# $\delta, \varepsilon$ -Unsaturated $\alpha, \beta$ -Diamino Acids as Building Blocks for the Asymmetric Synthesis of Diverse $\alpha, \beta$ -Diamino Acids

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**Supporting Information** 



**ABSTRACT:** A building block approach for the synthesis of  $\alpha,\beta$ -diamino acids is described, which involves the diastereodivergent preparation of two sets of orthogonally protected  $\delta,\varepsilon$ -unsaturated  $\alpha,\beta$ -diamino acids as templates for the preparation of 12 new  $\alpha,\beta$ -diamino acids of biological relevance using simple techniques.

 $\alpha$ -Amino acids are Nature's versatile building blocks that have found widespread use in the area of molecular design.<sup>1,2</sup> Thus, a number of synthetic building blocks and templates for the preparation of diverse natural and non-natural  $\alpha$ -amino acids have emerged over the last few decades.<sup>3</sup> In this regard, the  $\beta_{\gamma}$ unsaturated amino acid vinylglycine,<sup>4</sup> the  $\gamma$ , $\delta$ -unsaturated amino acid allylglycine and its congeners,<sup>5</sup> and the  $\delta$ , $\epsilon$ -unsaturated amino acid homoallylglycine<sup>6</sup> (Hag) have proved to be of distinct advantage as templates for many possible C-C and Chetero bond forming transformations. The biological relevance of  $\alpha_{\beta}\beta$ -diamino acids has similarly triggered synthetic activities, and a number of elegant methodologies based on the use of the aza-Mannich reaction,8 the aza-Henry reaction,9 chiral pool materials,<sup>10</sup> sigmatropic rearrangements,<sup>11</sup> cycloaddition reactions,<sup>12</sup> asymmetric catalytic transformations,<sup>13</sup> either in the context of synthesis of many important nature-inspired molecules or on their own merits, have been developed. Substrate- or reagent-controlled diastereodivergent synthesis of syn- and anti- $\alpha_{\beta}\beta$ -diamino acid derivatives have also been elegantly developed.<sup>14</sup> However, the use of  $\alpha_{\beta}$ -diamino acids as building blocks for the synthesis of other  $\alpha,\beta$ -diamino acids, in particular, through C-C bond formation, is less documented. Herein, we report two epimeric sets of orthogonally protected  $\alpha,\beta$ -diamino acids 7–8 and 11–12 (Scheme 1) as new building blocks for the synthesis of diverse  $\alpha,\beta$ -diamino acids.

The allylation of  $\alpha$ -chiral imines has emerged as an efficient method for the synthesis of enantio-enriched homoallylic amines.<sup>15</sup> On the basis of our continuing interest<sup>16</sup> in strategic stereodivergent allylation of  $\alpha$ -chiral imines, we studied the allylation reaction of the chiral imine **2**, prepared by

dehydrative condensation between Garner's aldehyde  $1^{17}$  and 4-methoxybenzyl amine. Thus, allylation of the imine 2 with allylzinc bromide under optimized reaction conditions provided the *syn*-homoallylic amine 3 as the major isomer (74%), together with a small amount of the *anti*-isomer 4 (12%). On the contrary, when allylation of 2 was carried out with allyl magnesium bromide, the homoallylic amine 4 was formed as the major isomer in a similar yield and diastereomeric excess. The products 3 and 4 were then separately converted to the desired building blocks over a three-step sequence involving protection of the  $\beta$ -nitrogen with Cbz-Cl, one-pot deprotection—oxidation of the resulting carboxylic acids 6 and 10.

The stereochemical assignment of the amines **3** and **4** was based on Cram's open chain and chelate models with further support from the synthetic work described later (Scheme 5). The protected pair of templates 7–8 and **11–12** exhibited hindered rotation, and significant signal multiplication occurred when the <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> at room temperature, questioning the diastereomeric purity of the products. However, recording their <sup>1</sup>H NMR spectra at higher temperature clearly established their homogeneity as a single set of signals was observed (Figure 1, Supporting Information). This kind of hindered rotation of *N*-carbamates is well-precedented.<sup>17c</sup>

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Scheme 1. Diastereodivergent Synthesis of  $\alpha_{\beta}\beta$ -Diamino Acid Building Blocks 7, 8, 11, and 12



Scheme 2. Diastereodivergent Synthesis of DAP and 2,3-Diaminosuberic Acid Derivatives<sup>a</sup>



<sup>&</sup>lt;sup>a</sup>Cat. 13 is benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium.

Addition of organometallic reagents to imines derived from Garner's aldehyde has been studied earlier with varying amounts of diastereoselectivity.<sup>18</sup> However, the present diastereodivergent allylation protocol is of significant advantage in the sense that reagent-controlled switching of diastereoselectivity was reported to be problematic in earlier instances.

Having access to the stereochemically pure *syn-* and *anti*diamino acid building blocks with orthogonal protection, we considered their conversion to other diamino acids. 2,6-Diaminopimelic acid (DAP) has found widespread utility as an important naturally occurring diamino acid.<sup>19</sup> However, exploration of other regio-isomeric pimelic acids (e.g., 2,3diaminopimelic acid) and homologues thereof remains important. We opted for a cross-metathesis (CM) reaction of the prepared building blocks 7, 8, 11, and 12 toward the fulfillment of some of these objectives in view of several elegant reports<sup>20</sup> on CM-mediated transformations of  $\alpha$ -amino acids and peptides. Thus, the CM reaction of 7 with *tert*-butyl acrylate proceeded better in the presence of Grubbs' second-generation catalyst 13 (G-II)<sup>21a</sup> under optimized conditions to provide the unsaturated ester 14 in good yield (82%) (Scheme 2). One-pot hydrogenolytic removal of the double protections on the  $\beta$ -nitrogen as well as saturation of the double bond in 14 delivered the diaminopimelic acid derivative 15. The attempted CM reaction of 7 with the terminal and nonconjugated olefin (Type-1 according to Grubbs' classification<sup>21b</sup>) benzyl butenoate proved to be a little sluggish, but efficacious. The CM product 16 was obtained in good yield but as an E/Z

mixture (84:16). One-pot hydrogenolytic removal of the *N*-Cbz, *N*-PMB, and *O*-Bn protection groups, as well as saturation of the double bond, proceeded well to produce the hitherto unknown 2,3-diaminosuberic acid derivative 17. The building block 11 was similarly converted into the epimeric diaminopimelic acid derivative 19 and the diaminosuberic acid derivative 21 through the CM products 18 and 20 in comparable overall yields. A variable-temperature <sup>1</sup>H NMR study on 18 revealed its *E*-geometry as a doublet of 16 Hz could be located at  $\delta$  5.45 in the <sup>1</sup>H NMR spectrum (Figure 2, Supporting Information).

 $\alpha,\beta$ -Diamino acids, wherein the  $\beta$ -nitrogen is part of a heterocyclic ring, have proven to be of importance in the design of modified peptides.<sup>22</sup> We realized that a cyclization involving the  $\beta$ -nitrogen and the remote carboxy function in 15 or 19 would constitute a short synthesis of piperidinyl glycines. Further, the synthetic brevity will not be compromised if the cyclization event could be conducted concurrently during the hydrogenolysis step. Thus, the CM product 22 (Scheme 3),

# Scheme 3. Synthesis of Two Diastereomeric Piperidinyl Glycine Derivatives



obtained from a reaction of 7 with methyl acrylate, on treatment with hydrogen in the presence of Pd-C in methanol underwent smooth conversion into the piperidone derivative 24 in a yield of 74% over a one-pot four-step sequence, the exact order of the chemical steps in this sequence being uncertain. Similarly, exhaustive hydrogenation of the benzyl acrylate derivative 23 under identical conditions led to the cyclized product 24 (70%), perhaps indicating that, at least in this instance, hydrogenolysis of an N-Cbz group is taking place faster than deprotection of the benzyl ester function as otherwise the cyclization event would be difficult to interpret.

Note

It was pleasing to note that the epimeric piperidinyl glycine derivative **26** could be obtained from **25** with similar efficiency.

As an extension, we considered the CM reaction of the prepared templates with styrene derivatives to obtain compounds reminiscent of DOPA and tyrosine. The CM reaction of 7 with 1,2-dimethoxy-4-styrylbenzene proceeded somewhat sluggishly, and the product 27 (Scheme 4) was obtained (E:Z = 89:11) in a modest yield of 65%. In an analogous event, the CM reaction of 7 with 1-methoxy-4styrylbenzene proceeded in a similar fashion to provide 28 (E:Z = 81:19). These CM products were then separately subjected to the one-pot, three-step deprotection-saturation cascade to obtain the desired DOPA and tyrosine analogues 29 and 30, respectively. The corresponding epimeric set of compounds, 33 and 34, were similarly prepared from 11 (Scheme 4). It is interesting to note that significant homodimerization of the styrene unit was observed, while dimerization products from either of the diamino acid building blocks 7 and 11 were almost undetected.

 $\alpha$ -Amino acid derivatives having a lipophilic side chain are receiving current attention in peptide engineering and tuning of biological activity.<sup>23</sup> Therefore, the preparation of the corresponding diamino acids remains important. We utilized the second set of templates 8 and 12 in this regard. Thus, the CM reaction of 8 with the unactivated olefin 1-decene proceeded in good yield, leading to 35 (Scheme 5). The one-





pot hydrogenolytic removal of the benzyl ester moiety, as well as saturation of the double bond, provided the free  $\beta$ -amino acid **36**. Compound **39** was similarly prepared from **12**. We opted to demonstrate the utility of these  $\beta$ -amino acid

#### Scheme 4. Diastereodivergent Synthesis of DOPA and Tyrosine Analogue



derivatives through their conversion to the corresponding  $\beta$ lactams in view of known importance of amino-substituted  $\beta$ lactams.<sup>24</sup> The building blocks 8 and 12 proved to be better since their reactive functionalities for lactam ring formation could be unraveled in a single hydrogenation step. The  $\beta$ -amino acids 36 and 39 thus obtained were cyclized in the presence of Mukaiyama's reagent to the desired targets 37 and 40, respectively (Scheme 5). In the <sup>1</sup>H NMR spectrum of 37, H<sub>a</sub> appeared as a double doublet (dd,  $J_{a,b} = 4.8$  Hz,  $J_{a,NH} = 8$  Hz), whereas, in the <sup>1</sup>H NMR spectrum of 40, H<sub>a</sub> appeared as a doublet ( $J_{a,NH} = 7.2$  Hz) indicating little coupling with H<sub>b</sub>. These data were diagonistic of their stereochemistry,<sup>25</sup> and hence of the newly created stereocenters in 3 and 4.

Interestingly, compound **37** formed gels with hydrocarbon solvents, including petroleum ether. From the SEM micrograph displayed in Figure 1, it is evident that this gel is microporous with pores measuring  $0.5-8 \ \mu m$  in diameter. Structurally similar organogels have found applications in oil-spill recovery.<sup>26</sup>



Figure 1. SEM micrograph of freeze-dried 37, demonstrating that the gel is composed of a network of interconnected pores.

In brief, we have developed efficient synthetic protocols to prepare a set of four orthogonally protected  $\delta_{,e}$ -unsaturated  $\alpha_{,\beta}$ -diamino acids as new building blocks and demonstrated their utility for the preparation of 12 new  $\alpha_{,\beta}$ -diamino acids of potential biological relevance having (i) a polar (CO<sub>2</sub>H) headgroup, (ii) a terminal aromatic residue, (iii) an appended piperidone ring, and (iv) a lipophilic side chain utilizing the cross-metathesis reaction as the key step. The versatile reactivity of the double bond should allow this building block approach suitable for the synthesis of other  $\alpha_{,\beta}$ -diamino acids and derivatives thereof for peptide engineering. The methodology developed may thus find several applications.

#### EXPERIMENTAL SECTION

**General.** Column chromatography was performed on silica gel, Merck grade 230–400 mesh. TLC plates were visualized with UV, in an iodine chamber, or with vaniline solution, unless noted otherwise. IR spectra were recorded using KBr disks, chloroform solution, or as neat samples. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 400 and 100 MHz, respectively. Several compounds reported herein exhibited extensive rotamerism complicating analysis of NMR spectra. However, recording such spectra at higher temperature (70–80 °C) resolved the problem in the majority of cases.

Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF, benzene, and ether were freshly distilled under argon from a purple solution of sodium benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

(R)-tert-Butyl-4-((S)-1-(4-methoxybenzylamino)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (3). A stirred solution of the Garner's aldehyde 1 (2.00 g, 8.73 mmol) in dry THF (30 mL) was cooled to 5 °C, and anhydrous MgSO<sub>4</sub> (4.20 g, 34.9 mmol) was added under an argon atmosphere. After stirring for 10 min, a solution of 4methoxybenzyl amine (1.32 g, 9.60 mmol) in THF (6 mL) was added dropwise over 10 min. The reaction mixture was then allowed to come to rt and was stirred for 20 h. It was filtered, and the filtrate was concentrated in vacuo, and diluted with dry THF (25 mL). The solution was cooled to -5 °C, and then a solution of allylzinc bromide [prepared in situ by treating allyl bromide (1.3 mL) with Zn dust (1.1 g) in dry THF (20 mL) at rt for 20 min] was added dropwise over 30 min. The mixture was stirred at this temperature for 6 h and then quenched by the slow addition of aq. NH<sub>4</sub>Cl solution (5 mL) before being extracted with EtOAc (2  $\times$  50 mL). The combined organic extract was washed with water (50 mL) and brine solution (50 mL) and dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated in vacuo to leave a crude product, which was purified by flash chromatography over silica gel using EtOAc/hexane (1:19) to give 3 (2.5 g, 74%), followed by 4 (0.4 g, 12%), both as oils. 3:  $[\alpha]_{D}^{25}$  – 17.0 (c 2.2, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3350, 2977, 2934, 1698, 1612, 1512, 1388 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO- $d_{61}$  400 MHz):  $\delta$  7.20 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.4 Hz, 2H), 5.79-5.70 (m, 1H), 5.10-5.07 (m, 2H), 4.02-3.98 (m, 2H), 3.90 (dd, J = 6.8, 9.2 Hz, 1H), 3.72 (s, 3H), 3.67-3.62 (m, 2H), 3.35-3.33 (br m, 1H), 2.97-2.93 (m, 1H), 2.31-2.27 (m, 1H), 1.95–1.92 (m, 1H), 1.42–1.23 (m, 15H).<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 75 MHz, 70 °C): δ 158.2, 152.1, 136.5, 133.1, 128.8, 116.5, 113.6, 93.5, 79.2, 63.4, 58.5, 57.2, 55.0, 50.8, 34.0, 28.0, 26.1. HRMS (QTOF ES<sup>+</sup>) found m/z 391.2594 (M + H)<sup>+</sup>; C<sub>22</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub> requires 391.2597.

(*R*)-tert-Butyl 4-((*R*)-1-(4-Methoxybenzylamino)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (4). The imine 2 was prepared as described above from the aldehyde 1 (1.0 g, 4.37 mmol), dry THF (20 mL), 4-methoxybenzyl amine (0.66 g, 4.80 mmol), and anhydrous MgSO<sub>4</sub> (2.1 g, 17.5 mmol). It was filtered under an inert atmosphere, and the filtrate was concentrated in *vacuo*, which was used as such in the next step.

To a stirred solution of allylmagnesium bromide (1 M, 9.0 mL, 8.75 mmol) in dry Et<sub>2</sub>O/THF (1:1) (15 mL) at -30 °C was added a solution of the imine 2 (1.5 g, 4.37 mmol) in dry  $Et_2O$  (5 mL) dropwise over 10 min under argon. After 8 h, the mixture was quenched with aq. NH<sub>4</sub>Cl solution (5 mL) and then extracted with EtOAc (2  $\times$  50 mL). The combined organic extract was washed with water (50 mL) and brine solution (50 mL) and dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silica gel using EtOAc/hexane (1:19) to give 3 (0.17 g, 10%), followed by 4 (1.28 g, 75%), both as oils. 4:  $[\alpha]_D^{25} - 41.4$  (c 1.2, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3345, 2977, 2933, 1697, 1612, 1512, 1388, 1366, 1248. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 7.18 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.82-5.77 (m, 1H), 5.04 (m, 2H), 4.03 (br m, 1H), 3.88-3.76 (m, 2H), 3.71 (s, 3H), 3.67–3.62 (m, 1H), 3.58 (d, J = 13.2 Hz, 1H), 3.34 (br m, 1H), 2.94-2.91 (m, 1H), 2.30-2.17 (m, 1H), 2.01-1.95 (m, 1H), 1.51–1.23 (m, 15H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 75 MHz, 70 °C): δ 158.0, 151.4, 136.0, 132.8, 128.7, 116.0, 113.4, 93.1, 78.8, 63.3, 59.4, 57.3, 54.7, 50.7, 36.1, 27.7, 26.2. HRMS (QTOF ES<sup>+</sup>) found m/z 391.2594  $(M + H)^{+}$ .  $C_{22}H_{35}N_2O_4$  requires 391.2597.

(*R*)-*tert*-Butyl 4-((S)-1-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (5). To a stirred solution of the amine 3 (2.5 g, 6.4 mmol) in EtOAc (15 mL) and water (2 mL) was added NaHCO<sub>3</sub> (1.10 g, 12.8 mmol), followed by benzyl chloroformate (1.10 mL, 7.7 mmol) slowly over 10 min at rt. The resulting mixture was stirred for 3 h before being diluted with water (10 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine solution (25 mL) and dried over (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated in *vacuo* to give a pale yellow crude product, which was purified by flash column chromatography using EtOAc/hexane (1:19) to give 5 (3.30 g, 98%) as a colorless oil.  $[\alpha]_{D}^{25}$  + 12.5 (*c* 1.1, CHCl<sub>3</sub>). IR (KBr): 2978, 2935, 1695, 1613, 1513, 1366, 1248 cm<sup>-1.</sup> <sup>1</sup>H NMR

(DMSO- $d_{6^{\circ}}$  300 MHz, 75 °C):  $\delta$  7.33 (br m, 5H), 7.21 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.42–5.29 (m, 1H), 5.16–5.04 (m, 2H), 4.98–4.52 (m, 2H), 4.57–4.52 (m, 1H), 4.29–4.23 (m, 1H), 4.14 (t, J = 5.7 Hz, 1H), 4.06–4.03 (m, 1H), 3.98–3.92 (m, 1H), 3.76 (m, 4H), 2.31–2.19 (m, 2H), 1.56 (s, 3H), 1.44 (s, 9H), 1.40 (s, 3H). <sup>13</sup>C NMR (DMSO- $d_{6^{\circ}}$  75 MHz, 75 °C):  $\delta$  158.1, 151.8, 136.4, 135.3, 130.4, 128.5 (2 rotamers), 127.8 (2 rotamers), 127.3, 115.8, 113.4, 92.9, 79.3, 66.1, 63.8, 59.1, 58.7, 54.8, 49.2, 31.6, 27.7, 26.5, 23.2. HRMS (QTOF ES<sup>+</sup>) found m/z 547.2781 (M + Na)<sup>+</sup>. C<sub>30</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>6</sub> requires 547.2784.

(2R,3S)-3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(tert-butoxycarbonylamino)hex-5-enoic Acid (6). Jones' reagent (3.0 mL) was added dropwise to a stirred solution of the acetonide 5 (1.00 g, 1.91 mmol) in acetone (12 mL) at 10 °C. The resulting mixture was stirred for 3 h at rt and then quenched with isopropanol (1.0 mL). The volatiles were evaporated in vacuo, and the residue was extracted with EtOAc ( $2 \times 20$  mL). The combined organic extract was washed with water  $(2 \times 10 \text{ mL})$  and the brine solution (10 mL) and dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated under reduced pressure to leave a crude viscous liquid, which was purified by flash chromatography over silica gel using EtOAc/hexane (2:3) to provide 6 (0.85 g, 81%) as a colorless gum.  $[\alpha]_D^{25}$  + 13.5 (c 1.0, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3361, 2977, 1745, 1700, 1612, 1513, 1367, 1248, 1162 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.72 (brm, 1H), 7.4-7.30 (m, 5H), 7.17 (d, J = 7.6 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 5.42-5.32 (m, 1H), 5.24-5.11 (m, 2H), 4.91 (d, J = 11.2 Hz, 2H), 4.72 (d, J = 15.2 Hz, 1H), 4.51 (t, J = 5.1 Hz, 1H), 4.07 (d, J = 15.2 Hz, 1H), 3.95-3.83 (m, 1H), 3.78 (s, 3H), 2.61-2.57 (m, 1H), 2.22-2.17 (m, 1H), 1.44 (s, 9H). <sup>13</sup>C NMR (100 MHz,  $CDCl_3$ ):  $\delta$  175.0, 159.1, 157.1, 156.3, 16.1, 133.6, 129.8, 129.3, 128.5, 128.1 127.9, 118.4, 113.9, 80.0, 67.7, 59.7, 56.4, 55.2, 52.5, 33.8, 28.4. HRMS (QTOF ES<sup>+</sup>) found m/z 521.2266 (M + Na)<sup>+</sup>, C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>7</sub> requires 521.2264.

(2R,3S)-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(tert-butoxycarbonylamino)hex-5-enoate (7). To a stirred solution of the carboxylic acid 6 (500 mg, 1.00 mmol) in dry DMF (6 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (652 mg, 2.00 mmol), followed by methyl iodide (125 µL, 2.00 mmol) dropwise at 0 °C. The resulting solution was stirred for 1 h at rt before being diluted with water (10 mL) and extracted with Et<sub>2</sub>O (2  $\times$  25 mL). The combined organic extract was washed with water (25 mL) and brine solution (25 mL) and dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography using EtOAc/hexane (1:9) to give 7 (0.5 g, 97%) as a colorless oil.  $[\alpha]_{D}^{25}$  + 4.5 (c 1.6, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3370, 2976, 2932, 1746, 1713, 1699, 1612, 1513, 1366, 1248, 1173 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.33-7.25 (m, 5H), 7.12 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 7.2 Hz, 2H), 6.43 (brm, 1H), 5.49-5.41 (m, 1H), 5.19-5.14 (m, 2H), 4.93 (d, J = 10.8 Hz, 2H), 4.61 (d, J = 15.2 Hz, 1H), 4.50-4.47 (m, 1H), 4.04-4.96 (m, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 2.54–2.29 (m, 2H), 1.42 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.5, 158.9, 156.6, 155.5, 136.0, 133.4, 129.3, 128.3, 127.9, 127.7, 118.1, 113.7, 79.4, 67.3, 59.7, 56.2, 55.0, 52.0, 51.7, 33.5, 28.1. HRMS  $(QTOF ES^+)$  found m/z 535.2422  $(M + Na)^+$ ,  $C_{28}H_{36}N_2NaO_7$ requires 535.2420.

(55,6*R*)-Benzyl 5-Allyl-4-(4-methoxybenzyl)-10,10-dimethyl-3,8-dioxo-1-phenyl-2,9-dioxa-4,7-diazaundecane-6-carboxylate (8). To a stirred solution of the carboxylic acid 6 (0.5 g, 1.0 mmol) in dry DMF (6 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (490 mg, 1.5 mmol), followed by benzyl bromide (180 µL, 1.5 mmol) dropwise at 0 °C, and the resulting solution was stirred for 1 h at rt before being diluted with water (10 mL) and extracted with Et<sub>2</sub>O (2 × 25 mL). The combined organic layer was washed with water (25 mL) and brine solution (25 mL) and dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated in *vacuo* to give the crude product, which was purified by flash chromatography using EtOAc/hexane (1:9) to give 8 (560 mg, 95%) as a colorless oil. [α]<sub>D</sub><sup>25</sup> + 16.6 (*c* 0.4, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 2977, 2931, 1712, 1514, 1250, 1164, 1029 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.34–7.30 (m, 10H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.40–5.33 (m, 1H), 5.20–5.09 (m, 4H), 4.90–4.85 (m, 2H), 4.54–4.64 (m, 2H), 3.93–3.90 (m, 1H), 3.76 (s, 3H), 2.54–2.51 (m, 1H), 2.19–2.16 (m, 1H), 1.42 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.2, 159.1, 156.8, 155.8, 136.2, 135.4, 133.6, 129.5, 129.4, 128.7, 128.6, 128.5, 128.4, 128.2, 127.9, 118.3, 113.8, 79.6, 67.6, 67.2, 60.0, 56.7, 55.2, 52.2, 33.8, 28.4. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 611.2738 (M + Na)<sup>+</sup>, C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>7</sub> requires 611.2733.

(*R*)-*tert*-Butyl 4-((*R*)-1-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (9). Compound 9 was prepared following the procedure described for compound 5. Yield = 1.29 g from 1.01 g of 4, 96%.  $[\alpha]_D^{25}$ – 20.2 (*c* 2.4, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): 2978, 2935, 1698, 1612, 1513, 1376, 1248 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz, 90 °C):  $\delta$  7.23 (*s*, 5H), 7.15 (d, *J* = 5.1 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.63–5.55 (m, 1H), 5.16 (*s*, 2H), 4.98–4.87 (m, 2H), 4.57–4.52 (m, 1H), 4.34–4.09 (m, 3H), 3.73 (*s*, 4H), 3.60–3.55 (m, 1H), 2.53–2.21 (m, 2H), 1.55– 1.49 (m, 15H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 75 MHz, 70 °C):  $\delta$  159.0, 156.8, 152.4, 137.2, 135.9, 131.1, 129.1, 128.8, 128.6, 128.0, 117.1, 114.3, 94.0, 80.0, 67.0, 65.7, 65.4, 59.7, 58.8, 55.5, 33.8, 28.4, 27.8, 23.9. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 547.2782 (M + Na)<sup>+</sup>. C<sub>30</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>6</sub> requires 547.2784.

(2*R*,3*R*)-3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(*tert*-butoxycarbonylamino)hex-5-enoic Acid (10). Compound 10 was prepared following the procedure described for compound 6. Yield = 0.75 g from 1.0 g of 9, 79%.  $[\alpha]_D^{25} - 17.8$  (*c* 0.9, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3366, 2975, 1745, 1702, 1611, 1513, 1367, 1247, 1164 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz, 70 °C):  $\delta$  7.32–7.30 (br m, 5H), 7.18 (m, 2H), 6.91–6.82 (m, 2H), 5.35–5.30 (m, 1H), 5.11 (s, 2H), 4.76– 4.72 (m, 2H), 4.50–4.45 (m, 2H), 4.34–4.21 (m, 2H), 3.71 (s, 3H), 2.48–2.32 (m, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 75 MHz, 70 °C):  $\delta$  172.7, 158.9, 156.4, 155.6, 137.2, 135.5, 131.0, 129.9, 128.6, 128.2, 127.8, 117.0, 114.0, 78.9, 66.9, 58.7, 56.5, 55.5, 49.7, 33.7, 28.7. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 521.2266 (M + Na)<sup>+</sup>, C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>7</sub> requires 521.2264.

(2*R*,3*R*)-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(*tert*-butoxycarbonylamino)hex-5-enoate (11). Compound 11 was prepared following the procedure described for compound 7. Yield = 483 mg from 500 mg of 10, 94%.  $[\alpha]_D^{25}$  – 13.3 (*c* 0.6, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 70 °C): δ 7.32– 7.26 (m, 5H), 7.14 (d, *J* = 11.2 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.40–5.29 (m, 1H), 5.10 (d, *J* = 3.6 Hz, 2H), 4.82–4.75 (m, 2H), 4.45–4.35 (m, 2H), 4.19–4.09 (m, 2H), 3.72 (s, 3H), 3.47 (s, 3H), 2.38–2.31 (m, 2H), 1.35 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 171.3, 158.8, 156.8 (156.2), 155.2, 136.4, 134.4, 130.1, 129.4, 129.1, 128.4, 128.0, 117.7, 113.7, 80.0, (67.7) 67.2, 59.9, 55.5, 55.2, 52.3, 50.2, 33.3, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 535.2418 (M + Na)<sup>+</sup>, C<sub>28</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>7</sub> requires 535.2420.

(5*R*,6*R*)-Benzyl 5-Allyl-4-(4-methoxybenzyl)-10,10-dimethyl-3,8-dioxo-1-phenyl-2,9-dioxa-4,7-diazaundecane-6-carboxylate (12). Compound 12 was prepared following the procedure described for compound 8. Yield = 566 mg from 500 mg of 10, 96%.  $[\alpha]_D^{25} - 7.3$  (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 70 °C):  $\delta$ 7.33-7.31 (m, 10H), 7.14 (d, *J* = 7.2 Hz, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.36-5.33 (m, 1H), 5.12-5.07 (m, 2H), 5.03-4.95 (m, 2H), 4.82-4.76 (m, 2H), 4.55-4.52 (m, 1H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.16-4.12 (m, 2H), 3.73 (s, 3H), 2.44-2.31 (m, 2H), 1.37 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (171.2) 170.8, 158.9, (156.7) 156.3, 155.3, 136.4, 135.3 (134.9), 134.4, 133.7, 130.1, 129.5, 129.1, 128.6 (overlap two signals), 128.4, 128.0, 117.8 (117.6), (113.9) 113.7, (80.2) 80.0, (67.7) 67.4, 67.3 (67.1), 59.9, 55.8, 55.2, 50.2, 33.4, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 611.2738 (M + Na)<sup>+</sup>, C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>7</sub> requires 611.2733.

(55,6*R*,*E*)-1-*tert*-Butyl 7-Methyl 5-((benzyloxycarbonyl)(4methoxybenzyl)amino)-6-(*tert*-butoxycarbonylamino)hept-2enedioate (14). *General Procedure for Cross-Metatheses*. Grubbs' second generation catalyst 13 (25 mg, 3 mol %) was added to a stirred solution of the olefin 7 (500 mg, 0.98 mmol) and *tert*-butyl acrylate (265  $\mu$ L, 1.96 mmol) in anhydrous and degassed CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at rt, and the reaction mixture was heated to reflux under argon for 3 h. It was then concentrated in *vacuo*, and the residue was purified by flash

chromatography over silica gel using EtOAc/hexane (1:9) to afford the  $\alpha,\beta$ -unsaturated ester 14 as a colorless oil (490 mg, 82%).  $[\alpha]_D^{25}$  –8.5 (c 0.8, CHCl<sub>3</sub>). IR (KBr): 3409, 2978, 2931, 1714, 1657, 1613, 1514, 1220, 1162 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.34–7.28 (m, 5H), 7.11 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 7.6 Hz, 2H), 6.48–6.41 (m, 2H), 5.59 (d, J = 15.2 Hz, 1H), 5.19–5.21 (m, 2H), 4.62 (d, J = 15.2 Hz, 1H), 4.11–4.05 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.66–2.63 (m, 1H), 2.42–2.40 (m, 1H), 1.45 (s, 9H), 1.42 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.4, 165.2, 159.2, 156.7, 155.6, 142.0, 136.1, 129.4, 129.0, 128.6, 128.2, 127.9, 126.1, 114.0 (113.9), 80.2, 79.8, 67.7, 59.1, 56.4, 55.2, 52.3, 52.0, 32.1, 28.3, 28.1. HRMS (QTOF ES<sup>+</sup>) found m/z 635.2941 (M + Na)<sup>+</sup>, C<sub>33</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 635.2945.

(2R.3S)-7-tert-Butyl 1-Methyl 3-Amino-2-(tert-butoxycarbonylamino)heptanedioate (15). Pd-C (10%) (15 mg) was added to a stirred solution of the  $\alpha_{,\beta}$ -unsaturated ester 14 (200 mg, mmol) in MeOH (4 mL), and the heterogeneous mixture was vigorously stirred under a hydrogen atmosphere for 8 h. It was then filtered through Celite, the filter cake was washed with MeOH (10 mL), and the filtrate was concentrated in vacuo to leave a crude product, which, on purification by column chromatography over neutral alumina using EtOAc/hexane (1:1), gave compound 15 (78 mg, 66%) as a colorless foam.  $[\alpha]_{D}^{25} - 26.1$  (c 0.8, CHCl<sub>3</sub>). IR (KBr): 3390, 2978, 2932, 1722, 1715, 1646, 1495, 1367, 1164 cm<sup>-1</sup>. <sup>1</sup>H NMR  $(CDCl_3, 400 \text{ MHz}): \delta 6.04 \text{ (s, 1H)}, 5.34 \text{ (d, } J = 9.2 \text{ Hz}, 1\text{H}), 4.38 \text{ (d, } J$ = 8.4 Hz, 1H), 3.84-3.80 (m, 1H), 3.78 (s, 3H), 3.74-3.72 (m, 1H), 2.41-2.39 (m, 1H), 2.31-2.25 (m, 1H), 1.94-1.92 (m, 2H), 1.72-1.61 (m, 2H), 1.46 (s, 18H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 172.6, 172.3, 156.0, 80.2, 79.8, 57.1, 52.4, 35.0, 33.1, 28.3, 28.2, 21.5. HRMS (QTOF ES<sup>+</sup>) found m/z 361.2335 (M + H)<sup>+</sup>,  $C_{17}H_{33}N_2O_6$  requires 361.2339.

(65, 7R)-1-Benzyl 8-Methyl 6-((Benzyloxycarbonyl)(4methoxybenzyl)amino)-7-(*tert*-butoxycarbonylamino)oct-3enedioate (16). Compound 16 was prepared following the procedure described for compound 14 but employing a reaction time of 12 h. Yield = 286 mg from 300 mg of 7, 74%.  $[\alpha]_D^{25} + 4.5$  (*c* 2.4, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): 3409, 2953, 2929, 1713, 1612, 1513, 1455, 1249, 1162 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.40–7.20 (m, 10H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 2H), 6.58–6.56 (m, 1H), 5.57–5.50 (m, 1H), 5.46–5.42 (m, 1H), 5.21–5.11 (m, 2H), 5.06–5.02 (m, 2H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.53–4.49 (m, 1H), 3.91 (d, *J* = 14.2 Hz, 2H), 3.73 (s, 3H), 3.63 (s, 3H), 2.85–2.84 (m, 2H), 2.41–2.28 (m, 2H), 1.36 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.6, 171.3, 159.1, 156.7, 155.8, 136.3, 135.9, 129.8, 129.6, 129.4, 128.6, 128.3, 128.0, 125.3, 114.0, 113.8, 79.5, 67.5, 66.3, 59.8, 56.6, 55.1, 52.2, 37.9, 32.3, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 683.2943 (M + Na)<sup>+</sup>, C<sub>37</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 683.2945.

(65,7*R*)-6-Amino-7-(*tert*-butoxycarbonylamino)-8-methoxy-8-oxo-octanoic Acid (17). Compound 17 was prepared following the procedure described for compound 15, using Pd(OH)<sub>2</sub> as catalyst, and the reaction time was 6 h. Yield = 65 mg from 200 mg of 16, 68%.  $[\alpha]_D^{25}$  + 13.5 (*c* 1.1, MeOH). IR (net): 3360, 2925, 2855, 1742, 1722, 1695, 1613, 1514, 1251, 1161 cm<sup>-1</sup>. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 4.48 (s, 1H), 3.80 (s, 3H), 3.64 (s, 1H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.71– 1.62 (m, 6H), 1.45 (s, 9H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz): δ 175.9, 169.9, 156.9, 80.3, 53.9, 52.2, 33.1, 29.1, 27.2, 24.4, 24.1. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 319.1862 (M + H)<sup>+</sup>, C<sub>14</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub> requires 319.1869.

(5*R*,6*R*,*E*)-1-*tert*-Butyl 7-Methyl 5-((Benzyloxycarbonyl)(4methoxybenzyl)amino)-6-(*tert*-butoxycarbonylamino)hept-2enedioate (18). Compound 18 was prepared following the procedure described for compound 14. Yield = 377 mg from 400 mg of 11, 79%.  $[\alpha]_D^{25} - 6.2$  (*c* 0.8, CHCl<sub>3</sub>). IR (KBr): 3408, 2978, 2930, 1714, 1657, 1612, 1514, 1221, 1164 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 70 °C):  $\delta$  7.35–7.31 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 3H)), 6.81 (d, *J* = 8.8 Hz, 2H), 6.42–6.34 (m, 1H), 5.45 (d, *J* = 15.6 Hz, 1H), 5.15 (s, 2H), 4.54–4.50 (m, 1H), 4.43 (d, *J* = 15.6 Hz, 1H), 4.21 (br d, *J* = 14.0 Hz, 2H), 3.74 (s, 3H), 3.53 (s, 3H), 2.51–2.48 (m, 2H), 1.41 (s, 9H), 1.39 (s, 9H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz, 25 °C):  $\delta$  171.8, 165.0, 158.8, 156.7, 155.8, 144.6, 137.0, 129.3, 128.8, 128.2, 128.1, 128.0, 124.8, 113.9, 79.7, 79.1, 67.3, 66.9, 55.4, 55.3, 52.3, 31.9, 28.5, 28.1. HRMS (QTOF ES<sup>+</sup>) found m/z 635.2946 (M + Na)<sup>+</sup>, C<sub>33</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 635.2945.

(2*R*,3*R*)-7-*tert*-Butyl 1-Methyl 3-Amino-2-(*tert*-butoxycarbonylamino)heptanedioate (19). Compound 19 was prepared following the procedure described for compound 15. Yield = 80 mg from 200 mg of 18, 68%.  $[\alpha]_D^{25} - 15.6$  (*c* 0.75, CHCl<sub>3</sub>). IR (KBr): 3394, 2978, 2933, 1722, 1715, 1644, 1495, 1366, 1166 cm<sup>-1.1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.37 (d, *J* = 8.0 Hz, 1H), 4.23 (q, *J* = 4.0 Hz, 1H), 3.71–3.66 (m, 4H), 2.97–2.95 (m, 1H), 2.16 (dt, *J* = 2.0, 7.6 Hz, 2H), 1.75–1.66 9m, 1H), 1.60–1.47 (m, 2H), 1.37 (s, 18H), 1.28– 1.17 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  172.7, 171.7, 155.7, 80.2, 80.0, 58.6, 53.6, 52.2, 35.2, 33.5, 28.3, 28.1, 21.9. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 361.2331 (M + H)<sup>+</sup>, C<sub>17</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub> requires 361.2339.

(*GR*, *7R*)-1-Benzyl 8-Methyl 6-((Benzyloxycarbonyl)(4methoxybenzyl)amino)-7-(*tert*-butoxycarbonylamino)oct-3enedioate (20). Compound 20 was prepared following the procedure described for compound 14. Yield = 270 mg from 300 mg of 11, 70%.  $[\alpha]_D^{25} - 8.2$  (*c* 0.5, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3410, 2954, 2932, 1713, 1612, 1513, 1456, 1249, 1161 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 70 °C): δ 7.35 (br m, 10H), 7.16 (d, *J* = 6.8 Hz, 3H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.32–5.30 (m, 1H), 5.14–5.02 (m, 5H), 4.53–4.42 (m, 2H), 4.12–4.03 (m, 2H), 3.76 (s, 3H), 3.51 (s, 3H), 2.85 (d, *J* = 6.4 Hz, 2H), 2.49–2.33 (m, 2H), 1.39 (s, 9H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz, 25 °C): δ 172.0, 171.3, 158.8, 156.7, 155.8, 137.2, 137.1, 136.5, 130.5, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 128.0, 124.7, 113.8, 79.0, 67.2, 66.7, 66.0, 63.4, 55.4, 55.3, 52.2, 37.7, 31.7, 28.6. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 683.2941 (M + Na)<sup>+</sup>, C<sub>37</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 683.2945.

(6*R*,*TR*)-6-Amino-7-(*tert*-butoxycarbonylamino)-8-methoxy-8-oxooctanoic Acid (21). Compound 21 was prepared following the procedure described for compound 17, using Pd(OH)<sub>2</sub>-C as catalyst. Yield = 31 mg from 100 mg of 20, 65%.  $[\alpha]_D^{25} + 9.1$  (*c* 1.15, MeOH). IR (net): 3360, 2925, 2855, 1742, 1722, 1695, 1613, 1514, 1251, 1161 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  12.02 (br m, 1H), 8.22 (m, 1H), 4.41 (dd, *J* = 4.0, 8.8 Hz, 1H), 3.59 (s, 3H), 3.57–3.54 (m, 1H), 2.11–2.08 (m, 2H), 1.49–1.21 (m, 17H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  174.7, 170.3, 156.2, 79.5, 55.0, 53.0, 51.5, 33.85, 33.8, 28.5, 24.5, 24.4. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 319.1864 (M + H)<sup>+</sup>, C<sub>14</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub> requires 319.1869.

(55,6*R*,*É*)-Dimethyl 5-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-6-(*tert*-butoxy shycarbonylamino)hept-2-enedioate (22). Compound 22 was prepared following the procedure described for compound 14. Yield = 370 mg from 400 mg of 7, 83%.  $[\alpha]_D^{25}$  + 4.6 (*c* 0.85, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3361, 2952, 2917, 1745, 1715, 1701, 1611, 1513, 1248, 1162 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.35–7.23 (m, 5H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.47–6.43 (m, 1H), 6.35 (d, *J* = 15.2 Hz, 1H), 5.62 (d, *J* = 15.2 Hz, 1H), 5.24–5.19 (m, 2H), 3.79 (s, 3H), 3.61 (s, 6H), 2.58–2.54 (m, 2H), 1.47 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.3, 166.2, 159.2, 156.6, 155.7, 143.6, 136.1, 129.6, 128.9, 128.6, 128.2, 127.9, 123.8, 114.0, 79.8, 67.7, 59.0, 56.6, 55.2, 52.4, 51.4, 32.1, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 593.2479 (M + Na)<sup>+</sup>, C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>NaO<sub>9</sub> requires 593.2475.

(55,6R,E)-1-Benzyl 7-Methyl 5-((Benzyloxycarbonyl)(4methoxybenzyl)amino)-6-(*tert*-butoxycarbonylamino)hept-2enedioate (23). Compound 23 was prepared following the procedure described for compound 14. Yield = 393 mg from 400 mg of 7, 78%.  $[\alpha]_D^{25} - 4.5$  (*c* 0.9, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3362, 2976, 2954, 1722, 1715, 1698, 1612, 1514, 1251, 1164 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.23–7.15 (m, 10H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 7.2 Hz, 2H), 6.45–6.41 (m, 1H), 6.32–6.30 (m, 1H), 5.58 (d, *J* = 15.2 Hz, 1H), 5.10–5.05 (m, 2H), 5.02–4.98 (m, 2H), 4.55 (d, *J* = 14.8 Hz, 1H), 4.46–4.44 (m, 1H), 3.90–3.86 (m, 2H), 3.62 (s, 3H), 3.56 (s, 3H), 2.48–2.46 (m, 2H), 1.32 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.3, 165.6, 159.2, 156.6, 155.6, 144.1, 136.1, 136.0, 129.6, 128.9, 128.6, 128.5, 128.2, 128.1, 127.9, 123.9, 114.0, 79.8, 67.7, 66.0, 59.0, 56.6, 55.1, 52.4, 52.2, 32.2, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 669.2786 (M + Na)<sup>+</sup>, C<sub>36</sub>H<sub>42</sub>N<sub>2</sub>NaO<sub>9</sub> requires 669.2788.

(R)-Methyl 2-(tert-Butoxycarbonylamino)-2-((S)-6-oxopiperidin-2-yl)acetate (24). Pd-C (10%) (16 mg) was added to a stirred solution of the  $\alpha_{\beta}$ -unsaturated ester 22 (200 mg, 0.35 mmol) or 23 (200 mg, 0.31 mmol) in MeOH (5 mL), and the heterogeneous mixture was vigorously stirred under a hydrogen atmosphere for 6 h. It was then filtered through Celite, the filter cake was washed with MeOH (10 mL), and the filtrate was concentrated in vacuo to leave a crude product, which, on purification by column chromatography over neutral alumina using EtOAc/hexane (3:2), gave compound 24 (74 mg, 74%) as a colorless foam.  $[\alpha]_{D}^{25} - 30.0$  (c 1.95, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3357, 2955, 1744, 1716, 1663, 1524, 1366, 1166 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.45 (s, 1H), 5.63 (d, I = 8.0 Hz, 1H), 4.39 (d, J = 7.6 Hz, 1H), 3.88 (brs, 1H), 3.79 (s, 3H), 2.41-2.25 (m, 2H), 1.93-1.92 (m, 2H), 1.73-158 (m, 2H), 1.45 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): *δ* 173.2, 171.2, 155.9, 80.4, 56.7, 54.1, 52.8, 31.2, 28.2, 25.2, 19.4. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 309.1423 (M + Na)<sup>+</sup>, C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>5</sub> requires 309.1426.

(5Ř,6Ř,E)-Ďimethyl 5-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-6-(tert-butoxycarbonylamino)hept-2-enedioate (25). Compound 25 was prepared following the procedure described for compound 14. Yield = 361 mg from 400 mg of 11, 81%.  $[\alpha]_{D}^{25}$ -15.3 ( $\stackrel{1}{c}$  0.8, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3363, 2954, 2917, 1744, 1716, 1701, 1611, 1512, 1248, 1166 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz, 70 °C): δ 7.32-7.25 (m, 5H), 7.11 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 6.40-6.34 (m, 1H), 5.49 (d, J = 15.6 Hz, 1H), 5.13 (s, 2H), 4.52-4.43 (m, 2H), 4.10-4.01 (m, 2H), 3.71 (s, 3H), 3.64-3.54 (m, 4H), 3.49 (s, 3H), 2.48–2.43 (m, 2H), 1.35 (s, 9H).  $^{13}\mathrm{C}$  NMR (DMSO-d<sub>6</sub>, 75 MHz, 70 °C): δ 171.6, 166.0, 159.1, 156.6, 155.1, 145.5, 137.0, 130.3, 129.8, 128.7, 128.2, 128.0, 122.9, 114.1, 79.3, 67.1, 58.2, 55.5, 52.2, 51.3, 50.1, 32.0, 28.5. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C):  $\delta = 171.2$ , 166.3, 159.0, 156.5, 155.1, 144.8 (144.5), 136.4 (136.0), 130.0, 129.4, 128.5, 128.0, 123.0, (113.9) 113.8, 80.1, 67.8, 67.3, 59.5, 55.3, 55.1, 52.4, 51.2, 31.9, 28.2. HRMS (QTOF ES<sup>+</sup>) found m/z 593.2476 (M + Na)<sup>+</sup>, C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>NaO<sub>9</sub> requires 593.2475.

(*R*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-((*R*)-6-oxopiperidin-2-yl)acetate (26). Compound 26 was prepared following the procedure described for compound 15. Yield = 66 mg from 200 mg of 25, 66%.  $[\alpha]_{25}^{25}$  – 8.5 (*c* 2.3, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3358, 2957, 1745, 1714, 1663, 1523, 1366, 1168 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.73 (s, 1 H), 5.71 (d, *J* = 8.0 Hz, 1H), 4.46 (dd, *J* = 4.4, 7.8 Hz, 1H), 3.79 (m, 4H), 2.41–2.27 (m, 2H), 1.94–1.92 (m, 1H), 1.80–1.77 (m, 2H), 1.45 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$ 172.6, 170.2, 155.7, 80.6, 56.6, 55.2, 52.8, 31.0, 28.2, 23.9, 19.4. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 309.1424 (M + Na)<sup>+</sup>, C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>5</sub> requires 309.1426.

(2R,3S)-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(tert-butoxycarbonylamino)-6-(3,4-dimethoxyphenyl)hex-5-enoate (27). Compound 27 was prepared following the procedure described for compound 14 but using 5 mol % of G-II catalyst 13 with 3 equiv of styrene derivative, and the refluxing time was 16 h. Yield = 164 mg from 200 mg of 7, 65%).  $[\alpha]_{\rm D}^{25} - 11.2$  (c 0.76, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3365, 2954, 2837, 1709, 1701, 1514, 1250, 1160, 1027, 755 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.42-7.21 (m, 5H), 7.01 (d, J = 7.6 Hz, 2H), 6.68-6.58 (m, 5H), 6.41 (br d, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.53-5.46 (m, 1H), 5.15-5.07 (m, 2H), 4.57-4.46 (m, 2H), 3.92-3.84 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 2.47–2.43 (m, 2H), 1.34 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.8, 159.0, 156.9, 155.8, 148.8, 148.5, 136.2, 132.7, 130.6, 129.6, 128.5, 128.1, 127.9, 123.4, 119.2, 113.9, 110.9, 108.7, 79.7, 67.5, 60.3, 56.7, 55.9, 55.8, 55.1, 52.3, 52.0, 32.9, 28.4. HRMS (QTOF ES<sup>+</sup>) found m/z 671.2940 (M + Na)<sup>+</sup>, C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 671.2945

[2*R*,3*S*,*E*]-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(*tert*-butoxycarbonylamino)-6-(4-methoxyphenyl)hex-5-enoate (28). Compound 28 was prepared following the procedure described for compound 27. Yield = (166 mg from 200 mg of 7, 69%). [ $\alpha$ ]<sub>D</sub><sup>25</sup> - 15.5 (*c* 0.5, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3374, 2954, 1711, 1513, 1249, 1174, 1033, 755 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.28–7.22 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.74–6.61 (m, 4H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 15.6 Hz, 1H), 5.49–5.45 (m, 2H), 5.17–5.06 (m, 2H), 4.57 (d, *J* = 15.2 Hz, 1H), 4.48 (t, J = 7.2 Hz, 1H), 3.95–3.88 (m, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.60–3.56 (m, 4H), 2.51–2.44 (m, 2H), 1.36 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.8, 159.0, 158.9, 156.9, 155.8, 138.2, 136.3, 132.4, 129.9 (129.8), 129.7 (129.4), 128.5, 128.1, 127.9, 127.3, 123.1, 113.9, 113.8, 79.7, 67.5, 60.2, 56.8, 55.3, 55.2, 52.3, 52.1, 32.9, 28.4. HRMS (QTOF ES<sup>+</sup>) found m/z 641.2836 (M + Na)<sup>+</sup>, C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>NaO<sub>8</sub> requires 641.2839.

(2*R*,3*S*)-Methyl 3-Amino-2-(*tert*-butoxycarbonylamino)-6-(3,4-dimethoxyphenyl)hexanoate (29). Compound 29 was prepared following the procedure described for compound 15. Yield = 49 mg from 100 mg of 27, 81%).  $[\alpha]_D^{25} - 8.6$  (*c* 0.9, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3387, 2972, 2932, 1709, 1516, 1393, 1367, 1260, 1159, 1029, 764 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.82–6.70 (m, 1H), 6.63 (d, *J* = 6.8 Hz, 2H), 5.36 (d, *J* = 8.8 Hz, 1H), 4.20 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 3.20 (brm, 1H), 2.55– 2.45 (m, 2H), 1.65–1.59 (m, 2H), 1.51–1.43 (m, 4H), 1.38 (s, 9H).<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  172.8, 156.0, 148.8, 147.1, 134.7, 120.1, 111.6, 111.1, 79.8, 57.5, 55.9, 55.8, 52.7, 52.4, 35.3, 34.0, 29.7, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 397.2332 (M + H)<sup>+</sup>, C<sub>20</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub> requires 397.2339.

(2*R*,3*S*)-Methyl 3-Amino-2-(*tert*-butoxycarbonylamino)-6-(4methoxyphenyl)hexanoate (30). Compound 30 was prepared following the procedure described for compound 15. Yield = (48 mg from 100 mg of 28, 80%).  $[\alpha]_D^{25} - 3.2$  (*c* 1.1, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3374, 2954, 1714, 1514, 1247, 1164, 1034, 758 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.87 (d, *J* = 6.0 Hz, 2H), 6.56 (d, *J* = 6.0 Hz, 2H), 6.28 (d, *J* = 6.0 Hz, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 3.62–3.55 (m, 4H), 3.53 (s, 3H), 2.35 (brm, 2H), 1.5 (brm, 4H), 1.21 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  170.2, 157.8, 155.9, 133.4, 129.3, 113.8, 80.4, 55.2 (two signals), 53.7, 34.4, 29.9, 28.3, 27.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 367.2225 (M + H)<sup>+</sup>, C<sub>19</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub> requires 367.2233.

(2R,3R)-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(tert-butoxycarbonylamino)-6-(3,4-dimethoxyphenyl)hex-5-enoate (31). Compound 31 was prepared following the procedure described for compound 27. Yield = 169 mg from 200mg of 11, 67%.  $[\alpha]_{D}^{25}$  -10.9 (c 0.69, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3384, 2971, 1709, 1516, 1393, 1367, 1261, 1160, 1029, 762 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 70 °C): δ 7.18–7.00 (m, 7H), 6.82–6.50 (m, 5H), 5.91 (d, J = 15.2 Hz, 1H), 5.48 (br m, 1H), 5.01 (s, 2H), 4.44–4.31 (m, 2H), 4.07-3.91 (m, 2H), 3.62-3.61 (overlapped two singlet, 6H), 3.49 (s, 3H), 3.40-3.33 (m, 4H), 2.42-2.31 (m, 2H), 1.25 (s, 9H).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz, 70 °C):  $\delta$  171.7, 159.0 (158.9), 156.8, 156.1, 149.6, 149.1, 137.2, 131.8, 131.0, 130.8, 129.9, 128.7, 128.2, (128.1) 128.0, 125.1, 119.4 (119.3), (114.2) 114.1, 113.0, 110.6, 79.1, 67.1, 67.0, 59.3, 56.4, 56.2, 55.4, 52.3, 52.1, 32.9, 28.6. HRMS (QTOF ES<sup>+</sup>) found m/z 671.2946 (M + Na)<sup>+</sup>, C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>NaO<sub>9</sub> requires 671.2945.

(2*R*,3*R*,*E*)-Methyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(*tert*-butoxycarbonylamino)-6-(4-methoxyphenyl)hex-5-enoate (32). Compound 32 was prepared following the procedure described for compound 27. Yield = (149 mg from 200 mg of 11, 62%). [*α*]<sub>2</sub><sup>55</sup> - 17.2 (*c* 0.4, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3374, 2956, 1711, 1513, 1249, 1174, 1034, 757 cm<sup>-1.</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.35-7.10 (m, 5H), 7.03-6.86 (m, 4H), 6.75-6.59 (m, 4H), 6.4 (m, 1H), 6.07-6.02 (m, 1H), 5.49-5.45 (m, 1H), 5.17-5.06 (m, 2H), 4.59-4.43 (m, 2H), 3.97-3.88 (m, 1H), 3.71 (s, 3H), 3.69-3.49 (m, 7H), 2.51-2.37 (m, 2H), 1.36 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.8 (171.4), 159.0, 158.9 (158.8), 156.9, 155.5, 136.3, 132.4, 130.0, 129.7, 129.3, 128.5, 128.4, 128.1 (128.0), 127.3, 127.27, 123.1, (113.9) 113.7, 80.1 (79.9), 67.5 (67.2), 60.1, 56.8, 55.7, 55.3, 55.2, 52.5 (52.3), 32.9, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 641.2842 (M + Na)<sup>+</sup>, C<sub>35</sub>H<sub>4</sub>/N<sub>2</sub>NaO<sub>8</sub> requires 641.2839.

(2*R*,3*R*)-Methyl 3-Amino-2-(*tert*-butoxycarbonylamino)-6-(3,4-dimethoxyphenyl)hexanoate (33). Compound 33 was prepared following the procedure described for compound 15. Yield = 48 mg, from 100 mg of 31, 78%).  $[\alpha]_D^{25} - 6.5$  (*c* 1.0, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3384, 2971, 1709, 1515, 1393, 1367, 1260, 1159, 1029, 766 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 25 °C):  $\delta$  6.77 (*d*, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 6.60 (*d*, *J* = 8.0 Hz, 1H), 4.32 (*d*, *J* = 8.4 Hz, 0.5H) {4.26 (*d*, *J* = 8.0 Hz, 0.5H)}, 3.99 (*dd*, *J* = 7.2, 9.6 Hz, 1H), 3.92 (*t*, *J* =

8.4 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.59–3.44 (m, 4H), 1.63–1.41 (m, 3H), 1.32–1.17 (m, 13H). NMR (DMSO- $d_6$ , 400 MHz, 70 °C):  $\delta$  = 6.84–6.68 (m, 3H), 4.36 (br m, 1H), 4.08–4.02 (m, 2H), 3.76–3.62 (m, 9H), 3.38 (m, 1H), 1.67–1.60 (m, 3H), 1.37 (br m, 13H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  172.0, 152.8, 148.8, 147.2, 134.3, 120.2, 111.7, 111.2, 80.4, 63.6 (63.4), 61.6 (61.1), 55.9, 55.8, 51.9 (51.7), 35.3, 29.3, 28.8, 28.3. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 397.2344 (M + H)<sup>+</sup>, C<sub>20</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub> requires 397.2339.

(2*R*,3*R*)-Methyl 3-Amino-2-(*tert*-butoxycarbonylamino)-6-(4methoxyphenyl)hexanoate (34). Compound 34 was prepared following the procedure described for compound 15. Yield = 43 mg from 100 mg of 32, 72%).  $[\alpha]_D^{25} - 4.2$  (*c* 0.8, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3374, 2956, 1714, 1513, 1247, 1164, 1032, 760 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 70 °C):  $\delta$  8.41 (brm, 2H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.51–4.47 (m, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.57–3.51 (m, 1H), 2.57–2.51 (m, 2H), 1.69–1.64 (m, 4H), 1.41 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 70 °C):  $\delta$  17.4, 158.1, 155.6, 133.9, 129.6, 114.3, 79.6, 55.6, 52.8, 52.0, 51.8, 34.3, 29.7, 28.6, 27.0. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 367.2229 (M + H)<sup>+</sup>, C<sub>19</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub> requires 367.2233.

(2R,3S)-Benzyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(tert-butoxycarbonylamino)tetradec-5-enoate (35). Compound 35 was prepared following the procedure described for compound 8 but using 3 equiv of 1-decene, 5 mol % of G-II catalyst 13, and a refluxing time of 12 h. Yield = 367 mg from 400 mg of 8, 77%.  $[\alpha]_{D}^{25}$  + 19.0 (c 1.1, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 2956, 2927, 1716, 1514, 1499, 1250, 1175, 1029 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$ 7.35–7.24 (m, 10H), 7.01 (d, J = 7.6 Hz, 2H), 6.75 (m, 3H), 6.65 (d, J = 4.0 Hz, 1H), 5.29-5.08 (m, 7H), 4.99-4.89 (m, 1H), 4.53-4.46 (m, 2H), 5.18-5.08 (m, 4H), 3.86-3.82 (m, 1H), 3.75 (br s, 4H), 2.44-2.41 (m, 1H), 2.23-2.18 (m, 1H), 1.80-1.72 (m, 2H), 1.43 (s, 9H), 1.33–1.21 (m, 12H), 0.87 (t, J = 6.0 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 171.4, 159.0, 156.9, 155.8, 136.3, 135.4, 135.3, 134.6, 129.5, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 124.7, 113.8, 79.5, 67.5, 67.1, 60.4, 56.9, 55.2, 52.3, 32.6, 31.9, 29.5, 29.3, 29.2, 28.4, 22.7, 14.2. HRMS (QTOF ES<sup>+</sup>) found m/z 723.3982 (M + Na)<sup>+</sup>, C<sub>42</sub>H<sub>56</sub>N<sub>2</sub>NaO<sub>7</sub> requires 723.3985.

(2*R*,35)-3-Amino-2-(*tert*-butoxycarbonylamino)tetradecanoic Acid (36). Compound 36 was prepared following the procedure described for compound 15 using Pd(OH)<sub>2</sub>-C as catalyst, and the reaction time was 10 h. Yield = 84 mg from 200 mg of 35, 82%. [α]<sub>D</sub><sup>25</sup> -17.3 (*c* 1.6, MeOH). IR (net): 3776, 3378, 2926, 2855, 1715, 1690, 1517, 1170, 1061 cm<sup>-1</sup>. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 4.19 (brs, 1H), 3.44 (brm, 1H), 1.60 (m, 1H), 1.47–1.37 (m, 12H), 1.22–1.20 (m, 16H), 0.80 (t, *J* = 6.4 Hz, 3H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz): δ 172.5, 156.4, 79.7, 54.6, 52.4, 31.7, 29.4 (two signals), 29.3, 29.1, 29.0, 28.8, 27.3, 25.2, 22.4, 13.1. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 381.2725 (M + Na)<sup>+</sup>, C<sub>19</sub>H<sub>38</sub>N<sub>2</sub>NaO<sub>4</sub> requires 381.2729.

tert-Butyl (3R,4S)-2-Oxo-4-undecylazetidin-3-ylcarbamate (37). To a stirred solution of 2-chloro-1-methylpyridinium iodide (142 mg, 0.56 mmol) and DIEA (75  $\mu$ L, 0.42 mmol) in dry CH<sub>3</sub>CN (30 mL), a solution of the amino acid 36 (100 mg, 0.28 mmol) in dry CH<sub>3</sub>CN (10 mL) was added slowly, and the resulting mixture was heated up to 70 °C for 1 h, by which time the solution became clear. The reaction mixture was allowed to come to rt, and stirring was continued for 15 h. Then, the volatiles were evaporated off under vacuum and the residue was extracted with EtOAc  $(2 \times 30 \text{ mL})$ . The organic part was washed with water  $(2 \times 25 \text{ mL})$  and brine solution (30 mL) and then dried (MgSO<sub>4</sub>). It was then filtered, and the filtrate was concentrated under reduced pressure to leave the crude product, which was purified by flash chromatography using EtOAc/hexane (15:85) to give the compound 37 (80 mg, 84%) as a colorless gel.  $[\alpha]_{D}^{25}$  -27.3 (c 0.9, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3328, 2958, 2927, 2855, 1763, 1697, 1525, 1367, 1251, 1169, 1050 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.04 (s, 1H), 5.12 (d, J = 8.0 Hz, 1H), 5.04 (dd, J = 4.8, 8.0 Hz, 1H), 3.75 (dt, J = 5.2, 7.6 Hz, 1H), 1.45 (s, 9H), 1.30-1.20 (m, 20H), 0.86 (t, J = 6.8 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$ 168.4, 155.2, 80.3, 60.1, 55.3, 31.9, 30.7, 29.63, 29.60, 29.52(overlap two signals), 29.50, 29.3, 28.2, 25.9, 22.7, 14.1. HRMS (QTOF ES<sup>+</sup>) found m/z 363.2620 (M + Na)<sup>+</sup>, C<sub>19</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>3</sub> requires 363.2624.

(2*R*,3*R*)-Benzyl 3-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(*tert*-butoxycarbonylamino)tetradec-5-enoate (38). Compound 38 was prepared following the procedure described for compound 35. Yield = 362 mg from 400 mg of 12, 76%.  $[\alpha]_{D}^{25}$  -5.7 (*c* 0.64, CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 2956, 2929, 1715, 1514, 1501, 1251, 1176, 1029 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.28–7.09 (m, 11H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.70–6.65 (m, 2H), 5.50 (d, *J* = 6.8 Hz, 1H), 5.19–4.79 (m, 6H), 4.59–4.52 (m, 1H), 4.25 (d, *J* = 16 Hz, 1H), 4.08 (d, *J* = 15.6 Hz, 1H), 3.67 (s, 3H), 2.46–2.18 (m, 2H), 1.70–1.64 (m, 2H), 1.34 (s, 9H), 1.27–1.04 (m, 12H), 0.79 (t, *J* = 6.8 Hz, 3H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta$  171.0, 158.2, 156.3, 155.3, 136.6, 135.6, 132.4, 130.0, 128.2 (two signals), 127.9 (two signals), 127.7, 27.4, 113.6, 113.3, 78.5, 66.7, 66.5, 66.2, 66.1, 55.4, 54.9, 31.9, 31.3, 28.9, 28.8, 28.6, 28.5, 28.0, 27.7, 27.5, 22.1. HRMS (QTOF ES<sup>+</sup>) found *m*/z 723.3981 (M + Na)<sup>+</sup>, C<sub>42</sub>H<sub>56</sub>N<sub>2</sub>NaO<sub>7</sub> requires 723.3985.

(2*R*,3*R*)-3-Amino-2-(*tert*-butoxycarbonylamino)tetradecanoic Acid (39). Compound 39 was prepared following the procedure described for compound 36. Yield = 81 mg from 200 mg of 38, 79%. [*α*]<sub>2</sub><sup>55</sup> -7.8 (*c* 0.72, MeOH). IR (net): 3778, 3374, 2929, 2855, 1717, 1694, 1517, 1172, 1061 cm<sup>-1.</sup> <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 4.19 (brs, 1H), 3.60 (brm, 1H), 1.54 (m, 2H), 1.38-1.30 (m, 11H), 1.29-1.10 (m, 16H), 0.80 (t, *J* = 6.4 Hz, 3H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz): δ 171.0, 157.0, 80.0, 54.9, 52.9, 31.7, 29.4 (two signals), 29.3, 29.1, 29.0, 28.7, 27.3, 24.9, 22.4, 13.2. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 381.2732(M + Na)<sup>+</sup>, C<sub>19</sub>H<sub>38</sub>N<sub>2</sub>NaO<sub>4</sub> requires 381.2729.

*tert*-Butyl (3*R*,4*R*)-2-Oxo-4-undecylazetidin-3-ylcarbamate (40). Compound 40 was prepared following the procedure described for compound 37. Yield = 76 mg from 100 mg of 39, 80%.  $[\alpha]_D^{25} + 9.0$  (*c* 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  6.45 (s, 1H), 5.33 (d, *J* = 7.2 Hz, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 3.56 (t, *J* = 5.6 Hz, 1H), 1.65–1.51 (m, 2H), 1.38 (s, 9H), 1.19 (brs, 18H), 0.81 (t, *J* = 6.4 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  167.9, 154.9, 80.3, 63.4, 58.6, 33.7, 31.9, 29.6, 29.5, 29.48, 29.4, 29.3, 28.3, 26.0, 22.7, 14.1. HRMS (QTOF ES<sup>+</sup>) found *m*/*z* 363.2626 (M + Na)<sup>+</sup>, C<sub>19</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>3</sub> requires 363.2624.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds 3–40, and HPLC chromatograms of compounds 3, 4, 7, 8, 11, 12, 14, 16, 18, 20, 22, 23, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, and 38 are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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