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ASYMMETRIC SYNTHESIS VIII [1] : BIOGENETICALLY PATTERNED APPROACH TO THE CHIRAL TOTAL SYNTHESIS OF (-)-PUMILIOTOXIN-C

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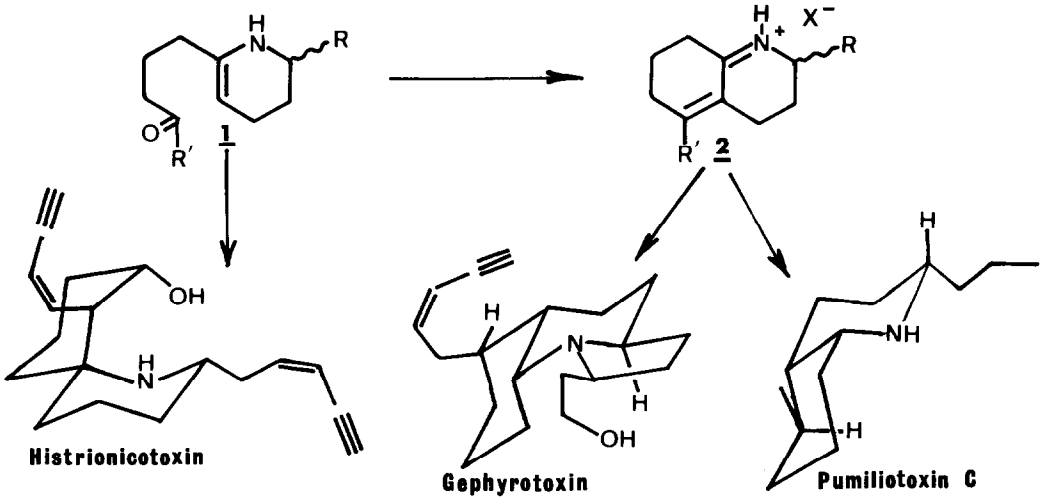
Abstract - (-)-Pumiliotoxin-C and the (+)-9,10-trans isomer 10 were prepared in six steps from the chiral (+)-2-cyano-6-oxazolopiperidine synthon 3.

Over the last two decades intense efforts have been directed towards the isolation, identification, pharmacological evaluation, and total synthesis of the extraordinary array of steroid and piperidine based alkaloids found in secretion from the skins of certain highly coloured neotropical frogs, the Dendrobatidae[2]. Three of the major groups of piperidine alkaloids present in skin extracts of these frogs, the histrionicotoxins, the gephyrotoxins, and in particular compounds of the pumiliotoxin-C class are considered to be related biogenetically through different modes of cyclization of an endocyclic piperidine enamine such as 1[3] (scheme 1). Although a number of synthetic routes to natural (-)-pumiliotoxin-C have been developed no chiral biomimetic synthesis of this alkaloid has been reported to our knowledge[4].



Scheme 1

In an earlier communication we demonstrated that the proposed transformation 1 → 2 could be mimicked by a highly efficient cyclization of an aminonitrile equivalent of enamine 1 on contact with alumina[3]. In a continuation of our research in this area we now wish to describe how this key reaction has been incorporated into a biomimetic approach to the synthesis of (-)-pumiliotoxin-C (PTX-C) and its (+)-9,10-trans isomer 10 in only six steps starting from our recently developed 1,4-dihydropyridine based synthon 3[5] (scheme 2).

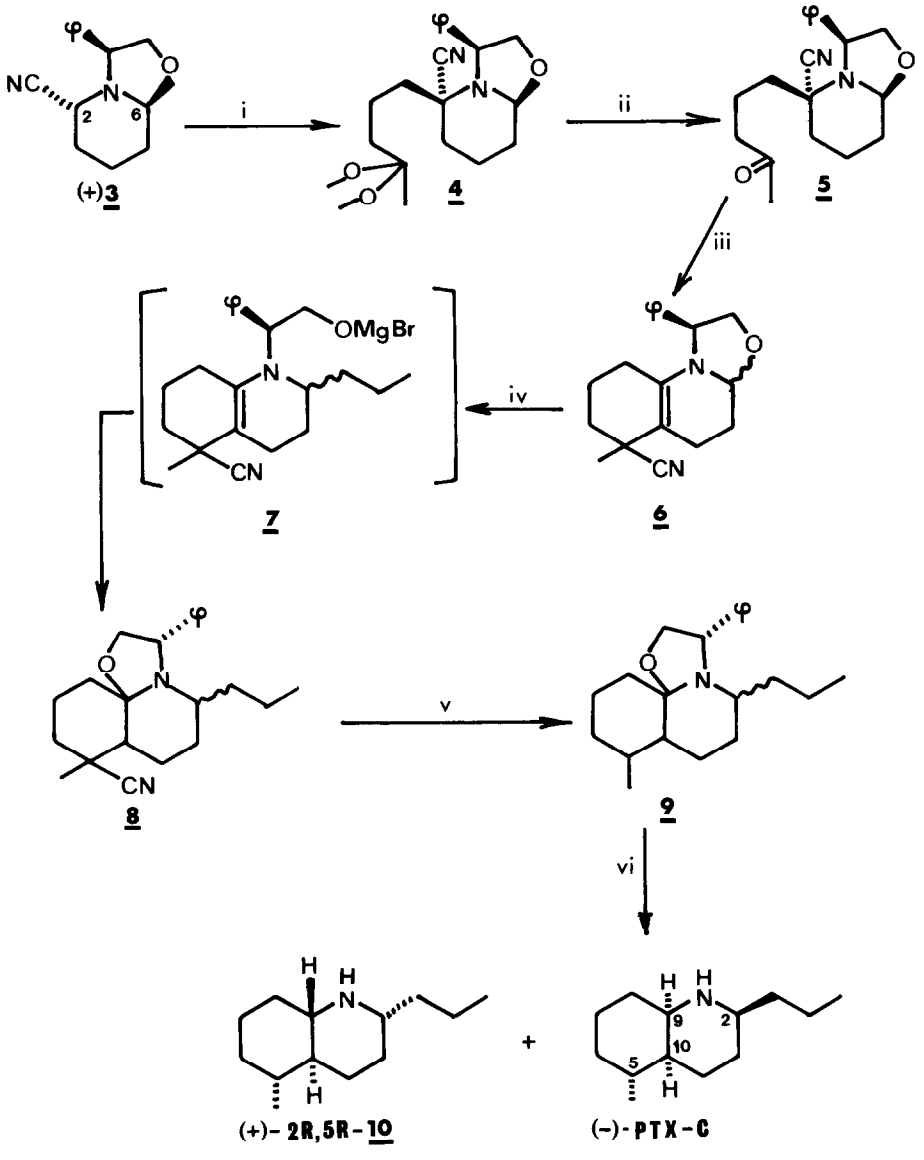
On reaction of the anion of 3 (scheme 2) with iodopentanone dimethyl ketal at -78°C for 1.5 hr followed by normal extractive work-up and flash column chromatography on silica-gel (hexane:ether/ 2:1) compound 4 was isolated as a colorless oil in 65% yield[6]. The stereochemistry at C-2 of this molecule was assigned on the basis of previous results. Treatment of 4 with $LiBF_4$ in acetonitrile -2% H_2O (60°C, 30min.) proved to be a very mild method for liberating the ketone function of intermediate 5 without disrupting the acid labile oxazolidine system[7]. As compound 5, obtained essentially pure in >95% yield[6], proved to be relatively sensitive it was immediately dissolved in CH_2Cl_2 and stirred as a slurry with alumina (Merck art. 1097, preactivated at 110°C for 45 min.) under argon at reflux temperature for 1.5hr. The expected cyanoenamine 6 was obtained pure in 55% yield after rapid filtration through a short column of silica-gel as an ~ 8:2 mixture of epimeric oxazolidines[6]. By trituration of this mixture with ether and crystallization of the residue from hot ether the major epimer (H-2 axial) was isolated as a colorless crystalline solid, mp. 138°C.

Reaction of this major component, or the mixture of epimers 6 with PrMgBr in ether (15°C, 1.5hr) resulted in both cases in the formation of compounds 8 isolated as a 7:3 mixture of isomers after flash chromatography on silica-gel (hexane:ether/8:2)[6]. Interestingly, introduction of the propyl side chain was accompanied by recyclization of the oxazolidine ring at C-10 of the intermediate enamine 7.

The two remaining steps involved i) treatment of the 8 mixture with Na/NH_3 liq. at -78°C for 1hr which produced compounds 9 in quantitative yield[6], and ii)complete cleavage of the oxazolidine system under hydrogenolysis conditions ($H_2/Pd(OH)_2$-C, CH_2Cl_2-CH_3OH). A 7:3 mixture of (+)-2R,5R-trans decahydroquinoline 10[8] and (-)-PTX-C[9] was thus obtained in a combined yield of > 95%. The two products were separated by column chromatography on alumina (300:1 ratio) eluting with $CHCl_3$:EtOAc (1:1).

Alternatively, by carefully separating the two isomers of 8 by preparative layer chromatography (silica ; hexane-ether [4:1]) followed by the transformaton of each isomer to the final products as above it was shown that the major isomer gave rise to compound 10, and the minor isomer to (-)-PTX-C.

Due to the complexity of the NMR data the relative stereochemistry at carbons-2,5,9 and -10 of 8 and 9 are at present unknown. However as the absolute configuration at C-2 are opposite in 10 and (-) PTX-C it was clear that the formation of an isomeric mixture of compounds 8 was a result of a lack of specificity in the Grignard reaction.



i) LDA, RX, -78°C, 1.5hr ; ii) $LiBF_4$, CH_3CN-2% H_2O, 60°C, 30min. ; iii) Al_2O_3, CH_2Cl_2, Δ, 1.5hr ; iv) PrMgBr, Et_2O, 15°C, 1.5hr ; v) Na, NH_3liq, -78°C, 1hr ; vi) H_2, $Pd(OH)_2$-C, CH_2Cl_2-MeOH.

SCHEME 2

This was not unexpected as the initial step in the reaction is the opening of the oxazolidine ring of 6 to give a near planar 3,4-dihydropyridinium ion.

Similarily, it cannot be determined as yet whether the decyanation of the two isomers of 8 occurs with retention or inversion of configuration. However the configuration at C-5 of 10 and PTX-C are identical which would indicate that the same process must be operating for both isomers of 8. This observation is revealing, as in our earlier studies[3] reduction of the C-9,10 bond of an enamine related to 7 preceeded the decyanation step, and the configuration at C-5 of the cis and trans products obtained were opposite. Furthermore the cis final product possessed the gephyrotoxin rather than PTX-C configuration due to the resultant 2,5-cis arrangement of the alkyl side chains. It would appear that prior elimination of CN from the minor tricyclic isomer of 8 favours generation of the desired 2,5-trans dialkyl substitution pattern of PTX-C.

Finally, it is interesting to note that trans-decahydroquinoline alkaloids of type 10 have been recently isolated for the first time from Dendrobatidae[10]. X-ray analysis of one of them [(+)-2,5-diallyl-trans-decahydroquinoline][11] showed that the absolute configuration at C-2, C-9 and C-10 is the same as for (+)-10.

References and Notes

1) For part VII see : J.L. MARCO, J. ROYER and H.-P. HUSSON, Tetrahedron Lett., 26, 6345 (1985).

2) a) B. WITKOP and E. GOSSINGER, The Alkaloids, 21, 190 (1983) Academic Press, Inc. A. BROSSI, Editor ; b) J.W. DALY, G.B. BROWN, M. MENSAH-DWUMAH and C.W. MEYERS, Toxicon, 16, 163 (1978) ; c) J.W. DALY, Fortschr. Chem. Org. Naturst., 41, 205 (1982).

3) a) D.H. GNECCO MEDINA, D.S. GRIERSON and H.-P. HUSSON, Tetrahedron Lett., 20, 2099 (1983) ; b) M. BONIN, R. BESSELIEVRE, D.S. GRIERSON and H.-P. HUSSON, Tetrahedron Lett., 24, 1493 (1983).

4) For reviews on the syntheses of PTX-C prior to 1983, see Ref. 2a ; more recent syntheses include : a) S. MASAMUNE, L.A. REED, J.T. DAVIS, W. CHOY, J. Org. Chem., 48, 4441 (1983) ; b) K. ABE, T. TSUGOSHI and N. NAKAMURA, Bull. Chem. Soc. Jpn., 57, 3351 (1984).

5) L. GUERRIER, J. ROYER, D.S. GRIERSON and H.-P. HUSSON, J. Am. Chem. Soc., 105, 7754 (1983) ; Readily available (+)-phenylglycinol rather than the (-) enantiomer was employed to prepare synthon (+)- 3 in order to have access to the natural (-) enantiomer of pumiliotoxin-C.

6) Satisfactory IR, ^{1}H and ^{13}C NMR, HR MS or microanalyses were obtained for all compounds described.

7) B.H. LIPSHUTZ, D.F. HARVEY, Synth. Comm., 12, 267 (1982).

8) a) G. HABERMEHL, H. ANDRES, K. MIYAHARA, B. WITKOP and J.W. DALY, Ann., 1577 (1976) ; b) 10, HCl : $[\alpha]_D^{20}$ + 25.8° (c 1.0, CH_3OH), mp 230°-235°C (hexane:ether).

9) PTX-C, HCl : $[\alpha]_D^{20}$ - 13.1° (c 1.0, CH_3OH), mp 220-225°C (hexane:Et_2O) ; lit[2c] $[\alpha]_D^{20}$ - 13.1° (c 1.0, CH_3OH), mp 230°-240°C.

10) J.W. DALY, personal communication.

11) I.L. KARLE, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C.

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