An Efficient Route to Either Enantiomer of trans -2-Aminocyclopentanecarboxylic Acid

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An Efficient Route to Either Enantiomer of *trans*-2-Aminocyclopentanecarboxylic Acid

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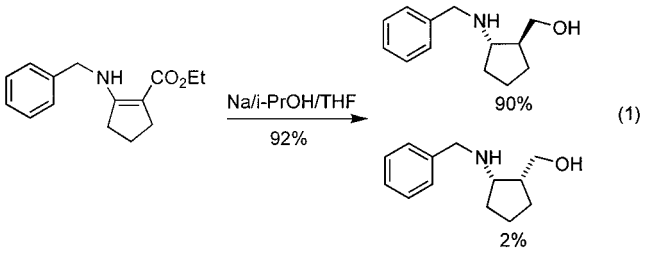
Oligomers of β-amino acids (β-peptides) can be designed to adopt a variety of secondary structures, helix, sheet, or turn, by proper choice of residue substitution pattern.[1] β-Peptide helices have proven to be very stable conformationally, with oligomers containing as few as six residues displaying high helix populations in aqueous solution.[2] The predictability and stability of β-peptide conformations have led recently to the design of specific β-peptides with useful biological activities.[3] Further exploration of β-peptide function will be facilitated by improvements in the synthesis of the requisite β-amino acids.[4]

We have shown that oligomers composed of *trans*-2-aminocyclopentanecarboxylic acid (ACPC) adopt a helical conformation that contains a network of 12-membered ring hydrogen bonds between backbone C=O and N−H groups (12-helix).[5] Use of a pyrrolidine-based analogue of ACPC allowed us to generate short water-soluble β-peptides and to demonstrate that these oligomers fold to the 12-helix in aqueous solution.[2] We have recently shown that an ACPC-containing β-peptide displays interesting antibiotic activity.[3c] The synthesis of protected ACPC derivatives we originally employed[5] was serviceable for moderate quantities of only the *R,R* enantiomer. Here, we report a more efficient synthesis of ACPC derivatives that gives access to either enantiomeric series in large quantities (> 20 g).

Scheme 1 shows our previous route to (*R,R*)-ACPC derivatives,[5] which is closely based on work of Tilley *et al.*[6] This route suffers from two major drawbacks. First, the scale is limited by the need for large volumes of water for the baker's yeast reduction[7] and by the tedious filtration, extraction and chromatography required. Second, (*S,S*)-ACPC derivatives are not available via this route. Inability to prepare (*S,S*)-ACPC and derivatives is a serious limitation in terms of biological applications because the 12-helix promoted by this ACPC enantiomer has the same helical sense as an α-helix formed by conventional peptides. 12-Helical β-peptides containing (*S,S*)-ACPC residues may serve as antagonists of protein−protein interactions that depend on α-helix recognition.

Several alternative asymmetric routes to ACPC have been reported,[8,9] but none is efficient enough for our long-term goals, which require that we be able to prepare multigram quantities of enantiomerically pure material in a few days from commerically available precursors. Work by Bartoli *et al.*[10] (eq 1) inspired the first new route



(1)

we explored. These workers demonstrated that the reduction of the cyclic β-enamino esters with sodium metal results in formation of *trans* γ-amino alcohols in high yield and with excellent diastereoselectivity. We hypothesized that replacement of benzylamine with enantiomerically pure α-methylbenzylamine[11] would result in reduction to produce predominantly *trans* diastereomeric γ-amino alcohols, which could be separated by simple recrystallization of the corresponding HCl salts. It seemed likely that, after purification, the desired γ-amino alcohol could be carried on to enantiomerically pure Fmoc-ACPC.

The results of this synthetic endeavor are summarized in Scheme 2. β-Ketoester **1** was allowed to react with (*S*)-α-methylbenzylamine in refluxing benzene with a catalytic amount of toluenesulfonic acid. The resulting enamine **6** was isolated as a yellow oil after distillation. The enamine was reduced with sodium in THF/^{i}PrOH to a diastereomeric mixture of four γ-amino alcohols. Unfortunately, this reaction also produced significant amounts of Birch reduction side products. Nevertheless, after HCl was added to the reaction mixture, the HCl salt of the desired amino alcohol could be obtained in 20% yield by multiple recrystallizations. The configuration of the desired diastereomer was confirmed by X-ray cystallog-

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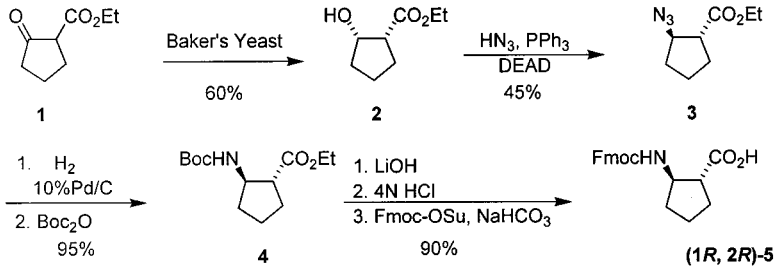
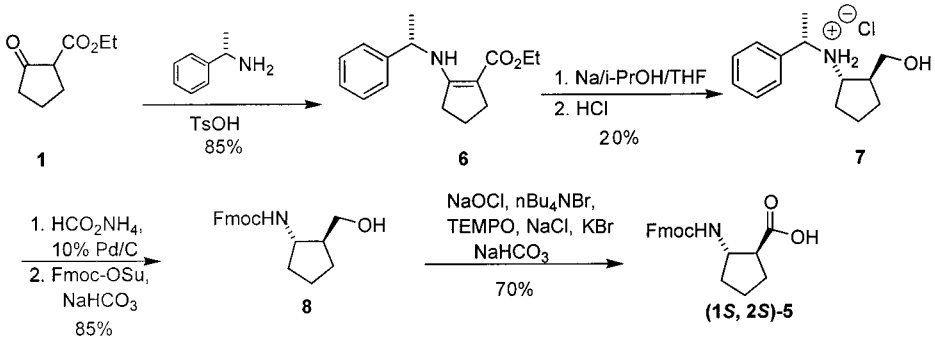
Scheme 1



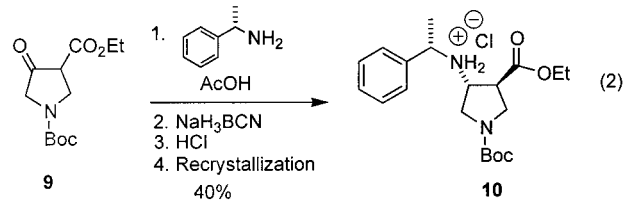
Scheme 2



raphy. Removal of the chiral auxiliary was accomplished by transfer hydrogenation, and the resulting primary γ-ammonium alcohol was protected with Fmoc-OSu. Finally, oxidation of the primary alcohol provided (*S*,*S*)-Fmoc-ACPC.

Although the route in Scheme 2 gives access to either enantiomer of ACPC, it suffers from low yields in the enamine reduction. In addition, when this reaction was run on a larger scale the yields declined because of Birch reduction. The reduction step could probably be improved with careful attention, but we decided to investigate another route.

The route in Scheme 3 was inspired by our recent success with reductive amination of β-ketoester **9** to β-aminoester **10** (eq 2).[12] Subjecting β-ketoester **1** to



reductive amination provided the β-aminoester **12** in 40% yield after chromatography. Alternatively we found that a three-step recrystallization of the HCl salt of the crude product afforded β-ammonium ester in 29% yield. Reductive removal of the chiral auxiliary followed by saponification and protection of the amine with Fmoc-OSu resulted in the desired (1*S*,2*S*)-Fmoc-ACPC in 25% overall yield from **1** without need for chromatography. ^{1}H NMR indicated that (1*S*,2*S*)-**5** prepared in this way was identical to (1*S*,2*S*)-**5** synthesized via the previous route (Scheme 2) as well as (1*R*,2*R*)-**5** from our original synthesis. Finally, the optical rotation of (1*S*,2*S*)-**5** was of the same magnitude as but opposite in sign to the optical rotation of (1*R*,2*R*)-**5**. Following the route in Scheme 3 but starting with (*R*)-(+)-α-methylbenzylamine provided (1*R*,2*R*)-**5**.

In summary, we have developed two new asymmetric routes that provide either enantiomer of Fmoc-ACPC, which is a building block for the solid-phase synthesis of β-peptides. The better of these syntheses allows preparation of multigram quantities of enantiomerically pure Fmoc-ACPC in four steps without the need for chromatography. This route will facilitate investigation of the conformational and biological properties of 12-helical β-peptides.

Experimental Section

General Procedures. Melting points were determined on a capillary melting point apparatus and are uncorrected. Optical rotations were measured using sodium light (D line, 589.3 nm). THF was distilled from sodium/benzophenone ketyl under N_2. All commercially available reagents and solvents were purchased from Aldrich and used without further purification, with the exception of 4 N HCl in dioxane, which was purchased from Pierce, and Fmoc-OSu, which was purchased from Advanced ChemTech. Analytical thin-layer chromatography (TLC) was carried out on Whatman TLC plates precoated with silica gel 60 (250 μm layer thickness). Visualization was accomplished using either UV lamp or potassium permanganate stain (2 g of $KMnO_4$, 13.3 g of K_2CO_3, 3.3 mL of 5% (w/w) NaOH, 200 mL of H_2O). Column chromatography was performed on EM Science silica gel 60 (230−400 mesh). Solvent mixtures used for TLC and column chromatography are reported in v/v ratios. Diastereomeric excesses were determined using ^{1}H NMR.

Ethyl 2-[(1′*S*)-Phenylethylamino]-cyclopent-1-ene Carboxylate (6). To a stirred solution of β-ketoester **1** (31 mL, 209 mmol) in benzene (135 mL) under N_2 atmosphere was added (*S*)-(−)-α-methylbenzylamine (25 mL, 194 mmol) and TsOH (25 mg). The resulting solution was heated to reflux for 16 h, during which time water was azeotropically removed via a Dean−Stark trap. After removal of the benzene under reduced pressure, the resulting orange oil was distilled (135 °C, 1 mmHg) to give **6** (42.7 g, 85%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 6.4 Hz, 1H), 7.33−7.18 (m, 5H), 4.53 (p, J = 7.1), 4.17 (m, 2H), 2.56−2.4 (m, 3H), 2.21 (m, 1H), 1.81−1.58 (m, 2H), 1.49 (d, J = 7.0 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 164.0, 145.1, 128.6, 126.9, 125.3, 93.4, 58.3, 54.2, 32.2, 28.8, 24.8, 20.8, 14.6.

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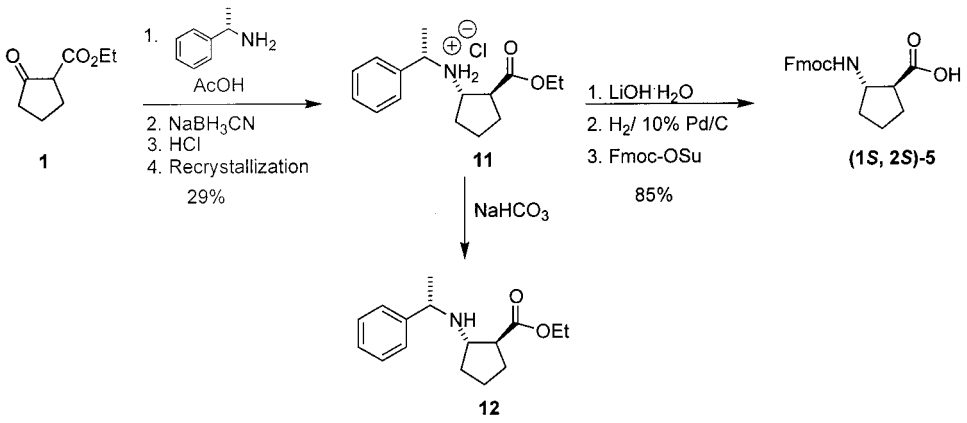
Scheme 3



(1*S*,2*S*)-2-Hydroxymethyl-cyclopentyl-[(1′*S*)-phenylethyl]-amine Hydrochloride (7). *β*-Enamino ester **6** (7.6 g, 29.3 mmol) was dissolved in a mixture of THF (75 mL) and *i*-PrOH (30 mL) under N_2. Sodium was added in 1 g portions until all of the starting material was consumed (5−7 h) according to TLC (6% MeOH in CH_2Cl_2, R_f = 0.9). The excess sodium was removed, and the reaction was quenched with 75 mL of saturated NH_4Cl. The organic layer was concentrated, and the residue was shaken with CH_2Cl_2. The organic layer was separated, washed with brine, and dried with K_2CO_3. After concentration, the orange oil was passed through a plug of silica, eluting with 10% MeOH in CH_2Cl_2. The eluted solution was concentrated to afford a yellow oil. The yellow oil was dissolved in 200 mL of EtOAc, and 7.5 mL of 4 N HCl in dioxane was added dropwise with stirring. The solution was stored at 0 °C for 2 h, and the resulting white solid was isolated by filtration and washed with ether. Multiple recrystallizations from MeOH/ether gave 1.49 g (20% yield) of *γ*-ammonium alcohol **7** as a white crystalline solid: mp 230−231 °C; ^{1}H NMR (300 MHz, D_2O) *δ* 7.55−7.49 (m, 5H), 4.53 (q, *J* = 6.8 Hz, 1H), 3.55 (m, 1H), 3.37 (m, 1H), 2.31 (m, 1H), 2.04−1.84 (m, 2H), 1.80−1.58 (m, 3H), 1.79 (d, *J* = 6.9 Hz, 3H), 1.52−1.42 (m, 1H); ^{13}C NMR (75 MHz, D_2O) *δ* 137.8, 131.0, 130.9, 128.9, 64.6, 61.4, 58.8, 46.3, 31.7, 28.8, 24.5, 20.1.

(1*S*,2*S*)-2-Hydroxymethyl-cyclopentyl-(9*H*-fluoren-9-yl-methoxy)-carbamate (8). *γ*-Ammonium alcohol **7** (1.1 g, 4 mmol) was dissolved in 35 mL of MeOH. 10% Pd/C (1.1 g) and HCO_2NH_4 (5.2 g, 83 mmol) were added, and the reaction mixture was heated at reflux until the starting material was completely consumed (3−4 h) according to TLC (20% MeOH in CH_2Cl_2, R_f = 0.22). After the reaction mixture had cooled to room temperature, the mixture was filtered through a pad of Celite, and the filtrate was concentrated to yield a white solid (0.6 g). The white solid was dissolved in a mixture of acetone (24 mL) and water (12 mL), and $NaHCO_3$ (1.5 g, 17.9 mmol) and Fmoc-OSu (1.48 g, 4.4 mmol) were added. The reaction mixture was stirred under N_2 for 24 h. The acetone was removed under reduced pressure, the residue was diluted with water, and the product was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting white solid was purified via chromatography (1:1 hexane/EtOAc, R_f = 0.28) to yield 1.1 g (85%) of **8** as a white solid: mp 140−141 °C (recrystallized from hexane/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.75 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.30 (td, *J* = 7.4 Hz, 1.4 Hz), 5.00 (d, *J* = 7.0 Hz, 1H), 4.41 (d, *J* = 6.8 Hz, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 3.73 (m, 1H), 3.59 (m, 1H), 3.48 (m, 2H), 2.03 (m, 1H), 1.79 (m, 2H), 1.59 (m, 2H), 1.5−1.3 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 157.0, 143.8, 141.3, 127.7, 127.1, 125.0, 120.0, 66.7, 64.3, 55.2, 49.9, 47.2, 33.1, 27.6, 22.6.

(1*S*,2*S*)- 2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-cyclopentane Carboxylate [(1*S*,2*S*)-5] from Alcohol 8. Alcohol **8** (535 mg, 1.59 mmol) was dissolved in CH_2Cl_2 (20 mL). To the resulting solution was added TEMPO (10 mg, 0.064 mmol), saturated $NaHCO_3$ (10 mL), KBr (50 mg, 0.42 mmol), and ^{n}Bu$_4$NBr (60 mg 0.19 mmol). The reaction mixture was cooled to 0 °C, and a solution of bleach (24 mL, 5.25% NaOCl by weight), saturated aqueous $NaHCO_3$ (15 mL), and saturated aqueous NaCl (30 mL) was added dropwise over 25 min. One hour after the final addition, the yellow solution was acidified with 1 N HCl to pH 3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the resulting oil was subjected to silica gel chromatography (6:3:0.5 hexane/EtOAc/AcOH, R_f = 0.33). Concentration of the appropriate fractions yielded 390 mg (70%) of (1*S*, 2*S*)-**5**: mp 164−165 °C (recrystallized from heptane/methanol); $[\alpha]^{23}_D$ = 36.3 (*c* 1.21, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) *δ* 7.87 (d, *J* = 7.2 Hz, 2H), 7.73−7.61 (m, 2H), 7.50−7.26 (m, 4H), 4.35−15 (m, 3H), 4.08−3.94 (m, 1H), 2.56 (q, 1H), 2.04−1.78 (m, 2H), 1.77−1.35 (m, 4H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) *δ* 175.98, 155.53, 143.97, 143.88, 140.75, 127.63, 127.09, 125.16, 120.13, 65.26, 55.41, 49.39, 46.76, 32.61, 28.48, 22.92; HRMS FAB *m*/*z* 374.0 [M + Na]$^+$.

Ethyl (1*S*,2*S*)-2-[(1′*S*)-Phenylethyl]-aminocyclopentane Carboxylate Hydrochloride (11). To a stirred solution of *β*-ketoester **1** (40 mL, 270 mmol) in absolute ethanol (320 mL) under N_2 was added (*S*)-(−)-α-methylbenzylamine (69.6 mL, 540 mmol) and glacial acetic acid (30.8 mL, 540 mmol). The reaction mixture was stirred at room temperature until the formation of the enamine was complete (2 h; monitored by TLC, 7:3 hexane/EtOAc, R_f = 0.22). The reaction mixture was diluted with 640 mL of absolute ethanol and heated to 72 °C, and sodium cyanoborohydride (42.4 g, 675 mmol) was then added to the reaction mixture in five portions over a 5 h period. The disappearance of enamine was monitored by TLC. Through the course of the reaction a solid formed on the surface that hindered efficient mixing of additional sodium cyanoborohydride. This solid could be broken up with a spatula or by use of a mechanical stirrer. When the reaction was complete (6−8 h), 200 mL of H_2O was added, and the ethanol was removed via rotary evaporation in a well ventilated hood (**Caution: Possible HCN evolution!!**). The resulting mixture was extracted with diethyl ether (700 mL). The ethereal solution was passed through a plug of silica, eluting with an additional 1.5 L of ether. The filtrate was concentrated, the resulting oil was dissolved in EtOAc (1.2 L), and 4 N HCl in dioxane (65 mL) was added dropwise at room temperature with stirring. The resulting solution was stored at 0 °C for 1 h. A white precipitate formed during this time. The solid was isolated by filtration and washed with EtOAc (200 mL). (The EtOAc filtrate was used to obtain a small amount of the 1*R*,2*R* diastereomer, as described below.) This solid could be purified by recrystallization from ethanol (75 g of solid in 450 mL ethanol). The resulting solid was filtered and washed with acetonitrile and then recrystallized from acetonitrile (27 g in 400 mL). After filtration and drying, 23 g of **11** was obtained as a white crystalline solid (29% yield from **1**). ^{1}H NMR of the corresponding free amine (**12**) indicated the diastereomeric excess to be > 99%. Characterization of **11**: mp 240−241 °C; ^{1}H NMR (300 MHz, CD_3OD) *δ* 7.53−7.40 (m, 5H), 4.44 (q, *J* = 6.6 Hz, 1H), 4.14 (m, 2H), 3.80 (dt, *J* = 8.1 Hz, 6.4 Hz, 1H), 3.11 (m, 1H), 2.27−2.00 (m, 2H), 1.89−1.59 (m, 7H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) *δ* 137.8, 130.6, 130.5, 128.7, 62.4, 60.4, 59.1, 48.6, 31.8, 31.1, 25.1, 20.2, 14.4.

Ethyl (1*S*,2*S*)-2-[(1′*S*)-Phenylethyl]-aminocyclopentane Carboxylate (12). A sample of **11** was mixed with an excess of

saturated $NaHCO_3$ solution, extracted into diethyl ether, dried over $MgSO_4$, and concentrated under reduced pressure to give **12** as a clear oil: R_f = 0.24, 7:3 hexane/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 4.18−4.03 (m, 2H), 3.83 (q, J = 6.6 Hz, 1H), 3.21 (q, J = 7.1 Hz, 1H), 2.56 (dt, J = 8.9 Hz, 7.0 Hz, 1H), 1.95 (m, 1H), 1.79 (m, 2H), 1.61 (m, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.29 (m, 1H), 1.23 (t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 145.8, 128.1, 126.6, 126.4, 61.5, 56.5, 51.2, 34.2, 26.7, 24.5, 23.5, 14.0.

The diastereomer of **12**, ethyl (1*R*,2*R*)-2-[(1′*S*)-phenylethyl]-aminocyclopentane carboxylate, was obtained in the following way for use as a standard in the NMR-based determination of the *de* of **12**. The EtOAc filtrate mentioned in the procedure for **11** was shaken with solid $NaHCO_3$, and the $NaHCO_3$ was then removed by filtration. The solution was concentrated, and the residue was purified by chromatography to give ethyl (1*R*,2*R*)-2-[(1′*S*)-phenylethyl]-aminocyclopentane carboxylate as a clear oil: R_f = 0.15, 7:3 hexane/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.10 (m, 2H), 3.79 (q, J = 6.7 Hz, 1H), 3.02 (q, J = 8.0 Hz, 1H), 2.50 (q, J = 8.4 Hz, 1H), 1.99−1.86 (m, 2H), 1.82−1.50 (m, 4H), 1.41 (m, 1H), 1.35 (d, J = 6.7 Hz, 3H), 1.23 (t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 145.3, 128.2, 126.7, 126.2, 60.1, 60.1, 51.0, 32.6, 27.9, 24.7, 23.0, 14.1.

(1*S*,2*S*)-2-(*9H*-Fluoren-9-ylmethoxycarbonylamino)-cyclopentane Carboxylate [(1*S*,2*S*)-5] from *β*-Ammonium Ester 11. Compound **11** (6.27 g, 21.0 mmol) was dissolved in THF/MeOH/H_2O (6:3:1, 100 mL), and the solution was cooled to 0 °C. LiOH·H_2O (4.41 g, 105 mmol) was added. The mixture was stirred at 0 °C for 9 h. Aqueous HCl (1 N, 110 mL) was added at 0 °C. The solvent was then removed on a vacuum rotary evaporator to give (1*S*,2*S*)-2-[(1′*S*)-phenylethyl]-aminocyclopentanecarboxylic acid as a white solid, which was used for the next step without further purification: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.12 (br s, 2H), 7.68−7.57 (m, 2H), 7.38−7.25 (m, 3H), 4.21 (m, 1H), 3.37−3.20 (m, 2H), 2.15−1.99 (m, 1H), 1.94−1.68 (m, 3H), 1.58 (d, J = 6.6 Hz, 3H), 1.64−1.47 (m, 1H), 1.45−1.28 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 175.21, 137.40, 128.89, 128.77, 128.29, 58.57, 56.76, 46.22, 31.13, 30.86, 24.44, 20.95; HRMS FAB m/z 256.3 $[M + Na]^+$.

The white solid was dissolved in 300 mL of 95% ethanol in a hydrogenation flask; 10% Pd−C (2.0 g) was added. The resulting mixture was shaken under H_2 (50 psi) for 48 h. After the reaction was complete (the disappearance of starting material was monitored by TLC), the mixture was filtered through Celite, and the filtrate was concentrated to obtain the HCl salt of (1*S*,2*S*)-aminocyclopentanecarboxylic acid as a white solid, which was used for the next step without further purification: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.68 (br s, 2H), 3.62−3.49 (q, 1H), 2.94−2.80 (m, 1H), 2.11−1.37 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 174.96, 53.38, 48.26, 30.85, 29.48, 23.49; HRMS FAB m/z 152.1 $[M + Na]^+$.

This solid was dissolved in acetone/H_2O (2:1, 300 mL) and cooled to 0 °C, and Fmoc-Osu (8.92 g, 26.4 mmol) and $NaHCO_3$ (17.1 g, 203 mmol) were added. The reaction mixture was stirred at 0 °C for 1 h and was then allowed to stir at room temperature overnight. Water (100 mL) was added. The acetone was removed under reduced pressure. The aqueous residue was diluted with water (300 mL) and stirred for 1 h with diethyl ether (300 mL). The layers were separated, and the aqueous layer was acidified with 1 N aqueous HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to give a white solid. The crude product was purified by crystallization from *n*-hexane/CH_2Cl_2 to afford 6.31 g (85%) of (1*S*,2*S*)-**5** as a white solid. This material was identical to the material produced from alcohol **8** (characterization above).

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Supporting Information Available: ^{1}H and ^{13}C NMR for compounds **5**−**7**, **11**, and **12,** as well as some additional intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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