Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2622–2633

Synthesis and conformational analysis of 3-hydroxypipecolic acid analogs via CSI-mediated stereoselective amination

In Su Kim, Joa Sub Oh, Ok Pyo Zee and Young Hoon Jung*

College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea

Received 9 December 2006; revised 16 January 2007; accepted 17 January 2007
Available online 20 January 2007

Abstract—A short and efficient stereoselective synthetic approach toward substituted piperidines, involving (2*S*,3*S*)-3-hydroxypipecolic acid **1**, (2*R*,3*S*)-3-hydroxypipecolic acid **3**, and their acid-reduced analogs **2** and **4**, has been developed. The requisite *anti*- and *syn*-1,2-amino alcohols **11** and **12** for the preparation of title four piperidine analogs **1**–**4** were synthesized via the regioselective and diastereoselective amination of *anti*- and *syn*-1,2-dibenzyl ethers **13** and **14** using chlorosulfonyl isocyanate (CSI). As a result, reaction of *anti*-1,2-dibenzyl ether **13** with CSI afforded exclusively the *anti*-1,2-amino alcohol **11** with the diastereoselectivity of 49:1 in toluene at −78 °C and *syn*-isomer **14** gave the *syn*-1,2-amino alcohol **12** as the major product with the diastereoselectivity of 12:1 in hexane at −78 °C. The result of these reactions could be explained by the neighboring group effect leading to retention of stereochemistry. In addition, conformational changes of *trans*-piperidine intermediate **9** in terms of the nature of *N*-protecting groups are described. The conformations of **9** and **24**–**28** were confirmed by ^{1}H NMR analysis and NOE correlation. Furthermore, the conformations of piperidines **18** and **23** with hydroxyl methyl substituent at C-2 were investigated by NMR spectroscopy.

1. Introduction

Polyhydroxylated piperidine alkaloids have been frequently reported in nature and synthesized in laboratories. Moreover, these alkaloids have received considerable attention as potential medical agents because of their interesting pharmacological properties.[1] Consequently, the therapeutic potentials of polyhydroxylated piperidine alkaloids have been the subject of intensive research, and various synthetic approaches to produce them have been reported.[2] In particular, stereoisomeric 3-hydroxypipecolic acids and their acid-reduced analogs, such as (2*S*,3*S*)-3-hydroxypipecolic acid (**1**), (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**), (2*R*,3*S*)-3-hydroxypipecolic acid (**3**), and (2*S*,3*S*)-2-hydroxymethylpiperidin-3-ol (**4**), are nitrogen-containing six-membered cyclic compounds that have been used as important synthetic building blocks for the preparation of many naturally occurring polyhydroxylated piperidine alkaloids. For example, *trans*-3-hydroxypipecolic acid (**1**) is a component of (−)-swainsonine (**5**),[3] which has α-D-mannosidase inhibitory activity, and *cis*-3-hydroxypipecolic acid (**3**) constitutes a part of the structure of the anti-tumor tetrazomine (**6**).[4] In addition, *trans*-3-hydroxypipecolic acid (**1**) and its reduced analog **2** have been used to prepare other natural products such as (+)-febrifugine (**7**),[5] a potent anti-malarial agent, and (+)-prosophylline (**8**),[6] which exhibits analgesic, anesthetic, and antibiotic activities (Fig. 1).

Due to the unique structural features of these piperidine alkaloids and their potent biological activities, several synthetic methods for stereoisomeric 3-hydroxypipecolic acid analogs have been recently developed. The majority of synthetic approaches for 3-hydroxypipecolic acids could be divided into three large categories, e.g., asymmetric synthesis for the construction of the stereogenic centers,[7] resolution via chemical and enzymatic processes,[8] and synthetic approaches using chiral pool.[4,9] In an example for asymmetric synthesis, Kumar and Bodas reported the total synthesis of both the enantiomers of *trans*-3-hydroxypipecolic acid employing Sharpless asymmetric dihydroxylation and epoxidation.[7a] However, most synthetic route to *trans*- and *cis*-3-hydroxypipecolic acids have relied upon the chiral pool, and asymmetric syntheses for them are rather scarce. Among the chiral starting materials used, the low-cost amino acids such as D- and L-serines were the most widely employed, since it allows the straightforward installation of β-hydroxy-α-amino acid framework. In a recent paper, Liang and Datta presented efficient synthetic strategies to both *trans*- and *cis*-3-hydroxypipecolic acid, starting from D-serine, via diastereoselective addition of homoallyl Grignard reagent.[9a] In another example, Jourdant and Zhu described the stereodivergent synthesis of both *trans*- and *cis*-3-hydroxypipecolic acid, using L-serine as a starting material.[9c]

Keywords: Chlorosulfonyl isocyanate; 3-Hydroxypipecolic acid; 2-Hydroxymethylpiperidin-3-ol; Amination.
* Corresponding author. Tel.: +82 31 290 7711; fax: +82 31 290 7773; e-mail: yhjung@skku.ac.kr

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.028

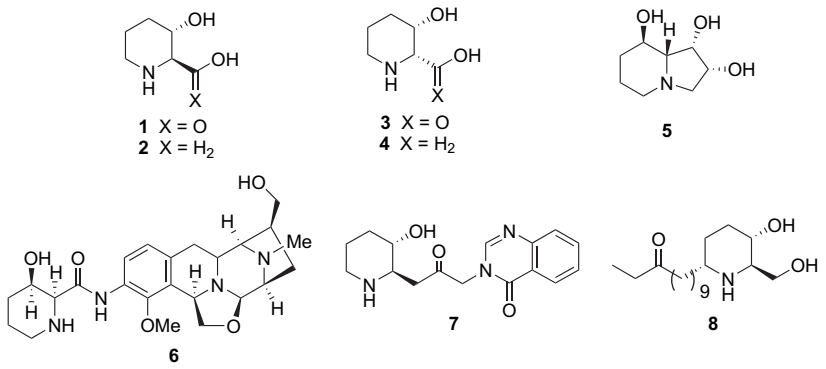


Figure 1. Structures of polyhydroxylated piperidine alkaloids.

In spite of the several syntheses of stereoisomeric 3-hydroxypipecolic acids, synthetic approaches for their reduced analogs **2** and **4** could be found in a few presentations.[10] In a representative example, Takahata et al. demonstrated asymmetric total synthesis of *trans*- and *cis*-2-hydroxymethylpiperidin-3-ol via diastereoselective addition of vinyl metals to Garner aldehyde derived from D-serine.[10a–c]

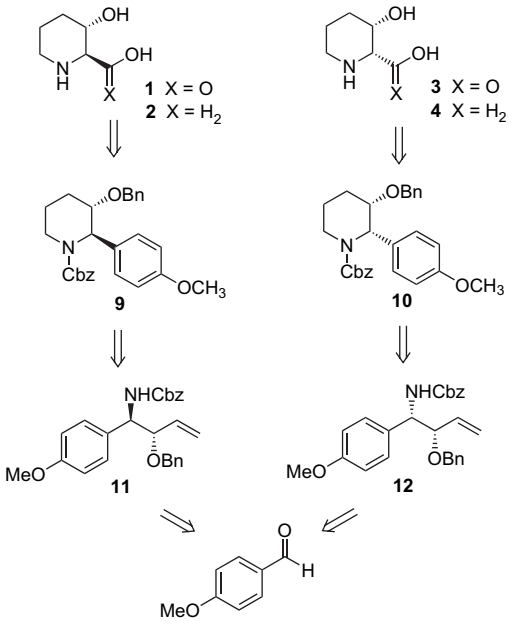
Recently, we demonstrated the regioselective and diastereoselective amination of a variety of allyl ethers using chlorosulfonyl isocyanate[11] and applied our CSI methodology to the synthesis of various polyhydroxylated alkaloids including (2*S*,3*S*)-3-hydroxypipecolic acid.[12] As a part of our research program aimed at developing the enantioselective syntheses of various polyhydroxylated alkaloids using our method of CSI-mediated stereoselective amination, we attempted to synthesize polyhydroxylated piperidine alkaloids, i.e., stereoisomeric 3-hydroxypipecolic acids and their acid-reduced analogs.

Herein, we describe the total synthesis of stereoisomeric piperidines **1**–**4** via the stereoselective synthesis of amino alcohols using chlorosulfonyl isocyanate, and the relation between conformational changes in the *trans*-piperidine intermediate **9** and the nature of *N*-protecting groups.

2. Results and discussion

Retrosynthetic analysis of the title piperidines **1**–**4** is shown in Scheme 1. Piperidine alkaloids **1**–**4** would be prepared by the regioselective and diastereoselective installation of a NHCbz moiety into *anti*-1,2-dibenzyl ether **13** and *syn*-1,2-dibenzyl ether **14**, which are both easily derived from commercially available *p*-anisaldehyde using chiral borane reagents,[13,14] to give the corresponding *anti*-1,2-amino alcohol **11** and *syn*-1,2-amino alcohol **12**. Ring-closing metathesis[15] of amino alcohols **11** and **12**, followed by Pt-catalyzed hydrogenation of the double bond was expected to afford the piperidine intermediates **9** and **10**, which in turn could be transformed into the desired piperidines **1**–**4** via the oxidation of the *p*-methoxyphenyl group.

In the initial studies, we investigated the regioselectivity and diastereoselectivity of the reaction of *anti*-1,2-dibenzyl ether **13** with CSI. As expected, the regioselectivity was completely controlled by the stability of the carbocation



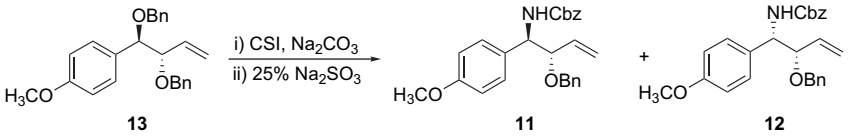
Scheme 1. Retrosynthetic analysis of **1**–**4**.

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 (**11** and **12**) 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 the favor of the desired *anti*-isomer **11**. 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 decreasing reaction temperature.

The reactions of *syn*-1,2-dibenzyl ether **14** with CSI were examined in various solvents and at different temperatures. Table 2 gives a summary of the results. In the case of **14**, *syn*-1,2-amino alcohol **12** was obtained as the major product, which had the same *syn*-stereochemistry as the starting material. Although the diastereoselective ratio of the

Table 1. CSI reactions of the *anti*-1,2-dibenzyl ether **13** in various solvents and at different temperatures[a]

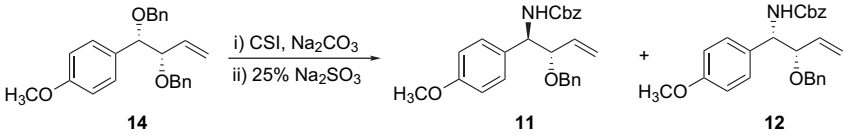


13 **11** **12**

Entry	Solvent	T (°C)	Time (h)	Yield[b] (%)	Ratio[c] (**11**:**12**)
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 with CSI (3.0 equiv) and Na_2CO_3 (4.5 equiv).
[b] Isolated yield of pure materials.
[c] Isomer ratio determined by ^{1}H NMR spectroscopy.

Table 2. CSI reactions of *syn*-1,2-dibenzyl ether **14** in various solvents and at different temperatures[a]



14 **11** **12**

Entry	Solvent	T (°C)	Time (h)	Yield[b] (%)	Ratio[c] (**11**:**12**)
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 with CSI (3.0 equiv) and Na_2CO_3 (4.5 equiv).
[b] Isolated yield of pure materials.
[c] Isomer ratio determined by ^{1}H NMR spectroscopy.

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[11a,16] 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 **12** 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 decreases, the attack of the vicinal OBn (the neighboring group effect) becomes faster than the nucleophilic attack and the diastereoselectivity of 1,2-amino alcohol increases. Therefore, this reaction is 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 from commercially available *p*-anisaldehyde (Scheme 2). *p*-Anisaldehyde was converted into the diol **15** with excellent diastereoselectivity (>99% ds by NMR analysis) and enantioselectivity (95% ee via the Mosher ester), as shown in the reported literature.[11a,b] Perbenzylation of the diol **15** gave the fully protected *anti*-1,2-dibenzyl ether **13** in excellent yield. The regioselective and diastereoselective CSI reaction of **13** was carried out in anhydrous toluene at −78 °C for 24 h, followed by the removal of the *N*-chlorosulfonyl moiety with aqueous 25% sodium sulfite, to afford the *anti*-1,2-amino alcohol **11** with excellent diastereoselectivity (*anti*/*syn*=49:1, 98% ds by NMR analysis) in 90% yield.

The allylation of **11** with allyl bromide afforded compound **16** in quantitative yield, and the cyclization of **16** was readily performed with a first-generation Grubbs catalyst to give the unsaturated piperidine **17** in 91% yield. Hydrogenation of the olefin **17** with platinum oxide,[5j] followed by the oxidation of **9** with $RuCl_3$ (0.15 equiv) and $NaIO_4$ (17 equiv) in $H_2O/CH_3CN/EtOAc$ (2:1:1)[17] gave the intermediate carboxylic acid, in which the benzyl group had been oxidized to benzoate.[18] The removal of the benzoyl and benzyloxycarbonyl groups with 6 N hydrochloric acid furnished crystalline *trans*-3-hydroxypipecolic acid **1**. The spectral properties (^{1}H and ^{13}C NMR) and specific rotation of

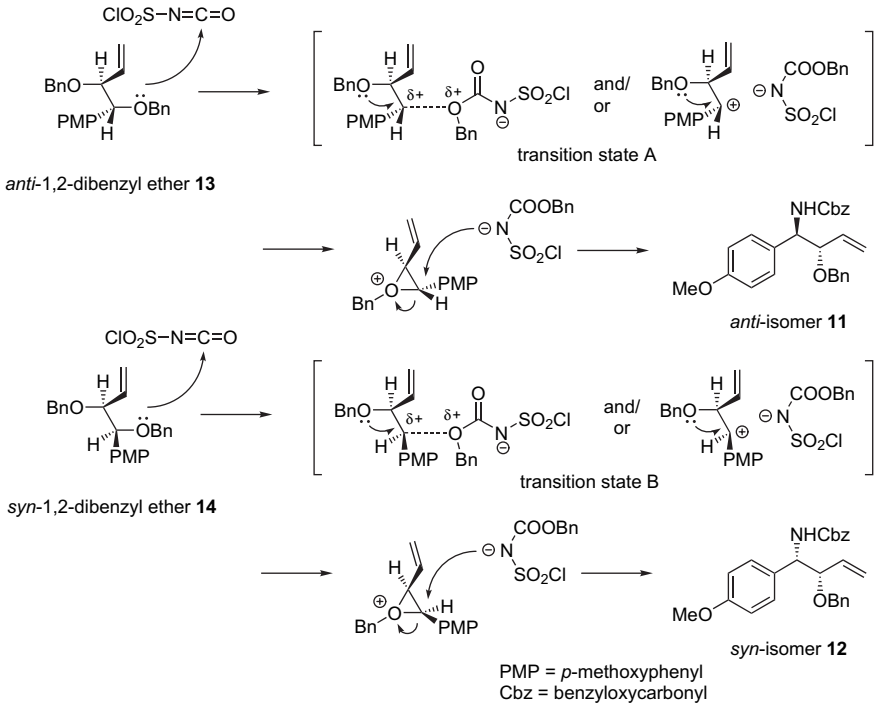
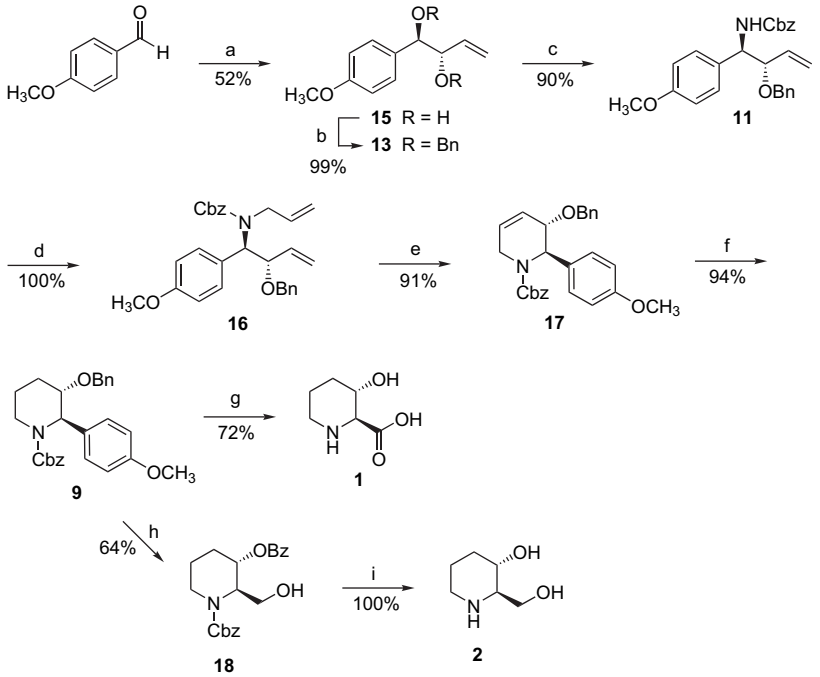


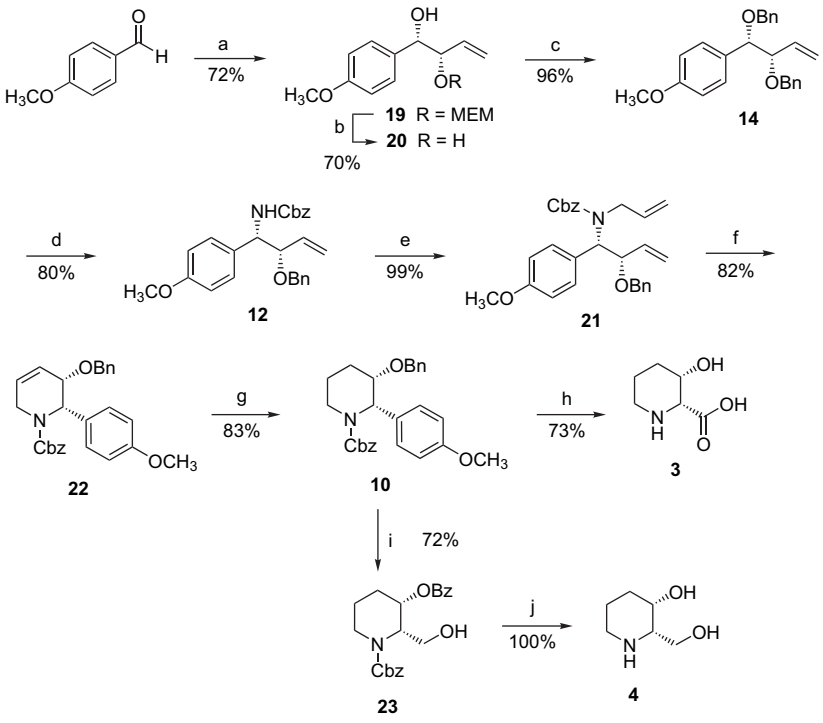
Figure 2. Neighboring group effect of nucleophilic attack on the *p*-methoxybenzylic carbocation.

synthesized compound **1** were in full agreement with the reported literature values.[9e]

Furthermore, the total synthesis of (2*R*,3*S*)-2-hydroxymethyl-piperidin-3-ol (**2**) was achieved from the piperidine **9** via a three-step procedure. Oxidation of the *p*-methoxyphenyl group of **9** gave the intermediate carboxylic acid, which was reacted with borane–tetrahydrofuran complex without purification to give the desired alcohol **18** in 64% overall yield. Finally, acid hydrolysis of **18** gave 2,3-*trans*-piperidine **2**, with specific rotation and spectral data (^{1}H and ^{13}C NMR) identical to those reported in the literature.[10a]



Scheme 2. Reagents and conditions: (a) (i) allyl(diisopropylamino)dimethylsilane, *n*-BuLi, TMEDA, (−)-*B*-methoxydiisopinocamphenylborane, $BF_3{\cdot}OEt_2$, Et_2O, −78 °C, 3 h; (ii) KF, $KHCO_3$, 30% H_2O_2, THF, MeOH, rt, 20 h; (b) NaH, BnBr, THF, DMF, rt, 11 h; (c) (i) CSI, Na_2CO_3, toluene, −78 °C, 24 h; (ii) 25% Na_2SO_3, rt, 24 h; (d) NaH, allyl bromide, THF, DMF, rt, 2 h; (e) first-generation Grubbs catalyst, CH_2Cl_2, rt, 4 h; (f) PtO_2, MeOH, rt, 1 h; (g) (i) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, rt, 4 h; (ii) 6 N HCl, reflux, 10 h; (h) (i) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, rt, 4 h; (ii) $BH_3{\cdot}THF$, THF, 0 °C, 24 h; (i) 6 N HCl, MeOH, reflux, 24 h.



Scheme 3. Reagents and conditions: (a) (i) 3-(2-methoxyethoxymethoxy)-propene, *s*-BuLi, (+)-*B*-methoxydiisopinocamphenylborane, $BF_3 \cdot OEt_2$, THF, −78 °C, 3 h; (ii) 3 M NaOH, 30% H_2O_2, rt, 8 h; (b) concd HCl, MeOH, rt, 1 h; (c) NaH, BnBr, THF, DMF, rt, 8 h; (d) (i) CSI, Na_2CO_3, hexane, −78 °C, 18 h; (ii) 25% Na_2SO_3, rt, 24 h; (e) NaH, allyl bromide, THF, DMF, rt, 1 h; (f) first-generation Grubbs catalyst, CH_2Cl_2, rt, 4 h; (g) PtO_2, MeOH, rt, 30 min; (h) (i) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, rt, 4 h; (ii) 6 N HCl, reflux, 24 h; (i) (i) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, rt, 4 h; (ii) $BH_3 \cdot THF$, THF, 0 °C, 24 h; (j) 6 N HCl, MeOH, reflux, 24 h.

For the synthesis of the 2,3-*cis*-piperidines **3** and **4** as 2-stereoisomeric forms of **1** and **2**, we focused on the preparation of *syn*-1,2-amino alcohol **12** via the CSI-mediated stereoselective amination of *syn*-1,2-dibenzyl ether **14**, because the stereochemistry of the starting material is retained through the neighboring group effect for polybenzyl ethers[12a] and 1,2-dibenzyl ethers.[12b] With this in mind, we initially prepared the enantiomeric pure monoprotected *syn*-vicinal diol to act as a precursor for *syn*-1,2-dibenzyl ether **14**. As shown in Scheme 3, alkoxyallylboration of *p*-anisaldehyde with (+)-*B*-γ-methoxyethoxymethoxyallyldiisopinocamphenylborane, prepared from (+)-*B*-methoxydiisopinocamphenylborane and lithiated allyl methoxyethoxymethoxyallyl ether in THF at −78 °C, followed by oxidation, provided the MEM-monoprotected diol **19** in 72% yield with high diastereoselectivity (>95% ds by NMR analysis) and enantioselectivity (90% ee via the Mosher ester).[14]

The MEM group of **19** was removed by acidic cleavage to afford the desired *syn*-vicinal diol **20** in 70% yield. The diol **20** was then perbenzylated with benzyl bromide in the presence of sodium hydride to afford *syn*-1,2-dibenzyl ether **14** in excellent yield, and treatment of **14** with CSI in the presence of anhydrous hexane at −78 °C, followed by reduction of the *N*-chlorosulfonyl group, furnished the desired *syn*-1,2-amino alcohol **12** with high diastereoselectivity (*syn*/*anti*=12:1, 92% ds by NMR analysis) in 80% yield. Allylation of **12** and subsequent ring-closing metathesis furnished unsaturated piperidine **22**. Fortunately, the minor trans-diastereomer **17** was completely removed (cat. 6%) by column chromatography. Hydrogenation of the olefin **22**, oxidation of its *p*-methoxyphenyl group, and removal of the protecting groups by acid hydrolysis gave (2*R*,3*S*)-3-hydroxypipecolic acid (**3**) in good yield.

In addition, the formation of (2*S*,3*S*)-2-hydroxymethylpiperidin-3-ol (**4**) was achieved, with good overall yields, through the same synthetic route applied to the synthesis of *trans*-2-hydroxymethylpiperidin-3-ol (**2**). The analytical data (^{1}H NMR, ^{13}C NMR, and specific rotation) of synthesized compounds **3** and **4** were in full agreement with reported literature values.[4a,10b]

Observations of vicinal coupling constants and NOE correlations in piperidine **9** produced interesting results. The conformation of **9** allowed a remarkably undistorted chair-like conformation with axially oriented bulky substituents, e.g., *p*-methoxyphenyl and benzyloxy groups (Fig. 3).

In order to confirm the interaction between the *p*-methoxyphenyl group at C-2 and the *N*-benzyloxycarbonyl group in **9**, we attempted to introduce various *N*-protecting groups

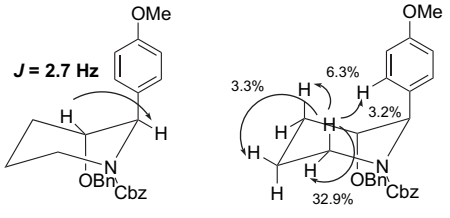
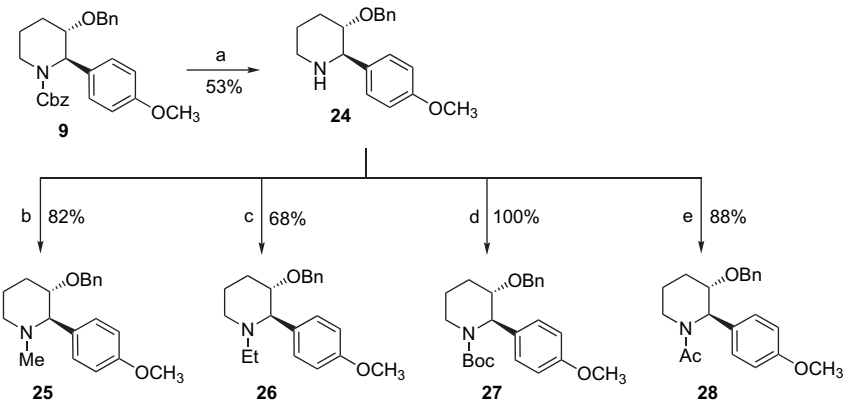


Figure 3. Conformational analysis of piperidine **9** through observations of vicinal coupling constants and NOE correlations.



Scheme 4. Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, rt, 1 h; (b) K_2CO_3, CH_3I, THF, 50 °C, 2 h; (c) K_2CO_3, C_2H_5I, THF, 50 °C, 3 h; (d) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 1 h; (e) Ac_2O, Et_3N, CH_2Cl_2, rt, 1 h.

into the piperidine **24**, prepared by cleavage of the *N*-benzyloxycarbonyl group of **9**, as illustrated in Scheme 4.

Palladium-catalyzed hydrogenation of the carbamate **9** afforded the piperidine **24**, which was transformed, according to the known synthetic methods, into the *N*-alkylated compounds **25** and **26**, and the *N*-acylated compounds **27** and **28**. The relative configurations and conformations of the piperidines **24**–**28** were determined from coupling constants between pairs of axial protons (J=9.0 Hz) or pairs of equatorial protons (J=2.7 Hz) in the piperidine ring (Fig. 4).

In case of the piperidine **24**, the conformation **29A** with two substituents in an equatorial orientation is strongly favored, because the alternative conformation **29B** is severely destabilized by 1,3-diaxial interaction. Therefore, *N*-alkylated piperidines **25** and **26** also exist in the conformation **29A**. However, *N*-acylated piperidines **27** and **28** took the conformation **29B**, as shown in piperidine **9**. Presumably, because of a strong $A^{(1,3)}$ strain between the *p*-methoxyphenyl group at C-2 and the *N*-acyl groups of **9**, **27**, and **28**, the *p*-methoxyphenyl group occupies the axial position via conformation **29B**.[19] In contrast, the piperidines **24**–**26** were dramatically converted into the chair conformation **29A** to avoid unfavorable 1,3-diaxial interactions between the *p*-methoxyphenyl group at C-2 and the hydrogens at C-4 and C-6.

In addition, the conformations of piperidines **18** and **23** were investigated by NMR spectroscopy. ^{1}H NMR spectra of *trans*-piperidine **18** ($J_{2eq,3eq}=J_{3eq,4eq}=J_{3eq,4ax}=1.5$ Hz) and *cis*-piperidine **23** ($J_{3ax,4ax}=12.0$ Hz) strongly suggested a significant conformational feature, i.e., the hydroxyl methyl substituent at C-2 was located axially (Fig. 5). As described in a previous paper,[20] the *N*-Cbz piperidine ring structure preferably adopts an axial conformation for the substituent at C-2 due to considerable steric hindrance between the *N*-Cbz group and its vicinal substituent.

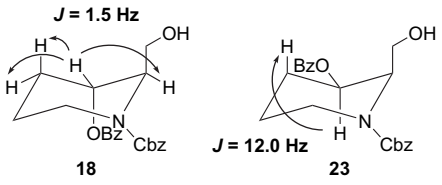


Figure 5. Conformation of the piperidines **18** and **23**.

3. Conclusion

We describe the flexible stereoselective total syntheses of (2*S*,3*S*)-3-hydroxypipecolic and (2*R*,3*S*)-3-hydroxypipecolic acids, and their acid-reduced analogs via the regioselective and diastereoselective amination of 1,2-dibenzyl ether using CSI, ring-closing metathesis, and oxidation of the *p*-methoxyphenyl group. In addition, we describe conformational changes in the *trans*-piperidine intermediate in terms of the nature of *N*-protecting groups. We believe that the described synthetic strategy can be applied to the preparation of various polyhydroxylated piperidine alkaloids or other natural products containing a nitrogen atom in the ring.

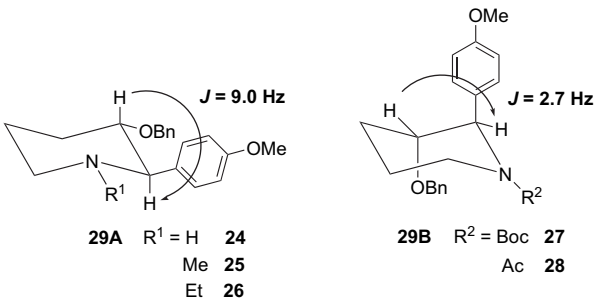


Figure 4. Conformational analysis of the piperidines **24**–**28**.

4. Experimental

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus and were not corrected. Nuclear magnetic resonance spectra

(^{1}H and ^{13}C NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, E. Merck). High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505, or JMS-600 spectrometer.

4.1.1. (1*R*,2*S*)-1-*p*-Methoxyphenylbut-3-ene-1,2-diol (15). To a stirred solution of allyl(diisopropylamino)dimethylsilane (5.10 mL, 20.86 mmol) in anhydrous Et_2O (25 mL) were added TMEDA (3.15 mL, 20.86 mmol) and *n*-butyllithium (13.04 mL, 20.86 mmol, 1.6 M in hexane) at 0 °C under N_2. The solution was stirred for 4 h at 0 °C and cooled to −78 °C. The reaction mixture was treated with (−)-*B*-methoxydiisopinocamphenylborane (7.85 g, 24.83 mmol) in anhydrous Et_2O (5 mL) and stirred at −78 °C for 2 h. To this solution were added boron trifluoride etherate (3.43 mL, 27.03 mmol) and a solution of *p*-anisaldehyde (2.00 g, 14.69 mmol) in anhydrous Et_2O (5 mL). The reaction mixture was stirred at −78 °C for 3 h. To this mixture were added THF (20 mL), MeOH (20 mL), KF (2.43 g, 41.87 mmol), $KHCO_3$ (4.19 g, 41.87 mmol), and 30% H_2O_2 (45 mL). The reaction mixture was stirred for 20 h at room temperature and cooled to 0 °C, and the excess H_2O_2 was quenched by the addition of $Na_2S_2O_3$. The mixture was diluted with EtOAc (100 mL) and filtered through Celite pad. The Celite pad was washed with EtOAc, the filtrate was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) and recrystallization (toluene) to give 1.48 g (52%) of the *anti*-diol **15** as a white solid. R_f=0.25 (hexane/EtOAc 1:1); mp 87–89 °C; $[\alpha]_D^{25}$ −73.2 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2) 3342, 2380, 2282, 1592, 1419, 1121, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95–1.97 (br, 1H), 2.29–2.31 (br, 1H), 3.82 (s, 3H), 4.30 (dd, 1H, *J*=6.0, 5.0 Hz), 4.70 (d, 1H, *J*=5.0 Hz), 5.25 (dd, 1H, *J*=10.5, 1.5 Hz), 5.33 (dd, 1H, *J*=17.5, 1.5 Hz), 5.85 (ddd, 1H, *J*=17.5, 10.5, 6.0 Hz), 6.91 (dd, 2H, *J*=7.0, 2.0 Hz), 7.30 (dd, 2H, *J*=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.51, 76.45, 77.54, 114.05, 118.08, 128.19, 132.10, 136.39, 159.63. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.22; H, 7.29.

4.1.2. (1*R*,2*S*)-1,2-Bis-benzyloxy-1-*p*-methoxyphenylbut-3-ene (13). To a solution of the diol **15** (5.84 g, 30.07 mmol) in anhydrous THF (50 mL) and DMF (50 mL) were added NaH (2.89 g, 72.16 mmol, 60% in mineral oil) and benzyl bromide (9.3 mL, 78.17 mmol) at 0 °C under N_2. The reaction mixture was stirred for 11 h at room temperature and quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (200 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 15:1) to afford 11.1 g (99%) of *anti*-1,2-dibenzyl ether **13** as colorless oil. R_f=0.30 (hexane/EtOAc 15:1); $[\alpha]_D^{25}$ −43.9 (*c* 0.2, $CHCl_3$); IR (neat) 3339, 2362, 1593, 1418, 1121, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.90 (dd, 1H, *J*=7.5, 6.5 Hz), 4.26 (d, 1H, *J*=12.0 Hz), 4.32 (d, 1H, *J*=12.0 Hz), 4.34 (d, 1H, *J*=6.5 Hz), 4.52 (d, 1H, *J*=12.0 Hz), 4.53 (d, 1H, *J*=12.0 Hz), 5.26 (dd, 1H, *J*=17.0, 1.0 Hz), 5.32 (dd, 1H, *J*=10.5, 1.0 Hz), 5.93 (ddd, 1H, *J*=17.0, 10.5, 7.5 Hz), 6.91 (dd, 2H, *J*=7.0, 2.0 Hz), 7.07 (dd, 2H, *J*=7.0, 2.0 Hz), 7.22–7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.52, 70.53, 70.79, 82.98, 83.68, 113.69, 118.76, 127.49, 127.63, 127.81, 127.89, 128.35, 128.47, 129.45, 131.65, 136.11, 138.61, 138.70, 159.47; HRMS (CI) Calcd for $C_{25}H_{25}O_3$ [M−H$^+$]: 373.1804, found: 373.1809.

4.1.3. (1*R*,2*S*)-Benzyl *N*-(2-benzyloxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (11). To a stirred solution of **13** (5.0 g, 13.35 mmol) in anhydrous toluene (67 mL) were added Na_2CO_3 (6.37 g, 60.08 mmol) and CSI (3.49 mL, 40.05 mmol) under N_2. The reaction mixture was stirred for 24 h at −78 °C, and quenched with H_2O (10 mL), when the reaction was completed by TLC monitoring. The aqueous layer was extracted with EtOAc (30 mL×2). The organic layer was added to a solution of aqueous 25% Na_2SO_3 (100 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford 5.02 g (90%, *anti*/*syn*=49:1) of *anti*-1,2-amino alcohol **11** as a white solid. R_f=0.25 (hexane/EtOAc 5:1); mp 110–112 °C; $[\alpha]_D^{25}$ −18.5 (*c* 0.2, $CHCl_3$); IR (CH_2Cl_2) 3340, 2367, 1593, 1417, 1121, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.11–4.13 (br, 1H), 4.37 (d, 1H, *J*=11.5 Hz), 4.63 (d, 1H, *J*=11.5 Hz), 4.79–4.81 (br, 1H), 5.03 (d, 1H, *J*=12.0 Hz), 5.09 (d, 1H, *J*=12.0 Hz), 5.28 (dd, 1H, *J*=10.5, 1.0 Hz), 5.32 (dd, 1H, *J*=17.5, 1.0 Hz), 5.48 (ddd, 1H, *J*=17.5, 10.5, 7.0 Hz), 5.56–5.59 (br, 1H), 6.86 (dd, 2H, *J*=7.0, 2.0 Hz), 7.25–7.37 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.47, 58.01, 66.99, 70.68, 82.48, 113.79, 116.53, 119.82, 127.83, 128.36, 128.63, 128.70, 129.44, 131.10, 135.26, 136.74, 139.10, 155.84, 159.19; HRMS (FAB) Calcd for $C_{26}H_{28}NO_4$ [M+H$^+$]: 418.2018, found: 418.2010.

4.1.4. (1*R*,2*S*)-Benzyl *N*-allyl-*N*-(2-benzyloxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (16). To a stirred solution of the carbamate **11** (10.8 g, 25.87 mmol) in anhydrous THF (65 mL) and DMF (65 mL) were added NaH (1.55 g, 38.81 mmol, 60% in mineral oil) and allyl bromide (3.36 mL, 38.81 mmol) at 0 °C under N_2. The reaction mixture was stirred for 2 h at room temperature and quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (130 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 8:1) to afford 11.9 g (100%) of **16** as colorless syrup. R_f=0.34 (hexane/EtOAc 8:1); $[\alpha]_D^{25}$ −24.5 (*c* 0.2, $CHCl_3$); IR (neat) 3343, 2381, 2284, 1593, 1418, 1211, 1041 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.62–3.67

(m, 1H), 3.74 (s, 3H), 3.74–3.78 (m, 1H), 4.31 (d, 1H, J=11.0 Hz), 4.48 (d, 1H, J=11.0 Hz), 4.50–4.63 (m, 1H), 4.82 (d, 1H, J=11.0 Hz), 4.93–5.05 (m, 1H), 5.07 (s, 2H), 5.30–5.40 (m, 3H), 5.73–5.76 (br, 1H), 6.86 (br d, 2H, J=6.0 Hz), 7.10 (br d, 2H, J=6.0 Hz), 7.21–7.34 (m, 10H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 47.95, 55.72, 62.53, 66.97, 70.55, 80.38, 114.13, 116.84, 120.62, 128.08, 128.29, 128.63, 128.79, 129.01, 130.64, 130.89, 135.57, 136.85, 137.59, 138.75, 156.33, 159.21; HRMS (FAB) Calcd for $C_{29}H_{32}NO_4$ [M+H$^+$]: 458.2331, found: 458.2332.

4.1.5. (2*R*,3*S*)-1-Benzyloxycarbonyl-(3-benzyloxy-2-*p*-methoxyphenyl)-1,2,3,6-tetrahydropyridine (17). To a stirred solution of **16** (5.4 g, 11.80 mmol) in anhydrous CH_2Cl_2 (118 mL) was added first-generation Grubbs catalyst (0.20 g, 0.24 mmol) under N_2. The reaction mixture was stirred for 4 h at room temperature and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford 4.6 g (91%) of the unsaturated piperidine **17** as colorless syrup. R_f=0.20 (hexane/EtOAc 5:1); $[\alpha]_D^{25}$ +2.9 (c 0.2, $CHCl_3$); IR (neat) 3342, 2379, 2282, 1592, 1418, 1121, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (d, 1H, J=19.0 Hz), 3.79 (s, 3H), 4.24 (d, 1H, J=5.0 Hz), 4.48 (d, 1H, J=19.0 Hz), 4.60 (d, 1H, J=11.5 Hz), 4.64–4.79 (br, 1H), 5.22 (s, 2H), 5.63–5.82 (br, 1H), 6.00–6.10 (br, 2H), 6.82 (d, 2H, J=9.0 Hz), 7.06–7.11 (br, 2H), 7.28–7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.05, 55.02, 55.49, 67.56, 70.93, 72.31, 114.05, 123.81, 127.96, 128.13, 128.21, 128.57, 128.70, 128.72, 129.24, 130.76, 136.91, 138.41, 156.02, 159.10; HRMS (FAB) Calcd for $C_{27}H_{27}NO_4Na$ [M+Na$^+$]: 452.1838, found: 452.1829.

4.1.6. (2*R*,3*S*)-1-Benzyloxycarbonyl-(3-benzyloxy-2-*p*-methoxyphenyl)piperidine (9). To a solution of the unsaturated piperidine **17** (1.73 g, 4.03 mmol) in anhydrous MeOH (40 mL) was added PtO_2 (46 mg, 0.20 mmol). The reaction mixture was stirred for 1 h under H_2 balloon at room temperature and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford 1.63 g (94%) of the piperidine **9** as colorless syrup. R_f=0.28 (hexane/EtOAc 5:1); $[\alpha]_D^{25}$ −55.2 (c 0.2, $CHCl_3$); IR (neat) 3339, 2365, 1593, 1418, 1121, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37–2.09 (m, 4H), 2.96 (dt, 1H, J=13.0, 3.0 Hz), 3.81 (s, 3H), 4.06–4.10 (br, 1H), 4.20 (br d, 1H, J=13.0 Hz), 4.60 (d, 1H, J=12.0 Hz), 4.71 (d, 1H, J=12.0 Hz), 5.19 (s, 2H), 5.64–5.66 (br, 1H), 6.87 (dd, 2H, J=7.0, 2.0 Hz), 7.10 (dd, 2H, J=7.0, 2.0 Hz), 7.27–7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.67, 24.41, 40.47, 55.52, 56.19, 67.37, 70.56, 74.10, 114.33, 127.68, 127.72, 127.79, 127.90, 128.01, 128.63, 130.48, 137.23, 138.85, 157.02, 158.67; HRMS (FAB) Calcd for $C_{27}H_{30}NO_4$ [M+H]$^+$: 432.2175, found: 432.2173.

4.1.7. (2*S*,3*S*)-3-Hydroxypipecolic acid (1). To a stirred solution of the piperidine **9** (1.0 g, 2.32 mmol) in a mixture of H_2O/CH_3CN/EtOAc (2:1:1 v/v/v, 140 mL) were added $NaIO_4$ (8.4 g, 39.39 mmol) and $RuCl_3$ (58 mg, 0.28 mmol). The reaction mixture was stirred for 4 h at room temperature, quenched with propan-2-ol, and filtered through Celite pad. The filtrate was concentrated in vacuo. The residue was dissolved in a solution of aqueous 6 N HCl (20 mL), and the resulting mixture was refluxed for 10 h. The reaction mixture was cooled in an ice bath, neutralized to pH 7 by the addition of an aqueous solution of 10 N NaOH (15 mL), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/30% NH_4OH 5:5:1) to afford 0.24 g (72%) of (2*S*,3*S*)-3-hydroxypipecolic acid (**1**) as a white solid. R_f=0.32 (EtOAc/MeOH/30% NH_4OH 5:5:1); mp 229–235 °C (decomp.); $[\alpha]_D^{20}$ +13.0 (c 0.5, 10% HCl) [lit.[9e] $[\alpha]_D^{20}$ +12.9 (c 0.23, 10% HCl)]; ^{1}H 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.

4.1.8. (2*R*,3*S*)-1-Benzyloxycarbonyl-(3-benzoyloxy-2-hydroxymethyl)piperidine (18). To a stirred solution of the piperidine **9** (1.0 g, 2.32 mmol) in a mixture of H_2O/CH_3CN/EtOAc (2:1:1 v/v/v, 140 mL) were added $NaIO_4$ (8.4 g, 39.39 mmol) and $RuCl_3$ (58 mg, 0.28 mmol). The reaction mixture was stirred for 4 h at room temperature, quenched with propan-2-ol, and filtered through a Celite pad. The filtrate was concentrated in vacuo. The residual viscous oil was used without purification in the next step. To a stirred solution of crude carboxylic acid (0.7 g, 1.83 mmol) in THF (12 mL) was slowly added borane–tetrahydrofuran complex (9.15 mL, 9.15 mol, 1.0 M in THF) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C and quenched with an aqueous solution of saturated NH_4Cl (6 mL). The aqueous layer was extracted with EtOAc (20 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford 0.46 g (54%) of the alcohol **18** as colorless syrup. R_f=0.32 (hexane/EtOAc 1:1); $[\alpha]_D^{25}$ +12.0 (c 0.5, $CHCl_3$); IR (CH_2Cl_2) 3436, 2943, 2356, 1963, 1703, 1435, 1271, 1116, 1068 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58–2.10 (m, 4H), 3.00–3.10 (m, 1H), 3.87 (dd, 2H, J=11.5, 7.5 Hz), 4.20-4.26 (br, 1H), 4.65 (t, 1H, J=7.5 Hz), 5.04–5.20 (br, 2H), 5.29 (d, 1H, J=1.5 Hz), 7.20–7.40 (m, 5H), 7.41 (dt, 2H, J=8.5, 1.5 Hz), 7.59 (dt, 1H, J=8.5, 1.5 Hz), 7.99 (dd, 2H, J=8.5, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.07, 25.06, 39.93, 57.03, 60.46, 67.54, 68.13, 127.87, 127.17, 128.64, 128.68, 129.88, 130.46, 133.30, 136.77, 156.24, 165.92; HRMS (FAB) Calcd for $C_{21}H_{24}NO_5$ [M+H$^+$]: 370.1654, found: 370.1649.

4.1.9. (2*R*,3*S*)-2-Hydroxymethylpiperidin-3-ol (2). A solution of the alcohol **18** (80 mg, 0.217 mmol) in a mixture of 6 N HCl (2.1 mL) and MeOH (2.1 mL) was refluxed for 24 h and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50Wx8 (H$^+$ form) using 0.5 M aqueous NH_4OH as eluant to afford 37 mg (100%) of (2*R*,3*S*)-2-hydroxymethylpiperidin-3-ol (**2**) as a white solid. R_f=0.20 ($CHCl_3$/MeOH/30% NH_4OH 5:1:0.1); mp 155 °C (decomp.); $[\alpha]_D^{25}$ +55.0 (c 0.1, MeOH) [lit.[10a] $[\alpha]_D^{19}$ +58.3 (c 1.06, MeOH)]; ^{1}H 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 (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.

4.1.10. (1*S*,2*S*)-2-(2-Methoxyethoxymethoxy)-1-*p*-methoxyphenylbut-3-en-1-ol (19). To a stirred solution of 3-(2-methoxyethoxymethoxy)-propene (3.4 g, 23.26 mmol) in anhydrous THF (43 mL) was added dropwise for 30 min *s*-BuLi (17.5 mL, 24.48 mmol, 1.4 M in cyclohexane) at −78 °C under N_2. The resulting bright yellow solution was stirred at −78 °C for 30 min. The reaction mixture was treated with (+)-*B*-methoxydiisopinocamphenylborane (8.8 g, 22.04 mmol) in anhydrous THF (25 mL) and stirred at −78 °C for 1 h. To this solution were added boron trifluoride etherate (4.4 mL, 34.89 mmol) and a solution of *p*-anisaldehyde (3.17 g, 22.04 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred at −78 °C for 3 h, and then slowly added a mixture of 3 M NaOH (10 mL) and 30% H_2O_2 (10 mL). The biphasic solution was stirred at room temperature for 8 h. The aqueous layer was separated and extracted with Et_2O (20 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford 4.75 g (72%) of the homoallylic alcohol **19** as colorless oil. R_f=0.29 (hexane/EtOAc 1:1); $[\alpha]_D^{29}$ +57.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3450, 2888, 2357, 1611, 1512, 1459, 1246, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.41 (s, 3H), 3.53 (t, 2H, J=4.5 Hz), 3.73–3.77 (m, 2H), 3.80 (s, 3H), 4.17 (t, 1H, J=7.0 Hz), 4.54 (t, 1H, J=7.0 Hz), 4.74 (d, 1H, J=6.5 Hz), 4.80 (d, 1H, J=6.5 Hz), 5.12–5.18 (m, 2H), 5.56 (ddd, 1H, J=17.0, 10.5, 7.0 Hz), 6.87 (dd, 2H, J=9.0, 2.0 Hz), 7.27 (dd, 2H, J=9.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.46, 59.21, 67.87, 72.03, 76.50, 82.86, 93.75, 113.82, 119.38, 128.60, 132.54, 134.52, 159.51; ESIMS *m*/*z* 305 [M+Na]$^+$.

4.1.11. (1*S*,2*S*)-1-*p*-Methoxyphenylbut-3-ene-1,2-diol (20). To a stirred solution of the homoallylic alcohol **19** (2.2 g, 7.792 mmol) in methanol (20 mL) was added a mixture of MeOH/H_2O/13 M HCl (8:1:1, 155 mL). The solution was stirred for 1 h at room temperature and diluted with H_2O (100 mL). The aqueous layer was extracted with Et_2O (200 mL×2). The organic layer was washed with H_2O, 5 M NaOH, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford 1.06 g (70%) of the *syn*-diol **20** as a white solid. R_f=0.28 (hexane/EtOAc 1:1); mp 48–52 °C; $[\alpha]_D^{29}$ +5.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3394, 2358, 1513, 1247, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.20 (ddt, 1H, J=7.5, 5.5, 1.5 Hz), 5.14 (dt, 1H, J=11.0, 1.5 Hz), 5.25 (dt, 1H, J=17.0, 1.5 Hz), 5.71 (ddd, 1H, J=17.0, 11.0, 5.5 Hz), 6.89 (dd, 2H, J=8.5, 2.5 Hz), 7.27 (dd, 2H, J=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.49, 77.00, 77.20, 114.06, 117.15, 128.44, 132.57, 136.67, 159.70; APCIMS *m*/*z* 193 [M−H]$^-$.

4.1.12. (1*S*,2*S*)-1,2-Bis-benzyloxy-1-*p*-methoxyphenylbut-3-ene (14). To a stirred solution of the diol **20** (0.7 g, 3.604 mmol) in anhydrous THF (7.2 mL) and DMF (7.2 mL) were added NaH (0.37 g, 9.370 mmol, 60% in mineral oil) and benzyl bromide (1.1 mL, 9.370 mmol) at 0 °C under N_2. The reaction mixture was stirred for 8 h at room temperature and quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (15 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 15:1) to afford 1.3 g (96%) of *syn*-1,2-dibenzyl ether **14** as colorless oil. R_f=0.26 (hexane/EtOAc 15:1); $[\alpha]_D^{29}$ +0.3 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3028, 2863, 2357, 1610, 1609, 1510, 1246, 1073 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.06 (t, 1H, J=7.0 Hz), 4.39 (d, 1H, J=12.0 Hz), 4.43 (d, 1H, J=7.0 Hz), 4.54 (d, 1H, J=12.0 Hz), 4.59 (d, 1H, J=12.0 Hz), 4.69 (d, 1H, J=12.0 Hz), 5.16–5.21 (m, 2H), 5.65 (ddd, 1H, J=16.5, 11.5, 7.0 Hz), 6.92 (dd, 2H, J=9.0, 2.5 Hz), 7.27–7.39 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.48, 70.85, 71.30, 83.77, 83.91, 113.77, 118.34, 127.50, 127.60, 127.83, 127.91, 128.43, 128.46, 129.45, 130.07, 135.52, 138.90, 139.91, 159.56; HRMS (CI) Calcd for $C_{25}H_{27}O_3$ [M+H$^+$]: 375.1960, found: 375.1953.

4.1.13. (1*S*,2*S*)-Benzyl *N*-(2-benzyloxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (12). To a stirred solution of **14** (1.20 g, 3.204 mmol) in anhydrous hexane (16 mL) were added Na_2CO_3 (1.53 g, 14.42 mmol) and CSI (0.84 mL, 9.612 mmol) under N_2. The reaction mixture was stirred for 18 h at −78 °C, and quenched with H_2O (2.5 mL), when the reaction was completed by TLC monitoring. The aqueous layer was extracted with EtOAc (8 mL×2). The organic layer was added to an aqueous solution of 25% Na_2SO_3 (15 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford 1.07 g (80%, *syn*/*anti*=12:1) of *syn*-1,2-amino alcohol **12** as a white solid. R_f=0.25 (hexane/EtOAc 5:1); mp 128–129 °C; $[\alpha]_D^{29}$ +24.8 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3367, 2358, 1689, 1523, 1257, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.97–4.01 (br, 1H), 4.24 (d, 1H, J=11.5 Hz), 4.55 (d, 1H, J=11.5 Hz), 4.79–4.81 (br, 1H), 5.07 (d, 1H, J=12.0 Hz), 5.12 (d, 1H, J=12.0 Hz), 5.31–5.36 (m, 2H), 5.68–5.70 (br, 1H), 5.87 (ddd, 1H, J=17.5, 11.0, 7.0 Hz), 6.88 (dd, 2H, J=8.5, 2.5 Hz), 7.16 (dd, 2H, J=8.5, 2.5 Hz), 7.25–7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.52, 58.29, 67.02, 71.04, 82.86, 113.92, 119.26, 127.84, 127.98, 128.26, 128.37, 128.53, 128.69, 132.97, 135.71, 136.80, 138.06, 156.31, 159.15; HRMS (FAB) Calcd for $C_{26}H_{28}NO_4$ [M+H$^+$]: 418.2018, found: 418.2016.

4.1.14. (1*S*,2*S*)-Benzyl *N*-allyl-*N*-(2-benzyloxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (21). To a stirred solution of the carbamate **12** (1.20 g, 2.874 mmol) in anhydrous THF (5.7 mL) and DMF (5.7 mL) were added NaH (0.15 g, 3.737 mmol, 60% in mineral oil) and allyl bromide (0.32 mL, 3.737 mmol) at 0 °C under N_2. The reaction mixture was stirred for 1 h at room temperature and quenched with H_2O (3 mL). The aqueous layer was extracted with EtOAc (15 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 8:1) to afford 1.3 g (99%) of **21** as colorless syrup. R_f=0.34 (hexane/EtOAc 8:1); $[\alpha]_D^{29}$ +62.6

(*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 2942, 2357, 1695, 1511, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.81–3.88 (m, 2H), 4.31–4.44 (m, 2H), 4.61–4.69 (m, 2H), 4.92–4.98 (m, 2H), 5.12–5.33 (m, 4H), 5.59–5.74 (m, 2H), 6.82–6.84 (br, 2H), 7.18–7.41 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.62, 55.41, 63.86, 67.28, 70.35, 79.70, 113.78, 116.18, 119.68, 127.61, 127.86, 128.00, 128.50, 128.58, 130.91, 135.69, 136.11, 137.21, 156.77, 159.26; HRMS (FAB) Calcd for $C_{29}H_{32}NO_4$ [M+H$^+$]: 458.2331, found: 458.2325.

4.1.15. (2*S*,3*S*)-1-Benzyloxycarbonyl-(3-benzyloxy-2-*p*-methoxyphenyl)-1,2,3,6-tetrahydropyridine (22). To a stirred solution of **21** (1.0 g, 2.186 mmol) in anhydrous CH_2Cl_2 (44 mL) was added first-generation Grubbs catalyst (90 mg, 0.109 mmol) under N_2. The reaction mixture was stirred for 4 h at room temperature and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the *cis*-piperidine **22** (0.77 g, 82%) and the *trans*-piperidine **17** (56 mg, 6.0%) as colorless syrup, respectively. R_f=0.30 (hexane/EtOAc 5:1); $[\alpha]_D^{29}$ +66.1 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 2357, 1697, 1511, 1303, 1181 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.38–3.42 (br, 1H), 3.80 (s, 3H), 4.23–4.28 (br, 1H), 4.50–4.63 (m, 3H), 5.17–5.23 (br, 2H), 5.70–5.72 (br, 1H), 6.00–6.03 (br, 1H), 6.82–6.84 (br, 2H), 7.18–7.52 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.90, 53.36, 55.42, 67.69, 71.00, 73.00, 113.62, 124.16, 127.90, 127.99, 128.20, 128.34, 128.59, 128.77, 129.01, 130.75, 136.78, 138.14, 155.92, 159.09; HRMS (FAB) Calcd for $C_{27}H_{28}NO_4$ [M+H$^+$]: 430.2018, found: 430.2024.

4.1.16. (2*S*,3*S*)-1-Benzyloxycarbonyl-(3-benzyloxy-2-*p*-methoxyphenyl)piperidine (10). To a stirred solution of the unsaturated piperidine **22** (0.70 g, 1.63 mmol) in anhydrous MeOH (16 mL) was added PtO_2 (18 mg, 0.081 mmol). The reaction mixture was stirred for 0.5 h under H_2 balloon at room temperature and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford 0.585 g (83%) of the piperidine **10** as colorless syrup. R_f=0.30 (hexane/EtOAc 5:1); $[\alpha]_D^{28}$ +50.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 2943, 2051, 1694, 1509, 1420, 1251, 1145, 1093, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.57–1.72 (m, 2H), 1.91–1.99 (m, 2H), 2.76 (dt, 1H, *J*=13.0, 3.5 Hz), 3.82-3.87 (m, 4H), 3.99 (br d, 1H, *J*=11.0 Hz), 4.60 (d, 1H, *J*=12.0 Hz), 4.70 (d, 1H, *J*=12.0 Hz), 5.19 (d, 1H, *J*=12.5 Hz), 5.22 (d, 1H, *J*=12.5 Hz), 5.77–5.81 (br, 1H), 6.87 (dd, 2H, *J*=9.5, 3.0 Hz), 7.27–7.40 (m, 10H), 7.54 (br d, 2H, *J*=9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.23, 26.15, 36.64, 55.45, 67.58, 70.82, 78.11, 113.93, 127.85, 128.04, 128.23, 128.63, 128.74, 129.76, 129.93, 137.02, 138.47, 156.02, 158.71; HRMS (FAB) Calcd for $C_{27}H_{30}NO_4$ [M+H]$^+$: 432.2175, found: 432.2182.

4.1.17. (2*R*,3*S*)-3-Hydroxypipecolic acid (3). To a stirred solution of the piperidine **10** (0.31 g, 0.718 mmol) in a mixture of H_2O/CH_3CN/EtOAc (2:1:1 v/v/v, 44 mL) were added $NaIO_4$ (2.61 g, 12.21 mmol) and $RuCl_3$ (18 mg, 0.086 mmol). The reaction mixture was stirred for 4 h at room temperature, quenched with propan-2-ol, and filtered through Celite pad. The filtrate was concentrated in vacuo. The residue (0.33 g) was dissolved in an aqueous solution of 6 N HCl (8.6 mL), and the resulting mixture was refluxed for 24 h. The reaction mixture was cooled in an ice bath, neutralized to pH 7 by the addition of an aqueous solution of 10 N NaOH (5.5 mL), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/30% NH_4OH 3:5:0.9) to afford 76 mg (73%) of (2*R*,3*S*)-3-hydroxypipecolic acid (**3**) as a gummy solid. R_f=0.26 (EtOAc/MeOH/30% NH_4OH 3:5:0.9); $[\alpha]_D^{28}$ +77.6 (*c* 0.5, 1 M HCl) [lit.[4a] $[\alpha]_D^{20}$ +58.3 (*c* 0.12, 1 M HCl)]; ^1H NMR (500 MHz, D_2O) δ 1.57–1.68 (m, 2H, H-4_{ax} and H-5_{ax}), 1.82–1.88 (m, 2H, H-4_{eq} and H-5_{eq}), 2.86 (ddd, 1H, *J*=13.0, 3.5, 3.0 Hz, H-6_{ax}), 3.27 (ddd, 1H, *J*=12.5, 2.5, 1.5 Hz, H-6_{eq}), 3.52 (d, 1H, *J*=1.5 Hz, H-2), 4.36 (d, 1H, *J*=2.0 Hz, H-3); ^{13}C NMR (125 MHz, D_2O) δ 16.10, 28.92, 43.81, 62.46, 64.32, 172.48; HRMS (FAB) Calcd for $C_6H_{12}NO_3$ [M+H$^+$]: 146.0817, found: 146.0816.

4.1.18. (2*S*,3*S*)-1-Benzyloxycarbonyl-(3-benzoyloxy-2-hydroxymethyl)piperidine (23). To a stirred solution of the piperidine **10** (0.3 g, 0.695 mmol) in a mixture of H_2O/CH_3CN/EtOAc (2:1:1 v/v/v, 44 mL) were added $NaIO_4$ (2.53 g, 11.82 mmol) and $RuCl_3$ (17 mg, 0.083 mmol). The reaction mixture was stirred for 4 h at room temperature, quenched with propan-2-ol, and filtered through Celite pad. The filtrate was concentrated in vacuo. The residual viscous oil was used without purification in the next step. To a stirred solution of crude carboxylic acid (0.32 g, 0.834 mmol) in THF (3.5 mL) was slowly added borane–tetrahydrofuran complex (1.4 mL, 1.390 mol, 1.0 M in THF) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C and quenched with an aqueous solution of saturated NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (10 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford 0.20 g (78%) of the alcohol **23** as colorless syrup. R_f=0.22 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$ −8.3 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3428, 2939, 2357, 1701, 1431, 1270, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55–1.66 (m, 2H), 1.78 (br d, 1H, *J*=11.5 Hz), 1.91–2.06 (m, 2H), 2.98 (ddd, 1H, *J*=13.5, 3.0, 2.5 Hz), 3.93–3.99 (m, 1H), 4.09–4.14 (br, 1H), 4.63–4.79 (br m, 2H), 4.86–5.00 (m, 2H), 5.08 (d, 1H, *J*=12.0 Hz), 7.24–7.30 (m, 5H), 7.40 (t, 2H, *J*=7.5 Hz), 7.55 (t, 1H, *J*=7.5 Hz), 7.98 (br d, 2H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.09, 28.84, 38.70, 54.82, 59.85, 67.60, 68.54, 128.00, 128.19, 128.60, 128.66, 129.92, 130.16, 133.25, 136.64, 155.98, 166.96; HRMS (FAB) Calcd for $C_{21}H_{24}NO_5$ [M+H$^+$]: 370.1654, found: 370.1659.

4.1.19. (2*S*,3*S*)-2-Hydroxymethylpiperidin-3-ol (4). A solution of the alcohol **23** (50 mg, 0.135 mmol) in a mixture of 6 N HCl (1.4 mL) and MeOH (1.4 mL) was refluxed for 24 h and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50Wx8 (H^+ form) using 0.5 M aqueous NH_4OH as eluant to afford 18 mg (100%) of (2*S*,3*S*)-2-hydroxymethylpiperidin-3-ol (**4**) as a gummy solid. R_f=0.32 ($CHCl_3$/MeOH/30% NH_4OH 5:1:0.1); $[\alpha]_D^{28}$ +10.8 (*c* 0.5, MeOH) [lit.[10b] $[\alpha]_D^{21}$ −12.4 (*c* 2.51, H_2O) for enantiomer of **4**]; ^1H NMR (500 MHz, D_2O) δ 1.57–1.63 (m, 2H), 1.77–1.84 (m, 2H), 2.80 (dt, 1H, *J*=12.5, 3.0 Hz), 3.03–3.07 (m, 1H), 3.20 (br d, 1H, *J*=11.0 Hz), 3.59 (dd, 1H, *J*=12.0, 3.5 Hz), 3.66 (dd, 1H, *J*=12.0, 5.5 Hz), 3.99

(s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 17.46, 29.13, 44.57, 60.47, 60.66, 63.53; HRMS (FAB) Calcd for $C_6H_{14}NO_2$ [M+H$^+$]: 132.1024, found: 132.1021.

4.1.20. (2*R*,3*S*)-3-Benzyloxycarbonyl-2-*p*-methoxyphenylpiperidine (24). To a stirred solution of **9** (0.45 g, 1.04 mmol) in anhydrous MeOH (5.2 mL) was added 10% Pd/C (0.16 g, 1.56 mmol). The reaction mixture was stirred for 1 h under H_2 balloon at room temperature and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$/MeOH 15:1) to afford 0.16 g (53%) of **24** as colorless syrup. R_f=0.27 ($CHCl_3$/MeOH 15:1); $[\alpha]_D^{29}$ −0.6 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 2922, 2855, 2358, 1604, 1456, 1375, 1248, 1096, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (ddd, 1H, *J*=13.0, 11.0, 4.0 Hz), 1.65 (ddt, 1H, *J*=13.0, 11.0, 4.0 Hz), 1.78 (ddd, 1H, *J*=11.0, 4.5, 2.5 Hz), 2.25 (dt, 1H, *J*=11.0, 2.5 Hz), 2.70 (dt, 1H, *J*=11.5, 2.5 Hz), 3.06 (br d, 1H, *J*=11.5 Hz), 3.33 (ddd, 1H, *J*=11.0, 9.0, 4.5 Hz), 3.47 (d, 1H, *J*=9.0 Hz), 3.84 (s, 3H), 4.08 (d, 1H, *J*=11.5 Hz), 4.25 (d, 1H, *J*=11.5 Hz), 6.89 (dd, 2H, *J*=9.0, 2.5 Hz), 6.98 (t, 2H, *J*=9.0 Hz), 7.21 (dt, 3H, *J*=9.0, 2.5 Hz), 7.37 (dd, 2H, *J*=9.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.34, 31.80, 46.97, 55.52, 67.23, 71.73, 80.28, 113.83, 127.50, 127.86, 128.32, 129.40, 134.58, 138.83, 159.31; HRMS (CI) Calcd for $C_{19}H_{24}NO_2$ [M+H$^+$]: 298.1807, found: 298.1804.

4.1.21. (2*R*,3*S*)-3-Benzyloxy-2-*p*-methoxyphenyl-1-methylpiperidine (25). To a solution of **24** (0.010 g, 0.034 mmol) in anhydrous THF (0.3 mL) were added potassium carbonate (14 mg, 0.102 mmol) and iodomethane (0.004 mL, 0.100 mmol) under N_2. The reaction mixture was stirred for 2 h at 50 °C and quenched with H_2O (1 mL). The aqueous layer was extracted with EtOAc (2 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$/MeOH 30:1) to afford 8.6 mg (82%) of **25** as colorless syrup. R_f=0.26 ($CHCl_3$/MeOH 30:1); $[\alpha]_D^{28}$ −29.4 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2) 2926, 2856, 2780, 1609, 1510, 1455, 1372, 1295, 1246, 1176, 1119, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (ddd, 1H, *J*=13.0, 12.0, 5.0 Hz), 1.74–1.80 (m, 2H), 2.02 (s, 3H), 2.13 (dt, 1H, *J*=11.5, 3.0 Hz), 2.21 (ddd, 1H, *J*=13.0, 10.0, 3.0 Hz), 2.73 (d, 1H, *J*=9.0 Hz), 2.97 (br d, 1H, *J*=13.0 Hz), 3.37–3.39 (br, 1H), 3.85 (s, 3H), 3.96 (d, 1H, *J*=12.0 Hz), 4.20 (d, 1H, *J*=12.0 Hz), 6.89–7.31 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.76, 31.09, 44.09, 55.51, 56.83, 71.96, 75.38, 80.78, 113.81, 127.47, 127.87, 128.27, 129.93, 128.78, 159.13; HRMS (CI) Calcd for $C_{20}H_{26}NO_2$ [M+H$^+$]: 312.1963, found: 312.1966.

4.1.22. (2*R*,3*S*)-3-Benzyloxy-1-ethyl-(2-*p*-methoxyphenyl)piperidine (26). To a solution of **24** (0.020 g, 0.067 mmol) in anhydrous THF (0.7 mL) were added potassium carbonate (37 mg, 0.268 mmol) and iodoethane (0.016 mL, 0.201 mmol) under N_2. The reaction mixture was stirred for 3 h at 50 °C and quenched with H_2O (1 mL). The aqueous layer was extracted with EtOAc (2 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$/MeOH 30:1) to afford 14.9 mg (68%) of **26** as colorless syrup. R_f=0.28 ($CHCl_3$/MeOH 30:1); $[\alpha]_D^{29}$ −15.4 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2) 2924, 2856, 2357, 1733, 1607, 1510, 1455, 1375, 1245, 1175, 1117, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.91 (br s, 3H), 1.29–1.42 (m, 1H), 1.64–1.67 (br, 1H), 1.80 (br d, 1H, *J*=13.0 Hz), 2.05–2.19 (br, 2H), 2.20 (br d, 1H, *J*=10.5 Hz), 2.54–2.57 (br, 1H), 3.00–3.07 (br m, 2H), 3.33–3.36 (br, 1H), 3.85 (s, 3H), 3.94 (d, 1H, *J*=12.0 Hz), 4.17 (d, 1H, *J*=12.0 Hz), 6.83–7.33 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.83, 23.81, 31.30, 48.39, 51.80, 55.51, 71.95, 72.73, 81.34, 113.77, 127.46, 127.93, 128.26, 130.09, 138.79; HRMS (CI) Calcd for $C_{21}H_{28}NO_2$ [M+H$^+$]: 326.2120, found: 326.2120.

4.1.23. (2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-(3-benzyloxy-2-*p*-methoxyphenyl)piperidine (27). To a solution of **24** (0.015 g, 0.050 mmol) in anhydrous CH_2Cl_2 (0.5 mL) were added di-*tert*-butyl dicarbonate (0.017 mL, 0.075 mmol) and triethylamine (0.014 mL, 0.100 mmol) under N_2. The reaction mixture was stirred for 1 h at room temperature and quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 6:1) to afford 20 mg (100%) of **27** as colorless syrup. R_f=0.24 (hexane/EtOAc 6:1); $[\alpha]_D^{28}$ −42.2 (*c* 0.2, $CHCl_3$); IR (CH_2Cl_2) 2923, 2856, 2358, 1688, 1607, 1511, 1456, 1414, 1366, 1250, 1172, 1133, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33–1.38 (br dt, 1H, *J*=13.0, 2.0 Hz), 1.46 (s, 9H), 1.58 (t, 1H, *J*=13.0, 2.0 Hz), 1.86 (dt, 1H, *J*=8.5, 1.5 Hz), 1.98–2.03 (m, 1H), 2.86 (dt, 1H, *J*=13.0, 3.0 Hz), 3.81 (s, 3H), 4.08 (dd, 1H, *J*=5.5, 2.5 Hz), 4.12 (br d, 1H, *J*=13.0 Hz), 4.62 (d, 1H, *J*=12.0 Hz), 3.76 (d, 1H, *J*=12.0 Hz), 5.57–5.59 (br, 1H), 6.88 (dd, 2H, *J*=9.0, 2.5 Hz), 7.11 (dd, 2H, *J*=9.0, 2.5 Hz), 7.29–7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.72, 24.62, 28.68, 39.98, 55.49, 55.65, 70.52, 74.23, 79.76, 114.24, 127.70, 127.78, 128.57, 131.14, 138.98, 156.40, 158.55; HRMS (CI) Calcd for $C_{24}H_{32}NO_4$ [M+H$^+$]: 398.2331, found: 398.2331.

4.1.24. (2*R*,3*S*)-1-Acetyl-(3-benzyloxy-2-*p*-methoxyphenyl)piperidine (28). To a solution of **24** (0.015 g, 0.050 mmol) in anhydrous CH_2Cl_2 (0.5 mL) were added acetic anhydride (0.007 mL, 0.075 mmol) and triethylamine (0.014 mL, 0.100 mmol) under N_2. The reaction mixture was stirred for 1 h at room temperature and quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford 17.5 mg (88%) of **28** as colorless syrup. R_f=0.25 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$ −64.8 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2) 2921, 2856, 2358, 1737, 1609, 1456, 1375, 1247, 1122, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41–2.13 (m, 4H), 2.28 (s, 3H), 2.71 (br t, 1H, *J*=12.0 Hz), 3.70 (br d, 1H, *J*=12.0 Hz), 3.81 (s, 3H), 4.17 (d, 1H, *J*=2.5 Hz), 4.61 (d, 1H, *J*=12.0 Hz), 4.72 (d, 1H, *J*=12.0 Hz), 5.06–5.08 (br, 1H), 6.88–7.39 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.62, 25.15, 31.81, 55.53, 60.54, 70.73, 73.41, 74.86, 114.58, 127.50, 127.89, 128.71, 129.50, 129.89, 138.67, 159.24, 170.10; HRMS (CI) Calcd for $C_{21}H_{26}NO_3$ [M+H$^+$]: 340.1912, found: 340.1915.

Acknowledgements

This research was supported by the Brain Korea 21 (BK21) Program and the Seoul Research and Business Development (Seoul R&BD) Program (10541).

References and notes

1. (a) Schneider, M. J. Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155–299; (b) Fodor, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, NY, 1985; Vol. 3, pp 1–90.
2. (a) Numata, A.; Ibuka, T. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1987; Vol. 31, Chapter 6; (b) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (c) Mitchison, A.; Nsdin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553; (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633; (e) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387; (f) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17; (g) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491; (h) Pinder, A. R. *Nat. Prod. Rep.* **1989**, *6*, 67.
3. (a) Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031; (b) Ferreira, F.; Greck, C.; Genêt, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.
4. (a) Scott, J. D.; Tipple, T. N.; Williams, R. M. *Tetrahedron Lett.* **1998**, *39*, 3659; (b) Scott, J. D.; Williams, R. M. *Tetrahedron Lett.* **2000**, *41*, 8413.
5. For recent references on the syntheses of febrifugine and/or isofebrifugine, see: (a) Katoh, M.; Matsune, R.; Honda, T. *Heterocycles* **2006**, *67*, 189; (b) Ashoorzadeh, A.; Caprio, V. *Synlett* **2005**, 346; (c) Katoh, M.; Matsune, R.; Nagase, H.; Honda, T. *Tetrahedron Lett.* **2004**, *45*, 6221; (d) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663; (e) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510; (f) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809; (g) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477; (h) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953; (i) Takeuchi, T.; Azuma, K.; Takakura, K.; Abe, H.; Kim, H.-S.; Wataya, Y.; Harayama, T. *Tetrahedron* **2001**, *57*, 1213; (j) Takeuchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193; (k) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989.
6. For recent references on the syntheses of prosophylline and/or deoxoprosophylline, see: (a) Angelique, J.; Jieping, Z. *Heterocycles* **2004**, *64*, 249; (b) Chavan, S. P.; Cheruchupally, P. *Tetrahedron Lett.* **2004**, *45*, 421; (c) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron* **2003**, *59*, 6445; (d) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982; (e) Koulocheri, S. D.; Magiatis, P.; Haroutounian, S. A. *J. Org. Chem.* **2001**, *66*, 7915; (f) Datta, A.; Kumar, J. S. R.; Roy, S. *Tetrahedron* **2001**, *57*, 1169.
7. (a) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360; (b) Bodas, M. S.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 8461.
8. (a) Quibell, M.; Benn, A.; Flinn, N.; Monk, T.; Ramjee, M.; Wang, Y.; Watts, J. *Bioorg. Med. Chem.* **2004**, *12*, 5689; (b) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413; (c) Knight, D. W.; Lewis, N.; ShareDavidHaigh, A. C. *Tetrahedron: Asymmetry* **1993**, *4*, 625.
9. (a) Liang, N.; Datta, A. *J. Org. Chem.* **2005**, *70*, 10182; (b) Haddad, M.; Larcheveque, M. *Tetrahedron Lett.* **2001**, *42*, 5223; (c) Zhu, J.; Jourdant, A. *Tetrahedron Lett.* **2000**, *41*, 7033; (d) Horikawa, M.; Busch-Peterson, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843; (e) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975; (f) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1996**, *37*, 4001; (g) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866.
10. (a) Takahata, H.; Banda, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199; (b) Takahata, H.; Banda, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527; (c) Takahata, H.; Banda, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603; (d) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401; (e) Banda, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817; (f) Enders, D.; Jegelka, U. *Synlett* **1992**, 999.
11. (a) Kim, I. S.; Kim, J. D.; Ryu, C. B.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2006**, *62*, 9349; (b) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025; (c) Kim, J. D.; Kim, I. S.; Hua, J. C.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2005**, *46*, 1079; (d) Kim, J. D.; Zee, O. P.; Jung, Y. H. *J. Org. Chem.* **2003**, *68*, 3721; (e) Kim, J. D.; Han, G.; Jeong, L. S.; Park, H.-J.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2002**, *58*, 4395; (f) Kim, J. D.; Lee, M. H.; Han, G.; Park, H.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2001**, *57*, 8257; (g) Kim, J. D.; Lee, M. H.; Lee, M. J.; Jung, Y. H. *Tetrahedron Lett.* **2000**, *41*, 5073.
12. (a) Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*, 4101; (b) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289.
13. (a) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243; (b) Previously, we demonstrated the asymmetric synthesis of *anti*-1,2-vicinal diol in Refs. 11a,b and 12b.
14. Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547 and references therein.
15. For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
16. (a) Winstein, S.; Allred, E.; Heck, R.; Grick, R. *Tetrahedron* **1958**, *3*, 1; (b) Krow, G. R.; Yuan, J.; Lin, G.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 1259; (c) Roberts, D. D. *J. Org. Chem.* **1997**, *62*, 1857.
17. (a) Nunez, M. T.; Mzrtin, V. S. *J. Org. Chem.* **1990**, *55*, 1928; (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. A. *J. Org. Chem.* **1981**, *46*, 3936.
18. (a) Chaudhuri, S. R.; Gurjar, M. K. *Tetrahedron Lett.* **2002**, *43*, 2435; (b) Schuda, P. F.; Cichowicz, M. B.; Heiman, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829.
19. For $A^{(1,3)}$ strain in *N*-acylpiperidines, see: Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445 and references therein.
20. Kiso, M.; Ando, K.; Inagaki, H.; Ishida, H.; Hasegawa, A. *Carbohydr. Res.* **1995**, *272*, 159.