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Asymmetric Synthesis of Functionalized *trans*-2,6-Disubstituted Piperidines with *N*-Sulfinyl δ-Amino β-Ketoesters. Synthesis of (–)-Lasubine I

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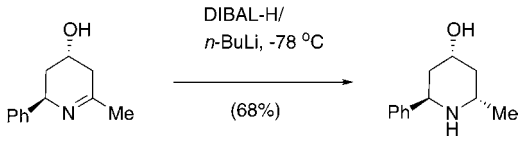
ABSTRACT



The hydroxy-directed reduction of 1,2-dehydropiperidines with the "ate" complex of DIBAL-H and *n*-BuLi affords functionalized *trans*-2,6-disubstituted piperidines. This methodology was employed in the asymmetric synthesis of the quinolizidine alkaloid (–)-lasubine I.

Piperidines are key structural units of numerous alkaloids and pharmaceuticals.[1] Simple 2,6-disubstituted piperidines, isolated from fire ant venom, are reported to possess a broad range of activities (necrotic, insecticidal, antibacterial, antifungal, anti-HIV).[2] Polyhydroxylated piperidines (azasugars) are potent inhibitors of carbohydrate-processing enzymes, which suggests they will find utility in treating viral infections, cancer, diabetes, and tuberculosis.[3] In addition, piperidines serve as building blocks for the synthesis of more complex alkaloids including the indolizidine and quinolizidine ring systems, which in themselves exhibit a broad range of biological activities.[4] As a consequence of the central role played by this ring system, numerous methods have been devised for the asymmetric syntheses of simple, unfunctionalized *cis*- and *trans*-2,6-disubstituted piperidines.[5] However, most of these approaches are target specific and few provide access to *trans*-2,6-disubstituted piperidines having ring functionality.[6] Such functionality is necessary for the construction of more complex bioactive alkaloids.

Recent efforts in our laboratory have focused on *N*-sulfinyl δ-amino β-ketoesters **1**, a new sulfinimine (*N*-sulfinyl imine) derived polyfunctionalized chiral building block for piperidine[7] and pyrrolidine[8] alkaloid syntheses (Scheme 1).[9] While these building blocks afforded mono- and bicyclic piperidine alkaloids with appropriate ring functionality for further

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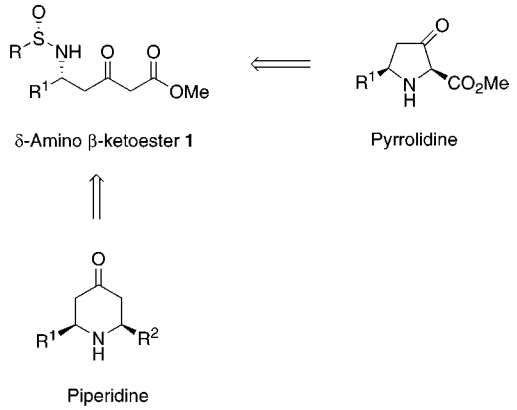
Scheme 1



elaboration, the 2,6-substituents always had the cis relationship.[7] We describe herein a new methodology for the construction of *trans*-2,6-disubstituted, ring functionalized piperidines and demonstrate the utility of the method with the asymmetric synthesis of lasubine I.

Yamamoto and co-workers reported the highly stereoselective reduction of 1,2-dehydropiperidines to *trans*-2,6-disubstituted piperidines using $Me_3Al-LiAlH_4$.[10] It was suggested that the bulky Lewis acid (Me_3Al) coordinates to the nitrogen lone pair and the resultant $A^{1,2}$-strain forces the C-6 substituent into the axial position, facilitating formation of the trans isomer. The situation for the reduction of a functionalized 1,2-dehydropiperidine is likely to be more complicated because of competition for the Lewis acid by the functional group. Nevertheless a proximate functionality, such as a hydroxyl group, could be used to direct the reduction to give the desired trans isomer. To test this idea *trans*- and *cis*-1,2-dehydropiperidines **5a** and **5b** were constructed as outlined in Scheme 2. Treatment of the *syn*- and *anti*-*δ*-amino *β*-hydroxy esters **2a**[7b] and **2b**[7b] with 10 equiv of lithium *N*,*O*-dimethylhydroxylamine afforded the corresponding Weinreb amides (+)-**3a** and (+)-**3b** in 90−98% isolated yields. The methyl ketones (+)-**4** were readily obtained in 88−94% yield on reaction of **3** with 10 equiv of MeMgBr at −78 °C. Removal of the *N*-sulfinyl group with 2 N HCl and neutralization with 28% NH_4OH gave the desired *trans*- and *cis*-1,2-dehydropiperidines **5a** and **5b**. The dehydropiperidines were isolated in crude form, dried ($MgSO_4$), and immediately added, via cannula, to the appropriate reducing system at −78 °C. These results are summarized in Table 1.

Yamamoto observed that the hydride system $LiAlH_4/Me_3Al$ reduces unfunctionalized 1,2-dehydropiperidines with nearly complete trans selectivity while DIBAL-H gave exclusively the cis product.[10] We have observed quite different results for the reduction of 4-hydroxy 1,2-dehydropiperidines **5**. Thus reduction of *trans*-**5a** with 7.0 equiv of $LiAlH_4$:Me_3Al (THF) gave 4-hydroypiperidines (+)-**6**:(−)-**7** in an 88:12 cis:trans ratio (Table 1, entry 1), while

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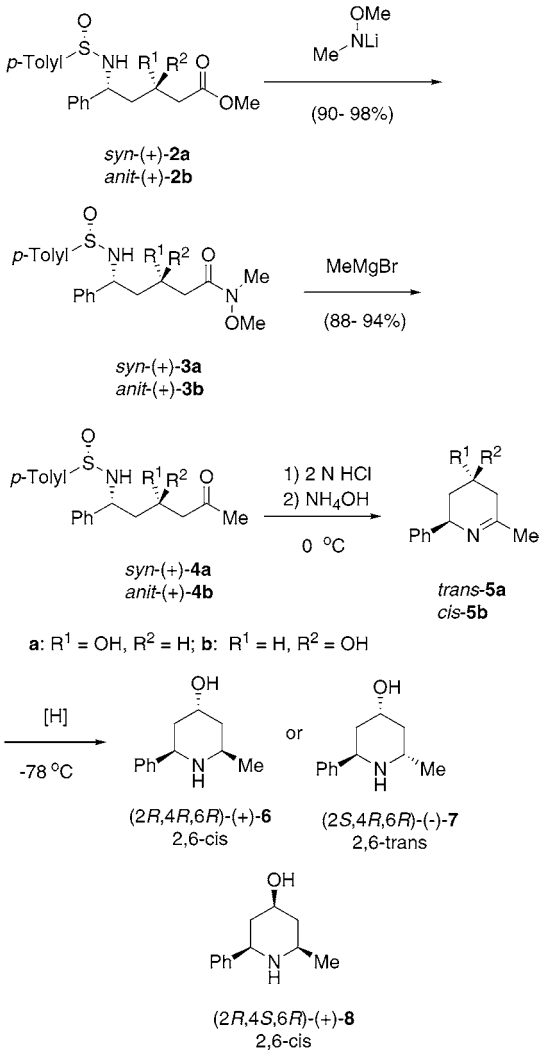
Scheme 2



DIBAL-H (CH_2Cl_2) gave a separable 30:70 mixture of cis:trans (+)-**6**:(−)-**7** (entry 4). The major isomer (2*S*,4*R*,6*R*)-(−)-**7** was isolated in 60% yield and its configuration was

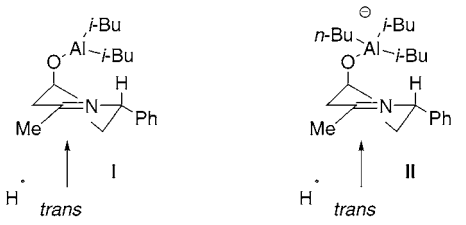
Table 1. Reduction of 4-Hydroxy-1,2-dehydropiperidines **5** at −78 °C

entry	5	hydride reagent	equiv (solvent)[a]	piperidine (% yield)[b] *cis*-6:*trans*-7[c]
1	**5a**	$LiAlH_4$:Me_3Al	7.0 (THF)	88:12 (60)
2		$NaBH_4$	1.0 (THF)	75:25 (70)
3		DIBAL-H	4.0 (THF)	99:1 (65)
4		DIBAL-H	4.0 (DCM)	30:70 (60
5		DIBAL-H	2.0 (DCM)[d]	99:1 (40)
6		DIBAL-H:Me_3Al	4.0 (DCM)	80:20 (60)
7		DIBAL-H	4.0 (PhMe)	83:17 (60)
8		DIBAL-H:*n*-BuLi	4.0 (Et_2O)	1:99 (68)
9	**5b**	DIBAL-H	4.0 (DCM)	(+)-**8**, 99:1 (58)
10		DIBAL-H:*n*-BuLi	4.0 (Et_2O)	(+)-**8**, 99:1 (68)

[a] Piperidine **5** added to the hydride reagent. [b] Isolated yield of the major isomer. [c] Ratio determined by ^1H NMR. [d] DIBAL-H added to the imine.

determined by NOE studies and by X-ray crystal structure analysis. Interestingly, carrying out the reduction of **5a** with DIBAL-H in THF or the addition of DIBAL-H (CH_2Cl_2) to the dehydropiperidine resulted in only the cis product (+)-**6** being identified (Table 1, entries 3 and 5).[11] Significantly, the "ate" complex, *i*-$Bu_2Al(H)$-*n*-BuLi, prepared by adding *n*-butyllithium to DIBAL-H,[12] reduced **5a** with complete trans selectivity affording (−)-**7** in 68% isolated yield (Table 1, entry 8). We suggest that these results can be explained in terms of alkoxy aluminum species I and II, which shield the top face of the C−N double bond with increasing steric bulk (Scheme 3). This added bulk would favor approach of

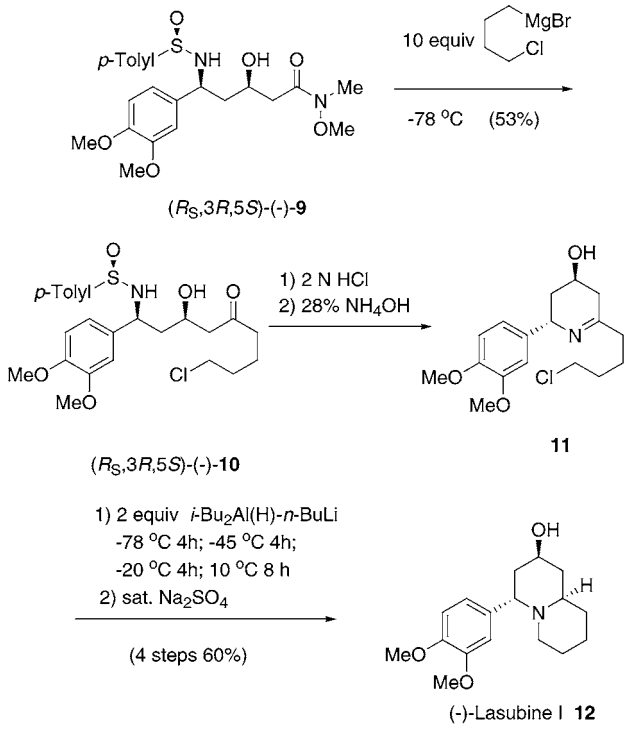
Scheme 3



the hydride reagent from the bottom, which would produce the trans product. Other alkoxy aluminum species including the ring-flipped chair and the twisted boat cannot, at this time, be ruled out. In support of these arguments is the fact that reduction of *cis*-**5b** with these reagent systems produces only *cis*-(2*R*,4*S*,6*R*)-(+)-2-methyl-6-phenylpiperidin-4-ol (**8**) (Table 1, entries 9 and 10). The structure (+)-**8** was supported by NOE and NOESY studies.[13]

(−)-Lasubine I (**12**), a member of the Lythraceae family of naturally occurring alkaloids that contain the 4-arylquinolizidine substructure, has been the subject of only a few asymmetric syntheses.[6a,b,e] The key step in Comin's synthesis was a diastereoselective (86% de) addition of a Grignard reagent to a chiral 1-acylpyridinium salt.[6e] An aza-Diels−Alder reaction employing a resolved chiral aldehyde tricarbonylchromium complex was also used in the synthesis of lasubine II (Scheme 4).[7b] The Weinreb amide was treated with 10 equiv of (4-chlorobutyl)magnesium bromide[14] in ether−THF at −78 °C to give the chloro ketone (−)-**10** in 53% yield following isolation by preparative TLC. Removal of the sulfinyl group with 2 N HCl and neutralizing with

Scheme 4



28% NH_4OH afforded 4-hydroxy 1,2-dehydropiperidine **11**, which was dried and immediately added to 2.0 equiv of the *i*-$Bu_2Al(H)$-*n*-BuLi complex in ether. After the addition was complete the reaction mixture was allowed to slowly warm to 10 °C (−78 °C, 4 h; −45 °C, 4 h; −20 °C, 4 h; 10 °C, 8 h). Deviations from this protocol resulted in reduced yields. Quenching and workup afforded (−)-lasubine I (**12**) as a single diastereomer in 60% yield for the four steps and with properties consistent with literature values.[6a,e]

In summary, the hydroxy-directed, highly diastereoselective trans reduction of 4-hydoxy 1,2-dehydropiperidines with the "ate" complex of DIBAL-H and *n*-BuLi is described. This new methodology affords functionalized *trans*-2,6-disubstitued piperidines and was employed in a concise asymmetric synthesis of the quinolizidine alkaloid (−)-lasubine I (**12**).

Acknowledgment. This work was supported by a grant from the National Institute of General Medical Sciences (GM51982).

Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, and the X-ray analysis of compound (−)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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