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PALLADIUM CATALYZED REDUCTIVE CYCLIZATION REACTION IN ALKALOID SYNTHESIS - AN ENANTIOSELECTIVE TOTAL SYNTHETIC ROUTE TO (+)-PUMILIOTOXIN C

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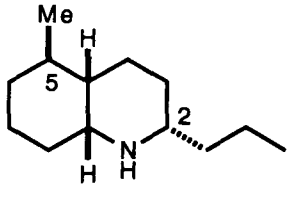
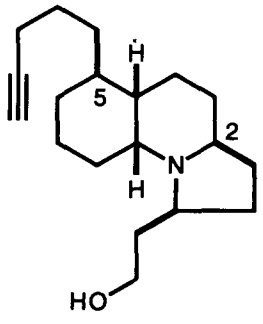
Abstract: Beginning with the chirally homogeneous cyclohexenol **3**, an enantioselective total synthetic route to (+)-pumiliotoxin C (**1**) has been described. Palladium catalyzed reductive cyclization reaction was employed to prepare a key component in the synthesis. Copyright © 1996 Elsevier Science Ltd

Owing to their intriguing pharmacological properties and unique structures, pumiliotoxin C (**1**) and gephyrotoxin (**2**) have proved to be challenges in organic synthesis.[1] Both arrow poison frog toxins (**1**) and (**2**) possess a *cis*-decahydroquinoline ring system with side chain substituents at the C-2 and C-5 positions (the C-2 side chain of **2** being attached at nitrogen). Pumiliotoxin C (**1**) has served as prototype for the synthesis of *cis*-decahydroquinoline alkaloids and has frequently been used to illustrate new methods for construction of decahydroquinoline ring system.



Pumiliotoxin C (1)



Gephyrotoxin (2)

Much effort has been devoted to the synthesis of the *cis*-decahydroquinoline alkaloids,[2] however, there remains conspicuous needs of general procedures to prepare both simple and complex congeners and flexible ones to synthesize topographical relatives.[3] We herein embark upon a program to develop a unified

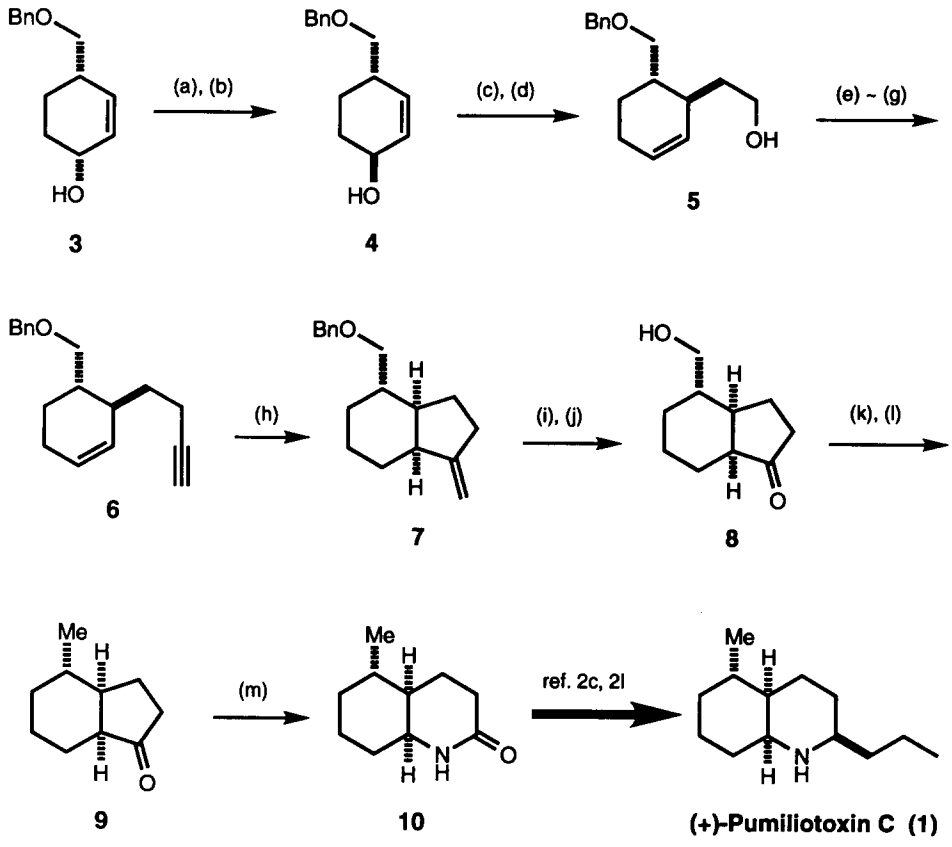
strategy for the synthesis of the *cis*-decahydroquinoline alkaloids employing palladium catalyzed reductive cyclization reaction as the key step. The target chosen to explore this approach was (+)-pumiliotoxin C (**1**).

The chirally homogeneous cyclohexenol **3**,[4] $[\alpha]_D^{27}$-5.0 (c 0.45, $CHCl_3$), prepared from (*R*)-(-)-pantolactone, was used as the starting material. The inversion of hydroxyl group in **3** under carefully controlled Mitsunobu reaction conditions[5] (*p*-nitrobenzoic acid, Ph_3P, DEAD, THF, -30 °C → rt; LAH, THF, 80% overall) resulted in the formation of the alcohol **4**, $[\alpha]_D^{27}$-82.8 (c 0.15, $CHCl_3$).[6] Thermal Claisen rearrangement of **4** with triethyl orthoacetate was next conducted in the presence of *o*-nitrophenol at 160 °C for 2 h to furnish the corresponding ester (78%), which was reduced with LAH to afford the alcohol **5**[6] in 91% yield. The compound **5** was converted efficiently into the bromide (CBr_4, Ph_3P, 86%), which was then replaced with lithium trimethylsilylacetylide in THF-HMPA (-78 °C → rt, 87%). The use of low temperature and of HMPA as cosolvent is critical to the success of this coupling process. Exposure of the resulting TMS-acetylene to 1N methanolic sodium hydroxide gave rise to the key enyne **6**, $[\alpha]_D^{22}$ +108.3 (c 0.31, $CHCl_3$), (92%).[6]

With **6** in hand, the pivotal palladium catalyzed reductive cyclization reaction[7] for the construction of the *cis*-decahydroquinoline ring system of (+)-pumiliotoxin C (**1**) was examined. As a result of testing, the cyclization of **6** in 1,2-dichloroethane (DCE) in the presence of $(dba)_3Pd_2$•$CHCl_3$ (2.5 mol %), *N, N'*-bis(benzylidene)ethylenediamine (BBEDA) (5.0 mol %), polymethylhydrosiloxane (PMHS) (10 eq.), and acetic acid (1 eq.) proceeded quite nicely to provide the *exo*-olefin **7**[6], $[\alpha]_D^{24}$+101.7 (c 0.43, $CHCl_3$), in 61% yield.

With the efficient synthesis of the *cis*-hydrindane derivative **7**, the stage was now set for the completion of the synthesis. The benzyl ether **7** was transformed to the keto alcohol **8**[6] by the standard procedure using sodium in liquid ammonia (88%), follwed by ozonolysis (O_3, MeOH, -78 °C; Me_2S, 65%). After treatment of **8** with 1,1'-thiocarbonyldiimidazole and 4-dimethylaminopyridine (DMAP), the corresponding thioimidazolide, obtained in 95% yield, was allowed to react with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in benzene under reflux, giving the ketone (+)-**9** (79%),[6] $[\alpha]_D^{23}$+80.7 (c 0.64, $CHCl_3$), which displays the same spectra with those provided by Mehta in a total synthesis of (±)-pumiliotoxin C (**1**).[2e, 8] Finally, Beckmann rearrangement of **9** to **10** was conducted, in 61% yield, under standard conditions.[2e] The analytical properties (^1H NMR, IR, MS) of (+)-**10**[6] were identical in all respects to those reported[2c] with the exception of the optical rotation, which was opposite in sign. Since the amide **10** has been transformed previously into pumiliotoxin C (**1**), [2c, 2e] the present enantioselective synthesis of **10** gives rise to the formal total synthetic route to (+)-pumiliotoxin C (**1**). Our methodology based upon

palladium catalyzed reductive cyclization reaction is believed to be an efficient tool in the synthesis of other complex *cis*-decahydroquinoline alkaloids, such as gephyrotoxin (**2**) and lepadin A.[9]



Reagents and conditions: (a) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF, -30 °C → rt. (b) LAH, THF. (c) $MeC(OEt)_3$, *o*-nitrophenol (cat.), 160 °C. (d) LAH, THF. (e) CBr_4, Ph_3P, CH_2Cl_2. (f) LiC≡CTMS, HMPA, THF, -78 °C → rt. (g) 1N NaOH, MeOH. (h) $(dba)_3Pd_2{\cdot}CHCl_3$ (2.5 mol %), BBEDA (5.0 mol %), PMHS (10 eq.), AcOH (1 eq.), DCE. (i) Na, Liq. NH_3, THF, -78 °C; NH_4Cl. (j) O_3, MeOH, -78 °C; Me_2S. (k) 1,1'-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux. (l) $^nBu_3SnH$, AIBN, C_6H_6, reflux. (m) $NH_2OH{\cdot}HCl$, NaOAc, MeOH; TsCl, NaOH, aq. THF.

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