Influence of ring size on the reduction of vinylogous urethanes. Applications to the synthesis of lupinine and epilupinine

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Dedicated with respect and affection to Professor Jimmy Bull on his retirement from the University of Cape Town

Abstract
Short syntheses of the quinolizidine alkaloids lupinine and epilupinine via alkyl 3-(2-thioxo-1-piperdinyl)propanoates and the vinylogous urethanes prepared from them are reported. Alkyl piperidin-2-ylideneacetates were found to undergo reduction of the C=C bond with lithium aluminium hydride more readily than their pyrrolidin-2-ylideneacetate analogues, a finding that is in line with reports of the relative reactivities of double bonds exocyclic to five- and six-membered rings.

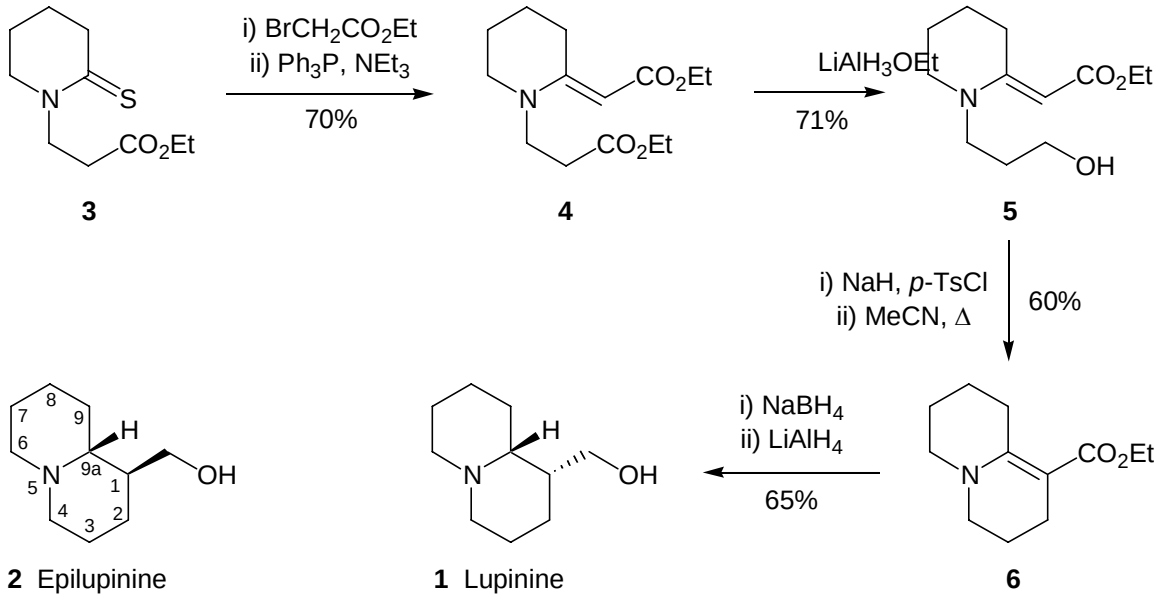
Keywords: Enaminones, epilupinine, lupinine, quinolizidine alkaloids, thiolactams, vinylogous urethanes

Introduction

The general approach to alkaloid and antibiotic synthesis explored in these laboratories over a number of years is based on the use of β-acylated enamines (enaminones) and related compounds as scaffolds upon which to build the more complex architectures found in a representative range of alkaloidal families.[1] The focus of our investigations has hitherto largely been on using 2-(acylmethylidene)pyrrolidines derived from pyrrolidine-2-thiones as versatile intermediates en route to target systems containing isolated or fused pyrrolidine rings,[2] for example, the 1-azabicyclo[4.3.0]nonane (indolizidine) nucleus.[3] Complementary explorations of piperidine-based precursors for the synthesis of the homologous 1-azabicyclo[4.4.0]decane (quinolizidine) ring system are under-represented in our work.[4] However, our recently reported observations of intriguing discrepancies in the behavior of five-membered and six-membered thiolactam precursors[5] have prompted us to examine the reactions of the latter class of

compounds and their 2-alkylidene derivatives more closely, and to pay more attention to their use in the synthesis of quinolizidine alkaloids. Some relevant results are reported in this article.

The quinolizidine ring system is well represented among alkaloids isolated from both plant and animal sources,[6] and novel strategies for the stereoselective synthesis of compounds containing this important structural motif continue to receive considerable attention.[7] The diastereomeric alkaloids lupinine **1** and epilupinine **2** (numbering scheme shown), the simplest members of the large group of alkaloidal metabolites of the Leguminosae (Fabaceae),[8] are exceptionally popular targets for synthesis, and are frequently used to exemplify emerging methodologies.[9] In fact, an early communication from these laboratories disclosed a simple synthesis of (±)-lupinine *rac*-**1** from the piperidine-2-thione **3** *via* the enaminone intermediates **4**–**6** (vinylogous urethanes) (Scheme 1).[10] However, full experimental details were never reported, the relatively unsophisticated spectroscopic techniques available at the time made the characterisation of compounds somewhat tentative, and the apparently stereoselective conversion of **6** into **1**, although precedented,[11] was not fully probed. We thus chose to re-investigate aspects of this synthesis, using the route as a framework within which to contextualise a further exploration of behavioral differences between five-and six-membered ring intermediates.

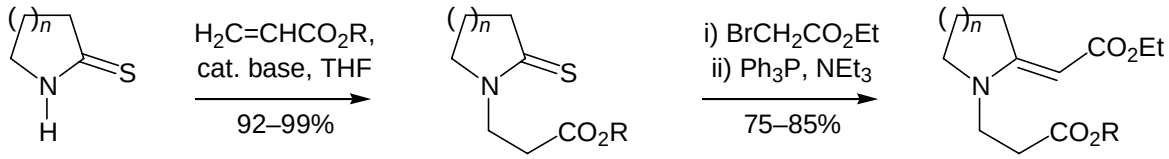


Scheme 1

Results and Discussion

The vinylogous urethanes on which this study is based were prepared in two steps from pyrrolidine-2-thione[12] **7a** or piperidine-2-thione[12] **7b**, conjugate addition of which to esters of acrylic acid was readily achieved by stirring the reactants together in dry tetrahydrofuran at

40 °C in the presence of a catalytic quantity of sodium hydride[13] or sodium hydroxide (Scheme 2). The *N*-alkyl products **3** and **8a–c** were isolated in yields of 92–99%. Conversion of these thiolactams into the vinylogous urethanes **4** and **9a–c** was accomplished in 75–85% overall yields by alkylation on sulfur with ethyl bromoacetate followed by Eschenmoser sulfide contraction[14] in the presence of triphenylphosphine and triethylamine. The (*E*)-geometry of the double bond in these products was inferred from the chemical shift of the hydrogen atoms at C-3 in the ring (δ *ca*. 3.1), the downfield shift of about 0.6 ppm relative to (*Z*)-analogues[14a] arising from the anisotropic deshielding effect of the carbonyl group.



7a *n* = 1
7b *n* = 2

3 *n* = 2; R = Et
8a *n* = 1; R = Et
8b *n* = 1; R = Bu^t
8c *n* = 2; R = Bu^t

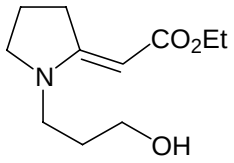
4 *n* = 2; R = Et
9a *n* = 1; R = Et
9b *n* = 1; R = Bu^t
9c *n* = 2; R = Bu^t

Scheme 2

A critical feature of the previously reported synthesis of lupinine shown in Scheme 1 was the chemoselective reduction of the saturated ester group of intermediate **4** while leaving the vinylogous urethane untouched. Our prior experience with pyrrolidine-based vinylogous urethanes led us to believe that the enaminone system in such compounds was robust enough to resist reduction with lithium aluminium hydride.[1,3b] Indeed, treatment of the pyrrolidinylidene compounds **9a** and **9b** with lithium aluminium hydride (1.1 equiv.) in tetrahydrofuran at room temperature was complete within 2 h, affording the same saturated alcohol **10** in yields of 73% and 79%, respectively; as expected, the vinylogous urethane was unaffected. However, it was disconcerting to discover that the piperidinylidene analogues **4** and **9c** were substantially less inert under the same conditions. The former, for instance, gave only a 3% yield of the expected product **5**, while the major product **11** (65%) resulted from reduction of both the saturated ester and the double bond of the vinylogous urethane. Even at a lower temperature (0 °C) and with a shorter reaction time (45 min), the yield of **5** was only 66%, while the over-reduced product **11** was still significant (26%). Interestingly, in the original lupinine synthesis reported from this laboratory[10] (Scheme 1), the reactivity of the reductant was tempered by the addition of an equivalent of ethanol[15] to give a 71% yield of **5**. Over-reduction was not mentioned, or, more probably, was not recognised. In the present work, attempts to moderate the reaction in other ways, *e.g.* by using Superhydride,® lithium pyrrolidineborohydride[16] or sodium borohydride in combination with lithium iodide,[17] failed to reduce either functional group. However, we were able to minimise over-reduction with lithium aluminium hydride by changing the solvent to a

mixture of toluene and diethyl ether. With a 2:1 ratio of these solvents, reduction of **4** at 0 °C for 45 min afforded **5** (58%) and **11** (27%); with a 4:1 ratio of solvents, the isolated yields were 62% and 13%, respectively.

The difference in reactivity of the exocyclic C=C bond in the five- and six-membered vinylogous urethanes **4** and **9a–c** is in line with Brown's observations about the stability and reactivity of double bonds that are exocyclic or endocyclic to rings of varying size.[18] Brown's carefully worded generalisation included the following statement: "*Reactions which involve the loss of an exo double bond will be favored in the 6-ring as compared to the corresponding 5-ring derivative*". Thus the greater lability of the piperidinylidene vinylogous urethanes towards conjugate reduction, though troublesome for our purposes, should perhaps not have surprised us. However, other factors may well make even this feature of enaminone reactivity unpredictable. For example, the vinylogous cyanamide **12a**, the reduction of which to the alcohol **13** proceeds in 74% yield,[4] is clearly far less susceptible to reduction of the C=C bond than the corresponding vinylogous urethane. To confirm this observation and complete our series of comparisons, we prepared the *tert*-butyl ester analogue **12b** in 75% yield by sulfide contraction between the piperidine-2-thione **8c** and bromoacetonitrile. Reduction of the ester group with lithium aluminium hydride in THF at room temperature, although affording only a 60% yield of **13**, gave no observable formation of the over-reduced product.



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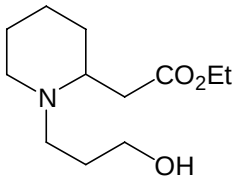

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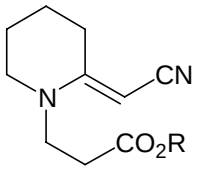
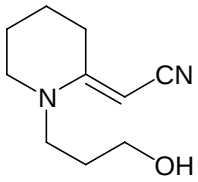


12a R = Et
12b R = Bu^t



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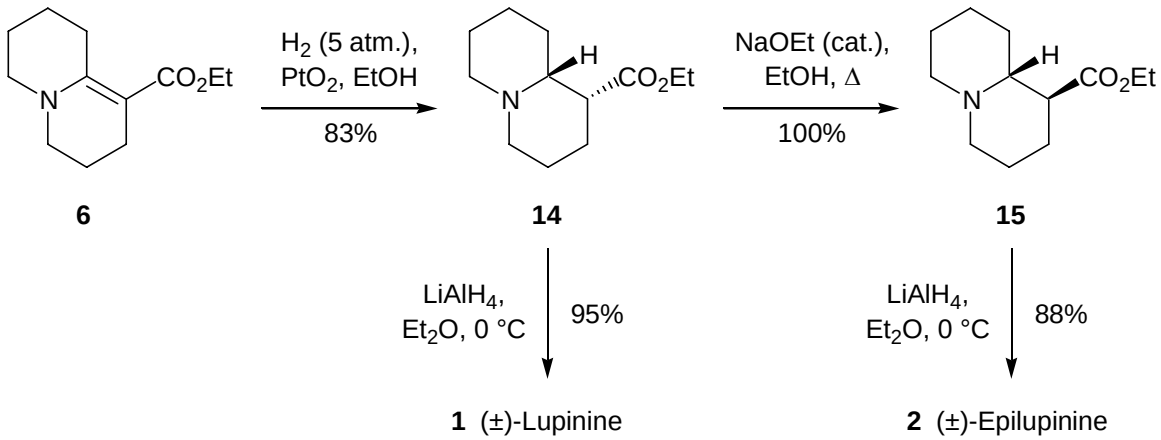
As originally performed, the cyclisation of alcohol **5** to give the quinolizidine ring system **6** (Scheme 1) entailed activation of the leaving group by initial conversion into a toluenesulfonate. We have subsequently found that this is not an ideal approach; since mixtures of toluenesulfonate and chloride products are formed, the latter in general not being sufficiently reactive to give efficient ring closure. Our preferred mode of activation is now via an alkyl iodide, which is formed *in situ* and immediately cyclised under appropriate conditions. In the present investigation, the alcohol **5** was treated with iodine, triphenylphosphine and imidazole, according to the method developed by Garegg and Samuelson[19] for preparing alkyl iodides from alcohols. When the reactants were heated in a 2:1 mixture of toluene and acetonitrile, the intermediate iodide cyclised spontaneously to give the 3,4,6,7,8,9-hexahydro-2*H*-quinolizine **6** in 74% yield. Although other workers have prepared compound **6** by different routes,[11,20,21] characterisation has hitherto been sketchy and ^{13}C NMR data have not previously been reported.

The selective conversion of **6** into the target quinolizidine alkaloids **1** and **2** demands that the reduction of the C=C bond proceed with reliable stereocontrol. Goldberg and Ragade reported that

stereocontrolled reduction of **6** with sodium borodeuteride gave the 9a-deuterated isotopomer of (±)-ethyl lupinoate **14** exclusively, a somewhat surprising result that was rationalised in terms of conformational effects and the preferred trajectory of hydride approach.[11] Lhommet and co-workers prepared **14** by catalytic hydrogenation of **6** over Raney nickel under harsh conditions (150 atm., 100 °C).[21b] Significantly, at a reaction temperature of 200 °C, they found that the sole product was (±)-ethyl epilupinoate **15**, in which the ester group occupies the thermodynamically favoured equatorial position. Furthermore, **14** could be epimerised to **15** merely upon heating at 200 °C. Less drastically, Goldberg and Lipkin accomplished epimerisation in unspecified yield by heating the lupinate ester **14** with sodium ethoxide in ethanol.[20]

We found that stereoselective *cis*-hydrogenation of the bicyclic vinylogous urethane **6** could be accomplished under far milder conditions than those employed by Lhommet's group. Hydrogenation over Adams catalyst in absolute ethanol at a hydrogen pressure of 5 atm afforded (±)-ethyl lupinoate **14** as the sole detectable isomer in a yield of 83% (Scheme 3). Moreover, in our hands the base-catalysed epimerisation with a catalytic quantity of sodium ethoxide in boiling ethanol gave a quantitative yield of the epilupinoate ester **15**. Although both isomers have been known for decades, reliable spectroscopic data are rare. Our spectroscopic data agreed well those of Lhommet[21b] and also Hua *et al.*,[22] who reported data for the enantiomerically pure compounds (–)-**14** and (+)-**15**. In the IR spectra, Bohlmann bands[23] in the region *ca.* 2750–2800 cm^{-1} indicated *trans*-fusion of the quinolizidine ring system.

Reduction of (±)-**14** and (±)-**15** to give (±)-lupinine **1** and (±)-epilupinine **2**, respectively, was most successfully achieved by the dropwise addition of the precursors in dry diethyl ether to a suspension of lithium aluminium hydride in ether at 0 °C, a "reverse addition" procedure recommended by Davies and Smyth.[24] The isolated yields of the two alkaloids were 95% and 88%, respectively. Spectroscopic data for these products, recorded in deuterated chloroform at 300 MHz, were in excellent agreement with those recorded at 400 MHz by Hua *et al.*[22] In addition, spectra recorded for lupinine in deuterated benzene accorded well with those reported at 600 MHz by Rycroft and Robins.[25]



Scheme 3

The methodology described in this article is conceptually and experimentally straightforward and the transformations are efficient. We are currently applying the principles elaborated above to the enantioselective synthesis of a suite of 1,4-disubstituted quinolizidine alkaloids recently isolated from the skins of poison-dart frogs.[26]

Experimental Section

General Procedures. All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) and diethyl ether were distilled from Na/benzophenone, dichloromethane, acetonitrile and triethylamine from CaH_2, and benzene and toluene from Na. Commercially available chemicals were used as received. Melting points, recorded on a Reichert hot-stage microscope apparatus, are uncorrected. TLC was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Column chromatography was carried out on silica gel 60, particle size 0.063–0.200 mm (conventional columns) or Whatman Partisil Prep 40, particle size 0.040–0.063 mm (flash columns). FTIR spectra were recorded on a Bruker Vector 22 spectrometer. NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C), Bruker AVANCE 300 (300.132 MHz for ^{1}H, 75.473 MHz for ^{13}C) or Bruker DRX 400 (400.132 MHz for ^{1}H, 100.625 MHz for ^{13}C) spectrometers. $CDCl_3$ was used as solvent and TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals. *J* values are given in Hz. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

General procedure for the *N*-alkylation of thiolactams with acrylate esters

To a stirred solution of pyrrolidine-2-thione[12] **7a** or piperidine-2-thione[12] **7b** (5–45 mmol scale) in dry THF (*ca.* 1.75 cm^3 per mmol of solute) was added a catalytic amount of NaH (60% dispersion in oil, *ca.* 0.05 equiv.) or NaOH, followed by the dropwise addition of the acrylate ester (1.2 equiv.). The mixture was stirred at 40 °C for 16 h before evaporating the solvent *in vacuo*. The resulting yellow residue was dissolved in Et_2O, and the resulting solution was washed with H_2O and saturated aqueous NaCl solution. The ethereal phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil, which was purified by column chromatography on silica gel using EtOAc–hexane (1:9 to 1:1) as eluent to give the following products:

Ethyl 3-(2-thioxo-1-piperidinyl)propanoate (3). (6.89 g, 92%), from piperidine-2-thione **7b** (4.00 g, 34.72 mmol), dry THF (60 cm^3), NaH dispersion (69 mg, 1.74 mmol) and ethyl acrylate (4.49 cm^3, 4.19 g, 41.67 mmol); pale yellow oil, R_f 0.56 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2947 (m, br), 1732 (s, C=O), 1520 (s), 1353 (m, C=S), 1184 (s), 1159 (s), 1098 (m) and 1051 (m); δ_H (400 MHz; $CDCl_3$) 4.19 (2H, t, *J* 6.9, chain NC*H*$_2$), 4.14 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.53 (2H, t, *J* 6.1, ring NC*H*$_2$), 2.97 (2H, t, *J* 6.5, C*H*$_2$C=S), 2.85 (2H, t, *J* 7.0, C*H*$_2$CO$_2$Et), 1.89 (2H, quintet, *J* 6.2, ring 5-H), 1.72 (2H, quintet, *J* 6.4, ring 4-H) and 1.27 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C

(100 MHz; $CDCl_3$) 199.9 (*C*=S), 171.6 (*C*=O), 60.6 (O*C*$H_2$$CH_3$), 51.8 (ring N*C*$H_2$), 50.7 (chain N*C*$H_2$), 41.6 (*C*$H_2$C=S), 30.7 (*C*$H_2$$CO_2$Et), 22.8 (ring C–5), 20.3 (ring C–4) and 14.0 (OCH_2*C*H_3). The spectroscopic data agree with those published previously.[4]

Ethyl 3-(2-thioxo-1-pyrrolidinyl)propanoate (8a). (0.85g, 92%), from pyrrolidine-2-thione **7a** (0.463 g, 4.58 mmol), dry THF (10 cm^3), NaOH (<10 mg) and ethyl acrylate (0.55 cm^3, 5.95 mmol); yellow oil, R_f 0.54 (EtOAc–hexane 1:1); ν_{max}(thin film)/cm^{-1} 2979 (m), 1732 (s, C=O), 1511 (m), 1379 (m), 1320 (m) and 1188 (m); δ_H (400 MHz; $CDCl_3$) 4.15 (2H, q, *J* 7.2, OC*H*$_2$$CH_3$), 4.01 (2H, t, *J* 6.8, chain NC*H*$_2$), 3.82 (2H, t, *J* 7.3, ring NC*H*$_2$), 3.01 (2H, t, *J* 7.9, C*H*$_2$C=S), 2.77 (2H, t, *J* 6.8, C*H*$_2$$CO_2$Et), 2.08 (2H, quintet, *J* 7.6, ring 4-H), 1.27 (3H, t, *J* 7.2, OCH_2C*H*$_3$); δ_C (50 MHz; $CDCl_3$) 201.4 (*C*=S), 171.2 (*C*=O), 60.6 (O*C*$H_2$$CH_3$), 55.6 (ring N*C*$H_2$), 44.7 (chain N*C*$H_2$), 43.5 (*C*$H_2$C=S), 30.8 (*C*$H_2$$CO_2$Et), 19.7 (ring C-4), 13.9 (OCH_2*C*H_3); *m*/*z* (EI) 201 (31%, M^+), 172 (21), 156 (26), 129 (24), 128 (100), 126 (14), 114 (26), 112 (33), 111 (39), 110 (17), 87 (14), 85 (84). The compound has previously been reported, but without spectroscopic characterisation.[27]

***tert*-Butyl 3-(2-thioxo-1-pyrrolidinyl)propanoate (8b).** (1.13 g, 99%), from pyrrolidine-2-thione **7a** (0.58 g, 5.73 mmol), dry THF (10 cm^3), NaH dispersion (11 mg, 0.29 mmol) and *tert*-butyl acrylate (1.00 cm^3, 0.88 g, 6.88 mmol); yellow oil, R_f 0.33 (EtOAc–hexane 3:7); ν_{max} (film)/cm^{-1} 2978 (m), 1726 (s, C=O), 1509 (m), 1367 (m), 1326 (m), 1289 (m), 1254 (m), 1154 (s) and 1120 (m); δ_H (400 MHz; $CDCl_3$) 3.98 (2H, t, *J* 6.8, chain NC*H*$_2$), 3.80 (2H, t, *J* 7.3, ring NC*H*$_2$), 3.00 (2H, t, *J* 7.9, C*H*$_2$C=S), 2.67 (2H, t, *J* 6.8, C*H*$_2$$CO_2$R), 2.06 (2H, quintet, *J* 7.6, ring H–4) and 1.46 (s, 9H, C*Me*$_3$); δ_C (50 MHz; $CDCl_3$) 201.4 (*C*=S), 170.7 (*C*=O), 81.1 (*C*Me_3), 55.6 (ring N*C*H_2), 44.8 (*C*H_2C=S), 43.8 (chain N*C*H_2), 32.3 (*C*$H_2$$CO_2$R), 27.9 (C*Me*$_3$) and 19.8 (ring C–4); *m/z* (EI) 229 (57%, M^+), 173 (34), 172 (38) 156 (42), 128 (100), 114 (10), 102 (14), 101 (6), 85 (17), 57 (14) (Found: M^+, 229.1140. $C_{11}H_{19}NO_2S$ requires 229.1137. $M^+ - CO_2Bu^t$, 128.0530. $C_6H_{10}NS$ requires 128.0534).

***tert*-Butyl 3-(2-thioxo-1-piperidinyl)propanoate (8c).** (10.57 g, 99%), from piperidine-2-thione **7b** (5.00 g, 43.40 mmol), dry THF (75 cm^3), NaH dispersion (87 mg, 2.17 mmol) and *tert*-butyl acrylate (7.60 cm^3, 6.71 g, 52.36 mmol); pale yellow solid, m.p. 55-56 °C (from pentane); R_f 0.66 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2950 (m), 1724 (s, C=O), 1521 (s), 1450 (s), 1360 (m, C=S), 1160 (m) and 966 (m); δ_H (400 MHz; $CDCl_3$) 4.16 (2H, t, *J* 7.0, chain NC*H*$_2$), 3.53 (2H, t, *J* 6.1, ring NC*H*$_2$), 2.97 (2H, t, *J* 6.5, C*H*$_2$C=S), 2.76 (2H, t, *J* 7.0, C*H*$_2$$CO_2$R), 1.88 (2H, quintet, *J* 6.4, ring 5–H), 1.72 (2H, quintet, *J* 6.4, ring 4–H) and 1.45 (9H, s, C*Me*$_3$); δ_C (100 MHz; $CDCl_3$) 199.7 (*C*=S), 170.9 (*C*=O), 80.7 (*C*Me_3), 51.7 (ring N*C*H_2), 50.8 (chain N*C*H_2), 41.6 (*C*H_2C=S), 31.8 (*C*$H_2$$CO_2$R), 27.9 (C*Me*$_3$), 22.8 (ring C–5) and 20.2 (ring C–4); *m*/*z* (EI) 243 (33%, M^+), 187(21), 186 (100), 170 (34), 142 (44), 116 (15), 115 (21), 82 (23) (Found: C, 59.51; H, 8.84; N, 5.76. $C_{12}H_{21}NO_2S$ requires C, 59.23; H, 8.70; N, 5.76%).

General procedure for the preparation of vinylogous urethanes from *N*-alkylthiolactams

Ethyl bromoacetate (1.1 equiv.) was added dropwise to a stirred solution of thiolactam **3** or **8a–c** (2–20 mmol scale) in dry CH_3CN (*ca.* 1.75 cm^3 per mmol of solute). The resulting solution was

stirred at room temperature for 16 h, after which S-alkylation was complete. The volatiles were removed *in vacuo* (oil pump), and the residue was thoroughly dried under vacuum. This salt was then re-dissolved in dry CH_3CN (*ca.* 1.75 cm^3 per mmol of solute), after which triphenylphosphine (1.1 equiv.) and triethylamine (1.1 equiv.) were added to induce sulfur extrusion. The resulting solution was left to stir at ambient temperature for 16 h (2.25 h for **8b**). H_2O (10–20 cm^3) was added, and the resulting solution was extracted repeatedly with CH_2Cl_2. The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel; CH_2Cl_2 or hexane–benzene (9:1) were used initially as eluents to remove triphenylphosphine and triphenylphosphine sulfides, after which the desired products were eluted with hexane–EtOAc mixtures (8:2 to 7:3). The following products were obtained:

Ethyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidinyl]propanoate (4). (4.63 g, 84%), from ethyl 3-(2-thioxo-1-piperidinyl)propanoate **3** (4.00 g, 18.55 mmol), ethyl bromoacetate (2.27 cm^3, 3.41 g, 24.43 mmol), dry CH_3CN (2 × 35 cm^3), PPh_3 (5.36 g, 20.43 mmol) and NEt_3 (2.85 cm^3, 2.07 g, 20.43 mmol); yellow oil, R_f 0.69 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2980 (w), 2943 (w), 1733 (m, C=O), 1681 (m, C=O), 1566 (s, C=C), 1187 (m), 1134 (s), 1096 (m), 1050 (m) and 790 (w); δ_H (400 MHz; $CDCl_3$) 4.55 (1H, s, =C*H*), 4.15 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 4.06 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.49 (2H, t, *J* 7.1, chain NCH_2), 3.27 (2H, t, *J* 6.1, ring NCH_2), 3.09 (2H, t, *J* 6.6, CH_2C=), 2.62 (2H, t, *J* 7.2, C$H_2$$CO_2$R), 1.76 (2H, quintet, *J* 6.2, ring 4-H), 1.62 (2H, quintet, *J* 6.4, ring 5-H) and 1.27 and 1.24 (6H, overlapping t, *J* 7.1, 2 × $OCH_2C$$H_3$); δ_C (100 MHz; $CDCl_3$) 171.5 (*C*=O, saturated ester), 168.6 (*C*=O, unsaturated ester), 161.3 (N*C*=CH), 82.0 (NC=*C*H), 60.5 and 57.9 (2 × OCH_2CH_3), 49.9 (ring NCH_2), 47.4 (chain NCH_2), 30.3 (CH_2CO_2R), 26.2 (CH_2C=), 23.2 (ring C–4), 19.3 (ring C–5), 14.5 and 14.0 (2 × $OCH_2$$CH_3$); *m/z* (EI) 269 (40%, M^+), 224 (62), 196 (100), 182 (50), 169 (31), 154 (7), 149 (15), 124 (20), 97 (48) (Found: M^+, 269.1626. $C_{14}H_{23}NO_4$ requires 269.1627).

Ethyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate (9a). (0.61 g, 83%), from ethyl 3-(2-thioxo-1-pyrrolidinyl)propanoate **8a** (0.58 g, 2.88 mmol), ethyl bromoacetate (0.35 cm^3, 0.53 g, 3.17 mmol), dry CH_3CN (2 × 5 cm^3), PPh_3 (0.83 g, 3.17 mmol) and NEt_3 (0.44 cm^3, 0.32 g, 3.17 mmol); waxy solid, m.p. 31–33 °C; R_f 0.54 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2980 (m), 1734 (s, C=O), 1638 (s, C=O), 1595 (s, C=C), 1377 (m), 1301 (m), 1250 (m), 1134 (s, br), 1052 (m) and 786 (m); δ_H (200 MHz; $CDCl_3$) 4.53 (1H, s, =C*H*), 4.15 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 4.09 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.50 (2H, t, *J* 9.0, chain NCH_2), 3.41 (2H, t, *J* 7.0, ring NCH_2), 3.13 (2H, td, *J* 7.8 and 1.1, CH_2C=), 2.58 (2H, t, *J* 7.0, C$H_2$$CO_2$R), 1.93 (2H, quintet, *J* 7.4, ring H-4) and 1.27 and 1.25 (6H, overlapping t, *J* 7.1, 2 × $OCH_2C$$H_3$); δ_C (50 MHz; $CDCl_3$) 171.4 (*C*=O, saturated ester), 169.1 (*C*=O, unsaturated ester), 164.3 (N*C*=CH), 78.1 (NC=*C*H), 60.7 and 58.1 (2 × OCH_2CH_3), 52.7 (ring NCH_2), 41.8 (chain NCH_2), 32.4 (CH_2C=), 30.8 (CH_2CO_2R), 21.0 (ring C–4), 14.6 and 14.0 (2 × $OCH_2$$CH_3$); *m/z* 255 (11%, M^+), 210 (17), 185 (39), 182 (17), 140 (31), 128 (20), 114 (20), 112 (42), 111 (55), 110 (20), 101 (28), 98 (100), 94 (18), 85 (17) (Found: C, 61.18; H, 8.23; N, 5.45. $C_{13}H_{21}NO_4$ requires C, 61.16; H, 8.29; N, 5.49%). The compound has previously been reported, but without spectroscopic data.[27]

***tert*-Butyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate (9b).** (0.44 g, 75%), from *tert*-butyl 3-(2-thioxo-1-pyrrolidinyl)propanoate **8b** (0.53 g, 2.31 mmol), ethyl bromoacetate (0.28 cm^3, 0.42 g, 2.54 mmol), dry CH_3CN (2 × 4 cm^3), PPh_3 (0.67 g, 2.54 mmol) and NEt_3 (0.35 cm^3, 0.26 g, 2.54 mmol); yellow oil, R_f 0.69 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2978 (m), 2935 (m), 1728 (s, C=O), 1685 (s, C=O), 1595 (s, C=C), 1368 (m), 1301 (m), 1249 (m), 1133 (s) and 1051 (m); δ_H (400 MHz; $CDCl_3$) 4.53 (1H, s, =C*H*), 4.09 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.45 (2H, t, *J* 7.0, chain NCH_2), 3.39 (2H, t, *J* 7.1, ring NCH_2), 3.13 (2H, t, *J* 7.8, CH_2C=), 2.49 (2H, t, *J* 7.0, C$H_2$$CO_2$R), 1.92 (2H, quintet, *J* 7.4, ring 4-H), 1.45 (9H, s, CMe_3), 1.25 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 170.7 (*C*=O, saturated ester), 169.3 (*C*=O, unsaturated ester), 164.5 (N*C*=CH), 81.0 (*C*Me_3), 78.1 (NC=*C*H), 58.2 (O*C*$H_2$$CH_3$), 52.7 (ring N*C*$H_2$), 42.0 (chain N*C*$H_2$), 32.5 (*C*$H_2$C=), 32.2 (*C*$H_2$$CO_2$R), 28.0 (C$Me_3$), 21.1 (ring C-4), 14.7 (OCH_2*C*H_3); *m/z* (EI) 283 (53%, M^+), 238 (36), 227 (17), 226 (10), 210 (43), 183 (18), 182 (100), 168 (35), 155 (62), 154 (38), 111 (11), 110 (17), 108 (19), 57 (14) (Found: M^+, 283.1788; $C_{15}H_{25}NO_4$ requires 283.1784)

***tert*-Butyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidinyl]propanoate (9c).** (0.94 g, 85%), from *tert*-butyl 3-(2-thioxo-1-piperidinyl)propanoate **8c** (900 mg, 3.70 mmol), ethyl bromoacetate (0.45 cm^3, 0.68.g, 4.07 mmol), dry CH_3CN (2 × 7 cm^3), PPh_3 (1.07 g, 4.07 mmol) and NEt_3 (0.58 cm^3, 0.41 g, 4.07 mmol); pale yellow oil, (R_f 0.37 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2978 (m), 2938 (m), 1728 (s, C=O), 1683 (s, C=O), 1568 (s, C=C), 1368 (m), 1332 (m), 1259 (m), 1135 (s, br), 1096 (m) and 1051 (m); δ_H (200 MHz; $CDCl_3$) 4.55 (1H, s, =C*H*), 4.06 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.45 (2H, t, *J* 7.1, chain NCH_2), 3.26 (2H, t, *J* 6.1, ring NCH_2), 3.09 (2H, t, *J* 6.5, CH_2C=), 2.54 (2H, t, *J* 7.1, C$H_2$$CO_2$R), 1.81–1.55 (4H, m, ring 4–H and 5–H), 1.46 (9H, s, CMe_3) and 1.24 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 170.9 (*C*=O, saturated ester), 168.8 (*C*=O, unsaturated ester), 161.5 (N*C*=CH), 82.0 (NC=*C*H), 80.9 (*C*Me_3), 58.1 (O*C*$H_2$$CH_3$), 50.0 (ring N*C*$H_2$), 47.5 (chain N*C*$H_2$), 31.7 (*C*$H_2$$CO_2$R), 28.0 (C$Me_3$), 26.3 (*C*$H_2$C=), 23.3 (ring C–5), 19.4 (ring C–4) and 14.6 (OCH_2*C*H_3); *m*/*z* (EI) 297 (35%, M^+), 252 (20), 241 (20), 224 (22), 197 (17), 196 (100), 182 (40), 169 (45), 168 (40), 122 (23), 97 (45) (Found, M^+, 297.1931. $C_{16}H_{27}NO_4$ requires 297.1940).

Ethyl (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanoate (10). (a) $LiAlH_4$ (37 mg, 0.97 mmol, 1.1 equiv.) was added to a stirred solution of *tert*-butyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate **9b** (0.25 g, 0.88 mmol) in dry THF (5 cm^3). The reaction mixture was stirred for 2 h at room temperature under a nitrogen atmosphere before being quenched with sequential additions of H_2O (0.037 cm^3), aqueous NaOH solution (15% w/v, 0.037 cm^3) and H_2O (0.112 cm^3). A white precipitate formed. The supernatant liquid was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product (0.19 g) was purified by column chromatography on silica gel using EtOAc–hexane (4:1) as eluent to give the alcohol **10** as a yellow oil (0.15 g, 79%). Recrystallisation from hexane–ethyl acetate afforded colourless needles, m.p. 62–63 °C; R_f 0.42 (EtOAc–hexane 4:1); ν_{max} (film)/cm^{-1} 3246 (m, br, OH), 2942 (m), 1660 (s, C=O), 1586 (s, C=C), 1463 (m), 1378 (m), 1296 (m), 1253 (m), 1140 (s) and 1056 (s); δ_H (200 MHz; $CDCl_3$) 4.55 (1H, br s, =C*H*), 4.07 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.65 (2H, t, *J*

6.1, C*H*$_2$OH), 3.41 (2H, t, *J* 7.1, chain NC*H*$_2$), 3.31 (2H, t, *J* 7.2, ring NC*H*$_2$), 3.14 (3H, br t, *J* 7.8, C*H*$_2$C= and O*H*), 1.95 (2H, quintet, *J* 7.5, C*H*$_2$CH$_2$OH), 1.81 (2H, quintet, *J ca.* 6.7, ring 4-H) and 1.25 (3H, t, *J* 7.1, OC*H*$_2$CH$_3$); δ_C (50 MHz; $CDCl_3$) 169.7 (*C*=O), 165.0 (N*C*=CH), 77.2 (NC=*C*H), 59.6 (*C*H$_2$OH), 58.2 (OC*H*$_2$CH$_3$), 52.7 (ring NC*H*$_2$), 43.0 (chain NC*H*$_2$), 32.6 (*C*H$_2$C=), 28.8 (*C*H$_2$CH$_2$OH), 20.9 (ring C–4) and 14.6 (OCH$_2$*C*H$_3$); *m*/*z* (EI) 213 (12%, M^+), 169 (41), 168 (36), 126 (27), 124 (12), 122 (13), 108 (19), 98 (12), 97 (100), 96 (85) (Found: C, 61.64; H, 8.67; N, 6.99. $C_{11}H_{19}NO_3$ requires C, 61.95; H, 8.98; N, 6.57%. Found:, M^+, 213.1355. $C_{11}H_{19}NO_3$ requires 213.1365). (b) When the reaction was repeated with ethyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate **9a** (0.31 g, 1.21 mmol) and $LiAlH_4$ (51 mg, 1.34 mmol, 1.1 equiv.) in dry THF (5 cm^3), the product **10** was obtained as a yellow oil (0.19 g, 73%).

Representative procedure for the reduction of ethyl 3-[(2*E*)-2-(2-ethoxy-2-oxoethylidene)piperidinyl]propanoate (4)

To a suspension of $LiAlH_4$ (21 mg, 0.55 mmol) in a mixture of dry toluene and dry Et_2O (4:1 v/v, 1 cm^3) at 0 °C was added a solution of the vinylogous urethane **4** (144 mg, 0.54 mmol) in the same solvent mixture (2 cm^3). The reaction mixture was stirred at 0 °C for 45 min before being quenched by the sequential addition of H_2O (0.021 cm^3), aqueous NaOH solution (15% w/v, 0.021 cm^3) and H_2O (0.063 cm^3). EtOAc (6.5 cm^3) was added, and the mixture was stirred at room temperature for 30 min before being filtering through celite. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel using EtOAc–hexane (4:1) as eluent to give recovered substrate **4** (6.5 mg, 4.5%) and the following two products:

Ethyl (2*E*)-[1-(3-hydroxypropyl)-2-piperidinylidene]ethanoate (5). (76 mg, 62%); pale yellow oil, R_f 0.24 (EtOAc–hexane 4:1); ν_{max} (film)/cm^{-1} 3419 (s, v br, OH), 2943 (s, br), 1656 (s, C=O), 1559 (s, C=C), 1489 (m), 1448 (m), 1358 (m), 1333 (m), 1278 (m), 1140 (s, br) and 1060 (s, br); δ_H (300 MHz; $CDCl_3$) 4.59 (1H, s, =C*H*), 4.05 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.69 (2H, t, *J* 6.0, C*H*$_2$OH), 3.31 (2H, t, *J* 7.4, chain NC*H*$_2$), 3.25 (2H, t, *J* 6.1, ring NC*H*$_2$), 3.09 (2H, t, *J* 6.6, C*H*$_2$C=), *ca.* 2.6 (v br s, O*H*), 1.85 (2H, *ca.* quintet, *J ca.* 6.7, C*H*$_2$CH$_2$OH), 1.76 (2H, *ca.* quintet, *J ca.* 6.1, ring 5-H), 1.64 (2H, *ca.* quintet, *J ca.* 6.4, ring 4-H) and 1.24 (3H, t, *J* 7.1, OC*H*$_2$CH$_3$); δ_C (75 MHz; $CDCl_3$) 169.1 (*C*=O), 162.0 (N*C*=CH), 81.1 (NC=*C*H), 59.9 (*C*H$_2$OH), 58.0 (OC*H*$_2$CH$_3$), 49. and 48.8 (2 × NC*H*$_2$), 28.2 (*C*H$_2$CH$_2$OH), 26.5 (*C*H$_2$C=), 23.2 (ring C–5), 19.4 (ring C–4) and 14.6 (OCH$_2$*C*H$_3$); *m/z* (EI) 227 (13%, M^+), 196 (27), 183 (26), 182 (72), 169 (14), 168 (11), 154 (11), 140 (100), 124 (10), 111 (30), 110 (18), 97 (28) (Found: M^+, 227.1519; $C_{12}H_{21}NO_3$ requires 227.1521).

Ethyl [1-(3-hydroxypropyl)-2-piperidinyl]acetate (11). (16.5 mg, 13%); yellow oil, R_f 0.13 (EtOAc–hexane 4:1); ν_{max} (film)/cm^{-1} 3395 (m, v br, OH), 2936 (s), 2859 (m), 1733 (s, C=O), 1446 (m), 1372 (m), 1301 (m), 1247 (m), 1162 (m, br), 1115 (m) and 1035 (m); δ_H (200 MHz; $CDCl_3$) 4.15 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.78 (2H, t, *J* 5.2, C*H*$_2$OH), 3.15–3.00 (1H, m, NC*H*), 2.88–2.35 (6H, m, 2 × NC*H*$_2$ and C*H*$_2$CO$_2$R), 1.78–1.46 (8H, m, remaining C*H*$_2$) and 1.26 (3H, t,

J 7.1, O*C*H$_2$CH$_3$), O*H* signal not located; δ_C (50 MHz; CDCl$_3$) 172.5 (*C*=O), 64.3 (*C*H$_2$OH), 60.4 (O*C*H$_2$CH$_3$), 57.3 (N*C*H), 54.3 (chain N*C*H$_2$), 49.2 (ring N*C*H$_2$), 34.4 (*C*H$_2$CO$_2$R), 30.7 (*C*H$_2$CH$_2$OH), 27.4 (ring C–3), 24.9 (ring C–5), 21.3 (ring C–4) and 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI) 229 (2%, M$^+$), 184 (21), 143 (9), 142 (100) (Found: M$^+$, 229.1674. $C_{12}H_{23}NO_3$ requires 229.1678).

***tert*-Butyl 3-[(2*E*)-2-(cyanomethylene)piperidinyl]propanoate (12b).** *tert*-Butyl 3-(2-thioxo-1-piperidinyl)propanoate **8c** (0.23 g, 0.95 mmol) and bromoacetonitrile (0.15 cm^3, 0.26 g, 2.15 mmol, 2.3 equiv.) in dry THF (2 cm^3) were stirred at room temperature under an atmosphere of N_2 for *ca*. 24 h until thin layer chromatographic analysis showed that salt formation was complete. The solvent was then evaporated *in vacuo* (oil pump). A solution of triethyl phosphite (0.18 cm^3, 0.17 g, 1.05 mmol) and NEt$_3$ (0.15 cm^3, 0.11 g, 1.05 mmol) in dry CH$_3$CN (2 cm^3) was added. The mixture was stirred at room temperature for 16 h. Dry Et$_2$O (*ca*. 2 cm^3) was added to precipitate triethylammonium bromide. The mixture was filtered through celite, and the solids were washed with Et$_2$O. The solvents were evaporated *in vacuo*, and the resulting orange oil was purified by column chromatography on silica gel using EtOAc–hexane (1:4) as eluent to give the product **12b** as a yellow oil (0.18 g, 75%); R_f 0.75 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2976 (m, br), 2189 (s, C≡N), 1725 (s, C=O), 1577 (s, C=C), 1368 (m), 1350 (m), 1331 (m), 1258 (m) and 1150 (s, br); δ_H (400 MHz; CDCl$_3$) 3.60 (1H, s, =C*H*), 3.37 (2H, t, *J* 7.1, chain NC*H*$_2$), 3.22 (2H, t, *J* 6.1, ring NC*H*$_2$), 2.66 (2H, t, *J* 6.5, C*H*$_2$C=), 2.49 (2H, t, *J* 7.1, C*H*$_2$CO$_2$R), 1.78 (2H, quintet, *J* 6.1, ring 5-H), 1.66 (2H, quintet, *J* 6.2, ring 4–H), 1.46 (9H, s, C*Me*$_3$); δ_C (100 MHz; CDCl$_3$) 170.6 (*C*=O), 161.2 (N*C*=CH), 122.2 (*C*≡N), 81.2 (*C*Me$_3$), 59.6 (NC=*C*H), 49.8 and 47.4 (2 × N*C*H$_2$), 31.5 (*C*H$_2$CO$_2$R), 28.1 (*C*H$_2$C=), 28.0 (C*Me*$_3$), 23.4 (ring C–5) and 19.6 (ring C–4).

(2*E*)-[1-(3-Hydroxypropyl)-2-piperidinylidene]ethanenitrile (13). A solution of ethyl 3-[(2*E*)-2-(cyanomethylene)piperidinyl]propanoate **12b** (0.20 g, 0.80 mmol) in dry THF (15 cm^3) was stirred at room temperature with LiAlH$_4$ (33 mg, 0.88 mmol, 1.1 equiv.) for 48 h under an atmosphere of N_2. The reaction was quenched with sequential additions of H$_2$O (0.5 cm^3), aqueous NaOH solution (15% w/v, 0.5 cm^3) and H$_2$O (1.5 cm^3). The resulting precipitate was removed by filtration through celite, and the solids were washed with CH$_2$Cl$_2$. The combined filtrates were dried (MgSO$_4$), filtered and evaporated *in vacuo* to yield a yellow oil that was purified by column chromatography on silica gel using EtOAc–hexane (4:1) as eluent to give the alcohol **13** as a yellow oil (87 mg, 60%); R_f 0.06 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 3425 (m, br, OH), 2946 (m, br), 2871 (m, br), 2184 (s, C≡N), 1574 (s, C=C), 1350 (m), 1334 (m), 1176 (m) and 1056 (m); δ_H (400 MHz; CDCl$_3$) 3.82 (1H, s, =C*H*), 3.64 (2H, t, *J* 5.9, C*H*$_2$OH), 3.25–3.21 (4H, m, 2 × NC*H*$_2$), *ca.* 2.85 (1H, br s, O*H*), 2.65 (2H, t, *J* 6.5, C*H*$_2$C=), 1.83–1.76 (4H, m, C*H*$_2$CH$_2$OH and ring 5-H), 1.68 (2H, quintet, *J* 6.3, ring 4-H); δ_C (100 MHz; CDCl$_3$) 161.6 (N*C*=CH), 123.0 (*C*≡N), 59.4 (*C*H$_2$OH), 57.8 (NC=*C*H), 49.5 and 48.6 (2 × N*C*H$_2$), 28.0 (*C*H$_2$C=), 27.9 (*C*H$_2$CH$_2$OH), 23.3 (ring C–5) and 19.4 (ring C–4). Spectroscopic data were in agreement with those published previously.[4]

Ethyl 3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylate (6). A solution of alcohol **5** (0.48 g, 2.11 mmol), PPh_3 (1.66 g, 6.34 mmol) and imidazole (0.43 g, 6.34 mmol) was prepared in a mixture of dry toluene and CH_3CN (1:2 v/v, 21 cm^3). Once the reactants had dissolved, iodine (1.07 g, 4.23 mmol) was added with stirring. The resulting brown solution was heated under reflux at 120 °C for 80 min before being cooled to room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (25 cm^3) and extracted with EtOAc (2 × 25 cm^3). The combined organic phases were washed with saturated aqueous $NaHSO_3$ solution (25 cm^3), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product (2.64 g) was purified by column chromatography on silica gel using CH_2Cl_2 to elute PPh_3, followed by EtOAc–hexane (1:1) to give the bicyclic product **6** as an orange oil (0.33 g, 74%); R_f 0.31 (EtOAc–hexane 1:1); ν_{max} (film)/cm^{-1} 2941 (m), 2857 (w), 1671 (s, C=O), 1556 (s, C=C), 1320 (m), 1285 (m), 1254 (s), 1153 (m), 1118 (s) and 1065 (m); δ_H (400 MHz; $CDCl_3$) 4.08 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.11 (2H, t, *J* 6.2, 4-H or 6-H), 3.07 (2H, t, *J* 5.8, 4-H or 6-H), 3.01 (2H, t, *J* 6.5, 9-H), 2.38 (2H, t, *J* 6.3, 2-H), 1.80–1.72 (4H, m, 3-H, 7-H), 1.61 (2H, *ca.* quintet, *J ca.* 6.3, 8-H) and 1.24 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 168.7 (*C*=O), 156.2 (C-9a), 91.4 (C-1), 58.2 (O*C*H$_2$CH$_3$), 51.0 (overlapping C-4, C-6), 27.6 (C-9), 23.5 (C-2), 23.2 and 21.2 (C-3, C-7), 20.4 (C-8) and 14.5 (OCH$_2$*C*H$_3$); *m*/*z* (EI) 209 (52%, M^+), 180 (65), 178 (30), 164 (70), 162 (25), 149 (28), 137 (64), 136 (100), 135 (22), 134 (45), 122 (22), 108 (20) (Found: M^+, 209.1420. $C_{12}H_{19}NO_2$ requires 209.1416). Apart from the ^{13}C NMR spectrum, which has not been reported before, spectroscopic data were in agreement with those published previously.[21]

Ethyl (1*R,9a*R**)-octahydro-2*H*-quinolizine-1-carboxylate (ethyl lupinoate) (14).** A solution of ethyl 3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylate **6** (0.28 g, 1.34 mmol) in absolute EtOH (15 cm^3) was stirred with Adams catalyst (67 mg) in an autoclave under H_2 gas (5 atm.) at room temperature for 16 h. The solution was filtered through celite and washed with ethanol. The combined filtrates were evaporated *in vacuo*, and the crude product (0.28 g) was purified by column chromatography on silica gel with EtOAc followed by MeOH–EtOAc (1:9) as eluents to give (±)-ethyl lupinoate **14** as a yellow oil (0.24 g, 83%); R_f 0.49 (MeOH–EtOAc 1:4); ν_{max} (film)/cm^{-1} 2935 (s), 2857 (m), 2803 (w, Bohlmann band), 2756 (m, Bohlmann band), 2680 (w, Bohlmann band), 1738 (s, C=O), 1444 (m), 1272 (m), 1223 (m), 1207 (m), 1155 (s), 1128 (s), 1112 (s) and 1035 (m); δ_H (400 MHz; $CDCl_3$; tentative assignments by correlation experiments) 4.15–4.04 (2H, m, OC*H*$_2$CH$_3$), 2.90–2.85 (2H, m, 4_{eq}-H and 6_{eq}-H), 2.50–2.47 (1H, m, C*H*CO$_2$Et), 2.20–2.05 (2H, m, 9a-H and 3-H), 2.05–1.87 (3H, m, 4_{ax}-H, 6_{ax}-H, 8-H), 1.72 (1H, br d, *J* 12.7, 9_{ax}-H), 1.70–1.55 (1H, m, 2-H), 1.55–1.45 (5H, m), 1.28–1.19 and 1.21 (4H, overlapping m and t, *J* 7.1, 9_{eq}-H and OCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 173.4 (*C*=O), 62.8 (C-9a) , 59.7 (O*C*H$_2$CH$_3$), 57.2 and 55.1 (C-4, C–6), 44.4 (*C*HCO$_2$Et), 29.0 (C–7), 26.4 (C–8), 25.0 (C–9), 24.5 (C–2), 22.1 (C–3) and 14.2 (OCH$_2$*C*H$_3$); *m/z* (EI) 211 (47%), 210 (28), 182 (72), 166 (44), 164 (22), 138 (47), 136 (37), 124 (21), 123 (21), 111 (59), 110 (47), 97 (65) (Found: M^+, 211.1572. $C_{12}H_{21}NO_2$ requires 211.1572). Spectroscopic data were in agreement with those reported by other workers, who did not attempt the assignment of NMR signals.[21,22]

Ethyl (1*R,9a*S**)-octahydro-2*H*-quinolizine-1-carboxylate (ethyl epilupinoate) (15).** A solution of ethyl (1*R**,9a*R**)-octahydro-2*H*-quinolizine-1-carboxylate **14** (0.34 g, 1.63 mmol) in absolute ethanol (6 cm^3) was added dropwise to a solution of NaOEt, prepared by dissolving a catalytic amount of Na (<5 mg) in absolute EtOH (6 cm^3). The resulting mixture was heated under reflux for 16 h before acidifying the solution with glacial acetic acid (30 drops). The solvent was evaporated *in vacuo*, and the resulting solid was extracted with CH_2Cl_2 (4 × 30 cm^3). The extracts were combined and evaporated *in vacuo*, and the crude product (0.70 g) was purified by column chromatography on silica gel with MeOH–EtOAc (1:9) as eluent to give (±)-ethyl epilupinoate **15** as a pale yellow oil (0.34 g, 100%); R_f 0.26 (MeOH–EtOAc 1:4); ν_{max} (film)/cm^{-1} 2939 (s), 2862 (m), 2803 (w, Bohlmann band), 2755 (w, Bohlmann band), 1732 (s, C=O), 1446 (m), 1373 (m), 1317 (m), 1260 (s), 1175 (s), 1146 (s), 1034 (m) and 733 (m); δ_H (200 MHz; $CDCl_3$) 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 3.09 (2H, br t, *J ca* 10.7, 4_{eq}-H and 6_{eq}-H), 2.57–2.49 (1H, m, $CHCO_2Et$), 2.34–2.19 (3H, m), 1.98–1.96 (1H, m), 1.85–1.65 (6H, m), 1.61–1.29 (3H, m) and 1.25 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 174.1 (*C*=O), 63.5 (C-9a), 60.4 (OCH_2CH_3), 55.9 and 55.2 (C-4 and C-6), 47.8 ($CHCO_2Et$), 29.5 (C-7), 28.2 (C-8), 24.4 (C-9), 23.6 (C-2), 23.3 (C-3) and 14.1 (OCH_2CH_3). Spectroscopic data were in agreement with those reported by other workers.[21,22]

(1*R,9a*R**)-Octahydro-2*H*-quinolizin-1-ylmethanol, (±)-lupinine (1).** A solution of ethyl (1*R**,9a*R**)-octahydro-2*H*-quinolizine-1-carboxylate **14** (0.11 g, 0.51 mmol) in dry Et_2O (2 cm^3) was added to a stirred suspension of $LiAlH_4$ (29 mg, 0.76 mmol, 1.5 equiv.) in dry Et_2O (1 cm^3) cooled to 0 °C. After 1 h, the reaction was quenched by sequential additions of H_2O (0.029 cm^3), aqueous NaOH solution (15% w/v, 0.029 cm^3) and H_2O (0.087 cm^3). A white precipitate formed. EtOAc (6 cm^3) was added, and after a further 30 min of stirring, the mixture was filtered through celite. The filtrate was evaporated *in vacuo*, and the crude product (0.10 g) was purified by column chromatography on silica gel with MeOH–EtOAc (1:4) as eluent to give (±)-lupinine **1** as a pale yellow oil (87 mg, 95%); R_f 0.33 (MeOH–EtOAc 1:4); ν_{max} (film)/cm^{-1} 3333 (m, v br, OH), 2934 (s), 2857 (m), 2806 (m, Bohlmann band), 2762 (m, Bohlmann band), 2677 (w, Bohlmann band), 1444 (m), 1351 (m), 1114 (m), 1088 (m), 1066 (m) and 1037 (s); δ_H (300 MHz; C_6D_6; assignments follow ref. 25) 4.76 (1H, br s, O*H*), 4.14 (1H, dd, *J* 10.7 and 6.1, CH_aH_bOH), 3.75 (1H, dd, *J* 10.7 and 2.0, CH_aH_bOH), 2.56–2.46 (2H, m, 4_{eq}-H, 6_{eq}-H), 2.31–2.17 (1H, m, 3_{ax}-H), 1.80–1.68 (3H, m), 1.62 (1H, dd, *J* 12.0 and 3.4, 4_{ax}-H), 1.60–1.50 (2H, m), 1.45–1.15 (6H, m) and 1.00 (1H, qt, *J* 12.5 and 3.8, 8_{ax}-H); δ_C (75 MHz; C_6D_6) 65.2 (C-9a and CH_2OH), 57.3 (C-4 and C-6), 39.1 (C-1), 31.2 (C-2), 29.9 (C-9), 25.9 (C-7), 25.0 (C-8) and 23.1 (C-3); δ_C (100 MHz; $CDCl_3$) 65.5 (CH_2OH), 64.9 (C–9a), 56.9 (C-4 and C-6), 38.2 (C-1), 30.9 (C-2), 29.4 (C-9), 25.4 (C-7), 24.5 (C-8) and 22.7 (C-3). Spectroscopic data were in agreement with those reported by other workers.[22,25]

(1*R,9a*S**)-Octahydro-2*H*-quinolizin-1-ylmethanol, (±)-epilupinine (2).** A solution of ethyl (1*R**,9a*S**)-octahydro-2*H*-quinolizine-1-carboxylate **15** (0.29 g, 1.39 mmol) in dry Et_2O (6 cm^3) was added to a stirred suspension of $LiAlH_4$ (63 mg, 1.67 mmol, 1.2 equiv.) in dry Et_2O (3 cm^3) cooled to 0 °C. After 75 min, the reaction mixture was filtered through celite, and solids were

and washed with undried (moist) Et_2O. The filtrate was evaporated *in vacuo* to yield epilupinine **2** as a chromatographically pure pale yellow oil (0.22 g, 88%) that decomposed if purification on silica gel was attempted; R_f 0.15 (*ca.* 1% aq. NH_3 in EtOAc); ν_{max} (film)/cm^{-1} 3342 and 3207 (m, v br, OH), 2930 (s), 2858 (m), 2807 (m, Bohlmann band), 2760 (m, Bohlmann band), 2678 (w, Bohlmann band), 1674 (m), 1443 (m), 1371 (m), 1296 (m), 1113 (m), 1093 (m), 1070 (m) and 1014 (w); δ_H (300 MHz; $CDCl_3$) 3.65 (1H, dd, *J* 10.8 and 3.6, C*H*$_a$H$_b$OH), 3.51 (1H, dd, *J* 10.8 and 6.0, CH$_a$*H*$_b$OH), 3.28 (1H, br s, O*H*), 2.80 (2H, br t, *J* 13.2, 4_{eq}-H and 6_{eq}-H), 2.04–1.98 (2H, m, 4_{ax}-H and 6_{ax}-H), 1.93–1.84 (2H, m), 1.79–1.57 (6H, m), 1.45–1.36 (1H, m, C*H*CH$_2$OH) and 1.23–1.16 (3H, m); δ_C (75 MHz; $CDCl_3$) 64.3 (C-9a), 64.0 (*C*H$_2$OH), 56.7 and 56.5 (C-4 and C-6), 43.8 (C-1), 29.5 and, 28.1 (C-2 and C-9), 25.4 (C-7), 24.8 (C-8) and 24.4 (C-3). Spectroscopic data were in agreement with those reported by other workers.[22]

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