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Enantioselective Syntheses of 2-Alkyl- and 2,6-Dialkylpiperidine Alkaloids: Preparations of the Hydrochlorides of (–)-Coniine, (–)-Solenopsin A, and (–)-Dihydropinidine

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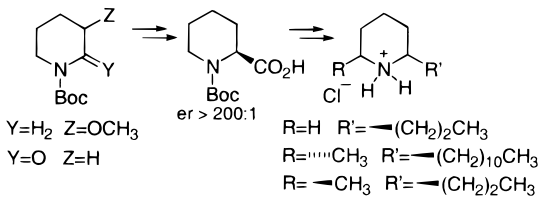
ABSTRACT



Sequences of lithiation–substitution, enantioselective hydrogenation, and diastereoselective lithiation–substitution provide efficient highly enantioselective syntheses of 2-substituted and *cis* and *trans* 2,6-disubstituted piperidines. The methodology is demonstrated by syntheses of (–)-coniine, (–)-solenopsin A, and (–)-dihydropinidine as their hydrochlorides.

Direct elaborations of *N*-Boc amines by lithiation−substitution reactions offer opportunities for convenient and efficient syntheses of alkaloid ring systems. The piperidine family, which includes many compounds with useful pharmacological properties, has been a target of particular interest.[1] Enantioselective syntheses of members of this family, (−)-coniine[2] (**1**), (−)-solenopsin A[2ab,3] (**2**) and (−)-dihydropinidine[2cd,4] (**3**) have been the focus of many studies.

We wish to report that lithiation−substitution and asymmetric hydrogenation can be used as key steps in convenient and efficient syntheses of highly enantioenriched 2-substituted and *cis* and *trans* 2,6-disubstituted piperidines from commercially available materials. This methodology is demonstrated for preparations of the hydrochlorides of the

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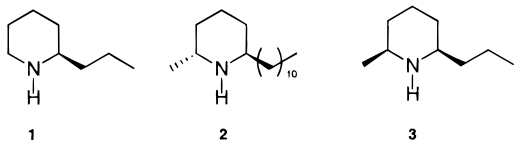
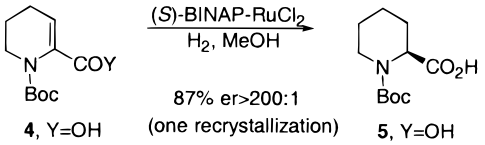
alkaloids **1**−**3** from *N*-Boc-3-methoxy piperidine and *N*-Boc-*δ*-valerolactam via (*S*)-*N*-Boc-pipecolic acid.



1 **2** **3**

Asymmetry is introduced into the piperidine ring by the enantioselective hydrogenation of 2-carboxy-*N*-Boc-1,4,5,6-tetrahydropyridine **(4)** with the Noyori catalyst[5] (*S*)-BINAP-$RuCl_2$ to yield (*S*)-*N*-Boc-pipecolic acid **(5)** in high enantioenrichment after one recrystallization as shown in Scheme 1. Prior to recrystallization, **5** is obtained in 95% yield with

Scheme 1



an er of 98:2 as shown in Table 1. The table also shows that reductions of the *N*-*tert*-butyl amide, the *N*-(3,5-dimethyl) phenyl amide, the *N*, *N*-diethyl amide, and the methyl ester corresponding to **4** with (*S*)-BINAP-$RuCl_2$ provided the

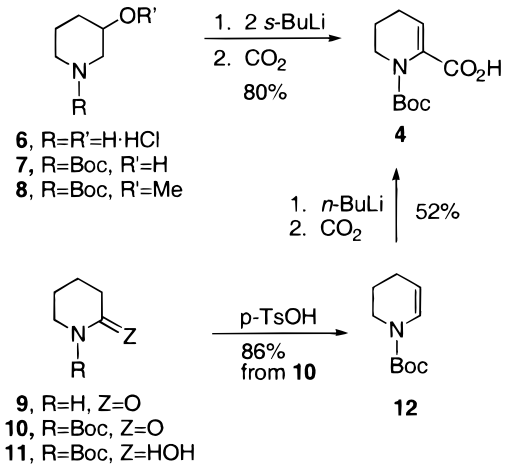
Table 1. Reduction of **4** and Derivatives with (*S*)-BINAP-$RuCl_2$

Y	yield (%)	er
OH	95	98:2
NH-*t*-Bu	99	98:2
NH-3,5-$Me_2C_6H_3$	78	96:4
$N(C_2H_5)_2$	83	87:13
OCH_3	66	73:27

expected enantioenriched reduction products in 99%, 78%, 83%, and 66% yields with ers of 98:2, 96:4, 87:13, and 73:27, respectively. Reductions of **4** with (*S*)-BINAP-Rh(I), (*R*, *R*)-DIPAMP-Rh(I) gave the racemic acid, while (*R*, *R*)-Me-DuPhos-Rh(I) afforded the product with an er of 71:29.[6] Reduction of 2-carboxymethyl-*N*-phenoxycarbonyl 1,4,5,6-tetrahydropyridine with (*R*)-BINAP-$RuCl_2$, as reported by Foti and Commins, gives an (*S*)-configured product in 52% yield with an er of 90:10.[7] It is interesting that their ester, which differs from the methyl ester of **4** only by a *tert*-butyl group vs a phenyl group on the *N*-carboxy function, gives a product that has the same configuration as we observe, although they use the catalyst of the opposite configuration.[7,8] Changes in the facial selectivity in reductions with chiral Ru(II) complexes at different pressures are known, although changes to this degree are unusual.[5b]

The precursor to (*S*)-*N*-Boc-pipecolic acid (**5**), 2-carboxy-*N*-Boc-1,4,5,6- tetrahydropyridine (**4**), was prepared by either of two methods as shown in Scheme 2. Following our

Scheme 2



previous report, 3-hydroxypiperidine hydrochloride (**6**) was reacted with $(Boc)_2O$ to afford **7** in 83% yield.[9] Treatment of **7** with sodium hydride and iodomethane gave **8** in 89% yield. The reaction of **8** with 2 equiv of *s*-BuLi/TMEDA (−78 °C, 5 h), followed by the addition of carbon dioxide, afforded **4** in 80% yield.[9] In an alternative sequence, *δ*-valerolactam (**9**) was reacted with $(Boc)_2O$ and DMAP in acetonitrile to afford **10** in 79% yield. Reduction with DIBALH gave lactamol **11,** which was dehydrated without purification with *p*-TsOH in toluene to provide the enecarbamate **12** in 86% yield from **10** following the procedure of Dieter.[10] When **12** was reacted with *s*-BuLi/TMEDA, under conditions similar to those used for the conversion of **8** to **4**, low yields of **4** were obtained. A yield of 52% of **4** was

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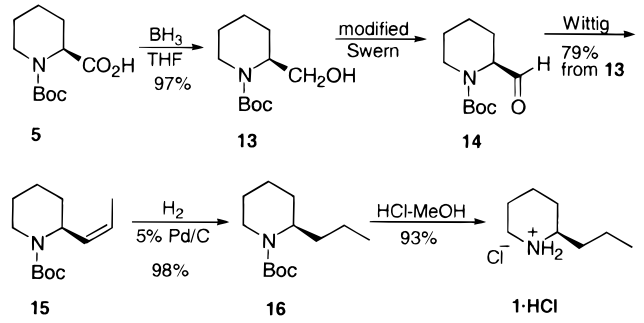
achieved in the reaction of **12** with *n*-BuLi/TMEDA (−65 to −30 °C, 30 min), followed by treatment with carbon dioxide. The crude product from this reaction contained approximately 25% 5-nonanone, based on its ^{1}H NMR spectrum, indicating that nucleophilic additions of *n*-BuLi to carbonyl groups can be competitive with the lithiation of **12** by *n*-BuLi.

The formation of **4** from **12** is considered to occur by metalation at the vinyl position, followed by reaction of the vinyllithium intermediate with carbon dioxide. A reasonable pathway for the conversion of **8** to **4** is initial lithiation adjacent to nitrogen followed by elimination of methoxide to afford **12**.[9] However, the lower yield of **4** from the direct reaction of **12** with *s*-BuLi (vide supra) and the failure of **12** to give increased yields of **4** in the presence of lithium methoxide suggests that these reactions have similar but different pathways.

The enantioselective formation of **5** combined with our previous studies of diastereoselectivities in lithiation−substitutions of substituted *N*-Boc-piperidines provides a basis for convenient syntheses of highly enantioenriched 2-substituted and 2,6-disubstituted piperidine alkaloids. The following syntheses are based on previous syntheses.[9]

(−)-Coniine Hydrochloride (1·HCl). Reduction of **5** with BH_3·THF provided alcohol **13** in 97% yield. The alcohol **13** was oxidized by the Katzenellenbogen modification of the Swern oxidation to provide aldehyde **14**, which was immediately reacted with the ylide of (ethyl)triphenylphosphonium bromide to afford **15** in 79% overall yield based on **13**.[2no,5,11] Catalytic hydrogenation of **15** with 5% Pd/C provided **16** in 93% yield as shown in Scheme 3. Treatment

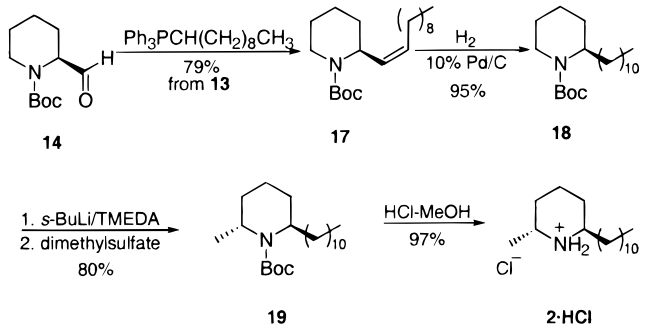
Scheme 3



of **16** with HCl−methanol afforded (−)-coniine hydrochloride (**1·HCl**) in 98% yield. The overall yield from **5** is 70%. Mp 219−220 °C (lit.[2c] 218−221 °C); $[\alpha]^{20}_D$ −6.5° (c = 1.0, EtOH) (lit.[2c] $[\alpha]^{20}_D$ −7.3° (c 1.0, MeOH)).

(−)-Solenopsin A Hydrochloride (2·HCl). Reaction of aldehyde **14** with the ylide of (decyl)triphenylphosphonium iodide afforded **17** in 79% yield.[12] Hydrogenation with 10% Pd/C then gave **18** in 95% yield. Lithiation of **18** with *s*-BuLi/TMEDA followed by treatment with dimethyl sulfate provided **19** in 80% yield as shown in Scheme 4.[3a,f,5]

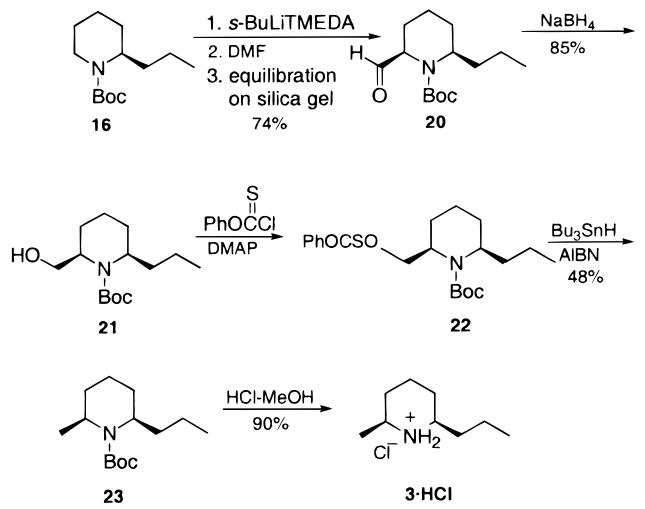
Scheme 4



Deprotection with HCl−MeOH gave (−)-solenopsin A hydrochloride (**2·HCl**) in 97% yield. The overall yield from **5** is 56%. Mp 148−149 °C (lit.[3c] 147−150 °C); $[\alpha]^{20}_D$ −8.2 (c 0.5, $CHCl_3$) (lit.[3c] $[\alpha]^{20}_D$ −7.7 (c 0.51, $CHCl_3$)).

(−)-Dihydropinidine Hydrochloride (3·HCl). Treatment of **16** with *s*-BuLi/TMEDA followed by DMF afforded a 10:90 *cis*−*trans* mixture of aldehydes, based on the ^{1}H NMR spectrum of the crude product. The aldehyde mixture was isomerized with silica gel to provide an 83:17 *cis*−*trans* mixture from which **20** was obtained in 74% yield by flash chromatography.[5,13] Reduction of **20** with sodium borohydride gave **21** in 85% yield. Deoxygenation of **21** was accomplished in two steps by a Barton deoxygenation.[14] Alcohol **21** was converted to the thionocarbonate **22** in 88% yield by the reaction with phenylchlorothionoformate/DMAP. Reduction with tributyltin hydride/AIBN followed by reflux with TBAF provided **23** in 48% yield. Deprotection of **23** with HCl−methanol afforded (−)-dihydropinidine hydrochloride (**3·HCl**) in 90% yield as shown in Scheme 5. The

Scheme 5



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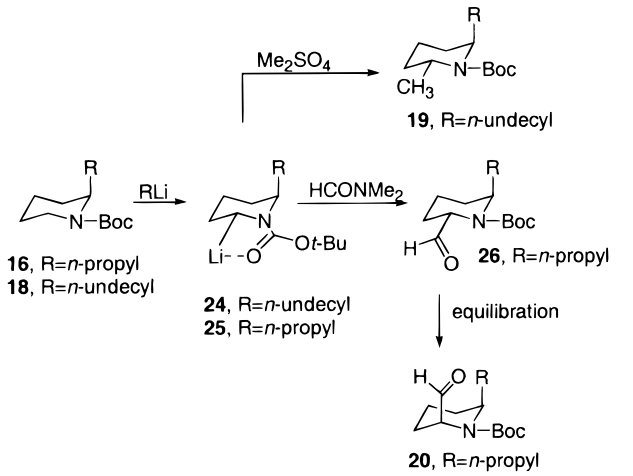
Scheme 6



overall yield from **5** was 17%. Mp 242−243 °C (lit.[4b] 234 °C); $[\alpha]^{20}_D$ −13.3° (*c* 1.0, EtOH) (lit.[4b] $[\alpha]^{20}_D$ −12.74° (*c* 0.47 EtOH)).

The flexibility of this methodology, in accessing both *cis* and *trans* 2,6-disubstituted piperidines, lies in the structure and reactivity of the intermediate lithiated *N*-Boc piperidines.[9] Lithiations of **16** and **18**, in which the 2-substituent is axial as a result of $A_{1,3}$ strain, provides **24** and **25** in which the lithium is equatorial.[9,15] Subsequent methylation of **24** occurs with retention of configuration to afford **19**. Similarly, **16** provides **26** via **25**. In this case, however, $A_{1,3}$ strain provides a driving force for equilibration to afford **20**.[9,15] The reactions are outlined in Scheme 6. The stereochemical outcomes of the reactions leading to *cis* or *trans* 2,6-disubstituted piperidines are consistent with principles that should be applicable to related systems.

Because both enantiomers of the catalyst are commercially available, both (*S*)-and (*R*)-*N*-Boc-pipecolic acid can be prepared with high enantiointegrity.[5] The diastereoselectivities of subsequent lithiation−substitution and equilibration allows a high degree of stereochemical control. Although the present syntheses afford alkyl-substituted piperidines, this approach can provide highly enantioenriched 2-substituted and *cis* and *trans* 2,6-disubstituted piperidine rings with many functionalities and with any desired absolute configuration.

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Supporting Information Available: Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org

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