quenched with 30% aqueous NH_4OH (50 mL) and extracted with CH_2Cl_2. The organic phases were washed with 30% NH_4OH and water, dried, evaporated, and flash chromatographed (Al_2O_3, CH_2Cl_2) to yield **40** (135 mg, 38%), which was identified by comparison of its spectral data to the ones previously obtained.

***cis*-4-[Bis(methoxycarbonyl)methyl]-3-(3-indolylmethyl)-1-methylpiperidine (41).** A solution of enamine **40** (250 mg, 0.70 mmol) in absolute EtOH (25 mL) was hydrogenated at room temperature in the presence of 10% Pd–C (56 mg). When the absorption ceased, the catalyst was filtered off, and the solution was evaporated and flash chromatographed (CH_2Cl_2–MeOH (93:7)) to give **41** (231 mg, 92%): IR ($CHCl_3$) 3475 (NH), 1732 cm^{-1} (CO); ^1H NMR (400 MHz) 1.79 (m, 1 H, 4-H), 1.90 (td, J = 12, 3 Hz, 1 H, 5-Ha), 2.01–2.20 (m, 1 H, 5-He), 2.15 (s, 3 H, NCH_3), 2.53 (dd, J = 14, 3 Hz, 1 H, 2-Ha), 2.70 (br d, J = 11 Hz, 1 H, 6-He), 2.85 (br t, J = 11 Hz, 1 H, 6-H), 3.05 (dd, J = 14, 8 Hz, 1 H, 2-He), 3.73 and 3.75 (2 s, 3 H each, OCH_3), 3.98 (d, J = 4 Hz, 2 H, $InCH_2$), 6.90 (s, 1 H, In-2H), 7.03 (d, J = 7 Hz, 1 H, In-6H), 7.09 (t, J = 7 Hz, 1 H, In-5H), 7.30 (t, J = 7 Hz, 1 H, In-4H), 7.50 (d, J = 7 Hz, 1 H, In-7H), 8.90 (br, 1 H, NH); ^{13}C NMR 27.2 (C-5), 27.3 (C-7), 38.6 (C-4), 40.3 (C-3), 46.0 (NCH_3), 52.7 (OCH_3), 55.1 (COCH), 55.1 (C-6), 60.3 (C-2), 111.2 (In-C7), 113.4 (In-C3), 118.1 (In-C5), 119.1 (In-C4), 121.2 (In-C6), 122.4 (In-C2), 127.8 (In-C3a), 136.4 (In-C7a), 168.8 (CO), 169.6 (CO); MS m/z (relative intensity) 358 (M^+, 6), 356 (7), 327 (4), 322 (8), 297 (4), 240 (15), 227 (45), 130 (31), 96 (100). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.98; H, 7.41; N, 7.80.

20-Deethylsilicine (20). A mixture of **41** (100 mg, 0.28 mmol) and PPA (2 mL) was stirred under argon atmosphere at 100 °C for 2 h. The cooled mixture was poured into ice–water, basified with potassium carbonate, and extracted with CH_2Cl_2. Evaporation of the dried (Na_2SO_4) organic extracts, followed by a flash chromatography (CH_2Cl_2–MeOH (9:1)) furnished **20** as an oil (30 mg, 40%): IR (NaCl) 1650 cm^{-1} (CO); ^1H NMR (1.54 (qd, J = 12, 4 Hz, 1 H, 20-Ha), 1.70–1.78 (m, 1 H, 15-H), 1.79 (br d, J = 12 Hz, 1 H, 20-He), 1.81 (t, J = 12 Hz, 1 H, 5-Ha), 1.91 (td, J = 12, 4 Hz, 1 H, 21-Ha), 2.12–2.21 (m, 1 H, 16-H), 2.36 (s, 3 H, NCH_3), 2.70 (dd, J = 18, 9 Hz, 1 H, 14-H), 2.72 (dd, J = 17, 9 Hz, 1 H, 6-H), 2.79 (dd, J = 18, 2 Hz, 1 H, 14-H), 2.87 (br d, J = 12 Hz, 1 H, 21-He), 3.03 (ddd, J = 12, 4, 2 Hz, 1 H, 5-He), 3.19 (dd, J = 17, 5 Hz, 1 H, 6-H), 7.11 (ddd, J = 8, 7, 2 Hz, 1 H, 10-H), 7.32 (td, J = 8, 1 Hz, 1 H, 11-H), 7.34 (dd, J = 7, 1 Hz, 1 H, 12-H), 7.60 (dd, J = 8, 1 Hz, 1 H, 9-H), 9.00 (br s, 1 H, NH); ^{13}C NMR 30.4 (C-6), 34.2 (C-16), 37.5 (C-14), 40.7 (C-15), 46.3 (NCH_3), 55.7 (C-21), 63.5 (C-5), 112.0 (C-12), 120.0 (C-10), 121.1 (C-9), 122.1 (C-7), 126.6 (C-11), 128.6 (C-8), 130.9 (C-2), 136.5 (C-13), 193.1 (CO); MS m/z (relative intensity) 268 (M^+, 85), 197 (18), 168 (44), 130 (36), 110 (53), 96 (100), 42 (99); calcd mass for $C_{17}H_{20}N_2O$ 268.1571, found 268.1583. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.08; H, 7.53; N, 10.46.

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Registry No. **1a**, 1620-40-2; **1b**, 5562-24-3; **2a**, 143924-08-7; **2b**, 143924-17-8; **2c**, 5083-55-6; **2c** alcohol, 4684-84-8; (±)-**3a**, 143924-09-8; (±)-**3b**, 143924-18-9; (±)-**3c**, 143924-20-3; (±)-**9a**, 143924-10-1; (±)-**9b**, 143924-19-0; (±)-**9c**, 137710-66-8; (±)-**20**, 137710-70-4; **24**, 143924-11-2; **24** ketone, 16498-68-3; (±)-**28**, 143924-12-3; (±)-**29a**, 143924-13-4; (±)-**29b**, 143924-21-4; (±)-**36a**, 143924-14-5; (±)-**36b**, 143924-22-5; (±)-**37a**, 143924-15-6; (±)-**37b**, 143924-23-6; (±)-**38**, 137710-67-9; (±)-**40**, 137710-68-0; (±)-**41**, 143924-16-7; 3-(chloromethyl)pyridine hydrochloride, 6959-48-4; 3-[(phenylsulfonyl)methyl]pyridine, 1620-51-5; 3-pyridylacetonitrile, 6443-85-2; indole, 120-72-9.

Supplementary Material Available: A 2D-NMR spectrum of 20-deethylsilicine (**20**) (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Orthogonally Protected N^3-(Carboxymethyl)-L-2,3-diaminopropanoic Acids and O-(Carboxymethyl)-L-serines for Solid-Phase Peptide Synthesis

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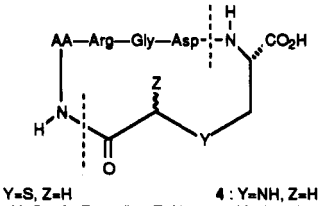
The syntheses of the orthogonally protected N^3-(carboxymethyl)-2,3-L-diaminopropanoic acids **18**, **19**, and **20** and O-(carboxymethyl)-L-serines **35** and **38** are described. All of the diaminopropanoic acids were prepared via reductive amination of the known oxazolidine aldehyde **9**. The carboxymethyl serines were prepared via O-alkylation of N-CBZ-L-serine. To enable incorporation of these amino acids into cyclic peptides, protecting group schemes were designed for compatibility with either Boc or Fmoc solid-phase peptide synthesis.

Introduction

As part of our program focused on the discovery and development of antithrombotic agents, we recently reported that cyclic thioether peptides **1** that incorporate the Arg-Gly-Asp (RGD) tripeptide sequence are potent inhibitors of fibrinogen binding to the platelet glycoprotein II_bIII_a (GP II_bIII_a) receptor.[1] In such peptides, potency in the platelet aggregation assay was sensitive to certain structural changes in the *S*-(carboxymethyl)cysteine bridge. For instance, sulfide oxidation followed by chromatographic separation gave sulfoxide **2b** (AA = D-Tyr)



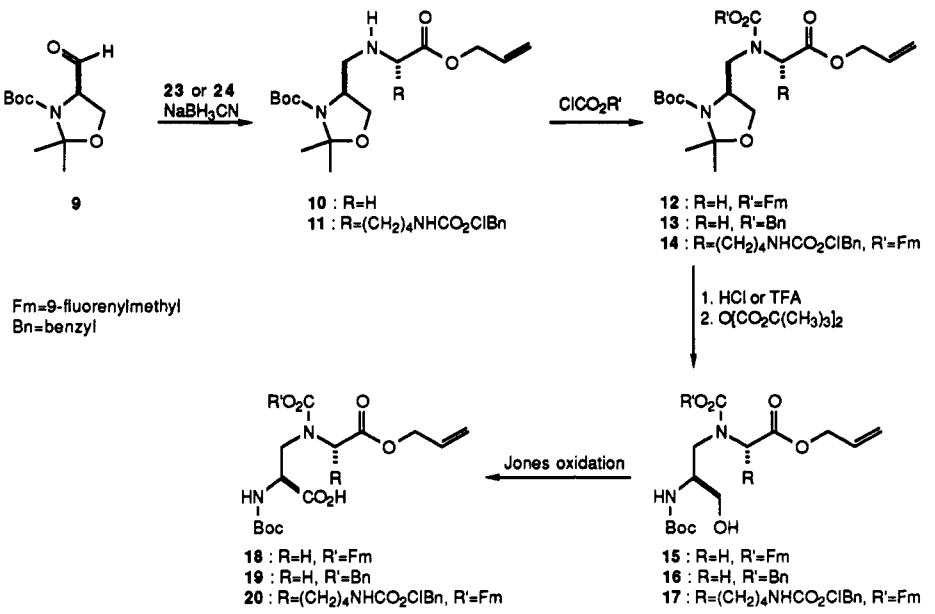
1 : Y=S, Z=H
2a : Y=S—O (R config), Z=H
2b : Y=S—O (S config), Z=H
3a : Y=S, Z=alkyl
3b : Y=S, Z=phenyl
3c : Y=S, Z=naphthyl
4 : Y=NH, Z=H
5 : Y=N-acyl or N-alkyl, Z=H
6 : Y=NH, Z=alkyl
7 : Y=N-acyl or N-alkyl, Z=alkyl
8 : Y=O, Z=H

which was 5-fold more potent than **1**. Incorporation of acetyl bridge substituents (Z) such as phenyl or naphthyl gave peptides **3b** and **3c** (AA = Gly) that were six and 50 times more potent, respectively, than the unsubstituted parent peptide **1**. Based upon these results, we sought to

(1) Barker, P. L.; Bullens, S.; Bunting, S.; Burdick, D. J.; Chan, K. S.; Deisher, T.; Eigenbrot, C.; Gadek, T. R.; Gantzos, R.; Lipari, M. T.; Muir, C. D.; Napier, M. A.; Pitti, R. M.; Padua, A.; Quan, C.; Stanley, M. S.; Struble, M.; Tom, J. Y. K.; Burnier, J. P. *J. Med. Chem.* **1992**, *35*(11), 2040–2048.

0022-3263/92/1957-6421$03.00/0

Scheme I



9

10 : R=H
11 : R=$(CH_2)_4NHCO_2CIBn$

12 : R=H, R'=Fm
13 : R=H, R'=Bn
14 : R=$(CH_2)_4NHCO_2CIBn$, R'=Fm

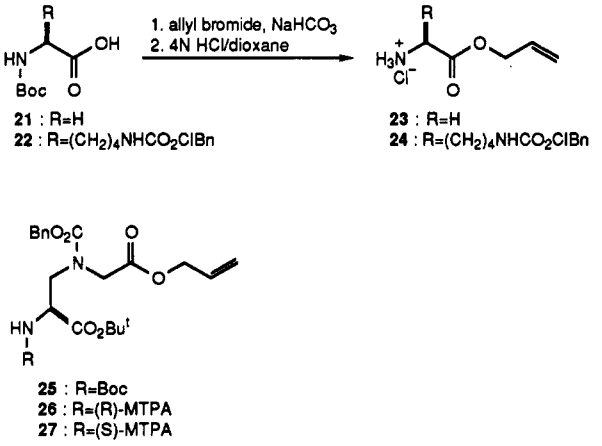
15 : R=H, R'=Fm
16 : R=H, R'=Bn
17 : R=$(CH_2)_4NHCO_2CIBn$, R'=Fm

18 : R=H, R'=Fm
19 : R=H, R'=Bn
20 : R=$(CH_2)_4NHCO_2CIBn$, R'=Fm

further investigate the structure–activity relationships (SAR) occurring in this region of the peptide in order to maximize potency. One rational approach substituted the heteroatoms N and O in place of sulfur to generate the peptides **4** and **8**. Comparison of the platelet antiaggregatory behavior of the sulfoxide **2b** relative to that of the sulfide **1** clearly demonstrated that heteroatom functionalization could create a more potent analogue. In this context, replacing the sulfur atom with nitrogen was an exciting prospect, since the resulting secondary amine could be readily acylated or alkylated (**5**), thus providing a handle on the peptide to which a variety of additional functional groups could be tethered. Such functional groups would be useful in probing for additional charged or hydrophobic binding interactions between the RGD peptide and GP II_bIII_a. From RGD peptides in the thioether series (i.e., **3a**, **3b**, **3c**) an SAR for alkyl and aryl substituents (Z) on the acetyl bridge had been generated and was available for comparison to analogous compounds in the amine series. However, it was not known how a charged species such as carboxyl or amine attached to this region of the molecule would influence the binding affinity. The SAR generated from the amine series would allow this determination. In order to interpret the SAR of RGD peptides containing acetyl bridge substituents and make valid comparisons with peptides **3a**, **3b**, and **3c**, the unambiguous assignment of stereochemistry at this position was crucial.

To design a straightforward synthetic strategy for these heteroatom and acetyl bridge-substituted peptides, we disconnected the cycle at the Asp carboxyl and AA amine, intending to incorporate the ether or amino group into the peptide as part of the C-terminal residue. This paper reports the synthesis of these heteroatom-containing amino acids, appropriately protected for compatibility with standard Fmoc or Boc solid-phase peptide synthesis (SPPS) techniques.[2] High-yielding routes to the orthogonally protected N^3-(carboxymethyl)-2,3-L-diaminopropanoic acids **18**, **19**, and **20** and the *O*-(carboxymethyl)-L-serines

Scheme II



21 : R=H
22 : R=$(CH_2)_4NHCO_2CIBn$

23 : R=H
24 : R=$(CH_2)_4NHCO_2CIBn$

25 : R=Boc
26 : R=(R)-MTPA
27 : R=(S)-MTPA

35 and **38** are described that provide mutligram quantities of enantiomerically pure material. Furthermore, the synthetic strategy developed for preparation of the diaminopropanoic acids enables the alkylated carboxymethyl substituent to be incorporated into the amino acid stereospecifically.

Results and Discussion

Amine Synthesis. As outlined in Scheme I, the synthetic strategy called for a reductive amination on the configurationally stable oxazolidine aldehyde **9**, which was prepared in three steps from commercially available Boc-D-serine.[3] The glycine allyl ester hydrochloride **23**, needed for the synthesis of **18** and **19**, was prepared from Boc-glycine **21** in 98% overall yield as detailed in Scheme II. Reductive amination[4] of oxazolidine **9** with **23** in the presence of $NaBH_3CN$ gave **10** (86%) which was protected with 9-fluorenylmethyl chloroformate and $NaHCO_3$ to afford carbamate **12** (94%). Initial attempts to hydrolyze the oxazolidine ring of **12** directly to the N^α-Boc amino alcohol **15** with hot allyl alcohol and catalytic *p*-toluenesulfonic acid were unsuccessful.[5] However, simultaneous

(2) (a) For a review of Fmoc SPPS, see: Fields, G. B.; Noble, R. L. *Int. J. Peptide Protein Res.* **1990**, *35*, 161–214. (b) Barany, G.; Kneib-Cordonier, N.; Mullen, D. G. *Int. J. Peptide Protein Res.* **1987**, *30*, 705–739. (c) Bodansky, M. *Principles of Peptide Synthesis*; Springer-Verlag: New York, 1984. (d) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.

(3) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361–2364.

(4) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

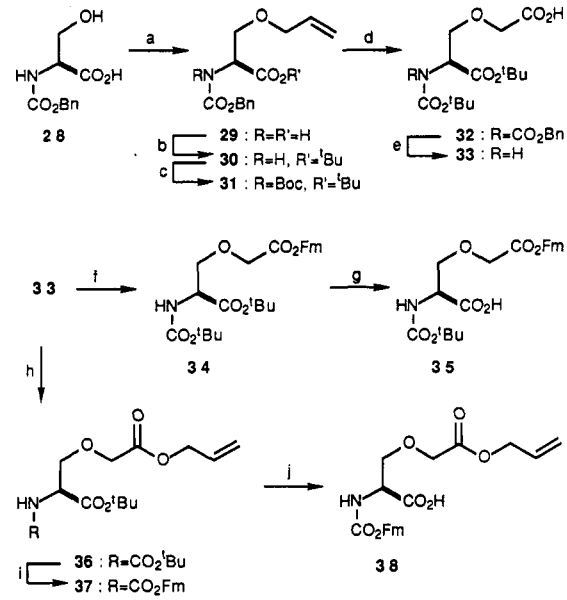
Boc cleavage and oxazolidine hydrolysis with trifluoroacetic acid (TFA) followed by reprotection with di-*tert*-butyl dicarbonate cleanly gave the alcohol **15** in 92% yield. Finally, Jones oxidation[6] of this alcohol gave the amino acid **18** (83%).

The orthogonal protecting group scheme of **18** was designed to facilitate and simplify the solid-phase preparation of a broad series of N-alkylated and N-acylated cyclic amino peptides such as **5**. After coupling the free α-carboxyl of diaminopropanoic acid **18** to the Boc-compatible solid support, the Fmoc could be cleaved with 20% piperidine/*N*,*N*-dimethylacetamide (DMA)[2a] without affecting the Boc or allyl ester functionalities. The resulting secondary amine could then be alkylated or acylated while the residue was attached to the resin. The side-chain allyl ester, being resistant to standard Boc SPPS conditions (α-amines are deprotected with TFA and residues coupled with (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), 1-hydroxybenzotriazole (HOBt), and 4-methylmorpholine (NMM)), would remain intact throughout the residue coupling sequence until the point of peptide cyclization. Cleavage of the allyl ester could be accomplished using $(Ph_3P)_4Pd$ in 20% piperidine/DMA,[7] and the resulting carboxylic acid cyclized onto the peptide amino terminus (BOP, HOBt, NMM).

For preparing N-substituted peptides, a benzyloxycarbonyl (CBZ) protection[2c] on the secondary amine would be more suitable than an Fmoc due to its stability in the presence of amines and $(Ph_3P)_4Pd$. Importantly, a CBZ group would also be resistant to TFA but could be removed with liquid HF used for cleaving the peptide from the solid support. The diaminopropanoic acid **19** was prepared from the amine **10** as shown in Scheme I. After treatment of the secondary amine **10** with benzyl chloroformate, the resulting carbamate **13** (91%) was hydrolyzed, reprotected, and oxidized to provide the carboxylic acid **19** in 75% yield.

For making the acetyl-substituted amino acid **20**, our synthetic strategy allowed both chiral centers to be prepared as separate fragments in enantiomerically pure form before coupling via reductive amination as detailed in Scheme I. The amine hydrochloride **24** was prepared by the same procedure described for the conversion of **21** to **23** (Scheme II). Hence, commercially available *N*-α-Boc-*N*-ε-(2-chloro-CBZ)-L-lysine (**22**) was esterified and deprotected to afford **24** (99% overall). Reductive coupling of **24** and the aldehyde **9** with $NaBH_3CN$, followed by protection of the resulting secondary amine with 9-fluorenylmethyl chloroformate gave the oxazolidine **14** (89% from **9**). For reasons that are unclear, the hydrolysis product from treating the Boc-oxazolidine **14** with TFA could not be N^{α}-protected to give **17**. However, 4 N HCl–dioxane afforded the crude amino alcohol hydrochloride, and treatment with di-*tert*-butyl dicarbonate and $NaHCO_3$ cleanly gave the *N*-Boc amino alcohol **17** in 89% yield. Oxidation of this alcohol with Jones reagent gave the multifunctional, orthogonally protected amino acid **20** in 75% yield from **17**. The protecting group scheme for the three amine and two carboxyl groups was designed to allow routine peptide synthesis and secondary amine functionalization on the solid support, thereby facilitating preparation of the cyclic peptide class **7**. 2-Chlorobenzyloxycarbonyl, a standard Boc SPPS amine protecting group, would be stable to the reaction conditions required for acylation or alkylation of the secondary amine and α-couplings of the amino acid residues, but would be removed by HF[2c] during peptide cleavage from the resin.

Scheme III[a]



[a] Key: (a) NaHMDS, allyl bromide (41%); (b) *tert*-butyl 2,2,2-trichloroacetimidate, $BF_3{\cdot}OEt_2$ (94%); (c) $O[CO_2C(CH_3)_3]_2$, DMAP (99%); (d) O_3; then $(CH_3)_2S$; then $RuCl_3{\cdot}H_2O$, $NaIO_4$, CH_3CN, CCl_4, H_2O (87%); (e) H_2/10% Pd–C (97%); (f) 9-fluorenemethanol, DCC, DMAP (90%); (g) TFA; then $O[CO_2C(CH_3)_3]_2$, $NaHCO_3$ (92%); (h) allyl bromide, $NaHCO_3$ (91%); (i) 4 N HCl–dioxane; then $ClCO_2Fm$, $NaHCO_3$ (84%); (j) TFA (93%).

To determine the enantiomeric purity of these analogues, the carboxylic acid **19** was first converted to the *tert*-butyl ester **25** with *tert*-butyl 2,2,2-trichloroacetimidate[8] (89%). Cleavage of the *N*-Boc group with 4 N HCl gave the amine hydrochloride which was treated independently with (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA)[9] to give the two diastereomeric amides **26** and **27**. ^1H NMR analysis showed the diastereomeric purity of these amides to be ≥95%. This degree of purity is equivalent to that seen by Garner[3] for the oxazolidine aldehyde **9**, indicating that the stereochemical integrity of the chiral center remains intact during the reductive amination and throughout the remainder of the synthesis. In addition, all intermediates in the conversion of the amine **11** to the amino acid **20** were diastereomerically pure by ^1H and ^{13}C NMR.

Ether Synthesis. As shown in Scheme III, both *N*-Boc-*O*-(carboxymethyl)-L-serine δ-fluorenylmethyl ester (**35**) and the *N*-Fmoc-*O*-(carboxymethyl)-L-serine δ-allyl ester (**38**) were prepared from a single commercially available starting material, *N*-CBZ-L-serine (**28**). Initial attempts at O-carboxymethylating **28** directly with either

(5) Similar oxazolidines have been cleaved with CH_3OH/cat. TsOH. (a) Frutos, M. P.; Fernandez, M. D.; Fernandez-Alvarez, E.; Bernabe, M. *Tetrahedron* **1992**, *48*, 1123–1130. (b) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C. G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729–5733.

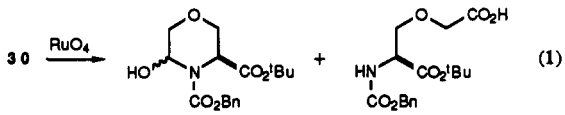
(6) Bladon, P.; Fabian, J. M.; Henbest, H. B.; Koch, H. P.; Wood, G. W. *J. Chem. Soc.* **1951**, 2402–2411.

(7) (a) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371–4372. For references on the usage of allyl-based side-chain protection for SPPS, see: (b) Lyttle, M. H.; Hudson, D. In *Peptides: Chemistry and Biology* (Proceedings of the 12th American Peptide Symposium); Smith, J. A., Rivier, J. E., Eds.; ESCOM: Leiden, 1992; 583–584. (c) Durette, P. L.; Baker, F.; Barker, P. L.; Boger, J.; Bondy, S. S.; Hammond, M. L.; Lanza, T. J.; Pessolano, A. A.; Caldwell, C. G. *Tetrahedron Lett.* **1990**, *31*, 1237–1240.

(8) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483–2486.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

benzyl bromoacetate or sodium iodoacetate were unsuccessful,[10] so an allyl group was chosen to serve as a latent carboxymethyl function. *N*-CBZ-*O*-allyl-L-serine (**29**) was prepared (41–45%) by sequential treatment of **28** with NaHMDS and allyl bromide.[11] The carboxyl group of **29** was treated with *tert*-butyl trichloroacetimidate to provide the α-*tert*-butyl ester **30** in 94% yield. Protection of the α-carboxyl at this point permitted the δ-carboxyl group, which was formed by terminal olefin oxidation later in the synthetic sequence, to be functionalized specifically. Oxidation of **30** with ruthenium tetraoxide[12] gave the aminol **39** as the major product and only meager amounts of the desired carboxylic acid **40** (eq 1). It seemed likely that



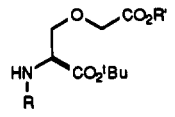
39 39% **40** 22%

additional amine protection prior to the olefin oxidation would prevent the carbamate from trapping the aldehyde oxidation intermediate, thereby leading to higher yields. To investigate this possibility, the carbamate **30** was protected, prior to oxidation, as the *N*-Boc derivative **31** (99%) by reaction with di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine (DMAP). When the fully protected amino olefin **31** was subjected to RuO_4, TLC analysis of the reaction mixture revealed multiple product formation. However, ozonolysis of the olefin followed by ruthenium tetraoxide oxidation cleanly gave the carboxylic acid **32** in 87% yield. Hydrogenolysis of the benzyloxycarbonyl group of **32** gave the *N*-Boc-*O*-(carboxymethyl)-L-serine **33** (97%), which served as the common intermediate for both the *N*-Boc and *N*-Fmoc carboxymethyl serine derivatives **35** and **38**, respectively.

The arrangement of protecting groups on **35** was established for compatibility with Boc-SPPS of cyclic ether peptides such as **8**. The side-chain 9-fluorenylmethyl ester could be selectively cleaved with piperidine, allowing solid-phase cyclization without deviating from the standard N^{α}-Boc synthetic method.[13] Side-chain esterification of the carboxylic acid **33** with 9-fluorenemethanol, 1,3-dicyclohexylcarbodiimide (DCC), and DMAP was followed by simultaneous Boc and *tert*-butyl ester hydrolysis with TFA. Finally, reprotection of the resulting amine with di-*tert*-butyl dicarbonate and $NaHCO_3$ gave the orthogonally protected carboxymethyl serine **35** in 83% yield from **33**.

For preparation of the *N*-Fmoc allyl ester **38**, the side-chain carboxyl of **33** was esterified with allyl bromide and $NaHCO_3$ in *N*,*N*-dimethylformamide (DMF) and the Boc group selectively removed in the presence of the *tert*-butyl ester with 4 N HCl–dioxane. The resulting amine was reprotected with 9-fluorenylmethyl chloroformate and finally the *tert*-butyl ester cleaved with TFA to afford **38** (71% from **33**). The product **38** could also be prepared by treatment of **36** with TFA followed by N-reprotection with 9-fluorenylmethyl chloroformate. However, this route yielded **38** as an impure oil even after a difficult chromatographic separation as compared to the crystalline product **38** isolated after treatment of **37** with TFA (Scheme III). Carboxymethyl serine **38**, protected with an N^{α}-Fmoc and a side-chain allyl ester, was fully compatible with Fmoc SPPS of cyclic ether peptides **8**.

To determine the enantiomeric purity of these carboxymethyl serines, the Mosher amides **43** and **44** were prepared from the carboxylic acid **32**. Selective N^{α}-Boc



41 : R=CO_2Bn, R'=H
42 : R=CO_2Bn, R'=$C(CH_3)_3$
43 : R=(R)-MTPA, R'=$C(CH_3)_3$
44 : R=(S)-MTPA, R'=$C(CH_3)_3$

cleavage of **32** with 4 N HCl–dioxane gave the *N*-CBZ-(carboxymethyl)serine **41** (85%). In order to inhibit lactamization during the final Mosher amidation, the side-chain carboxyl of **41** was also converted to a *tert*-butyl ester with *tert*-butyl 2,2,2-trichloroacetimidate to give **42** (89%). Hydrogenolysis of the benzyl carbamate **42** gave the free α-amine, which was independently treated with (*R*)-(–)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to give both possible Mosher amide diastereomers **43** and **44**, respectively. ^1H NMR analysis of the two diastereomers showed each to be 94% pure, indicating that the stereochemistry of the α-center remained intact during the strongly basic O-alkylation step.

Cyclic Peptide Synthesis. The utility of these carboxymethyl diaminopropanoic acids and carboxymethyl serines was demonstrated by their incorporation into cyclic RGD peptides. Shown in Scheme IV are the syntheses of the functionalized amino peptides **47** and **50**, and the ether peptide **52**.

Peptides **47** and **50** were both readily prepared from the diaminopropanoic acid **18**. After coupling the free α-carboxyl of **18** to hydroxymethyl resin with 1,3-diisopropylcarbodiimide (DIPC) and catalytic DMAP, the Fmoc group was selectively removed with 20% piperidine/DMA to give a secondary amine. Conversion of this secondary amine to its hydrochloride salt followed by reductive alkylation with benzaldehyde and $NaBH_3CN$ gave **45**, whereas acylation of the amine with benzoyl chloride in the presence of Et_3N afforded **48**. Employing standard Boc SPPS protocols, the Asp, Gly, Arg, and D-Val residues were coupled sequentially to the α-amine of **45** and **48** to give peptides **46** and **49**, respectively. Cleavage of the side-chain allyl esters of **46** and **49** was followed by N-terminal deprotection, peptide cyclization, and cleavage from the solid support to give the respective peptides **47** and **50**.

The ether peptide **52** was prepared from amino acid **35** or **38**. Detailed in Scheme IV is the synthesis starting from the *N*-Fmoc amino acid **38**. The α-carboxyl of **38** was linked to *p*-alkoxybenzyl alcohol (Wang) resin using DIPC and catalytic DMAP. After coupling the desired residues to the amino terminus utilizing standard Fmoc protocols to give **51**, the N-terminal Fmoc was removed with 20% piperidine/DMA and the side chain allyl ester cleaved with $(Ph_3P)_4Pd$. The resin beads were washed with dilute TFA/CH_2Cl_2 to remove piperidine salts, and the peptide was cyclized with BOP, HOBt, and NMM and then cleaved from the resin with TFA to afford **52**. The syn-

(10) O-Alkylation of *N*-benzoylserine with sodium iodoacetate in 12% yield has been reported: Shafer, J.; Baronowsky, P.; Laursen, R.; Finn, F.; Westheimer, F. H. *J. Biol. Chem.* **1966**, *241*, 421–427.

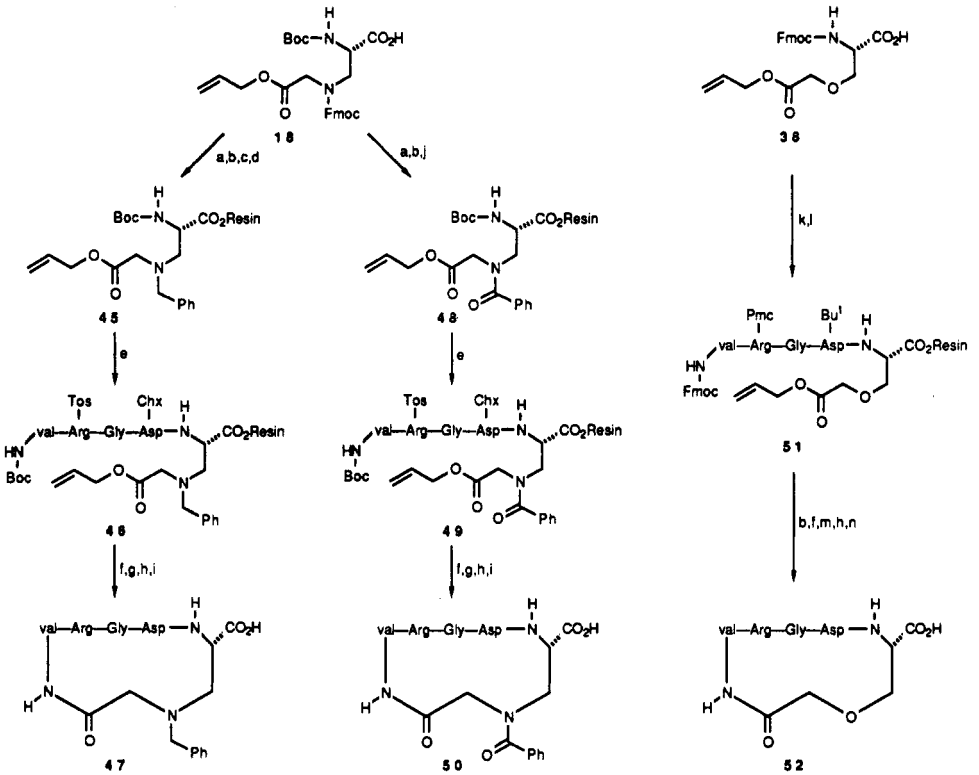
(11) For examples of serine O-alkylation with allyl bromide and benzyl bromide see: (a) Chen, S. T.; Wang, K. T. *Synthesis* **1989**, 36–37. (b) Sham, H. L.; Bolis, G.; Stein, H. H.; Fesik, S. W.; Marcotte, P. A.; Plattner, J. J.; Rempel, C. A.; Greer, J. *J. Med. Chem.* **1988**, *31*, 284–295. (c) Sugano, H.; Miyoshi, M. *J. Org. Chem.* **1976**, *41*, 2352–2353. (d) Hruby, V. J.; Ehler, K. W. *J. Org. Chem.* **1970**, *35*, 1690.

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(13) (a) Rovero, P.; Quartara, L.; Fabbri, G. *Tetrahedron Lett.* **1991**, *32*, 2639–2642. (b) Felix, A. M.; Wang, C.-T.; Heimer, E. P.; Fournier, A. *Int. J. Peptide Protein Res.* **1988**, *31*, 231–238.

(14) Kaiser, E.; Colescot, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.

Scheme IV[a]



[a] Key: (a) 1,3-diisopropylcarbodiimide, DMAP, hydroxymethyl resin; (b) 20% piperidine/DMA; (c) 4 N HCl–dioxane, CH_2Cl_2; (d) benzaldehyde, $NaBH_3CN$, DMF; (e) Boc peptide synthesis; (f) $(Ph_3P)_4Pd$, 20% piperidine/DMA; (g) 45% TFA/45% CH_2Cl_2/5% ethanedithiol/5% anisole; (h) BOP, HOBt, NMM; (i) HF; (j) benzoyl chloride, Et_3N; (k) 1,3-diisopropylcarbodiimide, DMAP, Wang resin; (l) Fmoc peptide synthesis; (m) 2% TFA/CH_2Cl_2; (n) 98% TFA/2% triethylsilane.

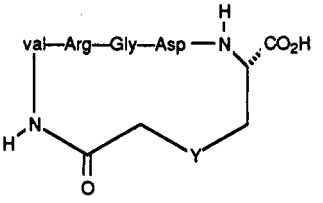
thesis of **52** from the Boc amino acid **35** was also performed and generally followed the steps shown for the preparation of peptides **47** and **50**. Thus, conversion of **35** into **52** was accomplished by carrying out steps a, e, b, g, h, and i in sequential order.

The RGD peptides **47**, **50**, and **52** were tested for biological activity and did inhibit fibrinogen binding to GP II_bIII_a in the ELISA assay (Table I).[1]

Conclusion

Synthetic routes to orthogonally protected N^3-(carboxymethyl)-2,3-L-diaminopropanoic acids and *O*-(carboxymethyl)serines have been described which provided multigram quantities of the enantiomerically pure amino acids. Reductive aminations of the aldehyde **9** with various amino acid allyl ester hydrochlorides were shown to be efficient routes to N^3-carboxymethylated diaminopropanoic acid derivatives. This route allowed the multiple amine and carboxylic acid functional groups present in the molecule to be suitably protected as dictated by standard SPPS technique. The synthesis detailed in Scheme I proceeded through an inversion of the functional groups present in D-serine. The carboxyl group of D-serine was converted into an aldehyde and then reductively aminated to become a side chain, and the hydroxymethyl side chain of serine served as the protected carboxyl group of the incipient L-amino acid. D-Amino acids frequently are important tools in studying structure–activity relationships in peptides. Although not carried out, this same route should be applicable to the preparation of D-amino acids from L-serine. Oxidation of *O*-allylserines was shown to be a useful method for preparing (carboxymethyl)serines on a large scale. Both N^α-Boc and N^α-Fmoc-(carboxymethyl)serines were available from the same synthetic intermediate. The synthetic route permitted the δ-carboxyl to be specifically esterified with groups orthogonal to the α-amine protections. The utility of the N^3-(carboxymethyl)-2,3-L-diaminopropanoic acids and (carboxymethyl)serines was demonstrated by employing them in the synthesis of cyclic RGD peptides. The synthesis of a broad range of cyclic RGD peptides and their biological profiles will be the subject of future reports.

Table I. Inhibition of GP II_bIII_a/Fibrinogen Binding



peptide	Y	ELISA IC_{50}, nM[a]
47	*N*-benzyl	10.0
50	*N*-benzoyl	5.6
52	O	9.7
53[b]	S[b]	2.0[b]

[a] Inhibition of GP II_bIII_a/fibrinogen binding; $n \geq 3$. Confidence limits ±25–30%. [b] See ref 1.

Experimental Section

N-CBZ-L-serine and *N*-Boc-D-serine were purchased from Bachem California. Anhydrous THF, acetonitrile, DMF, and toluene were purchased from Aldrich Chemical Co. Anhydrous ethyl ether was purchased from Mallinckrodt. Hydrogenations were performed on a Parr 3921 hydrogenation apparatus. Flash chromatography was performed using EM silica gel 60 (230–400 mesh). All concentrations were performed on a rotary evaporator.

Melting points were taken on a Laboratory Devices Mel-Temp II apparatus and are reported uncorrected. TLC analysis was

performed on Whatman silica gel 60A K6F plates and visualized by UV and/or charring with 0.2% ninhydrin in ethanol. Optical rotations were determined at ambient temperature with a Perkin-Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300-MHz VXR-300S spectrometer. Spectral data are reported in ppm from tetramethylsilane as follows: chemical shift, multiplicity (app = apparent, b = broad, s = singlet, d = doublet, t = triplet, q = quartet), coupling constant, and integration. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-HX110HF/HX110HF tandem MS/MS instrument using the positive-ion FAB technique. Combustion analyses were performed by Oneida Research Services, Inc., Whitesboro, NY.

Oxazolidine of N^2-(*tert*-Butoxycarbonyl)-N^3-(carboxymethyl)-(2*S*)-diaminopropan-1-ol Allyl Ester (10). A solution of 1,1-dimethylethyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**9**) (5.07 g, 22.1 mmol), glycine allyl ester hydrochloride (**23**) (16.8 g, 111 mmol), and $NaBH_3CN$ (1.39 g, 22.1 mmol) in methanol (65 mL) was stirred at room temperature for 1 h. The reaction mixture was evaporated, and the oily solid residue was partitioned between aqueous $NaHCO_3$ (18.6 g, 221 mmol in 170 mL H_2O) and ethyl ether (200 mL). The aqueous layer was extracted repeatedly (4 × 50 mL) with ethyl ether, and the combined organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, using 2:1 hexane–ethyl acetate) to yield 6.27 g (86%) of the amine **10** as a colorless oil: TLC R_f 0.26 (1:1 hexane–ethyl acetate); $[\alpha]^{22}_D$ +37° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 75 °C) δ 5.76–5.63 (m, 1 H), 5.10–4.94 (m, 2 H), 4.40 (app d, J = 5.9 Hz, 2 H), 3.85–3.66 (m, 3 H), 3.19 (ABq, $\Delta\nu_{AB}$ = 12.3, J_{AB} = 17.3 Hz, 2 H), 2.87–2.84 (m, 1 H), 2.64–2.57 (m, 1 H), 1.65 (s, 3 H), 1.49 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR (75.5 MHz, C_6D_6, 75 °C) δ 171.86, 152.13, 132.71, 117.83, 93.96, 79.36, 66.52, 64.98, 57.77, 51.81, 51.11, 28.51, 27.37, 24.07; IR (film) 3355, 1743, 1697, 1392, 1365, 1259, 1179, 1160, 1087 cm^{-1}. Anal. Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53: Found: C, 58.21; H, 8.58; N, 8.49.

Oxazolidine Amine 11. The aldehyde **9** (3.21 g, 14.0 mmol) was reductively aminated with **24** (27.4 g, 70.1 mmol) and $NaBH_3CN$ (0.970 g, 15.4 mmol) in CH_3OH (45 mL) and worked up as described previously for **10** to yield 7.48 g (94%) of the amine **11** as a colorless oil after flash chromatography (silica gel, using 2:1 hexane–ethyl acetate); TLC R_f 0.1 (2:1 hexane–ethyl acetate); $[\alpha]^{23}_D$ +19.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 75 °C) δ 7.33–6.79 (m, 4 H), 5.81–5.68 (m, 1 H), 5.25 (app s, 2 H), 5.15–4.98 (m, 2 H), 4.45 (app d, J = 5.9 Hz, 2 H), 4.39 (m, 1 H) 3.89–3.71 (m, 3 H), 3.14–2.93 (m, 4 H), 2.57–2.50 (m, 1 H), 1.66 (s, 3 H), 1.49 (s, 3 H), 1.44 (s, 9 H), 1.60–1.18 (m, 6 H); ^{13}C NMR (75.5 MHz, C_6D_6, 75 °C) δ 174.63, 156.07, 152.21, 135.53, 134.10, 132.80, 130.31, 129.67, 129.28, 126.87, 118.10, 94.01, 79.49, 66.68, 65.04, 63.90, 62.07, 58.25, 50.98, 41.19, 33.32, 29.95, 28.56, 27.39, 24.12, 23.24; IR (film) 3349 (broad), 1729, 1696, 1530, 1390, 1364, 1251, 1178, 1091 cm^{-1}. Anal. Calcd for $C_{28}H_{42}ClN_3O_7$: C, 59.20; H, 7.45; N, 7.40: Found: C, 58.90; H, 7.51; N, 7.22.

Oxazolidine of N^2-(*tert*-Butoxycarbonyl)-N^3-((9-fluorenylmethoxy)carbonyl)-N^3-(carboxymethyl)-(2*S*)-diaminopropan-1-ol Allyl Ester (12). The amine **10** (5.83 g, 17.8 mmol) was dissolved in 2:1 THF–H_2O (100 mL), and $NaHCO_3$ (3.00 g, 35.5 mmol) and 9-fluorenylmethyl chloroformate (5.52 g, 21.3 mmol) were added to a stirring solution of the amine (5.83 g, 17.8 mmol) in 2:1 THF–H_2O (100 mL). After 16 h at room temperature, the layers were separated, and the aqueous layer was washed with ethyl ether (50 mL), saturated with NaCl, and washed again with ethyl ether (2 × 50 mL). The combined organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (gradient elution, using 3:1, 1:1 hexane–ethyl ether) to afford 9.78 g (94%) of the N^3-Fmoc **12** as a colorless oil: TLC R_f 0.68 (ethyl ether); $[\alpha]^{22}_D$ –0.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.87–7.26 (m, 8 H), 5.92–5.81 (m, 1 H), 5.32–5.17 (m, 2 H), 4.58–4.51 (m, 2 H), 4.44–4.17 (m, 3 H), 4.04–3.72 (m, 5 H), 3.59–3.39 (m, 1 H), 3.21–3.00 (m, 1 H), 1.46 (s, 3 H), 1.37 + 1.34 (s, 12 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 168.54, 155.28, 150.85, 143.36, 143.32, 140.42, 131.79, 127.16, 126.59, 124.40, 124.36, 119.57, 117.55, 92.72, 79.00, 66.72, 64.89, 64.60, 54.78, 49.14, 48.49, 46.44, 27.58, 26.57, 23.10; IR (film) 1749, 1702, 1450, 1390, 1364, 1231, 1184, 1138 cm^{-1}; FAB MS MH$^+$ calcd for $C_{31}H_{39}N_2O_7$ 551.2757, found 551.2750.

Oxazolidine of N^2-(*tert*-Butoxycarbonyl)-N^3-(benzyloxycarbonyl)-N^3-(carboxymethyl)-(2*S*)-diaminopropan-1-ol Allyl Ester (13). The amine **10** (2.35 g, 7.16 mmol) was stirred with $NaHCO_3$ (1.2 g, 14.3 mmol) and benzyl chloroformate (1.18 mL, 1.41 g, 8.24 mmol) at room temperature for 16 h and then worked up according to the procedure described for the synthesis of **12**. Purification of the crude residue by flash chromatography (silica gel, using 3:1 hexane–ethyl ether) afforded 3.01 g (91%) of the carbamate **13**: TLC R_f 0.11 (3:1 hexane–ethyl ether); $[\alpha]^{23}_D$ + 1.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 7.41–7.28 (m, 5 H), 5.90–5.80 (m, 1 H), 5.28 (app d, J = 17.1 Hz, 1 H), 5.20 (app d, J = 10.7 Hz, 1 H), 5.09 (app s, 2 H), 4.58 (app d, J = 4.9 Hz, 2 H), 4.06 (ABq, $\Delta\nu_{AB}$ = 21.6, J = 17.6 Hz, 2 H), 4.04–3.98 (m, 1 H), 3.89–3.81 (m, 2 H), 3.59 (dd, J = 13.9, 8.1 Hz, 1 H), 3.32–3.27 (m, 1 H), 1.49 (s, 3 H), 1.41 (app s, 12 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 168.66, 155.28, 150.88, 136.11, 131.76, 127.82, 127.33, 126.91, 117.49, 92.76, 78.99, 66.34, 64.88, 64.54, 54.85, 49.29, 48.82, 27.58, 26.54, 23.11; IR (film) 1749, 1702, 1463, 1430, 1390, 1257, 1231, 1184, 1138, 1098, 1078 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_7$: C, 62.32; H, 7.41; N, 6.06: Found: C, 62.20; H, 7.36; N, 5.70.

Carbamate 14. The amine **11** (7.42 g, 13.1 mmol) was treated with $NaHCO_3$ (2.20 g, 26.2 mmol) and 9-fluorenylmethyl chloroformate (4.06 g, 15.7 mmol) in 2:1 THF–H_2O (75 mL) as described previously for the preparation of **12** to provide 9.77 g (95%) of the oxazolidine **14** as a colorless oil after silica flash chromatography (gradient elution, using 2:1, 1:1, 3:7 hexane–ethyl ether): TLC R_f 0.09 (1:1 hexane–ethyl ether); $[\alpha]^{23}_D$ –13° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 7.85–7.27 (m, 12 H), 7.05 (m, 1 H), 5.90–5.77 (m, 1 H), 5.27–5.17 (m, 2 H), 5.10 (app s, 2 H), 4.55–4.40 (m, 4 H), 4.21 (t, J = 5.1 Hz, 1 H), 3.91–3.71 (m, 4 H), 3.64–3.53 (m, 1 H), 3.20–2.90 (m, 3 H), 1.84–1.06 (m, 6 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 169.64, 164.25, 155.44, 150.83, 143.46, 143.34, 140.59, 134.38, 131.99, 129.24, 129.16, 128.88, 127.16, 126.80, 126.61, 124.30, 119.66, 117.49, 92.68, 79.22, 66.27, 64.80, 64.71, 62.26, 59.75, 55.23, 48.69, 46.61, ~40 (peak not resolved from solvent multiplet), 28.80, 28.63, 27.71, 26.71, 23.05; IR (film) 3355 (broad), 1730, 1697, 1451, 1392, 1365, 1246, 1173, 1146, 1106, 1073 cm^{-1}; FAB MS MH$^+$ calcd for $C_{43}H_{53}ClN_3O_9$ 790.3470, found 790.3508.

N^2-(*tert*-Butoxycarbonyl)-N^3-((9-fluorenylmethoxy)carbonyl)-N^3-(carboxymethyl)-(2*S*)-diaminopropan-1-ol Allyl Ester (15). Trifluoroacetic acid (300 mL) was added to a stirring solution of the *N*-Boc-oxazolidine **12** (9.75 g, 17.7 mmol) in methylene chloride (40 mL) at ambient temperature. After 45 min, the reaction was concentrated in vacuo, diluted with THF (100 mL) and H_2O (20 mL), and reconcentrated. Next, the residue was dissolved in 3:2 THF–H_2O (100 mL) and treated sequentially with di-*tert*-butyl dicarbonate (5.80 g, 26.6 mmol) and $NaHCO_3$ (3.13 g, 37.2 mmol). The reaction was stirred at room temperature for 16 h and then diluted with ethyl ether (100 mL). After separation of layers, the aqueous phase was saturated with NaCl and extracted again with ethyl ether (3 × 75 mL). The combined organic phase was dried ($MgSO_4$) and concentrated and the resulting residue purified by silica gel flash chromatography (gradient elution, using 1:1 hexane–ethyl ether, ethyl ether) to give 8.3 g (92%) of the alcohol **15** as a colorless oil: TLC R_f 0.34 (ethyl ether); $[\alpha]^{22}_D$ +6.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.90–7.27 (m, 8 H), 6.48 + 6.37 (d, J = 8.8, 8.3 Hz, respectively, 1 H), 5.95–5.82 (m, 1 H), 5.32–5.18 (m, 2 H), 4.76 + 4.66 (bt, J = 4.6, 5.4 Hz, respectively, 1 H), 4.58 + 4.53 (app d, J = 5.4, 4.8 Hz, respectively, 2 H), 4.34–4.16 (m, 3 H), 4.13–3.96 (m, 2 H), 3.70–3.56 (m, 1 H), 3.51–3.26 (m, 3 H), 3.19–3.08 (m, 1 H), 1.34 + 1.33 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 168.66, 155.35, 154.84, 143.40, 140.36, 131.91, 127.18, 126.64, 124.47, 119.57, 117.40, 77.47, 66.80, 64.47, 61.19, 51.23, 48.80, 46.41, 27.81; IR (film) 3409 (broad), 1749, 1709, 1477, 1450, 1364, 1244, 1184 cm^{-1}; FAB MS MH$^+$ calcd for $C_{28}H_{35}N_2O_7$ 511.2444, found 511.2455.

N^2-(*tert*-Butoxycarbonyl)-N^3-(benzyloxycarbonyl)-N^3-(carboxymethyl)-(2*S*)-diaminopropan-1-ol Allyl Ester (16). The oxazolidine **13** (2.77 g, 5.99 mmol) was cleaved with 4 N HCl–dioxane (20 mL) and then treated with di-*tert*-butyl dicarbonate (4.00 g, 18.3 mmol) and $NaHCO_3$ (1.28 g, 15.3 mmol) in 3:2 THF–H_2O (50 mL) as described for the preparation of **17**. Silica gel flash chromatography (gradient elution, using 1:1 hexane–ethyl ether, ethyl ether) of the residue provided 2.30 g

(91%) of the pure alcohol **16** as a colorless oil: TLC R_f 0.35 (ethyl ether); ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 7.37–7.27 (m, 5 H), 6.12 (d, J = 6.0 Hz, 1 H), 5.90–5.80 (m, 1 H), 5.30–5.16 (m, 2 H), 5.08 (app s, 2 H), 4.62–4.51 (m, 2 H), 4.42 (bs, 1 H), 4.09 (overlapping ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 18.6 Hz, 2 H), 3.75–3.64 (m, 1 H), 3.49 (dd, J = 14.2, 4.4 Hz, 1 H), 3.43–3.36 (m, 2 H), 3.27 (dd, J = 14.2, 8.1 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 168.75, 155.36, 154.86, 136.31, 131.88, 127.83, 127.23, 126.77, 117.35, 77.47, 66.17, 64.41, 61.20, 51.28, 49.05, 27.80; IR (film) 3675–3170, 1749, 1702, 1503, 1477, 1364, 1244, 1178 cm^{-1}; FAB MS MH$^+$ calcd for $C_{21}H_{31}N_2O_7$ 423.2131, found 423.2151.

Alcohol 17. The oxazolidine **14** (5.15 g, 6.54 mmol) was treated with 4 N HCl–dioxane (20 mL) and the mixture was stirred at room temperature for 1 h. The reaction was concentrated in vacuo, diluted with THF (50 mL) and H_2O (2 mL), stirred for 10 min, and reconcentrated. The residue was taken up in 3:2 THF–H_2O (50 mL) and treated with di-*tert*-butyl dicarbonate (2.85 g, 13.1 mmol) and $NaHCO_3$ (1.37 g, 16.3 mmol). The reaction was worked up as described for the synthesis of **15** and purified by flash chromatography (silica gel, using ethyl ether) yielding 4.89 g (89%) of the alcohol **17** as a colorless oil: TLC R_f 0.43 (ethyl ether); $[\alpha]^{23}_D$ −16° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 7.85–7.27 (m, 12 H), 6.98 (bs, 1 H), 5.98 (bd, J = 6.0 Hz, 1 H), 5.91–5.78 (m, 1 H), 5.28–5.15 (m, 2 H), 5.11 (overlapping ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 19.1 Hz, 2 H), 4.50–4.37 (m, 4 H), 4.32 (app t, J = 5.6 Hz, 1 H), 4.24 (app t, J = 5.4 Hz, 1 H), 4.09 (bm, 1 H), 3.66–3.56 (m, 1 H), 3.43 (dd, J = 14.7, 5.4 Hz, 1 H), 3.35–3.32 (m, 2 H), 3.09–2.97 (m, 3 H), 1.81–1.17 (m, 6 H), 1.35 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 169.85, 155.48, 155.33, 154.77, 143.47, 143.39, 140.44, 134.34, 131.98, 131.91, 129.16, 129.03, 128.77, 127.08, 126.70, 126.56, 124.29, 119.53, 117.12, 77.42, 66.37, 64.47, 62.17, 61.38, 60.09, 51.73, 48.53, 46.47, ~40 (peak not resolved from solvent multiplet), 28.87, 28.71, 27.80, 23.02; IR (film) 3350 (broad), 1702, 1516, 1477, 1450, 1244, 1171, 1058 cm^{-1}; FAB MS MH$^+$ calcd for $C_{40}H_{49}ClN_3O_9$ 750.3157, found 750.3160.

N^2-(*tert*-Butoxycarbonyl)-N^3-((9-fluorenylmethoxy)carbonyl)-N^3-(carboxymethyl)-L-2,3-diaminopropanoic Acid δ-Allyl Ester (18). The alcohol **15** (8.22 g, 16.1 mmol) was dissolved in acetone (120 mL) and cooled to −5 °C in an ice–salt water bath. Jones reagent (18.1 mL of 2.67 M, 48.4 mmol) was added over 15 min, the ice bath was removed, and the reaction was stirred at room temperature for 1.5 h before the excess Jones reagent was quenched with 2-propanol (9 mL). After being stirred for 2 h, the mixture was filtered and the green precipitate washed with ethyl ether (200 mL). The organic layer was washed twice with brine (2 × 30 mL), and these aqueous washings were added to the green precipitate dissolved in H_2O (100 mL). The total aqueous phase was saturated with NaCl and extracted with ethyl acetate (3 × 30 mL). All organic layers were combined, dried ($MgSO_4$), and evaporated to provide the crude carboxylic acid as a green oil which was purified by silica gel flash chromatography (gradient elution, using 1:1 hexane–ethyl ether, 500:400:100:6 hexane–ethyl ether–ethanol–acetic acid). Residual acetic acid was removed by repeatedly (3×) concentrating the product out of toluene and once out of 1:1 ethyl ether–hexane, affording 7.03 g (83%) of the carboxylic acid **18** as a pale yellow foam: TLC R_f 0.26 (500:400:100:6 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{23}_D$ +6.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.89–7.27 (m, 8 H), 6.99–6.95 (m, 1 H), 5.95–5.82 (m, 1 H), 5.32–5.18 (m, 2 H), 4.59 + 4.53 (app d, J = 5.4, 4.9 Hz, respectively, 2 H), 4.35–3.98 (m, 6 H), 3.91 (dd, J = 14.7, 4.9 Hz, 0.5 H), 3.76 (dd, J = 14.2, 4.4 Hz, 0.5 H), 3.38 (dd, J = 14.7, 9.3 Hz, 0.5 H), 3.27 (dd, J = 14.2, 9.3 Hz, 0.5 H), 1.35 + 1.34 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$) δ 172.32, 172.24, 169.11, 155.63, 155.43, 155.42, 143.67, 143.61, 140.70, 132.29, 132.23, 127.74, 127.64, 127.17, 127.07, 125.26, 124.86, 120.19, 120.09, 117.91, 117.77, 78.28, 78.20, 67.73, 67.19, 65.04, 64.90, 53.08, 52.72, 49.55, 49.10, 49.03, 48.55, 46.51, 46.44, 28.14, 27.86; IR (film) 3700–2300, 1749, 1709, 1477, 1450, 1370, 1244, 1191, 1164 cm^{-1}; FAB MS MH$^+$ calcd for $C_{28}H_{33}N_2O_8$ 525.2237, found 525.2249.

N^2-(*tert*-Butoxycarbonyl)-N^3-(benzyloxycarbonyl)-N^3-(carboxymethyl)-L-2,3-diaminopropanoic Acid Allyl Ester (19). The alcohol **16** (2.13 g, 5.04 mmol) in acetone (40 mL) was oxidized with 2.67 M Jones reagent (5.70 mL, 15.1 mmol) and worked up according to the procedure described for **18** to provide 1.80 g (82%) of the pure carboxylic acid **19** following silica gel flash chromatography (gradient elution, using ethyl ether, 500:400:100:5 hexane–ethyl ether–ethanol–acetic acid) and azeotropic removal of residual acetic acid with toluene: TLC R_f 0.11 (500:400:100:5 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{23}_D$ +19° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.37–7.25 (m, 5 H), 7.12 + 7.07 (d, J = 8.8, 8.3 Hz, respectively, 1 H), 5.95–5.76 (m, 1 H), 5.32–5.05 (m, 4 H), 4.59 + 4.54 (app d, J = 5.4, 4.9 Hz, respectively, 2 H), 4.37–4.01 (m, 3 H), 3.85–3.72 (m, 1 H), 3.39–3.27 (m, 1 H), 1.36 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$) δ 172.21, 172.18, 169.28, 169.14, 155.62, 155.49, 155.43, 136.59, 136.48, 132.30, 132.20, 128.37, 128.34, 127.81, 127.77, 127.22, 127.15, 117.87, 117.79, 78.34, 78.29, 66.68, 66.59, 64.98, 64.92, 52.85, 52.58, 49.51, 49.14, 48.34, 28.15, 27.87; IR (film) 3700–2300, 1749, 1716, 1477, 1457, 1410, 1370, 1244, 1191, 1164 cm^{-1}; FAB MS MH$^+$ calcd for $C_{21}H_{29}N_2O_8$ 437.1923, found 437.1921.

2,3-L-Diaminopropanoic Acid 20. The alcohol **17** (4.17 g, 5.56 mmol) in acetone (44 mL) was oxidized with 2.67 M Jones reagent (6.25 mL, 16.7 mmol) and worked up according to the procedure described for **18** to provide 3.20 g (75%) of the carboxylic acid **20** as a colorless foam following silica gel flash chromatography (gradient elution, using 1:1 ethyl ether–hexane, 500:400:100:5 hexane–ethyl ether–ethanol–acetic acid): TLC R_f 0.24 (500:400:100:5 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{23}_D$ −10° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 75 °C) δ 7.59–6.81 (m, 13 H), 5.93 (bs, 1 H), 5.79–5.67 (m, 1 H), 5.30 (overlapping ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 18.8 Hz, 2 H), 5.14 (app d, J = 17.4 Hz, 1 H), 5.01 (app d, J = 10.2 Hz, 1 H), 4.64–4.38 (m, 5 H), 4.16–4.05 (m, 2 H), 3.98–3.88 (m, 1 H), 3.79–3.64 (m, 1 H), 3.05–2.97 (m, 2 H), 1.39 (s, 9 H), 1.98–1.09 (m, 6 H); ^{13}C NMR (75.5 MHz, C_6D_6, 75 °C) δ 174.70, 171.04, 157.35, 156.84, 156.34, 144.57, 144.48, 141.89, 135.30, 134.07, 132.47, 130.38, 129.66, 129.36, 127.89, 127.45, 127.43, 126.99, 125.25, 125.18, 120.22, 118.23, 80.07, 68.08, 66.00, 64.27, 61.90, 54.93, 50.14, 47.85, 41.29, 29.92, 29.70, 28.54, 24.09; IR (film) 3700–2300, 3349, 1702, 1516, 1477, 1450, 1423, 1251, 1164 cm^{-1}; FAB MS MH$^+$ calcd for $C_{40}H_{47}ClN_3O_{10}$ 764.2950, found 764.2945. Anal. Calcd for $C_{40}H_{46}ClN_3O_{10}$: C, 62.86; H, 6.07; N, 5.50. Found: C, 62.48; H, 6.03; N, 5.22.

Glycine Allyl Ester Hydrochloride (23). A solution of Boc-glycine **21** (50.0 g, 285 mmol), $NaHCO_3$ (60.0 g, 713 mmol), and allyl bromide (120 mL, 168 g, 1.39 mol) in anhydrous DMF (600 mL) was stirred at 50 °C for 16 h and then concentrated in vacuo. The yellow residue was taken up in ethyl ether (600 mL), and insoluble salts were removed by filtration. The filtrate was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to yield 61.7 g (100%) of the crude allyl ester. This ester was treated with HCl (41.1 g, 1.13 mol) in dioxane (300 mL). After the ester was stirred at room temperature for 0.5 h, TLC (1:1 hexane–ethyl ether) indicated a complete reaction, and ethyl ether (500 mL) was added to the reaction mixture causing the product to precipitate. The product was collected by filtration, washed with ethyl ether, and dried in vacuo to provide 42.4 g (98%) of the glycine allyl ester hydrochloride **23** as a white crystalline solid: mp 74–76 °C; ^{1}H NMR (300 MHz, D_2O) δ 6.04–5.91 (m, 1 H), 5.42–5.31 (m, 2 H), 4.76–4.75 (m, 2 H), 3.96 (overlapping ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 19.6 Hz, 2 H). Anal. Calcd for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.65; N, 9.24: Found: C, 39.36; H, 6.66; N, 9.19.

N-ε-(2-Chloro-CBZ)-L-Lysine Allyl Ester Hydrochloride (24). Following the procedure described above for the preparation of **23**, N-α-Boc-N-ε-(2-chloro-CBZ)-L-lysine (**22**) (41.5 g, 100 mmol) was esterified with allyl bromide (61.0 mL, 84.7 g, 700 mmol) and $NaHCO_3$ (21.0 g, 250 mmol) in anhydrous DMF (200 mL). The Boc group was hydrolyzed with HCl (24.3 g, 667 mmol) in dioxane (180 mL) to provide 39.0 g (100%) of the lysine allyl ester hydrochloride **24** as a colorless cyrstalline solid: mp 128–129 °C; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 8.64 (bs, 3 H), 7.48–7.34 (m, 5 H), 5.99–5.86 (m, 1 H), 5.40–5.23 (m, 2 H), 5.07 (overlapping ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 19.5 Hz, 2 H), 4.72–4.61 (m, 2 H), 4.00 (app t, J = 6.1 Hz, 1 H), 3.01–2.95 (m, 2 H), 1.84–1.77 (m, 2 H), 1.41–1.26 (m, 4 H). Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_4$: C, 52.18; H, 6.18; N, 7.16: Found: C, 52.18; H, 6.21; N, 7.03.

N^2-(*tert*-Butoxycarbonyl)-N^3-(benzyloxycarbonyl)-N^3-(carboxymethyl)-L-2,3-diaminopropanoic Acid α-*tert*-Butyl δ-Allyl Diester (25). The carboxylic acid **19** (0.23 g, 0.53 mmol) was dissolved in methylene chloride (2 mL), and cyclohexane (4 mL) and *tert*-butyl 2,2,2-trichloroacetimidate (0.23 g, 1.1 mmol) were added. This reaction mixture was stirred at room tem-

perature for 30 h and then filtered and concentrated and the resulting residue purified by flash chromatography (silica gel, using 3:1 hexane–ethyl ether) to afford 0.23 g (89%) of the *tert*-butyl ester **25** as a colorless oil: TLC R_f 0.34 (1:1 hexane–ethyl ether); $[\alpha]^{23}_D$ −1.6° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 7.37–7.27 (m, 5 H), 6.75 (bs, 1 H), 5.91–5.79 (m, 1 H), 5.28 (app d, J = 17.1 Hz, 1 H), 5.19 (app d, J = 10.8 Hz, 1 H), 5.09 (br app s, 2 H), 4.58 (m, 2 H), 4.22–4.15 (m, 1 H), 4.10 (ABq, $\Delta\nu_{AB}$ = 16.3, J_{AB} = 18.1 Hz, 2 H), 3.80 (dd, J = 14.2, 5.4 Hz, 1 H), 3.39 (dd, J = 14.2, 8.5 Hz, 1 H), 1.39 (s, 9 H), 1.38 (s, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 75 °C) δ 169.26, 168.59, 155.13, 154.78, 136.08, 131.83, 127.83, 127.31, 126.82, 117.36, 80.52, 78.07, 66.38, 64.47, 49.19, 27.71, 27.23; IR (film) 3363 (broad), 1742, 1716, 1503, 1483, 1457, 1370, 1244, 1158 cm^{-1}; FAB MS MH^+ calcd for $C_{25}H_{37}N_2O_8$ 493.2549, found 493.2529.

N^2-Mosher Amides of N^3-(Benzyloxycarbonyl)-N^3-(carboxymethyl)-L-2,3-diaminopropanoic Acid α-*tert*-Butyl δ-Allyl Diester (26) and (27). The N^α-Boc *tert*-butyl ester **25** (0.077 g, 0.16 mmol) was treated with 4 N HCl–dioxane (2.5 mL) and the resulting mixture stirred at room temperature for 1 h. Volatiles were evaporated, and the residue was c[illegible]ed with THF (7 mL) and reconcentrated to a thick oil. The crude amine hydrochloride was dissolved in pyridine (1.5 mL), and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenacetyl chloride (0.059 g, 0.24 mmol) and triethylamine (0.060 g, 0.63 mmol) were added sequentially. After being stirred at room temperature for 16 h, the reaction was quenched with H_2O (1.5 mL). The mixture was diluted with ethyl ether (10 mL), the layers were separated, and the organic layer was washed successively with 10% HCl (3 × 5 mL), saturated $NaHCO_3$ (2 × 5 mL) and H_2O (5 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue eluted through a plug of silica gel, using 1:1 hexane–ethyl ether to provide 37 mg (39%) of the Mosher amide **26** as a colorless oil. The above procedure was repeated for the preparation of the (*S*)-Mosher amide **27**. The diastereomeric purity of each (*R*)- and (*S*)-Mosher amide derivative was determined by analysis with 300-MHz ^1H NMR. For each derivative, the signal corresponding to the NH and CH group was chosen for analysis, showing the diastereomeric excess to be ~94%.

(*R*)-Mosher amide (26): TLC R_f 0.35 (1:1 hexane–ethyl ether); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.82 + 8.76 (d, J = 8.3, 7.8 Hz, respectively, 1 H, NH), 7.64–7.20 (m, 10 H), 5.95–5.76 (m, 1 H), 5.32–4.95 (m, 4 H), 4.64–4.49 (m, 3 H), 4.14–3.26 (m, 7 H), 1.34 + 1.32 (s, 9 H).

(*S*)-Mosher amide (27): TLC R_f 0.35 (1:1 hexane–ethyl ether); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.67 + 8.61 (d, J = 8.8, 1 H, NH), 7.64–7.21 (m, 10 H), 5.91–5.73 (m, 1 H), 5.27–4.92 (m, 4 H), 4.81–4.69 (m, 1 H, CH), 4.58–4.41 (m, 2 H), 3.87–3.25 (m, 7 H), 1.38–1.34 (m, 9 H).

N-(Benzyloxycarbonyl)-O-allyl-L-serine (29). *N*-CBZ-L-serine (**28**) (25.0 g, 105 mmol) was dissolved in anhydrous DMF (500 mL) and cooled to −40 °C in an ethanol/H_2O–dry ice bath. A 1 M solution of NaHMDS (214 mL, 214 mmol) in THF was added over 15 min and the resulting solution stirred at −40 °C for 45 min. After rapid addition of freshly filtered (basic alumina) allyl bromide (9.9 mL, 13.9 g, 115 mmol), the reaction was warmed to room temperature, stirred for an additional 4 h, recooled to −40 °C, and quenched with acetic acid (6.6 mL, 6.9 g, 115 mmol) in THF (10 mL). The reaction was poured into 500 mL of ice water and extracted with ether (2 × 100 mL). After acidifying to pH 2 with concentrated HCl and saturating with NaCl, the aqueous solution was washed repeatedly with ether (5 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to a yellow oil. Purification of this oil by silica gel flash chromatography (gradient elution, using 2:1 hexane–ethyl ether, ethyl ether) yielded 12.0 g (41%) of the *O*-allylserine **29** as a colorless oil, which eventually crystallized upon standing at room temperature: mp 48–52 °C; TLC R_f 0.30 (500:400:100:5 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{23}_D$ +22° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (bs, 1 H), 7.35–7.25 (m, 5 H), 5.87–5.74 (m, 2 H), 5.24–5.13 (m, 2 H), 5.10 (ABq, $\Delta\nu_{AB}$ = 8.1, J_{AB} = 12.2 Hz, 2 H), 4.50 (ddd, J = 8.3, 3.4, 2.9 Hz, 1 H), 3.96 (app d, J = 5.9 Hz, 2 H), 3.90 (dd, J = 9.3, 2.9 Hz, 1 H), 3.66 (dd, J = 9.3, 3.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.37, 156.23, 135.97, 133.69, 128.44, 128.13, 128.01, 117.75, 72.28, 69.39, 67.15, 54.12; IR (film) 3680–2300 (broad), 1729, 1516, 1218, 1065 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 59.93; H, 6.07; N, 4.84.

N-(Benzyloxycarbonyl)-O-allyl-L-serine *tert*-Butyl Ester (30). *tert*-Butyl 2,2,2-trichloroacetimidate (18.5 g, 84.9 mmol) was added to a solution of the carboxylic acid **29** (11.8 g, 42.4 mmol) in methylene chloride (42 mL) and cyclohexane (84 mL) and the resulting mixture stirred at ambient temperature for 10 h. Next, boron trifluoride etherate (0.3 mL, 2.4 mmol) was added, and stirring was continued for 1 h. After being quenched with $NaHCO_3$ (0.6 g, 7.1 mmol), the reaction was filtered and concentrated in vacuo and the resulting residue purified by flash chromatography (silica gel, using 4:1 hexane–ethyl ether) affording 13.4 g (94%) of the *tert*-butyl ester **30** as a colorless oil: TLC R_f 0.19 (4:1 hexane–ethyl ether); $[\alpha]^{24}_D$ +13° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H), 5.89–5.76 (m, 1 H), 5.62 (d, J = 8.3 Hz, 1 H), 5.27–5.14 (m, 2 H), 5.12 (overlapping ABq, $\Delta\nu_{AB}$ ~ 0, J_{AB} = 12.5 Hz, 2 H), 4.37 (dt, J = 8.3, 2.9 Hz, 1 H), 4.04–3.89 (m, 2 H), 3.83 (dd, J = 9.3, 2.9 Hz, 1 H), 3.65 (dd, J = 9.3, 2.9 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.26, 155.95, 136.32, 134.03, 128.44, 128.05, 128.02, 117.21, 82.16, 72.16, 70.18, 66.85, 54.86, 27.94; IR (film) 3460–3260, 1729, 1510, 1218, 1158, 1065 cm^{-1}; FAB MS MH^+ calcd for $C_{18}H_{26}NO_5$ 336.1811, found 336.1831.

N-(Benzyloxycarbonyl)-N-(*tert*-butoxycarbonyl)-O-allyl-L-serine *tert*-Butyl Ester (31). The carbamate **30** (12.2 g, 36.3 mmol) was dissolved in acetonitrile (60 mL), and di-*tert*-butyl dicarbonate (10.3 g, 47.2 mmol) and 4-(dimethylamino)pyridine (0.44 g, 3.6 mmol) were added. After being stirred at ambient temperature for 3 days, the reaction mixture was concentrated under reduced pressure to yield a brown oil. Purification of the residue was performed by using flash chromatography (silica gel, using 9:1 hexane–ethyl ether) to provide 15.7 g (99%) of the *N*-Boc-*N*-CBZ-*O*-allylserine **31** as a colorless oil: TLC R_f 0.29 (4:1 hexane–ethyl ether); $[\alpha]^{22}_D$ −30° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5 H), 5.90–5.77 (m, 1 H), 5.30–5.10 (m, 5 H), 4.04–3.84 (m, 4 H), 1.46 (s, 9 H), 1.40 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.70, 153.80, 151.71, 135.34, 134.49, 128.43, 128.25, 128.18, 116.91, 83.42, 81.98, 71.75, 68.64, 68.15, 58.70, 27.88, 27.84; IR (film) 2977, 1736, 1702, 1397, 1370, 1350, 1291, 1231, 1158, 1118 cm^{-1}. Anal. Calcd for $C_{23}H_{33}NO_7$: C, 63.43; H, 7.64; N, 3.22. Found: C, 63.51; H, 7.78; N, 3.34.

N-(Benzyloxycarbonyl)-N-(*tert*-butoxycarbonyl)-O-(carboxymethyl)-L-serine α-*tert*-Butyl Ester (32). Ozone was passed through a stirring solution of the olefin **31** (15.5 g, 35.5 mmol) in methanol (200 mL) at −78 °C until a slight blue color persisted in the reaction medium, and then the ozone source was removed and the reaction immediately quenched with a precooled solution (−78 °C) of dimethyl sulfide (12.0 mL, 10.2 g, 163 mmol) in methanol (75 mL) and the resulting mixture warmed to room temperature over 14 h. Volatiles were removed under reduced pressure, and the residue was dissolved in ethyl ether (500 mL) and washed repeatedly with brine (5 × 30 mL). The ether layer was dried ($MgSO_4$) and concentrated in vacuo, providing the crude aldehyde as an oil. The aldehyde was dissolved in CCl_4 (70 mL), acetonitrile (70 mL), and H_2O (110 mL). To this heterogeneous mixture was added sodium periodate (15.2 g, 71.0 mmol) and $RuCl_3 \cdot H_2O$ (0.18 g, 0.85 mmol) and the reaction stirred vigorously for 2 h. The reaction was diluted with CH_2Cl_2 (250 mL) and H_2O (50 mL). After separation of layers, the aqueous phase was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to a black oil. This residue was purified by silica gel flash chromatography (gradient elution, using 1:1 hexane–ethyl ether, 500:400:100:5 hexane–ethyl ether–ethanol–acetic acid) yielding 13.9 g (87%) of the carboxylic acid **32** as a colorless oil, after residual acetic acid from the chromatography was removed by concentrating the product out of toluene (3×): $[\alpha]^{23}_D$ − 19° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (bs, 1 H), 7.37–7.27 (m, 5 H), 5.23 (ABq, $\Delta\nu_{AB}$ = 17.7, J_{AB} = 12.2 Hz, 2 H), 5.14 (dd, J = 7.3, 5.9 Hz, 1 H), 4.12 (dd, J = 10.0, 5.9 Hz, 1 H), 4.10 (ABq, $\Delta\nu_{AB}$ = 18.1, J_{AB} = 17.1 Hz, 2 H), 3.94 (dd, J = 10.0, 7.3 Hz, 1 H), 1.45 (s, 9 H), 1.41 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.68, 167.86, 153.58, 151.53, 134.95, 128.39, 128.33, 128.21, 83.92, 82.64, 69.95, 68.88, 67.86, 58.16, 27.72, 27.68; IR (film) 3700–2300, 1762, 1736, 1697, 1370, 1297, 1231, 1158, 1131 cm^{-1}; FAB MS MH^+ calcd for $C_{22}H_{32}NO_9$ 454.2076, found 454.2077.

***N*-(*tert*-Butoxycarbonyl)-*O*-(carboxymethyl)-L-serine α-*tert*-Butyl Ester (33).** The N^{α}-Boc-N^{α}-CBZ carboxylic acid **32** (12.0 g, 26.5 mmol) was dissolved in methanol (150 mmol) and transferred into a Parr shaker bottle. After adding 10% Pd–C (0.98 g), the mixture was shaken under an atmosphere of hydrogen at 50 psi for 1 h on the Parr apparatus. The catalyst was removed by filtration through Celite. The filter cake was washed with methanol and then with ethyl ether, and the combined filtrate and washings were concentrated in vacuo to yield an oil. Residual methanol was removed by diluting the oil with ethyl ether and hexane and reconcentrating to yield 8.19 g (97%) of the N^{α}-Boc-carboxylic acid **33** as a colorless oil, which was used without further purification in the next step: $[\alpha]^{22}_{D}$ +3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (bs, 1 H), 5.67 (d, *J* = 8.3 Hz, 1 H), 4.33 (m, 1 H), 4.12 (ABq, $\Delta\nu_{AB}$ = 7.2, J_{AB} = 17.1 Hz, 2 H), 3.98 (dd, *J* = 9.3, 3.4 Hz, 1 H), 3.77 (dd, *J* = 9.3, 3.4 Hz, 1 H), 1.48 (s, 9 H), 1.45 (s, 9 H); IR (film) 3700–2300, 1716, 1510, 1397, 1370, 1251, 1158 cm^{-1}; FAB MS MH^+ calcd for $C_{14}H_{26}NO_7$ 320.1709, found 320.1709.

***N*-(*tert*-Butoxycarbonyl)-*O*-(carboxymethyl)-L-serine α-*tert*-Butyl δ-Fluorenylmethyl Diester (34).** Dicyclohexylcarbodiimide (2.77 g, 13.4 mmol), and 9-fluorenemethanol (2.64 g, 13.4 mmol), and 4-(dimethylamino)pyridine (0.270 g, 2.24 mmol) were added sequentially to a stirring solution of the carboxylic acid **33** (3.57 g, 11.2 mmol) in methylene chloride (180 mL). After being stirred at ambient temperature for 48 h, the cloudy reaction mixture was filtered and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (silica gel, using 2:1 hexane–ethyl ether) afforded 5.03 g (90%) of the fluorenylmethyl ester **34** as colorless crystals: mp 80–82 °C; TLC R_f 0.28 (1:1 hexane–ethyl ether); $[\alpha]^{22}_{D}$ +5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.30 (m, 8 H), 5.51 (d, *J* = 8.3 Hz, 1 H), 4.46 (app d, *J* = 6.8 Hz, 2 H), 4.30 (ddd, *J* = 8.3, 3.4, 2.9 Hz, 1 H), 4.22 (app t, *J* = 6.8 Hz, 1 H), 4.13 (app s, 2 H), 3.96 (dd, *J* = 9.3, 3.4 Hz, 1 H), 3.73 (dd, *J* = 9.3, 2.9 Hz, 1 H), 1.48 (s, 9 H), 1.44 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.77, 169.27, 155.45, 143.36, 143.34, 141.22, 127.82, 127.11, 124.93, 124.90, 120.01, 82.15, 79.66, 71.96, 68.43, 66.55, 54.40, 46.63, 28.27, 27.92; IR (film) 3438, 1743, 1715, 1497, 1448, 1370, 1251, 1202, 1152, 1054 cm^{-1}. Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.82. Found: C, 67.48; H, 7.14; N, 2.68.

***N*-(*tert*-Butoxycarbonyl)-*O*-(carboxymethyl)-L-serine δ-Fluorenylmethyl Ester (35).** The *N*-Boc and *tert*-butyl ester groups of the carboxymethyl serine **34** (4.83 g, 9.71 mmol) were simultaneously removed by treating a solution of **34** in methylene chloride (30 mL) with trifluoroacetic acid (200 mL). After being stirred for 2 h, the reaction mixture was concentrated to a yellow oil. The residue was diluted with THF (150 mL) and reconcentrated in vacuo to provide a white solid. A 1:1 dioxane–H_2O solution (200 mL) was added to the solid, followed by di-*tert*-butyl dicarbonate (6.60 g, 30.2 mmol) and $NaHCO_3$ (3.39 g, 40.3 mmol). The reaction mixture was stirred at room temperature for 18 h and then concentrated. The resulting residue was dissolved in H_2O (100 mL) and carefully acidified with concentrated HCl to pH 4, causing the product to precipitate as an oil. This oil was extracted from the aqueous layer by washing with ethyl acetate (2 × 20 mL). Further acidification to pH 3 produced more precipitate, which again was extracted into several washings of ethyl acetate (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the resulting residue was achieved by using silica gel flash chromatography (gradient elution, using 2:1 ethyl ether–hexane, 900:100:5 ethyl ether–ethanol–acetic acid). Residual acetic acid was removed by repeatedly (3×) concentrating the product out of toluene and once out of 1:1 hexane–ethyl ether, affording 3.93 g (92%) of the *N*-Boc carboxylic acid **35** as a white foam: TLC R_f 0.17 (500:400:100:5 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{22}_{D}$ +11° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.78–7.26 (m, 8 H), 4.93 (s, 2 H), 4.49–4.39 (m, 2 H), 4.24–4.16 (m, 2 H), 4.10 (ABq, $\Delta\nu_{AB}$ = 12.0, J_{AB} = 16.6 Hz, 2 H), 3.86 (dd, *J* = 9.8, 4.4 Hz, 1 H), 3.69 (dd, *J* = 9.8, 3.9 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 174.77, 172.17, 157.84, 144.87, 142.53, 128.87, 128.23, 126.07, 126.04, 120.97, 80.62, 72.54, 69.16, 67.64, 55.61, 47.91, 28.69; IR (film) 3700–2300, 1743, 1715, 1448, 1251, 1216, 1166, 1138 cm^{-1}; FAB MS MH^+ calcd for $C_{24}H_{28}NO_7$ 442.1865, found 442.1834.

***N*-(*tert*-Butoxycarbonyl)-*O*-(carboxymethyl)-L-serine α-*tert*-Butyl δ-Allyl Diester (36).** The carboxylic acid **33** (3.97 g, 12.5 mmol) was dissolved in DMF (24 mL). Next, $NaHCO_3$ (1.83 g, 21.8 mmol) and allyl bromide (7.54 mL, 10.5 g, 87.1 mmol) were added to the reaction flask and the mixture was stirred at 50 °C for 4 h using an oil bath as the heat source. After the reaction mixture was concentrated under reduced pressure, the resulting residue was diluted with ethyl ether (75 mL), filtered, washed twice with brine, dried ($MgSO_4$), and concentrated. Purification of the oil was achieved using silica gel flash chromatography (gradient elution, using 3:1, 2:1 hexane–ethyl ether), yielding 4.07 g (91%) of the allyl ester **36** as a colorless oil: TLC R_f 0.31 (3:2 hexane–ethyl ether); $[\alpha]^{22}_{D}$ +4° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1 H), 5.52 (bd, *J* = 8.3 Hz, 1 H), 5.37–5.24 (m, 2 H), 4.65 (dt, *J* = 5.9, 1.5 Hz, 2 H) 4.30 (dt, *J* = 8.3, 3.4 Hz, 1 H), 4.11 (overlapping ABq, $\Delta\nu_{AB}$ = ~0, J_{AB} = 17.1 Hz, 2 H), 4.00 (dd, *J* = 9.3, 3.4 Hz, 1 H), 3.75 (dd, *J* = 9.3, 3.4 Hz, 1 H), 1.48 (s, 9 H), 1.46 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.60, 169.28, 155.44, 131.54, 118.87, 82.13, 79.63, 71.98, 68.40, 65.41, 54.39, 28.28, 27.91; IR (film) 3436, 3389, 1749, 1716, 1503, 1370, 1251, 1158 cm^{-1}. Anal. Calcd for $C_{17}H_{29}NO_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 57.13; H, 8.11; N, 3.80.

***N*-((9-Fluorenylmethoxy)carbonyl)-*O*-(carboxymethyl)-L-serine α-*tert*-Butyl δ-Allyl Diester (37).** The *N*-Boc *tert*-butyl ester **36** (3.28 g, 9.14 mmol) was stirred in a solution of 4 N HCl–dioxane (20 mL) for 1 h. Volatiles were removed under reduced pressure, the residue was diluted with THF (100 mL), and the solution was reconcentrated. The crude amine hydrochloride was dissolved in 1:1 dioxane–H_2O (100 mL). 9-Fluorenylmethyl chloroformate (2.95 g, 11.4 mmol) was then added followed by $NaHCO_3$ (2.69 g, 32.0 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with ethyl ether (100 mL), the layers were separated, and the aqueous layer was washed repeatedly (3 × 50 mL) with ethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by silica gel flash chromatography (gradient elution, using 4:1, 3:1, 2:1 hexane–ethyl ether) yielding 3.69 g (84%) of the *N*-Fmoc(carboxymethyl)serine **37** as colorless crystals: mp 46–48 °C; TLC R_f 0.10 (2:1 hexane–ethyl ether); $[\alpha]^{22}_{D}$ +10° (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.27 (m, 8 H), 5.99 (bd, *J* = 8.3 Hz, 1 H), 5.94–5.84 (m, 1 H), 5.35–5.23 (m, 2 H), 4.65 (app d, *J* = 5.9 Hz, 2 H), 4.43–4.31 (m, 3 H), 4.24 (app t, *J* = 7.3 Hz, 1 H), 4.12 (app s, 2 H), 4.07 (dd, *J* = 9.3, 2.9 Hz, 1 H), 3.78 (dd, *J* = 9.3, 2.5 Hz, 1 H), 1.48 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.66, 168.88, 155.96, 143.88, 143.75, 141.16, 131.45, 127.56, 126.95, 125.18, 125.15, 119.82, 118.91, 82.39, 71.81, 68.27, 67.04, 65.42, 54.75, 47.03, 27.87; IR (film) 3349, 1722, 1510, 1244, 1218, 1158, 1138, 1085, 1058 cm^{-1}; FAB MS MH^+ calcd for $C_{27}H_{32}NO_7$ 482.2179, found 482.2179. Anal. Calcd for $C_{27}H_{31}NO_7$: C, 67.35; H, 6.49; N, 2.91. Found: C, 67.77; H, 6.72; N, 2.68.

***N*-((9-Fluorenylmethoxy)carbonyl)-*O*-(carboxymethyl)-L-serine δ-Allyl Ester (38).** Trifluoroacetic acid (100 mL) was added to a stirring solution of the *tert*-butyl ester **37** (3.35 g, 6.96 mmol) in methylene chloride (20 mL). After the solution was stirred at room temperature for 40 min, volatiles were removed under reduced pressure giving a yellow oily solid, which was crystallized out of hexane–ethyl ether to provide 2.76 g (93%) of the pure carboxylic acid **38** as a white crystalline solid: mp 106–107 °C; TLC R_f 0.25 (500:400:100:5 hexane–ethyl ether–ethanol–acetic acid); $[\alpha]^{23}_{D}$ + 20° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.75–7.24 (m, 8 H), 5.98–5.85 (m, 1 H), 5.34–5.18 (m, 2 H), 4.92 (bs, 2 H), 4.62 (dt, *J* = 5.9, 1.5 Hz, 2 H), 4.39 (m, 1 H), 4.36–4.26 (m, 2 H), 4.21–4.08 (m, 3 H), 3.99 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.81 (dd, *J* = 9.8, 3.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.21, 171.93, 158.48, 145.25, 145.13, 142.48, 133.17, 128.74, 128.13, 126.31, 126.27, 120.88, 118.87, 72.20, 69.08, 68.14, 66.50, 55.63, 48.27; IR (KBr) 3700–2300, 1722, 1525, 1209, 1138 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.91; H, 5.44; N, 3.25.

***N*-(Benzyloxycarbonyl)-*O*-(carboxymethyl)-L-serine Di-*tert*-butyl Ester (42).** To a stirring solution of **32** (0.50 g, 1.1 mmol) in dioxane (5 mL) was added 4 N HCl–dioxane (5 mL) and the resulting mixture stirred at room temperature for 1 h. After the reaction was concentrated in vacuo, the crude product was diluted with THF (15 mL), reconcentrated, and purified using

silica gel flash chromatography (gradient elution, using 2:1 hexane–ethyl ether, 500:400:100:7 hexane–ethyl ether–ethanol–acetic acid). Residual acetic acid from the chromatography was removed by azeotroping the product out of toluene (2 × 50 mL). This procedure provided 0.33 g (85%) of the carboxylic acid **41** as a colorless oil. The *N*-(benzyloxycarbonyl)-*O*-(carboxymethyl)-L-serine α-*tert*-butyl ester (**41**) was dissolved in methylene chloride (1 mL) and cyclohexane (2 mL), and *tert*-butyl 2,2,2-trichloroacetimidate was added. This reaction mixture was stirred at room temperature for 30 h and then filtered and concentrated, and the resulting residue was purified by flash chromatography (silica gel, using 3:1 hexane–ethyl ether) to give 0.33 g (89%) of the di-*tert*-butyl ester **42** as colorless crystals: mp 35–37 °C; TLC R_f 0.17 (3:1 hexane–ethyl ether); $[\alpha]^{22}_D$ +1° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.33 (m, 5 H), 5.87 (d, J = 8.3 Hz, 1 H), 5.13 (ABq, $\Delta\nu_{AB} \sim 0$, J_{AB} = 12.5 Hz, 2 H), 4.35 (ddd, J = 8.3, 3.4, 2.9 Hz, 1 H), 3.99 (dd, J = 9.3, 3.4 Hz, 1 H), 3.94 (ABq, $\Delta\nu_{AB}$ = 11.2, J_{AB} = 16.6 Hz, 2 H), 3.76 (dd, J = 9.3, 2.9 Hz, 1 H), 1.48 (s, 9 H), 1.46 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.12, 169.02, 156.05, 136.42, 128.40, 127.95, 82.29, 81.81, 71.59, 68.88, 66.77, 54.87, 28.04, 27.91; IR (film) 3320, 2981, 1750, 1729, 1511, 1370, 1230, 1159, 1138 cm^{-1}. Anal. Calcd for $C_{21}H_{31}NO_7$: C, 61.60; H, 7.63; N, 3.42. Found: C, 61.35; H, 7.45; N, 3.05.

Preparation of the Mosher Amides of *O*-(Carboxymethyl)-L-serine Di-*tert*-butyl Diester (43) and (44). A solution of the *N*-(benzyloxycarbonyl)-*O*-(carboxymethyl)-L-serine Di-*tert*-butyl diester (**42**) (0.11 g, 0.27 mmol) in ethanol (30 mL) was hydrogenated on a Parr apparatus at 50 psi over 10% Pd–C (0.01 g) for 0.5 H. The catalyst was removed by filtration through Celite, and the filter cake was washed with ethanol. The combined filtrate and washings were concentrated in vacuo. The residue was diluted with THF and divided into two equal aliquots, and each was concentrated in vacuo. After each colorless crude residue was dissolved in pyridine (1 mL), one aliquot was treated with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenacetyl chloride (0.05 g, 0.20 mmol) and the other aliquot with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenacetyl chloride (0.05 g, 0.20 mmol). Each reaction was stirred at room temperature for 16 h and then worked up in the same way as follows. The reaction was quenched with H_2O (1.5 mL) and stirred for 0.5 h. After dilution with ethyl ether (10 mL) and separation of the layers, the organic layer was washed successively with 10% HCl (3 × 5 mL), saturated $NaHCO_3$ (2 × 5 mL), and H_2O (5 mL). The organic layer was dried ($MgSO_4$) and concentrated to a pale yellow oil.

The diastereomeric purity of each crude (*R*)- and (*S*)-Mosher amide derivative was determined by analysis with 300-MHz ^1H NMR. For each derivative, the signal corresponding to the OCH_3 group was chosen for analysis, showing the diastereomeric excess to be 94–95%.

(*R*)-Mosher amide of *O*-(carboxymethyl)-L-serine di-*tert*-butyl diester (43): ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.8 Hz, 1 H), 7.63–7.36 (m, 5 H), 4.63–4.58 (m, 1 H), 4.07 (dd, J = 9.3, 3.4 Hz, 1 H), 3.97 (app s, 2 H), 3.80 (dd, J = 9.3, 2.9 Hz, 1 H), 3.41 (m, 3 H, OCH_3), 1.47 (s, 9 H), 1.46 (s, 9 H).

(*S*)-Mosher amide of *O*-(carboxymethyl)-L-serine di-*tert*-butyl diester (44): ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.8 Hz, 1 H), 7.63–7.36 (m, 5 H), 4.62–4.57 (m, 1 H), 4.02 (dd, J = 9.3, 3.4 Hz, 1 H), 3.86 (ABq, $\Delta\nu_{AB}$ = 8.3, J_{AB} = 16.6 Hz, 2 H), 3.70 (dd, J = 9.3, 2.9 Hz, 1 H), 3.54 (m, 3 H, OCH_3), 1.49 (s, 9 H), 1.43 (s, 9 H).

Boc Synthesis of Peptides. Peptides were synthesized using standard Boc solid-phase peptide synthesis protocols. Boc groups were cleaved with a solution consisting of 45% TFA, 45% CH_2Cl_2, 5% ethanedithiol, and 5% anisole. Boc amino acid residues (3 equiv) were coupled with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 3 equiv), 1-hydroxybenzotriazole (HOBt, 3 equiv), and 4-methylmorpholine (NMM, 6 equiv). Side-chain protection was Arg(tosyl) and Asp(cyclohexyl). Couplings were monitored by a Kaiser ninhydrin test.[14]

Peptide 47. Amino acid **18** (4.00 g, 7.63 mmol) was coupled to hydroxymethyl resin (5.04 g, 2.52 mmol of 0.5 mequiv/g substitution) with DIPC (1.06 g, 8.40 mmol) and DMAP (0.065 g, 0.532 mmol) in CH_2Cl_2. To 0.25 mmol of amino acid **18** linked to hydroxymethyl resin was added 20% piperidine/DMA for 20 min and the resulting secondary amine converted to the hydrochloride salt by washing the beads (3×) with 0.5 mmol of HCl (4 N HCl–dioxane) in methylene chloride. Treatment of the amine hydrochloride with benzaldehyde (4.5 mmol) and $NaBH_3CN$ (1.5 mmol) gave the *N*-benzyl product. Asp(Chx), Gly, Arg(Tos), and D-Val residues were coupled sequentially using Boc SPPS. Cleavage of the allyl ester was accomplished with $(Ph_3P)_4Pd$ (0.1 mmol) in 20% piperidine/DMA. The amino terminus was deprotected with 45% TFA/45% CH_2Cl_2/5% ethanedithiol/5% anisole, whereupon the peptide was cyclized with BOP (2 mmol), HOBt (2 mmol), and NMM (4 mmol) and then cleaved with HF. Reversed-phase HPLC purification[1] of the crude product gave 26 mg (16%) of the pure peptide **47** as a white powder. Amino acid analysis, expected (found) 1 Arg (0.90), 1 Asp (0.96), 1 Gly (1.05), 1 Val (0.90); FAB mass spectrum m/z 662 $(M + H)^+$; t_R 27 min.

Peptide 50. As described previously for **47**, amino acid **18** (0.3 mmol) on hydroxymethyl resin was treated with 20% piperidine/DMA to generate the secondary amine. Acylation of the amine was performed with benzoyl chloride (2 mmol) and triethylamine (3 mmol) in CH_2Cl_2. Peptide synthesis, cyclization, cleavage and purification was carried out as described for **47** to yield 57 mg (28%) of **50** as a white powder. Amino acid analysis, expected (found) 1 Arg (1.01), 1 Asp (0.96), 2 Gly (1.74), 1 Val (0.94); FAB mass spectrum m/z 676 $(M + H)^+$; t_R 29 min.

Peptide 52. Following the procedure described for **47**, the amino acid **35** was coupled to hydroxymethyl resin. After sequential coupling of the Asp(Chx), Gly, Arg(Tos), and D-Val amino acid residues to resin-bound **35** (0.3 mmol), the side-chain 9-fluorenylmethyl ester was removed with 20% piperidine/DMA. N-Terminal deprotection, peptide cyclization, HF cleavage, and HPLC purification was performed as described previously for **47** and provided 32 mg (19%) of pure **52** as a white powder. Amino acid analysis, expected (found) 1 Arg (1.03), 1 Asp (1.00), 1 Gly (1.00), 1 Val (0.99); FAB mass spectrum m/z 573 $(M + H)^+$; t_R 15 min.

Fmoc Synthesis of 52. Amino acid **38** (3.82 g, 8.99 mmol) was coupled to *p*-alkoxybenzyl alcohol (Wang) resin (4.68 g, 3.00 mmol of 0.64 mequiv/g substitution) with DIPC (1.25 g, 9.90 mmol) and DMAP (0.073 g, 0.60 mmol) in CH_2Cl_2. The Fmoc group of resin-bound **38** (0.25 mmol) was cleaved with 20% piperidine/DMA. After the resin was rinsed free of excess piperidine, the Fmoc amino acids were coupled using BOP, HOBt, and NMM as for the Boc amino acids. The side-chain protection was Arg-(2,2,5,7,8-pentamethylchromanyl-6-sulfonyl) and Asp(*tert*-butyl). The peptide amino terminal Fmoc group was removed and the allyl ester cleaved with $(Ph_3P)_4Pd$. Piperidine salts were removed by repeated washing (3×) with 2% TFA/CH_2Cl_2 and the peptide cyclized with BOP, HOBt, and NMM. Cleavage of the peptide from the solid support with 2% triethylsilane/TFA gave 7 mg (5%) of the pure peptide **52** after reversed-phase HPLC purification.[1]

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Supplementary Material Available: ^{13}C and ^1H NMR spectra of new compounds for indication of purity (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.