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# The asymmetric synthesis of (−)-pumiliotoxin C using tandem catalysis

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**Abstract**—The potent neurotoxin (−)-pumiliotoxin C has been prepared in 8 steps starting from 2-cyclohexenone. Key steps are a tandem asymmetric conjugate addition–allylic substitution reaction and a tandem Heck-allylic substitution reaction.


## 1. Introduction

Among the alkaloids isolated from *Dendrobates* spp. (poison dart frogs), pumiliotoxin C (**1**), first isolated from *Dendrobates pumilio*, is one of the most prominent members.[1] Pumiliotoxin C is a potent neurotoxin that acts as a noncompetitive blocker for acetylcholine receptor-channels and therefore has attracted considerable attention from a pharmaceutical standpoint.[2] Because of its structure, a *cis*-fused perhydroquinoline skeleton featuring four stereogenic centers, an impressive effort has been devoted to the synthesis of **1**.[3] A number of total syntheses has been reported either of the racemate,[4] the natural enantiomer,[5] or its antipode.[6] The strategies applied for the synthesis of (−)-**1** until now relied on starting materials from the chiral pool, the use of chiral auxiliaries, for example, in the concise synthesis by Comins and coworkers,[7] or the application of a (enzymatic) kinetic resolution. No catalytic asymmetric synthesis of pumiliotoxin C is known (Fig. 1).

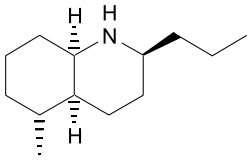
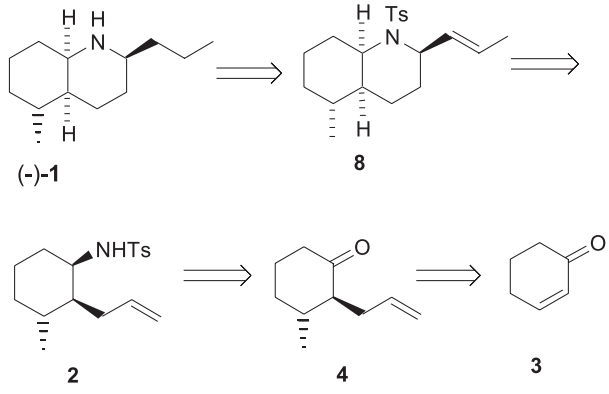


**Figure 1.** (−)-Pumiliotoxin (**1**).

Tandem[8] or domino[9] catalytic reactions comprise a rapidly growing field in organic synthesis. Especially the use of reactive intermediates, formed in the first step, for a subsequent reaction in a multistep conversion allows the preparation of complicated structures in a limited number of steps. The catalytic asymmetric synthesis of (−)-pumiliotoxin C (**1**) presented here is based on two tandem catalytic reactions elaborated upon in our laboratory. In the retrosynthetic scheme (Scheme 1), it is shown that the nitrogen containing six-membered ring in **1** can be constructed by a tandem Heck-allylic substitution reaction starting from **2**. Reduction of the double bond and detosylation leads directly to **1**. In turn, **2** can be prepared starting from 2-cyclohexenone **3** by a tandem asymmetric conjugate addition–allylic substitution reaction, followed by conversion of the carbonyl group into the required *N*-tosylamine.




**Scheme 1.** Retrosynthesis of **1**.

*Keywords*: Alkaloids; Heck-allylic substitution; Pumiliotoxin C.
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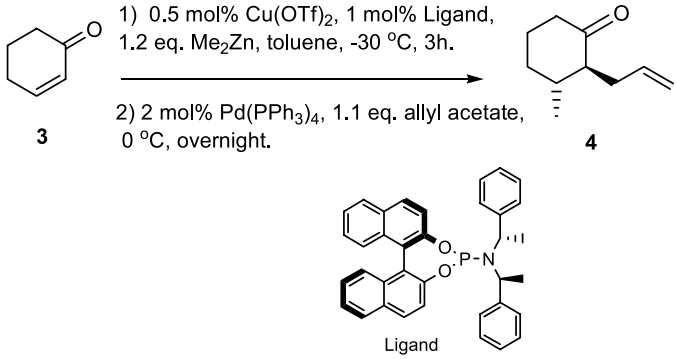



**Scheme 2.** Tandem asymmetric conjugate addition–allylic substitution reaction.

## 2. Results and discussion

The synthesis started with the copper-phosphoramidite catalyzed addition of dimethylzinc to 2-cyclohexenone (**3**, Scheme 2).[10] Using the depicted phosphoramidite ligand, this reaction proceeds with an excellent enantioselectivity of 96%. The resulting zinc enolate reacted with catalytic $Pd(PPh_3)_4$ and allyl acetate to give **4**.[11] This reaction was carried out on 5 g scale using 0.5 mol% of copper catalyst and 2 mol% of palladium catalyst and afforded **4** in 84% yield as a mixture of *trans*/*cis* isomers (ratio 8:1).

In order to convert ketone **4** into its corresponding amine **7** with the correct stereochemistry, several methods were applied. Whereas reduction of the corresponding oxime with $LiAlH_4$ led predominantly to the undesired isomer, reductive amination using Leuckart's method[12] was accompanied by the formation of side products. It was therefore decided to reduce **4** to alcohol **5** and use this in a subsequent Mitsunobu amination reaction (Scheme 3).

Reduction of **4** with $LiAlH_4$ at low temperature afforded **5** in virtually quantitative yield as a 2:1 mixture of diastereomers together with the residual diastereomer at C2. After purification by flash chromatography, **5** was isolated in 46% yield and 90% diastereomeric purity.

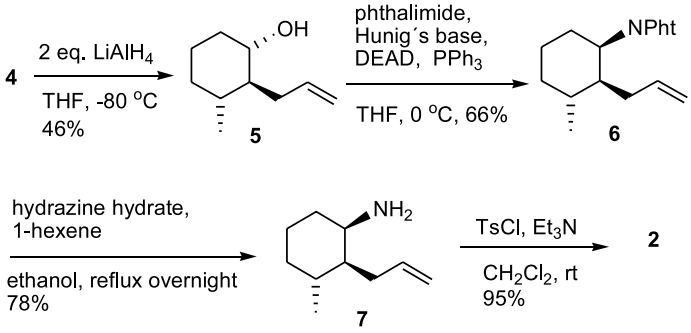
Alcohol **5** was subjected to Mitsunobu-type reactions.[13] As an *N*-tosyl functionality was required, initially both *N*-tosyl formamide[14] and *N*-tosyl *t*-butoxycarbamate[15] were explored as nucleophiles. After reaction, mild cleavage of the formyl or BOC group, respectively, would afford the corresponding tosyl amide. With cyclohexanol as a model substrate and using standard Mitsunobu conditions (DEAD, $Ph_3P$ and Hünig's base) the reaction with *N*-tosyl *t*-butoxycarbamate was successful, whereas *N*-tosyl formamide showed no reaction. Using **5** as the substrate, however, only a very slow reaction was observed and therefore these nucleophiles were abandoned.

Contrary, using phthalimide as the nucleophile, **6** was obtained in a reasonable yield (66%) and after hydrazinolysis and subsequent reaction of the amine **7** with tosyl chloride, **2** was obtained as a crystalline compound. In order to ascertain the correct 1,2-*cis*-2,3-*trans* stereochemistry of **2**, crystals were grown from heptane and an X-ray structure was obtained.[16] As can be seen in Figure 2, **2** possesses the desired relative and absolute stereochemistry. In addition, the crystallization increased the ee of **2** to >99.5% according to chiral HPLC analysis.

With **2** in hand, the tandem Heck-allylic substitution reaction was studied using 1-bromopropene as the alkenyl halide.[17,18] This palladium-catalyzed reaction was performed using the conditions initially developed by Larock and coworkers using tri-*o*-tolylphosphine as the ligand (Scheme 4).

In this mechanistically quite complicated reaction, the alkylpalladium species resulting from the Heck reaction rearranges to the corresponding allylic palladium intermediate by a β-hydride elimination–readdition mechanism (Fig. 3).[19]

Intramolecular attack of the deprotonated *N*-tosylamide affords the six-membered ring, thereby liberating the palladium catalyst. At the outset of the synthesis it was not clear which stereochemistry would result from this




**Scheme 3.**

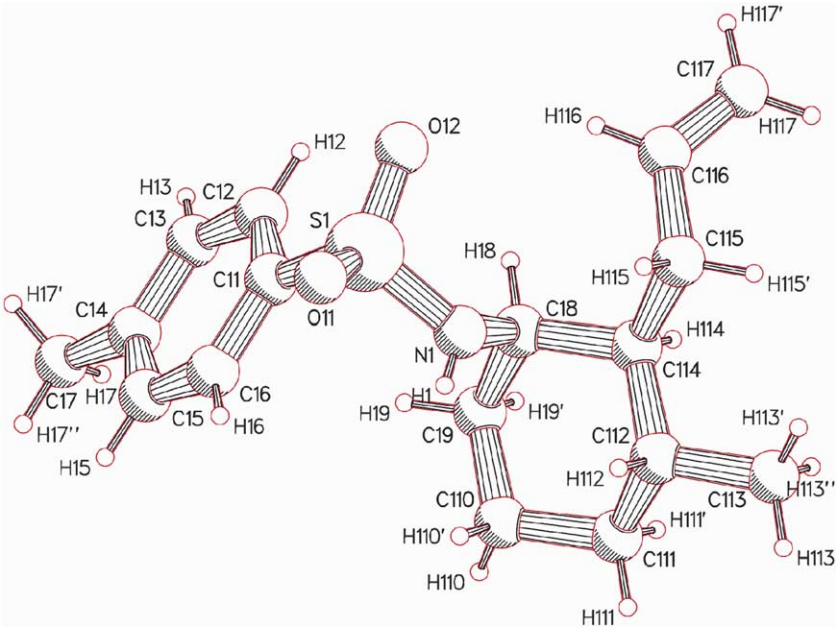
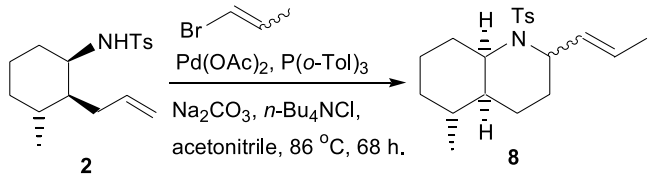



**Figure 2.** Ortep plot of the structure of **2**.




**Scheme 4.**

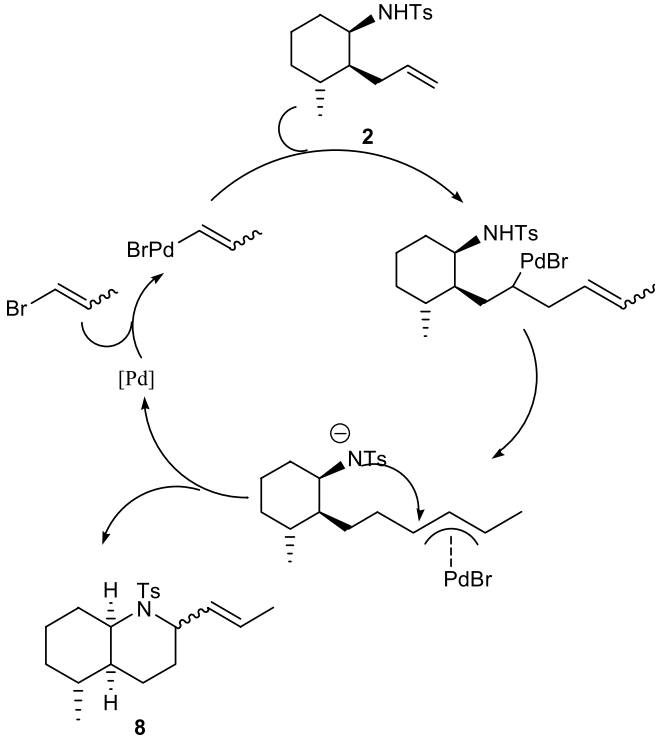
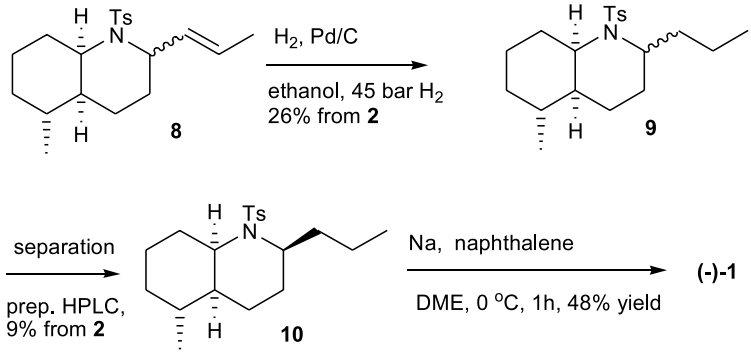



**Figure 3.** The Heck-allylic substitution reaction (ligands are omitted for clarity).




**Scheme 5.**

reaction and molecular models did not give a conclusive answer.

Inspection of the crude product mixture by GC-MS revealed that several stereoisomers of **8** had been formed in the reaction. As *cis*,*trans* isomers of the olefin moiety could not be excluded, it was decided to take the crude product through the next step without purification. Hydrogenation of the double bond with $H_2$ and Pd/C afforded a mixture that consisted mainly of two stereoisomers of **9**, according to GC-MS, and a number of side products that could not be identified (Scheme 5). One of the two stereoisomers of **9** could be purified by flash chromatography. After removal of the tosyl group by treatment with Na/naphthalene this isomer could tentatively be identified as 2-*epi*-pumiliotoxin according to GC-MS.[20]

As the other isomer of **9** could not be obtained pure by flash chromatography, preparative HPLC was applied. This afforded a pure isomer of **9** which, after removal of the tosyl group and purification by acid/base extraction, afforded (−)-**1** in 48% yield. All spectral data are in accordance with those reported in the literature.[21]

To conclude; a short, catalytic asymmetric synthesis of (−)-pumiliotoxin C has been developed that is based on two tandem catalytic reactions. Starting with an asymmetric conjugate addition–allylic substitution reaction, two stereocenters are created in high yield with excellent enantioselectivity and high diastereoselectivity. After functional group modification, a tandem Heck-allylic substitution reaction creates the perhydroquinoline skeleton, albeit in moderate yield, with both the natural and unnatural configuration at the C2 stereocenter. Two additional steps complete the synthesis of (−)-pumiliotoxin C.

## 3. Experimental

### 3.1. General

General experimental information: Unless noted otherwise, all materials were obtained from commercial suppliers and used without further purification. THF was dried and distilled from sodium/benzophenone, $CH_3CN$ and DME were dried and distilled from $CaH_2$ and ether was dried and distilled from $P_2O_5$. The *n*-$Bu_4NCl$ was crystallized by addition of dry ether to a saturated solution in reagent grade acetone and upon removal of the solvents dried at 70 °C under vacuum for 32 h. The needed volume of dry $CH_3CN$ to afford a 1 M solution was then added and the reagent kept and used as such. Dry $Na_2CO_3$ was purchased from commercial suppliers and stored in a Schlenk flask after further drying under vacuum at 120 °C for 24 h. Flash chromatography was performed on silica gel Merck Type 9385 230–400 mesh. All NMR spectra were recorded on a Varian XL 300 MHz in $CDCl_3$ solutions using the residual solvent peak as internal reference. Mass spectra and HRMS data were obtained using an AEI MS-902. Melting points were determined on a Mettler FP1.

**3.1.1. (2*S*, 3*R*)-2-Allyl-3-methylcyclohexanone (4).** $Cu(OTf)_2$ (94 mg, 0.26 mmol, 0.5 mol%) and (*R*,*S*,*S*)-phosphoramidite ligand[10a] (280 mg, 0.52 mmol, 1.0 mol%) were dissolved in dry toluene in a flame-dried Schlenk tube under an atmosphere of nitrogen. After stirring for 1 h at room temperature, the solution was cooled to −30 °C and freshly distilled 2-cyclohexenone (5.03 mL, 52 mmol) was added. After stirring for an additional 10 min at the same temperature, $Me_2Zn$ (31.2 mL of a 2 M solution in toluene, 62.4 mmol, 1.2 equiv) was added dropwise to the solution which turned bright yellow. After stirring for an additional 3 h at −30 °C, $Pd(PPh_3)_4$ (1.20 g, 1.04 mmol, 2.0 mol%) and allyl acetate (6.17 mL, 57.2 mmol, 1.14 equiv) were added. The resulting mixture was warmed to 0 °C and stirred overnight at this temperature. GC analysis of a reaction mixture aliquot on a DB-1 column showed complete conversion to the product with a *trans*/*cis* ratio of 8.5:1 (*trans*: $T_r$=12.28 min, *cis*: $T_r$=13.40 min). The reaction mixture was quenched by pouring it into 200 mL of 2 M aqueous HCl. The layers were separated, the aqueous layer was extracted with diethyl ether (4×100 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual zinc and palladium salts were removed by flash chromatography of the resulting yellow oil over a small column of silica, eluted with toluene. Crude yield: 7.51 g (49.3 mmol, 95%) of a yellowish oil, which was used without further purification. $^1H$ NMR of a sample purified by flash chromatography ($SiO_2$, hexanes:diethyl ether 3:1): $\delta_H$ 0.81 (3H, d, $J$=6.9 Hz, of minor diastereomer), 1.05 (3H, d, $J$=6.2 Hz), 1.43–1.59 (1H, m), 1.64–2.11 (6H, m), 2.21–2.40 (5H, m), 4.95–5.05 (2H, m), 5.74–5.85 (1H, m); $\delta_C$ 20.2 (q), 25.4 (t), 30.8 (t), 33.4 (t), 37.8 (d), 41.5 (t), 56.7 (d), 115.8 (t), 136.5 (d), 212.1 (s); *m*/*z* (EI) 152 ($M^+$, 23), 137 (100), 97 (54). An ee of 96.2% was determined by chiral GC

on a Chiraldex G-TA column, 30 m×0.25 mm, He-flow: 1.0 mL/min, 100 °C, 15 min, 10 °C/min, 150 °C, 30 min; $T_r$=13.14 min (major enantiomer), $T_r$=14.96 min (minor enantiomer), $T_r$=15.54 min (both enantiomers of the minor diastereomer).

**3.1.2. (1*S*,2*S*,3*R*)-2-Allyl-3-methylcyclohexanol (5).** To a stirred suspension of $LiAlH_4$ (3.74 g, 98.6 mmol) in 100 mL of THF at −80 °C in flame-dried glassware under a nitrogen atmosphere, was added in a dropwise fashion 7.5 g (49.3 mmol) crude **4** as a solution in 20 mL of THF. The reaction mixture was stirred at this temperature until the reaction was completed as indicated by TLC (approx. 3 h). The reaction was quenched by adding 2 mL of water, 1 mL of 15% aqueous NaOH after 15 min and 1 mL of water after an additional 30 min. This procedure avoids problems with aluminum salts. The resulting slurry was then divided between water and diethyl ether and the aqueous layer was extracted with diethyl ether (3×100 mL). After drying the combined organic layers over $MgSO_4$, the solvent was removed under reduced pressure yielding 7.26 g (47.1 mmol, 99%) of the crude product. The diastereomeric mixture was separated by flash chromatography ($SiO_2$, heptanes:diethyl ether 2:1) yielding **5** as a colorless oil which solidified upon standing at 5 °C. 3.5 g (22.6 mmol) of crystalline **5** was obtained, melting at ambient temperature. $^1$H NMR showed 90% diastereomeric purity. $^1$H NMR: $\delta_H$ 0.86–1.09 (3H, m), 0.96 (3H, d, $J$=5.3 Hz), 1.22–1.30 (4H, m), 1.58–1.79 (4H, m), 1.94–1.96 (1H, m), 2.22–2.30 (1H, m), 2.51–2.58 (1H, m), 3.38–3.44 (1H, m), 4.94–5.15 (2H, m), 5.82–5.97 (1H, m); $\delta_C$ 19.7 (q), 23.9 (t), 32.3 (t), 33.7 (d), 35.1 (t), 35.7 (t), 50.9 (d), 72.4 (d), 116.3 (t), 136.3 (d); *m/z* (CI) 172 $(M+NH_4)^+$. $[\alpha]_D=-8°$ ($c$=1.01, $CHCl_3$).

**3.1.3. 2-[(1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexyl]-1*H*-isoindole-1,3(2*H*)-dione (6).** To a solution of **5** (3.13 g, 20.3 mmol), triphenylphosphine (10.64 g, 40.58 mmol, 2 equiv), phthalimide (5.97 g, 40.58 mmol, 2 equiv) and distilled di-*i*-propylethylamine (7.1 mL, 40.58 mmol, 2 equiv) in 200 mL of THF in a flame-dried Schlenk tube under a nitrogen atmosphere was added dropwise via syringe diethyl azodicarboxylate (6.4 mL, 40.58 mmol, 2 equiv) over 15 min, allowing the reaction temperature to rise to 30 °C. After 3.5 h of stirring, no starting material remained as indicated by TLC. After evaporation of the solvent, 14.4 g of a viscous bright orange oil was obtained. After adding 100 mL of heptane, a yellow semi-solid, consisting of diethyl 1,2-hydrazinedicarboxylate and triphenylphosphine oxide, remained. After filtration and evaporating the mixture, 3.2 g of a yellow oil was obtained. Further extraction of the residue with heptane yielsded an additional 0.6 g of crude product. Purification by flash chromatography ($SiO_2$, heptanes:diethyl ether 5:1) yielded 3.79 g (13.38 mmol, 66%) of **6** as a colorless oil. $\delta_H$ 0.81–0.89 (2H, m), 1.16 (3H, d, $J$=7.0 Hz), 1.21–1.28 (2H, m), 1.57–1.81 (5H, m), 2.07–2.18 (2H m), 2.30–2.41 (1H, m), 2.60–2.72 (1H, m), 4.53–4.59 (1H, m), 4.58–4.96 (2H, m), 5.53–5.67 (1H, m), 7.67–7.72 (2H, m), 7.77–7.83 (2H, m); $\delta_C$ 19.2 (q), 21.0 (t), 25.6 (t), 26.5 (t), 30.3 (d), 34.7 (t), 44.2 (d), 50.9 (d), 115.6 (t), 122.8 (d), 131.8 (s), 133.6 (d), 137.5 (d), 169.2 (s); *m/z* (EI) 283 ($M^+$, 42), 186 (25), 136 ({M−phthaloyl-H}$^+$,100), 95 (44). HRMS 283.1565, $C_{18}H_{21}NO_2$ requires 283.1572.

**3.1.4. (1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexylamine (7).** To a solution of **6** (2.94 g, 10.38 mmol) and 1-hexene (6.5 mL, 51.5 mmol, 5 equiv) in 55 mL of ethanol in a 3-necked roundbottom flask under a nitrogen atmosphere, hydrazine hydrate (2.5 mL, 48.4 mmol, 4.7 equiv) was added. This mixture was heated at reflux overnight. After cooling, the solvent was removed under reduced pressure, and the remaining oil was taken up in 50 mL of ethyl acetate and extracted with 50 mL of 0.1 M aqueous NaOH. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated. 1.24 g (8.12 mmol, 78%) of **7** was obtained which was used without further purification. $\delta_H$ 0.80–1.02 (1H, m), 0.88 (3H, d, $J$=6.4 Hz), 1.12–1.23 (1H, m), 1.48–1.53 (6H, m), 1.58–1.63 (2H, br d, $J$=12.8 Hz), 1.87–1.98 (1H, m), 2.29–2.33 (1H, m), 3.05 (1H, m), 4.96–5.08 (2H, m), 5.72–5.82 (1H, m); $\delta_C$ 19.9 (t), 20.1 (q), 30.3 (d), 33.9 (t), 34.1 (t), 34.8 (t), 47.1 (d), 47.4 (d), 115.3 (t), 138.0 (d); *m/z* (CI) 154 $(M+H)^+$.

**3.1.5. *N*-[(1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexyl]-4-toluenesulfonamide (2).** To a solution of **7** (682 mg, 4.45 mmol) in 15 mL of dichloromethane was added *p*-toluenesulfonyl chloride (933 mg, 4.94 mmol, 1.1 equiv) and triethylamine (1.34 mL, 9.6 mmol, 2.2 equiv). The mixture was stirred for 60 h under a nitrogen atmosphere. After removal of the solvent, the residue was dissolved in diethyl ether (50 mL), and sequentially washed with 2 M aqueous HCl (2×50 mL), aqueous saturated sodium bicarbonate (2×50 mL) and brine (50 mL). After drying over $MgSO_4$, filtration and evaporation, an oil (1.39 g, 4.52 mmol) was isolated. Crystallisation from heptane afforded **2** (900 mg 2.93 mmol, 66%) as colorless crystals; mp 92–94 °C. A second crop of 395 mg (29%, 1.28 mmol) proved to be equally pure. $\delta_H$ 0.89 (3H, d, $J$=6.0 Hz), 0.95–1.01 (1H, m), 1.13–1.64 (8H, m), 1.91–2.01 (1H, m), 2.11–2.19 (1H, m), 2.43 (3H, s), 3.56–3.58 (1H, m), 4.79–4.82 (1H, m), 4.86–4.92 (2H, m), 5.56–5.71 (1H, m), 7.29 (2H, d, $J$=8.0 Hz), 7.78 (2H, d, $J$=7.3 Hz). $\delta_C$ 19.9 (t), 20.1 (q), 21.5 (q), 30.6 (t), 31.3 (d), 33.0 (t), 33.6 (t), 47.2 (d), 51.5 (d), 116.1 (t), 127.0 (d), 129.6 (d), 137.0 (d), 138.5 (s), 143.1 (s); *m/z* (EI) 307 ($M^+$,18), 155 ($Ts^+$, 44), 152 ({M−Ts}$^+$,100), 91 (tropylium$^+$, 57). HRMS 307.1599, $C_{17}H_{25}NO_2S$ requires 307.1606. Anal. Found: C, 66.26; H, 8.22; N, 4.56; S, 10.11. $C_{17}H_{25}NO_2S$ requires C, 66.41; H, 8.20; N, 4.56; S, 10.41. $[\alpha]_D=-36.8°$ ($c$=1.01, $CHCl_3$). An ee of 99.5% was determined by chiral HPLC on a Chiralpak AS column, 250×4.6 mm, eluted with *n*-heptane: *i*-propanol 95:5, flow: 1 mL/min, at 40 °C.

Selected X-ray data of **2**.[16] $C_{17}H_{25}NO_2S$, $M_r$=307.45, monoclinic, $P2_1$, $a$=11.3300(5), $b$=10.9724(5), $c$=13.7035(7) Å, $\beta$=98.732(1)°, $V$=1683.84(14) Å$^3$, $Z$=4, $D_x$=1.213 g cm$^{-3}$, $F(000)$=664, $\mu$=1.96 cm$^{-1}$, $\lambda$(Mo K$_\alpha$)=0.71073 Å, $T$=100(1) K, 16062 reflections measured, $GooF$=1.029, $wR(F^2)$=0.1700 for 8539 unique reflections and 392 parameters, 23 restraints and $R(F)$=0.0629 for 8285 reflections obeying $Fo\geq 4.0\sigma(Fo)$ criterion

of observability. The asymmetric unit consists of two molecules of the title compound.

**3.1.6. (2*S*,4a*S*,5*R*,8a*R*)-5-Methyl-1-(4-toluenesulfonyl)-2-*n*-propyl decahydro-quinoline (10).** A flame-dried reseal-able tube with a teflon cap was loaded with dry $Na_2CO_3$ (268 mg, 2.53 mmol, 3 equiv) and suspended in 1.41 mL of dry, distilled $CH_3CN$ under a nitrogen atmosphere. To the stirring mixture was then sequentially added tri-*o*-tolylphos-phine (154 mg, 0.51 mmol, 0.6 equiv), palladium acetate (5.08 mL of a 0.05 M stock solution in $CH_3CN$, 0.25 mmol, 0.3 equiv), tetra-*n*-butylammonium chloride (1.69 mL of a 1 M solution in $CH_3CN$, 1.69 mmol, 2 equiv), **2** (260 mg, 0.85 mmol), and 1-bromo-1-propene (0.29 mL, 3.39 mmol, 4 equiv, mixture of *cis* and *trans*). The amount of solvent was adapted so as to afford a 0.1 M solution of **2**. The mixture was then frozen at −40 °C, sealed under vacuum and slowly heated to 86 °C. After stirring at this temperature for 68 h, the mixture was flashed over a plug of silica with pentanes:ethyl acetate 1:1 and concentrated to afford 384 mg of a yellow oil. GC-MS analysis showed a 1:1 mixture of diastereomers with the correct mass ($m/z=347$) together with some unidentified side products. The product mixture was hydrogenated without further purification: 500 mg of the mixture was dissolved in 10 mL of ethanol, placed in an autoclave and 50 mg of 10% Pd/C was added. The mixture was stirred overnight at room temperature under 45 bar of hydrogen pressure. After filtration over a plug of silica with ethanol 132 mg (0.38 mmol, 26%) of a mixture of two epimers (**9**) with an $m/z$ of 349 (GC-MS) was obtained together with a number of side products that could not be identified. Purification by flash chromatography ($SiO_2$, hexanes:diethyl ether 10:1) afforded a pure compound that after removal of the tosyl group by Na/naphthalene (vide infra) gave 2-*epi*-pumiliotoxin C (*epi*-**1**).[20]

Separation of the remaining mixture by preparative HPLC yielded 26 mg (0.075 mmol) of **10** as a colorless solid. $\delta_H$ 0.93 (3H, d, $J=4.0$ Hz), 0.95 (3H, t, $J=4.0$ Hz), 1.07–1.83 (16H, m), 2.42 (3H, s), 3.95–4.04 (2H, m), 7.27 (2H, d, $J=8.1$ Hz), 7.71 (2H, d, $J=8.1$ Hz). $\delta_C$ 14.0 (q), 18.4 (q), 18.9 (q), 20.5 (t), 20.6 (t), 20.9 (t), 21.4 (d), 26.3 (t), 28.2 (t), 29.9 (t), 34.4 (d), 38.3 (t), 51.7 (d), 52.5 (d), 126.6 (d), 129.4 (d), 139.2 (s), 142.4 (s): $m/z$ (EI) 349 ($M^+$, 1.1), 306 ({M−*n*-Pr}$^+$, 100), 155 ($Ts^+$, 6), 135 (20), 91 (tropylium$^+$, 12). HRMS 349.2087. $C_{20}H_{31}NO_2S$ requires 349.2075.

**3.1.7. (2*S*,4a*S*,5*R*,8a*R*)-5-Methyl-2-*n*-propyl decahydro-quinoline, (−)-pumiliotoxin C (1).** Naphthalene (47.7 mg, 0.37 mmol, 5 equiv) was dissolved in 2 mL of dry and degassed DME under an argon atmosphere. To this solution was added metallic sodium (approx. 9 mg, 0.39 mmol, 5.2 equiv) in small slices and the mixture was sonicated until a deep-green solution of sodium naphthalenide had formed (5 min). The solution was then stirred for an additional 2 h at room temperature under argon, cooled to 0 °C and 26 mg of **10** (0.075 mmol) was added as a solution in 1 mL of dry DME. The mixture was stirred for 60 min at 0 °C and then quenched by adding 1 mL of saturated aqueous $NH_4Cl$. Subsequently, 5 mL of 2 M aqueous HCl was added and the aqueous layer was washed with heptane (3×5 mL). The aqueous layer was brought to pH 14 by addition of 10% aqueous NaOH followed by extraction with dichloromethane (4×5 mL). After drying over $MgSO_4$ and evaporation of the solvent, 7 mg (0.036 mmol, 48%) of pure (−)-pumiliotoxin C (**1**) was obtained. All spectroscopic data were in accordance with the literature. Comparison of the mass spectrum with the NIST Mass Spectral Library (1995) showed 94% correspondence.

$^1$H NMR: $\delta$ 0.85 (d, $J=6.3$ Hz, 3H), 0.91 (t, $J=6.5$ Hz, 3H), 1.08–1.18 (m, 2H), 1.26–1.49 (m, 8H), 1.52–1.69 (m, 5H), 1.81–1.98 (m, 2H), 2.53–2.56 (m, 1H), 2.85–2.86 (m, 1H). $^{13}$C NMR: $\delta$ 57.74 (d), 55.98 (d), 42.56 (d), 39.68 (t), 35.91 (t), 33.37 (t), 27.37 (d), 27.32 (t), 27.04 (t), 21.25 (t), 19.91 (q), 19.15 (t), 14.31 (q). The free amine was converted into its hydrochloride by bubbling HCl gas through a solution in *i*-propanol, giving a temperature rise to about 50 °C. After cooling in ice and no further observation of heat develop-ment, the solvent was removed under reduced pressure giving 5 mg of a yellowish solid. Crystallisation from *i*-propanol gave a tiny amount of small colorless needles, mp 190–191 °C (dec., lit.[5j] 220–225 °C).

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