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# N-Acyldihydropyridones as Synthetic Intermediates. A Short Synthesis of (±)-Pumiliotoxin C.

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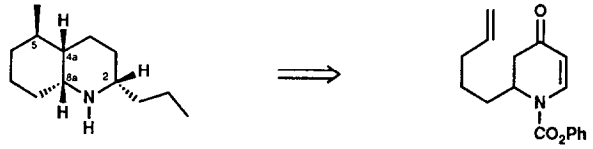
***Summary:*** *A stereocontrolled synthesis of (±)-pumiliotoxin C was achieved from 4-methoxypyridine in seven steps.*

We have been exploring the synthetic utility of N-acyl-2-alkyl-2,3-dihydro-4-pyridones. These readily available heterocycles have proven to be useful building blocks for the preparation of quinolizidine[1], indolizidine[2] and piperidine[3] alkaloids. In this communication we report a synthesis of a *cis*-decahydroquinoline alkaloid, pumiliotoxin C[4], via intermediate N-acyldihydropyridone **4**.

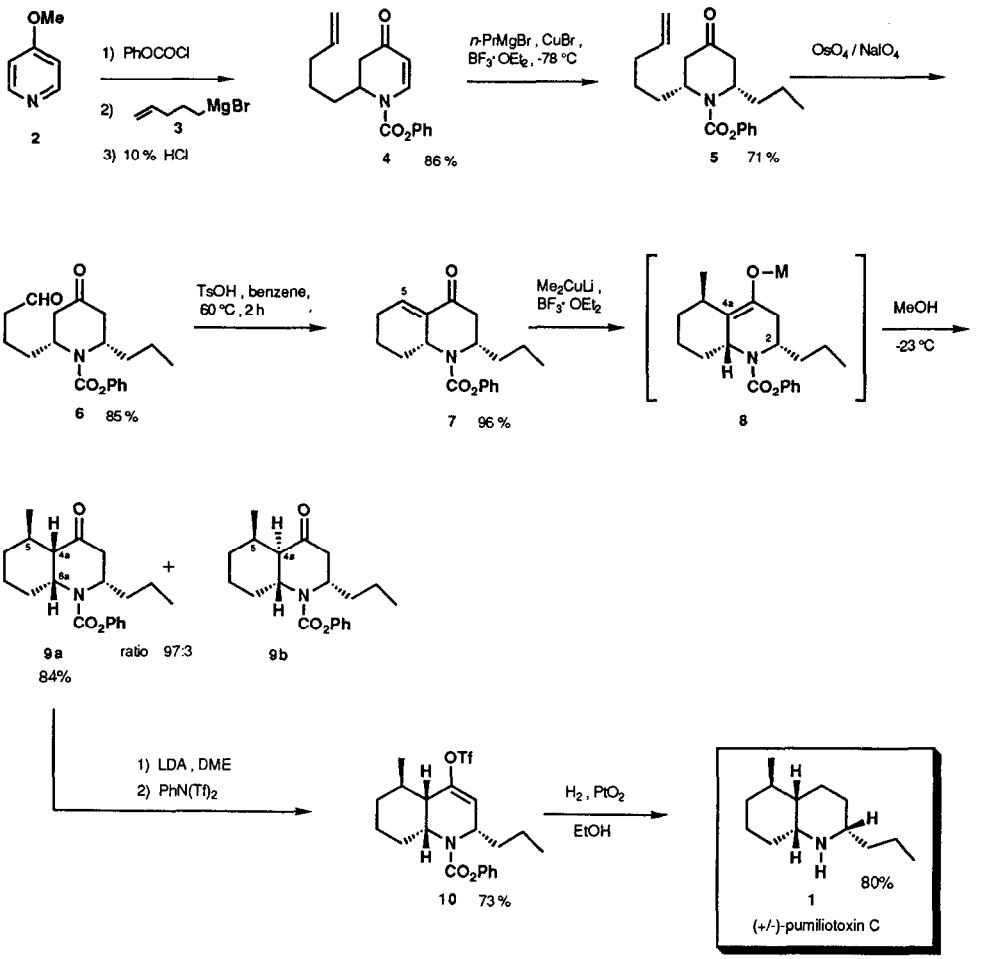



**1**
pumiliotoxin C

**4**

Dihydropyridone **4** was prepared in one step and in 86% yield from 4-methoxypyridine (**2**), Grignard reagent **3**, and phenyl chloroformate (THF, -23°C). Copper-mediated conjugate addition of *n*-propylmagnesium bromide to **4** in the presence of boron trifluoride etherate gave piperidone **5** in 71% yield. The stereoselectivity of this reaction was 11:1 in favor of the *cis* diastereomer **5**.[5] This selectivity was obtained by slow addition (2 h) of the Grignard reagent to a mixture of **4**, cuprous bromide, and boron trifluoride etherate in THF at -78°C. The stereochemical outcome of the cuprate reaction likely arises from a stereoelectronic effect. Due to $A^{(1,3)}$ strain between the C-2 substituent and the N-acyl group of **4**, the alkyl group at C-2 occupies the axial position. Stereoelectronically preferred[6] axial attack by the organocuprate on the α,β-enone function of **4** leads to the *cis* product.[1] Oxidative cleavage of the terminal olefin with $OsO_4/NaIO_4$ provided aldehyde **6**, which on treatment with *p*-toluenesulfonic acid gave enone **7** in near quantitative yield.

The synthetic plan called for introducing the C-5 methyl group via a conjugate addition to enone **7**. We anticipated a high degree of the desired stereoselectivity based on the premise that the conformation of **7** is restricted due to the presence of $A^{(1,3)}$ strain. Examination of the molecular mechanics derived structure **7** (MMX) shown in Figure 1[7] suggested that stereoelectronically preferred[6] axial attack of a methyl nucleophile at C-5 would lead to the desired stereochemical result. This analysis proved to be correct, as reaction of **7** with lithium dimethylcuprate and boron trifluoride etherate (THF, -78°C) gave enolate **8** in situ.[8] The last



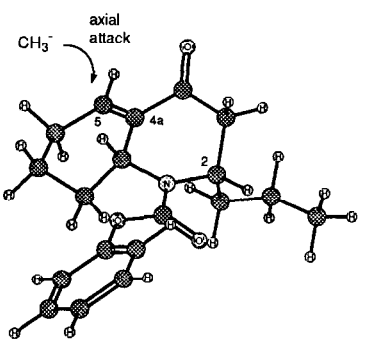




Fig. 1. Structure 7 (MMX)

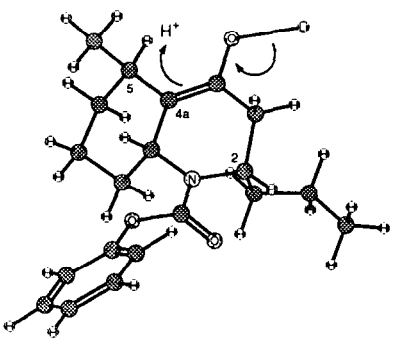
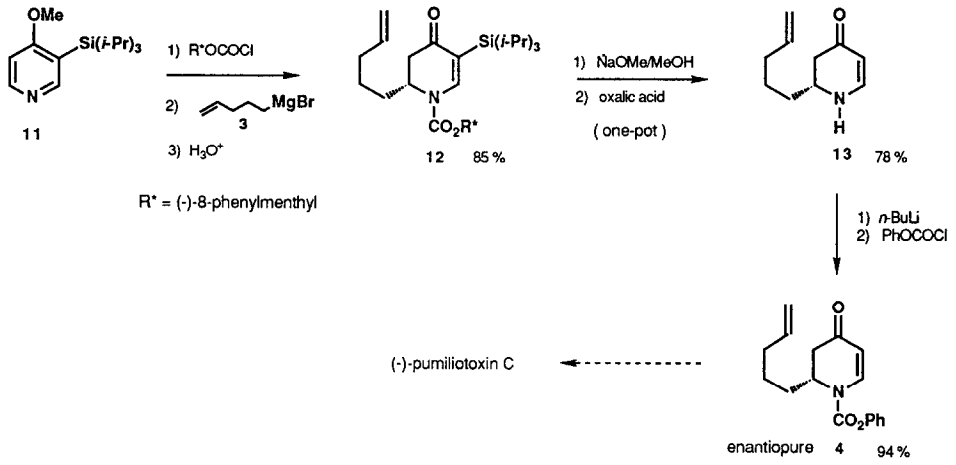



Fig. 2. Axial protonation of 8

stereogenic center at C-4a was introduced by protonation of enolate **8**. Stereoelectronically controlled[6] axial protonation at C-4a (relative to C-2) of **8** leads to the desired diastereomer **9a** (see Figure 2). On quenching **8** with aqueous $NH_4Cl$, an 85:15 mixture of ketones **9a** and **9b** was formed. The stereoselectivity of the protonation step was increased to 97:3 by quenching with anhydrous methanol at -23°C. An 84% yield of pure **9a** was isolated by radial PLC (silica gel, EtOAc/hexane).[9] To convert **9a** to pumiliotoxin C, the N-phenoxycarbonyl group and the oxygen of the keto carbonyl had to be removed. The ketone **9a** was converted to vinyl triflate **10** in 73% yield using McMurry's conditions.[10] *Catalytic hydrogenation of **10** over $PtO_2$ in ethanol gave (±)-pumiliotoxin C in 80% yield.* The reduction of vinyl triflates to alkanes under these conditions has been reported;[11] however, to our knowledge the reductive removal of an N-phenoxycarbonyl group via hydrogenation is novel.[12] Our synthetic (±)-pumiliotoxin C (**1**) showed spectral properties identical with those reported for natural material.[13-15] The hydrochloride of **1** was crystallized from 2-propanol/ether (3:1) and exhibited the same melting point range (mp 231- 233°) as described in the literature for the racemate (mp 231-233°).[13a]

By incorporating our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones,[16] the above racemic synthesis will be modified to provide natural (-)-pumiliotoxin C. Reaction of 4-methoxy-3-(triisopropylsilyl)pyridine,[16] the chloroformate of (-)-8-phenylmenthol,[16] and Grignard reagent **3** in THF/toluene at -78°C gave the dihydropyridone **12** in 99% crude yield and 91% de. Purification by radial PLC (silica gel, EtOAc/hexane) gave an 85% yield of pure diastereomer **12**. Treatment of **12** with sodium methoxide/methanol, followed by oxalic acid/methanol via a one-pot reaction, provided dihydropyridone **13** [$[\alpha]^{25}$ + 373 (*c* 0.74, $CHCl_3$)] in 78% yield. Conversion of **13** to enantiopure **4** [$[\alpha]^{25}$ - 137 (*c* 2.14, $CHCl_3$)] was carried out in 94% yield on treatment with *n*-BuLi and phenyl chloroformate. The enantioselective synthesis of (-)-pumiliotoxin C from enantiopure **4** is in progress and will be reported in due course.

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4. Pumiliotoxin C is one of the physiologically active alkaloids found in the skin secretions of neotropical "poison-dart" frogs belonging to the family *Dendrobatidae*. Daly, J.W.; Spande, T.F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1-274.

5. The stereochemistry of **5** was determined by comparing its NMR data with those of similar compounds reported in the literature, see: Comins, D.L.; Weglarz, M.A. J. Org. Chem. **1991**, 56, 2506 and ref. 1b.

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7. Molecular modeling was performed using PCMODEL (Serena Software, Bloomington, IN) and Chem3D (Cambridge Scientific Computing, Inc., Cambridge, MA).

8. The conjugate addition at C-5 appears to be completely stereospecific.

9. The stereochemistry of **9a** was assigned based on $^1$H NMR coupling constants: $J_{4a\text{-}8a}$ = 6.6 Hz and $J_{4a\text{-}5}$ = 11.7 Hz.

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13. For previous syntheses of pumiliotoxin C and leading references, see: (a) LeBel, N.A.; Balasubramanian, N. J. Am. Chem. Soc. **1989**, 111, 3363. (b) Schultz, A.G.; McCloskey, P.J.; Court, J.J. J. Am. Chem. Soc. **1987**, 109, 6493. (c) Bonin, M.; Royer, J.; Grierson, D.S.; Husson, H-P. Tetrahedron Lett. **1986**, 27, 1569. (d) See ref. 4 and references therein.

14. $^{13}$C NMR data for 1: (75 MHz, $CDCl_3$) δ 59.9, 57.8, 40.7, 34.7, 34.3, 29.0, 27.1, 25.1, 23.0, 20.4, 19.6, 19.0, 13.6.

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