(*R*,*R*,*R*)-2,5-Diaminocylohexanecarboxylic Acid, a Building Block for Water-Soluble, Helix-Forming *β*-Peptides

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Unnatural oligomers with discrete and predictable folding propensities ("foldamers") are subjects of considerable current interest.[1] Attention in our laboratory and several others has focused on oligomers of *β*-amino acids ("*β*-peptides").[1−3] We have shown, for example, that oligomers of *trans*-2-aminocyclohexanecarboxylic acid (ACHC) adopt a helical conformation that has approximately three residues per turn and contains a network of 14-membered ring hydrogen bonds between backbone C═O and N−H groups ("14-helix").[3] Independent studies by Seebach et al. demonstrate that *β*-peptides constructed from acyclic residues bearing a single α- or *β*-substitutent also adopt the 14-helical conformation.[2] Recent results from our laboratory show that acyclic residues have a lower intrinsic propensity for helical folding than do cyclohexane-based residues.[3b,4]

To pursue potential applications of 14-helical *β*-peptides, we must develop efficient syntheses of protected forms of ACHC and derivatives that bear substituents on the cyclohexyl ring. The "extra" substituents on ACHC derivatives should occupy equatorial positions on the cyclohexane ring in order to avoid steric repulsions with residues at positions i + 3 and/or i − 3 in the 14-helical conformation. The extensive literature on asymmetric synthesis of *β*-amino acids[5] suggests a few routes for preparation of enantiomerically pure ACHC.[6,7] Our previous efforts relied on a crystallization-based resolution of *N*-benzoyl-ACHC, which proved to be capricious.[3c] Excellent chemistry developed by Kobayashi et al.[7,8] seemed likely to provide a more secure route to protected versions of ACHC and to appropriately substituted derivatives. We now report a synthesis of a protected form of (*R*,*R*,*R*)-2,5-diaminocyclohexanecarboxylic acid (DCHC), a monomer that has allowed us to study 14-helix formation by short *β*-peptides in aqueous solution.[3b] We also report an improved synthesis of protected versions of ACHC itself.

Our approach relies on the method of Kobayashi et al. for enzymatic desymmetrization (via selective ester hydrolysis) of diester **1**.[7] For ACHC, the resulting chiral monoacid was subjected to a Curtius rearrangement, as previously reported[7] (Scheme 1). The resulting isocyanate can be converted to a Cbz-protected amino group via reaction with benzyl alcohol;[7] in our experience, however, **2** could not be easily purified from the excess benzyl alcohol needed for efficient trapping of the isocyanate. We therefore carried the impure material forward. (Attempts to trap the isocyanate with *tert*-butyl alcohol were low yielding.) After hydrogenation of **2**, to remove the alkene and the Cbz protecting group, benzyl alcohol was easily separated from the amine product by acid−base extraction. The amino group was then reprotected to yield **3**. Epimerization of **3** yielded **4**, which was contaminated with approximately 8% of **3**. One recrystallization provided pure **4**. Hydrolysis of the methyl ester provided Boc-ACHC that was comparable in terms of optical rotation to Boc-ACHC prepared by an alternative enantioselective route.[3c] Standard protecting group manipulations allowed conversion of **4** to **5a**, which could be hydrolyzed to provide Cbz-ACHC, **5b**.

To synthesize DCHC, which bears an "extra" amino group at the 5-position of the cyclohexyl ring, we first synthesized **6** from **2** using published procedures (Scheme 2).[8] The first step in the conversion involves hydrolysis of the methyl ester of **2**, and excess benzyl alcohol from the Curtius rearrangement was removed by an acid−base extraction after this hydrolysis. A one-pot procedure was developed to introduce a protected amino group stereospecifically at the 5-position. First, methanesulfonyl chloride (MsCl) was added to a solution of **6** at 0 °C, and then tetra-*n*-butylammonium azide was added at 0 °C. We believe that this reaction generates an allylic azide. All attempts to isolate this putative intermediate, however, were complicated by the presence of an additional isomer, presumably from sigmatropic rearrangement of the allylic azide moiety.[9] When the intermediate azide was reduced to the amine at 0 °C (with tri-*n*-butylphosphine and water), followed by treatment with di-*tert*-

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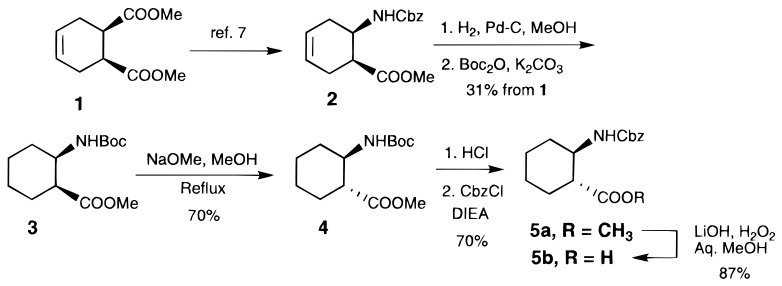
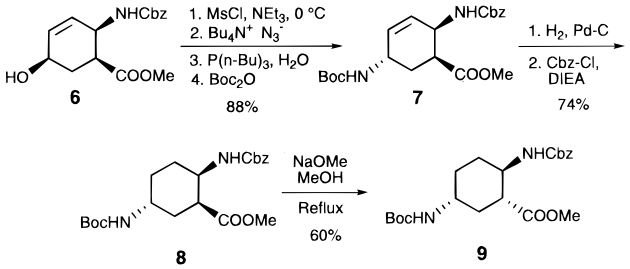
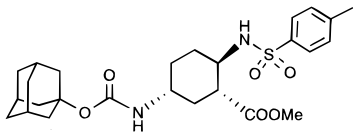
Scheme 1



Scheme 2



butyl-dicarbonate, **7** was isolated in pure form. Hydrogenation of **7** followed by reprotection with Cbz-Cl provided **8**, and epimerization yielded **9** (**8** was not detected after epimerization). The relative and absolute stereochemistry of **9** was verified by conversion to **10**, for which a crystal structure was obtained.



10

Short β-peptides containing DCHC and/or ACHC, which were constructed from building blocks that included **5b** and **9**, have been shown to display high population of the 14-helical conformation in aqueous solution.[3b] The water-solubility of these β-peptides depended upon protonation of the 5-amino group on the DCHC residue. This amino group can also serve as a point of attachment for a wide variety of "sidechains," which should allow us to use 14-helical β-peptides as scaffolds to display functional groups in specific and predictable arrangements.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured using sodium light (D line, 589.3 nm). Carbon NMR data were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with a phase angle of 135°: (C) not observed; (CH) positive; (CH_2) negative; (CH_3) positive. Dry methanol was prepared by distillation from $Mg(OMe)_2$ (Mg turnings (5 g), I_2 (0.5 g), methanol (100 mL)). Triethylamine (Et_3N) was distilled from CaH_2 and stored under N_2. Methanesulfonyl chloride (MsCl) was distilled from P_2O_5 and stored under N_2. Unless otherwise noted, all other commercially available reagents and solvents were purchased from Aldrich and used without further purification, except for 4 N HCl in dioxane, which was purchased from Pierce, and tetra-*n*-butylammonium azide, which was purchased from TCI America. 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 a UV lamp, 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), or ninhydrin stain (0.5 g of ninhydrin, 150 mL of *n*-butanol, 5 mL of glacial acetic acid). 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.

Compound 2 was prepared as described in ref 7; however, **2** could not be efficiently separated from residual benzyl alcohol used in the reported protocol. Therefore, impure **2** was carried on to the next step.

Compound 3. To a solution of **2** (ca. 18 mmol) in methanol (25 mL) was added 10% Pd−C (0.26 g). The mixture was shaken under H_2 (50 psi) for 18 h. The mixture was then filtered through a plug of glass wool, concentrated, and dried under vacuum to obtain a yellow liquid. Water was added to the liquid, and then 3 N HCl was added to the solution until a pH of 2 was obtained. The resulting solution was extracted twice with diethyl ether to remove benzyl alcohol. To the aqueous layer was added K_2CO_3 (in small amounts to avoid vigorous evolution of gas) until a pH of 9 was obtained. Dioxane was added, followed by Boc_2O (5.3 g, 22 mmol). The resulting solution was stirred for 20 h. The solution was then mixed with water and extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, concentrated, and dried under vacuum to obtain a viscous yellow liquid. The product was purified by SiO_2 column chromatography, eluting with 6:1 hexane/ethyl acetate. The fractions containing the desired product were combined and concentrated to afford 1.73 g of **3** as a clear oil (31% yield from **1**): $[\alpha]^{23}_D = 77.8$ (*c* 0.55, $CHCl_3$); IR (neat) 3445 (NH), 1716 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.32 (br, 1H), 3.85 (m, 1H), 3.69 (s, 3H), 2.79 (bq q, J = 4 Hz, 1H), 2.07−1.93 (m, 1H), 1.84−1.55 (m, 4H), 1.51−1.25 (m, 12H; includes large singlet at 1.43); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 174.3 (C), 155.2 (C), 79.0 (C), 51.4 (CH_3), 49.0 (CH), 44.8 (CH), 29.7 (CH_2), 28.3 (CH_3), 26.8 (CH_2), 23.7 (CH_2), 22.5 (CH_2); EI-MS *m*/*z* (M^+) calcd for $C_{13}H_{23}NO_4$ 257.1627, obsd 257.1628.

Compound 4. Sodium (0.17 g, 7.4 mmol) was placed into a flame-dried Schlenk flask outfitted with a condenser. The flask was cooled to 0 °C, and dry methanol (10 mL) was added. The mixture was kept under N_2 and vented to remove evolved gases until all of the sodium dissolved. In a separate flask, **3** (2.3 g, 8.9 mmol; dried under vacuum) was dissolved in dry methanol (10 mL) and transferred to the NaOMe solution via cannula. The resulting solution was refluxed for 5 h. After the solution was cooled to room temperature, 0.5 M aqueous NH_4Cl was added. The solvent was mostly removed on a rotary evaporator, and the precipitate was collected by suction filtration to obtain 2.0 g of white solid that contained **4** and about 8% **3**. The solid was recrystallized from *n*-heptane to afford 1.36 g (70% yield) of **4** as colorless crystals: mp 90 °C, $[\alpha]^{23}_D = -14$ (*c* 1.0, $CHCl_3$); IR (KBr) 3361 (NH), 1727 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.51 (br, 1H), 3.67 (s and m, 4H), 2.24 (dt, J = 12, 3.5 Hz, 1H), 2.09−1.99 (m, 1H), 1.96−1.85 (m, 1H), 1.81−1.52 (m, 2H), 1.51−1.29 (m, 11H; includes large singlet at 1.42), 1.27−1.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 174.4 (C), 154.9 (C), 79.2 (C), 51.7 (CH), 51.2 (CH_3), 50.1 (CH), 33.9 (CH_2), 28.4 (CH_2), 28.3 (CH_3), 24.7 (CH_2), 24.4 (CH_2); EI-MS *m*/*z* (M^+) calcd for $C_{13}H_{23}NO_4$ 257.1627, obsd 257.1628.

Compound 5a. To **4** (0.26 g, 1.0 mmol) was added 4 N HCl in dioxane (3 mL), and the resulting solution was stirred for 1 h (white solid precipitated during this time). The solvent was removed under a stream of N_2, and the residue was dried under vacuum. The residue was then suspended in CH_2Cl_2 (10 mL), and DIEA (0.55 mL, 3.1 mmol) was added, which caused the residue to dissolve. Benzylchloroformate (0.23 mL, 1.6 mmol)

was added, followed by DMAP (10 mg, 0.08 mmol). The resulting solution was stirred for 26 h; during this time the solution became yellow. The solution was then washed with 1 N HCl and with water, and the organic layer was dried over $MgSO_4$ and concentrated. The product was purified by SiO_2 column chromatography, eluting with 5:1 hexane/ethyl acetate. Fractions containing the product were combined and concentrated to afford 0.22 g (70% yield) of **5** as a white solid, which appeared to be pure by NMR. This material could be recrystallized from *n*-heptane without obvious improvement in purity: mp 79 °C; $[\alpha]^{23}_D = -18$ (*c* 0.9, $CHCl_3$); IR (KBr) 3331 (NH), 1733 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.27 (m, 5H), 5.07 (s, 2H), 4.08 (br, 1H), 3.73 (tdd, $J = 11$, 9, 4 Hz, 1H), 3.61 (s, 3H), 2.27 (td, $J = 11$, 3 Hz, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.81−1.49 (m, 3H), 1.47−1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 174.3 (C), 155.4 (C), 136.6 (C), 128.4 (CH), 128.0 (CH), 66.5 (CH_2), 51.7 (CH and CH_3), 49.7 (CH), 32.8 (CH_2), 28.6 (CH_2), 24.6 (CH_2), 24.3 (CH_2); EI-MS *m*/*z* (M^+) calcd for $C_{16}H_{21}NO_4$ 291.1471, obsd 291.1474.

Compound 5b. Methanol (50 mL) and water (17 mL) were added to **5a** (1.04 g, 3.57 mmol), followed by $LiOH \cdot H_2O$ (1.80 g, 42.9 mmol) and 26% aqueous H_2O_2 (2.3 mL, 18 mmol). The mixture was stirred at room temperature for 24 h. A solution of Na_2SO_3 (6.76 g, 53.7 mmol) in water (40 mL) was then added at 0 °C, and the mixture was stirred for 10 min. The methanol was removed via rotary evaporation, which caused formation of a precipitate. Aqueous sodium hydroxide solution was added with heating until the precipitate redissolved. The aqueous layer was washed twice with ethyl acetate. The organic layers were discarded, and the aqueous layer was cooled to 0 °C and acidified with 3 M HCl until white solid precipitated. This mixture was treated with ethyl acetate, which caused the precipitate to dissolve. The aqueous layer was acidified to pH 2 with 3 M HCl and re-extracted with the same ethyl acetate and then with four additional aliquots ethyl acetate. The organic extracts were combined, dried over $MgSO_4$, and concentrated. Toluene was added and removed via rotary evaporation three times to remove any acetic acid produced during the workup. The residue was dried under vacuum to afford 0.862 g (87% yield) of a white solid that appeared to be pure by NMR. This material could be recrystallized from ethyl acetate/hexane without obvious improvement in purity: mp 147−148.5 °C; $[\alpha]^{23}_D = -27.1$ (*c* 1, $CHCl_3$); IR (thin film) 3328 (NH), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.43 (br, 1H), 7.38−7.25 (m, 5H), 6.12, 5.25−4.85 (m, 3H), 3.85−3.63 (m, 1H), 2.38−2.19 (m, 1H), 2.13−1.92 (m, 2H), 1.79−1.48 (m, 3H), 1.46−1.10 (m, 3H); ^{13}C NMR (CD_3CN, 75.4 MHz) δ 175.9 (C), 156.5 (C), 138.4 (C), 129.4 (CH), 128.8 (CH), 128.6 (CH), 66.6 (CH_2), 52.4 (CH), 49.6 (CH), 33.4 (CH_2), 29.9 (CH_2), 25.5 (CH_2), 25.2 (CH_2); FAB-MS *m*/*z* calcd for $C_{15}H_{19}NO_4Na$ ($M + Na^+$) 300.1212, obsd 300.1221.

Compound 7. Dry CH_2Cl_2 (50 mL) was added to **6** (prepared according to ref 8; 2.2 g, 6.7 mmol), and the resulting solution was cooled to 0 °C. To this solution was added Et_3N (2.2 mL, 16 mmol) and then MsCl (1.3 mL, 16 mmol), and the resulting solution was stirred for 15 min at 0 °C, under N_2. In a separate flask, tetrabutylammonium azide (2.9 g, 10 mmol) was dissolved in CH_2Cl_2 (10 mL); this solution was added via cannula to the solution of mesylate. The resulting solution was stirred at 0 °C under N_2 for 1.5 h. To the solution was added P(*n*-Bu)$_3$ (5 mL, 20 mmol), followed by water (0.4 mL). The resulting solution warmed to room temperature and stirred under N_2 for 10 h. To this solution was added Boc_2O (4.4 g, 20 mmol), and the resulting solution was stirred open to air for 24 h. The solvent was removed on a rotary evaporator, 2:1 hexane/ethyl acetate (200 mL) was added, and the white solid that precipitated was collected by suction filtration. The filtrate was concentrated to obtain a yellow liquid that contained the product. The product was purified by SiO_2 column chromatography, eluting with 2:1 hexane/ethyl acetate. The fractions containing the product were collected and concentrated to afford 1.1 g of white solid. This material was recrystallized from *n*-heptane/benzene to afford 1.0 g (88% yield) of **7** as a white solid: mp 97−100 °C; $[\alpha]^{23}_D = -140.4$ (*c* 1.2, $CHCl_3$); IR (KBr) 3355 (NH), 1734 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.28 (m, 5H), 5.76 (*AB* quartet, $J = 10.5$ Hz, 1H), 5.72 (A*B* quartet, $J = 10.5$ Hz, 1H), 5.47 (br d, $J = 10$ Hz, 1H), 5.08 (s, 2H), 4.59 (m, 2H), 4.22 (m, 1H), 3.65 (s, 3H), 3.00 (m, 1H), 2.28 (ddd, $J = 14$, 8.5, 6 Hz, 1H), 1.83 (ddd, $J = 14$, 7, 3 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.9 (C), 155.8 (C), 155.0 (C), 136.3 (C), 130.2 (CH), 129.7 (CH), 128.5 (CH), 128.0 (CH), 79.7 (C), 66.8 (CH_2), 52.0 (CH_3), 46.8 (CH), 44.0 (CH), 41.8 (CH), 29.9 (CH_2), 28.3 (CH_3); EI-MS *m*/*z* ($M^+ - C_4H_9$) calcd for $C_{17}H_{20}N_2O_6$ 348.1321, obsd 348.1329; FAB-MS *m*/*z* 405.2 ($M + H^+$), 349.1 ($M + H^+ - C_4H_9$), 305.1 ($M + H^+ -$ Boc).

Compound 8. To a solution of **7** (1.1 g, 2.6 mmol) in methanol (25 mL) was added 10% Pd−C (0.24 g). The resulting mixture was shaken under H_2 (40 psi) for 12 h. The reaction was monitored by TLC (1:1 hexane/ethyl acetate). The reaction was judged to be complete when a single spot was observed at the origin of the TLC plate. If the reaction was not complete after 12 h, additional 10% Pd−C (0.05 to 0.1 g) was added, and the mixture was shaken for an additional 12 h. After the reaction was complete, the mixture was filtered through a plug of glass wool, and the filtrate was concentrated to obtain a thick oil. The oil was dissolved in CH_2Cl_2 (30 mL), and DIEA (1.9 mL, 6.2 mmol) was added, followed by benzylchloroformate (0.6 mL, 4.2 mmol) and DMAP (10 mg, 0.08 mmol). The resulting solution was stirred for 27 h; during this time the solution became orange. The solvent was removed on a rotary evaporator, methanol was added, and a white solid precipitated. The precipitate was collected by suction filtration to afford 0.78 g (74% yield) of **8** as a white solid that appeared to be pure by NMR. This material could be recrystallized from methanol without obvious improvement in purity: mp 184−185 °C, $[\alpha]^{23}_D = 5.0$ (*c* 1, $CHCl_3$); IR (KBr) 3357 (NH), 1730 (C═O), 1720 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.29 (m, 5H), 5.71 (br d, $J = 9$ Hz, 1H), 5.08 (s, 2H), 4.33 (br, 1H), 3.80 (tt, $J = 10$, 4.5 Hz, 1H), 3.72 (s, 3H), 3.46 (br, 1H), 2.95 (q, $J = 4.5$ Hz, 1H), 2.41 (br d, $J = 13$ Hz, 1H), 2.04−1.93 (m, 3H), 1.43 (s and m, 10H), 1.25 (qd, $J = 12$, 5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.6 (C), 155.7 (C), 155.0 (C), 136.5 (C), 128.5 (CH), 128.1 (CH), 79.4 (C), 66.7 (CH_2), 52.0 (CH_3), 49.7 (CH), 45.6 (CH), 43.5 (CH), 34.1 (CH_2), 31.7 (CH_2), 28.4 (CH_3), 27.8 (CH_2); EI-MS *m*/*z* ($M^+ + H^+$) calcd for $C_{21}H_{30}N_2O_6$ 406.2104, obsd 406.2105.

Compound 9. In a Schlenk flask outfitted with a condenser was placed **8** (0.69 g, 1.7 mmol), and this material was dried under vacuum overnight. Dry methanol (35 mL) was added to obtain a suspension. Sodium (0.2 g, 8.5 mmol) was placed into a separate flame-dried flask. The flask was cooled to 0 °C, and dry methanol (10 mL) was added. After the sodium dissolved, the NaOMe solution was added via cannula to the suspension of **8** in methanol. The resulting mixture was refluxed under N_2 for 5 h; the solution became clear soon after heating began. After the solution cooled to room temperature, 0.5 M aqueous NH_4Cl (45 mL) was added, and a white precipitate formed. The solid was collected by suction filtration, washed with additional water, and dried under vacuum. This material was recrystallized from methanol to afford 0.4 g (60% yield) of **9** as a white solid: mp 192−193 °C; $[\alpha]^{23}_D = 7.1$ (*c* 0.7, $CHCl_3$); IR (KBr) 3362 (NH), 3315 (NH), 1734 (C═O) $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.29 (m, 5H), 5.07 (s, 2H), 4.70 (br, 1H), 4.41 (br, 1H), 3.71 (m, 1H), 3.61 (s, 3H), 3.47 (br, 1H), 2.39 (td, $J = 12.5$, 4 Hz, 1H), 2.27−2.08 (m, 2H), 2.05−2.00 (m, 1H), 1.53−1.21 (m, 12H; includes large singlet at 1.43); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.1 (C), 155.5 (C), 155.1 (C), 136.5 (C), 128.5 (CH), 128.0 (CH), 79.5 (C), 66.7 (CH_2), 52.0 (CH_3), 51.2 (CH), 48.3 (CH), 47.9 (CH), 34.9 (CH_2), 31.5 (CH_2), 28.4 (CH_3); FAB-MS *m*/*z* 429.4 ($M + Na^+$), 373.3 ($M + Na^+ - C_4H_9$).

Compound 10. TFA (1.5 mL) was added to **9** (0.05 g, 0.13 mmol), and the resulting solution was stirred for 30 min. The solvent was removed under a stream of N_2, and the residue was dried under vacuum. The residue was dissolved in CH_2Cl_2 (10 mL), and DIEA (0.06 mL, 0.35 mmol) was added, followed by adamantylfluoroformate (0.03 g, 0.15 mmol) and DMAP (2 mg, 0.02 mmol). The resulting solution was stirred for 24 h. The solvent was removed on a rotary evaporator, and the product was purified by SiO_2 column chromatography eluting with 8:1 CH_2Cl_2/CH_3CN. The fractions containing the product were combined and concentrated to afford 0.05 g (84% yield) of white solid. The solid was dissolved in ethanol (4 mL), 10% Pd−C (0.01 g) was added, and the mixture was shaken under H_2 (40 psi) for 11 h. The mixture was the filtered through a plug of glass wool, and the filtrate was concentrated to obtain a white solid. The solid was dissolved in CH_2Cl_2 (5 mL), and DIEA (0.03 mL,

0.20 mmol) was added, followed by TsCl (0.04 g, 0.20 mmol) and DMAP (2 mg, 0.02 mmol). The resulting solution was stirred for 14 h. The solution was diluted with CH_2Cl_2 (30 mL) and washed with 1 N HCl. The organic layer was dried over $MgSO_4$, concentrated and dried under vacuum to obtain a yellow oil. This oil was purified by SiO_2 column chromatography, eluting with 6:1 CH_2Cl_2/ethyl acetate. The fractions containing the product were combined and concentrated to afford 0.02 g (61% yield from **9**) of clear oil. X-ray quality crystals of **10** were grown by vapor diffusion of 1:1 *n*-heptane/1,2-dichloroethane into a solution of **10** in 1,2-dichloroethane: mp 171−172 °C; IR (KBr) 3408 (NH), 3147 (NH), 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 4.67 (d, J = 7.5 Hz, 1H), 4.36 (br, 1H), 3.49−3.24 (m and s, 5H), 3.42 (s, 3H), 2.42 (s, 3H), 2.37 (td, J = 12, 3 Hz, 1H), 2.23−2.01 (m, 11H), 1.93 (m, 1H), 1.64 (m, 7H), 1.36 (q, J = 12 Hz, 2H), 1.18 (qd, J = 12, 3 Hz, 1H); FAB-MS m/z 527.2 ($M + Na^+$).

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Supporting Information Available: ^1H and ^{13}C NMR data (including DEPT-135) for compounds **3**−**10** and solid-state structure of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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