Tetrahedron 68 (2012) 280–286

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Synthesis of optically active homotryptophan and its oxygen and sulfur analogues

Koushik Goswami [a], Sibasish Paul [a], Sandesh T. Bugde [b,†], Surajit Sinha [a,*]

[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India
[b] Department of Chemistry, Goa University, Goa 403206, India

ARTICLE INFO

Article history:
Received 25 June 2011
Received in revised form 12 October 2011
Accepted 14 October 2011
Available online 29 October 2011

Keywords:
Unnatural amino acid
Homotryptophan
Alkynyloxazolidine
Sonogashira coupling
Larock's heteroannulation

ABSTRACT

D-Homotryptophan and its sulfur analogue have been synthesized by Sonogashira coupling between 3-iodoheteroarenes and ethynyloxazolidine followed by reduction of triple bond and oxidation of alcohol to acid. L-Homotryptophan and its oxygen analogue have been synthesized from silylated internal alkyne using Larock's heteroannulation as the key reaction. The alkynyloxazolidines were synthesized from L-serine and L-glutamic acid, respectively.

1. Introduction

Indoleamine 2,3-dioxygenase (IDO) is a heme-containing glycoprotein that uses superoxide to cleave the indole 2,3-double bond of L-tryptophan to kynurenine via the formation of *N*-formylkynurenine. Further metabolism of kynurenine produced anthranilic acid, quinolinic acid, and kynurenic acid and elevation of their concentration are known to be responsible for many inflammatory and neurodegenerative diseases including cancers. So, inhibitors of the IDO enzyme have important clinical implications as potential therapeutic agents.[1]

The crystal structure of tryptophan bound TDO (tryptophan 2,3-dioxygenase)[2] shows that the N1 nitrogen of the indole ring is hydrogen-bonded to the side chain of His55 (Fig. 1). Thus, *N*-methyl-tryptophan becomes inactive against TDO probably because the methyl group sterically interacts with this residue. His55 in TDO is replaced by Ser167 in IDO, which has a smaller side chain and creates a small pocket to accommodate the methyl group. This may be why *N*-methyl-tryptophan is the most potent inhibitor of IDO known till date.[3] A larger substrate binding pocket also may explain why IDO can accommodate many tryptophan analogues in its active site.

Recent study[4] shows that human IDO (hIDO) has two binding sites, an active and an inhibitory substrate binding site (Si site). Upon substrate binding, the protein undergoes conformational changes that allow Si site to accommodate a wide range of compounds of different structures and these can act as either an effector or an inhibitor. Due to this allosteric effect the design of compounds targeting the Si site may provide a handle to control the activity of catalytic active site. Tryptophan analogues constitute one class of IDO

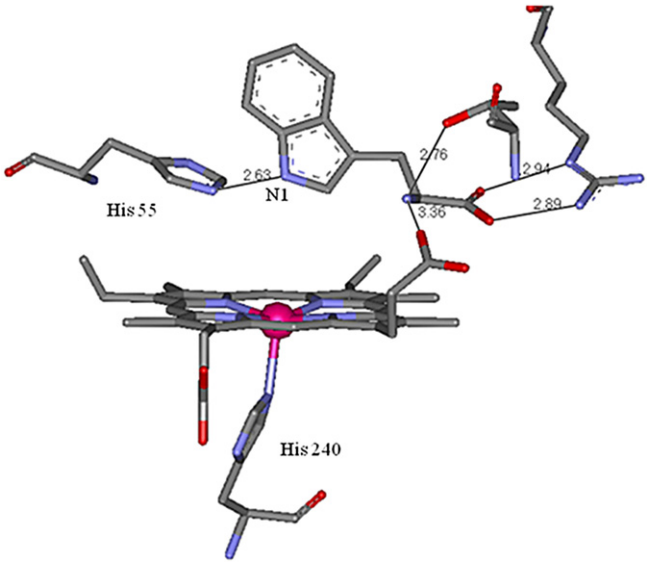


Fig. 1. Tryptophan bound TDO.

* Corresponding author. Tel.: +91 33 2473 4971; fax: +91 33 2473 2805; e-mail address: ocss5@iacs.res.in (S. Sinha).
† Determination of ee using HPLC.

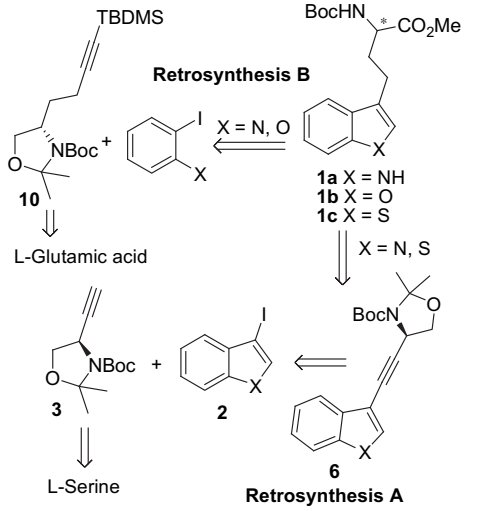
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.055

inhibitors.[5] Hence, synthesis as well as testing[3,6] of several tryptophan analogues have already been reported. Herein, we report the synthesis of optically active homotryptophan and its *O*, *S* analogues.

Except L-homotryptophan, the '*O*' and '*S*' analogues have not been reported so far. Cook and his group were the first to report the enantioselective synthesis of homotryptophan using a two-carbon homologation of an indole moiety to be followed by diasteroselective alkylation of the Schöllkopf chiral auxiliary.[6b,d] In our method, chiral center has been derived from naturally occurring amino acids L-serine and L-glutamic acid, respectively.

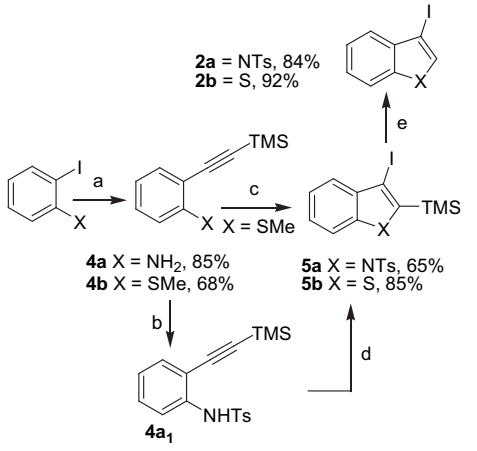
2. Results and discussion

Retrosynthetic strategy **A** was used for the synthesis of D-homotryptophan and its '*S*' analogue by way of intermediate **6** whereas that of **B** was used for L-isomer and its '*O*' analogue using Larock's heteroannulation as the key reaction. The masked form of alkynylated amino acids **3** and **10** has been used in order to avoid the epimerization at the α-C[6d] as well as intramolecular nucleophilic (O or N) attack to the Pd(II)/alkyne complexes[6c,e] (Scheme 1).



Scheme 1. Retrosynthetic pathway.

The synthesis of 3-iodoindole **2a** and 3-iodobenzothiophene **2b** has been described in Scheme 2. Protected 3-iodoindole **2a** was prepared from 2-iodoaniline according to Knight's procedure[7] with a slight modification.

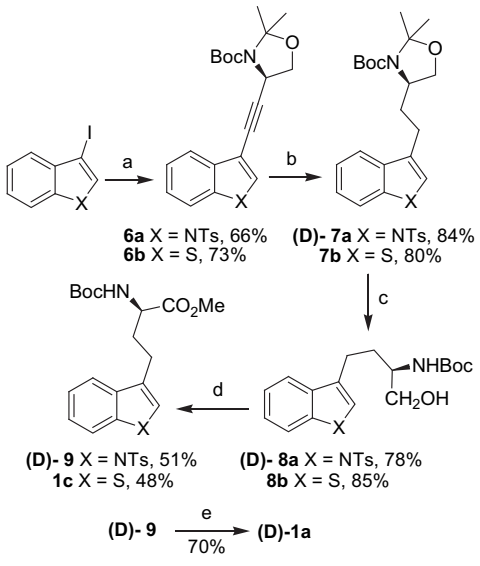


Scheme 2. Preparation of 3-iodobenzofused heterocycles. Reaction conditions: (a) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N; (b) TsCl, THF/pyridine mixture (8:2); (c) I_2, DCM; (d) I_2, K_2CO_3, CH_3CN; (e) TBAF, THF.

According to their procedure, tosyl-protected-2-iodoaniline was used as a starting material, which after Sonogashira coupling gave indole as the major product as was expected from the literature.[8] Interestingly, the unprotected 2-iodoaniline gave exclusively Sonogashira coupled product **4a**, which was then protected to obtain **4a$_1$**. After iodocyclization and silyl-deprotection, protected 3-iodoindole **2a** was obtained in 41% overall yield. Similarly, compound **2b**[9] was synthesized from 2-iodothioanisole according to Larock's methodology (Scheme 2).

To get efficient Sonogashira coupling[10] between 3-iodoindole **2a** and ethynyloxazolidine **3**,[11] choice of base was very important. We were pleased to find that the combination of diisopropylethylamine (DIPEA) and $Pd(OAc)_2$ gave **6a** in 66% yield.

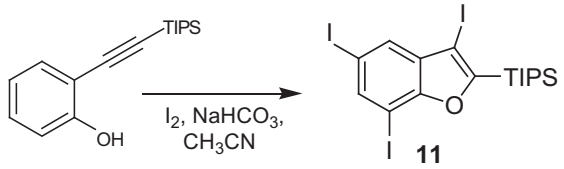
Comparable yield was also obtained when $PdCl_2(PPh_3)_2$ was used as a catalyst. Using the same protocol, **6b** was obtained in 73% yield. The presence of trimethylsilyl group at C-2 position of 3-iodoindole gave poor coupling yield (20%). Next step was the reduction of triple bond to single bond and it is worth to mention here that **6b** underwent smooth catalytic reduction[12] whereas **6a** gave problem. Initial attempt to reduce the triple bond of pure **6a** catalytically (Pd/C) using either triehylsilane[12] or hydrogen under atmospheric pressure[12] was not successful. Interestingly, the recovered starting material from the Pd/C reaction above smoothly afforded the reduced product on subsequent repetition of the same reaction. Following, it was revealed that prior treatment with activated charcoal was necessary to carry out the catalytic reduction of column purified **6a**. After charcoal treatment, triethylsilane-mediated reduction was completed within 15 min whereas atmospheric hydrogen pressure took overnight stirring. After acetal deprotection, oxidation followed by diazomethane treatment[13] tosyl-protected D-homotryptophan and its thio-analogue were obtained. Detosylation was carried out in the presence of Mg/MeOH/NH_4Cl[14a] to obtain D-homotryptophan derivative (D)-**1a** in 15.6% overall yield from **6a** (Scheme 3). Detosylation of (D)-**9** by TBAF/THF[14b] or Cs_2CO_3 in THF/MeOH[14c] failed. In both cases, the corresponding free acid was obtained. The 60% ee of (D)-**1a** was determined by HPLC using Chiralcel OD (250×4.6 mm) column.



Scheme 3. Synthesis of D-homotryptophan derivative and its sulfur analogue. Reaction conditions: (a) **3**, $Pd(OAc)_2$, PPh_3, CuI, DIPEA, 65 °C, 3.5–4 h; (b) 10% Pd/C, Et_3SiH, MeOH, 15 min, rt, for (D)-**7a**; 10% Pd/C, MeOH, H_2 (atmospheric pressure), overnight, rt, for **7b**; (c) PTSA, MeOH, 2 h, rt; (d) (i) 1 M Jones reagent, acetone, 0 °C, (ii) CH_2N_2, ether; (e) Mg, MeOH, NH_4Cl.

According to retrosynthetic route **A**, 3-iodobenzofuran was required for the synthesis of oxygen analogue **1b**. To the best of our

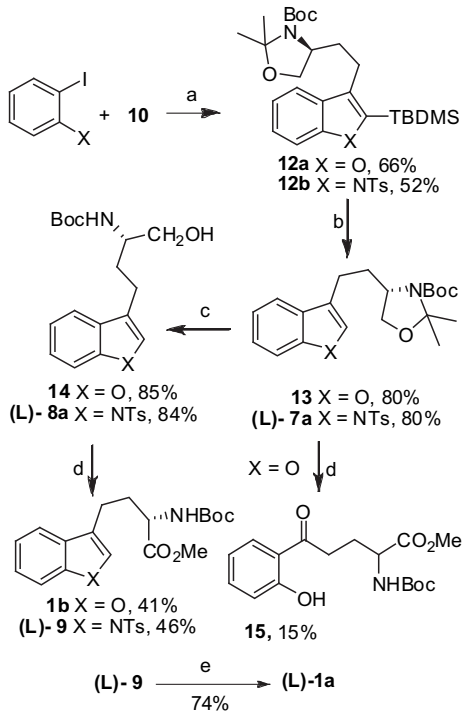
knowledge there is no suitable method for the synthesis of 3-iodobenzofuran. Larock attempted[15a] to synthesize this compound but landed with a complex mixture and Cacchi[15b] got aromatic electrophilic substituted product instead of iodocyclisation. To overcome the problem associated with trimethylsilylacetylene, we used triisopropylsilylacetylene and following Cacchi's method we obtained a complex mixture from where **11** was isolated in very small amount (Scheme 4). Next, we prepared 3-bromobenzofuran from benzofuran according to the literature procedure. Unfortunately, the coupling did not take place under standard Sonogashira conditions.



Scheme 4. Attempted synthesis of 3-iodobenzofuran.

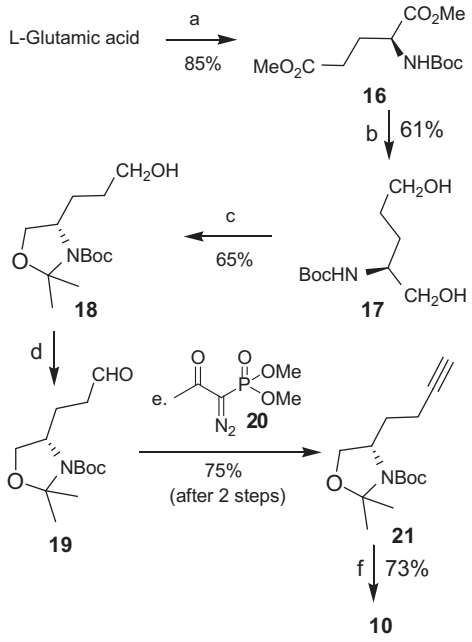
So, retrosynthetic strategy **B** was followed to prepare L-homotryptophan and its '*O*'-analogue using Larock's heteroannulation[16] as the key step.

According to Larock's protocol, 2-iodophenol was treated with silylated internal alkyne **10** to provide 2,3-disubstituted benzofuran **12a**, which after silyl-deprotection furnished **13**. Without deprotection of oxazolidine ring when **13** was subjected for Jones oxidation followed by diazomethane treatment, a complex mixture was obtained from where the keto-amino acid **15** was isolated in 15% yield. Interestingly, after acetal deprotection, the aminoalcohol **14**, under same oxidizing condition afforded the desired compound **1b** in 41% yield. Similarly L-homotryptophan derivative (L)-**1a** has been synthesized in 94% ee from *N*-tosyl-2-iodoaniline following the protocol as described for oxygen analogue (Scheme 5).



Scheme 5. Synthesis of L-homotryptophan derivative and its oxygen analogue. Reaction conditions: (a) $Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 80 °C, 12–20 h; (b) TBAF, THF, 1.5 h, rt; (c) PTSA, MeOH, 2 h, rt; (d) (i) 1 M Jones reagent, acetone, 0 °C, (ii) CH_2N_2, ether; (e) Mg, MeOH, rt.

The internal alkyne **10** was in turn synthesized from L-glutamic acid via the formation of aldehyde **19** (Scheme 6). The synthesis of aldehyde **19** has been previously reported[17] but the synthetic steps were different. The aldehyde was subsequently converted to alkyne using Bestmann–Ohira reagent[18] and silylation was carried out using a method reported for alkynylglycine derivatives.[19]



Scheme 6. Synthesis of silylated internal alkyne from L-glutamic acid. Reaction conditions: (a) (i) $SOCl_2$, MeOH, −5 °C to rt; (ii) Boc_2O, THF, Et_3N, 0 °C; (b) $LiBH_4$, THF/MeOH mixture, 0 °C; (c) 2,2-dimethoxypropane, $BF_3{\cdot}OEt_2$, acetone, rt, 2 h; (d) Dess–Martin periodinane, DCM, rt, 30 min (e) **20**, K_2CO_3, MeOH, 0 °C to rt, 4 h; (f) *n*-BuLi, THF, −78 °C, TBDMSCl, rt, 12 h.

3. Conclusion

In conclusion, the synthesis of optically active homotryptophan and its '*O*', '*S*' analogues is described. Though the synthesis of L-homotryptophan was reported by Cook and his group with a high overall yield (65%), but many functional groups may not survive under their conditions as strong reagents like *t*-BuLi and *n*-BuLi were used. Our synthetic route is mild and flexible and manipulation of starting materials can give several other tryptophan analogues.

4. Experimental section

4.1. General information

All reagents were purchased from commercial sources and used without further purification, unless otherwise stated. Petroleum ether (PE) refers to the fraction of petroleum boiling between 60 and 80 °C. THF is the abbreviation of tetrahydrofuran. All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents and standard syringe and septum techniques unless otherwise indicated. Organic extracts were dried over anhydrous Na_2SO_4 and then filtered prior to removal of all volatiles under reduced pressure on rotary evaporation. Chromatographic purification of products was accomplished using column chromatography on silica gels (mesh 100–200). Thin-layer chromatography (TLC) was carried out on aluminum sheets, Silica Gel 60 F_{254} (Merck; layer thickness 0.25 mm). Visualization of the developed chromatogram was performed by UV light and/or phosphomolybdic acid stains. Optical rotations were measured at

stated temperature and solvent; Concentration was in gm/100 mL when $[\alpha]_D$ was recorded. ^1H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively, using $CDCl_3$ as solvent. Chemical shifts (δ) are given in parts per million relative to the solvent residual peak or TMS as internal standard. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad.

4.2. Experimental procedure

*4.2.1. (R)-tert-Butyl-2,2-dimethyl-4-(2-(1-tosyl-1H-indol-3-yl)ethynyl)oxazolidine-3-carboxylate (**6a**).* To a stirred degassed solution of *N*-tosyl-3-iodoindole **2a** (170 mg, 0.43 mmol) and **3** (114 mg, 0.51 mmol) in diisopropylethylamine (5 mL) under nitrogen were added $Pd(OAc)_2$ (9.6 mg, 0.043 mmol), PPh_3 (45 mg, 0.17 mmol), and copper iodide (8 mg, 0.043 mmol), respectively. The yellowish solution was degassed again and heated at 65 °C for 4 h. The reaction mixture was diluted with ether and filtered through a Celite pad. After solvent evaporation in vacuo residue was directly charged in silica gel column, eluting with petroleum ether/AcOEt (9:1), to give **6a**, 158 mg (74%) as yellowish white foam.

Treatment of **6a** (yellowish white foam) with activated charcoal in methanol (5 mL) was performed and filtered through Celite. After solvent removal, the material was passed through a short silica gel column to get **6a**, 140 mg (66.2%) as white foam.

R_f (20% AcOEt/PE) 0.70; $[\alpha]_D^{26}$ −87.9 (*c* 1.07, $CHCl_3$); IR: (neat/$CHCl_3$) ν 2235, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, 1H, *J*=8.5 Hz), 7.75 (d, 2H, *J*=8.0 Hz),7.69 (s, 1H), 7.58 (d, 1H, *J*=7.5 Hz), 7.33 (t, 1H, *J*=7 Hz), 7.25 (m, 1H), 7.20 (d, 2H, *J*=8.0 Hz), 4.78–4.89 (br m, 1H), 4.10–4.14 (m, 2H), 2.31 (s, 3H), 1.69 (s, 3H), 1.50–1.54 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 145.4, 135.0, 134.3, 131.0, 130.1, 128.9, 127.0, 125.5, 123.8, 120.4, 113.7, 104.9, 94.6, 94.2*, 92.7, 80.8*, 80.4, 73.3, 69.1, 49.4, 28.6, 27.2*, 26.2, 25.4*, 24.5, 21.6 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{27}H_{30}N_2O_5SNa^+$=517.1773, found 517.1771.

*4.2.2. (R)-tert-Butyl 4-(2-(benzo[b]thiophen-3-yl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**6b**).* According to the procedure outlined for **6a**, 3-iodobenzo[*b*]thiophene **2b** (34 mg, 0.13 mmol) and **3** were heated for 3.5 h to yield the coupling product **6b** (34 mg, 73%) as white solid.

R_f (10% AcOEt/PE) 0.50; $[\alpha]_D^{26}$ −148.8 (*c* 0.30, $CHCl_3$); IR: (neat/$CHCl_3$) ν 2227,1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.84 (d, 1H, *J*=7.5 Hz), 7.57 (s, 1H), 7.37–7.44 (m, 2H), 4.83–4.93 (br m, 1H), 4.14–4.17 (m, 2H), 1.72 (s, 3H), 1.57 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 139.2, 138.7, 129.8, 125.0, 124.6, 122.8, 122.5, 117.8, 94.4, 90.9, 80.3, 75.8, 68.9, 49.2, 28.4, 27.1*, 26.1, 25.3*, 24.4 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{20}H_{23}NO_3SNa^+$=380.1296, found 380.1292.

*4.2.3. (R)-tert-Butyl 2,2-dimethyl-4-(2-(1-tosyl-1H-indol-3-yl)ethyl) oxazolidine-3-carboxylate (D)-**7a**.* To the methanolic solution of white foamy **6a** (140 mg, 0.28 mmol) were added 10% Pd/C (20 mg) followed by triethylsilane (0.44 mL, 2.8 mmol) dropwise under argon atmosphere. The reaction started with evolution of gas. After completion of the reaction (TLC), the reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The crude product was purified by short silica gel column chromatography, eluting with petroleum ether/AcOEt (9:1), to obtain 117 mg (84%) of (D)-**7a**, as white foam.

R_f (20% AcOEt/PE) 0.70; $[\alpha]_D^{26}$ −24.2 (*c* 1.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, 1H, *J*=8.0 Hz), 7.66 (d, 2H, *J*=8.0 Hz), 7.37 (d, 1H, *J*=7.5 Hz), 7.32 (s, 0.5H), 7.20–7.23 (m, 1.5H), 7.14 (br s, 1H), 7.10 (d, 2H, *J*=7.5 Hz), 3.66–3.93 (m, 3H), 2.56 (br s, 2H), 2.22 (s, 3H), 2.09 (br s, 0.5H), 1.95 (br s, 0.5H), 1.81–1.87 (m, 1H), 1.26–1.53 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 151.9*, 144.7, 135.5, 131.0, 130.9, 129.9, 126.8, 124.8, 124.7, 123.1, 122.7, 122.6, 122.4, 119.4, 113.9, 93.9, 93.4*, 80.2, 79.6*, 66.9, 57.5, 57.0*, 32.9, 32.2*, 28.5, 27.7, 26.9*, 24.6, 23.3*, 21.8, 21.6 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{27}H_{34}N_2O_5SNa^+$=521.2086, found 521.2086.

*4.2.4. (R)-tert-Butyl 4-(2-(benzo[b]thiophen-3-yl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (**7b**).* A solution of **6b** (34 mg, 0.095 mmol) in methanol (1.5 mL) containing 10% Pd/C (5 mg) was evacuated, before being exposed to hydrogen atmosphere and stirred for overnight under atmospheric hydrogen pressure. The suspension was filtered and the solvent was removed in vacuo. The crude residue was purified by short silica gel column chromatography, eluting with petroleum ether/AcOEt (95:5), to afford **7b** as a white solid (29 mg, 80%).

R_f (10% AcOEt/PE) 0.52; $[\alpha]_D^{26}$ −27.4 (*c* 1.24, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, 1H, *J*=7 Hz), 7.73 (d, 1H, *J*=7 Hz), 7.34–7.39 (m, 2H), 7.10 (s, 0.5H), 7.23 (s, 0.4H), 3.79–4.10 (m, 3H), 2.86 (br s, 2H), 2.10–2.26 (two br s, 1H), 1.96–2.03 (m, 1H), 1.38–1.63 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 152.0*, 140.7, 139.1, 139.0*, 135.9, 124.4, 124.3*, 124.0, 123.1, 123.0*, 121.6, 121.4, 94.0, 93.4*, 80.2, 79.8*, 67.0, 57.6, 57.2*, 33.1, 32.3*, 28.7, 28.6, 28.4, 27.8, 27.0*, 25.4, 24.7, 23.4* (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{20}H_{27}NO_3SNa^+$=384.1609, found 384.1608.

*4.2.5. tert-Butyl (R)-1-hydroxy-4-(1-tosyl-1H-indol-3-yl)butan-2-ylcarbamate (D)-**8a**.* To a solution of (D)-**7a** (350 mg, 0.7 mmol) in methanol (5 mL) was added *p*-toluensulfonic acid (PTSA) monohydrate (66 mg, 0.350 mmol) and stirred at rt for 2 h. The solution was then neutralized with saturated aqueous $NaHCO_3$, diluted with AcOEt (8 mL), and washed with brine (2×5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a silica gel column with petroleum ether/AcOEt (7: 3) to give (D)-**8a** (250 mg, 78%) as white foam.

R_f (30% AcOEt/PE) 0.20; $[\alpha]_D^{26}$−2.7 (*c* 1.22, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3404, 1693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J*=8 Hz), 7.73 (d, 2H, *J*=8 Hz), 7.45 (d, 1H, *J*=7.5 Hz), 7.34 (s, 1H), 7.29 (t, 1H, *J*=7.5 Hz), 7.20 (d, 1H, *J*=8.0 Hz), 7.17 (d, 2H, *J*=8.0 Hz), 4.89 (br s, 1H), 4.10–4.12 (m, 2H), 3.59 (dd, 1H, *J*=5.2, 10.5 Hz), 2.68–2.77 (m, 3H), 2.29 (s, 3H), 1.89–1.92 (m, 1H), 1.78–1.83 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 144.8, 135.4, 135.3, 130.9, 129.9, 126.8, 124.8, 123.1, 122.9, 122.6, 119.5, 113.8, 79.8, 65.6, 52.6, 30.9, 28.5, 21.6, 21.5; HRMS (ESI) $(M+Na)^+$ calculated for $C_{24}H_{30}N_2O_5SNa^+$=481.1773, found 481.1732.

*4.2.6. tert-Butyl (R)-4-(benzo[b]thiophen-3-yl)-1-hydroxybutan-2-ylcarbamate (**8b**).* Starting oxazolidine **7b** (29 mg, 0.08 mmol) according to the procedure described for (D)-**8a**, gave the aminoalcohol **8b** (22 mg, 85%) as white solid.

R_f (20% AcOEt/PE) 0.20; $[\alpha]_D^{26}$ +9.4 (*c* 2.41, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3352, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, 1H, *J*=7.5 Hz), 7.73 (d, 1H, *J*=8.0 Hz), 7.32–7.38 (m, 2H), 7.14 (s, 1H), 4.74 (br s, 1H), 3.60–3.74 (m, 3H), 2.88–2.97 (m, 2H), 2.41(br s, 1H), 1.95–2.01 (m, 1H), 1.85–1.89 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 140.5, 138.7, 135.7, 124.2, 123.8, 122.9, 121.5, 121.4, 79.7, 65.7, 52.5, 31.0, 28.3, 25.0; HRMS (ESI) $(M+Na)^+$ calculated for $C_{17}H_{23}NO_3SNa^+$=344.1296, found 344.1298.

*4.2.7. tert-Butyl (R)-1-(methoxycarbonyl)-3-(1-tosyl-1H-indol-3-yl) propylcarbamate (D)-**9**.* To a solution of aminoalcohol (D)-**8a** (42 mg, 0.092 mmol) in acetone (1.5 mL) at 0 °C was added freshly prepared Jones reagent (1 M, 0.28 mL, 0.28 mmol) dropwise under nitrogen. After completion of the reaction (TLC), it was quenched with isopropyl alcohol (0.3 mL) and partitioned with AcOEt (20 mL) and saturated NH_4Cl (7 mL). After stirring the solution for 1 h, the aqueous layer was separated and re-extracted with AcOEt (20 mL),

and the combined organic layers were dried, filtered, and concentrated in vacuo to about 7 mL in volume. The solution of the crude acid was cooled to 0 °C. Excess ethereal diazomethane was added, and the reaction mixture was stirred for 10 min. The diazomethane was blown off with nitrogen, the organic layer was washed with aqueous $NaHCO_3$ (7 mL), saturated NH_4Cl (7 mL), dried, filtered, and concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography, eluting with DCM/AcOEt (95:5), to afford (D)-**9** (23 mg, 51%) as white foam.

Comparable yield (48%) was obtained in two steps oxidation via the formation of aldehyde using Dess–Martin periodinane.

R_f (5% AcOEt/CH_2Cl_2) 0.85; $[\alpha]_D^{26}$ −17.8 (*c* 0.91, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3394, 1743, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J*=8.5 Hz), 7.75 (d, 2H, *J*=8.5 Hz), 7.44 (d, 1H, *J*=7.5 Hz), 7.34 (s, 1H), 7.30 (t, 1H, *J*=7.5 Hz), 7.20–7.24 (m, 3H,), 5.10 (br d, 1H, *J*=7.0 Hz), 4.38 (br d, 1H, *J*=5 Hz), 3.70 (s, 3H), 2.70–2.75 (m, 2H), 2.33 (s, 3H), 2.21 (br s, 1H), 1.98–2.01(m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 155.4, 144.8, 135.4, 130.8, 129.9, 126.9, 124.8, 123.13, 123.08, 121.6, 119.4, 113.9, 80.2, 53.2, 52.4, 32.1, 28.4, 21.6, 21.0; HRMS (ESI) $(M+Na)^+$ calculated for $C_{25}H_{30}N_2O_6SNa^+$=509.1722, found 509.1722.

*4.2.8. tert-Butyl (R)-1-(methoxycarbonyl)-3-(1H-indol-3-yl)propylcarbamate (D)-**1a**.* After the commencement of H_2 gas evolution from a mixture of activated Mg turnings (40 mg, 1.7 mmol) and dry methanol (2.5 mL) was added a solution of compound (D)-**9** (20 mg, 0.04 mmol) in methanol (1 mL) followed by (16 mg, 0.3 mmol) of ammonium chloride. The reaction mixture was stirred for 3 h at rt and was quenched with saturated ammonium chloride solution (2 mL). It was extracted with EtOAc (3×5 mL). The whole organic layers were washed with brine, dried, filtered, and concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography to afford (D)-**1a** (9.2 mg, 70%) as white foam. Enantiomeric excess (60% ee) was determined by HPLC with a Chiralcel OD (250×4.6 mm, particle size 10 μm) column (isopropanol/hexane=20:80, 1 mL/min), t_R (major)=11 min (D-isomer), t_R (minor)=17.76 min (L-isomer).

R_f (5% AcOEt/CH_2Cl_2) 0.60; $[\alpha]_D^{26}$ −18.6 (*c* 0.22, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3373, 3363, 1737, 1693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.57 (d, 1H, *J*=8.0), 7.34 (d, 1H, *J*=8.0 Hz), 7.19 (t, 1H, *J*=7.5 Hz), 7.11 (t, 1H, *J*=7.3 Hz), 7.02 (s, 1H), 5.09 (br d, 1H, *J*=7.0 Hz), 4.41 (br d, 1H, *J*=5 Hz), 3.67 (s, 3H), 2.83 (t, 2H, *J*=7.75 Hz), 2.22–2.26 (m, 1H), 2.02–2.08 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.6, 136.5, 127.4, 122.2, 121.8, 119.5, 118.9, 115.1, 111.3, 80.1, 53.4, 52.3, 33.1, 28.5, 21.1; HRMS (ESI) $(M+Na)^+$ calculated for $C_{18}H_{24}N_2O_4Na^+$=355.1634, found 355.1635.

*4.2.9. tert-Butyl (R)-1-(methoxycarbonyl)-3-(benzo[b]thiophen-3-yl) propylcarbamate (**1c**).* The aminoalcohol **8b** (20 mg, 0.064 mmol), similarly converted to methylester **1c** in 48% (10.8 mg) yield as white solid using the procedure described for (D)-**9**.

R_f (20% AcOEt/PE) 0.50; $[\alpha]_D^{26}$ −29.5 (*c* 0.34, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3367, 1761, 1681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, 1H, *J*=7.5 Hz), 7.71 (d, 1H, *J*=7.0 Hz), 7.32–7.39 (m, 2H), 7.14 (s, 1H), 5.14 (br d, 1H, *J*=7.0 Hz), 4.45 (br d, 1H, *J*=5 Hz), 3.71 (s, 3H), 2.88–2.93 (m, 2H), 2.28–2.30 (m, 1H), 2.07–2.10 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 155.4, 140.5, 138.7, 135.0, 124.3, 123.9, 122.9, 121.8, 121.5, 80.1, 53.2, 52.4, 32.2, 28.3, 24.3; HRMS (ESI) $(M+Na)^+$ calculated for $C_{18}H_{23}NO_4SNa^+$=372.1245, found 372.1241.

*4.2.10. (S)-tert-Butyl 4-(2-(2-(tert-butyldimethylsilyl)benzofuran-3-yl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (**12a**).* To a solution of 2-iodophenol (151 mg, 0.68 mmol) and (*S*)-*tert*-butyl-4-(4-(*tert*-butyldimethylsilyl)but-3-ynyl)-2,2-dimethyloxazolidine-3-carboxylate **10** (210 mg, 0.57 mmol) in dry DMF (3 mL) were added lithium chloride (24 mg, 0.57 mmol) and sodium carbonate (181 mg, 1.7 mmol). The reaction vessel was evacuated and flushed with argon three times. Palladium acetate (12.7 mg, 0.057) was added; the reaction mixture was again flushed with argon and heated at 80 °C for overnight. The reaction mixture was cooled to rt and the solvent was removed. The crude residue was subjected for column purification, eluting with petroleum ether/AcOEt (96:4), to afford **12a** as colorless oil (172 mg, 66%).

R_f (10% AcOEt/PE) 0.65; $[\alpha]_D^{27}$ +33.5 (*c* 1.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.59 (m, 1H), 7.47 (d, 1H, *J*=7.5 Hz), 7.23–7.28 (m, 1H), 7.22 (t, 1H, *J*=7.25 Hz), 3.88–4.06 (m, 3H), 2.79 (br s, 2H), 2.01 (br s, 2H), 1.45–1.66 (m, 15H), 0.99 (s, 9H), 0.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 156.2, 152.4, 152.0*, 130.7, 130.4*, 128.9, 124.4, 124.3*, 121.9, 119.7, 119.4*, 111.5, 111.4*,110.5, 94.0, 93.5*, 80.1, 79.7*, 67.2, 57.6, 57.4*, 34.9, 34.5*, 28.6, 28.4, 27.6, 26.9, 26.7, 26.6, 24.6, 23.3*, 21.4, 18.1, 17.6, −5.2; HRMS (ESI) $(M+Na)^+$ calculated for $C_{26}H_{41}NO_4SiNa^+$=482.2703, found 482.2704.

*4.2.11. (S)-tert-Butyl 4-(2-(2-(tert-butyldimethylsilyl)-1-tosyl-1H-indol-3-yl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (**12b**).* The heteroannulation for *N*-tosyl-2-iodoaniline was carried out on 0.134 mmol scale using 1.2 equiv of **10**, as described for compound **12a**. Yield: 52% (43 mg).

R_f (20% AcOEt/PE) 0.80; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.37–7.43 (m, 3H), 7.21 (br s, 1H), 7.16 (t, 1H, *J*=7.25 Hz), 7.06 (d, 2H, *J*=8.0 Hz), 3.80–4.14 (m, 3H), 2.87 (br m, 2H), 2.27 (s, 3H), 1.90 (br s, 2H), 1.48–1.62 (m, 15H), 1.07 (s, 9H), 0.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 152.1*, 143.9, 140.3, 139.2, 138.8*, 136.9, 136.0, 132.3, 129.3, 126.3, 125.3, 123.4, 119.4, 119.2*, 116.1, 116.0*, 94.1, 93.7*, 80.2, 80.0*, 67.2, 67.0*, 57.5, 34.4, 28.6, 27.5, 26.8*, 24.5, 23.4, 23.2*, 21.5, 19.0, 0.81 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{33}H_{48}N_2O_5SSiNa^+$=635.2951, found 635.2952.

*4.2.12. (S)-tert-Butyl 4-(2-(benzofuran-3-yl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate (**13**).* To a solution of **12a** (150 mg, 0.32 mmol) in THF (5 mL) was added tetrabutyl ammonium fluoride (0.4 mL of 1.0 M in THF, 0.4 mmol) at 0 °C and stirred at rt for 1 h. After removal of solvent the crude residue was charged directly into silica gel column, eluting with petroleum ether/AcOEt (94:6), to give **13** as a white solid (98 mg, 80%).

R_f (10% AcOEt/PE) 0.50; $[\alpha]_D^{26}$ +28.6 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.43–7.46 (m, 2H), 7.23–7.28 (m, 2H), 3.81–4.07 (m, 3H), 2.69 (br s, 2H), 2.20 (br s, 0.5H), 2.06 (br s, 0.5H), 1.94–2.00 (m, 1H), 1.39–1.65 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.5, 152.0*, 141.4, 141.1*, 128.2, 124.4, 124.3*, 122.4, 119.8, 119.6, 119.5, 111.6, 94.0, 93.4*, 80.2, 79.7*, 67.0, 57.6, 57.2*, 33.1, 32.4*, 28.6, 27.8, 27.0*, 24.7, 23.4*, 20.5 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{20}H_{27}NO_4Na^+$=368.1838, found 368.1838.

*4.2.13. (S)-tert-Butyl 2,2-dimethyl-4-(2-(1-tosyl-1H-indol-3-yl) ethyl)oxazolidine-3-carboxylate (L)-**7a**.* The silyl deprotection of **12b** was carried out as described above for compound **13** on 0.062 mmol scale. After silica gel chromatography (L)-**7a** was obtained as white foam (25 mg, 80%).

R_f (20% AcOEt/PE) 0.70; $[\alpha]_D^{26}$ +34.0 (*c* 1.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 1H, *J*=8.5 Hz), 7.75 (d, 2H, *J*=8.5 Hz), 7.46 (d, 1H, *J*=7.5 Hz), 7.39 (s, 0.5H), 7.31 (s, 1.5H), 7.16–7.24 (m, 3H), 3.74–3.93 (m, 3H), 2.64 (br s, 2H), 2.33 (s, 3H), 2.17 (br s, 0.5H), 2.02 (br s, 0.5H), 1.89–1.95 (m, 1H), 1.35–1.61 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 152.0*, 144.8, 135.6, 131.1, 129.9, 126.9, 126.4, 124.9, 124.8, 123.2, 122.8, 122.7, 122.4, 119.5, 113.9, 94.0, 93.5*, 80.3, 79.7*, 67.0, 57.6, 57.1*, 33.0, 32.3*, 28.6, 27.8, 27.0*, 26.0, 24.6, 23.3*, 22.8, 21.9, 21.7 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{27}H_{34}N_2O_5SNa^+$=521.2086, found 521.2085.

*4.2.14. tert-Butyl (S)-4-(benzofuran-3-yl)-1-hydroxybutan-2-ylcarbamate (**14**).* According to the procedure described for (D)-

8a, oxazolidine **13** (93 mg, 0.26 mmol) gave the aminoalcohol **14** (68 mg, 85%) as white solid.

R_f (20% AcOEt/PE) 0.20; $[\alpha]_D^{26}$ −14.4 (*c* 1.31, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3358, 1687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, 1H, *J*=7.5 Hz), 7.44–7.46 (m, 2H), 7.25–7.29 (m, 1H), 7.22 (t, 1H, *J*=7.5 Hz), 4.78 (br d, 1H, *J*=7.5 Hz), 3.58–3.70 (m, 3H), 2.71–2.78 (m, 2H), 2.58 (br s, 1H), 1.91–1.97 (m, 1H), 1.80–1.86 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 155.5, 141.4, 128.1, 124.3, 122.4, 119.7, 119.6, 111.6, 79.9, 65.7, 52.6, 31.1, 28.5, 20.3; HRMS (ESI) $(M+Na)^+$ calculated for $C_{17}H_{23}NO_4Na^+$=328.1525, found 328.1523.

*4.2.15. tert-Butyl (S)-1-hydroxy-4-(1-tosyl-1H-indol-3-yl)butan-2-ylcarbamate (L)-**8a**.* According to the procedure described for (D)-**8a**, oxazolidine (L)-**7a** (25 mg, 0.05 mmol) gave the aminoalcohol (L)-**8a** (19.3 mg, 84%) as white solid.

R_f (30% AcOEt/PE) 0.25; $[\alpha]_D^{26}$ +2.92 (*c* 2.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J*=8.5 Hz), 7.74 (d, 2H, *J*=8.5 Hz), 7.46 (d, 1H, *J*=8.0 Hz), 7.34 (s, 1H), 7.23 (t, 1H, *J*=7.5 Hz), 7.19–7.23 (m, 3H), 3.59–3.70 (m, 3H), 2.71–2.77 (m, 2H), 2.32 (s, 3H), 1.92–1.93 (m, 1H), 1.79–1.82 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 144.8, 135.51, 135.49, 130.9, 129.9, 126.9, 124.8, 123.2, 123.0, 122.5, 119.5, 113.9, 79.9, 65.9, 52.6, 30.9, 28.5, 21.7, 21.6; HRMS (ESI) $(M+Na)^+$ calculated for $C_{24}H_{30}N_2O_5SNa^+$=481.1773, found 481.1771.

*4.2.16. tert-Butyl (S)-1-(methoxycarbonyl)-3-(benzofuran-3-yl)propylcarbamate (**1b**).* According to the procedure outlined for ester (D)-**9**, aminoalcohol **14** (18.3 mg, 0.06 mmol) afforded the methyl-ester **1b** (8.2 mg, 41%) as white solid.

R_f (20% AcOEt/PE) 0.55; $[\alpha]_D^{26}$ +25.6 (*c* 0.53, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3369, 1759, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J*=7.5 Hz), 7.44–7.47 (m, 2H), 7.22–7.30 (m, 2H), 5.12 (br d, 1H, *J*=7.0 Hz), 4.42 (br d, 1H, *J*=4.5 Hz), 3.71 (s, 3H), 2.73–2.77 (m, 2H), 2.25–2.26 (m, 1H), 2.01–2.06 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 155.6, 141.6, 128.0, 124.4, 122.5, 119.6, 119.1, 111.7, 80.2, 53.4, 52.5, 32.2, 28.5, 28.2, 19.7; HRMS (ESI) $(M+Na)^+$ calculated for $C_{18}H_{23}NO_5Na^+$=356.1474, found 356.1474.

*4.2.17. tert-Butyl (S)-1-(methoxycarbonyl)-3-(1-tosyl-1H-indol-3-yl) propylcarbamate (L)-**9**.* Using the procedure outlined for ester (D)-**9**, aminoalcohol (L)-**8a** (19 mg, 0.041 mmol) afforded the ester (L)-**9** in 46% yield (9.1 mg) as white foam.

R_f (5% AcOEt/CH_2Cl_2) 0.80; $[\alpha]_D^{26}$ +26.8 (*c* 1.03, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3381, 1743, 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J*=8.0 Hz), 7.75 (d, 2H, *J*=8.0 Hz), 7.44 (d, 1H, *J*=7.5 Hz), 7.34 (s, 1H), 7.30 (t, 1H, *J*=8.0 Hz), 7.19–7.23 (m, 3H), 5.10 (br d, 1H, *J*=7.0 Hz), 4.37 (br s, 1H), 3.70 (s, 3H), 2.70–2.74 (m, 2H), 2.32 (s, 3H), 2.17–2.22 (m, 1H), 1.98–2.02 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 155.5, 144.9, 135.5, 130.8, 130.0, 127.0, 124.9, 123.2, 123.1, 121.7, 119.4, 113.9, 80.2, 53.3, 52.3, 32.2, 28.5, 21.7, 21.0; HRMS (ESI) $(M+Na)^+$ calculated for $C_{25}H_{30}N_2O_6SNa^+$=509.1722, found 509.1720.

*4.2.18. tert-Butyl (S)-1-(methoxycarbonyl)-3-(1H-indol-3-yl)propylcarbamate (L)-**1a**.* The tosyl deprotection of (L)-**9** was carried out as described above for compound (D)-**1a** on 0.022 mmol scale. After silica gel chromatography (L)-**1a** was obtained as white foam (5.4 mg, 74%). Enantiomeric excess (94% ee) was determined by HPLC with a Chiralcel OD (250×4.6 mm, particle size 10 μm) column (isopropanol/hexane=20:80, 1 mL/min), t_R (minor)=11.3 min (D-isomer), t_R (major)=17.6 min (L-isomer).

R_f (5% AcOEt/CH_2Cl_2) 0.60; $[\alpha]_D^{26}$ +26.6 (*c* 0.50, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3371, 1735, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.56 (d, 1H, *J*=7.5 Hz), 7.35 (d, 1H, *J*=8.0 Hz), 7.19 (t, 1H, *J*=7.5 Hz), 7.11 (t, 1H, *J*=7.5 Hz), 7.02 (s, 1H), 5.09 (d, 1H, *J*=7.5 Hz), 4.41 (d, 1H, *J*=5 Hz), 3.67 (s, 3H), 2.83 (t, 2H, *J*=7.75 Hz), 2.20–2.27 (m, 1H), 2.01–2.08 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.6, 136.5, 127.4, 122.2, 121.8, 119.4, 118.9, 115.0, 111.3, 80.1, 53.4, 52.3, 33.1, 28.5, 21.1; HRMS (ESI) $(M+Na)^+$ calculated for $C_{18}H_{24}N_2O_4Na^+$=355.1634, found 355.1633.

*4.2.19. tert-Butyl (S)-1-(methoxycarbonyl)-4-oxopentylcarbamate (**16**).* Freshly distilled thionyl chloride (0.60 mL, 8.16 mmol) was added dropwise with stirring to a cooled suspension of L-glutamic acid (1.0 g, 6.8 mmol) in anhydrous methanol (7 mL). The reaction mixture was stirred at rt for 2 h and was refluxed for 8 h. The solvent was removed under reduced pressure and co-evaporated with methanol (3×7 mL) to afford crude product as sticky liquid. To a solution of this crude product in THF (20 mL) were added triethylamine (2.0 mL, 14.6 mmol) and a solution of di-*tert*-butyl dicarbonate (1.78 g, 8.16 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at rt for 8 h. After completion of the reaction, solvent was removed in vacuo and the residue partitioned between AcOEt (20 mL) and water (20 mL). The aqueous phase was extracted with AcOEt (2×15 mL) and the combined organic layers were washed with 3% HCl (15 mL), saturated $NaHCO_3$ (15 mL), and brine (20 mL), dried (Na_2SO_4), and evaporation of the solvent gave **16** (1.5 g, 85%) as a colorless liquid.

$[\alpha]_D^{26}$ +13.7 (*c* 0.89, $CHCl_3$), lit.[20] $[\alpha]_D^{25}$ +12.5 (*c* 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (br d, 1H, *J*=6.4 Hz), 4.28 (br d, 1H, *J*=4.6 Hz), 3.69 (s, 3H), 3.63 (s, 3H), 2.33–2.42 (m, 2H), 2.10–2.16 (m, 1H), 1.86–2.00 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 172.7, 155.4, 80.0, 52.9, 52.4, 51.8, 30.1, 28.3, 27.7; HRMS (ESI) $(M+Na)^+$ calculated for $C_{12}H_{21}NO_6Na^+$=298.1267, found 298.1266.

*4.2.20. tert-Butyl (S)-1,5-dihydroxypentan-2-ylcarbamate (**17**).* To a solution of diester **16** (1.46 g, 5.33 mmol) in THF (20 mL) was added $LiBH_4$ portionwise at 0 °C followed by MeOH (0.37 mL) in THF (7 mL) dropwise and left for overnight stirring at rt. After solvent removal, ethyl acetate (50 mL) and water (60 mL) were added at 0 °C. The organic layer was then washed with brine (30 mL), dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed on silica gel (petroleum ether/AcOEt 1:1) to yield **17** (712 mg, 61%) as a sticky liquid.

IR: (neat/$CHCl_3$) ν 3340, 1687 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (br s, 1H), 3.56–3.61 (m, 5H), 3.39–3.42 (br m, 2H), 1.41–1.61 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 79.7, 65.0, 62.2, 52.4, 28.8, 28.5, 28.1; HRMS (ESI) $(M+Na)^+$ calculated for $C_{10}H_{21}NO_4Na^+$=242.1368, found 242.1367.

*4.2.21. (S)-tert-Butyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (**18**).* To a solution of diol **17** (1.1 g, 4.6 mmol) in a mixture of acetone (15 mL) and 2,2-dimethoxypropane (5 mL) was added $BF_3 \cdot OEt_2$ (0.03 mL) and the resulting solution was stirred for 2 h. After the consumption of starting material, solvent was removed and the residual oil was taken up in dichloromethane (15 mL). The resulting solution was washed with a mixture of saturated $NaHCO_3$ and H_2O (1:1, 10 mL), brine (10 mL), and dried over Na_2SO_4. After filtration and solvent removal, the crude oil was purified by column chromatography to give **18** (700 mg, 65%) as a colorless oil.

$[\alpha]_D^{26}$ +28.5 (*c* 0.89, $CHCl_3$), lit.[17] $[\alpha]_D^{25}$ +31 (*c* 1.0, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3444, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64–3.93 (m, 5H), 2.15 (br s, 2H), 1.49–1.61 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 151.8*, 93.7, 93.2*, 80.2, 79.5*, 67.1, 62.4, 57.1, 30.0, 29.7*, 29.4, 28.9*, 28.4, 27.5, 26.7*, 24.5, 23.2* (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{14}H_{25}NO_4Na^+$=282.1681, found 282.1681.

*4.2.22. (S)-tert-Butyl 4-(but-3-ynyl)-2,2-dimethyloxazolidine-3-carboxylate (**21**).* To a solution of aminoalcohol **18** (500 mg, 1.93 mmol) in dichloromethane (16 mL) was added solid periodinane (982 mg, 2.3 mmol) portionwise and stirred for 0.5 h. After consumption of starting material (TLC), it was diluted with ether (40 mL) and the resulting suspension was added to 1.3 M NaOH (16 mL). The reaction mixture was stirred for 15 min, ether layer

was washed with a mixture of 1.3 M NaOH (16 mL) and water (24 mL). The organic layer was dried, filtered, concentrated in vacuo, and used in the next step without further purification.

To a cooled (0 °C) stirred solution of above crude aldehyde **19** and phosphonate **20** (555 mg, 2.89 mmol) in MeOH (11 mL) was added K_2CO_3 (530 mg, 3.86 mmol) portionwise. The reaction mixture was stirred at 0 °C for 1 h, and then warmed to rt. Stirring was continued until the reaction was completed (~5 h) as indicated by TLC (9:1 petroleum ether/AcOEt). The mixture was then diluted with saturated aqueous NH_4Cl (15 mL) and extracted with diethyl ether (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a silica gel column with petroleum ether/AcOEt (95:5) to give **21** (370 mg, 75%, after two steps) as a crystalline solid.

R_f (10% AcOEt/PE) 0.60; $[\alpha]_D^{26}$ +1.41 (*c* 0.89, $CHCl_3$); IR: (neat/$CHCl_3$) ν 3308, 3263, 2117, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94–3.98 (m, 2H), 3.80–3.83 (m, 1H), 2.18–2.24 (m, 2H), 1.89–2.01 (m, 2H), 1.74–1.78 (m, 1H), 1.48–1.59 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 151.8*, 93.8, 93.3*, 83.7, 83.4*, 80.2, 79.8*, 69.0, 66.8, 57.1, 56.6*, 32.1, 31.7*, 28.6, 27.7, 26.9*, 24.5, 23.3*, 15.6 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{14}H_{23}NO_3Na^+$=276.1576, found 276.1573.

*4.2.23. (S)-tert-Butyl 4-(4-(tert-butyldimethylsilyl)but-3-ynyl)-2,2-dimethyloxazolidine-3-carboxylate (**10**).* To a solution of **21** (800 mg, 3.2 mmol) in anhydrous THF (10 mL) at −78 °C was added dropwise *n*-butyllithium (2.4 mL, 1.2 equiv, 1.6 M in hexane) followed by a solution of *tert*-butyl dimethyl silylchloride (528 mg, 1.1 equiv) in THF (5 mL) under an argon atmosphere. The reaction mixture was allowed to warm up to 25 °C and stirred overnight. Quenching was performed by the addition of cold water (15 mL). The aqueous phase was extracted with ethyl acetate (3×7 mL). The combined organic layers were dried, concentrated, and purified to yield **10** (857 mg, 73%) as a colorless oil.

R_f (10% AcOEt/PE) 0.75; $[\alpha]_D^{26}$ +3.04 (*c* 1.63, $CHCl_3$); IR: (neat/$CHCl_3$) ν 2173, 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.89–3.95 (m, 3H), 2.26–2.30 (m, 2H), 1.90–1.99 (m, 1H), 1.76 (m, 1H), 1.47–1.58 (m, 15H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 151.8*, 107.1, 106.5*, 93.8, 93.3*, 83.5, 80.2, 79.7*, 67.0, 57.6, 56.9*, 32.2, 32.1*, 28.6, 27.6, 26.9*, 26.2, 24.6, 23.3*, 17.1, 16.6, −4.4 (*asterisk denotes conformer peaks); HRMS (ESI) $(M+Na)^+$ calculated for $C_{20}H_{37}NO_3SiNa^+$=390.2440, found 390.2441.

Acknowledgements

S.S. thanks DST, India, for financial support by a grant [SR/S1/OC-38/2007]. K.G. and S.P. are thankful to CSIR for their fellowship.

Supplementary data

Spectroscopic data as well as copies of the spectra of all new compounds are provided. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.055.

References and notes

1. (a) Röhrig, U. F.; Awad, L.; Grosdidier, A.; Larrieu, P.; Stroobant, V.; Colau, D.; Cerundolo, V.; Simpson, A. J. G.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2010**, *53*, 1172; (b) Botting, N. P. *Chem. Soc. Rev.* **1995**, *24*, 401.
2. Forouhar, F.; Anderson, J. L. R.; Mowat, C. G.; Vorobiev, S. M.; Hussain, A.; Abashidze, M.; Bruckmann, C.; Thackray, S. J.; Seetharaman, J.; Tucker, T.; Xiao, R.; Ma, L. C.; Zhao, L.; Acton, T. B.; Montelione, G. T.; Chapman, S. K.; Tong, L. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 473.
3. Cady, S. G.; Sono, M. *Arch. Biochem. Biophys.* **1991**, *291*, 326.
4. Lu, C.; Lin, Y.; Yeh, S. R. *J. Am. Chem. Soc.* **2009**, *131*, 12866.
5. (a) Peterson, A. C.; Migawa, M. T.; Martin, M. J.; Hamaker, L. K.; Czerwinski, K. M.; Zhang, W.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1994**, *3*, 531; (b) Peterson, A. C.; Laloggia, A. J.; Hamaker, L. K.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1993**, *3*, 473.
6. (a) Podea, P. V.; Toşa, M. I.; Paizs, C.; Irimie, F. D. *Tetrahedron: Asymmetry* **2008**, *19*, 500; (b) Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781; (c) van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2004**, *346*, 823; (d) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525; (e) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717.
7. Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539.
8. Suzuki, N.; Yasaki, S.; Yasuhara, A.; Sakamoto, T. *Chem. Pharm. Bull.* **2003**, *51*, 1170.
9. Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905.
10. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467; (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
11. (a) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18; (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31; (c) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527; (d) Crisp, G. T.; Jiang, Y. L.; Pullman, P. J.; Savi, C. D. *Tetrahedron* **1997**, *53*, 17489.
12. (a) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599; (b) Sauvage, J. F.; Baker, R. H.; Hussey, A. S. *J. Am. Chem. Soc.* **1960**, *82*, 6090; (c) Jourdant, A.; Gonzalez-Zamora, E.; Zhu, J. *J. Org. Chem.* **2002**, *67*, 3163.
13. Dondoni, A.; Giovannini, P. P.; Massi, A. *Org. Lett.* **2004**, *6*, 2929.
14. (a) Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 5239; (b) Nishikawa, T.; Koide, Y.; Kanakubo, A.; Yoshimura, H.; Isobe, M. *Org. Biomol. Chem.* **2006**, *4*, 1268; (c) Bajwa, J. S.; Chen, G.-P.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425.
15. (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292; (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Morob, L. *Synlett* **1999**, 1432.
16. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
17. Truchot, C.; Wang, Q.; Sasaki, N. A. *Eur. J. Org. Chem.* **2005**, 1765.
18. (a) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721; (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
19. Meffre, P.; Gauzy, L.; Branquet, E.; Durand, P.; Goffic, F. L. *Tetrahedron* **1996**, *52*, 11215.
20. Varala, R.; Adapa, S. R. *Org. Process Res. Dev.* **2005**, *9*, 853.