Biomimetic Synthesis

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

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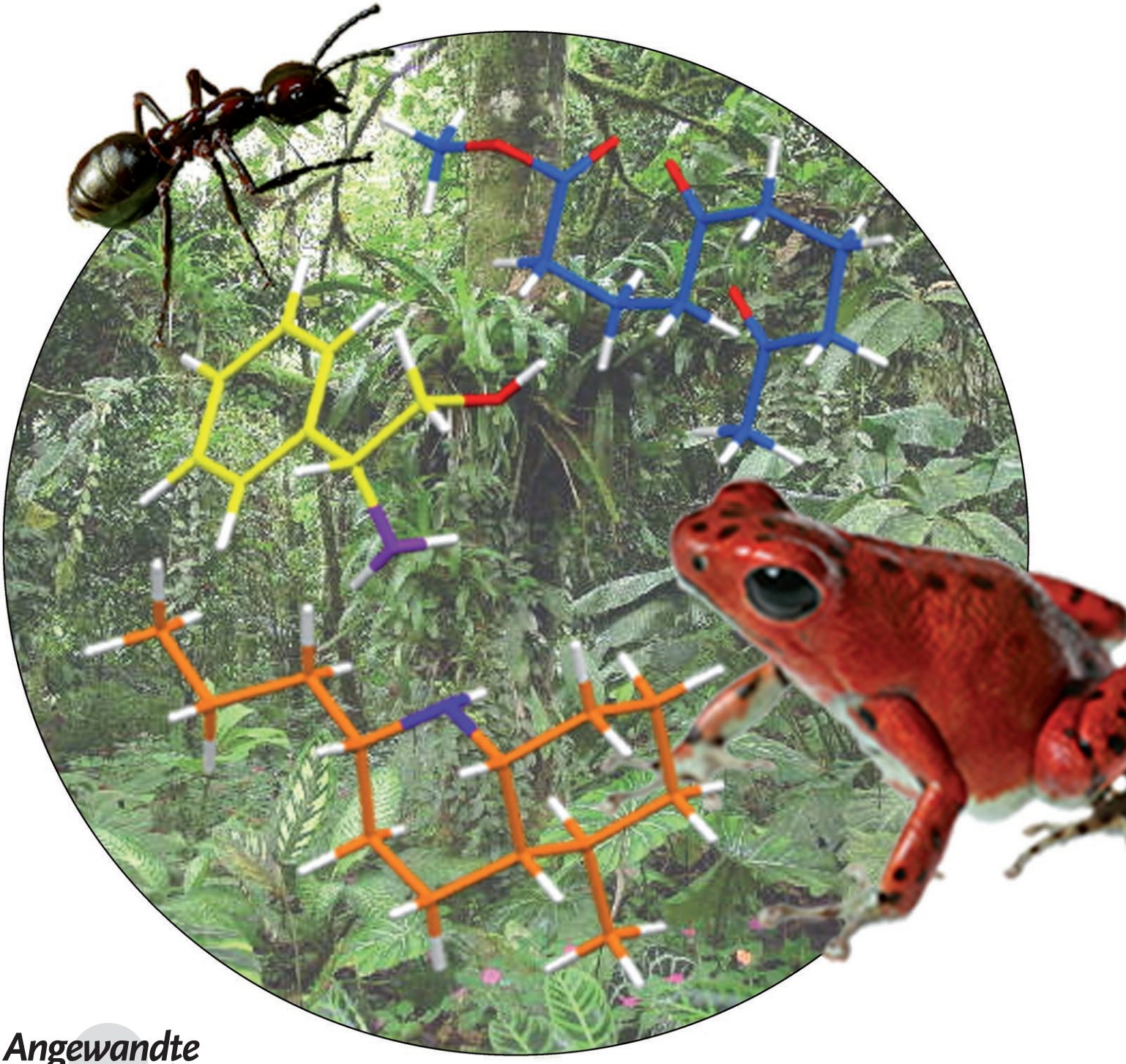
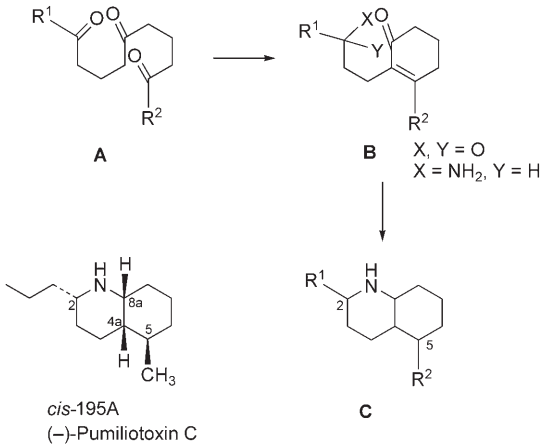


Frogs of the neotropical family Dendrobatidae produce a remarkably diverse array of biologically active alkaloids. One of the major classes of these amphibian alkaloids[1] are the decahydroquinolines, which have been isolated not only from skin extracts of dendrobatid and mantelline frogs,[2] but also from bufonid toads,[3] tunicates,[4] marine flatworms,[4b] and myrmicine ants.[5] They possess either a *cis* or *trans* decahydroquinoline ring fusion, with a side-chain substituent at both the C2 and C5 positions and, in the lepadin series,[4] an acylated hydroxy group at the C3 position. The most representative decahydroquinoline alkaloid is *cis*-195 A (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,[1] in particular after the discovery that some of these alkaloids also occur in ants, thus strengthening a dietary hypothesis for their origin in frogs.[5] 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]

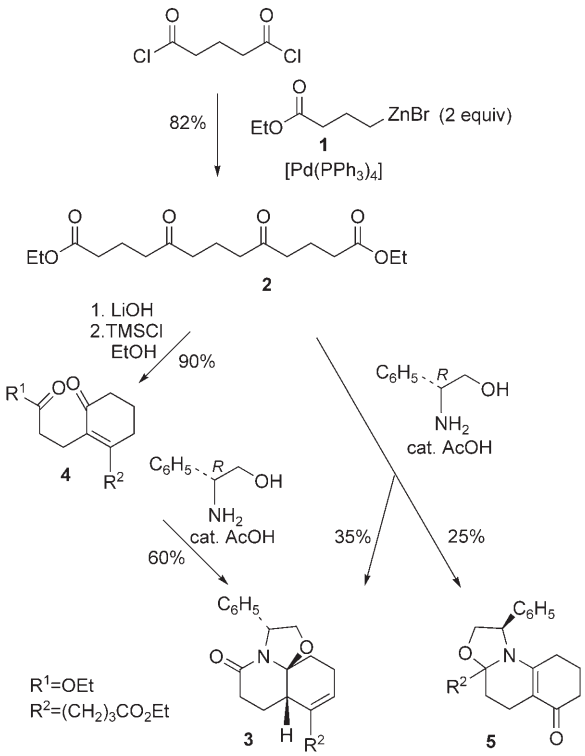
The structural diversity and pharmacological activity associated with this class of alkaloids, as well as the limited amounts available from natural sources, have stimulated considerable synthetic effort in this area,[9] including some biomimetic approaches.[10] In this context, we present herein a biomimetic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

Our synthetic approach involves the use of an appropriate 1,5-polycarbonyl derivative as a synthetic equivalent of the hypothetical biogenetic polyketide intermediate **A**, and (*R*)-phenylglycinol as a chiral latent form of ammonia, to induce



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

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**: $R^1 = OEt$; $R^2 = (CH_2)_3CO_2Et$), which was easily accessible in excellent yield (82%) by reaction of glutaryl dichloride with 4-ethoxy-4-oxobutylzinc bromide (**1**) in the presence of $[Pd(PPh_3)_4]$ as the catalyst (Scheme 2). To our delight, heating a benzene solution of **2** and (*R*)-phenylglycinol in a Dean–Stark apparatus in the presence of a catalytic amount of AcOH resulted in the straightforward construction of the hydroquinoline ring system, with gener-



Scheme 2. Biomimetic construction of the hydroquinoline ring system. See the Supporting Information for further details.

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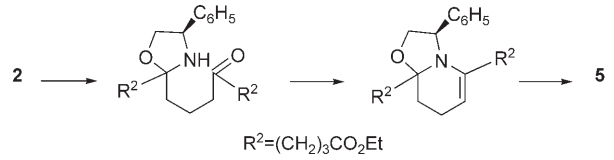
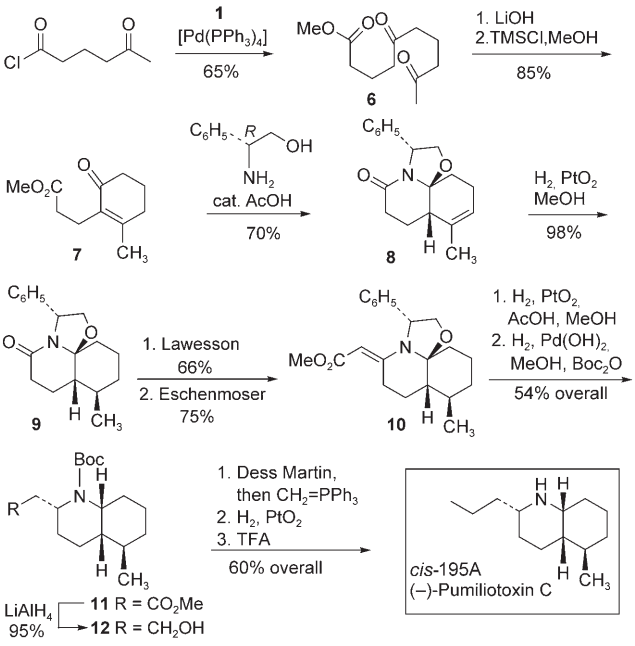
ation of two stereogenic centers, leading directly to the enantiopure tricyclic lactam **3** in 35% yield. Cyclohexenone **4** (22%) and hydroquinolone **5** (25% yield; nearly equimolecular mixture of stereoisomers) were also isolated. Formation of **3** can be rationalized by considering that, after an initial aldol cyclization from the symmetrical starting diketone **2**, the resulting δ 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 aqueous LiOH (1 mol L^{-1}) followed by reesterification, and then converted into lactam **3** (60% yield) by reaction with (*R*)-phenylglycinol in refluxing C_6H_6 containing a catalytic amount of 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.



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



Scheme 4. Biomimetic synthesis of decahydroquinoline *cis*-195A. TFA = trifluoroacetic acid, TMS = trimethylsilyl, Boc = *tert*-butyloxycarbonyl. See the Supporting Information for further details.

By choosing the appropriate 1,5-polycarbonyl derivative, the 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 the palladium-catalyzed coupling of 5-oxohexanoyl chloride with the functionalized organozinc derivative **1** and stereoselectively converted as in the above series into a tricyclic hydroquinolone lactam (**8**) in excellent overall yield. Thus, the initial aldol cyclocondensation took place in 85% yield, whereas cyclocondensation of the resulting cyclohexenone **7** with *R*-phenylglycinol led to lactam **8** in 70% yield in a process which again involved the generation of two stereogenic centers from an achiral precursor.[12] In this series, the configuration of the stereogenic ring-fusion carbon atoms generated in this step was unambiguously established by X-ray crystallographic analysis[13] of perhydroquinoline **9**, which was stereoselectively obtained in nearly quantitative yield by catalytic hydrogenation of **8**. The X-ray structure of **9** also made evident the *trans* relationship between the hydrogen atoms 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 hydroquinoline ring, ultimately leading to enantiopure 2,5-disubstituted *cis*-perhydroquinolines. Thus, **9** was converted into the corresponding thioamide, which was then subjected to Eschenmoser sulfide contraction[14] conditions ($BrCH_2CO_2Me$, $CHCl_3$; then $(MeO)_3P$, Et_3N, $CHCl_3$, reflux) to give β enamino ester **10** in 50% overall yield.

At this point, the complete relative stereochemistry of the target alkaloid *cis*-195A (pumiliotoxin C) was installed by hydrogenation of **10** in the presence of PtO_2 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 debenzylation with hydrogen and $Pd(OH)_2$ in the presence of Boc_2O led to the protected *cis*-perhydroquinoline **11**.

Finally, the conversion of ester **11** into pumiliotoxin C was accomplished in satisfactory overall yield by reduction to alcohol **12**, followed by methylenation of the corresponding aldehyde, subsequent catalytic hydrogenation of the resulting *N*-Boc-2-allylperhydroquinoline, and finally deprotection of the piperidine nitrogen. The NMR spectroscopy data and $[\alpha]_D^{22}$ value (–15.3, $c = 0.5$ in MeOH) of *cis*-195A (pumiliotoxin C) hydrochloride were consistent with those values reported in the literature.[11]

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.[15] These lactams are easily accessible by a cyclocondensation reaction of a δ oxoacid derivative with phenylglycinol. The use of diketo(di)esters **2** and **6** as the δ-oxoester partners in the cyclocondensation reactions reported herein allows the straightforward construction of the hydroquinoline ring system. These 1,5-polycarbonyl 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.

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[12] Minor amounts (ca. 18%) of the diastereoisomer at the hydroquinoline ring fusion positions were also isolated.

[13] The measurement was carried out on a Enraf–Nonius CAD4 diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation. The structure was solved by direct methods (SHELXS-86) after applying Lorentz, polarization, and absorption (empirical PSI scan method) corrections. Full-matrix least-squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and riding thermal parameters for H atoms (positioned at calculated positions) converged to a *R* factor of 0.0294 (calculated for the reflections with $I > 2\sigma(I)$). Crystal data: $C_{18}H_{23}NO_2$, orthorhombic, space group $P2_12_12_1$, $a = 7.863(6)$, $b = 13.811(9)$, $c = 14.249(9)$ Å, $V = 1547.4(18)$ Å^3, $\mu(Mo_{K\alpha}) = 0.079$ mm^{-1}, $\rho_{cald} = 1.225$ mg m^{-3}. Approximate dimensions: $0.52 \times 0.48 \times 0.39$ mm^3. Data collection was up to a resolution of $2\theta = 49.9°$ producing 1795 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.080 and -0.097 e Å^{-3}. CCDC-671493 (**9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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