Cyclization of 3-Aminoacrylates – Total Synthesis of Pumiliotoxin C and Related Stereoisomeric Compounds☆

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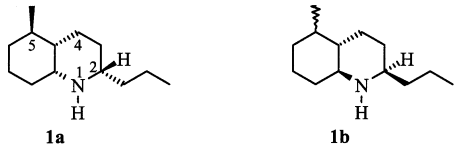
A method is described for the synthesis of pumiliotoxin C (**1a**) and related stereoisomeric compounds **1c**–**1f**. Starting from (+)- or (–)-3-methylcyclohexanone (**6a**,**b**), the oxo esters **7a** and **7b** were prepared. Condensation with (+)- or (–)-3-aminohexanol (**8a**,**b**) gave the stereoisomeric 3-aminoacrylates **9a**, **9b** and **9c**. The hydroxy group of the aminoacrylates was transformed into bromide using the tosylate method. Cyclization of the bromides led to unsaturated quinoline ring systems. Finally, decarboxylation and catalytic hydrogenation gave the different *cis*- and *trans*-fused stereoisomeric alkaloids of the pumiliotoxin C type. The structures were verified by X-ray analysis.

In 1969, pumiliotoxin C (PTX-C) (**1a**) (Scheme 1) was the first alkaloid to be isolated from the skin secretions of the Central American frog species *Dendrobates pumilio*, belonging to the family Dendrobatidae[1][2]. In the following years, investigation of amphibians of the genera *Dendrobates* and *Phyllobates* led to the discovery of hundreds of alkaloids, such as batrachotoxin, histrionicotoxin, and gephyrotoxin,[3][4] with highly interesting physiological properties. The significant neurological activities and the unusual *cis*-decahydroquinoline structure made PTX-C (**1a**) an interesting target for total synthesis. In 1994, the *trans* diastereomer of PTX-C, *trans*-195A (**1b**), was identified as the major alkaloid in skin extracts of the Peruvian frog *Epipedobates bassleri*[5]. The stereochemistry at C-5 has not been determined.

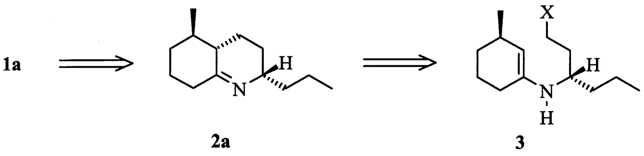
Scheme 1



It is commonly known that the physiological properties of pharmacons are strongly correlated with their stereochemistry, and so the aim of our work was to find a pathway for a flexible synthesis of substituted perhydroquinoline derivatives of the pumiliotoxin C group, enabling us to obtain the different possible stereoisomers of PTX-C (**1a**).

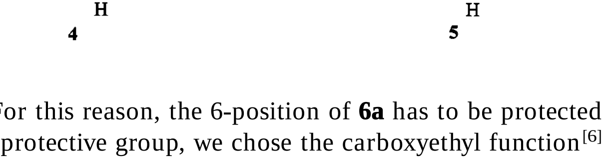
Retrosynthetic analysis of pumiliotoxin C led us to the precursor enamine **3** (Scheme 2).

Scheme 2



Enamine **3** (X = OH) is available by condensation of (*R*)-(+)-3-methylcyclohexanone (**6a**) with (*S*)-3-aminohexanol (**8a**) and already incorporates the required stereochemistry at C-2 and C-5 of PTX-C (**1a**). The configuration of these centres can be easily varied by using the corresponding enantiomers as starting materials. However, enamine cyclization of **3** would result in a 7-methyl-substituted quinoline derivative of type **5**, since cyclization at the sterically less hindered C-6 would be preferred. This is shown in Scheme 3 for the bromide **4**.

Scheme 3



For this reason, the 6-position of **6a** has to be protected. As protective group, we chose the carboxyethyl function[6]. It can be introduced into the molecule as easily as it can be

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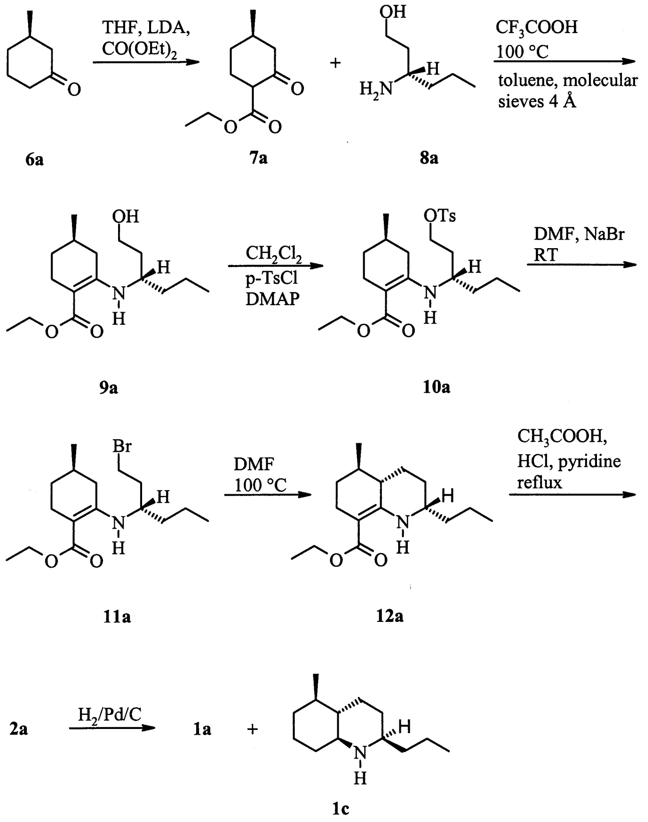
removed after cyclization. A hydroxy function in the side chain should enable us to introduce different leaving groups. These considerations led us to the key intermediate of our synthesis, the 3-aminoacrylate **9**.

Scheme 4



The stereochemistry of the *n*-propyl chain on C-2 of PTX-C (**1a**) was fixed by the two enantiomeric 3-aminohexanols (*S*-**8a** and *R*-**8b**) used for the formation of enamines with ketones *R*-**6a** and *S*-**6b**. The optically pure 3-aminohexanols (**8a**,**b**) were prepared as follows: Condensation of ethyl butyrylacetate with benzylamine in toluene gave ethyl 3-(benzylamino)-2-hexenoate in quantitative yield. Reduction of this compound with Na or LiAlH$_4$ gave racemic 3-(benzylamino)hexanol in 77% yield[7]. Separation of the enantiomers could be achieved by formation of diastereomeric salts with dibenzoyl tartrate and fractional crystallization from 60% ethanol. The optical purity was verified by NMR shift experiments of the free (*S*)- and (*R*)-3-aminohexanols (**8a**,**b**).

The (*R*)- and (*S*)-3-methylcyclohexanones (**6a**,**b**) could be synthesized by established procedures: (*R*)-(+)-methylcyclohexanone (**6a**) by retro-aldol reaction of (*R*)-(+)-pulegone[8]; the (−) isomer **6b** by oxidation of (−)-citronellol with pyridinium chlorochromate (PCC) to give (3*S*)-isopulegone[9], and retro-aldol reaction of the latter.

The protective ethoxycarbonyl function was introduced by deprotonation of the ketone (*R*)-**6a** with lithium diisopropylamide (LDA) and condensation of the anion with diethyl carbonate. Deprotonation with sodium hydride[10] proved to be ineffective because the ketone was reduced to the alkoxide, which reacted with the diethyl carbonate to give a mixed ester in yields of 40%.

For the synthesis of PTX-C (**1a**), we started with the oxo ester **7a** and aminohexanol (*S*)-**8a**. Heating a 1:1 mixture of these compounds in toluene, using molecular sieves as a water trap and trifluoroacetic acid as catalyst, led to the desired 3-aminoacrylate **9a** in 84% yield.

We then studied the behavior of the 3-aminoacrylate **9** under different conditions, with regard to its cyclization. Direct cyclization of **9** by acid catalysts in polar aprotic solvents was not successful. To achieve the cyclization of compound **9**, we had to convert the hydroxy group into a better leaving group. Tosylation was performed using *N*,*N*-dimethylaminopyridine (DMAP) as a base[11], furnishing tosylate **10a** in 86% yield; no tosylation of the nitrogen atom could be detected. The ethoxycarbonyl group not only protects C-6, but it also prevents reaction of electrophilic agents with the free electron pair of the nitrogen atom. Bromination could be easily performed by reaction of the tosylate with NaBr in DMF at room temperature, giving yields of 93%.

The cyclization of the bromide **11a** could be achieved at 100°C using degassed DMF as solvent and molecular sieves to prevent hydrolysis of the enamine by traces of water. The reaction proved to be stereoselective. The steric hindrance of the methyl and bromine substituents leads to a back-side attack of the side chain, to give the required stereochemistry for PTX-C (**1a**) at C-4a. The protective ethoxycarbonyl group proved to be ideal. Under the reaction conditions, the conjugated system is stable and the reaction leads to the desired quinoline derivative **12a** in high yields.

The next step of the synthesis was removal of the ethoxycarbonyl function. Refluxing **12a** for 48 h in acetic acid/HCl/pyridine gave the cyclic imine **2a** in 93% yield. Attempts to remove the ethoxycarbonyl function by the method described by Krapcho and Lovey[12] were not successful because the amine was oxidized to an aromatic compound.

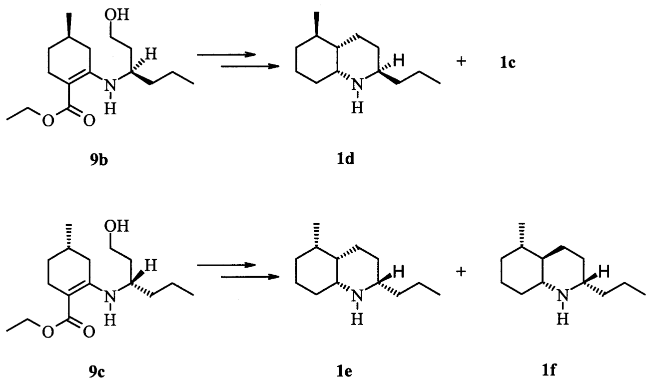
Finally, the imine double bond was hydrogenated using palladium on charcoal as catalyst. The hydrogenation afforded two diastereomeric alkaloids, *cis*-PTX-C (**1a**) and the *trans*-fused isomer **1c**. The spectra of the *cis* compound **1a** are identical to those of the natural product and X-ray analysis proved the structures of both compounds. We expected the reaction to be stereoselective, because the *n*-propyl chain should prevent the imine from coming into contact with the catalyst from the *endo* side. However, the palladium catalyst causes isomerization of the double bond. Hydrogenation of the isomerized imine affords the more stable *trans*-fused alkaloid **1c**.

The *trans* compound **1c** may be identical to the alkaloid *trans*-195A (**1b**) that was detected in *Epipedobates bassleri*, since the analytical methods used did not allow determination of the stereochemistry at C-5[5] of **1b**.

Starting from 3-aminoacrylate **9**, the overall yield of the two alkaloids was 57%. The *cis*/*trans* ratio was determined as 1:0.64.

In the same manner as described above, condensation of the β-oxo ester **7a** with (*R*)-3-aminohexanol (**8b**) and **7b** with (*S*)-**8a** afforded the stereoisomeric 3-aminoacrylates **9b** and **9c**, respectively. Cyclization, decarboxylation, and hydrogenation of the isomers **9b** and **9c** afforded the new *cis*-fused alkaloids **1d** and **1e**. As *trans*-fused alkaloids, we isolated **1c** once more, as well as its enantiomer **1f**.

Scheme 5



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Experimental Section

General: (*R*)-(+)- (**6a**)[8] and (*S*)-(−)-3-methylcyclohexanone (**6b**)[9] as well as (*S*)-(+)- (**8a**) and (*R*)-(−)-3-aminohexanol (**8b**)[7] were prepared according to literature procedures. Analogous procedures are described only once; the given yields are also valid for the reactions with the other isomers. Melting points: uncorrected. − IR: Bruker IFS 88. − NMR: Bruker AM 300 (300 MHz and 75 MHz, for ^{1}H and ^{13}C, respectively); $CDCl_3$ as solvent, TMS as internal standard. − MS: Finnigan MAT 312 and MAT 95 (70 eV).

Ethyl (4R)- (**7a**) *and Ethyl (4S)-4-Methyl-2-oxocyclohexane-1-carboxylate* (**7b**): A solution of 5.0 g (44.6 mmol) of 3-methylcyclohexanone (**6a** or **6b**) and 38g (0.32 mol) diethyl carbonate in 30 ml of THF was cooled to −78°C and 25 ml (50 mmol) of a 2 N solution of LDA in THF/hexane/ethylbenzene was slowly added by means of a syringe. The mixture was then allowed to warm to room temperature and was stirred for 16 h. After cooling with ice, the solution was neutralized with dilute acetic acid and extracted with diethyl ether. The ether was evaporated from the combined extracts and the crude oxo esters were purified by column chromatography (silica gel, diethyl ether/hexane, 1:10) to yield 6.43 g (78%) of a colorless liquid. − IR ($CHCl_3$): $\tilde{\nu}$ = 2928 cm^{-1}, 2872, 1744, 1717, 1656, 1616, 1457, 1422, 1404, 1369, 1276, 1217, 1101, 1086. − ^{1}H NMR ($CDCl_3$): δ = 12.19 (s, 1 H), 4.18 (q, *J* = 7 Hz, 2 H), 2.5−1.6 (m, 6 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.15 (m, 1 H), 1.00 (d, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 172.82 (s), 171.53 (s), 76.98 (d), 60.04 (d), 37.15 (t), 33.93 (t), 30.52 (t), 22.00 (t), 21.20 (q), 14.22 (q). − MS (70 eV); *m/z* (%): 184 (74) [M^+], 169 (7), 156 (23), 138 (100), 123 (14), 113 (19), 96 (49), 91 (21), 81 (75), 73 (9), 67 (52), 63 (10), 55 (43).

3-Aminoacrylate **9**: Under nitrogen, 3.0 g (16.3 mmol) oxo ester **7a** or **7b**, 1.9 g (16.3 mmol) (+)- or (−)-3-aminohexanol **8a**,**b** and two drops of trifluoroacetic acid were dissolved in 7 ml of toluene and heated to 100°C for 20 h. Molecular sieves (4 Å) were used to remove water. The solvent was subsequently removed in vacuo and the residual crude oil was purified by column chromatography on neutral aluminum oxide (activity grade V; eluent: diethyl ether/hexane, 1:1) to yield 3.86 g (84%) of a light-yellow oil. − Isomer **9a**: IR (film): $\tilde{\nu}$ = 3447 cm^{-1}, 2955, 2872, 2361, 2340, 1646, 1595, 1456, 1363, 1239, 1154, 1052, 961, 909, 879, 774, 720, 668. − ^{1}H NMR ($CDCl_3$): δ = 8.83 (d, *J* = 10 Hz, 1 H), 4.10 (q, *J* = 7 Hz, 2 H), 3.65 (m, 3 H), 2.48 (m, 2 H), 2.18 (dt, *J* = 12, *J* = 5 Hz, 1 H), 1.85−1.50 (m, 5 H), 1.50−1.30 (m, 4 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.08 (dq, *J* = 11, *J* = 6 Hz, 1 H), 1.00 (d, *J* = 6 Hz, 3 H), 0.90 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 171.99 (s), 159.43 (s), 88.83 (s), 59.80 (t), 58.61 (t), 48.63 (d), 39.52 (t), 39.10 (t), 34.99 (t), 31.08 (t), 28.60 (d), 23.89 (t), 21.89 (q), 19.14 (t), 14.68 (q), 14.15 (q). − MS (70 eV); *m/z* (%): 283 (45) [M^+], 268 (12), 254 (5), 240 (49), 238 (58), 226 (17), 210 (28), 194 (97), 192 (100), 182 (17), 176 (20), 168 (29), 154 (13), 138 (25), 136 (22), 122 (10), 110 (21), 95 (25), 81 (22), 67 (26). − HRMS: $C_{16}H_{29}NO_3$: calcd. 283.2147, found 283.2148. − Isomer **9b**: IR (film): $\tilde{\nu}$ = 3440 cm^{-1}, 2956, 2873, 2247, 1645, 1595, 1454, 1364, 1239, 1154, 1085, 1051, 910, 774, 733, 647. − ^{1}H NMR ($CDCl_3$): δ = 8.85 (d, *J* = 10 Hz, 1 H), 4.10 (q, *J* = 7 Hz, 2 H), 3.63 (m, 3 H), 2.42 (m, 2 H), 2.35−2.10 (m, 1 H), 2.00−1.50 (m, 5 H), 1.50−1.30 (m, 4 H), 1.22 (t, *J* = 7 Hz, 3 H), 1.15−1.00 (m, 1 H), 0.95 (q, *J* = 6 Hz, 3 H), 0.87 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.88 (s), 159.31 (s), 88.40 (s), 59.41 (t), 58.47 (t), 48.45 (d), 39.18 (t), 39.18 (t), 34.77 (t), 30.88 (t), 28.39 (d), 23.62 (t), 21.61 (q), 18.95 (t), 14.52 (q), 14.02 (q). − MS (70 eV); *m/z* (%): 283 (37) [M^+], 268 (5), 252 (4), 240 (44), 238 (57), 226 (12), 210 (32), 194 (100), 192 (93), 176 (23), 168 (22), 164 (30), 149 (37), 134 (19), 121 (9), 110 (21), 91 (68), 81 (24), 67 (32). − HRMS: $C_{16}H_{29}NO_3$: calcd. 283.2147, found 283.2148. − Isomer **9c**: IR (film): $\tilde{\nu}$ = 3440 cm^{-1}, 2956, 2873, 2247, 1645, 1595, 1454, 1364, 1239, 1154, 1085, 1051, 910, 774, 733, 647. − ^{1}H NMR ($CDCl_3$): δ = 8.59 (d, *J* = 9 Hz, 1 H), 4.05 (q, *J* = 7 Hz, 2 H), 3.55 (m, 3 H), 2.33 (m, 2 H), 2.11 (m, 1 H), 1.95−1.50 (m, 5 H), 1.50−1.25 (m, 4 H), 1.22 (t, *J* = 6 Hz, 3 H), 1.05 (m, 1 H), 0.93 (d, *J* = 6 Hz, 3 H), 0.85 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CHCl_3$): δ = 170.90 (s), 160.33 (s), 88.43 (s), 59.44 (t), 58.49 (t), 48.48 (d), 39.21 (t), 39.21 (t), 34.79 (t), 30.90 (t), 28.40 (d), 23.64 (t), 21.63 (q), 18.97 (t), 14.55 (q), 14.04 (q). − MS (70 eV); *m/z* (%): 283 (28) [M^+], 265 (7), 254 (3), 240 (33), 238 (38), 222 (21), 210 (28), 194 (61), 192 (69), 176 (46), 168 (18), 164 (22), 149 (49), 134 (29), 121 (13), 110 (20), 91 (100), 81 (31), 67 (38). − HRMS: $C_{16}H_{29}NO_3$: calcd. 283.2147, found 283.2148.

Tosylate **10**: To a stirred solution of 1.53 g (5.4 mmol) of 3-aminoacrylate **9** in 5 ml of anhydrous CH_2Cl_2 was added 1.24 g (6.5 mmol) of tosyl chloride, followed by a solution of 1.58 g (13 mmol) of DMAP in 2 ml of CH_2Cl_2. The resulting mixture was allowed to stir for 30 min. To remove the precipitate and to separate the product, the mixture was applied to a column of 100 g of neutral aluminium oxide (activity grade V; eluent: diethyl ether/hexane, 1:10) to yield 2.03 g (86%) of a colourless oil. − Isomer **10a**: IR (film): $\tilde{\nu}$ = 3250 cm^{-1}, 3160, 2957, 2873, 2251, 1643, 1597, 1455, 1361, 1237, 1189, 1178, 1155, 1120, 1052, 960, 919, 815, 773, 734, 664, 555. − ^{1}H NMR ($CDCl_3$): δ = 8.77 (d, *J* = 8 Hz, 1 H), 7.70 (d, *J* = 7 Hz, 2 H), 7.28 (d, *J* = 7 Hz, 2 H), 4.06 (m, 4 H), 3.57 (m, 1 H), 2.44 (s, 3 H), 2.39 (dt, *J* = 5, *J* = 18 Hz, 2 H), 2.14 (dt, *J* = 5, *J* = 11 Hz, 1 H), 1.88 (m, 1 H), 1.80−1.50 (m, 4 H), 1.45−1.25 (m, 4 H), 1.24 (t, *J* = 7 Hz, 3 H), 1.06 (m, 1 H), 0.97 (d, *J* = 6 Hz, 3 H), 0.87 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.88 (s), 159.08 (s), 144.76 (s), 132.91 (s), 129.81 (d), 129.81 (d), 127.80 (d), 127.80 (d), 89.22 (s), 67.54 (t), 58.54 (t), 47.62 (d), 39.38 (t), 35.78 (t), 34.75 (t), 30.88 (t), 28.42 (d), 23.73 (t), 21.73 (q), 21.56 (q), 18.90 (t), 14.58 (q), 14.00 (q). − MS (70 eV); *m/z*

(%): 437 (42) $[M^+]$, 422 (5), 395 (10), 364 (7), 348 (16), 322 (5), 300 (12), 282 (10), 266 (32), 250 (28), 238 (52), 222 (32), 212 (34), 192 (100), 176 (60), 164 (14), 150 (37), 136 (23), 122 (50), 109 (24), 91 (82), 81 (60), 67 (45). − HRMS: $C_{23}H_{35}NO_5S$: calcd. 437.2236, found 437.2237. − Isomer **10b**: IR (film): $\tilde{\nu}$ = 3250, 3160, 2957, 2873, 1643, 1597, 1455, 1237, 1189, 1178, 1155, 1120, 1052, 960, 919, 815, 773, 734, 664. − ^{1}H NMR ($CDCl_3$): δ = 8.77 (d, *J* = 8 Hz, 1 H), 7.56 (d, *J* = 7 Hz, 2 H), 7.30 (d, *J* = 7 Hz, 2 H), 4.06 (m, 4 H), 3.53 (m, 1 H), 2.42 (s, 3 H), 2.38 (dt, *J* = 5, *J* = 17 Hz, 2 H), 2.12 (m, 1 H), 1.86 (m, 1 H), 1.80−1.50 (m, 4 H), 1.50−1.25 (m, 4 H), 1.24 (t, *J* = 7 Hz, 3 H), 1.05 (d, *J* = 6 Hz, 1 H), 0.98 (d, *J* = 7 Hz, 3 H), 0.87 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.82 (s), 158.92 (s), 144.69 (s), 132.98 (s), 129.78 (d), 129.78 (d), 127.76 (d), 127.76 (d), 89.16 (s), 67.47 (t), 58.48 (t), 47.66 (d), 39.09 (t), 35.85 (t), 34.63 (t), 30.75 (t), 28.38 (d), 23.64 (t), 21.58 (q), 21.49 (q), 18.78 (t), 14.53 (q), 13.95 (q). − MS (70 eV); *m/z* (%): 437 (2) $[M^+]$, 423 (1), 348 (2), 338 (4), 302 (3), 291 (10), 266 (5), 232 (11), 212 (12), 192 (13), 184 (20), 176 (12), 169 (15), 155 (46), 138 (38), 123 (39), 109 (18), 97 (66), 91 (100), 81 (51), 79 (21), 69 (45). − HRMS: $C_{23}H_{35}NO_5S$: calcd. 437.2236, found 437.2332. − Isomer **10c**: IR (film): $\tilde{\nu}$ = 3250, 3160, 2957, 2873, 1643, 1597, 1455, 1237, 1189, 1178, 1155, 1120, 1052, 960, 919, 815, 773, 734, 664. − ^{1}H NMR ($CDCl_3$): δ = 8.72 (d, *J* = 8 Hz, 1 H), 7.73 (d, *J* = 7 Hz, 2 H), 7.25 (d, *J* = 7 Hz, 2 H), 4.08 (m, 4 H), 3.58 (m, 1 H), 2.42 (s, 3 H), 2.38 (m, 2 H), 2.11 (m, 1 H), 1.85 (m, 1 H), 1.80−1.50 (m, 4 H), 1.50−1.15 (m, 4 H), 1.22 (t, *J* = 7 Hz, 3 H), 1.02 (m, 1 H), 1.00 (d, *J* = 6 Hz, 3 H), 0.84 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.87 (s), 158.96 (s), 144.73 (s), 132.73 (s), 129.84 (d), 129.84 (d), 127.80 (d), 127.80 (d), 89.12 (s), 67.53 (t), 58.53 (t), 47.73 (d), 39.13 (t), 35.88 (t), 34.66 (t), 30.79 (t), 28.41 (d), 23.68 (t), 21.63 (q), 21.54 (q), 18.82 (t), 14.57 (q), 13.99 (q).

Bromide **11**: 2.03 g (4.64 mmol) of the tosylate **10** was dissolved in 20 ml of DMF and 0.72 g (7 mmol) of NaBr was added. The solution was stirred at room temperature for 20 h. To isolate the brominated compound, the whole mixture was applied to a column of 150 g of aluminium oxide (activity grade V; eluent: diethyl ether/hexane, 1:10) to give 1.5 g (93%) of a colourless oil. − Isomer **11a**: IR (film): $\tilde{\nu}$ = 3233 cm^{-1}, 3163, 2956, 2872, 1646, 1599, 1454, 1362, 1225, 1157, 1123, 1074, 962, 774, 733, 571. − ^{1}H NMR ($CDCl_3$): δ = 8.75 (d, *J* = 7 Hz, 1 H), 4.01 (q, *J* = 7 Hz, 2 H), 3.60 (m, 1 H), 3.32 (m, 2 H), 2.48 (m, 1 H), 2.32 (m, 1 H), 2.06 (m, 1 H), 2.00−1.50 (m, 6 H), 1.33 (m, 3 H), 1.14 (t, *J* = 8 Hz, 3 H), 1.00 (m, 1 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.79 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.77 (s), 159.05 (s), 89.07 (s), 58.41 (t), 49.42 (d), 39.26 (t), 39.07 (t), 34.87 (t), 30.85 (t), 30.73 (t), 28.39 (d), 23.64 (t), 21.67 (q), 18.89 (t), 14.48 (q), 13.92 (q). − MS (70 eV); *m/z* (%): 347 (24) $[M^+]$, 345 (22) $[M^+]$, 332 (14), 330 (14), 316 (4), 303 (18), 301 (27), 299 (15), 286 (3), 266 (37), 258 (41), 256 (41), 238 (51), 222 (7), 212 (9), 192 (100), 176 (18), 151 (7), 138 (14), 110 (16), 95 (20), 81 (17), 67 (19). − HRMS: $C_{16}H_{28}{}^{79}BrNO_2$: calcd. 345.1303, found 345.1304. − Isomer **11b**: IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 2872, 1646, 1599, 1454, 1362, 1225, 1157, 1123, 1074, 774, 733, 571. − ^{1}H NMR ($CDCl_3$): δ = 8.84 (d, *J* = 10 Hz, 1 H), 4.09 (q, *J* = 7 Hz, 2 H), 3.68 (m, 1 H), 3.41 (m, 2 H), 2.50−2.30 (m, 2 H), 2.19 (m, 1 H), 1.98 (m, 3 H), 1.68 (m, 2 H), 1.58−1.30 (m, 4 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.13 (m, 1 H), 1.01 (q, *J* = 7 Hz, 3 H), 0.89 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.96 (s), 159.12 (s), 89.05 (s), 58.58 (t), 49.68 (d), 39.48 (t), 39.01 (t), 34.90 (t), 30.89 (t), 30.77 (t), 28.45 (d), 23.64 (t), 21.63 (q), 18.97 (t), 14.62 (q), 14.08 (q). − MS (70 eV); *m/z* (%): 347 (21) $[M^+]$, 345 (22), 332 (34), 330 (35), 318 (4), 304 (19), 301 (29), 286 (3), 267 (7), 266 (36), 258 (47), 256 (46), 238 (50), 222 (15), 192 (100), 176 (36), 150 (9), 148 (9), 138 (14), 136 (13), 122 (17), 110 (17), 95 (22), 81 (21), 67 (20). − HRMS: $C_{16}H_{28}{}^{79}BrNO_2$: calcd. 345.1303, found 345.1304. − Isomer **11c**: IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 2872, 1646, 1599, 1454, 1362, 1225, 1157, 1123, 1074, 774, 733, 571. − ^{1}H NMR ($CDCl_3$): δ = 8.83 (d, *J* = 10 Hz, 1 H), 4.11 (q, *J* = 7 Hz, 2 H), 3.68 (m, 1 H), 3.42 (m, 2 H), 2.40 (m, 2 H), 2.16 (m, 1 H), 1.95 (m, 3 H), 1.67 (m, 2 H), 1.55−1.30 (m, 4 H), 1.22 (t, *J* = 7 Hz, 3 H), 1.10 (m, 1 H), 0.98 (d, *J* = 6 Hz, 3 H), 0.89 (t, *J* = 8 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 171.01 (s), 159.18 (s), 88.09 (s), 58.82 (t), 49.72 (d), 39.51 (t), 39.04 (t), 34.94 (t), 30.90 (t), 30.82 (t), 28.47 (d), 23.67 (t), 21.67 (q), 19.00 (t), 14.65 (q), 14.08 (q).

Cyclization: 2.04 g (5.9 mmol) of the bromide **11** was dissolved in 20 ml of degassed DMF and heated under nitrogen for 20 h at 100°C. To remove traces of water, molecular sieves (4 Å) were added. After cooling with ice, the mixture was made alkaline with potassium carbonate and extracted with diethyl ether. The combined ethereal extracts were dried with potassium sulfate and the solvent was removed by rotary evaporation. Chromatography of the crude product using neutral aluminium oxide (activity grade V; eluent: diethyl ether/hexane, 1:20) yielded 1.36 g (87%) of a light-yellow oil. − Isomer **12a**: IR (film): $\tilde{\nu}$ = 3259 cm^{-1}, 3170, 2958, 2929, 2872, 1648, 1601, 1462, 1363, 1271, 1248, 1209, 1103, 1052, 959, 782, 701, 668. − ^{1}H NMR ($CDCl_3$): δ = 8.90 (s, 1 H), 4.11 (m, 2 H), 3.25 (m, 1 H), 2.41 (m, 1 H), 2.20−2.00 (m, 2 H), 1.83 (m, 2 H), 1.63 (m, 2 H), 1.57−1.10 (m, 7 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 0.94 (t, *J* = 5 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.77 (s), 161.71 (s), 87.68 (s), 58.51 (t), 48.66 (d), 41.43 (d), 38.44 (t), 34.94 (d), 31.41 (t), 28.13 (t), 23.64 (t), 23.55 (t), 20.42 (q), 19.25 (t), 14.72 (q), 14.06 (q). − MS (70 eV); *m/z* (%): 265 (15) $[M^+]$, 250 (5), 236 (5), 222 (43), 192 (11), 176 (100), 163 (5), 150 (8), 134 (7), 123 (10), 109 (15), 95 (20), 82 (25), 69 (26). − HRMS: $C_{16}H_{27}NO_2$: calcd. 265.2042, found 265.2042. − Isomer **12b**: IR (film): $\tilde{\nu}$ = 3257 cm^{-1}, 3170, 2929, 1646, 1600, 1463, 1207, 1103, 1051, 963, 783, 702, 612. − ^{1}H NMR ($CDCl_3$): δ = 9.12 (br. s, 1 H), 4.13 (m, 2 H), 3.17 (m, 1 H), 2.40 (dd, *J* = 15, *J* = 6 Hz, 1 H), 2.33−2.16 (m, 1 H), 2.12−2.00 (m, 1 H), 1.95−1.85 (m, 1 H), 1.85−1.63 (m, 2 H), 1.60−1.10 (m, 7 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.19 (m, 1 H), 0.98 (d, *J* = 6 Hz, 3 H), 0.92 (t, *J* = 7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 171.05 (s), 160.41 (s), 89.37 (s), 58.89 (t), 52.88 (d), 43.91 (d), 40.18 (t), 33.71 (d), 31.93 (t), 30.32 (t), 25.83 (t), 24.02 (t), 20.14 (q), 18.83 (t), 14.88 (q), 14.13 (q). − MS (70 eV); *m/z* (%): 265 (17) $[M^+]$, 250 (25), 236 (5), 222 (45), 204 (5), 193 (13), 176 (100), 162 (3), 150 (8), 134 (6), 120 (5), 105 (11), 91 (8), 79 (10), 67 (8). − HRMS: $C_{16}H_{27}NO_2$: calcd. 265.2042, found 265.2042. − Isomer **12c**: IR (film): $\tilde{\nu}$ = 3260 cm^{-1}, 3169, 2929, 1648, 1600, 1464, 1363, 1211, 1052, 959, 783, 701, 621. − ^{1}H NMR ($CDCl_3$): δ = 9.10 (br. s, 1 H), 4.11 (m, 2 H), 3.15 (m, 1 H), 2.38 (dd, *J* = 15, *J* = 6 Hz, 1 H), 2.30−2.11 (m, 1 H), 2.05 (m, 1 H), 1.95−1.60 (m, 4 H), 1.60−1.11 (m, 7 H), 1.22 (t, *J* = 7 Hz, 3 H), 0.98 (d, *J* = 7 Hz, 3 H), 0.93 (t, *J* = 6 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 171.03 (s), 160.38 (s), 89.39 (s), 58.67 (t), 52.89 (d), 43.91 (d), 40.18 (t), 33.71 (d), 31.93 (t), 30.71 (t), 25.84 (t), 24.01 (t), 20.13 (q), 18.81 (t), 14.66 (q), 14.11 (q). − MS (70 eV); *m/z* (%): 265 (16) $[M^+]$, 250 (5), 236 (6), 222 (43), 220 (18), 205 (3), 192 (11), 176 (100), 163 (5), 150 (8), 134 (7), 123 (10), 109 (15), 95 (20), 82 (25), 69 (26). − HRMS: $C_{16}H_{27}NO_2$: calcd. 265.2042, found 265.2042.

Decarboxylation: Under nitrogen, 1.36 g (5.1 mmol) of the cyclized compound **12** was dissolved in 6 ml of glacial acetic acid. 1.5 ml of pyridine and 15 ml of 20% hydrochloric acid were added and the solution was refluxed for 48 h. The solvents were then evaporated in vacuo, the crude product was made alkaline with NaOH (30%), and extracted with diethyl ether. The combined ethereal extracts were dried with potassium sulfate and the solvent was evaporated. The residue was purified by column chromatography using aluminium oxide (activity grade IV; eluent: hexane/diethyl ether, 1:10) to yield 1.06 g (93%) of a light-yellow oil. − Isomer **2a**: IR ($CHCl_3$): $\tilde{\nu}$ = 3270 cm^{-1}, 2852, 2926, 1647, 1460, 1380, 1245, 1130, 960. − ^1H NMR ($CDCl_3$): δ = 3.35 (m, 1 H), 3.03 (m, 1 H), 2.59 (m, 1 H), 2.32 (d, *J* = 13 Hz, 1 H), 2.25−1.86 (m, 2 H), 1.85−1.50 (m, 5 H), 1.50−1.00 (m, 6 H), 0.88 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 172.35 (s), 57.03 (d), 44.12 (d), 38.74 (d), 35.02 (t), 34.84 (t), 27.24 (t), 26.15 (t), 24.03 (t), 22.16 (t), 19.92 (q), 18.86 (t), 13.43 (q). − MS (70 eV); *m/z* (%): 193 (9) [M^+], 188 (14), 178 (44), 174 (28), 172 (8), 164 (27), 161 (100), 151 (39), 145 (44), 136 (13), 122 (9), 108 (11), 95 (9), 91 (15), 77 (16), 67 (10). − HRMS: $C_{13}H_{23}N$: calcd. 193.1830, found 193.1829. − Isomer **2b**: IR ($CHCl_3$): $\tilde{\nu}$ = 3285 cm^{-1}, 2852, 2926, 1647, 1458, 1380, 1245, 1142, 953. − ^1H NMR ($CDCl_3$): δ = 3.38 (m, 1 H), 3.12 (m, 1 H), 2.42−2.30 (m, 2 H), 2.25−1.95 (m, 4 H), 1.95−1.55 (m, 4 H), 1.55−1.00 (m, 5 H), 0.93 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 171.51 (s), 57.62 (d), 44.98 (d), 40.22 (t), 40.03 (d), 39.07 (t), 34.88 (t), 27.43 (t), 26.03 (t), 25.92 (t), 19.60 (q), 19.06 (t), 14.05 (q). − MS (70 eV); *m/z* (%): 193 (7) [M^+], 188 (12), 178 (50), 161 (100), 146 (43), 122 (5), 108 (9), 95 (7), 77 (12), 67 (13). − Isomer **2c**: IR ($CHCl_3$): $\tilde{\nu}$ = 3285 cm^{-1}, 2852, 2926, 1647, 1458, 1380, 1245, 1142, 953. − ^1H NMR ($CDCl_3$): δ = 3.15 (m, 1 H), 2.87 (m, 1 H), 2.65 (m, 1 H), 2.34 (m, 1 H), 2.20−1.60 (m, 7 H), 1.60−1.00 (m, 6 H), 0.88 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 171.59 (s), 57.74 (d), 45.06 (d), 40.39 (t), 40.12 (d), 39.27 (t), 34.98 (t), 27.56 (t), 26.12 (t), 26.05 (t), 19.71 (q), 19.18 (t), 14.16 (q). − MS (90 eV); *m/z* (%): 193 (11) [M^+], 188 (13), 178 (47), 174 (28), 164 (25), 161 (100), 150 (39), 146 (44), 136 (13), 130 (8), 122 (8), 108 (11), 91 (15), 77 (14), 67 (12). − HRMS: $C_{13}H_{23}N$: calcd. 193.1830, found 193.1829.

Pumiliotoxin C and Isomers (**1**): 0.57 g of 10% Pd/C was stirred in 20 ml of ethanol under hydrogen until no further hydrogen was absorbed. A solution of 1.06 g of the imine in 5 ml of ethanol was then added by means of a syringe and the mixture was stirred for 24 h. The solution was subsequently filtered and the solvent was removed from the filtrate by rotary evaporation. The *cis* and *trans* isomers could be separated by column chromatography using aluminum oxide (activity grade III; eluent: hexane/diethylamine, 100:0.5). After removal of the solvents, the purified alkaloids were transformed into their more stable hydrochlorides by adding HCl/diethyl ether. Fractional crystallization afforded the alkaloids in yields of 50−60% (*cis*) or 30−40% (*trans*). PTX-C (**1a**)·HCl: m.p. 278°C (sealed capillary under N_2) − $[\alpha]^{20}_D$ = −12.9 (*c* = 0.6 in methanol). − IR ($CHCl_3$): $\tilde{\nu}$ = 2927 cm^{-1}, 2872, 2708, 2542, 1730, 1585, 1471, 1444, 1377, 1181, 1117, 998, 970. − ^1H NMR ($CDCl_3$): δ = 9.43 (br. s, 1 H, NH), 8.32 (br. s, 1 H, NH), 3.29 (d, *J* = 9 Hz, 1 H, 8a-H), 2.93 (br. s, 1 H, 2-H), 2.45−2.20 (m, 2 H, 8-H_2), 2.15−1.90 (m, 5 H, 3-H_2, 5-H, 9-H_2), 1.88−1.60 (m, 4 H, 4-H_2, 6-H_2), 1.60−1.15 (m, 5 H, 4a-H, 7-H_2, 10-H_2), 0.86 (t, *J* = 6 Hz, 3 H, 11-H_3), 0.82 (d, *J* = 4 Hz, 3 H, 12-H_3). − ^{13}C NMR ($CDCl_3$): δ = 60.09 (d, C-2), 58.05 (d, C-8a), 40.90 (d, C-4a), 34.89 (t, C-6), 34.36 (t, C-9), 29.14 (t, C-8), 27.15 (d, C-5), 25.23 (t, C-3), 23.15 (t, C-4), 20.46 (t, C-7), 19.76 (q, C-12), 19.11 (t, C-10), 13.73 (q, C-11). − MS (70 eV); *m/z* (%): 195 (22) [M^+], 180 (24), 166 (8), 152 (100), 135 (25), 124 (13), 109 (33), 95 (27), 79 (30), 67 (32). − $C_{13}H_{26}ClN$ (231.8): calcd. C 67.36, H 11.31, N 6.04; found C 67.24, H 11.16, N 6.51. − X-ray analysis[13]: $C_{13}H_{26}ClN$, mol. mass 231.8, monoclinic, space group: *P*21 (No. 4), unit cell dimensions: *a* = 8.607(3), *b* = 7.569(2), *c* = 11.596(4) Å, β = 109.84(3)°, *Z* = 2, D_x = 1.083 g/ml, diffractometer Stoe IPDS, structure solution by SHELXS-86, refinement by SHELXL-93, *R*1 = 0.0654, *wR*2 = 0.0768, absolute structure probably correct, Flack parameter *x* = −0.49(16). Good agreement was found with the structure determination of natural pumiliotoxin C hydrochloride[14]. − *trans*-PTX (**1c**)·HCl: m.p. 295°C (sealed capillary under N_2) − $[\alpha]^{20}_D$ = −27.3 (*c* = 0.6 in methanol) − IR ($CHCl_3$): $\tilde{\nu}$ = 3420 cm^{-1}, 2959, 2931, 2871, 2740, 2601, 2537, 1589, 1453, 1442.− ^1H NMR ($CDCl_3$): δ = 9.43 (br. s, 1 H, NH), 9.04 (br. s, 1 H, NH), 2.88 (br. s, 1 H, 2-H), 2.61 (br. s, 1 H, 8a-H), 2.43 (d, *J* = 9 Hz, 1 H, 8-Heq), 2.10 (m, 2 H, 4-Heq, 6-Heq), 2.00 (m, 1 H, 3-Heq), 1.90−1.55 (m, 5 H, 4-Hax, 6-Hax, 7-Heq, 8-Hax, 9-H), 1.53−1.20 (m, 4 H, 4a-H, 7-Hax, 10-H_2), 1.2−1.0 (m, 3 H, 3-Hax, 5-H, 9-H), 0.92 (t, *J* = 7 Hz, 6 H, 9-H_3, 12-H_3). − ^{13}C NMR ($CDCl_3$): δ = 61.75 (d, C-8a), 58.27 (d, C-2), 44.54 (d, C-4a), 36.58 (d, C-5), 35.07 (t, C-6), 34.18 (t, C-9), 29.94 (t, C-8), 28.07 (t, C-3), 27.25 (t, C-4), 24.12 (t, C-7), 18.82 (t, C-10), 18.82 (q, C-12), 11.87 (q, C-11). − MS (70 eV); *m/z* (%): 196 (3) [M^+ + 1], 195 (3) [M^+], 180 (1), 168 (3), 153 (13), 152 (100), 138 (5), 124 (3), 109 (6), 95 (3), 81 (4), 69 (7), 55 (7). − $C_{13}H_{26}ClN$ (231.8): calcd. C 67.36, H 11.31, N 6.04; found C 67.00, H 11.15, N 6.67. − X-ray analysis[13]: $C_{13}H_{26}ClN$, mol. mass 231.8, monoclinic, space group *P*21 (No.4), unit cell dimensions: *a* = 8.462(2), *b* = 7.353(1), *c* = 11.949(2) Å, β = 104.90(1)°, *Z* = 2, D_x = 1.071 g/ml, diffractometer Stoe IPDS, structure solution by SHELXS-86, refinement by SHELXL-93, *R*1 = 0.0357, *wR* = 0.0877, absolute structure determined, Flack parameter *x* = −0.09(8). − Isomer **1d**: m.p. 232°C (sealed capillary under N_2) − ^1H NMR ($CDCl_3$): δ = 9.50 (br. s, 1 H), 8.17 (br. s, 1 H), 3.34 (br. s, 1 H), 2.98 (br. s, 1 H), 2.50−2.23 (m, 2 H), 2.23−1.55 (m, 9 H), 1.55−1.10 (m, 5 H), 0.89 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 59.59 (d), 57.52 (d), 37.19 (t), 34.39 (t), 33.93 (t), 33.81 (d), 28.82 (t), 25.31 (d), 25.09 (t), 23.18 (t), 22.57 (q), 18.76 (t), 13.45 (q). − $C_{13}H_{26}ClN$ (231.8): C 67.36, H 11.31, N 6.04; found C 67.24, H 11.16, N 6.51. − Isomer **1e**: m.p. 201°C (sealed capillary under N_2) − IR ($CHCl_3$): $\tilde{\nu}$ = 2930 cm^{-1}, 2870, 2738, 2536, 1587, 1455, 1376, 957. − ^1H NMR ($CDCl_3$): δ = 9.32 (br. s, 1 H), 8.25 (br. s, 1 H), 3.24 (d, *J* = 10 Hz, 1 H), 2.86 (m, 1 H), 2.45−2.20 (m, 2 H), 2.20−1.85 (m, 5 H), 1.85−0.95 (m, 9 H), 0.85 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 60.00 (d), 57.81 (d), 40.69 (d), 34.76 (t), 34.56 (t), 29.02 (t), 27.07 (d), 25.07 (t), 23.00 (t), 20.33 (t), 19.70 (q), 19.01 (t), 13.67 (q). − $C_{13}H_{26}ClN$ (231.8): C 67.36, H 11.31, N 6.04; found C 67.26, H 11.14, N 6.63. − Isomer **1f**: Spectroscopic data and mp are identical to those of **1c** − $[\alpha]^{20}_D$ = +27.5 (*c* = 0.6 in methanol).

☆ Dedicated to Dr. *John W. Daly* on the occasion of his 65th birthday.

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[13] Crystallographic data (excluding structure factors) for the structures reported in this paper and further details of the structure investigation have been deposited with the Cambridge Crystal-

lographic Data Centre under the depository nos. CCDC-100476 (PTX-C) and -100463 (*trans*-PTX). Copies of the data can be obtained by E-mail from deposit@ccdc.cam.ac.uk.

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