Regioselective Haller–Bauer Cleavage in Tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,10-dione. A Total Synthesis of (±)-Pumiliotoxin C

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The toxic secretions of the neotropical "poison dart" frogs of *Dendrobates pumilio* and *Dendrobates auratus*, native to South and Central America are a rich source of diverse *cis*-decahydroquinoline based alkaloids.[1a] Pumiliotoxin C (**1**) is one of the simpler, relatively nontoxic, prototype members of this alkaloid family.[1a-e] In view of the interesting structural and stereochemical features, promising pharmacological activity profile, and scarce availability, these alkaloids have aroused a great deal of synthetic interest.[2] Indeed, **1** has been a favorite target of synthetic efforts in recent years and over a dozen syntheses in racemic[2a-c,e-h,j-l,n-p] as well as chiral[2d,i,m] form have been accomplished. Our interest in **1** emanated from our recently delineated strategy[3] for quick access to *cis*-hydrindanes through base mediated Haller–Bauer cleavage in tricyclo[5.2.1.0^{2,6}]decan-10-ones. We felt that this approach was readily adaptable for a concise synthesis of pumiliotoxin C (**1**) and related alkaloids and the present note records the successful attainment of this objective.

We have previously reported[3] that refluxing the readily available tricyclic dione **2**[4] with 30% aqueous NaOH in benzene and esterification furnished the *cis*-hydrindanone **3** *via* Haller–Bauer cleavage[5] and double bond isomerization to the conjugated position. However, we now find that when **2** was treated with 1% aqueous NaOH–benzene at room temperature for a prolonged period (24 h) and the product esterified with diazomethane, a 7:3 mixture of bicyclic esters **4** and **5** is obtained *via* regioselective Haller–Bauer cleavage. Pleasingly, double bond isomerization did not take place under these conditions but some epimerization of the ester group was encountered. From the practical point of view, the keto esters **4** and **5** were more conveniently separated and characterized as ketals **6** and **7**, respectively. The stereochemistry of the ester moiety in **4** and **5** was secured through catalytic hydrogenation of **7** to furnish a product which was identical (^{1}H and ^{13}C NMR) with that obtained from hydrogenation of the ketal of **3**. It is known that hydrogenation of *cis*-hydrindanes occurs preferentially from the *exo*-face; thus the reduction product of **3** and hence **5** has an *endo*-ester group.

The ester functionality in **6**, with correct stereochemistry at the three contiguous stereogenic centers for the synthesis of **1**, was first transformed to a methyl group. This transformation unexpectedly proved to be quite troublesome. However, a solution was found through LAH reduction to ketal alcohol **8** followed by conversion to the corresponding bromide and catalytic hydrogenation to **9**. Reductive removal of bromine in **9** was accomplished with $NaBH_3CN$ in HMPA[6] and aqueous acid workup furnished the *cis*-hydrindanone **10**, the key precursor of **1**. Beckmann rearrangement of **10** to **11** was conveniently accomplished *via* the oxime. The bicyclic lactam **11** was elaborated in three steps to **1** through the intermediacy of lactim ether **12** following a protocol similar to that described in the literature.[2e] The sample of **1** obtained by us was stereochemically homogenous and was characterized as its hydrochloride by comparison (^{1}H and ^{13}C NMR) with the literature data[2] for pumiliotoxin C hydrochloride.

In summary, we have achieved a short, straightforward synthesis of **1** which is amenable to scaleup and adaptable for the synthesis of other members of the *cis*-decahydroquinoline based natural products.

Experimental Section

2-*exo* and *endo*-Carbomethoxy-7-(ethylenedioxy)bicyclo-[4.3.0]non-3-ene (6 and 7). To a solution of **2** (1.25 g, 7.71 mmol) in benzene (50 mL) was added 20 mL of 1% aqueous NaOH and the mixture was stirred at rt for 24 h. The benzene layer was separated and the aqueous layer was acidified (pH ≃ 2) with dilute HCl. Extraction of the aqueous layer with ethyl acetate (3 × 50 mL), washing with brine, drying over Na_2SO_4, and removal of solvent furnished a mixture of acids. To a solution of a mixture of acids in dry ether was added an excess of distilled ethereal diazomethane at 0 °C until the yellow color persisted. After 30 min, excess diazomethane was destroyed by two drops of glacial acetic acid and the residue after the removal of solvent was filtered through a silica gel column (20 g, elution with 25% ethyl acetate–hexane) to furnish a mixture of esters **4** and **5** (980 mg, 65%).

To a solution of the above mixture of esters **4** and **5** (950 mg, 5.05 mmol) in benzene (100 mL) was added ethylene glycol (0.2 mL, 3.6 mmol) and a catalytic amount of *p*-TSA and the mixture was refluxed using a Dean–Stark water separator for 3 h. The cooled reaction mixture was washed with aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. Removal of solvent furnished a mixture of ketals **6** and **7**, which was separated on a silica gel column (20 g) eluting with 10% ethyl acetate–hexane. **6**: IR (neat) 3000, 1740, 1460, 1200 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89–5.79 (m, 1H), 5.67–5.59 (m, 1H), 3.91–3.85 (m, 4H), 3.68 (s, 3H), 2.98–2.91 (m, 1H), 2.15–1.35 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 128.9, 124.4, 116.6, 64.9, 64.8, 51.6, 49.8, 47.8, 40.4, 36.0, 27.8, 24.2. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.47; H, 7.60. **7**: IR (neat): 3000, 1740, 1460, 1200 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.92–5.83 (m, 1H), 5.72–5.64 (m, 1H), 3.91–3.89 (m, 4H), 3.69 (s, 3H), 2.71–2.59 (m, 2H), 2.20–1.01 (m, 7H); ^{13}C NMR (50

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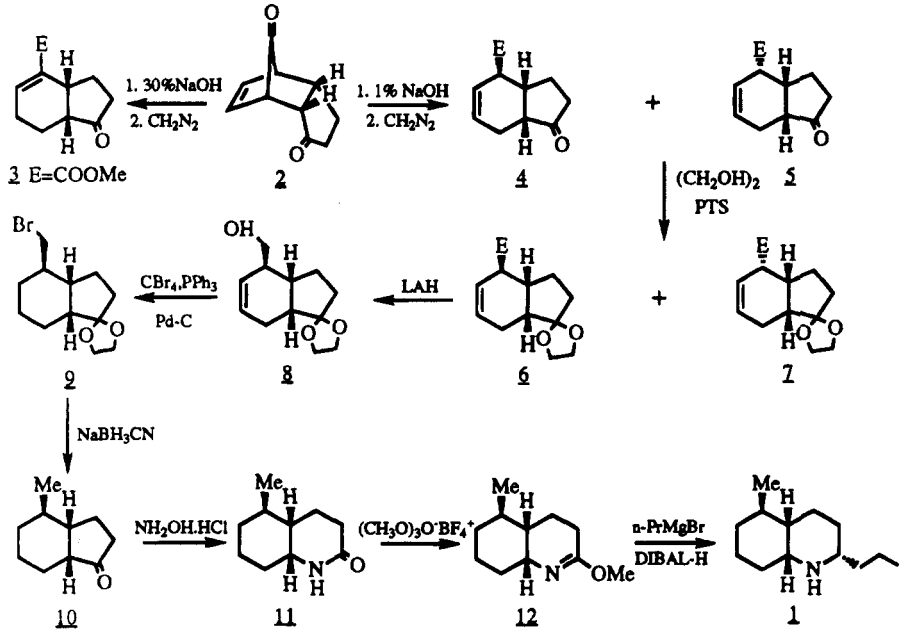
Scheme 1



MHz, $CDCl_3$) δ 174.8, 128.3, 122.6, 118.8, 64.8, 64.0, 51.9, 43.3, 40.1, 36.5, 33.4, 26.4, 21.5. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.42; H, 7.58.

2-*exo*-(Hydroxymethyl)-7-(ethylenedioxy)bicyclo[4.3.0]-non-3-ene (8). A solution of **6** (680 mg, 2.85 mmol) in dry THF (30 mL) and LAH (162 mg, 4.27 mmol) was refluxed overnight. The reaction mixture was quenched with saturated Na_2SO_4, extracted with ethyl acetate (3 × 50 mL), washed with brine, and dried over anhydrous Na_2SO_4 to furnish alcohol **8** (450 mg, 75%): IR (neat) 3300, 3000, 1300, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.85–5.78 (m, 1H), 5.62–5.56 (m, 1H), 3.95–3.81 (m, 4H), 3.72–3.64 (m, 1H), 3.54–3.46 (m, 1H), 2.20–1.20 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.8, 127.9, 117.0, 65.4, 64.9, 64.7, 48.2, 46.7, 40.3, 36.3, 27.4, 24.4. Anal. Calcd for $C_{13}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.48; H, 8.60.

2-*exo*-(Bromomethyl)-7-(ethylenedioxy)bicyclo[4.3.0]-nonane (9). To a solution of **8** (450 mg, 2.14 mmol) in dry CH_2Cl_2 (10 mL) was added PPh_3 (1.1 g, 4.28 mmol) and CBr_4 (1.4 g, 4.28 mmol) at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with brine, and dried over anhydrous Na_2SO_4. Removal of solvent and filtration through a silica gel column (10 g) furnished the unsaturated bromo ketal (400 mg, 70%): IR (neat) 3000, 1450, 1300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.85–5.78 (m, 1H), 5.62–5.52 (m, 1H), 3.90–3.50 (m, 4H), 3.36–3.29 (m, 2H), 2.40–1.20 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.8, 128.5, 116.8, 64.9, 64.8, 48.0, 45.6, 42.2, 37.3, 36.1, 26.8, 24.4. Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.76; H, 6.27. Found: C, 52.69; H, 6.25.

A solution of the above unsaturated bromomethyl ketal (400 mg, 1.46 mmol) in dry ethyl acetate (5 mL) was stirred at rt under a hydrogen atmosphere with 10% Pd/C (5 mg). After 10 min, the catalyst was filtered off and solvent removed to furnish saturated bromo ketal **9** (360 mg, 90%): IR (neat) 2900, 1450, 1300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.98–3.82 (m, 4H), 3.55–3.48 (m, 1H), 3.31–3.23 (m, 1H), 2.02–1.02 (m, 13H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 117.0, 65.0, 64.8, 52.5, 45.7, 45.5, 38.6, 35.9, 30.9, 26.3, 25.4, 24.2. Anal. Calcd for $C_{12}H_{19}O_2Br$: C, 52.38; H, 6.96. Found: C, 52.30; H, 6.92.

2-*exo*-Methylbicyclo[4.3.0]nona-7-one (10). To a solution of **9** (360 mg, 1.3 mmol) in dry HMPA (5 mL) was added $NaBH_3CN$ (163 mg, 2.6 mmol) and the mixture was stirred at 80 °C for 4 h. The reaction mixture was diluted with water and extracted with ether (3 × 50 mL). The ethereal extract was washed with dilute HCl and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and filtration through a silica gel column (2 g) furnished **10** (100 mg, 50%): IR (neat) 2930, 1740, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30–1.02 (m, 13H), 0.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 219.7, 50.2, 43.8, 34.7, 33.5, 32.2, 23.4, 22.7(2C), 20.6. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.72; H, 10.50.

2-Aza-7-*exo*-methylbicyclo[4.4.0]deca-3-one (11). A mixture of **10** (100 mg, 0.65 mmol), hydroxylamine hydrochloride (76 mg, 1.1 mmol), NaOAc (98 mg, 6 mmol), and methanol (3 mL) was stirred at rt for 45 min. The residue after evaporation of the solvent was diluted with water and extracted with ether (3 × 15 mL). Removal of ether furnished the crude oxime (115 mg). *p*-Toluenesulfonyl chloride (280 mg, 1.48 mmol) was added portionwise over 10 min to a stirred solution of the crude oxime (115 mg) and NaOH (135 mg, 3.4 mmol) in 10 mL dioxane/water 3:4 at 5 °C. The mixture was stirred at rt for 15 h and dioxane was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with brine. Removal of solvent and crystallization gave lactam **11** (70 mg, 65%): mp 149–150 °C; IR (KBr) 3178, 3074, 2926, 1674, 1479 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 3.65–3.60 (q, 1H), 2.33–2.26 (m, 2H), 2.12–1.95 (m, 1H), 1.79–1.34 (m, 9H), 0.95–0.92 (d, 3H, J = 6.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 52.3, 39.8, 33.7, 31.9, 27.6, 27.3, 23.2, 19.9, 19.3.

***dl*-Pumiliotoxin C (1).** The lactam **11** (30 mg, 0.17 mmol) was added to a stirred mixture of trimethyloxonium tetrafluoroborate (45 mg, 0.3 mmol), *N*-ethyldiisopropylamine (1 drop), and CH_2Cl_2 at 10 °C under N_2. After 1 h the mixture was diluted with CH_2Cl_2 and shaken with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and evaporation of solvent gave the crude lactim ether **12**. A solution of this lactim ether **12** in benzene (5 mL) was added to *n*-propylmagnesium bromide (2 mL, 0.5 mmol) [prepared by propyl bromide (0.2 mL) and magnesium (50 mg in ether)] and refluxed for 6 h. The cooled reaction mixture after dilution with ether was washed with aqueous $NaHCO_3$, dried, and evaporated to give crude imine. The crude imine in dry CH_2Cl_2 was cooled to −78 °C and DIBAL-H (1 equiv) was added under N_2. After 15 min, the reaction was quenched with MeOH and diluted with CH_2Cl_2, washed, and dried. Removal of the solvent and filtration through a silica gel column (500 mg) furnished free pumiliotoxin C (**1**), which for characterization was converted to its hydrochloride with dry HCl in ether and crystallized from 2-propanol/ether to give a white solid (7 mg, 45%): mp 235–238 °C [lit. 238–242 °C];[2e] IR (KBr) 3400, 2530, 1595, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.6 (br s, 1H), 8.3 (br s, 1H), 3.32–3.30 (br d, 1H), 3.12–2.90 (m, 1H), 2.61–1.10 (m, 13H), 0.94–0.92 (d, 3H, J = 6.8 Hz), 0.92–0.90 (d, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 60.1, 58.0, 40.9, 34.9, 34.4, 29.1, 27.3, 25.2, 23.2, 20.7, 19.7, 19.1, 13.7.

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