(zero time); 25-μL samples were withdrawn at different times and diluted in 10 mL of CH_2Cl_2. Mn porphyrin decomposition was followed by UV–vis spectroscopy in the 350–700-nm range, measuring the percentage decrease of the absorbance at the λ_{max} referred to the sample taken at zero time. Results are reported in Tables II and III.

Titration of HOCl Extracted in CH_2Cl_2. In a 100-mL round-bottomed flask, equipped with a magnetic stirrer, were poured 32 mL of CH_2Cl_2 and 40 mL of aqueous NaOCl (0.35 M) buffered at the desired pH. The mixture was vigorously stirred at 0 °C for 30 min; 30 mL of the CH_2Cl_2 solution were carefully separated and stirred for 10 min with an excess of acidic KI solution and titrated with 0.001 N aqueous $Na_2S_2O_3$. Results are reported in Table I.

Determination of Association Constants (K_1, β_2). The K_1 and β_2 values were determined as reported by Walker et al.[34] following the absorbance change of 1.0×10^{-5} M CH_2Cl_2 solution of Mn(TPP)Cl **1** and of Mn(T2,6Cl_2PP)Cl **2** at 477.6 and 477.9 nm, respectively, upon addition of the ligand CH_2Cl_2 solution. The concentration ranges of the latter were 2.10×10^{-4} to 3.15×10^{-2}, 4.02×10^{-4} to 5.25×10^{-2}, and 4.93×10^{-6} to 1.48×10^{-3} M for 1-IMH, 1-8, and 2-8, respectively. Titrations were recorded at 25 ± 0.2 °C under aerobic conditions.

Acknowledgment. We are grateful to Dr. Pier Lucio Anelli and Prof. Luigi Casella for helpful discussions and to Alessandro Maiocchi for determination of association constants.

Registry No. 1, 32195-55-4; 1·imidazole, 79969-69-0; 2, 91463-17-1; 2·imidazole, 118920-72-2; 2·8, 118920-73-3; 3, 118920-69-7; 4, 118920-70-0; 5, 118920-71-1; 6, 79968-43-7; 7, 85939-49-7; 8, 33529-01-0; 9, 3978-81-2; 10, 1008-88-4; 11, 23569-17-7; 12, 1131-48-2; cyclooctene, 931-88-4; 1-dodecene, 112-41-4; hypochlorous acid, 7790-92-3.

Supplementary Material Available: Visible spectrum changes by addition of increasing amounts of ligand 8 to a CH_2Cl_2 of Mn porphyrin 2; mole percent plot of monoligated Mn porphyrin 2 at varying ligand 8 concentration; plots of log $(A - A_0/A_\infty - A)$ vs log [L] of K_1 and β_2 calculation for Mn porphyrins 1 and 2 when *N*-hexylimidazole is the axial ligand (6 pages). Ordering information is given on any current masthead page.

Synthesis of 4-Substituted Prolines as Conformationally Constrained Amino Acid Analogues

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Anionic substitution of *N*-(9-(9-phenylfluorenyl))-protected glutamic acid esters proceeds without loss of optical integrity to give 4-substituted glutamic acid derivatives. The 4-methyl, propyl, cyanomethyl, and phenyl analogues have thus been prepared. Primarily by conversion to the corresponding 5-hydroxypentanoic acids and intramolecular nitrogen alkylation, 4-substituted prolines are obtained in an efficient and chirospecific manner. Because of the restricted side-chain mobility, these 4-substituted prolines behave as conformationally constrained amino acid analogues.

Introduction

Substituted prolines have elicited a wide range of interest. Several alkylated prolines are rare naturally occurring amino acids,[1] they are constituent amino acids in antibiotics,[2] and recently they have gained interest in the development of novel angiotensin converting enzyme inhibitors.[3] Proline itself plays a significant role in the biochemistry of proteins, inducing strong preference for secondary structural motifs (kinks in α-helices and reverse turns).[4] This property has marked effects, for instance, in collagen biosynthesis[5] and in protein folding,[6] and has also been implicated in certain peptide hormone recognition events.[7] Conformationally constrained peptides are emerging as useful tools in developing peptide-derived pharmaceutic agents.[8] Substituted prolines provide a new

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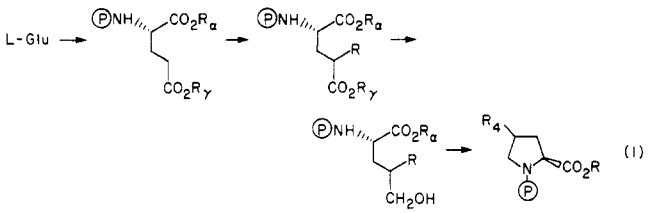
type of simple conformational constraint.

Asymmetric syntheses for 2-, 3-, and 5-substituted prolines exist,[9] but the syntheses of 4-substituted prolines[1,3,10] either provide racemic material or necessitate the use of expensive starting materials in lengthy and complex synthetic sequences. We now report an efficient synthetic protocol for 4-substituted prolines based on chirospecific transformations of glutamic acid.

A suitably protected glutamic acid derivative is alkylated or otherwise substituted at C-4 to provide 4-substituted glutamic acid derivatives. Selective reduction of the distal ester functionality is achievable with the proper choice of protecting groups, and finally ring closure to the proline completes the synthesis as shown in sequence 1. This



(1)

strategy allows flexibility in introducing substituents on the proline ring merely by the choice of the electrophile. The stereochemistry can be controlled, since the newly generated asymmetric center is epimerizable. Furthermore, previous results from our laboratory demonstrated that utilization of the 9-(9-phenylfluorenyl) (PhFl) group for nitrogen protection will prevent racemization at the α-center,[11] thus providing for the chirospecificity of the synthetic sequence.

Results and Discussion

The two esters of glutamic acid were differentiated to secure chemoselectivity in later stages of the synthesis. Glutamic acid was first converted to the γ-methyl glutamate **1** as described.[12] Protection of the nitrogen with the PhFl group was conducted by using a modification of the literature procedure.[11] We found that using the hydrochloride salt of the amino ester **1** gave less than 50% yields of N-PhFl derivative **2**. However, from the free amine **1**, the desired **2** was obtained in 84% yield. Care must be exercised in isolation. For a sucessful outcome it was crucial to adjust the pH of the aqueous phase in the extractions to the isoelectric point of **2**.[13] The α-carboxylic acid was converted to its *tert*-butyl ester with *O-tert*-butyl-*N,N'*-diisopropylisourea in dichloromethane to provide the key intermediate diester **3**. We have prepared **3** on scales of up to 30 g with 40–45% overall yield from glutamic acid.

The distal ester enolate anion[14] first generated with use of lithium diisopropylamide (LDA) as the base, but this led to varying yields in the alkylation coupled with extensive decomposition of diester **3**. With use of a weaker base, potassium hexamethyldisilazide (KMHDS, pK 26),[15] alkylation with methyl iodide gave a 95% yield of the diastereomeric mixture of **4a/5a** (ratio 1/2), which could not be easily separated at this stage. Similar alkylation

Scheme I. Synthesis of 4-Substituted Glutamates and 4-Substituted 2-Amino-5-hydroxypentanoic Acids

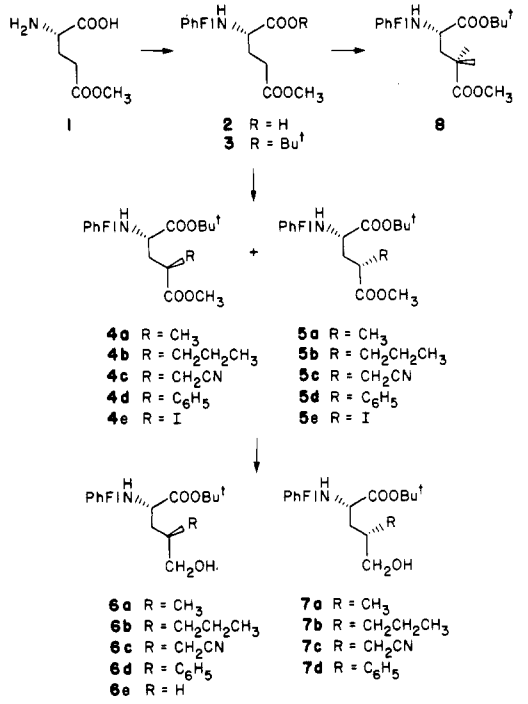
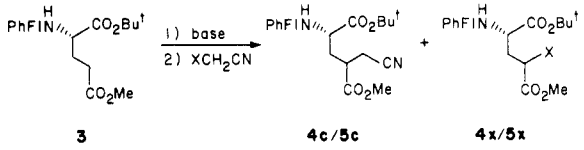


Table I. Alkylation of Diester 3 with Acetonitrile Derivatives



base	X	% yield[a] 3	4c/5c	4x/5x
KHMDS	Cl	24		
	Br	43	17	7
	I	<2		84
	$PhSO_2O$[b]	65		
LiHMDS	Br	36	13	6
LiTMP	Br	10	64	
	I	52		34

[a] Yields refer to isolated yields by MPLC chromatography. [b] Reference 16.

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(13) To estimate the isoelectric points of N-PhFl protected amino acids, we determined the pK's of N-PhFl-alanine to be 9.8 and 4.4 in dioxane–water, 1/3, giving a pI of 7.1. Under similar conditions we obtained for alanine a pI of 6.6. This information was used to select the pH for extracting the monoester from aqueous phase at pH 6.3.

(14) The γ-anion of protected glutamate has been used in the synthesis of γ-carboxyglutamic acid: Zee-Cheng, R. K. Y.; Olsen, R. E. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 1128. A similar protocol has recently been described for aldol type reactions: Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *J. Chem. Soc., Chem. Commun.* **1988**, 828.

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(16) Dodson, R. M.; Turner, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 4517.

Table II. Epimerization of γ-Methyl Glutamate Diastereomers 4a/5a

base	temp, °C	time, h	quench	ratio 4a/5a[a]
KHMDS	−78	0.7	Na_2SO_4, satd	1/3.0
LDA	−78	0.7	CH_3OH	1/2.3[b]
BMDA[c]	−78 → 0	2	CH_3OH	1/6.5
NaOMe/MeOH	20	20	H_3PO_4, 1 M	1/2.7

[a] Measured by integration of the methyl ester signals. The original ratio, as isolated from the alkylation reaction, was 1/2.8. [b] Extensive decomposition was observed. [c] BMDA = bromomagnesium diisopropylamide.

with propyl iodide gave only 58% of **4b/5b**, but utilization of propyl triflate improved the combined yield to 81% (ratio **4b/5b**, 1/3). Dialkylation was observed only in the methyl series, where a 3% yield of dimethyl derivative **8** was obtained.

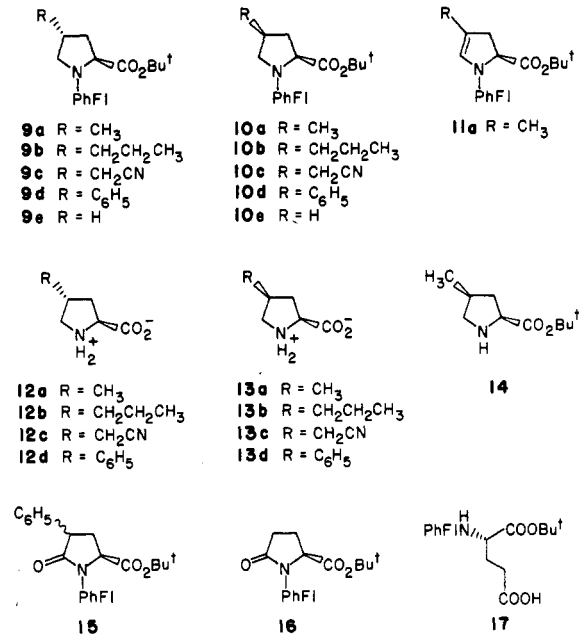
The cyanomethyl derivatives in the **c** series required more thorough investigations of the reaction conditions (Table I). The use of lithium 2,2,6,6-tetramethylpiperidie (LiTMP) as the base and bromoacetonitrile as the electrophile proved satisfactory. It is interesting to note that iodoacetonitrile proved to be more efficient as an iodinating reagent than iodine itself! Quenching the enolate anion with elemental iodine gave a 52% yield of **4e/5e**, whereas with iodoacetonitrile the yield was 84%.

The diastereomer ratios of anti/syn, **4/5**, in the alkylations varied very little, only from 4/6 in the methyl case to 1/3 in the propyl and cyanomethyl cases. We therefore briefly studied the possibility of epimerization at the newly generated γ-center. Although the proportion of the major syn isomer could be increased, the ratio could not be inverted (Table II).

We also wanted to explore the possibility of introducing an aryl substituent at the γ-carbon of glutamic acid and hence the 4-position of proline employing our strategy. Electrophilic arylation reagents based on chromium tricarbonyl complexes are known.[17] The simplest congener (benzene chromium tricarbonyl)[18] gave the 4-phenyl pyroglutamate **15** (11–17%), the nonarylated pyroglutamate **16** (37–43%), and the free γ-acid **17** (5–12%).[19] The pyroglutamate **15** was converted to 4-phenylproline derivative **10e** by reduction with BH_3·THF with a catalytic amount of $NaBH_4$. The stereochemistries of the phenyl compounds are tentatively assigned on the basis of chemical shift and coupling constant data.

Synthesis of Prolines. For the reduction of the alkylated glutamic acid derivatives **4/5**, diisobutylaluminum hydride (DIBAL) was initially used as the reducing agent. Instead of the desired hydroxypentanoic acids **6/7**, the cyclized compounds **9/10** were obtained in moderate yields (43–59%). The DIBAL functions as a Lewis acid, thereby activating the intermediate aldehyde toward intramolecular ring closure. Upon consumption of another equivalent of hydride, these intermediates provide the prolines **9/10**. From a diastereomeric mixture of γ-substituted glutamates, only one proline diastereomer was obtained accompanied by a small amount of the corresponding 4,5-dehydroproline **11**. Although this method provides a very short synthesis of prolines, the facts that only one diastereomer was produced and that some dehydroproline was also formed warranted further search for a more effective strategy for the ring closure.

Chart I. 4-Substituted Prolines



Lithium aluminum hydride (−78 to −20 °C, THF) proved more convenient in furnishing the hydroxy pentanoic acids **6/7** in yields varying from 54 to 95%.[20] Dehydroprolines **11** were not produced under these conditions, but in an attempted reduction of cyanomethyl derivative **4c/5c** to **6c/7c** at −95 °C, the dehydroproline **11c** was the major product.

Although separation of the diastereomers could be effected at any stage after alkylation, we have found it to be most convenient at the alcohol stage. We have, however, examined the reactions with each diastereomer and the diastereomer mixture, and no significant kinetic resolution was observed in any case at any stage.

For the ring closure, we decided to rely on a Mitsunobu type activation protocol.[21] Treatment of the amino alcohols **6/7** with triphenyl phosphine and carbon tetrabromide in THF in the presence of diisopropylethylamine led to clean and rapid ring closure to the penultimate proline derivatives **9/10**.[22] The case of intramolecular substitution of the nitrogen was surprising in view of inertness of similar N-PhFl compounds toward intermolecular alkylations.[23]

Final deprotection of **9/10** to the free prolines was effected simply by stirring with trifluoroacetic acid in dichloromethane at 20 °C to provide the free amino acids **12/13**. No cation scavenger was necessary in the simple alkyl cases, whereas the cyanomethyl derivatives required the use of thioanisole to scavenge the PhFl cation.[24] The nitrogen protecting group could be selectively removed by catalytic hydrogenation in acetic–methanol to give the proline esters **14/15**.[25]

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(19) These reactions have not been optimized. It is plausible that the phenylfluorenyl group interferes with the desired reaction through ligand exchange; quenching the reaction immediately after starting material had been consumed (TLC analysis) gave only the 4-iodo compounds **4e/5e**.

(20) 2-Amino-5-hydroxypentanoic acid is a competitive inhibitor of γ-cystathionase. For a synthesis, see: Barlos, K.; Mamos, P.; Papaioannou, D.; Patrianakou, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1583.

(21) Castro, B. R. *Org. React.* **1983**, *29*, 1.

(22) Diisopropylethylamine was required to consume the liberated HBr. Without added base, the cyclization yields remained below 50%.

(23) We have not been able to alkylate or acylate secondary PhFl-amines satisfactorily under any conditions.

(24) In different contexts, we have observed that under similar conditions but without a cation scavenger an alkyl nitrile reacts with the liberated PhFl cation to provide the corresponding PhFl amide.

Table III. ^{1}H NMR Data for 4-Substituted Prolines 12 and 13

compd	4-substn	H-2	H-3α	H-3β	H-4	H-5α	H-5β
12a	trans-CH_3	4.35	1.88	2.21	2.28	2.76	3.42
13a	cis-CH_3	4.33	2.54	1.66	2.40	2.88	3.45
12b	trans-$CH_2CH_2CH_3$	4.30	1.89	[2.14–2.26]		2.80	3.44
13b	cis-$CH_2CH_2CH_3$	4.17	2.38	1.50	2.16	2.75	3.29
12c	trans-CH_2CN	4.29	1.95	2.23	2.4–2.6	2.84	3.43
13c	cis-CH_2CN	4.15	2.47	1.60	2.2–2.5	2.81	3.30

Table IV. ^{13}C NMR Data for 4-Substituted Prolines 12 and 13

compd	4-substn	C-2	C-3	C-4	C-5	CO_2^-	other
12a	trans-CH_3	60.0	36.1	31.6	52.0	173.2	15.7
13a	cis-CH_3	59.8	36.0	32.9	51.9	171.9	15.6
12b	trans-$CH_2CH_2CH_3$	59.6	33.2	36.5	50.7	172.8	13.1, 20.5, 34.2
13b	cis-$CH_2CH_2CH_3$	59.4	33.6	37.8	50.6	171.6	13.1, 20.5, 34.3
12c	trans-CH_2CN	59.1	32.9	33.0	49.2	170.9	18.9, 118.8
13c	cis-CH_2CN	59.3	33.1	34.1	49.1	170.6	18.7, 118.6

The optical integrity of our synthetic route was proved with the *cis*-4-methylproline ester **15**. This was treated with α-phenylethyl isocyanate (*R* and *S* isomers separately), and the optical purity (probed by high-field NMR studies) was shown to be >99% (detection limit determined by doping experiment), thus proving the chirospecificity of the synthetic sequence.

NMR Spectroscopy. High-field (400-MHz) 2D NMR spectroscopy was used to assign the relative stereochemistry at the C-4 center.[26] All the ^{1}H resonances of **12a** and **13a** were first assigned on the basis of COSY experiments and coupling constant data.[27] Phase-sensitive NOESY[28] was then used to reveal the requisite data on close spatial proximity of various diagnostic protons to establish the structures of the two isomers as shown. Thus H-2 was uniquely identified by its chemical shift. The NOE cross peak with one (α) of the H-5's distinguished these protons. The H-3's also were distinguished from each other by the NOE cross peaks with H-5's. For the 4-substituent, the relative stereochemistry was directly determined from the NOE cross peaks with H-2 and H-4 or R-4. The stereochemistries of the intermediates in the methyl series were deduced from this information and chemical evidence. The structures of the propyl and cyanomethyl derivatives were assigned by comparison to the methyl series. Pertinent NMR data are given in Tables III and IV.

Conclusion

An efficient and versatile synthetic protocol for the production of 4-substituted prolines has been developed. Starting from *N*-(9-(9-phenylfluorenyl))glutamic acid esters, the desired prolines are obtained in optically pure form in four steps and good overall yields. These prolines are currently being evaluated for their ability to impose conformational constrainments on small peptides.

Experimental Section

All reactions requiring anhydrous conditions were conducted in flame-dried reaction vessels under a positive pressure of Ar. Solvents and reagents were distilled immediately prior to use: THF and ether from $LiAlH_4$; chloroform and trifluoromethanesulfonic anhydride from P_2O_5; acetonitrile, chlorotrimethylsilane, dichloromethane, tetramethylethylenediamine (TMEDA), and 2,2,6,6-tetramethylpiperidine (TMP) from CaH_2. After extractive isolation, the organic layers were dried over Na_2SO_4 for 30 min (with stirring), filtered, and evaporated in vacuo with a Berkeley rotary evaporator. Melting points were measured on a Büchi melting point apparatus with open-ended capillary tubes, and are uncorrected. Analytical TLC was conducted on Merck silica gel plates, and the R_f values refer to elution with 20% EtOAc in hexanes. Elemental analyses were performed at the UC Berkeley Analytical Laboratory.

NMR Spectroscopy. Proton and carbon NMR spectra were measured in 0.1 M solutions (in $CDCl_3$, unless otherwise indicated) on a Bruker AM 400 or 500 spectrometer, both using an Aspect 3000 computer equipped with an array processor. For proton spectra, eight scans of 10 ppm spectral width were acquired, using 32K data points. The FID signal was zero-filled to 64K and apodised with a convoluted Gaussian (line broadening −1.0, Gaussian broadening 0.25) function before FT. The chemical shifts are reported downfield from TMS as internal standard (δ 0.00 ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, as measured from spectra, are given in hertz. In aqueous solutions, the HDO resonance was used as a reference (T = 293 K, δ 4.65 ppm) for proton spectra, and dioxane (δ 66.5 ppm) for carbon spectra. Carbon multiplicites were determined by DEPT 90 and DEPT 135 experiments and are indicated as CH_3, CH_2, CH, and C. Chemical shifts for aromatic carbons are not reported.

***N*-(9-(9-Phenylfluorenyl))glutamic Acid γ-Methyl Ester (2).** To a suspension of glutamic acid γ-methyl ester **1** (12.09 g, 75 mmol) in 150 mL of chloroform was added chlorotrimethylsilane (8.58 g, 10.0 mL, 105 mol %) via syringe at room temperature. The heterogeneous reaction mixture was heated at reflux for 2 h and cooled to room temperature. Triethylamine (22.0 mL, 15.94 g, 157.5 mmol, 210 mol %) was added, followed by lead nitrate (14.9 g, 45 mmol, 60 mol %) and 9-bromo-9-phenylfluorene (28.9 g, 90 mmol, 120 mol %) in 150 mL of chloroform. The resulting mixture was vigorously stirred at room temperature for 87 h, after which 50 mL of methanol was added. After being stirred for another 15 min, the solution was filtered and the filtrate was concentrated. The residue was partitioned between 250 mL of ethyl acetate and 250 mL of 5% aqueous citric acid, the aqueous layer was discarded, and the organic solution was extracted successively with brine (2 × 100 mL) and water (2 × 50 mL). The combined aqueous layers were washed with ether (100 mL) and

(25) 5-Phenylproline was also prepared by reaction of γ-glutamate **17** with phenyllithium (THF, −78 °C, to room temperature). The solvents were evaporated, and the crude ketone was reduced with $NaBH_4$ in isopropanol (room temperature, overnight, 40% from **17**) to give a 1/1 mixture of diastereomeric alcohols: ^{1}H NMR δ 1.17 and 1.19 (s, 9 H), 1.40–2.00 (m, 4 H), 2.52 (t, J = 6 Hz) and 2.56 (dd, J = 4.7, 6.4 Hz) (1 H), 4.58 (dd, J = 4.8, 7.3 Hz) and 4.66 (dd, J = 4.0, 8.3 Hz) (1 H). The resulting 5-hydroxy-5-phenylpentanoic acid derivative was then cyclized as described to give 5-phenyl-*N*-(9-(9-phenylfluorenyl)proline *tert*-butyl ester: HRMS calcd for $C_{34}H_{34}NO_2$ (MH^+) 488.2589, found 488.2571. ^{1}H NMR less polar isomer: δ 1.48 (s, 9 H), 1.8–2.0 (m, 4 H), 3.52 (dd, 1 H, J = 6.0, 7.7 Hz), 4.07 (dd, 1 H, J = 1, 9.0 Hz), 6.50 (m, 1 H), 6.83 (m, 1 H), 6.95 (m, 16 H). More polar isomer: δ 1.18 (s, 9 H), 1.6–1.95 (m, 2 H), 2.47 (m, 1 H), 2.62 (m, 1 H), 4.34 (d, 1 H, J = 7.9 Hz), 4.78 (d, 1 H, J = 7.8 Hz), 6.45 (m, 2 H), 6.74 (m, 2 H), 6.84 (m, 1 H), 7.0–7.8 (m, 13 H).

(26) (a) Bax, A. *Two Dimensional Nuclear Magnetic Resonance in Liquids*; Delft University Press: Delft, Holland, 1982. (b) Wüthrich, K. *NMR of Proteins and Nucleic Acids*; John Wiley & Sons: New York, 1986.

(27) An earlier ^{1}H NMR study of 4-methylprolines has been conducted [Abraham, R. J.; McLauchlan, K. A.; Dalby, S.; Kenner, G. W.; Sheppard, R. C.; Burroughs, L. F. *Nature* **1961**, *192*, 1150]. Based on the current 2D NMR data, the assignments for the 3α and 3β protons have been changed (see Table III).

(28) Bodenhausen, G.; Kogler, H.; Ernst, R. R. *J. Magn. Reson.* **1984**, *58*, 370.

acidified to pH 6.3, and the product that separated as an oil was induced to crystallize by conducting a vigorous stream of nitrogen through the stirred mixture. The slightly off white solid was filtered and dried to give **2** (25.3 g, 84%): R_f 0.04; mp 142–143 °C; ^{1}H NMR δ 1.72 (dddd, 1 H, J = 14, 7, 7, 5 Hz), 1.84 (dddd, 1 H, J = 14, 7, 7, 7 Hz), 2.35 (ddd, 1 H, J = 12, 7, 7 Hz), 2.39 (ddd, 1 H, J = 12, 7, 7 Hz), 2.63 (dd, 1 H, J = 7, 5 Hz), 3.67 (s, 3 H), 7.15–7.75 (m, 13 H); ^{13}C NMR δ 28.5 (CH_2), 30.3 (CH_2), 51.9 (CH), 55.4 (CH_3), 72.8 (C), 174.4 (C), 177.2 (C). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.8; H, 5.9; N, 3.4.

α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-glutamate (3). To a stirred solution of γ-methyl ester **2** (1.50 g, 3.7 mmol) in 10 mL of dichloromethane was added *O*-*tert*-butyl *N*,*N*′-diisopropylisourea (2.0 g, 10 mmol) via syringe. The mixture was stirred at room temperature for 16 h, the diisopropylurea was filtered off, the filter cake was washed with dichloromethane (30 mL), and the filtrates were evaporated. The oily residue was passed through a column of silica gel, eluting with a mixture of ethyl acetate/hexanes, 1/2. The solvent was evaporated, and the colorless residue was crystallized from 15 mL of isooctane to give diester **3** (1.28 g, 75%): R_f 0.36; mp 100 °C; ^{1}H NMR δ 1.17 (s, 9 H), 1.65 (dddd, 1 H, J = 14, 7, 7, 6.3 Hz), 1.70 (dddd, 1 H, J = 14, 7, 7, 3.5 Hz), 2.37 (ddd, 1 H, J = 12, 7, 7 Hz), 2.43 (ddd, 1 H, J = 12, 7, 7 Hz), 2.51 (dd, 1 H, J = 6.3, 3.5 Hz), 3.64 (s, 3 H), 7.15–7.75 (m, 13 H); ^{13}C NMR δ 27.82 (CH_3), 30.35 (CH_2), 30.39 (CH_2), 51.45 (CH_3), 55.17 (CH), 72.87 (C), 80.72 (C), 173.93 (C), 174.84 (C). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8; N, 3.1. Found: C, 76.2; H, 6.8; N, 3.0.

(2*S*,4*R*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-methylglutamate (4a) and (2*S*,4*S*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-methylglutamate (5a). To a −78 °C solution of KHMDS (30 mL, 18 mmol, 180 mol %, 0.6 M in toluene) in 75 mL of THF was added a solution of **3** (4.58 g, 10 mmol) in 30 mL of THF over 5 min. The mixture was stirred at −78 °C for 1 h, and methyl iodide (1.25 mL, 2.84 g, 200 mol %) was added. Stirring was continued at −78 °C for another 3 h, after which the heterogeneous mixture was poured into a mixture of 100 mL of 0.5 M H_3PO_4 and 200 mL of ether. The organic phase was separated and washed with brine, and the combined aqueous phases were back extracted with a 100-mL portion of ether. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to give 5.56 g of faintly yellow oil. MPLC (SiO_2, 10% EtOAc in hexane) gave **4a**, **5a** as a colorless oil (4.44 g, 94%), as a 1/3 mixture of diastereomers. Anal. Calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.1; N, 3.0. Found: C, 76.4; H, 7.2; N, 2.9.

4a: R_f 0.38; ^{1}H NMR δ 1.07 (d, 3 H, J = 7 Hz), 1.17 (s, 9 H), 1.39 (ddd, 1 H, J = 4.6, 7.4, 13.6 Hz), 1.86 (ddd, 1 H, J = 5.1, 9.0, 13.6 Hz), 2.56 (dd, 1 H, J = 5.1, 7.4 Hz), 2.74 (m, 1 H), 3.56 (s, 3 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 18.07 (CH_3), 27.81 (CH_3), 35.61 (CH), 39.31 (CH_2), 51.38 (CH_3), 54.53 (CH), 72.97 (C), 80.56 (C), 175.15 (C), 176.70 (C).

5a: R_f 0.38; ^{1}H NMR δ 0.79 (d, 3 H, J = 7 Hz), 1.14 (s, 9 H), 1.33 (ddd, 1 H, J = 4.1, 7.5, 13.6 Hz), 1.89 (ddd, 1 H, J = 6.0, 10.4, 13.6 Hz), 2.47 (dd, 1 H, J = 4.1, 10.4 Hz), 2.71 (m, 1 H), 3.67 (s, 3 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 16.89 (CH_3), 27.81 (CH_3), 36.14 (CH), 38.85 (CH_2), 51.54 (CH_3), 54.30 (CH), 72.79 (C), 80.60 (C), 175.25 (C), 177.28 (C).

(2*S*,4*R*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-propylglutamate (4b) and (2*S*,4*S*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-propylglutamate (5b). To a −78 °C solution of KHMDS (7 mL, 4.2 mmol, 210 mol %, 0.6 M in toluene) in 15 mL of THF was added a solution of **3** (915 mg, 2 mmol) in 5 mL of THF over 5 min. The mixture was stirred at −78 °C for 1 h, and propyl triflate (770 mg, 4 mmol) was added. Stirring was continued for another 3 h. The heterogeneous mixture was poured into a mixture of 50 mL of 0.5 M H_3PO_4 and 50 mL of ether. The organic phase was separated and washed with brine, and the combined aqueous phases were back extracted with a 10-mL portion of ether. The combined organic phases were then dried, filtered, and evaporated to give 1.23 g of faintly yellowish oil. MPLC (SiO_2, 2% EtOAc in hexane) gave **4b** and **5b** as colorless oils (**4b** 170 mg, 17%; **5b** 640 mg, 64%). Anal. Calcd for $C_{32}H_{37}NO_4$: C, 76.9; H, 7.5; N, 2.8. Found: C, 76.9; H, 7.4; N, 2.8.

4b: R_f 0.38; ^{1}H NMR δ 0.88 (t, 3 H, J = 7 Hz), 1.18 (s, 9 H), 1.2–1.6 (m, 5 H), 1.84 (ddd, 1 H, J = 4.8, 4.8, 9.6 Hz), 2.55 (br t, 1 H), 2.63 (m, 1 H), 3.07 (br s, 1 H, NH), 3.60 (s, 3 H), 7.15–7.7 (m, 13 H); ^{13}C NMR δ 13.89 (CH_3), 20.24 (CH_2), 27.84 (CH_3), 35.15 (CH_2), 37.54 (CH_2), 41.03 (CH), 51.25 (CH_3), 54.77 (CH), 73.06 (C), 80.63 (C), 175.02 (C), 176.53 (C).

5b: R_f 0.38; ^{1}H NMR δ 0.80 (t, 3 H, J = 7 Hz), 1.13 (s, 9 H), 1.1–1.5 (m, 5 H), 1.83 (ddd, 1 H, J = 7.3, 6.0, 7.3 Hz), 2.45–2.65 (m, 2 H), 3.0 (br s, 1 H, NH), 3.66 (s, 3 H), 7.15–7.75 (m, 13 H); ^{13}C NMR δ 13.89 (CH_3), 20.30 (CH_2), 27.83 (CH_3), 34.49 (CH_2), 37.74 (CH_2), 42.03 (CH), 51.32 (CH_3), 54.72 (CH), 72.90 (C), 80.59 (C), 175.19 (C), 176.75 (C).

(2*S*,4*R*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-(cyanomethyl)glutamate (4c) and (2*S*,4*S*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-(cyanomethyl)glutamate (5c). A solution of **3** (4.58 g, 10 mmol) in 20 mL of THF was added to a −78 °C solution of lithium 2,2,6,6-tetramethylpiperidide (from 1.4 mL, 15 mmol, TMP and 10 mL of 1.5 M BuLi) in 100 mL of THF. After 30 min, bromoacetonitrile (1.4 mL, 2.5 g, 20 mmol) was added, and stirring was continued at −78 °C for another 2 h. Isolation as described above provided 5.10 g of crude product, which gave, after MPLC purification, **4c** (1.22 g, 25%) and **5c** (1.84 g, 37%). Anal. Calcd for $C_{31}H_{32}N_2O_4$: C, 75.0; H, 6.5; N, 5.6. Found: C, 75.2; H, 6.7; N, 5.6.

4c: R_f 0.24; ^{1}H NMR δ 1.20 (s, 9 H), 1.62 (ddd, 1 H, J = 4.9, 7.9, 13.8 Hz), 1.91 (ddd, 1 H, J = 5.0, 8.4, 13.8 Hz), 2.52 (dd, 1 H, J = 6.9, 16.9 Hz), 2.56 (dd, 1 H, J = 6.7, 16.9 Hz), 2.60 (dd, 1 H, J = 5.0, 7.9 Hz), 2.94 (dddd, 1 H, J = 4.9, 6.7, 6.9, 8.4 Hz), 3.63 (s, 3 H), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 20.10 (CH_2), 27.78 (CH_3), 36.52 (CH_2), 38.11 (CH), 52.21 (CH_3), 54.22 (CH), 72.94 (C), 81.43 (C), 117.56 (C), 172.78 (C), 174.24 (C).

5c: R_f 0.24; ^{1}H NMR δ 1.17 (s, 9 H), 1.51 (ddd, 1 H, J = 3.5, 9.7, 14.1 Hz), 1.92 (ddd, 1 H, J = 3.9, 10.6, 14.1 Hz), 1.95 (dd, 1 H, J = 4.3, 16.7 Hz), 2.04 (dd, 1 H, J = 8.0, 16.7 Hz), 2.34 (dd, 1 H, J = 3.5, 10.6 Hz), 3.12 (dddd, 1 H, J = 3.9, 4.3, 8.0, 9.7 Hz), 3.75 (s, 3 H), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 18.28 (CH_2), 27.76 (CH_3), 36.06 (CH_2), 38.02 (CH), 52.41 (CH_3), 53.35 (CH), 72.70 (C), 81.40 (C), 117.49 (C), 173.24 (C), 174.34 (C).

(2*S*,4*R*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-iodoglutamate (4e) and (2*S*,4*S*)-α-*tert*-Butyl γ-Methyl *N*-(9-(9-Phenylfluorenyl))-4-iodoglutamate (5e).

A. With I_2. To a −78 °C solution of KHMDS (26.7 mL, 16 mmol, 160 mol %, 0.6 M in toluene) in 50 mL of THF was added a solution of **3** (4.58 g, 10 mmol) in 25 mL of THF over 5 min. The mixture was stirred at −78 °C for 45 min and then cannulated into a solution of I_2 (3.17 g, 12.5 mmol, 125 mol %) in 50 mL of THF stirred at −78 °C. Stirring was continued at −78 °C for another 2 h, after which the heterogeneous mixture was poured into a mixture of 10 mL of 0.5 M H_3PO_4 and 25 mL of ether. The organic phase was separated and washed with brine, and the combined aqueous phases were back extracted with a 10-mL portion of ether. The combined organic phases were dried, filtered, and evaporated to give 5.82 g of yellow oil. MPLC (SiO_2, 15% EtOAc in hexane) gave a nearly 1/1 mixture of **4e** and **5e** as a white foam (3.02 g, 52%). Anal. Calcd for $C_{29}H_{30}INO_4$: C, 59.7; H, 5.2; N, 2.4. Found: C, 60.0; H, 5.4; N, 2.4.

4e: R_f 0.39; ^{1}H NMR δ 1.18 (s, 9 H), 2.03 (ddd, 1 H, J = 4.3, 8.5, 13.9 Hz), 2.35 (ddd, 1 H, J = 4.3, 10.4, 13.9 Hz), 2.45 (dd, 1 H, J = 4.3, 8.5 Hz), 3.59 (s, 3 H), 4.76 (dd, 1 H, J = 4.3, 10.5 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 14.58 (CH), 27.76 (CH_3), 42.52 (CH_2), 52.59 (CH_3), 56.06 (CH), 72.75 (C), 81.26 (C), 171.53 (C), 173.72 (C).

5e: R_f 0.39; ^{1}H NMR δ 1.14 (s, 9 H), 2.02 (ddd, 1 H, J = 4.3, 6.0, 14.4 Hz), 2.30 (ddd, 1 H, J = 8.0, 10.2, 14.4 Hz), 2.58 (dd, 1 H, J = 4.3, 10.2 Hz), 3.78 (s, 3 H), 4.44 (dd, 1 H, J = 6.0, 8.0 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 17.58 (CH), 27.76 (CH_3), 41.67 (CH_2), 52.77 (CH_3), 56.13 (CH), 72.71 (C), 81.12 (C), 172.19 (C), 173.95 (C).

B. With Iodoacetonitrile. To a stirred, cooled (−78 °C) solution of KHMDS (6 mL of 0.6 M in toluene) in 15 mL of THF, **3** (915 mg, 2 mmol) in 5 mL of THF was added. After 90 min at −78 °C, iodoacetonitrile was added, and the reaction mixture was stirred for another 2 h at this temperature, quenced by pouring into 50 mL of 0.5 M H_3PO_4, and extracted into ether (2 × 100 mL). The ether extracts were washed with brine (50 mL), dried,

filtered, and evaporated. Chromatography over silica (MPLC, 10% EtOAc in hexanes as eluant) gave **4e** (980 mg, 84%), identical with the material prepared previously.

***tert*-Butyl (2*S*,4*R*)-5-Hydroxy-4-methyl-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (6a) and *tert*-Butyl (2*S*,4*S*)-5-Hydroxy-4-methyl-2-(*N*-(9-(9-phenylfluorenyl))-amino)pentanoate (7a).** α-*tert*-Butyl γ-metyl *N*-(9-(9-phenylfluorenyl))-4-methylglutamate (**4a**/**5a**, 2.56 g, 5.4 mmol) was dissolved in 100 mL of THF, and the solution was cooled to −78 °C. Lithium aluminum hydride (515 mg, 13.6 mmol) was added, and the reaction mixture was stirred at −78 °C for 4 h. The reaction mixture was quenched with 4 mL of saturated aqueous Na_2SO_4, warmed to room temperature, and diluted with another 50 mL of saturated aqueous Na_2SO_4. The product was extracted into EtOAc (3 × 300 mL), and the combined organic layers were dried, filtered, and evaporated to give 2.42 g of white foam. Purification by MPLC (10% EtOAc in hexanes) gave in order of elution **11a** (63 mg, 7.1%), **8** (28 mg, 2.9%), **7a** (555 mg, 24%), **6a** (1.58 g, 66%). **6a**/**7a**: Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.5; H, 7.5; N, 3.2. Found: C, 78.6; H, 7.4; N, 3.1.

6a: R_f 0.09; mp 119–120 °C ($CHCl_3$–isooctane); ^1H NMR δ 0.79 (d, 3 H, *J* = 6.9 Hz), 1.25 (s, 9 H), 1.28 (ddd, 1 H, *J* = 4.9, 8.1, 14.4 Hz), 1.41 (ddd, 1 H, *J* = 3.6, 5.0, 14.4 Hz), 1.66 (m, 1 H), 2.70 (dd, 1 H, *J* = 5.0, 5.0 Hz), 3.22 (dd, *J* = 7.0, 10.7 Hz), 3.46 (dd, 1 H, *J* = 4.7, 10.7 Hz), 7.1–7.75 (m, 13 H); ^{13}C NMR δ 18.69 (CH_3), 27.82 (CH_3), 32.44 (CH), 39.83 (CH_2), 54.67 (CH), 67.82 (CH_2), 73.24 (C), 81.18 (C), 174.29 (C).

7a: R_f 0.09; ^1H NMR δ 0.61 (d, 3 H, *J* = 6.8 Hz), 1.16 (s, 9 H), 1.24 (m, 1 H), 1.53 (ddd, 1 H, *J* = 5.6, 10.2, 14.0 Hz), 1.78 (m, 1 H), 2.49 (dd, 1 H, *J* = 3.6, 10.2 Hz), 3.32 (dd, 1 H, *J* = 7.8, 10.2 Hz), 3.46 (dd, 1 H, *J* = 5.2, 10.4 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 17.43 (CH_3), 27.82 (CH_3), 33.14 (CH), 40.49 (CH_2), 55.02 (CH), 68.66 (CH_2), 72.94 (C), 80.71 (C), 175.54 (C).

8: R_f 0.38; mp 113–114 °C (isooctane); ^1H NMR δ 1.00 (s, 3 H), 1.09 (s, 9 H), 1.11 (s, 3 H), 1.43 (dd, 1 H, *J* = 4.1, 14.1 Hz), 2.04 (dd, 1 H, *J* = 9.6, 14.1 Hz), 2.68 (dd, 1 H, *J* = 4.1, 9.6 Hz), 3.76 (s, 3 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 23.59 (CH_3), 27.78 (CH_3), 28.03 (CH_3), 40.55 (C), 45.03 (CH_2), 51.67 (CH_3), 54.44 (CH), 72.97 (C), 80.26 (C), 172.25 (C), 178.32 (C). Anal. Calcd for $C_{31}H_{35}NO_4$: C, 76.7; H, 7.3; N, 2.9. Found: C, 76.9; H, 7.2; N, 2.9.

11a: R_f 0.52; ^1H NMR δ 1.24 (s, 9 H), 1.58 (d, 3 H, *J* = 1.2 Hz), 2.18 (dddd, 1 H, *J* = 1.4, 1.4, 7.8, 15.8 Hz), 2.52 (dddd, *J* = 1.4, 1.4, 10.0, 15.5 Hz), 3.04 (dd, 1 H, *J* = 7.8, 10.0 Hz), 5.82 (m, 1 H), 7.0–7.8 (m, 13 H).

***tert*-Butyl (2*S*,4*R*)-5-Hydroxy-4-propyl-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (7b).** α-*tert*-Butyl γ-methyl *N*-(9-(9-phenylfluorenyl))-4-propylglutamate (**5b**, 520 mg, 1.04 mmol) was dissolved in 20 mL of THF, and the solution was cooled to −20 °C. Lithium aluminum hydride (99 mg, 2.6 mmol) was added, and the reaction mixture was stirred at −20 °C for 4 h. The reaction mixture was quenched with 2 mL of saturated aqueous Na_2SO_4, and the solid sodium aluminum sulfate was filtered off. The filter cake was washed with EtOAc (3 × 50 mL), and the combined organic layers were dried, filtered, and evaporated to give 460 mg of white foam. Purification by MPLC (10% EtOAc in hexanes) gave **7b** (262 mg, 54%); R_f 0.11; ^1H NMR δ 0.73 (t, 3 H, *J* = 7.0 Hz), 0.9–1.3 (m, 5 H), 1.17 (s, 9 H), 1.3–1.6 (m, 2 H), 2.44 (dd, 1 H, *J* = 4.0, 5.4 Hz), 3.29 (dd, 1 H, *J* = 8.1, 10.3 Hz), 3.57 (dd, 1 H, *J* = 4.0, 10.3 Hz), 4.4 (br s, 1 H), 7.15–7.8 (m, 13 H); ^{13}C NMR δ 14.05 (CH_3), 19.89 (CH_2), 27.82 (CH_3), 34.76 (CH_2), 38.17 (CH), 39.14 (CH_2), 55.74 (CH), 66.52 (CH_2), 73.01 (C), 80.84 (C), 175.23 (C). Anal. Calcd for $C_{31}H_{37}NO_3$: C, 78.95; H, 7.91; N, 2.97. Found: C, 79.64; H, 7.79; N, 3.03.

***tert*-Butyl (2*S*,4*S*)-5-Hydroxy-4-propyl-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (6b).** As described for the preparation of **7b**, **4b** (173 mg, 0.35 mmol) was converted to **6b** (91 mg, 56%): R_f 0.10; ^1H NMR δ 0.83 (t, 3 H, *J* = 7.0 Hz), 0.8–1.3 (m, 5 H), 1.24 (s, 9 H), 1.5–1.6 (m, 2 H), 2.61 (dd, 1 H, *J* = 4.4, 5.0 Hz), 3.28 (dd, 1 H, *J* = 6.9, 10.9 Hz), 3.56 (dd, 1 H, *J* = 4.1, 10.9 Hz), 7.1–7.8 (m, 13 Hz); ^{13}C NMR δ 14.19 (CH_3), 20.13 (CH_2), 27.80 (CH_3), 35.38 (CH_2), 37.24 (CH), 37.92 (CH_2), 54.71 (CH), 65.97 (CH_2), 73.26 (C), 81.28 (C), 174.16 (C).

***tert*-Butyl (2*S*,4*R*)-5-Hydroxy-4-(cyanomethyl)-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (7c).** α-*tert*-Butyl γ-methyl *N*-(9-(9-phenylfluorenyl))-4-(cyanomethyl)glutamate (**5c**, 420 mg, 0.90 mmol) was dissolved in 20 mL of THF, and the solution was cooled to −40 °C. Lithium aluminum hydride (99 mg, 2.6 mmol) was added, and the reaction mixture was stirred at −40 °C for 2 h. The reaction mixture was quenched with 2 mL of saturated aqueous Na_2SO_4, and the solid sodium aluminum sulfate was filtered off. The filter cake was washed with EtOAc (3 × 50 mL), and the combined organic layers were dried, filtered, and evaporated to give 460 mg of white foam. Purification by MPLC (10% EtOAc in hexanes) gave **7c** (262 mg, 65%): R_f 0.04; ^1H NMR δ 1.18 (s, 9 H), 1.2–1.4 (m, 1 H), 1.49 (ddd, 1 H, *J* = 4.5, 9.6, 14.1 Hz), 1.86 (dd, 1 H, *J* = 7.1, 16.9 Hz), 2.03 (dd, 1 H, *J* = 4.6, 16.9 Hz), 2.20 (m, 1 H), 2.38 (dd, 1 H, *J* = 3.9, 9.6 Hz), 3.48 (dd, 1 H, *J* = 6.4, 10.7 Hz), 3.58 (dd, 1 H, *J* = 5.3, 10.8 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 18.18 (CH_2), 27.71 (CH_3), 34.08 (CH), 36.13 (CH_2), 53.62 (CH), 64.16 (CH_2), 72.79 (C), 81.19 (C), 118.27 (C), 174.89 (C). Anal. Calcd for $C_{30}H_{32}N_2O_3$: C, 76.9; H, 6.9; N, 6.0. Found: C, 77.0; H, 7.3; N, 5.7.

***tert*-Butyl (2*S*,4*S*)-5-Hydroxy-4-(cyanomethyl)-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (6c).** As described for the preparation of **7c**, **4c** (208 mg, 0.44 mmol) was converted to **6c** (135 mg, 67%): R_f 0.04; ^1H NMR δ 1.23 (s, 9 H), 1.1–1.4 (m, 1 H), 1.57 (ddd, 1 H, *J* = 4.4, 7.3, 14.2 Hz), 2.0 (m, 2 H), 2.33 (dd, 1 H, *J* = 6.6, 10.0 Hz), 2.54 (dd, 1 H, *J* = 4.2, 7.3 Hz), 3.33 (dd, 1 H, *J* = 4.4, 11.4 Hz), 3.39 (dd, 1 H, *J* = 5.5, 11.4 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 20.24 (CH_2), 27.71 (CH_3), 34.69 (CH), 35.88 (CH_2), 53.99 (CH), 63.01 (CH_2), 72.99 (C), 81.70 (C), 118.55 (C), 174.05 (C).

***tert*-Butyl (2*S*)-5-Hydroxy-2-(*N*-(9-(9-phenylfluorenyl))amino)pentanoate (6e).** As described for the preparation of **7c**, **4** (915 mg, 2 mmol) was converted to **6e** (868 mg, 95%): R_f 0.07; mp 123 °C (Et_2O); ^1H NMR δ 1.19 (s, 9 H), 1.4–1.7 (m, 4 H), 2.53 (dd, 1 H, *J* = 4.7, 6.8 Hz), 3.53 (m, 2 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 27.79 (CH_3), 28.37 (CH_2), 32.08 (CH_2), 55.61 (CH), 62.41 (CH_2), 73.02 (C), 80.79 (C), 178.84 (C). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.3; H, 7.3; N, 3.3. Found: C, 78.7; H, 7.3; N, 3.26.

(2*S*,4*R*)-4-Methyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (9a). As described for **10a**, **6a** (301 mg, 0.68 mmol) was transformed into **9a** (260 mg, 89%): R_f 0.56; ^1H NMR δ 0.86 (d, 3 H, *J* = 6.2 Hz), 1.2–1.4 (m, 1 H), 1.28 (s, 9 H), 1.66 (m, 1 H), 2.3–2.5 (m, 2 H), 3.16 (dd, 1 H, *J* = 1.2, 10.1 Hz), 3.25 (m, 1 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 16.74 (CH_3), 27.91 (CH_3), 32.04 (CH), 40.16 (CH_2), 57.17 (CH_2), 61.62 (CH), 76.49 (C), 79.43 (C), 175.49 (C).

(2*S*,4*R*)-4-Propyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (9b). As described for **10a**, **6b** (301 mg, 0.68 mmol) was transformed into **9c** (260 mg, 89%): R_f 0.55; ^1H NMR δ 0.81 (t, 3 H, *J* = 7.0 Hz), 1.28 (s, 9 H), 1.05–1.35 (m, 5 H), 1.68 (m, 1 H), 2.32 (m, 1 H), 2.37 (m, 1 H), 3.15 (dd, 1 H, *J* = 1.1, 9.9 Hz), 3.29 (m, 1 H), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 14.20 (CH_3), 21.57 (CH_2), 27.91 (CH_3), 35.16 (CH_2), 37.31 (CH), 38.33 (CH_2), 55.62 (CH_2), 61.35 (CH), 76.54 (C), 79.43 (C), 175.53 (C).

(2*S*,4*S*)-4-(Cyanomethyl)-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (9c). As described for **10a**, **6c** (301 mg, 0.68 mmol) was transformed into **9c** (260 mg, 89%): R_f 0.14; ^1H NMR δ 1.28 (s, 9 H), 1.54 (ddd, 1 H, *J* = 9.8, 12.0, 12.5 Hz), 1.81 (dddd, 1 H, *J* = 0.8, 1.3, 6.1, 12.5 Hz), 2.23 (dd, 1 H, *J* = 6.8, 16.9 Hz), 2.29 (dd, *J* = 6.2, 16.9 Hz), 2.56 (dd, *J* = 8.7, 10.1 Hz), 2.71 (dddddd, 1 H, *J* = 6.1, 6.6, 6.8, 6.8, 10.1, 12.2 Hz), 3.27 (dd, 1 H, *J* = 1.3, 9.8 Hz), 3.39 (ddd, 1 H, *J* = 0.8, 6.6, 8.7 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 19.85 (CH_2), 27.86 (CH_3), 33.80 (CH), 37.11 (CH_2), 54.30 (CH_2), 61.17 (CH), 76.36 (C), 80.11 (C), 117.92 (C), 174.61 (C).

(2*S*)-*N*-(9-(9-Phenylfluorenyl))proline *tert*-Butyl Ester (9e). (A) From 6e. As described for the preparation of **10a**, **6e** (75 mg, 0.18 mmol) was transformed into **9e** (68 mg, 95%): R_f 0.07; mp 64–66 °C; ^1H NMR δ 1.28 (s, 9 H), 1.55–1.75 (m, 3 H), 1.85 (m, 1 H), 2.83 (ddd, 1 H, *J* = 6.2, 9.1, 9.1 Hz), 3.16 (dd, 1 H, *J* = 3.2, 9.0 Hz), 3.23 (ddd, 1 H, *J* = 3.3, 6.6, 9.7 Hz), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 24.89 (CH_2), 27.91 (CH_3), 32.13 (CH_2), 50.22 (CH_2), 61.48 (CH), 76.88 (C), 79.47 (C), 175.58 (C). Anal. Calcd for $C_{28}H_{29}NO_2$: C, 81.7; H, 7.1; N, 3.4. Found: C, 81.7; H, 7.1; N, 3.1.

(B) With DIBAL. α-*tert*-Butyl γ-methyl *N*-(9-(9-phenylfluorenyl))glutamate (**3**, 980 mg, 2.14 mmol) was dissolved in 250 mL of THF. The solution was cooled to −40 °C, and DIBAL (35

mL, 35 mmol, 300 mol %, 1 M in hexane) was added via syringe at 4.4 mL min^{-1}. Stirring was then continued at −40 °C for 2 h. The reaction mixture was cannulated (Teflon cannula) into a stirred mixture of 100 mL of 1 M aqueous H_3PO_4 and 100 mL of ether. The organic layer was washed with brine, the combined aqueous phases were extracted with another 100-mL portion of ether, and the combined organic layers were dried, filtered, and evaporated to give a glassy semisolid material. This was applied onto a short column of silica and eluted with 10% EtOAc in hexanes to give 810 mg (81%) of **9e**.

(2*S*,4*S*)-4-Methyl-*N*-(9-(9-phenylfluorenyl))proline *t*-Butyl Ester (10a). To a stirred solution of alcohol **7a** (887 mg, 2 mmol) dissolved in 20 mL of THF were added triphenylphosphine (1.05 g, 4 mmol), carbon tetrabromide (1.33 g, 4 mmol), and diisopropylethylamine (700 μL, 517 mg, 4 mmol). The reaction mixture was stirred for 1 h at room temperature, diluted with 150 mL of ether, and extracted with 0.5 M H_3PO_4 (2 × 50 mL), saturated aqueous Na_2CO_3 (50 mL), and brine (50 mL). The combined acidic and brine washes were back extracted with another 100 mL of ether, and the organic solutions were combined, dried, filtered, and evaporated to give crude **10a**. Chromatography over silica (5% EtOAc in hexanes as eluant) gave **10a** (750 mg, 88%): R_f 0.52; mp 121 °C from 80% aqueous EtOH); ^1H NMR δ 0.94 (d, 3 H, J = 6.3 Hz), 1.20 (s, 9 H), 1.30 (m, 1 H), 1.96 (m, 1 H), 2.04 (m, 1 H), 2.97 (dd, 1 H, J = 8.2, 8.3 Hz), 3.01 (dd, 1 H, J = 9.4, 11.3 Hz), 3.31 (dd, 1 H, J = 7.0, 11.3 Hz), 7.0–7.8 (m, 13 H); ^{13}C NMR δ 17.30 (CH_3, 27.92 (CH_3), 33.26 (CH), 40.60 (CH_2), 59.07 (CH_2), 62.41 (CH), 77.44 (C), 79.39 (C), 175.56 (C). Anal. Calcd for $C_{29}H_{31}NO_2$: C, 81.9; H, 7.3; N, 3.3. Found: C, 82.0; H, 7.3; N, 3.3.

(2*S*,4*S*)-4-Propyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (10b). As described for the preparation of **10a**, **7b** (886 mg, 2 mmol) was transformed into **10b** (774 mg, 91%): R_f 0.49; ^1H NMR δ 0.83 (t, 3 H, J = 7.1 Hz), 1.20 (s, 9 H), 1.15–1.38 (m, 5 H), 1.85 (m, 1 H), 2.03 (m, 1 H), 2.95 (dd, 1 H, J = 7.9, 8.6 Hz), 3.03 (dd, 1 H, J = 9.6, 11.3 Hz), 3.34 (dd, 1 H, J = 7.0, 11.3 Hz), 7.0–7.8 (m, 13 H); ^{13}C NMR δ 14.15 (CH_3), 21.53 (CH_2), 27.91 (CH_3), 35.18 (CH_2), 38.57 (CH), 38.75 (CH_2)$_3$, 57.52 (CH_2), 62.17 (CH), 77.49 (C), 79.27 (C), 175.57 (C). Anal. Calcd for $C_{31}H_{35}NO_2$: C, 82.1; H, 7.8; N, 3.1. Found: C, 81.8; H, 8.1; N, 2.9.

(2*S*,4*R*)-4-(Cyanomethyl)-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (10c). As described for the preparation of **10a**, **7c** (150 mg, 0.32 mmol) was transformed into **10c** (124 mg, 87%): R_f 0.18; ^1H NMR δ 1.23 (s, 9 H), 1.53 (ddd, 1 H, J = 4.3, 4.6, 13.3 Hz), 2.07 (ddd, 1 H, J = 7.2, 10.0, 13.3 Hz), 2.30 (m, 1 H), 2.64 (dd, 1 H, J = 7.1, 16.8 Hz), 2.76 (dd, 1 H, J = 8.3, 16.8 Hz), 3.00 (dd, 1 H, J = 4.6, 10.0 Hz), 3.13 (dd, 1 H, J = 4.3, 10.3 Hz), 3.23 (dd, 1 H, J = 6.1, 10.3 Hz), 7.1–7.7 (m, 13 H); ^{13}C NMR δ 20.77 (CH_2), 27.82 (CH_3), 34.98 (CH), 36.45 (CH_2), 54.92 (CH_2), 60.36 (CH), 76.29 (C), 80.27 (C), 119.16 (C), 174.72 (C). Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 80.0; H, 6.7; N, 6.2. Found: C, 80.3; H, 7.1; N, 5.9.

(2*S*,4*R*)-4-Methylproline (12a). (2*S*,4*R*)-4-Methyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-butyl ester (**9a**, 221 mg, 0.5 mmol) was dissolved in 4 mL of CH_2Cl_2, and 1 mL of trifluoroacetic acid was added. The reaction mixture was stirred for 16 h and then partitioned between isooctane and water (5 mL each). The organic phase was extracted with 2 mL of H_2O, and the aqueous solutions were combined and evaporated to dryness in vacuo to give **12a** (56 mg, 87%): ^1H NMR δ (D_2O) 0.92 (d, 3 H, J = 6.6 Hz), 1.88 (ddd, 1 H, J = 8.6, 9.4, 13.3 Hz), 2.21 (dddd, 1 H, J = 0.9, 5.0, 7.2, 13.3 Hz), 2.28 (ddddq, 1 H, J = 6.6, 7.2, 7.2, 8.6, 8.8 Hz), 2.76 (dd, 1 H, J = 8.8, 11.5 Hz), 3.42 (dd, 1 H, J = 7.2, 11.5 Hz), 4.35 (dd, 1 H, J = 4.9, 9.6 Hz); ^{13}C NMR δ 15.75 (CH_3), 31.61 (CH), 36.07 (CH_2), 52.01 (CH_2), 59.98 (CH), 173.22 (C).

(2*S*,4*R*)-4-Propylproline (12b). As described for **12a**, **9b** (40 mg, 0.88 mmol) was transformed to **12b** (12 mg, 90%): ^1H NMR δ 0.72 (t, 3 H, J = 7.3 Hz), 1.06–1.30 (m, 4 H), 1.89 (m, 1 H), 2.14–2.26 (m, 2 H), 2.80 (dd, 1 H, J = 9.0, 11.5 Hz), 3.44 (dd, 1 H, J = 7.9, 11.5 Hz), 4.30 (dd, 1 H, J = 4.3, 9.6 Hz); ^{13}C NMR δ 13.12 (CH_3), 20.46 (CH_2), 33.51 (CH_2), 34.15 (CH_2), 36.45 (CH), 50.71 (CH_2), 59.62 (CH), 172.82 (C); HRMS calcd for $C_8H_{16}NO_2$ (MH^+) 158.1175, found 158.1178.

(2*S*,4*S*)-4-(Cyanomethyl)proline (12c). As described for **12a**, **9c** (150 mg, 0.32 mmol) was transformed to **12c** (96 mg, 67%): ^1H NMR δ 1.95 (ddd, 1 H, J = 9.0, 9.0, 13.8 Hz), 2.23 (ddd, 1 H, J = 5.2, 7.2, 13.8 Hz), 2.40–2.60 (m, 3 H), 2.84 (dd, 1 H, J = 8.8, 12.0 Hz), 3.43 (dd, 1 H, J = 7.3, 12.0 Hz), 4.29 (dd, 1 H, J = 5.0, 9.4 Hz); ^{13}C NMR δ 18.88 (CH_2), 32.87 (CH_2), 32.97 (CH), 49.24 (CH_2), 59.06 (CH), 118.83 (C), 170.93 (C); HRMS calcd for $C_7H_{11}N_2O_2$ (MH^+) 155.0830, found 155.0826.

(2*S*,4*S*)-4-Methylproline (13a). As described for **12a**, **10a** (221 mg, 0.5 mmol) was transformed to **13a** (58 mg, 90%): ^1H NMR (D_2O) δ 0.94 (d, 3 H, J = 6.7 Hz), 1.66 (ddd, 1 H, J = 9.6, 9.9, 13.1 Hz), 2.40 (ddddq, 1 H, J = 6.7, 7.4, 7.6, 9.9, 10 Hz), 2.54 (dddd, 1 H, $J \approx 1$, 7.6, 13.1 Hz), 2.88 (dd, 1 H, J = 10.0, 11.4 Hz), 3.45 (dd, 1 H, J = 7.4, 11.4 Hz), 4.33 (dd, 1 H, J = 8.4, 9.6 Hz); ^{13}C NMR δ 15.63 (CH_3), 32.89 (CH), 36.03 (CH_2), 51.92 (CH_2), 59.79 (CH), 171.93 (C).

(2*S*,4*S*)-4-Propylproline (13b). As described for **12a**, **10b** (134 mg, 0.3 mmol) was transformed to **13b** (44 mg, 95%): ^1H NMR δ 0.62 (t, 3 H, J = 7.2 Hz), 1.00–1.20 (m, 4 H), 1.50 (ddd, 1 H, J = 10, 10, 13.1 Hz), 2.16 (m, 1 H), 2.38 (ddd, J = 7.4, 7.4, 13.1 Hz), 2.75 (dd, 1 H, J = 10.1, 11.5 Hz), 3.29 (dd, 1 H, J = 7.5, 11.5 Hz), 4.17 (dd, 1 H, J = 8.2, 9.9 Hz); ^{13}C NMR δ 13.11 (CH_3), 20.48 (CH_2), 33.58 (CH_2), 34.25 (CH_2), 37.77 (CH), 50.62 (CH_2), 59.36 (CH), 171.61 (C).

(2*S*,4*R*)-4-(Cyanomethyl)proline (13c). As described for **12a**, **10c** (150 mg, 0.32 mmol) was transformed to **13c** (92 mg, 66%): ^1H NMR δ 1.60 (ddd, 1 H, J = 9.7, 9.7, 13.2 Hz), 2.27–2.55 (m, 3 H), 2.41 (m, 1 H), 2.81 (dd, 1 H, J = 9.5, 11.8 Hz), 3.30 (dd, 1 H, J = 7.3, 11.8 Hz), 4.15 (dd, 1 H, J = 8.0, 9.9 Hz); ^{13}C NMR δ 18.74 (CH_2), 33.09 (CH_2), 34.05 (CH), 49.06 (CH_2), 59.32 (CH), 118.64 (C), 170.62 (C).

(2*S*,4*S*)-4-Methylproline *tert*-Butyl Ester (14). The protected *cis*-4-methylproline (**10a**, 880 mg, 2 mmol) was dissolved in 15 mL of glacial acetic acid/methanol, 1/1, and 10% Pd/C (100 mg) was added. The reaction vessel was evacuated, and the atmosphere was replaced with hydrogen, repeating the process four times. The mixture was then stirred under a static atmosphere of H_2 (1 atm) for 24 h at room temperature. The reaction mixture was filtered through a pad of Celite, the filtrate was evaporated, and the residue was partitioned between 1 M AcOH (30 mL) and ether (3 × 50 mL). The aqueous layer was adjusted to pH ≈9.5 with saturated aqueous Na_2CO_3, and the product was extracted into 20% i-PrOH/$CHCl_3$ (2 × 50 mL), followed by final washing with $CHCl_3$ (50 mL). The organic extracts were combined, dried, filtered, and evaporated to give **14** (360 mg, 97%) as a viscous oil; ^1H NMR δ 1.01 (d, 3 H, J = 6.6 Hz), 1.35 (ddd, 1 H, J = 8.1, 8.1, 12.4 Hz), 1.47 (s, 9 H), 2.20 (m, 1 H), 2.29 (ddd, 1 H, J = 7.9, 7.9, 12.4 Hz), 2.55 (br s, 1 H), 2.61 (dd, J = 8.2, 9.8 Hz), 3.04 (dd, 1 H, J = 6.7, 9.8 Hz), 3.68 (dd, 1 H, J = 7.9, 8.1 Hz); ^{13}C NMR δ 18.08 (CH_3), 28.02 (CH_3), 34.27 (CH), 38.90 (CH_2), 54.50 (CH_2), 60.57 (CH), 80.95 (C), 174.83 (C).

***tert*-Butyl (2*S*)-4-Phenyl-*N*-(9-(9-phenylfluorenyl))-pyroglutamate (15).** To a cooled, stirred solution of KHMDS (6 mL, 3.6 mmol, 180 mol %, 0.6 M in toluene) in 15 mL of THF was added α-*tert*-butyl γ-methyl *N*-(9-(9-phenylfluorenyl))-glutamate (**3**, 915 mg, 2 mmol) in 5 mL of THF over 2 min. The mixture was stirred at −78 °C for 30 min, after which time η^6-benzene chromium tricarbonyl (857 mg, 4 mmol, 200 mol %) in 5 mL of THF was added. Stirring was continued for another 10 h at −78 °C, and a solution of iodine (4 g, 15.8 mmol, 790 mol %) in 5 mL of THF was slowly added. The cooling bath was removed, and stirring was continued at room temperature until gas evolution ceased (40 min). The mixture was then partitioned between saturated sodium thiosulfate and ether, and the organic layer was washed with 0.5 M H_3PO_4, dried, filtered, and evaporated to give a greenish oil. Rapid chromatography over silica gel gave 125 mg (13%) of pure **15**, along with **16** (364 mg, 43%) and **17** (96 mg, 11%).

15: R_f 0.18; mp 168–169 °C; ^1H NMR δ 1.25 (s, 9 H), 2.22–2.40 (m, 2 H), 3.89 (dd, 1 H, J = 1.5, 8.8 Hz), 3.95 (dd, 1 H, J = 8.6, 12.0 Hz), 7.15–7.85 (m, 18 H); ^{13}C NMR δ 27.54 (CH_3), 34.59 (CH_2), 47.10 (CH), 59.29 (CH), 73.48 (C), 81.57 (C), 171.29 (C), 176.13 (C). Anal. Calcd for $C_{34}H_{31}NO_3$: C, 81.4; H, 6.2; N, 2.8. Found: C, 81.2; H, 6.3; N, 2.8.

16: R_f 0.05; mp 199–202 °C; ^1H NMR δ 1.20 (s, 9 H), 1.83 (dddd, 1 H, J = 1.0, 1.2, 8.9, 13.0 Hz), 2.21 (dddd, 1 H, J = 9.2, 9.3, 11.9, 12.8 Hz), 2.32 (ddd, 1 H, J = 1.2, 9.2, 16.3 Hz), 2.66 (ddd, 1 H, J = 8.9, 11.9, 16.3 Hz), 3.88 (dd, 1 H, J = 1.0, 9.3 Hz), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 25.16 (CH_2), 27.49 (CH_3), 30.99 (CH_2), 61.66

(CH), 73.13 (C), 81.37 (C), 171.42 (C), 176.49 (C).

(2*S*,4*R*)-4-Phenyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (10d). To a solution of **15** (84 mg, 0.17 mmol) in 5 mL of dry THF were added BH_3·THF (1 M, 5 mL) and $NaBH_4$ (5 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 2 days. The reaction was quenched by pouring the mixture into 0.5 M H_3PO_4 (10 mL), and the product was extracted into ether (3 × 20 mL). Drying and evaporating gave a crude product mixture, which was purified by MPLC (2% EtOAc in hexane) to give pure **10d** (17 mg, 21 %) and recovered **15** (65 mg, 77%).

10d: R_f 0.52; ^{1}H NMR δ 1.31 (s, 9 H), 1.93 (m, 1 H), 2.78 (dd, 1 H, J = 8.3, 10.6 Hz), 3.36 (dd, J = 5.3, 6.0 Hz), 3.52 (dd, 1 H, J = 8.2, 9.0 Hz), 3.58 (m, 1 H); ^{13}C NMR δ 27.94 (CH_3), 38.49 (CH_2), 42.51 (CH), 56.82 (CH_2), 61.39 (CH), 79.81 (C), 175.22 (C); HRMS calcd for $C_{34}H_{34}NO_2$ (MH^+) 488.2589, found 488.2576.

(2*S*)-*N*-(9-(9-Phenylfluorenyl))glutamic Acid α-*tert*-Butyl Ester (17). The unsymmetrical diester **3** (2.29 g, 5 mmol) was dissolved in 40 mL of THF. Lithium hydroxide monohydrate (250 mg, 6 mmol) in 4 mL of distilled H_2O was added, and the reaction mixture was refluxed for 4 h. The solvent was evaporated, and the residue was partitioned between 100 mL of half saturated Na_2CO_3 and ether (50 mL). The aqueous layer was acidified to pH 6.5 with 1 M H_3PO_4 and extracted with EtOAc (2 × 100 mL), and the organic extracts were combined, dried, filtered, and evaporated to give **17** as a white foam (2.35 g, 106%); after 48 h in high vacuum (0.3 mmHg, 40 °C) 2.22 g (100%): R_f 0.49; mp 60–62 °C (EtOAc–isooctane); ^{1}H NMR δ 1.21 (s, 9 H), 1.6–1.85 (m, 2 H), 2.2–2.5 (m, 2 H), 2.58 (dd, 1 H, J = 4.7, 7.5 Hz), 7.2–7.8 (m, 13 H); ^{13}C NMR δ 27.76 (CH_3), 29.19 (CH_2), 31.57 (CH_2), 55.54 (CH), 72.97 (C), 81.63 (C), 173.83 (C), 177.39 (C). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.8; H, 6.6; N, 3.2. Found: C, 76.0; H, 6.9; N, 3.0.

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Registry No. **1**, 1499-55-4; **2**, 119595-72-1; **3**, 119595-73-2; **4a**, 119595-74-3; **4b**, 119619-09-9; **4c**, 119595-75-4; **4e**, 119595-76-5; **5a**, 119595-77-6; **5b**, 119595-78-7; **5c**, 119595-79-8; **5e**, 119595-80-1; **6a**, 119595-81-2; **6b**, 119595-82-3; **6c**, 119595-83-4; **6e**, 119595-84-5; **7a**, 119677-62-2; **7b**, 119595-85-6; **7c**, 119677-63-3; **8**, 119595-86-7; **9a**, 119595-87-8; **9b**, 119595-88-9; **9c**, 119595-89-0; **9e**, 119595-90-3; **10a**, 119677-64-4; **10b**, 119595-91-4; **10c**, 119595-92-5; **10d**, 119595-93-6; **11a**, 119595-94-7; **12a**, 23009-50-9; **12b**, 31101-27-6; **12c**, 119595-95-8; **13a**, 6734-41-4; **13b**, 6734-44-7; 13c, 119595-96-9; **14**, 119595-97-0; **15**, 119595-98-1; **16**, 119595-99-2; **17**, 119596-00-8; MeI, 74-88-4; F_3CSO_3Pr, 29702-90-7; $BrCH_2CN$, 590-17-0; 9-bromo-9-phenylfluorene, 55135-66-5; η^6-benzene chromium tricarbonyl, 12082-08-5.

Chirospecific Synthesis of β-Hydroxy α-Amino Acids

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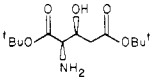
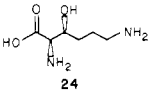
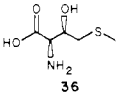
A variety of β-hydroxy α-amino acids have been synthesized with complete enantiomeric purity from L-serine. These include β-hydroxyglutamic acid, β-hydroxypipecolic acid, β-hydroxylysine, β-hydroxyproline, and β-hydroxymethionine. The syntheses proceed by the ready addition of vinyl- and allylmagnesium bromide and (methylthio)methyllithium to the carboxyl group of *N*-(phenylsulfonyl)serine to give high yields of the corresponding ketones. These particular organometallic reagents were chosen because by further manipulation they allow the introduction of a wide scope of functionalities. By judicious choice of reducing agent, either diastereomeric amino alcohol can be obtained with high preference on reduction of the amino ketone. The original serine primary hydroxyl group can then be selectively oxidized to give the amino acid in high overall yield and >99% ee.

Introduction

The chirospecific synthesis of β-hydroxy α-amino acids has long been of interest, sparked in part by the possible use of such compounds as potent enzyme inhibitors.[1a-c] Further interest stems from their use as attractive starting materials for chirospecific natural product synthesis. Their utility lies in their two set stereocenters and multifunctionalities, all of which are differentiable. Recently several syntheses of such compounds have appeared in the literature.[2-6] However, usually the synthesis of only one hydroxy amino acid is reported, and the possibility for generalization of the procedure is limited. We now report the

Table I. Summary of Yields in Synthetic Sequences

compounds	overal yield,[a] % syn diastereomer (anti)
 14	30 (24)
 19	33 (26)
 24	20 (16)
 29	37 (31)
 36	30 (24)

[a] From serine.

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