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Synthesis of Enantiopure Piperidines. Total Synthesis of (2*R*,6*S*)-2-Methyl-6-propylpiperidine [(-)-Dihydropinidine]

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Abstract: Enantiomerically pure 2-alkyl-, 3-alkyl-, 4-alkyl-, and *cis*-2,6-dialkylpiperidines are prepared from the chiral, non-racemic oxazolopiperidone **1**. An asymmetric synthesis of (2*R*,6*S*)-(-)-dihydropinidine is reported. Copyright © 1996 Elsevier Science Ltd

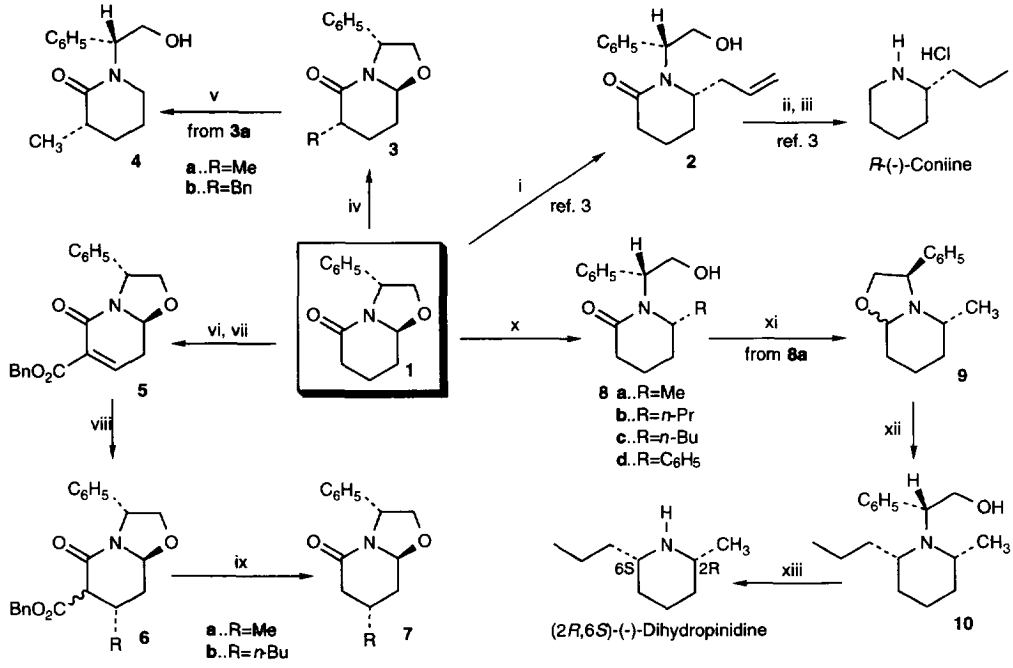
The piperidine ring is present in many natural products, in particular simple piperidine alkaloids, most of them displaying significant biological activities.[1] Accordingly, the development of homochiral piperidine building blocks, with the aim of synthesizing diversely substituted enantiopure piperidines, has received considerable synthetic attention over the last years.[2]

In a previous paper[3] we reported the preparation of several homochiral oxazolopiperidones and the synthesis of the 2-substituted piperidine alkaloid (*R*)-(-)-coniine. The key step was the stereoselective addition of an allylsilane to the chiral non-racemic bicyclic lactam **1** (Scheme 1).

In this paper we illustrate the potential of the homochiral lactam **1** for the synthesis of diversely substituted piperidines in enantiomerically pure form. Thus, treatment of **1** with LDA followed by alkylation of the resulting enolate with either methyl iodide or benzyl bromide gave the corresponding enantiopure 3-substituted piperidones **3a**[4] and **3b** in moderate chemical yield (40%)[5] but good stereoselectivity (only one diastereoisomer was observed by NMR).[6] The configuration of the new stereogenic center was determined by reducing the methylated bicyclic lactam **3a** to the known (α*R*,3*S*) hydroxy lactam **4**, whose configuration had been determined by X-ray analysis.[5]

The introduction of an alkyl substituent at the piperidine 4-position required the previous functionalization of this position, taking advantage of the lactam carbonyl group. For this reason, **1** was converted to the α,β-unsaturated lactam **5** by benzyloxycarbonylation followed by *in situ* selenation (77% yield), with subsequent elimination of phenylsulfenic acid by way of the corresponding selenoxide (>90%). Lactam **5** proved to be somewhat unstable, giving the corresponding 2-pyridone, and from the synthetic standpoint it was more convenient to use the crude material in the following reaction. The benzyloxycarbonyl group provides an additional and necessary activation towards the nucleophilic addition at C-4.[7] Thus, treatment of **5** with a lower-order heterocuprate, for instance lithium methylcyanocuprate, led to a 4:1 mixture of esters **6a** (50% yield), which was converted to the enantiopure 4-substituted piperidine **7a**[8] by

catalytic debenzylation followed by decarboxylation (70% yield). In a similar manner, the 4-butyl substituted piperidine **7b** was obtained in 45% overall yield operating from *n*-BuCu(CN)Li. The absolute configuration of C-7 in **7a** was deduced by NOE difference experiments. Thus, upon irradiation of the H-8a methine proton, the methyl hydrogens signal exhibited a 10% enhancement.



Scheme 1. *Reagents and conditions*: i) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2; ii) $LiAlH_4$, Et_2O, reflux; iii) H_2, Pd-C, MeOH, then HCl, MeOH; iv) LDA, RX, THF, -78°C; v) Et_3SiH, $TiCl_4$, CH_2Cl_2; vi) HMDSLi, $ClCO_2Bn$, THF, -78°C, then $BrSeC_6H_5$, THF, -78°C; vii) O_3, CH_2Cl_2; viii) RCuCNLi, THF, -78°C; ix) HCO_2NH_4, Pd-C, MeOH, then toluene, reflux; x) $R_2Cu(CN)Li_2$, $BF_3.Et_2O$, THF, -78°C; xi) Red-Al, THF; xii) *n*-PrMgBr, Et_2O, -60°C; xiii) H_2, $Pd(OH)_2$, MeOH, then HCl, MeOH.

With the final aim of preparing enantiopure *cis*-2,6-dialkylpiperidines, we then investigated the reaction of **1** with higher-order cyanocuprates as an alternative method for the preparation of 2-substituted piperidines. Thus, treatment of **1** with $Me_2Cu(CN)Li_2$ (3 equiv) in the presence of $BF_3.Et_2O$ led to the expected α-amidoalkylation product **8a**[9,10] in 67% yield (97:3; calculated by NMR). The α-substituted piperidines **8b**[10] (59%; 95:5), **8c** (65%; 93:7), and **8d** (75%; 9:1) were similarly obtained operating from the appropriate higher-order cyanocuprate. The absolute configuration of the new stereogenic center was assigned as *R* (for **8a-c**, but *S* for **8d**) because catalytic hydrogenation of **2**[3] gave the α-propyl substituted derivative **8b**.

Finally, a total synthesis of (2*R*,6*S*)-dihydropinidine,[11] the dihydro derivative[12] of the *cis*-2,6-dialkylpiperidine alkaloid (-)-pinidine,[13] was completed from the α-methyl substituted piperidine **8a**. Thus, reduction of **8a** with Red-Al (60% yield) followed by treatment of the resulting oxazolopiperidine **9** with propylmagnesium bromide gave alcohol **10** (73% yield). The *cis* relationship between the methyl and propyl substituents in **10** was evident from the difference between the ^{13}C-NMR chemical shifts corresponding to the methine (δ 65.0) and the methylene (δ 61.7) carbons of the chiral auxiliary.[14] Subsequent catalytic

debenzylation of **10** afforded (2*R*,6*S*)-dihydropinidine.[15,16] Our synthetic dihydropinidine was isolated as the hydrochloride, which showed $[\alpha]_D$ +12.2 (*c* 1.0, EtOH) {Lit.[12b] $[\alpha]_D$ +12.7 (*c* 1.07, EtOH)}[17] and possessed ^{1}H- and ^{13}C-NMR spectroscopic data identical to those reported for (±)-dihydropinidine.[18]

In summary, we have demonstrated the versatility of oxazolopiperidone **1** in the preparation of enantiopure 2-substituted, 3-substituted, 4-substituted, and *cis*-2,4-disubstituted piperidines.[19]

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(CH_3); 24.2 (C-7); 33.9 (C-8); 39.4 (C-6); 57.9 (C-3); 71.9 (C-2); 86.3 (C-8a); 125.7 and 128.7 (C-*o* and C-*m*); 127.4 (C-*p*); 139.8 (C-*ipso*); 169.4 (C=O). $[\alpha]^{22}_D$ -168 (*c* 0.5, MeOH).

9. **8a**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.20 (d, *J*=7.0 Hz, 3H, CH_3); 1.60-2.00 (m, 4H, H-4 and H-5); 2.48 (ddd, *J*=17.0, 10.0, 7.5 Hz, 1H, H-3); 2.54 (dddd, *J*=17.0, 8.0, 3.5, 1.0 Hz, 1H, H-3); 3.50 (m, 1H, H-6); 4.04 (ddd, *J*=12.0, 4.0, 3.5 Hz, 1H, CH_2O); 4.28 (ddd, *J*=12.0, 9.0, 7.0 Hz, 1H, CH_2O); 4.46 (dd, *J*=9.0, 4.0 Hz, 1H, OH); 4.60 (dd, *J*=7.0, 3.5 Hz, 1H, $NCHC_6H_5$); 7.20-7.40 (m, 5H, C_6H_5). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 16.0 (C-4); 19.6 (CH_3); 29.3 (C-5); 31.8 (C-3); 52.8 (C-6); 63.4 (CH_2O); 64.5 ($NCHC_6H_5$); 127.2 (C-*p*); 127.3 (C-*o*); 128.2 (C-*m*); 137.4 (C-*ipso*); 171.6 (C=O). $[\alpha]^{22}_D$ -19.5 (*c* 1.0, EtOH).
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