Total Synthesis of (±)-Pumiliotoxin C: An Electrochemical Approach

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Keywords: Electrochemistry / Metalation / Natural products / Pumiliotoxin C / Total synthesis

The total stereoselective synthesis of the decahydroquinoline alkaloid (±)-pumiliotoxin C (*cis*-**195A**, **1**) is described. The compound was prepared in 15 steps from the commercially available 4-piperidone ethylene ketal **2**, in an overall 5% yield. New C–C bonds in the α position relative to the nitrogen atom were formed by the metalation of aminonitriles **4** and **15**, which were themselves prepared electrochemically. The ease of this synthesis shows that the *N*-aryl group is an efficient nitrogen-protecting group that can be removed in the last step through a Birch dearomatization. In addition, the aryl substituent serves as an efficient activator of the nitrogen atom during the elaboration of aminonitriles **4** and **15**. The oxygen atom of the keto carbonyl group in octahydroquinolinone **10** was removed by an unprecedented two-step method involving a Shapiro reaction and a palladium-catalyzed reduction of the intermediate alkene **13**. Finally, the expected stereospecific alkylation–hydride reduction process of the *cis*-fused aminonitrile **15** established the *trans* relationship between the propyl group at C-2 and the methyl substituent at C-5.

Introduction

Frogs of the family Dendrobatidae, more commonly known as "poison-arrow frogs", produce a vast array of lipophilic alkaloids, many of which can be isolated from the glandular secretions of their skin. At least 20 structural classes have been detected, including histrionicotoxins, epibatidine, pyrrolizidines, decahydroquinolines, indolizidines, and other bicyclic alkaloids. To date, approximately 30 alkaloids have been assigned to the decahydroquinoline class; selected examples are given in Figure 1.[1]

The *cis*-decahydroquinoline ring is also found in the alkaloids of the gephyrotoxin family.[2] Among these alkaloids, the relatively nontoxic alkaloid pumiliotoxin C (**1**) is the most abundant in natural sources, and was the first to be isolated from the skin secretions of the brightly colored Panamanian frog *Dendrobates pumilio*.[3] The difficulty in isolating more than milligram quantities from natural sources led chemists to elaborate new chemical pathways for the formal or total synthesis of **1**. For this, one has to deal with the construction of the *cis*-decahydroquinoline ring and should also correctly orient the substituents borne by the C-2 and C-5 carbon atoms. These synthetic routes have included alkylation of *N*-formamidine derivatives,[4] aminocyclization reactions,[5] Haller–Bauer cleavage,[6] nitrogen fixation,[7] cycloaddition reactions,[8–11] Beckmann rearrangement of tetrahydroindenones,[12] [3,3]-sigmatropic rearrangements,[13] addition of Grignard reagents to pyridinium salts,[14] and biomimetic approaches.[15] In addition, several elegant, well-designed enantioselective syntheses of natural (–)-**1** have been reported in the last decade.[16–20]

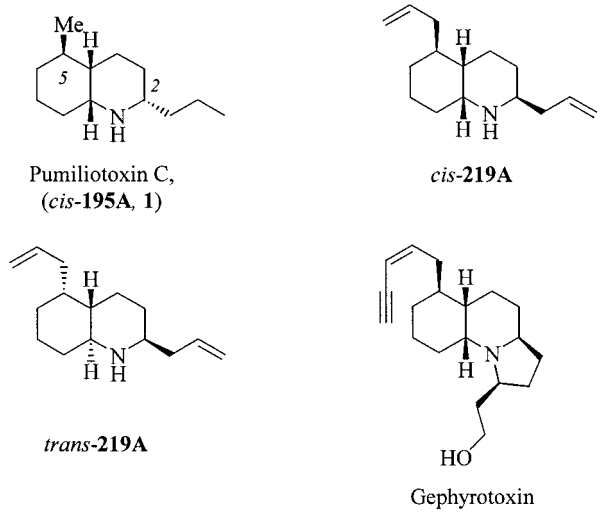

Figure 1. Structures of *cis*- and *trans*-decahydroquinoline alkaloids from dendrobatid frogs.

In a recent paper,[21] we showed that *cis*-2,6-dialkylpiperidines **III**, such as (±)-isosolenopsin A ($R^1 = C_{11}H_{23}$, $R^2 = CH_3$) and (±)-dihydropinidine ($R^1 = C_3H_7$, $R^2 = CH_3$), can be efficiently synthesized by anodic cyanation of *N*-phenyl-2-alkylpiperidine **I** (Scheme 1).

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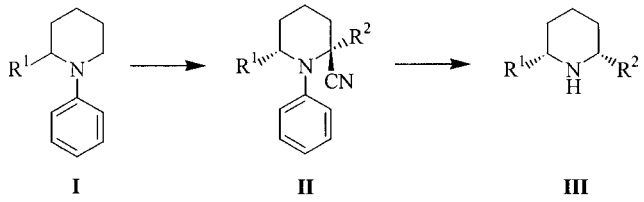
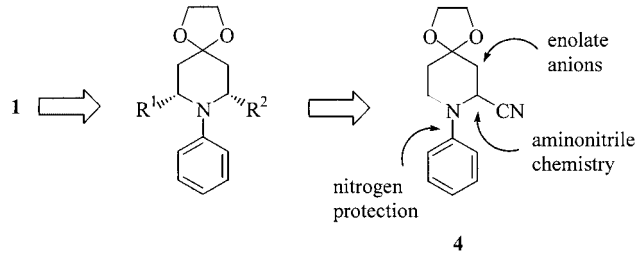
 DOI: 10.1002/ejoc.200400846



Scheme 1. Synthesis of 2,6-dialkylpiperidines.

The most attractive feature of this sequence is that the regiochemistry of cyanide introduction in **I** seems to be well adapted for the synthesis of **III**. In other words, a new C–C bond is created at C-6 regiospecifically, providing a reliable route from 2-alkylperidines **I** to the corresponding 2,6-dialkyl derivatives **III** via the bifunctional aminonitrile **II**. Our synthetic plan for the stereoselective synthesis of **1** is outlined in retrosynthesis (Scheme 2). It calls for aminonitrile **4** to be elaborated with a masked carbonyl function at C-4. The unmasked ketone ensures the elaboration of the bicyclic system, while aminonitrile chemistry affords 2,6-disubstituted products.



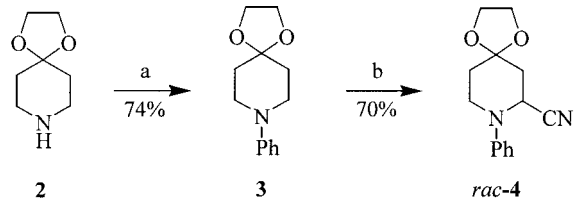
Scheme 2. Retrosynthetic analysis of (±)-pumiliotoxin C (**1**).

The stereochemical approach was to use the decahydroquinoline ring as a rigid template to control the *trans* relationship that should be established between the C-5 and C-2 chiral centers. The role of the cyclic ketal in the formation of piperidine **4** and in the stabilization of the lithiated aminonitrile (through coordination of Li with O) remained to be established. In this study, all compounds are racemic, and consequently, all the stereogenic units will be represented in a relative configuration.

Results and Discussion

Preparation and Alkylation of Aminonitrile 4

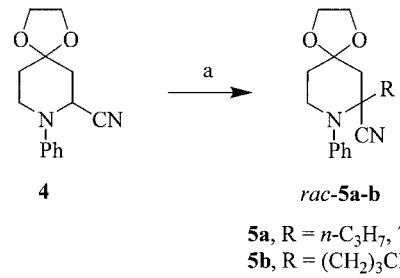
Access to the starting material proved to be straightforward (Scheme 3). The phenyl group was easily incorporated by the Caubère coupling of commercially available 4-piperidone ethylene ketal **2** with phenyl bromide (1.1 equiv.) in THF (50 °C, overnight), in the presence of a *t*BuONa/$NaNH_2$ mixture as the complex base.[22] Under these conditions, *N*-phenylpiperidone (**3**) was obtained in 74% yield after chromatographic purification.



Scheme 3. Synthesis of aminonitrile **4**. Reagents and conditions: (a) $NaNH_2$/*t*BuONa, C_6H_5Br, THF, 50 °C, overnight, 74%; (b) – 2 e^-, – H^+, MeOH, AcOLi (20 g L^{-1}), NaCN (6 equiv.), 70%.

For the synthesis of aminonitrile **4**, we used a large-scale method developed in our laboratory.[23] Before performing macroscale electrolyses, analytical investigations were carried out with a glassy carbon electrode at a scan rate of 50 mV s^{-1}. Amine **3** (1 g L^{-1}) was dissolved in methanol containing lithium acetate (20 g L^{-1}) as supporting electrolyte and sodium cyanide (6 equiv. per mol of substrate) as trapping agent. The voltammogram revealed a well-defined irreversible system at E_{p_A} = +0.95 V vs. SCE, followed by an ill-defined peak at E_{p_B} = +1.5 V vs. SCE. These data are in accordance with previous results obtained in our laboratory, which clearly showed that the first oxidation peak is attributable to the amine–iminium transformation, and the second oxidation peak corresponds to the oxidation of the α-aminonitrile system generated at peak A.[23] Taken together, these results indicate that a selective bielectronic process could be performed at peak A. Thus, a methanolic solution of **3** was percolated through a flow cell fitted with a porous graphite electrode as anode, and the current was calculated according to a bielectronic process (2 F mol^{-1}). After a single passage through the porous anode, the voltammogram recorded for the outlet solution showed the quasi disappearance of the first oxidation peak. Work-up and chromatographic purification over a silica column afforded the expected aminonitrile **4**, which was obtained as a viscous oil that solidified upon cooling (m.p. 118 °C, 70%). The ^1H NMR spectrum is consistent with a ring cyanation and includes a characteristic 2-H signal, which appears as a broad singlet at δ = 4.67 ppm (1 H).

We set bifunctional aminonitriles **5a**,**b** as initial synthetic targets of this study (Scheme 4).[24] There are two distinct processes for the synthesis of **5**: deprotonation and alkylation of the resulting carbanion. Table 1 details the effects



Scheme 4. Synthesis of aminonitriles **5a**,**b**. Reagents and conditions: (a) LDA (1.1 equiv.), RBr, THF, –20 °C, overnight, **5a** (R = n-C_3H_7, 75%), **5b** [R = $(CH_2)_3Cl$, 94%].

Table 1. Metalation and alkylation of α-aminonitrile **4**.

Entry	Deprotonation, T [°C] / t [h]	Additive	Electrophile	Alkylation, T [°C] / t [h]	Product yield[a][b], %
1	–40 / 2	–	n-C_3H_7Br	–20→20 / 2	**5a**, 40
2	–40 / 2	–	n-C_3H_7Br	–20→20 / 12	**5a**, 55
3	–40 / 1	HMPA[c]	n-C_3H_7Br	–20 / 12	**5a**, 60
4	–40 / 5	TMEDA[d]	n-C_3H_7Br	–20 / 12	**5a**, 10[e]
5	–20 / 2	–	n-C_3H_7Br	–20 / 12	**5a**, 75
6	–40 / 5	–	n-C_3H_7I	–20 / 12	**5a**, 72
7	–60 / 1	–	n-C_3H_7I	–20→20 / 5	**5a**, 75
8	–40 / 1	–	$Br(CH_2)_3Cl$	–20 / 12	**5b**, 94

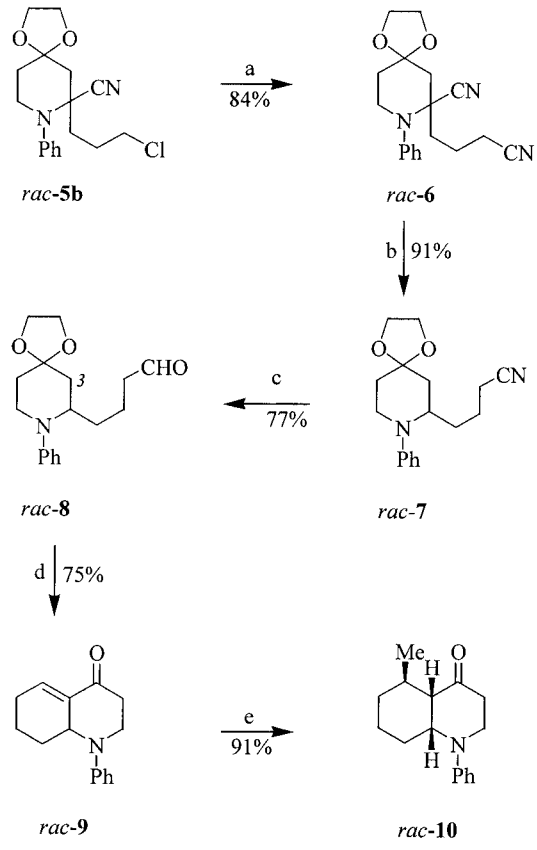
[a] All products were isolated and characterized by ^1H NMR spectroscopy. [b] Yields were determined after column chromatography through silica gel. [c] HMPA/THF (5:15). [d] 0.2 equiv. [e] Starting compound was recovered in 80% yield.

of temperature, electrophile structure, and solvent additives. All the experiments were carried out with 1.1 equiv. of LDA as base and THF as solvent. The deprotonation step was done at temperatures between –60 °C and –20 °C.

Treatment of the deep-orange anion solution obtained in this way with 1-bromopropane at –20 °C (no alkylation occurred below –30 °C), followed by continuous stirring at room temperature for 2 h (entry 1), gave the desired bifunctional aminonitrile **5a** in 40% yield, along with 30–40% of unreacted aminonitrile **4**. Prolonged treatment at room temperature (12 h, entry 2) did not significantly increase the yield (55%). Because of these anomalous results, and to eliminate or minimize the presence of **4**, we added HMPA or TMEDA, solvent additives that are commonly used to enhance the ionic character of the C–Li bond. Upon comparing entries 2 and 3, one sees that the presence of HMPA as co-solvent had little effect, while the addition of 0.2 equivalents of TMEDA (entry 4) led to an unexpectedly low 10% yield of **5a** accompanied by unreacted aminonitrile **4** (80%). Entry 5, however, clearly shows the effect of the temperature at which the electrophile was condensed onto the lithiated carbanion. Lowering the temperature to –20 °C for 12 h significantly improved the formation of aminonitrile **5a** (75%). These differences in reactivity can be interpreted in terms of electrophile reactivity. At elevated temperatures (entries 1 and 2), when the lithiated aminonitrile reacts with the alkyl halide (RBr) an elimination process (*E*2) occurs competitively. The nature of the electrophile also has an effect as the results (entries 6 and 7) indicate that the best yields were observed in the presence of iodopropane. These results confirm that when the piperidine ring is oxygenated, the $S_N/E2$ ratio is decreased substantially. Following these data, the alkylation of **4** with 1-bromo-4-chlorobutane was carried out at –20 °C for 12 h; the bifunctional aminonitrile **5b** was obtained in 94% yield after careful purification by column chromatography on silica gel. Having installed the requisite side chain in **5b**, we turned our attention to constructing octahydroquinolinone **10**.

Synthesis of Octahydroquinolinone 10

For the synthesis of **1**, we believed the best synthetic approach to be an intramolecular aldol annulation process between an aldehyde group, tethered by a three-carbon unit, and C-3 (Scheme 5).



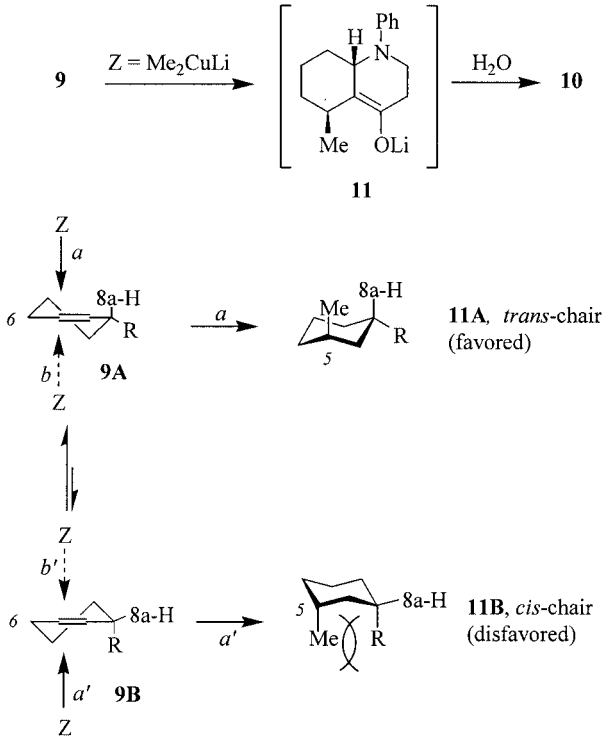
Scheme 5. Synthesis of octahydroquinolinone **10**. Reagents and conditions: (a) NaCN (3 equiv.), DMSO, nBu$_4$NI (10 mol-%), room temp., 48 h, 84%; (b) $NaBH_4$, (4 equiv.), EtOH, room temp., overnight, 91%; (c) Dibal-H (1.0 equiv.), CH_2Cl_2, –60 °C to –20 °C, overnight, 77%; (d) 1.5 M H_2SO_4/THF, 78 °C, 5 h, 75%; (e) Me_2-CuLi (2.2 equiv.), Et_2O,–15 °C, 30 min, 91%.

This conversion was accomplished by the displacement of the terminal chlorine atom in **5b** by cyanide in DMSO to afford the polar dinitrile **6** in 84% yield. On further treatment with four equivalents of $NaBH_4$, **6** gave the desired protected nitrile **7** in a satisfactory 37% yield from **2**. The synthesis of aldehyde **8** was carried out by the mild reduction of the terminal nitrile group with one equivalent of Dibal-H in CH_2Cl_2 at –20 °C, followed by the hydrolysis of

the intermediary iminium ion. Unfortunately, the reaction proved to be more difficult than anticipated, as it can not be reproduced easily. Thus, the yield of the aldehyde **8** varies with the scale of the reaction − it decreased from 95 to 55% starting from an increasing amount of nitrile **7** (0.70 to 7.06 mmol). The ^{1}H NMR spectrum of **8** is consistent with the structure assigned. Specifically, the aldehydic proton displays a characteristic triplet (J = 1.6 Hz) signal at δ = 9.69 ppm (1 H). The spectrum also contains a characteristic multiplet system at δ = 3.93–4.04 ppm (4 H), attributable to the ethylene ketal moiety.

For a simple and efficient synthesis of enone **9**, it was clear that both the ketone unmasking and the annulation process should be done in the same reaction vessel. To this end, the exposure of **8** to acidic conditions was investigated. Heating **8** in refluxing THF for 3 h in the presence of 1.5 M HCl resulted in the formation of **9** in a modest 30% yield, accompanied by several polar side-products that were easily separable by column chromatography. By using oxygen-free solvents and heating **8** for 5 h in a mixture containing H_2SO_4 in place of HCl, enone **9** was obtained in an improved 75% yield. Structural determination of **9** was straightforward. In the ^{13}C NMR spectrum, the C-4 and C-5 carbon atoms give resonance signals at δ = 199.09 and 138.18 ppm. In the ^{1}H NMR spectrum recorded in $CDCl_3$, 5-H exhibits a characteristic narrow multiplet signal at δ = 6.84 ppm (1 H).

For the stereoselective introduction of the C-5 methyl group in **9**, we turned to the conjugate addition of an organocuprate reagent, as reported by Comins[14] and Kunz.[18] The treatment of **9** with an ethereal solution containing 2.2 equiv. of Me_2CuLi at –15 °C for 30 min led, after the addition of an excess of water to the resulting enolate **11**, to the expected adduct **10**, with an excellent diastereoselectivity (*de* ≈ 99%), in 91% yield (Scheme 6). The ^{13}C NMR spectrum of **10** exhibits a set of 14 resonance lines, two of which are due to the C-4a and C-5 carbon atoms at δ = 55.67 and 26.78 ppm, respectively. The ^{1}H NMR spectrum of **10**, well resolved, allowed the complete assignment of all the signals. The most salient feature is the doublet signal (J = 7.4 Hz) at δ = 1.06 ppm (3 H) corresponding to the 5-Me group. The ^{1}H-^{1}H COSY spectrum shows that 8-Ha exhibits a well-defined quadruplet of doublets (^2J = ^3J = 11.6, ^3J = 3.5 Hz, 1 H) at δ = 1.37 ppm. Since 8-Ha exhibits two large coupling constants with its neighbors, it was concluded that it is in an axial position. These data allowed us to determine the stereochemistry of **10**. A NOESY experiment showed correlations between 5-Me, 4a-H, and 8a-H, which are typical of a *cis*-fused decahydroquinoline class, while a correlation between 2-Ha (δ = 3.50 ppm) and 8-Ha (δ = 1.37 ppm) indicated that these two protons are close (Figure 2).[25] Because this spatial relationship is possible only in conformer B, it was assumed that **10** had a gephyrotoxin-like conformation. At first sight, this result seemed to be contradictory. Eliel et al.[26] have extensively studied the conformational equilibrium of various substituted *cis*-decahydroquinolines. On the basis of ^{13}C NMR studies, they concluded, in the case of N-H or N-Me derivatives, that conformer A was energetically favored. Conversely, Booth et al.[27] have observed that when the nitrogen atom is substituted by larger groups, conformer B is preferred. These findings were confirmed by Meyers et al.,[4] who showed that in the case of *N*-formamidines and *N*-Boc derivatives, the *cis*-decahydroquinoline system exists predominantly in conformation B. These results agree with our observations, and support the fact that **10** would exist in conformation B with selectivity greater than 99%, as determined by ^{1}H NMR spectroscopy. Taken together, these results also indicate that the conjugate addition of Me_2CuLi to enone **9** proceeds in an efficient stereocontrolled mode (path *a*, Scheme 6).[28] The addition reaction between Me_2-CuLi (Z) and the ethylenic double bond in conformer **9A** yields the *trans*-axial/equatorial enolate **11A**, while the similar addition to conformer **9B** (path *a′*) leads to the energetically disfavored enolate **11B**, which suffers from unfavor-



Scheme 6. Stereochemical pathway for the addition of Me_2CuLi to hexahydroquinolinone **9**. For sake of simplicity only the cyclohexyl ring is represented.

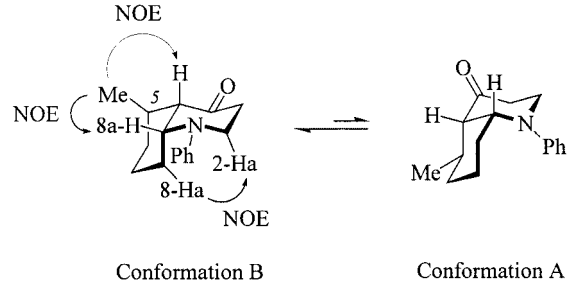


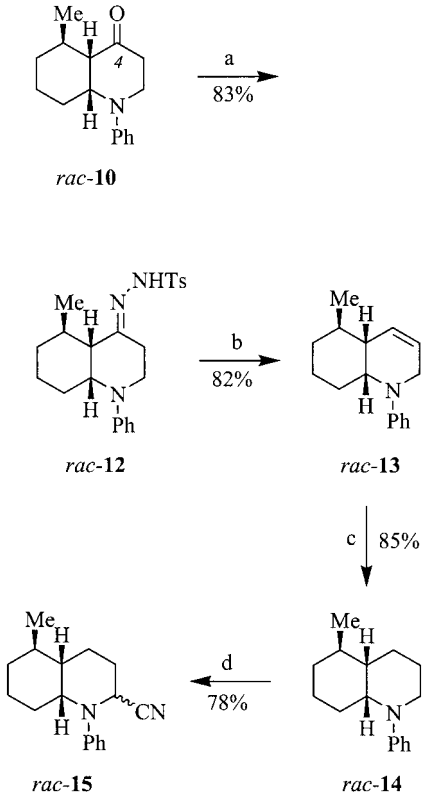
Figure 2. Conformational study of octahydroquinolinone **10**. Characteristic NOE effects are indicated.

able 1,3-diaxial interactions between the R group and the methyl substituent.[29]

Completion of the Synthesis of (±)-Pumiliotoxin C

Synthesis of Aminonitrile 15

For the synthesis of decahydroquinoline **1**, we thought to remove the undesired carbonyl group at C-4 (Scheme 7). Removal can be achieved classically by the Wolff–Kishner reduction or, more efficiently, by two-step methods involving the catalytic reduction of a vinyl triflate[14] or the desulfurization of a dithiolane[18] in the presence of Raney nickel.



Scheme 7. Synthesis of aminonitrile **15**. Reagents and conditions: (a) $TsNHNH_2$ (1.1 equiv.), EtOH, 78 °C, overnight, 83%; (b) *n*BuLi (2.2 equiv.), THF, –60 °C, 90 min, room temp., 2 h, 82%; (c) Pd/C (10%), MeOH, H_2 (1 atm.), 10 h, 85%; (d) – 2 e^-, – H^+, MeOH, AcOLi (20 g L^{-1}), NaCN (6 equiv.), 78%.

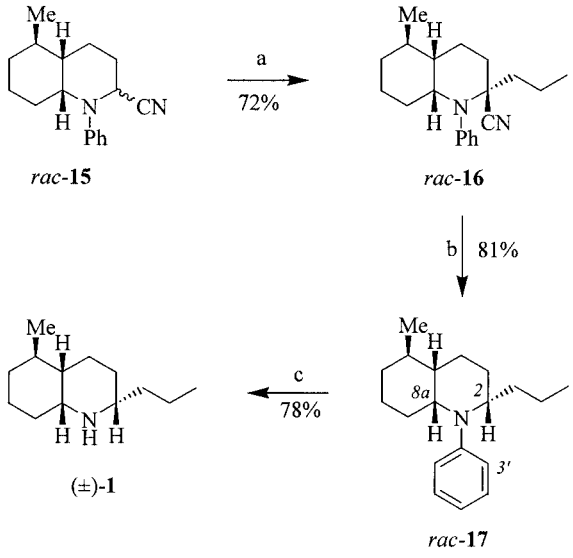
A new solution to this problem is the Shapiro reaction[30,31] followed by the catalytic reduction of an alkene derivative. Thus, heating **10** in refluxing ethanol, in the presence of 1.1 equiv. of tosylhydrazine, afforded tosylhydrazone **12** (83%) as a white solid which melts at 182–184 °C. The synthesis should give one geometric isomer in which the carbon–nitrogen double bond probably has an (*E*) configuration; no efforts were made to determine the geometry of this product. The Shapiro reaction was performed by treatment of a THF solution of **12** at –60 °C with 2.2 equiv. of *n*BuLi in THF followed by stirring for 2 h at room temperature, upon which N_2 evolved. The addition of water to the resulting vinyllithium salt yielded alkene **13** in a satisfactory 82% yield. Both the ^1H and ^{13}C NMR spectra indicated the presence of a single product, providing evidence that the double bond had formed regiospecifically. From the literature data,[32] this result was predictable and may arise from the *syn*-dianion effect. Several studies have shown that in ether solvents the geometry of the tosylhydrazone directs the regioselectivity of alkene formation. In the ^1H NMR spectrum of **13**, recorded in $CDCl_3$, the ethylenic protons are found at δ = 5.70 (1 H) and 5.88 ppm (1 H) as an AB resonance system ($J_{A,B}$ = 10.1 Hz). Interestingly, the Shapiro reaction is a particularly attractive method for elaborating a Δ^3-piperidine system, which upon functionalization of the alkene double bond enables the preparation of polysubstituted decahydroquinolines.

For our purposes, the alkene double bond in **13** was reduced by a palladium-catalyzed hydrogenation, affording decahydroquinoline **14** in 85% yield. Because it appeared difficult to stereoselectively introduce a propyl chain at the remaining carbon center (C-2),[4] we reasoned that the synthesis of aminonitrile **15** should constitute an attractive alternate process (Scheme 7). Our operating strategy rested on the assumption that **15** should be synthesized regioselectively, thus permitting the further incorporation of the requisite *n*-propyl chain through a nitrile-stabilized carbanion. Interestingly, the voltammogram of a methanolic solution of amine **14** displays a characteristic irreversible system at E_p = +0.95 V vs. SCE, once more indicating the formation of an iminium ion at the anode. Consequently, **14** was electrolyzed in an *undivided batch cell* at controlled potential (E_p = +0.80 V vs. SCE) in a similar medium to that used for the electrolysis of **3**. After the consumption of two Faradays per mol of substrate, aminonitrile **15** was obtained in a modest 45% yield as a mixture of two isomeric species. The ^1H NMR spectrum of that mixture revealed the presence of epimers at C-2 in a 6:4 ratio. Characteristic low-field signals attributed to the 2-H protons of each epimer are found at δ = 4.17 and 4.40 ppm, whereas the 8a-H proton signals resonate at δ = 3.55 and 4.01 ppm. Interestingly, this product distribution indicates that the formation of the intermediary iminium ion at the anode is highly regioselective. The presence of single adducts cyanated at C-2 reveals that favorable interactions occur between the partially occupied nitrogen lone-pair of the intermediary radical cation and the vicinal methylene protons at C-2. Hence, cyanation takes place at the less-substituted carbon atom.[33,34] Note that no detectable amount of the alternate regioisomer, which would result from a proton loss at C-8a, has ever been encountered.

To improve the yield of **14**, several experiments were undertaken. In one of these, we found that when the electrolysis was carried out at a planar vitreous electrode in a *divided cell* on a 2.80 mmol scale the yield of **15** reached 78%. These encouraging observations prompted us to incorporate the propyl chain at C-2 through the metalation of the aminonitrile function of **15**.

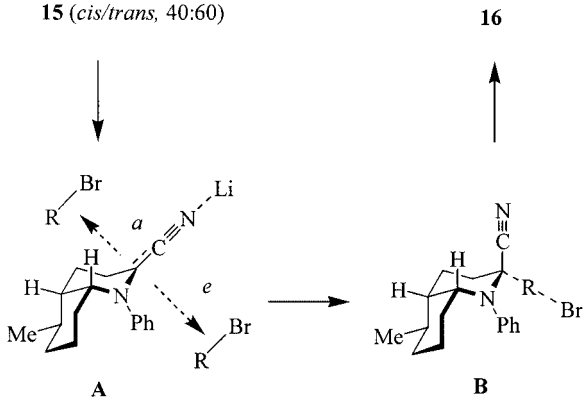
Synthesis of (±)-Pumiliotoxin C

The alkylation of a *cis*/*trans* mixture (40:60) of **15** in THF was performed by adding 1.5 equiv. of LDA, and then by condensing the resulting anion solution with propyl bromide at –20 °C overnight (Scheme 8). Workup yielded the bifunctional aminonitrile **16** (72%) as a single adduct (*de* ≈ 99%). The spectroscopic data (^{1}H, ^{13}C NMR) of this adduct are consistent with the formation of one geometric isomer, although the relative orientation of the side-chain substituent could not be determined from the ^{1}H NMR spectrum. Interestingly, single crystals were obtained by a slow crystallization of **16** from a mixture of diethyl ether and petroleum ether (Figure 3).



Scheme 8. Synthesis of (±)-pumiliotoxin C (**1**). Reagents and conditions: (a) LDA (1.5 equiv.), *n*-C_3H_7Br, THF, –20 °C, overnight, 72%; (b) EtOH, $NaBH_4$, (4.0 equiv.), room temp., overnight, 81%; (c) Li (130 equiv.), liq. NH_3/THF/EtOH (20:10:8), –40 °C, 1 h, H_2SO_4/H_2O/EtOH (0.5:5.0:4.5), 60 °C, 10 min, 78%.

A subsequent X-ray study of these crystals provided the final proof that our predictions were correct, as in the predominant conformation the propyl chain attached to C-2 and the methyl group attached to C-5 are equatorial, and hence mutually *trans*. In addition, aminonitrile **16** has the required pumiliotoxin-like conformation. The success of the alkylation lies also in the fact that both *cis*- and *trans*-**15** yield the same lithiated species **A**, which is attacked from the equatorial direction by the entering electrophile to produce the energetically favored reactant-like transition state **B** (Scheme 9). It should also be pointed out that in transition state **B**, a maximum orbital overlap between the axial cyano group and the nitrogen lone-pair is maintained.[35]



Scheme 9. Alkylation of aminonitrile **15**.

In the penultimate step, reduction of the aminonitrile system in **16** should occur with retention of configuration at C-2. Reasoning that in conformation **D** a severe synaxial interaction between the C-8–C-8a bond and the propyl chain borne by C-2 should place the intermediate iminium system in conformation **C**, we planned the hydride reduction of **16** (Scheme 10). Thus, treatment of **16** with an excess of $NaBH_4$ in ethanol resulted in the synthesis of de-

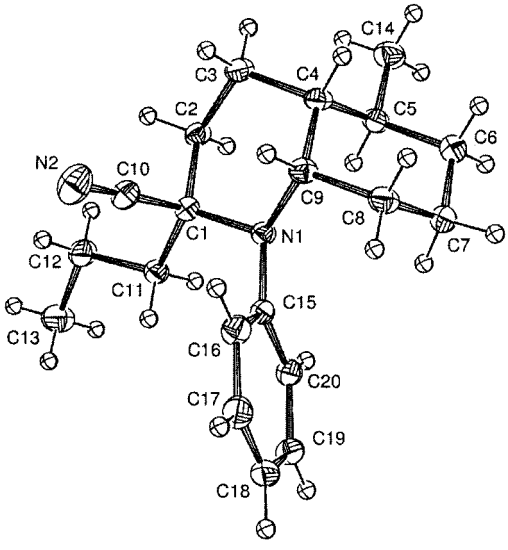
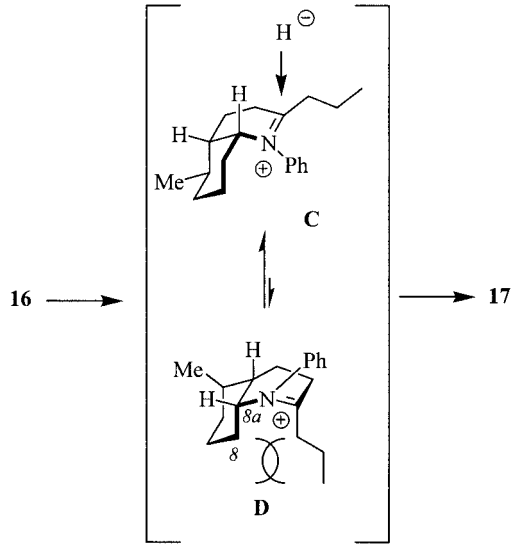


Figure 3. PLATON view of aminonitrile **16**.



Scheme 10. Hydride reduction of aminonitrile **16**.

cahydroquinoline **17** in 81% yield. Attack from the bottom face of the molecule, which would have generated the less thermodynamically stable isomer of **17**, was not observed.

Surprisingly, both the ^{1}H and ^{13}C NMR spectra of **17** display unresolved coalescent signals. For example, in the ^{1}H NMR spectrum, recorded in C_6D_6, diagnostic protons 2-H and 8a-H resonate as broadened singlets at δ = 3.00 (1 H) and 3.29 ppm (1 H), respectively. This anomalous behavior was also found in the broad-band decoupled ^{13}C NMR spectrum (C_6D_6, 300 K), in which the C-3′, C-2, and C-8a carbon atoms (Scheme 8) resonate as ill-defined systems at δ = 124.38, 60.90, and 59.44 ppm, respectively. However, heating the sample at 343 K induced decoalescence of these broad peaks and a sharpening of all the signals. We assessed our product ratio to be at least 99:1, but we were not able to determine the stereochemistry of **17** by spectroscopic means. After a few days, amine **17** crystallized as colorless plates (m.p. < 40 °C). An X-ray study of these plates revealed the stereochemical outcome of the reduction process. The ORTEP view clearly shows that the propyl chain is equatorial (Figure 4), indicating that the hydride anion was incorporated as shown in Scheme 10. Finally, the *N*-aryl bond in **17** was cleaved by the reductive dearomatization of the phenyl substituent in a single electron transfer. In a preceding report,[21] we noticed that reduction of the phenyl group of several *N*-phenyl-2,6-dialkylpiperidines was possible in a NH_3/THF/EtOH (20:10:4) mixture in the presence of 10 equiv. of Li. Under these reaction conditions, amine **17** was not completely reduced and a mixture of unstable enamines **18** and **19**, which were rapidly hydrolyzed in sulfuric acid medium (H_2SO_4/H_2O/EtOH, 0.5:4.5:5.0, Scheme 11), was obtained. Note that when ethanol was used as proton donor, over-reduction of an ethylenic double bond occurred (step c, Scheme 11) to yield substantial amounts of enamine **19** (30–40%).

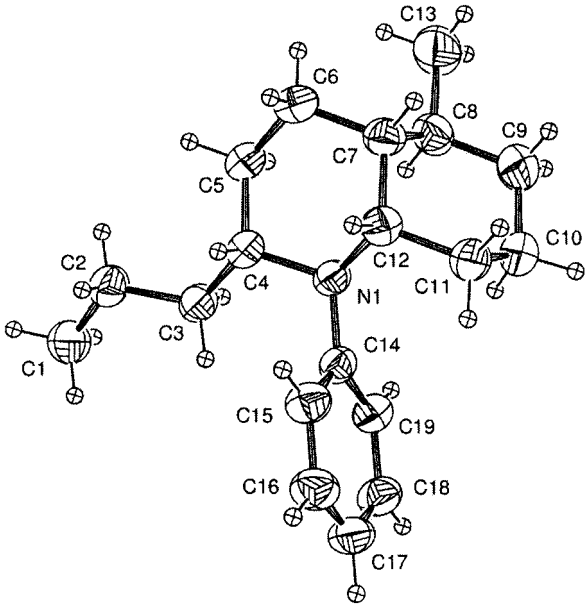
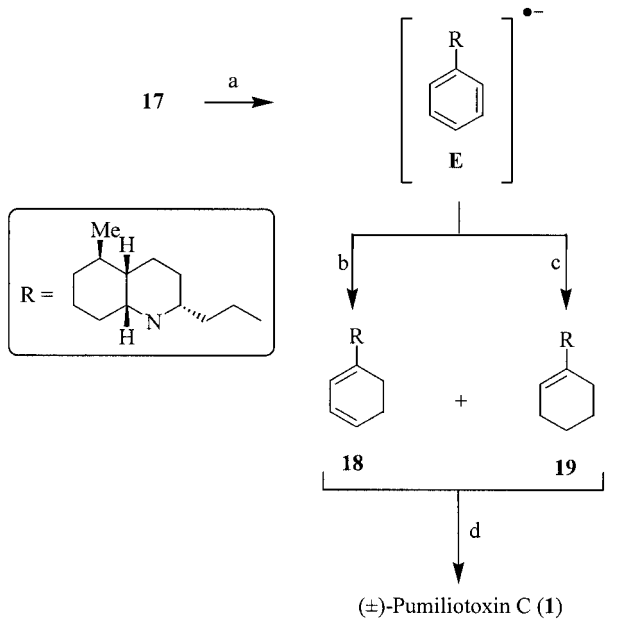


Figure 4. ORTEP drawing of decahydroquinoline **17**.



Scheme 11. Birch reduction of decahydroquinoline **17**. (a) + e^-; (b) + 2 H^+, + e^-; (c) + 4 H^+, + 3 e^-; (d) H_2SO_4/H_2O/EtOH (0.5:5.0:4.5), 60 °C, 10 min.

Workup afforded a crude mixture, which was purified by careful filtration through silica gel with diethyl ether and diethyl ether saturated with gaseous ammonia as successive eluents. The less-polar unreacted amine **17** eluted first, followed by **1**, which was isolated in a modest 25% yield. Nevertheless, the high-resolution mass spectrum supported the exact formula $C_{13}H_{25}N$, with M^+ at 195.1982. Realizing that protonation of the intermediate radical anion **E** (Steps b and c in Scheme 11) should constitute the driving force of the reduction process, we attempted to increase the efficiency of the Birch reduction. Thus, increasing the amount of ethanol twofold and performing the reduction with 130 equiv. of Li allowed us to prepare **1** in a much improved 78% yield, whose high-field ^{1}H NMR spectrum confirmed the molecular formula, and whose ^{13}C NMR spectrum was consistent with the literature values.[8]

Conclusions

In summary, an efficient, scalable, stereocontrolled synthesis of (±)-pumiliotoxin C, adaptable to the synthesis of an interesting set of decahydroquinolines, has been developed. Apart from the generally high yields in the individual steps, the most prominent features of the synthesis are (a) the viability of the aryl group as an efficient activator and protecting group of the nitrogen atom, (b) the unprecedented utilization of a regioselective Shapiro reaction to remove the carbonyl group embedded in a decahydroquinoline ring, and (c) the efficiency of α-aminonitrile chemistry for the α functionalization of 4-piperidone systems.

Experimental Section

General Techniques: Purification by column chromatography was performed with 70–230 mesh silica gel (Merck). TLC analyses were

carried out on alumina sheets precoated with silica gel 60 F_{254} and visualized with UV light; R_f values are given for guidance. IR spectra were recorded with a Perkin–Elmer FT-IR 16PC (KBr powder or dichloromethane). NMR spectra were recorded with a Bruker Avance DRX 500 FT spectrometer [500 MHz (^{1}H) and 100 MHz (^{13}C)], a Bruker AH 300 FT spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)], or a Bruker DPI 200 FT [200 MHz (^{1}H) and 50 MHz (^{13}C)]. Chemical shifts are expressed in ppm downfield from TMS; coupling constants (J) are given in Hertz. High resolution mass spectra were obtained with a Mat 311 double focusing instrument at the CRMPO with a source temperature of 170 °C. An ion accelerating potential of 3 kV and ionizing electrons of 70 eV were used. For air-sensitive reactions, all glassware was oven dried (120 °C) over a 24 h period and cooled under a stream of argon. All commercially available reagents were used as supplied. THF was distilled from sodium benzophenone ketyl and stored under an argon atmosphere. Methylene chloride and *tert*-butanol were distilled from calcium hydride. Diisopropylamine was distilled from potassium hydroxide. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C) homogeneous material. Air-sensitive reagents were transferred by syringe or with a double-ended needle.

8-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane (3): A THF (10 mL) solution containing *t*BuOH (2.59 g, 35 mmol) was added dropwise (by syringe) to a THF (30 mL) suspension of $NaNH_2$ (4.10 g, 105 mmol). The resulting mixture was stirred at room temperature for 1 h under an atmosphere of argon. 4-Piperidone ethylene ketal (**2**; 5.0 g, 35.0 mmol) and bromobenzene (6.03 g, 38.4 mmol) were added sequentially over a 15 min period. The solution was stirred at 50 °C overnight and the crude reaction mixture was quenched by the addition of an excess of water. The solution was extracted with diethyl ether (50 mL × 3). The combined organic layers were extracted with a 10% HCl solution (50 mL), which was made basic by the addition of NaOH pellets. The aqueous layer was extracted with diethyl ether (50 mL × 3) and the ethereal phases were dried with $MgSO_4$ and concentrated in vacuo to afford an oil, which was purified by column chromatography on silica gel (diethyl ether/petroleum ether, 35:65) to afford **3** (5.69 g, 74%) as a pale-yellow oil. R_f (diethyl ether/petroleum ether, 50:50) = 0.65. IR (KBr): $\tilde{\nu}$ = 1228, 1497, 1599, 2830, 2884, 2958 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.82 (t, J = 5.8 Hz, 4 H), 3.31 (t, J = 6.0 Hz, 4 H), 3.97 (s, 4 H), 6.82 (t, J = 7.2 Hz, 1 H), 6.93 (d, J = 7.9 Hz, 2 H), 7.24 (t, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 35.35, 48.19, 64.98, 107.63, 117.06, 119.17, 129.56, 151.43 ppm. HRMS ($C_{13}H_{17}NO_2$ [M$^+$]): calcd. for 219.1259; found 219.1264.

8-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carbonitrile (4): Compound **3** (6.9 g, 31.5 mmol) was dissolved in 2.0 L of methanol containing lithium acetate (20 g L^{-1}) and sodium cyanide (9.3 g, 190.0 mmol). The solution was filtered through a Millipore system (5 μm) and electrolyzed in a flow cell fitted with a graphite-felt anode (diameter 50 mm, thickness 12 mm). The flow rate of the solution (f) was regulated by a peristaltic pump at 5 mL min^{-1} and the current (i_{ox} = 253 mA) calculated[36] according to a bielectronic process. The outlet solution was concentrated under reduced pressure and the crude material was taken-up in water. The aqueous phase was extracted with dichloromethane (50 mL × 3) and the organic layers were dried with $MgSO_4$ and concentrated. The crude material was purified by column chromatography (dichloromethane/petroleum ether, 85:15) to yield aminonitrile **4** (5.35 g, 70%) as a white powder, m.p. 118 °C (diethyl ether). R_f (diethyl ether/petroleum ether, 50:50) = 0.24. IR (KBr): $\tilde{\nu}$ = 1369, 1494, 1600, 2226, 2836, 2894, 2973 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.85–2.27 (m, 4 H), 3.28–3.53 (m, 2 H), 3.96–4.13 (m, 4 H), 4.66–4.69 (m, 1 H), 6.98–7.36 (m, 3 H), 7.25–7.35 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 35.35, 37.31, 45.48, 50.75, 64.99, 65.27, 105.49, 117.77, 119.18, 123.02, 129.88, 149.25 ppm. HRMS ($C_{14}H_{16}N_2O_2$ [M$^+$]): calcd. for 244.1212; found 244.1210. $C_{14}H_{16}N_2O_2$: calcd. C 68.83, H 6.60, N 11.48; found C 68.81, H 6.52, N 11.23.

8-Phenyl-7-propyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carbonitrile (5a): *n*BuLi (1.6 M in hexane; 1.4 mL, 2.24 mmol) was added (by syringe) to a THF (5.0 mL) solution of diisopropylamine (0.38 mL, 0.27 g, 2.66 mmol) at –80 °C. The solution was stirred at that temperature for 15 min and was then allowed to warm to 0 °C over a 30 min period. The resulting LDA solution was transferred (with a double-ended needle) to a THF (10 mL) solution of **4** (0.5 g, 2.05 mmol) cooled to –55 °C. The solution was warmed to –20 °C for 2 h, and 1-bromopropane (0.22 mL, 0.30 g, 2.44 mmol) was added dropwise. The mixture was maintained at –20 °C for 12 h, and the reaction mixture was diluted with water (100 mL). The aqueous phase was extracted with diethyl ether (100 mL × 3), the combined organic layers were dried with $MgSO_4$, and the solvents evaporated in vacuo. The oily residue was purified by column chromatography (diethyl ether/petroleum ether, 45:55) to afford **5a** (0.44 g, 75%) as pale-yellow oil. R_f (diethyl ether/petroleum ether, 50:50) = 0.50. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.78 (t, J = 6.8 Hz, 3 H), 1.28–1.50 (m, 4 H), 1.79–1.84 (m, 2 H), 1.93 (td, J = 13.0, 5.0 Hz, 1 H), 2.13 (dd, J = 13.5, 2.5 Hz, 1 H), 3.59 (dm, J = 9.0 Hz, 1 H), 3.57 (td, J = 12.5, 2.8 Hz, 1 H), 3.92–4.11 (m, 4 H), 7.19–7.37 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.00, 17.05, 35.68, 42.12, 43.25, 50.08, 59.82, 64.32, 64.82, 105.86, 120.44, 126.68, 127.36, 129.00, 148.07 ppm.

7-(3-Chloropropyl)-8-phenyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carbonitrile (5b): LDA (1.5 M in cyclohexane; 16.5 mL, 24.75 mmol) was added (by syringe) to a THF (35.0 mL) solution of **4** (5.50 g, 22.54 mmol) cooled to –40 °C. The solution was stirred at that temperature for 1 h and 1-bromo-3-chloropropane (2.45 mL, 3.90 g, 24.80 mmol) was added dropwise. The mixture was maintained at –20 °C over a 12 h period, and was then diluted with water (100 mL). The aqueous phase was extracted with diethyl ether (100 mL × 3) and the combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The oily residue was purified by column chromatography (diethyl ether/petroleum ether, 50:55) to afford **5b** (6.77 g, 94%) as a pale-yellow oil. R_f (diethyl ether/petroleum ether, 40:60) = 0.27. IR (KBr): $\tilde{\nu}$ = 1105, 1142, 1227, 1365, 1495, 1598, 2831, 2883, 2957 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.57–1.98 (m, 7 H), 2.07 (dd, J = 13.5, 2.3 Hz, 1 H), 3.00 (dm, J = 13.5 Hz, 1 H), 3.25–3.41 (m, 2 H), 3.52 (td, J = 12.3, 3.2 Hz, 1 H), 3.90–4.11 (m, 4 H), 7.17–7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.37, 36.09, 37.86, 43.74, 44.73, 50.71, 59.75, 64.84, 65.31, 106.16, 119.99, 127.34, 127.70, 129.64, 148.26 ppm. HRMS ($C_{17}H_{21}ClN_2O_2$ [M$^+$]): calcd. for 320.1292; found 320.1269. $C_{17}H_{21}ClN_2O_2$: calcd. C 63.65, H 6.60, N 8.73; found C 63.30, H 6.66, N 8.35.

7-(3-Cyanopropyl)-8-phenyl-1,4-dioxa-8-azaspiro[4.5]decane-7-carbonitrile (6): Compound **5b** (1.94 g, 6.06 mmol) and NaCN (0.89 g, 18.16 mmol) were dissolved in DMSO (25 mL) in the presence of tetrabutylammonium iodide (10 mol-%). The reaction mixture was stirred at room temperature for 48 h, and was then quenched by the addition of water (100 mL). The product was extracted with diethyl ether (50 mL × 3), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by column chromatography (diethyl ether/petroleum ether, 15:85) to afford **6** (1.59 g, 84%) as a highly viscous oil. R_f (petroleum ether/diethyl ether, 30:70) = 0.26. IR (KBr): $\tilde{\nu}$ = 704, 774, 1143, 1492, 1630, 2245, 2960 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.56–1.93

(m, 7 H), 2.08 (dd, *J* = 13.5, 2.5 Hz, 1 H), 2.10–2.30 (m, 2 H), 3.00 (dm, *J* = 12.0 Hz, 1 H), 3.54 (td, *J* = 12.0, 2.8 Hz, 1 H), 3.92–3.97 (m, 2 H), 4.01–4.10 (m, 2 H), 7.20–7.37 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.00, 20.05, 35.59, 38.76, 43.28, 50.23, 59.22, 64.39, 64.86, 105.58, 118.77, 119.85, 127.06, 127.19, 129.30, 147.68 ppm. HRMS ($C_{18}H_{21}N_3O_2$ [M$^+$]): calcd. for 311.1634; found 311.1643. $C_{18}H_{21}N_3O_2$: calcd. C 69.43, H 6.80, N 13.49; found C 69.80, H 6.86, N 12.97.

4-(8-Phenyl-1,4-dioxa-8-azaspiro[4.5]dec-7-yl)butanenitrile (7): $NaBH_4$ (0.70 g, 18.50 mmol) was slowly added to an ethanol solution (20 mL) of **6** (1.43 g, 4.60 mmol). After the addition had been completed (approximately 15 min), the resulting mixture was stirred overnight and the solvent was then evaporated to dryness. The crude material was taken-up with a 15% ammonia solution (50 mL) and extracted with diethyl ether (50 mL × 3). The aqueous layer was removed and the combined organic phases were dried with anhydrous $MgSO_4$. The crude mixture was purified by column chromatography (petroleum ether/diethyl ether, 40:60) to afford **7** (1.20 g, 91%) as a colorless oil. R_f (petroleum ether/diethyl ether, 30:70) = 0.42. IR (KBr): $\tilde{\nu}$ = 755, 1141, 1499, 1597, 2244, 2957 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.51–1.71 (m, 2 H), 1.72–1.85 (m, 5 H), 1.96 (dd, *J* = 13.5, 5.4 Hz, 1 H), 2.24 (t, *J* = 7.2 Hz, 2 H), 3.15–3.28 (m, 1 H), 3.42 (dt, *J* = 13.0, 3.4 Hz, 1 H), 3.83 (q, *J* = 4.7 Hz, 1 H), 3.91–4.03 (m, 4 H), 6.86 (t, *J* = 7.3 Hz, 1 H), 6.95 (d, *J* = 7.9 Hz, 2 H), 7.25 (t, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.17, 22.84, 29.49, 33.95, 36.94, 43.32, 55.61, 63.91, 64.67, 107.42, 117.79, 119.74, 119.78, 129.30, 150.37 ppm. HRMS ($C_{17}H_{22}N_2O_2$ [M$^+$]): calcd. for 286.1681; found 286.1687. $C_{17}H_{22}N_2O_2$: calcd. C 71.30, H 7.74, N 9.78; found C 71.36, H 7.81, N 9.57.

4-(8-Phenyl-1,4-dioxa-8-azaspiro[4.5]dec-7-yl)-butanal (8): Dibal-H (1 M in toluene; 3.5 mL, 3.5 mmol) was added by syringe to a stirred solution of **7** (1.0 g, 3.5 mmol) in dichloromethane (15 mL), under an atmosphere of argon, at –60 °C. The temperature was then raised to –20 °C. After standing overnight at that temperature, the reaction was quenched by the addition of 20 mL of a 5% HCl solution. The aqueous phase was made basic by the addition of an excess of solid $NaHCO_3$, and extracted with dichloromethane (30 mL × 3). The organics were dried with $MgSO_4$ and concentrated in vacuo to give a slightly yellow oil, which upon purification by column chromatography (petroleum ether/diethyl ether, 20:80) yielded 0.78 g (77%) of **8**. R_f (petroleum ether/diethyl ether, 20:80) = 0.53. IR (KBr): $\tilde{\nu}$ = 703, 737, 1040, 1265, 1499, 1597, 1722, 2958, 3054 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.50–1.70 (m, 4 H), 1.75–1.85 (m, 3 H), 1.97 (dd, *J* = 14.3, 5.4 Hz, 1 H), 2.37 (t, *J* = 4.80 Hz, 2 H), 3.15–3.22 (m, 1 H), 3.38 (dt, *J* = 13.0, 3.4 Hz, 1 H), 3.79 (q, *J* = 4.70 Hz, 1 H), 3.93–4.04 (m, 4 H), 6.86 (t, *J* = 7.3 Hz, 1 H), 6.96 (d, *J* = 7.9 Hz, 2 H), 7.26 (t, *J* = 7.4 Hz, 2 H), 9.69 (t, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.24, 29.28, 34.16, 36.81, 43.76, 43.81, 56.06, 63.87, 64.62, 107.55, 118.02, 119.75, 129.20, 150.53, 202.52 ppm. HRMS ($C_{17}H_{23}NO_3$ [M$^+$]): calcd. for 289.1678; found 289.1683. $C_{17}H_{23}NO_3$: calcd. C 70.56, H 8.01, N 4.84; found C 70.94, H 8.14, N 4.53.

1-Phenyl-2,3,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (9): THF (5 mL) containing **8** (0.76 g, 2.63 mmol) and 50 mL of 1.5 M H_2SO_4 were added, under an argon atmosphere, to a flask equipped with a reflux condenser. The solution was refluxed under an argon atmosphere for 5 h. The reaction mixture was made basic by the addition of 50 mL of a saturated solution of Na_2CO_3. The aqueous phase was transferred to a separating funnel and extracted with diethyl ether (30 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (petroleum ether/diethyl ether, 40:60) to yield **9** (0.45 g, 75%) as a slightly yellow oil. R_f (petroleum ether/diethyl ether, 40:60) = 0.37. IR (KBr): $\tilde{\nu}$ = 700, 750, 1600, 1690, 2960, 2930, 3055 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.47 (qd, *J* = 10.60, 4.60 Hz, 1 H), 1.55–1.70 (m, 1 H), 1.86 (dt, *J* = 10.70, 4.0 Hz, 1 H), 1.90–2.01 (m, 1 H), 2.28–2.35 (m, 2 H), 2.62 (t, *J* = 6.10 Hz, 2 H), 3.39 (dt, *J* = 13.0, 6.0 Hz, 1 H), 3.63 (dt, *J* = 13.0, 5.5 Hz, 1 H), 4.04–4.10 (m, 1 H), 6.83–6.85 (m, 1 H), 6.95–7.03 (m, 3 H), 7.28–7.34 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.40, 25.86, 27.82, 39.70, 45.98, 58.05, 118.91, 121.15, 129.28, 137.79, 138.18, 149.45, 199.09 ppm. HRMS ($C_{15}H_{17}NO$ [M$^+$]): calcd. for 227.1310; found 227.1312. $C_{15}H_{17}NO$: calcd. C 79.26, H 7.54, N 6.16; found C 79.58, H 7.55, N 5.91.

(4a*S,5*R**,8a*R**)-5-Methyl-1-phenyloctahydroquinolin-4(1*H*)-one (10):** MeLi (1.5 M in diethyl ether; 17.8 mL, 26.70 mmol) was added to a cooled (–30 °C), stirred suspension of CuI (2.55 g, 13.40 mmol) in diethyl ether (30 mL). This mixture was stirred for 1 h, and then a solution of enone **9** (1.38 g, 6.08 mmol) in diethyl ether (20 mL) was added with a cannula and the reaction mixture was allowed to warm up to –15 °C. After 30 min, TLC monitoring showed the complete disappearance of starting material. The reaction mixture was quenched by the addition of a 10% NH_3 solution (50 mL) and was then extracted with dichloromethane (30 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude yellow oil was purified by column chromatography to afford **10** (1.35 g, 91%) as a slightly amber oil. R_f (petroleum ether/diethyl ether, 70:30) = 0.43. IR (KBr): $\tilde{\nu}$ = 740, 1265, 1600, 1715, 2850, 2930, 3055 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (d, *J* = 7.4 Hz, 3 H), 1.28–1.31 (m, 1 H), 1.37 (qd, *J* = 11.6, 3.5 Hz, 1 H), 1.51 (tt, *J* = 12.6, 3.5 Hz, 1 H), 1.58–1.70 (m, 3 H), 2.54 (dt, *J* = 9.7, 4.7 Hz, 1 H), 2.59–2.65 (m, 2 H), 2.67–2.75 (m, 1 H), 3.50 (ddd, *J* = 12.9, 9.0, 4.6 Hz, 1 H), 3.66 (dt, *J* = 12.9, 5.7 Hz, 1 H), 4.11–4.15 (m, 1 H), 6.91 (t, *J* = 7.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 7.32 (t, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 18.08, 20.17, 26.78, 27.66, 28.18, 40.13, 44.27, 55.67, 56.79, 116.66, 119.73, 129.34, 149.60, 209.94 ppm. HRMS ($C_{16}H_{21}NO$ [M$^+$]): calcd. for 243.1623; found 243.1630. $C_{16}H_{21}NO$: calcd. C 78.97, H 8.70, N 5.76; found C 78.81, H 8.62, N 5.51.

4-Methyl-*N*′-[(4*E*,4a*S,5*R**,8a*R**)-5-methyl-1-phenyloctahydroquinolin-4(1*H*)-ylidene]benzenesulfonohydrazide (12):** Octahydroquinolinone **10** (1.32 g, 5.43 mmol) was dissolved in 20 mL of EtOH and refluxed overnight in the presence of *p*-toluenesulfonohydrazide (1.11 g, 5.96 mmol). The solvent was evaporated in vacuo, and the resulting crude reaction mixture was taken up in a MeOH/H_2O (80:20) mixture. The crystalline product was filtered off to afford **12** as a white solid (1.86 g, 83%), m.p. 182–184 °C. R_f (petroleum ether/diethyl ether, 60:40) = 0.18. IR (KBr): $\tilde{\nu}$ = 700, 770, 1600, 1650, 2795, 2950, 3220 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.82 (d, *J* = 6.7 Hz, 3 H), 0.98–1.10 (m, 1 H), 1.20–1.60 (m, 5 H), 2.35–2.63 (m, 7 H), 3.10–3.34 (m, 2 H), 3.60–3.70 (m, 1 H), 6.85–6.98 (m, 3 H), 7.25–7.40 (m, 4 H), 7.90 (d, *J* = 8.0 Hz, 2 H), 8.00 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.74, 20.26, 21.62, 26.06, 27.94, 28.37, 28.96, 45.51, 49.26, 56.39, 117.78, 120.29, 128.20, 129.21, 129.52, 135.36, 144.03, 150.04, 159.65 ppm. HRMS ($C_{23}H_{29}N_3O_2S$ [M$^+$]): calcd. for 411.1981; found 411.1983.

(4a*R,5*R**,8a*R**)-5-Methyl-1-phenyl-1,2,4a,5,6,7,8,8a-octahydroquinoline (13):** Compound **12** (1.82 g, 4.43 mmol) in 30 mL of THF was added with a syringe to an oven-dried Schlenk tube cooled to –60 °C and filled with argon. Then, *n*BuLi (1.6 M *in* hexane; 6.09 mL, 9.74 mmol) was added. After stirring for 90 min at –60 °C, the solution was allowed to warm to room temperature and was stirred for 2 h. Then, it was quenched with an excess of water

(25 mL) and extracted once more with diethyl ether (50 mL × 3). The combined ethereal layers were dried with $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography (petroleum ether/diethyl ether, 70:30) to afford **13** (0.82 g) in 82% yield. R_f (petroleum ether/diethyl ether, 70:30) = 0.72. IR (KBr): $\tilde{\nu}$ = 705, 740, 1265, 1600, 2850, 2930, 3055 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.25 (d, J = 7.3 Hz, 3 H), 1.35–1.40 (m, 1 H), 1.55–1.60 (m, 5 H), 2.05–2.17 (m, 1 H), 2.55–2.62 (m, 1 H), 3.57 (dm, J = 17.4 Hz, 1 H), 3.90 (dq, J = 17.4, 3.2 Hz, 1 H), 4.12–4.23 (m, 1 H), 5.70 (dm, J = 10.1, 3.0 Hz, 1 H), 5.88 (dq, J = 10.1, 3.0 Hz, 1 H), 6.83 (t, J = 7.2 Hz, 1 H), 6.95 (d, J = 8.3 Hz, 2 H), 7.33 (t, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.63, 19.62, 22.07, 27.02, 34.50, 41.45, 44.24, 50.01, 114.00, 117.46, 124.15, 129.24, 130.27, 149.42 ppm. HRMS ($C_{16}H_{21}N$ [M^+]): calcd. for 227.1674; found 227.1669.

(4a*S,5*R**,8a*R**)-5-Methyl-1-phenyldecahydroquinoline (14):** Compound **13** (0.79 g, 3.48 mmol) was dissolved in 30 mL of methanol and was placed in a low-pressure hydrogenation apparatus in the presence of 0.080 g of Pd/C (10%). Stirring for 10 h under one atmosphere of H_2, and subsequent work-up, afforded a crude oil, which was purified by column chromatography (petroleum ether/diethyl ether, 98:2), to yield **14** (0.68 g, 85%) as a colorless oil. R_f (petroleum ether/diethyl ether, 98:2) = 0.29. IR (KBr): $\tilde{\nu}$ = 695, 740, 1265, 1600, 2850, 2985, 3055 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.16 (d, J = 7.25 Hz, 3 H), 1.21–1.31 (m, 1 H), 1.32–1.42 (m, 1 H), 1.43–1.56 (m, 3 H), 1.58–1.75 (m, 3 H), 1.77–1.92 (m, 4 H), 2.96 (td, J = 12.0, 3.0 Hz, 1 H), 3.34 (dt, J = 12.0, 3.4 Hz, 1 H), 4.00 (dt, J = 11.3, 3.4 Hz, 1 H), 6.78 (t, J = 7.2 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.26 (t, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.79, 20.93, 21.75, 26.28, 26.36, 27.88, 34.60, 42.47, 43.87, 54.77, 117.02, 118.88, 129.59, 151.61 ppm. HRMS ($C_{16}H_{23}N$ [M^+]): calcd. for 229.1831; found 229.1828.

5-Methyl-1-phenyldecahydroquinoline-2-carbonitrile (15): Decahydroquinoline **14** (0.64 g, 2.79 mmol) was dissolved in 250 mL of methanol containing 5 g of lithium acetate and 0.82 g (16.73 mmol) of NaCN. The solution was transferred into a divided cell and oxidized at a planar vitreous carbon electrode at +0.80 V vs. SCE. After the consumption of 660 Coulomb, the electrolysis was stopped and the solution was concentrated under reduced pressure. The crude material was taken-up with water (50 mL) and extracted with diethyl ether (50 mL × 3). The organics were dried with $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography (petroleum ether/diethyl ether, 95:5) to afford **15** (0.55 g, 78%) as a *cis*/*trans* mixture (40:60). R_f (petroleum ether/diethyl ether) = 0.40. IR (KBr): $\tilde{\nu}$ = 699, 769, 1491, 1596, 2222, 2228, 2865, 2935 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (d, J = 6.7 Hz, 3 H), 1.11 (d, J = 7.2 Hz, 3 H), 1.24–2.24 (m, 24 H), 3.55 (q, J = 3.0 Hz, 1 H), 3.95–4.08 (m, 1 H), 4.15–4.18 (m, 1 H), 4.40 (br. s, 1 H), 6.94–7.40 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.36, 19.70, 20.37, 20.44, 23.03, 23.53, 24.77, 27.80, 29.34, 29.48, 35.40, 42.04, 42.65, 54.22, 57.73, 118.20, 121.06, 125.85, 126.74, 129.13, 129.50, 147.73, 148.51 ppm. HRMS ($C_{17}H_{22}N_2$ [M^+]): calcd. for 254.1783; found 254.1790. $C_{17}H_{22}N_2$: calcd. C 80.27, H 8.72, N 11.01; found C 80.02, H 8.79, N 10.39.

(2*S,4a*S**,5*R**,8a*R**)-5-Methyl-1-phenyl-2-propyldecahydroquinoline-2-carbonitrile (16):** Aminonitrile **15** (0.55 g, 2.16 mmol, *cis*/*trans*, 40:60) was dissolved in 10 mL of THF in a Schlenk tube equipped with a rubber stopper and flushed with argon. The resulting solution was cooled to –60 °C and a solution of LDA [prepared from 1.6 M *n*BuLi in hexane (2.05 mL, 3.28 mmol) and diisopropylamine (0.52 mL, 0.37 g, 3.71 mmol)] in THF was added with a syringe. The anion solution was stirred at –60 °C for 1 h, 1-bromopropane (0.36 mL, 0.49 g, 3.95 mmol) was added, and the solution was placed at –20 °C overnight. Then, 15 mL of water was added, and the resulting solution was extracted with diethyl ether (50 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated to yield a crude orange oil, which was purified by column chromatography (petroleum ether/diethyl ether; 95:5) to afford **16** (0.46 g, 72%) as a viscous oil that solidified upon cooling. A further slow crystallization from a petroleum ether/diethyl ether (50:1) mixture afforded colorless crystals, which were analyzed by X-ray diffraction; m.p. 100–102 °C. R_f (petroleum ether/diethyl ether, 95:5) = 0.5 ppm. IR (KBr): $\tilde{\nu}$ = 700, 750, 1594, 2216, 2871, 2923 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.77 (t, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 1.22–1.55 (m, 10 H), 1.71 (dm, J = 14.0 Hz, 1 H), 1.77–2.00 (m, 3 H), 2.02–2.20 (m, 2 H), 3.55 (q, J = 2.6 Hz, 1 H), 7.00–7.70 (br. m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.10, 17.21, 19.67, 20.55, 24.10, 27.61, 30.54, 30.35, 35.72, 41.80, 42.96, 57.45, 63.44, 116.53, 120.98, 126.81, 128.81 (br), 145.55 ppm. HRMS ($C_{20}H_{28}N_2$ [M^+]): calcd. for 296.2252; found 296.2257.

(2*S,4a*S**,5*R**,8a*R**)-5-Methyl-1-phenyl-2-propyldecahydroquinoline (17):** $NaBH_4$ (0.23 g, 6.08 mmol) was added to an ethanol solution (10 mL) of aminonitrile **16** (0.46 g, 1.55 mmol). The solution was stirred at room temperature overnight and the solvent was then evaporated. The crude material was taken-up with water (50 mL) and extracted with diethyl ether (50 mL × 3). The organics were dried ($MgSO_4$) and concentrated to give an oily residue, which was purified by a rapid filtration through a chromatography column (petroleum ether) to yield **17** (0.34 g, 81%) as a colorless oil. Upon cooling, the oily product crystallized as colorless plates (m.p. < 40 °C) which were analyzed by X-ray diffraction. R_f (petroleum ether) = 0.42. IR (KBr): $\tilde{\nu}$ = 700, 745, 1595, 2795, 2860, 2930, 2955 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz, 343 K): δ = 0.82 (t, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.10–1.52 (m, 10 H), 1.55–1.70 (m, 2 H), 1.75–1.90 (m, 2 H), 2.00–2.10 (m, 1 H), 2.20–2.29 (m, 1 H), 2.98–3.03 (m, 1 H), 3.27–3.32 (m, 1 H), 7.02–7.07 (m, 1 H), 7.17–7.22 (m, 2 H), 7.25–7.31 (m, 2 H) ppm. ^{13}C NMR (C_6D_6, 125 MHz, 343 K): δ = 14.9, 19.08, 19.47, 20.83, 25.97, 27.08, 29.57, 30.02, 34.25, 37.01, 43.98, 59.44, 60.89, 123.17, 124.36, 128.77, 150.80 ppm. HRMS ($C_{19}H_{29}N$ [M^+]): calcd. for 271.2300; found 271.2290. $C_{19}H_{29}N$: calcd. C 84.07, H 10.77, N 5.16; found C 83.86, H 10.80, N 5.23.

(2*S,4a*S**,5*R**,8a*R**)-5-Methyl-2-propyldecahydroquinoline [(±)-Pumiliotoxin C] (1):** Absolute EtOH (8 mL), **17** (0.18 g, 0.66 mmol), and 20 mL of liquid ammonia were added, in that order, to a Schlenk tube containing 10 mL of THF at –40 °C. Lithium wire (0.91 g, 130 mmol) was then added in small pieces over a 1 h period, upon which the solution became blue. Stirring was continued for 1 h, and the solution was quenched with an excess of water (100 mL). The ammonia was allowed to evaporate, and the resulting crude mixture was extracted with diethyl ether (100 mL × 2). The organics were dried with $MgSO_4$ and concentrated to afford a mixture of crude enamines, which was dissolved in an H_2SO_4/H_2O/EtOH (0.5:5.0:4.5) mixture. The solution was heated at 60 °C for 10 min and the solvents were then evaporated. The hydrochloride **1** was dissolved in water (10 mL), and the solution was made basic (pH 12) by addition of NaOH pellets. The free amine **1** was extracted with diethyl ether (30 mL × 2) and the aqueous layer was discarded. The combined organic layers were dried ($MgSO_4$) and concentrated to afford crude **1**, which was purified by column chromatography with diethyl ether saturated with gaseous ammonia to give **1** (0.10 g, 78%) as a colorless oil whose NMR spectroscopic data were in agreement with those reported in the literature.[8] R_f (diethyl ether saturated with gaseous ammonia) = 0.60

Table 2. X-ray crystallographic data for **16** and **17**.

	16	**17**
Formula	$C_{20}H_{28}N_2$	$C_{19}H_{29}N$
Mol. mass	296.44	271.43
Cryst. syst.	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
D_x [Mg m^{-3}]	1.146	1.111
a [Å]	6.4442(1)	5.535(4)
b [Å]	10.6710(2)	8.364(4)
c [Å]	12.9573(2)	17.843(9)
α [°]	97.131(1)	84.47(4)
β [°]	91.583(1)	83.62(5)
γ [°]	102.251(1)	82.62(5)
V [Å^3]	862.28(2)	811.3(8)
Z	2	2
F(000)	324	300
μ [cm^{-1}]	0.65	0.63
λ(Mo-K_α) [Å]	0.71073	0.71073
T [K]	120	293
Crystal size [mm]	0.48 × 0.34 × 0.30	0.42 × 0.33 × 0.33
Radiation	Mo-K_α	Mo-K_α
Max. 2θ [°]	54	54
Scan	$\omega/2\Theta$ = 1	$\omega/2\Theta$ = 1
hkl range	0→80, –13→13, –16→16	0→7, –10→10, –22→22
$t_{max.}$ [s]	15	60
Reflections measured	7447	3906
Reflections observed [$I > 2.0\sigma(I)$]	3341	2906
Final R	0.042	0.042
Rw	0.140	0.113

IR (KBr): $\tilde{\nu}$ = 755, 1078, 1311, 1449, 2605, 2719, 2796, 2862, 2926 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.84 (d, J = 6.6 Hz, 3 H), 0.91 (t, J = 6.9 Hz, 3 H), 0.94 (qd, J = 10.0, 3.3 Hz, 1 H), 1.05–1.15 (m, 2 H), 1.30–1.42 (m, 8 H), 1.45–1.64 (m, 4 H), 1.82–1.90 (m, 1 H), 1.87–1.98 (dm, J = 11.0 Hz, 1 H), 2.52–2.58 (m, 1 H), 2.82–2.84 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.33, 19.16, 19.92, 21.27, 27.07, 27.38, 29.71, 33.44, 35.95, 39.76, 42.60, 55.97, 57.73 ppm. HRMS ($C_{13}H_{25}N$ [M$^+$]): calcd. for 195.1987; found 195.1982.

X-ray Crystallographic Study: Crystallographic data were collected on a Nonius Kappa CCDC (for **16**) or on an automatic diffractometer CAD4 Nonius (for **17**) with graphite-monochromated Mo-K_α radiation. Details are given in Table 2. The structures were solved with SIR-97,[37] which revealed the non-hydrogen atoms of the molecules. Refinement was performed by full-matrix least-squares techniques with SHELXL-97.[38] Atom scattering factors were taken from the International Tables for X-ray Crystallography.[39] Figures were drawn with PLATON98[40] or ORTEP-3 for Windows.[41] CCDC-221915 (**16**) and –226074 (**17**) contain 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.

Acknowledgments

N. G. would like to thank the MENRT for a grant.

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Received: November 29, 2004

