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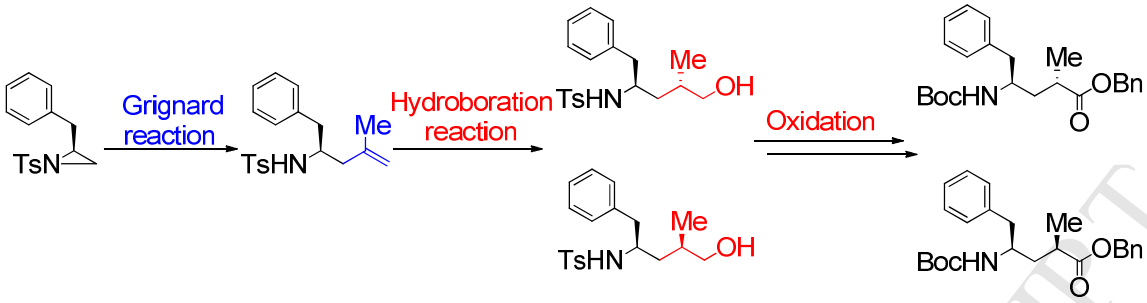
Graphical Abstract



Synthesis of tubuphenylalanine and *epi*-tubuphenylalanine via regioselective aziridine ring opening with carbon nucleophiles followed by hydroboration-oxidation of 1,1-substituted amino alkenes

Ramesh B. Reddy,[a] Premansh Dudhe,[a] Priyanka Chauhan,[a] Sagnik Sengupta,[a] and Chelvam Venkatesh*[,a,b]

[a] Discipline of Chemistry, Indian Institute of Technology Indore, Khandwa Road, Simrol, Indore-453 552, India.

[b] Discipline of Biosciences and Biomedical Engineering, Indian Institute of Technology Indore, Khandwa Road, Simrol, Indore-453 552, India.

*email: cvenkat@iiti.ac.in; fax: +91-731-2431482; Tel: +91-731-2438789

ABSTRACT

An efficient synthesis of *N*-Boc-tubuphenylalanine benzyl ester (*N*-Boc-Tup-OBn, **1a**) and *N*-Boc-*epi*-tubuphenylalanine benzyl ester (*N*-Boc-*epi*-Tup-OBn, **1b**) is reported herein. Regioselective aziridine **4** ring opening with carbon nucleophiles followed by hydroboration of 1,1-substituted aminoalkene **3** using 9-BBN and subsequent oxidation in an alkaline medium are used as the key steps to provide *N*-tosyl 1,4-aminoalcohols. The 1,4-aminoalcohols are successfully transformed into the desired products with an overall yield of 23% for **1a** and 11% for **1b** over 8 consecutive steps separately.

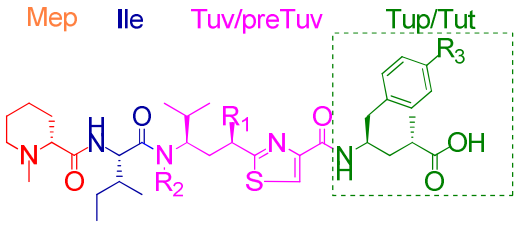
Keywords: Regioselective aziridine ring opening, Grignard reaction, Hydroboration, 9-BBN, Tubuphenylalanine, *epi*-Tubuphenylalanine

1. Introduction

Mitotic spindle microtubules are important drug targets in designing new anticancer therapy. Currently marketed anticancer drugs like paclitaxel and vinblastine work on suppression of microtubule dynamics in fast dividing cells leading to their apoptosis.[1] In the last decade, tubulysin compounds have emerged as a new class of highly potent cytotoxic peptides which can inhibit tubulin polymerisation more efficiently than vinca alkaloids.[2] However, the scarce supply of these natural anticancer agents has attracted the attention of medicinal chemists to develop novel routes towards the synthesis of a tubulysin family of natural products.[3]

Höfle and co-workers first isolated tubulysins from myxobacteria culture broths as antimitotic tetrapeptides.[4] Later, Müller and co-workers identified a gene cluster in myxobacteria with mixed non-ribosomal peptide synthetase-polyketide synthase system that is responsible for biosynthesis of tubulysin.[5] Interestingly, tubulysin was found to surpass cell growth inhibition activity of all the conventional anticancer natural products such as epothilones, vinblastine and taxol by a factor of 20 to 1000.[6] Tubulysin interacts with the eukaryotic cytoskeleton and prevents microtubule formation by binding with tubulin protein leading to apoptosis of cells.[7] The interesting biological activity of tubulysin and its derivatives justifies the rapidly growing interest in the development of novel chemosynthetic methods to access more potent tubulysin derivatives with cytotoxicity in the range of low nanomolar to picomolar concentrations.

The tubulysin scaffold is composed of four fragments: *N*-methyl-$_D$-pipecolic acid ($_D$-Mep), $_L$-isoleucine ($_L$-Ile), tubuvaline (Tuv), and tubuphenylalanine (Tup) or tubutyrosine (Tut) (Fig. 1) connected to each other through amide linkages. Mep is a carboxylic acid derivative of piperidine and is biosynthesized from $_L$-lysine[5a] whereas, isoleucine is a natural amino acid which provides necessary hydrophobic interactions in the tubulin protein binding pocket. Tubuvaline (Tuv) is the most complex component of tubulysin compounds with a thiazole ring containing a side chain chiral acetoxy carbon. The C-terminus fragments, Tup or Tut, are γ-amino acid homologous of phenylalanine and tyrosine, respectively. SAR studies[5b,8] have confirmed that few modifications in the *N*-terminus and Tuv units of the molecule are well tolerated and will not adversely affect the overall potency of the molecule. In contrast to this, the C-terminus end (Tup or Tut) has excellent scope for modifications. This part of the tubulysin natural products has been exploited to develop several new potent derivatives of this type of anticancer molecules.



Tubulysin	R_1	R_2	R_3
A	-OAc	$-CH_2OCOCH_2CH(CH_3)_2$	-OH
B	-OAc	$-CH_2OCOCH_2CH_2CH_3$	-OH
D	-OAc	$-CH_2OCOCH_2CH(CH_3)_2$	-H
U	-OAc	-H	-H
V	-OAc	-H	-H
Pretubulysin D	-H	-Me	-H

Fig. 1. Structure of tubulysin family of antimitotic agents.

Seiber and coworkers have designed pretubulysin photoaffinity probes by C-terminus modification for imaging studies using fluorescent labelling.[9] Leamon *et al.* have prepared targeted chemotherapeutic warheads of tubulysin derivatives and delivered to cancer cells via folic acid conjugation.[10]

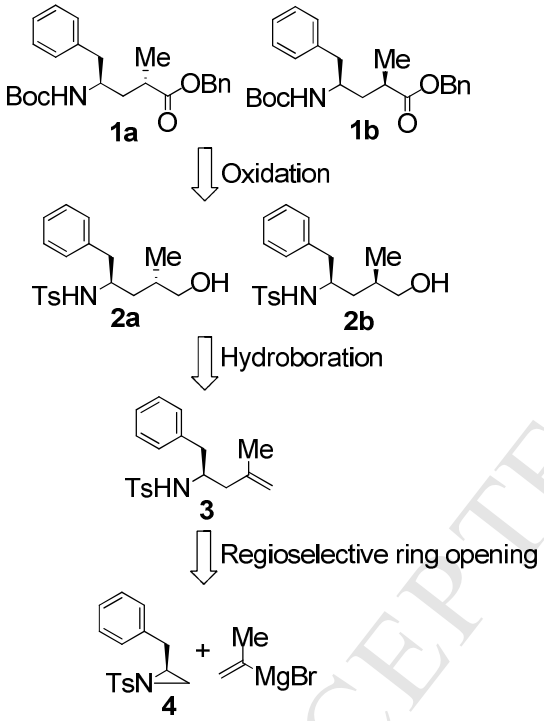
The existing methods for the synthesis of Tup and *epi*-Tup mostly employ chiral auxiliary controlled alkylation using SAMP-hydrazone or pseudoephedrine,[11] oxazolidinones,[12–13] and *tert*-butanesufinamide,[3c,14] along with substrate controlled diastereoselective methylation of chiral lactam,[15] diastereoselective hydrogenation,[3d,16] epoxide ring-opening[17] and Ireland-Claisen rearrangement of allyl ester of β-amino acid.[18] Recently, Park and co-workers have reported a chiral auxiliary-free direct synthetic pathway for the synthesis of tubuphenylalanine by Lewis acid-catalyzed Mukaiyama aldol condensation reaction.[19]

Although a variety of methods have been developed to date, there is enough scope to introduce refined synthetic protocols for a large-scale synthesis of these biologically active entities. Herein, we report a novel and high yielding synthetic route for the synthesis of tubuphenylalanine (Tup) and *epi*-tubuphenylalanine (*epi*-Tup) using hydroboration-oxidation of substituted alkene **3** as the crucial step without a chiral auxiliary in the substrate. Moreover, our synthetic route is efficient in terms of a number of the steps (8-steps) and overall yield (23%) compared to an earlier reported synthesis[20] of tubuphenylalanine fragment in 16-steps with an overall yield of 2.5%. This practical and efficient

synthesis of key components, **1a** and **1b,** will allow building a diverse set of new tubulysin architectures in the future.

2. Results and discussion

In order to develop a method for the synthesis of tubuphenylalanine (Tup) and its biologically active stereoisomer *epi*-tubuphenylalanine (*epi*-Tup), a simple retrosynthetic analysis of their closest precursors **2a** and **2b** are depicted in Scheme 1. According to this strategy, the crucial *N*-tosyl-1,4-amino alcohols **2a** and **2b** can be obtained from a common precursor, 1,1-disubstituted aminoalkene **3** through a regioselective hydroboration-oxidation reaction. Further, *N*-tosyl-benzylaziridine **4** could be a key starting material to obtain 1,1-disubstituted aminoalkene **3** via regioselective ring opening.

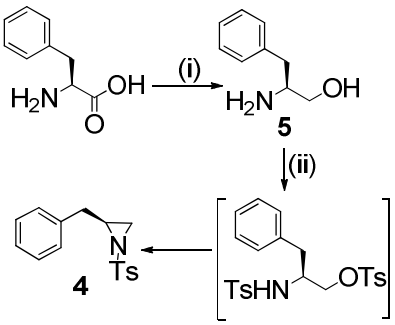


Scheme 1. Retrosynthetic analysis of *N*-Boc-Tup-OBn (**1a**) and *N*-Boc-*epi*-Tup-OBn (**1b**).

Since its inception in 1956, hydroboration reaction has made available many alkylated borane derivatives that are essential precursors for regio- and stereoselective introduction of hydroxy functionality in a substituted alkene.[21] Moreover, in 1979, Brown and co-workers reported pioneering studies on hydroboration of allene[22] using 9-BBN to address the drawbacks of previous hydroboration reactions that lacks regioselectivity. Further studies on the application of bicycloboranes have revealed that hydroboration of substituted terminal alkenes using 9-BBN generally results in the high

regioselective[23] preparation of organoboranes which can be easily oxidized to their corresponding alcohols in alkaline H_2O_2.[24]

We began our synthesis starting from L-phenylalanine to obtain the required 1,1-substituted aminoalkene **3** for hydroboration reaction. L-phenylalanine was converted to phenylalaninol **5** by performing reduction of acid functionality with $NaBH_4$ in the presence of I_2 under refluxing tetrahydrofuran in excellent yield. Without further purification, the hydroxy and amino functionalities in phenylalaninol **5** was tosylated using *p*-toluenesulfonyl chloride to give (*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropyl 4-methylbenzenesulfonate intermediate. The bis(tosyl) intermediate shown within parentheses was in situ cyclized by intramolecular sulfonamide nucleophilic attack on tosyl protected hydroxyl group in the presence of a mild base, Et_3N, to furnish *N*-Ts-benzylaziridine **4** in 85% isolated yield (Scheme 2).[25]



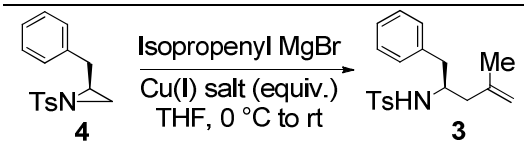
Scheme 2. Synthesis of (*S*)-2-benzyl-1-tosylaziridine (**4**). Reagents and conditions (i) $NaBH_4$, I_2, THF, 0 °C to reflux, 24 h, 96% (ii) Et_3N, TsCl, CH_3CN, 0 °C to rt, 1 h, 85%.

The key intermediate *N*-Ts-benzylaziridine **4** was thus prepared in gram scale to obtain the desired 1,1-substituted aminoalkene **3** which is an important substrate for regio- and stereoselective hydroboration reactions proposed to prepare **2a** and **2b**. Literature survey shows that there are few procedures for regioselective ring opening of aziridine by nucleophiles including Grignard reagents.[26] Cu (I) salts play an instrumental role in Grignard reactions for generating active organocuprate species. We have explored catalytic amounts of CuI, CuBr, and CuCN under different reaction conditions to prepare the desired alkene **3** in moderate to high yields (Table 1). The initial reaction was performed in the presence of CuI (Table 1, entry 1, 2) and after 12 h of reaction at room temperature, the expected aminoalkene **3** was isolated only in a moderate yield of 50-55%. However, no noticeable enhancement in the yield of **3** was observed when CuBr was used as a catalyst (Table 1, entry 3, 4). Copper(I)halides form homocuprates by the reaction of either copper(I) bromide or copper(I) iodide with a minimum of

two equivalents of Grignard reagents in ether or THF. The initially formed polymeric $(RCu)_n$ species were insoluble in Et_2O and THF, but dissolve only on addition of a second equivalent of Grignard reagent. The resultant organocuprates are thermally labile and generally prepared at low temperatures.[27] Because of this reason the yield of **3** was moderate when copper(I)halides were used as catalysts and require longer reaction time for completion (Table 1, entries 2, 4).

Interestingly, the yield of aminoalkene **3** has dramatically improved in the presence of CuCN (0.2 eq) to 90% within 2 h of the reaction time (Table 1, entry 6). The increase in yield of **3** is because when copper(I)halides were substituted with copper(I) cyanide as a catalyst, higher order cyanocuprates[28,29] were formed smoothly at 0 °C to rt. The cyanocuprates have higher thermal stability than homocuprates which are generally generated at a lower temperature. Moreover, cyanocuprates retain the reactivity of homocuprates as well as the stability of heterocuprates when copper(I)cyanide was used as the catalyst.

Table 1. Regioselective ring opening of (*S*)-2-Benzyl-1-tosylaziridine (**4**).



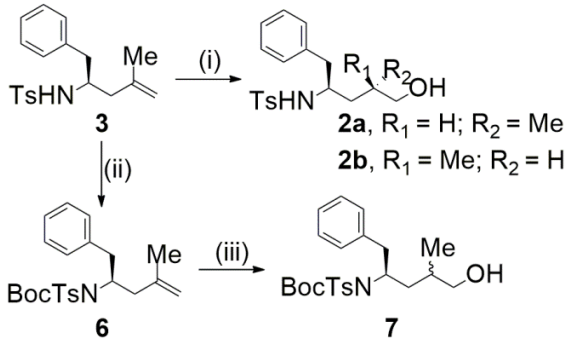
4 **3**

	Cu (I) salt (equiv.)	Rxn time	Grignard reagent (equiv.)	Yield of **3**[a]
1	CuI (0.1)	12 h	2.0	50%
2	CuI (0.2)	24 h	2.5	55%
3	CuBr (0.1)	12 h	2.0	60%
4	CuBr (0.2)	24 h	2.5	60%
5	CuCN (0.1)	2 h	1.5	73%
6	CuCN (0.2)	2 h	2.0	90%

[a] Isolated

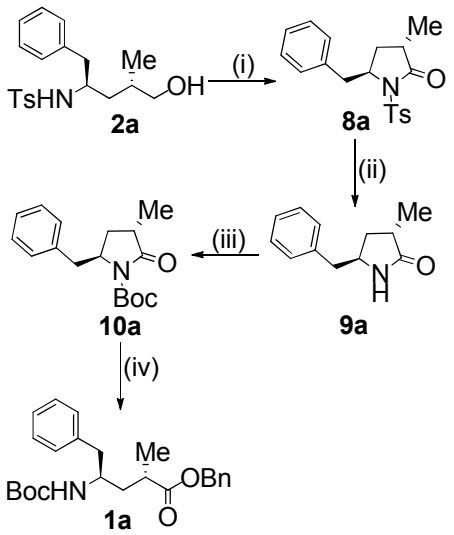
Substrate-controlled hydroboration can play a vital role in deciding the diastereoselectivity of formation of *N*-tosyl-1,4-amino alcohols, **2a**–**b**. Therefore, we plan to verify our hypothesis by preparing two differently protected amino alkenes such as **3** and **6**. Initially, *N*-tosyl protected alkene **3** was treated with Boc anhydride (Boc_2O) in the presence of dimethyl amino pyridine (DMAP) in dichloromethane to afford *N*-Boc-*N*-tosyl derivative of the alkene **6** in excellent yield.

The crucial hydroboration-oxidation of alkene functionality in **3** and **6** was realized later with 9-BBN. The hydroboration of **6** and subsequent oxidation using H_2O_2 in the presence of 2 M NaOH afforded 1,4-amino alcohols **7** (Scheme 3) only as a mixture of diastereomers in the ratio 2:1 (from ^{1}H NMR) in 70% yield. Moreover, the diastereomeric mixture of alcohols **7** remains non-separable by silica gel column chromatography.



Scheme 3. Synthesis of *N*-tosyl-1,4-amino alcohols, **2a**–**b** and **7.** Reagents and conditions (i) a. 9-BBN, THF, rt, 12 h b. 2 M NaOH, H_2O_2, 0 °C to rt, 12 h, 90%, *dr* = 2 :1 (ii) Boc_2O, DMAP, CH_2Cl_2, rt, 2 h, 97% (iii) a. 9-BBN, THF, rt, 12 h b. 2 M NaOH, H_2O_2, 0 °C to rt, 12 h, 70%, *dr* = 2:1 (non-separable).

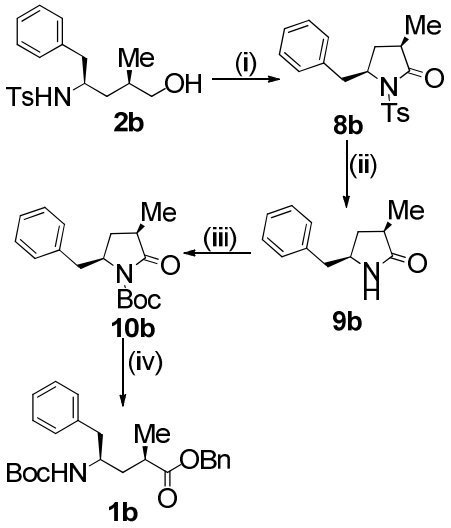
On the contrary, hydroboration-oxidation of alkene **3** in the presence of 9-BBN/2 M NaOH / 30% H_2O_2 smoothly resulted into a separable 2:1 diastereomeric mixture of 1,4-amino alcohols (**2a, 2b)** in a combined yield of 90%. After successful purification, 1,4-amino alcohol **2a** (Scheme 4) was subjected to oxidation reaction using pyridinium dichromate (PDC). During the oxidation of the primary hydroxyl group in **2a**, the primary alcohol forms chromate ester and subsequently oxidized to an unstable aldehyde. The unstable aldehyde undergoes further oxidation in the presence of PDC to form chromate carboxylic acid anhydride, [RC(O)OCrO_3H] followed by intramolecular cyclization with the NH-tosyl amino group to form *N*-Ts-γ-lactam **8a** as the only product.[30] Detosylation of **8a** was achieved with Mg/NH_4Cl via a single electron transfer mechanism under reflux conditions in methanol to provide **9a**.[31]



Scheme 4. Synthesis of *N*-Boc-Tup-OBn (**1a**). Reagents and conditions (i) PDC, DMF, rt, 12 h, 85% (ii) Mg, NH_4Cl, MeOH, reflux, 2 h, 84% (iii) Boc_2O, DMAP, DCM, rt, 2 h, 96% (iv) a. LiOH, H_2O_2, THF:H_2O (1:1), rt, 12 h b. BnBr, Et_3N, DCM, rt, 12 h, 75%.

The free NH group in **9a** was protected as NHBoc using Boc_2O and DMAP to afford **10a** in 95% yield. The Boc derivative of γ-lactam **10a** was reacted with LiOH in the presence of H_2O_2 to facilitate opening of lactam ring to provide carboxylic acid intermediate. Without isolation, the carboxylic acid intermediate was treated with benzyl bromide in the presence of a mild base, Et_3N, to afford *N*-Boc-Tup-OBn **1a** in 75% yield over two steps.

Zanda and coworkers[32] have established that the modification of Tup stereochemistry has only minor effects on the tubulysin cytotoxicity, this makes *epi*-tubuphenylalanine an important synthetic target. Therefore, in our synthetic strategy, 1,4-amino alcohol derivative **2b** was next subjected to synthetic transformations similar to the conversion of **2a** to **1a** as shown in Scheme 5. The primary alcohol **2b** was oxidized to chromate carboxylic acid anhydride, which undergoes in situ cyclisation to yield **8b**. Subsequent tosyl deprotection and Boc protection of amide NH yielded *N*-Boc γ-lactam **10b**. Lactam ring opening and benzyl protection at the C-terminus provided the desired molecule *N*-Boc-*epi*-Tup-OBn **1b** in good yield.



Scheme 5. Synthesis of *N*-Boc-*epi*-Tup-OBn (**1b**). Reagents and conditions (i) PDC, DMF, rt, 12 h, 83% (ii) Mg, NH_4Cl, MeOH, reflux, 2 h, 81% (iii) Boc_2O, DMAP, DCM, rt, 2 h, 99% (iv) a. LiOH, H_2O_2, THF:H_2O (1:1), rt, 12 h b. BnBr, Et_3N, DCM, rt, 12 h, 72%.

It was imperative to determine the stereochemistry of major (**2a**) and minor (**2b**) 1,4-aminoalcohol diastereoisomers. The stereochemistry was assigned by performing COSY and NOESY experiments on the lactams **8a** and **8b** (*N*-tosyl-5-benzyl-3-methylpyrrolidin-2-one). The NOE (Fig. 2) was observed between two protons at 3-H_a and 5-H_b in **8b**, whereas **8a** did not show any NOE between two protons 3-H_a and 5-H_b. The appearance of cross peaks off the diagonal peaks in **8b** for protons 3-H_a and 5-H_b indicated spatial coupling whereas its absence in **8a** confirmed the proposed *trans* stereo chemical arrangement of 3-H_a and 5-H_b protons in space. This study unequivocally established the stereochemistry of major and minor 1,4-aminoalcohols **2a** (2*R*, 4*S*) and **2b** (2*R*, 4*R*) respectively (see 2D-NMR data in supporting information).

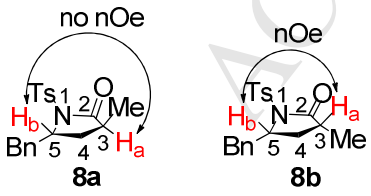


Fig. 2. Stereochemical assignments of **8a** and **8b** through ^1H-^1H COSY and NOESY studies.

3. Conclusions

In summary, we have developed a high yielding synthetic approach for C-terminus fragments of natural and synthetic tubulysins, i.e. tubuphenylalanine and *epi*-tubuphenylalanine via regioselective aziridine ring opening with carbon nucleophiles followed by hydroboration-oxidation of 1,1-substituted amino alkenes using 9-BBN. The chiral auxiliary-free synthetic protocol leads to overall good yields for both the biologically active γ-amino acids. These practical, concise and scalable synthetic steps have promising scope in the gram-scale synthesis of tubulysin and its derivatives.

4. Experimental Section

4.1. General information

All reactions were performed in oven-dried glassware under the inert atmosphere with magnetic stirring. Air and moisture-sensitive liquids and solutions were transferred via glass syringes. TLC was performed on 0.25 mm Merck TLC silica gel 60 F_{254} plates and visualized under UV light (254 nm) or by staining with bromocresol green, ninhydrin, $KMnO_4$. Flash chromatography was performed on 230–400 mesh silica gel. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Solvents were distilled using suitable drying agents (CaH_2 or Na wire, Mg turnings) under the nitrogen atmosphere. ^{1}H, ^{13}C-NMR, COSY, NOESY spectra were recorded on Avance III 400 MHz Ascend Bruker. Chemical shifts are expressed in ppm relative to TMS (^{1}H, 0 ppm) or solvent signals: $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.26 ppm) coupling constants are expressed in Hz. High-resolution mass spectra electrospray ionization (HRMS-ESI) performed on Bruker Daltonik LC/MS spectrometer. FT-IR spectra of samples dissolved in CH_2Cl_2 were recorded in using Fourier Transform Infrared-Attenuated Total reflection (FTIR-ATR) Spectrometer, Bruker (Tensor-27) over a range of 500–4000 cm^{-1}.

4.2. Experimental details and characterisation data

4.2.1. *(S)-2-Amino-3-phenylpropan-1-ol (**5**)*

$_{L}$-phenylalanine (5 g, 30 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottom flask under an inert atmosphere. The reaction mixture was cooled to 0 °C, and solid $NaBH_4$ (2.87 g, 75.70 mmol) was added to the reaction mixture in a single portion with stirring. A solution of Iodine (6.6 g, 52.5 mmol) in dry THF (30 mL) was added to the reaction mixture dropwise using dropping funnel over a period of 1 h. The reaction mixture was further heated to reflux on a preheated oil bath overnight. The reaction mixture was cooled to room temperature, and methanol (30 mL) was slowly

added until a clear solution is obtained. The solvent was evaporated under reduced pressure, and the resulting white paste was dissolved in 2 M NaOH (50 mL). The mixture was stirred at room temperature for 8 h. The aqueous phase was extracted with CH_2Cl_2 (100 × 3 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford $_L$-phenylalaninol (4 g, 96%) as a white solid, which was used in the next step without further purification. m.p. 90–94 C. TLC: R_f 0.19 (1:9, MeOH/CH_2Cl_2). $[\alpha]_D^{22.1}$ = −7.9 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3352 (O–H) 3279 (N–H), 3083, 3061, 3027, (=C–H), 2919, 2855(C–H), 1649 (N–H), 1551–1502 (C=C) 1452 (C–H), 1054 (C–O), 701 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.11 (m, 5H), 3.56 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.36–3.27 (dd, , *J* = 10.8, 8.0 Hz, 1H), 3.04 (brs, 1H), 2.72 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.45 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.97 (brs, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 129.2, 128.6, 126.4, 66.2, 54.2, 40.8 ppm. HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_{13}NO$ 152.1070, found 152.1101.

4.2.2. *(S)-2-Benzyl-1-tosylaziridine (**4**)*

4 Å molecular sieves (2 g) were flame dried in a 100 mL two neck round bottom flask under reduced pressure for 15-min or more until there is no sign of the appearance of water droplets or moisture in the flask. The heat dried molecular sieves were cooled to room temperature under inert atmosphere. CH_3CN (50 mL), magnetic bar and $_L$-phenylalaninol **5** (2.8 g, 18.5 mmol) were charged to this flask. The reaction mixture was briefly cooled to 0 °C, and Et_3N (7.7 mL, 55.55 mmol) and tosyl chloride (3.52 g, 18.5 mmol) were added sequentially via a syringe to the reaction mixture. The reaction mixture was warmed to room temperature and further stirred for 1 h. After complete consumption of $_L$-phenylalaninol, as confirmed by TLC, acetonitrile was evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL). The resultant precipitate and molecular sieves were filtered using Buchner funnel and washed with EtOAc (3 × 50 mL). The organic solvent was concentrated under reduced pressure and the crude mixture was purified by silica gel column chromatography (1:24 EtOAc/hexane) to afford 4 (4 g, 85%) as a white solid. m.p. 91–93 °C. TLC: R_f 0.21 (9:1, hexane/EtOAc). $[\alpha]_D^{22.0}$ = +16.4 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3029, (=C–H), 2922 (C–H), 1592, 1489, 1455 (C=C), 1317, 1157 (S=O), 712 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16–7.14 (m, 3H), 7.05–7.03 (m, 2H), 2.97–2.91 (m, 1H), 2.81 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.70 (d, *J* = 6.8 Hz, 1H), 2.68 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.42 (s, 3H), 2.16 (d, *J* = 4.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 144.3,

137.0, 134.8, 129.6, 128.7, 128.4, 127.8, 126.5, 41.1, 37.5, 32.8, 21.6 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{16}H_{17}NO_2S$ 310.0872, found 310.0883.

4.2.3. *(R)-4-Methyl-N-(4-methyl-1-phenylpent-4-en-2-yl) benzene sulfonamide (**3**)*

A 250 mL two neck round-bottom flask was charged with catalytic amount of CuCN (0.2 equiv.) under an inert atmosphere. *N*-Tosyl-benzylaziridine 4 (2.5 g, 8.7 mmol) dissolved in dry THF (50 mL) was added to the reaction mixture at 0 °C. Isopropenyl magnesium bromide (34.8 mL, 17.4 mmol, 0.5 M in THF) was added dropwise to the reaction mixture over a period of 20 minutes with stirring. The reaction mixture was allowed to warm to room temperature and further stirred for 2 h. After the consumption of *N*-Tosyl-benzylaziridine **4**, as confirmed by TLC, the reaction mixture was quenched with saturated NH_4Cl (30 mL) solution and further diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The organic layer was filtered, evaporated under reduced pressure, and the crude residue was purified over silica gel column chromatography (32:1 hexane/EtOAc) to afford the alkene **3** (2.1 g, 90%) as colorless liquid. TLC: R_f 0.17 (9:1, hexane/EtOAc). $[\alpha]_D^{22.2}$ = −1.5 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3284 (N–H), 3064, 3027 (=C–H), 2923, (C–H), 1649, 1604 (C=C) 1499–1451 (C–H), 1322, 1153 (S=O), 701 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.65 (d, *J* = 8.0 Hz, 2H), 7.26–7.19 (m, 5H), 7.07–7.05 (m, 2H), 4.76–4.67 (m, 2H), 4.32 (d, *J* = 5.6 Hz, 1H), 3.49–3.41 (m, 1H), 2.85, (dd, *J* = 13.6, 5.6 Hz, 1H)), 2.76, (dd, *J* = 13.6, 6.8 Hz, 1H) 2.41 (s, 3H), (dd, *J* = 14.0, 6.4 Hz, 1H), (dd, *J* = 14.0, 8.4 Hz, 1H), 1.38 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 143.2, 141.6, 137.2, 137.2, 129.5, 129.5, 128.4, 127.1, 126.5, 114.5, 52.6, 43.0, 41.2, 21.5, 21.5 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{19}H_{23}NO_2S$ 352.1342, found 352.1345.

4.2.4. *(R)-tert-Butyl (4-methyl-1-phenylpent-4-en-2-yl)(tosyl)carbamate (**6**)*

An oven dried 250 mL round-bottom flask was charged with a solution of alkene **3** (2.5 g, 7.59 mmol) in dry CH_2Cl_2 (50 mL). DMAP (0.185 g, 1.52 mmol) was added in single portion to the reaction mixture and Boc_2O (3.3 g, 15.2 mmol) was added using syringe. The reaction mixture was stirred at room temperature for 2 h. After the completion of reaction, CH_2Cl_2 was evaporated under reduced pressure and the residue was purified over silica gel column chromatography using 33:1 hexane/EtOAc mixture as eluent to afford **6** (3.1 g, 97%) as a colorless liquid. TLC: R_f 0.54 (9:1, hexane/EtOAc). $[\alpha]_D^{22.4}$ = −99.6 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3064, 3027 (=C–H), 2972, 2922, 2852 (C–H), 1727

(C=O), 1653 (C=C), 1493, 1455 (C–H), 1351, 1152 (S=O), 1088 (C–O), 673 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.20 (m, 5H), 7.18–7.00 (m, 4H), 5.00–4.80 (m, 3H), 3.32 (dd, *J* = 14.0, 9.6 Hz, 1H), 3.04 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.79 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.55 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.35 (s, 3H), 1.84 (s, 3H), 1.34 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 150.7, 143.2, 142.3, 139.1, 137.8, 129.6, 128.8, 128.6, 127.7, 126.5, 114.2, 83.9, 59.3, 42.0, 38.7, 27.9, 22.2, 21.4 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{24}H_{31}NO_4S$ 452.1866, found 452.2172.

4.2.5. *General procedure for hydroboration reactions*

9-BBN (3 equiv., 0.5 M THF solution) was added to a solution of alkene **3** or **6** (1.0 equiv.) in dry THF at room temperature. The resulting solution was further stirred for 12 h at the same temperature under nitrogen atmosphere. 2 M NaOH (3.5 equiv.) and 30% H_2O_2 (4 equiv.) were added at 0 °C to the reaction mixture and stirring was continued for 12 h at room temperature. The reaction mixture was quenched by adding saturated aq. NaCl (20 mL) at room temperature and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified using hexane:EtOAc as eluent over silica gel column chromatography.

4.2.5.1. *N-((2R,4S)-5-hydroxy-4-methyl-1-phenylpentan-2-yl)-4-methylbenzenesulfonamide (**2a**)*

According to the general procedure described in section 4.2.5, 9-BBN (38.2 mL, 19.1 mmol, 0.5 M THF solution) was added to alkene **3** (2.1 g, 6.37 mmol) in dry THF (20 mL) and stirred at room temperature for 12 h. 2 M NaOH (11.0 mL, 22.29 mmol) and 30% H_2O_2 (9.0 mL, 89.14 mmol) were added at 0 °C to the reaction mixture and stirred for 12 h at room temperature and worked up as mentioned in general procedure 4.2.5. The residue was purified over silica gel using column chromatography (3:1 hexane/EtOAc), to afford **2a** and **2b** as colorless liquid and pale yellow liquid respectively (9.1 g, combined yield 90 %, (**2a**:**2b** = 2:1). TLC: R_f 0.34 (1:1, hexane/EtOAc). $[\alpha]_D^{21.2}$ = −43.0 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3504 (N–H), 3277 (O–H), 3061, 3028 (=C–H), 2925, 2872 (C–H), 1598 (C=C), 1494, 1453, (C–H), 1320, 1152 (S=O), 1090 (C–O), 700 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.65 (d, *J* = 8.0 Hz, 2H), 7.26–7.19 (m, 5H), 6.69–6.97 (m, 2H), 4.66 (d, *J* = 7.2 Hz, 1H), 3.70–3.61 (m, 1H), 3.44 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.33 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.64–2.62 (m, 2H), 2.41 (s, 3H), 1.87–1.79 (m, 1H), 1.55–1.49 (m, 1H), 1.30–1.23 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 143.2, 137.8, 136.9, 129.6, 129.5, 128.5, 127.0,

126.6, 67.8, 52.9, 41.1, 39.1, 31.7, 21.5, 17.5 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{19}H_{25}NO_3S$ 370.1447, found 370.1448.

4.2.5.2. *N-((2R,4R)-5-hydroxy-4-methyl-1-phenylpentan-2-yl)-4-methylbenzenesulfonamide (**2b**)*

TLC: R_f 0.27 (1:1, hexane/EtOAc). $[\alpha]_D^{21.1}$ = +31.2 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3506 (N–H), 3283 (O–H), 3061, 3028 (=C–H), 2927, 2873 (C–H) 1598 (C=C), 1495, 1454, (C–H), 1322, 1154 (S=O), 1092 (C–O), 733 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.71 (d, *J* = 8.0 Hz, 2H), 7.27–7.18 (m, 5H), 7.02–7.01 (m, 2H), 4.85 (brs, 1H), 3.56–3.48 (m, 1H), 3.43 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.28 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.73 (dd, *J* = 13.6, 4.8 Hz 1H), 2.63 (dd, *J* = 13.6, 7.2 Hz 1H) 2.41 (s, 3H), 1.69 (brs, 1H), 1.64–1.57 (m, 1H), 1.55–1.48 (m, 1H), 1.22–1.16 (m, 1H), 0.68 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 143.2, 137.9, 137.2, 129.6, 129.5, 128.4, 127.0, 126.5, 68.1, 53.2, 42.3, 38.5, 32.3, 21.5, 16.4 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{19}H_{25}NO_3S$ 370.1447, found 370.1443.

4.2.5.3. *tert-Butyl ((2R)-5-hydroxy-4-(S or R)methyl-1-phenylpentan-2-yl)(tosyl)carbamate (**7**)* (*dr* = 2:1)

According to the general procedure described in section 4.2.5, 9-BBN (28.14 mL, 13.97 mmol, 0.5 M THF solution) was added to alkene **6** (2 g, 4.65 mmol) in dry THF (20 mL) in a round bottom flask (100 mL) at room temperature and stirred for 12 h. 2 M NaOH (8.14 mL, 16.28 mmol) was added followed by addition of 30% H_2O_2 (6.6 mL, 65.0 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and worked up as mentioned in general procedure 4.2.5. The crude residue was purified over silica gel column chromatography using 3:1 hexane/EtOAc mixture as eluent to afford colorless oil of **7** (1.65 g, 70%) as a diastereomeric mixture (2:1). TLC: R_f 0.23 (3:1, hexane/EtOAc). $[\alpha]_D^{22.2}$ = −49.8 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3564 (O–H), 3028 (=C–H) 2925, 2870 (C–H), 1722 (C=O), 1598 (C=C), 1494, 1453 (C–H), 1343, 1147 (S=O), 1085 (C–O), 669 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.23 (m, 6H), 7.05–6.99 (m, 3H), 4.93–4.86 (m, 1H), 3.63–3.55 (m, 1H), 3.54–3.47 (m, 1H), 3.37–3.28 (m, 1H), 3.02–2.97 (m, 1H), 2.36 (s, 3H), 1.97–1.91 (m, 2H), 1.84–1.79 (m, 1H), 1.55–1.50 (m, 1H), 1.34 (s, 9H), 1.04 (d, *J* = 6.4 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 1H)* ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 150.7, 143.4*, 143.3, 139.0, 137.5, 129.6, 128.9, 128.7, 127.9*, 127.8, 126.5, 84.2*, 84.1, 68.2*, 67.8, 59.2, 59.0*, 39.3, 37.4, 37.3*, 33.2*, 33.1, 29.6*, 27.9, 22.7*, 21.5, 21.4*, 17.4, 14.1* ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{24}H_{33}NO_5S$ 470.1970, found 470.2320. (*peaks from minor diastereoisomer)

4.2.6. *General procedure for the synthesis of N-Ts-γ-lactams **8a** and **8b***

Dry DMF (10 mL) was added to 1,4-amino alcohol (**2a** or **2b**, 1.0 equiv.) taken in a 100 mL round-bottom flask charged with a magnetic bead and the mixture was stirred at room temperature. Pyridinium dichromate (5.0 equiv.) was added to above reaction mixture in one portion and stirred for 24 h at the same temperature. After the complete consumption of 1,4-amino alcohol, the reaction mixture was quenched with cold water (10 mL). The aqueous layer was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with cold brine (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica gel column chromatography.

4.2.6.1. *(3S,5R)-5-Benzyl-3-methyl-1-tosylpyrrolidin-2-one (**8a**)*

According to the general procedure described in section 4.2.6, to a solution of 1,4-amino alcohol **2a** (500 mg, 1.43 mmol) in dry DMF (10 mL) taken in a round bottom flask (50 mL), PDC (2.7 g, 7.19 mmol) was added to the reaction mixture and stirred for 24 h at room temperature. The work up was performed as mentioned in the general procedure and the residue was purified over silica gel column chromatography (6:1 hexane/EtOAc) to afford lactam **8a** as colorless sticky liquid, (433 mg, 85%). TLC: R_f 0.53 (2:1, hexane/EtOAc). $[\alpha]_D^{20.4}$ = +97.8 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3062, 3028, (=C–H), 2931, 2874 (C–H) 1729 (C=O), 1597 (C=C), 1494, 1453 (C–H), 1352, 1159 (S=O), 711 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.0 (d, *J* = 8.4 Hz, 2H), 7.35–7.21 (m, 7H), 4.54 (td, *J* = 8.8, 3.2 Hz, 1H), 3.36 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.81 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.44 (s, 3H), 2.34–2.26 (m, 1H), 2.11–2.04 (m, 1H), 1.67–1.58 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.8, 145.0, 136.7, 136.0, 129.5, 129.5, 128.8, 128.3, 127.0, 58.8, 40.2, 35.7, 31.8, 21.6, 14.9 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{19}H_{21}NO_3S$ 366.1134, found 366.1138.

4.2.6.2. *(3R,5R)-5-Benzyl-3-methyl-1-tosylpyrrolidin-2-one (**8b**)*

According to the general procedure describe in section 4.2.6, to a solution of 1,4-amino alcohol **2b** (457 mg, 1.31 mmol) in dry DMF (10 mL) taken in a round bottom flask (50 mL), PDC (2.5 g, 6.57 mmol) was added to the reaction mixture and stirred for 24 h at room temperature. After workup, the residue was purified over silica gel column chromatography (6:1 hexane/EtOAc) to afford γ-lactam **8b** as white solid, (366 mg, 83 %). m.p. 122–124 °C. TLC: R_f 0.52 (2:1, hexane/EtOAc). $[\alpha]_D^{20.2}$ = +123.0 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3061, 3028, (=C–H), 2930, 2875 (C–H) 1732 (C=O), 1591 (C=C),

1494, 1454 (C–H), 1355, 1164 (S=O), 702 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.00 (d, *J* = 8.4 Hz, 2H), 7.35–7.22 (m, 7H), 4.48–4.41 (m, 1H), 3.84 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.63 (dd, *J* = 12.8, 10.0 Hz, 1H), 2.44 (s, 3H), 2.41–2.35 (m, 1H), 2.20–2.12 (m, 1H), 1.46–1.39 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.8, 145.0, 136.4, 136.1, 129.5 (2C*), 128.7, 128.3, 126.9, 59.6, 42.6, 36.9, 31.6, 21.6, 16.1 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{19}H_{21}NO_3S$ 366.1134, found 366.1140.

*higher intensity carbon

4.2.7. *General procedure for tosyl deprotection*

In a 100 mL round-bottom flask charged with magnetic bead, Mg turnings (10.0 equiv.) and NH_4Cl (5.0 equiv.), dry methanol was added under an inert atmosphere with stirring. A solution of Ts-γ-lactam (**8a** or **8b**, 1.0 equiv.) in dry methanol was added to the above suspension and stirred at room temperature for 10 minutes. The reaction mixture was further refluxed at 70 °C for 2 h. After complete consumption of Ts-γ-lactam (**8a** or **8b**), methanol was concentrated under reduced pressure and the crude residue was purified over silica gel column chromatography using hexane:EtOAc as eluent.

4.2.7.1. *(3S,5R)-5-Benzyl-3-methylpyrrolidin-2-one (**9a**)*

According to the general procedure described in section 4.2.7, *N*-tosyl- γ-lactam **8a** (350 mg, 1.02 mmol) in dry methanol (7 ml) was added to a suspension of Mg turnings (244 mg, 10.2 mmol) and NH_4Cl (273 mg, 5.0 mmol) in methanol (5 mL) taken in a 100 mL round bottom flask. The suspension was refluxed at 70 °C for 2 h under inert atmosphere and worked up as mentioned in the general procedure. The crude residue was purified over silica gel column chromatography (1:1 hexane/EtOAc) to afford 9a (161 mg, 84%) as colorless liquid. TLC: R_f 0.14 (1:3, hexane/EtOAc). $[\alpha]_D^{20.8}$ = −66.1 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3230 (N–H), 3028 (=C–H), 2928, 2871 (C–H), 1693 (C=O), 1456 (C–H), 701 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.23 (m, 3H), 7.21–7.15 (m, 2H), 5.87 (brs, 1H), 3.85–3.78 (m, 1H), 2.81 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.71 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.50–2.40 (m, 1H), 2.15–2.08 (m, 1H), 1.93–1.86 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.3, 137.6, 129.1, 128.8, 126.8, 53.4, 42.8, 35.1, 34.9, 16.2 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{12}H_{15}NO$ 212.1046, found 212.1059.

4.2.7.2. *(3R, 5R)-5-Benzyl-3-methylpyrrolidin-2-one (**9b**)*

According to the general procedure described in section 4.2.7, a solution of *N*-tosyl-γ-lactam **8b** (200 mg, 0.582 mmol)) in dry methanol (5 mL), was added to suspension of Mg turnings (140 mg, 5.82 mmol) and NH_4Cl (156 mg, 3 mmol) in methanol (5 mL) in a round bottom flask. The suspension was refluxed at 70 °C with stirring for 2 h under inert atmosphere and worked up as mentioned in the general procedure. The crude residue was purified over silica gel column chromatography (1:1 EtOAc/hexane) to afford **9b** (82 mg, 81%) as colorless liquid. TLC: R_f 0.14 (3:1, EtOAc/hexane). $[\alpha]_D^{20.6}$ = +83.2 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3230 (N–H), 3028 (=C–H), 2961, 2871 (C–H), 1693 (C=O), 1557–1456 (C–H), 701 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.22 (m, 3H), 7.20–7.12 (m, 2H), 5.96 (brs, 1H), 3.85–3.78 (m, 1H), 2.81 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.72 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.49–2.40 (m, 1H), 2.14–2.08 (m, 1H), 1.92–1.85 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 179.6, 137.6, 128.8, 128.8, 126.9, 53.7, 43.3, 37.0, 36.8, 15.9 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{12}H_{15}NO$ 212.1046, found 212.1055.

4.2.8. *General procedure for synthesis of **10a** and **10b***

Dry CH_2Cl_2 (10 mL) was added to γ-lactam (**9a** or **9b**, 1.0 equiv.) taken in a two-necked round bottom flask (100 mL) under inert atmosphere. The reaction mixture was cooled to 0 °C and solid DMAP (0.2 equiv.) was added dropwise to the reaction mixture in single portion with stirring followed by dropwise addition of Boc_2O (2.0 equiv.) using syringe. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. After the consumption of γ-lactam (**9a** or **9b**), the solvent was evaporated under reduced pressure using. The crude mixture was purified over silica gel column chromatography using hexane:EtOAc as eluent.

4.2.8.1. *(3S,5R)-tert-Butyl 5-benzyl-3-methyl-2-oxopyrrolidine-1-carboxylate (**10a**)*

According to the general procedure described in section 4.2.8, to a solution of γ-lactam **9a** (125 mg, 0.682 mmol) in dry CH_2Cl_2 (10 mL) in a round bottom flask (100 mL), DMAP (16.6 mg, 0.136 mmol) and Boc_2O (0.3 mL, 1.364 mmol) were added to the reaction mixture at 0 °C and further stirred at room temperature for 2.5 h. The solvent was evaporated under reduced pressure and the crude mixture was purified over silica gel column chromatography (8:1 hexane/EtOAc) to afford **10a** (190 mg, 96%) as colorless liquid. TLC: R_f 0.76 (1:1, hexane/EtOAc). $[\alpha]_D^{21.5}$ = +41.0 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3028 (=C–H), 2975, 2936 (C–H), 1785, 1711 (C=O), 1650 (C=C), 1455, 1305 (C–H), 1150 (C–O), 702 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.23 (m, 3H), 7.22–7.16 (m, 2H), 4.28 (td, *J* = 8.8, 3.2 Hz, 1H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.71 (dd, *J* = 13.2, 9.2 Hz, 1H),

2.44–2.35 (m, 1H), 2.04 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.58 (s, 9H), 1.54–1.42 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.6, 150.1, 137.4, 129.3, 128.7, 126.8, 82.9, 56.9, 39.2, 36.2, 30.7, 28.1, 15.3 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{17}H_{23}NO_3$ 312.1570, found 312.1657.

4.2.8.2. *(3R,5R)-tert-Butyl 5-benzyl-3-methyl-2-oxopyrrolidine-1-carboxylate (**10b**)*

According to the general procedure describe in section 4.2.8, to a solution of γ-lactam **9b** (70 mg, 0.261 mmol) in dry CH_2Cl_2 (10 mL) in a round bottom flask (100 mL), DMAP (6.37 mg, 0.05 mmol) and Boc_2O (0.12 mL, 0.522 mmol) were added to the reaction mixture at 0 °C and further stirred at room temperature for 2.5 h. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified over silica gel column chromatography (8:1 hexane/EtOAc) to afford **10b** (109 mg, 99%) as colorless liquid. TLC: R_f 0.76 (1:1, hexane EtOAc). $[\alpha]_D^{20.3}$ = +51.8 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3028 (=C–H), 2928, 2873 (C–H), 1746, 1711 (C=O), 1650 (C=C), 1494, 1455, 1305 (C–H), 1150 (C–O), 702 (=C–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.23 (m, 3H), 7.22–7.15 (m, 2H), 4.24–4.17 (m, 1H), 3.49 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.60 (dd, *J* = 13.2, 10 Hz, 1H), 2.54–2.44 (m, 1H), 2.17–2.09 (m, 1H), 1.60 (s, 9H), 1.40–1.33 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 177.2, 150.4, 137.0, 129.5, 128.6, 126.7, 83.1, 57.3, 41.3, 37.3, 30.5, 28.1, 16.6 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{17}H_{23}NO_3$ 312.1570, found 312.1574.

4.2.9. *General procedure for the synthesis of **1a** and **1b***

Dry THF (5mL) was added to *N*-Boc-γ-lactam (**10a** or **10b**, 1.0 equiv.) taken in a round-bottom flask (100 mL) with a magnetic bead. An aq.solution of LiOH (5.0 equiv.) and 30% aq.H_2O_2 (5.0 equiv.) were added to the reaction mixture at room temperature with constant stirring. The reaction mixture was stirred for further 12 h at room temperature, acidified with an aq. solution of 5% $KHSO_4$ (5 mL), and extracted with EtOAc (20 × 3 mL). The combined organic layers was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure to afford the intermediate carboxylic acid which was used as such for benzylation reaction without further purification. The intermediate crude carboxylic acid was dissolved in dry CH_2Cl_2 and Et_3N (2.0 equiv.) was added to the mixture with stirring at room temperature. BnBr (1.5 equiv.) was added to the reaction mixture via a syringe and stirred for 24 h at room temperature. The reaction mixture was quenched with cold water (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers was washed

with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified over silica gel column chromatography using hexane:EtOAc as eluent to afford **1a** or **1b**.

4.2.9.1. *(2S,4R)-Benzyl 4-((tert-butoxycarbonyl)amino)-2-methyl-5-phenylpentanoate (**1a**)*

According to the general procedure described in section 4.2.9, to a solution of *N*-Boc-γ-lactam **10a** (75 mg, 0.259 mmol) in THF (5 mL) in a round bottom flask, an aq.solution of LiOH (31 mg in 2 mL of H_2O, 1.29 mmol), 30% aq.H_2O_2 (1 mL) were added and the reaction mixture was stirred at room temperature for 12 h. After work up, as mentioned in general procedure, the solvent was evaporated under reduced pressure to afford the intermediate carboxylic acid. The crude carboxylic acid (75 mg, 0.243 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and Et_3N (0.06 mL, 0.486 mmol) was added to the mixture with stirring followed by addition of BnBr (0.04 mL, 0.364 mmol). The reaction mixture was stirred at room temperature for 24 h, worked up as mentioned in the general procedure. The crude residue was purified over silica gel column chromatography (11:1 hexane/EtOAc) to afford **1a** (72 mg, 75%) as pale yellow liquid. TLC: R_f 0.48 (2:1, hexane/EtOAc). $[\alpha]_D^{21.0}$ = +48.9 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3366 (N–H), 3062, 3029 (=C–H), 2973, 2931 (C–H), 1731, 1700 (C=O), 1651 (C=C), 1498, 1455 (C–H), 1167 (C–O), 698 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.13 (m, 10H), 5.15–5.04 (m, 2H), 4.30 (d, *J* = 7.6 Hz, 1H), 3.94–3.83 (m, 1H), 2.77–2.76 (d, *J* = 5.6 Hz, 2H), 2.69–2.59 (m, 1H), 1.94–1.88 (m, 1H), 1.50–1.41 (m, 1H), 1.38 (s, 9H), 1.17 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.0, 155.2, 137.8, 136.0, 129.4, 128.5, 128.3, 128.1 (2C*), 126.3, 79.1, 66.2, 49.7, 41.3, 37.9, 36.4, 28.3, 17.6 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. For $C_{24}H_{31}NO_4$ 420.2145, found 420.2160.

*higher intensity carbon

4.2.9.2. *(2R,4R)-Benzyl 4-((tert-butoxycarbonyl) amino)-2-methyl-5-phenylpentanoate (**1b**)*

According to the general procedure described in section 4.2.9, to a solution of *N*-Boc-γ-lactam **10b** (75 mg, 0.259 mmol) in THF (5 mL) in a round bottom flask, an aq.solution of LiOH (31 mg in 2 mL of H_2O, 1.29 mmol), 30% aq.H_2O_2 (1 mL) were added and the reaction mixture was stirred at room temperature for 12 h. After work up, as mentioned in general procedure, the solvent was evaporated under reduced pressure to afford the intermediate carboxylic acid. The crude carboxylic acid (75 mg, 0.243 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and Et_3N (0.06 mL, 0.486 mmol) was added to the mixture with stirring followed by addition of BnBr (0.04 mL, 0.364 mmol). The reaction mixture was

stirred at room temperature for 24 h, worked up as mentioned in the general procedure. The crude residue was purified over silica gel column chromatography (11:1 hexane/EtOAc) to afford **1b** (70 mg, 72%) as colorless liquid. TLC: R_f 0.48 (2:1, hexane/EtOAc). $[\alpha]_D^{21.4}$ = −43.7 (*c* 0.13, CH_2Cl_2). IR (CH_2Cl_2): 3366 (N–H), 3063, 3029 (=C–H), 2973, 2931 (C–H), 1729, 1699 (C=O), 1651 (C=C), 1496, 1454 (C–H), 1164 (C–O), 697 (=C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.13 (m, 10H), 5.15–5.04 (m, 2H), 4.30 (d, *J* = 7.6 Hz 1H), 3.96–3.81 (m, 1H), 2.77–2.76 (d, *J* = 5.6 Hz, 2H), 2.70–2.56 (m, 1H), 1.95–1.88 (m, 1H), 1.53–1.41 (m, 1H), 1.38 (s, 9H), 1.17 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.0, 155.2, 137.8, 136.0, 129.4, 128.5, 128.3, 128.1 (2C*), 126.3, 79.1, 66.2, 49.7, 41.3, 37.9, 36.4, 28.3, 17.6 ppm. HRMS (ESI) m/z $[M+Na]^+$ calcd. for $C_{24}H_{31}NO_4$ 420.2150, found 420.2160.

*higher intensity carbon

Conflict of Interest

Declarations of interest: none

Supplementary data

Electronic Supplementary Information (ESI) available: Copy of ^1H and ^{13}C NMR spectra of **1a, 1b, 2a, 2b, 3, 4, 5, 6, 7, 8a, 8b, 9a, 9b, 10a, 10b**.

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Legends

Table 1. Regioselective ring opening of (*S*)-2-Benzyl-1-tosylaziridine (**4**).

Fig. 1. Structure of tubulysin family of antimitotic agents.

Fig. 2. Stereochemical assignments of **8a** and **8b** through ^{1}H-^{1}H COSY and NOESY studies.

Scheme 1. Retrosynthetic analysis of *N*-Boc-Tup-OBn (**1a**) and *N*-Boc-*epi*-Tup-OBn (**1b**).

Scheme 2. Synthesis of (*S*)-2-benzyl-1-tosylaziridine (**4**). Reagents and conditions (i) $NaBH_4$, I_2, THF, 0 °C to reflux, 24 h, 96% (ii) Et_3N, TsCl, CH_3CN, 0 °C to rt, 1 h, 85%.

Scheme 3. Synthesis of *N*-tosyl-1,4-amino alcohols, **2a**–**b** and **7.** Reagents and conditions (i) a. 9-BBN, THF, rt, 12 h b. 2 M NaOH, H_2O_2, 0 °C to rt, 12 h, 90%, *dr*=2 :1 (ii) Boc_2O, DMAP, CH_2Cl_2, rt, 2 h, 97% (iii) a. 9-BBN, THF, rt, 12 h b. 2 M NaOH, H_2O_2, 0 °C to rt, 12 h, 70%, *dr*=2:1 (non-separable).

Scheme 4. Synthesis of *N*-Boc-Tup-OBn (**1a**). Reagents and conditions (i) PDC, DMF, rt, 12 h, 85% (ii) Mg, NH_4Cl, MeOH, reflux, 2 h, 84% (iii) Boc_2O, DMAP, DCM, rt, 2 h, 96% (iv) a. LiOH, H_2O_2, THF:H_2O (1:1), rt, 12 h b. BnBr, Et_3N, DCM, rt, 12 h, 75%.

Scheme 5. Synthesis of *N*-Boc-*epi*-Tup-OBn (**1b**). Reagents and conditions (i) PDC, DMF, rt, 12 h, 83% (ii) Mg, NH_4Cl, MeOH, reflux, 2 h, 81% (iii) Boc_2O, DMAP, DCM, rt, 2 h, 99% (iv) a. LiOH, H_2O_2, THF:H_2O (1:1), rt, 12 h b. BnBr, Et_3N, DCM, rt, 12 h, 72%.