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A Stereoselective Synthesis of *dl*-Pumiliotoxin C[1]

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dl-Pumiliotoxin C (**1**) was stereoselectively synthesized *via* 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**) which was prepared in two routes. The Diels–Alder reaction of 1,3-bis(trimethylsiloxy)-5-methylcyclohexa-1,3-diene (**6**) with acrylonitrile gave the cycloadducts (**7**) from which *anti*-8-methyl-*exo*-2-cyanobicyclo[2.2.2]oct-5-en-1-ol (**2**) was obtained in four steps. Treatment of the compound (**2**) with acid gave the keto-lactam (**5**). The Diels–Alder reaction of 1,3-bis(trimethylsiloxy)-1,3-butadiene (**11**) with ethyl crotonate furnished the adduct (**12**) from which the keto-lactam (**5**) was obtained *via* the compound (**19**) in seven steps. Reduction of the carbonyl group at the C_7 position and introduction of the *n*-propyl group at the C_2 position of the keto-lactam (**5**) gave *dl*-pumiliotoxin C.

Keywords——alkaloid; pumiliotoxin C; 5-methyl-2-propyldecahydroquinoline; nurve-muscle activity; stereoselective synthesis; Diels–Alder reaction; 1,3-dioxygenated-1,3-dienes

Structural elucidations and pharmacologies of the toxic alkaloids isolated from the colorful Central American arrow poison frogs have been extensively studied during the past years.[3–9] The pioneering studies of Witkop and his co-workers on the toxic alkaloids from the skin extracts of the arrow poison frogs, *Dendrobates pumilio*[3] and *D. auratus*[4,5] have led to the isolation of pumiliotoxin A, B, and C with high toxic activities. The structure possessing a novel *cis*-decahydroquinoline skeleton and the relative configuration of pumiliotoxine C (**1**) were first presented on the basis of a single crystal X-ray analysis of its hydrochloride in 1969.[3] There had been, however, some confusions on its absolute configuration in the literatures and the configurations (2*S*, 5*R*, 9*R*, and 10*S*) were unambiguously established in 1977 by another single crystal X-ray analysis[10] and its total synthesis.[11e] Recent investigations of the toxic constituents originated from *Dendrobates histrionicus* collected in Columbia have also resulted in the isolation of three analogs (Alkaloid I, II, and III[10]) of pumiliotoxin C.

1) A preliminary communication of this work appeared in *Tetrahedron Lett.*, **1976**, 3169.
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*
3) J.W. Daly, T. Tokuyama, G. Habermehl, I.L. Karle, and B. Witkop, *Ann.*, **729**, 198 (1969).
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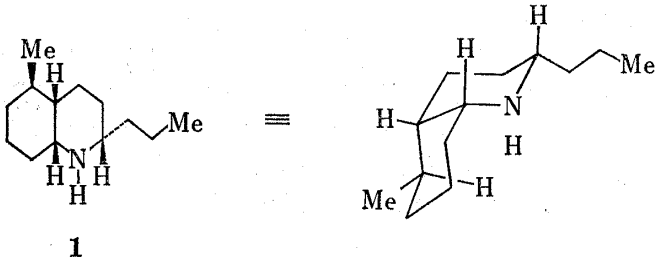
Interest in the synthesis of pumiliotoxin C increased not only due to the nurve-muscle activity of the toxin but for its unusual *cis*-decahydroquinoline structure. The synthetic study of the toxin has been undertaken in five laboratories with a remarkable degree of variety in the synthetic schemes culminating in eight syntheses.[1,11,12] Recently, we have reported a stereoselective synthesis of *dl*-pumiliotoxin C in a preliminary form and we now give a full detail of experiments which have led to the completion of the synthesis.



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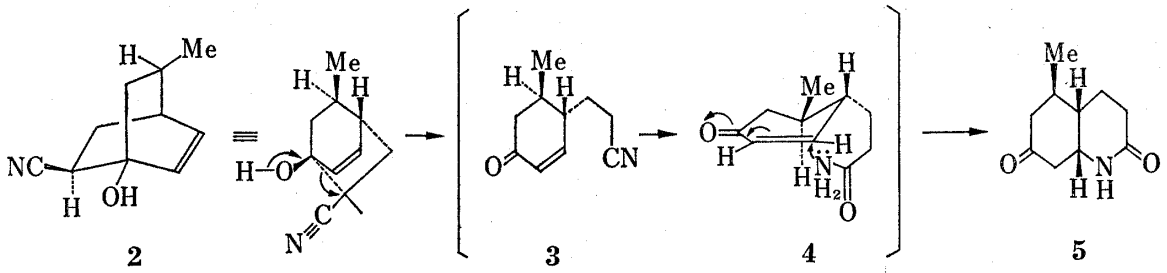
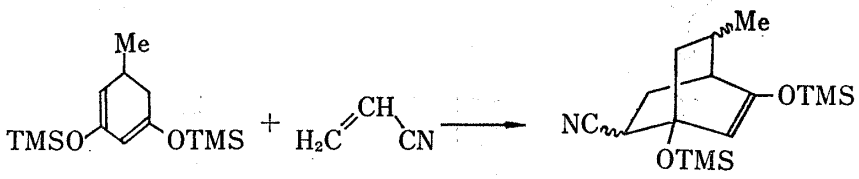


2 3 4 5

Chart 1

Our original plan to synthesize pumiliotoxin C (**1**) was based on that the keto-lactam (**5**) possessing three of four chiral centers of the toxin would be obtained from *anti*-8-methyl-*exo*-2-cyanobicyclo[2.2.2]oct-5-en-1-ol (**2**) through the retroaldol type bond cleavage and the subsequent reactions of hydrolysis of the nitrile (**3**) and the intramolecular Michael type addition of the amide (**4**) as shown in Chart 1.



6 7

8 : R=H
9 : R=$CH_2C_6H_5$ 10

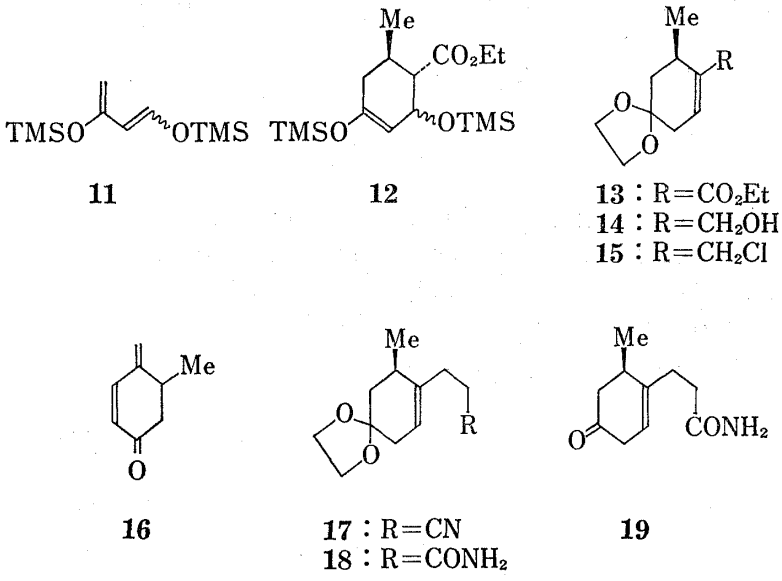
Chart 2

12) A private communication from Dr. K. Abe, Department of Chem., Faculty of Science, Osaka City University.

The starting material (**2**)[13] was prepared from a stereoisomeric mixture (**7**) owing to the configurations of the C_2–CN and C_8–Me groups, which was obtained by the Diels–Alder reaction of 1,3-bis(trimethylsiloxy)-5-methylcyclohexa-1,3-diene (**6**)[13,14] with acrylonitrile according to the procedure described in the preceding paper.[13]

Treatment of the hydroxy-nitrile (**2**) with a 15% perchloric acid solution in acetic acid at 100° yielded 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**) as a sole isolated product. The *cis* ring junction of the product (**5**) is anticipated since the intramolecular ring closure reaction gives usually the *cis* isomer.[15] This estimation was confirmed by the following chemical conversion result. Thus, reaction of the keto-lactam (**5**) with ethylene glycol in boiling benzene in the presence of *p*-toluenesulfonic acid gave the acetal (**8**), which was treated with sodium hydride–benzyl chloride to yield the N-benzyl compound (**9**). Deacetalization of **9** furnished the N-benzyl-ketolactam (**10**) which was identical in all respects with an authentic sample synthesized previously by the authors.[11a]

Much attention is being denoted to the preparation and utilization of functionalized-1,3-dienes in recent years.[16] Our interest in trimethylsiloxy-1,3-dienes for the Diels–Alder reactions prompted us to develop new acyclic 1,3-bis(trimethylsiloxy)-1,3-dienes with high reactivity and regioselectivity.[1,17] Another synthesis of the keto-lactam (**5**) using the acyclic diene, 1,3-bis(trimethylsiloxy)-1,3-butadiene (**11**), is shown in Chart 3. Thus, reaction of 1,3-bis(trimethylsiloxy)-1,3-butadiene (**11**), prepared from sodioacetoacetaldehyde[18] and trimethylchlorosilane, with ethyl crotonate in xylene at 170° afforded the regioselective cyclo-



11 **12** **13** : R=CO_2Et
14 : R=CH_2OH
15 : R=CH_2Cl

16 **17** : R=CN
18 : R=$CONH_2$ **19**

Chart 3

13) T. Ibuka, Y. Mori, T. Aoyama, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **26**, 456 (1978).
14) Other synthetic methods for 1,3-bis(trimethylsiloxy)cyclohexa-1,3-dienes: see *a*) S. Torkelson and C. Ainsworth, *Synthesis*, **1977**, 431; *b*) G.M. Rubottom and D.S. Krueger, *Tetrahedron Lett.*, **1977**, 611.
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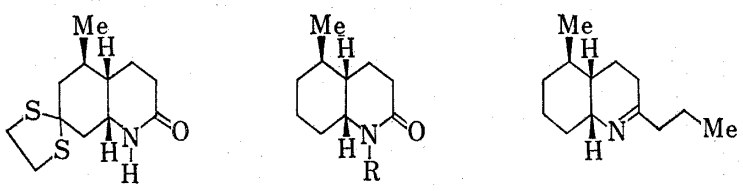
adduct (**12**) as a single product in 80% yield and no regioisomeric adduct was detected in the reaction product. The adduct (**12**) was converted into the ketal-ester (**13**) by refluxing with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid in 87% yield, which was reduced with lithium aluminum hydride to give the allyl alcohol (**14**). Treatment of the allyl alcohol (**14**) with *n*-butyllithium in tetrahydrofuran at −78°, followed by reaction with *p*-toluenesulfonyl chloride[19] at 0° gave the allyl chloride (**15**) in 59% overall yield. The allyl chloride (**15**) was unstable and it changed readily to the dienone (**16**) when kept on standing at room temperature. Cyanomethylenation of the allyl chloride (**15**) with cyanomethylcopper[20] furnished the γ,δ-unsaturated nitrile (**17**) in 80% yield. Reaction of the nitrile (**17**) with 30% hydrogen peroxide in methanolic sodium hydroxide gave the corresponding amide (**18**) which was treated with 1% hydrochloric acid to provide the γ,δ-unsaturated keto-amide (**19**) in 70% overall yield. No migration of the double bond to the α,β-position of the carbonyl group was observed under this acidic condition as can be seen from the infrared spectrum (IR; 1707 cm^{-1}, saturated ketone) and the nuclear magnetic resonance spectrum (NMR; δ 5.44, 1H, triplet, J=3.5 Hz, olefinic proton) of **19**. Treatment of the keto-amide (**19**) with borontrifluoride etherate or conc. hydrochloric acid at 0° yielded 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**) in *ca.* 30% yield. Although the optimum condition for this ring closure reaction was not settled, treatment of the amide (**19**) with sodium methoxide in refluxing methanol resulted in a more satisfactory yield (63%) of the keto-lactam (**5**) a sa single product. The presence of other possible stereoisomer of **5** was not revealed by the spectroscopic and chromatographic methods, suggesting that the cyclization of the keto-amide (**19**) would proceed *via* the intermediate (**4**).



20 **21** : R=H; **22** : R=COC_3H_7 **23**

Chart 4

Next, reduction of the C_7 carbonyl group and introduction of the *n*-propyl side chain at the C_2 position using the keto-lactam (**5**) were investigated. Thus, the keto-lactam (**5**) was converted to 5β-methyl-*cis*-decahydroquinoline-2-one (**21**) *via* the thioacetal (**20**) in 76% yield by the procedure previously reported.[11a] Treatment of **21** with sodium hydride–butyryl chloride in tetrahydrofuran–hexamethylphosphoric triamide (HMPA) gave the N-butyryl-lactam (**22**) in a high yield. Heating of **22** with CaO[21] on an open flame furnished the imine (**23**) and the recovered lactam (**21**) in 18% and 50% yields, respectively. Finally, catalytic hydrogenation of the imine (**23**) in 2 N hydrochloric acid over PtO_2 gave *dl*-pumiliotoxin C. *dl*-Pumiliotoxin C hydrochloride (mp 232°) derived from the free base was identical (IR, NMR, gas chromatography, and mixed melting point) with an authentic sample previously synthesized by the authors.[11a]

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. IR spectra were recorded on a Hitachi EPI-S spectrometer in $CHCl_3$. Unless otherwise specified, NMR

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spectra were measured on a Varian A-60 or HA-100D spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The abbreviations, s, d, t, q, and m in the NMR spectra signify singlet, doublet, triplet, quartet, and multiplet and the coupling constant (J) is measured in Hz. Mass spectra (MS) were recorded at 80 eV on a Hitachi RMU-6D mass spectrometer and abbreviation M^+ signifies a molecular ion. Column chromatographies were performed on silica gel (Mallinckrodt silicic acid, 100 mesh). Silica gel PF_{254} (Merck) or aluminum oxide PF_{254} (Merck) were used for preparative thin-layer chromatographies (TLC). Evaporative bulb to bulb distillations were carried out using a Büchi Kugelrohrofen distillation apparatus (Type KR) at the oven temperature and pressure indicated. Unless otherwise specified, the extracts were dried over anhydrous magnesium sulfate.

5β-Methyl-*cis*-decahydroquinoline-2,7-dione (5)——To a solution of 165 mg of the hydroxy-nitrile (**2**)[13] in 2 ml of acetic acid was added 0.4 ml of 70% $HClO_4$, and the mixture was heated at 100° for 5 hr. After cooling, the reaction mixture was made alkaline with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 80 mg of a crystalline solid. Recrystallization of the solid from acetone gave 67 mg of 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**) as colorless prisms, mp 197°. IR ν_{max} cm^{-1}: 3390 (NH), 1716 (CO), and 1660 (lactam CO). NMR δ: 1.07 (3H, m, C_5–CH_3), 4.02 (1H, m, C_{8a}–H), and 6.60—7.01 (1H, broad s, NH). MS *m/e*: 181 (M^+) and 124 (base peak). *Anal.* Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.11; H, 8.28; N, 7.88.

The Ketal-lactam (8)——To a solution of 50 mg of the keto-lactam (**5**) in 45 ml of dry benzene were added 1.0 ml of ethylene glycol and 15 mg of *p*-toluenesulfonic acid. The mixture was refluxed for 10 hr while water was azeotropically removed by a Dien–Stark apparatus. After cooling, the solvent was evaporated under reduced pressure. The residue was made alkaline with a 5% aq. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave a crystalline solid. Recrystallization of the solid from ether gave 44 mg of the ketal-lactam (**8**) as colorless needles, mp 166°. IR ν_{max} cm^{-1}: 3400 (NH) and 1650 (lactam CO). NMR δ: 0.97 (3H, d, J=6 Hz, C_5–CH_3), 3.65—4.00 (1H, m, C_{8a}–H), 3.91 (4H, s, $-OCH_2CH_2O-$), and 5.93—6.36 (1H, broad s, NH). MS *m/e*: 225 (M^+) and 113 (base peak). *Anal.* Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.71; H, 8.37; N, 6.30.

The N-Benzyl-ketal-lactam (9)——To a solution of 41 mg of the ketal-lactam (**8**) in 30 ml of dry benzene was added 170 mg of NaH (50% suspension in mineral oil). After the mixture was refluxed for 2 hr under argon, 446 mg of benzyl chloride was added, and the mixture was refluxed for 3.5 hr. Excess NaH was decomposed with water under ice cooling and the mixture was extracted with ether. The extract was washed with water, dried and evaporated. The residual oil was purified by preparative TLC (silica gel) to give 44 mg of the N-benzyl-ketal-lactam (**9**) as a colorless oil. IR ν_{max} cm^{-1}: 1625 (lactam CO). NMR δ: 1.03 (3H, d, J=6 Hz, C_5–CH_3), 3.43—3.86 (1H, m, C_{8a}–H), 3.88 (4H, s, $-OCH_2CH_2O-$), 4.11 and 5.22 (each 1H, d, J=15 Hz, benzylic protons), and 7.28 (5H, s, aromatic protons). MS *m/e*: 315 (M^+) and 91 (base peak).

The N-Benzyl-keto-lactam (10)——To a solution of 40 mg of the N-benzyl-ketal-lactam (**9**) in 1.5 ml of methanol was added 0.75 ml of 5% HCl and the mixture was warmed at 40° for 3.5 hr. After cooling, the reaction mixture was extracted with ether. The extract was washed with water, dried and evaporated to leave 40 mg of an oil. Purification of the oil by preparative TLC (silica gel) gave a crystalline solid. Recrystallization of the solid from ether gave 31 mg of the N-benzyl-keto-lactam (**10**) as colorless pillars, mp 85°. IR ν_{max} cm^{-1}: 1711 (CO) and 1631 (lactam CO). NMR δ: 0.92 (3H, d, J=7 Hz, C_5–CH_3), 3.47—3.93 (1H, m, C_{8a}–H), 3.99 and 5.26 (each 1H, d, J=15 Hz, benzylic protons), and 7.24 (5H, s, aromatic protons). MS *m/e*: 271 (M^+) and 91 (base peak). *Anal.* Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.27; H, 7.90; N, 5.24. This N-benzyl-keto-lactam (**10**) was identical in all respects with an authentic sample.[11a]

1,3-Bis(trimethylsiloxy)-1,3-butadiene (11)——Anhydrous $ZnCl_2$ (2.0 g) was added to 98 g of dry triethylamine, and the mixture was stirred for 30 min at room temperature. To the above mixture were added 35 g of sodioacetoacetaldehyde,[18] 500 ml of dry ether, and 104 g of trimethylchlorosilane. The mixture was stirred at 2° for 12 hr and then at room temperature for 36 hr. To the mixture was added 500 ml of dry ether, and the mixture was filtered. The filtrate was concentrated at a pressure of 5 mmHg below 50° to give a brown oil. Distillation of the oil gave 30 g of 1,3-bis(trimethylsiloxy)-1,3-butadiene (**11**) as a colorless oil, bp 58° (4 mmHg). The diene (**11**) was a diastereoisomeric mixture owing to (1*E*)-1,3-bis(trimethylsiloxy)-1,3-butadiene (9 parts) and (1*Z*)-1,3-bis(trimethylsiloxy)-1,3-butadiene (1 part) judging from its NMR spectrum. NMR δ: (1*E*)-diene, 0.20—0.22 (18H, $Me_3Si\times2$), 4.08 (2H, broad s, C_4–H), 5.53 (1H, d, J=11.5 Hz, C_2–H), and 6.74 (1H, d, J=11.5 Hz, C_1–H); (1*Z*)-diene, 0.20—0.22 [Me_3Si groups, overlapped with the signals of (1*E*)-diene], 4.33 (2H, broad s, C_4–H), 4.73 (1H, d of d, J=7.0 and 1.5 Hz, C_2–H), and 6.22 (1H, d, J=7.0 Hz, C_1–H). MS *m/e*: 230 (M^+) and 73 (base peak). *Anal.* Calcd. for $C_{10}H_{22}O_2Si_2$: C, 52.12; H, 9.62. Found: C, 52.41; H, 9.71.

The Cycloadduct (12)——A mixture of 2.3 g of the diene (**11**), 1.7 g of ethyl crotonate, and 4 ml of dry xylene was heated under argon in a sealed tube at 170° for 48 hr. The reaction mixture was concentrated under reduced pressure to give a pale yellow oil. Distillation of the oil gave 3.0 g of the gas chromatographically pure cycloadduct (**12**) as a colorless oil, bp 143° (5 mmHg). GC t_R (1.5% SE-30 glass column, 2 m, 150°): 9 min. Because of its highly moisture-sensitive property, the adduct (**12**) was directly used for the next step.

The Ketal-ester (13)——To a solution of 3.0 g of the cycloadduct (**12**) in 50 ml of benzene were added 1.08 g of ethylene glycol and 0.1 g of *p*-toluenesulfonic acid, and the mixture was refluxed for 10 hr. After

cooling, the mixture was concentrated under reduced pressure, made alkaline with a 5% aq. $NaHCO_3$ solution and extracted with ether. The extract was washed with water, dried and evaporated to give 2.9 g of an oily residue. The oil in pentane–$CHCl_3$ (1:1) was chromatographed on a silica gel column (3×20 cm) and the column was eluted with the same solvent. Concentration of the eluent gave an oil which was distilled to afford 2.0 g of the ketal-ester (**13**) as a colorless oil, bp 119° (5 mmHg). IR ν_{max} cm^{-1}: 1702 (CO). NMR δ: 1.20 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 1.28 (3H, t, J=7 Hz, –$CH_2C\underline{H}_3$), 3.97 (4H, s, –OCH_2CH_2O–), 4.19 (2H, q, J=7 Hz, –$C\underline{H}_2CH_3$), and 6.75 (1H, d of t, J=1 and 4 Hz, olefinic proton). MS *m/e*: 226 (M^+) and 86 (base peak). *Anal.* Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.29; H, 8.19.

The Allyl Alcohol (14)——To a suspension of 0.76 g of $LiAlH_4$ in 50 ml of dry ether was added a solution of 4.52 g of the ketal-ester (**13**) in 10 ml of dry ether. The mixture was stirred at 0° for 4 hr. The excess reagent was decomposed with wet ether, and the ether layer was washed with water, dried and evaporated to leave an oil. Distillation of the oil gave 2.96 g of the allyl alcohol (**14**) as a colorless oil, bp 128° (6 mmHg). IR ν_{max} cm^{-1}: 3550 and 3450 (OH). NMR δ: 1.10 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 2.07 (1H, s, OH, exchangeable with D_2O), 3.98 (4H, s, –OCH_2CH_2O–), 4.09 (2H, broad s, –CH_2O–), and 5.60 (1H, m, olefinic proton). MS *m/e*: 184 (M^+) and 86 (base peak).

The Allyl Chloride (15)——To a solution of 5.0 g of the allyl alcohol (**14**) in 10 ml of dry THF under argon were added at −78° 16 ml of a 1.8 M hexane solution of *n*-butyllithium and 6 ml of HMPA, and then a solution of 5.0 g of *p*-toluenesulfonyl chloride in 30 ml of dry ether. The mixture was stirred at −78° for 1 hr and then 12 hr at 0°. The reaction mixture was poured into ice-water and extracted with ether. The extract was washed with a 5% aq. $NaHCO_3$ solution and water, dried and evaporated under reduced pressure (below 30°). The oily residue in CH_2Cl_2 was chromatographed on a silica gel column (9×11 cm) and the column was eluted with CH_2Cl_2. The eluent was concentrated under reduced pressure to give 4.0 g of the allyl chloride (**15**) as a colorless oil. IR ν_{max} cm^{-1}: 1260, 1125, 1057, 1000, and 950. NMR δ: 1.14 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 3.97 (4H, s, –OCH_2CH_2O–), 3.96 and 4.23 (each 1H, d, J=11 Hz, –CH_2Cl), and 5.71 (1H, m, olefinic proton). MS *m/e*: 202 (M^+) and 86 (base peak).

The Dienone (16)——After being kept on standing at room temperature for 3 days, distillation of the allyl chloride (**15**) (3.0 g) gave 430 mg of the dienone (**16**) as a colorless oil, bp 75° (oven temperature of a Büchi Kugelrohrofen apparatus) at 15 mmHg. IR ν_{max} cm^{-1}: 1668 (CO). NMR δ: 1.22 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 5.37 (2H, t, J=1 Hz, *exo*-methylene protons), 5.93 (1H, t of d, J=1 and 10 Hz, C_3–H), and 7.10 (1H, d, J=10 Hz, C_2–H). MS *m/e*: 122 (M^+).

The γ,δ-Unsaturated Nitrile (17)——To 12 ml of 1.8 M hexane solution of *n*-butyllithium was added a solution of 0.82 g of acetonitrile in 10 ml of dry THF at −78° with stirring under argon. After stirring for 1 hr at −78°, the temperature of the mixture was raised up to −30° and 3.8 g of cuprous iodide was added. To a brick-colored solution of cyanomethylcopper was added a solution of 200 mg of the allyl chloride (**15**) in 5 ml of dry THF. The reaction mixture was stirred for 1.5 hr at −30° and then treated with aqueous ammonium chloride, and the solution was extracted with ether. The extract was washed with water, dried and evaporated to leave 210 mg of an oil, which was purified by preparative TLC [silica gel, developed with benzene–$CHCl_3$ (3:2)] to give 165 mg of the γ,δ-unsaturated nitrile (**17**) as a colorless oil. IR ν_{max} cm^{-1}: 2250 (CN). NMR δ: 1.09 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 3.95 (4H, s, –OCH_2CH_2O–), and 5.40 (1H, m, olefinic proton). MS *m/e*: 207 (M^+) and 86 (base peak). An analytical sample was obtained by bulb to bulb distillation, bp 108° (oven temperature) at 2 mmHg. *Anal.* Calcd. for $C_{11}H_{15}NO$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.81; H, 8.41; N, 6.48.

The Amide (18)——To a stirring solution of 93 mg of the nitrile (**17**) in 0.8 ml of methanol were added 0.4 ml of 5 M NaOH and 0.9 ml of 30% H_2O_2 at 0°. After stirring for 1 hr at 0°, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to give 91 mg of an oil. Purification of the oil by preparative TLC [silica gel, developed with acetone–$CHCl_3$ (1:1)] gave a crystalline mass. Recrystallization of the mass from ether gave 81 mg of the amide (**18**) as colorless plates, mp 97°. IR ν_{max} cm^{-1}: 3500, 3420 (NH_2), and 1680 (amide CO). NMR δ: 1.09 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 3.97 (4H, s, –OCH_2CH_2O–), 5.35 (1H, m, olefinic proton), and 5.70—6.43 (2H, broad s, NH_2). MS *m/e*: 225 (M^+) and 86 (base peak). *Anal.* Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.70; H, 8.46; N, 6.26.

The Keto-amide (19)——To a solution of 1.0 g of the amide (**18**) in 2.5 ml of acetone was added 2.0 ml of 1% HCl, and the mixture was allowed to stand at room temperature for 12 hr. The reaction mixture was concentrated under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave a crystalline solid. Recrystallization of the solid from ether gave 700 mg of the keto-amide (**19**) as colorless prisms, mp 69°. IR ν_{max} cm^{-1}: 3500, 3400 (NH_2), 1707 (CO), and 1680 (amide CO). NMR δ: 1.05 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 5.44 (1H, t, J=3.5 Hz, olefinic proton), and 5.50—6.25 (2H, broad s, NH_2). MS (M^+) *m/e*: Calcd. for $C_{10}H_{15}NO_2$: 181.1103. Found: 181.1103.

5β-Methyl-*cis*-decahydroquinoline-2,7-dione (5)——i) To a solution of 65 mg of the keto-amide (**19**) in 0.5 ml of dry methanol was added 1.5 ml of borontrifluoride etherate and the mixture was allowed to stand at room temperature for 3 hr. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 39 mg of a crystalline mass.

Recrystallization of the mass from acetone gave 20 mg of 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**), mp 197°, whose spectral data (IR and NMR) were identical with those of an authentic sample.[11a)]

ii) To a solution of 695 mg of the keto-amide (**19**) in 6 ml of dry methanol was added 25 mg of sodium methoxide and the mixture was refluxed for 40 min under argon. After cooling, the solvent was removed under reduced pressure, and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 690 mg of a crystalline solid. Recrystallization of the solid from acetone gave 438 mg of 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**), mp 197°. This dione (**5**) was identified with an authentic sample[11a)] by comparison of IR and NMR spectra.

The Thioacetal-lactam (20)——To a solution of 2.7 g of 5β-methyl-*cis*-decahydroquinoline-2,7-dione (**5**) in 100 ml of CH_2Cl_2 were added 2.5 ml of ethanedithiol and 1.9 ml of borontrifluoride etherate. The mixture was allowed to stand at room temperature for 42 hr and the mixture was washed with a 5% aq. NaOH solution and water. The solvent was evaporated to leave a crystalline solid. Recrystallization of the solid from ether–acetone (3:1) gave 3.6 g of the thioacetal-lactam (**20**) as colorless needles, mp 156°. IR ν_{max} cm^{-1}: 3400 (NH) and 1657 (lactam CO). NMR δ: 0.98 (3H, d, J=6 Hz, C_5–CH_3), 3.27 (4H, s, –SCH_2CH_2S–), 3.78 (1H, m, C_{8a}–H), and 5.61—6.03 (1H, broad s, NH). *Anal.* Calcd. for $C_{12}H_{19}NOS_2$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.04; H, 7.49; N, 5.42.

5β-Methyl-*cis*-decahydroquinoline-2-one (21)——To a solution of 3.6 g of the thioacetal-lactam (**20**) in 180 ml of ethanol was added 40 g of Raney W-2 nickel and the mixture was refluxed for 24 hr with stirring. After cooling, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was extracted with $CHCl_3$. The extract was washed with 1% hydrochloric acid, water, dried, and evaporated to leave a crystalline solid. Recrystallization of the solid from ether gave 1.9 g of 5β-methyl-*cis*-decahydroquinoline-2-one (**21**) as colorless plates, mp 152°. IR ν_{max} cm^{-1}: 3440 (NH) and 1650 (lactam CO). NMR δ: 0.92 (3H, d, J=6 Hz, C_5–CH_3), 3.63 (1H, m, C_{8a}–H), and 6.10—6.62 (1H, broad s, NH). MS *m/e*: 167 (M^+) and 124 (base peak). *Anal.* Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.99; H, 10.48; N, 8.43.

N-Butyryl-5β-methyl-*cis*-decahydroquinoline-2-one (22)——To a stirred suspension of 285 mg of NaH in 80 ml of dry THF was added 1.0 g of 5β-methyl-*cis*-decahydroquinoline-2-one (**21**) and the mixture was refluxed for 2 hr under argon. To the above mixture were added 0.95 g of butyryl chloride and 1.07 g of HMPA, and the mixture was refluxed for 3 hr. Excess NaH was decomposed with water under ice cooling and the mixture was extracted with $CHCl_3$. The extract was washed successively with a 5% aq. $NaHCO_3$ solution, 1% HCl, water, dried, and evaporated. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (4×26 cm) and the column was eluted with $CHCl_3$ to give 1.1 g of N-butyryl-5β-methyl-*cis*-decahydroquinoline-2-one (**22**) as a colorless oil. IR ν_{max} cm^{-1}: 1665 (imide CO). NMR δ: 0.93 (3H, t, J= 7 Hz, –$CH_2C\underline{H}_3$), 1.12 (3H, d, J=7 Hz, C_5–CH_3), and 4.37—4.77 (1H, m, C_{8a}–H). MS *m/e*: 237 (M^+) and 167 (base peak). An analytical sample was obtained by bulb to bulb distillation, bp 150° (oven temperature) at 1 mmHg. *Anal.* Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.94; H, 9.99; N, 6.00.

The Imine (23)——A mixture of 387 mg of the N-butyryl-lactam (**22**) and 400 mg of CaO was heated at 250—300° for 2 hr under argon. After cooling, the reaction mixture was acidified with 3.5% HCl and extracted with ether. The ether extract was washed with water, dried and evaporated to leave a crystalline mass. Recrystallization of the mass from ether gave 136 mg of 5β-methyl-*cis*-decahydroquinoline-2-one (**21**), mp 152°, which was identical in all respects with an authentic sample.[11a)] The aqueous acidic layer was made alkaline with 3% NH_4OH and extracted with ether. The extract was dried and evaporated to leave 170 mg of a pale yellow oil. Purification of the oil by preparative TLC (aluminum oxide, developed with $CHCl_3$) gave 57 mg of the imine (**23**) as a colorless oil. IR ν_{max} cm^{-1}: 1655 (C=N). NMR δ: 3.47 (1H, m, C_{8a}–H). MS *m/e*: 193 (M^+) and 122 (base peak).

***dl*-Pumiliotoxin C (1)**——A solution of 57 mg of the imine (**23**) in 5 ml of 2 N HCl was catalytically hydrogenated over 50 mg of PtO_2 at room temperature and atmospheric pressure for 7 hr. The catalyst was filtered off and the filtrate was made alkaline with 28% NH_4OH under ice cooling. The solution was extracted with CH_2Cl_2. The extract was dried and acidified with 1 ml of methanol saturated with hydrogen chloride. Evaporation of the solvent gave a crystalline residue. The residue in $CHCl_3$ was chromatographed on a silica gel column (0.5×1 cm) and the column was eluted with the same solvent. The solvent of the eluent was evaporated to give 67 mg of *dl*-pumiliotoxin C (**1**) hydrochloride. Recrystallization of the base hydrochloride from ethanol–ethyl acetate (1:3) gave *dl*-pumiliotoxin C hydrochloride as colorless needles, mp 232° (in a sealed capillary tube). IR ν_{max} cm^{-1}: 3600—3200 (NH), 1582, 1465, 1420, 962, and 942. NMR (100 MHz) δ: 0.89 (3H, d, J=6 Hz, C_5–CH_3), 0.92 (3H, t, J=6 Hz, –$CH_2C\underline{H}_3$), 2.97 (1H, broad s, $W_{1/2}$=15 Hz, C_2–H). The IR and NMR spectra of the synthetic *dl*-pumiliotoxin C hydrochloride were identical with those of the authentic *dl*-pumiliotoxin C hydrochloride previously synthesized by the authors.[11a)] *Anal.* Calcd. for $C_{13}H_{26}ClN$: C, 67.36; H, 11.31; N, 6.04. Found: C, 67.07; H, 11.32; N, 6.02.

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