Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates: The First Asymmetric Synthesis of *trans*-Decahydroquinoline Alkaloid (+)-219A

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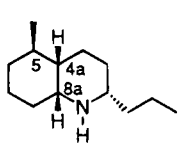
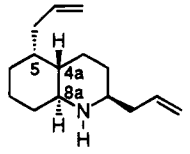
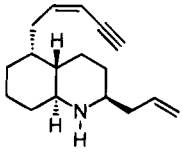
A remarkable number of physiologically active alkaloids are found in the skin secretions of neotropical frogs belonging to the family Dendrobatidae.[1] One major class of dendrobatid alkaloids is the 2,5-disubstituted *cis*-decahydroquinolines, e.g., pumiliotoxin C (**1**). Recently, *trans*-decahydroquinoline alkaloids, e.g., 2,5-diallyl-*trans*-decahydroquinoline (**2**, *trans*-219A) and 2-allyl-5-(pent-2-en-4-ynyl)-*trans*-decahydroquinoline (**3**, *trans*-243A),



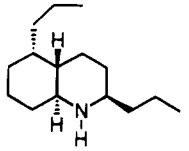
1 (-)-pumiliotoxin C



2 (+)-*trans*-219A



3 (+)-*trans*-243A

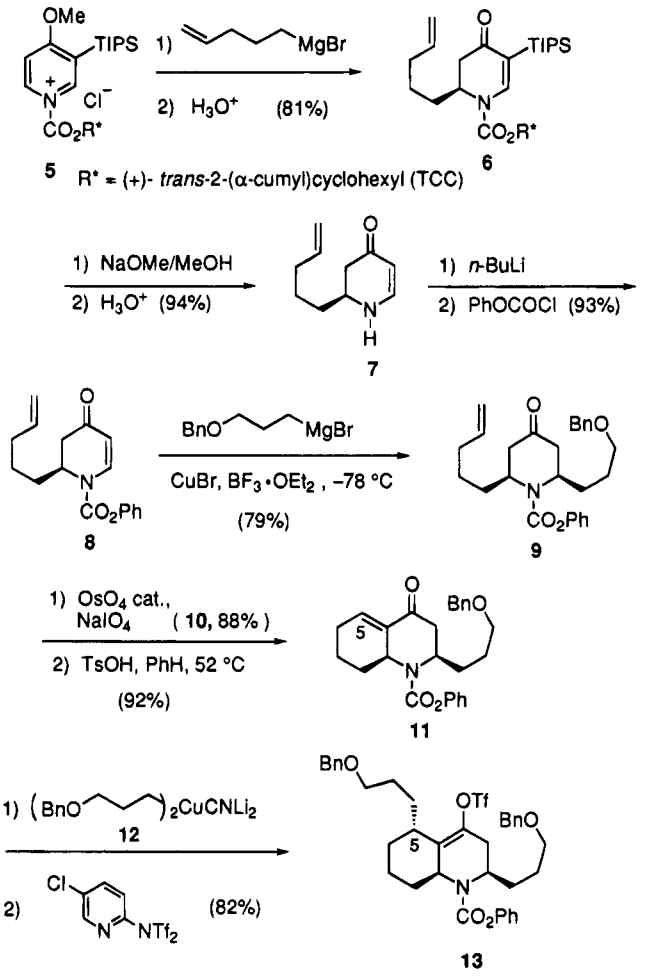


4 (+)-perhydro-219A

were isolated from *Dendrobates histrionicus* and the absolute configurations determined by X-ray crystallographic analysis.[2] Although considerable studies on the preparation of *cis*-decahydroquinoline alkaloids have appeared,[1,3] only one synthesis of a related *trans*-alkaloid, (+)-perhydro-219A (**4**), has been reported.[4] We recently developed a short, asymmetric route to the *cis*-decahydroquinoline alkaloid, (−)-pumiliotoxin C, from an enantiopure *N*-acyldihydropyridone intermediate.[3b] A complimentary strategy that also allows *N*-acyldihydropyridones to be utilized as building blocks for the synthesis of certain *trans*-decahydroquinolines has been under study in our laboratories. In this paper we report the first asymmetric synthesis of a naturally occurring *trans*-decahydroquinoline alkaloid of the Dendrobatidae family, (+)-*trans*-219A (**2**).

The strategy we used to prepare the *cis*-alkaloid pumiliotoxin C involved a conjugate addition reaction of a bicyclic enone and a stereoselective protonation of the resulting enolate to set the cis stereochemistry at C-4a and C-8a.[3] To arrive at the trans fused ring system of *trans*-219A, a plan was followed that included forming the bicyclic ring system through an intramolecular aldol condensation, stereospecific conjugate addition at C-5, and introduction of the required stereochemistry at C-4a through hydrogenation of an olefin bond.

Scheme 1



Reaction of homochiral 1-acylpyridinium salt **5**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[5] and the chloroformate of (+)-*trans*-2-(α-cumyl)-cyclohexanol (TCC),[6] with [5-(1-pentenyl)]magnesium bromide in THF/toluene at −78 °C gave the crude *N*-acyldihydropyridone **6** in 95% yield and 93% de (Scheme 1).

Purification by radial PLC (silica gel, EtOAc/hexanes) afforded an 81% yield of pure diastereomer **6** [mp 90–91.5 °C; $[\alpha]^{26}_D$ +81.7° (*c* 0.235, $CDCl_3$)]. Treatment of **6** with NaOMe/MeOH followed by aqueous 10% HCl provided dihydropyridone **7** [$[\alpha]^{24}_D$ −373° (*c* 2.77, $CHCl_3$)] in 94% yield via a one-pot reaction, and the chiral auxiliary, (+)-TCC, was recovered in 95% yield. Reacylation of **7** with *n*-butyllithium and phenyl chloroformate gave a 93% yield of enantiopure carbamate **8**.[3b] In the presence of boron trifluoride etherate, copper-mediated conjugate addition of [3-(benzyloxy)propyl]magnesium

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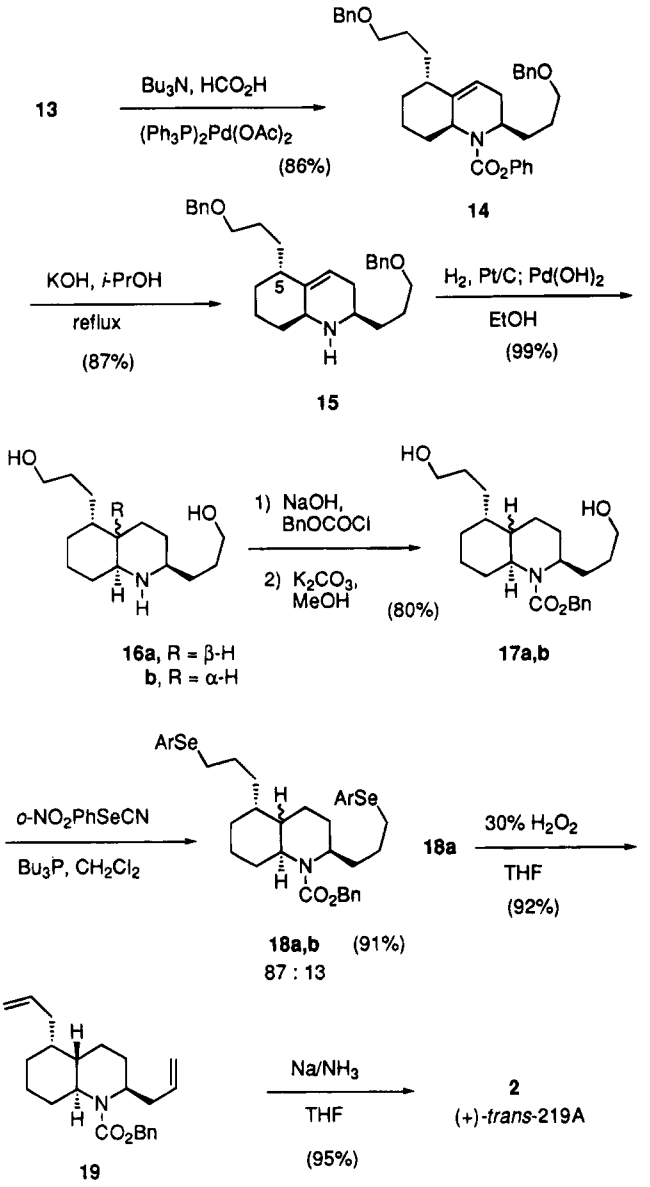
bromide[7] to **8** provided the *cis*-piperidone **9** in 79% yield.[8] Oxidative cleavage of the terminal alkene gave the aldehyde **10** (88% yield), which on treatment with *p*-toluenesulfonic acid in benzene afforded enone **11** [$[\alpha]^{23}_D$ +133° (*c* 0.305, $CHCl_3$)] in 92% yield. The stereocenter at C-5 was introduced stereoselectively by conjugate addition of the higher order cuprate[9] **12**[10] to **11** followed by trapping with *N*-(5-chloro-2-pyridyl)triflimide[11] to give vinyl triflate **13** in 82% yield. The vinyl triflate was converted to alkene **14** in 86% yield using Cacchi's procedure[12] (Scheme 2).

The phenyl carbamate of **14** was hydrolyzed with aqueous potassium hydroxide in 2-propanol under reflux for 6 days to afford an 87% yield of amine **15**. The reduction of **15** was anticipated to be stereoselective, for the side chain at C-5 is axial and blocks the bottom face of the olefin bond. Hydrogenation of **15** over 5% platinum on carbon and palladium hydroxide gave a mixture of the crude amino diols **16**, which was converted to carbamates **17** by triacylation and subsequent hydrolysis with potassium carbonate in methanol. The diol mixture was treated with tributylphosphine and *o*-nitrophenyl selenocyanate to give bisselenides **18** in 91% yield.[13] The ratio of diastereomers **18a** and **18b** was determined by ^1H NMR to be 87/13 in favor of the trans isomer **18a**. Oxidative elimination[13-14] of pure **18a** (79%) using aqueous hydrogen peroxide in THF provided a 92% yield of **19** after chromatography. The synthesis was completed by cleaving the *N*-(benzyloxycarbonyl) group. Treatment of **19** with sodium/ammonia gave alkaloid *trans*-219A (**2**) in 95% yield as a colorless oil [$[\alpha]^{24}_D$ +16.7° (*c* 0.305, MeOH) (lit.[2] $[\alpha]^{24}_D$ +9.7° (*c* 2.0, MeOH))]. All IR, MS, and NMR spectral data for our synthetic **2** were in agreement with the reported values.[2] A sample of synthetic **2** had identical MS and FTIR spectra and GC retention time as the natural material (see Acknowledgment).

The first asymmetric synthesis of alkaloid *trans*-219A has been accomplished in 14 steps and in 15% overall yield from readily available 4-methoxy-3-(triisopropylsilyl)pyridine. The basic strategy should be amenable to the enantioselective preparation of other alkaloids containing the *trans*-decahydroquinoline ring system, and efforts in this direction are underway in our laboratories.

Scheme 2



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Supplementary Material Available: Experimental details and physical data for the preparation of **2**, **6**–**11**, **13**–**15**, and **17**–**19** and copies of ^1H and ^{13}C NMR spectra (300 and 75 MHz) of compounds lacking analyses (33 pages).

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(7) The Grignard reagent was prepared from benzyl 3-bromopropyl ether (Aldrich) and magnesium turnings in THF at 0 °C.

(8) Stereoelectronically preferred axial attack by the organocuprate on the α,β-enone **8** gives the cis product; see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6. (b) See ref 3.

(9) Lipshutz, B. H. *Synlett* **1990**, 119 and references cited therein.

(10) The higher order cuprate **12** was prepared from [3-(benzyloxy)-propyl]lithium, prepared from 3-iodopropyl benzyl ether and *t*-BuLi in pentane/ether at −78 °C, and CuCN; see ref 9.

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