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The Isoxazoline-5-spirocyclopropane Route to (±)-Pumiliotoxin C

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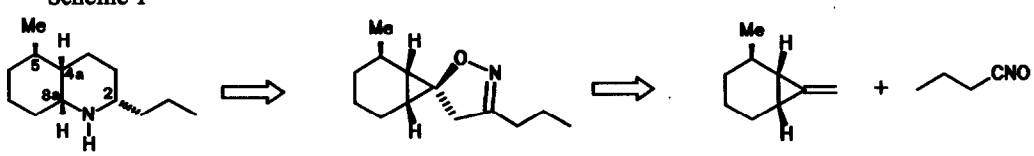
Abstract: A new total synthesis of (±)-Pumiliotoxin C has been achieved by the key thermal rearrangement of an appropriate 5-spirocyclopropane isoxazoline.

Pumiliotoxin C (1) is a relatively nontoxic alkaloid originally isolated from the skin of Amphibians of the genus *Dendrobates pumilio*. This compound represents the prototype of a wide class of decahydroquinoline alkaloids isolated from neotropical dendrobatid frogs.[1,2]

During the exploration of the synthetic applicability of the thermal rearrangement of 5-spirocyclopropane isoxazolines or isoxazolidines[3] we were able to show the utility of the method for the synthesis of quinolizidine[4] and indolizidine[5] alkaloids.

The retrosynthetic analysis for the synthesis of a quinoline skeleton requires the cycloaddition either of a nitrone or of a nitrile oxide to a substituted methylenenorcarane to give the respective 5-spirocyclopropane isoxazolidine or isoxazoline. The second route has been chosen to prepare (±)-Pumiliotoxin C since it might allow a better control of the relative stereochemistry of the four stereocenters (Scheme 1). Indeed, the *cis* C2-C4a stereochemistry might be obtained in the hydrogenation step. Furthermore, the *cis* C4a-C8a stereochemistry present in 1 should be obtained in the rearrangement step as previously proved with a model compound[6] and the *cis* C4a-C5 relationship derives from the starting methylenenorcarane 2.[7]

Scheme 1



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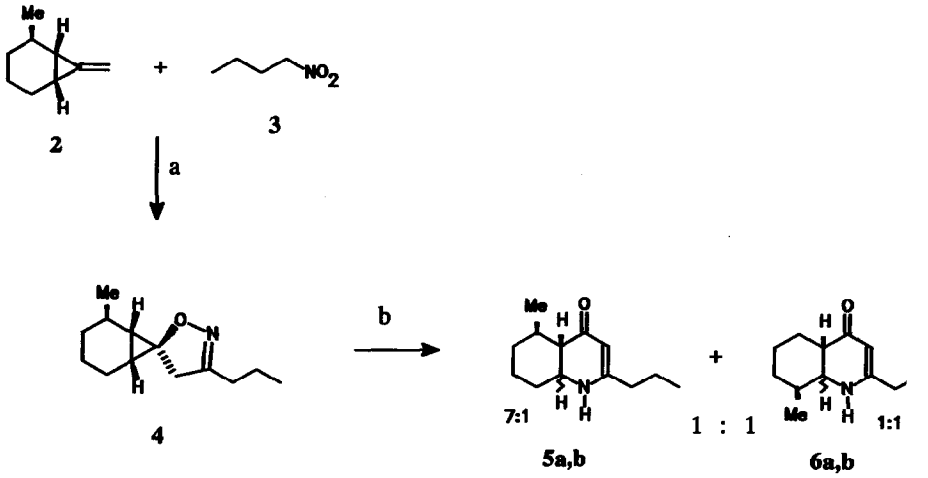
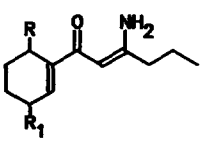
The cycloaddition of butyronitrile oxide, obtained from nitrobutane (3) by the Mukaiyama method,[8] to *exo*-2-methyl-7-methylenebicyclo[4.1.0]heptane[7] (2) afforded the spiroisoxazoline 4,[9] isolated in 50% yield. The structure was assigned on the basis of the chemical shifts of the isoxazoline

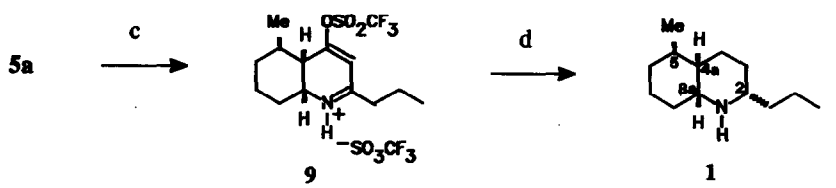


a) Benzene, PhNCO 2 eq., cat. NEt_3, rt, 16 h, 50%. b) Xylene, 140 °C, 36 h, 75%. c) $(CF_3SO_2)_2O$, CH_2Cl_2, 40 °C, 18 h, 100%. d) i: H_2, PtO_2 (25 mol%), MeOH, 1 atm, rt, 48 h; ii: Amberlite IRA-400, 75%.



7 R=Me R_1=H

8 R=H R_1=Me



methylene protons in the ^{1}H NMR spectrum (δ 2.86 and 2.75 ppm, AB system).[10] As was previously ascertained,[6] only the diastereoisomer **4** deriving from the attack of the nitrile oxide on the convex face of the methylenenorcarane was obtained.

Three of the stereocentres, then, are readily set up in isoxazoline **4** as it is necessary for the formation of Pumiliotoxin C. However, the methyl group on norcarane system in **4** is not able to discriminate between the two possible cleavages of the cyclopropane ring in the rearrangement step. In fact, by refluxing **4** in xylene (140 °C) for 36 h a 1:1 mixture of octahydroquinolinones **5**[9] and **6**[9] was obtained, albeit in good yield (75%). The quinolinones **5** and **6** were easily separated by flash chromatography. The quinolinone **5** was obtained as a 7:1 mixture of two diastereoisomers, evidenced exclusively by the ^{1}H NMR signals of 3-H enaminic proton (δ 4.87 for the major and δ 4.95 for the minor isomer) and 8-H proton. The assignment of the *cis*-fused ring structure to the major isomer **5a** was based on the previous results[6] and on the ^{1}H NMR spectrum. The 8a-H in **5a** (δ 3.77 ppm) appears as a broad singlet which is in accord with a small *cis* coupling constant with 4a-H. In the minor isomer **5b** the signal of 8a-H resonates at δ 3.23 ppm as a ddd (J = 15, 11, 4.5 Hz). The ring closure to give the quinolinone **6** occurs with no selectivity, as the *cis*-fused and *trans*-fused isomers were formed in equimolar amount. The assignment of the structure **5** or **6** to the two octahydroquinolinones was not a simple task. The mass spectrometry of the two isomers showed a significant difference only in the fragment at m/z 122, tentatively assigned the formula ($C_5H_5N^+$), that was much more abundant in **6** than in **5** (90% vs. 15%). The key diagnostic features were the ^{13}C NMR resonances of C4a and C8a carbon atoms of **5** and **6**. The two carbons resonate at δ 52.84 and 53.23 ppm for **5a**, and at δ 47.71 and 63.07 ppm and δ 43.24 and 59.47 ppm, respectively, for **6a** and **6b**. As it is apparent, the α methyl substitution deshields the C4a carbon in **5a**. When the methyl substitution is α to the C8a carbon the differentiation of the chemical shifts of C4a and C8a is increased, as evidenced in isomers **6a,b**. The expected[3,6] open chain side products **7** and **8** were isolated[9] in 15% yield, but they were found more abundant by running the rearrangement in FVT conditions (450 °C, 10^{-2} mmHg). The prolonged heating in refluxing xylene might, in fact, cause the ring closure of **7** and **8** by intramolecular Michael-type addition.[6]

The skeleton of the target molecule was then assembled in the ketone **5a** with the correct stereochemistry of three stereocentres. For the obtainment of Pumiliotoxin C a reduction of the double bond and of the ketone is required. The correct stereochemistry at C2 can be introduced by a selective catalytic reduction which should occur from the less hindered convex face of the molecule.[11] Our aim was to find a method for the stereoselective complete reduction of the enaminone functionality in a single step. To our knowledge, the most recent literature does not report any example for such reduction.[12] We thought, however, that the method of Jigajinni and Wightman[13] for the hydrogen catalyzed reduction of ketones via the corresponding enoltriflates might achieve our aims.

Treatment of quinolinone **5a** with trifluoromethanesulfonic anhydride gave quantitatively the iminium salt **9**, characterized by ^{1}H NMR and MS without purification. Hydrogenation of **9** under PtO_2 catalysis gave pure (±)-Pumiliotoxin C (**1**) in good yield (75%) after filtration of the catalyst and treatment of the methanolic solution with strongly basic Amberlite.[14] The resulting compound and its hydrochloride were identical by all spectroscopic and MS data with the natural alkaloid.[15,1]

Acknowledgment

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14. The conditions of this reaction have not been optimized. The study of this new reduction in a more generalized sense will be reported separately.
15. 1: ^{1}H NMR ($CDCl_3$): δ 3.08 (m, half-height width 8.5 Hz, 1 H), 2.75 (m, half-height width 21.3 Hz, 1 H), 2.18-0.72 (m, 16 H), 0.88 (t, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 3 H). MS: m/z (%) 195 ($M^{\cdot+}$, 1), 152 (100), 109 (14), 82 (17), 67 (26), 55 (40). 1 **HCl**: ^{1}H NMR ($CDCl_3$): δ 9.50 (br s, 1 H, NH), 3.38 (m, 1 H), 3.35 (s, 1H, NH), 3.07 (m, 1 H), 2.52-2.28 (m, 1 H), 2.27-0.78 (m, 15 H), 0.93 (t, J = 8 Hz, 3H), 0.91 (d, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 60.1 d, 58.2 d, 40.6 d, 34.7 t, 34.6 t, 29.1 t, 27.2 d, 25.3 t, 23.3 t, 20.7 t, 19.8 q, 18.9 t, 13.8 q.

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