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An efficient entry to highly substituted chiral 2-oxopiperazines from α-amino acids via iodocyclization

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ABSTRACT

A short and stereoselective route for the synthesis of 2-oxopiperazines is presented starting from different naturally abundant α-amino acids. The key synthetic steps involved amide coupling, Wittig reaction, HWE olefination, aza-Michael reaction, iodocyclization. This new pathway involving first report of iodocyclization to construct chiral substituted 2-oxopiperazines furnished final compounds in good yields.

1. Introduction

The piperazine moiety is very often found as important pharmacophore in a large number of biologically active molecules, including 5HTanxiolytics,[1] dopamine D3 agents,[2] Bcl-2 inhibitors,[3] cytochrome *c* inhibitor,[4] CNS compounds,[5] and HIV protease inhibitors,[6] antiproliferative agents,[7] quinolone antibiotics[8] etc.

The nitrogen-containing heterocycles offer a convenient core from which many compounds can be derived through convergent synthesis.[9] In this respect, piperazine is an important building block for generating libraries of compounds for the study of structure activity relationships (SAR).[9] Not only piperazine, but their keto analogues (oxopiperazine) also play an important role in drug development and found to be present in the core structure of many important bioactive natural products.[10–19] Particularly, the existence of substituted chiral 2-oxopiperazine nucleus in the skeleton of numerous natural products, such as pseudotheonamides A_1 and A_2 **1**–**2**,[10,11] (−)-A agelastatin A **3**,[12–14] marcfortine B **4**,[15] the Phakellin group **5**–**7**,[16–18] and guadinomine C_2 **8**[19] (Fig. 1) make them attractive targets. In addition, their crucial role in peptidomimetic chemistry for the discovery of novel, bioactive small molecules[20–24] is well established. Thus, oxopiperazines have gained a lot of importance as conformationally restricted peptidomimetics,[25] as fragments of natural products of diverse structural complexity and biological activities,[26] and also have been examined as ligands in enantioselective catalysis.[27] In case of peptidomimetic drugs, excellent examples, having 2-oxopiperazine template that conformationally mimics the dipeptide moiety, essentially include constrained substance P analogues,[28] farnesyltransferase (FTase)[29]

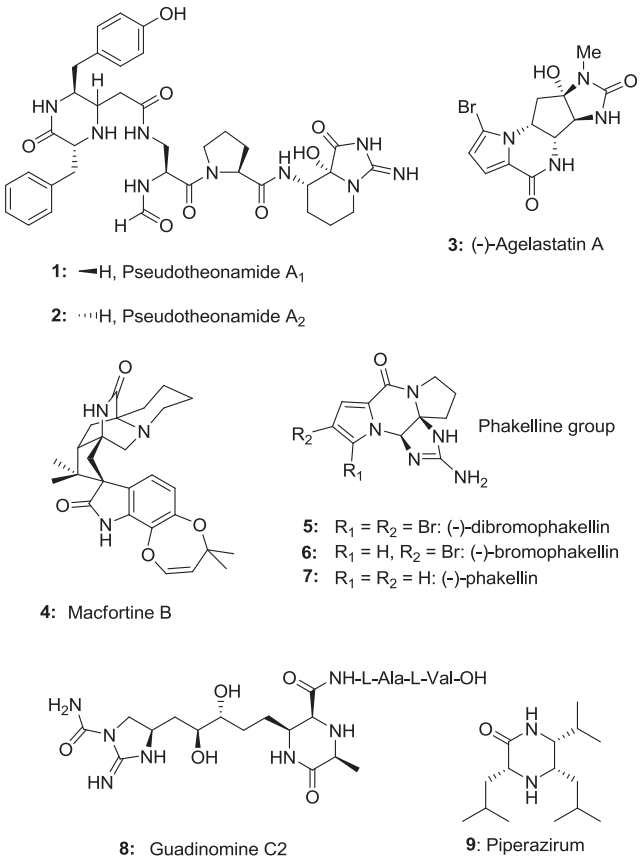

Fig. 1. Some important representatives of 2-oxopiperazines.

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and protein geranylgeranyltransferase-I (PGGTase-I)[30] inhibitors, compounds with dual farnesyltransferase/geranylgeranyltransferase-I inhibitory activity,[31] elastase,[32] factor Xa,[33] renin[34–36] and BACE1[37] inhibitors, melanocortin receptors (MCRs) agonists,[21] fibrinogen glycoprotein IIb–IIIa,[22,38] and neuropeptide S (NPS) receptor[39,40] antagonists.

Furthermore, bioactive drugs used for the treatment of central nervous system diseases are also highly enriched with the substituted oxopiperizines.[5] Besides; they are equally potential as cancer chemotherapeutic agents,[20,41] and are promising candidates for the treatment and prevention of numerous diseases, such as rheumatoid arthritis,[32] depression,[28] sexual disfunctions[21] or venous and arterial thrombosis.[33]

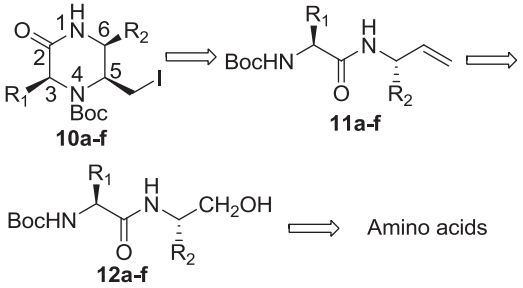
Because of their profound importance, many research groups were engaged in establishing efficient route to synthesize oxopiperazines.[9a,42] Despite this, there is a challenge to generate an efficient scalable route to substituted chirally pure 2-oxopiperazines. Our group is engaged to develop new synthetic methodology for the synthesis of chiral heterocycles and their bioevolution[43] and in continuation of this project, we wish to present here an elegant path to synthesize densely substituted chirally pure 2-oxopiperazines from commercially available α-amino acids utilizing amide coupling, methyl Wittig and iodocyclization[44] as the key reaction steps.

To further explore our synthetic methodology, we targeted the natural product piperazirum, a novel bioactive alkaloid from *Arum palaestinum* Boiss.[45] Piperazirum **9** was active against all examined cultured human cell lines using the SRB method,[46] such as A549 (non-small cell lung, ED_{50}=4.26±0.2 μM), SK-OV-3 (ovary, ED_{50}=1.38±0.1 μM), SK-MEL-2 (melanoma, ED_{50}=0.51±0.1 μM) and HCT-15 (colon, ED_{50}=2.47±0.3 μM).

2. Results and discussions

2.1. Retrosynthetic analysis

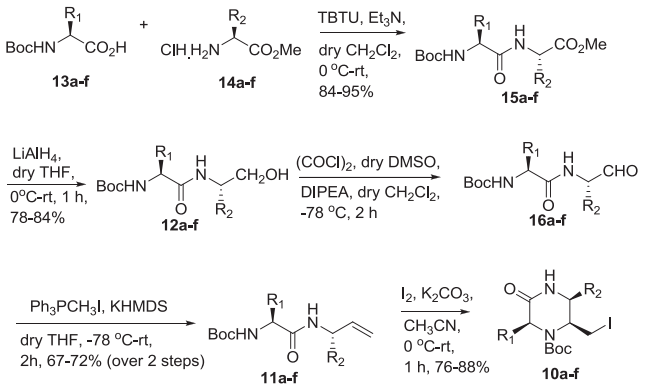
The retrosynthetic analysis suggests that the target 2-oxopiperazine derivatives, **10a–f** can be accessed via crucial diastereoselective iodocyclization reaction from the olefinic intermediates **11a–f**, which in turn can be obtained from the alcohols **12a–f** through Swern oxidation followed by methyl Wittig reaction. The intermediate alcohols **12a–f** can easily be furnished by amide coupling among different amino acid counter parts (Scheme 1).



Scheme 1. Retrosynthetic analysis of 2-oxopiperazine derivatives.

2.2. Synthesis of 2-oxopiperazine derivatives

To achieve the synthesis of various 2-oxopiperazine derivatives, we have taken different naturally abundant α-amino acids as starting materials. First, a number of amino acid methyl ester hydrochlorides (**14a–f**) were coupled with Boc protected amino acids (**13a–f**) through peptide coupling in presence of TBTU/Et_3N in dry CH_2Cl_2 to furnish compounds (**15a–f**) in excellent chemical yields (84–95%), which were subjected to $LiAlH_4$ mediated reduction of the ester functionality to furnish alcohols (**12a–f**) with very good yields (78–84%) within 1 h. In the next step, the derived alcohols (**12a–f**) were oxidized via Swern oxidation using oxalyl chloride/DMSO/DIPEA to provide aldehydes (**16a–f**), which were subsequently transformed into the olefinic compounds **11a–f** in good yields (67–72%, over two steps) utilizing methyl Wittig reaction in presence of Ph_3PCH_3I/KHMDS in 2 h. Now the stage was set for the crucial iodocyclization reaction to obtain the 2-oxopiperazine derivative **10a–f**. The crucial iodocyclization reaction of these olefinic compounds **11a–f** in the presence of K_2CO_3 (3 equiv)/I_2 (3 equiv) in CH_3CN delivered the targeted 2-oxopiperazine derivatives **10a–f** in satisfactory yields (76–88%) (Scheme 2).



Scheme 2. Synthesis of chiral 2-oxopiperazine derivatives **10a–f**.

It is believed that the iodocyclization reaction took place through the favoured six-membered cyclic transition state (**TS-2**, Fig. 2) compared to the disfavoured **TS-1** due to the presence of steric interaction between R_2 and Boc substituents. The regioselective 6-*exo*-*tet* cyclization mode provided the desired compounds where the newly generated stereocenter should be in *syn* fashion with the adjacent one. The other stereoisomers were isolated in very negligible yields via **TS-1**, which is energetically unfavourable. To further support the stereochemistry in the cyclic compounds, we have done COSY experiment with one of the 2-oxopiperazine derivative **10f** where the coupling constant value (*J* 5.19 Hz) between C–5H and C–6H clearly proved that the two adjacent H's are in *syn* fashion. Again, the kinetically favoured regioselective six-membered cyclization predominates over the seven-membered cyclization, which is kinetically unfavoured and expectedly seven-membered cyclic products were not found in any case (Table 1).

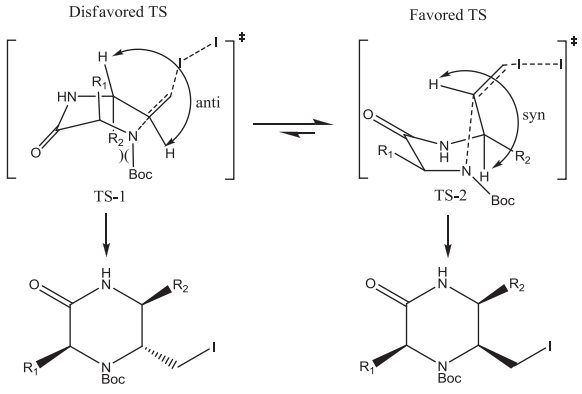
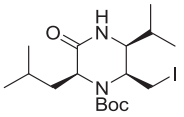
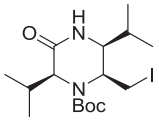
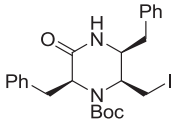
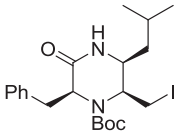
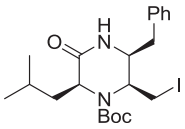
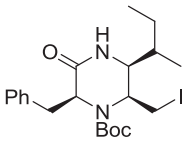
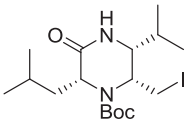


Fig. 2. Model for the diastereoselective iodocyclization reaction.

Table 1
Synthesized 2-oxopiperazine derivatives

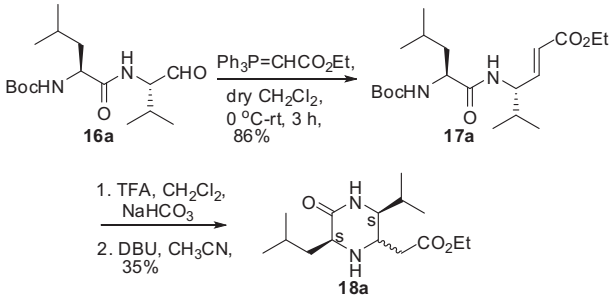
Entry	R_1	R_2	Compound no.	2-Oxopiperazine derivatives	Overall yield (%)	$[\alpha]_D^{25}$ in CH_3OH	de (%)[a]
1	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	**10a**		39.8	−24.7, (*c* 0.30)	>99
2	$-CH(CH_3)_2$	$-CH(CH_3)_2$	**10b**		40.8	−14.2, (*c* 0.41)	>99
3	$-CH_2Ph$	$-CH_2Ph$	**10c**		39.8	−10.8, (*c* 0.42)	>99
4	$-CH_2Ph$	$-CH_2CH(CH_3)_2$	**10d**		48.4	−14.7, (*c* 0.35)	>99
5	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	**10e**		42.0	−7.2, (*c* 0.51)	>99
6	$-CH_2Ph$	$-CH(CH_3)CH_2CH_3$	**10f**		42.5	−23.7, (*c* 0.18)	>99
7	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	**10g**		36.1	+24.6, (*c* 0.40)	>99

[a] Diastereomeric excess.

After successful achievement of the synthesis of 2-oxopiperazine derivatives, we turned our attention to achieve the synthesis of another kind of 2-oxopiperazines through aza-Michael cyclization. For the said purpose, we performed a model study on one of the previously prepared aldehyde **16a**.

Thus, aldehyde **16a** was transformed into α,β-unsaturated ester **17a** through Horner–Wadsworth–Emmons olefination in the presence of $Ph_3P{=}CHCO_2Et$ in dry CH_2Cl_2 in 2 h in excellent yield (86%) and then Boc was removed by the treatment of TFA to furnish free amine. Now the stage was set for the essential aza-Michael cyclization to furnish desired 2-ketopiperazine **18a**. This cyclization was examined in presence of different types of bases (DBU, DABCO, K_2CO_3) and Lewis acids ($BF_3{-}OEt_2$, $TiCl_4$). Unfortunately, the yields are very low (10–25%) except little bit improved in the case of DBU (35%). Nonetheless, we could achieve the chirally pure 2-oxopiperazines **18a** albeit in low yield (Scheme 3).

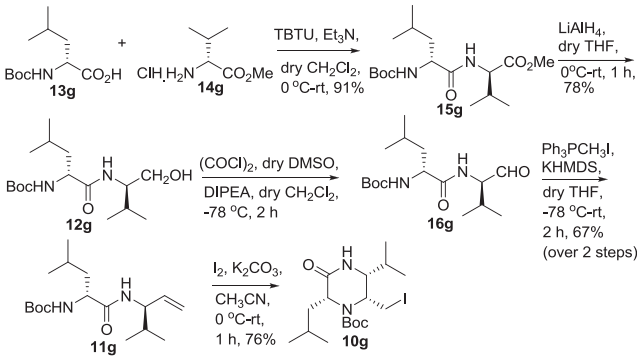
The synthetic methodology described above was also repeated with the (*R*)-amino acid in order to synthesize the target molecule piperazirum **9**. Thus (*R*)-leucine and (*R*)-valine provided the 2-oxopiperazie derivative **10g**, which could be utilized for total synthesis of the natural product, piperazirum. Efforts in this direction are currently underway (Scheme 4).



Scheme 3. Synthesis of 2-oxopiperazine **18a**.

3. Conclusions

In summary, we have developed a scalable synthetic route to 2-oxopiperazine derivatives involving amide coupling, Wittig olefination, aza-Michael reaction and iodocyclization as the key reaction steps. Iodocyclization played a crucial role to the formation of 2-oxopiperazine scaffolds resulting in good yield and this is the first report towards the synthesis of this type of cyclic skeletons.



Scheme 4. Synthesis of 2-oxopiperazine **10g**.

4. Experimental

4.1. General methods

Organic solvents were dried by standard methods. All the products were characterized by ^{1}H, ^{13}C, two-dimensional homonuclear COSY (correlation spectroscopy), IR, ESI-MS, HRMS. Analytical TLC was performed using 2.5×5 cm plates coated with a 0.25 mm thickness of silica gel ($60F_{254}$), visualization was accomplished with iodine and under UV lamp. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on Bruker Avance DPX 200FT, Bruker Robotics, Bruker DRX 300 and 400 Spectrometers at 200, 300 MHz (1H) and 50, 75 MHz (^{13}C). Experiments were recorded in $CDCl_3$ at 25 °C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton. For ^{13}C NMR reference $CDCl_3$ appeared at 77.16 ppm. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 25 °C in methanol as the solvent; concentrations mentioned are in g/100 ml.

4.1.1. General procedure for amide coupling of amino acids. To an ice cooled solution of *N*-Boc protected amino acids **13a**–**g** (4.32 mmol) in dry CH_2Cl_2 (25 ml), TBTU (6.48 mmol) and Et_3N (6.26 mmol) were added under N_2 atmosphere. Then the reaction mixture was stirred for 30 min at the same temperature. After that amino acid methyl ester hydrochlorides, **14a**–**g** (6.48 mmol) and Et_3N (6.48 mmol) were added. The whole mixture was stirred for 1 h at room temperature and water was added, the organic layer was separated, and the aqueous phase was extracted thrice with CH_2Cl_2 (3×50 ml). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure to obtain yellow crude product. The crude product was purified over silica gel column chromatography to furnish corresponding dipeptides **15a**–**g** as colourless solid in 84–95% yield.

*4.1.1.1. (S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-4-methylpentanamido)-3-methylbutanoate (**15a**).* Yield 93%; mp 143 °C; R_f (20% EtOAc/Hexane) 0.52; $[\alpha]_D^{22}$ −14.5 (*c* 0.50, CH_3OH); IR (KBr) 3338, 2977, 2366, 1759, 1688, 1645, 1551, 1179, 1020 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.74 (1H, br, s, NHBoc), 5.10 (1H, br, s, NHCO), 4.49 (1H, dd, J_1 8.76 Hz, J_2 5.04 Hz, $CHCH_2$), 4.12 (1H, s, $CHCO_2Me$), 3.69 (3H, s, OMe), 2.13 (1H, dd, J_1 12.09 Hz, J_2 6.63 Hz, $CHMe_2$), 1.65–1.58 (2H, m, CH_2CHMe_2), 1.49–1.46 (1H, m, $CHCMe_2$), 1.40 (9H, s, CMe_3), 0.91–0.85 (12H, m, Me_2CH); δ_C (75 MHz, $CDCl_3$) 173.3, 171.7, 155.9, 80.3, 63.7, 57.2, 53.5, 40.5, 28.8, 28.2, 24.7, 22.8, 19.5; *m*/*z* (ESI) 289.2 (100%), 345.3 (55%, MH^+), 367.4 (90%); HRMS (ESI): MH^+, found 345.2384 $C_{17}H_{33}N_2O_5$ requires 345.2389.

*4.1.1.2. (S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-3-methylbutanamido)-3-methylbutanoate (**15b**).* Yield 84%; mp 140 °C; R_f (20% EtOAc/Hexane) 0.53; $[\alpha]_D^{22}$ −10.9 (*c* 0.31, CH_3OH); IR (KBr) 3331, 3077, 2970, 2365, 1751, 1648, 1551, 1177, 1016 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.51 (1H, d, *J* 8.13 Hz, NHBoc), 5.14 (1H, d, *J* 8.61 Hz, NHCO), 4.54 (1H, dd, J_1 8.64 Hz, J_2 5.01 Hz, CHNHBoc), 3.96–3.91 (1H, m, $CHCO_2Me$), 3.73 (3H, s, OMe), 2.22–2.12 (2H, m, $CHMe_2$), 1.44 (9H, s, CMe_3), 0.98–0.90 (12H, m, Me_2CH); δ_C (75 MHz, $CDCl_3$) 172.1, 171.6, 155.7, 79.7, 60.0, 57.0, 52.0, 31.1, 30.5, 28.2, 19.1, 18.8; *m*/*z* (ESI) 275.0 (100%), 331.9 (35%, MH^+), 353.1 (90%); HRMS (ESI): MH^+, found 331.2237 $C_{16}H_{31}N_2O_5$ requires 331.2233.

*4.1.1.3. (S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanamido)-3-phenylpropanoate (**15c**).* Yield 90%; mp 112 °C; R_f (20% EtOAc/Hexane) 0.56; $[\alpha]_D^{22}$ −4.2 (*c* 0.30, CH_3OH); IR (KBr) 3485, 1743, 1660, 1365, 1170, 763 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.18–7.08 (8H, m, ArH), 6.93–6.90 (2H, m, ArH), 6.39 (1H, d, *J* 7.26 Hz, NHBoc), 4.99 (1H, d, *J* 5.34 Hz, CHNHBoc), 4.70 (1H, d, *J* 7.26 Hz, $CHCO_2Me$), 4.27 (1H, s, NHCO), 3.56 (3H, s, OMe), 3.01–2.93 (4H, m, CH_2Ph), 1.30 (9H, s, CMe_3); δ_C (50 MHz, $CDCl_3$) 171.3, 170.7, 155.1, 136.4, 135.5, 129.2, 129.1, 128.5, 128.4, 127.0, 126.8, 80.1, 55.6, 53.2, 52.1, 38.2, 37.8, 28.1; *m*/*z* (ESI) 370.1 (100%), 427.2 (50%, MH^+), 449.2 (95%); HRMS (ESI): MH^+, found 427.2237 $C_{24}H_{31}N_2O_5$ requires 427.2233.

*4.1.1.4. (S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanamido)-4-methylpentanoate (**15d**).* Yield 95%; mp 105 °C; R_f (20% EtOAc/Hexane) 0.50; $[\alpha]_D^{22}$ −10.5 (*c* 0.40, CH_3OH); IR (KBr) 3334, 2971, 2365, 1751, 1683, 1642, 1552, 1178, 1021 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.21–7.11 (5H, m, ArH), 6.45 (1H, d, *J* 7.29 Hz, NHBoc), 5.09 (1H, d, *J* 8.10 Hz, CHNHBoc), 4.47 (1H, dd, J_1 7.86 Hz, J_2 4.80 Hz, $CHCO_2Me$), 4.30 (1H, br s, NHCO), 3.60 (3H, s, OMe), 3.04–2.95 (2H, m, CH_2Ph), 1.53–1.37 (3H, m, CH_2CHMe_2), 1.32 (9H, s, CMe_3), 0.83–0.80 (6H, m, Me_2CH); δ_C (50 MHz, $CDCl_3$) 172.7, 170.9, 155.3, 136.5, 129.2, 128.4, 126.7, 80.0, 55.4, 52.1, 50.6, 41.3, 38.0, 28.1, 24.5, 22.6; *m*/*z* (ESI) 337.2 (100%), 393.3 (30%, MH^+), 415.4 (90%); HRMS (ESI): MH^+, found 393.2385 $C_{21}H_{33}N_2O_5$ requires 393.2389.

*4.1.1.5. (S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-4-methylpentanamido)-3-phenylpropanoate (**15e**).* Yield 89%; mp 87 °C; R_f (20% EtOAc/Hexane) 0.51; $[\alpha]_D^{22}$ −9.5 (*c* 0.21, CH_3OH); IR (KBr) 3335, 2974, 2366, 1755, 1688, 1644, 1551, 1178, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.18–7.16 (3H, m, ArH), 7.05–7.02 (2H, m, ArH) 6.47 (1H, d, *J* 6.84 Hz, NHBoc), 4.77 (2H, d, *J* 6.93 Hz, CH), 4.01 (1H, br s, NHCO), 3.63 (3H, s, OMe), 3.11–2.97 (2H, m, CH_2Ph), 1.88 (1H, buried s, $CHMe_2$), 1.57–1.53 (2H, m, CH_2CH), 1.36 (9H, s, CMe_3), 0.85–0.82 (6H, m, Me_2CH); δ_C (50 MHz, $CDCl_3$) 172.1, 171.6, 155.4, 135.7, 129.2, 128.4, 127.0, 79.9, 56.8, 52.9, 51.8, 41.1, 37.8, 28.2, 24.6, 22.8; *m*/*z* (ESI) 337.2 (100%), 393.1 (35%, MH^+), 415.4 (90%); HRMS (ESI): MH^+, found 393.2385 $C_{21}H_{33}N_2O_5$ requires 393.2389.

*4.1.1.6. (2S,3R)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanamido)-3-methylpentanoate (**15f**).* Yield 88%; mp 115 °C; R_f (20% EtOAc/Hexane) 0.58; $[\alpha]_D^{22}$ −15.5 (*c* 0.30, CH_3OH); IR (KBr) 3336, 2981, 2375, 1761, 1693, 1652, 1562, 1179, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.11 (5H, m, ArH), 6.47 (1H, d, *J* 7.95 Hz, NHBoc), 5.11 (1H, d, *J* 7.86 Hz, CHNHBoc), 4.43 (1H, dd, J_1 8.34 Hz, J_2 5.16 Hz, $CHCO_2Me$), 4.30 (1H, d, *J* 4.77 Hz, NHCO), 3.60 (3H, s, OMe), 2.98 (2H, d, *J* 5.94 Hz, CH_2Ph), 1.77–1.72 (1H, m, CHMeEt), 1.33 (9H, s, CMe_3), 1.08–0.98 (2H, m, CH_2Me), 0.82–0.74 (6H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 171.5, 171.1, 155.2, 136.6, 129.0, 128.0, 126.3, 79.4, 56.2, 55.3, 51.5, 37.8, 37.3, 27.9, 24.7, 14.9, 11.1; *m*/*z* (ESI) 337.2 (100%), 393.2 (30%, MH^+), 415.6 (90%); HRMS (ESI): MH^+, found 393.2384 $C_{21}H_{33}N_2O_5$ requires 393.2389.

*4.1.1.7. (R)-Methyl 2-((R)-2-(tert-butoxycarbonylamino)-4-methylpentanamido)-3-methylbutanoate (**15g**).* Yield 91%; mp 136 °C; R_f (20% EtOAc/Hexane) 0.52; $[\alpha]_D^{22}$ +14.2 (*c* 0.50, CH_3OH); IR (KBr) 3335, 2970, 2368, 1755, 1691, 1647, 1555, 1179, 1018 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.22 (1H, d, *J* 7.53 Hz, NHBoc), 5.71 (1H, d, *J* 7.44 Hz, CHNHBoc), 4.47–4.43 (1H, m, $CHCO_2Me$), 4.22 (1H, d, *J* 4.38 Hz, NHCO), 3.64 (3H, s, OMe), 2.08 (1H, dd, J_1 11.91 Hz, J_2 6.03 Hz, $CHMe_2$), 1.58–1.49 (3H, m, CH_2CHMe_2), 1.35 (9H, s, CMe_3),0.85 (12H, d, *J* 5.04 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 172.5, 172.0, 155.6, 79.7, 56.8, 52.9, 51.8, 40.6, 31.0, 28.1, 24.5, 22.7, 18.7; *m/z* (ESI) 289.1 (100%), 345.1 (55%, MH^+), 367.0 (90%); HRMS (ESI): MH^+, found 345.2386 $C_{17}H_{33}N_2O_5$ requires 345.2389.

4.1.2. General procedure of ester reduction. To an ice cooled solution of ester **15a**–**f** (2.90 mmol) in dry THF (30 ml), $LiAlH_4$ (3.19 mmol) was added slowly, and was allowed to stir at room temperature for 1 h. After completion of the reaction, it was quenched by slow addition of ethyl acetate and water. The aqueous layer was extracted with ethyl acetate thrice (3×50 ml), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure and subjected to silica jel column chromatography to obtain the alcohols **12a**–**g** in 78–84% yield.

*4.1.2.1. tert-Butyl (S)-1-((S)-1-hydroxy-3-methylbutan-2-ylamino)-4-methyl-1-oxopentan-2-ylcarbamate (**12a**).* Yield 79%; mp 122 °C; R_f (30% EtOAc/Hexane) 0.48; $[\alpha]_D^{22}$ −18.9 (*c* 0.30, CH_3OH); IR (KBr) 3327, 2977, 2369, 1685, 1639, 1537, 1397, 1254, 1179, 1024, 644 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.62 (1H, d, *J* 6.93 Hz, NHBoc), 5.13 (1H, br s, CHNHBoc), 4.08 (1H, d, *J* 3.27 Hz, NHCO), 3.67 (3H, br s, $CHCH_2OH$), 3.19 (1H, s, OH), 1.95–1.84 (1H, m, $CHMe_2$), 1.69–1.62 (2H, m, CH_2CH), 1.56–1.50 (1H, m, $CHMe_2$), 1.43 (9H, s, CMe_3),0.96–0.90 (12H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 173.3, 156.0, 80.3, 63.6, 57.1, 53.5, 40.5, 28.2, 24.7, 22.8, 19.5, 18.6; *m/z* (ESI) 261.1 (100%), 317.2 (30%, MH^+), 339.1 (40%); HRMS (ESI): MH^+, found 317.2435 $C_{16}H_{33}N_2O_4$ requires 317.2440.

*4.1.2.2. tert-Butyl (S)-1-((S)-1-hydroxy-3-methylbutan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**12b**).* Yield 83%; mp 145 °C; R_f (30% EtOAc/Hexane) 0.53; $[\alpha]_D^{22}$ −9.8 (*c* 0.15, CH_3OH); IR (KBr) 3323, 2968, 2365, 1686, 1635, 1532, 1369, 1298, 1176, 1020, 647 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.23 (1H, d, *J* 6.06 Hz, NHBoc), 5.00 (1H, d, *J* 4.74 Hz, NHCO), 3.79–3.74 (1H, m, CHNHBoc), 3.64–3.57 (3H, m, $CHCH_2OH$), 2.17 (1H, buried s, OH), 1.83–1.79 (2H, m, $CHMe_2$), 1.37 (9H, s, CMe_3),0.92–0.85 (12H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 172.4, 156.0, 79.8, 63.1, 60.7, 56.9, 30.2, 28.6, 28.1, 19.4, 19.2; *m/z* (ESI) 247.0 (100%), 303.9 (60%, MH^+), 325.1 (15%); HRMS (ESI): MH^+, found 303.2287 $C_{15}H_{31}N_2O_4$ requires 303.2284.

*4.1.2.3. tert-Butyl (S)-1-((S)-1-hydroxy-3-phenylpropan-2-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (**12c**).* Yield 80%; mp 145 °C; R_f (30% EtOAc/Hexane) 0.53; $[\alpha]_D^{22}$ −13.3 (*c* 0.31, CH_3OH); IR (KBr) 3461, 3335, 2963, 2363, 1658, 1532, 1386, 1048, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.21–7.04 (10H, m, ArH), 6.01 (1H, d, *J* 7.23 Hz, NHBoc), 5.02 (1H, d, *J* 7.02 Hz, NHCO), 4.19 (1H, d, *J* 6.78 Hz, CHNHBoc), 4.01–3.99 (1H, m, $CHCH_2OH$), 3.35 (2H, br s, CH_2OH), 2.91 (2H, d, *J* 7.05 Hz, CH_2Ph), 2.70–2.67 (2H, m, CH_2Ph) 2.38 (1H, buried s, OH) 1.33 (9H, s, CMe_3); δ_C (75 MHz, $CDCl_3$) 171.2, 155.4, 137.4, 136.7, 129.2, 129.1, 128.6, 128.5, 126.9, 126.5, 80.3, 63.1, 56.2, 52.6, 38.6, 36.7, 28.2; *m/z* (ESI) 343.0 (50%), 399.0 (80%, MH^+), 421.2 (95%); HRMS (ESI): MH^+, found 399.2288 $C_{23}H_{31}N_2O_4$ requires 399.2284.

*4.1.2.4. tert-Butyl (S)-1-((S)-1-hydroxy-4-methylpentan-2-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (**12d**).* Yield 84%; mp 129 °C; R_f (30% EtOAc/Hexane) 0.52; $[\alpha]_D^{22}$ −15.3 (*c* 0.34, CH_3OH); IR (KBr) 3462, 3336, 2966, 2365, 1659, 1535, 1383, 1049, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33–7.22 (5H, m, ArH), 6.04 (1H, d, *J* 8.04 Hz, NHBoc), 5.26 (1H, d, *J* 7.56 Hz, NHCO), 4.30 (1H, d, *J* 6.69 Hz, CHNHBoc), 3.95 (1H, d, *J* 3.00 Hz, $CHCH_2OH$), 3.47–3.39 (2H, m, CH_2OH), 3.11–2.98 (2H, m, CH_2Ph), 2.57 (1H, buried s, OH) 1.51 (1H, dd, J_1 13.29 Hz, J_2 6.63 Hz, $CHMe_2$), 1.41 (9H, s, CMe_3), 1.30–1.27 (2H, m, CH_2CHMe_2), 0.87 (6H, d, *J* 6.45 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 171.4, 155.4, 136.7, 129.2, 128.4, 126.7, 80.1, 65.0, 56.0, 49.7, 39.7, 38.3, 28.1, 24.5, 22.9; *m/z* (ESI) 309.2 (60%), 365.1 (70%, MH^+), 387.2 (90%); HRMS (ESI): MH^+, found 365.2438 $C_{20}H_{33}N_2O_4$ requires 365.2440.

*4.1.2.5. tert-Butyl (S)-1-((S)-1-hydroxy-3-phenylpropan-2-ylamino)-4-methyl-1-oxopentan-2-ylcarbamate (**12e**).* Yield 82%; mp 111 °C; R_f (30% EtOAc/Hexane) 0.49; $[\alpha]_D^{22}$ −17.5 (*c* 0.42, CH_3OH); IR (KBr) 3462, 3336, 2966, 2365, 1659, 1535, 1383, 1049, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.15 (5H, m, ArH), 6.72 (1H, br s, NHBoc), 5.07 (1H, br s, NHCO), 4.04 (2H, s, CHNH), 3.54 (2H, d, *J* 11.25 Hz, CH_2OH), 3.23 (1H, br s, OH), 2.80 (2H, d, *J* 6.63 Hz, CH_2Ph), 1.52 (3H, br s, CH_2CHMe_2), 1.35 (9H, s, CMe_3), 0.82 (6H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 172.9, 155.8, 137.7, 129.2, 128.4, 126.4, 80.1, 63.1, 53.4, 52.7, 41.0, 36.7, 28.2, 24.6, 22.7; *m/z* (ESI) 309.4 (60%), 365.2 (70%, MH^+), 387.2 (90%); HRMS (ESI): MH^+, found 365.2443 $C_{20}H_{33}N_2O_4$ requires 365.2440.

*4.1.2.6. tert-Butyl (S)-1-((2S,3R)-1-hydroxy-3-methylpentan-2-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (**12f**).* Yield 81%; mp 124 °C; R_f (30% EtOAc/Hexane) 0.51; $[\alpha]_D^{22}$ −18.5 (*c* 0.40, CH_3OH); IR (KBr) 3466, 3333, 2962, 2365, 1652, 1537, 1384, 1041, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23–7.15 (5H, m, ArH), 6.06 (1H, d, *J* 8.34 Hz, NHBoc), 5.20 (1H, d, *J* 7.38 Hz, NHCO), 4.24 (1H, d, *J* 6.90 Hz, CHNHBoc), 3.61 (1H, d, *J* 3.57 Hz, CHCHMeEt), 3.42 (2H, s, CH_2OH), 3.05–2.91 (2H, m, CH_2Ph), 2.46 (1H, br s, OH),1.46–1.34 (11H, m), 1.01–0.88 (1H, m, CHMeEt), 0.77–0.75 (6H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 171.6, 155.5, 136.7, 129.2, 128.6, 126.9, 80.3, 62.9, 56.3, 55.9, 38.3, 35.1, 28.1, 25.2, 15.3, 11.1; *m/z* (ESI) 309.3 (60%), 365.2 (70%, MH^+), 387.4 (90%); HRMS (ESI): MH^+, found 365.2444 $C_{20}H_{33}N_2O_4$ requires 365.2440.

*4.1.2.7. tert-Butyl (R)-1-((R)-1-hydroxy-3-methylbutan-2-ylamino)-4-methyl-1-oxopentan-2-ylcarbamate (**12g**).* Yield 78%; mp 120 °C; R_f (30% EtOAc/Hexane) 0.48; $[\alpha]_D^{22}$ +18.8 (*c* 0.26, CH_3OH); IR (KBr) 3325, 2970, 2366, 1688, 1635, 1534, 1392, 1250, 1176, 1027, 649 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.60 (1H, d, *J* 6.99 Hz, NHBoc), 5.12 (1H, br s, NHCO), 4.08 (1H, d, *J* 4.05 Hz, CHNHBoc), 3.69–3.60 (3H,m, $CHCH_2OH$), 3.07 (1H,buried s, OH), 1.89 (1H, dd, J_1 13.2 Hz, J_2 6.6 Hz, $CHMe_2$), 1.69–1.62 (2H, m, CH_2CH), 1.56–1.50 (1H, m, $CHMe_2$ (leucine)), 1.43 (9H, s, CMe_3),0.95–0.90 (12H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 173.3, 155.9, 80.3, 63.6, 57.1, 53.4, 40.5, 28.8, 28.2, 24.7, 22.8, 19.4; *m/z* (ESI) 261.2 (100%), 317.1 (30%, MH^+), 339.1 (40%); HRMS (ESI): MH^+, found 317.2436 $C_{16}H_{33}N_2O_4$ requires 317.2440.

4.1.3. General procedure for Swern oxidation. In an inert atmosphere, $(COCl)_2$ (4.74 mmol) was taken in dry CH_2Cl_2 (10 ml) cooled to −78 °C, dry DMSO (9.48 mmol) was added slowly. After 15 min, previously prepared alcohols 12a-g (3.16 mmol) in dry CH_2Cl_2 (20 ml) was added slowly. The reaction mixture was allowed to stir at the same temperature for 30 min, then DIPEA (12.64 mmol) was added. The reaction was then allowed to stir at the same temperature for 1.5 h. After completion, the reaction was quenched with slow addition of NH_4Cl solution, the aqueous layer was extracted with CH_2Cl_2 (3×30 ml), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and solvent was removed

under reduced pressure to furnish the crude aldehydes **16a**–**g**, which was used in the next step without further purification.

4.1.4. General procedure for Wittig reaction. To a solution of methyltriphenylphosphonium iodide (4.77 mmol) in dry THF (10 ml) under N_2 atmosphere, KHMDS solution (0.5 M in toluene) (3.97 mmol) was added slowly at −78 °C and stirred for 1 h. After the development of the deep yellow coloured solution, previously prepared aldehydes **16a**–**g** (1.59 mmol) in dry THF (15 ml) was added slowly to the reaction mixture at the same temperature and was allowed to stir for 2 h. After completion of the reaction, satd solution of ammonium chloride was added, extracted with ethyl acetate (3×20 ml). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and then solvent was removed under reduced pressure. The crude product was purified over silica gel column chromatography to furnish corresponding olefin **11a**–**g** as colourless solid in 67–72% yield.

*4.1.4.1. tert-Butyl (S)-4-methyl-1-((S)-4-methylpent-1-en-3-ylamino)-1-oxopentan-2-ylcarbamate (**11a**).* Yield 67%; mp 126 °C; R_f (15% EtOAc/Hexane) 0.62; $[\alpha]_D^{22}$ −16.8 (*c* 0.35, CH_3OH); IR (KBr) 3299, 2976, 2367, 1652, 1527, 1293, 1174, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.34 (1H, s, NHBoc), 5.78–5.70 (1H, m, CH=CH_2), 5.17–5.03 (3H, m, CH_2=, CHNHBoc), 4.33–4.31 (1H, m, CHCH=CH_2), 4.11 (1H, br s, NHCO), 1.84–1.68 (3H, m, CH_2CHMe_2, $CHMe_2$), 1.48–1.47 (1H, m, $CHMe_2$ (leucine)), 1.43 (9H, s, CMe_3), 0.95–0.87 (12H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 172.0, 155.9, 136.8, 115.4, 80.2, 56.3, 40.8, 32.1, 28.3, 24.8, 22.1, 18.7, 17.9; *m*/*z* (ESI) 257.3 (100%), 313.1 (25%, MH^+), 336.2 (40%); HRMS (ESI): MH^+, found 313.2489 $C_{17}H_{32}N_2O_3$ requires 313.2491.

*4.1.4.2. tert-Butyl (S)-3-methyl-1-((S)-4-methylpent-1-en-3-ylamino)-1-oxobutan-2-ylcarbamate (**11b**).* Yield 69%; mp 89 °C; R_f (15% EtOAc/Hexane) 0.62; $[\alpha]_D^{22}$ −12.8 (*c* 0.34, CH_3OH); IR (KBr) 3291, 2982, 2361, 1670, 1536, 1289, 1165, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.11 (1H, d, *J* 8.64 Hz, NHBoc), 5.80–5.69 (1H, m, CH=CH_2), 5.18–5.12 (3H, m, CH_2=, CHNHBoc), 4.37–4.32 (1H, m, CHCH=CH_2), 3.88–3.83 (1H, m, $CHMe_2$), 2.15 (1H, d, *J* 4.17 Hz, NHCO), 1.85–1.74 (1H, m, $CHMe_2$), 1.44 (9H, s, CMe_3), 0.97–0.88 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 171.1, 155.9, 136.6, 115.5, 79.8, 56.4, 32.0, 30.2, 28.2, 19.4, 18.7, 18.0; *m*/*z* (ESI) 242.1 (80%), 299.5 (30%, MH^+), 322.3 (65%); HRMS (ESI): MH^+, found 299.2337 $C_{16}H_{31}N_2O_3$ requires 299.2335.

*4.1.4.3. tert-Butyl (S)-1-oxo-3-phenyl-1-((S)-1-phenylbut-3-en-2-ylamino)propan-2-ylcarbamateas (**11c**).* Yield 70%; mp 140 °C; R_f (15% EtOAc/Hexane) 0.61; $[\alpha]_D^{22}$ −4.3 (*c* 0.26, CH_3OH); IR (KBr) 3293, 2975, 2363, 1653, 1520, 1290, 1170, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27–7.01 (10H, m, ArH), 5.82 (1H, d, *J* 7.14 Hz, NHBoc), 5.70–5.59 (1H, m, CH=CH_2), 5.04–4.83 (3H, m, CH_2=, CHNHBoc), 4.69 (1H, s, NHCO), 4.27 (1H, d, *J* 6.9 Hz, $CHCH_2Ph$), 2.99 (2H, d, *J* 5.97 Hz, CH_2Ph), 2.83–2.70 (2H, m, CH_2Ph), 1.39 (9H, s, CMe_3); δ_C (50 MHz, $CDCl_3$) 170.3, 155.2, 136.8, 129.4, 128.6, 128.3, 126.9, 126.6, 115.3, 80.2, 56.0, 51.9, 40.9, 38.3, 28.2; *m*/*z* (ESI) 338.9 (100%), 395.2 (20%, MH^+), 417.1 (30%); HRMS (ESI): MH^+, found 395.2332 $C_{24}H_{31}N_2O_3$ requires 395.2335.

*4.1.4.4. tert-Butyl (S)-1-((S)-5-methylhex-1-en-3-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (**11d**).* Yield 69%; mp 115 °C; R_f (15% EtOAc/Hexane) 0.60; $[\alpha]_D^{22}$ −7.8 (*c* 0.45, CH_3OH); IR (KBr) 3293, 2971, 2370, 1658, 1523, 1291, 1179, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30–7.19 (5H, m, ArH), 5.73 (1H, d, *J* 7.74 Hz, NHBoc), 5.62–5.51 (1H, m, CH=CH_2), 5.10–4.88 (3H, m, CH_2=, NHCO), 4.47–4.43 (1H, m, CHNHBoc), 4.29 (1H, dd, J_1 14.7 Hz, J_2 7.2 Hz, CHCH=CH_2), 3.07–3.04 (2H, m, CH_2Ph), 1.56–1.47 (1H, m, $CHMe_2$), 1.41 (9H, s, CMe_3), 1.30–1.25 (2H, m, CH_2CHMe_2), 0.89–0.86 (6H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 170.3, 155.4, 138.2, 136.7, 129.4, 128.6, 126.8, 114.4, 80.2, 56.1, 49.5, 43.9, 38.3, 28.2, 24.5, 22.7; *m*/*z* (ESI) 304.1 (80%), 361.2 (40%, MH^+), 383.2 (40%); HRMS (ESI): MH^+, found 361.2488 $C_{21}H_{33}N_2O_3$ requires 361.2491.

*4.1.4.5. tert-Butyl (S)-4-methyl-1-oxo-1-((S)-1-phenylbut-3-en-2-ylamino)pentan-2-ylcarbamate (**11e**).* Yield 72%; mp 123 °C; R_f (15% EtOAc/Hexane) 0.58; $[\alpha]_D^{22}$ −14.8 (*c* 0.20, CH_3OH); IR (KBr) 3296, 2968, 2375, 1666, 1527, 1292, 1177, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27–7.16 (5H, m, ArH), 6.16 (1H, d, *J* 7.8 Hz, NHBoc), 5.85–5.76 (1H, m, CH=CH_2), 5.16–5.06 (2H, m, CH_2=), 4.95–4.74 (2H, m, CHNHBoc, NHCO), 4.04–3.99 (1H, m, CHCH=CH_2), 2.91–2.80 (2H, m, CH_2Ph), 1.62–1.54 (2H, m, CH_2CHMe_2), 1.42 (9H, s, CMe_3), 1.34–1.30 (1H, m, $CHCH_2Me_2$), 0.92–0.83 (6H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 171.8, 155.6, 137.2, 129.4, 129.3, 128.3, 126.5, 115.0, 80.0, 53.1, 51.9, 41.0, 28.2, 24.5, 22.6, 22.2; *m*/*z* (ESI) 304.5 (100%), 361.3 (10%, MH^+), 383.2 (75%); HRMS (ESI): MH^+, found 361.2494 $C_{21}H_{33}N_2O_3$ requires 361.2491.

*4.1.4.6. tert-Butyl (S)-1-((3R,4R)-4-methylhex-1-en-3-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (**11f**).* Yield 71%; mp 115 °C; R_f (15% EtOAc/Hexane) 0.62; $[\alpha]_D^{22}$ −15.8 (*c* 0.60, CH_3OH); IR (KBr) 3297, 2972, 2371, 1660, 1526, 1299, 1175, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.20–7.12 (5H, m, ArH), 5.91 (1H, d, *J* 8.36 Hz, NHBoc), 5.56–5.45 (1H, m, CH=CH_2), 5.13–4.78 (3H, m, CH_2=, NHCO), 4.25 (2H, br s, CHCH=CH_2, $CHCH_2$), 2.99 (2H, d, *J* 6.66 Hz, CH_2Ph), 1.33 (11H, s, CMe_3, CH_2Me), 0.99–0.87 (1H, m, CHMeEt), 0.81–0.69 (6H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 170.4, 155.4, 136.7, 135.7, 129.3, 128.5, 126.7, 115.7, 80.1, 56.1, 55.5, 38.4, 38.2, 28.1, 25.0, 14.8, 11.4; *m*/*z* (ESI) 304.9 (100%), 361.2 (10%, MH^+), 383.1 (75%); HRMS (ESI): MH^+, found 361.2496 $C_{21}H_{33}N_2O_3$ requires 361.2491.

*4.1.4.7. tert-Butyl (R)-4-methyl-1-((R)-4-methylpent-1-en-3-ylamino)-1-oxopentan-2-ylcarbamate (**11g**).* Yield 67%; mp 98 °C; R_f (15% EtOAc/Hexane) 0.63; $[\alpha]_D^{22}$ +16.9 (*c* 0.31, CH_3OH); IR (KBr) 3295, 2974, 2366, 1655, 1521, 1291, 1175, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.21 (1H, br s, NHBoc), 5.73–5.62 (1H, m, CH=CH_2), 5.09–5.03 (2H, m, CH_2=), 4.90 (1H, br s, NHCO), 4.26–4.23 (1H, m, CHNHBoc), 4.01 (1H, br s, CHCH=CH_2), 1.83 (1H, s, $CHMe_2$, $CHMe_2$), 1.76–1.69 (1H, m, $CHMe_2$), 1.40 (2H, m, CH_2CHMe_2) 1.36 (9H, s, CMe_3), 0.86–0.80 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 172.1, 156.0, 136.8, 115.5, 80.5, 56.3, 32.1, 29.6, 28.3, 24.8, 22.8, 18.7, 17.8; *m*/*z* (ESI) 257.1 (100%), 313.2 (25%, MH^+), 336.1 (40%); HRMS (ESI): MH^+, found 313.2487 $C_{17}H_{33}N_2O_4$ requires 313.2491.

4.1.5. General procedure for iodocyclization. To an ice cooled solution of starting olefinic compounds **11a**–**g** (0.59 mmol) in acetonitrile (5 ml), K_2CO_3 (1.77 mmol) was added followed by I_2 (1.77 mmol) in argon atmosphere and keep stirring for 2 h. After the completion of reaction I_2 was quenched by satd $Na_2S_2O_3$ solution and extracted with ethyl acetate (3×25 ml), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure and the crude product was subjected to column chromatography to furnish the oily cyclic compounds **10a**–**g** in 76–88%.

*4.1.5.1. (3S,6S)-tert-Butyl 2-(iodomethyl)-6-isobutyl-3-isopropyl-5-oxopiperazine-1-carboxylate (**10a**).* Yield 70%; R_f (10% EtOAc/Hexane) 0.61; $[\alpha]_D^{22}$ −24.7 (*c* 0.30, CH_3OH); IR (Neat) 3498, 3242, 2995, 2363, 1649, 1454, 1122, 1029, 672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.01–4.93 (1H, m, NH), 4.45–4.32 (1H, m, $CHCH_2CHMe_2$), 4.28–4.23 (1H, m, $CHCH_2I$), 3.63–3.56 (1H, m, $CHCHMe_2$), 3.24–3.17 (2H, m, CH_2I), 1.82–1.50 (4H, m, $2CHMe_2$, CH_2CHMe_2), 1.44 (9H, s, CMe_3), 0.96–0.90 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 166.6, 155.2, 80.5, 80.3, 79.4, 47.4, 42.8, 32.1, 28.2, 24.7, 21.9, 18.2,

8.2; *m*/*z* (ESI) 383.3 (60%), 439.1 (100%, MH^+), 461.2 (20%); HRMS (ESI): MH^+, found 439.1454 $C_{17}H_{32}IN_2O_3$ requires 439.1458.

*4.1.5.2. (3S,6S)-tert-Butyl 2-(iodomethyl)-3,6-diisopropyl-5-oxopiperazine-1-carboxylate (**10b**).* Yield 71%; R_f (10% EtOAc/Hexane) 0.61; $[\alpha]_D^{22}$ −14.2 (*c* 0.41, CH_3OH); IR (Neat) 3492, 3245, 2999, 2368, 1646, 1452, 1128, 1022, 672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.05 (1H, d, *J* 9.09 Hz, NH), 4.31–4.24 (2H, m, $CHCH_2CHMe_2$, $CHCH_2I$), 3.61–3.57 (1H, m, $CHCHMe_2$), 3.22–3.19 (2H, m, CH_2I), 2.18–2.09 (1H, m, $CHMe_2$), 1.82–1.71 (1H, m, $CHMe_2$), 1.44 (9H, s, CMe_3), 1.01–0.91 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 165.3, 155.6, 80.9, 79.4, 53.9, 32.2, 30.9, 28.2, 19.0, 18.3, 17.6, 7.9; *m*/*z* (ESI) 369.0 (100%), 425.9 (100%, MH^+), 447.9 (10%); HRMS (ESI): MH^+, found 425.1306 $C_{16}H_{30}IN_2O_3$ requires 425.1301.

*4.1.5.3. (2S,5S)-tert-Butyl 2,5-dibenzyl-6-(iodomethyl)-3-oxopiperazine-1-carboxylate (**10c**).* Yield 69%; R_f (10% EtOAc/Hexane) 0.60; $[\alpha]_D^{22}$ −10.8 (*c* 0.42, CH_3OH); IR (Neat) 3492, 3245, 2998, 2365, 1642, 1455, 1119, 1029, 676 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29–7.15 (10H, m, ArH), 5.14–5.03 (1H, m), 4.65 (1H, br, s), 4.28–4.22 (1H, m), 3.95 (1H, d, *J* 6.12 Hz), 3.28–2.63 (6H, m, CH_2Ph, CH_2I), 1.42 (9H, s, CMe_3); δ_C (50 MHz, $CDCl_3$) 165.0, 155.4, 138.1, 136.2, 129.7, 129.5, 128.8, 128.5, 128.3, 126.8, 82.9, 79.8, 72.9, 49.9, 41.7, 29.7, 28.5, 7.1; *m*/*z* (ESI) 464.1 (60%), 521.1 (80%, MH^+), 543.3 (70%); HRMS (ESI): MH^+, found 521.1304 $C_{24}H_{30}IN_2O_3$ requires 521.1301.

*4.1.5.4. (2S,5S)-tert-Butyl 2-benzyl-6-(iodomethyl)-5-isobutyl-3-oxopiperazine-1-carboxylate (**10d**).* Yield 67%; R_f (10% EtOAc/Hexane) 0.63; $[\alpha]_D^{22}$ −14.7 (*c* 0.35, CH_3OH); IR (Neat) 3497, 3246, 2993, 2364, 1642, 1458, 1120, 1022, 679 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30–7.14 (5H, m, ArH), 5.05 (1H, br s, NH), 4.62–4.60 (1H, m, $CHCH_2Ph$), 4.19–4.14 (1H, m, $CHCH_2I$), 3.76–3.72 (1H, m, $CHCH_2CHMe_2$), 3.22–3.03 (4H, m, CH_2Ph, CH_2I), 1.82–1.72 (2H, m, CH_2CHMe_2), 1.40 (9H, s, CMe_3) 1.28–1.25 (1H, m, $CHMe_2$), 0.95–0.88 (6H, m, CH_3); δ_C (50 MHz, $CDCl_3$) 164.4, 155.2, 136.5, 129.6, 128.4, 126.9, 84.4, 79.8, 70.0, 49.9, 45.7, 38.8, 28.3, 24.5, 22.9, 6.86; *m*/*z* (ESI) 431.1 (60%), 487.1 (80%, MH^+), 510.2 (20%); HRMS (ESI): MH^+, found 487.1455 $C_{21}H_{32}IN_2O_3$ requires 487.1458.

*4.1.5.5. (3S,6S)-tert-Butyl 3-benzyl-2-(iodomethyl)-6-isobutyl-5-oxopiperazine-1-carboxylate (**10e**).* Yield 66%; R_f (10% EtOAc/Hexane) 0.62; $[\alpha]_D^{22}$ −7.2 (*c* 0.51, CH_3OH); IR (Neat) 3491, 3242, 2993, 2364, 1648, 1455, 1122, 1021, 675 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25–7.10 (5H, m, ArH), 4.91–4.88 (1H, m, NH), 4.34–4.32 (1H, m, $CHCH_2CHMe_2$), 4.16–4.14 (1H, m, $CHCH_2Ph$), 3.99–3.95 (1H, m, $CHCH_2I$), 3.01–2.65 (4H, m, CH_2I, CH_2Ph), 1.65–1.43 (3H, m, CH_2CHMe_2), 1.37 (9H, s), 0.90–0.84 (6H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 166.9, 155.0, 136.5, 129.5, 128.5, 126.7, 82.0, 79.6, 72.6, 42.7, 41.2, 35.3, 28.3, 24.5, 22.7, 7.3; *m*/*z* (ESI) 431.1 (50%), 487.9 (100%, MH^+), 510.1 (10%); HRMS (ESI): MH^+, found 487.1460 $C_{21}H_{32}IN_2O_3$ requires 487.1458.

*4.1.5.6. (2S,5S)-tert-Butyl 2-benzyl-5-sec-butyl-6-(iodomethyl)-3-oxopiperazine-1-carboxylate (**10f**).* Yield 70%; R_f (10% EtOAc/Hexane) 0.64; $[\alpha]_D^{22}$ −23.7 (*c* 0.18, CH_3OH); IR (Neat) 3497, 3246, 2993, 2364, 1642, 1458, 1120, 1022, 679 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.15 (5H, m, ArH), 5.06 (1H, d, *J* 6.75 Hz, NH), 4.55 (1H, d, *J* 6.30 Hz, $CHCH_2Ph$), 4.19 (1H, dd, J_1 10.89 Hz, J_2 5.40 Hz, $CHCH_2I$), 3.52 (1H, d, *J* 5.19 Hz, CHNH), 3.10–2.89 (4H, m, CH_2I, CH_2Ph), 1.44–1.40 (1H, m, CHMeEt), 1.32 (9H, s, CMe_3), 1.04–0.92 (2H, m, CH_2CH_3), 0.83–0.71 (6H, m); δ_C (75 MHz, $CDCl_3$) 165.1, 155.0, 136.3, 129.4, 128.3, 126.8, 80.97, 79.7, 76.2, 49.8, 38.9, 38.6, 28.3, 25.1, 14.5, 11.6, 7.9; *m*/*z* (ESI) 431.1 (60%), 487.0 (100%, MH^+), 510.3 (10%); HRMS (ESI): MH^+, found 487.1465 $C_{21}H_{32}IN_2O_3$ requires 487.1458.

*4.1.5.7. (3R,6R)-tert-Butyl 2-(iodomethyl)-6-isobutyl-3-isopropyl-5-oxopiperazine-1-carboxylate (**10g**).* Yield 76%; R_f (10% EtOAc/Hexane) 0.62; $[\alpha]_D^{22}$ +24.6 (*c* 0.40, CH_3OH); IR (Neat) 3497, 3243, 2994, 2362, 1643, 1451, 1120, 1028, 679 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.87 (1H, s, NH), 4.29 (1H, d, *J* 5.43 Hz, CHNBoc), 4.20–4.16 (1H, m, $CHCH_2I$), 3.52 (1H, d, *J* 5.25 Hz, CHNH), 3.19–3.08 (2H, m, CH_2I), 1.71–1.67 (2H, m), 1.55–1.45 (2H, m), 1.37 (9H, s, CMe_3), 0.89–0.83 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 166.7, 155.3, 80.6, 79.5, 47.4, 42.3, 32.1, 29.6, 28.2, 24.7, 21.9, 18.2, 8.2; *m*/*z* (ESI) 338.1 (60%), 439.9 (100%, MH^+), 461.3 (20%); HRMS (ESI): MH^+, found 439.1455 $C_{17}H_{32}IN_2O_3$ requires 439.1458.

4.1.6. Procedure for Horner–Wadsworth–Emmons olefination. To an ice cooled solution of the aldehyde **16a** (3.18 mmol) in dry CH_2Cl_2 (30 ml), Wittig reagent $Ph_3P{=}CHCO_2Et$ (4.13 mmol) was added and then allowed to stir at room temperature for 2 h. After completion of the reaction, solvent was removed under reduced pressure to obtain the crude product, which was purified by column chromatography to furnish the desired α,β-unsaturated ester **17a** in 86% yield.

*4.1.6.1. (S,E)-Ethyl 4-((S)-2-(tert-butoxycarbonylamino)-4-methylpentanamido)-5-methylhex-2-enoate (**17a**).* Yield 86%; R_f (25% EtOAc/Hexane) 0.51; $[\alpha]_D^{22}$ −15.9 (*c* 0.51, CH_3OH); IR (KBr) 3113, 2996, 2233, 1656, 1371, 1019, 770 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.02 (1H, d, *J* 7.59 Hz, NH), 6.81 (1H, dd, J_1 15.66 Hz, J_2 5.40 Hz, $CH{=}CHCO_2Et$), 5.86 (1H, d, *J* 15.60 Hz, $CHCO_2Et$), 5.36 (1H, d, *J* 6.60 Hz, NH), 4.48–4.42 (1H, m), 4.15–4.07 (3H, m), 1.85–1.75 (1H, m, $CHMe_2$), 1.59–1.45 (3H, m, CH_2CHMe_2), 1.36 (9H, s, CMe_3), 1.20 (3H, t, *J* 7.11 Hz, CH_3CH_2O), 0.87–0.81 (12H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 172.2, 166.1, 156.0, 146.6, 121.6, 79.1, 60.3, 54.9, 40.2, 32.1, 29.6, 28.2, 24.7, 22.8, 18.9, 17.85; *m*/*z* (ESI) 284.1 (60%), 385.2 (100%, MH^+), 407.1 (30%); HRMS (ESI): MH^+, found 385.2698 $C_{20}H_{37}N_2O_5$ requires 385.2702.

4.1.7. Procedure for aza-Michael reaction. To an ice cooled solution of **17a** (2.34 mmol) in dry CH_2Cl_2 (10 ml), 1:1 TFA in CH_2Cl_2 (10 ml) was added and allowed to stir at room temperature for 30 min. After completion of the reaction, solvent was removed and the crude residue was utilized in the next step without further purification.

The crude product obtained in the previous step was dissolved in CH_3CN (5 ml), cooled to 0 °C and then DBU (0.26 mmol) was added. The reaction mixture was allowed to stir at room temperature for 8 h. Water was added and the aqueous layer was extracted with ethyl acetate thrice, the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure. The crude product was purified by column chromatography to furnish the cyclic product **18a** in 26% over two steps.

*4.1.7.1. Ethyl-2-((3S,6S)-6-isobutyl-3-isopropyl-5-oxopiperazin-2-yl)acetate (**18a**).* R_f (60% EtOAc/Hexane) 0.42; $[\alpha]_D^{22}$ −26.8 (*c* 0.61, CH_3OH). IR (Neat) 3305, 3213, 2979, 2119, 1692, 1375, 1223, 1026, 768 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.30 (1H, s), 4.20–4.12 (2H, m), 3.49–3.38 (2H, m), 2.93–2.91 (1H, m), 2.57–2.54 (2H, m), 1.93–1.55 (5H, m), 1.27 (3H, t, *J* 7.14 Hz), 0.99–0.88 (12H, m); δ_C (75 MHz, $CDCl_3$) 173.6, 171.5, 62.0, 60.7, 52.8, 46.8, 40.6, 36.9, 30.4, 24.1, 23.4, 19.5, 14.1; *m*/*z* (ESI) 285.2, 20%, MH^+; HRMS (ESI): MH^+, found 285.2175 $C_{15}H_{29}N_2O_3$ requires 285.2178.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.09.109.

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