Asymmetric Synthesis of *trans*-2,3-Piperidinedicarboxylic Acid and *trans*-3,4-Piperidinedicarboxylic Acid Derivatives

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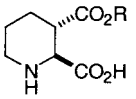
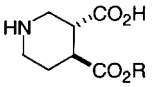
Asymmetric syntheses of (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (**1b**), (3*R*,4*S*)-4-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid (**2b**), and their corresponding *N*-Boc and *N*-Cbz protected analogues **8a**,**b** and **17a**,**b** are described. Enantiomerically pure **1b** has been synthesized in five steps starting from L-aspartic acid *β*-*tert*-butyl ester. Tribenzylation of the starting material followed by alkylation with allyl iodide using KHMDS produces the key intermediate **5a** in a 6:1 diastereomeric excess. Upon hydroboration, the alcohol **6a** is oxidized, and the resulting aldehyde **7** is subjected to a ring closure via reductive amination, providing **1b** in an overall yield of 38%. Optically pure **2b** has been synthesized beginning with *N*-Cbz-*β*-alanine. The synthesis involves the induction of the first stereogenic center using Evans's chemistry and sequential LDA-promoted alkylations with *tert*-butyl bromoacetate and allyl iodide. Further elaboration by ozonolysis and reductive amination affords **2b** in an overall yield of 28%.

Conformationally constrained amino acids are useful structural components for peptidomimetics and nonpeptide small molecules in drug discovery.[1] Incorporation of unnatural, nonproteinogenic amino acids into small peptides is expected to provide more druglike peptidomimetics with improved physiological and physiochemical properties such as binding affinity and metabolic stability.[2] In addition, cyclic amino acids may serve as a chemical platform for manipulation through the amino and carboxylic acid functionalities of hydrophobic and/or hydrophilic pendant substituents required for binding interactions with biological targets, making them ideal building blocks for the preparation of potential nonpeptide therapeutic agents using parallel synthesis or combinatorial chemistry methodologies.

2,3-Piperidinedicarboxylic acid and 3,4-piperidinedicarboxylic acid are structurally rigidified aspartic acid and aminomethyl-succinic acid derivatives, respectively. These heterocycles possess multiple functional groups for structural diversification and could be useful as scaffolds for construction of biologically active peptidomimetics or nonpeptide small molecule ligands. For example, (2*S*,3*S*)-2,3-piperidinedicarboxylic acid (**1a**) and (3*R*,4*S*)-3,4-piperidinedicarboxylic acid (**2a**) have been employed in our laboratory as templates for a series of protease inhibitors of therapeutic interest.[3] The common intermediates used are (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (**1b**) and (3*R*,4*S*)-4-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid (**2b**). The need for large quantities of enantiomerically pure **1b** and **2b** for structure−activity relationship (SAR) studies has led us to devise efficient synthetic methods to prepare these intermediates using readily accessible starting materials. Herein, we report asymmetric syntheses of **1b**, **2b** and their corresponding *N*-Boc and *N*-Cbz protected analogues starting from L-aspartic acid *β*-*tert*-butyl ester and *N*-Cbz-*β*-alanine, respectively.



1a R=H
1b R=*t*-Bu



2a R=H
2b R=*t*-Bu

(2*S*,3*S*)-2,3-Piperidinedicarboxylic Acid Derivatives. The synthesis of (2*S*,3*S*)-3-(methoxycarbonyl)-2-piperidinecarboxylic acid, the 3-methyl ester of **1a**, has been reported from (*S*)-2-phenylglycinol and dimethyl acetylenedicarboxylate involving an aza-annulation reaction.[4] In addition, 2-*tert*-butyl 3-methyl (2*S*,3*S*)-1-(9-phenylfluoren-9-yl)-2,3-piperidinedicarboxylate, another intermediate of **1a**, has been synthesized from L-aspartate.[5] For our purposes, *tert*-butyl protection at the 3-carboxylic acid is required for the target compound **1b**, which prompted us to consider an alternative synthetic route starting from the commercially available L-aspartic acid *β*-*tert*-butyl ester. Our plan was to introduce an allyl group at the *β*-carbon (C-3) of the L-aspartate followed by hydroboration of the olefin, oxidation of the resulting alcohol, and cyclization via reductive amination (Scheme 1). In this strategy, a suitable protecting group is required

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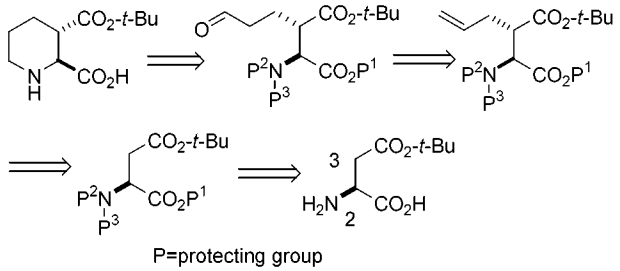
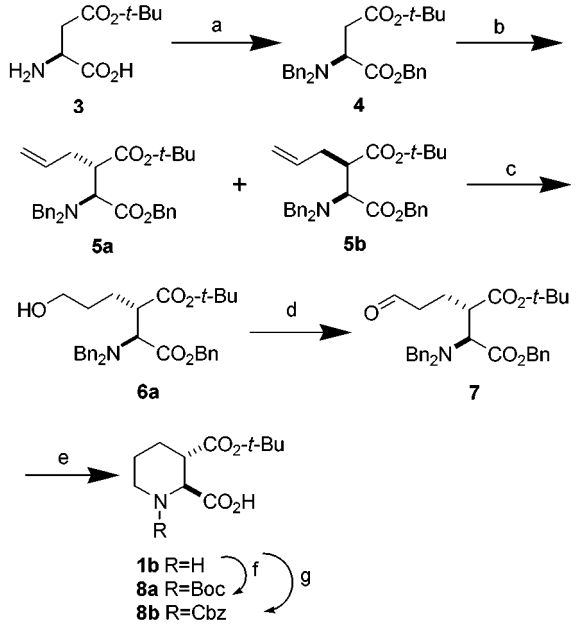
Scheme 1



to block alkylation at the α-carbon (C-2) of the aspartate and to influence the diastereomeric selectivity at C-3. Although Cbz has been shown to be able to block C-2 alkylation by deprotonation at the monoprotected α-amino, alkylation of N^{α}-Cbz-L-aspartate with an allyl halide produces the anti diastereomer as the major diastereomer with an *R*-configuration at C-3,[6] which is the opposite configuration in compound **1b**. Rapoport's 9-phenylfluoren-9-yl residue[7] is another amino protecting group that effectively suppresses α-deprotonation of α-amino acid derivatives and allows selective deprotonation at other acidic sites in the molecule. When the amino group of an L-aspartate was doubly protected with benzyl and 9-phenylfluoren-9-yl, alkylation of the aspartate derivative with allyl iodide using potassium hexamethyldisilazide (KHMDS) gives rise to the syn diastereomer as the major diastereomer (syn:anti = 10:1) with an *S*-configuration at C-3,[8] which is the desired configuration in compound **1b**. While extremely efficient on laboratory scale, however, 9-bromo-9-phenylfluorene is an expensive reagent unsuitable for large scale synthesis. We provide here an attractive procedure that employs dibenzyl protection for the α-amino of the aspartate.[9]

As depicted in Scheme 2, L-aspartic acid *β-tert*-butyl ester (**3**) was subjected to K_2CO_3-mediated benzylation with benzyl bromide in a mixed solvent system of DMF/DMSO (4:1) at 50 °C to produce the tribenzylated product **4** in 90% yield in one step. In this reaction, DMSO was required to enhance the solubility of the starting material **3**. Addition of 1.1 equiv of lithium hexamethyldisilazide (LHMDS) to a solution of **4** in THF at −78 °C followed by quenching with 1.2 equiv of allyl bromide at −30 °C gave rise to the syn (**5a**) and anti (**5b**) allylated products in a ratio of 1.5:1, the former being the desired diastereomer. Compounds **5a** and **5b** were inseparable by silica gel chromatography, and a mixture of **5a** and **5b** was obtained in 90% yield. Switching the electrophile from allyl bromide to allyl iodide had little effect on the diastereoselectivity. Significant improvement in diastereoselectivity was achieved when enolate formation was conducted using 1.2 equiv of KHMDS and 1.5 equiv of allyl iodide was employed as the electrophile. Under these conditions, a mixture of **5a** and **5b** was obtained in a 6:1

Scheme 2[a]



[a] Conditions: BnBr, K_2CO_3, DMF/DMSO (4:1), 50 °C, 90%; (b) KHMDS, allyl iodide, THF, 75%; (c) 9-BBN, THF, 78%; (d) PDC, CH_2Cl_2, 75%; (e) H_2, Pd−C, MeOH, 95%; (f) $(Boc)_2O$, NaOH/$NaHCO_3$, THF, H_2O, 85%; (g) CbzOSu, NMM, DMF, 82%.

excess of **5a** over **5b**. No diallylated product was formed under these conditions. However, use of 1.5 equiv of KHMDS and 1.5 equiv of allyl iodide resulted in formation of a significant amount (~20%) of diallylated product, which was derived from another alkylation of **5a** and **5b** at the C-3 center. These results reveal that the dibenzyl protected amino is sterically hindered enough to prevent alkylation at the C-2 center even in the presence of excess base. The difference in diastereofacial selectivity between the potassium enolate and lithium enolate can be explained by the hypothesis proposed by Chamberlin et al.[8] With the potassium enolate, formation of a seven-membered K-chelated cyclic enolate results in the preferential attack of the electrophile opposite to the bulky *N*,*N*-dibenzylamino residue to form **5a** as the major diastereomer. In contrast, the lithium enolate cannot form cyclic chelation because of its (*E*)-geometry and assumes a hydrogen-in-plane conformation. Consequently, electrophile attack is equally accessible from each side of the plane leading to formation of **5a** and **5b** in roughly similar amounts.

Hydroboration of the mixture of **5a** and **5b** produced the corresponding alcohols, which were easily separated by silica gel chromatography to provide the desired diastereomer **6a** in 78% yield. To convert the alcohol **6a** to an aldehyde, we examined several oxidation conditions including pyridinium dichromate (PDC),[10] Swern oxidation, sulfur trioxide pyridine complex[11] and Dess−Martin periodinane.[12] PDC was found to be superior to other conditions examined, providing the aldehyde **7** in 75% yield. When the aldehyde **7** was subjected to high-pressure hydrogenation in methanol using 10% Pd−C (29 wt %) as the catalyst, (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (**1b**) was obtained in 95% yield

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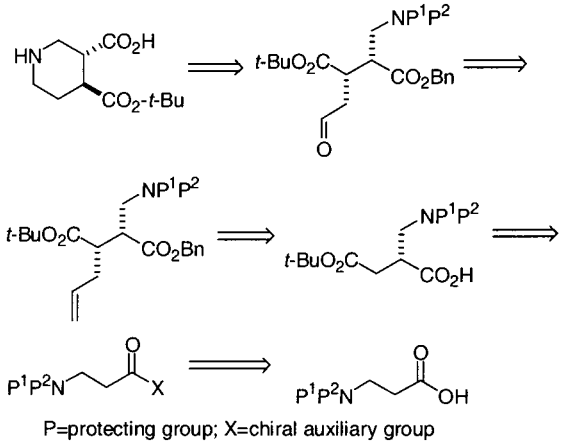
Scheme 3

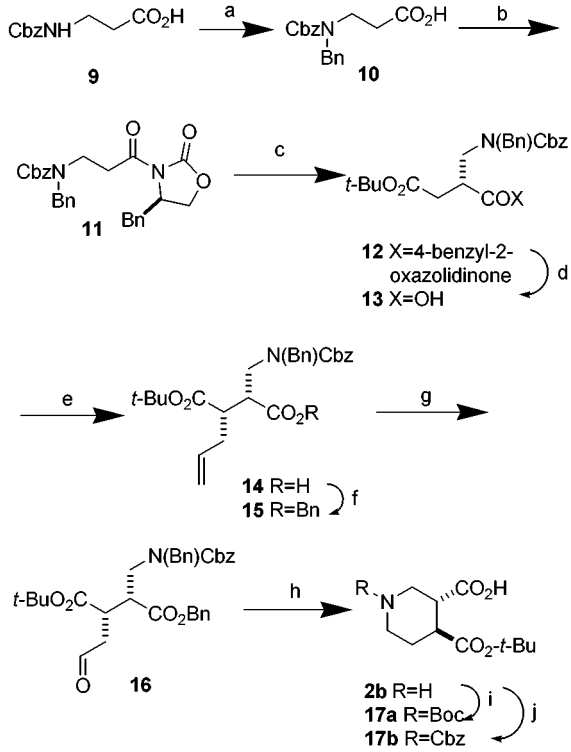


after overnight reaction. Longer reaction time was required to complete the reaction if less catalyst was used. The proton NMR spectrum of **1b** exhibits a large coupling constant between the C-2 and C-3 protons (8.5 Hz in CD_3-OD and 10.3 Hz in DMSO), clearly indicating an axial position for both hydrogens and in agreement with the trans stereochemistry reported previously.[4] Reaction of **1b** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] or *N*-(benzyloxycarbonyloxy)succinimide (CbzOSu) afforded the *N*-Boc and *N*-Cbz protected analogues **8a** and **8b**, respectively.

(3*R*,4*S*)-3,4-Piperidinedicarboxylic Acid Derivatives. To our knowledge, an asymmetric synthesis of *trans*-3,4-piperidinedicarboxylate has not been previously reported in the literature. Compound **2b** contains an embedded β-amino acid moiety, which immediately suggested the use of β-alanine as a starting point for sequential alkylations with *tert*-butyl bromoacetate and then with an allyl halide (Scheme 3). We planned to use Evans's chemistry[13] to introduce the first stereogenic center. The second stereogenic center could be then inducted during the dianion alkylation with an allyl eletrophile, the stereochemistry of which has been well established in the literature.[14] To avoid intramolecular cyclization, the β-amino group was doubly protected using benzyl and Cbz groups which could be later removed during piperidine ring formation by reductive amination. Dibenzyl protection for the β-amino was not feasible based on the consideration that the tertiary basic amino residue would not survive the ozonolysis conditions required to generate the aldehyde from the olefin moiety.

The synthesis started with commercially available *N*-Cbz-β-alanine (**9**), which was subjected to a benzylation in a mixed solvent of THF/DMF (4:1) to provide product **10** in 90% yield (Scheme 4). In the absence of DMF, the reaction was sluggish, requiring several days of reaction time to reach completion. In contrast, when DMF was used as the only solvent, *N*,*O*-dibenzylated product was obtained exclusively. Coupling of **10** with Evans's chiral auxiliary (*R*)-4-benzyl-2-oxazolidinone using pivaloyl chloride as the carboxyl activating agent[15] produced the alkylation precursor **11** in 88% yield. LDA-mediated alkylation of **11** with *tert*-butyl bromoacetate followed by $LiOH/H_2O_2$ hydrolysis gave rise to the succinic acid

Scheme 4[a]



[a] Conditions: (a) BnBr, NaH, THF/DMF (4:1), 90%; (b) (1) pivaloyl chloride, DIEA, THF, (2) (*R*)-4-benzyl-2-oxazolidinone, LiCl, 88%; (c) LDA, *tert*-butyl bromoacetate, THF, 75%; (d) LiOH, H_2O_2, THF, 90%; (e) LDA, allyl iodide, THF, 80%; (f) BnBr, DBU, benzene, 87%; (g) O_3, CH_2Cl_2, $P(PPh_3)_3$, 78%; (h) H_2, Pd−C, MeOH, 95%; (i) $(Boc)_2O$, NMM, THF, H_2O, 88%; (j) CbzOSu, NMM, DMF, 83%.

monoester **13** with an *R*-configuration. Intermediate **13** was subjected to enolate formation using 2.2 equiv of LDA followed by quenching with 1.5 equiv of allyl iodide, providing exclusively the desired syn diastereomer **14** in 80% yield after chromatography. The high diastereoselectivity is consistent with previous reports on alkylation of related succinic acid monoesters.[14,16] For comparison, the alkylation was found to be sluggish when allyl bromide was used as the electrophile. After conversion of the carboxylic acid **14** to a benzyl ester **15**, ozonolysis provided the aldehyde **16** in 85% yield. Reductive amination afforded the cyclized product **2b** as a TFA salt. The stereochemistry of **2b** was thoroughly investigated using 2D NMR experiments and clearly indicated the anti orientation of the C-3 and C-4 hydrogens, both adopting an axial position. Reaction of **2b** with $(Boc)_2O$ or CbzOSu furnished the *N*-Boc and *N*-Cbz protected analogues **17a** and **17b**, respectively.

In summary, enantiomerically pure (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (**1b**) has been synthesized in five steps in an overall yield of 38% starting from L-aspartic acid β-*tert*-butyl ester. Dibenzyl protection employed for the α-amino of the aspartate has proved to be able to direct regioselective alkylation at the C-3 center. Although this protection results in slightly

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lower diastereomeric excess (6:1) in allylation as compared with *N*-benzyl-*N*-9-phenylfluoren-9-yl protection (10:1 diastereomeric excess), it significantly shortens our synthetic sequence (one step from starting material **3** to the alkylation precursor **4**) and avoids the use of the expensive 9-bromo-9-phenylfluorene reagent. Beginning with *N*-Cbz-*β*-alanine, optically pure (3*R*,4*S*)-4-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid (**2b**) has been synthesized in eight steps in an overall yield of 28%. Compounds **1b**, **2b**, and their corresponding *N*-Boc and *N*-Cbz protected analogues **8a**,**b** and **17a**,**b** are novel conformationally rigidified amino acid derivatives which represent a useful source of chiral building blocks suitable for further synthetic elaboration in drug discovery.

Experimental Section

^{1}H NMR data were obtained at 300 MHz using a Varian VXR400 spectrometer and were referenced to TMS. 2D NMR experiments were operated at 399.735 MHz at 30 °C on a Varian Inova 400 spectrometer. Mass spectral data were obtained on either VG 70-VSE or Finnigan MAT 8230 mass spectrometers. Optical rotations were taken at 25 °C on a Perkin-Elmer 341 Polarimeter. Combustion analyses were performed by Quantitative Technologies, Inc, Bound Brook, NJ. Dry THF was distilled from calcium hydride. KHMDS and LHMDS (0.5 M in toluene and 1.0 M in THF, respectively) were used from fresh bottles purchased from Aldrich Chemical Co. Other solvents and reagents were used as purchased from commercial suppliers unless otherwise indicated. Yields quoted herein were isolated yields.

1-Benzyl 4-*tert*-Butyl (2*S*)-2-(Dibenzylamino)butanedioate (4). To a suspension of L-aspartic acid *β*-*tert*-butyl ester (25 g, 132 mmol) in DMF (200 mL) and DMSO (50 mL) was added benzyl bromide (79 mL, 462 mmol) followed by K_2CO_3 (55 g, 396 mmol). The mixture was mechanically stirred at 50 °C overnight. After being cooled to room temperature, insolubles were filtered off, and the filtrate was reduced to a small volume by evaporation under reduced pressure. The residue was diluted with water (500 mL), and the resulting solution was extracted with EtOAc three times. The combined organic phase was washed with brine three times, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel, eluting with 10% EtOAc/hexanes to provide 54.5 g (90%) of the tribenzylated product **4**. ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 5H), 7.30 (m, 10H), 5.32 (d, J = 12.4 Hz, 1H), 5.20 (d, J = 12.1 Hz, 1H), 3.95 (m, 1H), 3.80 (d, J = 13.9 Hz, 2H), 3.60 (d, J = 13.5 Hz, 2H), 2.87 (dd, J = 15.9 and 8.4 Hz, 1H), 2.62 (dd, J = 15.4 and 8.2 Hz, 1H), 1.40 (s, 9H). MS (ESI) m/z 460.1 (M + H)$^+$. Anal. Calcd for $C_{29}H_{33}NO_4$): C, 75.79; H, 7.24; N, 3.05. Found: C, 75.63; H, 7.20; N, 2.97.

4-Benzyl 1-*tert*-Butyl (3*S*)-2-Allyl-3-(dibenzylamino)-butanedioate (5). To a solution of **4** (30 g, 65.35 mmol) in freshly distilled dry THF (300 mL) at −78 °C was added a 0.5 M solution of KHMDS in toluene (157 mL). After stirring at −78 °C for 1 h, allyl iodide (9 mL, 98 mmol) was added. The temperature was raised to −30 °C and stirring was continued at −30 °C for 3 h. The reaction was quenched with 10% citric acid solution followed by dilution with brine. The resulting solution was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography on silica gel eluting with 20% EtOAc/hexanes provided 24.4 g (75%) of a mixture of **5a** and **5b** (6:1). ^{1}H NMR ($CDCl_3$) δ 7.6−7.2 (m, 15H), 5.4−5.1 (m, 3H), 4.90 (m, 2H), 4.00 (d, J = 13.8 Hz, 1/6 × 2H), 3.85 (d, J = 13.9 Hz, 5/6 × 2H), 3.61 (d, J = 11.1 Hz, 1/6 × 1H), 3.58 (d, J = 11.3 Hz, 5/6 × 1H), 3.36 (d, J = 13.6 Hz, 5/6 × 2H), 3.24 (d, J = 11.8 Hz, 1/6 × 2H), 2.95 (m, 1H), 2.65 (m, 1H), 2.20 (m, 1H), 1.42 (s, 1/6 × 9H), 1,31 (s, 5/6 × 9H). MS (ESI) m/z 500.1 (M + H)$^+$. Anal. Calcd for $C_{32}H_{37}NO_4$: C, 76.92; H, 7.46; N, 2.80. Found: C, 76.69; H, 7.32; N, 2.73.

1-Benzyl 4-*tert*-Butyl (2*S*,3*S*)-2-(Dibenzylamino)-3-(3-hydroxypropyl)butanedioate (6a). To a solution of the mixture of **5a** and **5b** (21 g, 42 mmol) in THF (50 mL) cooled in an ice bath was added a 0.5 M solution of 9-BBN (168 mL, 84 mmol). The mixture was allowed to stir at room-temperature overnight. After being cooled in an ice bath, a solution of NaOAc (69 g) in water (50 mL) was added followed by a solution of 33% H_2O_2 (68.5 mL). The mixture was stirred at room temperature for 3 h and extracted with EtOAc three times. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel, eluting with 30% EtOAc/hexanes to provide 16.9 g (78%) of the fast-moving isomer **6a** and 2.6 g (12%) of the slow-moving isomer **6b**. **6a**: ^{1}H NMR ($CDCl_3$) δ 7.5−7.2 (m, 15H), 5.24 (dd, J = 24.5,12.5 Hz, 2H), 3.82 (m, 2H), 3.80 (d, J = 13.5 Hz, 2H), 3.54 (d, J = 11.4 Hz, 1H), 3.47 (t, J = 6.6 Hz, 1H), 3.30 (d, J = 13.5 Hz, 2H), 2.85 (m, 1H), 1.9−1.4 (m, 4H), 1.34 (s, 9H). MS (ESI) m/z 518.1 (M + H)$^+$. Anal. Calcd for $C_{32}H_{39}NO_5$: C, 74.25; H, 7.59; N, 2.71. Found: C, 73.96; H, 7.85; N, 2.48. **6b**: ^{1}H NMR ($CDCl_3$) δ 7.5−7.2 (m, 15H), 5.22 (dd, J = 24.3 & 12.4 Hz, 2H), 4.00 (d, J = 13.2 Hz, 2H), 3.83 (m, 2H), 3.64 (d, J = 11.6 Hz, 1H), 3.47 (t, J = 6.6 Hz, 1H), 3.22 (d, J = 13.4 Hz, 2H), 2.84 (m, 1H), 1.9−1.4 (m, 4H), 1.41 (s, 9H). MS (ESI) m/z 518.1 (M + H)$^+$.

1-Benzyl 4-*tert*-Butyl (2*S*,3*S*)-2-(Dibenzylamino)-3-(3-oxopropyl)butanedioate (7). To a solution of **6a** (14.1 g, 27.3 mmol) in CH_2Cl_2 (400 mL) was added pyridinium dichromate (20.5 g, 54.5 mmol). The mixture was stirred at room temperature for 2 days and filtered through a pad of silica gel. The silica gel was thoroughly rinsed with CH_2Cl_2 and then $CHCl_3$. The combined filtrate was concentrated under reduced pressure. The residue was purified on silica gel eluting with 40% EtOAc/hexanes to provide 10.5 g (75%) of the aldehyde **7**. ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H), 7.5−7.2 (m, 15H), 5.26 (dd, J = 24.5 and 12.5 Hz, 2H), 3.80 (d, J = 13.6 Hz, 2H), 3.52 (d, J = 11.3 Hz, 1H), 3.30 (d, J = 13.1 Hz, 2H), 2.95 (m, 1H), 2.45 (m, 2H), 2.2−1.6 (m, 2H), 1.35 (s, 9H). MS (ESI) m/z 516.3 (M + H)$^+$. Anal. Calcd for $C_{32}H_{37}NO_5$: C, 74.54; H, 7.23; N, 2.72. Found: C, 74.82; H, 7.07; N, 2.61.

(2*S*,3*S*)-3-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic Acid (1b). To a solution of the aldehyde **7** (5.15 g, 10 mmol) in methanol (100 mL) in a Parr bottle was added 10% Pd−C (1.5 g). The mixture was stirred under H_2 at 50 psi overnight. The catalyst was filtered off, and the solution was concentrated under reduced pressure. The residue was washed with EtOAc to provide 2.2 g (95%) of the cyclized product **1b**. $[\alpha]_D$ +14.0° (c 0.35, MeOH). ^{1}H NMR (CD_3OD) δ 3.73 (d, J = 8.5 Hz, 1H), 3.32 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 1.93 (m, 1H), 1.83−1.72 (m, 2H), 1.67 (m, 1H), 1.48 (s, 9H). MS (ESI) m/z 230.1 (M + H)$^+$. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.74; H, 8.74; N, 5.92.

(2*S*,3*S*)-1,3-Bis(*tert*-butoxycarbonyl)-2-piperidinecarboxylic Acid (8a). To a solution of **1b** (1.15 g, 5 mmol) in THF (5 mL) and water (5 mL) cooled in an ice bath was added $NaHCO_3$ (0.84 g, 10 mmol) followed by di-*tert*-butyl dicarbonate (1.37 g, 6 mmol). The mixture was allowed to stir at room temperature overnight. After being cooled in an ice bath, a solution of 1 N HCl (12 mL) was slowly added with stirring. EtOAc was added. The separated organic phase was washed with brine three times, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel eluting with 5% MeOH/CH_2Cl_2 to provide 1.4 g (85%) of the *N*-Boc derivative **8a**. $[\alpha]_D$ +8.5° (c 0.40, MeOH). ^{1}H NMR ($CDCl_3$) δ 5.55 (bs, 1H), 5.12 (d, J = 10.4 Hz, 1H), 5.18 (m, 2H), 3.90 (m, 1H), 3.20 (m, 1H), 3.0−2.5 (m, 2H), 2.10 (m, 1H), 1.55 (m, 2H), 1.40 (s, 18H). MS (ESI) m/z 330.2 (M + H)$^+$. Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.36; H, 8.21; N, 4.26. Found: C, 58.55; H, 8.42; N, 4.55.

(2*S*,3*S*)-1-[(Benzyloxy)carbonyl]-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic Acid (8b). To a solution of **1b** (1.15 g, 5 mmol) in DMF (10 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.25 g, 5 mmol) followed by NMM (1.5 mL, 15 mmol). The mixture was stirred at room-temperature overnight. EtOAc was added. The solution was acidified with a solution of 1 N HCl and washed with brine three times, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel eluting with 5% MeOH/CH_2Cl_2 to give 1.5 g (82%) of

the *N*-Cbz derivative **8b**. $[\alpha]_D$ +1.2° (*c* 0.40, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.65 (bs, 1H), 7.35 (m, 5H), 5.50 (d, J = 15.4 Hz, 1H), 5.18 (m, 2H), 4.10 (m, 1H), 3.20 (m, 1H), 3.1−2.5 (m, 2H), 2.20 (m, 1H), 1.55 (m, 2H), 1.40 (s, 9H). MS (ESI) *m*/*z* 364.2 $(M + H)^+$. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.77; H, 7.14; N, 3.86.

3-{Benzyl[(benzyloxy)carbonyl]amino}propanoic Acid (10). To a solution of *N*-benzyloxycarbonyl-β-alanine (33.5 g, 150 mmol) in THF (400 mL) and DMF (100 mL) cooled in an ice bath was slowly added NaH (21.6 g, 60% in oil, 450 mmol). After stirring for 15 min, benzyl bromide (26.8 mL, 225 mmol) was added. The reaction was allowed to stir at room temperature overnight and quenched slowly by addition of water followed by 1 N HCl (pH = 3). The solution was extracted with EtOAc three times. The combined organic phase was washed with brine three times, dried ($MgSO_4$), and concentrated. Purification on silica gel eluting with 40% EtOAc/hexanes gave 42.2 g (90%) of the *N*-benzylated product **10**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 10H), 5.18 (d, J = 5.4 Hz, 2H), 4.50 (s, 2H), 3.50 (m, 2H), 2.52 (m, 2H). MS (ESI) *m*/*z* 314.1 $(M + H)^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.67; H, 6.17; N, 4.41.

Benzyl Benzyl{3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxopropyl}carbamate (11). To a solution of the carboxylic acid **10** (41.8 g, 133.5 mmol) and NEt_3 (40.5 mL, 400 mmol) in THF (500 mL) cooled at −30 °C was slowly added pivaloyl chloride (17.7 mL, 147 mmol). The mixture was stirred at −30 °C for 1 h at which time LiCl (6.22 g, 147 mmol) was added followed by (*R*)-(+)-4-benzyl-2-oxazolidinone (26 g, 147 mmol). The mixture was allowed to stir at room-temperature overnight. The volatiles were removed under reduced pressure. Water and EtOAc were added. The organic phase was separated, washed with brine, dried ($MgSO_4$), and concentrated. Purification on silica gel eluting with 40% EtOAc/hexanes gave 55.4 g (88%) of **11**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 15H), 5.20 (d, J = 13.6 Hz, 2H), 4.55 (m, 3H), 4.10 (m, 2H), 3.60 (m, 2H), 3.20 (m, 3H), 2.70 (m, 1H). MS (ESI) *m*/*z* 473.4 $(M + H)^+$. Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 70.86; H, 6.05; N, 5.79.

***tert*-Butyl (3*R*)-3-({Benzyl[(benzyloxy)carbonyl]amino}methyl)-4-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-4-oxobutanoate (12).** To a solution of diisopropylamine (5.33 mL, 52.8 mmol) in THF (75 mL) at −78 °C was added a solution of 2.5 M *n*-butyllithium (21.1 mL, 52.8 mmol). The solution was stirred at 0 °C for 30 min and after cooling back to −78 °C, a solution of **11** (22.7 g, 48 mmol) in THF (100 mL) was added. The mixture was stirred at −78 °C for 1 h at which time *tert*-butyl bromoacetate (7.8 mL, 52.8 mmol) was added. The solution was allowed to stir at −30 °C for 5 h and quenched by addition of an aqueous solution of citric acid. Following addition of EtOAc, the organic phase was separated, and the water layer was extracted with EtOAc three times. The combined organic phase was washed with 10% citric acid and brine, dried ($MgSO_4$), and concentrated. Silica gel chromatography eluting with 20% EtOAc/hexanes gave 21 g (75%) of the desired product **12**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 15H), 5.12 (m, 2H), 4.50 (m, 4H), 4.00 (m, 2H), 3.50 (m, 2H), 3.2.5 (m, 1H), 2.95 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H), 1.35 (s, 9H). MS (ESI) *m*/*z* 587.1 $(M + H)^+$. Anal. Calcd for $C_{34}H_{38}N_2O_7$: C, 69.61; H, 6.53; N, 4.78. Found: C, 69.86; H, 6.52; N, 4.64.

(2*R*)-2-({Benzyl[(benzyloxy)carbonyl]amino}methyl)-4-*tert*-butoxy-4-oxobutanoic Acid (13). To a solution of **12** (40.9 g, 69.8 mmol) in THF (150 mL)/water (120 mL) cooled in an ice bath was added a solution of 30% hydrogen peroxide (28.5 mL, 279 mmol). After the mixture was stirred for 5 min, a solution of LiOH (4.4 g, 105 mmol) in water (30 mL) was added. The mixture was allowed to stir at 0 °C for 2 h at which time sodium sulfite (35 g) was added. Stirring was continued for 30 min, The solution was acidified with 10% citric acid (pH = 3) and extracted with EtOAc three times. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Purification on silica gel eluting with 10% CH_3CN/CH_2Cl_2 followed with 10% $MeOH/CH_2Cl_2$ gave 26.8 g (90%) of the carboxylic acid **13**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 10H), 5.18 (s, 2H), 4.50 (m, 2H), 3.50 (m, 2H), 3.16 (m, 1H), 2.50 (m, 2H), 1.40 (s, 9H). MS (ESI) *m*/*z* 428.3 $(M + H)^+$. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.42; H, 6.79; N, 3.27. Found: C, 67.15; H, 6.71; N, 3.09.

(2*R*,3*S*)-2-({Benzyl[(benzyloxy)carbonyl]amino}methyl)-3-(*tert*-butoxycarbonyl)-5-hexenoic Acid (14). To a solution of diisopropylamine (4.6 mL, 32.9 mmol) in THF (18 mL) at −78 °C was added a solution of 2.5 M *n*-butyllithium (12.8 mL, 32.2 mmol). The solution was stirred at 0 °C for 30 min. After the mixture was cooled back to −78 °C, a solution of **13** (6.2 g, 14.6 mmol) in THF (30 mL) was added. The mixture was stirred at −78 °C for 60 min at which time allyl iodide (1.7 mL, 19 mmol) was added. After being stirred at −30 °C for 5 h, the solution was poured into a cold solution of 0.5 N HCl with vigorous stirring. EtOAc was added. The organic phase was separated, and the water layer was extracted with EtOAc twice. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel eluting with EtOAc/hexanes to give 5.45 g (80%) of the allylated product **14**. ^{1}H NMR ($CDCl_3$) δ 8.3 (bs, 1H), 7.30 (m, 10H), 5.65 (m, 1H), 5.22 (d, J = 12.4 Hz, 1H), 5.16 (m, 2H), 5.00 (d, J = 12.4 Hz, 1H), 4.72 (d, J = 14.7 Hz, 1H), 4.25 (d, J = 14.7 Hz, 1H), 3.70 (m, 1H), 3.40 (m, 1H), 3.15 (m, 1H), 2.67 (m, 1H), 2.00 (m, 2H), 1.25 (s, 9H). MS (ESI) *m*/*z* 468.3 $(M + H)^+$. Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.06; N, 2.99. Found: C, 69.70; H, 7.04; N, 2.96.

4-Benzyl 1-*tert*-Butyl (2*S*,3*R*)-2-Allyl-3-({benzyl[(benzyloxy)carbonyl]amino}methyl)butanedioate (15). A mixture of **14** (8.4 g, 18 mmol), benzyl bromide (4.3 mL, 35 mmol), and DBU (4.1 g, 27 mmol) in benzene (60 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduced pressure. The residue was purified on silica gel, eluting with 15% EtOAc/hexanes to give 8.7 g (87%) of the ester **15**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.0 (m, 15H), 5.60 (m, 1H), 5.2−4.8 (m, 6H), 4.60 (m, 1H), 4,25 (m, 1H), 3.50 (m, 2H), 3.10 (m, 1H), 2.80 (m, 1H), 2.20 (m, 2H). MS (ESI) *m*/*z* 558.2 $(M + H)^+$. Anal. Calcd for $C_{34}H_{39}NO_6$: C, 73.16; H, 6.99; N, 2.51. Found: C, 72.78; H, 7.04; N, 2.50.

1-Benzyl 4-*tert*-Butyl (2*R*,3*S*)-2-({Benzyl[(benzyloxy)carbonyl]amino}methyl)-3-(2-oxoethyl)butanedioate (16). Into a solution of **15** (4.3 g, 7.72 mmol) in CH_2Cl_2 (130 mL) at −78 °C was bubbled O_2 for 10 min, followed by O_3. The solution turned blue in 10 min and bubbling continued for additional 15 min. Nitrogen was then bubbled into the mixture until the blue color disappeared. Triphenylphosphine (1.91 g, 15.4 mmol) was added, and the solution was allowed to stir at room-temperature overnight. The reaction was quenched by addition of aqueous 1 N HCl solution. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. Chromatography on silica gel eluting with 20% EtOAc/hexanes gave 3.3 g (78%) of the aldehyde **16**. ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1H), 7.4−7.0 (m, 15H), 5.10 (m, 4H), 4.60 (m, 1H), 4.30 (m, 1H), 3.60 (m, 2H), 3.3−2.8 (m, 3H), 2.60 (m, 1H), 1.36 (s, 9H). MS (ESI) *m*/*z* 560.2 $(M + H)^+$. Anal. Calcd for $C_{33}H_{37}NO_7$: C, 70.84; H, 6.62; N, 2.50. Found: C, 70.56; H, 6.56; N, 2.48.

(3*R*,4*S*)-4-(*tert*-Butoxycarbonyl)-3-piperidinecarboxylic Acid (2b). To a solution of **16** (4.5 g, 8.0 mmol) in methanol (50 mL) was added TFA (0.7 mL) followed by 10% palladium on carbon (1.3 g). The mixture was stirred under hydrogen at 50 psi overnight. The catalyst was removed by filtration, and the solution was concentrated. The residue was washed with ether to give 1.7 g (95%) of the cyclized product **2b**. $[\alpha]_D$ +15.7° (*c* 0.236, MeOH). ^{1}H NMR (CD_3OD) δ 3.58 (m, 1H), 3.38 (m, 1H), 3.15−2.98 (m, 3H), 2.80 (m, 1H), 2.17 (m, 1H), 1.81 (m, 1H), 1.42 (s, 9H). MS (ESI) *m*/*z* 230.3 $(M + H)^+$. Anal. Calcd for $C_{11}H_{19}NO_4 \cdot CF_3CO_2H$: C, 45.48; H, 5.87; N, 4.08. Found: C, 45.70; H, 5.67; N, 4.03.

(3*R*,4*S*)-1,4-Bis(*tert*-butoxycarbonyl)-3-piperidinecarboxylic Acid (17a). To a suspension of **2b** (2.29 g, 10 mmol) in THF (10 mL) cooled in an ice bath was added a solution of 1 N NaOH (10 mL) followed by $NaHCO_3$ (1.68 g, 20 mmol) and di-*tert*-butyl dicarbonate (2.4 g, 11 mmol). After being stirred at room temperature for 5 h, the solution was cooled in an ice bath and acidified with 1 N HCl. EtOAc was added, and the separated organic phase was washed with brine three

times, dried ($MgSO_4$), and concentrated. Chromatography on silica gel eluting with 5% MeOH/CH_2Cl_2 provided 2.9 g (88%) of the *N*-Boc derivative **17a**. $[\alpha]_D$ −17.2° (*c* 0.40, MeOH). ^1H NMR ($CDCl_3$) δ 7.1 (bs, 1H), 4.25 (m, 1H), 4.02 (m, 1H), 2.8−2.6 (m, 4H), 1.96 (m, 1H), 1.46 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H). MS (ESI) *m*/*z* 330.2 $(M + H)^+$. Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.35; H, 8.20; N, 4.25. Found: C, 58.56; H, 8.28; N, 4.36.

(3*R*,4*S*)-1-[(Benzyloxy)carbonyl]-4-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic Acid (17b). To a solution of **2b** (1.45 g, 4.22 mmol) in DMF (10 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.16 g, 4.65 mmol) followed by NMM (1.72 mL, 17 mmol). After being stirred at room-temperature overnight, EtOAc was added. The solution was acidified with 1 N HCl, washed with brine three times, dried ($MgSO_4$), and concentrated. Purification on silica gel eluting with 5% MeOH/CH_2Cl_2 gave 1.4 g (83%) of the *N*-Cbz derivative **17b**. $[\alpha]_D$ −21.8° (*c* 0.30, MeOH). ^1H NMR ($CDCl_3$) δ 7.37 (m, 5H), 5.12 (m, 2H), 4.35 (m, 1H), 4.15 (m, 1H), 3.0−2.6 (m, 4H), 1.95 (m, 1H), 1.58 (m, 1H), 1.41 (s, 9H). MS (ESI) *m*/*z* 364.4 $(M + H)^+$. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.89; H, 6.86; N, 3.85.

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