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Diastereoselective synthesis of (2*S*,5*S*)- and (2*S*,5*R*)-*N*-benzyloxycarbonyl-5-hydroxypipecolic acids from *trans*-4-hydroxy-L-proline

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Abstract—An efficient diastereoselective synthesis of *cis*- and *trans*-5-hydroxy-(2*S*)-*N*-benzyloxycarbonyl pipecolic acids, starting from *trans*-4-hydroxy-L-proline is described. The key synthetic strategies involve the regioisomeric ring expansion of keto ester **8** and diastereoselective reduction of ketone **11** in high selectivity and yield.

1. Introduction

Diastereoselective syntheses of pipecolic acid and its derivatives have attracted considerable attention in organic, pharmaceutical, and medical chemistry due to their key biological roles as components of peptides, proteins, and other natural products.[1] Furthermore, functionalized pipecolic acids also represent key intermediates in the synthesis of conformationally constrained molecular scaffolds as elements in the design of small molecule combinational libraries.[2] A variety of routes for the synthesis of 5-substituted pipecolic acid and its derivatives were described in the literature.[3] Most of these methods are based on the intramolecular ring cyclization of N-protected diazoketone or alkyl halides derived from glutamic acid or glycinate chiral Schiff bases. Recently, Dhimane et al.[4] reported on the preparation of 5-substituted pipecolic acid derivatives from racemic *N*-Boc methylpipecolate in a diastereodivergent manner in high yield. Machetti et al.[5] introduced the preparation of *cis*- and *trans*-4-aminopipecolic acid, a conformationally constrained basic amino acid bearing orthogonal N-protection suitable for solid-phase peptide synthesis through a reductive amination and protection/deprotection method. The Valela group[6] developed a route to (2*S*,4*S*)- and (2*S*,4*R*)-4-hydroxy pipecolic acids from D-glucoheptono-1,4-lactone as a chiral template using β-elimination and diastereoselective hydrogenation.

In the context of our medicinal chemistry program dealing with the development of a new type of antimalarial derivatives, we require *cis*- and *trans*-5-hydroxypipecolic acid and its derivatives, as important fragments to generate novel cysteine protease inhibitors.[7] Herein, we report an efficient diastereoselective synthesis of *cis*- and *trans*-5-hydroxy-(2*S*)-*N*-benzyloxycarbonyl pipecolic acid, starting from *trans*-4-hydroxy-L-proline via regioisomeric ring expansion and diastereoselective reduction.

2. Results and discussion

To generate the Cbz-protected pipecolic acids, Cbz-*trans*-4-OTBS proline **2** was prepared from *trans*-4-hydroxy-L-proline **1**, which was protected with benzyloxycarbonyl chloride (Cbz–Cl) in the presence of sodium bicarbonate ($NaHCO_3$) to give the Cbz-protected acid,[8] which was subsequently treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine to give acid **2** in 91% (three steps) yield. Acid **2** was protected with

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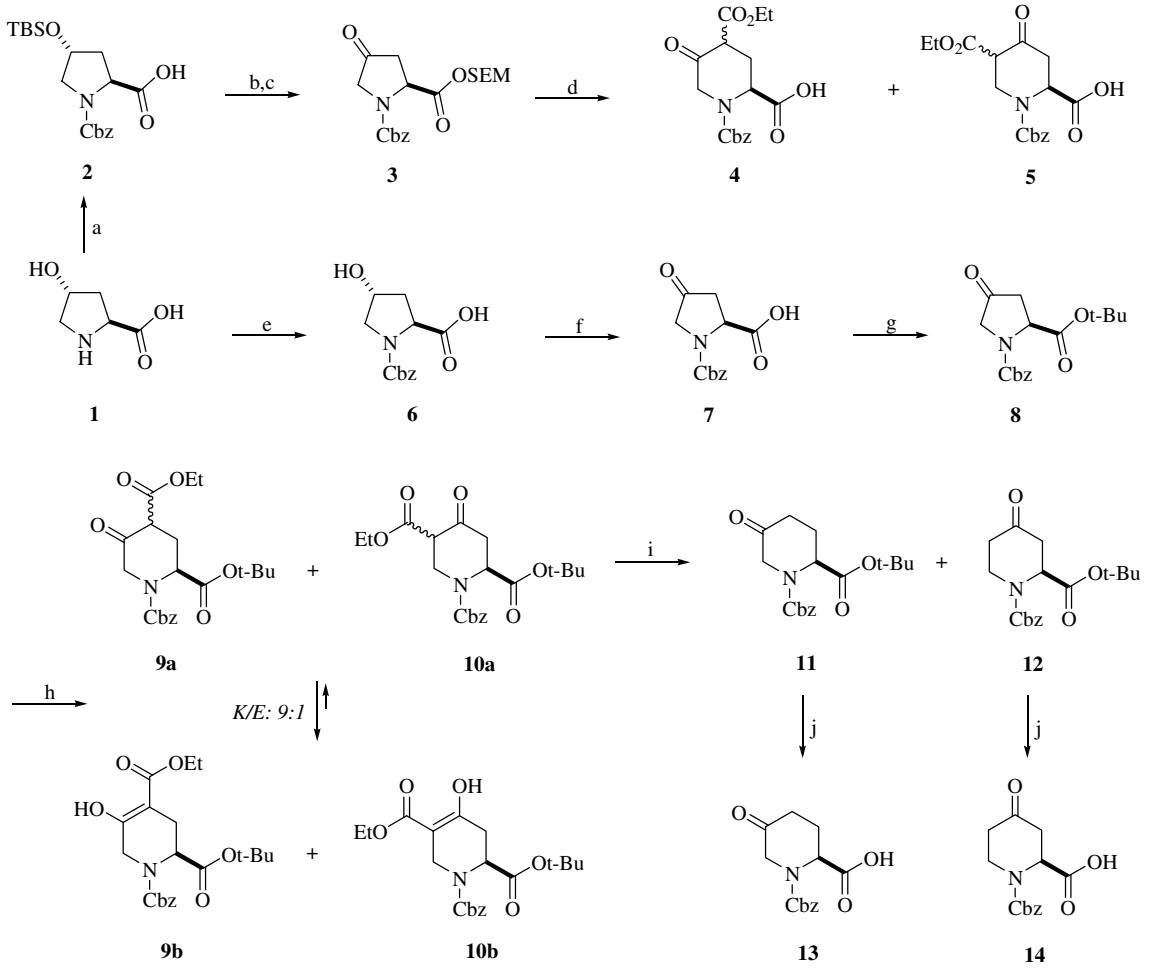
2-(trimethylsilyl)ethoxymethyl chloride (SEM–Cl) in the presence of diisopropylethylamine (DIPEA) to yield the fully protected compound, followed by hydrolysis with AcOH in THF/H_2O (8:2, v/v) to give the SEM ester, which was treated with tetrabutylammonium fluoride (TBAF) to give the secondary alcohol in 93% yield (two steps).

Oxidation of the alcohol was accomplished by using freshly prepared pyridinium chlorochromate (PCC) to afford ketone **3** in 89% yield.[9] Oxidation of the secondary alcohol was also attempted by using Dess–Martin periodinane (DMP), manganese dioxide (MnO_2), tetrapropylammonium perruthenate (TPAP), and Swern conditions. Although these latter conditions were more convenient due to the ease of handling and shorter reaction time, PCC conditions afforded a superior yield. Ketone **3** was subjected to ring expansion with boron trifluoride–diethyl etherate ($BF_3{\cdot}Et_2O$) and ethyl diazoacetate (EDA) to generate pipecolic acids **4** and **5** as a regioisomeric mixture (ratio, 1.3:1, 4:5) in 72% combined yield,[10] which could not be used efficiently for the preparation of pipecolic acids, due to inseparable regioisomeric mixtures by flash column chromatography. *N*-Cbz protection of **1** could also be achieved by treatment of Cbz–Cl in the presence of chlorotrimethylsilane (TMS–Cl) to give acid **6** in 95% yield (two steps). Acid **6** was oxidized by Jones reagent at 0 °C in acetone to generate keto acid **7** in 92% yield, which was treated with isobutylene in acidic media to afford keto ester **8** in 80% yield.[11] Keto ester **8** was treated with $BF_3{\cdot}Et_2O$ and EDA in ether to yield ring expansion regioisomeric keto–enol tautomers **9a** and **9b** and **10a** and **10b**. In this stage, we found that the keto–enol ratio of these mixtures is 9:1 based on ^1H NMR analysis. Decarboxylation of keto esters **9a** and **9b** and **10a** and **10b** was performed with NaCl in DMSO at 140 °C to give regioisomeric 4-ketone **11** and 5-ketone **12** (isolated ratio, 1.5:1, **11**:**12**) in 75% combined yield.[12] Regioisomers **11** and **12** were hydrolyzed using TFA in dichloromethane to give the corresponding acids **13** and **14** in 95% and 97% yields, respectively (Scheme 1).

With the 4- and 5-ketones **11** and **12** in hand, we turned our attention to formation of the desired *cis*- and *trans*-pipeco-

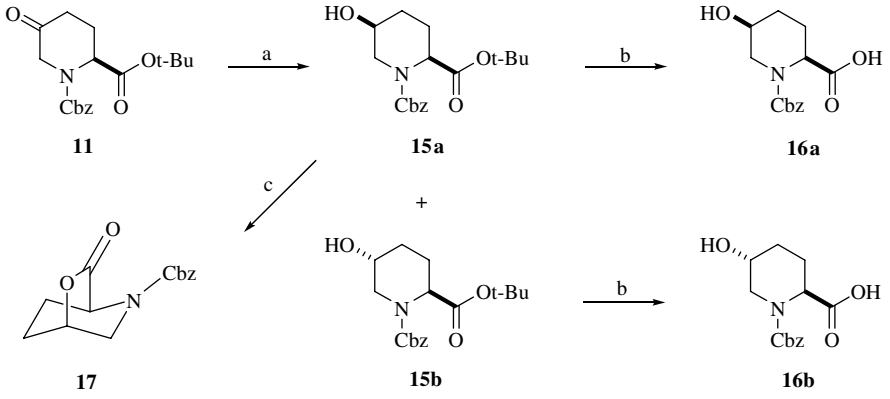


Scheme 1. Reagents and conditions: (a) Cbz–Cl, $NaHCO_3$, H_2O, toluene, rt, 16 h; then TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; then AcOH, THF/H_2O (8:2, v/v), 0 °C, 1 h, 91%; (b) SEM–Cl, DIPEA, CH_2Cl_2, 0 °C to rt, 1 h; then TBAF, THF, 0 °C, 1 h, 93%; (c) PCC, Florisil, CH_2Cl_2, rt, 16 h, 89%; (d) EDA, $BF_3{\cdot}Et_2O$, Et_2O, rt, 2 h, 72%; (e) TMS–Cl, DIPEA, CH_2Cl_2, reflux, 2 h; then, Cbz–Cl, 0 °C to rt, 16 h, 95%; (f) Jones Ox. acetone, 0 °C, 10 min, 92%; (g) isobutylene, H_2SO_4 (cat), CH_2Cl_2, rt, 16 h, 80%; (h) EDA, $BF_3{\cdot}Et_2O$, Et_2O, rt, 1 h, 90%; (i) NaCl, DMSO, H_2O (cat), 140 °C, 4 h, 75%; (j) TFA, CH_2Cl_2, rt, 2 h, 95% for **13**, 97% for **14**.

lic acid. Reduction of **11** was achieved with sodium borohydride in methanol to give *cis*-alcohol **15a** and *trans*-alcohol **15b** (97:3 ratio, **15a**:**15b**, 82% combined yield). The resulting diastereomeric mixture of the reduction products was successfully separated by column chromatography. Furthermore, *cis*-diastereomer **15a** could be identified via intramolecular lactonization, accomplished by refluxing for 1 h in benzene with a catalytic amount of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) to afford *N*-benzyloxycarbonyl lactone **17** in 90% yield,[3a,b] while no similar lactone could be obtained with *trans*-diastereomer **15b** as expected (Scheme 2).

In an attempt to improve further the selectivity of the reduction of 5-ketone **11** to *cis*-alcohol **15a** and *trans*-alcohol **15b** with a view to synthesize 5-hydroxypipecolates, other reducing agents were examined (Table 1). The best result was obtained with 5-ketone **11** in the presence of sodium borohydride in methanol at 0 °C to room temperature for 30 min (Table 1, entry 4). When the carbonyl group of ketone **11** was reduced using L-Selectride, K-Selectride, and Super-H in THF, the diastereomeric mixture of equatorial and axial alcohols **15a** and **15b** was generated, respectively, with 60:40 and 75:25 ratios in high yields (Table 1, entries 1–3). Among the sodium borohydride reagents considered, we have found that the bulkier reducing agents showed low diastereoselectivity and reduced yields, presumably due to steric coordinating effect (Table 1, entries 5–7).[13] Unfortunately, upon treatment of **11** with polymer bound-zinc borohydride (PB-$ZnBH_4$) or diisobutylaluminum hydride (DIBAL) in dichloromethane, the reaction led to the formation of undesired diol due to over reduction (Table 1, entries 8–9).

Likewise, treatment of 4-ketone **12** with sodium borohydride in methanol gave a diastereomeric mixture of the reduction product (2*S*,4*S*) 4-hydroxypipecolate **18a** and its (2*S*,4*R*)-diastereomer **18b** (95:5 ratio **18a**:**18b**, 86% combined yield), which was also cleanly separated by flash column chromatography. Stereoselective reduction of 4-ketone **12** with L-Selectride and Super-H in THF failed to enhance the diastereoselectivity (80:20 ratio, *cis*-**18a**:*trans*-**18b**, 96% combined yield for L-Selectride; 70:30 ratio, *cis*-**18a**:*trans*-**18b**, 88% combined yield for Super-H). Pure *cis*-**18a** and *trans*-**18b** were hydrolyzed by treatment with TFA-in dichloromethane to afford (2*S*,4*S*) 4-hydroxypipecolic

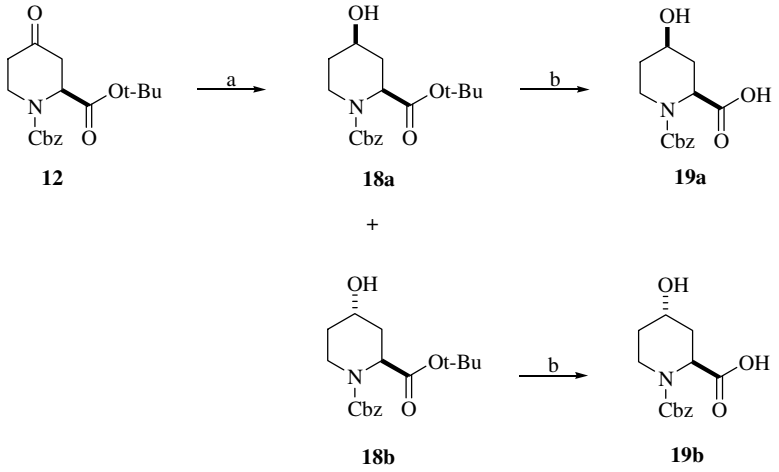


Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 30 min, 82%; (b) TFA, CH_2Cl_2, rt, 2 h, 90% for **16a**, 88% for **16b**; (c) *p*-TsOH, benzene, reflux, 1 h, 86%.

Table 1. Diastereoselective reduction of **11** with various reducing agents to generate **15a** and **15b**

Entry	Reducing agent[a]	Solvent	Temperature (°C)	Time (h)	Selectivity (*S*/*R*)[b]	Yield[c] (%)
1	Li–BH[CH(CH$_3$)CH$_2$CH$_3$]$_3$	THF	−45	0.5	60:40	92
2	K–BH[CH(CH$_3$)CH$_2$CH$_3$]$_3$	THF	−45	0.5	60:40	88
3	Li–BH(C$_2$H$_5$)$_3$	THF	−78 to 0	1	75:25	90
4	$NaBH_4$	MeOH	0 to rt	0.5	97:3	82
5	$NaBH_3CN$	MeOH	−45 to rt	0.5	95:5	60
6	NaBH(OAc)$_3$	MeOH	−45 to rt	0.5	90:10	25
7	Me$_4$NBH(OAc)$_3$	MeOH	0 to rt	5	—	—[d]
8	$ZnBH_4$	CH_2Cl_2	−45 to 10	1	Diol[e]	75
9	AlH[(CH$_3$)$_2$CHCH$_2$]$_2$	CH_2Cl_2	−45 to 10	1	Diol[e]	71

[a] L-Selectride: lithium tri-*sec*-butylborohydride; K-Selectride: potassium tri-*sec*-butylborohydride; Super-hydride: lithium triethylborohydride; $NaBH_4$: sodium borohydride; $NaBH_3CN$: sodium cyanoborohydride; NaBH(OAc)$_3$: sodium triacetoxyborohydride; Me$_4$NB(OAc)$_3$: tetramethylammonium triacetoxyborohydride; $ZnBH_4$: polymer bound-zinc borohydride (PB); DIBAL: diisobutylaluminum hydride.
[b] Diastereoselectivity.
[c] Isolated pure yield.
[d] No reaction.
[e] Over-reduction product.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 30 min, 86%; (b) TFA, CH_2Cl_2, rt, 2 h, 90% for **19a**, 88% for **19b**.

acid **19a** and (2*S*,4*R*) 4-hydroxypipecolic acid **19b** in 90% and 88% yields, respectively (Scheme 3).

3. Conclusion

In conclusion, we have developed a diastereoselective synthesis of (2*S*,4*S*)- and (2*S*,4*R*)-5-hydroxypipecolic acid through a regioisomeric ring expansion reaction and stereoselective reduction. This method is versatile and allows for the preparation of key fragments for enzyme inhibitor studies.

4. Experimental

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates from Analtech and visualized with a 254 nm UV light. Flash chromatography was carried out on silica gel 60 [Scientific Adsorbents Incorporated (SAI), particle size 32–63 μm, pore size 60 Å]. ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on a Bruker DPX 400, 500 at 400, 500 MHz, and 100, 125 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values are in hertz. Infrared (IR) spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded with a Waters Micromass ZQ LC-Mass system and Q-TOP micro mass spectrometer with electrospray interface and lockspray source. When necessary, chemicals were purified according to the reported procedures.[14]

4.1. (2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid 2

To a stirred solution of *trans*-4-hydroxy-L-proline **1** (2.0 g, 15.3 mmol) in water (30 mL) was added sodium bicarbonate (3.2 g, 38.0 mmol), followed by the addition of a solution of benzyl chloroformate (3.0 g, 17.5 mmol) in toluene (10 mL). The mixture was stirred at room temperature for 16 h. The two phases were separated and the aqueous phase extracted with ether (3 × 8 mL) and acidified to pH 2 with 3 M HCl solution. The oily residue was extracted with ethyl acetate (3 × 15 mL), and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used in the next reaction without purification. The residue was dissolved in dichloromethane (70 mL), and 2,6-lutidine (5.4 g, 50.5 mmol) was added, followed by TBSOTf (12.1 g, 45.9 mmol) at 0 °C. The mixture was warmed to room temperature for 30 min and stirred for 1 h. The reaction mixture was diluted with dichloromethane (35 mL) and washed with saturated aqueous NH_4Cl solution (35 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was treated with AcOH (9.1 mL) in THF/H_2O (90 mL, 8:2, v/v) at 0 °C and the mixture was stirred at 0 °C for 1 h. The resulting mixture was evaporated under reduced pressure and the residue was diluted with dichloromethane (70 mL) and washed with saturated aqueous NH_4Cl solution (40 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% methanol in dichloromethane) to give **2** (5.3 g, 91%) as a colorless oil. $R_f = 0.5$ (5% methanol/dichloromethane); $[\alpha]_D^{22} = -36.5$ (*c* 0.8, $CHCl_3$); IR (neat, NaCl) 3417, 3034, 2955, 2867, 1713, 1423, 1359, 1255, 1120, 1022, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) mixture of two rotamers δ 7.41–7.27 (m, 5H, Ar–H), 7.14 (br s, 1H, CO_2H), 5.26–5.13 (m, 2H, PhCH_2O), 4.57–4.42 (m, 2H, NCHCO$_2$H, CH$_2$CHOSi), 3.71–3.61 (m, 1H, NCH_2CHO), 3.57–3.42 (m, 1H, NCH_2CHO), 2.31–2.19 (m, 1H, NCHCH_2), 2.18–2.07 (m, 1H, NCHCH_2), 0.89 (s, 1/2 × 9H, SiCMe$_3$), 0.88 (s, 1/2 × 9H, SiCMe$_3$), 0.12 (s, 3H, Si–Me), 0.08 (s, 3H, Si–Me); ^{13}C NMR ($CDCl_3$, 125 MHz) mixture of two rotamers δ 177.4, 176.5, 175.9, 155.9, 154.4, 136.3, 136.1, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 70.4, 69.9, 67.8, 67.4, 58.5, 57.9, 55.4, 55.0, 40.2, 38.7, 18.4, 18.3, −3.2, −4.3, −4.4, −4.5; HRMS

calcd for $C_{19}H_{30}NO_5SiNa$: 380.1893 $[M+Na]^+$, found: 380.1888.

4.2. (2*S*)-4-Oxopyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(2-trimethylsilylethoxymethoxy) ester 3

To a stirred solution of acid **2** (7.6 g, 20.0 mmol) in dichloromethane (150 mL) was added DIPEA (2.8 g, 22.0 mmol), followed by the addition of a solution of SEM–Cl (3.7 g, 22.0 mmol) at 0 °C. The mixture was warmed to room temperature for 1 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous NH_4Cl solution (120 mL) and brine (120 mL). The organic phase was separated and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used in the next reaction without purification. The residue was dissolved in THF (180 mL) and treated with TBAF (38.8 g, 40.0 mmol, 1.0 M soln, in THF) at 0 °C. The mixture was stirred for 1 h, diluted with dichloromethane (150 mL), and washed with saturated aqueous NH_4Cl solution (150 mL) and brine (150 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 75:20:5; *n*-hexane–ethyl acetate–methanol, v/v) to give alcohol (7.3 g, 93%) as a pale yellow oil. To a stirred solution of alcohol (1.7 g, 4.3 mmol) in dry dichloromethane (50 mL) was added pyridinium chlorochromate (2.4 g, 10.8 mmol), followed by addition of Florisil (1.7 g) and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (10 mL) and filtered through Celite. The residue was treated with active carbon (2.2 g) and filtered again through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in *n*-hexanes) to give **3** (1.5 g, 89%) as a colorless oil. $R_f = 0.4$ (20% ethyl acetate/*n*-hexanes); $[\alpha]_D^{27} = -10.0$ (*c* 0.3, $CHCl_3$); IR (neat, NaCl) 3066, 3034, 2954, 2899, 1768, 1715, 1499, 1356, 1250, 1111, 1055, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) mixture of two rotamers δ 7.41–7.32 (m, 5H, Ar–H), 5.42 (d, $J = 6.0$ Hz, $1/2 \times 1H$, OCH_2O), 5.34 (d, $J = 6.0$ Hz, $1/2 \times 1H$, OCH_2O), 5.29–5.14 (m, 3H, OCH_2O, $PhCH_2O$), 4.89 (dd, $J = 11.0$, 10.0 Hz, 1H), 4.01–3.93 (m, 2H), 3.79–3.59 (m, 2H), 3.06–2.94 (m, 1H), 2.66 (d, $J = 2.5$ Hz, $1/2 \times 1H$), 2.62 (d, $J = 2.5$ Hz, $1/2 \times 1H$), 0.98 (t, $J = 8.0$ Hz, 1H), 0.92 (t, $J = 8.5$ Hz, 1H), 0.04 (s, 6H), 0.03 (s, 3H, $SiMe_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) mixture of two rotamers δ 207.0, 206.4, 170.8, 170.6, 154.7, 153.9, 135.8, 128.5, 128.2, 128.0, 90.3, 68.4, 67.9, 56.4, 56.3, 52.9, 52.7, 41.8, 40.8, 26.0, 18.4, −1.0; HRMS calcd. for $C_{19}H_{27}NO_6SiNa$: 416.1505 $[M + Na]^+$, found: 416.1441.

4.3. *N*-Benzyloxycarbonyl-4-ethoxycarbonyl-5-oxo-(*S*)-pipecolic acid 4/*N*-benzyloxycarbonyl-4-oxo-5-ethoxycarbonyl-(*S*)-pipecolic acid 5

To a stirred solution of ketone **3** (0.79 g, 2.0 mmol) in ether (7 mL) was added boron trifluoride–diethyl etherate (0.31 g, 2.2 mmol), followed by addition of ethyl diazoacetate (0.34 g, 3.0 mmol) at 5 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 60:30:10; *n*-hexane–ethyl acetate–methanol, v/v) to give **4** and **5** (0.51 g, 72%) as a viscous oil. $R_f = 0.1$ (60:30:10; *n*-hexane–ethyl acetate–methanol, v/v); $[\alpha]_D^{27} = +4.0$ (*c* 0.2, $CHCl_3$); IR (neat, NaCl) 3445, 2983, 1714, 1669, 1498, 1309, 1230, 1113, 1029, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 12.01 (br s, $2/3 \times 1H$), 7.49–7.46 (m, 5H), 5.24 (dd, $J = 11.5$, 12.0 Hz, 2H), 4.48–3.90 (m, 4H), 3.51 (dd, $J = 7.0$, 7.0 Hz, 1H), 3.01 (t, $J = 17.0$ Hz, $1/2 \times 1H$), 2.89 (t, $J = 17.0$ Hz, $1/2 \times 1H$), 2.79 (br s, $1/3 \times 1H$), 1.36–1.26 (m, 2H), 1.23 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 155.6, 135.8, 128.5, 128.2, 127.9, 127.8, 68.1, 66.0, 61.9, 61.8, 52.2, 43.6, 39.2, 30.2, 24.3, 15.6, 14.6; HRMS calcd for $C_{17}H_{20}NO_7$: 350.1240 $[M+H]^+$, found: 350.1264.

4.4. (2*S*)-4-Oxopyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester 8

A stirred solution of keto acid **7** (9.3 g, 35.4 mmol) in dry dichloromethane (71 mL) was cooled to 0 °C, and concentrated sulfuric acid (0.35 mL) was added dropwise. Isobutylene was bubbled into the solution until the volume of the mixture had increased by approximately 50%. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (140 mL) and washed with saturated aqueous Na_2CO_3 solution (120 mL) and water (120 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% ethyl acetate in *n*-hexanes) to give **8** (9.0 g, 80%) as a viscous bright yellow oil. $R_f = 0.4$ (30% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = +5.4$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3034, 2979, 1768, 1738, 1714, 1415, 1151, 1027, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) mixture of two rotamers δ 7.39–7.30 (m, 5H), 5.25–2.15 (m, 2H), 4.72 (dd, $J = 18.0$, 10.5 Hz, 1H), 4.03–3.89 (m, 2H), 2.99–2.84 (m, 1H), 2.55 (d, $J = 18.0$ Hz, 1H), 1.45 (s, $1/2 \times 9H$), 1.37 (s, $1/2 \times 9H$); ^{13}C NMR ($CDCl_3$, 125 MHz) mixture of two rotamers δ 207.7, 207.0, 170.3, 170.2, 154.7, 154.1, 136.0, 135.8, 128.4, 128.2, 128.0, 82.8, 67.7, 57.1, 53.0, 52.8, 41.6, 41.0, 28.2, 28.0; HRMS calcd for $C_{17}H_{22}NO_5$: 320.1498 $[M+H]^+$, found: 320.1495.

4.5. *N*-Benzyloxycarbonyl-4-ethoxycarbonyl-5-oxo-(*S*)-pipecolic acid *tert*-butyl ester 9a and 9b/*N*-benzyloxycarbonyl-4-oxo-5-ethoxycarbonyl-(*S*)-pipecolic acid *tert*-butyl ester 10a and 10b

To a stirred solution of keto ester **8** (6.0 g, 18.8 mmol) in ether (70 mL) was added dropwise boron trifluoride–diethyl etherate (2.8 g, 19.7 mmol), followed by addition of ethyl diazoacetate (3.2 g, 28.2 mmol) at 5 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether (70 mL) and washed with saturated aqueous NH_4Cl solution (100 mL) and brine (80 mL). The organic layer was separated, dried over

anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% ethyl acetate in *n*-hexanes) to give **9a** and **9b** and **10a** and **10b** as regioisomeric mixtures (6.9 g, 90%) of bright yellow oil. $R_f = 0.5$ (25% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = +22.4$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3034, 2979, 1733, 1714, 1668, 1630, 1407, 1310, 1155, 1066, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 12.1 (s, 1H), 7.42–7.30 (m, 5H), 5.24 (dd, $J = 13.0$, 16.5 Hz, 2H), 5.16–5.06 (m, $1/2 \times 1H$), 5.02–4.94 (m, $1/2 \times 1H$), 4.24 (dd, $J = 7.5$, 7.5 Hz, 2H), 4.10–3.85 (m, $3/2 \times 1H$), 3.61 (dd, $J = 7.0$, 7.0 Hz, $1/2 \times H$), 2.98 (t, $J = 15.5$ Hz, $2/3 \times 1H$), 2.80 (t, $J = 17.5$ Hz, $1/3 \times 1H$), 2.70 (dd, $J = 6.0$, 6.0 Hz, $1/3 \times 1H$), 2.52 (dd, $J = 5.0$, 5.0 Hz, $2/3 \times 1H$), 1.43 (s, $1/4 \times 9H$), 1.42 (s, $1/4 \times 9H$), 1.40 (s, $1/4 \times 9H$), 1.38 (s, $1/4 \times 9H$), 1.32 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.0, 170.9, 169.5, 168.8, 167.4, 166.7, 166.5, 166.1, 155.5, 155.0, 136.1, 136.0, 128.4, 128.1, 127.9, 127.7, 94.9, 94.5, 94.1, 82.5, 82.4, 82.2, 68.3, 67.9, 67.7, 67.3, 61.0, 60.6, 53.6, 53.1, 52.9, 52.6, 44.0, 43.8, 39.4, 39.0, 30.6, 28.3, 28.2, 24.4, 24.1, 15.4, 14.6; HRMS calcd for $C_{21}H_{28}NO_7$: 406.1866 $[M+H]^+$, found: 406.1859.

4.6. *N*-Benzyloxycarbonyl-5-oxo-(*S*)-pipecolic acid *tert*-butyl ester 11

To a stirred solution of keto-enol tautomers **9a** and **9b** and **10a** and **10b** (4.1 g, 10.1 mmol) in dimethylsulfoxide (10 mL) were added water (0.2 mL) and sodium chloride (0.6 g, 10.1 mmol) at room temperature. The mixture was heated at 140 °C for 4 h, and cooled to room temperature. The resulting reaction mixture was diluted with dichloromethane (150 mL) and washed with 50% aqueous NaCl solution (3×50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in *n*-hexanes) to give 5-ketone **11** (1.5 g, 45%) and 4-ketone **12** (1.0 g, 30%) as a colorless oil. $R_f = 0.27$ (20% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = -4.8$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3034, 2977, 2857, 1733, 1711, 1414, 1251, 1153, 1046, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.27 (m, 5H), 5.14 (dq, $J = 19.4$, 12.4 Hz, 2H), 4.74 (t, $J = 6.5$ Hz, $1/2 \times 1H$), 4.60 (t, $J = 6.5$ Hz, $1/2 \times 1H$), 4.38 (dd, $J = 39.2$, 19.0 Hz, 1H), 3.94 (dd, $J = 26.4$, 19.0 Hz, 1H), 2.50–2.03 (m, 4H), 1.44 (s, $1/2 \times 9H$), 1.36 (s, $1/2 \times 9H$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.9, 204.8, 170.5, 170.4, 155.5, 155.3, 136.0, 128.5, 128.2, 128.0, 127.9, 82.3, 67.7, 54.5, 54.1, 52.2, 51.8, 35.7, 35.5, 28.0, 27.9, 23.8, 23.7; HRMS calcd for $C_{18}H_{24}NO_5$: 334.1654 $[M+H]^+$, found: 334.1645.

4.7. *N*-Benzyloxycarbonyl-4-oxo-(*S*)-pipecolic acid *tert*-butyl ester 12

Bright yellow oil. $R_f = 0.24$ (20% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = -15.4$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3033, 2978, 2875, 1732, 1707, 1414, 1247, 1155, 1058, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.28 (m, 5H), 5.16 (dd, $J = 12.4$, 12.8 Hz, 2H), 5.03 (d, $J = 6.5$ Hz, $1/2 \times 1H$), 4.86 (t, $J = 5.5$ Hz, $1/2 \times 1H$), 4.11 (dd, $J = 8.0$, 7.5 Hz, 1H), 3.71 (dd, $J = 7.5$, 7.5 Hz, 1H), 2.85–2.62 (m, 2H), 2.60–2.43 (m, 2H), 1.43 (s, $1/2 \times 9H$), 1.36 (s, $1/2 \times 9H$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.4, 169.8, 155.6, 136.2, 128.5, 128.2, 128.0, 82.7, 67.8, 55.2, 41.2, 40.3, 39.5, 27.8; HRMS calcd for $C_{18}H_{24}NO_5$: 334.1654 $[M+H]^+$, found: 334.1647.

4.8. *N*-Benzyloxycarbonyl-4-oxo-(*S*)-pipecolic acid 13

To a stirred solution of 5-ketone **11** (0.25 g, 0.75 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (0.5 mL) at 5 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated in vacuo, and the residue was diluted with dichloromethane (35 mL) and washed with 2.5% aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in *n*-hexanes) to give 5-keto acid **13** (0.16 g, 95%) as a colorless oil. $R_f = 0.2$ (50% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = +0.4$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3600–3410, 3035, 2964, 1714, 1542, 1418, 1324, 1218, 1118, 1043, 879 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.67 (br s, 1H), 7.40–7.25 (m, 5H), 5.23–5.10 (m, 2H), 4.89 (t, $J = 6.4$ Hz, $2/3 \times 1H$), 4.78 (t, $J = 6.4$ Hz, $1/3 \times 1H$), 4.42 (dd, $J = 24.0$, 18.8 Hz, 1H), 4.00 (d, $J = 19.2$ Hz, 1H), 2.58–2.34 (m, 3H), 2.32–2.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7, 176.1, 155.9, 135.5, 128.8, 128.6, 128.0, 68.4, 53.5, 51.9, 35.6, 23.3; HRMS calcd for $C_{14}H_{16}NO_5$: 278.1028 $[M+H]^+$, found: 278.1049.

4.9. *N*-Benzyloxycarbonyl-4-oxo-(*S*)-pipecolic acid 14

Bright yellow oil; yield (0.17 g, 97%). $R_f = 0.2$ (50% ethyl acetate/*n*-hexanes); $[\alpha]_D^{25} = -19.6$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3433, 3034, 2961, 1727, 1704, 1542, 1423, 1317, 1251, 1186, 1057, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.30 (br s, 1H), 7.42–7.24 (m, 5H), 5.23–4.98 (m, 3H), 4.10 (t, $J = 6.0$ Hz, 1H), 4.68 (t, $J = 6.0$ Hz, 1H), 2.92–2.71 (m, 2H), 2.55–2.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.0, 174.1, 156.0, 155.4, 135.8, 128.6, 128.4, 128.0, 68.3, 54.3, 53.5, 40.8, 40.3, 39.4; HRMS calcd for $C_{14}H_{16}NO_5$: 278.1028 $[M+H]^+$, found: 278.1032.

4.10. General procedure for the preparation of *N*-benzyloxycarbonyl-(2*S*,5*S*)-5-hydroxypipecolic acid *tert*-butyl ester 15a and *N*-benzyloxycarbonyl-(2*S*,5*R*)-5-hydroxypipecolic acid *tert*-butyl ester 15b

To a stirred solution of 5-ketone **11** (0.33 g, 1.0 mmol) in the appropriate solvent (10 mL) was slowly added a reducing agent (1.2 mmol) at −78 to 0 °C. After the reaction was completed, the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and diluted with ethyl acetate (15 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 45% ethyl acetate in *n*-hexanes) to give *cis*-5-hydroxypipecolate **15a** and *trans*-5-hydroxypipecolate **15b**. Compound **15a**: viscous oil. $R_f = 0.41$ (45% ethyl acetate/*n*-hexanes); $[\alpha]_D^{26} = -27.9$ (*c* 2.0, $CHCl_3$); IR (neat,

NaCl) 3343, 3033, 2976, 2941, 2871, 1728, 1707, 1499, 1420, 1330, 1236, 1147, 1073, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.26 (m, 5H, Ar–H), 5.13 (dd, $J = 12.8$, 12.4 Hz, 2H, Bn), 4.78 (d, $J = 3.4$ Hz, $1/2 \times 1H$, H–2), 4.65 (d, $J = 3.4$ Hz, $1/2 \times 1H$, H–2), 4.20 (dd, $J = 12.0$, 14.4 Hz, 1H, H–5), 3.70–3.55 (m, 1H, H–6), 2.88 (t, $J = 11.6$ Hz, $1/2 \times 1H$, H–6), 2.78 (t, $J = 11.2$ Hz, $1/2 \times 1H$, H–6), 2.39 (br s, OH), 2.27 (t, $J = 11.5$ Hz, 1H, H–3), 1.97 (d, $J = 12.0$ Hz, 1H, H–4), 1.47 (s, $1/2 \times 9H$, *t*-Bu), 1.43 (s, $1/2 \times 9H$, *t*-Bu), 1.27 (dt, $J = 6.0$, 6.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 155.9, 136.5, 128.6, 128.0, 127.9, 81.9, 67.4, 66.6, 60.4, 54.2, 53.9, 48.1, 30.3, 29.9, 25.1, 24.9, 21.0; HRMS calcd for $C_{18}H_{25}NO_5Na$: 358.1630 $[M+Na]^+$, found: 358.1642. Compound **15b**: viscous oil. $R_f = 0.35$ (45% ethyl acetate/*n*-hexanes); $[\alpha]_D^{26} = -19.6$ (*c* 2.0, $CHCl_3$); IR (neat, NaCl) 3346, 3034, 2976, 2939, 1732, 1702, 1499, 1424, 1325, 1249, 1146, 1084, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.28 (m, 5H, Ar–H), 5.13 (dd, $J = 12.4$, 12.0 Hz, 2H, Bn), 4.89 (d, $J = 3.0$ Hz, $1/2 \times H$, H-2), 4.76 (d, $J = 3.0$ Hz, $1/2 \times H$, H–2), 4.1 (dd, $J = 13.6$, 13.6 Hz, 1H, H-5), 3.98 (d, $J = 36.8$ Hz, 1H, H-6), 3.33 (d, $J = 14.0$ Hz, $1/2 \times H$, H-6), 2.21 (d, $J = 14.0$ Hz, $1/2 \times H$, H-6), 2.16 (br s, OH), 2.27–1.88 (m, 2H, H-3), 1.80 (d, $J = 14.4$ Hz, 1H, H-4), 1.54 (d, $J = 14.0$ Hz, 1H, H-4) 1.47 (s, $1/2 \times 9H$, *t*-Bu), 1.43 (s, $1/2 \times 9H$, *t*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.8, 136.5, 128.5, 128.0, 127.8, 81.8, 67.4, 63.7, 54.9, 53.5, 47.8, 30.0, 27.1, 26.7, 20.3; HRMS calcd for $C_{18}H_{25}NO_5Na$: 358.1630 $[M+Na]^+$, found: 358.1645.

4.11. *N*-Benzyloxycarbonyl-(2*S*,5*S*)-5-hydroxypipecolic acid 16a

Acids **16a** and **16b** were prepared from *cis*-alcohol **15a** and *trans*-alcohol **15b** by the procedure described previously for preparing the acids **13** and **14**, respectively. Compound **16a**: yield; 88%. $R_f = 0.1$ (50% ethyl acetate/*n*-hexanes); mp 131–132 °C; $[\alpha]_D^{24} = 76.5$ (*c* 0.17, MeOH); IR (neat, NaCl) 3270, 3035, 2922, 1737, 1592, 1420, 1246, 1122, 1081, 854 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.52 (br s, 1H), 7.42–7.25 (m, 5H), 5.17 (s, 2H), 4.92 (d, $J = 5.5$ Hz, 1H), 4.75 (br s, 1H), 4.10 (d, $J = 14.0$ Hz, 1H), 3.98 (d, $J = 18.0$ Hz, 1H), 3.32–3.13 (m, 1H), 2.35–2.22 (m, 1H), 1.95 (t, $J = 13.0$ Hz, 1H), 1.72 (d, $J = 13.5$ Hz, 1H), 1.58 (t, $J = 13.5$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 171.9, 156.1, 155.9, 137.3, 128.4, 128.0, 127.6, 66.8, 61.5, 54.1, 53.7, 47.9, 47.5, 27.5, 27.3, 20.8; HRMS calcd for $C_{14}H_{17}NO_5Na$: 302.1004 $[M+Na]^+$, found: 302.1012.

4.12. *N*-Benzyloxycarbonyl-(2*S*,5*R*)-5-hydroxypipecolic acid 16b

Semisolid; yield; 88%. $R_f = 0.1$ (50% ethyl acetate/*n*-hexanes); $[\alpha]_D^{28} = -7.2$ (*c* 1.0, MeOH); IR (neat, NaCl) 3400, 3201, 3033, 2946, 1737, 1681, 1498, 1324, 1238, 1132, 1067, 856 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz): δ 10.45 (br s, 1H), 7.44–7.29 (m, 5H), 5.15 (s, 2H), 4.90 (dd, $J = 4.5$, 4.5 Hz, 1H), 4.87 (br s, 1H), 4.07 (d, $J = 13.5$ Hz, 1H), 3.96 (d, $J = 27.0$ Hz, 1H), 3.31 (d, $J = 13.5$ Hz, $2/3 \times 1H$), 3.17 (d, $J = 14.0$ Hz, $1/3 \times 1H$), 2.32–2.23 (m, 1H), 1.99 (t, $J = 14.0$ Hz, 1H), 1.75 (d, $J = 13.5$ Hz, 1H), 1.56 (t, $J = 13.5$ Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz): δ 172.0, 156.4, 156.8, 137.1, 128.2, 127.6, 127.4, 66.7, 62.9, 54.2, 53.9, 47.8, 47.6, 27.4, 27.3, 20.5; HRMS calcd for $C_{14}H_{17}NO_5Na$: 302.1004 $[M+Na]^+$, found: 302.1019.

4.13. Benzyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate 17

To a stirred solution of *cis*-alcohol **15a** (0.1 g, 0.3 mmol) in benzene (4 mL) was added *p*-toluenesulfonic acid monohydrate (0.01 g) and the mixture was refluxed for 1 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 5% aqueous sodium bicarbonate solution (2×10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 45% ethyl acetate in *n*-hexanes) to give *N*-Cbz lactone **17** (68 mg, 86%) as a colorless oil. $R_f = 0.35$ (45% ethyl acetate/*n*-hexanes); $[\alpha]_D^{26} = -10.0$ (*c* 2.0, $CHCl_3$); IR (neat, NaCl) 3034, 2947, 2889, 1771, 1707, 1418, 1348, 1292, 1136, 1080, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.30 (m, 5H), 5.17 (s, 2H), 4.89–4.68 (m, 2H), 3.71 (d, $J = 11.6$ Hz, 1H), 3.53 (d, $J = 11.6$ Hz, 1H), 2.30–2.18 (m, 1H), 2.17–1.97 (m, 2H), 1.81 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 154.3, 136.0, 128.6, 128.4, 128.3, 128.1, 73.6, 67.7, 50.5, 49.7, 47.5, 24.5, 23.6; HRMS calcd for $C_{14}H_{15}NO_4Na$: 284.0899 $[M+Na]^+$, found: 284.0913.

4.14. *N*-Benzyloxycarbonyl-(2*S*,4*R*)-4-hydroxypipecolic acid *tert*-butyl ester (18a)

Viscous oil; yield 86%. $R_f = 0.35$ (50% ethyl acetate/*n*-hexanes); $[\alpha]_D^{26} = -39.2$ (*c* 2.0, $CHCl_3$); IR (neat, NaCl) 3469, 3034, 2976, 2893, 1735, 1702, 1420, 1349, 1279, 1159, 1086, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 5H), 5.26–5.02 (m, 2H), 4.75 (d, $J = 4.5$ Hz, $1/2 \times 1H$), 4.63 (d, $J = 4.5$ Hz, $1/2 \times 1H$), 5.13 (s, 1H), 3.92 (t, $J = 18.0$ Hz, 1H), 3.48 (t, $J = 12.8$ Hz, $1/2 \times 1H$), 3.39 (t, $J = 12.8$ Hz, $1/2 \times 1H$), 2.50–2.25 (m, 2H), 1.88 (br s, 1H), 1.87–1.85 (m, 2H), 1.45 (s, $1/2 \times 9H$), 1.43 (s, $1/2 \times 9H$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 156.2, 136.7, 128.4, 128.1, 128.0, 127.9, 81.6, 67.2, 63.2, 54.9, 52.1, 51.8, 40.6, 35.8, 33.2, 31.2, 27.9; HRMS calcd for $C_{18}H_{26}NO_5$: 336.1811 $[M+H]^+$, found: 336.1824.

4.15. *N*-Benzyloxycarbonyl-(2*S*,4*R*)-4-hydroxypipecolic acid 19a

Acid **19a** was prepared from **18a** through hydrolysis similar to procedure for acid **16a**. White foam; yield 90%. $R_f = 0.1$ (50% ethyl acetate/*n*-hexanes); $[\alpha]_D^{26} = -17.1$ (*c* 2.0, MeOH); IR (neat, NaCl) 3423, 2925, 2856, 1682, 1431, 1357, 1282, 1142, 1084, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.31 (m, 5H), 5.14 (d, $J = 12.0$ Hz, 2H), 4.90 (br s, 1H), 4.12 (s, 1H), 3.86 (d, $J = 7.0$ Hz, 1H), 3.69–4.42 (m, 1H), 2.49 (t, $J = 7.5$ Hz, 1H), 1.88 (d, $J = 6.0$ Hz, 1H), 1.79–1.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 155.4, 141.9, 128.5, 128.1, 127.6, 66.8, 62.5, 54.3, 51.4, 36.0, 33.0, 31.2; HRMS calcd for $C_{14}H_{17}NO_5Na$: 302.1004 $[M+Na]^+$, found: 302.1015.

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