An efficient preparation of novel epoxyketone intermediates for the synthesis of carfilzomib and its derivatives

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A novel and efficient preparation of epoxyketone intermediates for the synthesis of carfilzomib and its derivatives has been developed. Compared to reported methods, this highly stereoselective, environmentally friendly, low-cost method can be used in scaling up the synthesis of carfilzomib and its derivatives.

Keywords: carfilzomib, epoxyketone derivatives, vanadium(III) acetylacetonate

The ubiquitin-proteasome pathway (UPP) is responsible for the intracellular protein degradation and regulation of pivotal transduction pathways associated with cell growth, survival, differentiation and apoptosis.[1,2] In this pathway, the 26S proteasome, consisting of a catalytic 20S particle and a 19S regulator particle, is the main proteolytic ingredient in eukaryotes. Three different proteolytic activities are localised to β-subunits of the 20S proteasome, namely β*1*, β*2* and β*5*, which are responsible for cleaving the chain after acidic amino acids, basic amino acids and hydrophobic amino acids respectively.[3,4] Based on this target, there has been a great deal of interest in developing structurally diverse proteasome inhibitors. Among these, a tripeptidyl epoxyketone, carfilzomib has been approved for the treatment of patients with relapsed and refractory multiple myeloma (MM) and mantle cell lymphoma (MCL).[5,6]

Carfilzomib represents a new generation of highly stereoselective and irreversible proteasome inhibitor and was approved on July 20, 2012 by the US Food and Drug Administration (FDA). Compared with bortezomib, carfilzomib (Fig. 1) can cause fewer side effects, especially lower rates of peripheral neuropathy. At the same time, it has enhanced tolerability and safety profiles.[7] Hence, it is considered to be a promising anticancer agent.

Epoxyketone fragments are extremely useful building blocks in the synthesis of carfilzomib and its derivatives. Several synthetic routes have been reported for the preparation of such key intermediates.[8–11] One representative method is shown in Scheme 1: firstly, condensation of *N*-Boc-protected leucine **A** with *N*, *O*-dimethylhydroxylamine hydrochloride gave the Weinreb amide **B**, which was then treated with isopropenylmagnesium bromide to give an α,β-unsaturated ketone **C**. After reducing the ketone in **C** with sodium borohydride and cerium chloride, to obtain the allylic alcohols **D** and **E.** Olefin **D** was epoxidised to give **F** using 3-chloroperoxybenzoic acid (mCPBA) or potassium peroxomonosulfate. Finally the hydroxyl group of epoxide **F** was oxidised to give the epoxyketone **G**. This method had several serious disadvantages. For example, a very expensive and unstable isopropenylmagnesium bromide was used in the production of intermediate **C** from **B**. Furthermore, a strong reducing agent $NaBH_4/CeCl_3{\cdot}7H_2O$ was employed in the reduction of the α,β-unsaturated ketone of intermediate **C** to a hydroxyl group, which led to the production of two diastereoisomers **D** and **E**. Hence flash chromatography was needed to purify the useful isomer **D**. From the viewpoint of drug economy, this synthetic route was not suitable for industrial scaling up of the preparation of a key intermediate for carfilzomib synthesis.

To avoid the above drawbacks, we describe here an economic and efficient method to produce the key intermediates under mild conditions.

Results and discussion

An epoxyketone is an important intermediate in carfilzomib synthesis. In a typical preparation of this key intermediate (Scheme 1), the formation of the unsaturated ketone **C** from amide **B** is a critical step, in which a four-fold excess of isopropenylmagnesium bromide was used. However, the high cost and difficulty in obtaining large amounts of the Grignard reagent made this an uneconomic route and encouraged us to find a more economic method. We have designed a novel process for the synthesis of the key intermediate for carfilzomib synthesis without the use of expensive reagents. As shown in Scheme 2, we chose the cheap and readily available ethylmagnesium bromide as a Grignard reagent to prepare the ethyl ketone **3** based on the literature method.[12] The reaction used 1 equiv. of the Grignard reagent to give a high yield (92%). An aldol condensation of compound $\mathbf{3R_1}$ with paraformaldehyde formed product $\mathbf{4R_1}$ in a yield of 92% (see experimental section). Aluminium isopropoxide and isopropanol were then employed to selectively reduce the

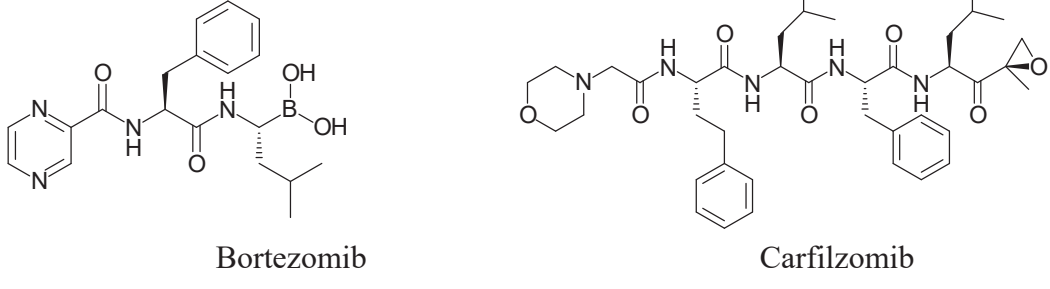

Fig. 1 Structures of bortezomib and carfilzomib.

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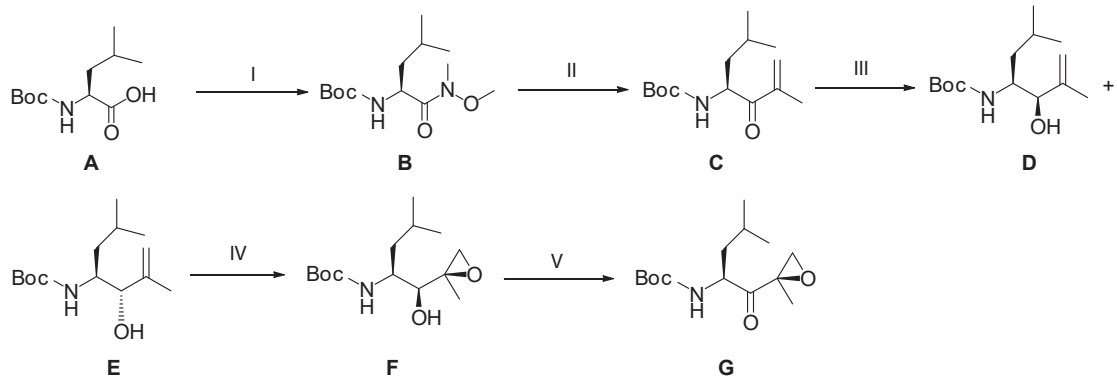
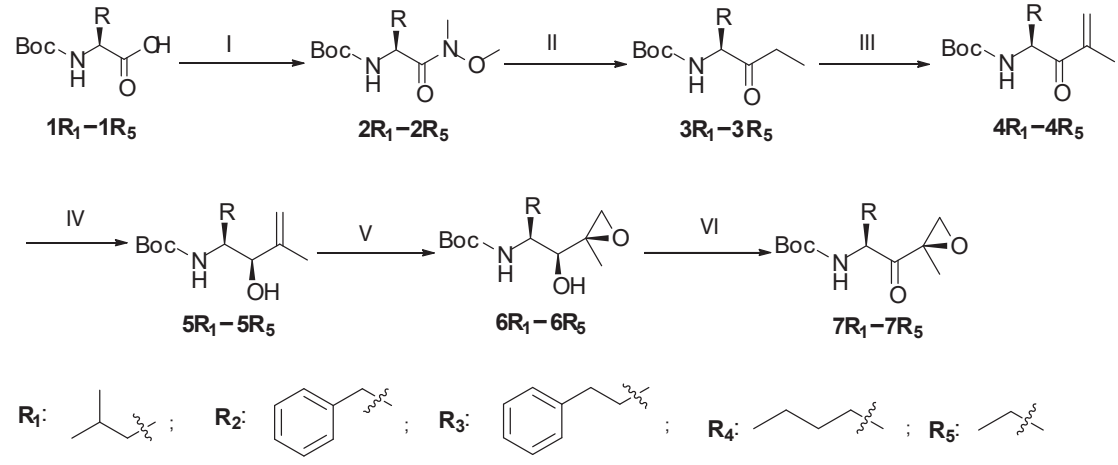


Scheme 1 Synthesis of epoxyketone fragments **G**: I, isobutyl chloroformate, *N*-methylmorpholine, dichloromethane (DCM), *N,O*-dimethylhydroxylamine hydrochloride; II, isopropenylmagnesium bromide, anhydrous tetrahydrofuran (THF); III, $NaBH_4$,$CeCl_3$·$7H_2O$, MeOH; IV, *m*CPBA, DCM, or potassium peroxomonosulfate, ethylenediaminetetraacetic acid (EDTA), $NaHCO_3$, acetone, H_2O; V, Dess–Martin, penodinane, MeCN.



Scheme 2 Synthesis of epoxyketone fragments ($7R_1$, $7R_2$, $7R_3$, $7R_4$ and $7R_5$): I, 1-hydroxybenzotriazole (HOBt), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *N,N*-diisopropylethylamine (DIPEA), DCM, 0 °C; II, anhydrous THF, ethylmagnesium bromide, –20 °C; III, piperidinium acetate, piperidine, paraformaldehyde, THF, 68 °C; IV, aluminium isopropoxide, isopropanol, toluene, 50 °C; V, *tert*-butyl hydroperoxide solution, vanadium(III) acetylacetonate, DCM; VI, pyridine sulfur trioxide, DIPEA, dimethyl sulfoxide.

α,β-unsaturated ketone of intermediate $4R_1$ to the alcohol $5R_1$ without the use of the strong reducing agent $NaBH_4/CeCl_3·7H_2O$. In this reduction, the *S* configuration of the intermediate $4R_1$ induces the generation of its neighbouring chiral centre. The formation of two stereoisomers was avoided and the workup was greatly simplified. Once the optically pure isomer $5R_1$ had been obtained, the newly generated *R* configuration of $5R_1$ induced the stereo-epoxidation. A single stereoisomeric epoxyl-alcohol $6R_1$ was obtained by oxidation with vanadium(III) acetylacetonate and *tert*-butyl hydroperoxide. Finally, commercially available pyridine:sulfur trioxide instead of the expensive Dess–Martin reagent was employed to oxidise the alcohol $6R_1$ to the ketone $7R_1$. In order to widen the new method, we also synthesised the aromatic compounds ($4R_2$–$7R_2$, $4R_3$–$7R_3$) and aliphatic compounds $4R_4$–$7R_4$ (Scheme 2). The results showed that the yields of the aliphatic substrates were generally higher than the aromatic compounds. This may be due to the effect of both steric and electronic factors in the reactions. However, more data are needed to define the mechanism.

Conclusions

A novel and efficient process for the synthesis of the epoxyketone fragment of carfilzomib and its derivatives has been developed. Compared with the conventional method, this new route is more economic and environmentally friendly and can be used in scaling up the synthesis of carfilzomib and its derivatives.

Experimental

Commercially available reagents were used directly without any purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel glass sheets (GF-254) and RP-18 F254s using UV light as a visualising agent, 15% ethanolic phosphomolybdic acid and heat as a developing agent. Column chromatography was performed on 200–300 mesh silica gel and an ODS C-18 column. Analytical reverse phase high-performance liquid chromatography (HPLC) was run using a Kromasil 100-5C18, 4.6 mm × 250 mm column eluting with a mixture of acetonitrile and 0.04% triflurooacetic acid. HPLC showed that the purity of all of the final products was greater than 95%. ^{1}H NMR spectra were measured on a Bruker Avance 400 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as the solvent. Mass spectra were determined on an Agilent Thermo MSQ PLUS mass spectrometer operating at an ionisation potential of 70 eV. High-resolution mass spectra were recorded on a ZAB-HS instrument using an electrospray source (ESI). Optical rotations were measured on a JASCO P-2000 polarimeter.

The general procedure for the preparation of fragments **7** followed the route described in Scheme 2.

*(*S*)*-tert-*Butyl{1-[methoxy(methyl)amino]-4-methyl-1-oxopentan-2-yl}carbamate* $2R_1$

N-Boc-protected amino acid $1R_1$ (7.5 mmol) was dissolved in dichloromethane (20 mL) and stirred at –10 °C. Then HOBt (7.5 mmol) and EDCI (11.3 mmol) were added. The reaction was carried out for 15 min, then *N, O*-dimethylhydroxylamine hydrochloride (7.5 mmol)

was added and after 15 min, DIPEA (18.9 mmol) was added. The reaction temperature was allowed to rise to room temperature 25 min later and the mixture was left overnight. The resulting mixture was washed with 1 M HCl (20 mL), 5% $NaHCO_3$ (20 mL) and saturated brine (20 mL) respectively and dried over anhydrous Na_2SO_4. It was filtered, and the solvent was evaporated to provide crude product **2R$_1$** which was used without further purification in the next reaction.

Colourless liquid; yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (–CH_3, d, *J* = 6.7 Hz, 3H), 0.95 (–CH_3, d, *J* = 6.5 Hz, 3H), 1.42 (–CH_3, s, 9H), 1.70 (–CH, dd, *J* = 13.0, 6.4 Hz, 1H), 3.19 (–CH_3, s, 3H), 3.78 (–CH_3, s, 3H), 4.71 (–CH, d, *J* = 4.3 Hz, 1H), 5.04 (–CONH, d, *J* = 9.1 Hz, 1H); MS (ESI) *m/z*: 275.2 [M + H]$^+$, 297.3 [M + Na]$^+$; HRMS calcd for $C_{13}H_{26}N_2O_4Na$ [M + Na]$^+$: 297.1784; found: 297.1782.

Compounds **2R$_2$–2R$_5$** were prepared from the corresponding amino acids and carboxylic acids following a similar procedure to that described for the synthesis of **2R$_1$**.

(S)-tert-*Butyl{1-[methoxy(methyl)amino]-1-oxo-3-phenylpropan-2-yl}carbamate* **2R$_2$**

Colourless liquid; yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (–CH_3, s, 9H), 2.87 (Ph–CH_2, dd, *J* = 13.2, 7.2 Hz, 1H), 3.05 (–Ph–CH_2, dd, *J* = 13.4, 5.9 Hz, 1H), 3.17 (–CH_3, s, 3H), 3.65 (–CH_3, s, 3H), 4.95 (–CONH, d, *J* = 7.1 Hz, 1H), 5.16 (–CH, d, *J* = 7.8 Hz, 1H), 7.23–7.09 (–Ph, m, 5H); MS (ESI) *m/z*: 309.3 [M + H]$^+$, 331.2 [M + Na]$^+$; HRMS calcd for $C_{16}H_{24}N_2O_4Na$ [M + Na]$^+$: 331.1628; found: 331.1630.

(S)-tert-*Butyl{1-[methoxy(methyl)amino]-1-oxo-4-phenylbutan-2-yl}carbamate* **2R$_3$**

Colourless liquid; yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (–CH_3, s, 9H). 2.03–2.01 (–CH_2, m, 2H), 2.71–2.68 (–CH_2, m, 2H), 3.16 (–CH_3, s, 3H), 3.62 (–CH_3, s, 3H), 4.68 (–CH, s, 1H), 5.22 (–CONH, d, *J* = 8.7 Hz, 1H), 7.22–7.07 (–Ph, m, 5H); MS (ESI) *m/z*: 323.2 [M + H]$^+$; HRMS calcd for $C_{17}H_{26}N_2O_4Na$ [M + Na]$^+$: 345.1784; found: 345.1797.

(S)-tert-*Butyl{1-[methoxy(methyl)amino]-1-oxohexan-2-yl}carbamate* **2R$_4$**

Colourless liquid; yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (–CH_3, dd, *J* = 9.5, 4.3 Hz, 3H), 1.27–1.24 (–CH_2, m, 2H), 1.34–1.31 (–CH_2, m, 2H), 1.42 (–CH_3, s, 9H), 1.51–1.48 (–CH_2, m, 1H), 1.68–1.65 (–CH_2, m, 1H), 3.19 (–CH_3, s, 3H), 3.76 (–CH_3, s, 3H), 4.66 (–CH, s, 1H), 5.13 (–CONH, d, *J* = 8.7 Hz, 1H); MS (ESI) *m/z*: 275.2 [M + H]$^+$, 297.3 [M + Na]$^+$; HRMS calcd for $C_{13}H_{26}N_2O_4Na$ [M + Na]$^+$: 297.1784; found: 297.1791.

(S)-tert-*Butyl{1-[methoxy(methyl)amino]-1-oxobutan-2-yl}carbamate* **2R$_5$**

Colourless liquid; yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (–CH_3, t, *J* = 7.5 Hz, 3H), 1.42 (–CH_3, s, 9H), 1.54 (–CH, dd, *J* = 20.2, 6.8 Hz, 1H), 1.80–1.70 (–CH, m, 1H), 3.19 (–CH_3, s, 3H), 3.74 (–CH_3, d, *J* = 13.1 Hz, 3H), 4.61 (–CH, s, 1H), 5.17 (–CONH, d, *J* = 8.2 Hz, 1H); MS (ESI) *m/z*: 247.3 [M + H]$^+$, 269.3 [M + Na]$^+$; HRMS calcd for $C_{11}H_{22}N_2O_4Na$ [M + Na]$^+$: 269.1471; found: 269.1474.

(S)-tert-*Butyl(2-methyl-5-oxoheptan-4-yl)carbamate* **3R$_1$**

The Weinreb amide **2R$_1$** (5.7 mmol) was dissolved in anhydrous THF (6 mL) and stirred at –20 °C. Ethylmagnesium bromide (17.1 mmol) was then added dropwise. The reaction was left for a further 20 min and then the temperature was allowed to rise to room temperature and the mixture was stirred overnight. The reaction was quenched with 1 M HCl (20 mL) at –20 °C and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to provide the crude product **3R$_1$**, which was purified by flash column chromatography with ethyl acetate and petroleum (V/V = 1:3).

Colourless liquid; yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (–CH_3, d, *J* = 6.6 Hz, 3H), 0.92 (–CH_3, d, *J* = 6.6 Hz, 3H), 1.03 (–CH_3, t, *J* = 7.2 Hz, 3H), 1.34–1.25 (–CH, m, 1H), 1.39 (–CH_3, s, 9H), 1.52–1.44 (–CH, m, 1H), 1.73–1.61 (–CH, m, 1H), 2.59–2.38 (–CH_2, m, 2H), 4.28 (–CH, dd, *J* = 9.0, 3.6 Hz, 1H), 5.04 (–CONH, d, *J* = 7.4 Hz, 1H). MS (ESI) *m/z*: 244.4 [M + H]$^+$, 266.3 [M + Na]$^+$; HRMS calcd for $C_{13}H_{25}NO_3Na$ [M + Na]$^+$: 266.1726; found: 266.1732.

Compounds **3R$_2$–3R$_5$** were prepared following a similar procedure to that described for the synthesis of **3R$_1$**.

(S)-tert-*Butyl(3-oxo-1-phenylpentan-2-yl)carbamate* **3R$_2$**

Colourless liquid; yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (–CH_3, t, *J* = 7.2 Hz, 3H), 1.41 (–CH_3, s, 9H), 2.38–2.34 (–CH_2, m, 2H), 2.97 (–Ph–CH_2, dd, *J* = 13.9, 6.3 Hz, 1H), 3.04 (–Ph–CH_2, dd, *J* = 13.8, 6.9 Hz, 1H), 4.54 (–CH, dd, *J* = 14.0, 6.9 Hz, 1H), 5.13 (–CONH, d, *J* = 7.4 Hz, 1H), 7.23–7.08 (–Ph, m, 5H); MS (ESI) *m/z*: 279.2 [M + H]$^+$, 301.2 [M + Na]$^+$; HRMS calcd for $C_{16}H_{23}NO_3Na$ [M + Na]$^+$: 300.1570; found: 300.1579.

(S)-tert-*Butyl(4-oxo-1-phenylhexan-3-yl)carbamate* **3R$_3$**

Colourless liquid; yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (–CH_3, t, *J* = 7.3 Hz, 3H), 1.45 (–CH_3, s, 9H), 1.81–1.78 (–CH_2, m, 1H), 2.19–2.16 (–CH_2, m, 1H), 2.48–2.45 (–CH_2, m, 2H), 2.64–2.60 (–Ph–CH_2, m, 2H), 4.38 (–CH, d, *J* = 4.2 Hz, 1H), 5.25 (–CONH, d, *J* = 7.4 Hz, 1H), 7.22–7.06 (–Ph, m, 5H); MS (ESI) *m/z*: 292.2 [M + H]$^+$, 314.2 [M +Na]$^+$; HRMS calcd for $C_{17}H_{25}NO_3Na$ [M + Na]$^+$: 314.1726; found: 314.1735.

(S)-tert-*Butyl(3-oxooctan-4-yl)carbamate* **3R$_4$**

Colourless liquid; yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (–CH_3, t, *J* = 7.0 Hz, 3H), 1.07 (–CH_3, t, *J* = 7.3 Hz, 3H), 1.25–1.20 (–CH_2, m, 2H), 1.34–1.30 (–CH_2, m, 2H), 1.43 (–CH_3, s, 9H), 1.50 (–CH_2, ddd, *J* = 11.5, 10.6, 5.9 Hz, 1H), 1.81–1.77 (–CH_2, m, 1H), 2.51–2.47 (–CH_2, m, 2H), 4.31 (–CH, dd, *J* = 11.9, 7.2 Hz, 1H), 5.17 (–CONH, d, *J* = 6.4 Hz, 1H); MS (ESI) *m/z*: 244.4 [M + H]$^+$, 266.3 [M + Na]$^+$; HRMS calcd for $C_{13}H_{25}NO_3Na$ [M + Na]$^+$: 266.1726; found: 266.1725.

(S)-tert-*Butyl(4-oxohexan-3-yl)carbamate* **3R$_5$**

Colourless liquid; yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (–CH_3, t, *J* = 7.5 Hz, 3H), 1.07 (–CH_3, t, *J* = 7.3 Hz, 3H), 1.43 (–CH_3, s, 9H), 1.62–1.53 (–CH, m, 1H), 1.83 (–CH, dd, *J* = 14.0, 7.0 Hz, 1H), 2.59–2.42 (–CH_2, m, 2H), 4.30 (–CH, dd, *J* = 11.9, 6.7 Hz, 1H), 5.22 (–CONH, s, 1H); MS (ESI) *m/z*: 216.3 [M + H]$^+$, 238.2 [M + Na]$^+$; HRMS calcd for $C_{11}H_{21}NO_3Na$ [M + Na]$^+$: 238.1413; found: 238.1412.

(S)-tert-*Butyl(2,6-dimethyl-3-oxohept-1-en-4-yl)carbamate* **4R$_1$**

A solution of compound **3R$_1$** (4 mmol) in anhydrous THF (10 mL) was heated with piperidinium acetate (14.8 mmol), piperidine (9.9 mmol) and paraformaldehyde (39.6 mmol). The reaction mixture was refluxed for 8 h at 68 °C. The solution was extracted with ethyl acetate (3 × 15 mL) and washed with 1 M HCl (40 mL) and brine (40 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by flash column chromatography with ethyl acetate and petroleum (V/V = 1:10) to give **4R$_1$**.

Colourless liquid; yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (–CH_3, d, *J* = 6.6 Hz, 3H), 0.99 (–CH_3, d, *J* = 6.6 Hz, 3H), 1.32 (–CH, ddd, *J* = 14.4, 9.6, 4.8 Hz, 1H), 1.42 (–CH_3, s, 9H), 1.50–1.44 (–CH, m, 1H), 1.76–1.71 (–CH, m, 1H), 1.89 (–CH_3, s, 3H), 5.05 (–CH, dd, *J* = 9.6, 3.6 Hz, 1H), 5.14 (–CH, d, *J* = 8.4 Hz, 1H), 5.87 (–CH, s, 1H), 6.07 (–CONH, s, 1H); MS (ESI) *m/z*: 256.3 [M + H]$^+$, 278.3 [M + Na]$^+$; HRMS calcd for $C_{14}H_{25}NO_3Na$ [M + Na]$^+$: 278.1726; found: 278.1734.

Compounds **4R$_2$–4R$_5$** were prepared following a similar procedure to that described for the synthesis of **4R$_1$**.

(S)-tert-*Butyl(4-methyl-3-oxo-1-phenylpent-4-en-2-yl)carbamate* **4R$_2$**

Colourless liquid; yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (–CH_3, s, 9H), 1.86 (–CH_3, s, 3H), 2.91–2.86 (–Ph–CH_2, m, 1H), 3.10–3.05 (–Ph–CH_2, m, 1H), 5.26 (–CONH, s, 1H), 5.33–5.29 (–CH, m, 1H), 5.85 (–CH_2, d, *J* = 1.2 Hz, 1H), 6.01 (–CH_2, s, 1H), 7.19–7.06 (–Ph, m, 5H); MS (ESI) *m/z*: 290.2 [M + H]$^+$, 312.3 [M + Na]$^+$; HRMS calcd for $C_{17}H_{23}NO_3Na$ [M + Na]$^+$: 312.1570; found: 312.1589.

(S)-tert-*Butyl(5-methyl-4-oxo-1-phenylhex-5-en-3-yl)carbamate* **4R$_3$**
Colourless liquid; yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (–CH_3, s, 9H), 1.87 (–CH_3, s, 3H), 2.05–2.01 (–CH_2, m, 2H), 2.64–2.60 (–CH_2, m, 2H), 5.06 (–CH, s, 1H), 5.35 (–CONH, s, 1H), 5.83 (–CH_2, s, 1H), 5.90 (–CH_2, s, 1H), 7.22–7.07 (–Ph, m, 5H); MS (ESI) *m/z*: 304.4 [M + H]$^+$, 326.4 [M + Na]$^+$; HRMS calcd for $C_{18}H_{25}NO_3Na$ [M + Na]$^+$: 326.1726; found: 326.1724.

(S)-tert-*Butyl(2-methyl-3-oxooct-1-en-4-yl)carbamate* **4R$_4$**
Colourless liquid; yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (–CH_3, t, *J* = 7.0 Hz, 3H), 1.25 (–CH_2, d, *J* = 2.5 Hz, 2H), 1.33–1.29 (–CH_2, m, 2H), 1.43 (–CH_3, s, 9H), 1.49–1.45 (–CH_2, m, 1H), 1.76–1.72 (–CH_2, m, 1H), 1.90 (–CH_3, s, 3H), 5.01 (–CH, dd, *J* = 12.5, 6.4 Hz, 1H), 5.28 (–CONH, d, *J* = 8.1 Hz, 1H), 5.88 (–CH_2, d, *J* = 0.9 Hz, 1H), 6.05 (–CH_2, s, 1H); MS (ESI) *m/z*: 256.3 [M + H]$^+$, 278.3 [M + Na]$^+$; HRMS calcd for $C_{14}H_{25}NO_3Na$ [M + Na]$^+$: 278.1726; found: 278.1725.

(S)-tert-*Butyl(5-methyl-4-oxohex-5-en-3-yl)carbamate* **4R$_5$**
Colourless liquid; yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (–CH_3, t, *J* = 7.5 Hz, 3H), 1.43 (–CH_3, s, 9H), 1.59–1.48 (–CH, m, 1H), 1.83 (–CH, dd, *J* = 12.5, 6.9 Hz, 1H), 1.90 (–CH_3, s, 3H), 4.98 (–CH, dd, *J* = 12.5, 7.4 Hz, 1H), 5.32 (–CONH, s, 1H), 5.88 (–CH, s, 1H), 6.05 (–CH, s, 1H); MS (ESI) *m/z*: 228.3 [M + H]$^+$, 250.2 [M + Na]$^+$; HRMS calcd for $C_{12}H_{21}NO_3Na$ [M + Na]$^+$: 250.1413; found: 250.1411.

tert-*Butyl [(3*R,*4*S*)-3-hydroxy-2,6-dimethylhept-1-en-4-yl]carbamate* **5R$_1$**
A mixture of aluminium isopropoxide (1 mmol) and isopropanol (9.5 mmol) in toluene (2 mL) was added dropwise to **4R$_1$** (1 mmol) in toluene (3 mL) at room temperature. The reaction mixture was then stirred at 50 °C overnight. The solution was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with 1 M HCl (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and the solvent was evaporated to give a yellow viscous oil, which was chromatographed with ethyl acetate and petroleum (V/V = 1:4) to give **5R$_1$**.

Colourless liquid; yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (–CH_3, d, *J* = 6.6 Hz, 3H), 0.90 (–CH_3, d, *J* = 6.6 Hz, 3H), 1.20–1.14 (–CH, m, 1H), 1.31–1.23 (–CH_2, m, 2H), 1.43 (–CH_3, s, 9H), 1.67–1.57 (–CH, m, *J* = 6.0, 3.6 Hz, 1H), 1.75 (–CH_3, s, 3H), 2.42 (–OH, s, 1H), 3.82 (–CH, t, *J* = 9.6 Hz, 1H), 4.14 (–CH, s, 1H), 4.70 (–CONH, d, *J* = 7.8 Hz, 1H), 4.93 (–CH_2, dd, *J* = 3.0, 1.2 Hz, 1H), 5.00 (–CH_2, s, 1H); MS (ESI) *m/z*: 258.3 [M + H]$^+$, 280.3 [M + Na]$^+$; HRMS calcd for $C_{14}H_{27}NO_3Na$ [M + Na]$^+$: 280.1883; found: 280.1888.

Compounds **5R$_2$–5R$_5$** were prepared following a similar procedure to that described for the synthesis of **5R$_1$**.

tert-*Butyl[(2*S,*3*S*)-3-hydroxy-4-methyl-1-phenylpent-4-en-2-yl] carbamate* **5R$_2$**
Colourless liquid; yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (–CH_3, s, 9H). 1.81 (–CH_3, s, 3H), 2.36 (–OH, s, 1H), 2.70 (–Ph–CH_2, s, 1H), 2.89 (–Ph–CH_2, dd, *J* = 14.3, 3.7 Hz, 1H), 3.98 (–CH, s, 1H), 4.20 (–CH, s, 1H), 4.64 (–CONH, s, 1H), 5.00 (–CH_2, s, 1H), 5.08 (CH_2, s, 1H), 7.24–7.10 (–Ph, m, 5H); MS (ESI) *m/z*: 292.2 [M + H]$^+$, 314.2 [M + Na]$^+$; HRMS calcd for $C_{17}H_{25}NO_3Na$ [M + Na]$^+$: 314.1726; found: 314.1729.

tert-*Butyl[(3*S,*4*R*)-4-hydroxy-5-methyl-1-phenylhex-5-en-3-yl] carbamate* **5R$_3$**
Colourless liquid; yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (–CH_3, s, 9H), 1.59 (–CH_2, s, 1H), 1.65 (–CH_3, d, *J* = 14.0 Hz, 3H), 1.80–1.76 (–CH_2, m, 1H), 2.15 (–OH, s, 1H), 2.59–2.54 (–Ph–CH_2, m, 1H), 2.75–2.70 (–Ph–CH_2, m, 1H), 3.79 (–CH, s, 1H), 4.12 (–CH, dd, *J* = 14.3, 7.2 Hz, 1H), 4.80 (–CONH, d, *J* = 8.8 Hz, 1H), 4.92 (–CH_2, dd, *J* = 2.7, 1.4 Hz, 1H), 5.01 (–CH_2, s, 1H), 7.23–7.08 (–Ph, m, 5H); MS (ESI) *m/z*: 306.3 [M + H]$^+$, 328.4 [M + Na]$^+$; HRMS calcd for $C_{18}H_{27}NO_3Na$ [M + Na]$^+$: 328.1883; found: 328.1881.

tert-*Butyl[(3*S,*4*S*)-3-hydroxy-2-methyloct-1-en-4-yl]carbamate* **5R$_4$**
Colourless liquid; yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (–CH_3, t, *J* = 6.7 Hz, 3H), 1.25 (–CH_2, s, 2H), 1.27 (–CH_2, s, 2H), 1.44 (–CH_3, s, 9H), 1.76 (–CH_3, s, 3H), 2.23 (–OH, d, *J* = 7.7 Hz, 1H), 3.74 (–CH, s, 1H), 4.14 (–CH, s, 1H), 4.65 (–CONH, s, 1H), 4.95 (–CH_2, d, *J* = 1.3 Hz, 1H), 5.01 (–CH_2, s, 1H); MS (ESI) *m/z*: 258.3 [M + H]$^+$, 280.3 [M + Na]$^+$; HRMS calcd for $C_{14}H_{27}NO_3Na$ [M + Na]$^+$: 280.1883, found: 280.1887.

tert-*Butyl[(3*S,*4*S*)-4-hydroxy-5-methylhex-5-en-3-yl] carbamate* **5R$_5$**
Colourless liquid; yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (–CH_3, t, *J* = 7.4 Hz, 3H), 1.44 (–CH_3, s, 9H), 1.54 (–CH, d, *J* = 3.4 Hz, 1H), 1.61 (–CH, d, *J* = 18.8 Hz, 1H), 1.76 (–CH_3, s, 3H), 2.21 (–CH, d, *J* = 7.4 Hz, 1H), 3.67 (–CH, s, 1H), 4.14 (–CH, s, 1H), 4.65 (–CONH, s, 1H), 4.94 (–CH, s, 1H), 5.01 (–CH, s, 1H). MS (ESI) *m/z*: 230.3 [M + H]$^+$, 252.2 [M + Na]$^+$; HRMS calcd for $C_{12}H_{23}NO_3Na$ [M + Na]$^+$ 252.1570; found: 252.1570.

tert-*Butyl{(1*S,*2*S*)-1-hydroxy-4-methyl-1-[(*R*)-2-methyloxiran-2-yl] pentan-2-yl}carbamate* **6R$_1$**
Compound **5R$_1$** (0.7 mmol) in DCM (3 mL) was treated with vanadium(III) acetylacetonate (0.14 mmol) at 0 °C under nitrogen. *tert*-Butyl hydroperoxide solution (2.1 mmol) was then added. The reaction mixture was allowed to warm to room temperature after 1 h and stirred overnight. The solution was extracted with DCM (3 × 10 mL). The combined organic phases were washed with sodium thiosulfate solution (3 × 20 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed with ethyl acetate and petroleum (V/V = 1:5) to give **6R$_1$**.

Colourless liquid; yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (–CH_3, d, *J* = 6.6 Hz, 3H), 0.91 (–CH_3, d, *J* = 6.6 Hz, 3H), 1.11–1.04 (–CH, m, 1H), 1.36 (–CH_3, s, 3H), 1.43 (–CH_3, s, 9H), 1.48–1.44 (–CH, m, 1H), 1.69–1.57 (–CH, m, 1H), 2.44 (–OH, s, 1H), 2.61 (–CH_2, d, *J* = 4.8 Hz, 1H), 2.97 (–CH_2, d, *J* = 4.8 Hz, 1H), 3.82 (–CH, d, *J* = 3.0 Hz, 1H), 3.95–3.85 (–CH, m, 1H), 4.88 (–CONH, d, *J* = 9.6 Hz, 1H); MS (ESI) *m/z*: 274.3 [M + H]$^+$, 296.4 [M + Na]$^+$; HRMS calcd for $C_{14}H_{27}NO_4Na$ [M + Na]$^+$ 296.1832; found: 296.1830.

Compounds **6R$_2$–6R$_5$** were prepared following a similar procedure to that described for the synthesis of **6R$_1$**.

tert-*Butyl{(1*R,*2*S*)-1-hydroxy-1-[(*R*)-2-methyloxiran-2-yl]-3-phenylpropan-2-yl}carbamate* **6R$_2$**
Colourless liquid; yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (–CH_3, s, 9H), 1.38 (–CH_3, s, 3H), 2.34 (–CH_2, s, 1H), 2.60 (–CH_2, d, *J* = 4.6 Hz, 1H), 2.75 (–Ph–CH_2, dd, *J* = 14.2, 9.5 Hz, 1H), 2.86 (–Ph–CH_2, dd, *J* = 14.0, 4.7 Hz, 1H), 3.01 (–OH, d, *J* = 4.6 Hz, 1H), 3.85 (–CH, d, *J* = 2.3 Hz, 1H), 4.12–4.08 (–CH, m, 1H), 4.87 (–CONH, d, *J* = 9.4 Hz, 1H), 7.25–7.06 (–Ph, m, 5H); MS (ESI) *m/z*: 308.2 [M + H]$^+$, 330.2 [M + Na]$^+$; HRMS calcd for $C_{17}H_{25}NO_4Na$ [M + Na]$^+$: 330.1675; found: 330.1690.

tert-*Butyl{(1*S,*2*S*)-1-hydroxy-1-[(*R*)-2-methyloxiran-2-yl]-4-phenylbutan-2-yl}carbamate* **6R$_3$**
Colourless liquid; yield 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.21 (–CH_3, m, 3H), 1.47 (–CH_3, s, 9H), 1.73–1.68 (–CH_2, m, 2H), 2.14 (–CH_2, s, 1H), 2.60–2.55 (–CH_2, m, 2H), 2.77–2.74 (–CH_2, m, 1H), 2.95 (–OH, d, *J* = 4.8 Hz, 1H), 3.85 (–CH, s, 1H), 3.89 (–CH, d, *J* = 10.2 Hz, 1H), 4.96 (–CONH, d, *J* = 9.2 Hz, 1H), 7.25–7.09 (–Ph, m, 5H); MS (ESI) *m/z*: 322.3 [M + H]$^+$, 344.2 [M + Na]$^+$; HRMS calcd for $C_{18}H_{27}NO_4Na$ [M + Na]$^+$: 344.1832; found: 344.1844.

tert-*Butyl{(1*R,*2*S*)-1-hydroxy-1-[(*R*)-2-methyloxiran-2-yl]hexan-2-yl}carbamate* **6R$_4$**
Colourless liquid; yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (–CH_3, t, *J* = 6.4 Hz, 3H), 1.23 (–CH_2, ddd, *J* = 11.3, 4.6, 2.3 Hz, 2H), 1.31–1.27 (–CH_2, m, 2H), 1.37 (–CH_3, s, 3H), 1.38–1.34 (–CH_2, m, 2H), 1.44 (–CH_3, s, 9H), 2.34 (–OH, d, *J* = 10.0 Hz, 1H), 2.62 (–CH_2, d, *J* = 4.8 Hz, 1H), 2.97 (–CH_2, d, *J* = 4.8 Hz, 1H), 3.75 (–CH, s, 1H), 3.80 (–CH, s, 1H), 4.90 (–CONH, d, *J* = 9.2 Hz, 1H); MS (ESI) *m/z*: 274.3 [M + H]$^+$, 296.4 [M + Na]$^+$; HRMS calcd for $C_{14}H_{27}NO_4Na$ [M + Na]$^+$: 296.1832; found: 296.1830.

tert-*Butyl{(1*R,2S*)-1-hydroxy-1-[(*R*)-2-methyloxiran-2-yl]butan-2-yl} carbamate* **6R$_5$**

Colourless liquid; yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (–CH_3, t, *J* = 7.4 Hz, 3H), 1.24 (–CH, s, 1H), 1.37 (–CH_3, s, 3H), 1.44 (–CH_3, s, 9H), 1.56–1.48 (–CH, m, 1H), 2.27 (–CH, s, 1H), 2.63 (–CH, d, *J* = 4.8 Hz, 1H), 2.96 (–CH, d, *J* = 4.8 Hz, 1H), 3.74 (–CH, t, *J* = 10.1 Hz, 1H), 3.81 (–CH, d, *J* = 2.7 Hz, 1H), 4.88 (–CONH, d, *J* = 9.1 Hz, 1H); MS (ESI) *m/z*: 246.3 $[M + H]^+$, 268.2 $[M + Na]^+$; HRMS calcd for $C_{12}H_{23}NO_4Na$ $[M + Na]^+$: 268.1519; found: 268.1522.

tert-*Butyl{(*S*)-4-methyl-1-[(*R*)-2-methyloxiran-2-yl]-1-oxopentan-2-yl}carbamate* **7R$_1$**

Compound **6R$_1$** (0.5 mmol) dissolved in dimethyl sulfoxide (DMSO) (3 mL) was treated with DIPEA (1.0 mmol). Pyridine:sulfur trioxide (2 mmol) was then slowly added. The mixture was stirred at room temperature overnight. The solution was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with 1 M HCl (10 mL) and saturated brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed with ethyl acetate and petroleum (V/V = 1:5) to give **7R$_1$**.

Colourless liquid; yield 91%; $[\alpha]_D^{24}$ = +54.4 (c = 0.5, CH_3CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (–CH_3, d, *J* = 6.4 Hz, 3H), 0.95 (–CH_3, d, *J* = 6.4 Hz, 3H), 1.21–1.11 (–CH, m, 1H), 1.39 (–CH_3, s, 9H), 1.49–1.44 (–CH, m, 1H), 1.50 (–CH_3, s, 3H), 1.83–1.64 (–CH, m, 1H), 2.87 (–CH, d, *J* = 4.8 Hz, 1H), 3.27 (–CH, d, *J* = 4.8 Hz, 1H), 4.30 (–CH, t, *J* = 9.6 Hz, 1H), 4.86 (–CONH, d, *J* = 8.0 Hz, 1H); MS (ESI) *m/z*: 272.3 $[M + H]^+$, 294.3 $[M + Na]^+$; HRMS calcd for $C_{14}H_{25}NO_4Na$ $[M + Na]^+$: 294.1675; found: 294.1678 (lit.[10] 294.1676).

Compounds **7R$_2$–7R$_5$** were prepared following a similar procedure to that described for the synthesis of **7R$_1$**.

tert-*Butyl{(*S*)-1-[(*R*)-2-methyloxiran-2-yl)]1-oxo-3-phenylpropan-2-yl}carbamate* **7R$_2$**

Colourless liquid; yield 69%; $[\alpha]_D^{24}$ = +13.8 (c = 0.25, CH_3CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (–CH_3, s, 9H). 1.50 (–CH_3, s, 3H), 2.73 (–CH_2, dd, *J* = 13.8, 7.7 Hz, 1H), 2.90 (–CH_2, d, *J* = 4.9 Hz, 1H), 3.10 (–Ph–CH_2, dd, *J* = 13.9, 5.0 Hz, 1H), 3.29 (–Ph–CH_2, d, *J* = 4.9 Hz, 1H), 4.58 (–CH, dd, *J* = 13.2, 8.0 Hz, 1H), 4.93 (–CONH, d, *J* = 7.7 Hz, 1H), 7.25–7.09 (–Ph, m, 5H); MS (ESI) *m/z*: 306.2 $[M + H]^+$, 328.2 $[M + Na]^+$; HRMS calcd for $C_{17}H_{23}NO_4Na$ $[M + Na]^+$: 328.1519; found: 328.1533.

tert-*Butyl{(*S*)-1-[(*R*)-2-methyloxiran-2-yl]-1-oxo-4-phenylbutan-2-yl} carbamate* **7R$_3$**

Colourless liquid; yield 75%; $[\alpha]_D^{24}$ = +7.0 (c = 0.5, CH_3CN); ^{1}H NMR (400 MHz, CDCl3): d 1.43 (–CH_3, s, 9H), 1.49 (–CH_3, s, 3H), 1.63–1.59 (–CH_2, m, 1H), 2.14 (–CH_2, s, 1H), 2.11–2.07 (–CH_2, m, 1H), 2.69–2.65 (–CH_2, m, 2H), 2.87 (–CH_2, d, *J* = 5.0 Hz, 1H), 3.21 (–CH_2, d, *J* = 4.8 Hz, 1H), 4.35 (–CH, d, *J* = 3.4 Hz, 1H), 5.02 (–CONH, d, *J* = 7.9 Hz, 1H), 7.24–7.09 (–Ph, m, 5H); MS (ESI) *m/z*: 320.3 $[M + H]^+$; HRMS calcd for $C_{18}H_{25}NO_4Na$ $[M + Na]^+$: 342.1675; found: 342.1687.

tert-*Butyl{(*S*)-1-[(*R*)-2-methyloxiran-2-yl]-1-oxohexan-2-yl} carbamate* **7R$_4$**

Colourless liquid; yield 87%; $[\alpha]_D^{24}$ = +39.1 (c = 0.5, CH_3CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90–0.86 (–CH_3, m, 3H), 1.30 (–CH_2, s, 2H), 1.34 (–CH_2, d, *J* = 7.6 Hz, 2H), 1.42 (–CH_3, s, 9H), 1.51 (–CH_3, s, 3H), 1.59 (–CH, s, 1H), 1.75–1.70 (–CH, m, 1H), 2.88 (–CH, d, *J* = 5.0 Hz, 1H), 3.25 (–CH, d, *J* = 4.8 Hz, 1H), 4.27 (–CH, t, *J* = 8.0 Hz, 1H), 4.92 (–CONH, d, *J* = 8.3 Hz, 1H); MS (ESI) *m/z*: 272.3 $[M + H]^+$, 294.3 $[M + Na]^+$; HRMS calcd for $C_{14}H_{25}NO_4Na$ $[M + Na]^+$: 294.1675; found: 294.1683.

tert-*Butyl{(*S*)-1-[(*R*)-2-methyloxiran-2-yl]-1-oxobutan-2-yl} carbamate* **7R$_5$**

Colourless liquid; yield 90%; $[\alpha]_D^{24}$ = +61.6 (c = 0.5, CH_3CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (–CH_3, t, *J* = 7.4 Hz, 3H), 1.42 (–CH_3, s, 9H), 1.48–1.45 (–CH, m, 1H), 1.53 (–CH_3, s, 3H), 1.88–1.79 (–CH, m, 1H), 2.90 (–CH, d, *J* = 5.0 Hz, 1H), 3.25 (–CH, d, *J* = 4.7 Hz, 1H), 4.27 (–CH, dd, *J* = 12.5, 8.1 Hz, 1H), 4.99 (–CONH, d, *J* = 7.4 Hz, 1H); MS (ESI) *m/z*: 266.2 $[M + Na]^+$; HRMS calcd for $C_{12}H_{21}NO_4Na$ $[M + Na]^+$: 266.1362; found: 266.1367.

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