A Short, Asymmetric Synthesis of (−)-Pumiliotoxin C

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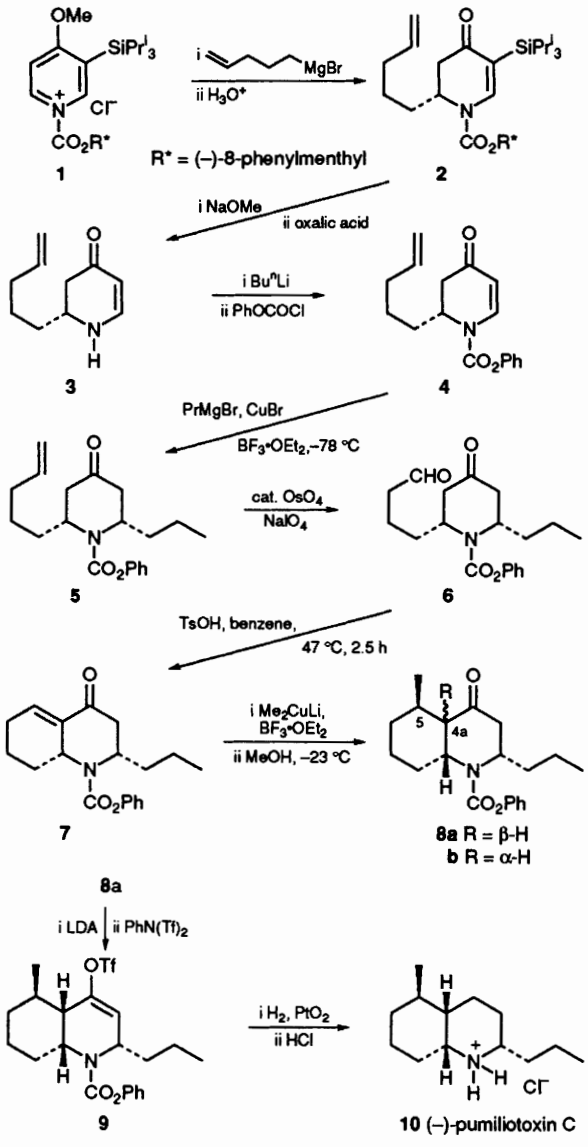
An asymmetric synthesis of (−)-pumiliotoxin C is accomplished in nine steps from 4-methoxy-3-(triisopropylsilyl)pyridine.

Pumiliotoxin C is one of the physiologically active alkaloids found in the skin secretions of neotropical frogs belonging to the family Dendrobatidae.[1] In this communication we report a short, enantioselective synthesis of this alkaloid using a strategy based on our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones.[2]

Reaction of homochiral 1-acylpyridinium salt **1**, prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine[2a] and the chloroformate of (−)-8-phenylmenthol,[3] with 5-(1-pentenyl)magnesium bromide in THF/toluene at −78 °C gave the *N*-acyldihydropyridone **2** in quantitative crude yield and 91% d.e. Purification by radial PLC (silica gel, EtOAc/hexane) provided an 89% yield of pure diastereoisomer **2**. Treatment of **2** with NaOMe/MeOH followed by oxalic acid provided dihydropyridone **3** {$[\alpha]_D^{25}$ + 373 (*c* 0.74, $CHCl_3$)} in 78% yield *via* a one-pot reaction. The chiral auxiliary, (−)-8-phenylmenthol, was recovered in 95% yield at this stage. The nitrogen of **3** was reacylated with *n*-butyllithium and phenyl chloroformate to give enantiopure carbamate **4** {$[\alpha]_D^{25}$ −137.4 (*c* 2.14, $CHCl_3$)} in 99% yield. In the presence of boron trifluoride etherate, copper-mediated conjugate addition of *n*-propylmagnesium bromide to **4** gave the *cis*-piperidone **5** in 88% yield. The diastereoselectivity was 11:1 in favour of *cis* addition.[4] The terminal alkene of **5** was oxidatively cleaved with $OsO_4/NaIO_4$ to provide aldehyde **6** (83% yield), which on treatment with *p*-toluenesulfonic acid gave enone **7** {$[\alpha]_D^{25}$ −164 (*c* 2.96, $CHCl_3$)} in 81% yield. The stereogenic centres at C-5 and C-4a were introduced in one reaction by conjugate addition of lithium dimethylcuprate to **7** followed by protonation (MeOH, −23 °C) of the intermediate enolate. The ketones **8a** and **8b** were formed in a ratio of 97:3. The ketone **8a** (87%) was converted to vinyl triflate **9** in 78% yield using LDA/$PhN(Tf)_2$.[5] Catalytic hydrogenation of **9** over PtO_2 in EtOH effected reduction of the vinyl triflate moiety and cleavage of the phenyl carbamate group to give (−)-pumiliotoxin C in one step.[6] Our synthetic (−)-pumiliotoxin C and its hydrochloride **10** showed spectral properties identical with those reported for the natural material.[1,7] The hydro-



Scheme 1

chloride **10** was recrystallized from propan-2-ol–diethyl ether (87% yield) and exhibited a melting point range (mp 237–239 °C; lit.[1a] mp 230–240 °C) and optical rotation {$[\alpha]_D^{22}$ −12.9 (*c* 0.35, MeOH); lit.[1c] $[\alpha]_D^{20}$ −13.1 (*c* 0.3, MeOH)} in agreement with literature data.†

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† Satisfactory IR, ^{1}H and ^{13}C NMR, HRMS or microanalyses were obtained for all compounds described.