Tetrahedron 65 (2009) 10074–10082

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient synthetic approach towards *trans*-$\beta^{2,3}$-amino acids and demonstration of their utility in the design of therapeutically important $\beta^{2,3}$-peptides and $\alpha,\beta^{2,3}$-peptide aldehydes

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ARTICLE INFO

Article history:
Received 12 June 2009
Received in revised form
11 September 2009
Accepted 17 September 2009
Available online 23 September 2009

Keywords:
trans-$\beta^{2,3}$-Amino acids
Betapeptides
Peptide aldehydes

ABSTRACT

An efficient synthetic approach towards *trans*-$\beta^{2,3}$-amino acids involving anti-selective aldol, azidation and controlled hydrolysis as key steps is discussed. Apart from structural elaboration of these building blocks to homo- and hetero-dipeptides, possibility of selective endocyclic cleavage of the chiral auxiliary was advantageously used in the preparation of α,β-hybrid peptide alcohols and corresponding aldehydes, which are promising candidates for biological evaluation against proteases of therapeutic interest.

1. Introduction

Similarity in the folding behaviour of β-peptides with that of their natural counterpart coupled with their superior stability in biological milieu has generated a great deal of interest in the design of structurally and functionally important molecular frameworks from β-amino acids.[1] Pioneering efforts, especially from the laboratories of Seebach, Gellman and De-Grado have laid a strong foundation to this area and have resulted in molecules with predictable conformational characteristics,[2] with potential application in drug design.[3] Important observations from studies on folding preferences of such oligomers include (i) 3_{14}-helices from β^3-peptides and $\beta^{2,3}$-peptides with like configurations at α- and β-positions,[4] (ii) extended structures when the monomeric $\beta^{2,3}$-amino acids have unlike configurations (*S*,*R* or *R*,*S*) at α- and β-centres,[1a,2d] and (iii) 10-membered turn if the amide bond is in between two substituted carbon atoms (i.e., $\beta^2\beta^3$-dipeptide).[5] Related studies have also shown that the presence of β-amino acids at specific locations in α-peptide hairpins or helices are tolerated without significant perturbation in the structure, highlighting the compatibility of such monomeric units with natural peptides in creating new hybrid molecules.[6] Further, unique aggregation characteristics of such molecules have extended their use beyond the realm of 'medicines' to 'material science' as shown by recent reports on liquid crystalline β-peptides.[7]

Anti-periplanar arrangement of side chains in *trans*-$\beta^{2,3}$-amino acids and tendency of their peptides to form extended structures suggest that such systems are ideal for creating new molecular topologies with tunable polarity characteristics.[1a,8] Among the notable approaches to prepare *trans*-$\beta^{2,3}$-amino acids,[9] the one developed by Ellman et al. makes use of Ti(O-*i*-Pr)$_3$ ester enolate addition to *tert*-butanesulfinyl imines, and has been shown to be applicable to a variety of substrates. New methods towards such building blocks using readily accessible chiral auxiliaries would be highly useful in structure design, and results from our investigation in this direction are discussed below.

2. Results and discussion

A sequence involving directed anti-aldol reaction of *N*-acyloxazolidinones with suitable aldehydes, followed by inversion at the β-carbon using amine equivalents was envisaged to give compounds of desired stereochemistry (Scheme 1). Possibility of modulating hydrolytic conditions to effect either exocyclic or endocyclic cleavage of the chiral auxiliary to prepare $\beta^{2,3}$-amino acids or α,β-hybrid systems was also explored.[10]

In a typical experiment, the acid chloride derived from valeric acid was reacted with in situ-generated anion of (4*S*)-4-benzyloxazolidin-2-one (**1**) to give **2a** quantitatively, which, when subjected to Evans $MgCl_2$ catalyzed anti-aldol reaction[11] with benzaldehyde

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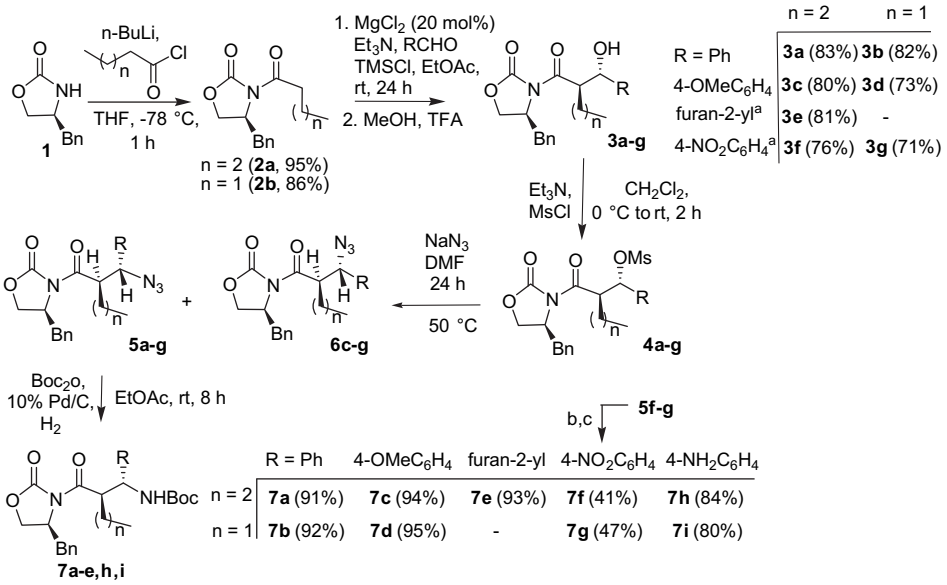
doi:10.1016/j.tet.2009.09.072



Scheme 1. Synthesis of β-[2,3]-amino acid precursors. (a) 0.3 equiv of $NaSbF_6$ used as additive, (b) PPh_3, THF–H_2O, (c) Boc_2o, EtOAc (2 steps).

afforded the alcohol **3a** in 83% yield (dr=91:9,[12] Scheme 1). Our initial attempts to invert the β-carbon configuration using amine equivalents under Mitsunobu-conditions proved ineffective, most likely due to steric reasons. A nucleophilic displacement route through mesylate **4a** using sodium azide was later considered, which afforded the desired isomer **5a** in 71% yield. Through a one-pot reduction–Boc-protection sequence,[13] this azide was converted to the *N*-protected β-amino acid precursor **7a** in 91% yield. Results from similar reaction sequences involving anisaldehyde, 2-furaldehyde, 4-nitrobenzaldehyde and other *N*-acyloxazolidinones are also presented in Scheme 1 and Table 1. Unlike mesylates **4a**–**e**, azidation of nitroderivatives **4f** and **4g** gave better conversion on using DMSO in place of DMF. Reactions in these cases however had to be stopped before the complete consumption of starting materials to avoid formation of side products such as 4-nitrobenzonitrile and *N*-acyloxazolidinones **2a**/**2b**. Selective reduction of the azide units in **5f** and **5g** was achieved under Staudinger reaction condition and the corresponding amines were converted to the Boc-derivatives **7f** (41%) and **7g** (47%) using Boc_2o. At the same time, simultaneous reduction of both nitro- and azide-units in these compounds under Pd–C/H_2 condition and subsequent selective Boc-protection of Cβ-NH_2 using 1 equiv of Boc_2o afforded the amino derivatives **7h** and **7i** as the major products.

Table 1
Azidation of mesylates **4a**–**g**

S. no.	*n*	R	Azide	dr (5:6)[a]	Yield (%)
1	2	Ph	**a**	—	71[b]
2	1	Ph	**b**	—	71[b]
3	2	4-$OMeC_6H_4$	**c**	61:39	79
4	1	4-$OMeC_6H_4$	**d**	63:37	75
5	2	Furan-2-yl	**e**	67:33	82
6	2	4-$NO_2C_6H_4$	**f**	95:5	75[c,d]
7	1	4-$NO_2C_6H_4$	**g**	97:3	84[c,d]

[a] Diastereomeric ratio was determined from ^{1}H NMR spectrum of the crude reaction mixture.
[b] Only the stereoisomer **5** was isolated.
[c] Based on the amount of recovered starting material.
[d] DMSO was used as the solvent.

The absolute stereochemistry of the alcohol **3c** and the corresponding azide **5c**, determined by X-ray crystallographic analysis (Fig. 1),[14] is in agreement with our expectations. In their ^{1}H NMR spectrum, the Cβ-H signal in compounds **5a**–**5g** appeared as a clear doublet with *J* values in the range of 8.4–10.0 Hz. The corresponding value in **6c**–**g** was 10.8 Hz consistent with the anti-periplanar positioning of Cα- and Cβ-hydrogens in these compounds. Interestingly, the use of L-phenylalanine derived chiral auxiliary in this strategy led to β[2,3]-amino acids having opposite relative stereochemistry compared to those prepared using *tert*-butanesulfinyl directing group, reported earlier.[9b] The decrease in stereoselectivity

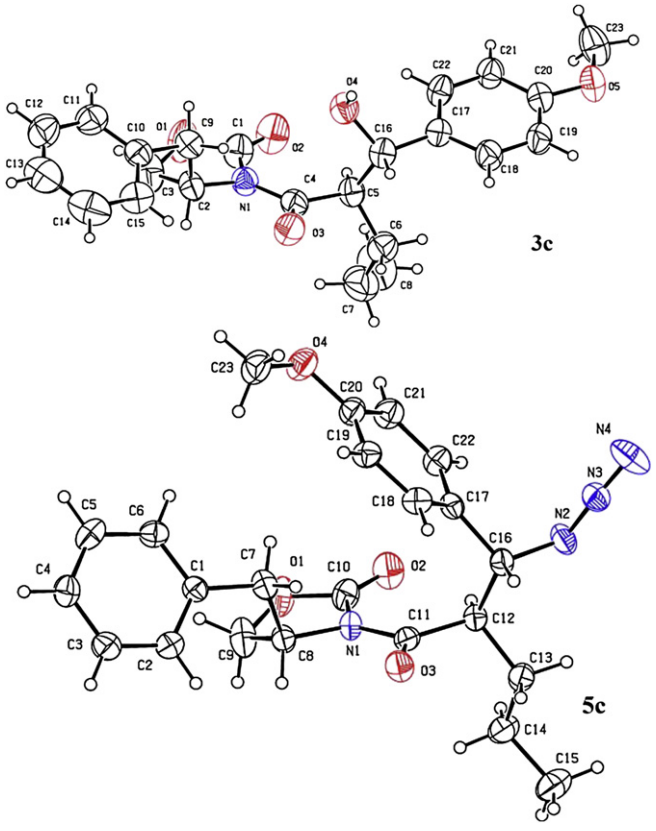
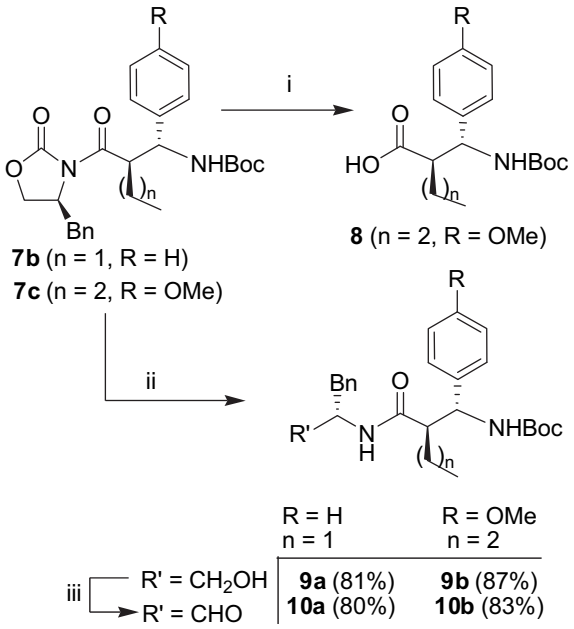


Fig. 1. ORTEP diagrams of compounds **3c** and **5c**.

during azidation of **4c**, **4d** and **4e** can be attributed to the preference towards a contact ion-pair mechanism during substitution.

As mentioned, an interesting aspect of this method is the possibility of adjusting reaction conditions to effect regioselective hydrolysis of the chiral auxiliary. Thus, exocyclic cleavage of **7c** using in situ-generated lithium hydroperoxide afforded the *N*-Boc amino acid (**8**) in 93% yields.[10] Hydrolysis of **7b** and **7c** using LiOH at the same time gave alcohols **9a** and **9b**, respectively, in high yields through endocyclic cleavage (Scheme 2). Peptide aldehydes such as **10a** and **10b**, which can be readily prepared from **9a** and **9b**, are potential candidates for targeting proteases of therapeutic interest.[15]

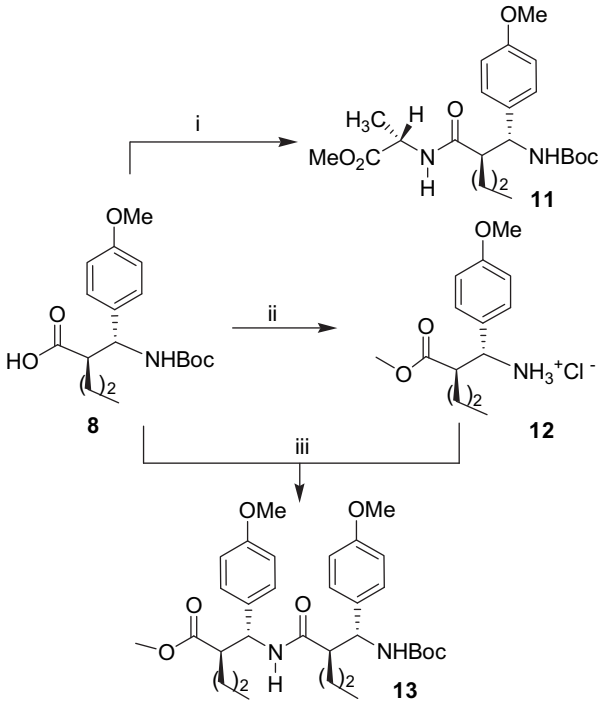


Scheme 2. Regioselective hydrolysis of the chiral auxiliary and preparation of α,β[2,3]-hybrid systems **9** and **10**: (i) H_2O_2, LiOH·H_2O, THF–H_2O (3:1), 0 °C to rt, 6 h, 93%; (ii) LiOH·H_2O, THF–H_2O (3:1), 0 °C to rt, 10 h; (iii) 2-iodoxybenzoic acid (IBX), DMSO, rt, 8 h.

Versatility of these β[2,3]-amino acid building blocks in the design of homo- and hetero-oligomers is demonstrated through preparation of compounds **11** and **13** as depicted in Scheme 3. The α,β-hybrid peptide **11** was prepared in 80% yield by reacting Boc-protected β[2,3]-amino acid **8** with the free amine from alanine methylester hydrochloride under EDCI/HOBt-mediated coupling condition. Our initial attempts to couple the free amine from **7c** with **8** gave only very low yields of the dipeptide, most likely due to increased steric bulk at the adjacent carbon atoms. To overcome this, **8** was first subjected to one-pot Boc-deprotection/esterification sequence using thionylchloride in methanol to get **12**, which was then coupled with **8** to afford the dipeptide **13** in 71% yield.

It is important to note that application of peptide alcohols,[16] β-peptides,[3e,3h,17] and α,β-hybrid systems[3b,3c,18] as drug candidates or their intermediates is well documented in literature, and the present strategy is expected to be useful in generating libraries of such compounds for biological evaluation.

To summarize, we delineate a useful method towards *trans*-β[2,3]-amino acids, their peptides and α,β[2,3]-hybrid systems through a unique route involving directed anti-aldol, stereo-selective inversion at the β-carbon and controlled hydrolysis as the key steps. Such molecules can find applications in the fields of drug design, and in creating well-defined molecular surfaces to understand phenomena like membrane-protein interaction.



Scheme 3. Synthesis of hybrid peptide **11** and *trans*-β[2,3] dipeptide **13**: (i) H_2NAlaO-Me·HCl, *i*-Pr_2NEt, EDCI, HOBt, CH_2Cl_2, 0 °C to rt, 27 h, 80%; (ii) $SOCl_2$, MeOH, 0 °C to rt, 24 h, 88%; (iii) *i*-Pr_2NEt, EDCI, HOBt, CH_2Cl_2, 0 °C to rt, 27 h, 71%.

3. Experimental

3.1. General procedures

All reactions were carried out under nitrogen atmosphere using dry solvents under anhydrous conditions, unless otherwise mentioned. Triethylamine and chlorotrimethylsilane were dried over calcium hydride and distilled under nitrogen atmosphere. HPLC-grade ethyl acetate from Finar chemicals Ltd., was used as received. Butyryl chloride, valeryl chloride and various aldehydes used in the reactions were also distilled before use. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (60 F254 grade) from Merck, and were analyzed using a 254 nm UV light. The chromatographic separation was carried out on 100–200 mesh silica gel. Melting points were obtained on electro-thermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz and 500 MHz instruments, and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, with *J* values in hertz. The splitting patterns in ^{1}H NMR spectra are reported as follows: s=singlet; d=doublet; t=triplet; q=quartet; qn=quintet; dd=doublet of doublet; ddd=doublet of doublet of doublet; dddd=doublet of doublet of doublet of doublet; br s=broad singlet; br d=broad doublet; br t=broad triplet; m=multiplet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$=77.0, DMSO-d_6=39.5) as the internal standard. High-resolution mass spectra (HRMS) were recorded on a Waters Q-Tof *micro*™ spectrometer with lock spray source. Infrared spectra were recorded using a Nicolet 6700 FT-IR spectrophotometer. Optical rotations were measured on an Autopol® IV automatic polarimeter from Rudolph Research Analytical with a cell of 50 mm path length and Elemental analysis was done on ThermoFinnigan FLASH EA 1112 CHNS analyser at IISc Bangalore, India.

The intensity data collection during X-ray crystallographic analysis was carried out on a Bruker AXS (kappa apex II) diffractometer[19] equipped with graphite monochromated Mo (K_α)

radiation. The data were collected for θ up to 25° for Mo Kα radiation. ω and φ scans were employed to collect the data. The frame width for ω was set to 0.5° for data collection. The frames were integrated and data were reduced for Lorentz and polarization correction using SAINT-Plus. The multi-scan absorption correction[20] was applied to data. All structures were solved using SIR-92 and refined using SHELXL-97.[21] The molecular and packing diagrams were drawn using ORTEP-3[22] (Oak Ridge Thermal Ellipsoid Plot) and Mercury 1.4.2. The non-hydrogen atoms were refined with anisotropic displacement parameter. All hydrogen atoms could be located in the difference Fourier map. However, the hydrogen atoms bonded to carbons were fixed at chemically meaningful positions and were allowed to ride with parent atom during the refinement.

3.2. Azidation of anti-aldol products[23]

*3.2.1. (S)-3-((R)-2-((R)-Azido(phenyl)methyl)pentanoyl)-4-benzyl oxazolidin-2-one (**5a**).* To a stirred solution of **3a** (400 mg, 1.09 mmol) in dry dichloromethane (4 mL) at 0 °C under N_2 atmosphere, was added triethylamine (0.30 mL, 2.18 mmol), followed by mesyl chloride (0.13 mL, 1.64 mmol). The reaction was monitored by TLC, and after complete consumption of the starting material (2 h), it was washed with 5% $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the mesylate **4a** as a gummy solid (470 mg, 97%). To a stirred solution of the above mesylate (400 mg, 0.89 mmol) in DMF (4 mL) was added NaN_3 (116.9 mg, 1.79 mmol) and the mixture was heated at 50 °C for 24 h. The reaction mixture was diluted with EtOAc (25 mL), washed with water (3 × 25 mL), followed by brine (25 mL) and then dried over anhydrous Na_2SO_4. It was filtered and concentrated under reduced pressure to get a residue, which was purified by chromatography on silica gel using 5% EtOAc/hexanes system to afford **5a** (250 mg, 71%) as a white crystalline solid; mp 57–59 °C; R_f (20% EtOAc/Hexane) 0.60; $[\alpha]_D^{30}$ +106.3 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2961, 2931, 2100, 1778, 1693, 1385, 1263, 1209, 1100, 733, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J*=7.2 Hz, Ph–*H*), 7.37 (t, 2H, *J*=7.2 Hz, Ph–*H*), 7.33 (d, 1H, *J*=6.8 Hz, Ph–*H*), 7.30–7.20 (m, 3H, Ph–*H*), 6.95 (d, 2H, *J*=7.6 Hz, Ph–*H*), 4.72 (d, 1H, *J*=9.6 Hz, PhC*H*N_3), 4.59–4.49 (m, 2H, $(PhCH_2)CH$ and $CH(CH_2CH_2CH_3)$), 4.05 (dd, 1H, *J*=8.9, 8.9 Hz, $(PhCH_2)CH(CH_aH_bO–)$), 3.96 (dd, 1H, *J*=2.6, 9.2 Hz, $(PhCH_2)CH(CH_aH_bO–)$), 2.61 (dd, 1H, *J*=3.2, 13.6 Hz, $(PhCH_aH_b)CH$), 1.94–1.83 (m, 3H, $(PhCH_aH_b)CH$ and $CH_2CH_2CH_3$), 1.38–1.25 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 152.8, 137.4, 135.1, 129.2 (2C), 128.9 (2C), 128.8 (3C), 128.1 (2C), 127.2, 68.1, 65.6, 54.9, 48.0, 36.9, 32.4, 20.1, 14.2; HRMS (ESI) exact mass calcd for $C_{22}H_{24}N_4O_3Na$ $[M+Na]^+$ 415.1746, found 415.1739.

*3.2.2. (S)-3-((R)-2-((R)-Azido(phenyl)methyl)butanoyl)-4-benzyloxazolidin-2-one (**5b**).* The alcohol **3b** (250 mg, 0.708 mmol) in dry dichloromethane (2.5 mL) was reacted with mesyl chloride (0.08 mL, 1.062 mmol) in presence of triethylamine (0.2 mL, 1.416 mmol) according to the procedure discussed above to get the mesylate **4b** as a yellow residue (290 mg, 95%). Compound **4b** (250 mg, 0.58 mmol) in DMF (2.5 mL) was subsequently subjected to azidation using NaN_3 (75.4 mg, 1.16 mmol) and the product mixture was chromatographed on silica gel using 5% EtOAc/hexanes system to afford **5b** as a white crystalline solid (155 mg, 71%); mp 125–128 °C; R_f (20% EtOAc/Hexane) 0.42; $[\alpha]_D^{30}$ +151.7 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3031, 2968, 2929, 2878, 2099, 1774, 1689, 1455, 1382, 1202, 1104, 1022, 740, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J*=7.0 Hz, Ph–*H*), 7.38 (t, 2H, *J*=7.2 Hz, Ph–*H*), 7.34–7.20 (m, 4H, Ph–*H*), 6.94 (d, 2H, *J*=8.0 Hz, Ph–*H*), 4.75 (d, 1H, *J*=10.0 Hz, PhC*H*N_3), 4.58–4.46 (m, 2H, $(PhCH_2)CH$ and $CH(CH_2CH_3)$), 4.06 (dd, 1H, *J*=8.0, 8.0 Hz, $(PhCH_2)CH(CH_aH_bO–)$), 3.97 (dd, 1H, *J*=2.8, 9.2 Hz, $(PhCH_2)CHCH_aH_bO–$), 2.62 (dd, 1H, *J*=3.2, 13.6 Hz, $(PhCH_aH_b)CH$), 2.01–1.83 (m, 3H, $(PhCH_aH_b)CH$ and CH_2CH_3), 0.95 (t, 3H, *J*=7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 152.8, 137.4, 135.1, 129.2 (2C), 128.9 (2C), 128.7 (3C), 128.0 (2C), 127.2, 67.6, 65.6, 54.9, 49.2, 36.9, 23.2, 11.0; HRMS (ESI) exact mass calcd for $C_{21}H_{22}N_4O_3Na$ $[M+Na]^+$ 401.1590, found 401.1590.

*3.2.3. (S)-3-((R)-2-((R)-Azido(4-methoxyphenyl) methyl) pentanoyl)-4-benzyloxazolidin-2-one (**5c**).* The alcohol **3c** (1 g, 2.52 mmol) in dry dichloromethane (10 mL) was reacted with mesyl chloride (0.29 mL, 3.78 mmol) in presence of triethylamine (0.70 mL, 5.04 mmol) according to the procedure discussed above to get the mesylate **4c** as a yellow residue (1.1 g, 92%). The compound **4c** (1 g, 2.1 mmol) in DMF (10 mL) was subsequently converted to the azide using NaN_3 (0.274 g, 4.2 mmol) to afford diastereomers **5c** and **6c** in 61:39 ratio (combined weight=700 mg, 79% yield). [Found: C, 65.40; H, 6.40; N, 11.94. $C_{23}H_{26}N_4O_4$ requires C, 65.39; H, 6.20; N, 13.26%.] mp 67–69 °C; R_f (20% EtOAc/Hexane) 0.57; $[\alpha]_D^{30}$ +136.3 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2959, 2933, 2872, 2099, 1775, 1692, 1610, 1513, 1384, 1248, 1208, 1100, 1031, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 2H, *J*=8.8 Hz, Ar–*H*), 7.30–7.22 (m, 3H, Ph–*H*), 6.95 (d, 2H, *J*=8.0 Hz, Ph–*H*), 6.89 (d, 2H, *J*=8.4 Hz, Ar–*H*), 4.68 (d, 1H, *J*=10.0 Hz, ArC*H*N_3), 4.60–4.49 (m, 2H, $(PhCH_2)CH$ and $CH(CH_2CH_2CH_3)$), 4.06 (dd, 1H, *J*=8.8, 8.8 Hz, $(PhCH_2)CH(CH_aH_bO–$)), 3.97 (dd, 1H, *J*=2.4, 8.8 Hz, $(PhCH_2)CH(CH_aH_bO–)$), 3.77 (s, 3H, 4-OCH_3–C_6H_4), 2.66 (dd, 1H, *J*=3.2, 13.2 Hz, $(PhCH_aH_b)CH$), 1.98 (dd, 1H, *J*=10.0, 13.6 Hz, $(PhCH_aH_b)CH$), 1.90–1.78 (m, 2H, $CH_2CH_2CH_3$), 1.39–1.24 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 159.9, 152.8, 135.1, 129.5, 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.2, 114.1 (2C), 67.7, 65.6, 55.3, 54.9, 48.0, 37.0, 32.5, 20.2, 14.2; HRMS (ESI) exact mass calcd for $C_{23}H_{26}N_4O_4Na$ $[M+Na]^+$ 445.1852, found 445.1855.

*3.2.3.1. (S)-3-((R)-2-((S)-Azido(4-methoxyphenyl)methyl)pentanoyl)-4-benzyloxazolidin-2-one (**6c**).* 91:9 mixture of **6c** and **5c** as per ^1H NMR; R_f (20% EtOAc/Hexane) 0.57; $[\alpha]_D^{30}$ −438.8 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2960, 2931, 2873, 2098, 1775, 1693, 1610, 1514, 1385, 1349, 1250, 1208, 1177, 1100, 831, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H, Ar–*H*), 7.30 (d, 3H, *J*=7.2 Hz, Ar–*H*), 6.95 (d, 2H, *J*=8.4 Hz, Ar–*H*), 4.80–4.73 (m, 1H, $(PhCH_2)CH(CH_2O)$), 4.67 (d, 1H, *J*=10.8 Hz, ArC*H*N_3), 4.56–4.50 (m, 1H, $CH(CH_2CH_2CH_3)$), 4.19 (d, 2H, *J*=4.8 Hz, $(PhCH_2)CH(CH_2O–)$), 3.84 (s, 3H, 4-OCH_3–C_6H_4), 3.44 (dd, 1H, *J*=3.2, 13.6 Hz, $(PhCH_aH_b)CH$), 2.80 (dd, 1H, *J*=10.0, 13.6 Hz, $(PhCH_aH_b)CH$), 1.60–1.49 (m, 1H, $CH_aH_bCH_2CH_3$), 1.20–1.10 (m, 3H, $CH_aH_bCH_2CH_3$ and $CH_2CH_2CH_3$), 0.75 (t, 3H, *J*=6.8 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 160.0, 153.3, 135.5, 129.5 (2C), 129.3 (2C), 128.9 (2C), 128.7, 127.3, 114.3 (2C), 68.7, 65.8, 55.7, 55.3, 47.3, 37.6, 32.2, 19.9, 14.0; HRMS (ESI) exact mass calcd for $C_{23}H_{26}N_4O_4Na$ $[M+Na]^+$ 445.1852, found 445.1855.

*3.2.4. (S)-3-((R)-2-((R)-Azido(4-methoxyphenyl)methyl) butanoyl)-4-benzyloxazolidin-2-one (**5d**).* The alcohol **3d** (500 mg, 1.30 mmol) in dichloromethane (10 mL) was reacted with mesyl chloride (0.15 mL, 1.96 mmol) in presence of triethylamine (0.37 mL, 2.61 mmol) according to the procedure discussed above to get the mesylate **4d** as a yellow residue (580 mg, 96%). The compound **4d** (580 mg, 1.26 mmol) in DMF (10 mL) was subsequently converted to the azide using NaN_3 (0.163 g, 2.52 mmol) to afford diastereomers **5d** and **6d** in 63:37 ratio (combined weight=384 mg, 75% yield); mp 112–114 °C; R_f (20% EtOAc/Hexane) 0.47; $[\alpha]_D^{30}$ +141.7 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2966, 2929, 2099, 2872, 2835, 1774, 1691, 1610, 1513, 1383, 1348, 1248, 1209, 1177, 1105, 1031, 830, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 2H, *J*=8.4 Hz, Ar–*H*), 7.29–7.20 (m, 3H, Ph–*H*), 6.94 (d, 2H, *J*=7.6 Hz, Ph–*H*), 6.90 (d, 2H, *J*=8.4 Hz, Ar–*H*), 4.71 (d, 1H, *J*=9.6 Hz, ArC*H*N_3), 4.55 (dddd, 1H, *J*=2.8, 2.8, 6.0, 10.8 Hz, $(PhCH_2)CH(CH_2O–)$), 4.48 (ddd, 1H, *J*=3.6, 9.6, 9.6 Hz, $CH(CH_2CH_3)$),

4.07 (dd, 1H, J=8.4, 8.4 Hz, (PhCH_2)CH(CH_aH$_b$O–)), 3.99 (dd, 1H, J=2.8, 9.2 Hz, (PhCH_2)CH(CH$_a$H$_b$O–)), 3.77 (s, 3H, 4-OCH_3–C$_6$H$_4$), 2.67 (dd, 1H, J=3.2, 13.6 Hz, (PhCH_aH$_b$)CH), 2.03 (dd, 1H, J=9.6, 13.6 Hz, (PhCH$_a$H$_b$)CH), 2.01–1.82 (m, 2H, CH_2CH$_3$), 0.95 (t, 3H, J=7.2 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.5, 159.9, 152.9, 135.1, 129.5, 129.3 (2C), 129.2 (2C), 128.9 (2C), 127.2, 114.1 (2C), 67.2, 65.6, 55.3, 54.9, 49.2, 37.0, 23.3, 11.0; HRMS (ESI) exact mass calcd for $C_{22}H_{24}N_4O_4Na$ [M+Na]$^+$ 431.1695, found 431.1688.

*3.2.4.1. (S)-3-((R)-2-((S)-Azido(4-methoxyphenyl) methyl)butanoyl)-4-benzyloxazolidin-2-one (**6d**).* mp 123–125 °C; R_f (20% EtOAc/Hexane) 0.47; $[\alpha]_D^{30}$ −104.3 (c 1, CHCl$_3$); IR (neat) ν_{max} 2966, 2913, 2099, 2835, 1778, 1694, 1513, 1388, 1250, 1210, 1108, 1031, 831, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.27 (m, 7H, Ar–H), 6.94 (d, 2H, J=8.6 Hz, Ar–H), 4.82–4.74 (m, 1H, (PhCH$_2$)CH–), 4.71 (d, 1H, J=10.8 Hz, ArCHN$_3$), 4.46 (ddd, 1H, J=4.0, 10.4, 10.4 Hz, CH(CH$_2$CH$_3$)), 4.20 (d, 2H, J=4.8 Hz, (PhCH$_2$)CH(CH_2O–)), 3.83 (s, 3H, 4-OCH_3–C$_6$H$_4$–), 3.43 (dd, 1H, J=3.2, 13.6 Hz, (PhCH_aH$_b$)CH), 2.82 (dd, 1H, J=10.0, 13.6 Hz, (PhCH$_a$H$_b$)CH), 1.59–1.47 (m, 1H, CH_aH$_b$CH$_3$), 1.34–1.24 (m, 1H, CH$_a$H$_b$CH$_3$), 0.78 (t, 3H, J=7.6 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.8, 160.0, 153.3, 135.4, 129.5 (2C), 129.3 (2C), 129.0 (2C), 128.7, 127.3, 114.3 (2C), 68.3, 65.8, 55.6, 55.3, 48.7, 37.7, 23.1, 10.8; HRMS (ESI) exact mass calcd for $C_{22}H_{24}N_4O_4Na$ [M+Na]$^+$ 431.1695, found 431.1702.

*3.2.5. (S)-3-((R)-2-((S)-Azido(furan-2-yl)methyl)pentanoyl)-4-benzyloxazolidin-2-one (**5e**).* The alcohol **3e** (300 mg, 0.84 mmol) in dry dichloromethane (3 mL) was reacted with mesyl chloride (0.1 mL, 1.26 mmol) in presence of triethylamine (0.23 mL, 1.68 mmol) according to the procedure discussed above to get the mesylate **4e** as a yellow viscous liquid (360 mg, 98%). This mesylate (350 mg, 0.805 mmol) in DMF (3.5 mL) was subjected to azidation using NaN$_3$ (104.6 mg, 1.609 mmol) and the product mixture was chromatographed on silica gel using 5% EtOAc/hexanes system to afford **5e** as a colourless viscous liquid (combined weight=252 mg, 82%; crude ^{1}H NMR showed the presence of diastereomers **5e** and **6e** in 67:33 ratio); R_f (20% EtOAc/Hexane) 0.47; $[\alpha]_D^{34}$ +130.8 (c 0.75, CHCl$_3$); IR (neat) 3015, 2961, 2913, 2871, 2099, 1775, 1692, 1384, 1203, 1102, 1010, 743, 701, 633 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, 1H, J=2.0 Hz, furan-H), 7.33–7.22 (m, 3H, Ph–H), 7.10 (d, 2H, J=6.8 Hz, Ph–H), 6.44 (d, 1H, J=3.2 Hz, furan-H), 6.36 (dd, 1H, J=2.0, 3.6 Hz, furan-H), 4.78 (d, 1H, J=10.0 Hz, CHN$_3$), 4.67–4.56 (m, 2H, (PhCH$_2$)CH(CH$_2$O–) and CH(C$_3$H$_7$)), 4.13 (dd, 1H, J=8.8, 8.8 Hz, (PhCH$_2$)CH(CH_aH$_b$O–)), 4.08 (dd, 1H, J=3.2, 9.2 Hz, (PhCH$_2$)CH(CH$_a$H$_b$O–)), 2.92 (dd, 1H, J=3.2, 13.6 Hz, (PhCH_aH$_b$)CH), 2.33 (dd, 1H, J=10.4, 13.6 Hz, (PhCH$_a$H$_b$)CH), 1.92–1.78 (m, 2H, CH_2CH$_2$CH$_3$), 1.41–1.30 (m, 2H, CH$_2$CH_2CH$_3$), 0.94 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.2, 152.8, 150.8, 143.0, 135.1, 129.3 (2C), 128.9 (2C), 127.3, 110.5, 108.9, 65.8, 60.1, 55.3, 45.5, 37.4, 32.2, 19.7, 14.2; HRMS (ESI) exact mass calcd for $C_{20}H_{22}N_4O_4Na$ [M+Na]$^+$ 405.1539, found 405.1542.

*3.2.5.1. (S)-3-((R)-2-((S)-Azido(furan-2-yl)methyl)pentanoyl)-4-benzyloxazolidin-2-one (**6e**).* 90:10 mixture of **6e** and **5e** as per ^{1}H NMR; R_f (20% EtOAc/Hexane) 0.47; $[\alpha]_D^{34}$ −62.7 (c 0.75, CHCl$_3$); IR (neat) 2954, 2927, 2865, 2100, 1779, 1694, 1388, 1207, 1105, 1012, 748 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, 1H, J=1.2 Hz, furan-H), 7.40–7.33 (m, 2H, Ph–H), 7.33–7.27 (m, 3H, Ph–H), 6.46 (d, 1H, J=3.2 Hz, furan-H), 6.41 (dd, 1H, J=1.6, 2.8 Hz, furan-H), 4.84 (d, 1H, J=10.4 Hz, CHN$_3$), 4.81–4.72 (m, 1H, (PhCH$_2$)CH–), 4.68 (ddd, 1H, J=3.6, 9.6, 9.6 Hz, CH(C$_3$H$_7$)), 4.25–4.18 (m, 2H, (PhCH$_2$)CH(CH_2O–)), 3.38 (dd, 1H, J=3.2, 13.6 Hz, (PhCH_aH$_b$)CH), 2.81 (dd, 1H, J=9.6, 13.6 Hz, (PhCH$_a$H$_b$)CH), 1.60–1.49 (m, 1H, CH_aH$_b$CH$_2$CH$_3$), 1.35–1.16 (m, 3H, CH$_a$H$_b$CH$_2$CH$_3$ and CH$_2$CH_2CH$_3$), 0.81 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.2, 153.0, 149.5, 143.5, 135.3, 129.5 (2C), 129.0 (2C), 127.3, 110.4, 110.1, 65.8, 61.2, 55.5, 45.5, 37.6, 32.2, 19.7, 14.1; HRMS (ESI) exact mass calcd for $C_{20}H_{22}N_4O_4Na$ [M+Na]$^+$ 405.1539, found 405.1538.

*3.2.6. (S)-3-((R)-2-((R)-Azido(4-nitrophenyl)methyl) pentanoyl)-4-benzyloxazolidin-2-one (**5f**).* The alcohol **3f** (1 g, 2.43 mmol) in dry dichloromethane (10 mL) was reacted with mesyl chloride (0.28 mL, 3.65 mmol) in presence of triethylamine (0.67 mL, 4.86 mmol) according to the procedure discussed above to get the mesylate **4f** as a yellow solid (1.18 g, 99%). The mesylate (280 mg, 0.571 mmol) in DMSO (5.6 mL) was subjected to azidation using NaN$_3$ (74.3 mg, 1.143 mmol) for 16 h and the product mixture was chromatographed on silica gel using 5–10% EtOAc/hexanes system to afford **5f** as a colourless viscous liquid (120 mg, 75% yield based on 64% consumption of the starting material). Crude ^{1}H NMR showed the presence of diastereomers **5f** and **6f** in 95:5 ratio. However, **6f** could not be isolated in pure form; R_f (20% EtOAc/Hexane) 0.33; $[\alpha]_D^{34}$ +94.5 (c 1, CHCl$_3$); IR (neat) 3028, 2961, 2924, 2864, 2102, 1775, 1692, 1605, 1523, 1386, 1350, 1255, 1209, 1103, 856, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25 (d, 2H, J=8.8 Hz, Ar–H), 7.65 (d, 2H, J=8.8 Hz, Ar–H), 7.30–7.22 (m, 3H, Ph–H), 6.99 (d, 2H, J=7.6 Hz, Ph–H), 4.97 (d, 1H, J=8.4 Hz, CHN$_3$), 4.59 (dddd, 1H, J=3.2, 3.2, 8.0, 10.8 Hz, (PhCH$_2$)CH(CH$_2$O–)), 4.39 (ddd, 1H, J=3.6, 8.4, 9.6 Hz, CH(C$_3$H$_7$)), 4.14 (dd, 1H, J=8.8, 8.8 Hz, (PhCH$_2$)CH(CH_aH$_b$O–)), 4.07 (dd, 1H, J=2.4, 8.8 Hz, (PhCH$_2$)CH(CH$_a$H$_b$O–)), 2.87 (dd, 1H, J=3.2, 13.2 Hz, (PhCH_aH$_b$)CH), 2.23 (dd, 1H, J=10.0, 13.6 Hz, (PhCH$_a$H$_b$)CH), 1.96–1.86 (m, 1H, CH_aH$_b$CH$_2$CH$_3$), 1.75–1.66 (m, 1H, CH$_a$H$_b$CH$_2$CH$_3$), 1.35–1.20 (m, 2H, CH$_2$CH_2CH$_3$), 0.91 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.7, 152.9, 147.9, 144.9, 134.6, 129.1 (2C), 129.0 (2C), 128.8 (2C), 127.5, 123.9 (2C), 66.6, 65.9, 55.2, 48.3, 37.3, 31.1, 20.0, 14.1; HRMS (ESI) exact mass calcd for $C_{22}H_{23}N_5O_5Na$ [M+Na]$^+$ 460.1597, found 460.1594.

*3.2.7. (S)-3-((R)-2-((R)-Azido(4-nitrophenyl)methyl)butanoyl)-4-benzyloxazolidin-2-one (**5g**).* The alcohol **3g** (1 g, 2.51 mmol) in dry dichloromethane (10 mL) was reacted with mesyl chloride (0.29 mL, 3.77 mmol) in presence of triethylamine (0.69 mL, 5.02 mmol) according to the procedure discussed above to get the mesylate **4g** as a yellow solid (1.15 g, 96%). The mesylate (250 mg, 0.525 mmol) in DMSO (5 mL) was subjected to azidation using NaN$_3$ (68 mg, 1.049 mmol) for 12 h and the product mixture was chromatographed on silica gel using 5–10% EtOAc/hexanes system to afford **5g** as a white crystalline solid (138 mg, 84% yield based on 74% consumption of the starting material). Crude ^{1}H NMR showed the presence of diastereomers **5g** and **6g** in 97:3 ratio. However, **6g** could not be isolated in pure form; mp 85–87 °C; R_f (20% EtOAc/Hexane) 0.30; $[\alpha]_D^{30}$ +132.3 (c 1, CHCl$_3$); IR (neat) 3036, 2971,2925, 2868, 2103, 1776, 1692, 1523, 1386, 1347, 1209, 1105, 852, 746, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25 (d, 2H, J=8.8 Hz, Ar–H), 7.65 (d, 2H, J=8.8 Hz, Ar–H), 7.32–7.22 (m, 3H, Ph–H), 6.98 (d, 2H, J=7.2 Hz, Ph–H), 4.99 (d, 1H, J=8.4 Hz, CHN$_3$), 4.60 (dddd, 1H, J=2.8, 2.8, 6.0, 10.8 Hz, (PhCH$_2$)CH(CH$_2$O–)), 4.35 (ddd, 1H, J=3.6, 9.2, 9.2 Hz, CH(C$_2$H$_5$)), 4.14 (dd, 1H, J=8.8, 8.8 Hz, (PhCH$_2$)CHCH_aH$_b$O–), 4.07 (dd, 1H, J=2.4, 8.8 Hz, (PhCH$_2$)CHCH$_a$H$_b$O–), 2.87 (dd, 1H, J=3.2, 13.2 Hz, (PhCH_aH$_b$)CH), 2.26 (dd, 1H, J=9.6, 13.2 Hz, (PhCH$_a$H$_b$)CH), 2.02–1.89 (m, 1H, CH$_a$H$_b$CH$_3$), 1.88 1.76 (m, 1H, CH$_a$H$_b$CH$_3$), 0.93 (t, 3H, J=7.6 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.5, 153.0, 147.9, 145.0, 134.6, 129.1 (2C), 128.9 (2C), 128.8 (2C), 127.5, 123.9 (2C), 66.2, 65.9, 55.1, 49.6, 37.3, 22.1, 10.9; HRMS (ESI) exact mass calcd for $C_{21}H_{21}N_5O_5Na$ [M+Na]$^+$ 446.1440, found 446.1438.

3.3. Conversion of azides to Boc-protected β-amino acid precursors

*3.3.1. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-phenylpentylcarbamate (**7a**).* To a solution of **5a** (40 mg, 0.102 mmol) and Boc$_2$O (33.4 mg, 0.153 mmol) in EtOAc

(0.5 mL) at room temperature was added 10% Pd/C (4 mg) and the solution was stirred under an atmosphere of hydrogen for 8 h. After the completion of the reaction, the catalyst was removed by filtration through Celite, the filtrate evaporated under reduced pressure and the resulting residue was purified by chromatography on silica gel column using 15% EtOAc/hexanes solvent system to get **7a** (43 mg, 91%) as a white crystalline solid. [Found: C, 69.48; H, 7.56; N, 5.92. $C_{27}H_{34}N_2O_5$ requires C, 69.50; H, 7.35; N, 6.00%.] mp 123–124 °C; R_f (20% EtOAc/Hexane) 0.37; $[\alpha]_D^{30}$ +29.0 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3371, 2961, 2930, 2872, 1773, 1693, 1496, 1384, 1350, 1248, 1165, 1099, 1015, 735, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 2H, *J*=6.8 Hz, Ph–*H*), 7.37–7.21 (m, 6H, Ph–*H*), 7.10 (d, 2H, *J*=6.4 Hz, Ph–*H*), 5.26 (br t, 1H, PhC*H*NHBoc), 5.07 (d, 1H, *J*=9.2 Hz, PhCHN*H*Boc), 4.60 (br t, 1H, $(PhCH_2)CH(CH_2O-)$), 4.34 (br t, 1H, $CH(CH_2CH_2CH_3)$), 4.14–4.03 (m, 2H, $(PhCH_2)CH(CH_2O-)$), 2.96 (d, 1H, *J*=13.2 Hz, $PhCH_aH_bCH$), 2.25 (t, 1H, *J*=11.6 Hz, $PhCH_aH_bCH$), 1.92–1.81 (m, 1H, $CH_aH_bCH_2CH_3$), 1.39 (s, 9H, $NH(C{=}O)OC(CH_3)_3$), 1.40–1.10 (m, 3H, $CH_aH_bCH_2CH_3$ and $CH_2CH_2CH_3$), 0.85 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.1, 153.2, 140.5, 135.6, 129.3 (2C), 128.9 (4C), 128.5, 127.4, 127.2, 126.8, 79.7, 66.0, 55.7, 55.3, 48.9, 37.2, 29.0, 28.3 (3C), 20.8, 14.1; HRMS (ESI) exact mass calcd for $C_{27}H_{34}N_2O_5Na$ $[M+Na]^+$ 489.2365, found 489.2359.

*3.3.2. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-phenylbutylcarbamate (**7b**).* The above one-pot reduction–Boc-protection procedure was repeated with a solution of **5b** (100 mg, 0.265 mmol) and Boc_2O (0.09 mL, 0.397 mmol) in EtOAc (1 mL) to get **7b** (110 mg, 92%) as a white crystalline solid. [Found: C, 69.05; H, 7.35; N, 6.43. $C_{26}H_{32}N_2O_5$ requires C, 69.00; H, 7.13; N, 6.19%.] mp 145–147 °C; R_f (20% EtOAc/Hexane) 0.33; $[\alpha]_D^{30}$ +43.2 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3382, 3019, 2971, 2925, 2856, 1777, 1698, 1499, 1386, 1215, 1169, 1103, 1014, 760. 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H, *J*=7.2 Hz, Ph–*H*), 7.36–7.20 (m, 6H, Ph–*H*), 7.09 (d, 2H, *J*=6.0 Hz, Ph–*H*), 5.25 (br t, 1H, *J*=6.8 Hz, PhC*H*NHBoc), 5.06 (d, 1H, *J*=9.2 Hz, PhCHN*H*Boc), 4.61 (br t, 1H, $(PhCH_2)CH(CH_2O-)$), 4.29 (br t, 1H, $CH(CH_2CH_3)$), 4.13–4.03 (m, 2H, $(PhCH_2)CH(CH_2O-)$), 2.93 (d, 1H, *J*=12.8 Hz, $PhCH_aH_bCH$), 2.24 (t, 1H, *J*=12.0 Hz, $PhCH_aH_bCH$), 1.93–1.83 (m, 1H, $CH_aH_bCH_3$), 1.60–1.42 (br s, 1H, $CH_aH_bCH_3$), 1.39 (s, 9H, $NH(C{=}O)OC(CH_3)_3$), 0.87 (t, 3H, *J*=6.8 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 155.1, 153.2, 140.5, 135.5, 129.2 (3C), 128.9 (3C), 128.5, 127.4, 127.1, 126.9, 79.7, 65.9, 55.6, 55.2, 50.5, 37.1, 28.3 (3C), 20.3, 11.8; HRMS (ESI) exact mass calcd for $C_{26}H_{32}N_2O_5Na$ $[M+Na]^+$ 475.2209, found 475.2201.

*3.3.3. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(4-methoxy phenyl)pentylcarbamate (**7c**).* The reduction–Boc-protection procedure was repeated with a solution of **5c** (200 mg, 0.47 mmol) and Boc_2O (0.16 mL, 0.71 mmol) in EtOAc (2 mL) to get **7c** (220 mg, 94%) as a white crystalline solid. [Found: C, 68.08; H, 7.45; N, 5.57. $C_{28}H_{36}N_2O_6$ requires C, 67.72; H, 7.31; N, 5.64%.] mp 68–70 °C; R_f (20% EtOAc/Hexane) 0.27; $[\alpha]_D^{30}$ +35.6 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3375, 2962, 2872, 1774, 1697, 1512, 1386, 1365, 1246, 1210, 1167, 1099, 1031, 833, 762, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H, Ar–*H*), 7.09 (d, 2H, *J*=6.4 Hz, Ar–*H*), 6.86 (d, 2H, *J*=8.4 Hz, Ar–*H*), 5.19 (br t, 1H, 4-$OMeC_6H_4CH$NHBoc), 5.01 (d, 1H, *J*=8.4 Hz, 4-$OMeC_6H_4CHN$*H*Boc), 4.60 (br t, 1H, $(PhCH_2)CH(CH_2O)$), 4.31 (br t, 1H, $CH(CH_2CH_2CH_3)$), 4.13–4.05 (m, 2H, $(PhCH_2)CH(CH_2O-)$), 3.76 (s, 3H, 4-OCH_3–C_6H_4–), 2.98 (d, 1H, *J*=12.8 Hz, $PhCH_aH_bCH$), 2.27 (t, 1H, *J*=10.8 Hz, $PhCH_aH_bCH$), 1.90–1.80 (m, 1H, $CH_aH_bCH_2CH_3$), 1.39 (s, 9H, $NH(C{=}O)OC(CH_3)_3$), 1.50–1.10 (m, 3H, $CH_aH_bCH_2CH_3$ and $CH_2CH_2CH_3$), 0.86 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 158.9, 155.1, 153.2, 135.5, 132.7, 129.2 (2C), 128.9 (3C), 127.9, 127.1, 113.8 (2C), 79.6, 65.9, 55.2, 55.1 (2C), 48.8, 37.2, 29.1, 28.3 (3C), 20.7, 14.1; HRMS (ESI) exact mass calcd for $C_{28}H_{36}N_2O_6Na$ $[M+Na]^+$ 519.2471, found 519.2465.

*3.3.4. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(4-methoxyphenyl) butylcarbamate (**7d**).* The reduction–Boc-protection procedure was repeated with **5d** (25 mg, 0.0613 mmol) and Boc_2O (20 mg, 0.0919 mmol) in EtOAc (0.5 mL) to get **7d** (28 mg, 95%) as a white crystalline solid. [Found: C, 67.17; H, 7.31; N, 5.99. $C_{27}H_{34}N_2O_6$ requires C, 67.20; H, 7.10; N, 5.81%.] mp 137–139 °C; R_f (20% EtOAc/Hexane) 0.23; $[\alpha]_D^{30}$ +35.4 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3371, 2974, 2932, 2875, 2836, 1776, 1698, 1513, 1388, 1367, 1246, 1169, 1105, 1034, 832, 763, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H, Ar–*H*), 7.08 (d, 2H, *J*=6.0 Hz, Ar–*H*), 6.86 (d, 2H, *J*=8.4 Hz, Ar–*H*), 5.19 (br t, 1H, 4-$OMeC_6H_4CH$NHBoc), 5.00 (d, 1H, *J*=8.4 Hz, 4-$OMeC_6H_4CHN$*H*Boc), 4.61 (br t, 1H, $(PhCH_2)CH(CH_2O-)$), 4.26 (br t, 1H, $CH(CH_2CH_3)$), 4.14–4.00 (m, 2H, $(PhCH_2)CH(CH_2O-)$), 3.76 (s, 3H, 4-OCH_3–C_6H_4), 2.97 (d, 1H, *J*=12.8 Hz, $PhCH_aH_bCH$), 2.26 (t, 1H, *J*=11.2 Hz, $PhCH_aH_bCH$), 1.91–1.80 (m, 1H, $CH_aH_bCH_3$), 1.54 (br s, 1H, merged with water peak, $CH_aH_bCH_3$), 1.39 (s, 9H, $NH(C{=}O)OC(CH_3)_3$), 0.87 (t, 3H, *J*=6.8 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 158.9, 155.1, 153.2, 135.5, 132.8, 129.2 (2C), 128.9 (3C), 128.0, 127.1, 113.9 (2C), 79.6, 65.9, 55.3, 55.2 (2C), 50.6, 37.2, 28.3 (3C), 20.4, 11.8; HRMS (ESI) exact mass calcd for $C_{27}H_{34}N_2O_6Na$ $[M+Na]^+$ 505.2315, found 505.2305.

*3.3.5. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(furan-2-yl) pentylcarbamate (**7e**).* The reduction–Boc-protection procedure was repeated with **5e** (100 mg, 0.262 mmol) and Boc_2O (0.09 mL, 0.392 mmol) in EtOAc (1 mL) to get **7e** (110 mg, 93%) as a colourless viscous liquid; R_f (20% EtOAc/Hexane) 0.40; $[\alpha]_D^{34}$ +39.1 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3363, 3028, 2967, 2929, 2872, 1777, 1701, 1498, 1387, 1210, 1169, 1101, 1013, 742, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (br s, 1H, furan-*H*), 7.34–7.28 (m, 2H, Ph–*H*), 7.27–7.22 (m, 1H), 7.18 (d, 2H, *J*=7.2 Hz, Ph–*H*), 6.30 (dd, 1H, *J*=3.2, 2.0 Hz, furan-*H*), 6.25 (d, 1H, *J*=3.2 Hz, furan-*H*), 5.38 (dd, 1H, *J*=9.6, 7.2 Hz, C*H*NHBoc), 5.06 (d, 1H, *J*=10.0 Hz, CHN*H*Boc), 4.62 (dddd, 1H, *J*=3.2, 3.2, 6.8, 13.6 Hz, $(PhCH_2)CH(CH_2O-)$), 4.34 (br s, 1H, $CH(C_3H_7)$), 4.16–4.07 (m, 2H, $(PhCH_2)CH(CH_2O-)$), 3.23 (d, 1H, *J*=12.8 Hz, $(PhCH_aH_b)CH$), 2.50 (t, 1H, *J*=11.6 Hz, $(PhCH_aH_b)CH$), 1.93–1.85 (m, 1H, $CH(CH_aH_bCH_2CH_3)$), 1.42 (s, 9H, $NH(C{=}O)OC(CH_3)_3$), 1.40–1.15 (m, 3H, $CH(CH_aH_bCH_2CH_3)$ and $CH(CH_2CH_2CH_3)$), 0.88 (t, 3H, *J*=7.2 Hz, $CH(CH_2CH_2CH_3)$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 155.0, 153.2, 141.9 (2C), 135.8, 129.3 (2C), 128.9 (2C), 127.1, 110.3, 106.6, 79.8, 66.0, 55.5, 50.1, 47.4, 37.4, 29.3, 28.2 (3C), 20.4, 14.1; HRMS (ESI) exact mass calcd for $C_{25}H_{33}N_2O_6$ $[M+H]^+$ 457.2339, found 457.2336.

*3.3.6. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(4-nitrophenyl)pentylcarbamate (**7f**).* To a stirred mixture of **5f** (65 mg, 0.149 mmol) in dry THF was added triphenylphosphine (46.8 mg, 0.179 mmol) and water (26.8 mg, 1.49 mmol). The reaction mixture was stirred at room temperature for 30 min, then heated to 60 °C and continued stirring at the same temperature for 10 h. The solvent was removed under reduced pressure, EtOAc (1 mL) and Boc_2o (0.05 mL, 0.223 mmol) were added to the residue and the mixture was stirred for 6 h at room temperature. Excess solvent was evaporated and the crude product was purified by column chromatography using 10% EtOAc/Hexanes as mobile phase to give **7f** as a white crystalline solid (31 mg, 41%); mp 155–157 °C; R_f (20% EtOAc/Hexane) 0.40; $[\alpha]_D^{30}$ +2.6 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3365, 3032, 2966, 2930, 2871, 1774, 1697, 1521, 1387, 1348, 1251, 1166, 1104, 1017, 858, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J*=8.4 Hz, Ar–*H*), 7.64 (d, 2H, *J*=8.4 Hz, Ar–*H*), 7.21–7.35 (m, 3H, Ph–*H*), 7.14 (d, 2H, *J*=6.4 Hz, Ph–*H*), 5.42 (br s, 1H, C*H*NHBoc), 5.21 (d, 1H, *J*=8.4 Hz, CHN*H*Boc), 4.69 (br s, 1H, $(PhCH_2)CH(CH_2O-)$), 4.31–4.13 (m, 3H, $(PhCH_2)CH(CH_2O-)$ and $CH(C_3H_7)$), 3.15 (d, 1H, *J*=12.4 Hz, $(PhCH_aH_b)CH$), 2.55 (t, 1H, *J*=10.8 Hz, $(PhCH_aH_b)CH$), 1.87

(ddd, 1H, J=4.4, 12.4, 12.4 Hz, CH(CH_aH$_b$CH$_2$CH$_3$)), 1.39 (s, 9H, NH(C=O)OC(CH_3)$_3$), 1.40–1.00 (m, 3H, CH(CH$_a$$H_bCH_2CH_3$) and CH(CH$_2CH_2CH_3$)), 0.82 (t, 3H, J=6.8 Hz, CH(CH$_2$CH$_2$CH_3)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.6, 155.0, 153.3, 148.0, 147.2, 135.1, 129.2 (2C), 129.0 (2C), 127.6 (2C), 127.4, 123.7 (2C), 80.3, 66.3, 55.4, 54.9, 48.4, 37.4, 28.2 (3C), 27.4, 20.8, 13.9; HRMS (ESI) exact mass calcd for $C_{27}H_{33}N_3O_7Na$ [M+Na]$^+$ 534.2216, found 534.2212.

*3.3.7. tert-Butyl(1R,2R)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(4-nitrophenyl)butylcarbamate (**7g**).* The reduction–Boc-protection procedure for converting **5f** to **7f** was repeated with **5g** (50 mg, 0.118 mmol) to get **7g** as a white crystalline solid (28 mg, 47%); mp 139–141 °C; R_f (20% EtOAc/Hexane) 0.25; $[\alpha]_D^{30}$ +4.6 (c 1, CHCl$_3$); IR (neat) ν_{max} 3363, 3032, 2974, 2930, 2871, 1774, 1697, 1521, 1387, 1348, 1214, 1166, 1109, 1014, 856, 701 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21 (d, 2H, J=8.8 Hz, Ar–H), 7.63 (d, 2H, J=8.4 Hz, Ar–H), 7.34–7.24 (m, 3H, Ph–H), 7.13 (d, 2H, J=6.0 Hz, Ph–H), 5.42 (br s, 1H, CHNHBoc), 5.21 (d, 1H, J=8.8 Hz, CHNHBoc), 4.70 (br s, 1H, (PhCH$_2$)CH(CH$_2$O–)), 4.30–4.10 (m, 3H, (PhCH$_2$)CH(CH_2O–)) and CH(C$_2$H$_5$)), 3.13 (d, 1H, J=12.8 Hz, (PhCH_aH$_b$)CH), 2.54 (t, 1H, J=10.4 Hz, (PhCH$_a$$H_b$)CH), 1.91–1.84 (m, 1H, CH(CH_aH$_b$CH$_3$), 1.39 (s, 10H, NH(C=O)OC(CH_3)$_3$ and CH(CH_aH$_b$CH$_3$)), 0.84 (t, 3H, J=7.2 Hz, CH(CH$_2$CH_3)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.4, 155.0, 153.3, 148.1, 147.2, 135.0, 129.2 (3C), 129.0 (2C), 127.6, 127.4, 123.7 (2C), 80.3, 66.2, 55.3, 54.8, 50.1, 37.4, 28.2 (3C), 18.9, 11.9; HRMS (ESI) exact mass calcd for $C_{26}H_{31}N_3O_7Na$ [M+Na]$^+$ 520.2060, found 520.2056.

*3.3.8. tert-Butyl (1R,2R)-1-(4-aminophenyl)-2-((S)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)pentylcarbamate (**7h**).* The reduction–Boc-protection procedure was repeated with a solution of **5f** (25 mg, 0.057 mmol), 10% Pd/C (5 mg) and Boc$_2$O (12.5 mg, 0.057 mmol) in EtOAc (1 mL) to get 7H (23 mg, 84%) as a brown viscous liquid; R_f (40% EtOAc/Hexane) 0.37; $[\alpha]_D^{30}$ +31.7 (c 1, CHCl$_3$); IR (neat) ν_{max} 3368, 2966, 2929, 2870, 1773, 1697, 1624, 1516, 1386, 1250, 1212, 1168, 1101, 1016, 833, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32–7.21 (m, 3H, Ar–H), 7.17 (d, 2H, J=7.6 Hz, Ar–H), 7.09 (d, 2H, J=6.4 Hz, Ar–H), 6.62 (d, 2H, J=8.4 Hz, Ar–H), 5.11 (br s, 1H, ArCHNHBoc), 4.97 (br s, 1H, ArCHNHBoc), 4.62–4.56 (m, 1H, (PhCH$_2$)CH), 4.30 (br s, 1H, CH(CH$_2$CH$_2$CH$_3$)), 4.15–4.02 (m, 2H, (PhCH$_2$)CH(CH_2O–)), 3.62 (br s, 2H, Ar–NH_2), 2.99 (d, 1H, J=12.4 Hz, (PhCH_aH$_b$)CH), 2.26 (br s, 1H, (PhCH$_a$$H_b$)CH), 1.89–1.79 (m, 1H, CH(CH_aH$_b$CH$_2$CH$_3$)), 1.50–1.34 (m, 1H, CH(CH$_a$$H_bCH_2CH_3$)), 1.40 (s, 9H, NH(C=O)OC(CH_3)$_3$), 1.33–1.19 (m, 2H, CH$_2$CH_2CH$_3$) 0.86 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.8, 155.2, 153.2, 145.7, 135.8, 130.5, 129.3 (2C), 128.9 (2C), 127.9 (2C), 127.1, 115.0 (2C), 79.5, 65.9, 55.4, 55.2, 49.0, 37.2, 29.4, 28.3 (3C), 20.8, 14.1; HRMS (ESI) exact mass calcd for $C_{27}H_{36}N_3O_5$ [M+H]$^+$ 482.2655, found 482.2659.

*3.3.9. tert-Butyl(1R,2R)-1-(4-aminophenyl)-2-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl) butylcarbamate (**7i**).* The reduction–Boc-protection procedure was repeated with a solution of **5g** (25 mg, 0.059 mmol), 10% Pd/C (5 mg) and Boc$_2$O (13.6 mg, 0.059 mmol) in EtOAc (1 mL) to get **7i** (22 mg, 80%) as a brown viscous liquid; R_f (40% EtOAc/Hexane) 0.33; $[\alpha]_D^{34}$ +35.1 (c 1, CHCl$_3$); IR (neat) ν_{max} 3364, 2969, 2925, 2857, 1774, 1698, 1622, 1512, 1382, 1212, 1170, 1103, 1014, 830, 753, 704 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.20 (m, 3H, Ar–H), 7.17 (d, 2H, J=7.6 Hz, Ar–H), 7.10 (d, 2H, J=6.4 Hz, Ar–H), 6.63 (d, 2H, J=8.4 Hz, Ar–H), 5.12 (t, 1H, J=6.8 Hz, ArCHNHBoc), 4.98 (d, 1H, J=9.2 Hz, ArCHNHBoc), 4.61 (br s, 1H, (PhCH$_2$)CH), 4.24 (br s, 1H, CH(CH$_2$CH$_3$)), 4.12–4.03 (m, 2H, (PhCH$_2$)CH(CH_2O–)), 3.66 (br s, 2H, Ar–NH_2), 2.97 (d, 1H, J=13.2 Hz, (PhCH_aH$_b$)CH), 2.26 (t, 1H, J=11.2 Hz, (PhCH$_a$$H_b$)CH), 1.90–1.80 (m, 1H, CH(CH_aH$_b$CH$_3$)), 1.61 (br s, 1H, CH$_a$$H_bCH_3$), 1.39 (s, 9H, NH(C=O)OC(CH_3)$_3$), 0.87 (t, 3H, J=6.8 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.6, 155.1, 153.2, 145.7, 135.7, 130.5, 129.3 (2C), 128.9 (2C), 127.9 (2C), 127.1, 115.0 (2C), 79.5, 65.9, 55.3, 55.2, 50.6, 37.1, 28.3 (3C), 20.6, 11.8; HRMS (ESI) exact mass calcd for $C_{26}H_{34}N_3O_5$ [M+H]$^+$ 468.2498, found 468.2496.

3.4. Regioselective hydrolysis of oxazolidinone ring

*3.4.1. (R)-2-((R)-(tert-Butoxycarbonylamino)(4-methoxyphenyl) methyl)pentanoic acid (**8**).* To a solution of **7c** (250 mg, 0.50 mmol) in 3:1 THF–H$_2$O (10 mL) at 0 °C was added 30% H$_2$O$_2$ (0.16 mL, 5 mmol), followed by 2.0 equiv of LiOH.H$_2$O (42.2 mg, 1.00 mmol). The mixture was stirred for 1 h, allowed to warm to room temperature and continued stirring at that temperature for 5 h. After completion of the reaction, the excess peroxide was quenched at 0 °C with 1 mL of 1.5 N aq Na$_2$SO$_3$. The solvents were removed under reduced pressure, the residue extracted with CH$_2$Cl$_2$ to remove the oxazolidinone chiral auxiliary and the aqueous layer was acidified using solid KHSO$_4$ (pH 1–2). This was extracted with EtOAc (3 × 10 mL), dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure to get the carboxylic acid **8** as a white solid (157 mg, 93%). [Found: C, 64.27; H, 8.10; N, 4.36. $C_{18}H_{27}NO_5$ requires C, 64.07; H, 8.07; N, 4.15%.] R_f (40% EtOAc/Hexane) 0.37; $[\alpha]_D^{30}$ +41.4 (c 1, CHCl$_3$); IR (neat) ν_{max} 2960, 2933, 2873, 1704, 1613, 1513, 1393, 1367, 1247, 1165, 1035, 832, 733 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.19 (d, 2H, J=8.4 Hz, Ar–H), 6.75 (d, 2H, J=8.8 Hz, Ar–H), 5.15 (br s, 1H, NHBoc), 4.82 (br s, 1H, Ar–CHNHBoc), 3.71 (s, 3H, 4-OCH_3–C$_6$H$_4$), 2.70 (br s, 1H, CH(CH$_2$CH$_2$CH$_3$)COOH), 1.64–1.54 (m, 1H, CH_aH$_b$CH$_2$CH$_3$), 1.50–1.15 (m, 3H, CH$_a$$H_bCH_2CH_3$ and CH$_2$CH_2CH$_3$), 1.33 (s, 9H, NH(C=O)OC(CH_3)$_3$), 0.83 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3), carboxylic acid proton was not seen; ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.4, 158.9, 155.2, 132.1, 127.9 (2C), 113.8 (2C), 79.8, 55.3, 55.2, 51.2, 30.6, 28.3 (3C), 20.7, 13.9; HRMS (ESI) exact mass calcd for $C_{18}H_{27}NO_5Na$ [M+Na]$^+$ 360.1787, found 360.1787.

*3.4.2. tert-Butyl(1R,2R)-2-((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)-1-phenylbutylcarbamate (**9a**).* To a stirred solution of **7b** (50 mg, 0.11 mmol) in THF (2 mL) at 0 °C was added a solution of LiOH (9.28 mg, 0.22 mmol) in 0.5 mL of water. After allowing the mixture to warm to room temperature, the stirring was continued for another 10 h. The solution was then concentrated, the precipitated product was filtered, washed with water, followed by hexanes and dried under reduced pressure to get **9a** (38 mg, 81%) as a white amorphous solid; R_f (10% MeOH/CHCl$_3$) 0.57; $[\alpha]_D^{30}$ −0.78 (c 1, CH$_3$OH); IR (neat) ν_{max} 3363, 3328, 2962, 2950, 2932, 2864, 1681, 1639, 1520, 1289, 1168, 1070, 1040, 1014, 698, 643 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32–7.24 (m, 5H, Ph–H), 7.24–7.17 (m, 3H, Ph–H), 7.07 (d, 2H, J=6.4 Hz, Ph–H), 5.46 (d, 2H, J=7.2 Hz, CH(Bn)NH(C=O) and CHNHBoc), 4.82 (br s, 1H, PhCHNHBoc), 3.98 (br s, 1H, CH(CH$_2$OH)), 3.47 (br s, 2H, CH_2OH), 2.59 (br s, 2H, CH_2Ph), 2.40 (br s, 1H, CH(CH$_2$CH$_3$)), 2.33 (br s, 1H, CH$_2$OH), 1.63–1.50 (br s, 2H, CH_2CH$_3$), 1.41 (s, 9H, NH(C=O)OC(CH_3)$_3$), 0.84 (t, 3H, J=7.2 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$+CD$_3$OD) δ 172.9, 155.8, 143.0, 137.4, 128.3 (2C), 127.4 (2C), 127.3 (1C), 126.4 (3C), 125.3 (2C), 78.5, 61.2, 56.2, 54.4, 51.6, 35.6, 27.0 (3C), 21.8, 10.4; HRMS (ESI) exact mass calcd for $C_{25}H_{34}N_2O_4Na$ [M+Na]$^+$ 449.2416, found 449.2411.

*3.4.3. tert-Butyl(1R,2R)-2-((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)-1-(4-methoxyphenyl) pentylcarbamate (**9b**).* To a stirred solution of **7c** (100 mg, 0.20 mmol) in THF (4 mL) at 0 °C was added a solution of LiOH (16.9 mg, 0.40 mmol) in 1.5 mL of water. After allowing the mixture to warm to room temperature, the stirring was continued for another 10 h. The solution was then concentrated, the precipitated product was filtered, washed with water, followed by hexanes and dried under reduced pressure to get **9b** (83 mg, 87%) as a white amorphous solid. [Found: C, 69.09; H, 8.08; N, 6.02. $C_{27}H_{38}N_2O_5$ requires C, 68.91; H, 8.14; N, 5.95%.] R_f (10% MeOH/CHCl$_3$) 0.52; $[\alpha]_D^{30}$ +12.99 (c 1, CH$_3$OH); IR (neat) ν_{max} 3349, 3315, 2956, 2933, 1678, 1637, 1513, 1454, 1299, 1244, 1167, 1019, 830,

698, 644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 3H, Ar–*H*), 7.09 (d, 4H, *J*=8.0 Hz, Ar–*H*), 6.82 (d, 2H, *J*=8.4 Hz, Ar–*H*), 5.48 (br d, 1H, N*H*(C=O)CH(C_2H_5)), 5.41 (br s, 1H, C*H*NHBoc), 4.74 (br s, 1H, ArCHN*H*Boc), 3.99 (br s, 1H, C*H*(CH_2OH)), 3.77 (s, 3H, 4-OCH_3–C_6H_4), 3.51 (br s, 2H, CH_2OH), 2.78–2.53 (br d, 2H, CH_2Ph), 2.48 (br s, 2H, C*H*(CH_2CH_3) and CH_2OH), 1.41 (br s, 11H, NH(C=O)OC(CH_3)$_3$ and C$H_2CH_2CH_3$), 1.25–1.15 (m, 2H, $CH_2CH_2CH_3$), 0.83 (t, 3H, *J*=6.8 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 173.3, 158.6, 155.7, 137.8, 132.7, 128.9 (2C), 128.1 (2C), 127.8 (2C), 126.1, 113.4 (2C), 79.4, 62.5, 56.1, 54.9, 53.3, 52.2, 36.2, 30.9, 28.0 (3C), 20.3, 13.7; HRMS (ESI) exact mass calcd for $C_{27}H_{38}N_2O_5Na$ $[M+Na]^+$ 493.2678, found 493.2676.

3.5. Conversion of alcohols to aldehydes

*3.5.1. tert-Butyl(1R,2R)-2-((S)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-1-phenylbutylcarbamate (**10a**).* To a stirred solution of **9a** (25 mg, 0.0587 mmol) in DMSO (0.6 mL) was added 2-iodoxybenzoic acid (IBX, 19.7 mg, 0.070 mmol) at room temperature. After stirring for 8 h, the reaction mixture was admixed with water (25 mL) and EtOAc (25 ml). The precipitate formed was filtered off, the organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by chromatography on silica gel using 0.5% CH_3OH–$CHCl_3$ solvent system to get **10a** as a white solid (20 mg, 80%); R_f (5% MeOH/$CHCl_3$) 0.38; $[\alpha]_D^{30}$ −1.3 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3357, 2973, 2932, 2809, 1736, 1676, 1644, 1521, 1362, 1294, 1257, 1172, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H, C*H*O), 7.33–7.17 (m, 8H, Ph–*H*), 6.92 (br s, 2H, Ph–*H*), 5.86 (br s, 1H, N*H*CH(Bn)CHO), 5.26 (br s, 1H, Ar–C*H*NHBoc), 4.85 (br s, 1H, ArCHN*H*Boc), 4.57 (q, 1H, *J*=6.5 Hz, ($PhCH_2$)C*H*(CHO)), 2.96 (dd, 1H, *J*=5.8, 13.8 Hz, PhC$H_a$$H_b$), 2.78 (br s, 1H, PhC$H_a$$H_b$), 2.43 (br s, 1H, C*H*($CH_2CH_3$)), 1.62 (2H, C$H_2CH_3$, merged with H_2O peak), 1.40 (s, 9H, NH(C=O)OC(CH_3)$_3$), 0.87 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 172.5, 155.2, 135.5 (2C), 129.2 (2C), 128.8 (2C), 128.5 (2C), 127.6, 127.1, 126.9 (2C), 79.8, 59.4, 56.6, 55.2, 35.2, 28.3 (3C), 22.1, 12.0; HRMS (ESI) exact mass calcd for $C_{25}H_{33}N_2O_4$ $[M+H]^+$ 425.2440, found 425.2440.

*3.5.2. tert-Butyl(1R,2R)-1-(4-methoxyphenyl)-2-((S)-1-oxo-3-phenylpropan-2-ylcarbamoyl)pentylcarbamate (**10b**).* Oxidation of alcohol **9b** (40 mg, 0.085 mmol) using IBX (28 mg, 0.102 mmol) according to the above procedure gave **10b** (33 mg, 83%) as a white solid; R_f (10% MeOH/$CHCl_3$) 0.39; $[\alpha]_D^{30}$ +7.0 (*c* 1, CH_3OH); IR (neat) ν_{max} 3363, 3313, 2958, 2921, 2864, 1673, 1633, 1516, 1415, 1250, 1170, 1014, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H, C*H*O), 8.31 (d, 1H, *J*=7.2 Hz, N*H*CH(Bn)CHO), 7.29 (d, 1H, *J*=9.6 Hz, Ar–CHN*H*C=O), 7.22–7.10 (m, 5H, Ar–*H*), 6.97 (d, 2H, *J*=7.2 Hz, Ar–*H*), 6.78 (d, 2H, *J*=8.8 Hz, Ar–*H*), 4.75–4.50 (m, 1H, Ar–C*H*NHBoc), 3.91 (br s, 1H, ($PhCH_2$)C*H*(CHO)), 3.69 (s, 3H, 4-OCH_3–C_6H_4–), 2.90 (dd, 1H, *J*=4.8, 14.4 Hz, PhC$H_a$$H_b$), 2.65–2.50 (m, 2H, PhC$H_a$$H_b$ and C*H*(C_3H_7)), 1.60–1.40 (m, 2H, C$H_2CH_2CH_3$), 1.35 (s, 9H, NH(C=O)OC(CH_3)$_3$), 1.30–1.10 (m, 2H, $CH_2CH_2CH_3$), 0.81 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.1, 173.2, 158.0, 155.1, 137.7, 134.4, 128.8 (2C), 128.5 (2C), 128.0 (2C), 126.0, 113.0 (2C), 77.6, 59.4, 55.5, 54.9, 51.3, 33.2, 31.5, 28.2 (3C), 19.8, 14.1; HRMS (ESI) exact mass calcd for $C_{27}H_{37}N_2O_5$ $[M+H]^+$ 469.2702, found 469.2702.

3.6. Preparation of α,β^{2,3}-hybrid peptide 11 and *trans*-β^{2,3}-dipeptide 13

*3.6.1. (S)-Methyl-2-((R)-2-((R)-(tert-butoxycarbonyl amino)(4-methoxyphenyl)methyl)pentanamido)propanoate (**11**).* To a mixture of **8** (15 mg, 0.045 mmol), alanine methylester hydrochloride (6.8 mg, 0.049 mmol) and 1-hydroxybenzotriazole (HOBT, 8.65 mg, 0.064 mmol) in dry CH_2Cl_2 at 0 °C was added *i*-Pr_2NEt (0.02 ml, 0.111 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI, 12.3 mg, 0.064 mmol). The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 24 h. It was then diluted with CH_2Cl_2, washed with 5% HCl (10 mL) followed by saturated $NaHCO_3$ solution (10 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, solvent evaporated under reduced pressure and the resulting residue was purified by chromatography on silica gel column using 0.5% MeOH-$CHCl_3$ solvent system to get **11** (15 mg, 80%) as a white solid; R_f (5% MeOH/$CHCl_3$) 0.58; $[\alpha]_D^{30}$ +5.4 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3350, 2924, 2856, 1748, 1679, 1643, 1523, 1456, 1252, 1171, 1026, 829, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, 2H, *J*=8.4 Hz, Ar–*H*), 6.82 (d, 2H, *J*=8.8 Hz, Ar–*H*), 5.81 (br s, 1H, N*H*CH(Me)-CO_2Me), 5.19 (br s, 1H, CHN*H*Boc), 4.73 (br s, 1H, ArC*H*NHBoc), 4.41 (qn, 1H, *J*=6.7 Hz, NHC*H*(Me)-CO_2Me), 3.77 (s, 3H, 4-OC$H_3$$C_6H_4$), 3.70 (s, 3H, –COOC$H_3$), 2.47 (br s, 1H, C*H*($C_3H_7$)), 1.75–1.50 (m, 2H, C$H_2CH_2CH_3$), 1.40 (s, 9H, NH(C=O)OC(CH_3)$_3$), 1.28–1.17 (m, 2H, $CH_2CH_2CH_3$), 1.06 (br s, 3H, CH(CH_3)$COOCH_3$), 0.89 (t, 3H, *J*=7.6 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.0, 158.9, 155.3, 133.0, 128.0 (2C), 113.7 (2C), 79.6, 56.3, 55.3, 53.5, 52.4, 47.6, 31.0, 28.3 (3C), 20.8, 18.1, 14.1; HRMS (ESI) exact mass calcd for $C_{22}H_{34}N_2O_6Na$ $[M+Na]^+$ 445.2315, found 445.2312.

*3.6.2. (1R,2R)-2-(Methoxycarbonyl)-1-(4-methoxyphenyl)pentan-1-aminium chloride (**12**).* To a stirred solution of **8** (100 mg, 0.297 mmol) in dry methanol (2 mL) at 0 °C under nitrogen atmosphere was added thionylchloride (0.11 mL, 1.485 mmol). After 1 h, the mixture was allowed to warm to room temperature and stirring was continued for another 24 h. Removal of solvent under reduced pressure gave an off-white semi solid, which was washed with diethyl ether to give **12** as a white spongy solid (75 mg, 88%). [Found: C, 57.39; H, 7.58; N, 5.05. $C_{14}H_{22}NO_3Cl$ requires C, 58.43; H, 7.71; N, 4.87%.] $[\alpha]_D^{30}$ −2.2 (*c* 1, CH_3OH); IR (neat) ν_{max} 2863, 2658, 2605, 1728, 1612, 1513, 1431, 1303, 1248, 1174, 1029, 986, 833, 758 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.34 (d, 2H, *J*=8.8 Hz, Ar–*H*), 7.05 (d, 2H, *J*=8.8 Hz, Ar–*H*), 4.52 (d, 1H, *J*=9.2 Hz, ArC*H*), 3.84 (s, 3H, 4-OC$H_3$$C_6H_4$–), 3.55 (s, 3H, COOC$H_3$), 3.19 (ddd, 1H, *J*=6.4, 9.2, 9.2 Hz, C*H*(C_3H_7)$COOCH_3$), 1.76–1.65 (m, 2H, C$H_2CH_2CH_3$), 1.42–1.27 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, 3H, *J*=7.6 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, D_2O) δ 174.6, 159.7, 128.7 (2C), 126.7, 114.6 (2C), 55.9, 55.4, 52.5, 50.1, 30.7, 19.7, 12.9; HRMS (ESI) exact mass calcd for $C_{14}H_{22}NO_3$ $[M+H]^+$ 252.1600 (for free amine), found 252.1597.

*3.6.3. (R)-Methyl-2-((R)-((R)-2-((R)-(tert-butoxycarbonyl amino)(4-methoxy phenyl)methyl)pentanamido)(4-methoxyphenyl) methyl)pentanoate (**13**).* To a mixture of **8** (29 mg, 0.087 mmol), **12** (25 mg, 0.087 mmol) and HOBT (14 mg, 0.104 mmol) in dry CH_2Cl_2 at 0 °C under anhydrous conditions was added *i*-Pr_2NEt (0.037 mL, 0.218 mmol) and EDCI (20 mg, 0.104 mmol). The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 24 h. It was then diluted with CH_2Cl_2 and washed with 5% HCl (10 mL) followed by saturated $NaHCO_3$ solution (10 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, solvent evaporated under reduced pressure and the resulting residue was purified by chromatography on silica gel column using 0.5–1% MeOH–$CHCl_3$ solvent system in a gradient mode to give **13** (35 mg, 71%) as a white spongy solid; R_f (5% MeOH/$CHCl_3$) 0.55; $[\alpha]_D^{30}$ +86.4 (*c* 0.9, CH_3OH); IR (neat) ν_{max} 3365, 3329, 2955, 2929, 2870, 2835, 1734, 1680, 1637, 1517, 1461, 1295, 1249, 1168, 1019, 826, 560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CD_3OD) δ 7.49 (d, 1H, *J*=7.2 Hz, ArCHN*H*), 7.00 (br s, 2H, Ar–*H*), 6.75 (br s, 2H, Ar–*H*), 6.65 (d, 2H, *J*=7.6 Hz, Ar–*H*), 6.54 (d, 2H, *J*=6.8 Hz, Ar–*H*), 6.15 (br s, 1H, N*H*Boc), 4.90 (d, 1H, *J*=9.2 Hz, ArC*H*NHC(O)), 4.55 (br s, 1H, ArC*H*NHBoc), 3.78 (s, 3H, 4-OCH_3–C_6H_4–), 3.67 (s, 3H, 4-OCH_3–C_6H_4), 3.42 (s, 3H, COOCH_3), 2.67 (ddd, 1H, *J*=3.6, 10.7, 10.7 Hz, C*H*(C_3H_7)CONH), 2.52 (br s, 1H, C*H*(C_3H_7)$COOCH_3$), 1.78–1.67 (br s, 1H, propyl CH), 1.67–1.52 (m, 2H, Propyl CH), 1.50–1.14 (m, 5H, Propyl CH), 1.37 (s,

9H, NH(C=O)OC(CH_3)$_3$), 0.94 (t, 3H, J=6.8 Hz, $CH_2CH_2CH_3$), 0.86 (t, 3H, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD) δ 174.1, 172.7, 158.1, 158.0, 132.7, 131.5, 127.5 (2C), 127.4 (2C), 113.0 (4C), 79.1, 56.2, 54.5, 54.3, 53.4, 53.2, 51.1, 51.0, 30.9 (2C), 27.7 (3C), 20.3, 20.1, 13.5, 13.3; HRMS (ESI) exact mass calcd for $C_{32}H_{46}N_2O_7Na$ $[M+Na]^+$ 593.3203, found 593.3210.

Acknowledgements

Financial support of this work by the Department of Science and Technology (DST), INDIA (Grants SR/S1/OC-13/2007) is gratefully acknowledged. We thank Mr. V. Ramkumar, IIT Madras for his help during X-ray crystallographic analysis. D. Balamurugan thanks DST for the research fellowship.

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.09.072.

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