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TETRAHEDRON: *ASYMMETRY*

Synthesis of chiral nonracemic 4-*trans*-substituted pipecolic acid derivatives†

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Abstract

The syntheses and resolutions of enantiomerically enriched 4-phenyl, 4-*tert*-butyl, and 4-isopropyl pipecolic acids are described. Optically active diastereomers were prepared by diastereomeric salt formation with the chiral base, L-tyrosine hydrazide, to provide Cbz or Boc protected 4-*cis*-D-pipecolic acid derivatives in >98% ee. Subsequent esterification followed by sodium methoxide catalyzed epimerization provided the isomeric 4-*trans*-L-pipecolic esters. In addition, an efficient synthesis of 4-phenyl-*cis*-pipecolic acid is described.

1. Introduction

As part of our program[1] to synthesize high-affinity ligands for specifically designed mutants of the intracellular protein FKBP12, we required efficient access to various 4-aryl/alkyl-*trans*-L-pipecolic acid derivatives in high enantiopurity. The synthesis of substituted pipecolic acids has received heightened attention[2] over the last decade as the use of these building blocks in the synthesis of peptidomimetics continues unabated. Research in the area of 4-substituted pipecolic acids alone has resulted in novel therapeutically relevant agents (Fig. 1) in areas such as HIV-1 protease inhibition (Palinavir), *N*-methyl-D-aspartic acid (NMDA) receptor antagonism (Selfotel), and thrombin inhibition (Argatroban). With the exception of Argatroban, however, which incorporates the (2*R*,4*R*) 4-methyl-2-piperidinecarboxylate (4-MPE), few examples exist in the literature specifically relating to the targeted synthesis of 4-*trans*-substituted pipecolic acids.[3,4]

We describe a synthetic protocol (outlined in Scheme 1) to obtain the 4-isopropyl, 4-*tert*-butyl, and 4-phenyl *trans*-substituted pipecolic acids, starting from 4-*cis*-substituted pipecolic acids, which are readily accessible via a variety of well documented methods (**A**).[2] These adducts may then be derivatized

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† Dedicated to Professor Ralph F. Hirschmann on the occasion of his receipt of the 1999 Arthur C. Cope Award.

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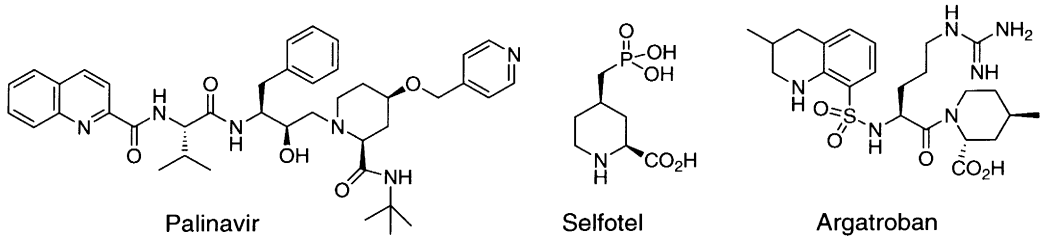
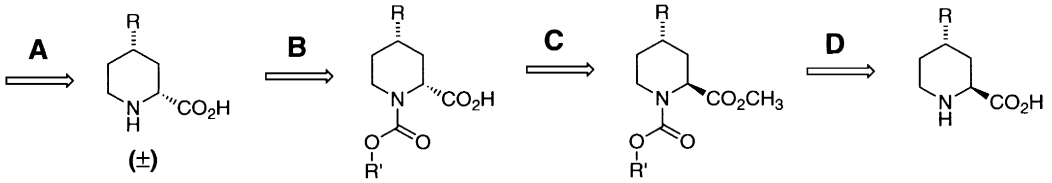


Fig. 1.

as their respective benzyl or *tert*-butyl carbamates and resolved to afford diastereomerically enriched products of the unnatural 2*R* configuration (**B**). Subsequent esterification and epimerization to the more thermodynamically stable 4-*trans*-substituted pipecolic acids then provides the natural 2*S* configuration (**C**). Final synthetic manipulation of the *N*-protected amino ester to the desired functionality for further chemical elaboration is then easily attended (**D**).

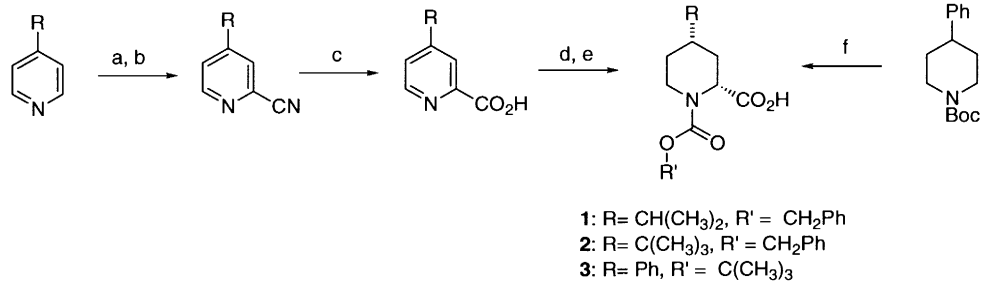


Scheme 1.

2. Results and discussion

2.1. *Synthesis of* cis-*substituted pipecolic acids*

Both the 4-isopropyl, and the known 4-*tert*-butyl,[5] *cis*-pipecolic acids were prepared by the method of Schuman and co-workers[5] from commercially available 4-alkylpyridines (Scheme 2). The resulting amino acids were then derivatized as their benzyl carbamates under standard Schotten–Baumann conditions[6] in order to provide a chromophore for aid in chiral HPLC analysis.



Scheme 2. Reagents and conditions: (a) H_2O_2, HOAc; (b) TMSCN, CH_2Cl_2, $(CH_3)_2NCOCl$; (c) HCl, H_2O, reflux; (d) H_2, PtO_2, $EtOH/H_2O$; (e) CbzCl, H_2O, NaOH; (f) *sec*-BuLi, Et_2O, TMEDA, $CO_{2(g)}$

Due to the problematic nature of the reduction of 4-phenylpyridine, we investigated alternate methods of synthesis of 4-phenylpipecolic acid. While a five-step, 50% overall yield, synthesis of (±)-*cis*-4-phenylpipecolic acid has been reported by Nazih and co-workers,[7] it also utilizes 4-phenylpyridine as its starting material which must be reduced via an *N*-acyl-dihydropyridine followed by a two-stage oxidative

transformation of a 2-(phenyldimethylsilyl)methyl group to generate the 2-carboxyl group of pipecolic acid. We opted, therefore, to utilize an alternative protocol involving the direct carboxylation of the fully saturated piperidine derivative (Scheme 2). It is well known from the work of Beak, Seebach, and Meyers that the dipole-stabilized carbanion resulting from removal of the α′-proton of appropriately *N*-protected 4-substituted piperidines may be trapped by various electrophiles resulting in a highly selective 2,4-*syn*-equatorial relationship.[8] We have found that the anion resulting from deprotonation of *N*-Boc-4-phenylpiperidine with *sec*-BuLi and TMEDA in ether solution readily reacted at −78°C with gaseous carbon dioxide to provide the *cis*-4-phenylpipecolic acid derivative, **3**, which could be crystallized from the crude reaction mixture in 61% yield. The pipecolyl C-2 proton of **3** exhibited the expected coupling constants with the adjacent methylene of 10.5 and 5.6 Hz, indicating an equatorial disposition of the carboxyl group. Likewise, adducts **1** and **2** exhibited similar coupling constants of 8.1, 6.5, and 10.7, 5.9 Hz, respectively. In point of interest, Fraser, in some of the earliest work in the field of α-amino carbanions,[9] reported the carboxylation of *N*-nitroso-4-phenylpiperidine with carbon dioxide to afford exclusively the 2-*trans*-carboxy derivative in good yield. This method would afford ready access to (±)-*trans*-4-phenylpipecolic acid.

2.2. *Resolution of* cis-*substituted pipecolic acids*

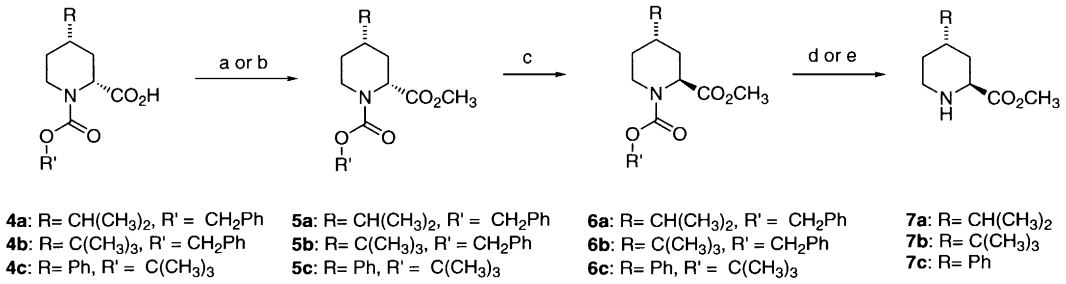
With the desired 4-substituted pipecolic acids in hand, we took advantage of the known ability of L-tyrosine hydrazide to resolve the unnatural D form of either the benzyl or *tert*-butyl carbamate of pipecolic acid[10] as well as benzyl carbamate derivative of D-proline.[11] Treatment of **1**–**3** with 0.9 equiv. of L-tyrosine hydrazide in refluxing methanol resulted in an optically enhanced salt complex (~1:1 complex by proton NMR) with an enrichment of 85, 79, and 40% ee, respectively. Recrystallization of the diastereomeric salts provided material of 98, 99.0, and 82% ee, respectively. A second recrystallization for the salts derived from **1** and **3** then afforded material of 99.0 and 98.5% ee, respectively. The overall non-optimized yields for the free acids **4a**–**c** were 37, 50 and 50% of theoretical. It should be noted that resolution of the benzyl carbamate analogue of compound **3** does provide the identical diastereomer.

2.3. *Epimerization of* cis-*substituted pipecolic acids*

The resolved *cis*-D-amino acids **4a**–**c** were converted to their corresponding *trans*-L-isomers by catalytic epimerization with sodium methoxide via their respective methyl esters **5a**–**c** (Scheme 3). Although all acids could be converted to their corresponding methyl esters via a DCC/DMAP coupling in excellent yields without detectable epimerization, we found it expedient to effect conversion of the acid stable benzyl carbamates **4a** and **4b** by use of thionyl chloride in methanol. Equilibration of **5a**–**c** to the thermodynamically more stable axially substituted adducts **6a**–**c**, thus relieving $A^{1,3}$ strain,[12] occurs in ~98% yield (as evidenced by proton NMR analysis) with isolated yields of 95, 83, and 93%, respectively. The pipecolyl C-2 protons of **6a**–**c** exhibited the expected range of coupling constants with the adjacent methylene of 4.5–5 Hz indicating an axial disposition of the carboxymethyl group. Removal of the carbamate protecting groups by either catalytic hydrogenation or acid deprotection afforded the free amines **7a**,**b** and hydrochloride **7c** which served as key starting materials for our research program.

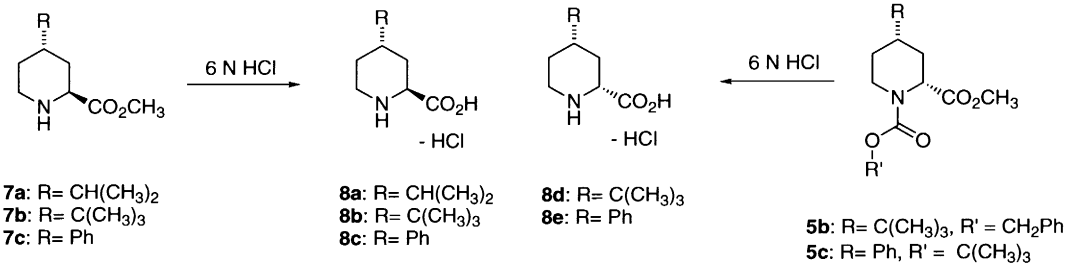
2.4. *CD analysis*

In order to provide additional support[13] in assigning the absolute stereochemistry of **7a**–**c**, we investigated the use of chiroptical methods of assignment. It is well known that circular dichroism



Scheme 3. Reagents and conditions: (a) MeOH, $SOCl_2$; (b) MeOH, DCC, DMAP, CH_2Cl_2, 0°C; (c) NaOMe, MeOH; (d) 10% Pd/C, H_2, MeOH; (e) $HCl_{(g)}$, CH_2Cl_2, 0°C

(CD) can be used to rapidly assign the absolute configuration of α-amino acids. All naturally occurring and most synthetic α-amino acids, specifically reported are 2- or 6-alkyl substituted pipecolic acids,[14] exhibit a diagnostic positive Cotton effect, generally attributed to the n–π* transition of the carboxyl group, centered near 203 nm for the zwitterionic form in water and 210–208 nm for acidic solutions. To this end, all three amino esters, as well as carbamates **5b** and **5c**, were hydrolyzed with 6 N HCl to provide the amino acid hydrochlorides **8a**–**e** (Scheme 4). CD spectra of **8a**,**b** in water exhibited the expected positive Cotton effect at 209 nm and were essentially identical with both L-pipecolic acid hydrochloride and (2*S*,4*S*) *trans*-4-methyl-L-pipecolic acid hydrochloride which was prepared via an asymmetric Aza-Diels–Alder protocol as described by Bailey and co-workers.[4,15] In contrast, controls **8d** and D-pipecolic acid hydrochloride exhibited negative Cotton effects at 208 and 210 nm, respectively. Due to the presence of a chiroptically interfering chiral aromatic group in adduct **8c** and its previously reported enantiomer **8e**,[7] they were further derivatized as their *N*-2,4-dinitrophenyl (DNP) derivatives by the use of Sanger's reagent.[16] A diagnostic negative Cotton effect in the range of 400–325 nm is observed for DNP-derivatized cyclic L-amino acids with a specific study of pipecolic acid and closely related analogues having been performed by Nagai and Kani.[17] The DNP derivative of L-pipecolic acid and **8c** exhibited essentially identical CD spectra in methanol with a negative Cotton effect occurring in the 400–325 nm region. Conversely, both the DNP derivative of D-pipecolic acid and **8e** exhibited a positive Cotton effect over this region.



Scheme 4.

In summary, we have described a useful preparative procedure for the synthesis of (±) *cis*-4-phenylpipecolic acid as well as a general strategy for the resolution of various 4-substituted *cis*-D-pipecolic acids and an efficient conversion to their corresponding *trans*-L-pipecolic acid isomers.

3. Experimental

All reagents and solvents were obtained from commercial sources and used without further purification. All melting points were measured on a Laboratory Devices MEL-TEMP II apparatus and are uncorrected. All IR spectra were recorded on a Perkin–Elmer 1600 Series FT-IR and ^{1}H, ^{19}F, and ^{13}C spectra on a Bruker ARX-300 instrument. Chemical shifts are reported downfield from tetramethylsilane. Low resolution mass spectra (LRMS) were obtained on a Micromass Platform II quadrupole mass spectrometer operating in electrospray mode while high resolution mass spectra (HRMS) were obtained on a Micromass LCT time-of-flight (TOF) mass spectrometer operating in electrospray mode. Data for HRMS were recorded at a nominal mass resolution of 5000 and internally calibrated using reference ions from poly(ethylene glycol) or poly(propylene glycol) as appropriate. Optical rotations, using a Perkin–Elmer 341 polarimeter, as well as elemental analyses, were obtained from Robertson Microlit Labs (Madison, NJ, USA). CD spectra were obtained on a Jasco J-710 spectropolarimeter using substrate concentrations of ~1–3 mg/mL and a 0.1 cm pathlength. Flash chromatography was performed on silica gel (Merck, 230–400 mesh). Analytical TLC was performed on silica gel 60 F_{254} plates (Merck). Chiral HPLC was performed on Chiral Technologies Inc., (Exton, PA, USA) analytical columns.

3.1. *(2*R,*4*S*)*-cis-*4-(2-Propyl)-1,2-piperidinedicarboxylic acid, 1-(phenylmethyl) ester (**4a**)*

A solution of racemic Cbz-protected amino acid **1** (23.6 g, 77.3 mmol) in MeOH (200 mL) was treated with L-tyrosine hydrazide (13.6 g, 69.6 mmol) and the mixture heated at reflux until a homogeneous solution was achieved. The solution was allowed to cool and the precipitated salt collected (~13 g) to afford material of 85% ee. Recrystallization from MeOH (75 mL) afforded material (~8 g) of 98% ee. A final recrystallization from MeOH (75 mL) afforded material (~7 g) of 99% ee. The free acid was obtained by partitioning between EtOAc (100 mL) and 1 N HCl (100 mL). The organic phase was washed with additional 1 N HCl (50 mL) followed by a brine solution (3×50 mL) then dried over Na_2SO_4, filtered, and concentrated for material (4.4 g, 37% of theoretical) of similar diastereomeric purity (99.0% ee by Chiralpak AD HPLC, 20% *iso*-PrOH/hexane, 0.2% TFA, retention time 5.3 min for the (2*S*)-L-enantiomer and 6.2 min for the (2*R*)-D-enantiomer. Chiralcel OD HPLC may also be used, 20% EtOH/hexane, 0.2% TFA, retention time 4.3 min for the (2*S*)-L-enantiomer and 10.9 min for the (2*R*)-D-enantiomer): $[\alpha]_D^{25}$=+42.8 (c=1.06, $CHCl_3$); TLC (MeOH:$CHCl_3$, 5:95) R_f=0.25; IR (neat) 2960, 1710, 1425, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 9.58 (br s, 1H), 7.31 (s, 5H), 5.13 (s, 2H), 4.35 (t, J=8.1 Hz, 1H), 3.64 (br s, 1H), 3.43 (br s, 1H), 2.08–2.00 (m, 1H), 1.78–1.71 (m, 2H), 1.54–1.31 (m, 3H), 0.90–0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 178.4, 157.0, 136.8, 128.9, 128.4, 127.9, 67.9, 55.8, 40.7, 38.5, 31.2, 29.2, 26.8, 20.4, 20.3; LRMS (ES−): $(M-H)^-$ 304; HRMS (ES+): $(M+H)^+$ calcd: 306.1705; meas.: 306.1692.

3.2. *(2*R,*4*S*)*-cis-*4-(*tert-*Butyl)-1,2-piperidinedicarboxylic acid, 1-(phenylmethyl) ester (**4b**)*

A solution of racemic Cbz-protected amino acid **2** (7.18 g, 22.5 mmol) in MeOH (50 mL) was treated with L-tyrosine hydrazide (3.95 g, 20.2 mmol) and the mixture heated at reflux until a homogeneous solution was achieved. The solution was allowed to cool and the precipitated salt collected (~4 g) to afford material of 79% ee. Recrystallization from MeOH (50 mL) afforded material (~3 g) of 99% ee. The free acid was isolated (1.78 g, 50% of theoretical) as described for compound **4a** (99.0% ee by Chiralcel OD HPLC, 10% 2-propanol/hexane, 0.2% TFA, retention time 6.0 min for the (2*S*)-L-enantiomer and 15.1 min for the (2*R*)-D-enantiomer): $[\alpha]_D^{25}$=+55.2 (c=1.00, $CHCl_3$); TLC (MeOH:$CHCl_3$, 5:95) R_f=0.25;

IR (neat) 2960, 1710, 1430, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 10.88 (br s, 1H), 7.33 (s, 5H), 5.14 (s, 2H), 4.26 (dd, J=10.8, 6.3 Hz, 1H), 3.64 (br s, 1H), 3.46 (br s, 1H), 2.13–2.08 (m, 1H), 1.83–1.80 (m, 1H), 1.60–1.48 (m, 1H), 1.41–1.25 (m, 2H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 178.4, 156.5, 136.4, 128.5, 128.0, 127.8, 67.5, 56.7, 42.0, 40.9, 32.6, 26.9, 24.2; LRMS (ES+): $(M+Na)^+$ 342; (ES−): $(M-H)^-$ 318; HRMS (ES+): $(M+H)^+$ calcd: 320.1862; meas.: 320.1862.

*3.3. (2*R,*4*S*)*-cis-*4-Phenyl-piperidine-1,2-dicarboxylic acid, 1*-tert-*butyl ester (**4c**)*

A solution of 4-phenyl-piperidine-1,2-dicarboxylic acid, 1-*tert*-butyl ester (26.1 g, 100 mmol) in diethyl ether (200 mL) was cooled to −78°C and treated with TMEDA (15.1 mL, 100 mmol) followed by slow addition of a 1.3 M cyclohexane solution of *sec*-butyllithium (92.3 mL, 120 mmol) solution over a 30 min period. The reaction mixture was allowed to slowly warm to −20°C and kept at this temperature for 30 min, after which time the solution was re-cooled to −78°C and the solution purged with gaseous carbon dioxide for 15 min. The mixture was removed from the cooling bath and allowed to warm to 0°C when it was poured onto a biphasic mixture of EtOAc (200 mL) and 1 N HCl (500 mL). The organic component was further washed with 1 N HCl (2×200 mL) followed by a brine solution (3×100 mL), dried over Na_2SO_4, filtered, and evaporated to afford a crude oil. The crude product was diluted with EtOAc (25 mL) and allowed to crystallize to afford 16.2 g (53%) of product as a colorless solid **3**. A second crop (2.5 g, 8%) of product was obtained on sitting for two days. The resolution of acid **3** was achieved as follows. A solution of the Boc-protected amino acid (18.0 g, 59.0 mmol) in MeOH (125 mL) was treated with L-tyrosine hydrazide (10.4 g, 53.1 mmol) and the mixture heated at reflux until a homogeneous solution was achieved. The solution was allowed to cool and the precipitated salt collected (15.1 g) to afford material of ~40% ee. Recrystallization from MeOH (100 mL) afforded material (9.6 g) of ~80% ee. A final recrystallization from MeOH (75 mL) afforded material (7.2 g). The free acid was isolated (4.5 g, 50% of theoretical) as an oil as described for compound **4** (98.5% ee by Chiralpak AD HPLC, 10% 2-propanol/hexane, 0.1% TFA, retention time 7.2 min for the (2*R*)-D-enantiomer and 9.9 min for the (2*S*)-L-enantiomer): mp (2*R/S* racemate) 112.5–113°C; $[\alpha]_D^{25}$=+19.4 (c=1.03, $CHCl_3$); TLC (EtOAc) R_f=0.45; IR (neat) 2975, 1700, 1395, 1250, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 11.69 (br s, 1H), 7.32–7.17 (s, 5H), 4.19 (dd, J=10.5, 5.6 Hz, 1H), 3.83–3.75 (m, 1H), 3.49–3.26 (m, 1H), 2.82–2.72 (m, 1H), 2.26 (dt, J=13.4, 4.1 Hz, 1H), 2.08–1.95 (m, 2H), 1.85–1.74 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 178.3, 156.0, 144.6, 128.6, 126.8, 126.6, 81.2, 56.7, 42.0, 38.5, 33.6, 30.8, 28.2; LRMS (ES−): $(M-H)^-$ 304. Anal. calcd for $C_{17}H_{23}NO_4$ (2*R/S* racemate): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.8; H, 7.48; N, 4.40.

*3.4. (2*R,*4*S*)*-cis-*4-(2-Propyl)-1,2-piperidinedicarboxylic acid, 2-methyl, 1-(phenylmethyl) ester (**5a**)*

A solution of the resolved acid **4a** (6.50 g, 21.3 mmol) in MeOH (30 mL) was added via a syringe to a −20°C solution of MeOH (25 mL) containing thionyl chloride (5.07 g, 42.6 mmol). The solution was allowed to warm to room temperature and stirred for 16 h, after which time the reaction was evaporated and the crude material flash chromatographed on silica gel (15% then 25% EtOAc/hexane) to afford product (6.34 g, 93%) as an oil: TLC (EtOAc:hexane, 15:85) R_f=0.29; IR (neat) 2955, 2870, 1745, 1710, 1415, 1330, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.33 (s, 5H), 5.18–5.07 (m, 2H), 4.30 (dd, J=8.1, 6.5 Hz, 1H), 3.66 (br s, 4H), 3.50 (br s, 1H), 2.02–1.95 (m, 1H), 1.79–1.69 (m, 2H), 1.55–1.38 (m, 2H), 1.36–1.30 (m, 1H), 0.89–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.6, 156.7, 136.9, 128.8, 128.4, 128.3, 67.7, 56.1, 52.4, 40.8, 38.7, 30.9, 29.5, 27.0, 20.4; LRMS (ES+): $(M+H)^+$ 320, $(M+NH_4)^+$ 337, $(M+Na)^+$ 342; HRMS (ES+): $(M+H)^+$ calcd: 320.1862; meas.: 320.1847.

3.5. (2R,4S)-cis-4-(tert-Butyl)-1,2-piperidinedicarboxylic acid, 2-methyl, 1-(phenylmethyl) ester (**5b**)

Prepared from **4b** by the method described for compound **5a**. Product (2.0 g, 85%) was isolated as an oil: TLC (EtOAc:hexane, 15:85) R_f=0.29; IR (neat) 2960, 2870, 1750, 1700, 1420, 1335, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.33 (s, 5H), 5.18–5.06 (m, 2H), 4.18 (dd, J=10.7, 5.9 Hz, 1H), 3.66 (br s, 3H), 3.53 (br s, 2H), 2.06–2.02 (m, 1H), 1.81–1.71 (m, 1H), 1.54–1.42 (m, 1H), 1.38–1.31 (m, 2H), 0.85 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.6, 156.7, 136.9, 128.8, 128.4, 128.3, 67.7, 57.5, 52.4, 42.6, 41.7, 32.9, 27.6, 27.3, 24.8; LRMS (ES+): $(M+H)^+$ 334, $(M+NH_4)^+$ 351, $(M+Na)^+$ 356; HRMS (ES+): $(M+H)^+$ calcd: 334.2018; meas.: 334.2032.

3.6. (2R,4S)-cis-4-Phenyl-piperidine-1,2-dicarboxylic acid, 1-tert-butyl ester, 2-methyl ester (**5c**)

A solution of acid **4c** (2.5 g, 8.19 mmol), MeOH (398 μL, 9.82 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (8.0 mL) at 0°C was treated with DCC (1.77 g, 8.60 mmol). The mixture was allowed to stir for 2 h, after which time it was allowed to warm to room temperature, diluted with EtOAc (25 mL), and filtered through a plug of Celite. The filtrate was concentrated and the crude material flash chromatographed on silica gel (10% then 20% EtOAc/hexane) to afford product (2.40 g, 92%) as an oil: TLC (EtOAc:hexane, 1:9) R_f=0.19; IR (neat) 2975, 1750, 1700, 1455, 1400, 1365, 1250, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.33–7.17 (s, 5H), 4.20 (dd, J=9.9, 5.5 Hz, 1H), 3.81–3.74 (m, 1H), 3.64 (s, 3H), 3.53–3.46 (m, 1H), 2.85–2.75 (m, 1H), 2.27–2.18 (m, 1H), 2.09–2.01 (m, 2H), 1.89–1.77 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.7, 156.0, 144.6, 128.6, 126.9, 126.5, 80.6, 56.6, 51.9, 41.9, 38.2, 33.6, 30.5, 28.3; LRMS (ES+): $(M+Na)^+$ 342; HRMS (ES+): $(M+H)^+$ calcd: 320.1862; meas.: 320.1876.

3.7. (2S,4S)-trans-4-(2-Propyl)-1,2-piperidinedicarboxylic acid, 2-methyl, 1-(phenylmethyl) ester (**6a**)

A solution of aminoester **5a** (6.00 g, 18.8 mmol) in MeOH (6.0 mL) was treated with a 25 wt% methanolic solution of sodium methoxide (430 μL) and allowed to stir at room temperature for four days. The reaction mixture was then partitioned between EtOAc (50 mL) and 1 N HCl (50 mL). The organic phase was washed with additional 1 N HCl (50 mL) followed by a brine solution (2×50 mL) then dried over Na_2SO_4, filtered, and concentrated for crude material containing an ~2:98 ratio of *cis*:*trans* isomers. The crude material was flash chromatographed on silica gel (15% then 20% EtOAc/hexane) to afford product (5.68 g, 95%) as an oil: TLC (EtOAc:hexane, 15:85) R_f=0.33; IR (neat) 2955, 1745, 1705, 1420, 1335, 1225, 1170, 1100 cm^{-1}; ^1H NMR (1:1 mixture of rotamers, $CDCl_3$, 300 MHz) 7.35 and 7.31 (s, 5H), 5.49 (s, 2H), 5.01 and 4.90 (d, J=4.6 and 4.6 Hz, 1H), 4.13 (t, J=19.2 Hz, 1H), 3.73 and 3.67 (s, 3H), 3.10–2.91 (m, 1H), 2.22 (t, J=13.3 Hz, 1H), 1.71–1.60 (m, 1H), 1.49–1.35 (m, 2H), 1.19–1.09 (m, 2H), 0.88–0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.6, 156.8 and 156.2, 137.1, 128.9, 128.4, 128.2, 67.7 and 67.6, 55.3 and 55.1, 52.5, 42.4, 39.1, 32.5, 30.8 and 30.6, 28.6 and 28.3, 19.9 and 19.9; LRMS (ES+): $(M+H)^+$ 320, $(M+NH_4)^+$ 337; HRMS (ES+): $(M+H)^+$ calcd: 320.1862; meas.: 320.1848.

3.8. (2S,4S)-trans-4-(tert-Butyl)-1,2-piperidinedicarboxylic acid, 2-methyl, 1-(phenylmethyl) ester (**6b**)

Prepared from **5b** by the method described for compound **6a**. Product (5.2 g, 83%) was isolated as an oil: TLC (EtOAc:hexane, 15:85) R_f=0.33; IR (neat) 2955, 1745, 1710, 1420, 1330, 1265, 1170, 1090 cm^{-1}; ^1H NMR (1:1 mixture of rotamers, $CDCl_3$, 300 MHz) 7.35 and 7.31 (s, 5H), 5.16 (s, 2H), 5.03 and 4.91 (d, J=4.8 and 4.8 Hz, 1H), 4.21–4.10 (m, 1H), 3.73 and 3.67 (s, 3H), 3.10–2.90 (m, 1H), 2.31–2.22

(m, 1H), 1.73–1.62 (m, 1H), 1.46–1.35 (m, 1H), 1.22–1.01 (m, 2H), 0.85 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.2, 156.8 and 155.8, 136.7, 128.5, 128.0, 127.8, 67.3 and 67.2, 55.1 and 54.9, 52.1, 42.7, 42.3 and 42.2, 32.0, 28.1 and 28.0, 27.1, 26.1 and 25.8; LRMS (ES+): $(M+Na)^+$ 356; HRMS (ES+): $(M+H)^+$ calcd: 334.2018; meas.: 334.2007.

*3.9. (2S,4S)-*trans*-4-Phenyl-piperidine-1,2-dicarboxylic acid, 1-*tert*-butyl ester, 2-methyl ester (**6c**)*

Prepared from **5c** by the method described for compound **6a**. Product (1.85 g, 93%) was isolated as an oil: TLC (EtOAc:hexane, 1:9) R_f=0.29; IR (neat) 2975, 1745, 1695, 1455, 1395, 1365, 1235, 1160 cm^{-1}; ^{1}H NMR (1:1 mixture of rotamers, $CDCl_3$, 300 MHz) 7.33–7.17 (s, 5H), 5.07 and 4.88 (d, J=5.0 and 5.1 Hz, 1H), 4.19 and 4.08 (d, J=12.9 and 13.2 Hz, 1H), 3.78 and 3.76 (s, 3H), 3.16 and 3. 08 (td, J=13.1, 2.8 and 13.2, 2.9 Hz, 1H), 2.55 (tt, J=12.6, 3.2 Hz, 1H), 2.44–2.38 (m, 1H), 2.04–1.80 (m, 2H), 1.68–1.57 (m, 1H), 1.50 and 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.8 and 172.2, 155.8 and 155.4, 145.0, 128.6, 126.7, 126.6, 80.2, 55.2 and 54.0, 52.2, 42.2 and 41.4, 38.7 and 38.6, 34.0 and 33.8, 32.5 and 32.2, 28.4; LRMS (ES+): $(M+Na)^+$ 342; HRMS (ES+): $(M+H)^+$ calcd: 320.1862; meas.: 320.1851.

*3.10. (2S,4S)-*trans*-4-(2-Propyl)-2-piperidinecarboxylic acid, methyl ester (**7a**)*

A solution of the Cbz-protected aminoester **6a** (6.00 g, 18.8 mmol) in MeOH (30 mL) was treated with 10 wt% Pd/C (600 mg) and purged with hydrogen for 10 min followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 4 h. The reaction mixture was filtered through a pad of Celite, the filtrate evaporated, and material flash chromatographed on silica gel (5% then 10% MeOH/CH_2Cl_2) to afford product (3.0 g, 86%) as a liquid: TLC (MeOH:$CHCl_3$, 5:95) R_f=0.25; IR (neat) 2955, 1735, 1465, 1370, 1210, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.73 (s, 3H), 2.91 (dt, J=7.3, 3.5 Hz, 1H), 2.78 (td, J=11.3, 2.4 Hz, 1H), 2.24 (s, 1H), 2.13 (dd, J=13.1, 2.3 Hz, 1H), 1.60 (dd, J=10.4, 2.4 Hz, 1H), 1.57–1.40 (m, 2H), 1.24 (qd, J=11.4, 4.3 Hz, 1H), 1.15–1.06 (m, 1H), 0.90–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 175.0, 56.1, 51.8, 42.9, 39.3, 32.2, 30.3, 28.9, 19.7, 19.5; LRMS (ES+): $(M+H)^+$ 186; HRMS (ES+): $(M+H)^+$ calcd: 186.1494; meas.: 186.1503.

*3.11. (2S,4S)-*trans*-4-(*tert*-Butyl)-2-piperidinecarboxylic acid, methyl ester (**7b**)*

Prepared from **6b** by the method described for compound **7a**. Product (378 mg, 85%) was isolated as a liquid: TLC (MeOH:$CHCl_3$, 5:95) R_f=0.25; IR (neat) 3352, 2955, 1735, 1470, 1365, 1215, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.74 (s, 3H), 2.95 (dt, J=6.8, 3.4 Hz, 1H), 2.77 (td, J=12.0, 2.6 Hz, 1H), 2.32 (s, 1H), 2.22 (dd, J=13.1, 2.6 Hz, 1H), 1.63 (dt, J=12.5, 2.7 Hz, 1H), 1.49 (td, J=12.7, 5.3 Hz, 1H), 1.24 (qd, J=12.2, 4.3 Hz, 1H), 1.02 (tt, J=12.3, 3.1 Hz, 1H), 0.86 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 174.3, 56.7, 52.0, 43.7, 32.5, 28.1, 27.4, 27.0; LRMS (ES+): $(M+H)^+$ 200; HRMS (ES+): $(M+H)^+$ calcd: 200.1650, meas.: 200.1660.

*3.12. (2S,4S)-*trans*-4-Phenyl-piperidine-2-carboxylic acid, methyl ester hydrochloride (**7c**)*

A solution of the Boc-protected aminoester **6c** (435 mg, 1.36 mmol) in CH_2Cl_2 (15 mL) at 0°C was treated with a steam of gaseous HCl for 5 min. The mixture was allowed to warm to room temperature and stirred for 1 h, after which time it was diluted with CH_2Cl_2 (10 mL) and concentrated to afford product: (free base, MeOH:$CHCl_3$, 7.5:92.5) R_f=0.36; IR (free base, neat) 3185, 2950, 1740, 1600, 1450, 1245, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.56 (br s, 1H), 9.57 (br s, 1H), 7.35–7.22 (s, 5H), 4.71

(br s, 1H), 3.89 (s, 3H), 3.67 (d, J=12.1 Hz, 1H), 3.47–3.43 (s, 1H), 2.74–2.67 (m, 1H), 2.62–2.46 (m, 2H), 2.35–2.24 (m, 1H), 2.03 (d, J=13.5 Hz, 1H); ^{1}H NMR (free base, $CDCl_3$, 300 MHz) 7.34–7.19 (s, 5H), 6.70 (br s, 1H), 4.19 (br s, 1H), 3.83 (s, 3H), 3.35–3.10 (m, 2H), 2.66–2.62 (m, 1H), 2.41 (d, J=12.6 Hz, 1H), 2.24–2.21 (m, 1H), 2.05–1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.7, 142.7, 128.8, 127.2, 126.7, 54.3, 53.3, 41.6, 37.2, 31.3, 29.2; ^{13}C NMR (free base, $CDCl_3$, 75 MHz) 172.2, 144.6, 128.6, 126.8, 126.6, 55.3, 52.5, 42.4, 38.4, 32.8, 31.5; LRMS (ES+): $(M+H)^+$ 220; HRMS (ES+): $(M+H)^+$ calcd: 220.1337; meas.: 220.1332.

3.13. (2S,4S)-trans-4-(2-Propyl)-piperidine-2-carboxylic acid, hydrochloride (**8a**)

A solution of aminoester **7a** (200 mg, 1.08 mmol) in 6 N HCl (2 mL) was heated at 95°C for 6 h then evaporated to a free flowing powder: $[\alpha]_D^{25}$=+16.3 (c=1.01, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.81 (br s, 1H), 9.88 (br s, 1H), 8.83 (br s, 1H), 4.20 (t, J=4.2 Hz, 1H), 3.11–2.96 (m, 2H), 1.99 (d, J=13.8 Hz, 1H), 1.74–1.64 (m, 2H), 1.51–1.36 (m, 2H), 1.14–1.05 (m, 1H), 0.79 (d, J=2.4 Hz, 3H), 0.77 (d, J=2.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) 169.5, 52.8, 40.2, 36.4, 30.1, 27.1, 24.2, 19.0; ^{1}H NMR (D_2O, 300 MHz) 4.37 (t, J=4.7 Hz, 1H), 3.45–3.28 (m, 2H), 2.34 (br d, J=14.6 Hz, 1H), 1.95 (br dd, J=14.5, 2.3 Hz, 1H), 1.89–1.79 (m, 2H), 1.68–1.51 (m, 2H), 1.46–1.34 (m, 1H), 0.97 (d, J=4.5 Hz, 3H), 0.95 (d, J=4.5 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz) 172.0, 54.9, 41.9, 37.1, 30.5, 28.2, 25.3, 19.2; HRMS (ES+): $(M+H)^+$ calcd: 172.1337; meas.: 172.1346.

3.14. (2S,4S)-trans-4-(tert-Butyl)-piperidine-2-carboxylic acid, hydrochloride (**8b**)

Prepared from **7b** by the method described for compound **8a**: $[\alpha]_D^{25}$=+14.5 (c=0.96, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.89 (br s, 1H), 10.14 (br s, 1H), 8.86 (br s, 1H), 4.34 (d, J=3.1 Hz, 1H), 3.20 (d, J=12.2 Hz, 1H), 3.05 (t, J=11.8 Hz, 1H), 2.15 (d, J=13.6 Hz, 1H), 1.79–17.0 (m, 2H), 1.52 (qd, J=12.9, 4.1 Hz, 1H), 1.07 (t, J=12.3 Hz, 1H), 0.82 (s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz) 169.4, 53.1, 40.5, 40.4, 31.4, 26.3, 25.0, 22.3; ^{1}H NMR (D_2O, 300 MHz) 4.48 (d, J=3.9 Hz, 1H), 3.47 (br d, J=12.4 Hz, 1H), 3.31 (td, J=13.1, 3.1 Hz, 1H), 2.47 (br dd, J=14.6, 2.4 Hz, 1H), 2.00 (br dt, J=14.0, 2.4 Hz, 1H), 1.74 (td, J=12.8, 5.5 Hz, 1H), 1.50 (qd, J=13.0, 4.6 Hz, 1H), 1.29 (tt, J=12.4, 2.6 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (D_2O, 75 MHz) 171.7, 55.3, 42.6, 41.0, 31.6, 26.4, 26.1, 23.6; HRMS (ES+): $(M+H)^+$ calcd: 186.1494; meas.: 186.1503.

3.15. (2S,4S)-trans-4-Phenyl-piperidine-2-carboxylic acid, hydrochloride (**8c**)

Prepared from **7c** by the method described for compound **8a**: $[\alpha]_D^{25}$=+50.4 (c=1.02, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.98 (br s, 1H), 10.17 (br s, 1H), 8.95 (br s, 1H), 7.29–7.24 (m, 2H), 7.18–7.13 (m, 3H), 4.32 (t, J=3.5 Hz, 1H), 3.17 (d, J=4.4 Hz, 2H), 2.69–2.62 (m, 1H), 2.18–2.15 (m, 2H), 1.99–1.79 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) 170.0, 144.1, 129.0, 127.1, 126.9, 53.7, 41.1, 36.4, 31.1, 28.9; ^{1}H NMR (D_2O, 300 MHz) 7.52–7.37 (m, 5H), 4.49 (dd, J=5.0, 3.5 Hz, 1H), 3.53–3.49 (m, 2H), 2.97 (tt, J=11.5, 3.5 Hz, 1H), 2.48 (dd, J=14.7, 1.8 Hz, 1H), 2.27 (qd, J=11.9, 5.3 Hz, 1H), 2.18–1.96 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) 171.5, 143.7, 129.4, 127.6, 127.2, 55.0, 42.0, 36.2, 31.4, 28.9; HRMS (ES+): $(M+H)^+$ calcd: 206.1181; meas.: 206.1170.

8c-DNP: TLC (MeOH:$CHCl_3$, 1:9) R_f=0.30; IR (neat) 2935, 1715, 1605, 1520, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.74 (d, J=2.2 Hz, 1H), 8.31 (dd, J=9.1, 2.2 Hz, 1H), 7.35–7.24 (m, 6H), 4.32 (s, 1H), 3.74–3.65 (m, 1H), 3.48 (d, J=12.4 Hz, 1H), 2.77 (br s, 1H), 2.51 (d, J=13.1 Hz, 1H), 2.29–2.18 (m, 1H), 2.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 176.2, 150.0, 143.8, 139.8, 139.2, 128.8, 128.3,

127.0, 126.7, 123.3, 121.7, 61.3, 48.4, 38.2, 34.0, 32.1; HRMS (ES+): $(M+H)^+$ calcd: 372.1195; meas.: 372.1208.

*3.16. (2*R,*4*S)-cis-*4-(*tert-*Butyl)-piperidine-2-carboxylic acid, hydrochloride (**8d**)*

Prepared from **5b** by the method described for compound **8a**: $[\alpha]_D^{25}=-13.7$ (c=0.98, MeOH); ^{1}H NMR (D_2O, 300 MHz) 3.94 (dd, J=11.7, 2.6 Hz, 1H), 3.61 (dt, J=13.0, 3.9 Hz, 1H), 3.05 (td, J =12.8, 3.0 Hz, 1H), 2.44 (br d, 1H), 2.04 (br d, 1H), 1.58–1.46 (m, 3H), 0.96 (s, 9H); ^{13}C NMR (D_2O, 75 MHz) 172.6, 58.2, 44.5, 44.2, 31.9, 27.8, 26.6, 23.1; HRMS (ES+): $(M+H)^+$ calcd: 186.1494; meas.: 186.1503.

*3.17. (2*R,*4*S)-cis-*4-Phenyl-piperidine-2-carboxylic acid, hydrochloride (**8e**)*

Prepared from either **5c** or **4c** by the method described for compound **8a**: $[\alpha]_D^{25}=-33.4$ (c=0.99, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.93 (br s, 1H), 9.67 (br s, 1H), 9.42 (br s, 1H), 7.41–7.36 (m, 2H), 7.31–7.27 (m, 3H), 4.14 (br s, 1H), 3.42 (d, J=12.4 Hz, 1H), 3.08–2.99 (m, 2H), 2.31 (d, J=13.4 Hz, 1H), 2.07–1.86 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) 170.3, 144.4, 129.0, 127.0, 126.9, 56.4, 43.7, 39.2, 33.0, 28.7; ^{1}H NMR (D_2O, 300 MHz) 7.49–7.37 (m, 5H), 4.12 (dd, J=12.8, 3.2 Hz, 1H), 3.67 (qd, J=12.9, 2.1 Hz, 1H), 3.25 (td, J=13.1, 3.1 Hz, 1H), 3.08 (tt, J=12.3, 3.6 Hz, 1H), 2.25 (dq, J=14.0, 3.2 Hz, 1H), 1.85 (d, J=14.5 Hz, 1H), 2.01–1.88 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) 172.1, 144.0, 129.4, 127.7, 127.1, 57.9, 44.2, 39.8, 33.1, 29.0; HRMS (ES+): $(M+H)^+$ calcd: 206.1181; meas.: 206.1189.

8e-DNP: $[\alpha]_D^{25}=-326.7$ (c=1.046, MeOH); TLC (MeOH:$CHCl_3$, 1:9) R_f=0.30; IR (neat) 2940, 1715, 1600, 1520, 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.66 (d, J=2.3 Hz, 1H), 8.31 (dd, J=8.9, 2.0 Hz, 1H), 7.34–7.22 (m, 6H), 4.08 (dd, J=10.2, 3.4 Hz, 1H), 3.69–3.58 (m, 1H), 2.99–2.80 (m, 2H), 2.39 (d, J=12.8 Hz, 1H), 2.10–1.98 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 175.7, 150.7, 143.5, 142.5, 128.7, 127.8, 127.0, 126.8, 122.8, 122.0, 62.1, 54.0, 40.3, 36.6, 31.5; HRMS (ES+): $(M+H)^+$ calcd: 372.1195; meas.: 372.1211.

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