Synthesis of a Homologous Series of Side-Chain-Extended Orthogonally Protected Aminooxy-Containing Amino Acids

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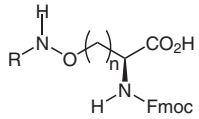
Abstract: Practical methodology is reported for the synthesis of a homologous series of side-chain-extended amino acids containing aminooxy functionality bearing orthogonal protection suitable for Fmoc peptide synthesis. These reagents may be useful for the preparation of libraries containing fragments joined by peptide linkers.

Key words: oxime, peptidomimetic, aldehydes, combinatorial chemistry

Fragment-based approaches to drug discovery have gained increasing importance in the pharmaceutical industry.[1] Tethered libraries represent a subclass of fragment-based methodologies. However, to date, tethered libraries have typically employed structurally simple linker elements, consisting mainly of polymethylene segments bearing terminal aminooxy groups that serve as anchoring points for fragment attachment.[2] However, increased library complexity, leading potentially to enhanced bioactivities, may be possible by combining the structural diversity of peptide scaffolds together with linker-based functionalized oxime ethers. Amino acids **1a–f** and **2a** were designed to serve as key components of linker-based peptide libraries by providing protected aminooxy groups appended onto the peptide backbone via methylene chains of increasing lengths (Figure 1). Final tethered products would be obtained by acid-catalyzed oxime ether deprotection and conjugation with fragment libraries. However, only the core structures of **1a**,[3] **1c**[4], and **1d**[5] are known in the literature and efficient syntheses of the series **1a–f** and **2a** have not yet been reported. Practical methodology for the preparation of **1a–f** and **2a** bearing orthogonal protection designed for Fmoc-based peptide synthesis was the focus of the current study.

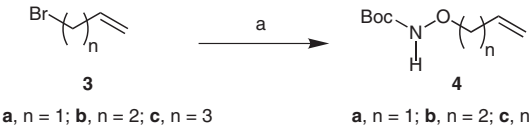


1, R = Boc: **2**, R = Mtt

a, n = 1; **b**, n = 2; **c**, n = 3; **d**, n = 4; **e**, n = 5; **f**, n = 6

Figure 1 Structures of protected aminooxy amino acid analogues

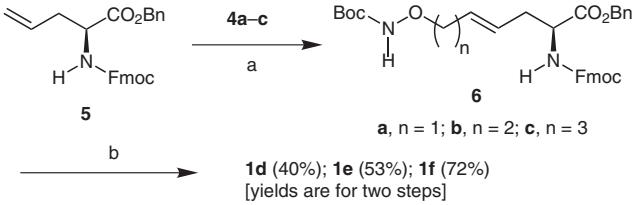
Cross metathesis (CM) has found wide application for coupling through highly efficient carbon–carbon bond formation.[6] A CM approach for the synthesis of target compounds **1d–f** required the *N*-Boc-protected aminooxy building blocks **4a–c**,[7] which could be obtained by reaction of the corresponding bromides **3a–c** with *N*-Boc-hydroxylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 (Scheme 1).[8] The CM coupling of *N*-Fmoc-L-allylglycine *O*-benzyl ester (**5**)[6c] with five equivalents of the respective substrates **4a–c** in refluxing CH_2Cl_2 using 5% Grubbs 2nd generation catalyst, [$(PCy_3)(Im(Mes)_2)Ru{=}CHPh$)][9] provided the products **6a–c** (Scheme 2), which were contaminated with small quantities of unwanted material resulting from homodimerization of reagent **4**. It was advantageous to subject the crude mixtures directly to hydrogenation to provide the easily purified final products **1d–f**. Based on combined yields over two steps, it was found that CM efficiency improved with increasing substrate chain length (**1d**, 40% yield; **1e**, 53% yield and **1f**, 72% yield).



3 **4**

a, n = 1; **b**, n = 2; **c**, n = 3 **a**, n = 1; **b**, n = 2; **c**, n = 3

Scheme 1 *Reagents and conditions*: (a) Boc-NHOH, DBU, CH_2Cl_2.



5 **6**

a, n = 1; **b**, n = 2; **c**, n = 3

1d (40%); **1e** (53%); **1f** (72%) [yields are for two steps]

Scheme 2 *Reagents and conditions*: (a) Grubbs 2nd generation catalyst, CH_2Cl_2, Δ; (b) H_2, Pd/C, EtOH.

The shorter homologues **1a–c** were prepared from L-serine (Ser), L-homoserine (HSer) and L-glutamic acid (Glu), respectively. Near quantitative conversion of Ser to *N*-Trt-L-serine *O*-methyl ester (*N*-Trt-Ser-OMe, **7**[10]) and reaction with *N*-hydroxyphthalimide under Mistunobu conditions, provided the globally-protected product **8** (79% yield, Scheme 3). Use of the *N*-Trt group was to minimize unwanted β-elimination during the Mitsunobu reaction.[11] Having served its purpose, the *N*-Trt group was

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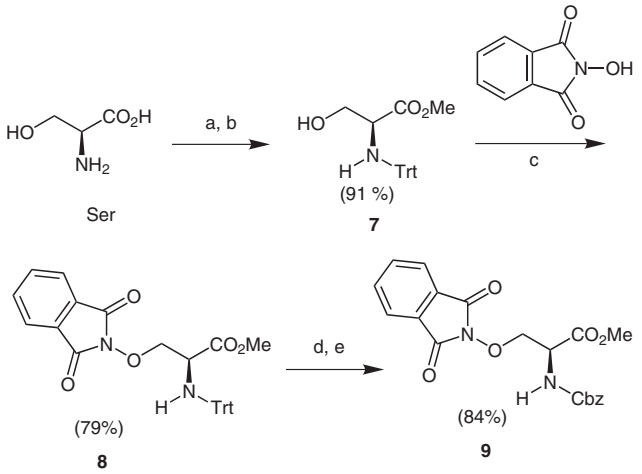
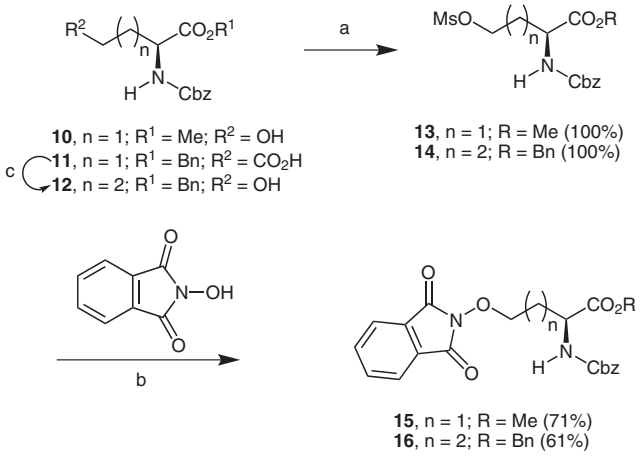


Scheme 3 *Reagents and conditions*: (a) HCl, MeOH; (b) TrtCl, Et_3N; (c) Ph_3P, DEAD; (d) HCl (37%), CH_2Cl_2; (e) CbzCl, THF, H_2O.

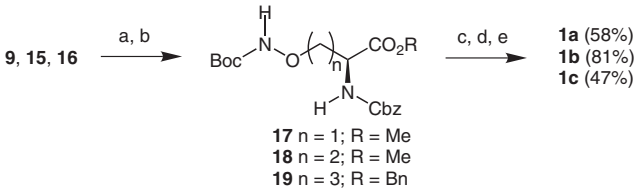
replaced by Cbz protection to provide intermediate **9** (84% yield).

Conversion of HSer to *N*-Cbz-L-homoserine *O*-methyl ester (*N*-Cbz-HSer-OMe, **10**) was by literature procedures,[12] while the side chain-elongated analogue **12** was obtained from commercially available *N*-Cbz-Glu-OBn (**11**)[13] by reduction of the free carboxylic acid group (Scheme 4).[14] When direct transformation of **10** to the phthalimidooxy product **15** under Mitsunobu conditions was accompanied by poor yields and the formation of cyclized by-products, the alcohols **10** and **12** were converted in quantitative yield to the corresponding mesyl esters **13** and **14**.[15] Subsequent nucleophilic displacement using *N*-hydroxyphthalimide provided **15** and **16**, respectively, in approximately 60–70% yields.[12]



Scheme 4 *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2; (b) DBU, DMF; (c) $ClCO_2Et$, 4-methylmorpholine, THF followed by $NaBH_4$, MeOH.

To complete the synthesis of the target compounds, the phthalimidooxy intermediates **9**, **15**, and **16** were cleaved by treatment with methylhydrazine in CH_2Cl_2 at 0 °C, then protected as their *N*-Boc derivatives **17**–**19** by reaction with Boc anhydride (near quantitative yields for two steps, Scheme 5). Cleavage of the amino acid methyl esters of **17** and **18** (LiOH in aqueous THF) followed by Cbz hydrogenolysis and reprotection as the *N*-Fmoc derivatives provided the final products **1a** and **1b** in 58% and 81% yields over three steps. Hydrogenation of **19** and *N*-Fmoc reprotection gave **1c** directly (47% yield).



Scheme 5 *Reagents and conditions*: (a) $MeNHNH_2$, CH_2Cl_2; (b) Boc_2O, Et_3N, THF; (c) LiOH, THF, H_2O; (d) H_2, Pd/C, MeOH; (e) FmocOSu, dioxane.

To determine whether the DBU/DMF conditions resulted in racemization at the α-amino center, **1c** was evaluated for enantiomeric purity as follows. Phenylalanine dipeptides were prepared by solid-phase techniques (Figure 2), and the resulting diastereomers were separated by reverse-phase HPLC (Figure 3). Analysis of the racemic D,L-phenylalanine containing dipeptides **20** indicated good separation of diastereomers. The dipeptide **22**, prepared using enantiomerically pure L-phenylalanine, did not show detectable diastereomeric contamination, indicating that the ee value of **1c** is >98%.

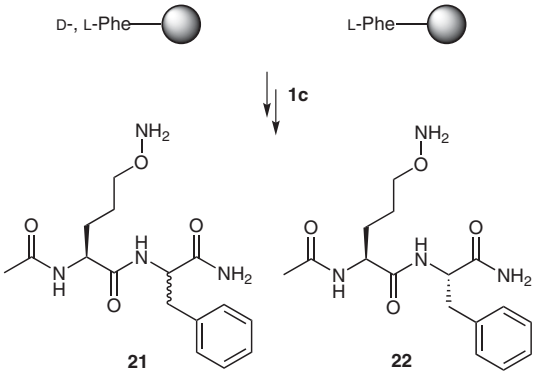


Figure 2 Determination of enantiomeric purity of **1c**

Use of the Boc-protected aminooxy-containing analogue **1a** in solid-phase peptide synthesis is potentially limited by β-elimination during piperidine-mediated Fmoc deprotection. Indeed, attempted incorporation on NovaSyn® TGR resin of **1a** in place of threonine in the Tsg101-binding peptide, FITC-Ava-PEPTAPPEE-amide[16] gave only product resulting from β-elimination.[17] Therefore, the aminooxy Boc protecting group in **1a** was replaced with the more electron-donating 4-methyltriphenylmethyl (Mtt) (final product **2a**). This was achieved by deprotection of phthalamide **9** using methylhydrazine in CH_2Cl_2 followed by reaction with MttCl (*i*-Pr_2EtN, CH_2Cl_2) to give the corresponding Mtt-protected aminooxy analogue **20** in quantitative yield (Scheme 6). Conversion to the

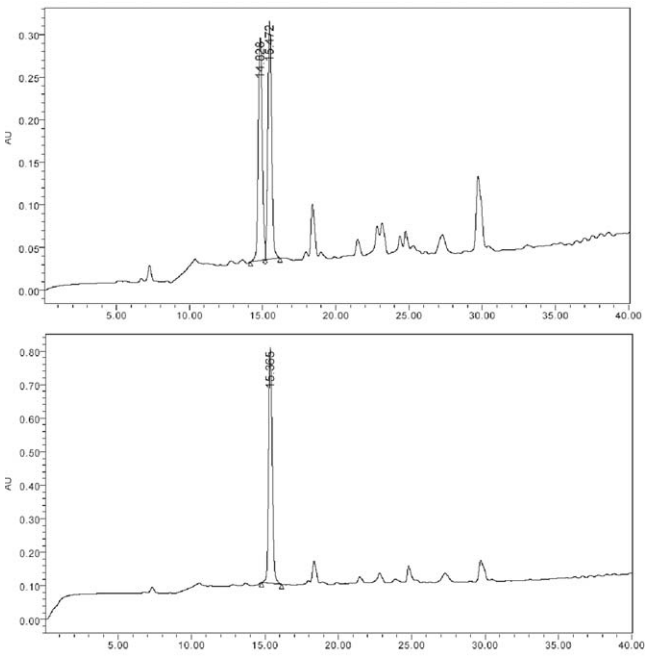
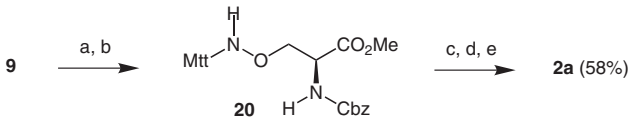


Figure 3 HPLC chromatograms of **21** (top) and **22** (bottom). Identity of the 3 major peaks were confirmed by ESI mass spectra [337.1 $(M + H)^+$ and 359.1 $(M + Na)^+$]

N-Fmoc final product **2a** was as described above for the preparation of target compounds **1a–c**. Repeating the synthesis of the Tsg101-binding peptide described above using **2a** rather than **1a** gave the desired aminooxy-containing peptide as the major product with no β-elimination side product as detected by HPLC.[18]



Scheme 6 *Reagents and conditions*: a) $MeNHNH_2$, CH_2Cl_2; (b) MttCl, *i*-Pr_2EtN, CH_2Cl_2; (c) LiOH, THF, H_2O; (d) H_2, Pd/C, MeOH; (e) FmocOSu, dioxane.

In conclusion, the practical synthesis of a homologous series of aminooxy-containing amino acid analogues has been reported herein. These analogues are intended to serve as valuable building blocks for the post solid-phase construction of tethered oxime-based peptide libraries.

All experiments involving moisture-sensitive compounds were conducted under dry conditions (positive argon pressure) using standard syringe, cannula, and septa protocols. All anhydrous solvents were obtained commercially (Aldrich) and used directly. HPLC-grade hexanes, EtOAc, CH_2Cl_2, and MeOH were used in chromatography. Analytical TLC was performed using Analtech precoated plates (Uniplate, silica gel GHLF, 250 microns) containing a fluorescence indicator. NMR spectra were recorded using a Varian Inova 400 MHz spectrometer. Coupling constants are reported in hertz, and peak shifts are reported in δ (ppm). Low-resolution mass spectra (ESI) were measured with using an Agilent 1200 LC/MSD-SL system, and high-resolution mass spectra (ESI or APCI) were measured by the University of California Riverside Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside CA, 92521. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm and IR spectra were obtained neat using a Jasco FT-IR/615 spectrometer.

Compounds 4a–c; General Procedure

To a mixture of alkenyl bromide **3a–c** (10 mmol) and *N*-Boc-hydroxylamine (25 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C, was added DBU (7.5 mL) carefully. The mixture was warmed to r.t. and stirred overnight. The mixture was diluted with EtOAc (150 mL), washed with H_2O (50 mL) and brine (50 mL), and purified by silica gel column chromatography (hexanes–EtOAc) to yield **4a–c** as colorless oils.

***N*-(Prop-2-en-1-yloxy)carbamic Acid 1,1-Dimethylethyl Ester (4a)[7]**

Prepared from **3a**; yield: 1.18 g (68%).

IR (KBr): 3290.9, 2979.5, 2361.4, 1717.3, 1456.0, 1368.3, 1249.7, 1165.8, 1107.9, 928.6 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (br s, 1 H), 5.88 (m, 1 H), 5.28–5.18 (m, 2 H), 4.27 (dd, *J* = 6.2, 1.0 Hz, 2 H), 1.41 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.74, 132.52, 119.54, 81.37, 77.24, 28.08.

ESI-MS (+): *m*/*z* = 196.1 $(M + Na)^+$.

***N*-(But-3-en-1-yloxy)carbamic Acid 1,1-Dimethylethyl Ester (4b)[7]**

Prepared from **3b**; yield: 1.10 g (59%).

IR (KBr): 3297.7, 2979.5, 1721.2, 1478.2, 1368.3, 1245.8, 1165.8, 1108.9, 773.3 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 1 H), 5.74 (m, 1 H), 5.03 (m, 1 H), 4.96 (m, 1 H), 3.81 (t, *J* = 6.8 Hz, 2 H), 2.30 (m, 2 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.90, 134.31, 116.64, 81.36, 75.45, 32.40, 28.09.

ESI-MS (+): *m*/*z* = 210.1 $(M + Na)^+$.

***N*-(Pent-4-en-1-yloxy)carbamic Acid 1,1-Dimethylethyl Ester (4c)[7]**

Prepared from **3c**; yield: 1.20 g (60%).

IR (KBr): 3300.6, 2978.5, 1721.2, 1368.3, 1246.8, 1166.7, 1108.9, 912.2, 775.2 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 5.71 (m, 1 H), 4.92 (m, 1 H), 4.86 (m, 1 H), 3.75 (t, *J* = 6.6 Hz, 2 H), 2.04 (m, 2 H), 1.62 (m, 2 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.90, 137.80, 114.90, 81.41, 75.96, 29.92, 28.13, 27.12.

ESI-MS (+): *m*/*z* = 224.1 $(M + Na)^+$.

Amino Acids 1d–f; General Procedure

A solution of alkene **4a–c** (5.0 equiv) and the protected allylglycine **5**[6c] (1.0 equiv) in anhyd CH_2Cl_2 (20 mL) was degassed under argon (5 min), then the Grubbs 2nd generation catalyst $[(PCy_3)(Im(Mes)_2)Ru{=}CHPh]$[9] (0.05 equiv) was added and the mixture was refluxed for 8 h. The solvent was evaporated by rotary evaporation and the residue was purified by silica gel column chromatography (hexanes–EtOAc) to yield crude **6a–c** as colorless oils. Without further purification, a solution of **6** in EtOH (10 mL) was hydrogenated at r.t. under 1 atm H_2 over 10% Pd/C (1 h). The catalyst was removed by filtration and the filtrate was concentrated and purified by silica gel column chromatography (CH_2Cl_2–MeOH) to yield **1d–f** as white waxes.

(3*S*)-3-Carboxy-12,12-dimethyl-10-oxo-8,11-dioxa-2,9-diazadecanoic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (1d)

Prepared from **4a** in 40% yield over 2 steps; $[\alpha]_D^{20}$ +9.60 (*c* 0.70, $CHCl_3$).

IR (KBr): 3296.7, 2923.6, 1701.9, 1522.5, 1449.2, 1160.9, 909.3, 733.8 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.55 Hz, 2 H), 7.59 (dd, *J* = 7.07, 4.13 Hz, 2 H), 7.38 (t, *J* = 7.46 Hz, 2 H), 7.29 (t, *J* = 7.45 Hz, 2 H), 7.18 (br s, 1 H), 5.67 (d, *J* = 7.95 Hz, 1 H), 4.40–4.38 (m, 3 H), 4.20 (m, 1 H), 3.84 (t, *J* = 5.97 Hz, 2 H), 1.91 (m, 1 H), 1.76 (m, 1 H), 1.68–1.59 (m, 3 H), 1.54–1.46 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.16, 157.53, 156.35, 143.75, 143.61, 141.24, 127.67, 127.04, 125.05, 119.93, 82.30, 76.09, 67.17, 53.60, 47.05, 31.71, 28.16, 27.24, 21.58.

ESI-MS (+): *m*/*z* = 507.2 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{26}H_{32}N_2O_7$ + Na $(M + Na)^+$: 507.2107; found: 507.2104.

(3*S*)-3-Carboxy-13,13-dimethyl-11-oxo-9,12-dioxa-2,10-diazadecanoic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (1e)

Prepared from **4b** in 53% yield over 2 steps; $[\alpha]_D^{20}$ +7.04 (*c* 0.48, $CHCl_3$).

IR (KBr): 3285.1, 2933.2, 2364.3, 1700.9, 1521.6, 1449.2, 1162.8, 909.3, 732.8 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.55 Hz, 2 H), 7.66–7.50 (m, 3 H), 7.37 (m, 2 H), 7.29 (t, *J* = 7.41 Hz, 2 H), 5.54 (d, *J* = 8.13 Hz, 1 H), 4.55–4.30 (m, 3 H), 4.19 (m, 1 H), 3.82 (m, 2 H), 1.88 (m, 1 H), 1.72 (m, 1 H), 1.64–1.55 (m, 2 H), 1.46 (s, 9 H), 1.44–1.35 (m, 3 H), 1.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.23, 157.51, 156.22, 143.76, 143.61, 141.24, 127.69, 127.04, 125.04, 119.93, 82.16, 76.44, 67.11, 53.66, 47.06, 31.96, 28.17, 27.50, 25.30, 24.77.

ESI-MS (+): *m*/*z* = 521.2 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{27}H_{34}N_2O_7$ + Na $(M + Na)^+$: 521.2264; found: 521.2261.

(3*S*)-3-Carboxy-14,14-dimethyl-12-oxo-10,13-dioxa-2,11-diazadecanoic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (1f)

Prepared from **4c** in 72% yield over 2 steps; $[\alpha]_D^{20}$ +7.67 (*c* 1.11, $CHCl_3$).

IR (KBr): 3292.9, 2928.4, 1702.8, 1450.2, 1248.7, 1162.9, 1107.9, 909.3, 731.9 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.47 Hz, 2 H), 7.64–7.51 (m, 3 H), 7.37 (t, *J* = 7.32 Hz, 2 H), 7.29 (d, *J* = 2.29 Hz, 2 H), 5.55 (br s, 1 H), 4.57–4.27 (m, 3 H), 4.19 (t, *J* = 6.84 Hz, 1 H), 3.80 (t, *J* = 6.44 Hz, 2 H), 1.86 (m, 1 H), 1.70 (m, 1 H), 1.64–1.52 (m, 2 H), 1.52–1.41 (m, 10 H), 1.41–1.19 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.31, 156.15, 143.70, 141.24, 127.67, 127.04, 125.10, 119.93, 113.43, 81.82, 76.60, 67.04, 47.10, 32.13, 28.76, 28.20, 27.74, 25.49, 24.94.

ESI-MS (+): *m*/*z* = 535.2 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{28}H_{36}N_2O_7$ + Na $(M + Na)^+$: 535.2420; found: 535.2414.

***N*-(Triphenylmethyl)-L-serine Methyl Ester (7)[10]**

To cooled MeOH (100 mL) at 0 °C was added acetyl chloride (10.0 mL) dropwise. The resulting solution was stirred for 15 min, then L-Serine (5.0 g, 47.6 mmol) was added and the solution was stirred at reflux for 2 h and then cooled to r.t. The solvent was evaporated to provide H-Ser-OMe·HCl as a white solid (7.40 g, quant). To a suspension of this material (1.50 g, 9.74 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (3.0 mL, 21.4 mmol) and trityl chloride (2.90 g, 10.22 mmol) and the mixture was stirred overnight at r.t. The mixture was diluted with EtOAc (200 mL), washed with H_2O (50 mL) and brine (50 mL). The solvent was evaporated and the residue purified by silica gel column chromatography (hexanes–EtOAc) to yield **7** as a white solid (3.20 g, 91%); $[\alpha]_D^{20}$ +3.02 (*c* 1.80, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 6 H), 7.27–7.17 (m, 9 H), 3.69 (m, 1 H), 3.55 (m, 2 H), 3.27 (s, 3 H), 2.96 (br s, 1 H), 2.29 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.90, 145.57, 128.72, 127.91, 126.59, 70.94, 64.92, 57.78, 51.96.

ESI-MS (+): *m*/*z* = 384.1 $(M + Na)^+$.

***O*-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*N*-(triphenylmethyl)-L-serine Methyl Ester (8)**

To a solution of alcohol **7** (2.80 g, 7.76 mmol), *N*-hydroxyphthalimide (2.53 g, 15.51 mmol), and Ph_3P (4.50 g, 17.06 mmol) in THF (100 mL) at 0 °C under argon was slowly added diethyl azodicarboxylate (DEAD) (40% in toluene, 7.80 mL, 17.06 mmol). The mixture was warmed to r.t. and stirred overnight. The mixture was diluted with EtOAc (200 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Purification by silica gel column chromatography (hexanes–EtOAc) provided **8** as a white wax; 3.10 g (79%); $[\alpha]_D^{20}$ +39.6 (*c* 1.34, $CHCl_3$).

IR (KBr): 2360.4, 1735.6, 1026.9, 701.0 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 2 H), 7.74–7.72 (m, 2 H), 7.55–7.52 (m, 6 H), 7.27–7.23 (m, 6 H), 7.19–7.15 (m, 3 H), 4.48 (dd, *J* = 9.2, 4.0 Hz, 1 H), 4.13 (dd, *J* = 9.2, 6.0 Hz, 1 H), 3.70 (m, 1 H), 3.42 (s, 3 H), 3.10 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.51, 162.94, 145.58, 134.46, 128.82, 128.72, 127.90, 126.49, 123.48, 80.18, 71.20, 55.74, 52.15.

ESI-MS (+): *m*/*z* = 529.1 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{31}H_{26}N_2O_5$ + Na $(M + Na)^+$: 529.1739; found: 529.1760.

***O*-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*N*-[(phenylmethoxy)carbonyl]-L-serine Methyl Ester (9)**

To a solution of **8** (2.00 g, 3.95 mmol) in CH_2Cl_2 (50 mL) at r.t. was added 37% HCl (0.50 mL) and the suspension was stirred for 1 h and then quenched by the addition of sat. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation and the residue was dissolved in THF (30 mL) with H_2O (10 mL). To this solution was added $NaHCO_3$ (498 mg, 5.92 mmol) and benzyl chloroformate (0.59 mL, 4.15 mmol) and the mixture was stirred overnight at r.t. THF was removed by rotary evaporation and the resulting aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by silica gel column chromatography (hexanes–EtOAc) to yield **9** as a viscous colorless oil (1.32 g, 84%); $[\alpha]_D^{20}$ +31.8 (*c* 0.75, $CHCl_3$).

IR (KBr): 3366.1, 2954.4, 2363.3, 1727.9, 1516.7, 1211.1, 1054.9, 876.5, 698.1 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 2 H), 7.67–7.65 (m, 2 H), 7.30–7.20 (m, 5 H), 6.26 (d, *J* = 8.8 Hz, 1 H), 5.07 (s, 2 H), 4.73 (dd, *J* = 10.6, 3.0 Hz, 1 H), 4.57 (m, 1 H), 4.33 (dd, *J* = 10.6, 3.4 Hz, 1 H), 3.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.56, 163.19, 156.11, 136.21, 134.76, 128.56, 128.45, 128.06, 127.97, 123.71, 77.61, 67.11, 53.45, 52.80.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{20}H_{18}N_2O_7$ + Na $(M + Na)^+$: 421.1011; found: 421.1007.

Mesyl Esters 13 and 14; General Procedure

To a solution of *N*-Cbz-L-homoserine *O*-methyl ester (**10**)[12] or 5-hydroxy-*N*-[(phenylmethoxy)carbonyl]-L-norvaline (**12**;[14] 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added Et_3N (1.5 equiv) and $MeSO_3Cl$ (1.2 equiv) and the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (100 mL), the CH_2Cl_2 layer was washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and the solvent evaporated. Purification of the residue obtained by silica gel column chromatography (hexanes–EtOAc) provided **13** (from **10**) and **14** (from **12**) as viscous colorless oils.

***N*-Benzyloxycarbonyl-*O*-mesyl-L-serine Methyl Ester (13)**

Prepared from **10** (2.70 g, quant); $[\alpha]_D^{20}$ +5.0 (*c* 0.30, $CHCl_3$).

IR (KBr): 3327.6, 2940.0, 1696.1, 1538.0, 1341.3, 1172.5, 1005.7, 740.5 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5 H), 5.61 (d, *J* = 6.0 Hz, 1 H), 5.11 (s, 2 H), 4.50 (m, 1 H), 4.28 (m, 2 H), 3.76 (s, 3 H), 2.96 (s, 3 H), 2.33 (m, 1 H), 2.14 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.73, 171.86, 155.93, 135.97, 128.55, 128.29, 128.12, 67.21, 65.69, 52.76, 50.76, 37.14, 31.79.

ESI-MS (+): *m*/*z* = 368.0 $(M + Na)^+$.

5-[(Methylsulfonyl)oxy]-*N*-[(phenylmethoxy)carbonyl]-L-norvaline Phenylmethyl Ester (14) Prepared from **12** (3.95 g, quant). This material was used in the next step without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 10 H), 5.36 (d, *J* = 8.0 Hz, 1 H), 5.18 (m, 2 H), 5.11 (s, 2 H), 4.45 (q, *J* = 8.0 Hz, 1 H), 4.20 (t, *J* = 8.0 Hz, 2 H), 2.95 (s, 3 H), 2.01 (m, 1 H), 1.84–1.70 (m, 3 H).

ESI-MS: *m*/*z* = 525.1 $(M + Na^+)$.

Phthalimidoxy Intermediates 15 and 16; General Procedure

To a solution of *N*-hydroxyphthalimide (2.0 equiv) in DMF (10 mL) at r.t. was added a solution of DBU (2.0 equiv) in DMF (10 mL). The mixture was cooled to 0 °C and stirred for 30 min, then a solution of either **13** (to prepare **15**) or **14** (to prepare **16**) (1.0 equiv) in DMF (10 mL) was added dropwise. The mixture was warmed to r.t. and stirred for 2 d. The solution was diluted with EtOAc (200 mL) and the organic layer was washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). Purification of the residue obtained by evaporation of the solvent by silica gel column chromatography (hexanes–EtOAc) provided products **15** and **16** as white solids.

***O*-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*N*-[(phenylmethoxy)carbonyl]-L-homoserine Methyl Ester (15)[12]**

Prepared from **13** (2.20 g, 71%); $[\alpha]_D^{20}$ +8.6 (*c* 1.95, $CHCl_3$).

IR (KBr): 3331.4, 2364.3, 2343.1, 1725.0, 1682.6, 1529.3, 1216.9, 698.1 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.74 (m, 2 H), 7.71–7.67 (m, 2 H), 7.31–7.22 (m, 5 H), 6.16 (d, *J* = 8.4 Hz, 1 H), 5.07 (s, 2 H), 4.58 (q, *J* = 6.8 Hz, 1 H), 4.26 (m, 2 H), 3.70 (s, 3 H), 2.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.02, 163.47, 156.14, 136.39, 134.60, 128.74, 128.40, 127.97, 127.91, 123.60, 74.98, 66.85, 52.55, 51.44, 30.19.

ESI-MS (+): *m*/*z* = 435.1 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{21}H_{20}N_2O_7$ + Na $(M + Na)^+$: 435.1168; found: 435.1176.

5-[(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)oxy]-*N*-[(phenylmethoxy)carbonyl]-L-norvaline Phenylmethyl Ester (16)

Prepared from **14** (2.70 g, 61%); $[\alpha]_D^{20}$ –16.34 (*c* 0.35, $CHCl_3$); mp 101–105 °C.

IR (neat): 3324, 3066, 3033, 2965, 2936, 2361, 2336, 1725, 1698, 1539, 1276, 1186, 1127, 1018, 876, 736, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.80 (m, 2 H), 7.76–7.73 (m, 2 H), 7.40–7.29 (m, 10 H), 5.47 (d, *J* = 8.0 Hz, 1 H), 5.20 (s, 2 H), 5.10 (s, 2 H), 4.49 (m, 1 H), 4.19 (m, 2 H), 2.16 (m, 1 H), 2.02 (m, 1 H), 1.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.95, 163.57, 155.94, 136.23, 135.23, 134.45, 128.86, 128.56, 128.44, 128.38, 128.23, 128.06, 127.98, 123.50, 67.20, 66.91, 53.63, 28.83, 24.28.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{28}H_{26}N_2O_7$ + Na $(M + Na)^+$: 525.1638; found: 525.1641.

Protected Amino Esters 17–20; General Procedure

To a solution of intermediates **9**, **15**, or **16** (1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C was added methylhydrazine (1.5 equiv) and the mixture was stirred at 0 °C (1 h). The mixture was passed through Celite and the filtrate was concentrated and dried under high vacuum (30 min). For product **20** see below. For products **17**–**19**, the residue was redissolved in THF (50 mL) and to this was added Et_3N (2.0 equiv) and Boc_2O (2.0 equiv) and the solution was stirred overnight at r.t. The mixture was diluted with EtOAc (200 mL) and washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Purification by silica gel column chromatography (hexanes–EtOAc) provided **17**–**19** as viscous colorless oils. For product **20**, the residue mentioned above prepared by the treatment of **9** with methylhydrazine was dissolved in CH_2Cl_2 (10 mL) and to this was added DIPEA (2.0 equiv) and 4-methyltrityl chloride (1.2 equiv) and the mixture was stirred for 1 h at r.t. The mixture was diluted with EtOAc (100 mL) and washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). Purification of the residue obtained by evaporation of the solvent by column chromatography (hexanes–EtOAc) using Et_3N-pretreated silica gel provided **20** as a white wax.

3-{[(1,1-Dimethylethoxy)carbonyl]aminooxy}-*N*-[(phenylmethoxy)carbonyl]-L-serine Methyl Ester (17)

Prepared from **9** (1.05 g, 95%); $[\alpha]_D^{20}$ –11.7 (*c* 1.33, $CHCl_3$).

IR (KBr): 3297.7, 2978.5, 2361.4, 1716.3, 1519.6, 1210.1, 1055.8, 775.2 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.31–7.23 (m, 5 H), 6.18 (d, *J* = 8.4 Hz, 1 H), 5.09 (s, 2 H), 4.54 (m, 1 H), 4.19 (dd, *J* = 7.2, 4.4 Hz, 1 H), 4.03 (dd, *J* = 11.0, 3.4 Hz, 1 H), 3.70 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.54, 156.87, 156.32, 136.24, 128.44, 128.06, 127.97, 82.30, 75.89, 67.00, 53.18, 52.60, 28.09.

ESI-MS (+): *m*/*z* = 391.1 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{17}H_{24}N_2O_7$ + Na $(M + Na)^+$: 391.1481; found: 391.1482.

4-{[(1,1-Dimethylethoxy)carbonyl]aminooxy}-*N*-[(phenylmethoxy)carbonyl]-L-homeserine Methyl Ester (18)

Prepared from **15** (0.90 g, 97%); $[\alpha]_D^{20}$ +5.8 (*c* 0.65, $CHCl_3$).

IR (KBr): 3308.3, 2977.6, 2361.4, 1703.8, 1527.4, 1246.7, 1162.9, 739.6 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1 H), 7.37–7.26 (m, 5 H), 6.10 (d, *J* = 7.6 Hz, 1 H), 5.12 (s, 2 H), 4.52 (dd, *J* = 13.6, 6.4 Hz, 1 H), 4.00–3.87 (m, 2 H), 3.73 (s, 3 H), 2.12 (m, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.56, 156.94, 156.13, 136.34, 128.41, 128.00, 127.91, 81.88, 72.87, 66.81, 52.44, 51.62, 30.28, 28.12.

ESI-MS (+): *m*/*z* = 405.1 $(M + Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{18}H_{26}N_2NaO_7$ + Na $(M + Na)^+$: 405.1638; found: 405.1647.

5-{[(1,1-Dimethylethoxy)carbonyl]aminooxy}-*N*-[(phenylmethoxy)carbonyl]-L-norvaline Phenylmethyl Ester (19)
Prepared from **16** (1.85 g, 80%); $[\alpha]_D^{20}$ –5.92 (*c* 0.58, $CHCl_3$).

IR (neat): 3310, 3065, 3034, 2976, 2940, 2881, 1711, 1523, 1454, 1367, 1247, 1165, 1110, 1044, 911, 734, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 10 H), 7.15 (s, 1 H), 5.56 (d, 1 H, *J* = 8.0 Hz), 5.22–5.13 (m, 2 H), 5.10 (s, 2 H), 4.42 (q, *J* = 8.0 Hz, 1 H), 3.81 (t, *J* = 6.0 Hz, 2 H), 2.23–1.92 (m, 1 H), 1.90–1.80 (m, 1 H), 1.72–1.60 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.15, 157.00, 156.05, 136.22, 135.27, 128.56, 128.44, 128.39, 128.23, 128.07, 81.70, 75.74, 67.09, 66.93, 53.77, 29.00, 28.14, 27.57, 23.93.

ESI-MS: *m*/*z* = 495.1 (M + Na^+).

HR-ESI/APCI MS: *m*/*z* calcd for $C_{25}H_{32}N_2O_7$ + Na (M + $Na)^+$: 495.2107; found: 495.2110.

3-[(Diphenyl-*p*-tolylmethyl)aminooxy]-*N*-[(phenylmethoxy)carbonyl]-L-serine Methyl Ester (20)
Prepared from **9** (1.31 g, quant); $[\alpha]_D^{20}$ +6.5 (*c* 1.08, $CHCl_3$).

IR (KBr): 3402.8, 2949.6, 1717.3, 1509.0, 1208.2, 1058.7, 698.1 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.16 (m, 15 H), 7.13 (AB, $J_{A,B}$ = 8.4 Hz, 2 H), 7.05 (AB, $J_{A,B}$ = 8.4 Hz, 2 H), 6.69 (s, 1 H), 5.40 (d, *J* = 8.8 Hz, 1 H), 5.06 (m, 2 H), 4.52 (m, 1 H), 3.91 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.84 (dd, *J* = 10.8, 3.6 Hz, 1 H), 3.59 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 156.0, 144.2, 141.1, 136.6, 136.3, 129.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.8, 127.0, 73.9, 67.0, 53.8, 52.5, 21.0.

ESI-MS (+): *m*/*z* = 547.2 (M + $Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{32}H_{32}N_2O_5$ + Na (M + $Na)^+$: 547.2209; found: 547.2213.

Amino Acids 1a–c and 2a; General Procedure
To a solution of intermediates **17**, **18**, or **20** (1.0 equiv) in THF (10 mL) containing H_2O (10 mL) at 0 °C was added $LiOH·H_2O$ (1.2 equiv) and the mixture was stirred at 0 °C (2 h). THF was removed by rotary evaporation and the residual aqueous phase was washed with Et_2O (50 mL) and then acidified to pH 3–4 by the addition of aq 1 N HCl (Note: For **20** aq sat. NH_4Cl was used rather than aq 1 N HCl.) The mixture was extracted with EtOAc (3 × 50 mL) and the combined EtOAc extracts were washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). The organic phase was concentrated and the residue was dissolved in MeOH (20 mL) and stirred with 10% Pd/C under 1 atm H_2 (2 h). (Note: The preparation of **1c** began at this point by the direct hydrogenation of **19**.) The Pd/C was removed by filtration and the filtrate was concentrated and the residue was dissolved in dioxane (10 mL) and H_2O (10 mL). To this was added 9-fluorenylmethylsuccinimidyl carbonate (FmocOSu) (1.1 equiv) and $NaHCO_3$ (2.0 equiv) and the mixture was stirred overnight at r.t. The reaction solution was acidified to pH 3–4 by the addition of aq 1 N HCl (Note: For **2a** aq sat. NH_4Cl was used rather than aq 1 N HCl.) The mixture was extracted with EtOAc (3 × 50 mL) and the combined EtOAc extracts were washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). Purification by silica gel column chromatography (CH_2Cl_2–MeOH) provided final products **1a–c** and **2a** as viscous colorless oils. Lyophilization from MeCN–H_2O provided white powders, which were suitable for solid-phase applications.

(3*S*)-3-Carboxy-9,9-dimethyl-7-oxo-5,8-dioxa-2,6-diazadecanoic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (1a)
Prepared from **17** (0.62 g, 58% yield over 3 steps); $[\alpha]_D^{20}$ +4.4 (*c* 1.30, $CHCl_3$).

IR (KBr): 3288.0, 2977.6, 2364.3, 1700.9, 1521.6, 1449.2, 1160.0, 734.7 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (br s, 1 H), 7.30 (d, *J* = 7.6 Hz, 2 H), 7.65–7.50 (m, 2 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.30–7.17 (m, 2 H), 6.48 (br s, 1 H), 4.54 (m, 1 H), 4.37 (m, 2 H), 4.28 (dd, *J* = 11.4, 3.4 Hz, 1 H), 4.22 (d, *J* = 7.2 Hz, 1 H), 4.02 (dd, *J* = 11.4, 5.4 Hz, 1 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.29, 156.56, 143.70, 143.56, 141.25, 127.72, 127.07, 125.14, 119.95, 83.81, 75.79, 67.45, 52.73, 46.98, 28.02, 27.55.

ESI-MS (+): *m*/*z* = 465.1 (M + $Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{23}H_{26}N_2O_7$ + Na (M + $Na)^+$: 465.1638; found: 465.1636.

(3*S*)-3-Carboxy-10,10-dimethyl-8-oxo-6,9-dioxa-2,7-diazadecanoic Acid 1-(9*H*-fluoren-9-ylmethyl) Ester (1b)
Prepared from **18** (1.60 g, 81% yield over 3 steps); $[\alpha]_D^{20}$ +9.0 (*c* 0.79, $CHCl_3$).

IR (KBr): 3296.7, 2977.6, 2355.6, 1700.9, 1523.5, 1160.9, 1106.9, 909.3, 735.7 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.6 Hz, 2 H), 7.69–7.60 (m, 2 H), 7.52 (m, 1 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 6.67 (br s, 1 H), 4.55 (m, 1 H), 4.43–4.28 (m, 2 H), 4.20 (t, *J* = 7.4 Hz, 1 H), 3.96 (m, 2 H), 2.15 (m, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.64, 157.92, 156.86, 143.81, 143.67, 141.23, 127.68, 127.07, 125.21, 119.91, 106.60, 82.81, 73.12, 67.37, 51.77, 47.00, 29.68, 28.12, 27.54.

ESI-MS (+): *m*/*z* = 479.1 (M + $Na)^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{24}H_{28}N_2O_7$ + Na (M + $Na)^+$: 479.1794; found: 479.1808.

(3*S*)-3-Carboxy-11,11-dimethyl-9-oxo-7,10-dioxa-2,8-diazadecanoic Acid 1-(9*H*-Fluoren-9-ylmethyl) Ester (1c)
Prepared from **19** (0.82 g, 47% yield over 2 steps); $[\alpha]_D^{20}$ +0.152 (*c* 0.77, $CHCl_3$); mp 55–65 °C.

IR (neat): 3295, 2977, 2941, 2879, 1710, 1525, 1451, 1368, 1249, 1165, 1110, 1043, 758, 739, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.6 Hz, 2 H), 7.62–7.56 (m, 2 H), 7.39 (t, *J* = 6.8 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 5.74 (s, 1 H), 4.56–4.32 (m, 3 H), 4.22 (t, *J* = 6.8 Hz, 1 H), 3.91 (s, 2 H), 2.16–2.04 (m, 1 H), 1.96–1.84 (m, 1 H), 1.78–1.68 (m, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.44, 156.49, 143.85, 141.20, 127.63, 127.04, 125.14, 119.88, 82.09, 75.80, 67.12, 53.72, 47.05, 38.33, 30.89, 28.76, 28.17, 23.90.

ESI-MS: *m*/*z* = 493.1 (M + Na^+).

HR-ESI/APCI MS: *m*/*z* calcd for $C_{25}H_{30}N_2O_7$ + Na (M + $Na)^+$: 493.1951; found: 493.1957.

3-[(Diphenyl-*p*-tolylmethyl)aminooxy]-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-serine (2a)
Prepared from **20** (0.40 g, 58% yield over 3 steps); $[\alpha]_D^{20}$ –9.4 (*c* 0.75, $CHCl_3$).

IR (KBr): 3404.7, 2365.3, 1706.7, 1508.1, 1229.4, 1056.8, 700.0 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.91 (dd, *J* = 7.4, 2.2 Hz, 1 H), 7.71 (t, *J* = 5.4 Hz, 1 H), 7.65 (m, 1 H), 7.45–7.16 (m, 16 H), 7.09–

7.00 (m, 5 H), 5.02 (dd, *J* = 16.2, 12.6 Hz, 1 H), 4.32–4.18 (m, 3 H), 3.84 (m, 1 H), 3.60 (t, *J* = 9.6 Hz, 1 H), 2.25 (s, 1.6 H), 2.21 (s, 1.4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4, 156.6, 145.1, 144.3, 142.0, 141.2, 137.4, 136.0, 129.2, 128.8, 128.5, 128.2, 128.1, 127.9, 127.5, 127.0, 125.7, 120.5, 74.1, 73.4, 66.3, 65.9, 54.3, 47.0, 21.0.

ESI-MS (+): *m*/*z* = 621.2 (M + Na)$^+$.

HR-ESI/APCI MS: *m*/*z* calcd for $C_{38}H_{34}N_2O_5$ + Na (M + Na)$^+$: 621.2365; found: 621.2368.

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(17) The major fraction obtained by HPLC purification of the peptide resulting using **1a** to replace the Thr residue, provided a mass spectral molecular ion (*m*/*z* = 1422.4) that was 31 amu lower than expected for the correct product (*m*/*z* = 1453.5). This is consistent with β-elimination of $HONH_2$ followed by reduction of the resulting double bond during under the reducing conditions of resin cleavage using triethylsilane.
(18) The major fraction obtained by HPLC purification of the peptide resulting from the use of **2a** to replace the Thr residue, provided mass spectral molecular ions consistent with the desired peptide product [*m*/*z* = 1454.5, (M + H) and 1476.5 (M + Na)].