Stereoselective Synthesis of 3-Substituted 2-Aminocyclopentanecarboxylic Acid Derivatives and Their Incorporation into Short 12-Helical β-Peptides That Fold in Water

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Abstract: A stereoselective synthetic route is reported for the introduction of side chains at the 3-position of trans-2-aminocyclopentanecarboxylic acid (ACPC). Ring opening of the aziridine 2-benzyloxymethyl-6-azabicyclo[3.1.0]hexane with selected nucleophiles occurs in a regioselective manner and provides ACPC precursors with functional groups at the 3-position, trans to the 2-amino group. Oligomers composed of the 3-substituted ACPC residues maintain the 12-helical conformation displayed by the nonsubstituted analogues, as shown by their similar circular dichroism signatures. The added diversity of the new residues provides good dispersion of NMR signals, allowing the assignment of nearly all the NOE signals of a selected hexamer in aqueous solution. The NOEs between protons on nonadjacent residues are characteristic of the 12-helix. 3-Substituted ACPC residues allow one to arrange specific functional groups in a geometrically defined fashion, which should facilitate the design of β-peptides for biological applications.

Introduction

Unnatural oligomers with discrete folding propensities (“foldomers”) have received much attention in recent years.†‡ β-Peptide foldamers constructed from β-amino acids constrained with five-membered rings (Figure 1), like trans-2-aminocyclopentanecarboxylic acid (ACPC) and trans-3-aminopyrrolidino-4-carboxylic acid (APC), adopt a robust helical conformation defined by 12-membered-ring hydrogen bonds, C==O(i) → N−H(i + 3) (“12-helix”).§ Helical structure can be observed with as few as six residues in aqueous solution,§ which makes these oligomers attractive as scaffolds for biological applications. Antimicrobial activity paralleling that of natural host-defense peptides has been reported for a 12-helical β-peptide composed of ACPC and APC.¶ Several groups have reported biological applications for non-12-helical β-peptides composed of acyclic β-amino acids.⁵–⁷

Figure 1. β-Amino acids, with a five-membered constraint.

To enhance the utility of 12-helical β peptides, we are developing strategies for appending functionality at specific sites along the helix. Recently we showed that diversity can be introduced into 12-helical β-peptides by sulfonylation of the ring nitrogen of APC or by introduction of a few acyclic β-amino acids among ACPC and/or APC residues (the latter approach is limited by diminution of 12-helical stability).⁹ Here we demonstrate a complementary strategy, side chain introduction at the 3-position of ACPC.

At the outset it was not clear that side chain introduction at the 3-position would be tolerable by the 12-helix, given the proximity of the substitution site to the backbone nitrogen. We were motivated to explore this possibility because success would provide a geometrically defined way to place functional groups

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along the 12-helical framework without diminishing the backbone’s intrinsic folding preference.

Results and Discussion

Monomers 1–3 were prepared enantioselectively, starting with the alkylation of sodium cyclopentadienide by benzylichloromethyl ether (Scheme 1). This step is generally plagued by the formation of a significant amount of the double-bond isomerized side product. Previous work has shown that isomerization could be avoided by simply switching from the traditional THF alkylation solvent to DMF, which removes the need to work with the toxic thallium compounds. The resulting diene was then converted to alcohol 4 in 77% yield via asymmetric hydroboration–oxidation with (+)-Ipc2BH, according to the procedure of Biggadike et al. Use of (−)-Ipc2BH provided the enantiomer of 4. Tosylation of the alcohol followed by recrystallization from heptane gave the tosylate in >99% ee. The tosylate was reduced to the highly enantiopure alkene 5 with LiAlH₄.

Conversion to cis-epoxide 6 (Scheme 2), previously performed by Colombini et al., from racemic 5, employs a Sharpless chlorohydroxylation. Epoxide ring opening with NaN₃ followed by alcohol activation with MsCl yielded a 2:3 regioisomeric mixture of azido-mesylates, which was converted to 7 by azide reduction and concomitant ring-closing mesylate displacement.

Conversion of 7 to the tert-butyl carbamate allowed facile ring opening with BF₃ and an alcohol (Scheme 2). This reaction gave only one product, the regiochemistry of which was established crystallographically in the case of methanol as the nucleophile. Crystals were obtained by slow evaporation of CHCl₃ from racemic 8. Analysis of the X-ray diffraction data confirmed the positions of the substituents on the ring as well as their cis/trans relationships.

The ring-opened intermediates 8 and 9 were converted to their respective N-Boc-β-amino acids by removal of the benzylic protecting group followed by oxidation. A protecting group change from Boc to FMoc afforded β-amino acid derivatives (e.g., 12 and 13) suitable for solid-phase synthesis. Access to an alternative type of side chain began with reaction of 7 with Cbz-Cl, followed by aziridine ring opening with cyanide. Reduction of the nitrite to the amine, followed by Boc protection, yielded 15. Removal of the benzyl and Cbz groups with Na/NH₃, followed by Fmoc protection of the resulting free amine and oxidation of the alcohol, produced 16. The routes in Scheme 2 should provide access to a wide range of 3-substituted ACPC residues.

To determine whether 3-substituted ACPC residues would be compatible with the 12-helical conformation, we first prepared two hexamers, Ac-(APC-1)-NH₂ and Ac-(3-ACPC)-NH₂. The CD signatures of these two hexamers in water (Figure 2) were similar to that of Ac-(APC-ACPC)-NH₂, which is known to be 12-helical.

We prepared hexamer 17 (Figure 3), which contains residues 1–3, for NMR analysis. We anticipated that the high chemical diversity of 17 (five different residues) would lead to dispersion in the proton NMR spectrum, which is critical for structural analysis. Indeed, nearly all proton resonances could be resolved in the NMR spectrum of 17 in 9:1 H₂O:D₂O (6 mM peptide, 100 mM acetate buffer (pH 3), 4 °C). Two-dimensional NMR data, including NOESY and ROESY, provided information about the three-dimensional structure of 17. NOEs between protons on residues that are not adjacent in sequence are particularly informative. All possible C₆H₄ → NH₁₂, C₆H₄ → NH₁₃, and C₆H₄ → C₆H₁₊₂ NOEs were observed (a few were ambiguous due to NMR resonance overlap). These three sets of NOEs are characteristic of the 12-helical conformation.

No NOEs inconsistent with the 12-helical conformation were observed. It is very likely that β-peptide 17 interconverts between 12-helical and unfolded states rapidly on the spectroscopic time scale under the conditions used for the NMR studies. We cannot rule out the possibility that the conformational ensemble includes states that are partially 12-helical and partially unfolded, along with the fully folded state and a completely unfolded state. The abundance of NOEs, particularly at the terminal residues, suggests that 17 is very well structured in aqueous solution.

Conclusions

We have shown that diversity can be conveniently introduced into 12-helical β-peptides in a geometrically defined way, while retaining the conformational preorganization provided by the five-membered ring, by placing side chains at the 3-position of the ring, trans to the 2-amino group. Employing aziridine 7 as a divergence point allows for various nucleophiles to be introduced. The capacity to produce a large pool of diverse monomers will prove important in preparing libraries of β-peptides to be screened for biological activities.

Experimental Section

General Procedures. Reagents were obtained from Aldrich Chemical Co. and were used without further purification, except 4 N HCl in dioxane, which was purchased from Pierce. Melting points (mp) were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer. Chemical
shifts were reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). 1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a Bruker AC-300 (300 MHZ) spectrometer. Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with phase angles of 90° and 135°. Mass spectra (MS) were obtained using an electrospray ionization (ESI) mass spectrometer. Molecular ions are reported as the sodium salt with molecular weights 22.9898 greater than the actual compound molecular weight. Analytical thin-layer chromatography was carried out on Whatman TLC plates precoated with silica gel 60 (250 μm thickness). Visualization was performed using a UV lamp or potassium permanganate stain. Column chromatography was performed on EM Science silica gel 60 (230–400 mesh). Solvent mixtures for chromatography are reported as v/v ratios. THF, benzene, and Et2O, used as reaction solvents, were distilled from sodium/benzophenone under nitrogen immediately prior to use. CH2Cl2, NEt3, and pyridine used as reaction solvents were distilled from CaH over nitrogen immediately prior to use.

Figure 2. Circular dichroism of Ac-(APC-ACPC)3-NH2, Ac-(APC-1)-NH2, and Ac-(3-ACPC)-NH2, 0.07 mM in H2O (25 °C). Data were obtained on an Aviv instrument with 1 mm path length cells. Data were normalized for peptide concentration and number of residues.
2-(Benzyloxymethyl)cyclopent-3-enol (4). Sodium cyclopentadiene (25 mL, 2 M in THF from Aldrich) was added dropwise to a solution of benzylichloromethyl ether\(^2\) (13.9 mL, 75 mmol) in DMF (125 mL) at \(-40^\circ\)C. After 15 min of vigorous stirring at \(-40^\circ\)C, the reaction mixture was quenched by pouring it into pentane (400 mL); ice water (200 mL). After shaking and allowing the phases to separate, the organic layer was washed twice with 200 mL of ice water and dried over MgSO\(_4\) with stirring, maintaining the temperature below 0 \(^\circ\)C to avoid isomerization of the product. After removal of the drying agent by filtration, the pentane was removed under reduced pressure at 0 \(^\circ\)C. The resulting yellow oil was diluted into THF (200 mL), cooled to \(-78^\circ\)C, and added via cannula to a suspension of (+)-IPC-BH\(_{14}\) (14.3 g, 50 mmol) in THF (300 mL) at \(-78^\circ\)C.\(^3\) The mixture was allowed to warm slowly to \(-10^\circ\)C and stirred for 48 h at that temperature. The reaction was then quenched by addition of MeOH (20 mL), followed by 3 M NaOH (20 mL) and 30\% H\(_2\)O\(_2\) (20 mL). After 12 h of vigorous stirring at room temperature, the THF was removed under reduced pressure. The remaining aqueous suspension was partitioned between EtOAc (350 mL) and saturated aqueous NaCl. The organic layer was dried with MgSO\(_4\), followed by removal of the solvent at reduced pressure. The remaining oil was chromatographed on silica gel with 3:1 hexanes:EtOAc. A pale yellow oil was recovered (7.41 g, 73\%). Chiral HPLC analysis (Chiracel OD 4.6 mm, 95:5 hexanes:PrOH, 1 mL/min) revealed a product of 97\% ee (retention time for the major enantiomer, 13.3 min, and for the minor enantiomer, 16.1 min). HRMS (ESI): [MNa]\(^+\) calculated 227.1048, found 227.1059.

**Figure 3.** NOEs between residues that are not adjacent in the sequence observed for 17 in 9:1 H\(_2\)O:D\(_2\)O. Dashed lines indicate NOEs that are ambiguous because of resonance overlap. Data were obtained on a Varian 600 MHz spectrometer.


The combined filtrate at reduced pressure, leaving a clear oil (3.23 g, 77\%). HRMS (ESI): [MNa]\(^+\) calculated 211.1099, found 211.1097. \(^1\)HNMR (CDCl\(_3\), 300 MHz, room temperature): \(\delta\) 1.57 (1H, m), 2.03 (1H, m), 2.33 (2H, m), 2.99 (1H, br), 3.36 (2H, m), 4.53 (2H, s), 5.72 (1H, m), 5.80 (1H, m), 7.25–7.35 (5H, m). \(^13\)C NMR: \(\delta\) 26.5 (CH\(_2\)), 31.7 (CH\(_3\)), 46.0 (CH), 72.9 (CH\(_2\)), 74.3 (CH\(_3\)), 127.3 (CH), 127.4 (CH), 128.1 (CH), 131.9 (CH), 138.5 (C) (note: in the aromatic region, some signals may represent more than one carbon).

2-(Benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (6). To a \(-78^\circ\)C solution of 5 (3.12 g, 16.6 mmol) and tert-butyl hydroperoxide (4 mL, 5–6 M in nonane) in CH\(_2\)Cl\(_2\) (250 mL) was added TCI (2.73 mL, 25 mmol) dropwise over 5 min.\(^4\) After 15 min, the reaction was quenched by transfer via cannula into a mixture of vigorously stirred Et\(_2\)O saturated aqueous Na\(_2\)SO\(_4\). After the mixture was stirred for 15 min, the Et\(_2\)O layer was washed with saturated aqueous Na\(_2\)SO\(_4\) and saturated aqueous NaCl. The organic layer was dried over MgSO\(_4\). Removal of the organic solvent at reduced pressure produced a yellow oil that was dissolved in benzene (160 mL). To the solution was added potassium tert-butoxide (3.92 g, 35 mmol). The suspension was stirred at room temperature for 2.5 h and then quenched with H\(_2\)O. The organic layer was then washed with saturated aqueous NaCl and dried over MgSO\(_4\). Upon removal of the solvent, a pale yellow oil (98.2 cis:trans mixture) was obtained, which was carried on without further purification (2.88 g, 85\%). HRMS (ESI): [MNa]\(^+\) calculated 227.1048, found 227.1050.

**2-(Benzyloxymethyl)-6-azabicyclo[3.1.0]hexane (7).** To a solution of compound 6 (9.79 g, 48 mmol) in 8:1 MeOH:H\(_2\)O (200 mL) were added Na\(_2\)S (15.0 g, 230 mmol) and NH\(_4\)Cl (6.0 g, 112 mmol).\(^5\) The mixture was heated to reflux for 15 h. The MeOH was then removed under reduced pressure, leaving a yellow oil, which was partitioned between EtOAc and H\(_2\)O. The organic layer was separated, washed with saturated aqueous NaCl, and dried over MgSO\(_4\). Removal of the solvents, followed by chromatography of the azido alcohols with 4:1 hexanes:EtOAc, gave as a clear oil a 3:2 mixture of diastereomers (10.1 g, 41 mmol, 85\%). The mixture of azido alcohols (7.13 g, 29 mmol) was dissolved in pyridine (25 mL) and cooled to 0 \(^\circ\)C. Methane sulfonyl chloride (2.72 mL, 35 mmol) was added dropwise to the solution, after which the reaction solution was allowed to warm slowly to room temperature. After being stirred for 2 h at room temperature, the mixture was diluted into 200 mL of EtOAc and extracted three times with saturated aqueous CuSO\(_4\) solution. The organic layer was then washed with saturated aqueous NaCl and dried over MgSO\(_4\). Removal of the solvents gave an oil that was taken up in THF (50 mL) and added dropwise to a suspension of LAH (4.26 g, 112 mmol) in THF (150 mL) at 0 \(^\circ\)C. The reaction mixture was stirred at room temperature for 5 h. Excess LAH was slowly quenched with 1 M NaOH at 0 \(^\circ\)C until the suspension appeared completely white. The suspension was filtered through Celite, and the isolated solid was washed with ether. The filtrate solvents were removed under reduced pressure, and the resulting oil was chromatographed on silica gel with EtOAc and then 5:1 EtOAc:MeOH, yielding a clear oil, which contains a 2\% cis impurity carried over from the epoxide formation (4.8 g, 84\%). HRMS (ESI): [MNa]\(^+\) calculated 226.1208, found 226.1218. \(^1\)HNMR (CDCl\(_3\), 300 MHz, room temperature): \(\delta\) 0.40 (1H, br), 1.39–1.47 (2H), 1.63–1.85 (2H), 2.42–2.48 (2H, m), 3.28–3.38 (2H, abx, \(J_{\text{HH}} = 9.3\) Hz, \(J_{\text{Hz}} = 7.5\) Hz, \(J_{\text{Hz}} = 6.9\) Hz), 4.52 (2H, s), 7.26–7.36 (5H). \(^13\)C NMR: \(\delta\) 21.8 (CH\(_3\)), 25.8 (CH\(_3\)), 35.1 (CH), 37.8 (CH), 40.0 (CH), 71.9 (CH), 72.9 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 138.3 (C) (note: in the aromatic region, some signals may represent more than one carbon).

[2-(Benzyloxymethyl)-5-methoxycyclopentyl]carbamic Acid tert-Butyl Ester (8). To a solution of 7 (1.90 g, 9.4 mmol) in MeOH (50 mL)
mL) were added NEt₃ (1.31 mL, 9.4 mmol) and di-tert-butyl dicarbonate (2.18 g, 10.0 mmol). The reaction stirred at room temperature for 2 h. The MeOH was then removed under reduced pressure, and the remaining oil was taken up in EtOAc, washed with saturated aqueous NaCl, and dried over MgSO₄. The solvent was removed under reduced pressure, leaving a yellow oil, which was chromatographed on silica gel with 5:1 hexanes:EtOAc to give the Boc-aziridine intermediate as a clear oil (2.38 g, 84%). A solution of CH₂Cl₂ (50 mL) and the Boc-aziridine intermediate (1.00 g, 3.3 mmol) was cooled to –78 °C. BF₃·OEt₂ (16.5 mmol) was added, followed by slow addition of BF₃·Et₂O (2.10 mL, 16.5 mmol). After 5 min, the reaction was quenched with addition of saturated aqueous NaHCO₃ addition. The mixture was allowed to warm to room temperature with stirring. The organic layer was separated, washed with saturated aqueous NaHCO₃, and dried over MgSO₄. Removal of the organic solvent left a yellow oil, which was chromatographed on silica gel with 3:1 hexanes:EtOAc, yielding a clear oil (0.96 g, 87%). HRMS (ESI): [M+Na]⁺ calculated 358.1994, found 358.1980. ²H NMR (CDCl₃, 300 MHz, room temperature): δ 1.49 (9H, s), 1.5–2.05 (5H, 3.35 (3H), 3.41 (1H, m), 3.59 (3H), 4.51 (2H, s), 7.25–7.35 (5H). ¹³C NMR: δ 25.7 (CH₃), 28.3 (CH₃), 29.2 (CH₂), 45.2 (CH₂), 56.7 (CH₃), 59.6 (CH), 72.8 (CH₂), 73.0 (CH), 86.7 (CH₃), 127.3 (CH₃), 127.4 (CH₂), 132.8 (CH), 138.4 (C), 155.1 (C) (note: in the aromatic region, some signals may represent more than one carbon).

[2-(Benzoxymethyl)-5-phenoxycyclopentyl]carbamic Acid tert-Butyl Ester (9). CH₂Cl₂ (50 mL) and phenol (3.10 g, 33 mmol) were cooled to –78 °C. BF₃·OEt₂ (16.5 mmol) was added, followed by slow addition of the Boc-aziridine intermediate (prepared as described in the procedure for 8) (0.9 g, 3.0 mmol) dissolved in CH₂Cl₂ (10 mL). After the addition was complete, saturated aqueous NaHCO₃ was added to the solution to quench the reaction. The mixture was allowed to warm to room temperature with vigorous stirring. The organic layer was separated, washed twice with 1 M NaOH and then saturated aqueous NaCl, and dried over MgSO₄. Solvents were removed under reduced pressure. The recovered oil was chromatographed on silica gel with 6:1 hexane:EtOAc, yielding a white crystalline solid (74%). Mp: 183–185 °C (recrystallized from MeOH:EtOH). HRMS (ESI): [M+Na]⁺ calculated 404.1630, found 404.1646. ²H NMR (pyridine-d₅, 300 MHz, room temperature): δ 1.89–2.16 (3H), 2.38 (1H, m), 3.36 (1H, m), 3.41 (1H, s), 4.04, (1H, q, J = 6.6 Hz), 6.40 (1H, d, J = 8.1 Hz), 4.63 (2H, d, J = 8.4 Hz), 9.44 (1H, m), 7.26 (2H, d, J = 7.8 Hz), 7.39 (2H, t, J = 7.8 Hz), 7.65 (2H, t, J = 7.8 Hz), 7.84 (2H, d, J = 7.8 Hz), 8.84 (1H, d, J = 9.6 Hz). ¹³C NMR: δ 27.3 (CH₃), 30.9 (CH₃), 48.4 (CH₂), 50.2 (CH₂), 57.4 (CH₂), 62.1 (CH), 66.8 (CH₂), 87.5 (CH), 120.9 (CH), 126.2 (CH), 128.0 (CH), 128.5 (CH), 142.2 (CH), 145.1 (CH), 145.3 (C), 157.3 (C), 177.5 (C) (note: in the aromatic region, some signals may represent more than one carbon).

2-[(2-(4-Fluoren-9-ylmethoxy)carbonylamino)-3-phenoxycyclopentylene]carboxylic Acid (10). A solution of 4 N HCl in dioxane was added to 10 (176 mg, 0.68 mmol), and the resulting solution was stirred for 1 h. The HCl/dioxane was then blown off with a stream of N₂. The white powdery residue was taken up in 2:1 acetone:H₂O (20 mL). To this solution were added NaHCO₃ (118 mg, 1.4 mmol) and Fmoc-OSu (229 mg, 0.68 mmol). The reaction mixture was stirred at room temperature for 16 h, and the acetonitrile was then removed under reduced pressure. The remaining aqueous suspension was extracted with CHCl₃ (20 mL). The organic layer was washed with saturated aqueous NaCl and dried over MgSO₄. Removal of the solvents under reduced pressure, followed by chromatography with 100% CHCl₃:AcOH, yielded a white solid (232 mg, 61%). Mp: 189–190 °C (recrystallized from MeOH:H₂O). HRMS (ESI): [M+Na]⁺ calculated 404.1474, found 404.1464. ²H NMR (pyridine-d₅, 300 MHz, room temperature): δ 1.89–2.16 (3H), 2.38 (1H, m), 3.36 (1H, m), 3.41 (1H, s), 4.04, (1H, q, J = 6.6 Hz), 4.30 (1H, t, J = 8.1 Hz), 4.63 (2H, d, J = 8.4 Hz), 9.44 (1H, m), 7.26 (2H, d, J = 7.8 Hz), 7.39 (2H, t, J = 7.8 Hz), 7.65 (2H, t, J = 7.8 Hz), 7.84 (2H, d, J = 7.8 Hz), 8.84 (1H, d, J = 9.6 Hz). ¹³C NMR: δ 27.3 (CH₃), 30.9 (CH₃), 48.4 (CH₂), 50.2 (CH₂), 57.4 (CH₂), 62.1 (CH), 66.8 (CH₂), 87.5 (CH), 120.9 (CH), 126.2 (CH), 128.0 (CH), 128.5 (CH), 142.2 (CH), 145.1 (CH), 145.3 (C), 157.3 (C), 177.5 (C) (note: in the aromatic region, some signals may represent more than one carbon).

2-(2-Benzoxymethyl-5-cyanocyclopentyl)carbamic Acid tert-Butyl Ester (11). This compound was prepared by a procedure similar to that used to prepare 10. Purification was performed by chromatography on silica gel with 100:1 CHCl₃:AcOH, yielding a white solid (83%), which was recrystallized from heptane:EtOAc. Mp: 135–136 °C. HRMS (ESI): [M+Na]⁺ calculated 344.1474, found 344.1482. ²H NMR (CDCl₃, 300 MHz, room temperature): δ 1.45 (9H, s), 1.89–2.28 (4H), 3.04 (1H, br), 4.06 (1H, br), 4.67 (1H, br), 5.05 (1H, br), 6.80 (2H, m), 6.95 (1H, m), 7.27 (2H, m). ¹³C NMR: δ 26.8 (CH₂), 28.9 (CH₃), 29.1 (CH₂), 50.2 (CH), 57.2 (CH), 61.5 (CH), 79.5 (CH), 87.5 (CH), 156.9 (CH), 175.8 (C) (note: in the aromatic region, some signals may represent more than one carbon).
organic solvent produced a clear oil that was purified by chromatography on silica gel, eluting with 6:1 hexanes:EtOAc. A clear oil product was obtained (7.5 g, 93%). The oil was found to be 99.4% ee by chiral HPLC (Chiral OD column, 95:5 hexanes/proH, 1 mL/min; retention time for the major enantiomer, 18.7 min, and for the minor enantiomer, 16.8 min). The Cbz-aziridine intermediate (4.80 g, 14.2 mmol) was dissolved in DMSO (120 mL). To the solution were added KCN (4.8 g, 74 mmol) and NH₄Cl (0.85 g, 16 mmol). 18-Crown-6 (19.5 g, 74 mmol) was then added to the reaction mixture, and the resulting mixture was heated at 80°C for 6 h. The reaction mixture was then poured into 300 mL of H₂O. The aqueous layer was extracted with 300 mL of Et₂O. The organic layer was washed with saturated aqueous NaCl and dried over MgSO₄. Removal of the Et₂O under reduced pressure gave a tan solid (4.7 g, 90%). This material could be recrystallized from heptane:EtOAc to give pure white crystals. Mp: 111–112°C. HRMS (ESI): [MNa]⁺ calculated 387.1763, found 387.1781. ¹H NMR (CDCl₃, 300 MHz, room temperature): δ 1.65 (1H, m), 1.91–2.03 (2H), 2.14 (1H, m), 2.23 (1H, br), 3.02 (1H, br), 3.48 (2H, d, J = 5.4 Hz), 3.91 (1H, d, J = 8.4 Hz), 4.48 (2H, s), 5.00 (1H, br), 5.10 (2H, s), 7.27–7.35 (10H). ¹³C NMR: δ 26.1 (CH₃), 27.8 (CH₂), 34.1 (CH), 44.2 (CH), 59.4 (CH), 66.8 (CH₂), 70.9 (CH), 73.1 (CH₂), 121.3 (C), 124.9 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 135.9 (C), 137.9 (C), 155.5 (C) (note: in the aromatic region, some signals may represent more than one carbon).

2-Benzoylxyloxyethyl-5-(tert-butoxy carbonylamino)methyl)cyclopentyl]carbamic Acid Benzyl Ester (15). THF (78 mL) was added to 14 (4.7 g, 12.9 mmol), and the resulting solution was cooled to 0°C. BH₃THF (78 mL, 1 M in THF) was then added dropwise with stirring. The reaction mixture was allowed to stir at room temperature for 5 h and then quenched by slow addition of 6 M HCl (aqueous) until all the excess borane was destroyed. The solution was then made basic with 1 M NaOH and extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaCl and dried over MgSO₄. After removal of the solvent under reduced pressure, the crude oil was dissolved in 50 mL of MeOH. NEt₃ (2.7 mL, 15 mmol) was added, and the solution was heated to 80°C. BH₃THF (78 mL, 1 M in THF) was then added dropwise with stirring. The reaction mixture was allowed to evaporate from the flask with stirring at room temperature. The remaining suspension was taken up in EtOAc and filtered. Removal of the EtOAc under reduced pressure yielded a yellow solid, which was dissolved in 3:1 acetone:H₂O (200 mL) containing NaHCO₃ (0.84 g, 10 mmol). Fmoc-OSu (1.82 g, 5.4 mmol) was added, and the solution was allowed to stir overnight at room temperature. The acetone was then removed under reduced pressure, and the remaining aqueous mixture was washed with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried over MgSO₄. After removal of the organic solvent at reduced pressure, the remaining yellow solid was recrystallized from heptane:EtOAc to afford a white solid (1.2 g, 47%). CH₂Cl₂ (40 mL) was added to the white solid (1.1 g, 2.36 mmol), and the resulting solution was cooled to 0°C. KBr (27 mg, 0.23 mmol), (n-Bu)₂NBr (32 mg, 0.1 mmol), and TEMPO (8 mg, 0.05 mmol) were added to the solution. Saturated aqueous NaHCO₃ was then added (10 mL), followed by dropwise addition of a combined solution of 5% NaClO (10.5 mL), saturated aqueous NaHCO₃ (10 mL), and saturated aqueous NaCl (10 mL). The reaction mixture turned a light yellow color. After 10 min, the reaction was quenched with 0.5 M HCl. The resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried over MgSO₄. Removal of solvent under reduced pressure yielded a white solid, which was chromatographed on silica gel with CHCl₃ and then CHCl₃ containing 1% AcOH, to give a white foamy solid (0.65 g, 57%). Recrystallization from CHCl₃/MeOH gave a white powdery solid. Mp: 150–152°C. HRMS (ESI): [MNa]⁺ calculated 503.2158, found 503.2141. ¹H NMR (pyridine-d₅, 300 MHz, room temperature): δ 1.48 (9H, s), 1.78 (1H, m), 1.95–2.23 (3H), 2.45 (1H, m), 3.33 (1H, m), 3.47 (1H, m), 3.78 (1H, m), 4.31 (1H, m), 4.57 (2H, m), 4.65 (1H, m), 7.29 (2H, d, J = 7.5 Hz), 7.39 (2H, t, J = 6.6 Hz), 7.62 (2H, t, J = 6.6 Hz), 7.82 (2H, d, J = 7.5 Hz), 8.86 (1H, d, J = 7.8 Hz). ¹³C NMR: δ 26.5 (CH₃), 27.2 (CH₂), 27.9 (CH₃), 40.9 (CH), 45.5 (CH), 46.6 (CH), 56.1 (CH₂), 66.8 (CH), 69.3 (CH₂), 82.9 (C), 119.8 (CH), 124.9 (CH), 127.0 (CH), 127.6 (CH), 141.1 (C), 143.2 (C), 154.2 (C), 155.1 (C), 178.5 (C) (note: in the aromatic region, some signals may represent more than one carbon).

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Supporting Information Available: ¹H and ¹³C spectra of all numbered intermediates in Schemes 1 and 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.