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An efficient stereoselective synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid using chlorosulfonyl isocyanate

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Abstract—An efficient stereoselective syntheses of (2*S*,3*S*)-3-hydroxypipecolic acid and (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol were achieved from *p*-anisaldehyde via the regioselective and diastereoselective introduction of an N-protected amine group using chlorosulfonyl isocyanate, ring-closing methathesis, and oxidation of *p*-methoxyphenyl group as the key steps.

Chiral hydroxylated piperidines are important core structures that are found in many bioactive natural and non-natural compounds. These compounds have received considerable attention on account of their many pharmacological properties.[1] Therefore, many novel asymmetric synthetic methods have been developed for their synthesis.[2] (2*S*,3*S*)-3-Hydroxypipecolic acid (**1**)[3] and (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**)[4] are nitrogen-containing six-membered cyclic compounds that have been used as important synthetic building blocks for the preparation of many naturally occurring alkaloids such as (+)-febrifugine (**3**),[5] a potent antimalarial agent, and (+)-prosophylline (**4**),[6] which exhibit analgesic, anesthetic, and antibiotic activities (Fig. 1).

As a part of our research program aimed at developing enantioselective syntheses of polyhydroxylated alkaloids, we became interested in developing an efficient route for synthesizing polyhydroxylated piperidine alkaloids such as (2*S*,3*S*)-3-hydroxypipecolic acid (**1**) and (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**).

This letter reports the novel enantioselective syntheses of **1** and **2** using Brown's asymmetric aldol reaction as a source of chirality and the regioselective and diastereoselective amination using chlorosulfonyl isocyanate (CSI).[7]

Scheme 1 outlines the retrosynthetic analyses of compounds **1** and **2**. The common intermediate **5** would be derived from the protected 1,2-amino alcohol **6a** by N-allylation and ring-closing methathesis. Compound **6a** would be prepared via the regioselective and diastereoselective installation of NHCbz group into *anti*-1,2-dibenzyl ether **7** using CSI reaction.

In the initial studies, the regioselectivity and diastereoselectivity of the reaction of *anti*-1,2-dibenzyl ether **7**

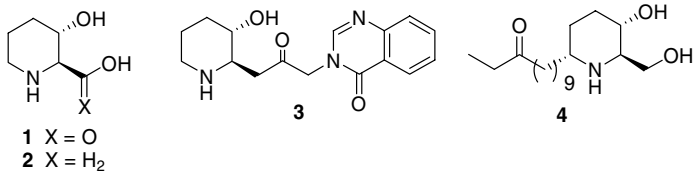

Figure 1. Structure of polyhydroxylated piperidines.

Keywords: Chlorosulfonyl isocyanate; 3-Hydroxypipecolic acid; Amination; Diastereoselectivity.
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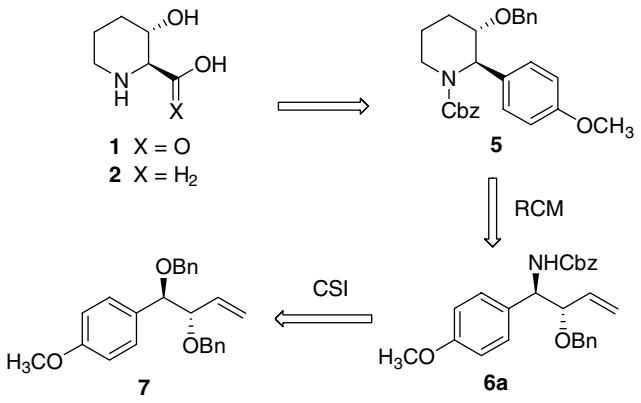


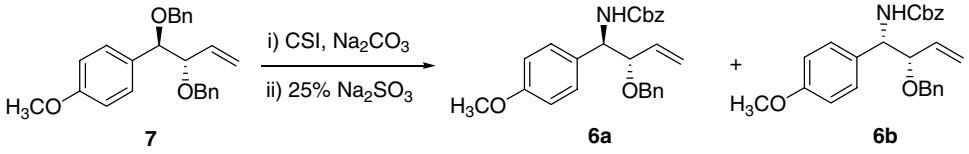
Scheme 1. Retrosynthetic analyses of **1** and **2**.

with CSI were investigated. As expected, the regioselectivity was completely controlled by the stability of the carbocation intermediate, and the diastereoselectivity differed widely according to the effects of the solvent and temperature, as summarized in Table 1.

As shown in entries 1 and 4, the reaction in methylene chloride at 0 °C gave the corresponding diastereoisomers (**6a** and **6b**) as an *anti*/*syn* mixture of 8:1 in 87% yield, and the reaction in hexane at 0 °C furnished an *anti*/*syn* mixture of 13:1 in favor of the desired *anti*-isomer **6a**. In particular, the reaction in toluene at −78 °C (entry 8) produced a significantly higher diastereoselectivity of 49:1 in 90% yield. Table 1 shows the successful attempts to optimize the diastereoselectivity by varying the solvent and temperature. Consequently, *anti*-diastereoselectivity increased with decreasing polarity of the solvent or by decreasing the reaction temperature.

The reactions of *syn*-1,2-dibenzyl ether **8** with CSI were examined in various solvents and at different temperatures. Table 2 gives a summary of the results. In the case of **8**, *syn*-1,2-amino alcohol **6b** was obtained as the

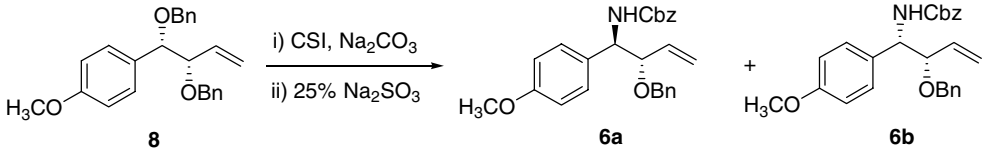
Table 1. CSI reactions of the *anti*-1,2-dibenzyl ether **7** in various solvents and at different temperatures[a]



Entry	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	Ratio[c] (**6a**:**6b**)
1	CH_2Cl_2	0	1	87	8:1
2	$CHCl_3$	0	3	94	10:1
3	Et_2O	0	6	81	11:1
4	Hexane	0	8	80	13:1
5		−78	12	82	25:1
6	Toluene	0	8	80	25:1
7		−40	16	90	38:1
8		−78	24	90	49:1

[a] All reactions were carried out at 0 °C with CSI (3.0 equiv) and Na_2CO_3 (4.5 equiv).
[b] Isolated yield of pure materials.
[c] Isomer ratio determined by ^1H NMR spectroscopy.

Table 2. CSI reactions of the *syn*-1,2-dibenzyl ether **8** in various solvents and at different temperatures[a]



Entry	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	Ratio[c] (**6a**:**6b**)
1	CH_2Cl_2	0	1	93	1:1.3
2	$CHCl_3$	0	3	94	1:1.6
3	Et_2O	0	6	93	1:1.7
4	Toluene	0	9	85	1:1.9
5		−78	24	90	1:4.6
6	CCl_4	0	11	80	1:2.2
7	Hexane	0	2.5	79	1:6.3
8		−78	18	80	1:12

[a] All reactions were carried out at 0 °C with CSI (3.0 equiv) and Na_2CO_3 (4.5 equiv).
[b] Isolated yield of pure materials.
[c] Isomer ratio determined by ^1H NMR spectroscopy.

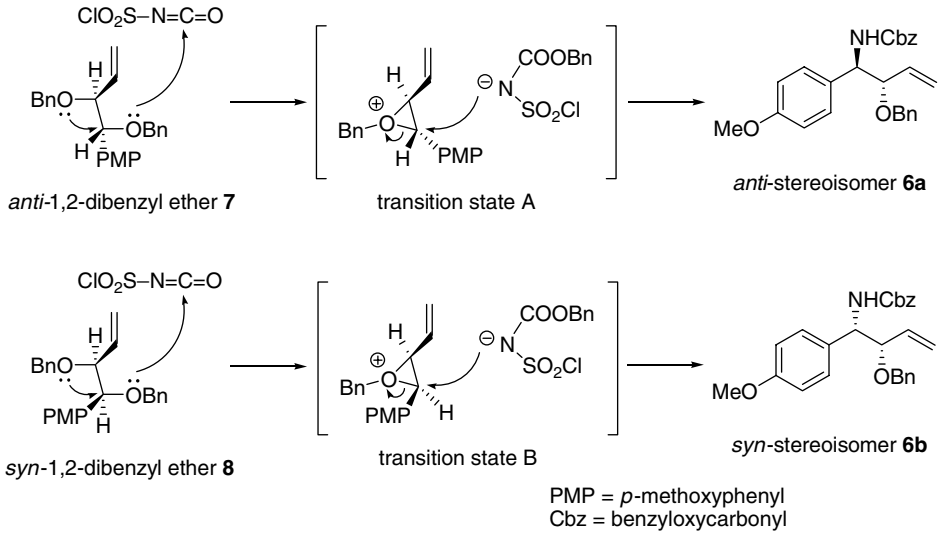


Figure 2. Neighboring group effect of nucleophilic attack on the *p*-methoxybenzylic carbocation.

major product, which had the same *syn*-stereochemistry as the starting material.

Although the diastereoselective ratio of the *syn*-1,2-dibenzyl ether was reduced when compared with the *anti*-stereoisomer, the reaction in hexane at −78 °C (entry 8) afforded the *syn*-isomer as the major product with a high diastereoselectivity of 1:12 in 80% yield.

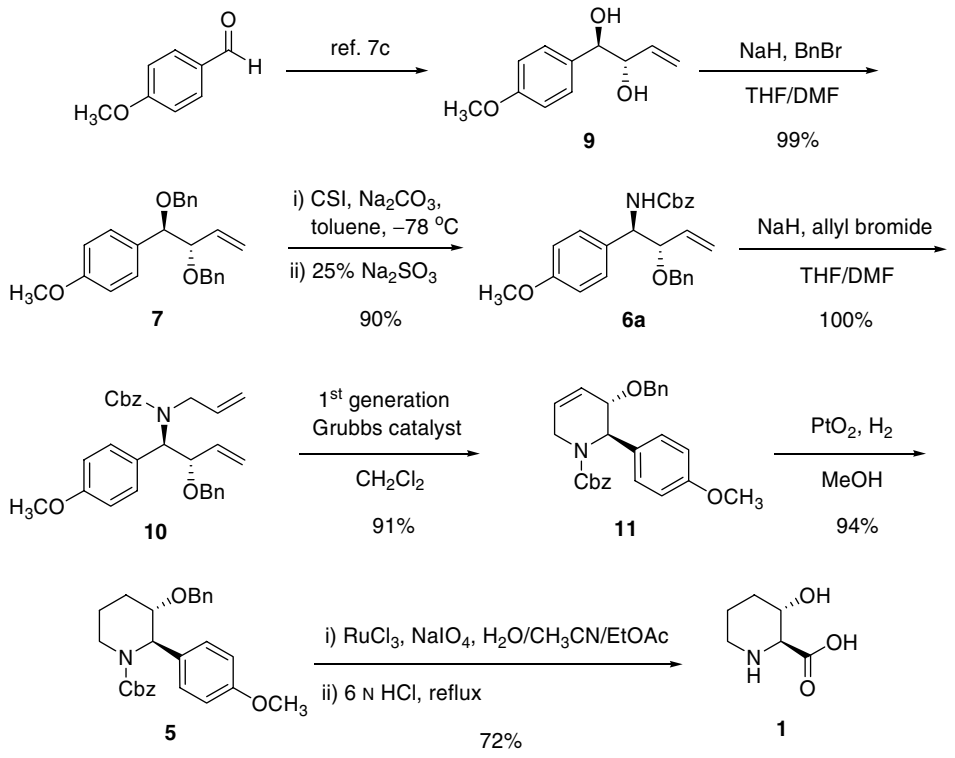
Tables 1 and 2 show that the diastereoselectivity of these reactions can be explained by the neighboring group effect[7c,8] and a partial S_N1 mechanism, where the NHCbz group orientation retains its original configuration in benzyl ether via a double inversion of the configuration, as shown in Figure 2. The reduced diastereoselectivity of compound **8** may have been caused by the increased steric repulsion between the two bulky substituents, which were placed in the cis-form (transition state B). As the polarity of the solvent decreased, there was a larger increase in the rate of vicinal OBn attack (the neighboring group effect) than nucleophile attack, which increased the diastereoselectivity. Therefore, these reactions are more efficient in non-polar solvents.

Based on the above results, the total syntheses of (2*S*,3*S*)-3-hydroxypipecolic acid (**1**) and (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**) were achieved using *p*-anisaldehyde as the starting material (Scheme 2). *p*-Anisaldehyde was converted into the diol **9** with high enantioselectivity (95% ee via the Mosher ester) and diastereoselectivity (>99% ds) according to the known procedure.[7c] Benzylation of the diol **9** with benzyl bromide and sodium hydride in DMF and THF gave the fully protected *anti*-1,2-dibenzyl ether **7** in 99% yield. The regioselective and diastereoselective CSI reaction of **7** was carried out on anhydrous toluene at −78 °C for 24 h, which was followed by desulfonylation with an aqueous solution of 25% sodium sulfite to afford the Cbz-protected amine **6a** with a high diastereoselectivity (*anti*/*syn* = 49:1, 98% ds) in 90% yield.

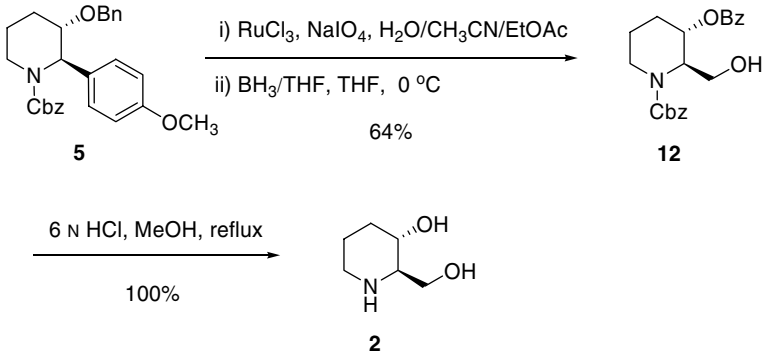
The allylation of NHCbz with allyl bromide afforded compound **10**, in a quantitative yield, which was readily cyclized by using first-generation Grubbs catalyst to give the unsaturated piperidine **11** in 91% yield. Hydrogenation of the olefin **11** with platinum oxide,[5i] followed by oxidation with $RuCl_3$ (0.15 equiv) and $NaIO_4$ (17 equiv) in $H_2O/CH_3CN/EtOAc$ (2:1:1)[9] gave the intermediate carboxylic acid, in which the benzyl group had been oxidized to the benzoate.[10] The removal of the benzoyl and benzyloxycarbonyl group with 6 N hydrochloric acid furnished *trans*-pipecolic acid **1** as a crystalline form, mp 229–235 °C (MeOH) [lit.[3b] 232–236 °C]; $[\alpha]_D^{25}$ +13.0 (*c* 0.5, 10% aq HCl) [lit.[3b] $[\alpha]_D^{25}$ +13.5 (*c* 0.5, 10% aq HCl)]. The spectral properties (^1H and ^{13}C NMR) of synthetic compound **1** were in full agreement with the reported literature values.[11]

The total synthesis of (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**) was achieved from the piperdine **5** via a three-step synthesis, as illustrated in Scheme 3. Oxidation of *p*-methoxyphenyl group of **5** under the above-mentioned reaction condition[9] gave the intermediate carboxylic acid, which was reacted with borane–tetrahydrofuran complex without purification to give the desired alcohol **12** in 64% overall yield. Acid hydrolysis of **12** gave 2,3-*trans*-piperidine **2**, with the specific rotation and spectral data (^1H and ^{13}C NMR), identical to those reported in the literature.[12]

In conclusion, we reported an efficient stereoselective syntheses of (2*S*,3*S*)-3-hydroxypipecolic acid and (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol via the regioselective and diastereoselective introduction of an N-protected amine group using the reaction of *anti*-1,2-dibenzyl ether with CSI, ring-closing methathesis, and oxidation of *p*-methoxyphenyl group. We believe that our synthetic strategy can be applied to the preparation of various polyhydroxylated piperidine alkaloids or other natural products containing a nitrogen atom in the ring.



Scheme 2. Total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**1**).



Scheme 3. Total synthesis of (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.040.

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11. Analytical data for **1**: $R_f = 0.32$ (EtOAc/MeOH/30% NH_4OH 5:5:1); mp 229–235 °C (decomp); $[\alpha]_D^{25}$ +13.0 (*c* 0.5, 10% HCl); ^1H NMR (500 MHz, D_2O) δ 1.59–1.67 (m, 2H, H-4_{ax} and H-5_{ax}), 1.84–1.95 (m, 2H, H-4_{eq} and H-5_{eq}), 3.02 (ddd, 1H, $J = 11.0$, 7.0, 2.5 Hz, H-6_{ax}), 3.25–3.30 (m, 1H, H-6_{eq}), 3.53 (d, 1H, $J = 6.5$ Hz, H-2), 4.05–4.08 (br, 1H, H-3); ^{13}C NMR (125 MHz, D_2O) δ 18.50, 28.32, 42.60, 62.10, 66.04, 172.12; HRMS (CI) Calcd for $C_6H_{12}NO_3$ [M+H$^+$] 146.0817, found 146.0817.
12. Analytical data for **2**: $R_f = 0.20$ ($CHCl_3$/MeOH 5:1); mp 155 °C (decomp); $[\alpha]_D^{25}$ +55.0 (*c* 0.1, MeOH); ^1H NMR (500 MHz, D_2O) δ 1.53–1.60 (m, 1H), 1.71–1.76 (m, 1H), 1.99 (dt, 1H, $J = 14.5$, 3.5 Hz), 2.14–2.19 (m, 1H), 2.93 (dt, 1H, $J = 13.0$, 3.5 Hz), 2.98 (ddd, 1H, $J = 9.5$, 6.5, 3.5 Hz), 3.33 (br dd, 1H, $J = 13.0$, 3.5 Hz), 3.74 (dt, 1H, $J = 9.5$, 4.5 Hz), 3.85 (dd, 1H, $J = 12.5$, 6.5 Hz), 3.98 (dd, 1H, $J = 12.5$, 3.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ 21.22, 31.01, 43.90, 58.97, 61.97, 65.48; HRMS (CI) Calcd for $C_6H_{14}NO_2$ [M+H$^+$] 132.1024, found 132.1024.