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Tetrahedron 61 (2005) 8226–8230
Tetrahedron

Annulation of pyrrole: application to the synthesis of indolizidine alkaloids

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Received 3 March 2005; revised 31 May 2005; accepted 9 June 2005

Available online 29 June 2005

Abstract—The nucleophilicity of pyrrole has been exploited to rapidly assemble the bicyclic skeleton of the indolizidine alkaloids. The key sequence is the annulation of a second ring onto pyrrole from a γ-lactone and has been exploited in the synthesis of the natural products (±)-monomorine and (±)-indolizidine 209D.

1. Introduction

Indolizidine alkaloids such as those derived from amphibians and ants have proved popular targets for total synthesis for both conformation of structure and investigation of the potent biological activity that many of these possess.[1] They have also been exploited to highlight new synthetic methods.[1] Many of the alkaloids isolated possess alkyl substituents around the bicyclic core such as the 5-alkyl substituted derivative assigned as indolizidine 209D[2] and the Pharaoh's ant trail pheromone (+)-monomorine,[3] which is a 3,5-dialkyl indolizidine (Fig. 1).

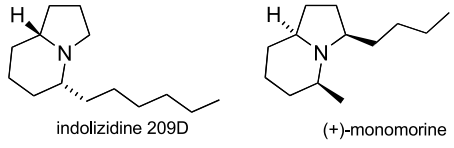
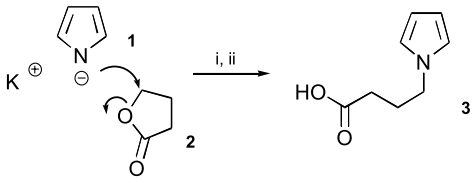


Figure 1.

The synthesis of bicyclic alkaloids from pyrrole derivatives has been reported to be an effective method for the synthesis of indolizidine alkaloids.[4] The pyrrole unit provides a template not only to form a second ring but also to reveal the saturated heterocycle by hydrogenation. One of the most efficient methods for the formation of the indolizidine skeleton was reported by Jefford[5] and Taylor,[6] who have shown that the activation of the carboxylate group of a γ-pyrrolic ester with boron tribromide promoted cyclisation onto the nucleophilic pyrrole ring. By developing a short synthesis of the appropriately substituted γ-pyrrolic esters, a rapid synthesis of the indolizidine skeleton of targeted alkaloids could be developed (Scheme 1).



Scheme 1. Reagents: (i) 160 °C; (ii) H_3O^+(90%).

Recently, the unusual S_N2 type ring opening of γ-butyrolactone (**2**) with the potassium salt of pyrrole (**1**), as reported by Li and Snyder,[7] has been exploited on a multi-gram scale to give the γ-pyrrolic acid **3** as a key intermediate in the synthesis of the naturally occurring alkaloid rhazinal, which posseses anti-mitotic properties.[8] Therefore, we set about investigating the extension of the lactone ring opening to substituted γ-pyrrolic acid derivatives, particularly those bearing a substituent at the γ-position of the lactone. This could be exploited to introduce a substituent at C-5 of an indolizidine simply by the choice of lactone. The reaction of substituted lactones has not been reported and it would be expected that the size of the substituent at the γ-position may inhibit the reaction if the process is truly an S_N2 type substitution. Subsequent conversion of the γ-pyrrolic acids to an ester, and Lewis acid mediated intramolecular acylation onto the nucleophilic pyrrole would yield the bicyclic structure. The availability and low cost of numerous substituted lactones that could be used to target indolizidine alkaloids warranted investigation into a rapid synthesis of these natural products via γ-pyrrolic esters.

Keywords: Pyrrole; Indolizidines; Alkaloids; γ-Lactones.
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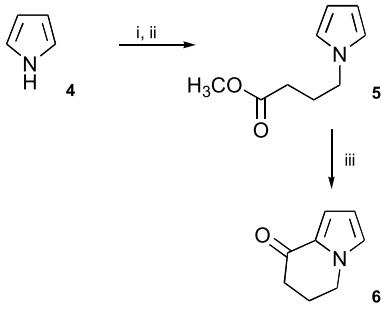
doi:10.1016/j.tet.2005.06.026

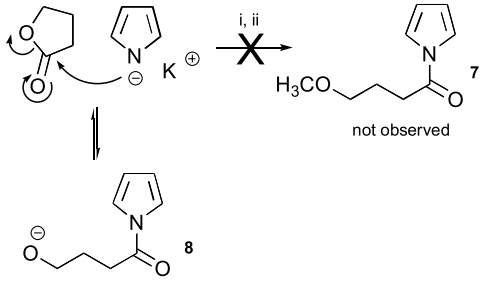
2. Results and discussion

Initial studies were carried out on the ring opening of γ-butyrolactone to form the unsubstituted indolizidine **6**. While the original reaction was carried out under solventless conditions, we investigated the use of a solvent to facilitate the formation of the desired ester directly from the crude reaction mixture. We found that reaction of the potassium salt of pyrrole with γ-butyrolactone at 160 °C in DMF affected the desired ring opening and addition of methyl iodide to the cooled mixture alkylated the intermediate carboxylate salt (Scheme 2).



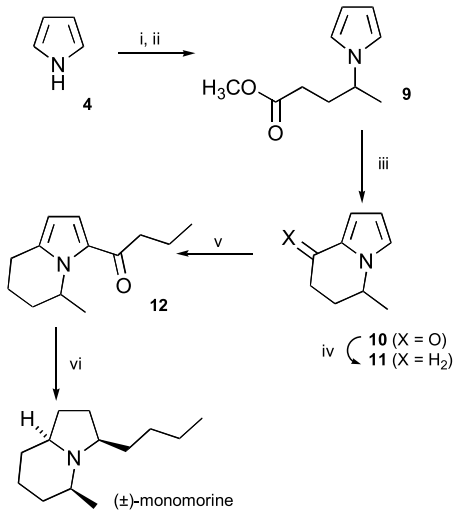
Scheme 2. Reagents: (i) KH, DMF, 0 °C then γ-butyrolactone, 160 °C, 4 h; (ii) CH_3I (excess) 18 °C (61%); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (91%).

It was interesting to note that no acyl pyrrole **7** was observed on the treatment of the reaction mixture with methyl iodide as might have been expected by trapping the, presumably kinetically favoured, acyl nucleophilic ring opened product (**8**) of the lactone. (Scheme 3) This indicates that the equilibrium favours the starting materials and results in the thermodynamically favoured γ-pyrrolic ester as the only observed product. This gave the methyl ester **5** in 61% yield in one step, making it a viable method for the synthesis of this type of compound. The γ-pyrrolic ester was then cyclised by treatment with boron tribromide[5] to yield the indolizidine **6** as indicated by desymmetrisation of the pyrrole ring in the ^1H NMR spectrum and a shift of the carbonyl stretch in the IR spectrum to 1651 cm^{-1}. Therefore, in two short steps we have achieved the annulation of pyrrole to form the indolizidine skeleton in 56% overall yield. As a result, we then investigated the application of this reaction to substituted lactones.



Scheme 3. Reagents: (i) DMF, 160 °C, 4 h; (ii) CH_3I (excess) 18 °C.

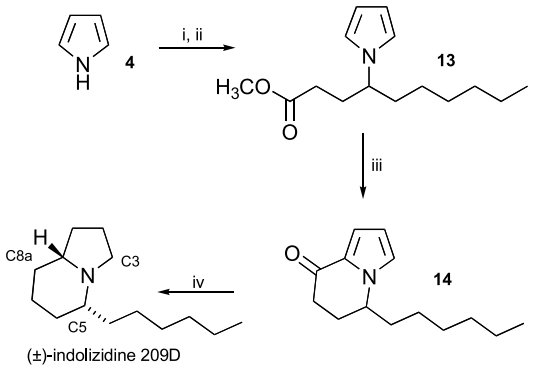
The reaction of the potassium salt of pyrrole with (±)-γ-valerolactone, which bears a methyl substituent at C-5 of the lactone, under the reaction conditions reported above yielded the γ-pyrrolic ester **9**[9] in low yield. Not surprisingly, the extra bulk at the γ-position of the lactone hindered the reaction and reduced the yield dramatically giving support for the S_N2 mechanism. To overcome this, the reaction was repeated under the conditions of Li and Snyder[7] to give the intermediate acid, which was then converted directly to the ester **9** in 48% over two steps. Clearly the substituted lactones require more forcing conditions but the γ-pyrrolic esters can be formed in reasonable yields and this has been carried out on a multi-gram scale. Cyclisation of the ester **9** gave the 5-substituted indolizidine **10** as expected in high yield (Scheme 4).



Scheme 4. Reagents: (i) KH, 0 °C; and then γ-valerolactone, 160 °C, 4 h (60%); (ii) K_2CO_3, DMF, CH_3I (excess) 18 °C (80%); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (90%); (iv) $NaBH_3CN$, ZnI_2, CH_2Cl_2, 45 °C (73%); (v) butyryl chloride, AgOTf, CH_2Cl_2, 0 °C (20%); (vi) Ref. 9: Pd/C, H_2 (55 psi), CH_3OH, catalytic H_2SO_4.

To exploit this method for the synthesis of natural products, we targeted the Pharaoh's ant pheromone monomorine that bears a methyl substituent at C-5. To achieve this synthesis, the carbonyl group adjacent to the pyrrole was removed by reduction with $ZnI_2/NaBH_3CN$[10] to activate C-3 of the indolizidine (**11**) to introduce a butyl substituent. Initially, we investigated Vilsmeier–Haack formylation and Wittig olefination to introduce the butyl chain required, however, formylation was low yielding and not regioselective occurring equally at C-2 and C-3. This was surprising as we expected formylation to occur exclusively at C-3 based upon a similar reaction for the synthesis of rhazinal,[8] consequently the methyl group at C-5 must hinder attack at this position. Surprisingly, the activation of an acid chloride, butyryl chloride, by typical Lewis acids such as $AlCl_3$ and $ZnCl_2$ proved unsuccessful. However, the use of silver triflate promoted the reaction to give the desired acylated product **12** in 20% yield (40% based upon starting material consumed). The selective acylation at C-3 of the indolizidine was indicated by the coupling constant of 4.2 Hz for the two protons of the pyrrole moiety. The ketone **12** has previously been hydrogenated stereoselectively by Muchowski[9] to yield monomorine. Thus, in five short steps we have accomplished the formal synthesis of this 3,5-dialkyl indolizidine (Scheme 5).

We then investigated the formation of the 5-hexyl



Scheme 5. Reagents: (i) KH, 0 °C; and then γ-decanolactone, 160 °C, 4 h; (ii) K_2CO_3, DMF, CH_3I (excess) 18 °C (30% over two steps); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (90%); (iv) Pd/C, H_2 (40 psi) CH_3CO_2H (90%).

substituted derivative 209D from the commercially available (±)-γ-decanolactone. The yield for the formation of the ester **13** in this instance was reduced further to 30% over two steps. The cause is most likely attributed to the increasing bulk of the C-4 substituent on the lactone therefore suggesting a limit to the size of the substituent at this position. Cyclisation of the ester **13** proceeded in high yield to give the 5-hexyl indolizidine **14**, which was then hydrogenated with palladium on carbon,[11] with high diastereoselectively, to yield (±)-indolizidine 209D. The assignment was confirmed by comparison of the ^{13}C NMR spectrum with that of both possible diastereomers.[12] (Table 1). In particular, the resonances of the three carbon atoms attached to nitrogen, (C3, C5 and C8a) resonating at 50.7, 63.9 and 65.4 ppm, respectively, are diagnostic for the formation of the desired diastereomer. The chemical shifts of these carbon atoms in the other possible isomer are 48.8, 55.1 and 55.5 ppm, respectively.[12b] Therefore, the racemic alkaloid was formed in 24% yield over four steps from commercial starting materials. The low yield of the lactone ring opening is offset by low cost of the reagents and the fact that the reaction can be carried out on a significant scale to enable the total synthesis of the targeted alkaloids in a few short steps. One downfall is that enantio-pure lactones are extremely expensive therefore limiting the method to the formation of racemic products at the present time. We are currently engaged in overcoming this problem to develop an asymmetric synthesis of γ-pyrrolic esters.

Table 1. ^{13}C NMR comparison of synthetic (±)-indolizidine 209D[a]

Smith et al.	Polniaszek et al.[12b]
65.4	65.1
63.9	63.9
50.7	51.6
33.8	34.7
31.8	31.9
30.0	31.1
29.8	30.9
29.7	30.6
29.5	29.8
25.9	25.9
24.3	24.8
22.6	22.7
20.2	20.5
14.1	14.2

[a] ^{13}C NMR δ (75 MHz, $CDCl_3$).

3. Conclusions

In conclusion, we have performed a rapid annulation of lactones onto pyrrole to yield 5-substituted indolizidines via γ-pyrrolic esters in only a few sequential synthetic steps. While the yields are not consistently high for the proposed S_N2 ring opening of the substituted lactones, the low cost and availability of the starting substrates makes this a viable entry into γ-pyrrolic esters as the reactions can be readily carried out on a multi-gram scale. These derivatives have been manipulated to complete a formal synthesis of (±)-monomorine and the total synthesis of (±)-indolizidine 209D.

4. Experimental

4.1. General experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus spectrometer operating at 300 and 75 MHz, respectively. Infrared spectroscopy was recorded on a Perkin–Elmer, paragon 1000 FT-IR as neat films on sodium chloride plates unless otherwise stated. High resolution and Low resolution mass spectroscopy was performed on a Kratos Concept ISQ mass instrument. Melting points were carried out on a Yanagimoto micro melting point apparatus and are uncorrected. Chemicals and reagents were purchased from Aldrich and used as received unless otherwise stated. Solvents were purified by standard literature methods before use.[13] Organic extracts were dried with anhydrous magnesium sulfate unless otherwise stated. Column chromatography was carried out using Merck Silica gel (40–63 μm).

4.2. General procedure for the *N*-alkylation of pyrrole

Method A. Pyrrole (0.200 g, 2.99 mmol) was added dropwise to a suspension of potassium hydride (0.120 g, 2.99 mmol) in anhydrous DMF (2 mL) under an atmosphere of nitrogen at 0 °C. The solution was stirred at room temperature for 10 min, γ-butyrolactone (0.256 g, 2.99 mmol) added and the mixture heated on an oil bath at 160 °C for 4 h. The solution was cooled to room temperature, methyl iodide (0.053 mL, excess) added and the mixture stirred overnight at room temperature. Water (10 mL) was added and the product extracted with 1:1 ethyl acetate/hexanes (3×10 mL). The organic extract was dried and evaporated to give the crude product, which was purified by flash chromatography on silica (eluent: ethyl acetate/hexanes, 1:9) to give **5** as a colourless oil in 61% yield. ν_{max}(neat)/cm^{-1} 1737; ^1H NMR spectrum (300 MHz, $CDCl_3$): 2.05–2.15 (m, 2H), 2.30 (t, J=6.9 Hz, 2H), 3.70 (s, 3H), 3.96 (t, J=6.9 Hz, 2H), 6.17 (apparent t, 2H), 6.66 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 27.0, 31.0, 48.7, 51.9, 108.5, 120.7, 173.5.

Method B. Pyrrole (3.30 g, 49 mmol) was added dropwise to solid potassium hydride (1.96 g, 49 mmol) under a nitrogen atmosphere and the mixture stirred at room temperature for 1 h. γ-Valerolactone (4.90 g, 62 mmol) was added and the mixture heated on an oil bath at 160 °C for 4 h. $NaHCO_3$ (5%) solution (50 mL) was added carefully and extracted

with dichloromethane (3×20 mL). The aqueous layer was retained, acidified with 2 M HCl and extracted with dichloromethane (3×20 mL). The organic extract was dried and evaporated to give the crude acid that was dissolved in DMF (20 mL), potassium carbonate (excess) and methyl iodide (4 equiv) added and stirred overnight at room temperature. The reaction mixture was worked up the same as for method A to yield the methyl ester as a colourless oil **9**[9] in 48% yield. ν_{max}(neat) 1733 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.45 (d, $J=6.9$ Hz, 3H), 1.94–2.08 (m, 2H), 2.10–2.18 (m, 2H), 3.64 (s, 3H), 4.10 (m, 1H), 6.14 (apparent t, 2H), 6.67 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 22.2, 30.5, 33.2, 51.6, 54.5, 107.9, 118.4, 173.5.

4.2.1. 8-Oxo-5,6,7,8-dehydroindolizidine (6). Boron tribromide (0.718 mL, 7.60 mmol) was added dropwise to a solution of **5** (1.16 g, 6.91 mmol) in dichloromethane (20 mL) under an atmosphere of nitrogen at 0 °C. The mixture was stirred at this temperature for 10 min and the reaction quenched by the careful addition of water (10 mL) followed by 2 M Na_2CO_3 (10 mL). The product was extracted with dichloromethane (2×20 mL), the organic extract dried and evaporated to give the crude product, which was purified by passing through a plug of silica gel (eluent: ethyl acetate/hexanes, 1:1) to give the indolizidine **6** in 91% yield as a colourless oil that solidified on storage in the refrigerator. ν_{max}(neat) 1651 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 2.20–2.29 (m, 2H), 2.56 (t, $J=6.9$ Hz, 2H), 4.09 (t, $J=6.0$ Hz, 2H), 6.22 (dd, $J=3.9$, 2.4 Hz, 2H), 6.83–6.84 (m, 1H), 6.98 (dd, $J=3.9$, 1.2 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 23.4, 36.1, 45.0, 110.2, 113.8, 125.9, 130.2, 187.2.

4.2.2. 5-Methyl-8-oxo-5,6,7,8-dehydroindolizidine (10). The γ-pyrrolic ester **9** was reacted under the same conditions as for **6** to give the product **10**, which was recrystallised from ether/hexanes (10:3) to yield the titled product as a colourless solid in 90% yield: mp=98–100 °C, [Found $M^{\cdot+}$, 149.0837 $C_9H_{11}NO$ requires 149.0840]; ν_{max}(neat) 1644 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.55 (d, $J=6.3$ Hz, 3H), 1.97–2.09 (m, 1H), 2.24–2.34 (m, 1H), 2.46–2.70 (m, 2H), 4.20–4.31 (m, 1H), 6.24 (dd, $J=2.4$, 4.2 Hz, 1H), 6.92–6.93 (m, 1H), 7.00 (dd, $J=2.2$, 4.2 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$: 20.6, 30.8, 34.5, 50.5, 110.4, 114.1, 124.1, 130.4, 187.2; *m/z* (EI) 149(100%), 134(30), 106(50), 93(40), 80(25), 67(30).

4.2.3. 5-Methyl-5,6,7,8-dehydroindolizidine (11). Sodium cyanoborohydride (0.10 g, 1.59 mmol) was added to a solution of the indolizidine **10** (0.20 g, 1.34 mmol) and zinc iodide (0.41 g, 1.28 mmol) in dichloromethane under an atmosphere of nitrogen (20 mL) and the mixture refluxed for 6 h. Water (10 mL) was added and the product extracted with dichloromethane (2×10 mL), the organic extract dried and evaporated to give the crude product. The indolizidine **11** was purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes, 1:4) to give the product as a colourless, unstable oil that was used immediately. ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.52 (d, $J=6.3$ Hz, 3H), 1.60–1.80 (m, 2H), 1.91–2.10 (m, 1H), 2.04–2.13 (m, 1H), 2.69–2.80 (m, 2H), 4.04–4.17 (m, 1H), 5.92 (br s, 1H), 6.17 (s, 1H), 6.67 (br s, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 19.9, 22.3, 23.6, 32.0, 50.4, 103.7, 107.4, 116.7, 129.5.

4.2.4. 5-Methyl-3-butyryl-5,6,7,8-dehydroindolizidine (12). Butyryl chloride (0.019 mL, 0.17 mmol) was added dropwise to a solution of indolizidine **11** (16 mg, 0.12 mmol) and silver triflate (52 mg, 0.20 mmol) in dichloromethane (1 mL) under an atmosphere of nitrogen and the mixture stirred at room temperature overnight. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The organic extract was dried and evaporated to give the crude product, which was purified by flash chromatography (eluent: ethyl acetate/hexanes, 1:9) to give unreacted starting material (50%) and **12** as a colourless oil in 20% yield. [Found $M^{\cdot+}$, 205.1471 $C_{13}H_{19}NO$ requires 205.1467]; ν_{max}(neat)/cm^{-1} 1643; ^1H NMR spectrum (300 MHz, $CDCl_3$): 0.96 (t, $J=7.5$ Hz, 3H), 1.33 (d, $J=6.6$ Hz, 3H), 1.60–2.03 (m, 6H), 2.61–2.80 (m, 1H), 2.70 (t, $J=7.5$ Hz, 2H), 2.86–2.97 (m, 1H), 5.26–5.32 (m, 1H), 5.86 (d, $J=4.2$ Hz, 1H), 6.98 (d, $J=4.2$ Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 15.0, 19.3, 22.0, 23.8, 29.3, 41.1, 49.6, 106.5, 120.5, 189.7, C3 and C8a not observed.

4.2.5. Methyl 4-(pyrrol-1-yl) decanoate (13). The γ-pyrrolic ester **13** was isolated as a colourless oil in 30% overall yield from pyrrole by Method B: [Found $M^{\cdot+}$, 251.1887 $C_{15}H_{25}NO_2$ requires 251.1885]; ν_{max}(neat)/cm^{-1} 1740; ^1H NMR spectrum (300 MHz, $CDCl_3$) 0.85 (m, 3H), 1.14–1.36 (m, 8H), 1.70–1.78 (m, 2H), 1.89–2.14 (m, 4H), 3.64 (s, 3H), 3.79–3.88 (m, 1H), 6.14 (apparent t, 2H), 6.62 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 22.6, 26.2, 29.0, 30.5, 31.6, 31.7, 36.7, 51.6, 59.6, 107.8, 118.8, 173.7; *m/z* (EI) 251(50%), 220(25), 164(100), 134(15), 106(35), 94(70), 81(50), 67(40).

4.2.6. 5-Hexyl-8-oxo-5,6,7,8-dehydroindolizidine (14). The product was formed by the same conditions as reported for compound **6**. Indolizidine **14** was isolated as a colourless oil in 90% yield: [Found $M^{\cdot+}$, 219.1617 $C_{14}H_{21}NO$ requires 219.1622]; ν_{max}(neat)/cm^{-1} 1662; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.51 (d, $J=6.3$ Hz, 3H), 1.69–1.83 (m, 8H), 1.84–1.97 (m, 1H), 2.06–2.16 (m, 1H), 2.30–2.42 (m, 1H), 2.51 (ddd, $J=17.7$, 9.3, 4.3 Hz, 1H), 2.67 (ddd, $J=17.7$, 10.2, 4.3 Hz, 1H), 4.15 (m, 1H), 6.24 (dd, $J=3.9$, 2.4 Hz, 1H), 6.91 (dd, $J=2.4$, 1.5 Hz, 1H), 7.01 (dd, $J=3.9$, 1.5 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 22.5, 26.0, 27.7, 29.1, 31.6, 33.3, 34.3, 54.8, 110.1, 114.3, 125.0, 130.2, 187.2 *m/z* (EI) 219(30%), 191(20), 148(65), 134(95), 106(100), 93(60), 67(30).

4.2.7. Indolizidine 209D. The indolizidine **14** (27 mg, 0.12 mmol) was dissolved in acetic acid (10 mL), Pd/carbon (20 mg of 5%) added and hydrogenated at 40 psi on a Parr shaker hydrogenator for 10 h. The catalyst was removed by filtration through Celite and the solvent removed. The residue was dissolved in 2 M Na_2CO_3 (10 mL) and extracted with dichloromethane (3×10 mL). The organic extracts were dried (Na_2SO_4), evaporated and the product purified by flash chromatography (eluent: dichloromethane/methanol/ammonia, 95:4.75:0.25) to give indolizidine 209D as a colourless oil in 90% yield; ^1H NMR spectrum (300 MHz, $CDCl_3$): 0.86 (t, $J=6.9$ Hz, 3H), 1.16–1.46 (m,

13H), 1.50–1.96 (m, 8H), 2.02–2.20 (m, 2H), 3.37 (td, $J=$ 9.3, 2.1 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.1, 20.2, 22.6, 24.3, 25.9, 29.5, 29.7, 29.8, 30.0, 31.8, 33.8, 50.7, 63.9, 65.4.

Acknowledgements

The authors thank the University of Tasmania for funding. P.P.M. is thankful to The University of Warwick for a travel award and O.R.S. to the School of Chemistry for a Summer Scholarship.

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