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Synthesis of enantiomerically pure *cis*-2,4-disubstituted piperidines: extension of chiral homoenolate alkylations toward the preparation of nitrogen heterocycles

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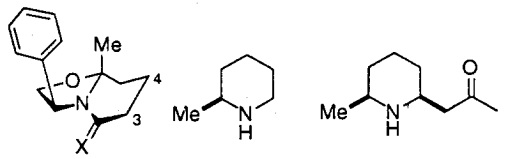
Abstract

Enantiomerically pure *cis*-2,4-disubstituted piperidines were synthesized from chiral thiolactam **2** in six steps via a highly diastereoselective homoenolate alkylation which set the stereochemistry at the C4 carbon. In addition, two cleavage methods were used to cleave the lactam to the desired piperidines with a high level of diastereoselection at the newly created C2 stereocenter.

Chiral piperidines occupy a unique place in many naturally occurring and biologically important compounds, and methods for their asymmetric syntheses have been reviewed recently.[1,2] Our program utilizing chiral, non-racemic bicyclic lactams for the preparation of nitrogen-containing heterocycles, bicyclic lactams **1** and **2**, have served as key sources for the preparation of 2-substituted piperidines [(−)-coniine **3**, and *cis*-2,6-disubstituted piperidines including (+)-pinidinone[3] **4**].



1: X = O
2: X = S

3 **4**

We have recently described the use of homoenolates derived from chiral bicyclic lactams as useful precursors for the preparation of chiral, nonracemic 5-substituted cyclohexenones and various carbocycles.[4] As an extension of this methodology, we felt that a variation of reductive cleavage conditions of the chiral auxiliary could produce 2,4-disubstituted piperidones and piperidines. Since very few general methods exist to install functionality at the 4-position of piperidine ring systems,[5,6] we felt that this was a worthwhile endeavor.

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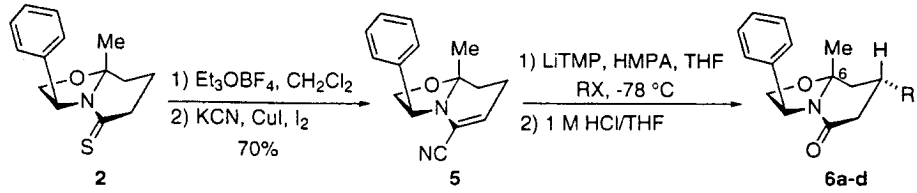
Treatment of thiolactam **2**[7] with Meerwein's reagent[8] followed by displacement with KCN in the presence of CuI and I_2 afforded α-cyanoenamine **5** in good overall yield (Scheme 1).[9] Further treatment of the α-cyanoenamine with 1.2 equiv. of LiTMP in the presence of HMPA followed by addition of various electrophiles afforded the 4-substituted products **6** as *single diastereomers*. Aqueous acidic hydrolysis of the crude alkylated products in THF returned the lactam **6** in good overall yields over the two steps (Table 1). The absolute stereochemistry of the newly created 4-carbon of lactam **6a** was determined by conversion to a known 5-substituted cyclohexenone[10] and the stereochemistry of the remaining examples (**6b–d**) was assigned by analogy.[11]



Scheme 1.

Efforts were subsequently focused upon the simultaneous reductive cleavage of the ring C–O bond as well as the carbonyl group to reach the piperidine nucleus as reported earlier.[12] However, the use of bulky reducing agents (DibAl and RedAl) failed to reduce the ring C–O bond, while treatment with more reactive reducing agents (AlH_3 and BH_3) afforded poor to modest diastereomeric ratios (1:1–6:1) at the C6 stereocenter of the newly created piperidine ring. An alternative reductive strategy was sought to try to circumvent the poor diastereoselection observed at the C6 stereocenter.

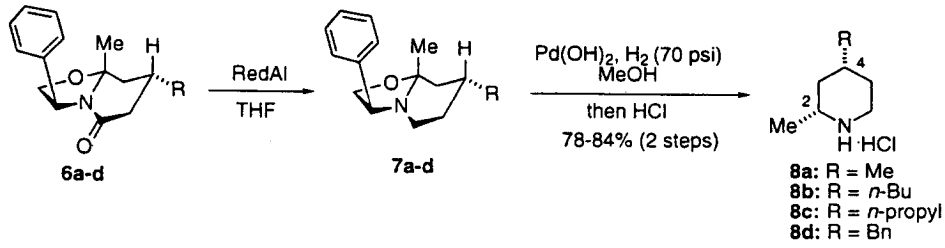
Treatment of **6a–d** with RedAl (10 equiv.) in THF at rt afforded oxazolidines **7a–d**[13] which were directly subjected to hydrogenolysis conditions to afford the piperidine hydrochloride salts **8a,b** as single diastereomers (^1H and ^{13}C NMR). While the absolute stereochemistry at C4 had been previously established,[4] it remained to determine the relative stereochemistry between the C2 and C4 substituents of piperidine products **8a–d**. It is well documented that the C2 and C6 carbon resonances in the ^{13}C NMR are diagnostic for the determination of different stereoisomers of 2,4-dimethyl piperidines.[14] Piperidine **8a** exhibited chemical shifts of 52.1 and 46.8 ppm for C2 and C6, respectively, which were in excellent agreement with reported values (C2=52.1 and C6=46.7 ppm) for *cis*-2,4-dimethyl piperidine.[14–16] Moreover, the literature values for C2 and C6 (46.1 and 41.6 ppm, respectively) for the *trans*-2,4-dimethyl piperidine lie outside the values observed for **8a–d**.[14] In addition, piperidines **8b–d** exhibited almost identical chemical shift data for C2 and C6 as **8a** indicative of a *cis*-relationship between the two substituents (Scheme 2).

In order to more clearly understand the observed diastereoselection in the reduction step, various other reducing agents were examined. Treatment of the 6-methyl lactams **6b,d** under dissolving metal

Table 1
Alkylation and hydrolysis of **5**

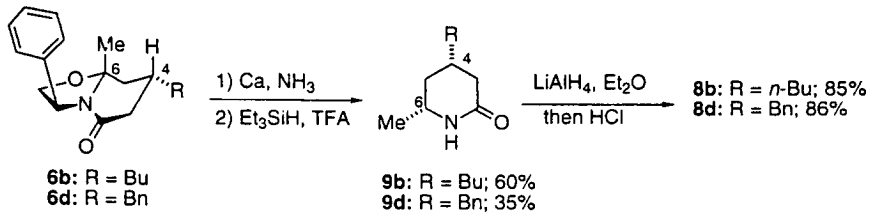
Entry	Electrophile	Yield (% 6)	Diast. Ratio[1]
a	MeI	40	>20:1
b	*n*-BuI	56	>20:1
c	AllylBr	66	>20:1
d	BnBr	76	>20:1

[1]Diastereomeric ratios determined by ^1H NMR and GC analysis.



Scheme 2.

conditions (Ca/NH_3) followed by addition of Et_3SiH/TFA afforded the 4,6-disubstituted-2-piperidones **9b,d** in moderate yields (Scheme 3).[17] Reduction of piperidones **9b,d** with $LiAlH_4$ in refluxing Et_2O afforded the desired piperidine hydrochloride salts **8b,d** whose physical properties (^1H NMR, ^{13}C NMR, $[\alpha]_D^{23}$, and mp) were identical to those reported for the piperidine hydrochlorides prepared in Scheme 2.[10c]



Scheme 3.

The observed diastereoselection in the creation of the C2 stereocenter in **8** via these two protocols can be explained by assuming that the bulky hydride reagent (Et_3SiH) can only approach the iminium ion derived from **6** from the *exo* face (top) or face severe steric interactions with the 4-substituent, *R*, which resides on the *endo* face. A similar argument has been presented in related systems.[17]

In summary, we have prepared chiral non-racemic 2,4-*cis*-disubstituted piperidines in several steps from thiolactam **2** by employing a highly diastereoselective homoenolate alkylation to **6**. This is equivalent to substitution at the 4-position of the piperidine ring. Two different reduction methods have been successfully employed to cleave the ring C–O bond to ultimately set the stereochemistry at the C2 center of the piperidine ring. The inversion of the methyl group in **6** appears to be controlled by the 4-substituent on **6**. Furthermore, a practical synthesis of chiral, non-racemic *cis*-4,6-disubstituted-2-piperidones **9** has been achieved. Additional studies to extend this methodology to more highly functionalized piperidine systems are currently underway and will be reported in due course.

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