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ARTICLE TYPE

# Stereoselective Synthesis of *O*-Tosyl Azabicyclic Derivatives *via* Aza Prins Reaction of Endocyclic *N*-Acyliminium Ions: Application to the Total Synthesis of (±)-*epi*-Indolizidine 167B and 209D

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A diastereoselective protocol has been established for the synthesis of 4-*O*-tosyl piperidine containing hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one and 1,3,4,10*b*-tetrahydropyrido[*2,1-a*]isoindol-6(2*H*)-one derivatives *via* the aza-Prins cyclization reaction of cyclic *N*-acyliminium ions mediated by *p*-toluene sulphonic acid (*p*-TSA) under mild conditions. The reaction is highly diastereoselective and gives excellent yields. This method has been applied to an efficient total synthesis of the indolizidine alkaloids, (±)-*epi*-indolizidine 167B and 209D.

## Introduction

Piperidines and their derivatives are extremely important building blocks in the synthesis of natural products,[1] biologically active compounds and drug intermediates.[2] These piperidine units are also present in many of the known alkaloids.[3] For example, dienomycin C (**1**), an alkaloid isolated from the *Streptomyces* strain MC67-C1, has been found to exhibit antibacterial activity against some strains of *Mycobacterium tuberculosis.*[4] Haloperidol (**2**) a neuroleptic drug, containing a 4-hydroxy piperidine moiety, is used in the treatment of delirium.[5] Apart from these, some amino- and hydroxylated piperidines show potent antineoplastic and antitumor activities.[6] Fused piperidines such as the alkyl indolizidine alkaloids (**3p-q**), isolated from the skin secretions of certain neotropical frogs of the Dendrobatidae family, represent a class of noncompetitive blockers of neuromuscular transmission.[7] Their epimers, alkyl *epi*-indolizidines (***epi*-3p-q**) are popular synthetic targets and many approaches have been published towards their synthesis.[8] Another class of piperidine containing alkaloids called quinolizidines (**4**), isolated from bacteria, fungi, plants, invertebrates and vertebrates, act as non-competitive blockers of nicotinic receptors.[9] Several research groups had reported that 4-substituted piperidines could be synthesized in the presence of Lewis and Brønsted acids *via* the aza-Prins cyclization reaction of homoallyl amine or *N*-acyl iminium ion precursors and then trapping the carbocations generated during these reactions, with various nucleophiles such as hydroxy,[10] halo,[11] aryl,[12] nitrile,[13] formate and acetate groups.[14] Alternatively, 4-substituted piperidines containing bicyclic systems are also accomplished *via* endo-trig (aza-Prins) cyclization of *N*-homoallyl cyclic *N*-acyliminium ions[15] followed by trapping with various nucleophiles such as formate,[16] hydroxy,[17] and halo[18] groups under Brønsted and Lewis acidic conditions. Apart from these methods, piperidine containing systems were also achieved by ene cyclizations,[19] alkyne-aza Prins cyclizations,[20] aza-Michael reactions[21] and by other methods.[22] Although there are many methods for the construction of piperidine rings using Lewis and Brønsted acids, the use of *p*-TSA in the Prins reaction is very limited.[23,24] Padwa *et al.* reported the dual role of *p*-TSA *via* tandem Pummerer/Mannich cyclization cascade of α-sulfinylamides for the synthesis of tosylated azabicyclic compounds.[24] The harsh reaction conditions, lack of selectivity, and poor yields limit the scope of these methods towards the application in natural product synthesis.[10-18] The direct insertion of a tosylate group at the C-4 position of the piperidine ring of azabicyclic compounds using the aza-Prins cyclization has not been explored. Presently we are involved in stereoselective

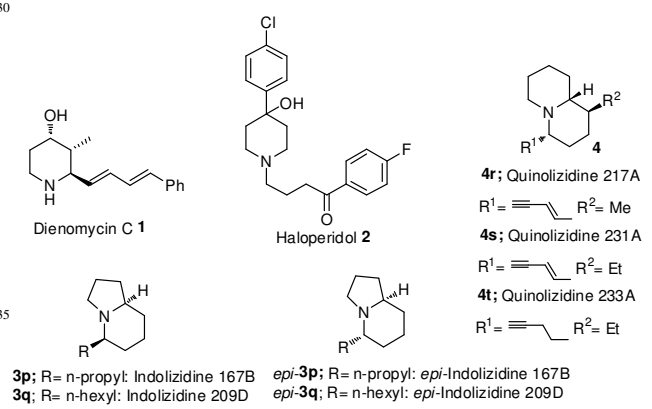



**Fig. 1** Some piperidine containing alkaloids

synthesis of tetrahydropyrans *via* the Prins cyclization reaction[25] and very recently reported a methodology for the synthesis of amido/phenyl azabicyclic compounds *via* the aza-Prins-Ritter/Friedel-Crafts cyclization reactions.[26] In this paper we wish to report the dual role of *p*-TSA for the synthesis of *O*-tosylated azabicyclic compounds *via* the aza-Prins cyclization in which the *p*-TSA acts as Brønsted acid as well as a nucleophile.

## Results and discussion

Initially, we reacted 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one with 1.2 equivalents of *p*-TSA in dichloromethane at room temperature and the reaction proceeded smoothly to afford (7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl 4-methylbenzene-sulfonate in 79% yield with a disteriomeric ratio of 85:15. Using the same solvent at reflux temperature resulted in 88% yield, without any change in diastereomeric ratio.

With the established optimal reaction conditions in hand, a variety of regioselectively reduced homoallyl imides derived from cyclic imides and homoallyl alcohols were evaluated as substrates and the results are summarized in Table 1. All the substrates produced cyclized products in moderate to high yields without formation of any elimination products.[18a, 27] The substrates having no substitution (entries 1, 7, and 11) at the α-position to nitrogen gave excellent yields with dr of 50:50 to 90:10. This is due to the absence of a 1,3-diaxial interaction between the axial hydrogen at the α-position to nitrogen and the incoming tosyl group (Scheme 1).[26,28] On the other hand, 5-hydroxy-1-(3-methylbut-3-en-1-yl) pyrrolidin-2-one (entry 6) failed to give the desired product, because of steric crowding between the bulky tosyl group and the tertiary carbocation formed during the reaction, instead starting material was recovered in 97%. Reactions of the substrates having alkyl and aryl substitutions at the α-position to nitrogen afforded the desired products with good yields and produced only a single diastereomer. In cases of aromatic substitution, the substrates having electron withdrawing aromatic substituents (entries 2, 3, 10 and 12) gave slightly higher yields, compared to unsubstituted phenyl (entry 13) and electron donating aromatic substituents (entries 5 and 15). There was no effect of the size of the cyclic imides such as succinimide, glutarimide and pthalimide on yields and diastereoselectivities.

The stereochemistry of compound **6n** was confirmed by $^{1}H$, $^{13}C$ and NOESY experiments. A strong NOE between the $H_{10}$ hydrogen at C-10 of the piperidine ring and the $H_7$ hydrogen at C-7

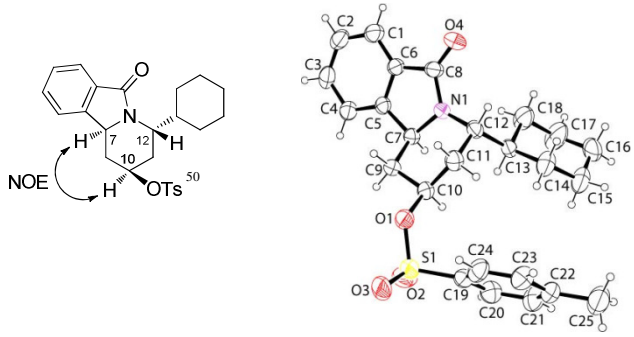
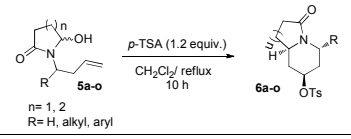
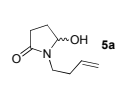
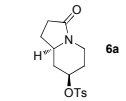
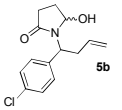
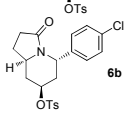
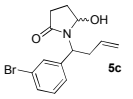
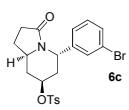
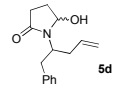
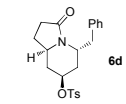
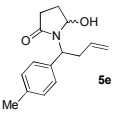
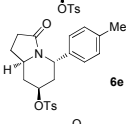
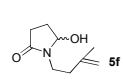
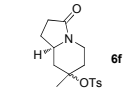
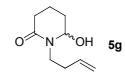
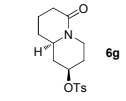
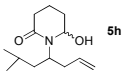
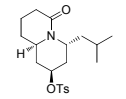
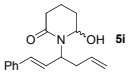
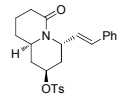
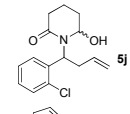
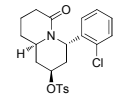
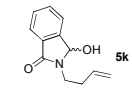
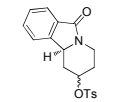
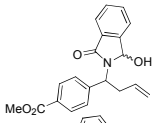
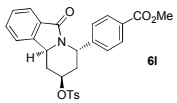
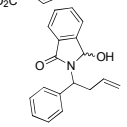
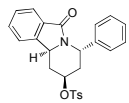
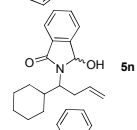
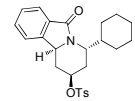
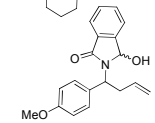
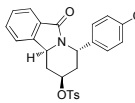



**Fig. 2** NOE and X-ray crystallographic structure of **6n**

**Table 1** Synthesis of *O*-Tosylated azabicyclic compounds *via* aza-Prins cyclization reaction

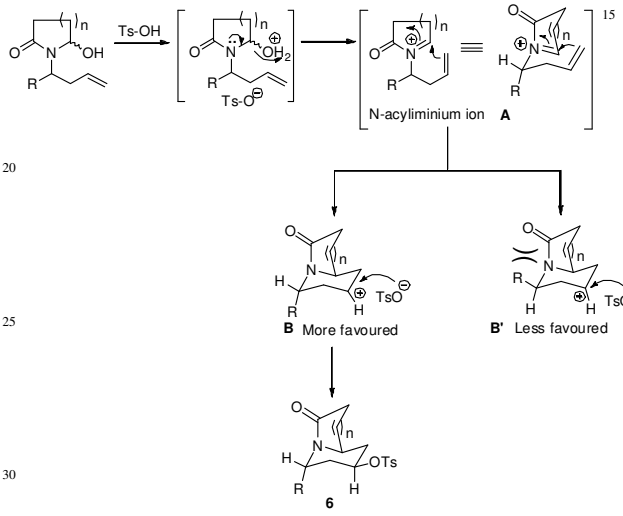



| S.No. | Substrate **5** | Product **6** | dr[a] | (%) Yield[b] |
|---|---|---|---|---|
| 1 |  **5a** |  **6a** | 85:15 | 88 |
| 2 |  **5b** |  **6b** | 100:0 | 75 |
| 3 |  **5c** |  **6c** | 100:0 | 78 |
| 4 |  **5d** |  **6d** | 100:0 | 81 |
| 5 |  **5e** |  **6e** | 100:0 | 59 |
| 6 |  **5f** |  **6f** | --- | 0 |
| 7 |  **5g** |  **6g** | 90:10 | 80 |
| 8 |  **5h** |  **6h** | 100:0 | 86 |
| 9 |  **5i** |  **6i** | 100:0 | 68 |
| 10 |  **5j** |  **6j** | 100:0 | 74 |
| 11 |  **5k** |  **6k** | 50:50 | 79 |
| 12 |  **5l** |  **6l** | 100:0 | 83 |
| 13 |  **5m** |  **6m** | 100:0 | 70 |
| 14 |  **5n** |  **6n** | 100:0 | 87 |
| 15 |  **5o** |  **6o** | 100:0 | 54 |

[a]Ratio is determined by $^{1}H$ NMR. [b]Yield refers to isolated yield.

of the ring junction of compound **6n** indicates the *cis* relationship between these two hydrogens. Similarly there was no observation of an NOE between $H_{10}$ and $H_{12}$ or between $H_7$ and $H_{12}$ of the piperidine ring. This clearly supports the *trans* relationship between tosyl and cyclohexyl groups. Finally the stereochemistry of the compound **6n** was confirmed by X-ray crystallographic analysis (Figure 2).[29]

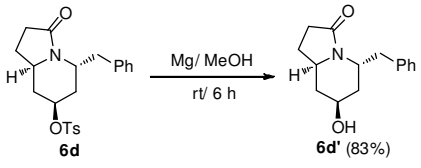
The mechanism of the reaction can be explained as follows. The starting material carbinol in the presence of *p*-TSA gives the corresponding *N*-acyliminium ion intermediate **A.** This intermediate undergoes a 6-endo-trig cyclization to give the more stable chair like intermediate **B**, with the R substituent axial, due to more steric crowding and strong angular strain between the




**Scheme 1** Plausible reaction mechanism

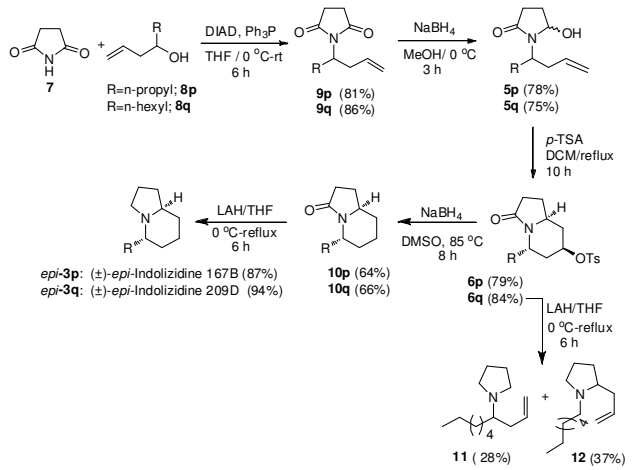
substituent **R** and the lactam carbonyl group.[26,28] The tosyl nucleophile attacks the carbocation intermediate **B** in an equatorial fashion to give the respective tosyl substituted azabicyclic compound **6**.

The conversion of the tosyl group to a hydroxy group was performed for compound (5*R**,7*S**,8a*R**)-5-benzyl-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate *(***6d)** by treating with Mg/MeOH at room temperature to give corresponding alcohol (5*R**,7*S**,8a*R**)-5-benzyl-7-hydroxyhexahydroindolizin-3(2*H*)-one (**6d'**) in 83% yield with retention of configuration (Scheme 2).[30] The configuration of the compound **6d'** was confirmed by NOESY experiment (see SI).




**Scheme 2** Deprotection of tosyl group

A number of protocols have been developed for the total synthesis of indolizidine 167B and 209D alkaloids and their epimers.[8] The present methodology was utilized for the synthesis of *epi*-indolizidine 167B and 209D. The secondary homoallyl alcohols **8p-q** were reacted with commercially available succinimide under Mitsunobu reaction conditions[31] to give the corresponding homoallyl imides **9p-q**. The imides **9p-q** were reduced with $NaBH_4$ to the corresponding carbinols **5p-q**.[32] The carbinols **5p-q** were then subjected to the aza-Prins cyclization reaction in the presence of *p*-TSA to give exclusively a single isomer of the tosylated azabicyclic products **6p-q**. To achieve our target, we followed a $LiAlH_4$ reduction procedure for the reduction of both lactam and tosyl groups.[33,34] Unfortunately, compound **6q**, could not be converted into the desired product and instead ring opening products **11** and **12** were isolated in 28% and 37% yields, respectively. After the failure of this reduction strategy, the tosyl group was first removed by using $NaBH_4$ in DMSO at 80° C to yield corresponding lactams **10p-q**.[35] The lactams **10p-q** were




**Scheme 3** Synthesis of (±)-*epi*-Indolizidine 167B and 209D

then finally reduced by LAH under reflux[34] to give the target alkaloids (±)-*epi*-indolizidine 167B (***epi*-3p**) and 209D (***epi*-3q**) in 87% and 94% yields, respectively. The spectral data were in agreement with the literature.[8]

## Conclusions

In conclusion, we have demonstrated the dual role of *p*-TSA in endo-trig cyclization reaction for the synthesis of 4-*O*-tosyl piperidine containing hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one and 1,3,4,10*b*-tetrahydropyrido[*2,1-a*]isoindol-6(2*H*)-one derivatives. This methodology could be useful for accessing other substituted azabicyclic alkaloids by manipulating the tosyl group. This methodology was successfully applied for the total synthesis of (±)-*epi*-indolizidine 167B and 209D in good yields.

## Experimental section

**General Information**: All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel

$GF_{254}$ (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for $^1H$ (600 MHz, 400 MHz) or $^{13}C$ (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

**Synthesis of starting materials**

The homoallyl imides and carbinol imides were synthesized using literature procedures and the structure of the known compounds **5a-o** were confirmed by comparison of their spectral data ($^1H$ NMR and $^{13}C$ NMR) with those reported.[26]

**Typical procedure for the synthesis of (7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate (6a)**

To a solution of 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (78 mg, 0.5mmol) in dichloromethane (3 mL) was added *p*-toluenesulfonic acid monohydrate (114 mg, 0.6mmol) at once. The reaction mixture was stirred at reflux temperature. The progress of the reaction was monitored by TLC with ethyl acetate as eluent. The reaction was completed in 10 h and after completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2x10 mL). The organic layer was washed with brine (5 mL), dried over ($Na_2SO_4$) and evaporated to leave the crude product, which was purified by column chromatography using ethyl acetate as eluent over silica gel to give the (7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate in (136 mg, 88%) as a white solid, mp 97-99 °C; $^1H$ NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 1.37 (q, *J* = 12.0 Hz, 1 H), 1.51 (dt, *J* = 12.0 and 5.6 Hz, 1 H), 1.56–1.67 (m, 1 H), 1.87–1.92 (m, 1 H), 2.15–2.22 (m, 2 H), 2.32-2.37 (m, 2 H), 2.43 (s, 3 H), 2.59 (dt, *J* = 11.6 and 2.4 Hz, 1 H), 3.42–3.50 (m, 1 H), 4.10 (dd, *J* = 13.6 and 5.2 Hz, 1 H), 4.52 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); $^{13}C$ NMR (150 MHz, $CDCl_3$) (major diastereomer) δ 21.7, 24.4, 30.0, 30.9, 37.2, 39.7, 55.1, 78.1, 127.7 (2C), 130.1 (2C), 134.2, 145.1, 173.4; IR (KBr, neat) 2925, 1685, 1597, 1455, 1358, 1189, 1175, 946, 858, 671, 555 $cm^{-1}$; HRMS (ESI) calcd for $C_{15}H_{19}NO_4S$ $(M + H)^+$ 310.1108, found 310.1100. ESI-MS: *m/z* (relative intensity): 332.2 ($(M + Na)^+$, 100%), 310.2 ($(M + H)^+$, 21%), 242.3 (19), 201.2 (52), 160.1 (58).

**(5*S**,7*S**,8a*R**)-5-(4-chlorophenyl)-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate (6b)**

Colourless gum; yield 157 mg, 75%; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.49 (q, *J* = 12.0 Hz, 1 H), 1.66–1.75 (m, 2 H), 1.88 (dt, *J* = 12.0 and 5.6 Hz,1 H), 2.16 (dd, *J* = 11.6 and 6.0 Hz, 1 H), 2.24 (dd, *J* = 12.4 and 6.0 Hz, 1 H), 2.48 (s, 3 H), 2.49–2.53 (m, 2 H), 3.47–3.54 (m, 1 H), 4.48 (tt, *J* = 11.6 and 4.0 Hz,1 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.9, 24.4, 29.9, 33.5, 39.8, 49.0, 52.2, 75.0 127.7 (2C), 128.0 (2C), 128.8, 129.2 (2C), 130.2 (2C), 133.5, 136.2, 145.3, 174.2; IR (KBr, neat) 2924, 1691, 1597, 1492, 1414, 1359, 1189, 1175, 1095, 951, 835, 575, 555 $cm^{-1}$; HRMS (ESI) calcd for $C_{21}H_{22}ClNO_4S$ $(M + H)^+$ 420.1031, found 420.1031. ESI-MS: *m/z* (relative intensity): 442.2 ($(M + Na)^+$, 100%), 420.2 ($(M + H)^+$, 39%), 311.2 (19), 272.1 (24), 270.1 (54), 248.1 (24), 117.1 (33).

**(5*S**,7*S**,8a*R**)-5-(3-bromophenyl)-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate (6c)**

Colourless gum; yield 180 mg, 78%; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.50 (q, *J* = 12.0 Hz, 1 H), 1.66–1.76 (m, 1 H), 1.88 (ddd, *J* = 18.0, 12.0 and 6.0 Hz, 1 H), 2.17–2.23 (m, 1 H), 2.25–2.32 (m, 1 H), 2.48 (s, 3 H), 2.50-2.55 (m, 2 H), 3.52-3.61 (m, 1 H), 4.45-4.50 (tt, *J* = 11.6 and 3.6 Hz, 1 H), 5.48 (d, *J* = 5.6 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 7.14-7.19 (m, 2 H), 7.37-7.41 (m, 3 H), 7.78 (d, *J* = 8.4 Hz, 2 H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 21.9, 24.4, 29.8, 33.5, 39.9, 49.2, 52.3, 75.1, 123.4, 125.0, 127.9 (2C), 129.3, 130.3 (2C), 130.7, 130.9, 133.9, 140.2, 145.3, 174.2; IR (KBr, neat) 2924, 1691, 1596, 1419, 1359, 1189, 1176, 949, 855, 671, 554 $cm^{-1}$; HRMS (ESI) calcd for $C_{21}H_{22}BrNO_4S$ $(M + H)^+$ 464.0526, found 464.0529. Found: C, 54.41; H, 4.77; N, 2.99; S, 6.87. Calc. for $C_{21}H_{22}BrNO_4S$: C, 54.32; H, 4.79; N, 3.02; S, 6.91.

**(5*R**,7*S**,8a*R**)-5-benzyl-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate (6d)**

White solid, mp 115-117 °C; yield 162 mg, 81%; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.37-1.49 (m, 2 H), 1.57–1.67 (m, 1 H), 1.74 (ddd, *J* = 13.6, 11.2 and 3.2 Hz, 1 H), 2.16–2.27 (m, 1 H), 2.29–2.37 (m, 3 H), 2.47 (s, 3 H), 2.58 (dd, *J* = 12.8 and 10.4 Hz,1 H), 2.72 (dd, *J* = 13.2 and 6.0 Hz,1 H), 3.67–3.75 (m, 1 H), 4.45 (pentet, *J* = 5.2 Hz, 1 H), 4.82 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 7.00-7.03 (m, 2 H), 7.21-7.26 (m, 3 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.8, 24.8, 30.2, 31.7, 37.1, 39.9, 48.9, 52.1, 75.6, 126.8, 127.7 (2C), 128.6 (2C), 129.1 (2C), 130.1 (2C), 134.1, 137.2, 145.0, 173.2; IR (KBr, neat) 2926, 1682, 1598, 1495, 1417, 1359, 1189, 1174, 1097, 948, 816, 675, 555 $cm^{-1}$; HRMS (ESI) calcd for $C_{22}H_{25}NO_4S$ $(M + H)^+$ 400.1577, found 400.1577. ESI-MS: *m/z* (relative intensity): 422.2 ($(M + Na)^+$, 100%), 400.3 ($(M + H)^+$, 41%), 251.2 (15), 250.2 (55), 228.2 (33), 102.2 (30).

**(5*S**,7*S**,8a*R**)-3-oxo-5-(*p*-tolyl)octahydroindolizin-7-yl 4-methylbenzenesulfonate (6e)**

Pale yellow gum; yield 118 mg, 59%; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.48 (q, *J* = 12.0 Hz, 1 H), 1.63–1.72 (m, 1 H), 1.85 (ddd, *J* = 18.4, 12.8 and 6.0 Hz, 1 H), 2.13–2.27 (m, 3 H), 2.32 (s, 3 H), 2.49 (s, 3 H), 2.50-2.55 (m, 2 H), 3.49-3.57 (m, 1 H), 4.52-4.56 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 5.46 (d, *J* = 4.8 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 7.6 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.1, 21.9, 24.3, 30.0, 33.3, 40.0, 49.2, 52.1, 75.5, 126.1 (2C), 128.0 (2C), 129.3, 129.7 (2C), 130.1 (2C), 134.3, 137.2, 145.2,

174.1; IR (KBr, neat) 2923, 1689, 1597, 1416, 1359, 1188, 1176, 948, 856, 680, 556 $cm^{-1}$; HRMS (ESI) calcd for $C_{22}H_{25}NO_4S$ (M + H)$^+$ 400.1577, found 400.1577. ESI-MS: *m/z* (relative intensity): 422.2 ((M + Na)$^+$, 100%), 400.3 ((M + H)$^+$, 60%), 250.2 (84), 228.2 (46), 136.1 (19).

**(2*R**,9a*R**)-6-oxooctahydro-1*H*-quinolizin-2-yl 4-methylbenzenesulfonate (6g)**

Colorless gum; yield 129 mg, 80%; $^1$H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 1.45−1.56 (m, 2 H), 1.60−1.68 (m, 1 H), 1.74−1.82 (m, 2 H), 1.85−2.11 (m, 3 H), 2.23−2.39 (m, 3 H), 2.43 (s, 3 H), 3.21−3.28 (m, 1 H), 4.53 (tt, *J* = 11.6 and 4.4 Hz,1 H), 4.72−4.79 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H); $^{13}$C NMR (150 MHz, $CDCl_3$) (major diastereomer) δ 19.0, 21.5, 29.6, 31.4, 32.6, 39.6 (2C), 54.0, 78.3, 127.4 (2C), 129.8 (2C), 134.0, 144.8, 169.3; IR (KBr, neat) 2948, 1636, 1452, 1356, 1269, 1176, 1093, 941, 849, 817, 670 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{21}NO_4S$ (M + H)$^+$ 324.1264, found 324.1262. ESI-MS: *m/z* (relative intensity): 346.2 ((M + Na)$^+$, 100%), 324.2 ((M + H)$^+$, 66%), 279.2 (28), 215.2 (37), 174.1 (55), 152.1 (41).

**(2*S**,4*R**,9a*R**)-4-isobutyl-6-oxooctahydro-1*H*-quinolizin-2-yl 4-methylbenzenesulfonate (6h)**

White solid, mp 122-124 ˚C; yield 163 mg, 86%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 1.12-1.32 (m, 2 H), 1.31−1.42 (m, 2 H), 1.44-1.64 (m, 3 H), 1.72-1.82 (m, 2 H), 1.93-2.00 (m, 1 H), 2.07−2.14 (m, 1 H), 2.26−2.39 (m, 2 H), 2.45 (s, 3 H), 3.40−3.47 (m, 1 H), 4.75 (tt, *J* = 11.6 and 4.8 Hz, 1 H), 5.04 (q, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.7, 22.5, 22.8, 25.1, 30.1, 33.1, 34.3, 39.3, 40.2, 46.4, 49.4, 76.0, 127.7 (2C), 130.0 (2C), 134.2, 145.0, 169.5; IR (KBr, neat) 2954, 1637, 1456, 1360, 1176, 1094, 945, 873, 817, 673 $cm^{-1}$; HRMS (ESI) calcd for $C_{20}H_{29}NO_4S$ (M + H)$^+$ 380.1890, found 380.1890. ESI-MS: *m/z* (relative intensity): 402.3 ((M + Na)$^+$, 100%), 380.3 ((M + H)$^+$, 9%), 271.2 (46), 246.2 (51), 230.2 (84), 208.2 (38).

**(2*S**,4*S**,9a*R**)-6-oxo-4-((E)-styryl)octahydro-1*H*-quinolizin-2-yl 4-methylbenzenesulfonate (6i)**

Colorless gum; yield 144 mg, 68%; $^1$H NMR (600 MHz, $CDCl_3$) δ 1.52-1.61 (m, 2 H), 1.65-1.75 (m, 1 H), 1.80 (ddd, *J* = 18.6, 13.2 and 6.0 Hz, 2 H), 1.96-2.05 (m, 1 H), 2.07-2.11 (m, 1 H), 2.18-2.22 (m, 1 H), 2.35-2.41 (m, 1 H), 2.46 (s, 3 H), 2.47-2.51 (m, 1 H), 3.48−3.54 (m, 1 H), 4.78 (tt, *J* = 11.4 and 4.2 Hz, 1 H), 5.76 (dd, *J* = 3.6 and 2.4 Hz, 1 H), 5.92 (dd, *J* = 16.2 and 3.6 Hz, 1 H), 6.25 (dd, *J* = 16.2 and 1.8 Hz, 1 H), 7.27 (d, *J* = 7.2 Hz, 3 H), 7.31-7.38 (m, 4 H), 7.81 (d, *J* = 8.4 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.4, 29.9, 30.3, 33.2, 34.4, 40.2, 49.4, 50.7, 75.8, 126.5 (2C), 127.2, 127.9 (2C), 128.1, 128.8 (2C), 130.2 (2C), 132.1, 134.2, 136.3, 145.2, 169.9; IR (KBr, neat) 2924, 1635, 1456, 1359, 1176, 1045, 948, 755, 704 $cm^{-1}$; HRMS (ESI) calcd for $C_{24}H_{27}NO_4S$ (M + H)$^+$ 426.1734, found 426.1734. ESI-MS: *m/z* (relative intensity): 448.3 ((M + Na)$^+$, 100%), 426.3 ((M + H)$^+$, 38%), 317.3 (30), 276.2 (65), 150.1 (58), 122.1 (30).

**(2*S**,4*S**,9a*R**)-4-(2-chlorophenyl)-6-oxooctahydro-1*H*-quinolizin-2-yl 4-methylbenzenesulfonate (6j)**

Colorless gum; yield 160 mg, 74%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.54−1.65 (m, 2 H), 1.72 (q, *J* = 12.0 Hz, 1 H), 1.76-1.84 (m, 1 H), 1.87-1.97 (m, 2 H), 2.01-2.08 (m, 1 H), 2.10-2.23 (m, 2 H), 2.40−2.48 (m, 4 H), 3.73−3.81 (m, 1 H), 4.67 (tt, *J* = 10.4 and 4.4 Hz, 1 H), 6.05 (dd *J* = 6.8 and 2.8 Hz, 1 H), 7.03-7.07 (m, 1 H), 7.17-7.20 (m, 2 H), 7.24-7.27 (m, 2 H), 7.29-7.33 (m, 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.8, 30.3, 32.9, 33.8, 39.6, 50.4, 52.9, 75.6, 126.90, 126.93, 127.7 (2C), 128.5, 130.0 (2C), 130.9, 133.1, 133.9, 137.8, 145.1, 169.9; IR (KBr, neat) 2925, 1643, 1443, 1356, 1177, 1039, 950, 846, 759 $cm^{-1}$; HRMS (ESI) calcd for $C_{22}H_{24}ClNO_4S$ (M + H)$^+$ 434.1187, found 434.1189. ESI-MS: *m/z* (relative intensity): 456.2 ((M + Na)$^+$, 100%), 434.2 ((M + H)$^+$, 95%), 334.2 (24), 284.2 (24), 262.2 (52), 118.2 (40).

**(2*R**,10b*S**)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl 4-methylbenzenesulfonate and (2*S**,10b*S**)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl 4-methylbenzenesulfonate (6k, mixture of isomers with 50:50 ratio)**

White solid, mp 129−131 ˚C; yield 141 mg, 79%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.35 (q, *J* = 12.0 Hz, 1 H), 1.59 (dd, *J* = 12.0 and 5.6 Hz, 1 H), 1.89−2.03 (m, 1 H), 2.47 (s, 3 H), 2.60-2.72 (m, 1 H), 2.98 (t, *J* = 12.8 Hz, 0.5 H), 3.27 (t, *J* = 12.8 Hz, 0.5 H), 4.31-4.38 (m, 1 H), 4.48 (dd, *J* = 13.6 and 4.8 Hz, 0.5 H), 4.62-4.69 (m, 0.5 H), 4.78-4.87 (m, 0.5 H), 5.01 (brs, 0.5 H), 7.34-7.41 (m, 3 H), 7.43-7.49 (m, 1 H), 7.50-7.56 (m, 1 H), 7.82 (d, *J* = 7.2 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.8 (2C), 29.8, 31.5, 33.8, 36.2, 36.5, 37.8, 53.2, 56.7, 75.9, 78.0, 121.8 (2C), 123.9, 124.0, 127.7 (2C), 127.8 (2C), 128.5, 128.7, 130.1 (2C), 130.2 (2C), 131.5, 131.8, 131.9, 132.1, 133.8, 134.0, 144.0, 145.0, 145.2, 145.3, 166.1, 166.2; IR (KBr, neat) 2925, 1689, 1597, 1421, 1362, 1290, 1189, 1175, 1097, 989, 947, 899, 851, 761, 734, 689, 671 $cm^{-1}$; HRMS (ESI) calcd for $C_{19}H_{19}NO_4S$ (M + H)$^+$ 358.1108, found 358.1109. ESI-MS: *m/z* (relative intensity): 380.2 ((M + Na)$^+$, 100%), 358.2 ((M + H)$^+$, 78%), 249.2 (27), 208.1 (60), 186.1 (83), 132.1 (12).

**Methyl 4-((2*R**,4*S**,10b*S**)-6-oxo-2-(tosyloxy)-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-4-yl)benzoate (6l)**

Colorless gum; yield 204 mg, 83%; $^1$H NMR (600 MHz, $CDCl_3$) δ 1.48 (q, *J* = 12.0 Hz, 1 H), 1.95-2.32 (m, 1 H), 2.53 (s, 3 H), 2.66 (dd, *J* = 12.0 and 3.0 Hz, 2 H), 3.93 (s, 3 H), 4.37 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 4.72 (tt, *J* = 11.4 and 3.6 Hz, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.91−7.94 (m, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.9, 33.8, 38.0, 48.9, 52.4, 54.3, 75.2, 122.1, 124.5, 126.4 (2C), 128.1 (2C), 129.0, 129.6, 130.3 (2C), 130.4 (2C), 131.3, 132.3, 133.7, 143.4, 144.4, 145.5, 166.7, 167.1; IR (KBr, neat) 2924, 1721, 1693, 1597, 1467, 1411, 1362, 1280, 1189, 1176, 1112, 964, 853, 754, 665 $cm^{-1}$; HRMS (ESI) calcd for $C_{27}H_{25}NO_6S$ (M + H)$^+$ 492.1475, found 492.1483. ESI-

MS: *m*/*z* (relative intensity): 514.3 ((M + Na)$^+$, 100%), 492.3 ((M + H)$^+$, 80%), 342.3 (71), 320.2 (57), 310.4 (20).

**(2*R**,4*S**,10b*S**)-6-oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl 4-methylbenzenesulfonate (6m)**

Pale yellow gum; yield 151 mg, 70%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.47 (q, *J* = 12.0 Hz, 1 H), 1.92-2.00 (m, 1 H), 2.52 (s, 3 H), 2.65 (dd, *J* = 12.4 and 4.0 Hz, 2 H), 4.38 (dd, *J* = 12.4 and 3.6 Hz, 1 H), 4.81 (tt, *J* = 11.2 and 4.0 Hz, 1 H), 5.83 (d, *J* = 5.6 Hz, 1 H), 6.97–7.01 (m, 2 H), 7.23–7.28 (m, 3 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.50–7.59 (m, 2 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.92 (d, *J* = 7.2 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.9, 33.7, 38.1, 48.9, 54.2, 75.5, 122.1, 124.5, 126.3 (2C), 127.7, 128.1 (2C), 128.9, 129.1 (2C), 130.2 (2C), 131.6, 132.1, 133.8, 138.1, 144.5, 145.3, 167.0; IR (KBr, neat) 2924, 1692, 1407, 1361, 1177, 1095, 963, 854, 696, 661 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{23}NO_4S$ (M + H)$^+$ 434.1421, found 434.1425. ESI-MS: *m*/*z* (relative intensity): 456.2 ((M + Na)$^+$, 100%), 300.2 (17), 284.2 (62), 211.3 (18), 168.2 (50).

**(2*R**,4*S**,10b*S**)-4-cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl 4-methylbenzene-sulfonate (6n)**

Colorless solid, mp 169-171 ˚C; yield 191 mg, 87%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.86–1.13 (m, 5 H), 1.22-1.28 (m, 1 H), 1.30-1.41 (m, 3 H), 1.42–1.55 (m, 2 H), 1.59-1.71 (m, 2 H), 1.98-2.05 (m, 1 H), 2.47 (s, 3 H), 2.69-2.76 (m, 1 H), 4.16 (dd, *J* = 10.4 and 5.6 Hz, 1 H), 4.41 (dd, *J* = 12.4 and 3.2 Hz, 1 H), 4.81-4.91 (m, 1 H), 7.36-7.41 (m, 3 H), 7.47 (t, *J* = 8.4 Hz, 1 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.81-7.86 (m, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.8, 25.8, 26.0 (2C), 29.7, 30.0, 31.8, 38.0, 38.5, 52.1, 54.1, 75.7, 121.9, 124.1, 128.0 (2C), 128.7, 130.1 (2C), 131.7, 131.8, 133.8, 144.3, 145.3, 166.7; IR (KBr, neat) 2928, 1689, 1410, 1361, 1179, 1096, 966, 941, 853, 827, 737, 691 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{29}NO_4S$ (M + H)$^+$ 440.1890, found 440.1893. ESI-MS: *m*/*z* (relative intensity): 462.3 ((M + Na)$^+$, 100%), 440.3 ((M + H)$^+$, 93%), 331.3 (16), 290.2 (31), 268.2 (45).

**(2*R**,4*S**,10b*S**)-4-(4-methoxyphenyl)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl 4-methylbenzene-sulfonate (6o)**

Colorless gum; yield 125 mg, 54%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.44 (q, *J* = 12.0 Hz, 1 H), 1.93 (ddd, *J* = 18.4, 13.2 and 6.0 Hz, 1 H), 2.51 (s, 3 H), 2.63 (dd, *J* = 10.8 and 2.0 Hz, 2 H), 3.78 (s, 3 H), 4.35 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 4.84 (tt, *J* = 11.2 and 4.0 Hz, 1 H), 5.78 (d, *J* = 5.6 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 6.8 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.49–7.58 (m, 2 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 6.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.9, 33.7, 38.0, 48.3, 54.1, 55.4, 75.6, 114.4 (2C), 122.1, 124.4, 127.5 (2C), 128.1 (2C), 128.9, 130.0, 130.2 (2C), 131.6, 132.0, 133.9, 144.4, 145.3, 158.9, 166.9; IR (KBr, neat) 2924, 1692, 1512, 1467, 1407, 1360, 1249, 1188, 1176, 1033, 964, 854, 738, 693, 665 cm$^{-1}$; HRMS (ESI) calcd for $C_{26}H_{25}NO_5S$ (M + H)$^+$ 464.1526, found 464.1528. ESI-MS: *m*/*z* (relative intensity): 486.3 ((M + Na)$^+$, 100%), 464.3 ((M + H)$^+$, 14%), 355.2 (11), 314.2 (53), 184.1 (10).

**(5*R**,7*S**,8a*R**)-5-benzyl-7-hydroxyhexahydroindolizin-3(2H)-one (6d')**

Colorless liquid; yield 51 mg, 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.17 (q, *J* = 12.0 Hz, 1 H), 1.30-1.37 (m, 1 H), 1.60–1.69 (m, 1 H), 1.89-1.93 (m, 1 H), 2.18–2.28 (m, 2 H), 2.29–2.37 (m, 2 H), 2.72 (dd, *J* = 13.6 and 10.0 Hz,1 H), 2.82 (dd, *J* = 13.6 and 6.8 Hz,1 H), 3.72–3.80 (m, 1 H), 4.11 (tt, *J* = 11.6 and 4.4 Hz, 1 H), 4.51-4.58 (m, 1 H), 7.20-7.32 (m, 5 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 25.1, 30.6, 35.4, 37.5, 42.9, 49.3, 52.7, 64.9, 126.8, 128.8 (2C), 129.3 (2C), 138.1, 173.6; IR (KBr, neat) 2923, 1659, 1453, 1421, 1286, 1081, 1027, 751, 701 cm$^{-1}$; HRMS (ESI) calcd for $C_{15}H_{19}NO_2$ (M + H)$^+$ 246.1489, found 246.1498. ESI-MS: *m*/*z* (relative intensity): 268.2 ((M + Na)$^+$, 100%), 246.2 ((M + H)$^+$, 25%), 224.2 (8), 202.2 (7), 137.4 (11).

**Synthesis of (±)-*epi*-Indolizidine 167B and 209D**

**General procedure for the synthesis of 9p and 9q from 7**

To a solution of $PPh_3$ (1.0 equiv.) and succinimide (1.0 equiv.) in THF (0.3 M), homoallyl alcohol **7** (1.0 equiv.) was added slowly under $N_2$ atmosphere. The reaction mixture was cooled to 0 °C and DIAD (1.0 equiv.) in THF (0.5 M) was added slowly. The reaction mixture was allowed to warm to room temperature and was stirred for 6 h. After completion of reaction, solvent was removed in rotary evaporator and crude product was directly subjected to column chromatography using ethyl acetate and hexane as eluents to give corresponding homoallyl imides.

**1-(Hept-1-en-4-yl)pyrrolidine-2,5-dione (9p)**

Pale yellow liquid; yield 794 mg, 81%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.6 Hz, 3 H), 1.14–1.26 (m, 2 H), 1.54–1.63 (m, 1 H), 1.91–2.01 (m, 1 H), 2.33–2.40 (m, 1 H), 2.60 (s, 4 H), 2.63–2.73 (m, 1 H), 4.09–4.17 (m, 1 H), 4.93–5.00 (m, 2 H), 5.56−5.66 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.9, 28.0 (2C), 33.3, 36.1, 52.0, 117.7, 135.0, 177.8 (2C); IR (KBr, neat) 2960, 2873, 1700, 1396, 1371, 1190, 1124, 920, 820 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{17}NO_2$ (M + H)$^+$ 196.1332, found 196.1333. Found: C, 67.73; H, 8.77; N, 7.14. Calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17.

**1-(Dec-1-en-4-yl)pyrrolidine-2,5-dione (9q)**

Yellow liquid; yield 1.13 g, 86%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 6.8 Hz, 3 H), 1.11-1.25 (m, 8 H), 1.55–1.65 (m, 1 H), 1.87–1.98 (m, 1 H), 2.30–2.38 (m, 1 H), 2.59 (s, 4 H), 2.60–2.69 (m, 1 H), 4.04–4.13 (m, 1 H), 4.90–4.99 (m, 2 H), 5.53–5.65 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.6, 28.0 (2C), 28.9, 31.2, 31.7, 36.1, 52.3, 117.6, 134.9, 177.7 (2C); IR (KBr, neat) 2928, 2857, 1704, 1397, 1372, 1177, 1143, 994, 918, 820 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{23}NO_2$ (M + H)$^+$ 238.1802, found 238.1799. Found: C, 70.79; H, 9.79; N, 5.95. Calc. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90.

**General procedure for the synthesis of 5p and 5q from 9p and 9q**

To a stirred solution of **9p-q** (1.0 equiv.) in MeOH (0.4 M) at 0°C was added $NaBH_4$ (2.0 equiv.). The reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction, the reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic phases were washed with brine, dried over $Na_2SO_4$ and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents to give the homoallyl carbinols **5p-q**.

**1-(Hept-1-en-4-yl)-5-hydroxypyrrolidin-2-one (5p, mixture of isomers with 50:50 ratio)**

Pale yellow gum; yield 614 mg, 78%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.16–1.28 (m, 2 H), 1.30–1.41 (m, 1 H), 1.49–1.70 (m, 2 H), 1.75–1.93 (m, 1 H), 2.19–2.37 (m, 2 H), 2.41–2.52 (m, 1 H), 2.57–2.68 (m, 1 H), 3.94–4.01 (m, 0.5 H), 4.02–4.09 (m, 0.5 H), 5.01–5.11 (m, 2 H), 5.23 (t, *J* = 4.8 Hz, 1 H), 5.65−5.75 (m, 0.5 H), 5.78−5.88 (m, 0.5 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 19.8, 20.0, 29.0 (2C), 29.3, 29.4, 33.3, 36.4, 36.5, 39.1, 52.2, 52.3, 82.5, 82.6, 116.9, 117.0, 135.6, 136.1, 176.0, 176.1; IR (KBr, neat) 2958, 1664, 1449, 1281, 1182, 1064, 989, 915, 787 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{19}NO_2$ $(M + H)^+$ 198.1489, found 198.1492. Found: C, 67.04; H, 9.69; N, 7.06. Calc. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10.

**1-(Dec-1-en-4-yl)-5-hydroxypyrrolidin-2-one (5q, mixture of isomers with 60:40 ratio)**

Pale yellow gum; yield 717 mg, 75%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3 H), 1.20-1.35 (m, 7 H), 1.50–1.58 (m, 0.6 H), 1.62–1.70 (m, 1 H), 1.74–1.80 (m, 0.4 H), 1.86–1.94 (m, 1 H), 2.15–2.35 (m, 3 H), 2.43 (t, *J* = 7.2 Hz, 1 H), 2.49–2.68 (m, 2 H), 3.89–4.00 (m, 1 H), 4.75 (brs, 1 H), 4.98–5.10 (m, 2 H), 5.23 (brs, 1 H), 5.63−5.74 (m, 0.4 H), 5.75−5.86 (m, 0.6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 13.93, 13.95, 22.50, 22.55, 26.5, 26.6, 28.9, 29.0, 29.20, 29.22, 29.28, 29.32, 31.0, 31.6, 31.7, 34.1, 36.4, 39.0, 52.2, 52.4, 82.3, 82.4, 116.5, 116.7, 135.6, 136.0, 175.5, 175.6; IR (KBr, neat) 2957, 1669, 1458, 1281, 1166, 1065, 990, 915, 786 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{25}NO_2$ $(M + H)^+$ 240.1958, found 240.1957. ESI-MS: *m*/*z* (relative intensity): 262.2 ($(M + Na)^+$, 61%), 240.2 ($(M + H)^+$, 66%), 222.2 (100), 210.3 (61), 185.2 (27), 130.2 (79).

**Synthesis of 6p and 6q from 5p and 5q:**

Compounds **5p** and **5q** were cyclized in dichloromethane under the same reaction conditions as described in general procedure for **6a-o** to provide **6p** and **6q** in 79% and 84% yields, respectively.

**(5*S**,7*S**,8a*S**)-3-oxo-5-propyloctahydroindolizin-7-yl 4-methylbenzenesulfonate (6p)**

Colorless liquid; yield 834 mg, 79%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.12-1.20 (m, 2 H), 1.24–1.33 (m, 2 H), 1.39-1.46 (m, 1 H), 1.54–1.65 (m, 2 H), 1.77–1.82 (m, 1 H), 2.17-2.25 (m, 2 H), 2.37 (dd, *J* = 9.2 and 7.6 Hz, 2 H), 2.46 (s, 3 H), 3.58-3.66 (m, 1 H), 4.26 (q, *J* = 6.8 Hz, 1 H), 4.73 (tt, *J* = 12.0 and 4.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.5, 21.7, 24.4, 30.1, 33.1, 34.0, 40.0, 47.2, 51.6, 75.7, 127.7 (2C), 130.0 (2C), 134.2, 145.0, 173.5; IR (KBr, neat) 2926, 1684, 1599, 1458, 1420, 1360, 1177, 1096, 946, 848, 816, 678 cm−1; HRMS (ESI) calcd for $C_{18}H_{25}NO_4S$ $(M + H)^+$ 352.1577, found 352.1579. ESI-MS: *m*/*z* (relative intensity): 374.2 ($(M + Na)^+$, 100%), 352.2 ($(M + H)^+$, 46%), 243.2 (55), 202.2 (32), 180.2 (37).

**(5*S**,7*S**,8a*S**)-5-hexyl-3-oxooctahydroindolizin-7-yl 4-methylbenzenesulfonate (6q)**

Pale yellow liquid; yield 990 mg, 84%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.07-1.15 (m, 1 H), 1.16–1.46 (m, 10 H), 1.52-1.65 (m, 2 H), 1.76–1.83 (m, 1 H), 2.15–2.26 (m, 2 H), 2.36 (dd, *J* = 9.6 and 8.0 Hz, 2 H), 2.45 (s, 3 H), 3.58-3.65 (m, 1 H), 4.22 (q, *J* = 7.2 Hz, 1 H), 4.72 (tt, *J* = 11.6 and 4.4 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.6, 22.5, 24.3, 26.1, 28.9, 30.1, 30.9, 31.6, 33.8, 40.0, 47.3, 51.5, 75.7, 127.6 (2C), 129.9 (2C), 134.1, 145.0, 173.3; IR (KBr, neat) 2928, 1688, 1417, 1361, 1288, 1177, 1095, 946, 851, 678 cm−1; HRMS (ESI) calcd for $C_{21}H_{31}NO_4S$ $(M + H)^+$ 394.2047, found 394.2047. Found: C, 64.19; H, 7.93; N, 3.52; S, 8.09. Calc. for $C_{21}H_{31}NO_4S$: C, 64.08; H, 7.94; N, 3.56; S, 8.15.

**General procedure for the synthesis of 10p and 10q from 6p and 6q**

To a stirred solution of **6** (1.0 equiv.) in DMSO (0.2 M), $NaBH_4$ (3.0 equiv.) was added slowly. The reaction mixture was stirred at 85°C for 8 h. After completion of the reaction, the reaction mixture was washed with brine solution and then extracted with ethylacetate. The combined organic phases were dried over $Na_2SO_4$ and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents to give **10p** and **10q**.

**(5S*,8a*R**)-5-propylhexahydroindolizin-3(2*H*)-one (10p)**

Colorless liquid; yield 231 mg, 64%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.6 Hz, 3 H), 1.07-1.44 (m, 5 H), 1.46–1.64 (m, 5 H), 1.80-1.87 (m, 1 H), 2.09–2.21 (m, 1 H), 2.31–2.39 (m, 2 H), 3.52-3.60 (m, 1 H), 4.20 (q, *J* = 6.8 Hz,1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.0, 19.7, 25.3, 27.5, 30.4, 32.3, 33.9, 48.0, 53.3, 173.8; IR (KBr, neat) 2933, 1682, 1418, 1371, 1306, 1271, 1155, 1078, 749 cm−1; HRMS (ESI) calcd for $C_{11}H_{19}NO$ $(M + H)^+$ 182.1539, found 182.1533. ESI-MS: *m*/*z* (relative intensity): 204.2 ($(M + Na)^+$, 100%), 182.2 ($(M + H)^+$, 61%), 168.2 (44), 166.2 (15).

**(5*S**,8a*R**)-5-hexylhexahydroindolizin-3(2*H*)-one (10q):**

Colorless liquid; yield 294 mg, 66%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 3 H), 1.06-1.26 (m, 9 H), 1.36–1.62 (m, 7 H), 1.78-1.86 (m, 1 H), 2.11–2.20 (m, 1 H), 2.33 (dd, *J* = 9.2 and 7.6 Hz, 2 H), 3.51-3.59 (m, 1 H), 4.17 (q, *J* = 6.8 Hz,1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.0, 22.6, 25.3, 26.3, 27.4, 29.2, 30.1, 30.3, 31.8, 33.9, 48.1, 53.2, 173.5; IR (KBr, neat) 2928, 1684, 1416, 1306, 1269, 1020, 738 cm−1; HRMS (ESI) calcd for $C_{14}H_{25}NO$ (M + H)$^+$ 224.2009, found 224.2009. ESI-MS: *m/z* (relative intensity): 246.2 ((M + Na)$^+$, 95%), 224.2 ((M + H)$^+$, 52%), 210.2 (100), 204.2 (48), 168.2 (43).

**General procedure for synthesis of *epi*-3p and *epi*-3q from 10p and 10q**

Lactams **10p-q** (1.0 equiv.) in THF (0.2 M) were added slowly to a strried suspension of $LiAlH_4$, (3.0 equiv.) in THF (0.3 M) under $N_2$ atmosphere at 0 °C and the reaction mixture was allowed to reflux for 6 h. After completion of reaction the excess LAH was quenched with ethylacetate at 0°C. The reaction mixture was filtered through celite pad. The solvent was removed in rotary evaporator, the residue was purified by column chromatography on neutral alumina to give the *epi*-**3p** and *epi*-**3q**.

**(5*S**,8a*R**)-5-propyloctahydroindolizine (*epi*-3p)**

Colorless liquid; yield 145 mg, 87%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.2 Hz, 3 H), 1.03-1.15 (m, 2 H), 1.21–1.33 (m, 3 H), 1.35-1.49 (m, 3 H), 1.52–1.59 (m, 3 H), 1.65–1.76 (m, 3 H), 2.33-2.41 (m, 1 H), 2.55 (q, *J* = 9.2 Hz,1 H), 2.74 (ddd, *J* = 11.6, 8.4 and 3.2 Hz, 1 H), 2.86 (ddd, *J* = 12.8, 6.8 and 3.6 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.5, 20.9, 21.0, 25.8, 27.7, 30.8, 31.4, 48.8, 55.1, 55.3; IR (KBr, neat) 2868, 2802, 1459, 1378, 1263, 1142, 1091, 896, 740 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{21}N$ (M + H)$^+$ 168.1747, found 168.1756. ESI-MS: *m/z* (relative intensity): 168.2 ((M + H)$^+$, 100%), 144.2 (23), 130.2 (45), 126.2 (44).

**(5*S**,8a*R**)-5-hexyloctahydroindolizine (*epi*-3q)**

Colorless liquid; yield 196 mg, 94%; $^1$H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.13-1.18 (m, 2 H), 1.24–1.38 (m, 9 H), 1.41-1.55 (m, 3 H), 1.56–1.66 (m, 3 H), 1.71–1.82 (m, 3 H), 2.43-2.48 (m, 1 H), 2.63 (dd, *J* = 17.4 and 9.6 Hz,1 H), 2.81 (ddd, *J* = 12.0, 9.0 and 3.0 Hz, 1 H), 2.90 (ddd, *J* = 13.2, 6.0 and 2.4 Hz, 1 H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 14.3, 19.6, 21.1, 22.9, 23.8, 27.8, 27.9, 29.9, 30.9, 31.4, 32.1, 49.0, 55.4, 55.7; IR (KBr, neat) 2927, 2857, 2802, 1460, 1378, 1262, 1148, 1088, 749 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{27}N$ (M + H)$^+$ 210.2216, found 210.2222. ESI-MS: *m/z* (relative intensity): 210.3 ((M + H)$^+$, 50%), 204.2 (100), 202.2 (15), 182.2 (22), 145.0 (9).

**1-(Dec-1-en-4-yl)pyrrolidine (11)**

Pale yellow liquid; yield 58 mg, 28%; $^1$H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.25-1.37 (m, 7 H), 1.40–1.46 (m, 1 H), 1.65-1.71 (m, 2 H), 1.95-2.02 (m, 4 H), 2.42–2.48 (m, 1 H), 2.51-2.57 (m, 1 H), 2.79 (brs, 1 H), 3.02 (brs, 4 H), 5.13-5.19 (m, 2 H), 5.80-5.88 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.8, 23.7 (2C), 25.9, 29.7, 31.3, 31.9, 35.8, 51.5 (2C), 63.9, 117.4, 135.3; IR (KBr, neat) 2923, 2856, 1632, 1457, 1030, 738, 610 cm−1; HRMS (ESI) calcd for $C_{14}H_{27}N$ (M + H)$^+$ 210.2216, found 210.2218. ESI-MS: *m/z* (relative intensity): 210.2 ((M + H)$^+$, 100%), 168.2 (77), 97.1 (17), 83.1 (21).

**2-Allyl-1-heptylpyrrolidine (12)**

Pale yellow liquid; yield 77 mg, 37%; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.23-1.35 (m, 10 H), 1.96–2.06 (m, 4 H), 2.16-2.30 (m, 2 H), 2.70-2.90 (m, 3 H), 3.20–3.35 (m, 2 H), 5.18 (d, *J* = 10.0 Hz, 1 H), 5.27 (d, *J* = 17.2 Hz, 1 H), 5.67-5.79 (m, 1 H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 14.2, 21.9, 22.8, 27.0, 27.6, 29.2, 30.0, 31.9, 36.8, 53.8, 54.4, 65.9, 117.9, 134.6; IR (KBr, neat) 2924, 2854, 1628, 1465, 1018, 734, 611 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{27}N$ (M + H)$^+$ 210.2216, found 210.2221. ESI-MS: *m/z* (relative intensity): 210.2 ((M + H)$^+$, 100%), 168.2 (24).

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## Notes and references

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