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Sequential deprotection–cyclisation reaction: stereoselective synthesis of azabicyclic β-enamino ester derivatives and (−) indolizidine 209D

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ABSTRACT

This paper describes a new strategy for the stereoselective synthesis of pyrrolizidine and indolizidine based enamino esters and their acyl derivatives from L-proline. The key reaction in this process involves deprotection followed by ring closure of cyclic *N*-Boc amino-β-ketoesters. Also, the synthesis of 5*R*,9*R*-(−)-indolizidine 209D has been accomplished using this protocol.

1. Introduction

Heterocyclic β-enamino esters have widespread applications in organic synthesis because of their versatile reactivity both as nucleophiles and electrophiles.[1] They also act as valuable intermediates in the total synthesis of natural products.[2] Eschenmoser coupling reaction[3] was the well established method for the preparation of heterocyclic β-enamino esters and their acyl derivatives (Knoevenagel type adducts). This reaction, which serves as the key step in the synthesis of various natural products,[4] has some limitations—formation of a mixture of geometrical isomers, long reaction times, moderate yields and isolation of by-products.[5] Recently, Varga and co-workers[6] reported the synthesis of indolizidine β-enamino ester **2** (Fig. 1) as a mixture of *E* and *Z* isomers in 3:1 ratio using Eschenmoser coupling reaction. So several methodologies have been developed for the synthesis of pyrrolidine and piperidine based enamino esters and their acyl derivatives.[7] Hart et al. developed an efficient methodology for the preparation of Knoevenagel type adducts **3** (Fig. 1) from (methylthio)alkylideniminium salts and active methylene compounds,[7a,8] though the geometry around the double bond has not been elaborated. Lhommet and co-workers reported the synthesis of pyrrolidine and piperidine based β-enamino esters **4** (Fig. 1) from ω-halogeno-β-keto esters and alkyl amines.[7d,9] Recently, Lee and co-workers reported the one pot synthesis of *exo*-cyclic enamino esters from nitrile derivatives via Blaise reaction intermediate.[9c] In a review recently published by Murthy et al., they presented the synthesis and application of β-enamino carbonyl compounds.[9d] As pyrrolizidine and indolizidine alkaloids have a wide and varied distribution in nature and display a broad range of interesting biological activities, novel strategies for the synthesis of these azabicyclic skeletons continue to receive considerable attention.[10]

Pyrrolizidine β-enamino ester **5** (Fig. 1) has been used for the total synthesis of Symchiral[11] and indolizidine β-enamino ester **6**

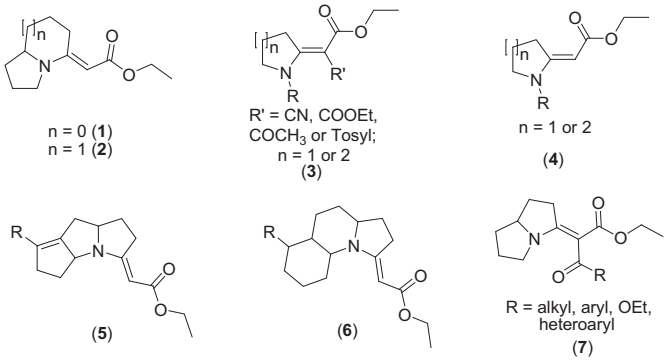

Fig. 1. Vinylogous urethanes and related Knoevenagel type adducts.

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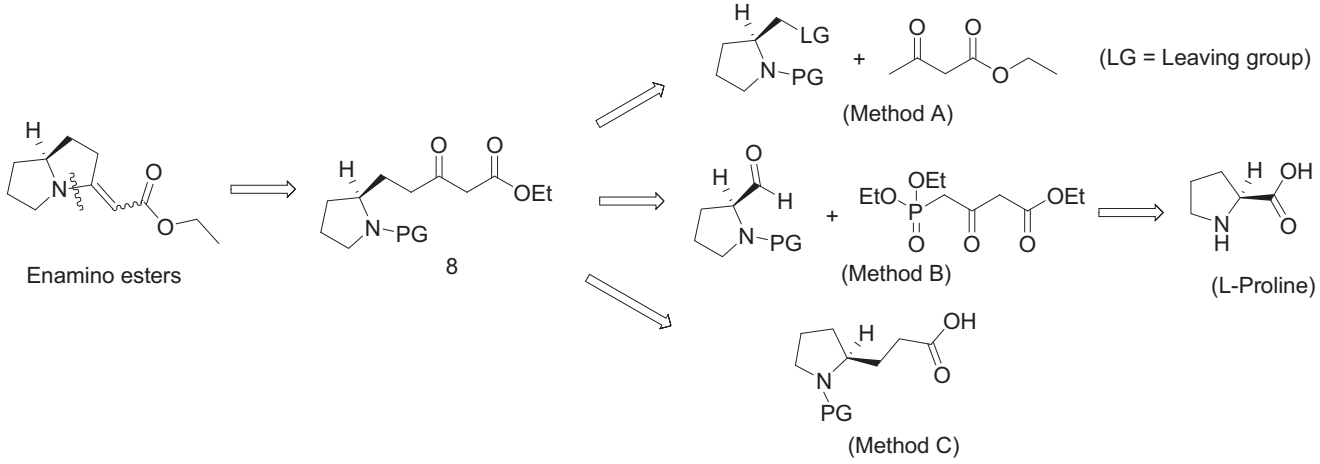
(Fig. 1) has been employed in the synthesis of Dendrobatid alkaloids, such as Gephyrotoxin and Dihydrogephyrotoxin.[2c] In this article, we wish to report a convenient and efficient method for the stereoselective synthesis of pyrrolizidine and indolizidine based β-enamino esters (**1** & **2**) and Knoevenagel type adducts (**7**) (Fig. 1) from readily available starting materials. The application of this protocol to synthesise indolizidine alkaloids has also been explored.

2. Results and discussion

Retrosynthetic analyses of azabicyclic enamino esters are illustrated in Scheme 1. We envisioned that the chiral enamino ester could be constructed from the chiral β-keto ester **8**, which could be obtained from commercially available L-proline. Three routes were designed to obtain β-keto ester **8**, the intermediate precursor of the desired β-enamino ester. Method A: regioselective alkylation of dimetalated ethyl acetoacetate with a chiral pyrrolidine derivative; Method B: hydrogenation of a Nazarov-type reagent, which could be prepared by Wittig–Horner–Emmons reaction between γ-phosphorylated ethyl acetoacetate and a chiral carboxaldehyde; Method C: from propionic acid derivatives.

obtained compounds treated with ethyl acetoacetate dianions[13] in THF at 0 °C. However no reaction took place even at 60 °C with different solvents. In the case of nosylate derivative (**13**), a complex reaction mixture was observed even at 0 °C in THF. The tosylate **12** was then converted into halides **14** and **15** by refluxing with LiBr in acetone and LiI in THF, respectively. The halide derivatives **14** and **15** also failed to give **8** with ethyl acetoacetate dianions. Thus the direct synthesis of β-keto ester **8** by C–C bond formation between ethyl acetoacetate dianions and electrophilic reagents **11**–**15** could not be achieved under the reported reaction conditions.

The synthesis of **8** was then tried from a Nazarov type reagent, a derivative of the ethyl 3-oxo-4-pentenoate. Incidentally, various methods are available for the synthesis of Nazarov's reagents,[14] which act as useful intermediates for the synthesis of various natural products.[15] Wittig–Horner–Emmons reaction has been chosen in the present study for the synthesis of Nazarov type reagent. From the known *N*-Boc-(*S*)-prolinal **16**, prepared from L-proline,[12] **8** was obtained as depicted in Scheme 3. The phosphonate reagent **17** (ethyl 4-(diethylphosphono)acetoacetate) was prepared in quantitative yield from commercially available diethyl phosphite and ethyl 4-chloroacetoacetate in the presence of sodium hydride.[14f]



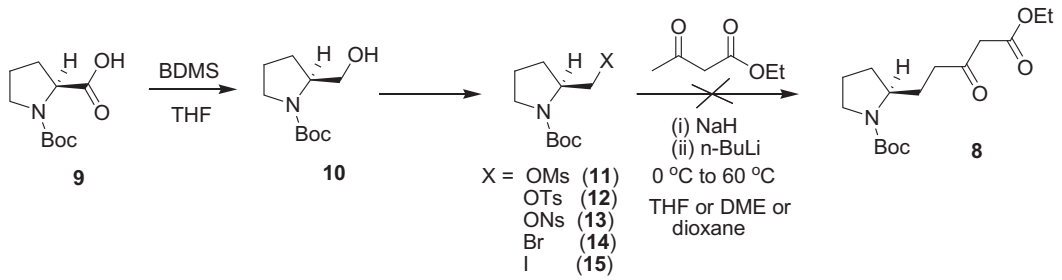
Scheme 1. Retrosynthetic analyses for enamino ester construction.

The cyclisation of **8** can be achieved by a protocol involving sequential N-deprotection followed by acid mediated condensation between the nucleophilic amine and the keto group of the β-keto ester.

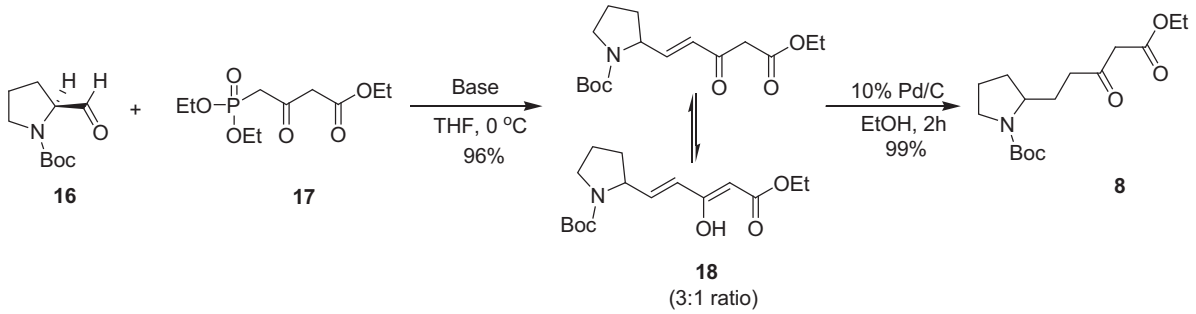
The essential intermediate **8** was attempted from *N*-Boc-L-proline as shown in Scheme 2. According to a known procedure,[12] the reduction of *N*-Boc-L-proline (**9**) was carried out without racemisation to get *N*-Boc-L-prolinol **10**. The hydroxy group of **10** was then converted into sulfonate esters **11**/**12**/**13** and the

The Horner–Wadsworth–Emmons reaction between *N*-Boc-(*S*)-prolinal **16** and the reagent **17** with sodium hydride proceeded smoothly to furnish γ,δ-unsaturated β-keto ester **18** in 96% yield. The ^{1}H NMR spectrum of **18** reveals the presence of keto and enol forms in nearly 3:1 ratio.

The reduction of the double bond was readily achieved by hydrogenation of **18** in ethanol (Pd/C, H_2 (40 psi), 2 h), affording **8** in quantitative yield. The enantiomeric purity of product **8**, determined by chiral HPLC analysis, was found to be 16% ee (ratio 58:42%). The

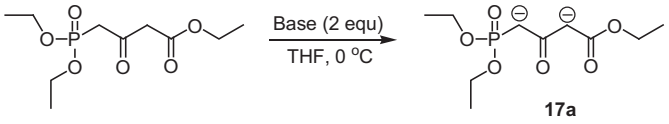


Scheme 2. Alkylation of dimetalated ethyl acetoacetate.



Scheme 3. Synthesis of β-keto ester intermediate **8** through Nazarov reagent.

epimerisation could have occurred during the condensation stage. Other strong bases, such as *t*-BuOK and *n*-BuLi also led to **8** in 20% ee and 15% ee, respectively. Wittig–Horner–Emmons reaction of enantiopure aldehyde normally affords the corresponding olefin without affecting the chiral purity,[16] the observed epimerisation may be due the dianionic ylide (**17a**) used in this condensation reaction (Scheme 4).



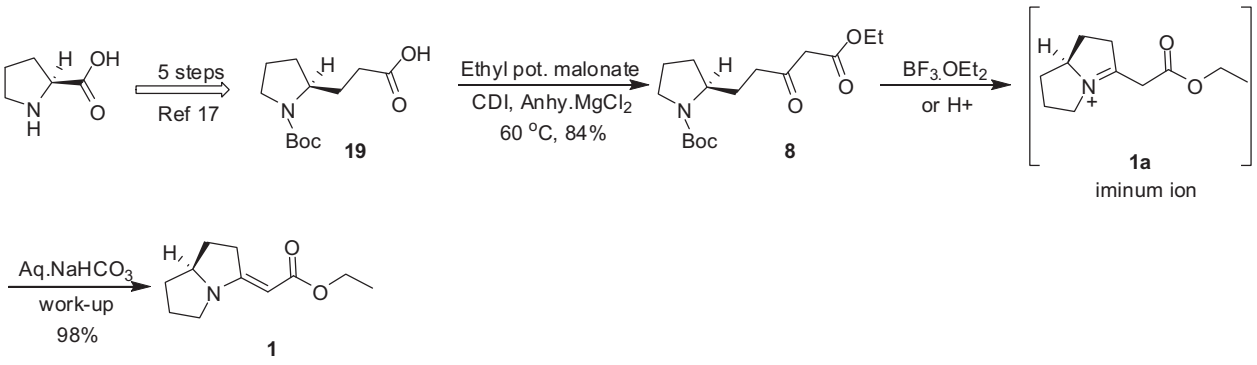
Scheme 4. Generation of dianionic phosphonate **17a**.

Enantiopure **8** was obtained starting from the alkanoic acid **19**. Thus, **19** prepared from L-proline,[17] was allowed to react with 1,1′-carbonyl diimidazole (CDI) in THF to yield the imidazolide, which was treated in situ with ethyl potassium malonate and anhydrous $MgCl_2$ affording 84% of **8** with an enantiomeric excess of 99%. The deprotective cyclisation of **8** using Brønsted acid (TFA, HCl or TfOH) or Lewis acid ($BF_3 \cdot OEt_2$) in dichloromethane led to the formation of iminium ion **1a** and this, on neutralisation with aqueous bicarbonate, afforded the pyrrolizidine β-enamino ester **1** in 98% yield (Scheme 5). No epimerisation was observed in this step (>99% ee).

The observed optical rotation of the β-enamino ester **1** is $[\alpha]_D^{25}$ −100.8 (*c* 0.5, CH_2Cl_2). The stereochemistry around the double bond was assigned as *E* on the basis of ^{1}H NMR data. The chemical shift value of the olefinic hydrogen of **1** is 4.44 ppm in $CDCl_3$. The reported chemical shift value of the pyrrolizidine enamino ester is 4.42 ppm for *E* isomer.[11]

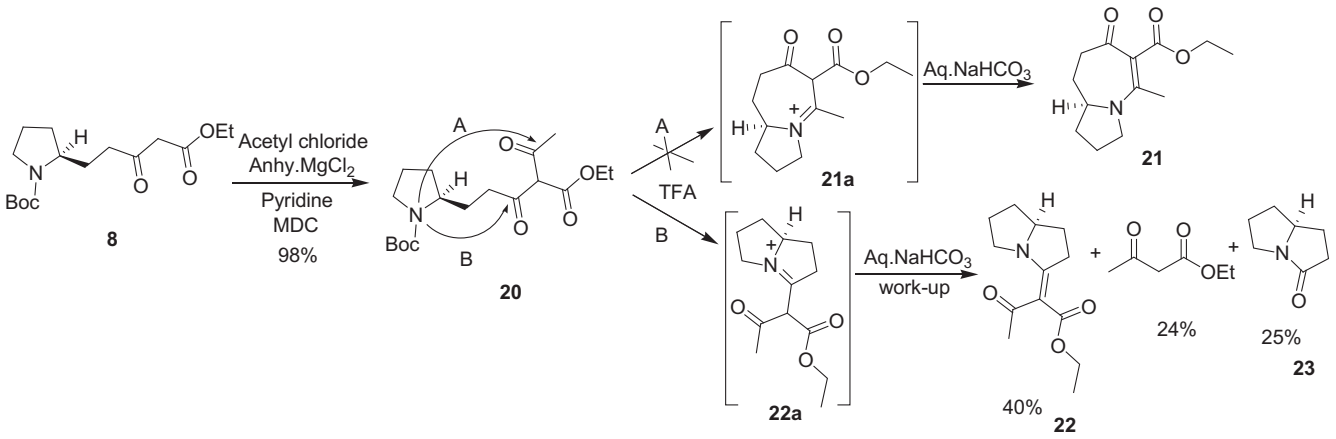
Selective C-acylation and aroylation of 1,3-dicarbonyl compounds with acid chloride using anhydrous magnesium chloride[18] or $SmCl_3$[19] are known. Acetylation of **8** under these conditions followed by subsequent deprotection and cyclisation may lead to either **21** or **22** (Scheme 6). Anticipating this to happen, acetylation of **8** was carried out with acetyl chloride in the presence of anhydrous magnesium chloride and pyridine in methylene dichloride and afforded **20** in 98% yield. **20** underwent deprotective cyclisation with trifluoroacetic acid providing the corresponding iminium ion **22a**, which on neutralisation afforded the pyrrolizidine core **22** beside considerable amount of ethyl acetoacetate and pyrrolizin-3-one **23**. The anticipated azepine skeleton **21** has not been formed at all, pathway B being preferred to A.

Aromatic acid chlorides were also employed for acylation and thus the treatment of **8** with benzoyl chloride under the same condition yielded 39% of **24**, 22% of **25** and 23% of **23** (Scheme 7). However, when the reaction mixture (iminium ion **24a**) was neutralized with aqueous Et_3N (5% solution) instead of aqueous $NaHCO_3$, it is found that the formation of the by-products was marginally reduced giving **24** in 60% yield, whereas when the reaction mixture was stirred with a mixture of water and ethyl acetate (1:1) for about 30 min, **24** was isolated as the exclusive product (95%). It is clear that when aqueous basic solution was employed for neutralisation of the iminium ion, apart from the formation of **24**, the nucleophilic attack of water on **24a** is also competing yielding **23** and **25**. But when a mixture of water–ethyl acetate was

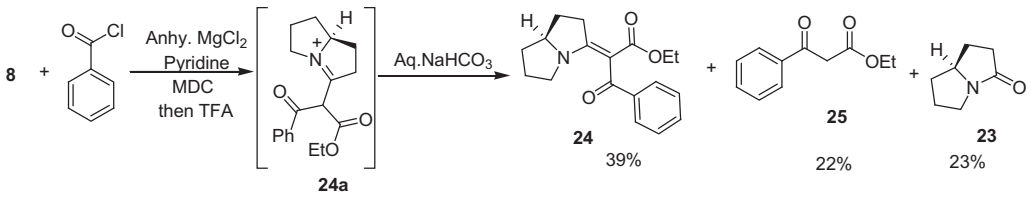


Scheme 5. Synthesis of pyrrolizidine β-enamino ester **1**.

The deprotective cyclisation of **8** was characterised by the absence of active $-CH_2-$ proton signal at δ 3.58 ppm and the presence of sharp singlet at δ 4.44 ppm in **1**, which corresponds to the =CH proton. The formation of product was further supported by the appearance of −CH=CH− signals at δ 78.8 and 169.5 ppm, which is reliable for β-enamino esters.



Scheme 6. Acetylation followed by deprotective cyclisation of **8**.

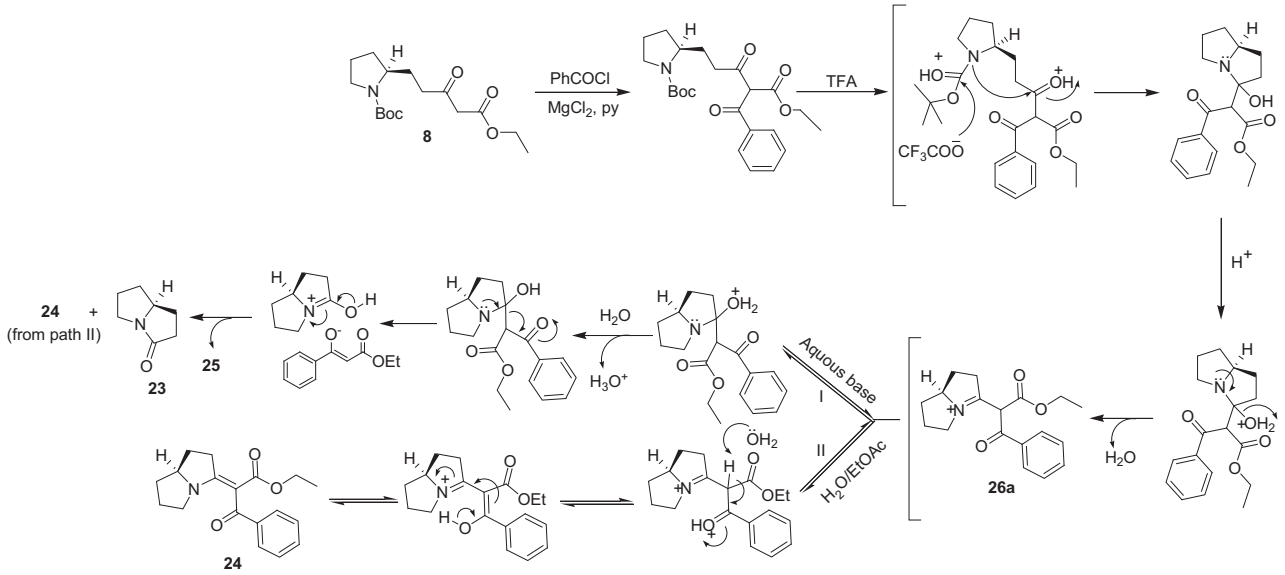


Scheme 7. Benzoylation followed by deprotective cyclisation of **8**.

employed, the iminium ion **24a** just got neutralised through the keto–enol tautomerism and a nucleophilic attack by water molecule on the electron deficient azomethine carbon was not favoured. The enantiomeric purity of product **24** was determined by chiral HPLC analysis, the enantiomeric excess being>99%. The observed optical rotation of the β-enamino ester **24** is $[\alpha]_D^{25}$ −63.7 (*c* 0.46, CH_2Cl_2). The mechanism of formation of **23**, **24** and **25** from **8** is shown in Scheme 8.

Using the optimised reaction conditions, various aroyl chlorides were treated with **8** (obtained from method B) and the corresponding pyrrolizidine based Knoevenagel type adducts prepared are shown in Fig. 2. Even the introduction of strong electron withdrawing substituents, such as nitro, formyl and trifluoromethyl groups at different positions of the aryl ring in order to achieve the azepine skeleton **21a** (cyclisation through path A) was not successful and in all cases the corresponding pyrrolizidines were obtained (**26**–**30**). Other aromatic and heteroaromatic acid chlorides have also been successfully tested in this reaction (**31**–**35**). In all the cases, only the *E* isomers were obtained as demonstrated by single crystal X-ray crystallographic study of **28**[20] (Fig. 3).

The reaction between β-keto ester **8** (obtained from method C) and chloroacetyl chloride in anhydrous $MgCl_2$/pyridine/MDC



Scheme 8. Proposed mechanism for the formation of **23**, **24** and **25**.

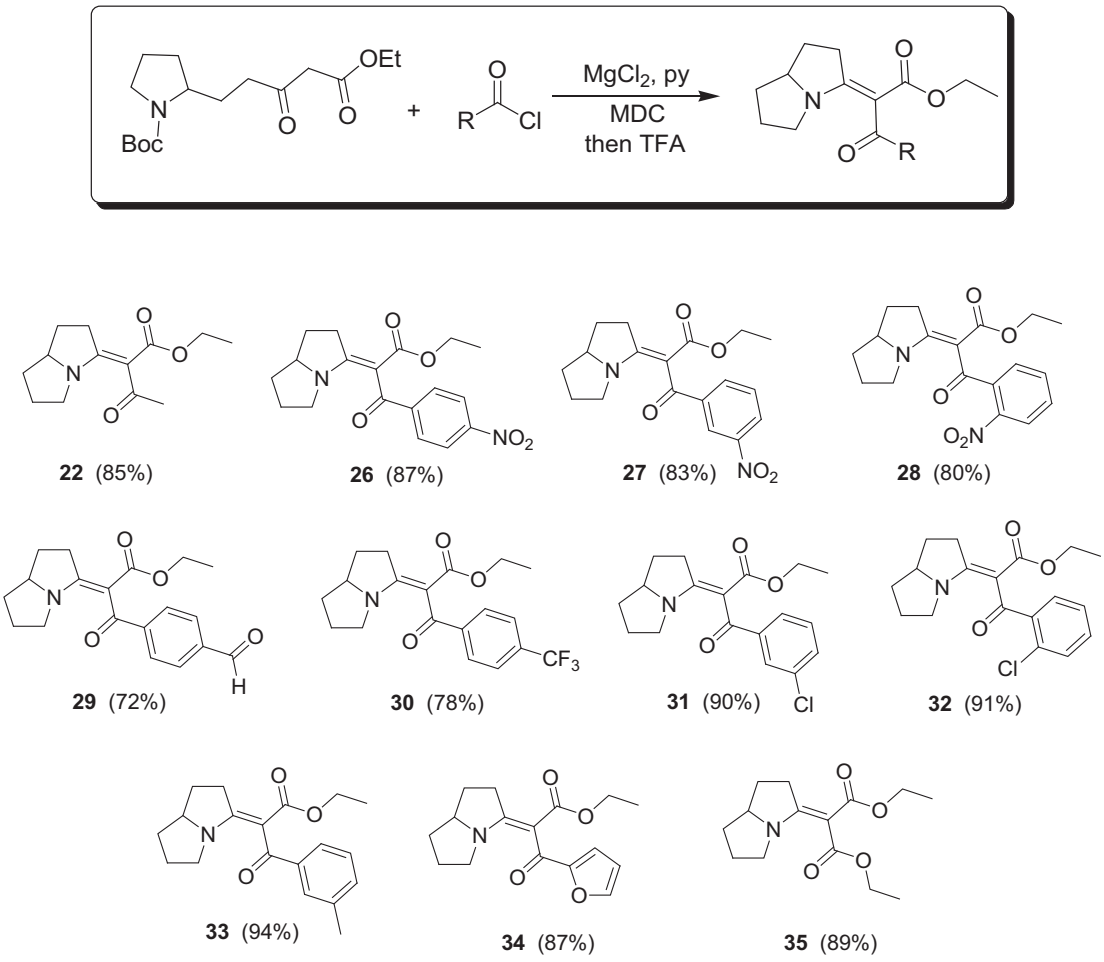


Fig. 2. Synthesis of pyrrolizidine based Knoevenagel type adducts (**22**, **26**–**35**).

medium yielded 82% of the furanone intermediate **36** after 5 h through the sequential C-acylation and O-alkylation. The deprotection of **36** was carried out with trifluoroacetic acid and the subsequent cyclisation at 50 °C afforded 71% of the tricyclic system with an azepine skeleton, **37** (Scheme 9). When the reaction between 3-chloropropionyl chloride and **8** was attempted, the pyranone intermediate **38** failed to give the cyclisation compound **40** even after 10 h reflux in MDC or EtOH (Scheme 9).

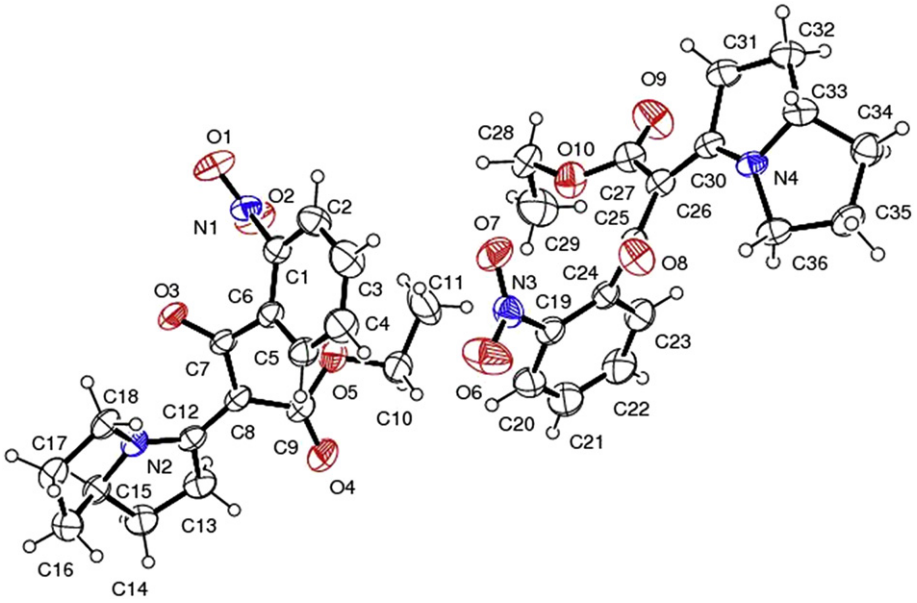
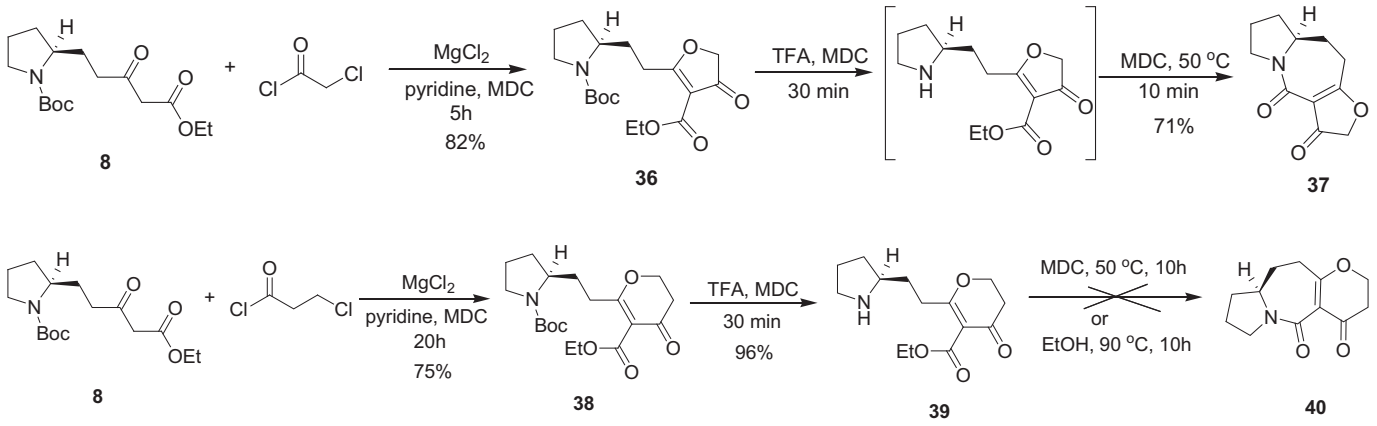


Fig. 3. ORTEP diagram of **28** (CCDC number 880531).



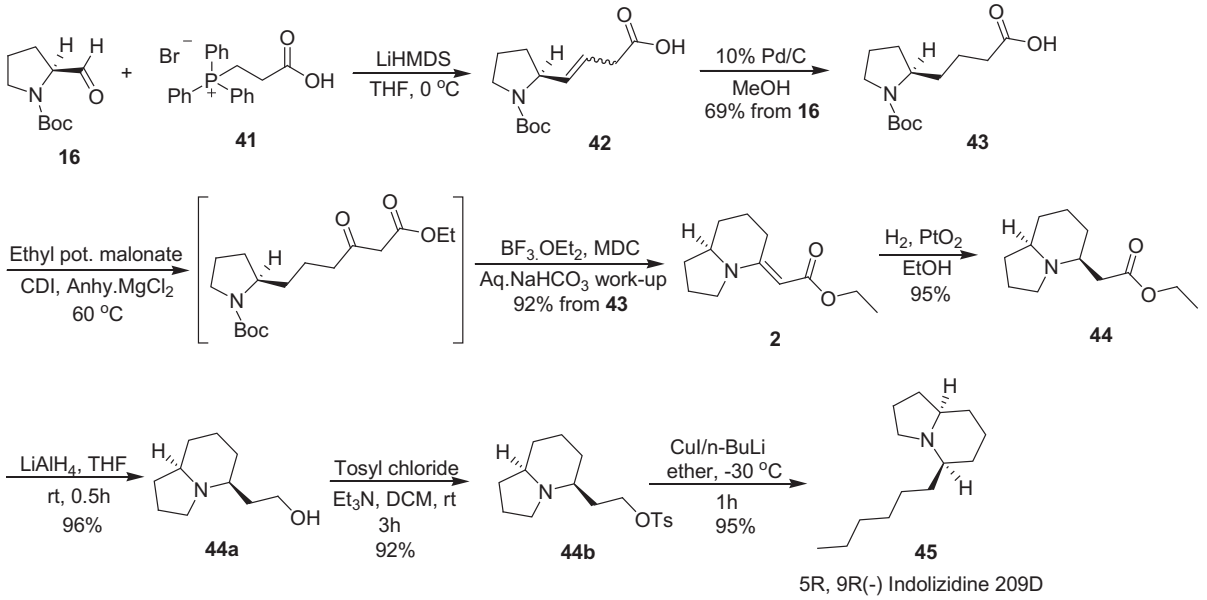
Scheme 9. Synthesis of azepine skeleton from **8**.

To demonstrate the synthetic utility of this approach, we achieved the enantioselective synthesis of (5*R*,9*R*)-(−) indolizidine 209D. (−)Indolizidine 209D acts as a noncompetitive blocker of neuromuscular transmission.[21] Wittig reaction between *N*-Boc-(*S*) prolinal and (2-carboxyethyl)-triphenylphosphonium bromide **41**[22] in the presence of sodium hydride or *t*-BuOK in DMSO at various temperature (between 0 °C and 60 °C) did not yield the product **42**. However in presence of LiHMDS in THF at 0 °C the reaction yielded **42** as a mixture of *E* and *Z* isomers. The mixture of the geometrical isomers was then hydrogenated with Pd/C and H_2 (40 psi) to afford **43** in 69% from **16**. **43** on reaction with 1,1′-carbonyl diimidazole (CDI) in THF afforded the corresponding imidazolide, which on in situ treatment with ethyl potassium malonate and anhydrous $MgCl_2$ yielded the *β*-keto ester. The subsequent deprotective cyclisation by boron trifluouride etherate yielded indolizidine *β*-enamino ester **2** in 92% from **43** (Scheme 10).

This transformation leads to the *E* isomer of **2** alone and the geometry of the double bond has been confirmed by the comparison of the spectral data with those available in the literature.[6] This way of getting **2** seems to be stereoselective as the reported method of preparing **2** leads to a diastereomeric mixture of *E* and *Z* in the ratio 3:1.[6] Diastereoselective hydrogenation of the *β*-enamino ester **2** was achieved by PtO_2/H_2 and the observed optical rotation of **44** ($[\alpha]_D^{25}$ −52.2 (*c* 1.4, CH_2Cl_2)) matched with that available in the litrature.[23] According to the known procedure,[23] the 5-substituted indolizidine **44** was converted into indolizidine alkaloid **45**, (5*R*, 9*R*)-(−) indolizidine 209D, whose physical and spectral data[24] match with the reported one. The observed optical rotation $[\alpha]_D^{25}$ −77.8 (*c* 0.4, CH_2Cl_2) is also in consistent with the previously reported [reported $[\alpha]_D^{25}$ −77.1 (*c* 0.34, CH_2Cl_2),[24b] $[\alpha]_D^{25}$ −89.6 (*c* 1.88, CH_2Cl_2)[24c]].

3. Conclusion

An efficient route to pyrrolizidine and indolizidine based vinylogous urethanes and Knoevenagel type adducts has been accomplished from readily available L-proline. This methodology, an alternative to Eschenmoser reaction, provides the (*E*)-isomer as the sole product. The synthetic utility of this protocol has demonstrated by the stereoselective synthesis of 5*R*, 9*R*-(−)-indolizidine 209D. We have also developed a practical route for the synthesis of naturally occurring pyrrolizidine, indolizidine and azepine skeletons from L-proline.



Scheme 10. Synthesis of 5*R*, 9*R*-(−) indolizidine **209D**.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on 400 or 300 MHz and ^{13}C NMR spectra were recorded on 100 or 75 MHz in DMSO-d_6 or $CDCl_3$ using 300 MHz or 400 MHz spectrometer. Chemical shifts are reported in δ (parts per million) relative to TMS. Electrospray ionization (ESI) mass spectra were obtained on Agilent mass spectrometer. Infrared spectra were recorded on a Shimadzu FT-IR instrument (KBr pellet) and the band positions are reported in reciprocal of centimetres (cm^{-1}). Melting points were determined on a melting point apparatus (Inlab Pvt Ltd, India) equipped with a thermometer and were uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyzer. The single crystal X-ray diffraction was done on a Bruker Axs Kappa Apexll CCD diffractometer, SAIF in Indian Institute of Technology Madras. Silica gel-G plates (Merck) were used for TLC; here UV and/or $KMnO_4$ were used as revealing agents. All reactions were carried out in a nitrogen atmosphere. Solvents and reagents were dried and purified prior to use: tetrahydrofuran and ether (distilled from sodium/benzophenone); dichloromethane (distilled from CaH_2). All the reagents and solvents were purchased from commercial sources and the compounds **11**,[25a] **12**,[25b] **14**,[25c] **15**,[25a] were prepared by literature procedure.

*4.1.1. Synthesis of (S)-tert-butyl 2-((E)-4-(ethoxycarbonyl)-3-oxobut-1-enyl)pyrrolidine-1-carboxylate (**18**) (mixture of keto–enol form).* To a slurry of sodium hydride (0.42 g, 17.4 mmol) (60% dispersion in mineral oil) in dry THF (20 mL) cooled to 5 °C was added phosphonate **17**[14f] (3.1 g, 11.6 mmol) in dry THF (10 mL) dropwise over a period of 1 h under nitrogen atmosphere and stirred for 0.5 h. Then *N*-Boc-(*S*)-prolinal **16** (2.3 g, 11.6 mmol) in dry THF (10 mL) was added dropwise over a period of 0.5 h and stirred at 5 °C for 1 h. The reaction mixture was poured into water (200 mL) and acidified (pH=5) with dil HCl (2% aqueous solution) and extracted with ethyl acetate (2×200 mL). The combined organic layer was washed with water (3×200 mL), brine solution (1×100 mL), dried over anhydrous Na_2SO_4 and concentrated to give **18** (3.45 g, 96%) as yellow oil. R_f (5% MeOH/DCM) 0.52; Keto form: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (3H, t, J=7.1 Hz, CH_3), 1.34 (9H, s, Boc-H), 1.75–1.77 (3H, m, CH_2), 2.05–2.07 (1H, m, CH_2), 3.26–3.29 (2H, m, CH_2), 3.75 (2H, s, CH_2), 4.09 (2H, q, J=7.1 Hz, OCH_2), 4.31–4.33 (1H, m, CH), 5.94–5.97 (1H, m, =CH), 6.82 (1H, dd, J=15.8, 5.9 Hz, =CH). Enol form: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (3H, t, J=7.1 Hz, CH_3), 1.40 (9H, s, Boc-H), 1.77–1.79 (3H, m, CH_2), 2.07–2.09 (1H, m, CH_2), 3.27–3.29 (2H, m, CH_2), 4.18 (2H, q, J=7.1 Hz, OCH_2), 4.39–4.41 (1H, m, CH), 5.25 (1H, s, =CH), 6.20–6.23 (1H, m, =CH), 6.44–6.47 (1H, m, =CH); (one enolic OH proton was not seen in ^{1}H NMR) ESI-m/z calcd for $[C_{16}H_{25}NO_5+H]^+$ 312.2, found 312.1.

*4.1.2. Synthesis of tert-butyl 2-(4-(ethoxycarbonyl)-3-oxobutyl)pyrrolidine-1-carboxylate (**8**) (mixture of enantiomers).* A suspension of **18** (3.3 g, 10.6 mmol) and 10% Pd–C (0.33 g, 10 wt %) in anhydrous ethanol (100 mL) was stirred under hydrogen atmosphere (40 psi) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to give pure **8** (3.3 g, 99%) as colourless oil (58:42 ratio of enantiomers) (enantiomeric purity—see Supplementary data).

*4.1.3. Synthesis of (S)-tert-butyl 2-(4-(ethoxycarbonyl)-3-oxobutyl) pyrrolidine-1-carboxylate (**8**) (single enantiomer).* To a suspension of carbonyl diimidazole (1.5 g, 9.1 mmol) in dry THF (15 mL) was added a solution of **19** (2 g, 8.2 mmol) in dry THF (15 mL) and stirred at room temperature for 2 h. To this reaction mixture, ethyl potassium malonate (0.73 g, 4.3 mmol) and anhydrous $MgCl_2$ (1.5 g, 9.1 mmol) were added. The resulting mixture was stirred at 60 °C for 2 h, poured into water (10 mL) and acidified with 5% aqueous HCl to pH 2–3. The mixture was extracted with dichloromethane (2×20 mL), the combined organic layer was washed water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (5% ethyl acetate/hexanes) to obtain the desired **8** (2.4 g, 92%) as colourless oil (enantiopurity is >99%). [Found: C, 61.37; H, 8.70; N, 4.48. $C_{16}H_{27}NO_5$ requires C, 61.32; H, 8.68; N, 4.47%]; R_f (100% DCM) 0.35; IR (KBr) 2976, 2934, 1744, 1716, 1690, 1478, 1454, 1395, 1367 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (3H, t, J=7.1 Hz, CH_3), 1.39 (9H, s, Boc-H), 1.50–1.55 (2H, m, CH_2), 1.76–1.84 (4H, m, CH_2), 2.48–2.53 (2H, m, CH_2), 3.22–3.24 (2H, m, CH_2), 3.58 (2H, s, CH_2), 3.62–3.65 (1H, m, CH), 4.08 (2H, q, J=7.1 Hz, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 22.6, 23.6, 28.1, 29.3, 30.3, 46.5, 48.8, 56.3, 60.4, 78.2, 153.9, 167.3, 203.1; ESI-m/z calcd for $[C_{16}H_{27}NO_5+H]^+$ 314.2, found 314.1.

*4.1.4. Synthesis of (E)-ethyl 2-((S)-tetrahydro-1H-pyrrolizin-3(6H)-ylidene) acetate (**1**).* A solution of **8** (0.5 g, 1.6 mmol) in dry MDC (20 mL) was cooled to 5 °C and dry HCl gas was purged for 5 min. The resulting mixture was stirred at 5 °C for 30 min, poured into saturated $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (2×60 mL). The combined organic layer was washed with water (3×70 mL), brine solution (1×50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to obtain the desired **1** (0.305 g, 98%) as light-yellow oil. [Found: C, 67.71; H, 8.81; N, 7.73. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%]; R_f (100% DCM) 0.43; $[\alpha]_D^{25}$ −100.8 (*c* 0.5, CH_2Cl_2); IR (KBr) 2931, 2857, 1685, 1598, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz, CH_3), 1.23–1.26 (1H, m, CH_2), 1.51–1.57 (1H, m, CH_2), 2.02–2.12 (1H, m, CH_2), 2.13–2.23 (3H, m, CH_2), 2.96–3.06 (2H, m, CH_2), 3.06–3.16 (1H, m, CH_2), 3.76 (1H, dd, J=17.2, 8.8 Hz, CH_2), 3.85–3.90 (1H, m, CH), 4.08 (2H, q, J=7.1 Hz, OCH_2), 4.44 (1H, s, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 28.5, 29.7, 32.0, 36.2, 44.0, 58.4, 66.2, 78.8, 163.8, 169.5; ESI-m/z calcd for $[C_{11}H_{17}NO_2+H]^+$ 196.1, found 196.1.

*4.1.5. General procedure for the synthesis of Knoevenagel adducts **22**, **24**, **26**–**35**.* To the stirring suspension of anhydrous $MgCl_2$ (1.6 mmol) in dry MDC (20 mL) at 5 °C, **8** (1.6 mmol) was added in dry MDC (5 mL) followed by the addition of pyridine (3.2 mmol) over a period of 20 min. After the mixture was stirred for 30 more min at 5 °C, acid chloride (1.7 mmol) in MDC (2 mL) was added. The resulting mixture was stirred for 15 min at 5 °C and then at room temperature for 5 h. The resulting suspension was acidified (pH=3) with dil HCl (2% solution) and washed with water (2×10 mL). To the organic layer was added TFA (2 mL) and stirred at room temperature for 1 h. The reaction mixture was added into water (150 mL) & ethyl acetate (150 mL) mixture and stirred at room temperature for 30 min. The organic layer was washed with water (3×150 mL), brine solution (1×100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography with MDC/MeOH (99/1) as eluent to give the product.

*4.1.6. (E)-Ethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxobutanoate (**22**).* Colourless oil; [found: C, 65.85; H, 8.09; N, 5.91. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%]; R_f (2% MeOH/DCM) 0.34; IR (KBr) 2973, 2927, 1688, 1633, 1531, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, J=7.2 Hz, CH_3), 1.42–1.44 (1H, m, CH_2), 1.56–1.66 (1H, m, CH_2), 2.06–2.20 (4H, m, CH_2), 2.28 (3H, s, CH_3), 2.70–2.77 (1H, m, CH_2), 2.92–3.01 (1H, m, CH_2), 3.36–3.41 (1H, m, CH_2), 4.09–4.17 (2H, m, CH_2 & CH), 4.18–4.24 (2H, m, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.7, 27.2, 30.7, 30.9, 38.2, 47.8, 59.7, 68.9, 99.99, 166.6, 169.3, 195.4; ESI-m/z calcd for $[C_{13}H_{19}NO_3+H]^+$ 238.1, found 238.1.

*4.1.7. (E)-Ethyl 2-((S)-tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxo-3-phenylpropanoate (**24**).* Colourless semi-solid; [found: C,

72.26; H, 7.09; N, 4.69. $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68%]; R_f (2% MeOH/DCM) 0.43; $[\alpha]_D^{25}$ −63.7 (*c* 0.46, CH_2Cl_2); IR (KBr) 2925, 1683, 1626, 1598, 1578, 1538, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, t, *J*=7.2 Hz, CH_3), 1.43 (1H, td, *J*=10.0, 1.6 Hz, CH_2), 1.63–1.73 (1H, m, CH_2), 2.09–2.19 (2H, m, CH_2), 2.19–2.26 (2H, m, CH_2), 2.58–2.62 (1H, m, CH_2), 2.97–3.06 (1H, m, CH_2), 3.28–3.32 (1H, m, CH_2), 3.78–3.84 (2H, m, OCH_2), 4.12–4.16 (1H, m, CH), 4.29 (1H, ddd, *J*=18.0, 9.6, 1.1 Hz, CH_2), 7.34–7.38 (2H, m, Ar–H), 7.40–7.44 (1H, m, Ar–H), 7.74 (2H, dd, *J*=8.4, 1.4 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 27.5, 27.9, 31.6, 37.9, 47.9, 59.4, 69.5, 97.5, 128.0, 128.3, 131.0, 142.7, 166.1, 169.3, 194.2; ESI-*m*/*z* calcd for $[C_{18}H_{21}NO_3+H]^+$ 300.1, found 300.1.

*4.1.8. (E)-Ethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-(4-nitrophenyl)-3-oxopropanoate (**26**).* Yellow semi-solid; [found: C, 62.82; H, 5.86; N, 8.15. $C_{18}H_{20}N_2O_5$ requires C, 62.78; H, 5.85; N, 8.13%]; R_f (2% MeOH/DCM) 0.37; IR (KBr) 2921, 1687, 1629, 1591, 1584, 1529, 1502 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.70 (3H, t, *J*=7.2 Hz, CH_3), 1.48–1.53 (1H, m, CH_2), 1.68–1.74 (1H, m, CH_2), 2.11–2.30 (4H, m, CH_2), 2.59–2.64 (1H, m, CH_2), 3.00–3.09 (1H, m, CH_2), 3.18–3.22 (1H, m, CH_2), 3.77 (2H, q, *J*=7.2 Hz, OCH_2), 4.16–4.22 (2H, m, CH_2 & CH), 7.82 (2H, d, *J*=8.7 Hz, Ar–H), 8.31 (2H, d, *J*=8.7 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 27.0, 27.5, 31.2, 38.1, 48.1, 59.4, 69.8, 96.8, 123.1, 128.5, 148.6, *167.6, 168.5, 190.8; ESI-*m*/*z* calcd for $[C_{18}H_{20}N_2O_5+H]^+$ 345.1, found 345.1.

*4.1.9. (E)-Ethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-(3-nitrophenyl)-3-oxopropanoate (**27**).* Yellow semi-solid; [found: C, 62.83; H, 5.86; N, 8.14. $C_{18}H_{20}N_2O_5$ requires 62.78; H, 5.85; N, 8.13%]; R_f (2% MeOH/DCM) 0.37; IR (KBr) 2922, 1688, 1628, 1592, 1585, 1524, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (3H, t, *J*=7.2 Hz, CH_3), 1.47–1.52 (1H, m, CH_2), 1.71–1.76 (1H, m, CH_2), 2.15–2.29 (4H, m, CH_2), 2.57–2.61 (1H, m, CH_2), 3.01–3.09 (1H, m, CH_2), 3.32–3.35 (1H, m, CH_2), 3.85 (2H, m, OCH_2), 4.19–4.21 (1H, m, CH), 4.32 (1H, dd, *J*=18.2, 9.4 Hz, CH_2), 7.55 (1H, t, *J*=8.2 Hz, Ar–H), 8.03 (1H, dd, *J*=8.2, 1.3 Hz, Ar–H), 8.27 (1H, dd, *J*=8.2, 1.3 Hz, Ar–H), 8.53 (1H, t, *J*=1.3 Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.5, 26.5, 27.2, 30.6, 37.8, 47.7, 58.6, 69.5, 95.3, 121.8, 125.0, 129.8, 133.8, 144.0, 147.4, 166.8, 167.5, 189.2; ESI-*m*/*z* calcd for $[C_{18}H_{20}N_2O_5+H]^+$ 345.1, found 345.1.

*4.1.10. (E)-Ethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-(2-nitrophenyl)-3-oxopropanoate (**28**).* Yellow solid; mp 107–108 °C; [found: C, 62.82; H, 5.86; N, 8.15. $C_{18}H_{20}N_2O_5$ requires C, 62.78; H, 5.85; N, 8.13%]; R_f (2% MeOH/DCM) 0.37; IR (KBr) 2925, 1689, 1631, 1596, 1588, 1520, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, t, *J*=7.2 Hz, CH_3), 1.51–1.54 (1H, m, CH_2), 1.69–1.79 (1H, m, CH_2), 2.16–2.31 (4H, m, CH_2), 3.08–3.20 (2H, m, CH_2), 3.67–3.81 (3H, m, CH_2 & OCH_2), 4.25–4.33 (2H, m, CH & CH_2), 7.25 (1H, d, *J*=7.8 Hz, Ar–H), 7.43 (1H, t, *J*=7.8 Hz, Ar–H), 7.58 (1H, t, *J*=7.8 Hz, Ar–H), 8.02 (1H, d, *J*=7.8 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 26.5, 27.0, 30.8, 39.3, 48.5, 59.3, 70.0, 97.7, 123.7, 127.6, 128.1, 133.1, 141.4, 146.2, 167.8, 170.1, 187.3; ESI-*m*/*z* calcd for $[C_{18}H_{20}N_2O_5+H]^+$ 345.1, found 345.1.

*4.1.11. (E)-Ethyl 3-(4-formylphenyl)-2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxopropanoate (**29**).* Pale-yellow sticky; [found: C, 69.75; H, 6.49; N, 4.29. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28%]; R_f (2% MeOH/DCM) 0.39; IR (KBr) 2925, 1705, 1686, 1621, 1595, 1572, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, t, *J*=7.0 Hz, CH_3), 1.43–1.50 (1H, m, CH_2), 1.69–1.75 (1H, m, CH_2), 2.15–2.29 (4H, m, CH_2), 2.59–2.66 (1H, m, CH_2), 3.01–3.06 (1H, m, CH_2), 3.35–3.38 (1H, m, CH_2), 3.76–3.86 (2H, m, OCH_2), 4.18–4.24 (1H, m, CH), 4.30 (1H, dd, *J*=18.3, 9.2 Hz, CH_2), 7.83 (2H, d, *J*=8.2 Hz, Ar–H), 7.88 (2H, d, *J*=8.2 Hz, Ar–H), 10.06 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 27.3, 27.8, 31.6, 38.2, 48.3, 59.6, 69.9, 97.2, 128.5, 129.6, 137.5, 148.4, 167.5, 169.0, 192.2, 192.5; ESI-*m*/*z* calcd for $[C_{19}H_{21}NO_4+H]^+$ 328.1, found 328.1.

*4.1.12. (E)-Ethyl 3-(4-(trifluoromethyl)phenyl)-2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxopropanoate (**30**).* Pale-yellow semi-solid; [found: C, 62.16; H, 5.50; N, 3.82. $C_{19}H_{20}F_3NO_3$ requires C, 62.12; H, 5.49; N, 3.81%]; R_f (2% MeOH/DCM) 0.41; IR (KBr) 2929, 1681, 1623, 1599, 1575, 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, t, *J*=7.1 Hz, CH_3), 1.45–1.50 (1H, m, CH_2), 1.69–1.77 (1H, m, CH_2), 2.14–2.29 (4H, m, CH_2), 2.56–2.63 (1H, m, CH_2), 2.99–3.08 (1H, m, CH_2), 3.33–3.36 (1H, m, CH_2), 3.81 (2H, q, *J*=7.1 Hz, OCH_2), 4.17–4.19 (1H, m, CH), 4.31 (1H, dd, *J*=18.1, 9.6 Hz, CH_2), 7.62 (2H, d, *J*=8.0 Hz, Ar–H), 7.80 (2H, d, *J*=8.0 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 27.3, 27.8, 31.6, 38.1, 48.2, 59.6, 69.8, 97.0, 125.0, 125.5, 128.3, 132.2, 146.2, 167.2, 169.0, 192.3; ESI-*m*/*z* calcd for $[C_{19}H_{20}F_3NO_3+H]^+$ 368.1, found 368.1.

*4.1.13. (E)-Ethyl 3-(3-chlorophenyl)-3-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxopropanoate (**31**).* Colourless semi-solid; [found: C, 64.81; H, 6.05; N, 4.21. $C_{18}H_{20}ClNO_3$ requires C, 64.77; H, 6.04; N, 4.20%]; R_f (2% MeOH/DCM) 0.42; IR (KBr) 2927, 1686, 1621, 1594, 1571, 1536, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, t, *J*=7.2 Hz, CH_3), 1.40–1.49 (1H, m, CH_2), 1.64–1.75 (1H, m, CH_2), 2.12–2.25 (4H, m, CH_2), 2.55–2.62 (1H, m, CH_2), 2.97–3.07 (1H, m, CH_2), 3.28–3.34 (1H, m, CH_2), 3.78–3.93 (2H, m, OCH_2), 4.11–4.20 (1H, m, CH), 4.28 (1H, dd, *J*=18.0, 9.5 Hz, CH_2), 7.30 (1H, t, *J*=7.8 Hz, Ar–H), 7.38–7.41 (1H, m, Ar–H), 7.59–7.62 (1H, m, Ar–H), 7.71 (1H, t, *J*=1.7 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 27.4, 27.9, 31.6, 38.1, 48.1, 59.5, 69.7, 96.8, 126.3, 128.3, 129.3, 130.8, 134.1, 144.6, 166.8, 168.9, 192.3; ESI-*m*/*z* calcd for $[C_{18}H_{20}ClNO_3+H]^+$ 334.1, found 334.1.

*4.1.14. (E)-Ethyl 3-(2-chlorophenyl)-3-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxopropanoate (**32**).* White solid; mp 81–82 °C; [found: C, 64.82; H, 6.06; N, 4.21. $C_{18}H_{20}ClNO_3$ requires C, 64.77; H, 6.04; N, 4.20%]; R_f (2% MeOH/DCM) 0.41; IR (KBr) 2929, 1687, 1623, 1591, 1573, 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, t, *J*=7.2 Hz, CH_3), 1.50–1.55 (1H, m, CH_2), 1.71–1.76 (1H, m, CH_2), 2.16–2.29 (4H, m, CH_2), 2.87–2.90 (1H, m, CH_2), 3.03–3.07 (1H, m, CH_2), 3.53–3.57 (1H, m, CH_2), 3.77 (2H, q, *J*=7.2 Hz, OCH_2), 4.20–4.24 (1H, M, CH), 4.34 (1H, dd, *J*=18.4, 8.7 Hz, CH_2), 7.22–7.25 (2H, m, Ar–H), 7.31–7.38 (2H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 26.7, 27.2, 31.1, 38.4, 48.3, 59.4, 69.8, 99.4, 126.1, 128.3, 129.2, 129.4, 130.7, 143.5, 168.5, 168.6, 189.6; ESI-*m*/*z* calcd for $[C_{18}H_{20}ClNO_3+H]^+$ 334.1, found 334.1. HRMS calculated for $C_{18}H_{21}ClNO_3$ (M^++Na) 356.1029, found 356.1042.

*4.1.15. (E)-Ethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxo-m-tolylpropanoate (**33**).* Yellow semi-solid; [found: C, 72.87; H, 7.42; N, 4.48. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%]; R_f (2% MeOH/DCM) 0.45; $[\alpha]_D^{25}$ −11.9 (*c* 0.4, CH_2Cl_2); IR (KBr) 2931, 1690, 1627, 1594, 1570, 1531, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, t, *J*=7.2 Hz, CH_3), 1.40–1.45 (1H, m, CH_2), 1.65–1.73 (1H, m, CH_2), 2.08–2.15 (3H, m, CH_2), 2.17–2.26 (1H, m, CH_2), 2.37 (3H, s, CH_3), 2.59–2.62 (1H, m, CH_2), 2.97–3.06 (1H, m, CH_2), 3.28–3.31 (1H, m, CH_2), 3.76–3.90 (2H, m, OCH_2), 4.12–4.15 (1H, m, CH), 4.26 (1H, dd, *J*=18.3, 8.7 Hz, CH_2), 7.24–7.27 (2H, m, Ar–H), 7.55 (1H, m, Ar–H), 7.58 (1H, s, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 21.4, 27.7, 28.0, 31.6, 37.8, 47.9, 59.3, 69.4, 97.2, 125.7, 127.9, 128.9, 131.8, 137.7, 142.6, 165.8, 169.3, 194.4; ESI-*m*/*z* calcd for $[C_{19}H_{23}NO_3+H]^+$ 314.1, found 314.1.

*4.1.16. (E)-Ethyl 3-(furan-2-yl)-2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene)-3-oxopropanoate (**34**).* Brown solid; mp 74–75 °C; [found: C, 66.47; H, 6.64; N, 4.85. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%]; R_f (2% MeOH/DCM) 0.40; IR (KBr) 2919, 1685, 1624, 1598, 1574, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J*=7.1 Hz, CH_3), 1.38–1.43 (1H, m, CH_2), 1.62–1.68 (1H, m, CH_2), 2.08–2.21

(4H, m, CH_2), 2.63–2.66 (1H, m, CH_2), 2.96–3.01 (1H, m, CH_2), 3.31–3.34 (1H, m, CH_2), 3.94–4.07 (2H, m, OCH_2), 4.08–4.14 (1H, m, CH), 4.23 (1H, dd, J=17.9, 9.3 Hz, CH_2), 6.46 (1H, dd, J=3.4, 0.6 Hz, Ar–H), 6.98 (1H, d, J=3.4 Hz, Ar–H), 7.46 (1H, d, J=0.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.3, 27.7, 31.3, 37.5, 47.7, 59.4, 69.3, 96.2, 111.7, 114.7, 144.2, 155.6, 165.1, 168.7, 180.8; ESI-m/z calcd for $[C_{16}H_{19}NO_4+H]^+$ 290.1, found 290.1.

*4.1.17. Diethyl 2-(tetrahydro-1H-pyrrolizin-3(6H)-ylidene) malonate (**35**).* Colourless oil; [found: C, 62.94; H, 7.94; N, 5.25. $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24%]; R_f (2% MeOH/DCM) 0.33; IR (KBr) 2929, 1675, 1631, 1585, 1571, 1555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, t, J=7.1 Hz, CH_3), 1.2–1.38 (1H, m, CH_2), 1.54–1.60 (1H, m, CH_2), 2.02–2.19 (4H, m, CH_2), 2.91–3.02 (2H, m, CH_2), 3.33 (1H, td, J=11.4, 3.0 Hz, CH_2), 3.95–4.02 (2H, m, CH & CH_2), 4.12–4.24 (4H, m, OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 27.6, 28.1, 31.3, 37.7, 46.3, 59.9, 68.7, 90.1, 163.5, 168.2; ESI-m/z calcd for $[C_{14}H_{21}NO_4+H]^+$ 268.1, found 268.1.

*4.1.18. General procedure for the synthesis **36**, **37**, **38** and **39**.* To the stirring suspension of anhydrous $MgCl_2$ (1.6 mmol) in dry MDC (20 mL) at 5 °C, **8** (1.6 mmol) was added in dry MDC (5 mL) followed by the addition of pyridine (3.2 mmol) over a period of 20 min. After the mixture was stirred for 30 more min at 5 °C, chloroacetyl chloride or 3-chloropropionyl chloride (1.7 mmol) in MDC (2 mL) was added. The resulting mixture was stirred for 15 min at 5 °C and then at room temperature for 5–20 h. The resulting suspension was acidified (pH=3) with dil HCl (2% solution) and washed with water (2×10 mL) and concentrated in vacuo. The crude product was purified by column chromatography using MDC/MeOH as eluent to give pure **36** or **38**. To the Boc compound **36** or **38** in MDC (10 mL) was added TFA (2 mL) and the obtained solution stirred at room temperature for 1 h. The reaction mixture was added into water and basified (pH=9) with aqueous $NaHCO_3$. The resulting mixture was extracted with DCM (2×150 mL), the combined organic layer was washed with water (2×100 mL), brine solution (1×100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo at 50 °C. The residue was purified by column chromatography with MDC/MeOH (99/1) as eluent to give **37** or **39**.

*4.1.19. (S)-tert-Butyl 2-(2-(3-(ethoxycarbonyl)-4,5-dihydro-4-oxofuran-2-yl)ethyl)pyrrolidine-1-carboxylate (**36**).* Colourless sticky; [found: C, 61.22; H, 7.72; N, 3.97. $C_{18}H_{27}NO_6$ requires C, 61.17; H, 7.70; N, 3.96%]; R_f (2% MeOH/DCM) 0.28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (3H, t, J=7.0 Hz, CH_3), 1.38 (9H, s, Boc-H), 1.69–1.78 (4H, m, CH_2), 1.94 (2H, br, CH_2), 2.94 (1H, br, CH_2), 3.21–3.28 (3H, m, CH_2), 3.73 (1H, br, CH), 4.17 (2H, q, J=7.0 Hz, OCH_2), 4.78 (2H, s, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 22.6, 28.1, 29.8, 29.9, 30.5, 46.3, 56.2, 59.6, 76.0, 78.3, 108.1, 153.5, 161.7, 195.7, 200.0; ESI-m/z calcd for $[C_{18}H_{27}NO_6+H]^+$ 354.2, found 354.1.

*4.1.20. (8aS)-6,7,8,8a,9,10-Hexahydro-4H-furo[2,3-e]pyrrolo[1,2-a]azepine-3,4(2H)-dione (**37**).* White solid; mp 147–149 °C; [found: C, 63.81; H, 6.34; N, 6.78. $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76%]; R_f (5% MeOH/DCM) 0.21; IR (KBr) 1729, 1658, 1563, 1472, 1353, 1329, 1300 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41–1.53 (1H, m, CH_2), 1.62–1.73 (1H, m, CH_2), 2.08–2.27 (4H, m, CH_2), 2.98–3.08 (1H, m, CH_2), 3.47 (1H, br, CH_2), 4.11 (2H, br, CH & CH_2), 4.32 (3H, br, OCH_2 & CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.4, 27.2, 29.7, 37.8, 49.0, 70.5, 70.8, 87.3, 167.2, 173.0, 192.0; ESI-m/z calcd for $[C_{11}H_{13}NO_3+H]^+$ 208.1, found 208.1.

*4.1.21. (S)-tert-Butyl 2-(2-(3-(ethoxycarbonyl)-5,6-dihydro-4-oxo-4H-pyran-2-yl)ethyl)pyrrolidine-1-carboxylate (**38**).* Colourless sticky; [found: C, 62.16; H, 7.98; N, 3.82. $C_{19}H_{29}NO_6$ requires C, 62.11; H, 7.96; N, 3.81%]; R_f (2% MeOH/DCM) 0.29; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (3H, t, J=6.7 Hz, CH_3), 1.35 (9H, s, Boc-H), 1.58 (2H, br, CH_2), 1.76 (2H, br, CH_2), 1.88 (2H, br, CH_2), 2.33 (2H, br, CH_2), 2.53 (2H, br, $COCH_2$), 3.19–3.24 (2H, m, CH_2), 3.67 (1H, br, CH), 4.14 (2H, q, J=6.7 Hz, OCH_2), 4.51 (2H, t, J=6.3 Hz, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 22.5, 23.4, 28.1, 29.3, 30.0, 34.9, 46.0, 46.2, 56.2, 60.6, 67.9, 78.5, 112.6, 165.2, 176.9, 187.7; ESI-m/z calcd for $[C_{19}H_{29}NO_6+H]^+$ 368.2, found 368.1.

*4.1.22. Ethyl 5,6-dihydro-4-oxo-2-(2-((S)-pyrrolidin-2-yl)ethyl)-4H-pyran-3-carboxylate (**39**).* Colourless sticky; [found: C, 62.95; H, 7.94; N, 5.25. $C_{14}H_{21}NO_4$ C, 62.90; H, 7.92; N, 5.24%]; R_f (10% MeOH/DCM) 0.19; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (3H, t, J=7.1 Hz, CH_3), 1.30–1.40 (1H, m, CH_2), 1.50–1.60 (1H, m, CH_2), 1.98–2.50 (4H, m, CH_2), 2.59–2.72 (3H, m, $COCH_2$ & CH_2), 2.80–2.89 (1H, m, CH_2), 3.10–3.14 (1H, m, CH_2), 3.58–3.64 (2H, m, OCH_2), 3.92 (1H, dd, J=17.5, 9.2 Hz, CH_2), 4.02–4.11 (3H, m, OCH_2 & CH), 4.36 (1H, br, D_2O exchangeable, NH); ^{13}H NMR (100 MHz, DMSO-d_6) δ 14.2, 26.4, 27.0, 30.3, 37.8, 45.5, 47.3, 58.2, 59.1, 68.6, 99.1, 165.1, 168.4, 195.2; ESI-m/z calcd for $[C_{14}H_{21}NO_4+H]^+$ 268.1, found 268.1.

*4.1.23. Synthesis of 4-((R)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl) butanoic acid (**43**).* To a suspension of (2-carboxyethyl)triphenylphosphonium bromide **41** (18.8 g, 45 mmol) in dry THF (120 mL) at −10 °C, under nitrogen atmosphere, was added LiHMDS (12.5 g, 75 mmol). The mixture was stirred for 45 min, and a solution of *N*-Boc-*S*-prolinal **16** (3 g, 15 mmol) in dry THF (50 mL) was added over a period of 30 min. The resulting mixture was stirred at 0 °C for 1 h and then quenched by the addition of 5% aqueous HCl. To the resultant mixture, ethyl acetate (300 mL) was added, the organic layer was separated and washed with saturated $NaHCO_3$ solution (2×150 mL). The combined washings were acidified (pH=2) with dil HCl (5% aqueous solution) and extracted with ethyl acetate (2×200 mL). The organic layer was washed with water (1×150 mL), brine solution (1×100 mL), dried over anhydrous Na_2SO_4 and concentrated to give crude **42** (3.1 g) as yellow oil. Crude **42** (3 g, 12 mmol) in ethanol (150 mL) was stirred at room temperature with 10% Pd–C (0.3 g) in hydrogen atmosphere (40 psi) for 2 h. The catalyst was filtered off, washed with ethanol (20 mL) and the combined filtrate and washing was concentrated. The residue was purified by column chromatography (1% MeOH/DCM) to yield **43** (2.7 g, 69% from **16**) as a colourless sticky product. [Found: C, 60.72; H, 9.03; N, 5.45. $C_{13}H_{23}NO_4$ C, 60.68; H, 9.01; N, 5.44%]; R_f (2% MeOH/DCM) 0.29; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12–1.15 (1H, m, CH_2), 1.38 (9H, s, Boc-H), 1.43–1.53 (2H, m, CH_2), 1.54–1.68 (2H, m, CH_2), 1.70–1.85 (3H, m, CH_2), 2.21 (2H, t, J=7.2 Hz, CH_2), 3.17–3.32 (2H, m, CH_2), 3.62 (1H, m, CH), 12.01 (1H, s, D_2O exchangeable, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.8, 22.7, 28.2, 30.2, 30.5, 35.3, 46.6, 56.4, 78.1, 153.8, 176.8; ESI-m/z calcd for $[C_{13}H_{23}NO_4-H]^+$ 256.1, found 256.1.

*4.1.24. Synthesis of (E)-ethyl 2-((R)-hexahydroindolizin-5(1H)-ylidene) acetate (**2**).*[6] To a suspension of carbonyl diimidazole (0.69 g, 4.3 mmol) in dry THF (5 mL) was added a solution of **43** (1 g, 3.9 mmol) in dry THF (5 mL) and stirred at room temperature for 2 h. To this reaction mixture, ethyl potassium malonate (0.73 g, 4.3 mmol) and anhydrous $MgCl_2$ (0.41 g, 4.3 mmol) were added. The resulting mixture was stirred at 60 °C for 2 h, poured into water (10 mL) and acidified with 5% aqueous HCl to pH 2–3. The mixture was extracted with dichloromethane (2×20 mL), the combined organic layer was washed water, dried over anhydrous Na_2SO_4 and then cooled to 5 °C, and $BF_3{\cdot}OEt_2$ (1.5 mL, 11.7 mmol) was added, stirred for 1 h. The mixture was then poured into saturated $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (2×60 mL). The combined organic layer was washed with water (3×60 mL), brine solution (1×60 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography with hexane/ethyl acetate (90/10) as eluent to obtain the desired **2** (0.75 g, 92%) as light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25

(3H, t, J=7.1 Hz, CH_3), 1.28–1.31 (1H, m, CH_2), 1.36–1.43 (1H, m, CH_2), 1.51–1.62 (1H, m, CH_2), 1.79–1.91 (2H, m, CH_2), 1.98–2.10 (3H, m, CH_2), 2.92 (1H, ddd, J=14.7, 10.9, 7.1 Hz, CH_2), 3.22–3.29 (4H, m, CH & CH_2), 4.09 (2H, q, J=7.2 Hz, OCH_2), 4.37 (1H, br, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 20.2, 22.7, 26.1, 29.3, 33.3, 47.9, 58.1, 59.1, 81.2, 160.8, 169.1. ESI-m/z calcd for $[C_{12}H_{19}NO_2+H]^+$ 210.1, found 210.1. This could be the E form as assigned earlier,[6] though there are small variation in the ^{1}H NMR data.

*4.1.25. Synthesis of ethyl 2-((5S, 8aR)-octahydroindolizin-5-yl)acetate (**44**).*[6] A mixture of **2** (1 g, 4.8 mmol) and PtO_2 (0.1 g) in anhydrous ethanol (100 mL) was stirred under hydrogen atmosphere (70 psi) at room temperature for 4 h. The catalyst was filtered off, the filtrate was concentrated to give pure **44** (0.95 g, 95%) as a light-yellow oil. $[\alpha]_D^{25}$ −52.2 (c 1.4, CH_2Cl_2) [reported $[\alpha]_D^{25}$ −51.3 (c 1.34, CH_2Cl_2)[23]]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24–1.26 (1H, m, CH_2), 1.28 (3H, t, J=7.2 Hz, CH_3), 1.30–1.32 (2H, m, CH_2), 1.40–1.47 (1H, m, CH_2), 1.66–1.93 (7H, m, CH_2), 2.06–2.08 (1H, m, CH_2), 2.29 (1H, m, CH_2), 2.48 (1H, m, CH_2), 2.70 (1H, dd, J=14.8, 4.9 Hz, CH_2), 3.15 (1H, td, J=7.8, 2.1 Hz, CH_2), 4.14 (2H, q, J=7.2 Hz, OCH_2); ESI-m/z calcd for $[C_{12}H_{21}NO_2+H]^+$ 212.2, found 212.1.

*4.1.26. Synthesis of 2-((5S,8aR)-octahydroindolizin-5-yl)ethanol (**44a**).* The title compound was prepared according to the known literature procedure.[23] Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06–1.10 (2H, m, CH_2), 1.18–1.24 (2H, m, CH_2), 1.40–1.42 (1H, m, CH_2), 1.54–1.62 (3H, m, CH_2), 1.67–1.78 (5H, m, CH_2), 1.86–1.89 (1H, m, CH_2), 1.97–1.99 (1H, m, CH), 3.08–3.11 (1H, m, CH), 3.33–3.46 (2H, m, CH_2), 4.35 (1H, br, D_2O exchangeable, OH).

*4.1.27. Synthesis of 2-((5S,8aR)-octahydroindolizin-5-yl)ethyl 4-methylbenzenesulfonate (**44b**).* The title compound was prepared according to the known literature procedure.[23] Light-yellow sticky. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.01 (2H, m, CH_2), 1.05–1.12 (1H, m, CH_2), 1.12–1.24 (1H, m, CH_2), 1.39–1.42 (1H, m, CH_2), 1.50–1.85 (8H, m, CH_2), 1.88–1.91 (2H, m, CH_2 & CH), 2.42 (3H, s, CH_3), 2.89–2.91 (1H, m, CH), 4.05–4.09 (2H, t, CH_2), 7.49 (2H, d, J=8.2 Hz, Ar–H), 7.79 (2H, d, J=8.2 Hz, Ar–H).

*4.1.28. Physical and spectroscopic data for (5R, 8aR)-5-hexyl-octahydroindolizine (**45**).*[24] The title compound was prepared according to the known literature procedure.[23] yellow oil; $[\alpha]_D^{25}$ −77.8 (c 0.4, CH_2Cl_2) [reported $[\alpha]_D^{25}$ −77.1 (c 0.34, CH_2Cl_2),[24b] $[\alpha]_D^{25}$ −89.6 (c 1.88, CH_2Cl_2)[24c]]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (3H, t, J=7.1 Hz, CH_3), 1.00–1.07 (2H, m, CH_2), 1.13–1.24 (11H, m, CH_2), 1.50–1.61 (4H, m, CH_2), 1.68–1.78 (3H, m, CH_2), 1.85 (3H, t, J=8.5 Hz, CH_2), 3.08 (1H, td, J=8.2, 2.8 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.6, 22.8, 24.9, 26.03, 29.9, 30.7, 31.05, 31.2, 32.04, 34.8, 51.7, 64.1, 65.2; ESI-m/z calcd for $[C_{14}H_{27}N+H]^+$ 210.2, found 210.1.

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Supplementary data

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