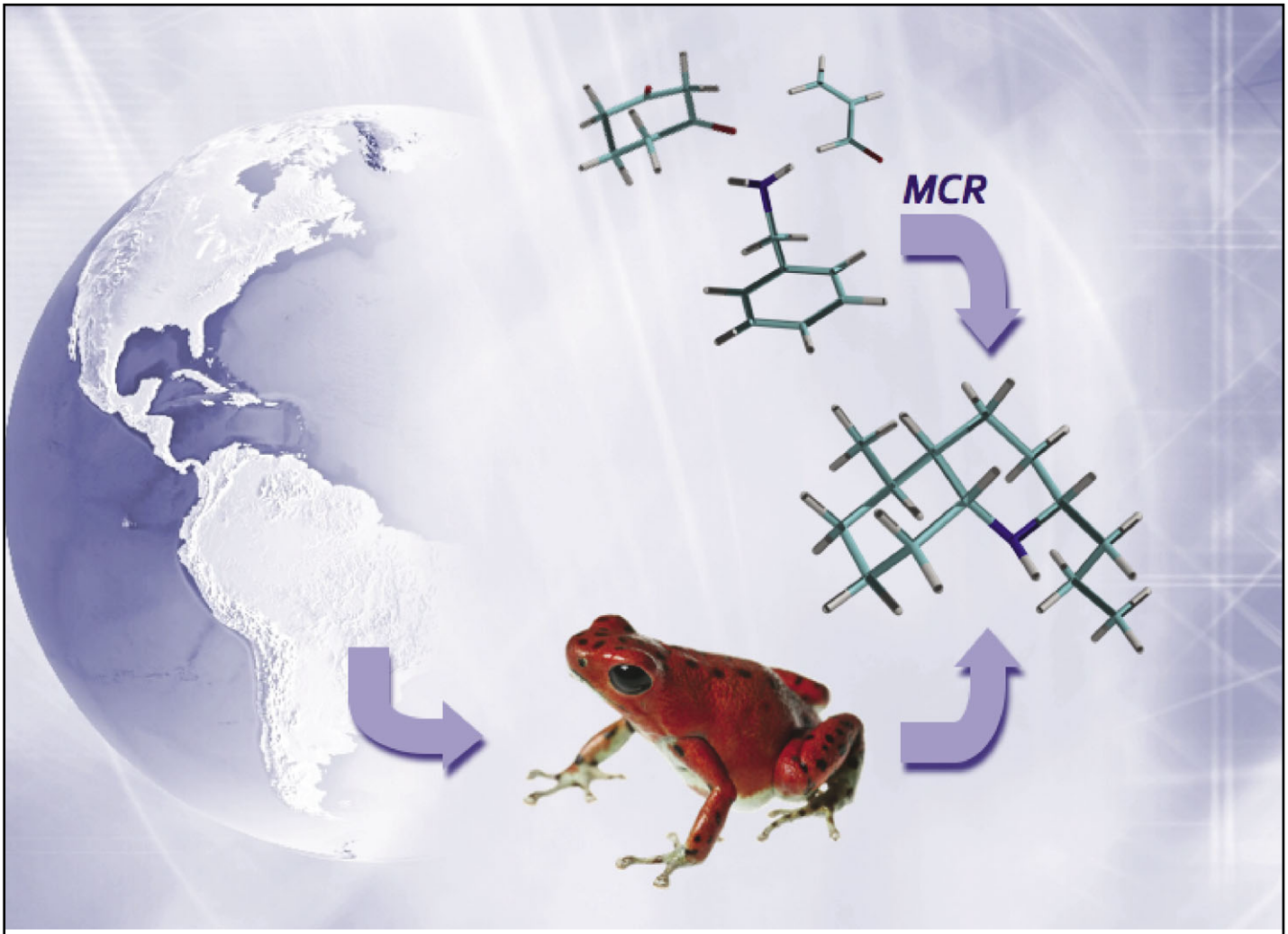

Showcasing research from the laboratory of J. Carlos Menéndez from Universidad Complutense, Madrid, Spain

Brief, efficient and highly diastereoselective synthesis of (±)-pumiliotoxin C based on the generation of an octahydroquinoline precursor *via* a four-component reaction

Pumiliotoxin C is one of the bioactive metabolites isolated from Central and South American poison dart frogs. A concise and diastereoselective synthesis of this alkaloid was developed, exploiting the high synthetic efficiency associated to a new multicomponent synthesis of octahydroquinolines. Image credit: Dong Lin © California Academy of Sciences.

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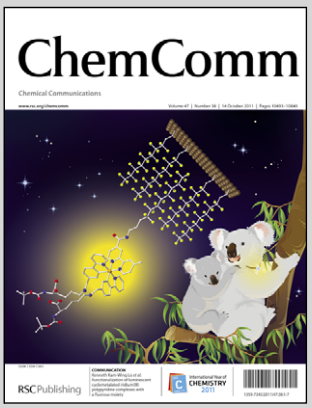

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Brief, efficient and highly diastereoselective synthesis of (±)-pumiliotoxin C based on the generation of an octahydroquinoline precursor *via* a four-component reaction†

Swarupananda Maiti and J. Carlos Menéndez*

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A short and highly diastereoselective synthesis of the amphibian alkaloid pumiliotoxin C is described, based on the preparation of an octahydroquinoline derivative through a four-component reaction. The route proceeds in 66% overall yield from 1,3-cyclohexanedione and includes two hydrogenation steps, whose stereochemical outcome was controlled *via* nitrogen acylation.

The decahydroquinoline ring system is the key structural fragment of many biologically active alkaloids[1] isolated from skin extracts of dendrobatid or mantelline frogs (Fig. 1). It has also been obtained from bufonids and other organisms such as tunicates, marine flatworms, and myrmicine ants. In many cases, these natural products have potent pharmacological activities, particularly as nicotinic receptor antagonists.[2] Their ecological and pharmacological importance, coupled with their challenging structures, has spurred a large amount of work aimed at the synthesis of these alkaloids. One of the most representative members of the group is *cis*-decahydroquinoline 195A, also known as pumiliotoxin C. This compound is isolated from frogs of the *Dendrobatidae* family,[3] which probably obtain the alkaloid from ants in their diet and accumulate it in their skins to serve as a passive chemical defense.[4] In spite of its small size, the concise construction of pumiliotoxin C poses an interesting synthetic challenge because it contains four stereocenters, three of which are contiguous, and it has received much attention from the synthetic community in recent years.[5] However, most of these syntheses require lengthy routes and only one of them[6] is focused on achieving synthetic efficiency by application of the contemporary methods involving the generation of several bonds in a single operation,[7] such as multicomponent reactions. Indeed, while this type of methodology is finding widespread application in library synthesis,[8] its systematic use in target-oriented synthesis, and specially in the construction of natural products, is still at its early stages.[9] In this context, the purpose of our work was to design and translate into practice a short synthesis of pumiliotoxin C having a multi-component reaction as the pivotal transformation. Thus, our synthetic strategy was based on the bond-creating reactions summarized in Scheme 1, featuring as the key step the one-pot conversion of 1,3-cyclohexanedione into a octahydroquinoline derivative through the generation of one C–C, two C–N and one C–O bonds in a single synthetic operation. This planned reaction can be viewed as an extension of our recently described synthesis of 6-alkoxy-1,4,5,6-tetrahydropyridines based on a CAN-catalyzed four-component reaction between primary amines, acyclic 1,3-dicarbonyl compounds, α,β-unsaturated aldehydes and alcohols.[10]

The translation of our four-component tetrahydropyridine synthesis to a cyclic 1,3-diketone substrate, leading to a new entry into 1,2,3,4,5,6,7,8-octahydroquinolines, turned out to

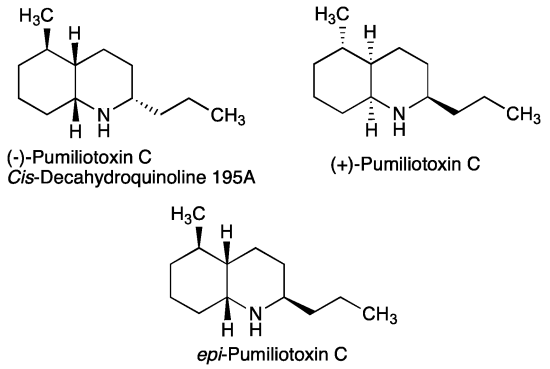
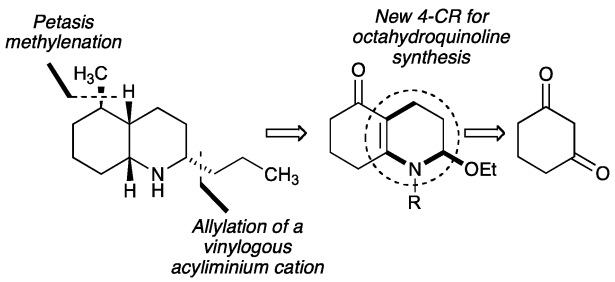


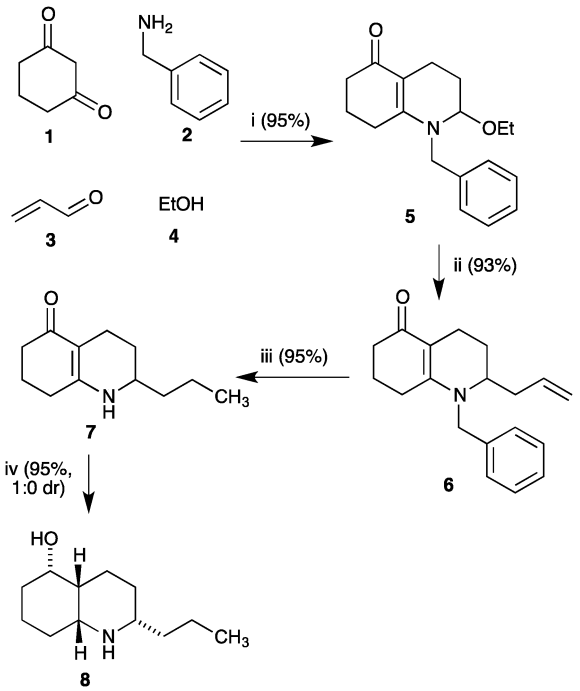
Fig. 1 Structure of (−)-pumiliotoxin C and some related natural products.



Scheme 1 Synthetic plan for the construction of pumiliotoxin C.

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, Madrid, Spain. E-mail: josecm@farm.ucm.es; Fax: +34 913941822; Tel: + 34 913941840

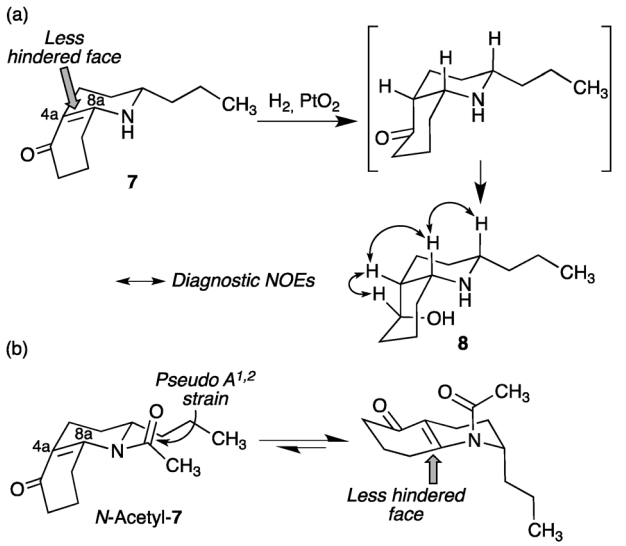
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of representative spectra. See DOI: 10.1039/c1cc11246e



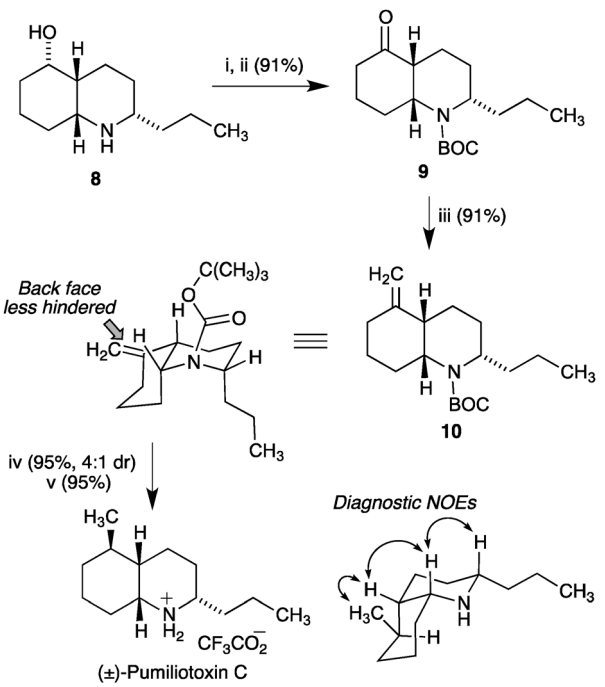
Scheme 2 Diastereoselective construction of intermediate **8**. *Reagents and conditions*: (i) **1** + **2** + **4**, $In(OTf)_3$ (5 mol%), DCM, rt, 1 h, then **3**, rt., 5 h. (ii) Allyltrimethylsilane, $BF_3{\cdot}Et_2O$, DCM, rt, 4 h. (iii) H_2 (60 psi), Pd–C (10%), AcOH, 50 °C, 15 h. (iv) H_2 (90 atm), Pt–C (5%), 50 °C, 24 h.

be non-trivial, since the application of our standard conditions led only to extensive decomposition of the starting materials. After some experimentation, we discovered that indium triflate (5 mol%) was an excellent catalyst for the desired transformation, and allowed to effect the reaction between 1,3-cyclohexanedione **1**, benzylamine **2**, acrolein **3** and ethanol **4**, affording a 95% yield of octahydroquinoline derivative **5**. Incorporation of the three-carbon chain at C-2 was achieved in 93% yield by allylation of **5** with allyltrimethylsilane in the presence of boron trifluoride, a transformation that has some interest because of the absence of literature precedent for nucleophilic additions mediated by vinylogous acylation intermediates onto polyhydroquinoline systems. Compound **6** obtained from this reaction was *N*-debenzylated to **7** by hydrogenolysis, and this intermediate was transformed into **8** in a second hydrogenation step, with complete diastereoselectivity (Scheme 2).

The stereochemistry of the crucial reduction of the C_{4a}–C_{8a} internal double bond was deduced from NOE experiments and can be explained by assuming that the major conformer for the ring system is the one with an equatorial arrangement for the propyl substituent, in which the top face is more accessible to the hydrogenation catalyst (Scheme 3a). Interestingly, the stereochemical outcome observed by us for the reduction of the internal double bond is the opposite to the one previously described for an *N*-acyl derivative of the same compound **7**. This difference can be explained through a conformational change caused by the strain between the *N*-acyl and C_2-propyl groups in *N*-acetyl-**7**, leading to the acyl substituent preferring an axial arrangement



Scheme 3 (a) Stereochemical study of compound **8** and proposed explanation for its formation. (b) Explanation found in ref. 6 for the stereochemical outcome of the reduction of the C_{4a}–C_{8a} internal double bond of the *N*-acetyl derivative of compound **7**, which was opposite to the one observed by us.



Scheme 4 Final stages of the synthesis of (±)-pumiliotoxin C. *Reagents and conditions*: (i) BOC_2O, K_2CO_3, CH_3CN, reflux, 24 h. (ii) Dess–Martin periodindane, DCM, rt, 4 h. (iii) Cp_2TiMe_2, toluene, reflux, 20 h. (iv) H_2 (1 atm), PtO_2, MeOH, rt, 1 h. (v) CF_3CO_2H, DCM, rt, 4 h.

(Scheme 3b).[6] This effect was exploited at a later stage of our synthesis.

The completion our synthesis is summarized in Scheme 4. The *N*-BOC derivative of compound **8** was transformed into **9** by oxidation with the Dess–Martin reagent. A Petasis methylenation reaction[11] of **9** afforded **10**,[12] which was

transformed into the natural product by diastereoselective hydrogenation of the exocyclic double bond and a final *N*-deprotection. An attempt was made to transform **8** directly into pumiliotoxin C *via* a methylenation–reduction sequence, avoiding the *N*-protection step, but in this case the final hydrogenation lacked diastereoselectivity. Presumably, the presence of the *N*-BOC substituent led to a diastereoselective hydrogenation by forcing the system to exist predominantly in a conformation where, in agreement with the previously mentioned literature precedent,[6] the carbamate substituent blocked the top face of the molecule.

In conclusion, we have developed a very short, diastereoselective synthesis of the amphibian alkaloid pumiliotoxin C. The main features of the route were: (i) a novel synthesis of 1,2,3,4,5,6,7,8-octahydroquinonines based on an indium triflate-catalyzed four-component reaction that generated one C–C, two C–N and one C–O bonds; (ii) the attachment of a three-carbon chain to the octahydroquinoline C-2 position based on a nucleophilic attack of an allylsilane onto a vinylogous acyliminium intermediate; (iii) two diastereoselective hydrogenation steps, whose outcome was tuned through the presence or absence of an *N*-acyl substituent. The overall yield of our route was 66% from 1,3-cyclohexanedione, making it the most efficient synthesis of pumiliotoxin C to date.

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