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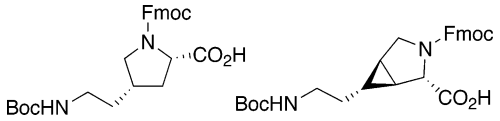
Synthesis of Conformationally Constrained Lysine Analogues

Rakesh Ganorkar, Amarnath Natarajan, Ahmed Mamai, and José S. Madalengoitia*

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

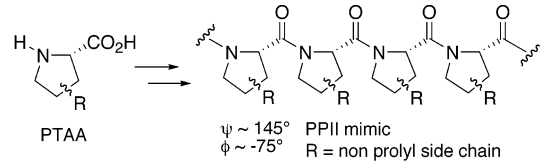
jmadalen@uvm.edu

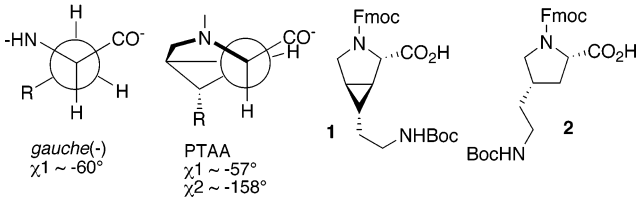
Received January 31, 2006



The synthesis of two conformationally constrained lysine analogues is reported. The synthesis of the novel analogue **1** based on the 3-aza-bicyclo[3.1.0]hexane system is accomplished from the known tricycle **3** in eight steps. The synthesis of the analogue **2** is accomplished in eight steps from 4-hydroxy proline. Both analogues are synthesized appropriately protected for Fmoc/Boc solid-phase peptide synthesis.

The poly-L-proline (PPII) secondary structure has received much attention in the past decade because of its role in mediating a number of signal transduction pathways.[1−3] Within this context, our group has been developing a program focused on the design and synthesis of PPII mimics as inhibitors of these signaling pathways. Our strategy for the construction of PPII mimics involves first the synthesis of peptides from what we call proline-templated amino acids (PTAAs) and then the synthesis of peptides from PTAAs. OligoPTAAs are designed to preferentially populate the PPII conformation in solution because ϕ is constrained $\sim -75°$ by the pyrrolidine ring and ψ is constrained $\sim 145°$ by the pseudo-A(1,3) strain. The utility of these PPII mimics is highlighted by a recent report from our group that uses oligoPTAAs to provide compelling evidence that cGMP-dependent protein kinase (PKG) binds peptide substrates in the PPII conformation.[4] In this paper, we report the synthesis of two lysine PTAA analogues (**1** and **2**), one of which (**1**) was critical to probe the active-site occupancy requirements of PKG. The lysine PTAA analogue **1** is designed to mimic a gauche(−) $\chi 1$ angle, whereas the analogue **2** roughly mimics a gauche(+) $\chi 1$ angle.





We envisioned that the synthesis of the lysine analogue **1** could be accomplished from the tricycle **3**, available in six steps from pyroglutamic acid in multigram quantities.[5] The ester functionality is selectively reduced with $LiEt_3BH$ at −78 °C affording the alcohol **4** in 84% yield (Scheme 1). The corresponding aldehyde **5** was also isolated in small amounts (∼5%, even with 6 equiv of $LiEt_3BH$).[6] We next explored the Mitsunobu reaction of the alcohol **4** with "HCN" as a means to introduce what would eventually become both the ϵ-carbon and the side-chain nitrogen. However, when alcohol **2** was subjected to Mitsunobu conditions using acetone cyanohydrin as the cyanide source, the major product isolated was the reduced DEAD adduct **6**.[7] Further attempts to modify the conditions were unsuccessful in furnishing the desired nitrile. Because the direct conversion of the alcohol to the nitrile proved elusive, we next explored the two-step process in which the alcohol could be converted to a suitable leaving group and then displaced with cyanide. Attempts to generate the tosylate with 1.1 equiv of TsCl and 1.1 equiv of Et_3N in CH_2Cl_2 at room temperature resulted in mixtures of the desired tosylate, the chloride **7**, and recovered starting material.[8] Not surprisingly, shorter reaction times resulted in the recovery of large amounts of starting material, and longer reaction times favored the production of the chloride. Unfortunately, the chloride could not be displaced by cyanide under a number of conditions examined. The chloride to nitrile transformation could be effected by first converting the chloride to an iodide (NaI, acetone) and then displacing the iodide with Bu_4NCN in an overall yield of 75% (data not shown). Because this procedure added an extra step, additional avenues into the nitrile were explored. We found that the mesylation of alcohol **4** with MsCl proceeds smoothly to yield the mesylate **8** (70%) as well as the chloride **7** (10−15%, Scheme 1), which was easily separable by flash chromatography. The introduction of the nitrile function was next explored. Although the reaction of mesylates with NaCN in DMSO represents a standard method for the synthesis of nitriles,[9] in

(1) For a PPII review, see: Siligardi, G.; Drake, A. F. *Pept. Sci.* **1995**, *37*, 281.

(2) For a survey of PPII helices in globular proteins, see: Adzhubei, A. A.; Sternberg, M. J. *J. Mol. Biol.* **1992**, *229*, 472.

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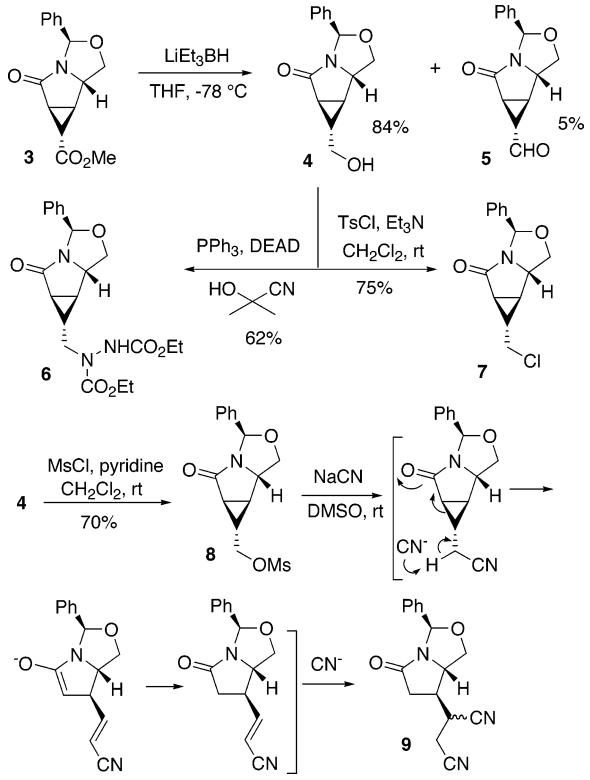
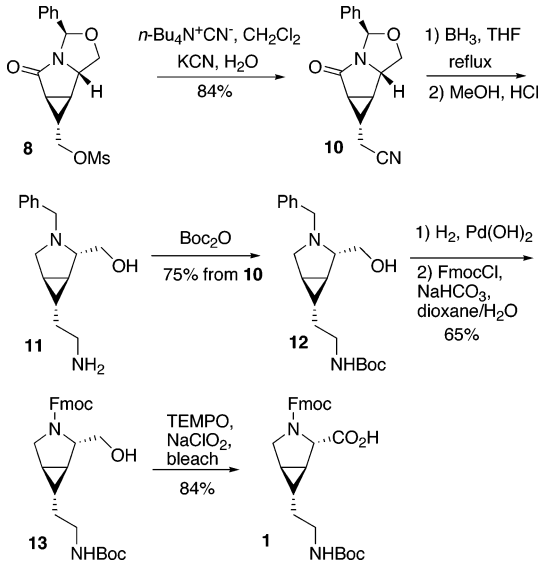
10.1021/jo060210f CCC: $33.50
Published on Web 06/02/2006

SCHEME 1



SCHEME 2



our system, the use of a stoichiometric amount of NaCN resulted in a mixture of products and the use of an excess of NaCN resulted in the isolation of compounds **9** as a 1:1 mixture of diastereomers. The formation of diastereomers **9** suggests that the naked anion is basic enough to deprotonate α to the nitrile promoting a retro-Michael ring opening to give, after protonation of the enolate, the α,*β*-unsaturated nitrile. Under the reaction conditions, cyanide then adds to the α,*β*-unsaturated nitrile in a Michael fashion affording the dinitrile compounds **9** as an approximate 1:1 mixture of diastereomers.

The incorporation of the final carbon and nitrogen was accomplished by the use of 0.3 equiv of Bu_4NCN in CH_2Cl_2/saturated aqueous KCN to give the nitrile **10**. Under these conditions, the dinitrile compounds do not form because the CN^- concentration is lower and the ionic association with the ammonium cation most likely attenuates the basicity of the cyanide anion (in contrast to the "naked" cyanide anion in DMSO). With the final carbon and nitrogen in place, the structure was elaborated to the desired PTAA. Complete reduction of the functionality in nitrile, amide, and oxazolidine functionality was accomplished with 3.5 equiv of BH_3 in refluxing THF to give the amino alcohol **11**.[10] The crude amine was then *N*-Boc protected with Boc_2O to give the prolinol **12** in 75% yield for both steps. Interestingly, N-debenzylation failed to proceed under standard conditions (H_2, Pd−C) or under other conditions (NH_4HCO_2H, Pd−C, MeOH, reflux) that had previously worked for us with troublesome N-debenzylations. In this instance, however, N-debenzylation was effected with H_2 and Pearlman's catalyst in methanol. The resultant secondary amine was protected with FmocCl to yield the alcohol **13** in 65% yield over both steps. Finally, the alcohol was oxidized to the carboxylic acid with TEMPO/NaOCl/$NaOCl_2$ to give the novel lysine PTAA **1** in 84% yield suitably protected for Fmoc/Boc solid-phase peptide synthesis.[11]

The synthesis of an analogue of 2,4-*cis*-lysine PTAA **2** (the *N*,*N*′-diBoc analogue) has been previously reported in the literature in 18 steps,[12] and during the preparation of this manuscript, a synthesis of the unprotected isomer by a route similar to ours was published.[13] We had originally envisioned that a short synthesis could be adapted starting from 4-hydroxy proline as the 4-position was appropriately functionalized for further elaboration into the lysine side-chain functionality. Protection of the α-nitrogen with CbzCl afforded the carbamate **15** in 99% yield. Protection of the carboxylic acid group was accomplished with BnBr and $NaHCO_3$ in DMF with a catalytic amount of NaI to give the benzyl ester **16** in 80% yield. Oxidation of the hydroxyl group was accomplished with trifluoroacetic anhydride, DMSO, and Et_3N to give the ketone **17** in 82% yield (Caution! Stench). To functionalize the 4-position with the desired two carbons and a nitrogen, we carried out a stabilized Wittig reaction that afforded the conjugated nitriles **18a** as a mixture of *cis*/*trans*-alkene isomers and the unconjugated nitrile **18b** as a 60:40 (**18a**/**18b**) mixture in 89% overall yield. The assignment is based in part on the nitrile stretching frequencies. The isomers **18a** exhibit an IR band at 2221 cm^{-1} consistent with a conjugated nitrile, whereas the isomer **18b** exhibits an IR band at 2254 cm^{-1} consistent with an unconjugated nitrile. In McCafferty's synthesis, an *N*-Boc-4-keto proline methyl ester is subjected to an analogous Wittig reaction under conditions that are essentially the same as ours, but only the presence of cis/trans isomers is reported. From an examination of their data, we suspect that the compound they assign as the *Z*-nitrile might indeed be the isomers with the exocyclic double bond because the reported IR band is at 2221 cm^{-1}. It is also possible that the isomer assigned as the *E*-nitrile could be the isomer with the endocyclic double bond because the reported IR frequency is 2251 cm^{-1}

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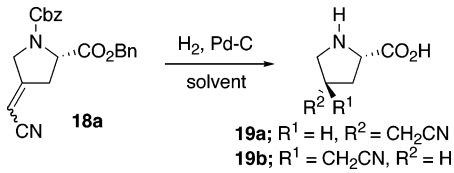
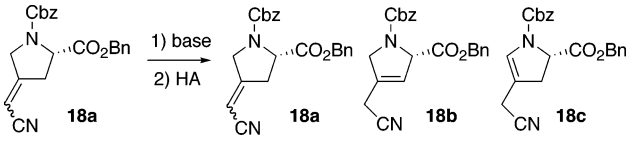
TABLE 1. Solvent Effects on the Diastereomer Ratio for the Hydrogenation of Nitrile 18a



solvent	**19b/19a**
EtOAc	1:0.4
EtOH	1:1
AcOH	1:1
i-PrOH	1:1.7
EtOH/H_2O (1:1)	1:2.4
H_2O	1:2.5

TABLE 2. Isomerization Experiments



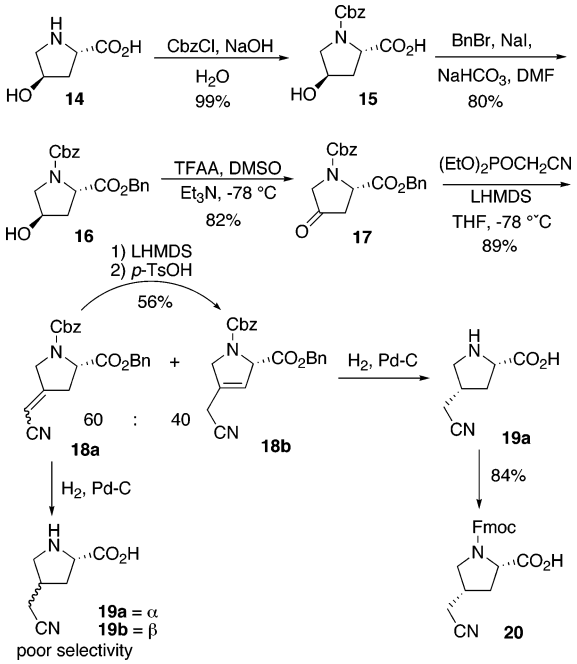
entry	base	HA	**18a/18b/18c**	conditions	% yield (**18b**)
1	LDA	AcOH	1.4:1:0.35	a[a]	20
2	LDA	TFA	0.8:1:0.23	a	25
3	LHMDS	*p*-TsOH	0.55:1:0.23	a	44
4	LHMDS	TfOH	0.4:1:0.17	a	39
5	LHMDS	*p*-TsOH	0.28:1:0.09	b[b]	56

[a] Condition a: 1.1 equiv of base is added to a solution of **18a** at −78 °C. After 30 min, this solution is transferred via cannula to a THF solution containing 2 equiv of acid at −78 °C. The reaction mixture is then allowed to warm to room temperature and quenched with water. [b] Condition b: 1.1 equiv of base is added to a solution of **18a** at −78 °C. After 30 min, this solution is transferred via cannula to a THF solution containing 2 equiv of acid at −78 °C. The reaction mixture is quenched with water and then allowed to warm to room temperature.

(**18b** exhibits an IR band at 2254 cm^{-1}). In addition, the alkene resonance is reported at 5.78−5.82 ppm, and the alkene resonance of **18b** appears at 5.74 ppm. In the McCafferty synthesis, the alkene isomers are hydrogenated to give a mixture of the 2,4-cis and 2,4-trans isomers. It has been our experience that similar compounds are not readily separable by flash chromatography (data not shown). Thus, to obtain a practical synthesis of this PTAA, we next explored conditions for the stereoselective reduction of the double bond with concomitant hydrogenolysis of the benzyl and Cbz groups in **18a**. Table 1 displays some of these results in which a clear solvent preference was noted. However, under none of the conditions explored did we obtain acceptable levels of diastereoselectivity. In contrast, when the nitrile **18b** was subjected to hydrogenation conditions, it cleanly afforded the 2,4-cis diastereomer **19a** with no detectable 2,4-trans diastereomer **19b**.

As the quick completion of the synthesis appeared possible from the nitrile **18b**, the isomerization of the α,*β*-unsaturated nitrile **18a** to the *β*,*γ*-unsaturated nitrile **18b** was explored (Table 2). Surprisingly, when the nitrile **18a** was enolized with LDA and kinetically protonated with AcOH, it afforded a 1.4:1:0.35 mixture of isomers (**18a**−**c**) in which the majority of products arose from α-protonation.[14] To optimize conditions, we investigated quenching with different acids and noticed that the ratio of the desired isomer increased with the acidity of the quenching acid (TfOH > *p*-TsOH > TFA > AcOH); however, the isolated yield of **18b** was highest when quenching with *p*-TsOH (entry 4). The final optimization of this reaction was accomplished by transferring the anion to a solution containing 2 equiv of *p*-TsOH at −78 °C and then quenching the reaction with water at −78 °C. Under these conditions, the desired isomer **18b** was obtained in 56% yield from **18a**.

SCHEME 3



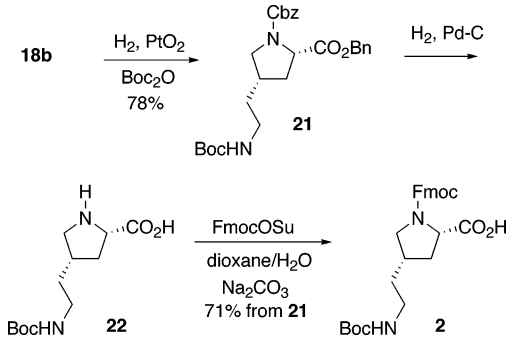
After optimization of the isomerization of **18a** to **18b**, we explored the completion of the synthesis of PTAA **2** through the intermediate **19a** (Scheme 3). At this point, all that remained in the synthesis was to protect the α-nitrogen, reduce the nitrile to a primary amine, and protect this side-chain amine. Protection of the α-nitrogen was accomplished by subjecting the amine **19a** to Fmoc-OSu and Na_2CO_3 in a 1:1 dioxane/H_2O mixture furnishing the carbamate **20** in 84% yield. Unfortunately, the carbamate **20** was not obtained in acceptable levels of purity even after extensive purification efforts. Moreover, alternative Fmoc-protection conditions fared no better in providing materials of higher purity. We also explored pressing on to the final PTAA **2** with the hopes of perhaps purifying the material at this point, but again, the PTAA could not be obtained in acceptable levels of purity for use in solid-phase peptide synthesis.

As an alternative strategy, we investigated reduction of the double bond and nitrile functionalities with PtO_2 and H_2 in the presence of Boc_2O. This reaction cleanly afforded the *N*-Boc carbamate **21** (Scheme 4) in 78% yield. Hydrogenolysis of the Cbz and benzyl protection groups was then accomplished with H_2 and Pd−C to give the amino acid **22**. Finally, protection of the amine with Fmoc-OSu afforded the PTAA **2** suitably protected for Fmoc/Boc solid-phase peptide synthesis in 71% yield from the intermediate **21**.

In conclusion, we report the synthesis of novel amino acid **1** in 14 steps from pyroglutamic acid and a synthesis of the PTAA **2** in eight steps from 4-hydroxyproline. This amino acid has proven critical in elucidating the conformation in which peptide

(14) The assignment of isomer **18c** is tentative. We were not able to isolate and definitively characterize this isomer.

SCHEME 4



substrates bind to the active site of PKG. We expect both PTAAs to be useful in a number of additional applications.

Experimental Section

(2*S*)-4-Cyanomethelene-pyrrolidine-1,2-dicarboxylic Acid Dibenzyl Ester (18a) and (2*S*)-4-Cyanomethyl-2,5-dihydro-pyrrole-1,2-dicarboxylic Acid Dibenzyl Ester (18b). Diethyl cyanomethylphosphonate (19.3 mL, 119 mmol) was added to a solution of LHMDS (109 mL of 1.0 M solution) in dry THF (60 mL) at −78 °C. After 30 min, a solution of ketone **17** (35.1 g, 99.2 mmol) in dry THF (50 mL) was added dropwise to the solution of the phosphonate anion. The reaction mixture was allowed to warm to room temperature, and after 90 min at room temperature, the reaction mixture was quenched with 10% HCl (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give 42.5 g of the crude product. The crude residue was purified by flash chromatography (2% EtOAc in CH_2Cl_2) to afford a 3:2 mixture of *cis*/*trans*-alkene isomers **18a** (20 g) and the unconjugated nitrile **18b** (13.33 g) (89% yield for both) as colorless solids. **18a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.19 (10H, m), 5.15−4.95 (5H, m), 4.6−4.5 (0.5H, 0.5H, t), 4.37 (0.5H, 0.5H, d), 4.19−4.14 (0.5H, 0.5H, d), 3.01−2.87 (1.5H, m), 2.66 (0.5H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (cis and trans conformers) 170.28, 170.15, 161.3, 161.0, 160.3, 160.2, 153.4, 153.3, 153.9, 135.5, 135.4, 134.6, 134.5, 127.2, 127.1, 127.0, 114.9, 114.6, 92.5, 92.3, 66.4, 66.1, 58.1, 57.7, 57.4, 50.6, 50.4, 50.0, 49.8, 35.8, 35.2, 35.0, 34.4 ppm; IR film 2221, 1745, 1710 cm^{-1}; MS (MALDI) 399.0 (M + 23), 377.1 (M + H). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.03; H, 5.32; N, 7.42. **18b**: $[\alpha]^{25}_D = -22.2°$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.20 (10H, m), 5.75−5.73 (1H, d), 5.13−5.07 (5H, m), 4.23−4.13 (2H, m), 3.00 (2H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.8, 168.5, 153.3, 152.9, 135.8, 135.7, 135.0, 134.8, 132.2, 132.1, 127.99, 127.86, 127.79, 127.7, 127.6, 127.34, 127.28, 127.1, 121.9, 121.8, 115.4, 66.64, 66.57, 66.5, 66.2, 65.8, 54.4, 53.9 ppm; IR film 2254, 1551, 1712 cm^{-1}; MS (MALDI) 399.0 (M + 23), 377.0 (M + H). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 66.92; H, 5.32; N, 7.42.

Enolization and Kinetic Protonation (18b). A solution of conjugated nitrile **18a** (4.93 g, 13.1 mmol) in dry THF (15 mL) was added to a cooled solution of LHMDS (14.4 mL of 1 M solution) in dry THF (20 mL) at −78 °C. After 15 min at −78 °C, this solution was transferred via a dry ice-cooled cannula into a flask containing a solution of *p*-TsOH (4.98 g, 26.2 mmol) in dry THF (25 mL) at −78 °C. Water (50 mL) was added at −78 °C, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography (2% EtOAc in CH_2Cl_2) to yield 2.78 g (56%) of pure product **18b**.

(2*S*,4*S*)-4-(2-*tert*-Butoxycarbonylamino-ethyl)-pyrrolidine-1,2-dicarboxylic Acid Dibenzyl Ester (21). A solution of the unconjugated nitrile **18b** (1.0 g, 2.7 mmol) was dissolved in MeOH (40 mL). To this solution was added platinum dioxide (0.121 g, 0.532 mmol), followed by di-*tert*-butyl dicarbonate (1.16 g, 5.32 mmol). The reaction mixture was stirred under an H_2 atmosphere for 48 h. The resulting mixture was then filtered through Celite, and the Celite plug was washed with ethyl acetate (3 × 30 mL). The filtrate was concentrated to yield the corresponding Boc-protected product **21**. The crude residue was purified by flash column chromatography (10% EtOAc in CH_2Cl_2) to yield 1.0 g (78%) of pure product **21**: $[\alpha]^{25}_D = -48.0°$ (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.18 (10H, m), 5.19−5.09 (2H, m), 4.99−4.97 (2H, m), 4.88−4.84 (1H, m), 4.34−4.29 (1H, dt), 3.84−3.77 (1H, dq), 3.09−3.03 (3H, m), 2.44−2.42 (1H, m) 2.13 (1H, m), 1.57−1.47 (3H, m), 1.40−1.39 (9H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 172.3, 172.0, 155.6, 154.3, 153.7, 136.3, 136.1, 135.4, 135.2, 128.2, 128.1, 128.06, 127.98, 127.9, 127.8, 127.7, 127.6, 127.4, 78.7, 66.74, 66.66, 66.4, 66.3, 59.0, 58.7, 52.1, 51.7, 38.8, 36.6, 36.0, 35.6, 35.3, 32.8, 32.7, 29.3, 28.1; IR film 3363 (br), 2975, 1749, 1706 cm^{-1}. MS (MALDI) 505.58 (M + 23), 383.00 (M-Boc). Anal. Calcd for $C_{27}H_{34}N_2O_6$: C, 67.20; H, 7.10; N, 5.81. Found: C, 66.91; H, 7.02; N, 5.85.

(2*S*,4*S*)-4-(2-*tert*-Butoxycarbonylamino-ethyl)-pyrrolidine-1,2-dicarboxylic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (2). The protected amino acid **21**, 0.29 g (0.62 mmol), was dissolved in EtOH (10 mL) and added to a flask containing 10 mol % of Pd−C (0.11 g). An H_2 atmosphere was then applied. After 2 h, the catalyst was removed by filtration through a pad of Celite and the Celite plug was washed with MeOH (2 × 15 mL). The filtrate was concentrated, and 10% Pd−C (0.11 g) was added, followed by MeOH (10 mL). The mixture was again subjected to an H_2 atmosphere for another 30 min. The reaction mixture was filtered through Celite, and the Celite plug was washed with MeOH (2 × 15 mL). The filtrate was concentrated to give 0.16 g of crude product **22** that was used in the next step without further purification. MS (MALDI): 259.2 (M + H), 281.2 (M + 23). The amino acid **22** (0.16 g, 0.62 mmol) was dissolved in water (4 mL). To this solution was added Na_2CO_3 (0.13 g, 1.2 mmol), followed by a solution of Fmoc-OSu (0.25 g, 0.74 mmol) in dioxane (10 mL) over a period of 2 h. After 2 additional hours, the resulting solution was diluted with water (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The resulting material was purified by column chromatography (10% MeOH in CH_2Cl_2) to finally obtain 0.21 g (71%) of **2** as a colorless solid: $[\alpha]^{25}_D = -53.0°$ (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (2H, d), 7.59 (2H, m), 7.39−7.31 (4H, m), 4.39−4.10 (4H, m), 3.71 (0.7H, 0.3H s), 3.34 (0.7H, 0.3H s), 3.08 (3H, m), 2.42 (0.7H, 0.3H s), 2.13 (0.7H, 0.3H s), 1.62−1.57 (3H, m), 1.46 (9H, s) ppm; ^{13}C NMR (125 MHz, CD_3OD) 183.6, 182.4, 160.9, 159.7, 159.1, 148.0, 147.7, 147.6, 145.09, 145.05, 144.9, 131.4, 130.7, 128.8, 128.6, 124.0, 123.4, 82.5, 71.6, 71.5, 65.1, 64.4, 56.3, 56.0, 42.6, 21.1, 39.8, 39.6, 39.4, 36.5, 31.4 ppm; IR film 3355 (br), 1684 cm^{-1}; MS (MALDI) 503.71 (M + 23); HRMS calcd for $C_{27}H_{32}N_2O_6$ [M + H]$^+$ 480.2216, found 480.2218.

Acknowledgment. Financial support for this work was provided by CHE-0411831 from the NSF. HRMS was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H NMR spectra for **1**, **4**−**13**, and **17**; ^{1}H NMR spectra for **2**, **18a**, **18b**, **19a**, **19b**, and **21**; ^{13}C NMR spectra for **1**, **2**, **4**, **5**, **7**, **8**, **10**−**13**, **18a**, **18b**, and **21**; and HMQC for **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060210F