Pergamon

Tetrahedron Letters 39 (1998) 8085–8088

TETRAHEDRON LETTERS

A Short Synthesis of the Marine Bioactive Metabolite (+/-) Girolline

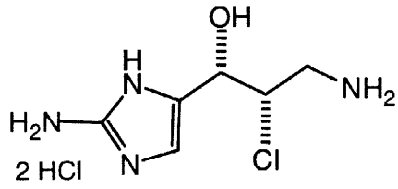
S. Marchais, A. Al Mourabit*, A. Ahond, C. Poupat and P. Potier

Institut de Chimie des Substances Naturelles du C.N.R.S.,
BP 1, 91198 Gif-sur-Yvette, France

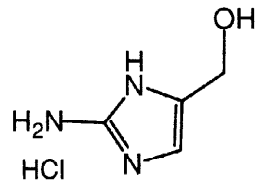
Received 4 August 1998; accepted 28 August 1998

Abstract : A new 2 step synthesis of (+/-) girolline **1** starting from the easily available α-chloro-β-aminoaldehyde **4** and 2-aminoimidazole **5** is described. The reaction of **4** with **5**, followed by deprotection, affords the *threo* diastereoisomer.

Several 2-aminoimidazole compounds which display potent biological activities have been isolated from various marine Sponges : oroidine[1-3], keramadine[3-5], palau'amine[6] are examples. Related to these compounds is girolline **1** [7], isolated from *Cymbastela cantharella* (previously *Pseudaxinyssa cantharella*) which shows potent *in vitro* cytotoxicity and *in vivo* antitumor activity [8]. However, phase I clinical trials with girolline have been discontinued because of unfavorable side effects; nevertheless, girolline and its analogues remain interesting biological tools.



1



2

Our efforts have been focused not only on the synthesis of the natural product but also on functional analogues containing 2-aminoimidazole. Several total syntheses of both racemic girolline **1** [9] as well as the natural enantiomer[10] have already been reported. Recently, Olofson and al.[11] obtained (+/-) girolline as the minor (+/-) *threo* diastereomer in a 9 / 1 mixture of *erythro* / *threo* diastereomers.

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

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01814-0

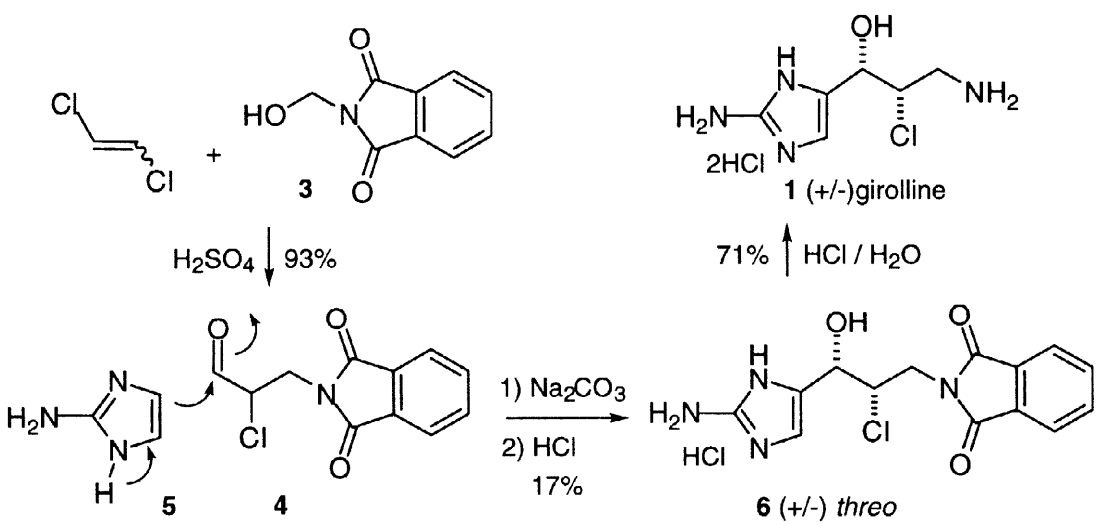
Although girolline appears structurally simple, its synthesis was more difficult than expected and required the choice of appropriate protecting groups. These difficulties arise mainly from the density of functionalities and the rapid decomposition of 4(5)-substituted 2-aminoimidazole derivatives under basic conditions. Thus, the final step in any synthesis of girolline should be performed under acidic conditions. Based on our prior investigations to find a general preparative method for 2-aminoimidazole marine compounds and derivatives, it indeed appeared that the stability of 2-aminoimidazoles functionalized in position 4(5) is pH sensitive. Thus, the previously prepared simple derivative 2-aminoimidazol-4(5)-methanol **2** [3, 12] and girolline **1** itself, are very unstable above pH 7. The use of **2** as starting material in the synthesis of various 2-aminoimidazole marine alkaloids is thereby limited by low reaction yields and difficulties in product purification.

In our previous syntheses [9a, 10b], we preferred to prepare the non-aminated imidazole intermediates and to introduce the amine function through azidation of the C-2 carbanion of N-1 protected imidazoles. Later on, Little and Webber [13] described a convenient preparation of 2-aminoimidazole derivatives using a cyclization reaction of α-haloketones and N-acetylguanidine.

The discovery by Xu and coworkers[14] that 2-aminoimidazole could undergo nucleophilic addition in reactions analogous to those of enamines with aldehydes, offered the promise of an easy access to girolline and analogues.

We now report the facile and rapid synthesis of (+/-) girolline **1** from commercially available starting materials and using convenient acidic or basic conditions in water as solvent.

The starting compound, α-chloro-β-aminoaldehyde **4**, was synthesized from N-(hydroxymethyl)phthalimide **3** using a described procedure [15, 16]. The published yield of the reaction (53%) could be increased by up to ca. 40% when the reaction was initiated at 0° C and maintained at this temperature during the addition of 1,2-dichloroethylene to a solution of **3** in sulfuric acid. The work-up of the reaction mixture is critical to the success of the reaction : after the slow addition of the acid solution to a stirred mixture of ice and water, the precipitated white solid product was filtered and washed with portions of ice-cold ethyl ether.



The base-promoted condensation of the α-chiral chloroaldehyde **4** with 2-aminoimidazole **5** in the presence of Na_2CO_3 provides the chlorohydrin **6**[17] in 17% yield after purification. The low yield is due to the instability of the β-phthalimido-α-chloroaldehyde **4** and the reaction product **6** under basic conditions. Only the *threo* isomer is observed. In addition to the presence of the large chlorine atom, participation of the phthalimide by hydrogen bond interaction with the 2-aminoimidazole may explain the high observed diastereoselectivity.

The amine function was deprotected by heating **6** for 4h at 100°C in 6N HCl. Evaporation and chromatography on silica gel (butanol / ethyl acetate / water : 4 / 1 / 5) followed by filtration on Sephadex LH20 (methanol) afforded (+/-) girolline in 71% yield. NMR and MS data of synthetic girolline were in agreement with those reported for the natural product [7]. Current efforts are focused on enhancing the yield of condensation of the α-chiral aldehydes with 2-aminoimidazole and the synthesis of analogues of girolline.

In conclusion, a concise total synthesis of (+/-) girolline has been developed which requires only three steps carried out in water under acidic and basic conditions. Analogues of girolline should thus now become available with very high diastereoselectivities from different α,β- functionalized aldehydes and 2-aminoimidazole.

References and notes :

1. Garcia E. E.; Benjamin L. E.; Fryer R. I. *J. Chem. Soc. Chem. Comm.*. **1973,** 78-79
2. Daninos-Zeghal S.; Al Mourabit A.; Ahond A.; Poupat C.; Potier P. *Tetrahedron*, **1997**, *53*, 7605-7614 and cited references
3. De Nanteuil G.; Ahond A.; Guilhem G.; Poupat C.; Tran Huu Dau.; Potier P.; Pusset M.; Pusset J.; Laboute P. *Tetrahedron*, **1985**, *41*, 6019-6033
4. Nakamura H.; Ohizumi Y.; Kobayashi J.; , Hirata Y. *Tetrahedron Lett.*, **1984**, *25*, 2475-2478
5. Lindel T.; Hochgürtel H. *Tetrahedron Lett.*, **1998**, *39*, 2541-2544
6. a) Kinnel R. B.; Gehrken H-P.; Scheuer P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376-3377
   b) Kinnel R. B.; Gehrken H-P.; Swali R.; Shoropowski G.; Scheuer P. J. *J. Org. Chem.* **1998**, *63*, 3281-3286
7. a) Ahond A.; Bedoya-Zurita M.; Colin M.; , Fizames C.; Laboute P.; Lavelle F.; Laurent D.; Poupat C.; Pusset M.; Pusset J.; Thoison O.; Potier P. *C. R. Acad. Sci. Paris, série II* **1981**, *307*, 145-148
   b)Chiaroni A.; Riche X.; Ahond A.; Poupat C.; Pusset M.; Potier P. *C. R. Acad. Sci. Paris, série II* **1981**, *312*, 49 - 53
8. Colson G.; Raboult L.; Lavelle F.; Zerial A. *Biochem. Pharmacol.* **1992**, *43*, 1717-1723
9. a) Bedoya-Zurita M.; Ahond A.; Poupat C.; Potier P. *Tetrahedron* , **1989**, *45*, 6713-6720
   b) Commerçon, A. ; Guéremy, C. *Tetrahedron Lett.* **1991,** *32*, 1419-1422
10. a) Commerçon, A. ; Paris, J. M. *Tetrahedron Lett.* **1991,** *32*, 4905-4906
    b) Ahond A.; Al Mourabit A.; Bedoya-Zurita M.; Heng R.; Marques-Braga R.; Poupat C.; Potier P. *Tetrahedron,* **1992**, *48*, 4327-4346.
11. Olofson A.; Yakushijin K.; Horne , D. A. *J. Org. Chem* , **1997**, *62*, 7918-7919
12. Daninos S.; Al Mourabit A.; Ahond A.; Bedoya-Zurita M.; Poupat C.; Potier P. *Bull Soc. Chim. Fr.* **1994**, *131*, 590-599

13. Little T. L.; Webber S. E. *J. Org. Chem* , **1994**, *59*, 7299-7305
14. Xu Y.-Z.; , Yakushijin K.; Horne D. A. *Tetrahedron Lett.*, **1993,** *34*, 6981-6984
15. Bott K. *Chem. Ber.*, **1973**, *106*, 2513-2522
16. Selected experimental data for **4 :**
    IR (KBr) : 1764, 1700, 1610; **MS** EI m/z (%) = 239, 237 $(M)^+$, 212, 210, 203, 161 (100%) ;
    ^{1}H NMR (250 MHz, $CDCl_3$) : δ = 9.60 (d, J = 2 Hz, 1H), 7.98-7.74 (m, 4H), 4.66 (dt, J = 2 and 6.5 Hz 1H), 4.34-4.11 (m, 2H); **^{13}C NMR** (62.5 MHz, $CDCl_3$) : δ = 193.1, 167.7, 134.5, 131.7, 123.8, 59.4, 38.8.
17. Compound **6** was prepared by the following procedure :
    To a solution of 2-aminoimidazole sulfate **5** (204 mg 1.54 mmol) in 4 ml water, was added 164 mg (1 equiv.) of Na_2CO_3. After stirring for 10 min at room temperature, 444 mg (1.2 equiv.) of α-chloro β-phthalimidoaldehyde **4** are added. After 4h, 2N HCl solution is added to the mixture which is then evaporated to dryness under vacuum ; the residue is chromatographed on silica gel (ethyl acetate / butanone / formic acid / water : 5 / 3 / 0.5 / 0.5). 84 mg (17%) of **6** are obtained : **MS** FAB (thioglycerol + NaI + MeOH), m/z = 345, 343 $(M + Na)^+$, 323, 321 $(M + H)^+$, 305, 303 $(M + H - H_2O)^+$; **^{1}H NMR** (250 MHz, CD_3OD) : δ = 7.88 - 7.71 (m. 4H), 6.88 (s, 1H) ; 4.68 (dd, J = 4 and 8 Hz,1H) ; 4.29 (m, 1H) ; 4.02 (m, 2H) ; **^{13}C NMR** (62.5 MHz, CD_3OD) : δ = 169.4, 148.9, 135.5, 133.1, 124.2, 114.1, 99.0 and 98.8, 61.3 and 61.05, 41.0 and 40.8.