would derive. The synthesis of dibromophakelline **2** by Foley and Büchi[19], by oxidation of the non-natural dihydrooroidin, is the first example of the chemical link between "linear" and polycyclic molecules.



Scheme 1

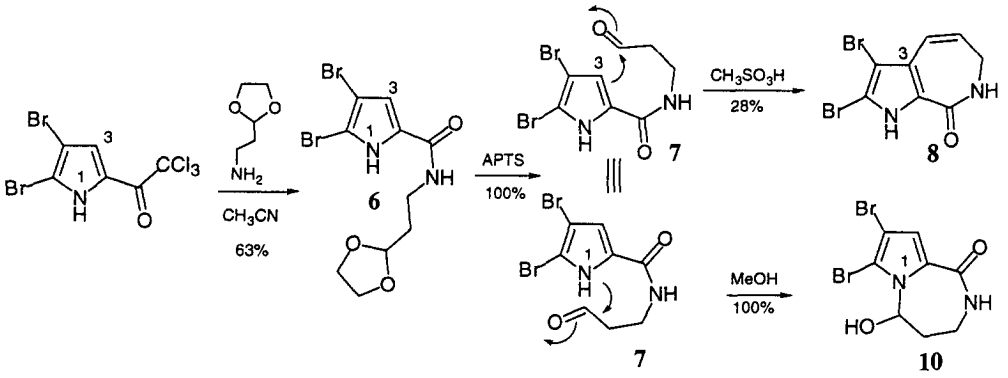
This group of molecules contains two structural types derived from oroidin **5** through a pyrrolic N_1 or C_3 intramolecular cyclisation.

In the context of the synthesis of oroidin derivatives[20], the search for a controlled regioselective intramolecular cyclisation became the focus in our investigation. The aldehyde **7**[21] has been used to prepare **8** and **10** (*Scheme* 2). When treated as described previously[21] with methanesulfonic acid, the aldehyde **7** undergoes

* Fax : (33) 01 69 07 72 47. e-mail : Ali.Almourabit@icsn.cnrs-gif.fr

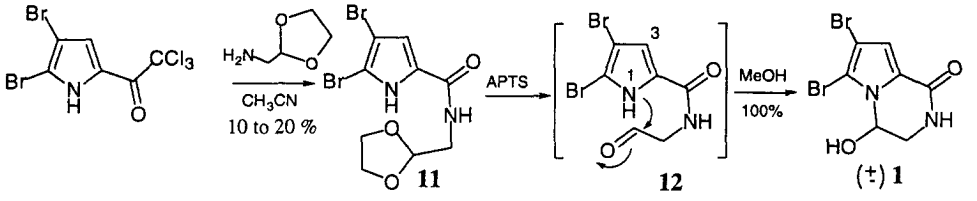
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01092-8

ring closure with C_3 position of the pyrrole and yields the odiline-like compound **8**. When treated with methanol at room temperature, carbinolamine **10**[22] was obtained quantitatively.



Scheme 2

Analogous reactions afforded the homologous natural six-membered carbinolamine longamide **1** (*Scheme* 3). The intermediate **11**[23] was obtained in poor yield. The amidic linkage by coupling the amine unit with the pyrrole moiety suffers probably from steric hindrance.



Scheme 3

The spectral data of synthetic longamide **1** were in agreement with those reported[1] for the natural product. Longamide **1** was described[1] as an optically active compound. In attempt to separate the enantiomers, chiral resolution of the synthetic racemate was performed by HPLC using a chiral column[24] and eluting with heptane / isopropanol : 85 / 15. (+) and (-) longamide were separated as shown in *Fig.*1.

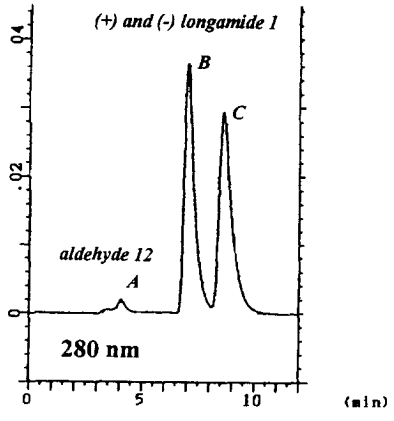
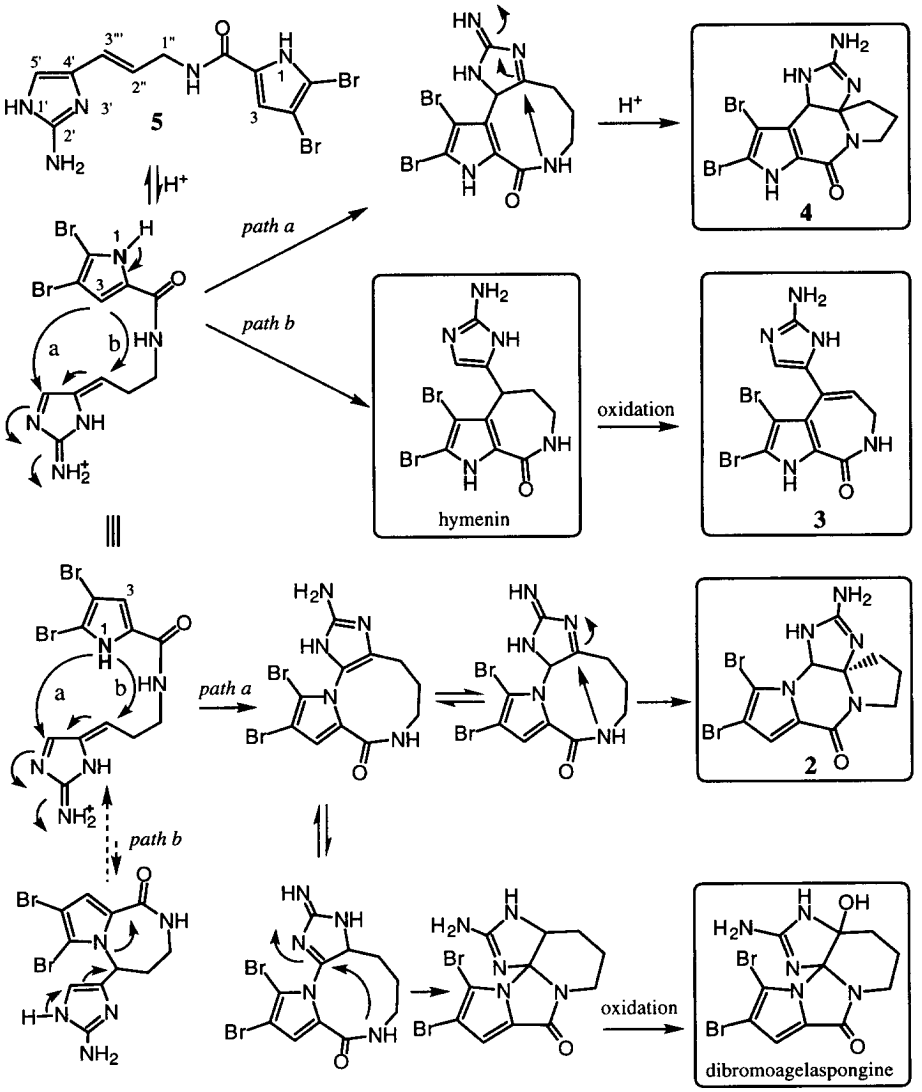


***Fig.*1 : Chiral HPLC[24] resolution of longamide 1**
UV detection (280 nm). **B** and **C** correspond to enantiomers of longamide **1**. Their racemisation occurs through the intermediate aldehyde **12** in 10 min.

The resulting analytically separated (+) and (-) enantiomers racemise in a few minutes (<10min). Each of them was collected and immediately re-injected on the same chiral column and revealed that the ratio of (+) and (-) forms of longamide **1** was ca. 1 : 1. The tendency of the carbinolamine to racemise through ring-chain

tautomerism, explains the fast racemisation, also observed in the used HPLC conditions with the natural product, kindly provided by Prof. Fattorusso.

This observed ring-chain tautomerism would appear to be usable for a biomimetic synthesis of other polycyclized 2-aminoimidazolopyrrole systems. The chemical pathway, starting from oroidin, depicted in *Scheme* 4 is plausible. The common key step appears to be the ring-chain tautomerism in an intramolecular cyclisation between pyrrolic N_1/C_3 and the electrophilic 4(5) substituted 2-aminoimidazole (*Scheme* 4).



Scheme 4

In summary, the marine natural product carbinolamine longamide **1** was synthesized by regioselective pyrrolic N_1 intramolecular cyclisation. Rapid racemisation through "ring - chain" tautomerism was observed by chiral HPLC analysis. Structure analysis of the oroidin group alkaloids clearly shows the central role of pyrrolic N_1 / C_3 nucleophilicity in their formation. These results, in combination with the biomimetic chemical pathway presented here, provide some ideas for the synthesis of more complex alkaloids of this class.

Acknowledgement : we thank M.-T. Adeline for HPLC separation and Pr. Fattorusso for sending us a natural sample of longamide.

References and notes :

1. a) Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron Letters,* **1995**, *36*, 7893-7896. b) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod.*, **1998**, *61*, 1433-1434.
2. Sharma, G. M.; Burkholder, P. R. *Chem. Commun.*, **1971**, 151-152.
3. Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.*, **1977**, *42*, 4118 - 4124.
4. De Nanteuil G.; Ahond A.; Guilhem J.; Poupat, C.; Tran Huu Dau E.; Potier P.; Pusset M.; Pusset J.; Laboute P. *Tetrahedron*, **1985**, *41*, 6019 - 6033.
5. Albizati, K. F.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 4163 - 4164.
6. Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *Chem. Comm.*, **1971**, 1129 - 1130.
7. Garcia, E. E.; Benjamin, L. E.; Fryer, R. I., *J. Chem. Soc. Chem. Comm.*, **1973**, 78 - 79.
8. Cimino, G.; De Stefano, S.; Minale, L.; Sodano, G. *Comp. Biochem. Physiol.*, **1975**, *50B*, 279 - 285.
9. Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Letters*, **1982,** *23*, 767-768.
10. Hooper, J. N. A.; Bergquist, P. R. *Memoirs of the Queensland Museum*, **1992**, *32*, 99 - 137.
11. Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, K.; Wakamatsu, K.; Miyazawa, T. *Experientia*, **1986**, *42*, 1064 - 1065.
12. Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes R. G.Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.*, **1991**, *56*, 2965 - 2975.
13. Rosa, R.; Silva, W.; Escalona de Motta, G.; Rodriguez, A. D.; Morales, J. J.; Ortiz, M. *Experientia*, **1992**, *48*, 885 - 887.
14. Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.*, **1993**, *115*, 3376 - 3377.
15. Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O.; Carnuccio, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 799 - 804.
16. Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod.*, **1996**, *59*, 501 - 503.
17. Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M., Kyogoku, Y. *Chem. Pharm. Bull.*, **1983**, *31*, 2321 - 2328.
18. Braekman, J.-C.; Daloze, D.; Stoller, C.; Van Soest, R. W. M. *Bioch. Syst. Ecol.*, **1992**, *20*, 417 - 431.
19. Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.*, **1982**, *104*, 1776 - 1777.
20. Daninos-Zegal, S.; Al Mourabit, A.; Ahond, A. ; Poupat, C.; Potier, P. *Tetrahedron,* **1997**, *53*, 7605 - 7614 and references cited herein.
21. Xu, Y. -Z.; Phan, G.; Yakushijin, K.; Horne, D. A. *Tetrahedron Letters*, **1994**, *35*, 351 - 354.
22. Selected experimental data for **10 : IR** (Nujol) : 1644; **FAB MS** m/z = 327, 325, 323 $(M+H)^+$, 277, 251, 185; **HR MS** calcd. for $C_8H_8Br_2N_2O_2$, 322.9031, found 322.9048. **^{1}H NMR** (200 MHz, CD_3OD) : 6.73 (s, 1H), 4.57 (t, J = 5 Hz, 1H), 3.37 (t, J = 7 Hz, 2H), 1.77-1.90 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) : 161.6, 114.0, 104.3, 36.3, 33.6.
23. Selected experimental data for **11: IR** (KBr) : 1630; **CI MS** m/z : 357, 355, 353 $(M+H)^+$, 277, 275; **^{1}H NMR** (250 MHz, $CDCl_3 + CD_3OD$), 6.67 (s, 1H), 5.00 (t, J = 4 Hz, 1H), 4.04 - 3.88 (m, 4H), 3.59 (d, J = 4 Hz, 2H); **^{13}C NMR** (62.5 MHz, $CDCl_3 + CD_3OD$) : 160.1, 126.6, 113.4, 105.1, 101.7, 99.0, 65.2, 41.3.
24. The separation of the 2 diastereoisomers was realized on Chiralpak OT (+) chiral column, diameter 0.46, length 25 cm Daicel Chemical Industries Ltd, T = 0°C, Flux 1 mL / min, pressure 700 psi, retention time 8 min and10 min, detection UV λ = 280 nm.