

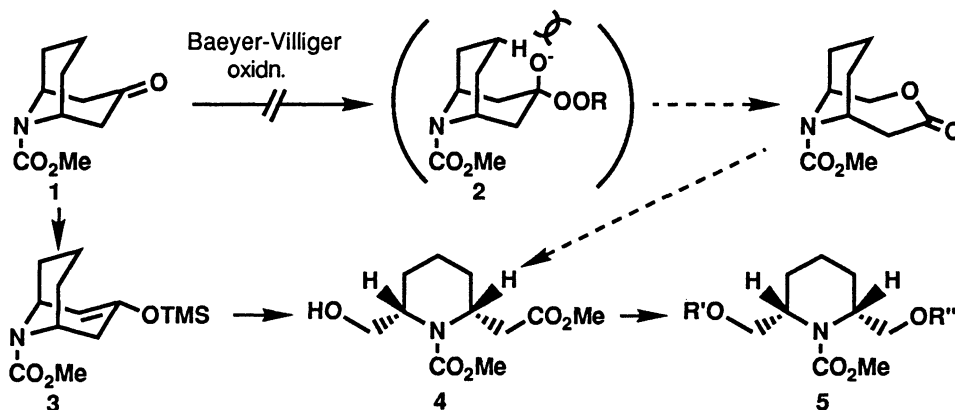
Asymmetric Cleavage of 9-Azabicyclo[3.3.1]nonan-3-one into *cis*-2,6-Disubstituted Piperidine. A Facile Approach to a Chiral Building Block for Alkaloid Synthesis

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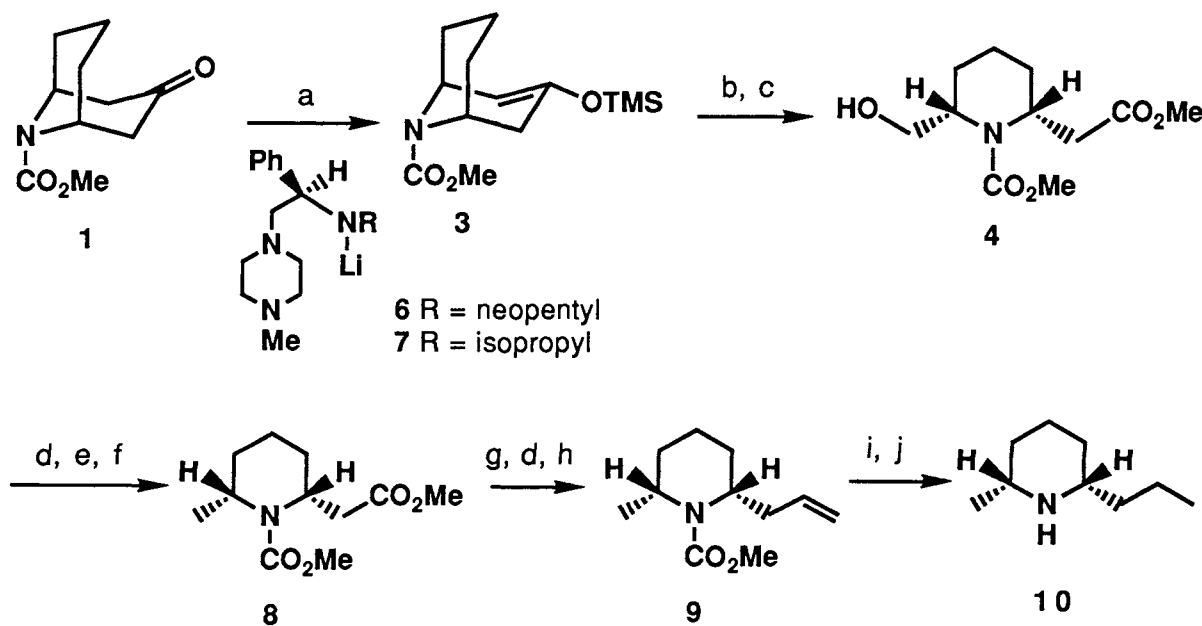
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An asymmetric cleavage of the 'fork head' ketone of 9-azabicyclo[3.3.1]nonan-3-one gave a *cis*-2,6-disubstituted piperidine derivative in 93% ee, which was transformed to the *cis*-2,6-bis(hydroxymethyl)piperidine derivative, a versatile chiral building block.

The 9-azabicyclo[3.3.1]nonan-3-one (**1**) could be an important synthon for the synthesis of natural products¹⁾ of the *cis*-2,6-disubstituted piperidine system. There lacks, however, any simple method for α -ketonic cleavage of its piperidone ring since the bicyclo[3.3.1]nonan-3-one system including **1** displays anomalous inactivity against the Baeyer-Villiger oxidation.²⁾ As for the enol ether route for the α -ketonic cleavage, an azabicyclo[3.3.1]nonan-2-one approach to the *cis*-3,5-disubstituted piperidine system *via* the ozonolytic cleavage of the enol ether of its 'non-fork head' ketone has been reported,³⁾ however, a similar cleavage of the σ -symmetric 'fork head' ketone system has never been examined to date. Recently, Koga and co-workers reported the kinetic deprotonation of prochiral 4-substituted cyclohexanones by chiral lithium amides in reasonably high enantiomeric excess (ee).^{4,5)} This method provides an excellent way to achieve the enantioselective construction of optically active compounds from *meso* ketones having a σ -plane. We examined the application of this method to the 9-azabicyclo[3.3.1]nonan-3-one system with a view for obtaining the chiral building block **5** for the syntheses of piperidine and indolizidine alkaloids focussing much attention because of a variety of their biological activities. In the present communication, we describe the asymmetric cleavage of the 'fork head' ketone in **1** through the enantioselective deprotonation and also its transformation into the versatile chiral building block bearing σ -symmetry.



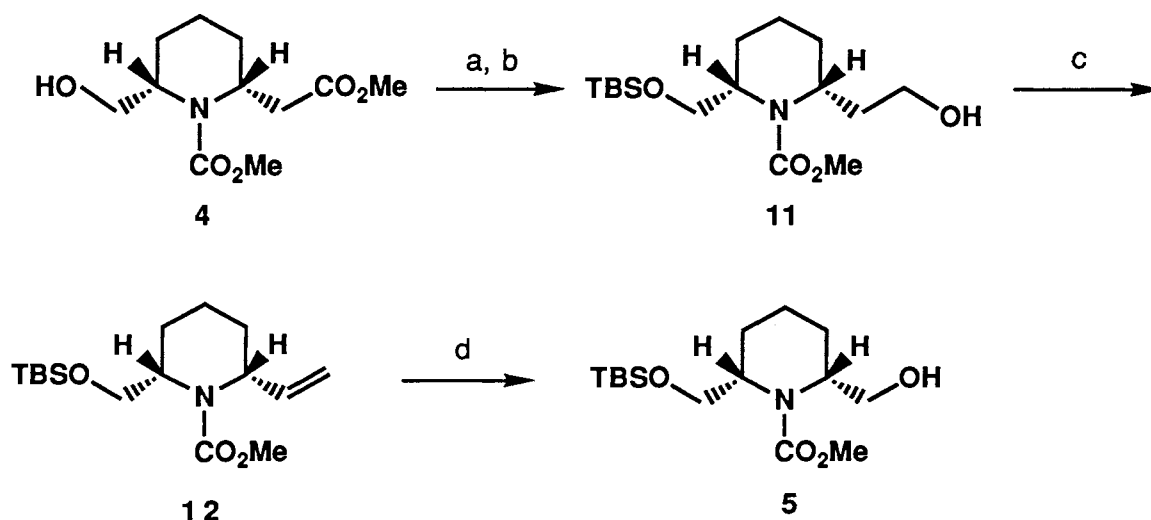
The treatment of a 9-azabicyclo[3.3.1]nonan-3-one (**1**) with a chiral lithium amide (**6**) and excess trimethylsilyl chloride (TMSCl) in tetrahydrofuran (THF) at $-100\text{ }^{\circ}\text{C}$ according to the method of Koga⁴) gave the corresponding trimethylsilyl enolate **3**⁶) in 93% ee^{7,8}) (94% yield) as shown in Scheme 1. Ozonolysis of **3** in CH_2Cl_2 at $-78\text{ }^{\circ}\text{C}$ followed by sodium borohydride reduction gave an acid, which was esterified using diazomethane to afford the piperidine derivative **4**, $[\alpha]_{\text{D}}^{26} -4.4^{\circ}$ ($c\ 0.18$, CHCl_3), in 60% yield. The absolute configuration of **4** was determined by its chemical correlation to (+)-dihydropinidine, the dihydro derivative of (-)-pinidine isolated from various species of *Pinus* plants.⁹) The conversion of the hydroxyl on **4** into the methyl group was carried out by the following sequences. The aldehyde obtained from the Swern oxidation of **4** was treated with ethanedithiol and boron trifluoride etherate to give the thioacetal, which was subjected to desulfurization with Raney nickel to afford an α -methyl piperidine (**8**) in 63% yield. Reduction of **8** with lithium triethylborohydride (Super-Hydride) in THF at $0\text{ }^{\circ}\text{C}$ followed by the Swern oxidation of the resulting alcohol gave an aldehyde, which was subjected to the Wittig reaction to afford the olefin **9** in 60% yield. The catalytic hydrogenation of **9** over 5% Pd/C and removal of the methoxycarbonyl group with trimethylsilyl iodide (TMSI)¹⁰) furnished (+)-dihydropinidine (**10**) in 87% yield. Synthetic (+)-dihydropinidine hydrochloride had a value of $[\alpha]_{\text{D}}^{26} +11.6^{\circ}$ ($c\ 0.15$, EtOH), which is parallel to that $[[\alpha]_{\text{D}}^{25} +12.8^{\circ}$ ($c\ 1.07$, EtOH)]¹¹) published for an authentic specimen from natural (-)-pinidine, and possessed the spectral properties (^1H and ^{13}C NMR and mass) identical with those for (\pm)-dihydropinidine.^{12a}) Thus the absolute configuration of **4** was determined to be *2R* and *6S*.



Reagents and conditions: a) lithium amide (**6**), TMSCl, $-100\text{ }^{\circ}\text{C}$; b) O_3 , CH_2Cl_2 -MeOH (10:1), $-78\text{ }^{\circ}\text{C}$ and then NaBH_4 ; c) CH_2N_2 ; d) $(\text{COCl})_2$, DMSO, Et_3N , -78 to $0\text{ }^{\circ}\text{C}$; e) ethanedithiol, $\text{BF}_3\cdot\text{OEt}_2$; f) Raney nickel (W-4); g) Super-Hydride, THF, $0\text{ }^{\circ}\text{C}$; h) $\text{CH}_2=\text{PPh}_3$, $0\text{ }^{\circ}\text{C}$ -rt; i) H_2 , 5% Pd/C; j) TMSI, CHCl_3

Scheme 1.

Next, we examined the transformation of **4** into the divergent piperidine synthon **5** (Scheme 2). Protection of the hydroxyl in **4** with *t*-butyldimethylsilyl chloride (TBSCl) followed by reduction with Super-Hydride gave the alcohol **11** in 78 % yield. Dehydration of **11** was effected by treatment with *o*-nitrophenyl selenocyanate followed by oxidation with H₂O₂¹³ to produce the olefin **12** in 71% yield. Ozonolysis of **12** and subsequent reduction with sodium borohydride gave **5**¹⁴ in 94% yield.



Reagents and conditions: a) TBSCl, DMAP, Et₃N; b) Super-Hydride, THF, 0 °C; c) *o*-NO₂PhSeCN, *n*-Bu₃P and then H₂O₂; d) O₃, CH₂Cl₂-MeOH(10:1), -78 °C and then NaBH₄

Scheme 2.

This piperidine derivative **5** can be one of the important chiral building blocks for the synthesis of many naturally occurring piperidine alkaloids, and it would be possible to synthesize both enantiomers of natural products possessing the *cis*-2,6-disubstituted piperidine skeleton from **5** since it has the equivalent functional groups on the 2 and 6 positions. The enantioselective synthesis of piperidine alkaloids from **5** is now being examined.

We are grateful to Professor K. Koga, Tokyo University, for his useful advices for the preparation and properties of the chiral amines **6** and **7**, and indebted to Professor C. Kibayashi, Tokyo College of Pharmacy, for his kindly providing us with the ¹H and ¹³C NMR chart of (±)-dihydropinidine.

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