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An Efficient, Stereoselective Synthesis of the Hydroxyethylene Dipeptide Isostere Core for the HIV Protease Inhibitor A-792611

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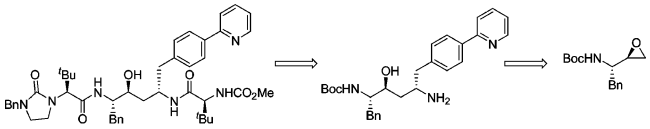
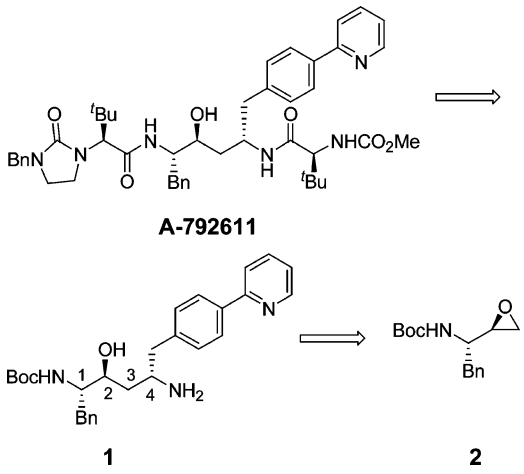


A stereoselective synthesis of the hydroxyethylene dipeptide isostere **1** is described. The route employs a substrate-directed kinetic protonation of an α/γ-substituted lactone to afford the desired stereochemistry. A method for converting the diastereomerically enriched intermediate lactone to the ring-open form with retention of stereochemistry is demonstrated. A novel procedure for utilizing *N*,*N*-dibromo-5,5-dimethylhydantoin in Hofmann rearrangements is disclosed. This route was used to prepare amino alcohol **1**, the core portion of the HIV protease inhibitor A-792611, in 46% yield from phenylalanine-derived epoxide **2**.

Drug cocktails of HIV protease inhibitors in combination with reverse transcriptase inhibitors have proven to be highly effective in halting the progression of HIV disease. HIV protease inhibitors are peptidomimetic structures, which contain nonhydrolyzable portions that bind to the protease enzyme and disable it from producing the proteins necessary for replication. Current combination treatments of protease inhibitors and reverse transcriptase inhibitors have been shown to reduce the viral load to below detectable levels for extended periods of time. Further research in the discovery of HIV protease inhibitors is directed toward the development of drugs with improved bioavailability, effectiveness toward resistant strains of the virus, and a reduction in side effects.[1] Work at Abbott Laboratories led to the identification of A-792611, a highly potent and selective HIV protease inhibitor, as a promising candidate to achieve these goals (Scheme 1).[2]

To support drug development efforts, we required a robust and efficient route to A-792611, the key to which would be the synthesis of the amino alcohol core **1**. Phenylalanine-derived epoxide **2** is an effective starting material to access hydroxyethylene dipeptide isosteres such as **1**, as it possesses the desired 1,2-*anti* stereochemistry and appropriate functionality for the introduction of the required carbon−carbon bond at C-3. However, the application of existing technology to make hydroxyethylene dipeptide isostere cores from epoxide **2** produced **1** in a 1.6:1 mixture of diastereomers at C-4.[2a,3] Our goal was to develop a diastereoselective synthesis of **1** that exploits the stereochemistry of epoxide **2**. Herein, we report the stereoselective preparation of **1** in 46% overall yield and 97:3 dr.

SCHEME 1



Lactone **5** was prepared from epoxide **2** by modified literature procedures.[2a,3] Thus, epoxide **2** is treated with diethylmalonate to give lactone **3** as a 1:1 mixture of C-3 epimers (Scheme 2). Alkylation of lactone **3** with 2-(α-bromotolyl)pyridine furnishes quaternary intermediate **4**. Ester hydrolysis is followed by pH adjustment with acetic acid, which after warming effects decarboxylation to provide lactone **5**. Based on literature precedent, it was not evident what mixture of C-3 stereoisomers would be obtained at this step.[3,5c] We were pleased to find that **5** is formed in a 5:1 diastereomeric ratio favoring the desired C-3 epimer, as indicated by HPLC analysis of the crude reaction mixture.[4,5] We were able to enhance the 5:1 dr by recrystallization from acetonitrile/water to afford **5** in 97:3 dr with greater than 95% recovery of the desired diastereomer.

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(4) Samples of each diastereomer were isolated by flash column chromatography and the relative stereochemistry was assigned by 2D NMR experiments; see the Supporting Information for details.

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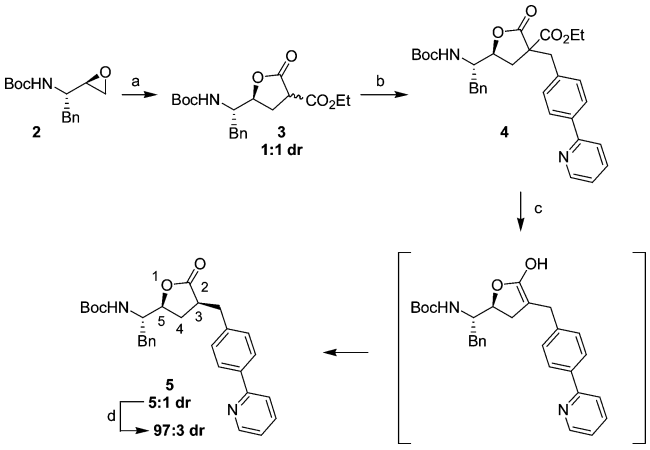
SCHEME 2[a]



[a] Reagents and conditions: (a) diethyl malonate, NaOEt, EtOH, 0 °C, 78%; (b) 2-(α-bromotolyl)pyridine, NaOEt, EtOH, 0 °C; (c) (i) LiOH·H_2O, (ii) AcOH, 60 °C, 82% from **3**; (d) recrystallization from 1:1 acetonitrile/H_2O, 75−35 °C, 95% recovery of *syn*-isomer.

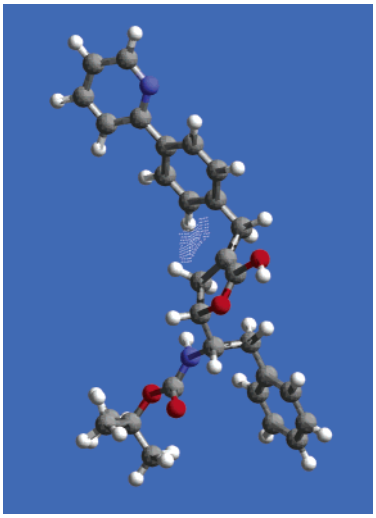


FIGURE 1. Enol surface accessibility.

The diastereoselective step of this process is the protonation of the enol produced by decarboxylation (Scheme 2).[6] Cerius[2] molecular mechanics modeling of the enol intermediate shows that in the lowest energy conformation the *si*-face of the enol is shielded by the C-5 substituent (Figure 1). Surface accessibility of this conformation was determined by the Connolly method with a 1.4 Å probe radius. Points at which a 1.4 Å sphere is able to approach C-3 on either face of the enol double bond are illustrated by white dots. The results indicate that in the lowest energy conformation, the *re*-face is the only available surface for electrophilic attack. This is consistent with the formation of the 3*R* isomer as the predominant kinetic product, as is observed.

Existing procedures for the conversion of lactones such as **5** to amino alcohols employ a basic hydrolysis reaction to obtain the corresponding acid−alcohol (Scheme 3).[2a,3,7] Our optimized conditions for this transformation were to treat **5** with a minimal amount of LiOH·H_2O in NMP. Care was taken in this step to minimize the reaction time, as the resulting acid-alcohol **6** decomposed to form the carbamate byproduct **7** as the reaction approached completion. Acid−alcohol **6** undergoes facile lactonization under neutral to acidic conditions and therefore had to be trapped in situ with excess TBSCl to afford **8**. ^{1}H NMR analysis of the crude reaction mixture after TBS protection indicated that the diastereomeric ratio had deteriorated from 5:1 to 1.6:1;[8] the epimerization presumably occurred during the basic hydrolysis reaction. Intermediate **8** was converted to Cbz-protected alcohol **9** via a Curtius rearrangement. Product **9** was also obtained in a 1.6:1 mixture of diastereomers. As Curtius rearrangements are known to proceed with retention of stereochemistry, this result further supports the LiOH-mediated epimerization of lactone **5**.

We sought an alternative method for the opening of the lactone ring that would retain the stereochemistry of lactone **5**. Ideally, ammonolysis would afford the corresponding primary amide, which after protection and Hofmann degradation would directly give amino alcohol **1**. Treatment of **5** with either ammonium hydroxide or with 7 M ammonia/methanol afforded poor conversion to the desired amide product. Ammonolysis in neat ammonia, however, cleanly produces amide product **10** as a crystalline solid in 96% yield and with little to no epimerization (Scheme 4).[9] Treatment of amide **10** with 2.5 equiv of triethylsilyl chloride in NMP provides substrate **11** for the Hofmann degradation reaction.

The use of NaOH/Br_2 effected the desired Hofmann degradation in reasonable, though somewhat variable yields. This prompted us to investigate alternative procedures. *N*-Bromosuccinimide has successfully been employed in Hofmann reactions to produce carbamates under anhydrous conditions. However, the reactivity of NBS with hydroxide complicates the use of this reagent in the aqueous reaction conditions employed to produce primary amine products.[10] We turned our attention to the use of *N*,*N*-dibromo-5,5-dimethylhydantoin (DBH, **12**), a commodity chemical comparably priced to Br_2, as an oxidant. While DBH has been used as an electrophilic brominating reagent for aromatic rings, alkenes, and ketones, we have not found precedent for its use in Hofmann reactions. The advantage of working with this crystalline, nontoxic reagent is that it can be easily weighed out and does not require special handling

(5) For alternate diastereoselective routes to α/γ-substituted lactones, see: (a) Haug, B. E.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4783−4786. (b) Brewer, M.; James, C. A.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4779−4782. (c) Nadin, A.; Sánchez López J. M.; Neduvelil, J. G.; Thomas, S. R. *Tetrahedron* **2001**, *57*, 1861−1864. (d) Ghosh, A. K.; Fidanze, S. *J. Org. Chem.* **1998**, *63*, 6146−6152. (e) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654. (f) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 351−352. (g) Ghosh, A. K.; McKee, S. P.; Thompson, W. J.; Darke, P. L.; Zugay, J. C. *J. Org. Chem.* **1993**, *58*, 1025−1029. (h) Kano, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1991**, *32*, 233−236. (i) Ghosh, A. K.; McKee, S. P.; Thompson. W. J. *J. Org. Chem.* **1991**, *56*, 6500−6503. (j) Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803−1806.

(6) For a discussion of stereoselective kintetic protonation of enolates, see: (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268. (b) Takano, S., Kudo, J., Takahashi, M., Ogasawara, K. *Tetrahedron Lett.* **1986**, *27*, 2405−2408. (c) Baker, W. R., Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739−8756.

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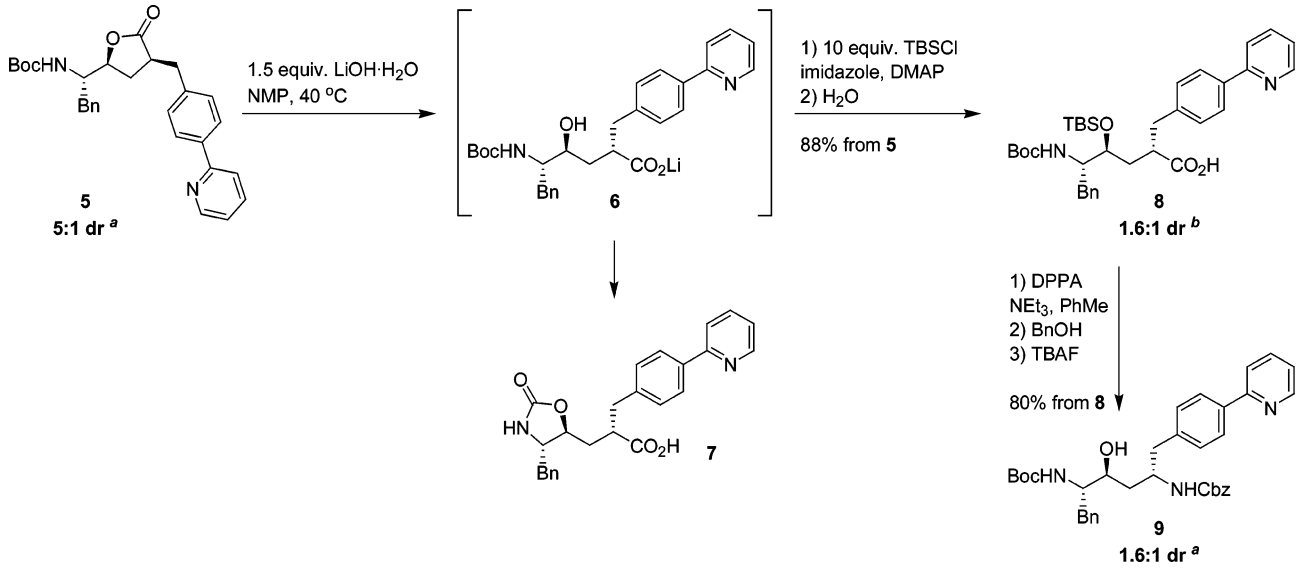
(8) ^{1}H NMR in DMSO-d_6 at 107 °C. Boc-peaks coalesced to two sharp peaks at 0.93 and 0.91 ppm.

(9) Amide **10** slowly converts back to lactone **5** in protic solvents such as methanol but is stable in the solid form and in aprotic solvents. The ammonolysis reaction was run in DME to afford **10** as a slurry without an increase in reaction time.

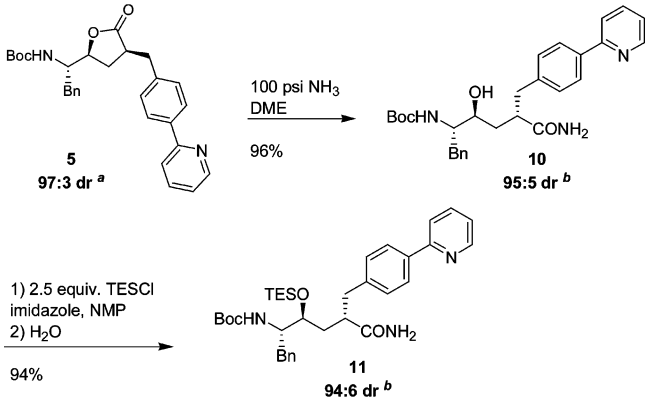
(10) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, R. A.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 7947−7948.

SCHEME 3



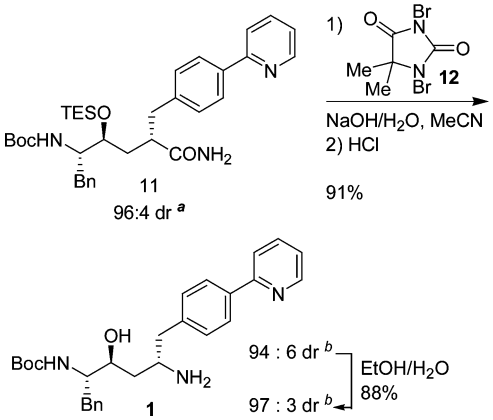
[a] Molar ratio as determined by HPLC assay vs external standards. [b]As determined by ^{1}H NMR analysis.

SCHEME 4



[a] Molar ratio as determined by HPLC assay vs external standards. [b] Ratio of HPLC peak area percents at 200 nm.

SCHEME 5



[a] Ratio of HPLC peak area percents at 200 nm. [b] Molar ratio as determined by HPLC assay vs external standards.

precautions. Additionally, given that there are two reactive bromines per molecule, substoichiometric quantities may be employed, and the water-soluble des-bromohydantoin byproduct is easily separated from the organic product.

We found that treatment of amide **11** with 0.6 equiv of DBH in a 1:2 mixture of 1 M NaOH/acetonitrile cleanly affords the TES-protected amine product (Scheme 5).[11] The reaction mixture is adjusted to pH 2−3 with HCl to cleave the silyl ether. After an aqueous workup, an HPLC assay of the crude product solution shows that the desired product **1** is obtained in a 91% two-step yield with a 94:6 dr. Recrystallization of the crude product from EtOH/H_2O gives **1** in 88% isolated yield and 97:3 dr. The diatereomeric ratio is further enriched by subsequent recrystallizations in the synthetic sequence. This five-step sequence from lactone **5** affords **1** in a 75% yield with high diastereomeric purity.

In summary, an efficient procedure for the preparation of the amino alcohol core **1** in high diastereomeric purity from epoxide **2** was developed. The route features a substrate directed kinetic enol protonation of a α/γ-substituted lactone to afford the desired C3-stereochemistry. A mild method for the conversion of diastereomerically enriched lactone **5** to the ring-open form with retention of stereochemistry was demonstrated. *N*,*N*-Dibromo-5,5-dimethylhydantoin was utilized as a novel reagent for Hofmann rearrangements, offering advantages over existing reagents in terms of safety, convenience, and reproducibility. This route affords amino alcohol **1** in 97:3 dr and in 46% yield from epoxide **2**.

(11) The scope and mechanism of the use of *N*,*N*-dibromo-5,5-dimethylhydantoin for Hofmann reactions is under investigation.

Experimental Section

{1-[5-Oxo-4-(4-pyridin-2-ylbenzyl)tetrahydrofuran-2-yl]-2-phenylethyl}carbamic Acid *tert*-Butyl Ester (5). A 22 L Morton flask was charged with **3** (1.0 kg, 2.65 mol, 1.0 equiv), 2-(α-bromotolyl)pyridine (658 g, 2.65 mol, 1.0 equiv), and EtOH (200 proof, 8.4 L). The contents of the flask were mixed for 15 min and cooled to 0 °C. A solution of NaOEt (95%, 190 g, 2.65 mol, 1.0 equiv) in EtOH (200 proof, 1.7 L) was added over 2 h, maintaining an internal temperature of <5 °C. The reaction mixture was stirred at 5 °C until the starting materials were consumed, as determined

by HPLC analysis (3 h). LiOH·H_2O (539 g, 12.8 mol, 4.8 equiv) was added portionwise over ~5 min, and the mixture was stirred for 2 h. Acetic acid (770 g, 12.8 mol) was added, and the reaction mixture was heated to 60 °C for 16 h to effect the decarboxylation. The resulting slurry was diluted with water (10 L), maintaining an internal temperature of 50 °C. The suspension was cooled to room temperature over 3 h and then filtered. The filter cake was washed with a 1:1 mixture of EtOH/H_2O (5.0 L) and heptane (5.0 L) and then dried under vacuum at 55 °C with a N_2 bleed. The desired product was obtained as a white crystalline solid (1.130 kg, 88.9:11.1 3*R*/3*S* isomers). The product was suspended in 1:1 MeCN/H_2O (22.6 L) and heated to 75 °C for 1 h. The slurry was cooled to 35 °C over 5 h and filtered. The filter cake was washed with 1:1 MeCN/H_2O (4.5 L), heptane (4.5 L), and dried under vacuum at 55 °C with a N_2 bleed for 1.5 days. The desired product was obtained as a white solid (1.060 kg, 97.5:2.5 3*R*/3*S* isomers, 84%). The dr was determined by normal-phase HPLC analysis: YMC-Pack, silica, 250 × 4.6 mm, 5 μm particle size, observing at 215 nm, 10 μm injection volume. Mobile phase: 10% IPA/hexane, isocratic method, 7 min run time. (3*R*)-Isomer elutes at 5.25 min; (3*S*)-isomer elutes at 6.05 min: mp 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.77−1.90 (m, 1H), 2.11 (ddd, J = 12.97, 8.64, 5.97 Hz, 1 H), 2.73 (dd, J = 13.86−9.88 Hz, 1 H), 2.79−3.02 (m, 3H), 3.32 (dd, J = 13.86, 3.84 Hz, 1 H), 3.95 (q, J = 8.42, 1H), 4.32 (ddd, J = 10.15, 5.97, 1.58, 1H), 4.61 (d, J = 9.74 Hz, 1H), 7.15−7.3 (m, 8H), 7.64−7.75 (m, 2H), 7.90 (ddd, J = 8.37, 2.06, 1.97 Hz, 2H), 8.85 (ddd, J = 4.77, 1.75, 1.03 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 30.8, 36.2, 39.5, 42.6, 53.3, 77.7, 79.8, 120.0, 121.7, 126.4, 126.9, 128.3, 128.8, 129.0, 136.3, 136.8, 137.5, 138.9, 149.2, 155.3, 156.5, 177.2; MS-ESI 473 (M + 1); $[\alpha]^{25}_D$ = +75.44 (*c* 0.98, $CHCl_3$).

[(1*S*,2*S*,4*S*)-1-Benzyl-4-carbamoyl-2-hydroxy-5-(4-pyridin-2-ylphenyl)pentyl]carbamic Acid *tert*-Butyl Ester (10). A stainless steel bomb was charged with lactone **5** (38 g, 80.4 mmol, 1.0 equiv), DME (380 mL, 0.2 M), and ammonia (380 mL, 133 psi) and stirred at ambient temperature for 48 h. The reaction vessel was carefully vented; the desired product was obtained as a slurry in DME. The product solution was dissolved in NMP (380 mL, 0.2 M), and the residual ammonia and DME were removed by distillation. An HPLC assay of the crude reaction mixture vs an external standard showed the product was formed in 95.4% yield (37.55 g) in a 94.6:5.4 dr (HPLC area % at 220 nm), with 4.7 mol % residual starting material (**5**). The crude product mixture was used in the next step without further purification. Crystalline **10** was obtained by filtration of the DME slurry and drying the resulting wet cake at 50 °C, 20 mmHg (76% isolated yield, 19% loss to DME liquors): mp 163 °C; ^{1}H NMR (400 MHz, DMSO-d_6, rotamers) δ 1.30 (br s, 1.0 H), 1.27 (br s, 1.1 H), 1.29 (br s, 6.9 H), 1.41−1.52 (m, 1 H), 1.64 (ddd, J = 13.86, 7.34, 7.07 Hz, 1 H), 2.58−2.81 (m, 5 H), 3.49−3.57 (m, 1 H), 3.74 (ddd, J = 14.41, 9.19, 2.33 Hz, 1 H), 4.58 (d, J = 6.31 Hz, 1 H), 5.81 (d, J = 9.74 Hz, 0.1 H), 6.31−6.39 (m, 0.9 H), 6.60−6.77 (m, 1 H), 7.10−7.28 (m, 7 H), 7.30 (ddd, J = 7.20, 4.87, 1.10 Hz, 1 H), 7.80−7.99 (m, 4 H), 8.60−8.65 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.2, 36.2, 36.7, 37.6, 43.6, 55.0, 68.9, 77.2, 119.4, 121.9, 125.2, 125.6, 127.4, 128.6, 128.7, 135.7, 136.5, 139.0, 140.6, 148.8, 154.7, 154.8, 155.3, 175.7; $[\alpha]^{25}_D$ = −30.44 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{29}H_{35}N_3O_4$: C, 71.14; H, 7.21; N, 8.58. Found: C, 70.98; H, 6.99; N, 8.53.

[(1*S*,2*S*,4*S*)-1-Benzyl-4-carbamoyl-5-(4-pyridin-2-ylphenyl)-2-triethylsilanyloxypentyl]carbamic Acid *tert*-Butyl Ester (11). Imidazole (22.5 g, 331.0 mmol, 5.0 equiv) was added to the crude NMP solution of **10** (32.4 g, 66.2 mmol, 1.0 equiv), triethylsilyl chloride was added (27.8 mL, 165.5 mmol, 2.5 equiv), and the reaction solution was stirred at ambient temperature until **10** was consumed, as determined by HPLC analysis (1 h). H_2O (150 mL) was added, and the solution was allowed to stir for an additional 15 min. An addition 150 mL of H_2O was added, and then the crude reaction mixture was extracted with MTBE (300 mL). The aqueous layer was extracted with MTBE (150 mL), and the combined organic layers were then washed with H_2O (3 × 150 mL). The organic layer was chase distilled with MeCN (3 × 100 mL), redissolved in 200 mL of MeCN, and used in the next step without further purification. An HPLC assay of the MeCN product solution showed the product was formed in 95.3% yield (42.97 g) in a 94.1:5.9 dr (HPLC area % at 220 nm). Analytically pure material was obtained by column chromatography for use as an external standard (50% EtOAc/hexane with 1% v/v NEt_3, R_f = 0.25): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64−0.70 (m, 6 H), 0.95−1.03 (m, 9 H), 1.28 (s, 1 H), 1.37 (s, 8 H), 1.64 (ddd, J = 13.41, 10.33, 3.57 Hz, 1 H), 1.88−1.97 (m, 1 H), 2.45−2.56 (m, 1 H), 2.65−2.90 (m, 4 H), 3.73 (dd, J = 10.09, 3.77 Hz, 1 H), 3.86−3.94 (m, 1 H), 4.79−4.95 (m, 3 H), 7.11−7.27 (m, 8 H), 7.64−7.76 (m, 2 H), 7.86 (d, J = 8.10 Hz, 2 H), 8.65 (ddd, J = 4.84, 1.68, 0.89 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.6, 7.4, 28.6, 37.7, 39.6, 40.1, 44.9, 54.0, 70.5, 79.2, 120.0, 121.6, 126.0, 126.7, 128.0, 128.9, 129.0, 136.3, 137.2, 138.4, 139.8, 149.2, 155.5, 156.8, 175.5; $[\alpha]^{25}_D$ = +9.12 (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{35}H_{49}N_3O_4Si$: C, 69.61; H, 8.18; N, 6.96. Found: C, 69.26; H, 8.28; N, 6.86.

[(1*S*,2*S*,4*S*)-4-Amino-1-benzyl-2-hydroxy-5-(4-pyridin-2-ylphenyl)pentyl]carbamic Acid *tert*-Butyl Ester (1). The crude MeCN solution of **11** was diluted to 0.16 M with additional MeCN (152 mL). *N*,*N*-Dibromo-5,5-dimethylhydantoin (**12**) (9.6 g, 33.7 mmol, 0.6 equiv) was added; the suspension was stirred until it became homogeneous. A 1 M NaOH solution (339 mL, 339 mmol, 6.0 equiv) was then added, and the resulting biphasic solution was stirred at ambient temperature until the reaction was complete as determined by HPLC analysis (30 min). The reaction was then adjusted to pH 2−3 with HCl (37 wt % in H_2O, 31.7 mL, 392.7 mmol, 7.0 equiv) and stirred until the TES-deprotection was complete (4 h). The crude reaction mixture was extracted with MTBE (150 mL) to remove the silyl byproducts. EtOAc (300 mL) was added to the aqueous layer, followed by 2 M NaOH (84 mL, 168 mmol, 3.0 equiv) to achieve a pH of 9−10. The layers were separated, and the aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with a 10 wt % NaCl solution (3 × 150 mL). The organic solution was chase distilled with EtOH (300 mL) and then dissolved in EtOH (130 mL). A HPLC assay of the EtOH solution vs an external standard shows a 91.2% crude assay yield (22.1 g of 1,3-trans product **1**, 1.53 g of 1,3-cis product, 93.5:6.5 dr). The EtOH solution was heated to 70 °C and H_2O (195 mL, 1.5:1 H_2O/EtOH) was added dropwise, during which time the crystallization nucleated. The suspension was held at 70 °C for 2 h and then cooled to ambient temperature at 10 °C/h. The product was then filtered and dried at 50 °C, 20 mmHg. The desired product was obtained in 87.8% yield (24.06 g, 97:3 dr): mp 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34−1.60 (m, 11 h), 2.46 (dd, J = 13.52 Hz, 1H), 2.79−2.92 (m, 3 H), 3.00−3.11 (br s, 1 H), 3.49 (m, 1 H), 3.66 (q, J = 8.05 Hz, 1 H), 3.79 (d, J = 10.43 Hz, 1 H), 4.89 (br s, 1 H), 5.08 (d, J = 9.47 Hz, 1 H), 7.12−7.23 (m, 4 H), 7.24−7.31 (m, 4 H), 7.65−7.76 (m, 2 H), 7.84−7.94 (m, 2 H), 8.66 (ddd, J = 4.77, 1.68, 0.96 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.7, 39.0, 39.5, 47.2, 54.1, 56.4, 71.4, 78.9, 120.1, 121.8, 125.8, 126.8, 128.0, 129.3, 129.4, 136.4, 137.5, 138.4(8), 138.5(4), 149.3, 155.5, 156.6; $[\alpha]^{25}_D$ = +4.96 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{28}H_{35}N_3O_3$: C, 72.86; H, 7.64; N, 9.10. Found: C, 72.70; H, 7.96; N, 9.11.

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Supporting Information Available: Analytical methods, experimental procedures for the preparation of **3**, and 2D NMR data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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