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Stereoselective Total Synthesis of *cis*- and *trans*-3-Hydroxypipecolic Acid

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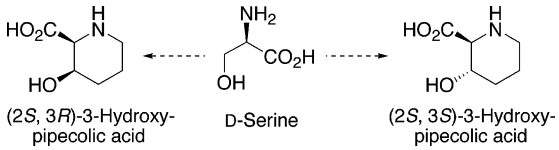

3-Hydroxypipecolic acid, a nonproteinogenic cyclic α-amino acid, is a common structural moiety found in a large number of natural and synthetic compounds of medicinal significance. Utilizing D-serine as a chiral template, the present research describes efficient and straightforward routes to *cis*- and *trans*-3-hydroxypipecolic acids in enantiopure form. The key steps in the syntheses involve chelation-controlled addition of a homoallyl Grignard reagent to a protected serinal derivative toward stereoselective formation of the corresponding *syn*-amino alcohol adduct **3**. On the other hand, zinc borohydride-mediated chelation-controlled reduction of a serine-derived α-aminoketone precursor leads to the formation of the corresponding *anti*-amino alcohol adduct **4** with high stereoselectivity. Following an efficient sequence of reactions, the above amino alcohol derivatives were subsequently transformed to the corresponding cis- and trans- title compounds, respectively.

The hydroxypipecolic acid structural framework is found in a wide variety of natural and synthetic compounds of biomedical significance.[1] In conformational and ligand binding studies involving bioactive peptides and peptidomimetics, these chimeric amino acid building blocks are often utilized as hydroxylated homoproline analogues or as constrained analogues of serine.[2] Consequently, development of methods for the stereoselective construction of various hydroxypipecolic acids is an active area of research.[3] In particular, 3-hydroxypipecolic acid, a cyclic β-hydroxy-α-amino acid derivative, has been the target of several synthetic efforts[4] due to the presence of this structural motif in compounds with diverse biological activities.[5] For example, the antitumor antibiotic tetrazomine contains a *cis*-3-hydroxypipecolic acid component,[4f] whereas (−)-swainsonine, a potent inhibitor of α-D-mannosidase, is derivable from the corresponding trans-configured 3-hydroxypipecolic acid.[6]

Among the several syntheses of the various stereoisomeric 3-hydroxypipecolic acids reported in the literature,[4] a majority of the approaches have utilized chiral building blocks as starting materials for the desired synthesis. In a very efficient example, Williams and co-workers[4g] have developed a short-step sequence to both the enantiomers of *trans*-3-hydroxypipecolic acids, employing the enantiomeric, commercially available (albeit relatively expensive: 1 g = $64.40−$67.40; Aldrich catalog) (2*S*,3*R*)- and (2*R*,3*S*)-benzyl-6-oxo-2,3-diphenyl-4-morpholinecarboxylates as chiral starting materials. In another example, in an L-serine-mediated chiral pool approach, Jourdant and Zhu developed synthetic routes to both *cis*- and *trans*-3-hydroxypipecolic acids in 15 and 13 linear reaction steps, respectively.[4e] In a recent publication, Kumar and Bodas described asymmetric synthetic routes to both the enantiomers of *trans*-3-hydroxypipecolic acids in about 15 reaction steps.[4a] Except for the above-mentioned syntheses by Williams and co-workers (five steps, 25−28% overall yields),[4g] most of the other reported (stereoselective) syntheses of the 3-hydroxypipecolic acids required 9−15 reaction steps, affording the desired products in approximately 10−30% overall yields.[4]

In continuation of our interest in the amino acid chiral template-assisted synthesis of natural and nonnatural bioactive compounds,[7] we have developed efficient routes to both the *cis*-(2*S*,3*R*)- and *trans*-(2*S*,3*S*)-3-hydroxy-

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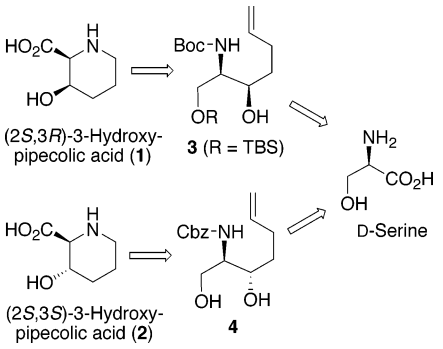


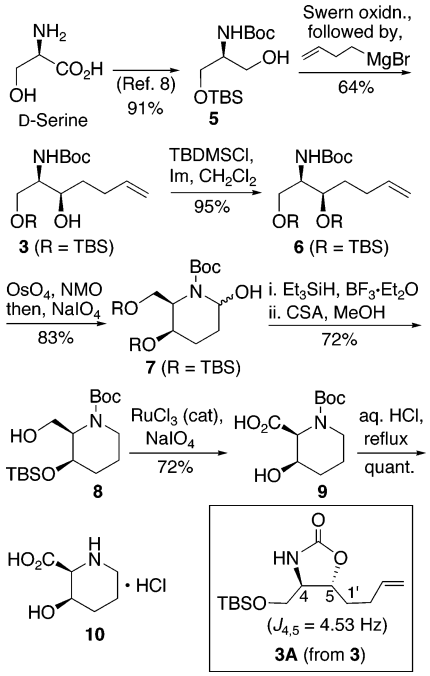
FIGURE 1. Retrosynthetic strategy and approach.

pipecolic acid (**1** and **2**; Figure 1) in enantiomerically pure form. Our synthetic strategy (Figure 1) and the details of the syntheses are described herein.

Starting from D-serine, a key step in the synthesis of **1** was envisioned to be the initial formation of the *syn*-amino alcohol intermediate **3** through a stereocontrolled addition of homoallylmagnesium bromide to an appropriately protected D-serinal derivative. Subsequent heterocyclization involving the strategically located amine functionality and the terminal olefinic moiety is expected to afford the desired cis-product **1**. Similarly, stereoselective construction of the *trans*-amino alcohol derivative **4**, utilizing a chelation-controlled reduction of an appropriate ketone intermediate, followed by heterocyclization would result in the corresponding *trans*-3-hydroxypipecolic acid (**2**).

Accordingly, synthesis of the *cis*-pipecolic acid derivative **1** was initiated by conversion of readily available D-serine to the corresponding protected aminodiol **5** (Scheme 1).[8] The next critical step in the sequence required stereoselective construction of the *syn*-1,2-amino alcohol functionality as depicted in the desired intermediate **3**. In previous research from our group, we demonstrated that under appropriate reaction conditions, reaction of in situ generated N-protected chiral α-aminoaldehydes with Grignard reagents results in a chelation-controlled addition of the organometallic nucleophile to the aldehyde carbonyl, leading to the formation of the corresponding enantiopure 1,2-amino alcohol adduct with high syn-selectivity.[9] Following this protocol, oxidation of **5** to the corresponding aldehyde and its reaction with an excess of homoallylmagnesium bromide afforded the required *syn*-amino alcohol derivative **3** with good diastereoselection (>9:1). The assigned stereochemistry of **3** was confirmed by its conversion to the corresponding oxazolidinone **3A** and subsequent ^{1}H NMR study, wherein the coupling constant between the ring protons ($J_{4,5}$ = 4.53 Hz, after decoupling H-5 from 1′-CH_2) was in good agreement with the reported values.[10] Protection of the

SCHEME 1



secondary hydroxy group of **3** afforded the silyl ether derivative **6** in high yield. As per our synthetic strategy, the Boc-amino group and the terminal olefinic moiety of the δ-alkenylcarbamate **6** represent strategic functionalities to achieve the required six-membered heterocyclic ring-forming reaction. Accordingly, treatment of **6** with catalytic osmium tetroxide followed by oxidative cleavage of the resulting diol with silica gel supported sodium periodate[11] resulted in the direct formation of the cyclic carbinolamine **7** in good overall yield. Reductive deoxygenation[12] of **7** was found to form a mixture of two products containing the expected amine derivative along with some quantities of the further silyl-deprotected (at the primary hydroxy site) product **8**. To simplify the purification process, the crude reaction mixture from the above reaction was therefore directly treated with camphorsulfonic acid[13] to cleanly afford the selectively deprotected free primary alcohol derivative **8** in good overall yield.

Subsequent oxidation of the primary hydroxy group under standard conditions[14] provided the corresponding carboxylic acid **9**. Interestingly, the secondary silyl ether linkage was found to be cleaved during the reaction.[15] Considering that, under similar reaction conditions, the silyl ether group remained unaffected in case of the corresponding trans-product (vide infra), the newly generated syn-oriented carboxylic acid moiety of **9** probably facilitated cleavage of the neighboring silyl ether functionality. Finally, acidic hydrolysis of the carbamate culminated in an efficient synthesis of the desired (2*S*,3*R*)-*cis*-3-hydroxypipecolic acid hydrochloride **10**.

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(9) For representative examples, see: (a) Datta, A.; Veeresa, G. *J. Org. Chem.* **2000**, *65*, 7609. (b) Kiran Kumar, K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899. (c) Ravi Kumar, J. S.; Datta, A. *Tetrahedron Lett.* **1999**, *40*, 1381 and references therein. For a pioneering report, see: Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939.

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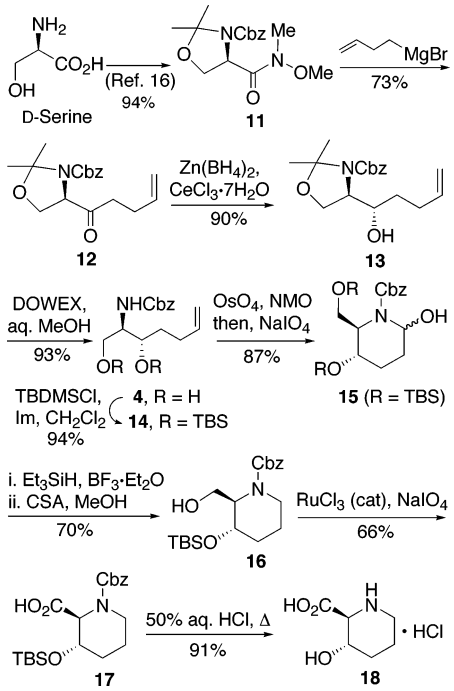
SCHEME 2



A slightly different strategy was followed to achieve the formation of the pivotal *anti*-amino alcohol derivative **13**, as needed for the synthesis of the target *trans*-3-hydroxypipecolic acid (**2**). Thus, following a reported method,[16] D-serine was converted to the corresponding N,O-protected Weinreb amide **11** (Scheme 2). Its conversion to the known ketone **12**, via addition of homoallylmagnesium bromide, was achieved under standard reaction conditions.[10] Stereoselective formation of the 1,2-*anti*-amino alcohol functionality was achieved by reduction of the ketone **12** with zinc borohydride, affording the product **13** with high stereocontrol (>93:7).[7b,c,10]

Selective removal of the acetonide protecting group to form **4**, and subsequent silyl protection of the resulting primary hydroxyl functionality, afforded the fully protected aminodiol **14** in high overall yield. Following the same sequence of reactions as described in Scheme 1, heterocyclization to form the piperidine framework **15** and its deoxygenation resulted in the mono-*O*-silyl-protected piperidine derivative **16**. Subsequent conversion of the primary hydroxy group to carboxylic acid afforded the N,O-diprotected hydroxypipecolic acid **17**. Notably, unlike in the case of the corresponding cis-derivative **8** (Scheme 1), during the present reaction the secondary silyloxy functionality remained unaffected. Finally, simultaneous removal of both the protecting groups under acidic conditions completed the synthesis of the target (2*S*,3*S*)-*trans*-3-hydroxypipecolic acid hydrochloride **18**.

In conclusion, starting from readily available D-serine and following a practical sequence of reactions, efficient synthetic routes to enantiopure *cis*- and *trans*-3-hydroxypipecolic acids have been developed. In terms of brevity and efficiency (*cis*-**10**: 11 steps, 24% overall; *trans*-**18**: 12 steps, 20% overall), the described methods compare well with the literature reported routes[4] and are expected to be attractive alternatives to the existing methods for the synthesis of the title compounds. Additionally, starting from L-serine, the above method can also be readily extended to synthesize the corresponding enantiomers of both the 3-hydroxypipecolic acids described, thereby providing easy access to all possible stereoisomers of these novel amino acid derivatives of structural and biological significance.

Experimental Procedure

(2*R*,3*R*)-2-(*tert*-Butoxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxyhept-6-ene (3). To a stirred solution of oxalyl chloride (2.43 mL, 27.88 mmol) in anhydrous CH_2Cl_2 (50 mL) at −78 °C under nitrogen atmosphere was added DMSO (2.33 mL, 32.8 mmol) dropwise. After being stirred for 30 min, a solution of the amino alcohol **5**[8] (5 g, 16.4 mmol) in CH_2Cl_2 (97 mL) was added to the reaction mixture over 30 min. The mixture was then warmed to −35 °C and stirred for 30 min at the same temperature, followed by dropwise addition of diisopropylethylamine (14.9 mL, 114.8 mmol) over 5 min. The reaction mixture was then warmed to 0 °C over 15 min and transferred through a cannula to a room-temperature solution of homoallymagnesium bromide (prepared from Mg (3.9 g, 164 mmol) and 4-bromo-1-butene (8.26 mL, 82 mmol) in THF (54 mL)). After being stirred for 2 h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL). The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum, and the residue was purified by careful flash column chromatography (EtOAc/hexane = 15:85) to yield the aminodiol derivative **3** as a light yellow oil (3.8 g, 64%): $[\alpha]_D^{25}$ −23 (*c* 1.3, $CHCl_3$); IR (neat) 3442, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.45 (s, 9H), 1.47−1.63 (m, 2H), 2.14−2.19 (m, 2H), 3.38 (s, 1H), 3.52 (br s, 1H), 3.79−3.97 (m, 3H), 4.95−5.19 (m, 2H), 5.12 (d, J = 8.8 Hz, 1H), 5.78−5.98 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2, 18.5, 26.1, 26.2, 28.5, 28.8, 30.2, 33.4, 53.8, 66.9, 73.1, 79.7, 115.3, 138.6, 156.4; HRMS calcd for $C_{18}H_{37}NO_4SiNa$ *m/z* (M + Na) 382.2390, found 382.2376.

Conversion of 6 to the Piperidinol Derivative 7. Step 1. To a room-temperature solution of **6** (320 mg, 0.68 mmol) and NMO (228 mg, 1.69 mmol) in acetone/H_2O (4 mL/1 mL) was added OsO_4 (5% solution in toluene, 0.173 mL, 0.0195 mmol) with stirring. The yellow solution slowly turned orange. After being stirred for 2 h, the reaction mixture was diluted with EtOAc (10 mL) followed by the addition of 10% aqueous $NaHSO_3$ (1 mL). The resulting mixture was allowed to stir for a few minutes, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude diol thus obtained was carried to the next step without further purification.

Step 2. Silica gel-supported $NaIO_4$ (1.36 g; prepared according to ref 11) was added to a room-temperature solution of the diol (~345 mg, 0.68 mmol; as obtained from the above reaction) in

(15) One of the reviewers of the manuscript wondered why the free secondary hydroxy group (at C-3) of compound **9**, generated during the conversion of **8** → **9**, did not undergo further oxidation to the corresponding ketone derivative. A couple of plausible explanations could be as follows: (i) the relatively short reaction time employed for the conversion of **8** → **9** (30 min) could probably be insufficient for carrying out the two-step process of initial cleavage of the silyl protecting group to unmask the hydroxy and subsequent oxidation of this relatively hindered secondary hydroxy to the corresponding ketone. (ii) A second possibility could be an intramolecular hydrogen bond interaction between the favorably placed (and newly generated) carboxylic acid moiety at C-2 and the free hydroxy group at C-3 of compound **9**, resulting in the prevention or rate retardation of the oxidation of the hydroxy group. However, additional experiments will have to be carried out to find out the exact reason for the above reaction stopping at product **9**.

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CH_2Cl_2 (5 mL). After being stirred for 90 min, the reaction mixture was filtered through a sintered funnel, the residue was washed thoroughly with $CHCl_3$, and the combined filtrate was concentrated under vacuum. The residual oil was purified by flash column chromatography (EtOAc/hexane = 5:95 to 10:90) to afford the cyclic carbinolamine **7** as a light yellow oil (269 mg, 83% over two steps): IR (neat) 3400, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (mixture of anomers) δ 0.07, 0.10, and 0.12 (3s, 12H), 0.91 and 0.94 (2s, 18H), 1.49 (s, 9H), 1.51−1.70 (m, 2H), 1.84−1.92 (m, 1H), 2.14 (m, 1H), 3.71−3.83 (m, 2H), 4.08−4.19 (m, 2H), 5.37 (d, J = 10.5 Hz, 1H), 5.49−5.63 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of anomers) δ −4.9, −4.6, 18.5, 18.7, 25.4, 26.2, 26.3, 28.7, 31.6, 55.6, 61.1, 69.8, 73.2, 80.9, 155.4; calcd for $C_{23}H_{50}NO_5Si_2$ *m/z* (M + H) 476.3228, found 476.3242.

Reductive Deoxygenation of the Carbinolamine 7 To Form the Piperidine Diol 8. A solution of **7** (250 mg, 0.53 mmol) and triethylsilane (0.17 mL, 1.06 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to −78 °C, and borontrifluoride etherate (0.15 mL, 1.17 mmol) was added to it dropwise under nitrogen atmosphere. After being stirred for 30 min at the same temperature, a second lot of triethylsilane (0.17 mL, 1.06 mmol) and borontrifluoride etherate (0.15 mL, 1.17 mmol) were added to the reaction mixture. The resulting mixture was stirred for 3 h at −78 °C, followed by quenching the reaction with saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was dissolved in MeOH/CH_2Cl_2 (2 mL:2 mL) and cooled to 0 °C followed by addition of camphorsulfonic acid (4 mg, 0.07 mmol) with stirring. The reaction mixture was maintained at pH 3 at 0 °C for 2 h and then brought to neutral pH with the addition of saturated aqueous $NaHCO_3$ (2 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 2:8 to 4:6) to yield the piperidine **8** as a colorless oil (132 mg, 72%): $[\alpha]^{25}_D$ −16 (*c* 0.7, $CHCl_3$); IR (neat) 3454, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.1 and 0.12 (2s, 6H), 0.91 (s, 9H), 1.48 (s, 9H), 1.68−1.76 (m, 4H), 2.45 (s, 1H, exchangeable with D_2O), 2.63−2.78 (m, 1H), 3.63−4.02 (m, 4H), 4.29−4.52 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.6, −5.5, 18.0, 23.9, 25.8, 28.4, 28.9, 29.2, 38.0, 39.4, 55.7, 56.6, 59.2, 70.0, 70.8, 80.0, 155.2, 156.0; HRMS calcd for $C_{17}H_{35}N_1O_4SiNa$ *m/z* (M + Na) 368.2233, found 368.2214.

Oxidation of 8 to (2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-3-hydroxypipecolic Acid (9). To a suspension of $NaIO_4$ (235 mg, 1.1 mmol) in $CH_3CN/CCl_4/H_2O$ (4.8 mL; 1:1:10) was added $RuCl_3 \cdot H_2O$ (11.4 mg, 0.055 mmol) in small portions, and the mixture was stirred at room temperature for 45 min. The resulting solution was added to the alcohol **8** (191 mg, 0.55 mmol) dissolved in CH_3CN (3 mL), followed by the addition of a second portion of $NaIO_4$ (118 mg, 0.55 mmol). The resulting mixture was stirred at room temperature for 30 min and filtered through Celite, and the Celite layer was washed thoroughly with EtOAc. The combined filtrate was dried over Na_2SO_4 and concentrated. The crude product thus obtained was purified by flash column chromatography (MeOH/$CHCl_3$ = 5:95 to 20:80) to yield the pure acid **9** (97 mg, 72%) as a semisolid: $[\alpha]^{25}_D$ −8 (*c* 0.6, $CHCl_3$); IR (neat) 3365, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 1.47 (s, 9 H), 1.50−1.60 (m, 2H), 1.64−1.78 (m, 1H), 1.83−1.94 (m, 1H), 2.88−3.08 (m, 1H), 3.75 (br s, 1H), 3.87 (d, J = 7.6 Hz, 1H), 4.71−4.86 (m, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) (mixture of rotamers) δ 22.9, 23.4, 24.8, 29.3, 29.4, 29.8, 39.5, 40.6, 57.4, 58.7, 71.8, 78.0, 79.9, 155.7, 155.8, 174.5, 174.7; HRMS calcd for $C_{11}H_{19}NO_5Na$ *m/z* (M + Na) 268.1161, found 268.1162.

(2*S*,3*R*)-3-Hydroxypipecolic Acid Hydrochloride (10). The Boc-protected acid **9** (78 mg, 0.32 mmol) was taken in 6 N HCl (10 mL) and heated at 70 °C for 2 h. The reaction mixture was cooled to room temperature and extracted once with CH_2Cl_2 (10 mL) to remove any organic soluble impurities. Concentration of the aqueous layer under high vacuum followed by overnight drying under high vacuum afforded the product **10** as a light yellow solid (57 mg, quantitative): $[\alpha]^{25}_D$ −25 (*c* 1.3, H_2O); ^1H NMR (400 MHz, D_2O) δ 1.53−1.72 (m, 2H), 1.73−1.90 (m, 2H), 2.82−2.94 (m, 1H), 3.24−3.34 (m, 1H), 3.93 (s, 1H), 4.42 (s, 1H); ^{13}C NMR (100.6 MHz, D_2O) δ 16.0, 28.5, 43.9, 60.9, 64.0, 170.5; HRMS calcd for $C_6H_{12}NO_3$ *m/z* (M + H) 146.0817 (free amine + H), found 146.0814.

Reduction of Ketone 12 to the *anti*-Amino Alcohol Derivative 13. To a solution of the homoallyl ketone **12** (540 mg, 1.70 mmol) in MeOH (10 mL) was added $CeCl_3 \cdot 7H_2O$ (190 mg, 0.51 mmol) in one portion, and the resulting solution was cooled to 0 °C with continuous stirring. An ethereal solution of zinc borohydride (0.20 M in Et_2O, 25.5 mL, 5.10 mmol) was then added dropwise to the reaction mixture (30 min), and stirring was continued at the same temperature for another 2 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl solution (10 mL), and the resulting solution was allowed to attain room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude residue by flash chromatography (EtOAc/hexane = 15:85 to 30:70) yielded the pure amino alcohol **13** as a light yellow oil (488 mg, 90%): $[\alpha]^{25}_D$ 27.5 (*c* 1.13, $CHCl_3$); IR (neat) 3471, 1681; ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.47−1.65 (m, 8H), 2.01−2.30 (m, 2H), 3.58 (br s, 1H), 3.77−4.17 (m, 4H), 4.91−5.23 (m, 4H), 5.65−5.93 (m, 1H), 7.31−7.41 (m, 5H); ^{13}C NMR(100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 22.9, 24.4, 26.3, 30.2, 32.0, 32.9, 61.2, 62.8, 64.0, 64.7, 67.0, 67.8, 71.4, 72.1, 94.6, 115.0, 128.1, 128.2, 128.3, 128.6, 134.9, 137.1, 137.9, 138.4, 154.2, 155.1; HRMS calcd for $C_{18}H_{26}N_1O_4$ *m/z* (M + H) 320.1862, found 320.1852.

Conversion of the Carbinolamine 15 to the Piperidine Derivative 16. Starting from the carbinolamine derivative **15** (375 mg, 0.74 mmol), we followed the same procedure as that for compound **8**. Column chromatographic purification resulted in the piperidine **16** (196 mg, 70%) as a colorless oil: $[\alpha]^{25}_D$ −11 (*c* 1, $CHCl_3$); IR (neat) 3439, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.32−1.42 (m, 1H), 1.56−1.69 (m, 2H), 1.89−2.04 (m, 1H), 2.83−3.01 (m, 1H), 3.70−3.82 (m, 2H), 3.93 (s, 1H), 4.0−4.14 (m, 1H), 4.22−4.34 (m, 1H), 5.15 (dd, J = 12.5 and 18.1 Hz, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ −4.6, −4.5, 18.4, 19.6, 26.1, 28.5, 40.5, 60.9, 65.5, 67.5, 128.1, 128.3, 128.8, 137.3, 157.3; HRMS calcd for $C_{20}H_{34}NO_4Si$ *m/z* (M + H) 380.2257, found 380.2254.

(2*S*,3*S*)-3-Hydroxypipecolic Acid Hydrochloride (18). The N,O-protected piperidine carboxylic acid derivative **17** (100 mg, 0.25 mmol) was taken in 6 N HCl (6 mL) and refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted once with CH_2Cl_2 (10 mL) to remove any organic soluble impurities. The aqueous layer was concentrated under vacuum, and the residue dried under high vaccum overnight to afford the desired product **18** as a light yellow solid (41 mg, 91%): $[\alpha]^{25}_D$ 14.2 (*c* 0.95, H_2O); ^1H NMR (400 MHz, D_2O) δ 1.50−1.68 (m, 2H), 1.82−1.94 (m, 2H), 2.90−3.00 (m, 1H), 3.19−3.30 (m, 1H), 3.72 (d, J = 7.6 Hz, 1H), 3.94−4.03 (m, 1H); ^{13}C NMR (100.6 MHz, D_2O) δ 19.0, 29.2, 42.9, 61.1, 65.9, 170.1; HRMS calcd for $C_6H_{12}NO_3$ *m/z* (M + H) 146.0817, found 146.0808.

Supporting Information Available: General experimental methods, experimental procedures and characterization data for compounds **6**, **12**, **4**, **14**, **15**, and **17**, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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