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Convergent asymmetric synthesis of indolizidines from (*S*)-5-(tosylmethyl)-2-pyrrolidinone: synthesis of (−)-δ-coniceine

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Abstract—The enantiomerically pure (*S*)-5-(tosylmethyl)-2-pyrrolidinone **2**, prepared from commercially available (*S*)-pyroglutaminol, is dialkylated at the nitrogen atom and the α-sulfonyl position using several dielectrophiles using sodium hydride as the base to diastereoselectively afford indolizidine derivatives **5** and the less common hexahydropyrrolo[1,2-*a*]azepin-3-one **6** in moderate to good yield. This domino process has been applied to the synthesis of (−)-δ-coniceine.

1. Introduction

The family of indolizidine alkaloids[1] is present in the skins of central and South American frogs, fungi and plants. Depending on their structure, they possess a variety of important biological activities. Alkylated indolizidines **I**–**IV** are non-competitive blockers of nicotinic acetyl choline receptor channels in muscle and ganglia membranes.[2] Hydroxylated derivatives **V**–**VIII** are inhibitors of glycosidases with potential antibacterial, antitumoral, antiviral, antiinflammatory or antidiabetic activity and act as anti-HIV agents[3] (Fig. 1). These alkaloids are very important targets in organic synthesis due to their scarcity in natural sources and their important physiological effects. The majority of strategies for constructing indolizidines are based on divergent methods for particular structures. However, convergent methods are especially appropriate for the preparation of a variety of structurally similar alkaloids from a common precursor. This objective can be easily achieved starting from either proline[4a–f] or pyroglutamic acid[4g–h] and using a three-carbon fragment for the construction of the six-membered ring.[4] In this context, we have recently described that (*E*)-5-tosyl-4-pentenamide **1** can be cyclised to 2-(tosylmethyl)-γ-lactam **2** by means of treatment with sodium hydride and, after reaction with 1,3-dielectrophiles, transformed stereoselectively into indolizidine derivatives **3** (Scheme 1).[5]

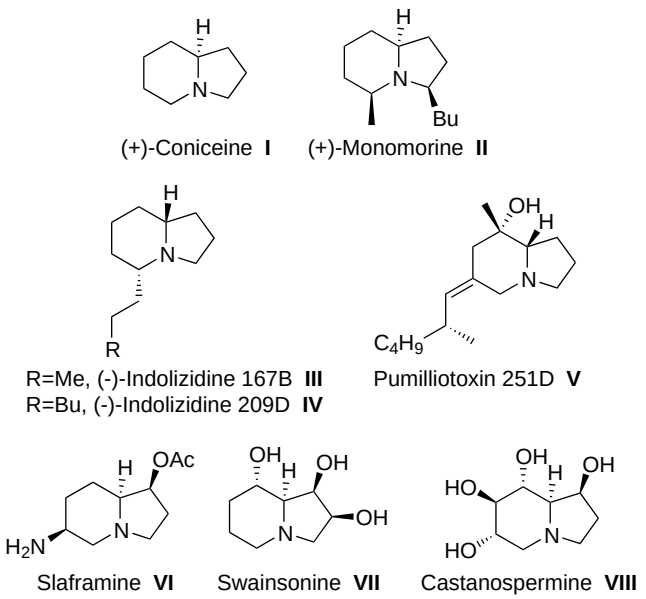
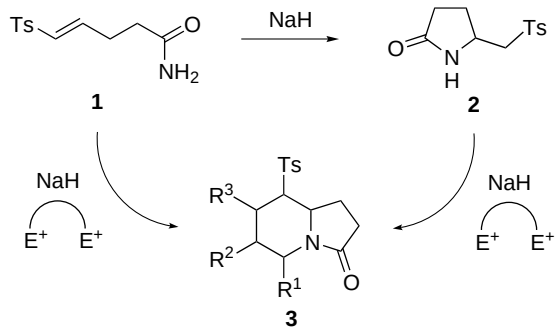


Figure 1. Selected examples of naturally occurring indolizidines.



Scheme 1.

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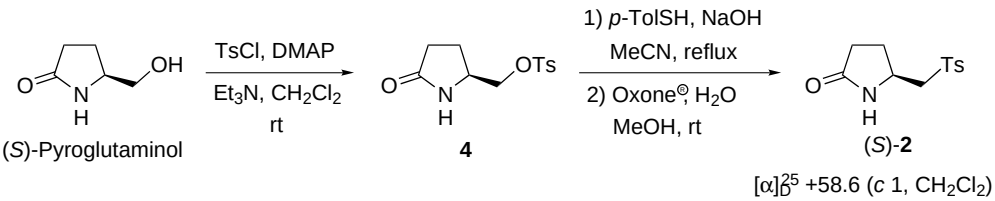
Herein, we report the preparation of optically active indolizidines starting from a chiral sulfone (*S*)-5-(tosylmethyl)-2-pyrrolidinone (*S*)-**2** from inexpensive (*S*)-pyroglutamic acid[6] and its application to the asymmetric synthesis of different indolizidines such as the simplest indolizidine alkaloid (−)-δ-coniceine **I**.[7,8]

2. Results and discussion

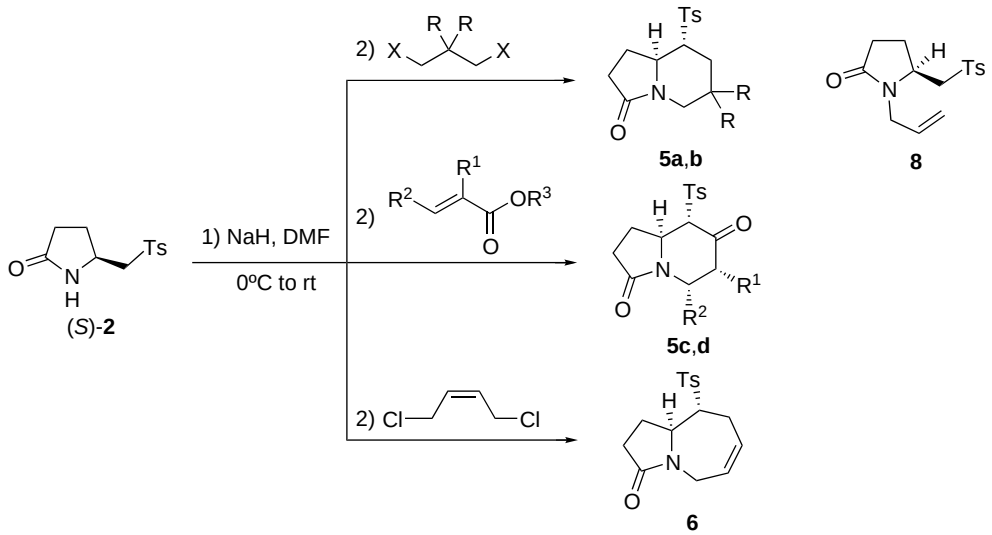
For the synthesis of (*S*)-2-(tosylmethyl)-γ-lactam **2**, (*S*)-pyroglutaminol[9] was used as the starting material, which was treated with *p*-toluenesulfonyl chloride, triethylamine and a catalytic amount of 4-(*N*,*N*′-dimethylamino)pyridine (DMAP) in dichloromethane, at room temperature, affording tosylate **4** in 60% yield.[10] Compound **4** underwent nucleophilic displacement by *p*-methylthiophenol under basic media followed by oxidation with oxone® giving enantiomerically pure sulfone (*S*)-**2** in 90% overall yield (Scheme 2).[11]

This synthesis was preferred to that employing the nucleophilic substitution reaction of sodium *p*-toluenesulfinate onto homochiral (*S*)-**5**-(bromomethyl)-2-pyrrolidinone[12] because higher purity of the crude sulfone (*S*)-**2** was obtained. Subsequent reaction of compound **2**, generated with 1,3- and 1,4-dielectrophiles in the presence of 2 equiv. of sodium hydride (60% dispersion in mineral oil) in DMF, gave the indolizidine derivatives **5** and hexahydropyrrolo[1,2-*a*]azepin-3-one **6**, respectively, in moderate to good yields (Scheme 3 and Table 1). Despite the fact that lithium hexamethyldisilazide is the most suitable base for deprotonating similar sulfones,[13] sodium hydride (used as a 60% dispersion in mineral oil) gave the best results. Other bases, such as *n*-BuLi, phosphazene bases and *tert*-BuOK, using a wide range of temperatures (from −78 to 50°C) did not improve on the results obtained using sodium hydride. Using 1,3-dielectrophiles such as 1,3-dihalogenides and α,β-unsaturated esters, indolizidine derivatives **5** were diastereoselectively obtained through a stepwise dialkylation. The first substitution reaction corresponded to that of sodium amide, rather than the α-sulfonyl carbanion,[14] as shown by the large amounts of dehydroiodinated compound **8**[5] (c.a. 40% yield) which were isolated in the reaction of **2** with 1,3-diiodopropane (Table 1, entry 1 and Scheme 3). The side product **8** was obtained in almost quantitative yield when 95% sodium hydride was employed instead of a 60% dispersion in mineral oil. Use of 2-(chloromethyl)-3-chloropropene as the dielectrophile, in the presence of sodium iodide (2 equiv.), afforded enantiomerically pure *exo*-methylene indolizidine **5b** in 85% yield (Table 1, entry 2).

Using α,β-unsaturated esters as the dielectrophile afforded highly functionalised indolizidine derivatives by employing substoichiometric amounts of base for the Michael addition step. Thus, *n*-butyl methacrylate generated a 10:1 *cis*/*trans* mixture of diastereomers in low yield (Scheme 3, Table 1, entry 3). In the case of methyl crotonate the reaction took place more rapidly,

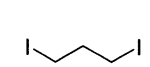
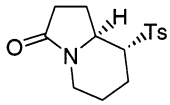
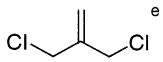
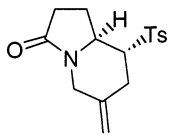
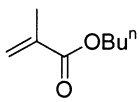
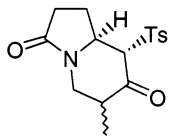
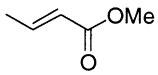
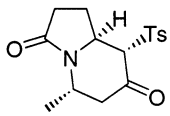
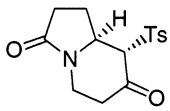
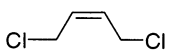
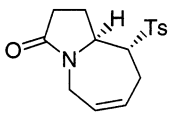


Scheme 2.



Scheme 3. R = H, =CH_2; R^1, R^2 = H, Me; R^3 = *n*-Bu, Me.

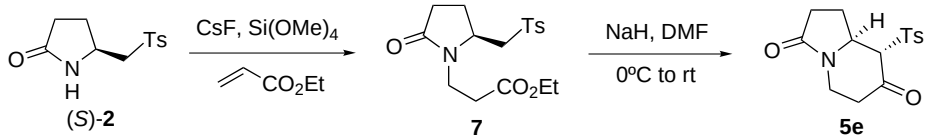
Table 1. Diastereoselective synthesis of indolizidine derivatives **5** and hexahydropyrrolo[1,2-*a*]azepin-3-one **6**

Entry	Dielectrophile	NaH (equiv.)	Time (h)	Product No	Structure	Yield (%)[a]	R_f[b]	$[\alpha]_D^{25}$
1		2	4	**5a**		60[c]	0.28	-58.1[d]
2		2	10	**5b**		85	0.33	+6.1[d]
3		1.2	4	**5c**		35[f]	0.49	—
4		1.2	1	**5d**		60[g]	0.59	+2.2[h]
5		2	24	**5e**		72[j]	0.39	+10.3[d]
6		3	16	**6**		54	0.67	-13.5[k]

[a] Isolated yield after flash chromatography (silica gel).
[b] Using ethyl acetate as eluent.
[c] A 40% of compound **8** was also obtained
[d] (*c* 1, CH_2Cl_2)
[e] 2.5 Equivalents of NaI were added.
[f] Obtained as a 10:1, *cis*:*trans* mixture of diastereomers.
[g] Only one diastereomer was detected.
[h] (*c* 0.7, CH_2Cl_2).
[i] Starting from crude compound **7** (Scheme 4).
[j] Overall yield from sulfone **2**.
[k] (*c* 0.9, CH_2Cl_2)

leading to higher conversions of the all-*cis*-diastereoisomer **5d** (Scheme 3, Table 1, entry 4). The moderate yields obtained when using acrylic esters were presumably caused by a retro-Michael reaction before cyclisation. This drawback, which was especially important in the case of ethyl acrylate, was overcome by employing an alternative two-step procedure based on the use of caesium fluoride and tetramethoxysilane.[15a,b] This methodology became particularly useful in organic synthesis for the conjugate addition of amides to Michael acceptors.[15c,d] Thus, Michael adduct **7** was generated in quantitative yield and further anionic cyclisation with sodium hydride (1 equiv.) in DMF, gave the indolizidine derivative **5e** in 72% overall yield (Scheme 4 and Table 1, entry 5). Again, only one diastereomer was detected in the crude product by NMR analysis. In contrast, use of butyl methacrylate, methyl fumarate and methyl maleate gave very disappointing results, probably the related retro-Michael addition was much faster in those examples under basic reaction conditions.

When (*Z*)-1,4-dichloro-2-butene was allowed to react with sulfone (*S*)-**2**, in the presence of NaH, functionalised hexahydropyrrolo[1,2-*a*]azepin-3-one **6** was isolated in 54% yield (Scheme 3, Table 1, entry 6). The rare hexahydropyrrolo[1,2-*a*]azepin-3-one or 1-azabicyclo[5.3.0.]decane system is not a common skeleton but



Scheme 4.

it is present in some natural products and compounds with biological interest such as thyroliberin,[16] *stemona* alkaloids[17] and a novel alkaloid 275A.[18] Because a few procedures are described focussed on the synthesis of this heterocyclic array,[6,19] this process proved to be a valuable alternative route to prepare them in a stereocontrolled manner. However, when 1,4-diiodobutane was employed the corresponding dehydroiodinated product was obtained.

The stereochemistry of pure **6** and pure compounds **5** was deduced by NOESY experiments and by analysing, in the case of compounds **5**, the coupling constant values between the α-sulfonyl proton and the ring junction methyne proton ($J_{trans}=10.4$ Hz).[5] Irrespective of the chosen method (one-pot or sequentially via **7**) the diastereomeric excess, determined by ^{1}H NMR (500 MHz) from the crude reaction mixtures of the products **5** and **6**, was higher than 98%. Molecular mechanical and semi-empirical PM3 calculations[20] predicted that the *trans* arrangement for compound **5a** is thermodynamically more stable (about 2 kcal/mol) than the undetected diastereoisomer *cis*-**5a**.

We then applied the methodology developed to the synthesis of (−)-δ-coniceine **I** starting from indolizidine derivative **5a**. The reduction of the arylsulfonyl group with 6% sodium amalgam/Na_2HPO_4[5] gave intermediate lactam **9** in 51% yield and final amide reduction was accomplished with lithium aluminium hydride[7b] affording (−)-δ-coniceine **I** in 85% yield[21] (Scheme 5).

3. Conclusions

The dialkylation of optically pure sulfone (*S*)-**2** with 1,3-dielectrophiles represents a concise, accessible and straightforward convergent methodology for preparing diastereoselectively sulfonylated optically active indolizidine derivatives, which are precursors of naturally occurring indolizidine alkaloids. The most simple indolizidine alkaloid (−)-δ-coniceine is prepared in only three steps following this short synthetic route. The functionalised hexahydropyrrolo[1,2-*a*]azepin-3-one skeleton can be easily obtained by reaction of (*S*)-**2** with (*Z*)-1,4-dichloro-2-butene.

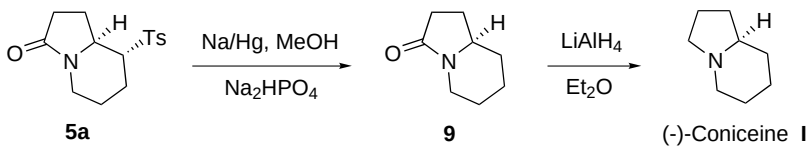
4. Experimental

4.1. General

Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 P-FT and only the structurally important peaks are listed. NMR spectra were performed on a Bruker AC-300 and DRX-500. $CDCl_3$ as solvent and TMS as internal standard were employed unless otherwise stated. Optical rotations were measured on a Jasco DIP-1000 polarimeter. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed by the Microanalyses Service of the University of Alicante. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm). Commercially available anhydrous DMF (Aldrich) was used without any other treatment.

4.2. Synthesis of (5*S*)-5-[(*p*-toluenesulfonyl)oxymethyl]-2-pyrrolidinone 4[22]

To a stirred solution of (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (2.2 g, 20 mmol), triethylamine (3.3 mL, 24 mmol) and DMAP (0.12 g, 1.2 mmol) in dichloromethane (90 mL) at 0°C, *p*-toluenesulfonyl chloride (3.7 g, 0.02 mol) was slowly added. The mixture was stirred at room temperature for 24 h. The organic phase was sequentially washed with aqueous HCl (2 M 3×10 mL), water (2×10 mL), $NaHCO_3$ (3×10 mL) and brine (2×10 mL). The solvent was dried (Na_2SO_4) and evaporated in vacuo affording **4**. Colourless prisms, mp 117–118°C (*n*-hexane/ethyl acetate). $[\alpha]_D$ +16.5 (*c* 2.5, EtOH), {lit.[10b] $[\alpha]_D$ +16.8 (*c* 2.6, EtOH)}. Calculated for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.2; H, 5.9; N, 5.7; S, 11.7%. IR (CH_2Cl_2) ν_{max}: 3265, 3179, 1665, 1298 and 1146 cm^{-1}. ^{1}H NMR (300 MHz) δ_H: 1.71–1.82 [m, 1H, 1×CH_2CHN], 2.21–2.35 (2m, 3H, 1×CH_2CHN, CH_2CO), 2.46 (s, 3H, CH_3Ar), 3.86–3.89 (m, 2H, CH_2S), 4.03–4.06 (m, 1H, CHN), 6.68 (s, 1H, NH), 7.37 and 7.79 (2d, $J=8.2$ Hz, 4H, ArH). ^{13}C NMR (75



Scheme 5.

MHz) δ_C: 21.6 (CH_3Ar), 22.7, 29.1 [$(CH_2)_2$], 52.6 (CHN), 71.9 (CH_2S), 127.9, 130.1, 132.4, 145.4 (ArC) and 177.6 (CO). MS m/z: 269 (M^+, 2), 239 (17), 97 (10), 91 (32), 85 (17), 84 (100), 73 (64), 65 (15) and 41 (27).

4.3. Synthesis of (5*S*)-5-[(*p*-toluenesulfonyl)methyl]-2-pyrrolidinone 2

Tosylate **4** (3.6 g, 13.4 mmol) and *p*-toluenethiol (2.9 g, 23 mmol) were dissolved in acetonitrile (75 mL) and sodium hydroxide (1.1 g, 27.5 mmol) was added. The resulting suspension was stirred under reflux for 24 h. Acetonitrile was removed and ethyl acetate (30 mL) was poured into the flask. The organic layer was washed with water (3×10 mL) and evaporated in vacuo giving crude sulfide. Without any other purification, this thioether (3 g, 13 mmol) was dissolved in a 1:1 mixture of methanol and water (150 mL) and oxone® (4.9 g, 8 mmol) was slowly added at 0°C and the reaction was stirred for 12 h at room temperature. Methanol was evaporated in vacuo and the aqueous solution was extracted with ethyl acetate (3×20 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure giving (*S*)-**2** as a colourless solid. Prisms, mp 139–140°C (*n*-hexane/diethyl ether). Calculated for $C_{12}H_{15}NO_3S$: C, 56.9; H, 6.0; N, 5.5; S, 12.6. Found: C, 56.5; H, 5.9; N, 5.2; S, 12.3%. IR (CH_2Cl_2) ν_{max}: 3278, 3177, 1660, 1301 and 1147 cm^{-1}. ^1H NMR (300 MHz) δ_H: 1.79, 2.34 [2m, 4H, $(CH_2)_2$], 2.48 (s, 3H, CH_3Ar), 3.23 (m, 2H, CH_2S), 4.10 (m, 1H, CHN), 6.53 (s, 1H, NH); 7.41 and 7.80 (2d, $J=8.2$ Hz, 4H, ArH). ^{13}C NMR (75 MHz) δ_C: 21.6 (CH_3Ar), 27.1, 29.1 [$(CH_2)_2$], 48.5 (CHN), 61.7 (CH_2S), 127.9, 130.2, 135.6, 145.5 (ArC) and 176.9 (CO). MS m/z: 253 (M^+, 0.4%), 98 (50), 97 (96), 92 (14), 91 (32), 84 (100), 69 (30), 65 (21), 55 (23) and 41 (12).

4.4. Synthesis of indolizidine derivatives 5a–5d and hexahydropyrrolo[1,2-*a*]azepin-3-one 6. General procedure

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, see Table 1) in anhydrous DMF, under a nitrogen atmosphere, was added a solution of sulfone (*S*)-**2** (247 mg, 1 mmol) in anhydrous DMF (3 mL) at 0°C. The mixture was stirred at the same temperature for 0.5 h. The dielectrophile (1.1 mmol) was then added stirring the resulting mixture for times depicted in Table 1 (see text). Saturated aqueous ammonium chloride (20 mL) and ethyl acetate (15 mL) were added. The organic phase was washed with water (2×20 mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography eluting with mixtures of *n*-hexane/ethyl acetate affording compounds **5a**–**5d** and **6**.

4.4.1. (8*R*,8a*S*)-8-(*p*-Toluenesulfonyl)perhydro-3-indolizidinone 5a. Colourless needles, mp 172–173°C (*n*-hexane/ethyl acetate). Calculated for $C_{15}H_{19}NO_3S$: C, 61.4; H, 6.5; N, 4.7; S, 10.9. Found: C, 61.1; H, 6.4; N, 4.8; S, 10.7%. IR (film) ν_{max}: 1673, 1287 and 1143 cm^{-1}. ^1H NMR (300 MHz) δ_H: 1.26–2.11, 2.34–2.55 [2×m with s at 2.48, 12H, CH_3Ar, $(CH_2)_2HCHN$, $(CH_2)_2CO$], 2.84 (ddd, $J=12.2$, 10.4 and 3.7 Hz, 1H, CHS), 3.68 (dt, $J=10.4$ and 7.3 Hz, 1H, CHN), 4.10 (dd, $J=13.4$ and 4.3 Hz, 1H, HC*H*N), 7.40 and 7.76 (2d, $J=7.9$, 4H, ArH); δ_c 21.6 (CH_3Ar), 23.3, 25.2, 25.3, 29.9 [$(CH_2)_2CO$, $(CH_2)_2CHS$], 39.1 (CH_2N), 56.0 (CHS), 66.8 (CHN), 128.8, 129.9, 134.2, 145.3 (ArC), and 173.6 (CO). MS m/z: 293 (M^+, 0.1%), 138 (17), 137 (100) and 136 (21). HRMS found: 293.1089. $C_{15}H_{19}NO_3S$ requires 293.1086.

4.4.2. (8*R*,8a*S*)-6-Methylene-8-(*p*-toluenesulfonyl)perhydro-3-indolizidinone 5b. Pale yellow oil. IR (film) ν_{max}: 3062, 1599, 1687, 1290 and 1144 cm^{-1}. ^1H NMR (300 MHz) δ_H: 1.91–2.10, 2.36–2.61 [2×m with s at 2.49, 9H, CH_3Ar, $(CH_2)CHS$, $(CH_2)_2CO$], 2.95 (ddd, $J=12.2$, 10.4, 4.3 Hz, 1H, CHS), 3.20 (d, $J=14.0$ Hz, 1H, *H*CHN), 3.81 (dt, $J=10.4$ and 7.3 Hz, 1H, CHN), 4.49 (d, $J=14.0$ Hz, 1H, HC*H*N), 4.85, 4.99 (2×s, 2H, CH_2=C), 7.42 and 7.77 (2×d, $J=7.9$ Hz, 4H, ArH). ^{13}C NMR (75 MHz) δ_c: 21.6 (CH_3Ar), 24.8, 30.1, 33.3 [$(CH_2)_2CO$, CH_2CHS], 45.2 (CH_2N), 55.7 (CHS), 66.7 (CHN), 113.7, 134.1 (C=CH_2), 128.8, 130.1, 136.7, 145.5 (ArC) and 173.1 (CO). MS m/z: 304 (M^+–1, 1%), 150 (22), 149 (100), 148 (84), 134 (13), 91 (13) and 65 (10). HRMS found: 305.1080. $C_{16}H_{19}NO_3S$ requires 305.1086.

4.4.3. (6*S*,8*S*,8a*S*)-6-Methyl-8-(*p*-toluenesulfonyl)perhydro-3,7-indolizidinedione *cis*-5c. Colourless oil. IR (film) ν_{max}: 1719, 1682, 1311 and 1149 cm^{-1}. ^1H NMR (300 MHz) δ_H: 1.01 (d, $J=6.1$ Hz, 3H, CH_3CH), 2.46–2.73 (m with s at 2.46, 9H, CH_3Ar, CH_2CH_2CO, CH_3CH, *H*CHN), 3.92 (d, $J=10.1$ Hz, 1H, CHS), 4.25 (m, 1H, CHN), 4.41 (dd, $J=12.4$ and 6.0 Hz, 1H, HC*H*N), 7.38 and 7.94 (2d, $J=7.9$ Hz, 4H, ArH). ^{13}C NMR (75 MHz) δ_c: 11.0 (CH_3CN), 21.7 (CH_3Ar), 25.7, 29.6, [$(CH_2)_2$], 44.6 (CH_2N), 44.8 (CH_3CH), 58.3 (CHS), 75.8 (CHN), 129.6, 129.7, 135.8, 145.5 (ArC), 173.4 (NCO) and 198.2 (*C*OCHS). MS m/z: 321 (M^+, 4%), 166 (100), 165 (36), 164 (74), 150 (10), 137 (17), 124 (16), 91 (20), 84 (16), 65 (11), 55 (12) and 41 (12). HRMS found: 321.1039. $C_{16}H_{19}NO_4S$ requires 321.1035.

4.4.4. (5*S*,8*R*,8a*S*)-5-Methyl-8-(*p*-toluenesulfonyl)perhydro-3,7-indolizidinedione 5d. Colourless oil. IR (film) ν_{max}: 1729, 1678, 1302 and 1148 cm^{-1}. ^1H NMR (300 MHz) δ_H: 1.28 (d, $J=6.4$ Hz, 3H, CH_3CHN), 2.20, 2.65 [3×m with s at 2.45, 9H, CH_3Ar, $(CH_2)_2$, CH_2CHNCH_3], 3.75 (d, $J=9.8$ Hz, 1H, CHS), 4.38 (m, 1H, $CHNCH_3$), 4.75 (ddd, $J=9.8$, 7.9 and 3.9 Hz, 1H, CHSC*H*N), 7.38 and 7.76 (2×d, $J=8.4$ Hz, 4H, ArH). ^{13}C NMR (75 Mz) δ_c: 19.6 (CH_3CHN), 21.7 (CH_3Ar), 25.5, 29.4 [$(CH_2)_2$], 45.2 (CHS), 45.2 (CH_2CHNCH_3), 52.8 ($CHNCH_3$), 76.2 (CHN), 129.2, 129.9, 134.6, 145.9 (ArC), 173.5 (NCO) and 198.4 (*C*OCHS). MS m/z: 321 (M^+, 3%), 167 (11), 166 (100), 165 (93), 164 (14), 150 (65), 137 (13), 124 (23), 122 (12), 110 (11), 91 (31), 84 (16), 69 (11), 65 (13), 55 (14) and 41 (14). HRMS found: 321.1046. $C_{16}H_{19}NO_4S$ requires 321.1040.

4.4.5. (9*R*,9a*S*)-9-(*p*-Toluenesulfonyl)-2,3,5,8,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-3-one 6. Pale yellow oil. IR (film) ν_{max}: 1672, 1615, 1289 and 1147. ^1H NMR (300 MHz) δ_H: 2.06–2.20 (m, 1H, 1×CH_2CH_2CO),

2.31–2.42 (m, 3H, 1×CH_2CH$_2$CO, CH_2CO), 2.48 (s, 3H, CH_3Ar), 3.02–3.18 (m, 1H, H_2CCHSO$_2$), 3.36–3.50 (m, 1H, H_2CCHSO$_2$), 3.61–3.73 (m, 1H, CHS), 4.01–4.23 (m, 2H, CH$_2$N), 4.62–4.78 (m, 1H, HCN), 5.40–5.83 (2m, 2H, *H*C=C*H*), 7.43 and 7.87 (2d, $J=8.2$ Hz, 4H, ArH). ^{13}C NMR (75 MHz) δ_c: 21.7 (*C*H$_3$Ar), 24.7 (*C*H$_2$CHN), 29.1 (*C*H$_2$CO), 37.7 (*C*H$_2$CHSO$_2$), 52.9 (CHSO$_2$), 58.8 (CH$_2$N), 77.4 (CHN), 127.1, 127.9 (HC=CH), 130.1, 130.2, 145.4, 160.6 (ArC) and 174.5 (C=O). MS *m*/*z*: 305 (M$^+$, 83), 266 (689), 255 (24), 254 (28), 231 (27), 219 (24), 169 (38), 155 (369), 148 (42), 139 (30), 137 (36), 136 (69), 122 (21), 111 (26), 110 (36), 108 (30), 105 (23), 98 (269, 95 (23), 91 (30), 90 (22), 84 (54), 79 (34), 69 (59), 67 (36), 66 (22), 65 (39), 63 (21), 55 (100), 53 (67), 43 (46), and 41 (46). HRMS found: 305.1087. $C_{16}H_{19}NO_3S$ requires 305.1086.

4.5. Synthesis of (8*S*,8a*S*)-8-(*p*-toluensulfonyl)perhydro-3,7-indolizidinedione 5e

A suspension of pyrrolidone (*S*)-**2** (144 mg, 0.75 mmol), CsF (106 mg, 0.7 mmol) in tetramethylorthosilicate[15c,d] (1 mL) was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous ammonium chloride (15 mL). Ethyl acetate (20 mL) was added and the resulting organic solution washed with water (4×20 mL) and dried (Na_2SO_4) then evaporated in vacuo furnishing the intermediate Michael adduct, which was treated without any additional purification with sodium hydride (60% dispersion in mineral oil, 27 mg, 0.63 mmol) in anhydrous DMF and stirred under an inert atmosphere for 24 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). Ethyl acetate (10 mL) was added and the resulting organic solution washed with water (2×20 mL), dried (Na_2SO_4) and evaporated in vacuo affording a residue, which was purified by flash chromatography eluting with *n*-hexane/ethyl acetate. Compound **5e** was obtained as pale yellow oil. IR (film) ν_{max}: 1725, 1667, 1297 and 1143 cm^{-1}. ^{1}H NMR (300 MHz) δ_H: 2.23–2.31 (m, 1H, CCH_2CH$_2$CO), 2.47–2.51 (m with s at 2.48, 8H, CH_3Ar, 1×CCH_2CH$_2$CO, 2×CH_2CO), 3.23–3.33 (m, 1H, 1×CH$_2$N), 3.81 (d, $J=9.8$ Hz, 1H, CHS), 4.10–4.21 (m, 1H, 1×CH$_2$N), 4.54–4.62 (m, 1H, CHN), 7.39 and 7.81 (2d, $J=8.2$, 4H, ArH). ^{13}C NMR (75 MHz) δ_c: 21.7 (*C*H$_3$Ar), 26.3 (CH$_2$CHN), 29.5 (CH$_2$CO), 37.6 (CH_2CH$_2$N), 38.8 (CH$_2$N), 55.8 (CHN), 77.2 (CHS), 129.4, 129.8, 139.9, 144.1 (ArC), 167.2 (NCO) and 210.3 (CO). MS *m*/*z*: 307 (M$^+$, 53), 306 (72), 305 (96), 280 (45), 267 (24), 266 (33), 255 (69), 243 (45), 236 (28), 230 (41), 219 (23), 217 (31), 205 (21), 193 (50), 181 (69), 155 (23), 150 (89), 148 (40), 136 (87), 130 (71), 122 (22), 119 (61), 111 (41), 108 (29), 107 (26), 106 (33), 105 (42), 97 (24), 92 (27), 91 (100), 84 (52), 83 (26), 82 (30), 80 (35), 79 (23), 70 (46), 69 (31), 67 (46), 55 (49), 43 (72) and 41 (84). HRMS found: 307.0887. $C_{15}H_{17}NO_4S$ requires 307.0878.

4.6. Synthesis of (8a*R*)-perhydro-3-indolizidinone 9

To a suspension of (6%) sodium amalgam (1.9 g, 5 mmol) and Na_2HPO_4 (287 mg, 2 mmol) in anhydrous methanol (10 mL), under a nitrogen atmosphere, was added a solution of sulfone **5a** (73 mg, 0.25 mmol) in anhydrous methanol at 0°C. The reaction mixture was stirred at room temperature for 48 h. Water was added (15 mL) and the suspension filtrated through a Celite path. Ethyl acetate was added and the resulting organic solution washed with water (2×20 mL), dried (Na_2SO_4) and evaporated in vacuo. The obtained residue was purified by flash chromatography eluting with mixtures of *n*-hexane/ethyl acetate affording lactam **9**. Oil, $[\alpha]_D^{25}$ −33.5 (*c* 0.2, $CHCl_3$) {lit[7c] $[\alpha]_D^{25}$ +35.4 (*c* 0.2, $CHCl_3$) for (+)-enantiomer}. IR (film) ν_{max}: 1650 cm^{-1}. ^{1}H NMR (300 MHz) δ_H: 1.10 (m, 1H, 1×CH_2CHN), 1.09–2.39 (m, 9H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CN and 1×CH_2N), 2.63 (m, 1H, 1×CH_2N), 3.40 (m, 1H, 1×CH_2N) and 4.08 (m, 1H, CHN). ^{13}C NMR (75 MHz) δ_c: 24.4 (*C*H$_2$CH$_2$CO), 25.3 (*C*H$_2$CH$_2$N), 29.7 (*C*H$_2$CO), 30.3 (*C*H$_2$CHN), 46.2 (CH$_2$N), 56.1 (CHN) and 173.0 (CO). MS *m*/*z*: 139 (M$^+$, 64), 138 (80), 124 (14), 110 (13), 96 (20), 84 (26), 83 (66), 82 (23), 69 (17), 68 (29), 67 (11), 57 (13), 56 (62), 55 (95), 53 (19), 41 (100) and 40 (23). HRMS found: 139.0980. $C_8H_{13}NO$ requires 139.0984.

4.7. δ-(−)-Coniceine I[7]

To a suspension of lithium aluminium hydride (42 mg, 0.88 mmol) in anhydrous ether (10 mL), under a nitrogen atmosphere at 0°C, a solution of lactam **9** (30 mg, 0.22 mmol) in anhydrous ether (7 mL) was added slowly. The resulting mixture was stirred at room temperature for 24 h. After hydrolysis with saturated aqueous ammonium chloride (10 mL), ethyl acetate (15 mL) was added and the mixture was stirred under reflux for 0.5 h. The organic phase was separated, dried (Na_2SO_4) and evaporated in vacuo furnishing pure δ-(−)-coniceine. ^{1}H NMR (300 MHz) δ_H: 1.09–1.40 (m, 8H, 4×CH$_2$), 1.57–1.78 (m, 6H, 2×CH$_2$N and CH_2CH) and 2.21–2.35 (m, 1H, CHN). $[\alpha]_D^{25}$ −10.1 (*c* 1.8, EtOH) {lit.[7l] $[\alpha]_D^{25}$ −10.2 (*c* 1.77, EtOH)}.

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