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2-(*N*-Allylaminomethyl)cinnamaldehydes as substrates for syntheses of aza-polycycles via intramolecular cycloaddition reactions☆

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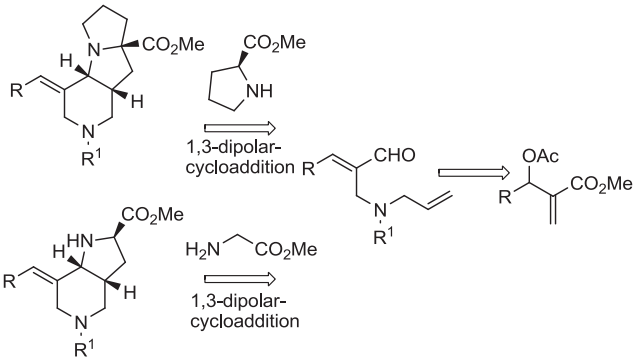
ABSTRACT

Syntheses of a variety of aza-polycycles employing 2-(*N*-allylaminomethyl)cinnamaldehydes derived from Morita–Baylis–Hillman adducts of acrylates via intramolecular 1,3-dipolar cycloaddition, or Aza-Diels–Alder or domino Knoevenagel/hetero Diels–Alder cycloaddition reactions are described. Whereas the Aza-Diels–Alder afforded a mixture of cis- and trans-isomers of substituted 1,2,3,4,4a,5,10,10a-octahydrobenzo[*b*][1,6]naphthyridines, the 1,3-dipolar cycloaddition and domino Knoevenagel/hetero Diels–Alder were diastereoselective to produce exclusively cis-derivatives of 1,2,3,4,4a,6,7,8,9,9a-decahydro-1*H*-pyrido[3,4-*b*]pyrrolizine-8a-carboxylates and 3,4,4a,5,7,8,9,10b-octahydro-1*H*-chromeno[3,4-*c*]pyridin-10(2*H*)-ones, respectively.

1. Introduction

The intramolecular cycloaddition is considered to be a robust strategy for accomplishing the synthesis of complex heterocycles.[1] In general; the reaction involves formation of at least two chemical bonds and a new ring system with high regio- and stereoselectivity. Amongst a wide spectrum of intramolecular cycloaddition reactions, the ones performed with the azomethine ylides are very popular as they result in pyrrolidine core, which is part of several alkaloid natural products.[2] Essentially this reaction is realized from a substrate carrying a dipole and a dipolarophile together. Remarkable influence of Morita–Baylis–Hillman (MBH) reaction on development of strategies for preparing heterocycles has motivated several research groups to perform intramolecular cycloaddition reactions on MBH derivatives for the synthesis of a number of polycycles.[3] A critical analysis of these protocols however, reveals that the azomethine ylides participating in these cycloaddition reactions originates from the formyl group present either in the aromatic system or the heteroaromatic system. Although in a recent report it was demonstrated that a formyl group in carbohydrate-based substrate can also be employed to prepare azomethine ylide, which participate in such cycloaddition reaction to give sugar-containing aza-polycyclic compounds,[4] there is lack of investigation on reaction of azomethine ylide dipole originating from MBH derivative containing an alkenylic formyl group. In context of our work concerning the exploitation of substituted allylamines derived from MBH adducts for constructing aza-heterocycles,[5] it occurred to us that the 2-(*N*-allylaminomethyl)cinnamaldehydes produced from the MBH adducts of acrylates can undergo intramolecular cycloaddition to furnish pyrido[3,4-*b*]pyrrolizine and pyrrolo[3,2-*c*]pyridine. Such target compounds are reported to be associated with anti-inflammatory (oxygenase inhibitors), anti-tumour (alkylating) agents and CNS activity.[6a–c] A retrosynthetic scheme outlining the rational of the envisaged approach is presented in Scheme 1. Herein we present the results of



Scheme 1. Retrosynthetic plan for the synthesis of pyrido[3,4-*b*]pyrrolizine and pyrrolo[3,2-*c*]pyridine.

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our study towards successful use of 2-(allyl(substituted amino) methyl)-3-arylacrylaldehyde for the intramolecular cycloaddition reactions. To extend the scope of the methodology, during the course of this study we also prepared 2-((substituted(3-methylbut-2-enyl)amino)methyl)-cinnamaldehyde and examined its application towards Aza-Diels–Alder (ADA) and Domino Knoevenagel/hetero Diels–Alder reactions.

2. Results and discussion

The work towards the desired objective commenced from the MBH acetates **1a**–**d**, which were transformed to allylamines **2a**–**d**,**3a** via S_N2'-reaction with benzylamine or tosylamine, respectively, following the reported procedures.[7a,b] The stereochemistry of these amines was assigned to be *E* exclusively.[7a] The reaction of substituted allylamines with allyl bromide in the presence of K_2CO_3 in DMF at room temperature afforded (*E*)-methyl 2-((*N*-allyl(substituted) amino)methyl)-cinnamates (**4a**–**d**,**5a**). To reduce the ester to formyl group, **4a**–**d**,**5a** were initially treated with DIBAL-H at room temperature to afford the corresponding alcohols **6a**–**d**,**7a**, which were then oxidized in the presence of MnO_2 to furnish (*E*)-2-((allyl(benzyl) amino)methyl)-cinnamaldehyde **8a**–**d**,**9a** (Scheme 2). Next with the required aldehydes in hand, their intramolecular cycloadditions through formation of azomethine ylides were investigated. Initially **8a** was treated with methyl proline ester in the presence of Et_3N in toluene at reflux. The reaction was completed in 12 h and afforded a product, which was isolated in 33% yield. Structure elucidation of the isolated product via spectroscopic analysis led us to establish the structure of the compound as **10a**. Importantly, the reaction was observed to be diastereoselective to furnish the cis-isomer only. The assignment of cis stereochemistry to the protons at the ring junctions of **10a** was initially made by analogy with the stereochemistry observed for conventional azomethine ylide cycloadditions in similar systems[8] and further corroborated by the coupling constant value of 5.1 Hz between them, which is consistent with a cis ring fusion. The relative stereochemistry of the ester group was assigned to be cis on the basis of the fact that the intramolecular cycloaddition proceeds through an ylide with *S*-shaped geometry (Fig. 1).

It has been reported that such cycloaddition reactions proceed more efficiently under microwave (MW) irradiation.[9] Therefore, in an attempt to increase the yield of the product we investigated the reaction of **8a** with methyl proline ester under MW irradiation. To our delight the reaction was complete in 30 min to afford **10a**, which was isolated in 68% yields. With the optimized condition in hand we tested the protocol with other substrates **8b**–**d**,**9a**. It was satisfying to note that the reaction between **8b**–**d**,**9a** and methyl proline ester under MW conditions afforded the expected polycycles **10b**–**d**,**11a** in good yields. All reactions were found to be diastereoselectives to afford the cis-isomers exclusively. Subsequently with the objective to increase the scope of the reactions, we considered replacing the methyl proline ester with methyl glycine ester as it would lead to bicyclic products instead of tricyclic compounds. Therefore reactions of **8a** and **9a** with methyl glycine ester under MW were examined. Expectedly here too reactions were diastereoselectives and afforded the corresponding products **12a** and **13a** as cis-isomer in good yield.

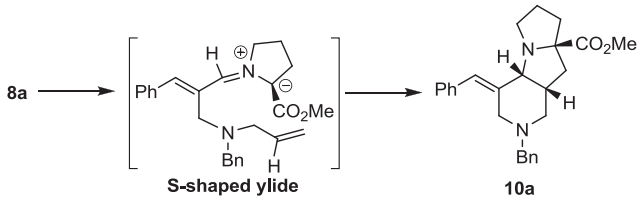
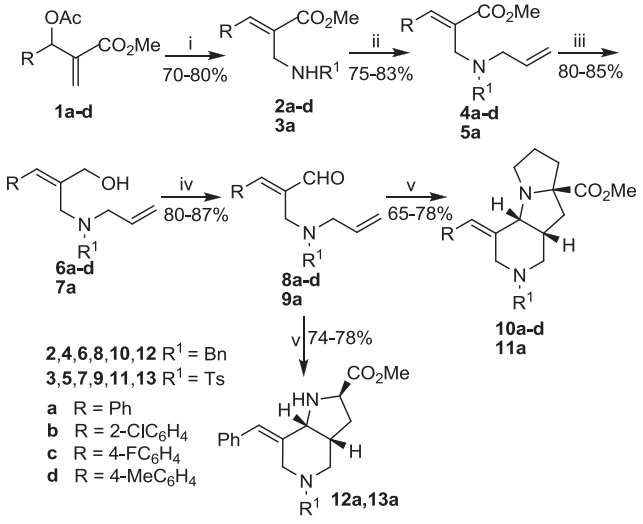
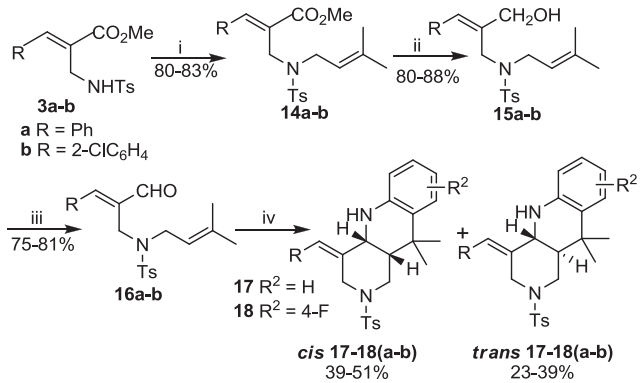


Fig. 1. Preferred geometry for the formation of **10a**.

The success with 1,3-dipolar cycloaddition, provoked us to investigate the utility of the same substrates for ADA reactions, which would lead to new tetrahydroquinoline derivatives.[10] Therefore the reaction of aldehyde **9a** with aniline was examined in the presence of several Lewis acids in dry MeCN. Unfortunately all attempt led to the formation of a mixture of products, which could not be isolated in pure form. It is widely reported that amines activated with prenyl group are better substrate for ADA reaction.[11] Thus, starting from **3a**,**b** prenyl derivatives **16a**,**b** were prepared as described above and in Scheme 3. Initially the ADA of **16a** with aniline was attempted in the presence of $Yb(OTf)_3$[12] but the reaction failed and a mixture of products was isolated. This led us to examine TFA and different Lewis acids including $InCl_3$, $Sc(OTf)_3$, $BiCl_3$ for the success of the reaction. It was interesting to discover that the reaction proceeded smoothly in the presence of $BiCl_3$ but in the presence of all other additives the reaction did not go beyond the formation of imine. Under the influence of $BiCl_3$, the reaction furnished the expected product **17a** as diastereomeric mixture in good yields (Scheme 3). Pure cis and trans isomers were isolated via silica gel based column chromatography. Next, to examine the scope of this reaction, only a limited study was performed. In the first opportunity, in place of aniline, the reaction of **16a** with 4-fluoroaniline was carried out. Expectedly this reaction too furnished the corresponding product



Scheme 2. Reagents and conditions: (i) $BnNH_2$, MeOH, rt, 1–2 h or $TsNH_2$, K_2CO_3, THF, 75 °C, 2 h; (ii) allyl bromide, K_2CO_3, DMF, rt, 2 h; (iii) DIBAL-H, PhMe, 0 °C-rt, 0.5 h; (iv) MnO_2, CH_2Cl_2 (dry), rt, 2 h; (v) methyl proline/glycine ester hydrochloride, Et_3N, PhMe, MW, 120 °C, 0.5–1 h.



Scheme 3. Reagents and conditions: (i) prenyl bromide, K_2CO_3, DMF, rt, 2–2.5 h; (ii) DIBAL-H, PhMe, 0 °C-rt, 0.5 h; (iii) MnO_2, CH_2Cl_2 (dry), rt, 2 h; (iv) $ArNH_2$, $BiCl_3$, MeCN, rt, 3–4 h.

18a as diastereomeric mixture, which was separated via column chromatography. In the second sequence another aldehyde **16b** was synthesized and subjected to reaction with aniline and 4-fluoroaniline. Likewise this aldehyde also furnished the respective adducts **17b** and **18b** as diastereomeric mixture in good yields. Both the cis and trans isomers were readily separated. In order to unambiguously assign the structure of the products a single crystal X-ray analysis of *cis*-**18a** was carried and the result is presented in Fig. 2.[13]

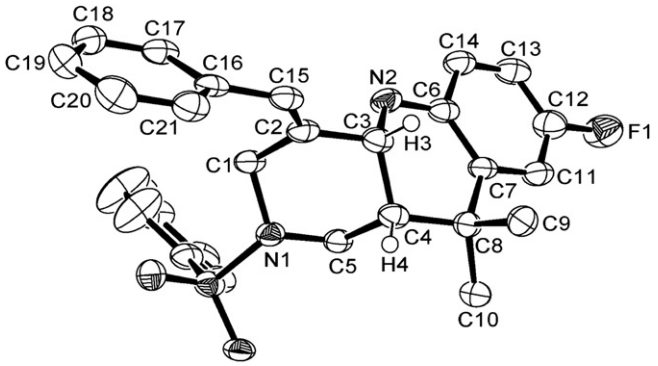
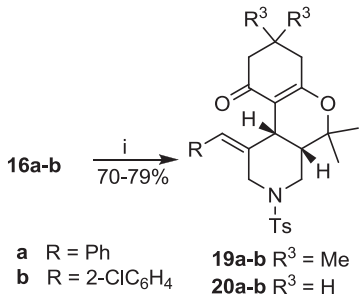


Fig. 2. Ortep structure of *cis*-**18a** at 35% probability level.

Finally, the utility of the aldehyde **16a**,**b** in domino Knoevenagel/Hetero Diels–Alder reactions was investigated. The optimization study was carried out using **16a** and 5,5-dimethyl-1,3-cyclohexanedione. After conducting a series of reactions for optimization, it was discovered that **16a** reacts with 5,5-dimethyl-1,3-cyclohexanedione in the presence of piperidine as a catalyst in toluene under MW condition to afford the product **19a** stereoselectively as cis-isomer (Scheme 4). The cis stereochemistry of **19a** was confirmed via literature precedence[14] and corroborated by carrying out detailed NMR experiments (see Supplementary data). To test the scope of the method **16b** was reacted with 5,5-dimethyl-1,3-cyclohexanedione and both **16a** and **16b** were reacted with 1,3-cyclohexanedione. It was satisfying to note that all reactions smoothly afford the respective products **19b** and **20a**,**b** as cis-isomer exclusively.



Scheme 4. (i) Substituted 1,3-cyclohexanedione, piperidine, PhMe, MW, 120 °C, 0.5–2 h.

3. Conclusions

In summary we have demonstrated for the first time that the β-allylaminoaldehydes derived from Morita–Baylis–Hillman adducts can be employed as substrates for the synthesis of aza-polycycles via different classes of cycloaddition reactions. As demonstrated these 2-(*N*-allylaminomethyl)cinnamaldehydes can be readily synthesized. Importantly, the 1,3-dipolar cycloaddition and domino Knoevenagel/hetero Diels–Alder were diastereoselective to produce exclusively cis-products. Further exploration towards the synthetic utility of these 2-(*N*-allylaminomethyl)cinnamaldehydes is underway in our laboratory.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin–Elmer's RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The detailed 2D NMR experiments were conducted on Bruker-400 MHz spectrometer. The ESMS were recorded on MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded as EI-HRMS on a JEOL system or as DART-HRMS (recorded as ES$^+$) on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having DART (Direct Analysis in Real Time) source. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL *III* microanalyzer. The room temperature varied between 20 °C and 35 °C. The stereochemistry displayed in the products is relative and not absolute.

4.2. General procedure for the synthesis of 4a–d,5a as exemplified by 4a

To a stirred solution of **3a** (1.00 g, 3.56 mmol) in anhyd DMF (8 mL) was added K_2CO_3 (0.74 g, 5.34 mmol) and the mixture was stirred for 10 min. Then allyl bromide (0.37 mL, 4.27 mmol) was added and the mixture was stirred at room temperature for 2 h. When the reaction was complete, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated to obtain the crude product. Purification via column chromatography over silica gel (100–200 mesh) using EtOAc/hexanes (1:9, v/v) as the eluent furnished pure **4a** (0.91 g, 80%) as colourless oil.

*4.2.1. Methyl (E)-2-[(N-allyl-N-benzylamino)methyl]-3-phenylprop-2-enoate (**4a**).* R_f=0.45 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1710 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.04 (d, 2H, J=6.5 Hz, CH_2), 3.53 (d, 4H, J=1.9 Hz, 2× CH_2), 3.80 (s, 3H, OCH_3), 5.06–5.11 (m, 2H, =CH_2), 5.79–5.93 (m, 1H, =CH), 7.21–7.36 (m, 8H, ArH), 7.59 (dd, 2H, J_1=6.5 Hz, J_2=1.5 Hz, ArH), 7.74 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.9, 56.7, 58.0, 62.3, 117.4, 126.8, 128.0, 129.1, 129.9, 130.5, 133.4, 135.7, 139.0, 139.5, 142.4, 169.5 ppm. MS (ES): m/z=322.1 [M+1]$^+$. $C_{21}H_{23}NO_2$ (321.1729): calcd C 78.47, H 7.21, N 4.36; found C 78.63, H 7.02, N 4.23.

*4.2.2. Methyl (E)-2-[(N-allyl-N-benzylamino)methyl]-3-(2-chlorophenyl)prop-2-enoate (**4b**).* This compound was isolated in 75% yield (1.69 g from 2.00 g) as brown oil. R_f=0.44 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1723 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.27 (d, 4H, J=1.3 Hz, 2× CH_2), 3.60 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.05–5.16 (m, 2H, =CH_2), 5.83–5.97 (m, 1H, =CH), 7.34–7.49 (m, 9H, ArH), 7.82 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=45.4, 52.2, 52.3, 57.9, 116.4, 128.7, 129.0, 129.7, 130.8, 135.2, 136.7, 142.2, 168.7 ppm. MS (ES): m/z=356.3 [M+1]$^+$. $C_{21}H_{22}ClNO_2$ (355.1339): calcd C 70.88, H 6.23, N 3.94; found C 70.93, H 6.30, N 3.83.

*4.2.3. Methyl (E)-2-[(N-allyl-N-benzylamino)methyl]-3-(4-fluorophenyl)prop-2-enoate (**4c**).* This compound was isolated in

83% yield (0.94 g from 1.00 g) as brown oil. R_f=0.44 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1715 (CO_2Me) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.12 (d, 2H, J=6.3 Hz, CH_2), 3.44 (d, 4H, J=1.0 Hz, 2× CH_2), 3.67 (s, 3H, OCH_3), 5.15–5.24 (m, 2H, =CH_2), 5.76–5.93 (m, 1H, =CH), 7.00–7.09 (m, 3H, ArH), 7.21–7.31 (m, 7H, =CH and ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.7, 52.5, 56.3, 57.8, 115.7, 117.8, 123.9, 124.0, 127.1, 128.3, 129.1, 129.8, 129.9, 135.6, 139.3, 169.3 ppm. MS (ES): m/z=340.3 $[M+1]^+$. $C_{21}H_{22}FNO_2$ (339.1635): calcd C 74.31, H 6.53, N 4.13; found C 74.39, H 6.42, N 4.22.

*4.2.4. Methyl (E)-2-[(N-allyl-N-benzylamino)methyl]-3-(4-methylphenyl)prop-2-enoate (**4d**).* This compound was isolated in 83% yield (2.36 g from 2.50 g) as brown oil. R_f=0.42 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1710 (CO_2Me) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.38 (s, 3H, CH_3), 3.04 (d, 2H, J=6.6 Hz, CH_2), 3.54 (s, 4H, 2× CH_2), 3.79 (s, 3H, OCH_3), 5.07–5.12 (m, 2H, =CH_2), 5.81–5.95 (m, 1H, =CH), 7.15–7.26 (m, 7H, ArH), 7.53 (d, 2H, J=8.0 Hz, ArH), 7.73 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.4, 50.1, 51.9, 56.7, 58.0, 117.5, 126.8, 128.0, 129.1, 129.9, 130.5, 132.5, 133.4, 135.7, 139.0, 139.5, 142.4, 169.5 ppm. MS (ES) m/z=336.0 $[M+1]^+$. $C_{22}H_{25}NO_2$ (335.1885): calcd C 78.77, H 7.51, N 4.18; found C 78.85, H 7.43, N 4.33.

*4.2.5. Methyl (E)-2-[(N-allyl-N-4-methylphenylsulfonamido)methyl]-3-phenylprop-2-enoate (**5a**).* This compound was isolated in 75% yield (0.84 g from 1.00 g) as a white solid, mp 142–143 °C. R_f=0.35 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1713 (CO_2Me) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.44 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 4.24 (s, 2H, CH_2), 4.90–4.95 (m, 2H, =CH_2), 5.46–5.59 (m, 1H, =CH), 7.22–7.26 (m, 2H, ArH), 7.41 (br s, 5H, ArH), 7.55 (d, 2H, J=8.2 Hz, ArH), 7.80 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 43.6, 51.4, 52.3, 118.5, 127.7, 128.3, 128.8, 129.3, 129.7, 130.0, 133.6, 134.7, 136.4, 143.4, 143.7, 168.2 ppm. MS (ES): m/z=385.9 $[M+1]^+$. $C_{21}H_{23}NO_4S$ (385.1348): calcd C 65.43, H 6.01, N 3.63; found C 65.55, H 6.12, N 3.51.

4.3. General procedure for the synthesis of 6a–d,7a, 15a,b as exemplified by 6a

To a stirred solution of **4a** (0.80 g, 2.49 mmol) in toluene (20 mL), was added 1.0 M DIBAL-H in toluene (6.23 mL, 6.23 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 30 min. When the reaction was completed as monitored by TLC, the reaction mixture was quenched with MeOH (15 mL) and the separated precipitate was filtered through Celite. The filtrate was evaporated under reduced pressure to obtain a residue, which upon column chromatography over silica gel (100–200 mesh) using EtOAc/hexanes (1:4, v/v) as the eluent furnished **6a** (0.58 g, 80%) as brown oil.

*4.3.1. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-phenylprop-2-en-1-ol (**6a**).* R_f=0.31 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3430 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.00 (d, 2H, J=6.4 Hz, CH_2), 3.41 (s, 2H, CH_2), 3.50 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 5.10–5.18 (m, 2H, =CH_2), 5.72–5.87 (m, 1H, =CH), 6.73 (s, 1H, =CH), 7.16 (d, 2H, J=7.0 Hz, ArH), 7.28–7.37 (m, 8H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=52.7, 56.5, 58.3, 69.5, 119.1, 127.0, 127.4, 128.2, 128.5, 129.0, 129.2, 130.6, 136.7, 137.5 ppm. MS (ES): m/z=294.2 $[M+1]^+$. $C_{20}H_{23}NO$ (293.1780): calcd C 81.87, H 7.90, N 4.77; found C 81.92, H 8.10, N 4.63.

*4.3.2. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(2-chlorophenyl)prop-2-en-1-ol (**6b**).* This compound was isolated in 85% yield (1.33 g from 1.70 g) as brown oil. R_f=0.25 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3567 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.99 (d, 2H, J=6.4 Hz, CH_2), 3.27 (s, 2H, CH_2), 3.47 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 5.11–5.17 (m, 2H, =CH_2), 5.72–5.89 (m, 1H, =CH), 6.69 (s, 1H, =CH), 7.09–7.12 (m, 1H, ArH), 7.22–7.42 (m, 8H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=53.1, 56.6, 58.4, 69.0, 119.2, 126.5, 127.6, 127.8, 128.8, 129.3, 129.6, 131.2, 134.1, 134.6, 135.4, 138.3, 139.3 ppm. MS (ES): m/z=328.4 $[M+1]^+$. $C_{20}H_{22}ClNO$ (327.1390): calcd C 73.27, H 6.76, N 4.27; found C 73.15, H 6.84, N 4.18.

*4.3.3. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(4-fluorophenyl)prop-2-en-1-ol (**6c**).* This compound was isolated in 80% yield (0.59 g from 0.80 g) as red oil. R_f=0.20 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3569 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.17 (d, 2H, J=6.4 Hz, CH_2), 3.37 (s, 2H, CH_2), 3.67 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 5.24–5.28 (m, 2H, =CH_2), 5.84–5.99 (m, 1H, =CH), 6.47 (s, 1H, =CH), 7.10–7.13 (m, 1H, ArH), 7.23–7.29 (m, 8H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=56.3, 58.3, 61.5, 63.0, 115.4, 115.7, 119.4, 123.5, 124.0, 127.7, 128.8, 129.3, 129.4, 129.5, 131.0, 134.4, 139.4 ppm. MS (ES): m/z=312.3 $[M+1]$.$C_{20}H_{22}FNO$ (311.1685): calc C 77.14, H 7.12, N 4.50; found C 77.20, H 7.06, N 4.55.

*4.3.4. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(4-methylphenyl)prop-2-en-1-ol (**6d**).* This compound was isolated in 80% yield (1.10 g from 1.50 g) as reddish brown oil. R_f=0.29 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3402 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.36 (s, 3H, CH_3), 2.99 (d, 2H, J=6.4 Hz, CH_2), 3.40 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 5.10–5.17 (m, 2H, =CH_2), 5.74–5.87 (m, 1H, =CH), 6.68 (s, 1H, =CH), 7.06 (d, 2H, J=7.9 Hz, ArH), 7.15 (d, 2H, J=7.9 Hz, ArH), 7.24–7.32 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.3, 52.8, 56.6, 58.3, 69.4, 118.8, 127.4, 128.6, 129.0, 129.2, 130.4, 133.9, 134.7, 136.7, 137.2, 138.2 ppm. MS (ES): m/z=308.0 $[M+1]^+$. $C_{21}H_{25}NO$ (307.1936): calcd C 82.04, H 8.20, N 4.56; found C 82.23, H 8.05, N 4.63.

*4.3.5. (E)-2-{[N-Allyl-(N-tosyl)amino]methyl}-3-phenylprop-2-en-ol (**7a**).* This compound was isolated in 80% yield (0.59 g from 0.80 g) as colourless oil. R_f=0.20 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3655 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=2.42 (s, 3H, CH_3), 3.63 (d, 2H, J=6.7 Hz, CH_2), 4.01 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 4.56 (dd, 1H, J_1=17.0 Hz, J_2=1.3 Hz, CH_2), 4.76 (dd, 1H, J_1=10.1 Hz, J_2=1.2 Hz, =CH_2), 5.19–5.39 (m, 1H, =CH), 6.78 (s, 1H, =CH), 7.07–7.11 (m, 2H, ArH), 7.22–7.30 (m, 5H, ArH), 7.65 (dd, 2H, J_1=6.6 Hz, J_2=1.7 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 43.8, 50.6, 65.1, 77.5, 119.8, 127.3, 127.4, 128.5, 129.0, 130.0, 131.4, 131.5, 136.3, 136.9, 143.8 ppm. MS (ES): m/z=357.9 $[M+1]^+$. $C_{20}H_{23}NO_3S$ (357.1399); calcd C 67.20, H 6.49, N 3.92; found C 67.28, H 6.53, N 3.83.

*4.3.6. (E)-2-{[N-3-Methylbut-2-enyl-(N-tosyl)amino]methyl}-3-phenylprop-2en-ol (**15a**).* This compound was isolated in 88% yield (1.23 g from 1.50 g) as colourless oil. R_f=0.25 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3454 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.68 (d, 2H, J=6.7 Hz, CH_2), 4.02 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 4.63–4.68 (m, 1H, =CH), 6.74 (s, 1H, =CH), 7.09 (d, 2H, J=6.8 Hz, ArH), 7.22–7.31 (m, 5H, ArH), 7.63 (d, 2H, J=8.2 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=17.6, 21.6, 25.6, 44.2, 45.7, 65.1, 118.0, 126.6, 127.2, 127.3, 128.2, 129.0, 129.8, 130.5, 136.2, 136.6, 137.28, 137.31, 143.5 ppm. MS (ES) m/z=385.6 $[M+1]^+$. $C_{22}H_{27}NO_3S$ (385.1712): calcd C 68.54, H 7.06, N 3.63; found C 68.42, H 6.92, N 3.72.

*4.3.7. (E)-2-{[N-3-Methylbut-2-enyl-(N-tosyl)amino]methyl}-3-(2-chlorophenyl)prop-2-en-ol (**15b**).* This compound was isolated in 80% yield (1.12 g from 1.50 g) as colourless oil. R_f=0.23 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=3459 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.69 (d, 2H, J=6.7 Hz, CH_2), 3.92 (s, 2H, CH_2), 4.38 (d, 2H, J=6.9 Hz, CH_2), 4.56–4.61 (m, 1H, =CH), 6.75 (s, 1H, =CH), 7.04–7.07 (m, 1H,

ArH), 7.17–7.37 (m, 5H, ArH), 763 (d, 2H, J=8.2 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=18.0, 21.7, 25.8, 30.5, 41.2, 67.7, 119.1, 125.7, 126.4, 126.8, 127.4, 127.6, 128.5, 129.8, 137.3, 137.8, 143.5 ppm. MS (ES) m/z=420.1 $[M+1]^+$. $C_{22}H_{26}ClNO_3S$ (419.1322): calcd C 62.92, H 6.24, N 3.34; found C 62.84, H 6.18, N 3.39.

4.4. General procedure for the formation of 8a–d,9a and 16a–b as exemplified by 8a

To a stirred solution of **6a** (0.40 g, 1.37 mmol) in dry DCM (10 mL) at room temperature was added activated MnO_2 (1.78 g, 20.55 mmol) and the reaction was continued at same temperature for 1 h. When the reaction was completed as monitored by TLC, the reaction mixture was diluted with DCM and filtered through Celite. The filtrate was evaporated to afford the crude product as oil. Purification by column chromatography over silica gel (100–200 mesh) using EtOAc/hexanes (1:9, v/v) as the eluent furnished **8a** (0.34 g, 85%) as brown oil.

*4.4.1. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-phenylprop-2-enal (**8a**).* R_f=0.40 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1679 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.06 (d, 2H, J=6.6 Hz, CH_2), 3.50 (s, 2H, CH_2), 3.54 (s, 2H, CH_2), 5.11–5.17 (m, 2H, =CH_2), 5.86–5.99 (m, 1H, =CH), 7.26 (s, 7H, ArH), 7.39–7.41 (m, 4H, =CH and ArH), 9.59 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=47.4, 57.1, 58.4, 118.0, 127.0, 128.1, 128.6, 129.3, 130.2, 131.4, 134.6, 135.5, 138.9, 139.3, 153.8, 195.4 ppm. MS (ES): m/z=292.1 $[M+1]^+$. $C_{20}H_{21}NO$ (291.1623): calcd C 82.44, H 7.26, N 4.81; found C 82.36, H 7.33, N 4.92.

*4.4.2. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(2-chlorophenyl) prop-2-enal (**8b**).* This compound was isolated in 87% yield (1.04 g from 1.20 g) as brown oil. R_f=0.38 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1667 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.00 (d, 2H, J=6.5 Hz, CH_2), 3.41 (s, 2H, CH_2), 3.50 (s, 2H, CH_2), 5.07–5.13 (m, 2H, =CH_2), 5.78–5.89 (m, 1H, =CH), 7.22–7.46 (m, 8H, ArH), 7.72 (s, 1H, =CH), 8.13 (dd, 1H, J_1=7.6 Hz, J_2=1.5 Hz, ArH), 9.67 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=47.4, 57.1, 58.6, 118.2, 126.9, 127.2, 128.4, 129.4, 129.8, 131.1, 132.6, 135.6, 139.3, 140.6, 144.0, 148.9, 195.2 ppm. MS (ES): m/z=326.1 $[M+1]^+$. $C_{20}H_{20}ClNO$ (325.1233): calcd C 73.72, H 6.19, N 4.30; found C 73.85, H 6.25, N 4.17.

*4.4.3. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(4-fluorophenyl) prop-2-enal (**8c**).* This compound was isolated in 87% yield (0.43 g from 0.50 g) as brown oil. R_f=0.35 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1667 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.04 (d, 2H, J=6.5 Hz, CH_2), 3.42 (d, 2H, J=1.1 Hz, CH_2), 3.52 (s, 2H, CH_2), 5.10–5.26 (m, 2H, =CH_2), 5.85–5.93 (m, 1H, =CH), 7.10–7.18 (m, 2H, ArH), 7.23–7.38 (m, 7H, ArH), 7.62 (s, 1H, =CH), 9.62 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=47.6, 52.1, 57.2, 118.3, 127.2, 128.4, 128.5, 129.0, 129.4, 132.2, 132.5, 132.8, 135.6, 135.9, 139.3, 139.5, 139.7, 192.7 ppm. MS (ES): m/z=310.2 $[M+1]^+$. $C_{20}H_{20}FNO$ (309.1529): calcd C 77.64, H 6.52, N 4.53; found C 77.83, H 6.46, N 4.64.

*4.4.4. (E)-2-{[N-Allyl-(N-benzyl)amino]methyl}-3-(4-methylphenyl) prop-2-enal (**8d**).* This compound was isolated in 88% yield (0.87 g from 1.00 g) as brown oil. R_f=0.42 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1679 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.40 (s, 3H, CH_3), 3.06 (d, 2H, J=6.5 Hz, CH_2), 3.49 (s, 2H, CH_2), 3.54 (s, 2H, CH_2), 5.11–5.17 (m, 2H, =CH_2), 5.87–6.00 (m, 1H, =CH), 7.19–7.27 (m, 7H, ArH), 7.35 (s, 1H, =CH), 7.77 (d, 2H, J=8.1 Hz, ArH), 9.56 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.8, 47.7, 57.3, 58.6, 76.9, 118.2, 127.1, 128.3, 128.5, 128.9, 129.5, 129.6, 130.3, 131.8, 132.1, 135.8, 138.2, 139.7, 141.1, 154.4, 195.7 ppm. MS (ES): m/z=306.1 $[M+1]^+$. $C_{21}H_{23}NO$ (305.1780): calcd C 82.58, H 7.59, N 4.59; found C 82.44, H 7.68, N 4.72.

*4.4.5. (E)-2-{[N-Allyl-(N-tosyl)amino]methyl}-3-phenylprop-2-enal (**9a**).* This compound was isolated in 80% yield (0.40 g from 0.50 g) as a white solid, mp 66–67 °C. R_f=0.30 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1681 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.44 (s, 3H, CH_3), 3.69 (d, 2H, J=6.0 Hz, CH_2), 4.20 (s, 2H, CH_2), 4.91–5.00 (m, 2H, =CH_2), 5.50–5.59 (m, 1H, =CH), 7.26–7.31 (m, 2H, ArH), 7.47–7.52 (m, 4H, ArH), 7.62 (d, 2H, J=8.2 Hz, ArH), 7.73–7.76 (m, 2H, =CH and ArH), 9.49 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ=21.7, 41.7, 51.4, 118.0, 127.9, 129.1, 129.9, 130.9, 131.0, 133.75, 133.78, 135.3, 135.7, 143.8, 154.6, 194.5 ppm. MS (ES): m/z=355.9 $[M+1]^+$. $C_{20}H_{21}NO_3S$ (355.1242): calcd C 67.58, H 5.95, N 3.94; found C 67.60, H 6.00, N 3.82.

*4.4.6. (E)-2-{[N-3-Methylbut-2-enyl-(N-tosyl)amino]methyl}-3-phenylprop-2-enal (**16a**).* This compound was isolated in 81% yield (1.05 g from 1.30 g) as a white solid, mp 90–93 °C. R_f=0.30 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1682 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.47 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.68 (d, 2H, J=6.3 Hz, CH_2), 4.21 (s, 2H, CH_2), 4.81–4.83 (m, 1H, =CH), 7.26–7.29 (m, 2H, ArH), 7.46–7.51 (m, 4H, ArH), 7.61 (d, 2H, J=8.2 Hz, ArH), 7.71–7.74 (m, 2H, =CH and ArH), 9.50 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=18.0, 21.8, 25.7, 41.5, 46.7, 120.0, 127.9, 129.1, 129.8, 130.9, 131.1, 133.9, 135.7, 135.8, 135.9, 143.6, 153.7, 194.2 ppm. MS (ES) m/z=384.1 $[M+1]^+$. $C_{22}H_{25}NO_3S$ (383.1555): calcd C 68.90, H 6.57, N 3.65; found C 68.97, H 6.52, N 3.61.

*4.4.7. (E)-2-{[N-3-Methylbut-2-enyl-(N-tosyl)amino]methyl}-3-(2-chlorophenyl)prop-2-enal (**16b**).* This compound was isolated in 75% yield (0.75 g from 1.00 g) as a white solid, mp 95–96 °C. R_f=0.29 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1680 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.50 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.66 (d, 2H, J=6.6 Hz, CH_2), 4.12 (s, 2H, CH_2), 4.74–4.78 (m, 1H, =CH), 7.25–7.27 (m, 2H, ArH), 7.37–7.43 (m, 3H, ArH), 7.44–7.50 (m, 2H, ArH), 7.71 (s, 1H, =CH), 7.76–7.79 (m, 1H, ArH), 9.56 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=17.9, 21.6, 25.7, 41.2, 46.6, 119.2, 127.1, 127.6, 129.65, 129.73, 131.3, 131.7, 132.1, 134.3, 135.9, 136.5, 138.1, 143.5, 148.8, 193.7 ppm. MS (ES) m/z=418.1 $[M+1]^+$. $C_{22}H_{24}ClNO_3S$ (417.1165): calcd C 63.22, H 5.79, N 3.35; found C 63.28, H 5.82, N 3.41.

4.5. General procedure for the formation of 10a–d, 11a, 12a and 13a as exemplified by 10a

A heterogeneous suspension of **8a** (0.25 g, 0.86 mmol), methyl proline ester hydrochloride (0.28 g, 1.72 mmol) and TEA (0.24 mL, 1.72 mmol) in 5 mL of toluene was irradiated in a sealed tube with microwaves for 30 min at 120 °C. After cooling to room temperature, the solvent was evaporated under reduced pressure and the reaction mixture was diluted with 10 mL of water and extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated under reduced pressure. Further purification of the crude product by column chromatography over silica gel over silica gel (230–400 mesh) using EtOAc/hexanes (1:4, v/v) as the eluent furnished **10a** (0.23 g, 68%) as reddish brown oil.

*4.5.1. (cis)-Methyl (E) 2-benzyl-4-benzylidene-1,2,3,4,4a,6,7,8,9,9a-decahydro-1H-pyrido[3,4-b]pyrrolizine-8a-carboxylate (**10a**).* R_f=0.23 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1725 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.56 (d, 1H, J=11.2 Hz, CH_2), 1.72–1.82 (m, 2H, CH_2), 1.94 (d, 1H, J=4.4 Hz, CH_2), 2.01–2.09 (m, 1H, CH_2), 2.44 (d, 2H, J=8.8 Hz, CH_2), 2.62–2.67 (m, 1H, CH), 2.76–2.80 (m, 1H, CH_2), 3.09–3.16 (m, 2H, CH_2), 3.20–3.25 (m, 1H,

CH_2), 3.51 (d, 2H, J=13.3 Hz, CH_2), 3.65 (d, 1H, J=13.5 Hz, CH_2), 3.72 (s, 3H, OCH_3), 4.12 (d, 1H, J=5.1 Hz, CH), 6.55 (s, 1H, ArH), 7.23–7.35 (m, 8H, ArH), 7.80 (d, 2H, J=7.3 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=27.2, 38.2, 40.9, 41.4, 51.3, 52.0, 58.6, 61.5, 62.3, 75.6, 127.2, 127.3, 128.1, 128.4, 129.2, 129.6, 136.2, 177.7 ppm. MS (ES): m/z=403.3 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{26}H_{31}N_2O_2$ 403.2386; found 403.2380.

*4.5.2. (cis)-Methyl (E) 2-benzyl-4-(2-chlorobenzylidene)-1,2,3,4,4a,-6,7,8,9,9a-decahydro-1H-pyrido[3,4-b]pyrrolizine-8a-carboxylate (**10b**).* This compound was isolated in 72% yield (0.48 g from 0.50 g) as reddish brown oil. R_f=0.20 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1724 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.56 (d, 1H, J=11.4 Hz, CH_2), 1.76–1.83 (m, 1H, CH_2), 1.93–1.98 (m, 2H, CH_2), 2.07–2.14 (m, 1H, CH_2), 2.38–2.45 (m, 2H, CH_2), 2.58–2.64 (m, 1H, CH), 2.75 (dd, 1H, J_1=11.6 Hz, J_2=4.2 Hz, CH_2), 3.06–3.09 (m, 1H, CH), 3.18–3.28 (m, 2H, CH_2), 3.51 (d, 2H, J=13.2 Hz, CH_2), 3.64–3.71 (m, 4H, CH_2 and OCH_3), 4.00 (d, 1H, J=5.3 Hz, CH), 6.82 (s, 1H, =CH), 7.17–7.23 (m, 2H, ArH), 7.28–7.36 (m, 6H, ArH), 8.41–8.44 (m, 1H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=27.4, 38.4, 41.3, 41.7, 49.2, 51.6, 52.2, 56.6, 58.8, 61.5, 62.3, 76.0, 126.7, 127.4, 127.9, 128.6, 128.7, 129.3, 129.4, 131.8, 134.2, 134.4, 177.8 ppm. MS (ES): m/z=437.3 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{26}H_{30}ClN_2O_2$ 437.1996; found 437.2005.

*4.5.3. (cis)-Methyl (E) 2-benzyl-4-(4-fluorobenzylidene) 1,2,3,4,4a,-6,7,8,9,9a-decahydro-1H-pyrido[3,4-b]pyrrolizine-8a-carboxylate (**10c**).* This compound was isolated in 65% yield (0.31 g from 0.35 g) as reddish brown oil. R_f=0.23 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1725 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.57 (d, 2H, J=11.2 Hz, CH_2), 1.76–1.83 (m, 2H, CH_2), 2.03–2.11 (m, 2H, CH_2), 2.39–2.46 (m, 2H, CH_2), 2.60–2.65 (m, 1H, CH), 2.79 (dd, 1H, J_1=10.2 Hz, J_2=3.0 Hz, CH_2), 3.07–3.10 (m, 1H, CH_2), 3.14–3.26 (m, 2H, CH_2), 3.51 (d, 1H, J=13.2 Hz, CH_2), 3.62 (d, 1H, J=17.8 Hz, CH_2), 3.70 (s, 3H, OCH_3), 4.06 (d, 1H, J=4.9 Hz, CH), 6.73 (s, 1H, =CH), 7.01–7.12 (m, 2H, ArH), 7.21–7.35 (m, 7H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=22.9, 27.3, 29.5, 32.1, 38.4, 41.2, 52.2, 56.7, 58.8, 62.4, 75.9, 115.1, 124.0, 127.4, 128.6, 129.0, 129.1, 129.4, 131.5, 177.8 ppm. MS (ES): m/z=421.3 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{26}H_{30}FN_2O_2$ 421.2291; found 421.2295.

*4.5.4. (cis)-Methyl (E) 2-benzyl-4-(4-methylbenzylidene) 1,2,3,4,4a,-6,7,8,9,9a-decahydro-1H-pyrido[3,4-b]pyrrolizine-8a-carboxylate (**10d**).* This compound was isolated in 70% yield (0.57 g from 0.60 g) as reddish brown oil. R_f=0.24 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1731 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.56 (d, 1H, J=11.2 Hz, CH_2), 1.74–1.81 (m, 1H, CH_2), 1.90–1.94 (m, 1H, CH_2), 2.05 (d, 1H, J=11.4 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.42 (d, 2H, J=11.0 Hz, CH_2), 2.60–2.65 (m, 1H, CH_2), 2.76–2.79 (m, 1H, CH_2), 3.11 (d, 2H, J=13.8 Hz, CH_2), 3.19–3.31 (m, 1H, CH), 3.49 (d, 2H, J=13.1 Hz, CH_2), 3.63 (d, 1H, J=6.1 Hz, CH_2), 3.67 (d, 1H, J=5.6 Hz, CH_2), 3.73 (s, 3H, OCH_3), 4.12 (d, 1H, J=4.9 Hz, CH), 6.51 (s, 1H, =CH), 7.13 (d, 2H, J=7.9 Hz, ArH), 7.26–7.37 (m, 5H, ArH), 7.71 (d, 2H, J=8.0 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.4, 27.4, 38.5, 41.0, 51.5, 52.3, 58.8, 75.8, 127.4, 128.5, 129.0, 129.4, 129.67, 129.72, 131.6, 133.6, 137.2, 178.0 ppm. MS (ES): m/z=417.4 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{27}H_{33}N_2O_2$ 417.2542; found 417.2550.

*4.5.5. (cis)-Methyl (E) 4-benzylidene-2-tosyl-1,2,3,4,4a,6,7,8,9,9a-decahydro-1H-pyrido[3,4-b]pyrrolizine-8a-carboxylate (**11a**).* This compound was isolated in 78% yield (0.36 g from 0.35 g) as a white solid, mp 141–142 °C. R_f=0.15 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1725 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.65–1.75 (m, 2H, CH_2), 1.77–1.92 (m, 2H, CH_2), 2.35–2.41 (m, 1H, CH_2), 2.44 (s, 3H, CH_3), 2.48–2.57 (m, 2H, CH and CH_2), 2.70–2.77 (m, 1H, CH_2), 2.88–2.93 (m, 1H, CH_2), 3.01–3.05 (m, 1H, CH_2), 3.37 (dd, 1H, J_1=12.2 Hz, J_2=5.0 Hz, CH_2), 3.65–3.73 (m, 4H, CH_2 and OCH_3), 4.12–4.16 (m, 2H, CH and CH_2), 6.61 (s, 1H, =CH), 7.24–7.35 (m, 5H, ArH), 7.66–7.71 (m, 4H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 27.2, 37.5, 40.3, 41.7, 47.9, 50.8, 52.3, 52.5, 58.2, 75.9, 127.8, 127.9, 128.4, 129.6, 129.8, 130.0, 133.1, 134.3, 135.6, 143.8, 177.1 ppm. MS (ES) m/z=467.3 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{26}H_{31}N_2O_4S$ 467.2005; found 467.2012.

*4.5.6. (cis)-Methyl (E) 5-benzyl-7-benzylidene-2,3,3a,4,5,6,7,7a-octahydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**12a**).* This compound was isolated in 74% yield (0.23 g from 0.25 g) as brown oil. R_f=0.15 (EtOAc/hexanes 1:4, v/v). IR (Neat): ν_{max}=1725 (CO_2Me), 3415 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.61 (dd, 1H, J_1=12.7 Hz, J_2=4.8 Hz, CH_2), 1.91 (d, 1H, J=10.8 Hz, CH_2), 2.24 (t, 2H, J=9.7 Hz, CH_2), 2.64 (dd, 1H, J_1=11.5 Hz, J_2=4.1 Hz, CH), 3.08 (d, 1H, J=14.1 Hz, CH_2), 3.25–3.30 (m, 1H, CH), 3.50 (d, 1H, J=12.7 Hz, CH_2), 3.61 (d, 1H, J=13.0 Hz, CH_2), 3.77 (s, 3H, OCH_3), 3.80 (s, 1H, CH), 3.88 (d, 1H, J=3.7 Hz, CH), 6.54 (s, 1H, =CH), 7.21–7.35 (m, 8H, ArH), 7.45 (d, 2H, J=8.6 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=34.9, 38.8, 52.5, 54.9, 57.8, 58.2, 58.8, 62.6, 123.4, 127.2, 127.3, 127.4, 128.4, 128.5, 128.7, 129.0, 129.5, 130.1, 134.5, 136.7, 138.0, 175.7 ppm. MS (ES): m/z=363.4 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{23}H_{27}N_2O_2$ 363.2073; found 363.2071.

*4.5.7. (cis)-Methyl (E) 7-benzylidene-5-tosyloctahydro-2,3,3a,4,-5,6,7,7a-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**13a**).* This compound was isolated in 81% yield (0.29 g from 0.30 g) as a white solid, mp 139–140 °C. R_f=0.10 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1725 (CO_2Me), 3423 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.64 (dd, 1H, J_1=13.1 Hz, J_2=5.2 Hz, CH_2), 2.16–2.30 (m, 2H, CH_2), 2.39–2.47 (m, 4H, CH and CH_3), 3.44 (d, 1H, J=12.7 Hz, CH_2), 3.53 (dd, 1H, J_1=11.7 Hz, J_2=5.3 Hz, CH_2), 3.68 (s, 3H, OCH_3), 3.77–3.82 (m, 1H, CH), 3.87 (d, 1H, J=4.7 Hz, CH), 4.11 (d, 1H, J=12.4 Hz, CH_2), 6.66 (s, 1H, =CH), 7.26–7.34 (m, 7H, ArH), 7.68 (d, 2H, J=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 33.3, 38.3, 47.0, 50.1, 52.4, 56.9, 58.4, 127.7, 127.9, 128.6, 128.8, 130.0, 131.6, 131.9, 134.1, 135.9, 143.8, 175.0 ppm. MS (ES): m/z=427.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{23}H_{27}N_2O_4S$ 427.1692; found 427.1695.

4.6. General procedure for the formation of 14a–b as exemplified by 14a

To a stirred solution of **3a** (1.00 g, 2.90 mmol) in anhyd DMF (8 mL) was added K_2CO_3 (0.48 g, 3.48 mmol) and the mixture was stirred for 10 min at room temperature. Then prenyl bromide (0.40 mL, 3.48 mmol) was added and mixture was stirred at same temperature for 2 h. When the reaction was complete, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated to obtain the crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc/hexanes (1:9, v/v) as the eluent to yield **14a** (0.96 g, 80%) as a white solid.

*4.6.1. (E)-Methyl 2-{[4-methyl-N-(3-methylbut-2-enyl)phenylsulfonamido]methyl}-3-phenylprop-2-enoate (**14a**).* Mp 82–83 °C. R_f=0.40 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1711 (CO_2Me) cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.49 (s, 6H, 2× CH_3), 2.41 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2), 4.24 (s, 2H, CH_2), 4.77–4.84 (m, 1H, =CH), 7.21–7.27 (m, 2H, ArH), 7.39–7.45 (m, 5H, ArH), 7.54 (d, 2H, J=8.3 Hz, ArH), 7.79 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=17.9, 21.7, 25.8, 43.6, 46.5, 52.2, 119.9, 127.7, 128.5, 128.7, 129.3, 129.6, 130.0, 134.7, 136.0, 136.7, 143.2, 143.3,

168.1 ppm. MS (ES): m/z=413.7 $[M+1]^+$. $C_{23}H_{27}NO_4S$ (413.1661): calcd C 66.80, H 6.58, N 3.39; found C 66.74, H 6.65, N 3.33.

*4.6.2. (E)-Methyl 3-(2-chlorophenyl)-2-{[4-methyl-N-(3-methylbut-2-enyl)phenylsulfonamido]methyl}prop-2-enoate (**14b**).* This compound was isolated in 83% yield (1.96 g from 2.00 g) as a white solid, mp 83–84 °C. R_f=0.38 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1713 (CO_2Me) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.51 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.74 (d, 2H, J=6.6 Hz, CH_2), 4.13 (s, 2H, CH_2), 4.72–4.77 (m, 1H, =CH), 7.21 (d, 2H, J=8.1 Hz, ArH), 7.30–7.33 (m, 2H, ArH), 7.40–7.47 (m, 2H, ArH), 7.54 (d, 2H, J=8.2 Hz, ArH), 7.85 (s, 1H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=18.0, 21.7, 25.8, 43.6, 46.5, 52.5, 119.4, 126.9, 127.6, 129.6, 129.7, 130.2, 130.8, 131.2, 133.3, 134.2, 136.3, 136.9, 139.7, 143.1, 167.1 ppm. MS (ES): m/z=448.1 $[M+1]^+$. $C_{23}H_{26}ClNO_4S$ (447.1271): calcd C 61.67, H 5.85, N 3.13; found C 61.73, H 5.91, N 3.01.

4.7. General procedure for the formation of 17–18(a–b) as exemplified by 17a

To a stirred solution of **16a** (0.25 g, 0.65 mmol) in dry MeCN (20 mL) was added aniline (0.06 mL, 0.65 mmol) at room temperature under N_2 atmosphere in the presence of molecular sieves. The reaction mixture was stirred for 20 min and then to it $BiCl_3$ (0.02 g, 0.065 mmol) was added and the reaction was continued at the same temperature. After the completion of the reaction as monitored by the TLC, the reaction mixture was filtered through a bed of Celite. The filtrate was diluted with H_2O (15 mL) and extracted with EtOAc (2×10 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product as oil. Purification by column chromatography over silica gel (230–400 mesh) using EtOAc/hexanes (3:97, v/v) as the eluent furnished pure (*cis*)-**17a** (0.13 g, 43%) and (*trans*)-**17a** (0.09 g, 30%) as a white solid.

*4.7.1. (cis)-4-(E) Benzylidene-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**17a**).* Mp 193–195 °C. R_f=0.15 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3389 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=1.29 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.87–1.97 (m, 1H, CH), 2.38 (s, 3H, CH_3), 2.43 (d, 1H, J=12.0 Hz, CH_2), 3.34 (d, 2H, J=13.2 Hz, CH_2), 3.85 (dd, 1H, J_1=11.5 Hz, J_2=4.3 Hz, CH_2), 4.19 (d, 1H, J=3.0 Hz, CH_2), 4.71 (d, 1H, J=13.7 Hz, CH_2), 6.40 (dd, 1H, J_1=7.9 Hz, J_2=1.2 Hz, ArH), 6.63–6.70 (m, 2H, =CH and ArH), 6.91–7.00 (m, 1H, ArH), 7.14 (dd, 1H, J_1=7.9 Hz, J_2=1.4 Hz, ArH), 7.19–7.25 (m, 2H, ArH), 7.30–7.44 (m, 5H, ArH), 7.53 (d, 2H, J=8.4 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.0, 34.6, 34.8, 42.3, 43.4, 45.3, 54.4, 114.0, 117.9, 126.3, 127.1, 127.6, 127.7, 127.8, 128.8, 129.1, 129.3, 129.9, 134.9, 135.3, 135.8, 142.0, 143.5 ppm. MS (ES) m/z=459.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{31}N_2O_2S$ 459.2106; found 459.2103.

*4.7.2. (trans)-4-(E) Benzylidene-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,-10a-octahydrobenzo[b][1,6]naphthyridine (**17a**).* Mp 191–192 °C. R_f=0.15 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3389 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.15 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.79 (d, 1H, J=11.9 Hz, CH), 2.40 (s, 3H, CH_3), 2.47 (d, 1H, J=11.9 Hz, CH_2), 3.59 (d, 2H, J=11.8 Hz, CH_2 and NH), 3.82 (dd, 1H, J_1=11.4 Hz, J_2=3.2 Hz, CH_2), 4.15 (d, 1H, J=12.1 Hz, CH_2), 4.66 (d, 1H, J=2.4 Hz, CH), 6.41 (d, 1H, J=8.2 Hz, ArH), 6.62–6.68 (m, 2H, =CH and ArH), 6.94 (t, 1H, J=7.3 Hz, ArH), 7.10 (d, 1H, J=7.7 Hz, ArH), 7.19–7.35 (m, 7H, ArH), 7.65 (d, 2H, J=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.2, 34.58, 34.62, 43.6, 44.7, 46.0, 49.1, 114.1, 118.0, 126.5, 127.0, 127.7, 127.8, 128.7, 130.0, 130.2, 134.75, 134.82, 135.6, 142.0, 143.7 ppm. MS (ES) m/z=459.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{31}N_2O_2S$ 459.2106; found 459.2103.

*4.7.3. (cis)-4-(E)-(2-Chlorobenzylidene)-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**17b**).* This compound was isolated in 51% yield (0.15 g from 0.25 g) as a white solid, mp 125–127 °C. R_f=0.30 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3361 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.93–1.97 (m, 1H, CH), 2.37 (s, 3H, CH_3), 2.46 (d, 1H, J=11.9 Hz, CH_2), 3.31 (d, 1H, J=13.0 Hz, CH_2), 3.84 (dd, 1H, J_1=11.7 Hz, J_2=3.8 Hz, CH_2), 4.27 (d, 1H, J=2.8 Hz, CH), 4.47 (d, 1H, J=12.8 Hz, CH_2), 6.41 (d, 1H, J=8.0 Hz, ArH), 6.64–6.69 (m, 2H, =CH and ArH), 6.95 (t, 1H, J=7.3 Hz, ArH), 7.13 (d, 1H, J=7.6 Hz, ArH), 7.20–7.35 (m, 4H, ArH), 7.41 (t, 2H, J=5.0 Hz, ArH), 7.52 (d, 2H, J=8.2 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.0, 34.6, 34.8, 42.5, 43.5, 45.5, 54.0, 114.1, 118.0, 126.3, 126.4, 127.1, 127.2, 127.7, 129.4, 129.7, 130.0, 131.2, 134.0, 134.1, 134.7, 136.9, 141.9, 143.6 ppm. MS (ES) m/z=493.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{29}ClFN_2O_2S$ 493.1717; found 493.1713.

*4.7.4. (trans)-4-(E)-(2-Chlorobenzylidene)-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**17b**).* This compound was isolated in 39% yield (0.13 g from 0.25 g) as a white solid, mp 129–130 °C. R_f=0.30 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3405 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.11 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.78–1.81 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.44 (d, 1H, J=13.5 Hz, CH_2), 3.67 (d, 1H, J=12.4 Hz, CH_2), 3.83 (dd, 1H, J_1=11.8 Hz, J_2=2.8 Hz, CH_2), 4.24 (d, 1H, J=12.8 Hz, CH_2), 4.39 (d, 1H, J=2.4 Hz, CH), 6.38 (d, 1H, J=7.9 Hz, ArH), 6.63–6.66 (m, 2H, =CH and ArH), 6.90–6.95 (m, 1H, ArH), 7.07–7.12 (m, 2H, ArH), 7.19–7.29 (m, 4H, ArH), 7.39 (dd, 1H, J_1=6.6 Hz, J_2=2.3 Hz, ArH), 7.67 (d, 2H, J=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ=21.8, 22.9, 26.2, 29.6, 29.9, 32.2, 34.7, 43.4, 44.7, 46.3, 48.6, 114.3, 118.2, 126.5, 126.8, 127.1, 127.8, 129.3, 129.9, 130.1, 130.3, 134.0, 134.2, 134.9, 136.6, 142.0, 143.7 ppm. MS (ES) m/z=493.0 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{29}ClFN_2O_2S$ 493.1717; found 493.1715.

*4.7.5. (cis)-4-(E) Benzylidene-8-fluoro-10,10-dimethyl-2-tosyl-1,2,3,-4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**18a**).* This compound was isolated in 42% yield (0.13 g from 0.25 g) as a white solid, mp 200–202 °C. R_f=0.29 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3409 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.29 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.89–1.93 (m, 1H, CH), 2.39 (s, 3H, CH_3), 2.45 (d, 1H, J=12.0 Hz, CH_2), 3.33 (d, 1H, J=13.0 Hz, CH_2), 3.56 (s, 1H, NH), 3.83 (dd, 1H, J_1=11.3 Hz, J_2=3.9 Hz, CH_2), 4.15 (d, 1H, J=2.7 Hz, CH), 4.70 (d, 1H, J=12.5 Hz, CH_2), 6.30–6.35 (m, 1H, ArH), 6.61–6.70 (m, 2H, =CH and ArH), 6.84 (dd, 1H, J_1=10.4 Hz, J_2=2.9 Hz, ArH), 7.22 (d, 2H, J=7.9 Hz, ArH), 7.28–7.33 (m, 3H, ArH), 7.38–7.43 (m, 2H, ArH), 7.53 (d, 2H, J=7.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 25.9, 34.6, 34.8, 42.2, 43.2, 44.9, 54.3, 112.8, 113.6, 114.7, 127.7, 127.8, 128.8, 128.9, 129.1, 129.3, 129.9, 134.8, 135.1, 135.7, 138.1, 138.2, 143.6, 154.6, 157.7 ppm. MS (ES) m/z=477.0 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{30}FN_2O_2S$ 477.2012; found 477.2015.

*4.7.6. (trans)-4-(E) Benzylidene-8-fluoro-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**18a**).* This compound was isolated in 32% yield (0.10 g from 0.25 g) as a white solid, mp 209–210 °C. R_f=0.28 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3412 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.14 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.77–1.81 (m, 1H, CH), 2.40–2.43 (m, 4H, CH_3 and CH_2), 3.49–3.56 (m, 2H, CH_2 and NH), 3.56 (s, 1H, NH), 3.80 (dd, 1H, J_1=11.7 Hz, J_2=3.3 Hz, CH_2), 4.14 (d, 1H, J=12.9 Hz, CH_2), 4.62 (d, 1H, J=2.6 Hz, CH), 6.30–6.35 (m, 1H, ArH), 6.65–6.67 (m, 2H, =CH and ArH), 6.80 (dd, 1H, J_1=10.1 Hz, J_2=2.7 Hz, ArH), 7.18 (d, 2H, J=7.0 Hz, ArH), 7.26–7.35 (m, 4H, ArH), 7.65 (d, 2H, J=8.2 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.8, 25.8, 26.1, 34.3, 35.0, 44.3, 45.4, 46.0, 49.0, 114.7, 119.1, 127.5, 127.8, 127.9, 128.7, 128.8, 129.1, 129.88, 129.94, 130.0, 130.2, 134.7, 135.3, 143.7, 146.0 ppm. MS (ES)

m/*z*=477.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{30}FN_2O_2S$ 477.2012; found 477.2010.

*4.7.7. (cis)-4-(E)-(2-Chlorobenzylidene)-8-fluoro-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**18b**).* This compound was isolated in 39% yield (0.12 g from 0.25 g) as a white solid, mp 201–202 °C. R_f=0.30 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3389 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.30 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.93–1.97 (m, 1H, CH), 2.38 (m, 3H, CH_3), 2.42 (d, 1H, *J*=12.0 Hz, CH_2), 3.29 (d, 1H, *J*=13.0 Hz, CH_2), 3.59 (s, 1H, NH), 3.83 (dd, 1H, J_1=11.5 Hz, J_2=3.5 Hz, CH_2), 4.23 (d, 1H, *J*=2.6 Hz, CH), 4.46 (d, 1H, *J*=12.9 Hz, CH_2), 6.32–6.36 (m, 1H, ArH), 6.65–6.70 (m, 2H, =CH and ArH), 6.84 (dd, 1H, J_1=10.1 Hz, J_2=2.7 Hz, ArH), 7.21–7.33 (m, 4H, ArH), 7.41 (t, 2H, *J*=7.3 Hz, ArH), 7.53 (d, 2H, *J*=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.0, 34.6, 34.9, 42.4, 43.3, 45.1, 54.1, 112.5, 112.8, 113.7, 114.0, 114.7, 114.8, 126.4, 127.2, 127.7, 128.86, 128.93, 129.4, 129.7, 130.0, 131.2, 134.0, 134.6, 136.8, 138.0, 143.7, 157.7 ppm. MS (ES) *m*/*z*=511.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{29}ClFN_2O_2S$ 511.1622; found: 511.1620.

*4.7.8. (trans)-4-(E)-(2-Chlorobenzylidene)-8-fluoro-10,10-dimethyl-2-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[b][1,6]naphthyridine (**18b**).* This compound was isolated in 32% yield (0.10 g from 0.25 g) as a white solid, mp 196–197 °C. R_f=0.29 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=3389 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.11 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.77–1.81 (m, 1H, CH), 2.41 (s, 3H, CH_3), 2.47 (d, 1H, *J*=12.0 Hz, CH_2), 3.43 (s, 1H, NH), 3.66 (d, 1H, *J*=12.6 Hz, CH_2), 3.81 (dd, 1H, J_1=11.7 Hz, J_2=3.6 Hz, CH_2), 4.22 (d, 1H, *J*=12.4 Hz, CH_2), 4.35 (d, 1H, *J*=2.1 Hz, CH), 6.28–6.33 (m, 1H, ArH), 6.61–6.66 (m, 2H, =CH and ArH), 6.79 (dd, 1H, J_1=10.1 Hz, J_2=2.7 Hz, ArH), 7.08–7.11 (m, 1H, ArH), 7.20–7.30 (m, 4H, ArH), 7.38–7.41 (m, 1H, ArH), 7.67 (d, 2H, *J*=8.2 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.1, 34.4, 34.9, 43.3, 44.3, 46.3, 48.5, 112.6, 112.9, 113.6, 114.0, 114.9, 115.0, 126.8, 127.1, 127.8, 129.1, 129.3, 129.9, 130.0, 130.3, 134.0, 134.1, 134.9, 136.6, 138.1, 143.7, 157.8 ppm. MS (ES): *m*/*z*=511.0 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{29}ClFN_2O_2S$ 511.1622; found 511.1615.

4.8. General procedure for the formation of 19–20(a–b) as exemplified by 19a

A heterogeneous suspension of **16a** (0.25 g, 0.65 mmol), 3,3-dimethyl cyclohexane 1,3-dione (0.06 g, 0.46 mmol) and piperidine (0.26 mL, 2.60 mmol) in 5 mL of toluene was irradiated in a sealed tube with microwaves for 30 min at 120 °C. After cooling to room temperature, the solvent was evaporated under reduced pressure and the reaction mixture was diluted with 10 mL of water and extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated under reduced pressure. Further purification of the crude product by column chromatography over silica gel over silica gel (230–400 mesh) using EtOAc/hexanes (1:4, v/v) as the eluent furnished **19a** (0.26 g, 79%) as a white solid.

*4.8.1. (cis)-1 (Z)-Benzylidene-5,5,8,8-tetramethyl-3-tosyl-3,4,4a,5,-7,8,9,10b-octahydro-1H-chromeno[3,4-c]pyridin-10(2H)-one (**19a**).* Mp 223–224 °C. R_f=0.23 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1650 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.49 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.78–1.82 (m, 1H, CH_2), 1.92–2.24 (m, 5H, CH and CH_2), 2.40 (s, 3H, CH_3), 2.69 (d, 1H, *J*=11.9 Hz, CH_2), 3.81 (dd, 1H, J_1=11.5 Hz, J_2=4.2 Hz, CH_2), 3.87 (br s, 1H, CH), 4.02 (d, 1H, *J*=11.5 Hz, CH_2), 6.67 (s, 1H, =CH), 7.26–7.37 (m, 7H, ArH), 7.63 (d, 2H, *J*=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ=21.7, 25.9, 26.0, 30.2, 30.4, 31.5, 41.1, 43.0, 43.3, 51.2, 51.5, 78.4, 107.1, 126.8, 128.1, 128.2, 128.4, 128.6, 129.0, 129.3, 129.8, 132.3, 134.3, 137.3, 143.9, 170.0, 196.9 ppm. MS (ES) *m*/*z*=506.0 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{30}H_{36}NO_4S$ 506.2365; found 506.2360.

*4.8.2. (cis)-1 (Z)-(2-Chlorobenzylidene)-5,5,8,8-tetramethyl-3-tosyl-3,4,4a,5,7,8,9,10b-octahydro-1H-chromeno[3,4-c]pyridin-10(2H)-one (**19b**).* This compound was isolated in 74% yield (0.26 g from 0.25 g) as a white solid, mp 241–242 °C. R_f=0.20 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1658 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.51 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.87–2.21 (m, 6H, CH and CH_2), 2.40 (s, 3H, CH_3), 2.74 (d, 1H, *J*=11.5 Hz, CH_2), 3.62 (br s, 1H, CH), 3.80 (dd, 1H, J_1=11.2 Hz, J_2=3.9 Hz, CH_2), 4.09 (d, 1H, *J*=12.1 Hz, CH_2), 6.65 (s, 1H, =CH), 7.15–7.17 (m, 2H, ArH), 7.26–7.38 (m, 3H, ArH), 7.52–7.55 (m, 1H, ArH), 7.65 (d, 2H, *J*=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 26.0, 26.1, 30.2, 30.7, 31.5, 41.0, 42.9, 43.3, 50.8, 51.5, 78.5, 107.0, 126.0, 126.5, 128.2, 128.3, 129.5, 129.8, 131.3, 134.3, 135.6, 136.0, 143.8, 196.9 ppm. MS (ES) *m*/*z*=540.2 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{30}H_{35}ClNO_4S$ 540.1975; found 540.1978.

*4.8.3. (cis)-1 (Z)-Benzylidene-5,5-dimethyl-3-tosyl-3,4,4a,5,7,8,9,-10b-octahydro-1H-chromeno[3,4-c]pyridin-10(2H)-one (**20a**).* This compound was isolated in 71% yield (0.22 g from 0.25 g) as a yellow solid, mp 240–241 °C. R_f=0.17 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1649 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.10 (s, 3H, CH_3), 1.25–1.33 (s, 4H, CH_2 and CH_3), 1.74–1.77 (m, 1H, CH_2), 1.85–1.90 (m, 1H, CH_2), 2.23–2.26 (m, 4H, CH_2), 2.35 (s, 1H, CH), 2.44 (s, 3H, CH_3), 2.91 (d, 1H, *J*=10.8 Hz, CH_2), 3.81 (dd, 1H, J_1=9.9 Hz, J_2=4.3 Hz, CH_2), 3.90 (br s, 1H, CH), 4.00 (d, 1H, *J*=13.2 Hz, CH_2), 6.62 (s, 1H, =CH), 7.26–7.34 (m, 7H, ArH), 7.67 (d, 2H, *J*=8.0 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=18.0, 20.7, 21.7, 25.9, 28.5, 36.6, 45.4, 49.6, 79.8, 111.1, 117.1, 118.5, 123.6, 127.4, 128.1, 129.0, 129.5, 129.8, 131.5, 136.96, 137.0, 138.3, 143.4, 171.5, 194.8 ppm. MS (ES) *m*/*z*=478.0 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{32}NO_4S$ 478.2052; found 478.2049.

*4.8.4. (cis)-1 (Z)-(2-Chlorobenzylidene)-5,5-dimethyl-3-tosyl-3,4,-4a,5,7,8,9,10b-octahydro-1H-chromeno[3,4-c]pyridin-10(2H)-one (**20b**).* This compound was isolated in 70% yield (0.23 g from 0.25 g) as a white solid, mp 204–205 °C. R_f=0.21 (EtOAc/hexanes 1:4, v/v). IR (KBr): ν_{max}=1657 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.08 (s, 3H, CH_3), 1.26–1.34 (s, 4H, CH and CH_3), 1.82–1.88 (m, 2H, CH_2), 2.22–2.26 (m, 4H, 2× CH_2), 2.43 (s, 4H, CH and CH_3), 2.98 (d, 1H, *J*=12.5 Hz, CH_2), 3.66 (br s, 1H, CH), 3.77 (d, 1H, *J*=9.7 Hz, CH_2), 4.04 (d, 1H, *J*=12.2 Hz, CH_2), 6.60 (s, 1H, =CH), 7.16–7.18 (m, 2H, ArH), 7.26–7.38 (m, 3H, ArH), 7.55 (d, 1H, *J*=7.5 Hz, ArH), 7.69 (d, 2H, *J*=9.0 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=20.7, 21.8, 25.8, 26.0, 29.7, 30.9, 37.9, 41.2, 42.6, 50.3, 78.3, 108.2, 125.8, 126.5, 128.0, 128.4, 129.5, 129.8, 131.3, 134.0, 134.2, 135.6, 136.0, 143.8, 171.7, 197.2 ppm. MS (ES) *m*/*z*=512.1 $[M+1]^+$. DART-HRMS $[ES^+]$: calcd for $C_{28}H_{31}ClNO_4S$ 512.1584; found 512.1587.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra and details of 2D experiments of **11a** and **19b** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.01.016. These data include MOL files and InChiKeys of the most important compounds described in this article.

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13. Crystal data of compound **18a** (crystallized from $CHCl_3$): $C_{28}H_{29}FN_2O_2S$, M=476.59, Monoclinic, P–1, a=33.877(7), b=7.9404(15), c=19.868(4) Å, α=90.00, β=95.989(7), γ=90.00, V=5315.4(18) Å^3, Z=8, D_x=1.191 g cm^{-3}, μ (Mo Kα)=0.155 mm^{-1}, F (000)=2016.0 colorless block, dimension 0.28×0.20×0.14 mm, 5212 reflections measured (R_{int}=0.0605), 5212 unique, wR_2=0.1806, conventional R=0.0652 on F^2 values of 3328 reflections with $I>2\sigma(I)$, $(\Delta/\sigma)_{max}$=000), S=1.053 for all data and 307 parameters. Unit cell determination and intensity data collection (2θ=50°) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997) for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 860024).
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