A Biomimetic Enantioselective Approach to the Decahydroquinoline Class of Dendrobatid Alkaloids**

Mercedes Amat*, Rosa Grieria, Robert Fabregat, Elies Molins, and Joan Bosch*

* [*] Prof. Dr. M. Amat, Dr. R. Grieria, R. Fabregat, Prof. Dr. J. Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona Av. Joan XXIII s/n, 08028-Barcelona (Spain)
Fax: (+34)93-402-45-39
E-mail: amat@ub.edu
www.ub.edu/farmacogrupo/amatbosch/index.htm

Financial support from the Ministry of Science and Technology (Spain)-FEDER (Project CTQ2006-02390/BQU) and the DURSI, Generalitat de Catalunya (Grant 2005SGR-0603) is gratefully acknowledged.

Supporting information for this article (experimental details, and copies of 1H and 13C NMR spectra) is available on the WWW under http://www.angewandte.org or from the author.

Frogs of the neotropical family Dendrobatidae produce a remarkably diverse array of biologically active alkaloids. One of the major classes of these amphibian alkaloids[1] are the decahydroquinolines, which have been isolated not only from skin extracts of dendrobatid and mantelline frogs[2,3] but also from bufoind toads,[1,2,4] marine flatworms,[4a,5] and myrmicine ants.[5] They possess either a cis or trans decahydroquinoline ring fusion, with a side chain substituent at both the C-2 and C-5 positions and, in the lepadin series,[3,4] an acylated hydroxy group at the C-3 position. The most representative decahydroquinoline alkaloid is cis-195A (formerly called pumiliotoxin C), first isolated in 1969 from a Panamanian population of Dendrobates pumilio.[6]

The source of amphibian alkaloids remains an unresolved and challenging question,[10] in particular after the discovery that some of these alkaloids also occur in ants, thus strengthening a dietary hypothesis for their origin in frogs.[1] Although there are no conclusive studies concerning the biosynthesis of these toxins and, consequently, little is known about the biosynthetic pathways, there has been speculation as to possible derivation from the polyketide route by aminocyclization of polycarbonyl intermediates (A), leading to either 2,5-disubstituted decahydroquinolines (C) or spiropiperidines (histrionicotoxins).[1a,b,7] In accordance with this hypothesis, a plausible biosynthetic pathway to the decahydroquinoline class of dendrobatid alkaloids is depicted in Scheme 1.[8]

The structural diversity and pharmacological activity associated with this class of alkaloids, as well as the limited amounts available from natural sources, have stimulated considerable synthetic effort in this area,[9] including some biomimetic approaches.[10] In this context we present herein a biomimetic enantioselective approach to the decahydroquinoline class of dendrobatid alkaloids, which has culminated in the biocatalytic synthesis of (--)pumiliotoxin C.[11]

Our synthetic approach involves the use of an appropriate 1,5-poly carbonyl derivative as a synthetic equivalent of the hypothetical biogenetic polyketide intermediate A and (R)-phenylglycinol as a chiral latent form of ammonia to induce the key enantioselective biomimetic aminocyclization to the target hydroquinoline system. To evaluate the feasibility of our proposal, we initially used 1,5-tetracarbonyl compound 2 [A: R1 = OEt; R2 = (CH2)3CO2Et], which was easily accessible in excellent yield (82%) by reaction of glutaryl dichloride with 4-ethoxy-4-oxobutyrobromide (1) in the presence of Pd(PPh3)4 as the catalyst (Scheme 2).

To our delight, heating a benzene solution of 2 and (R)-phenylglycinol under Dean-Stark conditions in the presence of a catalytic amount of AcOH, resulted in the straightforward construction of the hydroquinoline ring system, with generation of two stereogenic centers, leading directly to the enantiopure tricyclic lactam 3 in 35% yield. Cyclohexenone 4 (22% yield) and hydroquinoline 5 (25% yield; nearly equimolecular mixture of stereoisomers) were also isolated. Formation of 3 can be rationalized by considering that, after an initial aldol cyclization from the symmetrical starting diketone 2, the resulting 8-oxoester 4 undergoes a phenylglycinol-promoted cyclocondensation reaction, in a process that mimics the proposed biosynthetic pathway depicted in Scheme 1. In accordance with this interpretation, 2 was first cyclized to cyclohexenone 4 in excellent yield (90%), by treatment with 1N aqueous LiOH followed by reestification, and then converted to lactam 3 (60% yield) by reaction with (R)-phenylglycinol in refluxing CsHx-cat. AcOH.[12] On the other hand, the formation of 5 in the direct reaction of 2 with (R)-phenylglycinol is a consequence of the initial generation of an oxazolidine, which then undergoes two successive cyclizations as depicted in Scheme 3.

By choosing the appropriate 1,5-poly carbonyl derivative, the above biomimetic double cyclocondensation can be adapted to the enantioselective synthesis of a variety of 2,5-disubstituted decahydroquinoline derivatives, as exemplified by the synthesis of the decahydroquinoline alkaloid cis-195A outlined in Scheme 4. The required diketoester 6 was prepared in 65% yield by Pdcatalyzed coupling of 5-oxohexanoyl chloride with the functionalized organozinc derivative 1 and stereoselectively converted as in the above series to a tricyclic hydroquinoline lactam (8) in excellent overall yield. Thus, the initial aldol cyclocondensation took place in

((Catch Phrase))

DOI: 10.1002/anie.200((will be filled in by the editorial staff))
85% yield, whereas cyclocondensation of the resulting cyclohexene 7 with R-phenylglycinol led to lactam 8 in 70% yield in a process again involving the generation of two stereogenic centers from an achiral precursor. In this series the configuration of the stereogenic ring fusion carbons generated in this step was unambiguously established by X-ray crystallographic analysis of perhydroquinoline 9, which was stereostructurally obtained in nearly quantitative yield by catalytic hydrogenation of 8. The X-ray structure of 9 also made evident the trans relationship between the hydrogens at the 4a and 5 positions of the quinoline ring.

The lactam carbonyl present in tricyclic lactam 9 allows the introduction of substituents at the 2-position of the perhydroquinoline ring, ultimately leading to enantiopure 2,5-disubstituted cis-perhydroquinolines. Thus, 9 was converted to the corresponding thioamide, which was then subjected to Eschenmoser sulfide contraction conditions (BrCH2CO2Me, CHCl3; then (MeO)2P, EtN, CHCl3, reflux) to give β-elimino ester 10 in 50% overall yield.

At this point the complete relative stereochemistry of the target alkaloid cis-195A (pumilotoxin C) was installed by hydrogenation of 10 in the presence of PtO2 under acidic conditions, which brought about both the stereoselective reduction of the vinylogous urethane double bond and cleavage of the oxazolidine C–O bond. A subsequent debenzylization with hydrogen and Pd(OH)2 in the presence of Boc2O led to the protected cis-perhydroquinoline 11.

Finally, the conversion of ester 11 to pumilotoxin C was accomplished in satisfactory overall yield by reduction to alcohol 12, followed by methylation of the corresponding aldehyde, subsequent catalytic hydrogenation of the resulting N-Boc-2-allylperhydroquinoline, and finally deprotection of the piperidine nitrogen. The NMR data and [α]D202 value (~15.3, c = 0.5 in MeOH) of cis-195A (pumilotoxin C) hydrochloride were coincident with those reported in the literature.

The above results significantly expand the scope and potential of phenylglycinol-derived oxazolopiperidone lactams as chiral building blocks for the enantioselective synthesis of complex piperidine-containing derivatives. These lactams are easily accessible by a cyclocondensation reaction of a ω-oxoacid derivative with phenylglycinol. The use of diketide diesters 2 and 6 as the ω-oxoester partners in the cyclocondensation reactions reported herein allows the straightforward construction of the hydroquinoline ring system. These 1,5-polyarylmethoxy derivatives mimic the biogenetic intermediates A (Scheme 1) by undergoing a biomimetic double cyclization that reproduces the key step of the biosynthesis of the decahydroquinoline class of dendrobatid alkaloids.

**Scheme 1.** A hypothetical biosynthetic pathway to the decahydroquinoline class of dendrobatid alkaloids.

**Scheme 2.** Biomimetic construction of the hydroquinoline ring system.

**Scheme 3.** Plausible mechanism for the formation of 5.

**Scheme 4.** Biomimetic synthesis of decahydroquinoline cis-195A [(-)-Pumiliotoxin C].
A Biomimetic Enantioselective Approach to the Decahydroquinoline Class of Dendrobatid Alkaloids**

M. Amat,* R. Griera, R. Fabregat, E. Molins, J. Bosch*

The hypothetical key step of the biosynthesis of the decahydroquinoline dendrobatid alkaloids from 1,5-polycarbonyl derivatives is mimicked by using (R)-phenylglycinol as a chiral latent form of ammonia in a double cyclocondensation reaction.

Keywords: Alkaloids · Biomimetic synthesis · Pumiliotoxin C · Decahydroquinolines · Phenylglycinol

Scheme 1. A hypothetical biosynthetic pathway to the decahydroquinoline class of dendrobatid alkaloids.
Scheme 2. Biomimetic construction of the hydroquinoline ring system.

Scheme 3. Plausible mechanism for the formation of 5.

Scheme 4. Biomimetic synthesis of decahydroquinoline cis-195A [(−)-Pumiliotoxin C].