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Synthesis of epoxy and aziridino malonyl peptidomimetics

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ABSTRACT

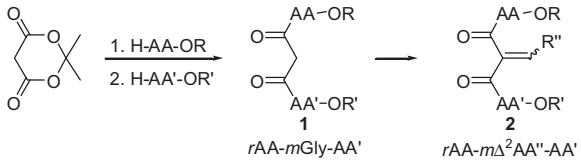
Short malonyl dehydro peptides have been epoxidized using H_2O_2/Na_2WO_4 dihydrate. The obtained diastereomeric epoxides were separated by HPLC and successfully tested in the ring opening reaction with *N*-Boc L-cysteine methyl ester, to indicate their electrophilic behavior. Moreover, by a simple two-step reaction, the epoxy malonyl peptides can be converted into the corresponding aziridino malonyl peptides.

1. Introduction

Peptides possess a broad spectrum of biological roles. The pharmacological properties of most peptides preclude their use as drugs. During the last 20 years peptidomimetics have aroused interest as compounds able to resolve applicative problems related to low bioavailability and short biological half-life of natural peptides.

Most peptidomimetics[1] have been used as enzyme inhibitors especially proteases, which are involved in numerous important physiological processes including protein turnover, digestion, blood coagulation and wound healing, fertilization, cell differentiation and growth, cell signaling, the immune response, and apoptosis.[2] These peptidomimetics present a functional group, usually an electrophilic moiety, which reacts with a nucleophilic amino acid within the active site of the enzyme.[3] Screenings of electrophilic building blocks have revealed that the activity of the small heterocyclic ring has been enhanced when they are linked to appropriate amino acids, substrate analogue peptides or peptidomimetics.[4] Therefore, peptidyl epoxides were found to be stable under various conditions, including in human serum.[5]

Recently we have reported an efficient method for the construction of short dehydro malonyl peptides (MDHPs) *r*AA-*m*Δ^2AA″-AA' **2**[6] by a Knoevenagel condensation reaction between non-symmetric malonyl peptides (*r*AA-*m*Gly-AA′)[7,8] and different aldehydes (Scheme 1).

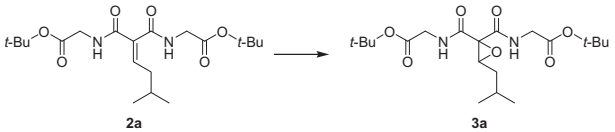


Scheme 1.

Carrying on our studies in this field, the synthesis of more complex peptidomimetics characterized by a retro-peptide modification and an oxirane ring was considered starting from the reported MDHPs by epoxidation reaction of the alkene.

2. Results and discussion

Inspired by our results on the epoxidation of the alkylidene and arylidene cyano acetates carrying L-α-amino ester residues by using *m*-CPBA and K_2CO_3,[9] the symmetric *N*,*N*′-Boc protected malonyl dehydrodipeptide **2a** was chosen to test the epoxidation reaction conditions (Scheme 2).



Scheme 2.

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Surprisingly, the dehydro malonyl peptide did not react with *m*-CPBA and K_2CO_3 and **2a** was quantitatively recovered. Therefore, the epoxidation was attempted using different reaction conditions.

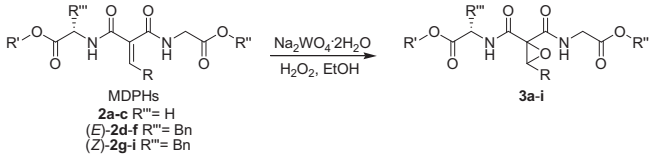
First, hydrogen peroxide was considered and different solvents, organic or inorganic bases, and reaction temperatures were tested as reported in Table 1. The reaction was performed in the presence of 1 M solution of NaOH,[10] but ^{1}H NMR spectroscopy and ES Q-TOF MS analyses on the crude mixtures showed a complex mixture of different compounds (entry 2).

Table 1
Optimization of epoxidation reaction conditions

Entry	Oxidant	Base	Solvent	*T* (°C)	Time	Yield (%)
1	*m*-CPBA	K_2CO_3	CH_2Cl_2	25	24 h	—
2	H_2O_2	NaOH	MeOH	25	17 h	—
3	H_2O_2	DABCO	CH_3CN	25	15 d	35
4	H_2O_2	K_2CO_3	EtOH	45	6 h	23
5	H_2O_2	K_2CO_3	EtOH	45	15 d	30
6	H_2O_2	$Na_2WO_4\cdot 2H_2O$	EtOH	78	6 h	98

The use of DABCO gave the expected epoxy peptide **3a** in unsatisfactory yields and long times (15 d). Also the reaction performed using potassium carbonate and/or heating the mixture for a long time gave poor yields. Finally, an equivalent of Na_2WO_4 dihydrate[11] gave the expected epoxy peptide **3a** in high yield (98%), after 6 h at reflux in EtOH.[12]

Using the optimal conditions, the epoxidation reactions were performed on symmetric malonyl dehydro peptides **2a**–**c** and on non-symmetric analogous compounds **2d**–**i** (Scheme 3), after separation of *E* and *Z* isomers[13] by flash chromatography on silica gel. The results are reported in Table 2.



Scheme 3.

Table 2
Epoxidation of malonyl dehydro peptides

Entry	MDPH	R	R′	R″	Epoxide	Yield (%)	dr
1	**2a**	*i*-Bu	*t*-Bu	*t*-Bu	**3a**	98	—
2	**2b**	Ph	*t*-Bu	*t*-Bu	**3b**	95	—
3	**2c**	(*R*)-2,2-Dimethyl-1, 3-dioxolan-4-yl	*t*-Bu	*t*-Bu	**3c**	79	>19:1
4	(*E*)-**2d**	*i*-Bu	Me	Me	**3d**	97	1.8:1
5	(*E*)-**2e**	Ph	Me	Me	**3e**	83	1.3:1
6	(*E*)-**2f**	Ph	Me	*t*-Bu	**3f**	72	1.5:1
7	(*Z*)-**2g**	*i*-Bu	Me	Me	**3g**	87	1.7:1
8	(*Z*)-**2h**	Ph	Me	Me	**3h**	94	1.2:1
9	(*Z*)-**2i**	Ph	Me	*t*-Bu	**3i**	83	1.4:1

In all cases the expected epoxides **3** were obtained in good yields and the diastereomeric ratios were determined on the crude mixtures by HPLC-RI analyses. A moderate diastereoselectivity was observed, except for **3c** (entry 3). Nevertheless, we underline that, at this stage of the research, it is important to access each of the new diastereomeric epoxides **3d**–**i**, considering the possible different biological behavior between stereoisomers. In fact, it is well-known that the potency and selectivity of enzyme inhibitors can be affected by the conformation of inhibitors. For compounds **3d**–**i**, separation conditions by HPLC using an analytical column have been found for each diastereomeric couple.

Regarding **3c** (Fig. 1), the *R* configuration of the new chiral center of the major isomer obtained can be assigned by ^{1}H NMR

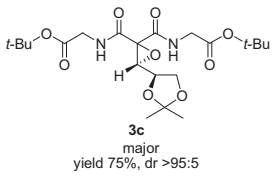
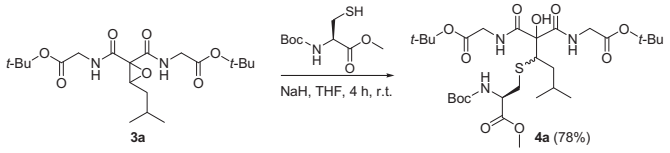


Fig. 1.

spectroscopy analysis. In fact, the epoxide proton of the major isomer presents a coupling constant (J=7.7 Hz) higher than that of the minor isomer (J=4.7 Hz) and compatible with that reported in the literature for the *anti* isomer of similar epoxides.[14]

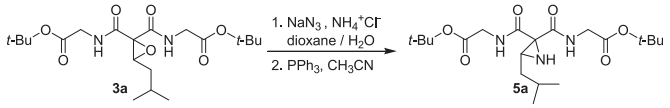
The selective ring opening reactions[15] of the 1,3-dioxolane ring, followed by oxidation of the primary alcohol, can provide a new scaffold carrying an α-hydroxy moiety for the construction of more complex compounds with potential pharmacological activity.

To mimic the nucleophilic attack of the thiolate group within the cysteine proteases on oxiranes as recently suggested by molecular mechanics and semiempirical quantum mechanic studies,[16] *N*-Boc L-cysteine methyl ester was treated with NaH in dry THF and then **3a** was added to the solution.[17] After 4 h, ^{1}H NMR spectroscopy and ES Q-TOF MS analyses performed on the crude mixture, confirmed the expected diastereomeric mixture **4a** (Scheme 4), suggesting the effective potential cysteine protease inhibitor activity also for the epoxy malonyl peptides here reported.



Scheme 4.

Moreover, these compounds can be regarded as new intriguing building blocks for the construction of more complex bioorganic molecules or as ideal substrates to obtain peptidomimetics carrying different heterocyclic rings (Scheme 5). Thus, the reaction of **3a** with sodium azide followed by reduction with triphenylphosphine led to the analogous aziridino retro-peptide **5a**.[18]



Scheme 5.

3. Conclusion

In conclusion, starting from short malonyl dehydro peptides (MDPHs), new peptidomimetics characterized by a retro-peptide modification and an oxirane ring have been obtained. The functionalization of the double bond leads to the synthesis of more complex molecules by an epoxidation reaction performed with Na_2WO_4 dihydrate. The diastereomeric epoxides, that can be separated by HPLC, have been demonstrated to be reactive substances toward L-cysteine, suggesting their possible activities as inhibitors of cysteine proteases. Finally, aziridino malonyl peptides can be synthesized by a simple two-step reaction from epoxy analogues.

4. Experimental section

4.1. General

IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer in $CHCl_3$ as the solvent. ^{1}H NMR spectra were recorded at

Varian Gemini 200 and Varian XL-300 MHz and ^{13}C NMR spectra at 50 and 75 MHz. The NOESY experiments were performed at Bruker 300 MHz. $CDCl_3$ 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. HPLC analyses were performed with an instrument Varian 9002 equipped with a Varian 9050 RI-4 differential refractometer, or a Varian 9050 UV/Vis detector using an analytical column (3.9×300 mm, flow rate 1.3 mL/min). Eluents were mixtures of HPLC grade hexane and ethyl acetate. NaH (55–65% suspension in mineral oil) was washed twice with pentane and dried under nitrogen.

4.2. Synthesis of epoxy malonyl peptides (3a–i). General procedure

A round-bottom flask was charged with a solution of a malonyl dehydro peptide **2a–i** (0.5 mmol) in 1 mL of EtOH and sodium tungstate dihydrate (0.5 mmol) and 0.40 mL of 40% hydrogen peroxide. The reaction mixture was warmed at 70–80 °C and followed by ^1H NMR spectroscopy analysis. After 6 h the disappearance of the vinyl proton signal was observed. After removal of the solvent, 10 mL of diethyl ether was added and the crude mixture was washed with water (2×10 mL) and dried over $MgSO_4$ to give the epoxide.

*4.2.1. Di-tert-butyl 2,2′-[(3-isobutyloxirane-2,2-diyl)bis(carbonylimino)] diacetate (**3a**).* Yield: 0.203 g, 98%; light yellow oil; ν_{max}: 3401, 3318, 1736, 1689 cm^{-1}. HRMS (ESI Q-TOF) calcd for $C_{20}H_{34}N_2NaO_7$ $(M+Na)^+$: 437.2264; found: 437.2273; δ_H 0.95 (d, *J*=6.6 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.47 (s, 18H), 1.57–1.64 (m, 2H), 1.75–1.92 (m, 1H), 3.32 (t, *J*=6.1 Hz, 1H), 3.81–4.16 (m, 4H), 7.63–7.69 (m, 1H, NH), 7.94–8.00 (m, 1H, NH); δ_C 22.2, 22.5, 26.3, 28.0 (6), 35.5, 41.9, 42.0, 59.9, 64.2, 82.3, 82.4, 165.5, 166.2, 167.8, 168.0.

*4.2.2. Di-tert-butyl 2,2′-[(3-phenyloxirane-2,2-diyl)bis(carbonylimino)] diacetate (**3b**).* Yield: 0.206 g, 95%; deep yellow oil; ν_{max}: 3401, 3330, 1730, 1689 cm^{-1}. HRMS (ESI Q-TOF) calcd for $C_{22}H_{30}N_2NaO_7$ $(M+Na)^+$: 457.1951; found: 457.1948; δ_H 1.42 (s, 9H), 1.48 (s, 9H), 3.52–4.14 (m, 4H), 4.44 (s, 1H), 7.29–7.42 (m, 5H), 8.17–8.22 (m, 2H, 2NH); δ_C 27.9 (3), 28.0 (3), 41.7, 42.2, 62.1, 64.2, 82.5 (2), 126.7 (2), 128.2 (2), 128.8, 131.5, 164.2, 165.1, 167.6, 168.0.

*4.2.3. Di-tert-butyl 2,2′-{[(3S)-3-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)oxirane-2,2-diyl]bis(carbonylimino)}diacetate (**3c**).* Yield: 0.182 g, 79%; deep yellow oil; ν_{max}: 3404, 3324, 1735, 1687 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{21}H_{34}N_2NaO_9$ $(M+Na)^+$: 481.2162; found: 481.2159. Major: δ_H 1.43 (s, 6H), 1.47 (s, 18H), 3.41 (d, *J*=7.7 Hz, 1H), 3.60–3.67 (m, 2H), 3.88–4.01 (m, 4H), 4.02–4.17 (m, 1H), 7.75–7.82 (m, 1H, 1NH), 8.05–8.11 (m, 1H, 1NH); δ_C 25.9 (2), 29.4 (3), 29.5 (3), 41.3, 41.7, 62.5, 66.3, 70.8, 72.0, 81.9, 82.0, 113.4, 168.7, 169.3, 175.8, 176.5. Minor: δ_H 1.43 (s, 6H), 1.47 (s, 18H), 3.34 (d, *J*=4.7 Hz, 1H), 3.60–3.67 (m, 2H), 3.78–3.85 (m, 4H), 4.19–4.34 (m, 1H), 7.61–7.67 (m, 1H, 1NH), 7.75–7.82 (m, 1H, 1NH); δ_C 26.4 (2), 28.6 (3), 29.4 (3), 41.2, 41.8, 62.6, 66.3, 70.8, 72.1, 81.9, 82.2, 113.9, 169.2, 169.5, 175.5, 176.2.

*4.2.4. Methyl (2S)-2-({[(2R,3R)(2S,3S)-3-isobutyl-2-{[(2-methoxy-2-oxoethyl)amino]carbonyl}oxiran-2-yl]carbonyl}amino)-3-phenylpropanoate (**3d**).* Yield: 0.204 g, 97%; yellow oil; ν_{max}: 3405, 3328, 1736, 1695 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{21}H_{28}N_2NaO_7$ $(M+Na)^+$: 443.1794; found: 443.1801. Major: δ_H 0.91 (d, *J*=6.7 Hz, 6H), 1.50–1.63 (m, 2H), 1.67–1.88 (m, 1H), 2.94–3.27 (m, 2H), 3.14–3.20 (m, 1H), 3.72 (s, 3H), 3.73 (s, 3H), 4.14–4.27 (m, 2H), 4.75–4.88 (m, 1H), 7.23–7.29 (m, 5H), 7.68–7.86 (m, 2H, 2NH); δ_C 22.2, 22.5, 26.3, 35.4, 37.9, 41.2, 52.4, 53.4, 59.9, 61.5, 64.4, 127.2, 128.6 (2), 129.2 (2), 135.7, 165.2, 166.0, 168.8, 171.2. Minor: δ_H 0.96 (d, *J*=6.7 Hz, 6H), 1.50–1.63 (m, 2H), 1.67–1.88 (m, 1H), 2.94–3.27 (m, 2H), 3.03–3.10 (m, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 4.00–4.13 (m, 2H), 4.75–4.88 (m, 1H), 7.08–7.16 (m, 5H), 7.68–7.86 (m, 2H, 2NH); δ_C 22.2, 22.5, 26.2, 35.4, 37.8, 41.0, 52.4, 53.2, 59.9, 61.5, 64.4, 127.1, 128.6 (2), 129.2 (2), 135.6, 165.4, 166.0, 169.2, 171.0.

*4.2.5. Methyl (2S)-2-{[(2R,3R)(2S,3S)-(2-{[(2-methoxy-2-oxoethyl)amino]carbonyl}-3-phenyloxiran-2-yl)carbonyl]amino}-3-phenylpropanoate (**3e**).* Yield: 0.183 g, 83%; deep yellow oil; ν_{max}: 3413, 3331, 1743, 1672, 1645 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{23}H_{24}N_2NaO_7$ $(M+Na)^+$: 463.1481; found: 463.1477. Major: δ_H 2.92–3.31 (m, 2H), 3.76 (s, 6H), 4.06–4.17 (m, 2H), 4.39 (s, 1H), 4.82–4.98 (m, 1H), 7.25–7.47 (m, 10H), 7.88–8.03 (m, 2H, 2NH); δ_C 29.7, 41.1, 52.4, 53.5 (2), 61.5, 64.4, 126.8 (2), 127.2, 128.3 (2), 128.6, 128.9 (2), 129.3 (2), 131.4, 135.7, 163.9 (2), 165.0 (2). Minor: δ_H 2.92–3.31 (m, 2H), 3.75 (s, 6H), 4.19–4.26 (m, 2H), 4.45 (s, 1H), 4.82–4.98 (m, 1H), 7.12–7.23 (m, 10H), 7.88–8.03 (m, 2H, 2NH); δ_C 29.7, 41.1, 52.4, 53.4 (2), 61.6, 64.3, 126.7 (2), 127.3, 128.2 (2), 128.6, 128.7 (2), 129.3 (2), 131.3, 135.8, 163.8 (2), 165.1 (2).

*4.2.6. Methyl (2S)-2-{[(2R,3R)(2S,3S)-(2-{[(2-tert-butoxy-2-oxoethyl)amino]carbonyl}-3-phenyloxiran-2-yl)carbonyl]amino}-3-phenylpropanoate (**3f**).* Yield: 0.173 g, 72%; deep yellow oil; ν_{max}: 3402, 3326, 1738, 1694 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{26}H_{30}N_2NaO_7$ $(M+Na)^+$: 505.1951; found: 505.1949. Major: δ_H 1.49 (s, 9H), 2.93 (d, *J*=6.0 Hz, 2H), 3.58 (s, 3H), 3.96–4.03 (m, 2H), 4.39 (s, 1H), 4.83–4.94 (m, 1H), 6.87–6.93 (m, 5H), 7.29–7.37 (m, 5H), 7.83–7.90 (m, 1H, 1NH), 8.17–8.23 (m, 1H, 1NH); δ_C 29.2 (3), 38.3, 41.3, 53.1, 54.7, 61.3, 64.5, 82.5, 126.8 (2), 127.2, 128.3 (2), 128.5, 128.7 (2), 129.2 (2), 131.3, 135.7, 163.9 (2), 165.0 (2). Minor: δ_H 1.49 (s, 9H), 2.93 (d, *J*=6.0 Hz, 2H), 3.53 (s, 3H), 3.96–4.03 (m, 2H), 4.45 (s, 1H), 4.83–4.94 (m, 1H), 6.78–6.84 (m, 5H), 7.16–7.25 (m, 5H), 7.48–7.56 (m, 1H, 1NH), 8.26–8.31 (m, 1H, 1NH); δ_C 29.5 (3), 37.6, 41.5, 53.1, 54.8, 61.5, 64.4, 82.6, 126.7 (2), 127.3, 128.2 (2), 128.5, 128.8 (2), 129.3 (2), 131.4, 135.6, 163.8 (2), 165.1 (2).

*4.2.7. Methyl (2S)-2-({[(2R,3S)(2S,3R)-3-isobutyl-2-{[(2-methoxy-2-oxoethyl)amino]carbonyl}oxiran-2-yl]carbonyl}amino)-3-phenylpropanoate (**3g**).* Yield: 0.183 g, 87%; yellow oil; ν_{max}: 3401, 3330, 1731, 1695 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{21}H_{28}N_2NaO_7$ $(M+Na)^+$: 443.1794; found: 443.1798. Major: δ_H 0.88 (d, *J*=6.4 Hz, 3H), 0.92 (d, *J*=6.4 Hz, 3H), 1.22–1.32 (m, 2H), 1.63–1.84 (m, 1H), 2.94–3.31 (m, 3H), 3.72 (s, 6H), 4.02 (d, *J*=5.5 Hz, 2H), 4.78–4.93 (m, 1H), 7.22–7.34 (m, 5H), 7.86–8.03 (m, 2H, 2NH); δ_C 23.4 (2), 23.7, 32.6, 38.3, 42.1, 54.6, 58.7 (2), 63.2, 66.3, 128.5, 129.1 (2), 129.9 (2), 136.3, 167.7, 169.4, 170.6, 171.5. Minor: δ_H 0.86 (d, *J*=6.4 Hz, 3H), 0.95 (d, *J*=6.4 Hz, 3H), 1.22–1.32 (m, 2H), 1.53–1.61 (m, 1H), 2.94–3.31 (m, 3H), 3.72 (s, 6H), 4.05 (d, *J*=5.5 Hz, 2H), 4.76–4.91 (m, 1H), 7.11–7.19 (m, 5H), 7.86–8.03 (m, 2H, 2NH); δ_C 23.4 (2), 23.7, 32.5, 38.2, 41.9, 54.2, 58.6 (2), 63.4, 66.3, 128.3, 129.0 (2), 129.9 (2), 136.2, 167.5, 169.4, 170.4, 171.5.

*4.2.8. Methyl (2S)-2-{[(2R,3S)(2S,3R)-(2-{[(2-methoxy-2-oxoethyl)amino]carbonyl}-3-phenyloxiran-2-yl)carbonyl]amino}-3-phenylpropanoate (**3h**).* Yield: 0.207 g, 94%; deep yellow oil; ν_{max}: 3396, 3328, 1742, 1696 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{23}H_{24}N_2NaO_7$ $(M+Na)^+$: 463.1481; found: 463.1484. Major: δ_H 2.93 (d, *J*=6.0 Hz, 2H), 3.54 (s, 6H), 4.17–4.29 (m, 2H), 4.39 (s, 1H), 4.81–4.96 (m, 1H), 6.87–6.96 (m, 5H), 7.24–7.40 (m, 5H), 7.88–7.99 (m, 1H, 1NH), 8.20–8.28 (m, 1H, 1NH); δ_C 38.0, 41.5, 53.4 (2), 53.6, 61.6, 66.8, 126.9 (2), 128.3, 128.6 (2), 129.0, 129.2 (4), 131.6, 136.7, 170.8 (2), 176.0 (2). Minor: δ_H 2.93 (d, *J*=6.0 Hz, 2H), 3.59 (s, 6H), 4.06–4.14 (m, 2H), 5.08–5.20 (m, 1H), 6.78–6.85 (m, 5H), 7.15–7.23 (m, 5H), 7.46–7.57 (m, 1H, 1NH), 8.29–8.36 (m, 1H, 1NH); δ_C 38.2, 41.6, 53.3 (2), 53.6, 61.6, 66.8, 126.8 (2), 128.4, 128.5 (2), 129.0, 129.3 (4), 131.7, 136.7, 171.6 (2), 176.3 (2).

*4.2.9. Methyl (2S)-2-{[(2R,3S)(2S,3R)-(2-{[(2-tert-butoxy-2-oxoethyl)amino]carbonyl}-3-phenyloxiran-2-yl)carbonyl]amino}-3-phenylpropanoate (**3i**).* Yield: 0.200 g, 83%; deep yellow oil; ν_{max}: 3402, 3326,

1738, 1694 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{26}H_{30}N_2NaO_7$ $(M+Na)^+$: 505.1951; found: 505.1947. Major: δ_H 1.42 (s, 9H), 2.92–3.30 (m, 2H), 3.74 (s, 3H), 4.13–4.26 (m, 2H), 4.39 (s, 1H), 4.83–4.97 (m, 1H), 6.86–6.94 (m, 5H), 7.24–7.48 (m, 5H), 7.93–8.08 (m, 2H, 2NH); δ_C 28.0 (3), 38.0, 41.8, 52.4, 53.5, 61.6, 64.2, 82.5, 126.8 (2), 128.2, 128.6 (2), 128.9, 129.3 (4), 131.4, 135.6, 163.8, 164.9, 170.7, 171.2. Minor: δ_H 1.41 (s, 9H), 2.92–3.30 (m, 2H), 3.75 (s, 3H), 4.13–4.26 (m, 2H), 4.45 (s, 1H), 5.31–5.38 (m, 1H), 6.78–6.85 (m, 5H), 7.12–7.22 (m, 5H), 7.93–8.08 (m, 2H, 2NH); δ_C 29.7 (3), 38.0, 41.8, 52.5, 53.5, 61.6, 64.3, 82.5, 126.7 (2), 128.2, 128.6 (2), 128.7, 129.3 (4), 131.4, 135.7, 163.7, 165.0, 170.6, 171.1.

*4.2.10. tert-Butyl [(2-{[(2-tert-butoxy-2-oxoethyl)amino]carbonyl}-2-hydroxy-(R,S)-3-({2-[tert-butoxycarbonylamino]-3-methoxy-3-oxopropyl}thio)-5-methylhexanoyl)amino]acetate (**4a**).* Yield: 0.269 g, 83%; deep yellow oil; ν_{max}: 3402, 3326, 1738, 1694 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{29}H_{51}N_3NaO_{11}S$ $(M+Na)^+$: 672.3142; found: 672.3138. Major: δ_H 0.84–0.92 (m, 6H), 1.43 (s, 18H), 1.45 (s, 9H), 1.63–1.75 (m, 2H), 1.81–1.95 (m, 1H), 2.25 (br, 1H, 1 OH), 2.90–3.00 (m, 1H), 3.26–3.37 (m, 2H), 3.75 (s, 3H), 3.88–3.96 (m, 4H), 5.68–5.83 (m, 1H), 7.67–7.81 (m, 3H, 3NH); δ_C 23.6 (2), 24.7, 27.8 (3), 28.1 (6), 29.5, 30.1, 42.1, 42.2 (2), 52.4, 53.3, 80.0, 82.2 (two), 125.3, 154.9, 167.4, 167.8, 169.5, 170.3, 171.2. Minor: δ_H 0.84–0.92 (m, 6H), 1.44 (s, 18H), 1.46 (s, 9H), 1.63–1.75 (m, 2H), 1.81–1.95 (m, 1H), 2.25 (br, 1H, 1 OH), 2.90–3.00 (m, 1H), 3.47–3.62 (m, 2H), 3.75 (s, 3H), 3.97–4.04 (m, 4H), 5.68–5.83 (m, 1H), 7.67–7.81 (m, 3H, 3NH); δ_C 23.6 (2), 24.7, 27.8 (3), 28.1 (6), 29.5, 30.1, 42.0, 42.2 (2), 52.4, 53.3, 79.7, 82.2 (2), 125.3, 155.1, 167.4, 167.9, 169.6, 170.5, 171.1.

*4.2.11. Di-tert-butyl 2,2′-[(3-isobutylaziridine-2,2-diyl)bis(carbonylimino)]diacetate (**5a**).* Yield: 0.144 g, 70%; yellow oil; ν_{max}: 3443, 3400, 1740, 1697 cm^{-1}. HRMS (ES Q-TOF) calcd for $C_{20}H_{35}N_3NaO_6$ $(M+Na)^+$: 436.2424; found: 436.2421; δ_H 0.85–0.94 (m, 6H), 1.40 (s, 18H), 1.54 (dd, J=5.8 Hz, J=7.4 Hz, 2H), 1.72–1.81 (m, 1H), 2.57–2.82 (m, 1H), 3.24–3.29 (m, 1H), 3.89 (dd, J=5.5, 18.3 Hz, 4H), 7.90–7.94 (m, 1H, 2NH); δ_C 22.2 (2), 22.4, 27.9 (6), 41.6, 41.8 (2), 53.3, 64.1, 81.6 (2), 165.3, 166.0, 167.7, 167.9.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.097.

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