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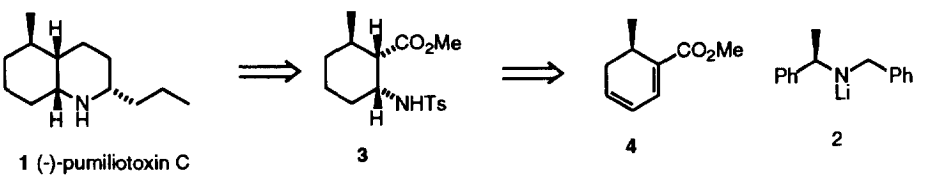
A Formal Synthesis of (-)-Pumiliotoxin C

Stephen G. Davies* and Gurdip Bhalay

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

Abstract: An asymmetric synthesis of an advanced intermediate in the synthesis of natural (-)-pumiliotoxin C has been achieved in six steps and in 61% overall yield employing as the key step a highly diastereoselective lithium amide 1,4-conjugate addition to a dienoic ester derived from (*R*)-(+)-pulegone.

(-)-Pumiliotoxin C **1** is isolated from the skin secretions of the neotropical Panamanian 'poison dart' frog *Dendrobates pumilio*.[1] This is a representative member of a major class of alkaloids which contain the *cis*-decahydroquinoline skeleton. The pharmacological activity associated with this alkaloid together with the isolation of only milligram quantities from natural sources has inspired a number of asymmetric syntheses.[2] Herein is described an approach towards (-)-pumiliotoxin C **1** which has emerged from our previously described methodology for homochiral β-amino acid synthesis using lithium (*R*)-(α-methylbenzyl)benzylamide **2** as a chiral ammonia equivalent in conjugate additions.[3] This diastereoselective synthesis defines a practical method for obtaining substantial quantities of precursors to (-)-pumiliotoxin C **1** and congeners, required for pharmacological activity and structural investigation. Schultz *et al* employed *ent*-**3** in their synthesis of unnatural (+)-pumiliotoxin C *ent*-**1**.[4] We envisaged (Scheme 1) the absolute configurations of the *cis*-β-amino acid moiety as being derivable from the 1,4-addition of **2** to the dienoic ester **4** with the stereochemistry of the remaining, methyl bearing, stereogenic centre being derived from natural (*R*)-(+)-pulegone the precursor of **4**.

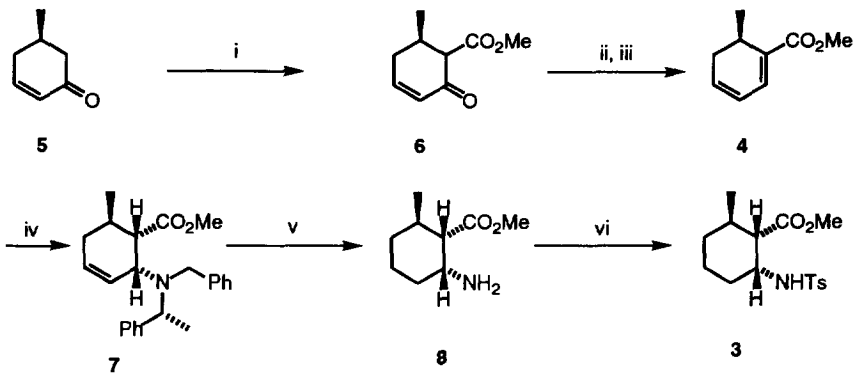


1 (-)-pumiliotoxin C **3** **4** **2**

Scheme 1

The homochiral diene **4**, (Scheme 2) was prepared starting from (+)-(*R*)-5-methylcyclohex-2-en-1-one **5** prepared as reported from (*R*)-(+)-pulegone.[5] Conversion to the β-ketoester **6** was achieved by deprotonation of **5** ($LiNPr^i_2$, THF, HMPA, -78°C) and treatment of the resulting enolate with methyl cyanoformate.[6] This underwent smooth acylation to afford methyl 6-(6*R*)-methyl-2-oxo-3-cyclohexenecarboxylate **6** in good yield (88%). Reduction of the keto functionality in **6** under Luche conditions[7] ($NaBH_4$, MeOH, $CeCl_3.7H_2O$) resulted in the rapid formation of the corresponding alcohol as a mixture of diastereomers (96%). Treatment of this mixture with methanesulphonyl chloride (MsCl, Et_3N, Et_2O, 0°C) gave the mesylate derivative, which was then treated with DBU without purification to give the diene product **4** (94%) after column chromatography, $[\alpha]_D^{23}$ = +95.8 (c = 1.17, $CHCl_3$). Reaction of this homochiral diene **4** with lithium (*R*)-(α-methylbenzyl)benzylamide **2** (THF, -78°C, 1h) followed by quenching with 2,6-di-*tert*-butylphenol gave the

adduct **7** $[\alpha]_D^{23}$ = -226.0 (c = 1.17, $CHCl_3$) in 86% yield and >95% d.e. Olefin reduction and hydrogenolytic removal of the benzyl groups (Pd-C, MeOH, 5bar H_2) resulted in smooth conversion to the saturated homochiral cyclohexyl β–amino ester **8** (97%) $[\alpha]_D^{22}$ = -31.0 (c = 1.07, $CHCl_3$). Finally conversion to the N-tosyl derivative under standard reaction conditions (TsCl, Et_3N, DCM, 20°C) afforded the desired intermediate **3** $[\alpha]_D^{23}$ = -34.3 (c = 1.20, $CHCl_3$) in excellent yield (92%). The spectroscopic data were in good agreement with those reported for *ent*-**3**[4], with the exception of opposite specific rotation {lit.[4] $[\alpha]_D^{22}$ = +34.9 (c = 1.17, $CHCl_3$)}.



Scheme 2[8]

Reagents: i, $LiNPr^i_2$, THF, HMPA, -78°C, MeOCOCN; ii, $NaBH_4$, MeOH, $CeCl_3.7H_2O$, 10mins; iii, MsCl, Et_3N, Et_2O, 0°C, 1h, then DBU; iv, **3**, THF, -78°C, 1h then 2,6-di-*tert*-butylphenol; v, 10% Pd-C, MeOH, 5bar H_2, 16h; vi, TsCl, Et_3N, DCM, 20°C, 48h.

In summary we have developed a convenient strategy (six steps, 61% overall yield) for the enantioselective synthesis of an advanced intermediate[4] towards (-)-pumiliotoxin C **1** and in general towards the *cis*-decahydroquinoline skeleton.

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8. All new compounds were fully characterised including elemental analysis.

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