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A Chirospecific Synthesis of (-)-Pinidine

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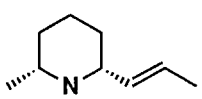
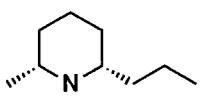
Abstract: A chirospecific synthesis of the *cis*-2,6-dialkylpieperidine alkaloids **1** and **2** has been achieved in eight steps (23%) and six steps (32%) from the known iodide **3**, respectively.

Alkaloids containing a 2,6-disubstituted piperidine ring are abundant in nature and many of them exhibit significant biological activity.[1] Although numerous *cis*-2,6-disubstituted piperidines can be stereoselectively prepared in racemic mode, their asymmetric synthesis has received less attention, a single example of enantioselective synthesis of (-)-pinidine (**1**), isolated from *Pinus* sp.[2], having recently been reported.[3] During the course of our program directed towards the design and development of new tactics for the asymmetric synthesis of biologically active nitrogen-containing compounds,[4] we have accomplished an asymmetric synthesis of **1** and dihydropinidine (**2**)[5] utilising the stereoselective intramolecular amidomercuration of a 5-pentenylcarbamate.



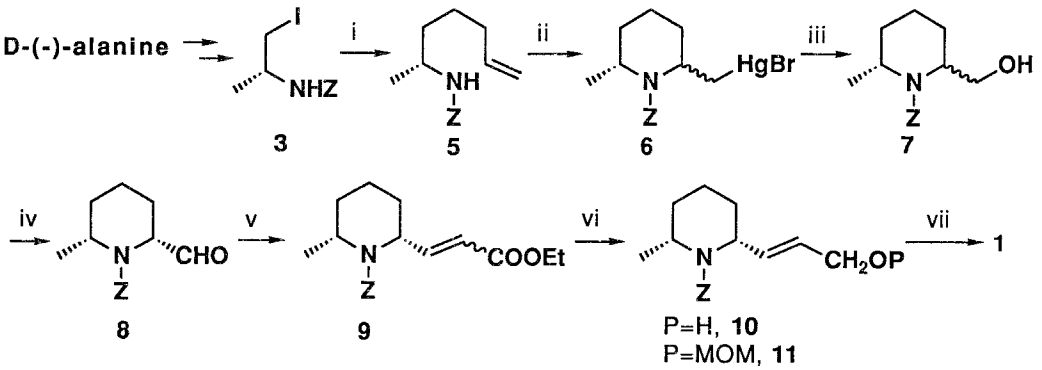
1



2

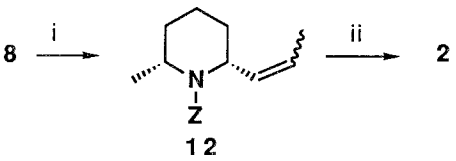
The diastereoselective electrophilic heterocyclization that proceeds with asymmetric induction is commonly employed to control the relative stereochemistry of ring appendages on the heterocycles formed and is increasingly recognized as an attractive protocol for stereoselective synthesis of biologically active heterocycles.[6] Among them, the intramolecular amidomercuration of 5-pentenylcarbamates to generate the 2,6-disubstituted piperidine system proceeds with low selectivity under conditions of kinetic control, but cyclization under conditions of thermodynamic control highly favors the *cis* isomers.[7] Accordingly, we examined the thermodynamically controlled amidomercuration of α-alkylated 5-pentenylcarbamates derived from α-amino acid as a chiral educt.[8]

Our synthesis of **1** began with the coupling reaction between the known iodide **3**[9], prepared from D-(-)-alanine and homoallylmagnesium bromide (**4**). The CuI-mediated coupling reaction of **3** with **4** in tetrahydrofuran (THF) at -40 °C provided 1-methyl-5-pentenylcarbamate **5** in 94% yield. The carbamate **5** underwent the cyclization induced by mercuric trifluoroacetate (nitromethane/room temp. /20 h) followed by treatment with aq. NaBr to provide the organomercurial bromide **6**, which was oxidatively demercurated (O_2/$NaBH_4$/DMF)[10] to afford a 5.5:1 (*cis*:*trans*) mixture of diastereomeric 2,6-disubstituted piperidines. The pure diastereomer *cis*-**7**[$[\alpha]_D^{26}$ -12.9 (*c* 2.1 MeOH)] was isolated by chromatography in 53% yield from **5**. The Swern oxidation of *cis*-**7** provided the aldehyde **8**. The introduction of *E* -olefin on **8** was performed by the Horner-Emmons reaction using diisopropyl (ethoxycarbonylmethyl)phosphonate[11] to furnish the α,β-unsaturated ester **9** (*E*:*Z*=13:1) in 93% yield from *cis*-**7**. The reduction of *E*-**9** with DIBALH provided the allyl alcohol **10** (88%), which was treated with MOMCl/Hünig base to afford the *O*-protected olefin **11** in 84% yield from **9**. Finally, exposure of **11** to Li/NH_3 caused both debenzyloxycarbonylation and reductive cleavage of the allylic C-O bond to give the desired (-)-pinidine (**1**)[12]{$[\alpha]_D^{25}$ -9.8 (*c* 1.2, EtOH), lit.[2a] $[\alpha]_D^{25}$ -10.5 (*c* 1.88, EtOH)**1**-HCl [$[\alpha]_D^{25}$ -9.0 (*c* 0.47, EtOH), lit.[2a]$[\alpha]_D^{26}$ -9.5 (*c* 5.3, EtOH)] } in 65% yield.



i homoallylmagnesium bromide (**4**)/ CuI; ii 1) $Hg(OCOCF_3)_2/MeNO_2$; 2) $NaHCO_3/NaBr$; iii $O_2/NaBH_4/DMF$; iv $(COCl)_2/DMSO/Et_3N$; v $(i\text{-}PrO)_2POCH_2COOEt/NaH$; vi 1) DIBALH; 2) MOMCl/$i\text{-}Pr_2NEt$; vii Li/NH_3

In addition, the synthesis (+)-dihydropinidine (**2**) was achieved in two steps from **8**. The elongation by a C_2 unit on **8** by the Wittig reaction provided the olefin **12** (*Z*:*E*=4:1), which was exposed to $Pd(OH)_2$ under hydrogen to give **2**[12] { **2**-HCl mp 246-247 °C, lit.[2a] 247-248 °C; $[\alpha]_D^{26}$ +12.7 (c 1.00 EtOH), lit.[13] +12.8 (*c* 1.07, EtOH)}in 74% yield from **7**.



i $Ph_3P^+EtCl^-/n\text{-}BuLi$; ii $H_2/Pd(OH)_2$

In conclusion, the chirospecific synthesis of the *cis*-2,6-dialkylpieperidine alkaloids **1** and **2** has been performed in eight steps (21%) and six steps (37%) starting from the known iodide **3**, respectively. This method would be applied to the synthesis of a variety of chiral *cis*-2,6-dialkylpiperidines or indolizidines by using α-amino acids as chiral educts and these results will be disclosed in due course.

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