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ORIGINAL ARTICLE

Synthesis of *gem*-diamino acid derivatives by a Hofmann rearrangement

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Abstract Starting from commercially available *N*-protected L-α-amino acids, *N*,*N*′-protected *gem*-diaminic units were obtained by a two-step methodology. A Hofmann reaction performed using a primary alcohol as the solvent to trap the isocyanate intermediate represents the key step of the new synthetic procedure. Then, the methodology was applied to α-carbamoyl α′-carboxyl aziridines, also functionalized with L-α-amino esters and stable *gem*-diaminic units characterized by an aziridine ring and by a retro-peptide modification were obtained. The use of the latter units in the retro-peptide chemistry allows to obtain modified peptides containing an aziridine ring able to behave as an electrophilic site and as a biomimetic structural analog of proline.

Keywords Aminals · Amino acids · Aziridines · Peptidomimetics

Introduction

Peptidomimetics typically are small protein-like molecules designed to mimic natural peptides or proteins. Their structure was derived from natural peptides and they should have the ability to bind to their natural targets in the same way as the natural sequences and hence should produce similar biological effects. It is possible to design these molecules in such a way that they show similar biological effects as their peptide role models but with enhanced properties like a higher proteolytic stability, higher bioavailability and also often with improved selectivity or potency (Grauer and König 2009; Liskamp et al. 2011; Deshmukh and Purohit 2012). In the field of peptidomimetic synthesis, many efforts have been devoted to design and obtain retro-peptidic structures that are characterized by two inversion points of a natural peptide sequence, namely a malonyl residue and a *gem*-diaminic residue. *gem*-Diaminoalkyl and malonyl units can be inserted in the terminal positions or within the peptide sequence to give partially modified retro-peptides in all cases. In fact, the incorporation of a *gem*-diaminoalkyl residue and a malonyl unit results in a good structural complementarity between the parent peptide and the modified retro isomer (Chorev and Goodman 1993; Fletcher and Campbell 1998; Volonterio et al. 2003; Gilmore et al. 2006).

Recently, a new and efficient strategy to synthesize non-symmetric malonyl peptidic units (Fioravanti et al. 2007) and their further modifications (Fioravanti et al. 2010a, b) have been reported by us. To the best of our knowledge, only few methods are reported in the literature to synthesize *gem*-diaminic residues. The most common approach starts from an α-aminoacyl azide that undergoes a Curtius rearrangement at high temperatures to give the corresponding *gem*-diaminic unit as a hydrochloride salt after an acid solution workup (De Bons and Loudon 1980; Chorev and Goodman 1983), usually highly unstable and not storable (Fife et al. 1978; Moad and Benkovic 1978; Moutevelis-Minakakis and Photaki 1985). *gem*-Diamines have also been synthesized by a Mannich condensation of *N*-protected α-aminoacidic amides and benzotriazole with aldehydes, followed by a treatment with a methanolic NH_3

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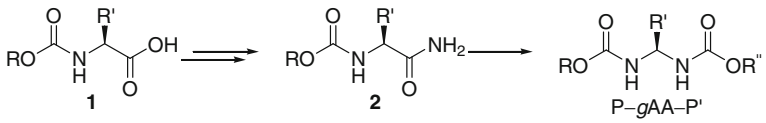
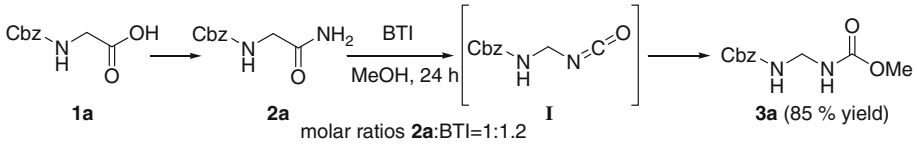
Scheme 1 *N*,*N*′-protected *gem*-diaminic units by a two-step methodology



Scheme 2 Hofmann rearrangement of **2a**



solution (Rowland et al. 2005) or through a Brønsted acid-catalyzed imine amidation reaction (Katritzky et al. 1990).

Results and discussion

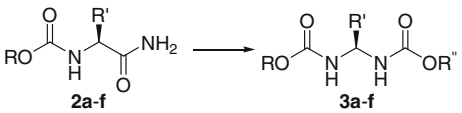
Continuing our studies on the retro-peptide synthesis, we here report a new two-step methodology (Scheme 1) involving α-aminoacidic amides **2** considered in a Hofmann rearrangement reaction to obtain stable *N*,*N*′-protected *gem*-diaminic units starting from commercially available *N*-protected L-α-amino acids **1** (Zhu et al. 2011).

N-Carboxybenzylglycine (**1a**) was chosen as suitable substrate to find the optimal reaction conditions and was converted into the corresponding amide **2a** by classical procedures (North and Pattenden 1990). Then, an opportune alcohol such as methanol was considered to trap the classical isocyanate intermediate **I** that is formed in the Hofmann rearrangement (Myers et al. 2004; Angelici et al. 2008). Under these conditions stable *N*,*N*′-protected *gem*-diaminic building blocks can be directly obtained, stored and deprotected just before use. So, the Hofmann reaction was successfully performed at room temperature, using a slight excess of [bis(trifluoroacetoxy)iodo]benzene (BTI) and the expected stable *N*,*N*'-protected aminal **3a** was obtained in good yields (Scheme 2).

Then, the reaction was performed starting from some different α-aminoacidic amides using allyl alcohol also as the solvent. In all cases *gem*-diaminic units were obtained in satisfactory yields and with total retention of the α-amino acid configuration, as required by the Hofmann transposition (Gribble 2009). The results are reported in Table 1.

As reported in Table 1, *gem*-diaminic units **3a–f**, that can be stored for long times (2 months), have always two different protecting groups on the nitrogen atoms and therefore they can be selectively deprotected to undergo a coupling reaction giving partially modified retro-peptides. To test this, **3f** was successfully considered in a tandem deprotection–coupling reaction (Thieriet et al. 1999) with 2,5-dioxopyrrolidin-1-yl ethyl malonate **4** to give *gem*-diaminic unit **5** (Scheme 3).

Table 1 Synthesis of stable *N*,*N*′-protected aminals



Entry	R	R′	R″	P–*g*AA–P′	Yield (%)
1	Bn	H	Me	**3a**	85
2	Bn	H	Allyl	**3b**	83
3	*t*-Bu	H	Me	**3c**	78
4	*t*-Bu	Bn	Me	**3d**	67
5	*t*-Bu	*i*-Pr	Me	**3e**	74
6	*t*-Bu	H	Allyl	**3f**	81

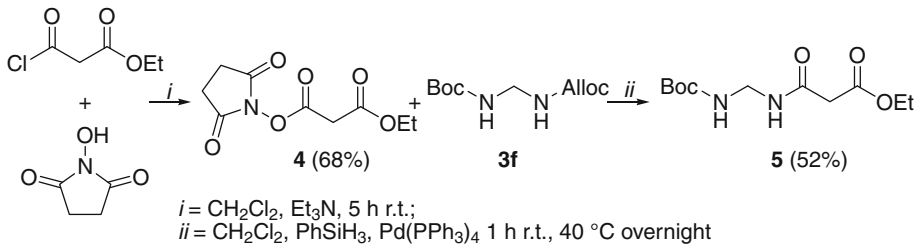
Interested in extending our studies, our synthetic strategy was also applied to α-alkoxycarbonyl α′-carbamoyl aziridines (Fioravanti et al. 2008, 2009), more complex compounds that can be regarded as interesting building blocks for the synthesis of modified retro-peptides containing electrophilic sites. Their synthesis was obtained by direct amination reaction of the corresponding (*E*)-acrylonitriles (Fioravanti et al. 2004) using ethyl nosyloxycarbamate ($NsONHCO_2Et$, $Ns = 4\text{-}NO_2C_6H_4SO_2$) as the aminating agent under heterogeneous conditions (Pellacani et al. 2011). The aziridination reactions take place with total retention of the starting alkene configuration.

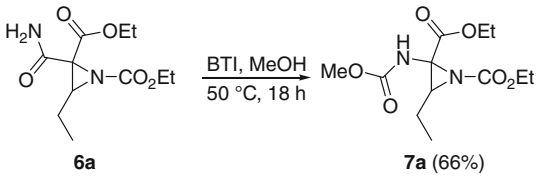
After selective hydrolysis of the cyano group to amide group, the Hofmann rearrangement was performed on **6a** following the standardized conditions, but after 24 h the expected product **7a** was observed only in unsatisfactory yield (≤21 %), as detected by ^{1}H NMR spectra. No better results were observed even by increasing the molar amounts of BTI and/or lengthening the reaction times. Finally **7a** was obtained in satisfactory yields (66 %) by heating the reaction mixture at 50 °C during 18 h (Scheme 4).

The reaction was extended also to different substituted α-carbamoyl α′-carboxyl aziridines, and the results are reported in Table 2.

The Hofmann rearrangement has been successful also with *gem*-dicarbamoyl aziridines carrying a natural amino acid residue (entries 5–8), leading to complex and

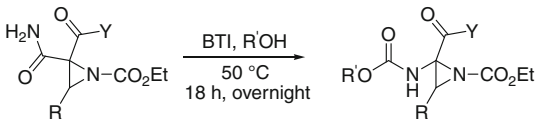
Scheme 3 Synthesis of **5** by a tandem deprotection–coupling reaction

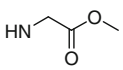
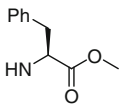
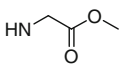
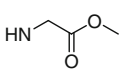




Scheme 4 Hofmann rearrangement of **6a**

Table 2 Synthesis of α-carbamoyl α′-carboxyl aziridines



Entry	6[a]	Y	R	R′	7	Yields (%)
1	**a**	OEt	Et	Me	**a**	66
2	**b**	OEt	Et	Allyl	**b**	58
3	**c**	OEt	*i*-Bu	Me	**c**	64
4	**d**	OEt	*i*-Bu	Allyl	**d**	49
5	**e**		*i*-Bu	Me	**e**	45
6	**f**[b]		*i*-Bu	Me	**f**	53
7	**g**		*i*-Bu	Allyl	**g**	59
8	**h**		Ph	Allyl	**h**	56

[a] Reaction time, 18 h for entries 1–4; overnight for entries 5–8

[b] Diastereomeric ratio ≥95 % determined by ^{1}H NMR spectroscopy of the crude mixtures

interesting *gem*-diaminic units characterized by three different sites of molecular grown.

Conclusion

In conclusion, the synthesis of stable *gem*-diaminic units by a Hofmann reaction performed under very mild conditions was successfully reported. The reaction was extended also to different substituted α-carbamoyl α′-carboxyl aziridines, leading to the synthesis of *gem*-diaminic units characterized by an aziridine ring and a retro-peptide modification. The former represents an important feature for the synthesis of modified peptides containing electrophilic sites that undergo ring opening reactions with a wide range of nucleophiles like potential protease inhibitors (Martina et al. 2005). Moreover it is known that alkoxycarbonyl aziridines represent biomimetic proline analogs, as shown by the comparison between the conformations of the aziridine carboxylic acid containing peptides and the corresponding proline peptides (Okawa and Nakajima 1981).

Experimental

IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer with $CHCl_3$ as the solvent. ^{1}H NMR spectra were recorded at 200 and 300 MHz and ^{13}C NMR spectra at 50 and 75 MHz with Varian Gemini and Varian XL instruments. $CDCl_3$ was used as the solvent and $CHCl_3$ as the internal standard. HRMS and ES Q-TOF analyses were performed using a Micromass Q-TOF spectrometer equipped with an ESI source and a syringe pump. Compounds **6a**–**h** were obtained as reported before (Fioravanti et al. 2008).

Synthesis of *N,N′*-protected *gem*-diamines **3**: general procedure

To a solution of *N*-protected α-amino acid (0.78 mmol) in 2 mL of anhydrous THF, triethylamine (1 mmol) was slowly added. Then, the solutions were cooled at −78 °C under a nitrogen atmosphere and ethyl chloroformate (0.9 mmol) was added dropwise. The reaction mixtures were allowed to warm to −30 °C over 3 h and a 30 % ammonia solution (8.8 mL) was added. The reactions were allowed to warm to room temperature and stirred for 1 h. The solvents were evaporated in vacuo, the residues recovered with EtOAc (10 mL), washed with H_2O (4 × 10 mL) and dried over Na_2SO_4. The recombined organic layers were concentrated in vacuo. The obtained α-aminoacidic amides (1 mmol) were added to a solution of

[bis(trifluoroacetoxy)iodo]benzene (BTI, 1.2 mmol) in 2.5 mL of the opportune alcohol. The reactions were checked by ^{1}H NMR and ES Q-TOF analyses. After 6 h, the solvent was evaporated in vacuo and the residues were stirred with dry diethyl ether (30 min) at room temperature and then filtered off.

*Benzyl methyl methylenebiscarbamate (**3a**)*

Yellow oil, 85 %. IR: 3436, 3354, 1713, 1678 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.68 (s, 3 H), 4.42–4.61 (m, 2 H), 5.11 (s, 2 H), 5.71 (br, 2 H), 7.33–7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 53.5, 56.1, 66.9, 126.2 (2 C), 128.4, 129.0 (2 C), 139.9, 155.2, 156.1. HR-MS HR-MS (ESI-TOF) (*m/z*) calcd for $C_{11}H_{14}N_2NaO_4$ $(M + Na)^+$: 261.0851; found, 261.0857.

*Allyl benzyl methylenebiscarbamate (**3b**)*

Orange oil, 83 %. IR: 3435, 3351, 1712, 1676 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.94–4.15 (m, 2 H), 4.39–4.60 (m, 2 H), 4.96–5.08 (m, 2 H), 5.15–5.34 (m, 2 H), 5.81–5.98 (m, 1 H), 6.14 (br, 2 H), 7.35–7.41 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 42.1, 64.3, 66.7, 108.9, 129.5 (2 C), 130.2, 134.7 (2 C), 135.0 (allylic CH), 138.1, 154.8, 156.0. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{13}H_{16}N_2NaO_4$ $(M + Na)^+$: 287.1008; found, 287.1012.

*tert-Butyl methyl methylenebiscarbamate (**3c**)*

Yellow oil, 78 %. IR: 3433, 3355, 1712, 1677 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.44 (s, 9 H), 3.61 (s, 3 H), 4.40–4.64 (m, 2 H), 6.27 (br, 2 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 27.7 (3 C), 53.5, 56.1, 81.8, 158.2, 159.1. HR-MS (ESI-TOF) (*m/z*) calcd for $C_8H_{16}N_2NaO_4$ $(M + Na)^+$: 227.1008; found, 227.1002.

*tert-Butyl methyl [(1 S)-2-phenylethane-1, 1-diyl]biscarbamate (**3d**)*

Orange oil, 67 %. IR: 3435, 3353, 1713, 1679 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.42 (s, 9 H), 2.92–3.18 (m, 2 H), 3.63 (s, 3 H), 5.67–6.11 (m, 1 H), 7.01 (br, 2 H), 7.32–7.41 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 27.5 (3 C), 42.1, 49.6, 63.3, 81.8, 126.8, 128.3 (2 C), 129.0 (2 C), 135.8, 158.1, 159.0. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{15}H_{22}N_2NaO_4$ $(M + Na)^+$: 317.1477; found, 317.1481.

*tert-Butyl methyl[(1 S)-2-methylpropane-1, 1-diyl]biscarbamate (**3e**)*

Deep yellow, 74 %. IR: 3435, 3353, 1716, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.82–0.90 (m, 6 H), 1.43 (s, 9 H), 2.06–2.18 (m, 1 H), 3.63 (s, 3 H), 5.58–6.17 (m, 1 H), 7.01 (br, 2 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 15.6 (2 C), 27.5 (3 C), 30.7, 51.4, 62.5, 81.8, 156.9, 158.0. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{11}H_{22}N_2NaO_4$ $(M + Na)^+$: 269.1477; found, 269.1483.

*Allyl tert-butyl methylenebiscarbamate (**3f**)*

Yellow oil, 81 %. IR: 3431, 3349, 1713, 1677 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.41 (s, 9 H), 4.36–4.42 (m, 2 H), 4.60–4.65 (m, 2 H), 5.15–5.34 (m, 2 H), 5.80–5.91 (m, 1 H), 7.05 (br, 2 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 27.9 (3 C), 42.1, 66.7, 80.7, 116.4, 135.0, 154.8, 156.0. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{10}H_{18}N_2NaO_4$ $(M + Na)^+$: 253.1164; found, 253.1160.

Synthesis of ethyl 3-({[(*tert*-butoxycarbonyl)amino]methyl}amino)-3-oxopropanoate (**5**)

To a solution of ethyl 3-chloro-3-oxopropanoate (10 mmol) and Et_3N (11 mmol) in anhydrous CH_2Cl_2, *N*-hydroxysuccinimide (11 mmol) was added and the reaction mixture was stirred at room temperature (5 h). After evaporating the solvent, the crude mixture was extracted with brine and **4** was used without further purification. Then, to a solution of **3f** in anhydrous CH_2Cl_2 and under an argon atmosphere 2 eq of $PhSiH_3$, 1.1 eq of **4** and 2 mol % of $Pd(PPh_3)_4$ were added at room temperature. After 1 h of stirring, the reaction was refluxed overnight. The crude mixture was washed with H_2O and dried over Na_2SO_4 and the solvent removed in vacuo. A fast purification on silica gel (hexane/EtOAc = 1:1) gave the purified expected compound.

*2,5-Dioxopyrrolidin-1-yl ethyl malonate (**4**)*

Pale oil, 68 %. IR: 1735, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.21 (t, $J = 7.1$, 3 H); 2.77 (s, 4 H); 3.60 (s, 2 H); 4.15 (q, $J = 7.1$, 2 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 14.1, 26.3 (2 C), 38.4, 61.5, 168.9, 169.4 (2 C), 180.2. HR-MS (ESI-TOF) (*m/z*) calcd for $C_9H_{11}NNaO_6$ $(M + Na)^+$: 252.0484; found, 252.0492.

*Ethyl 3-({[(tert-butoxycarbonyl)amino]methyl}amino)-3-oxopropanoate (**5**)*

Deep yellow oil, 52 %. IR: 3448, 3375, 1719, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.23 (t, $J = 7.1$, 3 H); 1.41 (s, 9 H); 3.65 (s, 2 H); 4.16 (q, $J = 7.1$, 2 H); 4.30–4.61 (m, 2 H), 7.03 (br, 2 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 13.9; 28.1 (3 C); 48.8; 61.4; 65.6, 80.0; 158.9; 172.3; 172.9. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{11}H_{20}N_2NaO_5$ $(M + Na)^+$: 283.1270; found, 283.1276.

Synthesis of N,N′-protected gem-diamines **7**: *general procedure*

To a solution of BTI (1.2 mmol) in 2.5 mL of the opportune alcohol, aziridine **6** (1 mmol) was added. The reactions were warmed at 50 °C and checked by ^{1}H NMR and ES Q-TOF analyses. After 18 h, the solvent was evaporated in vacuo and the crude was purified by flash chromatography on silica gel (hexane/EtOAc = 3:7).

*Diethyl 3-ethyl-2-[(methoxycarbonyl)amino]aziridine-1, 2-dicarboxylate (**7a**)*

Deep yellow oil, 66 %. IR: 3518, 1772, 1731 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.12 (t, J = 6.6 Hz, 3 H), 1.26 (t, J = 7.4 Hz, 3 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.72–1.81 (m, 2 H), 3.09 (t, J = 6.5 Hz, 1 H), 3.68 (s, 3 H), 4.07–4.42 (m, 4 H), 6.54 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 8.9, 13.8, 14.3, 22.0, 41.2, 51.9, 61.4, 61.9, 62.8, 155.2, 171.9, 172.4. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{12}H_{20}N_2NaO_6$ $(M + Na)^+$: 311.1219; found, 311.1227.

*Diethyl 2-{[(allyloxy)carbonyl]amino}-3-ethylaziridine-1,2-dicarboxylate (**7b**)*

Deep yellow oil, 58 %. IR: 3521, 1770, 1732, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.14 (t, J = 6.6 Hz, 3 H); 1.28 (t, J = 7.4 Hz, 3 H), 1,32 (t, J = 7.0 Hz, 3 H), 1.68–1.79 (m, 2 H), 3.11 (t, J = 6.5 Hz, 1 H), 3.95–4.17 (m, 2 H), 4.20–4.55 (m, 4 H), 5.15–5.33 (m, 2 H), 5.83–5.98 (m, 1 H), 6.56 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 9.1, 15.5, 16.0, 22.1, 41.3, 61.4, 61.9, 62.8, 66.9, 116.8, 135.2, 155.3, 169.9, 171.6. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{14}H_{22}N_2NaO_6$ $(M + Na)^+$: 337.1376; found, 337.1384.

*Diethyl 3-isobutyl-2-[(methoxycarbonyl)amino]aziridine-1,2-dicarboxylate (**7c**)*

Deep yellow oil, 64 %. IR: 3516, 1771, 1734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.77 (d, J = 6.5 Hz, 6 H), 1.26 (t, J = 7.4 Hz, 3 H), 1,34 (t, J = 7.0 Hz, 3 H), 1.52–1.68 (m, 1 H), 1.72–1.81 (m, 2 H), 3.11 (t, J = 6.5 Hz, 1 H), 3.69 (s, 3 H), 4.05–4.41 (m, 4 H), 6.54 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 13.8, 14.3, 22.3 (2 C), 28.2, 37.2, 41.2, 52.2, 61.4, 61.9, 62.8, 155.2, 171.9, 172.4. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{14}H_{24}N_2NaO_6$ $(M + Na)^+$: 339.1532; found, 339.1538.

*Diethyl 2-{[(allyloxy)carbonyl]amino}-3-isobutylaziridine-1,2-dicarboxylate (**7d**)*

Deep yellow oil, 49 %. IR: 3515, 1774, 1731, 1638 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.75 (d, J = 6.5 Hz, 6 H), 1.24 (t, J = 7.4 Hz, 3 H), 1.33 (t, J = 7.0 Hz, 3 H), 1.51–1.69 (m, 1 H), 1.73–1.82 (m, 2 H), 3.12 (t, J = 6.5 Hz, 1 H), 3.96–4.15 (m, 2 H), 4.20–4.45 (m, 4 H), 5.36–5.43 (m, 2 H), 5.81–6.02 (m, 1 H), 7.04 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 13.8, 14.3, 22.3 (2 C), 28.2, 37.2, 41.2, 61.4, 61.9, 62.8, 66.7, 108.5, 136.5, 155.2, 171.9, 172.4. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{16}H_{26}N_2NaO_6$ $(M + Na)^+$: 365.1689; found, 365.1693.

*Ethyl 3-isobutyl-2-[(methoxycarbonyl)amino]-2-{[(2-methoxy-2-oxoethyl)amino]carbonyl}aziridine-1-carboxylate (**7e**)*

Deep yellow oil, 45 %. IR: 3424, 3041, 1748, 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.87 (d, J = 6.5 Hz, 6 H), 1.27 (t, J = 7.4 Hz, 3 H), 1.56–1.78 (m, 1 H), 2.28 (t, J = 6.9 Hz, 2 H), 3.24 (t, J = 7.1 Hz, 1 H), 3.62 (s, 3 H), 3.68 (s, 3 H), 4.02–4.13 (m, 4 H), 8.15 (br, 1 H), 8.43 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 14.3, 22.2 (2 C), 23.6, 36.7, 38.1, 40.1, 52.7, 53.3, 61.3, 62.2, 154.3, 155.2, 171.9, 172.3. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{15}H_{25}N_3NaO_7$ $(M + Na)^+$: 382.1590; found, 382.1587.

*Ethyl 2-[(methoxycarbonyl)amino]-2-({[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino}carbonyl)-3-(2-methylpropyl)aziridine-1-carboxylate (**7f**)*

Orange oil, 53 %. IR: 3426, 3401, 1736, 1731 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 1.02 (d, J = 6.6 Hz, 6 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.53-1.83 (m, 2 H), 1.86–1.95 (m, 1 H), 3.14 (dd, J = 7.4 Hz, 1 H), 3.16–3.29 (m, 2 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 4.04 (q, J = 7.1 Hz, 2 H), 4.80-4.92 (m, 1 H), 7.01–7.64 (m, 5 H), 8.80 (br, 1 H), 9.43 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 14.5, 22.1 (2 C), 23.6, 29.7, 31.9, 37.6, 47.3, 52.5, 53.6, 61.6, 63.0, 127.4, 129.0 (2 C), 130.2 (2 C), 137.5, 154.8, 155.2, 172.2, 172.5. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{22}H_{31}N_3NaO_7$ $(M + Na)^+$: 472.2060; found, 472.2065.

*Ethyl 2-[(allyloxycarbonyl)amino]-3-isobutyl-2-(2-methoxy-2-oxoethylcarbamoyl)aziridine-1-carboxylate (**7g**)*

Deep yellow oil, 59 %. IR: 3424, 3403, 1746, 1699, 1638 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.88 (d, J = 6.5 Hz, 6 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.57–1.79 (m, 1 H), 2.21–2.30 (m, 2 H), 3.23 (t, J = 7.1 Hz, 1 H), 3.68 (s, 3 H), 3.84–4.01 (m, 2 H), 4.05-4.15 (m, 4 H), 5.15–5.32 (m, 2 H), 5.82–5.96 (m, 1 H), 8.10 (br, 1 H), 8.33 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 14.3, 22.1(2 C), 23.8, 35.9, 38.3, 41.1, 52.0, 61.6, 61.2, 66.9, 115.6, 134.9, 155.5, 155.8, 171.5, 172.1. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{27}N_3NaO_7$ $(M + Na)^+$: 408.1747; found, 408.1752.

*Ethyl 2-[(allyloxycarbonyl)amino]-2-(2-methoxy-2-oxoethylcarbamoyl)-3-phenylaziridine-1-carboxylate (**7h**)*

Deep yellow oil, 56 %. IR: 3422, 3400, 1746, 1698, 1636 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz, δ): 1.35 (t, $J = 7.1$ Hz, 3 H), 3.20 (s, 1 H), 3.69 (s, 3 H), 3.84–4.03 (m, 2 H), 4.06–4.17 (m, 4 H), 5.13–5.36 (m, 2 H), 5.81–5.98 (m, 1 H); 7.15–7.43 (m, 5 H), 7.99 (br, 1 H), 8.09 (br, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 13.8, 35.9, 41.1, 52.1, 61.6, 61.2, 66.9, 115.6, 128.3, 129.6 (2 C), 133.1 (2 C), 135.0, 138.6, 155.5, 155.8, 171.5, 172.1. HR-MS (ESI-TOF) (*m/z*) calcd for $C_{19}H_{23}N_3NaO_7$ $(M + Na)^+$: 428.1434; found, 428.1441.

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Conflict of interest The authors declare that they have no conflict of interest.

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