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Preparation and reductive transformations of vinylogous sulfonamides (β-sulfonyl enamines), and application to the synthesis of indolizidines

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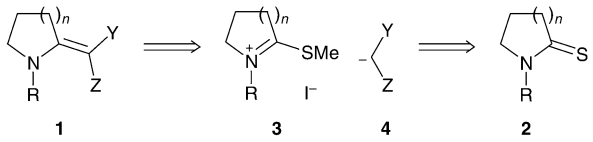
Condensation between the methiodide salts of 1-alkylpyrrolidine-2-thiones and ethyl [(4-methylphenyl)sulfonyl]acetate or 1-[(4-methylphenyl)sulfonyl]propan-2-one afforded several 2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidines in good yield. These β-sulfonyl enamines are sufficiently nucleophilic for cyclisation with internal electrophiles to give sulfone-substituted indolizines, potentially useful scaffolds for alkaloid synthesis. The carbon–carbon double bond in vinylogous sulfonamides was reduced stereoselectively either by catalytic hydrogenation or by treatment with sodium borohydride to yield β-sulfonyl amines. The sulfone group in β-acyl-β-sulfonyl enamines could be removed by hydrogenolysis with sodium amalgam in THF–methanol to give enaminones.

Introduction

Enaminones (β-acylated enamines; vinylogous amides, urethanes and ureas) of general structure N–C=C–C=O are readily prepared intermediates that have found widespread application in organic synthesis because of their versatile reactivity both as nucleophiles and as electrophiles.[1] We ourselves have described several applications of these systems in the synthesis of alkaloids and other nitrogen heterocycles.[2–4] Related systems N–C=C–Z (Z = CN, NO_2) have also featured in our work,[2,5] and we have recently started to explore the applicability of vinylogous sulfonamides (Z = SO_2Ar) in alkaloid synthesis. By incorporating the sulfone group into our systems, we intend to take advantage of two of its most valuable properties: its ability to form α-sulfonyl anions that one can exploit in a variety of synthetically useful transformations; and its ready removal by reductive or, less commonly, oxidative methods once it has served its purpose.[6] While the chemistry of vinylogous sulfonamides and their tautomers has received limited attention in the literature,[7,8] uses in the synthesis of alkaloids are rare. They feature most prominently in several syntheses of pyrrolidine, piperidine, indolizidine, quinolizidine and quinolinone alkaloids by Back and co-workers, where they are encountered as intermediates formed by the conjugate addition of amines to alkynylsulfones.[9] In this article we describe model studies on the synthesis of vinylogous sulfonamides such as **1**, their cyclisation to form indolizidines, a common motif in alkaloid systems,[10] and several further transformations of the products.

Results and discussion

In view of our long-term interest in indolizidine alkaloid synthesis, the vinylogous sulfonamides chosen as models for the present studies incorporate the pyrrolidine motif, as shown in **1** (*n* = 1; Y = SO_2Ar; Z = H). Whereas analogous enaminones **1** (*n* = 1, 2; Y = COR, COAr, CO_2R; Z = H) are readily prepared by Eschenmoser condensation (sulfide contraction) between the corresponding thiolactams **2** (*n* = 1, 2) and α-halomethylcarbonyl compounds,[11] this method fails with α-halomethylsulfones, which react unusually poorly with nucleophiles.[12] However, if thiolactams are activated by pretreatment with electrophiles such as iodomethane, the resulting thioiminium salts **3** can then undergo Knoevenagel-like condensation with relatively acidic compounds such as nitromethane or 1,3-dicarbonyl compounds **4** (Y, Z = CO_2R', COMe, CN, NO_2) to produce β-substituted enamines.[13] We envisaged that this method could be applied to the synthesis of vinylogous sulfonamides **1** (Y = SO_2Ar, Z = H) by using the anions of suitable α-sulfonyl esters or α-sulfonyl ketones **4** (Y = SO_2Ar, Z = COR′) as nucleophilic partners, followed by removal of the carbonyl-containing substituent (Scheme 1). A related condensation, involving the reaction of phenylsulfonylacetonitrile with 1-methylpyrrolidine-2-thione in the presence of silver carbonate, has been reported by Brillon and Sauvé.[14]



1 **3** **4** **2**

Scheme 1

The thiolactams chosen for these model studies, prepared from the corresponding lactams by thionation with phosphorus pentasulfide, included 1-methylpyrrolidine-2-thione[15] **5**, 3-(2-thioxopyrrolidin-1-yl)propyl acetate[16] **6** and ethyl 3-(2-thioxopyrrolidin-1-yl)propanoate[4] **7**. The nucleophilic partners, ethyl [(4-methylphenyl)sulfonyl]acetate[17] **8** and 1-[(4-methylphenyl)sulfonyl]propan-2-one[18] **9**, were prepared in 89% and 98% yields, respectively, by reaction of sodium 4-methylbenzenesulfinate with ethyl bromoacetate or chloroacetone according to reported procedures. Treating the thiolactams with an excess of iodomethane in dry tetrahydrofuran followed by removal of the solvent *in vacuo* afforded the moisture-sensitive methiodide salts, which were used without further purification. The salts were then treated with the sulfones in the presence of base at room temperature (Scheme 2). Optimal yields were obtained with triethylamine as base and dichloromethane as solvent, and reactions generally went to completion if left for *ca.* 72 h.

Excellent yields of products **10** and **11** (>90%) were obtained from the reaction of the sulfonyl ester **8** with thiones **5** and **6**, respectively. The products were obtained as single geometric isomers—probably, for steric reasons, the (*E*)-isomers as illustrated, although efforts to establish the geometry

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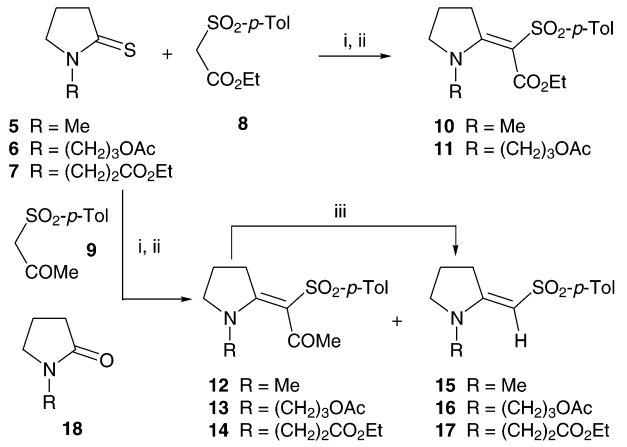
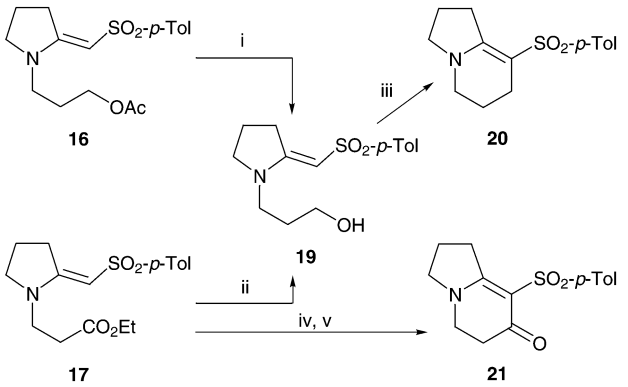


Scheme 2 *Reagents and conditions*: i, MeI, THF, 0 °C, 1–17 h; ii, add **8** or **9**, NEt_3, CH_2Cl_2, rt, 72 h (yields: **10**, 90%; **11**, 95%; **12** + **15**, 11% + 81%; **13** + **16**, 5% + 81%; **14** + **17**, 5% + 70%); iii, TFA, 80–90 °C, 30 min (yields: **15**, 85%; **16**, 87%; **17**, 92%).



Scheme 3 *Reagents and conditions:* i, K_2CO_3, MeOH, rt, 1 h (96%); ii, $LiAlH_4$, THF, rt, 15 h (94%); iii, PPh_3, Im, I_2 MeCN, reflux, 2 h (80%); iv, KOH, EtOH, reflux, 30 min, then HCl; v, K_2CO_3, Ac_2O, MeCN, 50 °C, 2 h, rt, 21 h (71% over 2 steps).

by NMR spectroscopic methods gave ambiguous results. However, attempts to remove the ester group by hydrolysis and decarboxylation failed. With the keto sulfone **9**, the expected products **12**–**14**, formed as single geometric isomers and again assumed to be (*E*) for steric reasons, were always accompanied by the vinylogous sulfonamides **15**–**17**, reflecting spontaneous deacetylation under the reaction conditions. The relative amounts of the two products varied from reaction to reaction, the amount of deacylated product increasing with time. However, the combined yield of the products was in general high. Spontaneous deacetylation has previously been observed with related products derived by condensing lactim ethers with ethyl acetoacetate or acetylacetone,[19,20] and can in fact be promoted by treatment with trifluoroacetic acid. In our hands, the acetyl groups could also be removed easily and cleanly from compounds **12**–**14** by treating them with trifluoroacetic acid at 80–90 °C for 30 min. The overall yields of compounds **15**–**17** by this two-step condensation–deacetylation process were in the range 74–90%. More conveniently but less efficiently, if the mixture of products from the condensation reaction was not separated, but instead treated immediately with trifluoroacetic acid, the overall yields of **15**–**17** were 5–10% lower. In addition, if the condensation between **9** and the methiodide salts was carried out in dichloromethane with potassium carbonate as base, the deacylated products were isolated almost exclusively, although also in diminished yield. The illustrated (*E*)-geometry of the deacylated products **15**–**17** was inferred from the chemical shift of the ring protons at C-3 (*ca.* δ 3.0), the downfield shift of about 0.5 ppm relative to a (*Z*)-analogue[7] arising from the anisotropic deshielding effect of the sulfonyl group. This phenomenon is well precedented with related (*E*)- and (*Z*)-enaminones.[11a] It should be noted that attempts to purify the acetyl products **12**–**14** were usually pointless, as further handling encouraged decomposition; lactams **18** were frequently detected in the NMR spectra after attempted purification.

With compounds **16** and **17** in hand, the next objective was to examine whether the vinylogous sulfonamide unit displayed sufficient "enamine" character to participate in intramolecular cycloalkylation and cycloacylation, respectively, to produce hexahydroindolizine systems. However, because the acetate substituent of the former was not expected to function as a leaving group, an alternative was sought. Hydrolysis of **16** with potassium carbonate in methanol afforded the corresponding alcohol **19** as a brownish oil in 96% yield (Scheme 3). Compound **19** could also be obtained in 94% yield by reducing ethyl 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propanoate **17** with lithium aluminium hydride in THF at room temperature for 15 h; remarkably, the vinylogous sulfonamide was not reduced under these conditions (*vide infra*).

When the alcohol was treated with iodine, triphenylphosphine and imidazole in boiling acetonitrile for 2 h,[21] the desired bicyclic product, 8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydroindolizine **20**, was obtained *via* the detectable but unisolated iodoalkyl intermediate as a crystalline solid in 80% yield. For the acylative cyclisation, the ester group of **17** was hydrolysed with ethanolic potassium hydroxide solution, and the crude potassium carboxylate was heated with acetic anhydride in acetonitrile at 50 °C. Cyclisation of the mixed anhydride intermediate gave 8-[(4-methylphenyl)sulfonyl]-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **21** in 71% overall yield.

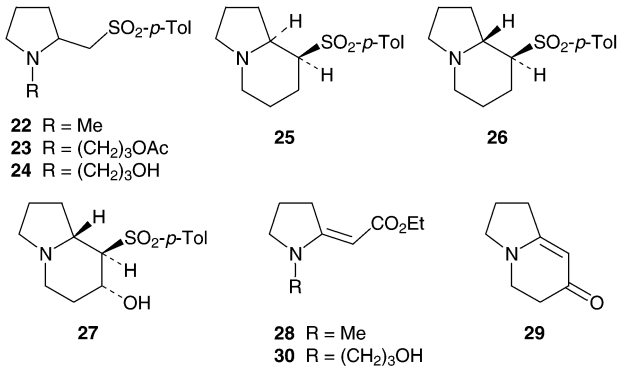
If vinylogous sulfonamides are to be effective intermediates for alkaloid synthesis, then two additional transformations require investigation: the reduction of the C=C double bond, and the removal of the sulfonyl substituent. We have previously achieved the reduction of various enaminones by catalytic hydrogenation or upon treatment with complex metal hydrides.[2] In the present work, we found that catalytic hydrogenation of the simple monocyclic compounds **15** and **16** required some forcing, eventually being accomplished at a pressure of 7.5–10 atm in glacial acetic acid over platinum dioxide. The tertiary amines **22** and **23** were isolated in yields of 84% and 98%, respectively. Reduction of **15** with sodium borohydride in methanol also gave **22**, but in 68% yield, whereas the reduction of the acetoxypropyl compound **16** under these rather basic conditions not only reduced the alkene bond but also cleaved the acetate from the side chain to give alcohol **24** in 85% yield.

With potential alkaloid precursors such as the sulfonylated indolizines **20** and **21**, the reduction of the double bond must be stereoselective, especially if additional substituents are present on the bicyclic nucleus. Our previously published work includes examples of stereocontrolled reduction of analogous bicyclic vinylogous urethanes[22] and cyanamides.[5] We found that the expected *cis*-selective hydrogenation of bicyclic vinylogous sulfonamide **20** under similar conditions to those described above afforded compound **25**, a crystalline solid, in 65% yield. In the ^1H NMR spectrum, the signals for the two methine hydrogen atoms showed a mutual coupling constant of *ca.* 4.6 Hz, confirming that they do not share a *trans*-diaxial relationship. Somewhat surprisingly in view of our experience with vinylogous urethanes, the identical product was obtained in 75% yield when the reduction was performed with sodium borohydride in methanol. In this case, however, the *trans*-dihydrogenated diastereomer **26** was also obtained as a minor product (7%). Interestingly, in a single attempt at oxidative removal of the sulfone from **25** by treatment with *n*-butyllithium and bis(trimethylsilyl) peroxide,[23] only the *trans*-product **26** was recovered in 84% yield, indicating an easy base-induced epimerisation. We have previously experienced similar epimerisations with alkyl indolizidine-8-carboxylates[4,22] and quinolizidine-1-carbonitrile.[5] The equatorial disposition

of the sulfone substituent in **26** presumably makes this the thermodynamically preferred isomer.

The oxoindolizidine **21** proved to be completely resistant to catalytic hydrogenation. However, with sodium borohydride in methanol, a single diastereomeric product was isolated as a clear oil in 64% yield, the ketone also undergoing reduction under these conditions. It was not possible to assign the stereochemistry unambiguously from the NMR spectrum because of overlapping signals, but thermodynamic considerations suggest structure **27**, in which the substituents on the *trans*-fused indolizidine nucleus occupy equatorial positions.

While reductive removal of sulfones from saturated carbon sites is a common synthetic transformation,[24] there are fewer reported examples of the hydrogenolysis of alkenylsulfones, and apparently none involving vinylogous sulfonamides. Although we explored several methods for removing the sulfone group from several of our vinylogous sulfonamides, the most successful involved treatment with sodium amalgam and disodium hydrogen phosphate in THF–methanol at ambient temperature, according to a procedure devised by Trost *et al.*[25] Under these conditions **10** and **21** yielded the corresponding desulfonylated products **28** and **29** in yields of 86% and 77%, respectively, while the acetate **11** underwent concomitant ester hydrolysis to give the alcohol **30** in 87% yield. Products **28** and **30** were once again obtained as (*E*)-isomers; but this finding implies nothing about the geometry of precursors **10** and **11**, since it is known that stereochemistry is not necessarily preserved in the desulfonylation of vinylsulfones with metal amalgams.[26] In these three examples, the products are all comparatively stable enaminones, the spectroscopic data for which agreed with those published elsewhere. Some attempts to desulfonylate vinylogous sulfonamides not bearing the additional stabilising substituent (*e.g.*, **20**) gave ambiguous results, probably because of the susceptibility of the unstabilised enamine product to hydrolysis.



In conclusion, we have demonstrated that vinylogous sulfonamides of the type that might be suitable for use in alkaloid synthesis are readily accessible, and are sufficiently nucleophilic for reaction with internal electrophiles to give useful indolizidine scaffolds for further elaboration. The carbon–carbon double bond can be reduced in a stereocontrolled fashion, and the sulfone group can be removed hydrogenolytically under suitable conditions. Investigations into the application of these results in the synthesis of several alkaloids are now under way.

Experimental

All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) was distilled from Na/benzophenone, and dichloromethane, acetonitrile and triethylamine from CaH_2. 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 Bruker Vector 22 or Bruker IFS 25 spectrometers. NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C) or a Bruker DRX 400 (400.132 MHz for ^{1}H, 100.625 MHz for ^{13}C). $CDCl_3$ 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 preparation of vinylogous sulfonamides

To a stirred solution of 1-alkylpyrrolidine-2-thione (*ca.* 2–11 mmol scale) in distilled THF (5–10 cm^3) was added excess iodomethane (1.7–2.0 equiv.) at 0 °C. In some cases the α-(methylthio)iminium salt precipitated out almost immediately, but in general the reaction was allowed to proceed until TLC showed complete consumption of the thiolactam (1–17 h). The solvent and other volatiles were removed by evaporation, and the residue was dissolved in CH_2Cl_2 (10–20 cm^3). A solution of the sulfones **8** or **9** (1 equiv.) and dry distilled NEt_3 (2 equiv.) in CH_2Cl_2 (5–20 cm^3) was added, and the reaction mixture was stirred at ambient temperature for 72 h. The resulting solution was then washed with water (*ca.* 50 cm^3), and the aqueous phase was extracted with further portions of CH_2Cl_2 (3 × 40 cm^3). The combined organic phases were dried (Na_2SO_4 or $MgSO_4$), filtered and evaporated *in vacuo*. The resulting crude products were when purified by chromatography on silica gel with hexane–EtOAc mixtures as eluent. The following results were recorded.

Ethyl [(4-methylphenyl)sulfonyl](1-methylpyrrolidin-2-ylidene)acetate **10** (3.17 g, 90%) was obtained from 1-methylpyrrolidine-2-thione **5** (1.26 g, 10.9 mmol) and iodomethane (2.65 g, 18.7 mmol) in THF (10 cm^3) stirred at 0 °C for 1 h, followed by evaporation of the solvent, dissolution in CH_2Cl_2 (20 cm^3) and addition of ethyl [(4-methylphenyl)sulfonyl]acetate **8** (2.64 g, 10.9 mmol) and NEt_3 (2.22 g, 21.9 mmol) in CH_2Cl_2 (20 cm^3); needles, mp 102–104 °C (from EtOAc–hexane) (Found: C, 59.0; H, 6.6; N, 4.0. $C_{16}H_{21}NO_4S$ requires C, 59.4; H, 6.5; N, 4.3%); R_f 0.24 (EtOAc); ν_{max} (KBr)/cm^{-1} 2983 (m), 2940 (m), 1741 (s), 1684 (s), 1597 (m), 1327 (s), 1303 (m), 1152 (s), 1086 (m), 1026 (m) and 816 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.79 (2H, d, *J* 8.3, Ar 2-H/6-H), 7.24 (2H, d, *J* 8.3, Ar 3-H/5-H), 4.02 (2H, q, *J* 7.1, OCH_2CH$_3$), 3.67 (2H, t, *J* 7.2, NCH_2), 3.41 (2H, t, *J* 7.8, CH_2C=), 2.97 (3H, s, NCH_3), 2.39 (3H, s, ArCH_3), 2.08 (2H, quintet, *J ca.* 7.3, CH$_2$CH_2CH$_2$) and 1.09 (3H, t, *J* 7.1, OCH$_2$CH_3); δ_C (50 MHz; $CDCl_3$; Me_4Si) 170.2 (C=O), 163.6 (N*C*=C), 142.5 and 142.0 (Ar*C*), 128.8 and 126.8 (Ar*C*H), 94.8 (NC=*C*), 60.2 (O*C*H$_2$CH$_3$), 57.6 (N*C*H$_2$), 39.6 (N*C*H$_3$), 36.2 (*C*H$_2$C=), 21.4 (Ar*C*H$_3$), 20.3 (CH$_2$*C*H$_2$CH$_2$) and 14.0 (OCH$_2$*C*H$_3$); *m/z* 323 (1%, M$^+$), 178 (16), 155 (47), 105 (19), 91 (100) and 65 (12) (Found: M$^+$, 323.1196. $C_{16}H_{21}NO_4S$ requires 323.1191).

Ethyl [1-(3-acetoxypropyl)pyrrolidin-2-ylidene][(4-methylphenyl)sulfonyl]acetate **11** (1.93 g, 95%) was obtained from 3-(2-thioxopyrrolidin-1-yl)propyl acetate **6** (1.00 g, 4.97 mmol) and iodomethane (1.25 g, 8.81 mmol) in THF (10 cm^3) stirred at 0 °C for 1 h, followed by evaporation of the solvent, dissolution in CH_2Cl_2 (20 cm^3) and addition of ethyl [(4-methylphenyl)sulfonyl]acetate **8** (1.09 g, 4.50 mmol) and NEt_3 (1.04 g, 9.29 mmol) in CH_2Cl_2 (5 cm^3); straw-coloured oil; R_f 0.20 (EtOAc–hexane, 1 : 1); ν_{max} (film)/cm^{-1} 2985 (m), 2942 (m), 1741 (s), 1597 (m), 1327 (s), 1303 (m), 1152 (m), 1085 (m), 1026 (m) and 815 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.77 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.24 (2H, d, *J* 8.1, Ar 3-H/5-H), 4.07 (2H, q, *J* 7.1, OCH_2CH$_3$), 3.99 (2H, t, *J* 6.1, CH_2OAc), 3.60 (2H, t, *J* 7.2, NCH_2), 3.36 (2H, t, *J* 7.5, NCH_2), 3.27 (2H, t, *J* 7.8, CH_2C=), 2.38 (3H, s, ArCH_3), 1.99 (3H, s, O$_2$CCH_3), 2.02–1.91 (4H, m, 2 × CH$_2$CH_2CH$_2$) and 1.15 (3H, t, *J* 7.1,

OCH_2CH_3); δ_C (100 MHz; $CDCl_3$; Me_4Si) 169.9 and 167.2 (2 × *C*=O), 163.5 (N*C*=C), 142.0 and 141.3 (Ar*C*), 128.2 and 126.0 (Ar*C*H), 95.0 (NC=*C*), 61.0 (OCH_2CH_3), 59.7 (CH_2OAc), 54.1 (ring NCH_2), 47.3 (chain NCH_2), 35.4 (CH_2C=), 24.8 and 20.6 (2 × $CH_2CH_2CH_2$), 20.0 and 19.6 (ArCH_3 and O_2CCH_3) and 13.3 (OCH_2CH_3); *m/z* (EI) 409 (1.3%, M^+), 364 (11), 350 (46), 254 (14), 210 (12), 194 (24), 169 (11), 168 (100), 122 (28), 120 (12) and 91 (16) (Found: M^+, 409.1546. $C_{20}H_{27}NO_6S$ requires 409.1559).

1-[(4-Methylphenyl)sulfonyl]-1-(1-methylpyrrolidin-2-ylidene) propan-2-one **12** (0.33 g, 11%) and *(2E)-1-methyl-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidine* **15** (2.03 g, 81%) were obtained from 1-methylpyrrolidine-2-thione **5** (1.15 g, 9.98 mmol) and iodomethane (1.52 g, 10.71 mmol) in THF (10 cm^3) stirred at 0 °C for 1.5 h, followed by evaporation of the solvent, dissolution in CH_2Cl_2 (10 cm^3) and addition of 1-[(4-methylphenyl)sulfonyl]propan-2-one **9** (2.12 g, 10.0 mmol) and NEt_3 (2.02 g, 20.0 mmol) in CH_2Cl_2 (10 cm^3). The compounds were separated by chromatography on silica gel with hexane–EtOAc mixtures as eluent. Compound **12**: clear oil, R_f 0.52 (EtOAc–hexane, 1 : 1), decomposing on attempted purification; ν_{max} (film)/cm^{-1} 2926 (w), 1720 (m), 1676 (s), 1598 (m), 1424 (m), 1402 (m), 1320 (s), 1302 (s), 1146 (s), 1086 (m) and 670 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) discernible signals at 7.73 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.28 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.78 (2H, t, *J* 7.4, NCH_2), 3.31 (2H, t, *J* 7.6, CH_2C=), 2.95 (3H, s, NCH_3), 2.40 (3H, s, ArCH_3), 2.31 (3H, s, $COCH_3$) and 2.07 (2H, quintet, *J ca.* 7.2, $CH_2CH_2CH_2$); δ_C (50 MHz; $CDCl_3$; Me_4Si) 189.3 (*C*=O), 174.4 (N*C*=C), 142.7 and 142.3 (Ar*C*), 129.5 and 125.8 (Ar*C*H), 104.0 (NC=*C*), 58.2 (NCH_2), 40.5 (NCH_3), 36.9 (CH_2C=), 30.3 (*C*OMe), 21.4 (ArCH_3), 20.1 (ring C-4); *m/z* 293 (<1%, M^+), 212 (17), 169 (31), 155 (58), 148 (31), 122 (17), 107 (10), 105 (23), 92 (14), 91 (100) and 89 (11) (Found: M^+, 293.1078. $C_{15}H_{19}NO_3S$ requires 293.1086). Compound **15**: colourless spars, mp 80–81 °C (from EtOAc–hexane); R_f 0.24 (EtOAc–hexane, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3012 (w), 2926 (w), 2860 (w), 1588 (s), 1300 (m), 1282 (m), 1132 (m) and 1082 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.82 (2H, d, *J* 8.3, Ar 2-H/6-H), 7.30 (2H, d, *J* 8.3, Ar 3-H/5-H), 4.87 (1H, s, =C*H*), 3.40 (2H, t, *J* 7.1, NCH_2), 3.05 (2H, t, *J* 7.8, CH_2C=), 2.79 (3H, s, NCH_3), 2.43 (3H, s, ArCH_3) and 1.95 (2H, quintet, *J ca.* 7.4, $CH_2CH_2CH_2$); δ_C (50 MHz; $CDCl_3$; Me_4Si) 161.9 (N*C*=CH), 143.4 and 141.8 (Ar*C*), 129.3 and 126.1 (Ar*C*H), 86.7 (NC=*C*H), 54.5 (NCH_2), 33.2 (NCH_3), 31.0 (CH_2C=), 21.4 (ArCH_3) and 20.8 (ring C-4); *m/z* (EI) 252 (12%, $M^+ + 1$), 251 (68, M^+), 187 (21), 186 (18), 160 (6), 112 (9), 105 (12), 96 (100), 94 (14) and 91 (12) (Found: M^+, 251.0968. $C_{13}H_{17}NO_2S$ requires 251.0980).

3-(2-{1-[(4-Methylphenyl)sulfonyl]-2-oxopropylidene}pyrrolidin-1-yl)propyl acetate **13** (50 mg, 6%) and *3-((2E)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate* **16** (710 mg, 81%) were obtained from 3-(2-thioxopyrrolidin-1-yl)propyl acetate **6** (525 mg, 2.60 mmol) and iodomethane (740 mg, 5.21 mmol) in THF (10 cm^3) stirred at 0 °C for 1 h, followed by evaporation of the solvent, dissolution in CH_2Cl_2 (15 cm^3) and addition of 1-[(4-methylphenyl)sulfonyl]propan-2-one **9** (550 mg, 2.59 mmol) and NEt_3 (530 mg, 5.24 mmol) in CH_2Cl_2 (5 cm^3). The compounds were separated by chromatography on silica gel with hexane–EtOAc mixtures as eluent. Compound **13**: clear oil, R_f 0.56 (EtOAc–MeOH, 10 : 1), 0.31 (EtOAc), decomposing on attempted purification; ν_{max} (film)/cm^{-1} 2956 (w), 2930 (w), 1738 (s), 1684 (s), 1464 (m), 1428 (m), 1366 (m), 1320 (m), 1290 (m), 1242 (s), 1154 (m), 1086 (m) and 1046 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) discernible signals at 7.72 (2H, d, *J* 8.3, Ar 2-H/6-H), 7.27 (2H, d, *J* 8.3, Ar 3-H/5-H), 4.05 (2H, t, *J* 6.1, CH_2OAc), 3.78 (2H, t, *J* 7.3, NCH_2), 3.42 (2H, t, *J* 6.9, NCH_2), 3.29 (2H, t, *J* 7.8, CH_2C=), 2.41 (3H, s, ArCH_3), 2.31 (3H, s, =CCOCH_3), 2.17–2.04 and 2.06 (5H, overlapping m and s, CH_2CH_2OAc and O_2CCH_3) and 2.01-1.81 (2H, m, ring $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 189.1 (=C*C*OCH_3), 174.5 (O*C*OCH_3), 170.7 (N*C*=C), 142.4 and 142.3 (Ar*C*), 129.4 and 125.6 (Ar*C*H), 104.0 (NC=*C*), 61.5 (CH_2OAc), 55.0 (ring NCH_2), 49.5 (chain NCH_2), 37.3 (CH_2C=), 30.1 (=CCO*C*H_3), 25.1 (CH_2CH_2OAc), 21.2, 20.7 and 20.1 (ArCH_3, OCOCH_3 and ring C-4); *m/z* (EI) 379 (<1%, M^+), 276 (11), 213 (17), 187 (25), 186 (100), 185 (15), 155 (22), 148 (31), 144 (18), 142 (14), 127 (19), 126 (99), 125 (95), 124 (18), 112 (25), 110 (10), 105 (20), 99 (31), 98 (96), 97 (24) and 91 (64) (Found: M^+, 379.1448. $C_{19}H_{25}NO_5S$ requires 379.1453). Compound **16**: colourless needles, mp 92–93 °C (from EtOAc–hexane) (Found: C, 60.5; H, 6.9; N, 4.0. $C_{17}H_{23}NO_4S$ requires C, 60.5; H, 6.9; N, 4.15%); R_f 0.29 (EtOAc–hexane, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3014 (w), 2974 (w), 1736 (m), 1582 (s), 1230 (s), 1132 (m), 1082 (m), and 576 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.75 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.25 (2H, d, *J* 8.2, Ar 3-H/5-H), 4.94 (1H, s, =C*H*), 4.04 (2H, t, *J* 6.1, CH_2OAc), 3.36 (2H, t, *J* 7.0, NCH_2), 3.20 (2H, t, *J* 7.2, NCH_2), 3.00 (2H, t, *J* 7.8, CH_2C=), 2.40 (3H, s, ArCH_3), 2.05 (3H, s, O_2CCH_3) and 1.95–1.85 (4H, overlapping quintets, *J ca.* 7.2, 2 × $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 170.8 (*C*=O), 161.3 (N*C*=CH), 143.2 and 141.8 (Ar*C*), 129.2 and 125.9 (Ar*C*H), 86.8 (NC=*C*H), 61.5 (CH_2OAc), 52.6 (ring NCH_2), 43.1 (chain NCH_2), 31.1 (CH_2C=), 25.1 (chain $CH_2CH_2CH_2$), 21.3 (ArCH_3) and 20.8 (OCOCH_3) and 20.7 (ring C-4); *m/z* (EI) 337 (4%, M^+), 279 (13), 278 (76), 182(14), 168 (23), 138 (15), 123 (24), 122 (41), 108 (14) 97 (10), 96 (100) and 91 (20) (Found: M^+, 337.1336. $C_{17}H_{23}NO_4S$ requires 337.1348).

Ethyl 3-(2-{1-[(4-methylphenyl)sulfonyl]-2-oxopropylidene} pyrrolidin-1-yl)propanoate **14** (28 mg, 5%) and *ethyl 3-((2E)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propanoate* **17** (350 mg, 70%) were obtained from ethyl 3-(2-thioxopyrrolidin-1-yl)propanoate **7** (300 mg, 1.49 mmol) and iodomethane (230 mg, 1.62 mmol) in THF (10 cm^3) stirred at 0 °C for 17 h, followed by evaporation of the solvent, dissolution in CH_2Cl_2 (15 cm^3) and addition of 1-[(4-methylphenyl)sulfonyl]propan-2-one **9** (320 mg, 1.51 mmol) and NEt_3 (260 mg, 2.57 mmol). The compounds were separated by chromatography on silica gel with hexane–EtOAc mixtures as eluent. Compound **14**: yellow oil; R_f 0.86 (EtOAc–hexane, 1 : 1), decomposing on attempted purification; ν_{max} (film)/cm^{-1} 2976 (w), 2938 (w), 2872 (w), 1664 (s), 1606 (s), 1376 (m), 1300 (m), 1268 (m), 1248 (m), 1204 (m), 1144 (s) and 1056 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) discernible signals at 7.73 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.28 (2H, d, *J* 8.2, Ar 3-H/5-H), 4.16 (2H, q, *J* 7.2, OCH_2CH_3), 3.78 (2H, t, *J* 7.3, NCH_2), 3.63 (2H, t, *J* 6.7, NCH_2), 3.27 (2H, t, *J* 7.8, CH_2C=), 2.72 (2H, t, *J* 6.7, CH_2CO_2Et), 2.41 (3H, s, ArCH_3), 2.31 (3H, s, $COCH_3$), 2.08–2.03 (2H, m, *J ca.* 7.5, $CH_2CH_2CH_2$) and 1.28 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$; Me_4Si) 189.4 (*C*OCH_3), 174.1 (*C*O_2Et), 170.7 (N*C*=C), 142.4 and 142.3 (Ar*C*), 129.4 and 125.7 (Ar*C*H), 104.4 (NC=*C*), 60.9 (OCH_2CH_3), 55.6 (ring NCH_2), 47.8 (chain NCH_2), 37.3 (CH_2C=), 30.3 and 30.2 (CH_2CO_2Et and COCH_3), 21.3 (ArCH_3), 20.1 ($CH_2CH_2CH_2$) and 14.0 (OCH_2CH_3). Compound **17**: clear oil, hardening to a low-melting wax (Found: C, 60.3: H, 6.7; N, 3.9. $C_{17}H_{23}NO_4S$ requires C, 60.5; H, 6.97; N, 4.15%); R_f 0.80 (EtOAc); ν_{max} (film)/cm^{-1} 2982 (m), 2936 (w), 1728 (s), 1678 (s), 1598 (m), 1496 (m), 1464 (m), 1444 (m), 1426 (m), 1376 (m), 1320 (s), 1292 (s), 1256 (m), 1190 (s), 1156 (s) and 1086 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.75 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.27 (2H, d, *J* 8.2, Ar 3-H/5-H), 4.93 (1H, s, =C*H*), 4.11 (2H, q, *J* 7.2, OCH_2CH_3), 3.43 and 3.39 (4H, overlapping t, *J ca.* 7.0, 2 × NCH_2), 2.99 (2H, t, *J* 7.8, CH_2C=), 2.54 (2H, t, *J* 6.9, CH_2CO_2Et), 2.39 (3H, s, ArCH_3), 1.89 (2H, quintet, *J ca.* 7.4, $CH_2CH_2CH_2$) and 1.24 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$; Me_4Si) 171.1 (*C*=O), 160.9 (N*C*=CH), 143.1 and 141.9 (Ar*C*), 129.3 and 126.0 (Ar*C*H), 87.3 (NC=*C*H), 60.9 (OCH_2CH_3), 52.9 (ring NCH_2), 42.0 (chain NCH_2), 31.0 and 30.8 (CH_2C= and CH_2CO_2Et), 21.3 (ArCH_3), 20.9 ($CH_2CH_2CH_2$) and 14.1

(OCH_2CH_3); *m/z* (EI) 337 (28%, M^+), 250 (9), 183 (10), 182 (100), 172(11), 171 (47), 154 (16), 136 (12), 110 (43), 109 (16), 108 (57), 96 (11), 94 (11), 92 (11) and 91 (64) (Found: M^+, 337.1341. $C_{17}H_{23}NO_4S$ requires 337.1348).

General procedure for the deacetylation of acetylated vinylogous sulfonamides

A solution of the acetylated vinylogous sulfonamides **12**–**14** in trifluoroacetic acid (4 cm^3 per mmol of reactant) was heated at reflux for 30 minutes at 80 °C. The reaction mixture was cooled, made basic with aq. Na_2CO_3 solution (10%), extracted with dichloromethane (3 × 30 cm^3), dried ($MgSO_4$) and filtered. The solvent was removed on the rotary evaporator to give the desired vinylogous sulfonamides as chromatographically pure compounds. The yields of products **15**–**17** were 85%, 87% and 92%, respectively. Characterisation of these compounds was dealt with in the previous section.

3-((2*E*)-2-{[(4-Methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate 16: representative one-pot procedure

A solution of 3-(2-thioxopyrrolidin-1-yl)propyl acetate **6** (0.50 g, 2.48 mmol) in THF (10 cm^3) was stirred with iodomethane (0.63 g, 4.44 mmol) at ice-bath temperature for 1 h. The solvent was removed *in vacuo*, and the resulting salt was dissolved in acetonitrile (15 cm^3). 1-[(4-Methylphenyl)sulfonyl]propan-2-one **9** (0.55 g, 2.59 mmol) and NEt_3 (0.52 g, 5.14 mmol) were added, and the solution was stirred under nitrogen at room temperature for 14 h. The solvent was removed *in vacuo*, and the residue was heated in trifluoroacetic acid (10 cm^3) at 80–90 °C for 1 h. The reaction mixture was cooled, made basic with aq. Na_2CO_3 solution (10%), then extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with EtOAc–MeOH (10 : 1) as eluent to give *3-((2E)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate* **16** (0.54 g, 65%) as colourless needles, mp 92–93 °C; characterisation as described above.

3-((2*E*)-2-{[(4-Methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propan-1-ol 19

(a) A solution of 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate **16** (180 mg, 0.53 mmol) in methanol (15 cm^3) containing K_2CO_3 (1.07 g, 7.74 mmol) was stirred for 1 h at ambient temperature. Inorganic solids were removed by filtration and the solvent was evaporated *in vacuo*. The dark viscous residue was dissolved in $CHCl_3$ (25 cm^3), and the resulting solution was washed with saturated aq. NaCl solution (10 cm^3). The phases were separated, and the aqueous layer was back-extracted with $CHCl_3$ (3 × 10 cm^3). The organic extracts were then combined, dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound **19** as a chromatographically pure pale brown oil (150 mg, 96%); R_f 0.23 (EtOAc); ν_{max} (film)/cm^{-1} 3483 (br m), 2944 (m), 2930 (w), 2876 (w), 1584 (s), 1290 (s), 1276 (s), 1128 (s), 1080 (s) and 846 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.74 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.24 (2H, d, *J* 8.2, Ar 3-H/5-H), 4.97 (1H, s, =C*H*), 3.62 (2H, t, *J* 5.9, CH_2OH), 3.37 (2H, t, *J* 7.0, NCH_2), 3.25 (2H, t, *J* 7.2, NCH_2), 2.97 (2H, t, *J* 7.5, CH_2C=), 2.45 (1H, br s, OH), 2.39 (3H, s, $ArCH_3$), 1.89 (2H, quintet, *J ca.* 7.4, ring $CH_2CH_2CH_2$) and 1.77 (2H, quintet, *J ca.* 7.5, chain $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 161.6 (NC=CH), 143.3 and 141.7 (Ar*C*), 129.3 and 125.9 (Ar*C*H), 85.9 (NC=*C*H), 59.5 (CH_2OH), 52.8 (ring NCH_2), 43.2 (chain NCH_2), 31.2 (CH_2C=), 28.7 (CH_2CH_2OH), 21.3 ($ArCH_3$) and 20.8 (ring C-4); *m/z* (EI) 295 (2%, M^+), 140 (10), 126 (11), 111 (90), 97 (9), 96 (100) and 91 (12) (Found: M^+, 295.1240. $C_{15}H_{21}NO_3S$ requires 295.1242).

(b) A solution of ethyl 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propanoate **17** (1.50 g, 4.45 mmol) in THF (20 cm^3) was stirred at room temperature with $LiAlH_4$ (0.25 g, 6.59 mmol) under nitrogen for 15 h. Water (0.5 cm^3), aq. NaOH solution (2.0 M; 0.5 cm^3) and water (1.5 cm^3) were then sequentially added to the reaction mixture. The solids were removed by filtration through celite and washed with CH_2Cl_2 (20 cm^3). Evaporation of the filtrate gave a brown oil, which was purified by column chromatography with EtOAc as eluting solvent. *3-((2E)-2-{[(4-Methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propan-1-ol* **19** was obtained as a pale brown oil (1.24 g, 94%); characterisation as described above.

1,2,3,5,6,7-Hexahydroindolizin-8-yl 4-methylphenyl sulfone 20

3-((2*E*)-2-{[(4-Methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propan-1-ol **19** (200 mg, 0.68 mmol) was dissolved in freshly distilled acetonitrile (10 cm^3), to which was added triphenylphosphine (530 mg, 2.02 mmol, 3.0 equiv.), imidazole (230 mg, 3.38 mmol, 5.0 equiv.) and iodine (340 mg, 1.34 mmol, 2.0 equiv.) at about 5 min intervals. This mixture was heated at reflux under nitrogen for 2 h. The solvent was then removed *in vacuo*, and the residue was partitioned between water (30 cm^3) and CH_2Cl_2 (30 cm^3). The aqueous phase was separated and back-extracted with dichloromethane (2 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated to yield a viscous oil, which was purified by column chromatography on silica gel with $CHCl_3$–EtOH (5 : 1) as eluent. The cyclised product, *1,2,3,5,6,7-hexahydroindolizin-8-yl 4-methylphenyl sulfone* **20** (150 mg, 80%), was obtained as colourless needles, mp 105–106 °C; R_f 0.35 (EtOAc–hexane, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2949 (m), 2849 (m), 1593 (s), 1295 (s), 1143 (m), 1123 (m), 1078 (m), 1000 (w), 811 (m), 660 (m), 590 (m) and 535 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.69 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.24 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.27 (2H, t, *J* 7.0, 3-H), 3.12–3.09 (4H, m, 1-H and 5-H), 2.39 (3H, s, $ArCH_3$), 2.32 (2H, t, *J* 6.1, 7-H), 1.92 (2H, quintet, *J ca.* 7.5, 2-H) and 1.81 (2H, br quintet, *J ca.* 6.1, 6-H); δ_C (50 MHz; $CDCl_3$; Me_4Si) 155.6 (C-8a), 141.8 and 141.7 (Ar*C*), 129.2 and 126.1 (Ar*C*H), 92.5 (C-8), 52.8 (C-3), 44.6 (C-5), 31.2 (C-1), 22.0, 21.4 and 21.2 (C-2, C-6, C-7) and 20.9 ($ArCH_3$); *m/z* (EI) 278 (13%, $M^+ + 1$), 277 (71, M^+), 153 (11), 122 (80), 121 (100), 120 (55) and 91 (8) (Found: M^+, 277.1131. $C_{15}H_{19}NO_2S$ requires 277.1136).

8-[(4-Methylphenyl)sulfonyl]-2,3,5,6-tetrahydroindolizin-7(1*H*)-one 21

A solution of ethyl 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propanoate **17** (300 mg, 0.89 mmol) in ethanolic KOH solution (1.0 M; 20 cm^3) was heated at reflux under nitrogen for 30 min. The solvent was removed *in vacuo,* and the residue was partitioned between water (40 cm^3) and CH_2Cl_2 (40 cm^3). The aqueous phase was washed with CH_2Cl_2 (2 × 40 cm^3), then acidified to pH 5 with conc. aq. HCl and extracted with CH_2Cl_2 (3 × 40 cm^3) and EtOAc (40 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to afford 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propanoic acid as a viscous yellow oil. This oil and acetic anhydride (0.10 g, 1.02 mmol) were dissolved in acetonitrile (20 cm^3), K_2CO_3 (130 mg, 0.94 mmol) was added, and the mixture was stirred at 50 °C for 2 h and at room temperature for a further 21 h. The solvent was removed *in vacuo*, and the residue was partitioned between water (40 cm^3) and CH_2Cl_2 (2 × 30 cm^3). The organic fractions were combined, dried ($MgSO_4$) and evaporated to give a brown oil, which was purified by column chromatography on silica gel with EtOAc–MeOH (4 : 1) as eluent. *8-[(4-Methylphenyl)sulfonyl]-2,3,5,6-tetrahydroindolizin-7(1H)-one* **21** (183 mg, 71%) was obtained as a chromatographically pure off-white solid, mp 243–244 °C; R_f = 0.44 (EtOAc–MeOH, 4 : 1); ν_{max} (film)/cm^{-1} 1638 (s), 1573 (s), 1460 (m), 1364 (m), 1299 (m), 1185 (m), 1143 (s), 1080 (m),

1040 (w), 666 (m) and 598 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.89 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.24 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.60 (2H, t, *J* 7.3, 3-H), 3.53 and 3.48 (4H, overlapping t, *J ca.* 7.7, 1-H and 5-H), 2.47 (2H, t, *J* 7.8, 6-H), 2.37 (3H, s, ArCH_3) and 2.16 (2H, quintet, *J ca.* 7.5, 2-H); δ_C (50 MHz; $CDCl_3$; Me_4Si) 184.5 (*C*=O), 170.4 (C-8a), 142.6 and 141.0 (Ar*C*), 128.8 and 127.4 (Ar*C*H), 106.8 (C-8), 54.6 (C-3), 43.8 (C-5), 34.9 and 34.0 (C-1, C-6), 21.4 (ArCH_3) and 21.0 (C-2); *m/z* (EI) 291 (1.6%, M^+), 227 (21), 226 (100) and 91 (4) (Found: M^+, 291.0927. $C_{15}H_{17}NO_3S$ requires 291.0929).

Catalytic hydrogenation of vinylogous sulfonamides: general procedure

The vinylogous sulfonamide was dissolved in absolute ethanol containing a suspension of platinum dioxide catalyst (10–15% by mass of starting material). The mixture was then stirred under a blanket of hydrogen at a pressure of 7.5–10 atm until TLC indicated complete consumption of starting material (12–48 h). The catalyst was removed by filtration through celite, and the filtrate was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel. The following results were recorded.

4-Methylphenyl (1-methylpyrrolidin-2-yl)methyl sulfone **22** (210 mg, 84%) was obtained by hydrogenating (2*E*)-1-methyl-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidine **15** (250 mg, 0.99 mmol) in absolute ethanol (20 cm^3) over PtO_2 (25 mg) at 10 atm for 48 h. After work-up and chromatography with EtOAc–MeOH (10 : 1) as eluent, the product was isolated as colourless spars, mp 77–78 °C (Found: C, 62.1; H, 7.6; N, 5.55; S, 12.9. $C_{13}H_{19}NO_2S$ requires C, 61.6; H, 7.6; N, 5.5; S, 12.7%); R_f 0.35 (EtOAc–MeOH, 10 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3424 (br, OH), 2967 (m), 2792 (m), 1645 (m), 1598 (m), 1456 (m), 1302 (s), 1148 (s), 1087 (m), 820 (m), 773 (m), 664 (m) and 563 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.79 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.36 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.37 (1H, dd, *J* 14.0 and 2.5, C$H_aH_bSO_2$), 3.03 and *ca.* 2.99 (2H, dd, *J* 14.0 and 9.6, and m, C$H_aH_bSO_2$ and NCH_aH_b), 2.61-2.56 (1H, m, NC*H*), 2.46 (3H, s, ArCH_3), 2.24 (3H, s, NCH_3), 2.15 (1H, distorted td, *J ca.* 9.2 and 8.1, NCH_aH_b), 2.11–2.01, 1.78–1.66 and 1.65–1.56 (1H, 2H and 1H, 3 × m, remaining H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 144.6 and 137.0 (Ar*C*), 129.9 and 127.9 (Ar*C*H), 60.6 (*C*H_2SO_2), 60.2 (C-2), 56.1 (C-5), 40.2 (N*C*H_3), 31.5 (C-3), 22.5 (Ar*C*H_3) and 21.6 (C-4).

3-(2-{[(4-Methylphenyl)sulfonyl]methyl}pyrrolidin-1-yl)propyl acetate **23** (357 mg, 98%) was obtained by hydrogenating 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate **16** (360 mg, 1.07 mmol) in absolute ethanol (30 cm^3) over PtO_2 (36 mg) at 7.5 atm for 24 h. After work-up and chromatography with EtOAc as eluent, the product was isolated as a yellow oil; R_f 0.39 (EtOAc); ν_{max} (film)/cm^{-1} 2961 (m), 2812 (m), 1738 (s), 1598 (m), 1368 (m) and 1303 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.71 (2H, d, *J* 8.3, Ar 2-H/6-H), 7.29 (2H, d, *J* 8.3, Ar 3-H/5-H), 3.98 (2H, br t, *J* 6.3 with fine coupling, CH_2OAc), 3.23 (1H, dd, *J* 13.3 and 2.3, C$H_aH_bSO_2$), 3.00–2.90 (2H, m, C$H_aH_bSO_2$ and ring NCH_aH_b), 2.78–2.72 (1H, m, NC*H*), 2.62 (1H, dt, *J* 12.1 and 8.0, chain NCH_aH_b), 2.38 (3H, s, ArCH_3), 2.30–1.70 and 1.95 (7H, overlapping m and s, ring and chain NCH_aH_b and O_2CCH_3, among others) and 1.70–1.52 (4H, m, remaining H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 170.8 (*C*=O), 144.5 and 136.9 (Ar*C*), 129.7 and 127.6 (Ar*C*H), 62.2 (*C*H_2OAc), 60.9 (*C*H_2SO_2), 58.6 (N*C*H), 52.6 and 50.3 (2 × N*C*H_2), 30.9 (ring C-3), 27.5 (*C*H_2CH_2OAc), 22.7 (ring C-4), 21.4 (Ar*C*H_3) and 20.7 (O_2CCH_3); *m/z* (EI) 339 (7%, M^+), 254 (7), 253 (16), 252 (100) and 170 (40) (Found: M^+, 339.1500. $C_{17}H_{25}NO_4S$ requires 339.1504).

(8R,8aR*)-8-[(4-Methylphenyl)sulfonyl]octahydroindolizine* **25** (130 mg, 65%) was obtained by hydrogenating 1,2,3,5,6,7-hexahydroindolizin-8-yl 4-methylphenyl sulfone **20** (200 mg, 0.72 mmol) in absolute ethanol (5 cm^3) over PtO_2 (30 mg) at 7.5 atm for 24 h. After work-up and chromatography with EtOAc–MeOH (10 : 1) as eluent, the product was isolated as colourless needles, mp 101–102 °C (from EtOAc–hexane) (Found: C, 64.0; H, 7.6; N, 4.9; S, 11.3. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; N, 5.0; S, 11.5%); R_f 0.33 (EtOAc–MeOH, 10 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2963 (m), 1597 (s), 1300 (s), 1146 (s), 1085 (m) and 817 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.78 (2H, d, *J* 8.1, Ar 2-H/6-H), 7.35 (2H, d, *J* 8.1, Ar 3-H/5-H), 3.57 (1H, dt, *J* 9.7 and *ca.* 4.6, C*H*SO_2; assignment confirmed by HETCORR), 3.12 (1H, ddd, *J* 10.9, 6.6 and *ca.* 4.6, 8a-H; assignment confirmed by HETCORR), 2.86 (1H, ddd, *J* 11.0, 6.6 and 4.8, 3-H_{eq}), 2.63 (1H, br dt, *J ca.* 11.6 and 9.0, 3-H_{ax}), 2.50–2.40 and 2.45 (5H, overlapping m and s, 5-H and ArCH_3), 2.15–1.95, 1.95–1.80 and 1.80–1.65 (7H, clusters of m, 1-H, 2-H, 6-H, 7-H_{eq}) and 1.50 (1H, m, 7-H_{ax}?); δ_C (100 MHz; $CDCl_3$; Me_4Si) 144.4 and 135.8 (Ar*C*), 129.6 and 128.3 (Ar*C*H), 62.1 (C-8; assignment confirmed by DEPT), 58.9 (C-8a; assignment confirmed by DEPT), 53.9 (C-3), 48.0 (C-5), 23.7, 22.1, 21.4, 21.3 (ArCH_3) and 20.1.

Reduction of vinylogous sulfonamides with sodium borohydride: general procedure

A solution of the vinylogous sulfonamide in methanol (15 cm^3 per mmol of reactant) was stirred with sodium borohydride (1–1.5 equiv.) under nitrogen at ambient temperature until TLC indicated consumption of the starting material. The reaction mixture was acidified with aq. HCl (1.0 M), filtered through celite and evaporated *in vacuo*. The residue was partitioned between aq. Na_2CO_3 solution (10%; 50 cm^3) and dichloromethane (3 × 40 cm^3). The organic fractions were combined, washed with water (20 cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography on silica gel. The following results were recorded.

4-Methylphenyl (1-methylpyrrolidin-2-yl)methyl sulfone **22** (170 mg, 68%) was obtained by reducing (2*E*)-1-methyl-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidine **15** (250 mg, 0.99 mmol) in methanol (15 cm^3) with sodium borohydride (59 mg, 1.56 mmol) for 30 min. After work-up and chromatography on silica gel with EtOAc–MeOH (10 : 1) as eluent, the product was isolated as colourless needles, mp 77–78 °C; characterisation as described above.

3-(2-{[(4-Methylphenyl)sulfonyl]methyl}pyrrolidin-1-yl)propan-1-ol **24** (270 mg, 85%) was obtained by reducing 3-((2*E*)-2-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidin-1-yl)propyl acetate **16** (360 mg, 1.07 mmol) in methanol (20 cm^3) with sodium borohydride (47 mg, 1.24 mmol) for 1 h. After work-up and chromatography on silica gel with EtOAc–MeOH (10 : 1) as eluent, the product was isolated as a yellow oil; R_f 0.25 (EtOAc); ν_{max} (film)/cm^{-1} 3417 (br m), 2956 (m), 1644 (m), 1597 (m), 1304 (m), 1147 (s), 1086 (m) and 1064 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.79 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.37 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.75–3.67 (3H, m, CH_2OH and C$H_aH_bSO_2$), 3.39 (1H, dd, *J* 13.9 and 2.5, C$H_aH_bSO_2$), 3.19 (1H, ddd, *J* 9.6, 6.2 and 3.6, chain NCH_aH_b), 3.07 (1H, dd, *J* 13.9 and 9.5, ring NCH_aH_b), 2.90–2.84 (2H, m, NC*H* and NCH_aH_b), 2.46 (4H, overlapping s, O*H* and ArCH_3), 2.16 (1H, distorted td, *J ca.* 9.0 and 7.8, chain NCH_aH_b), 2.05 (1H, ddd, *J* 15.7, 12.5 and 7.9, ring 3-H_a), 1.83-1.71 (4H, m, ring 4-H and CH_2CH_2OH) and 1.70-1.52 (1H, m, ring 3-H_b); δ_C (100 MHz; $CDCl_3$; Me_4Si) 144.7 and 136.9 (Ar*C*), 129.9 and 127.8 (Ar*C*H), 63.8 (CH_2OH), 60.8 (*C*H_2SO_2), 59.2 (N*C*H), 54.1 and 53.0 (2 × N*C*H_2), 31.1 and 29.4 (ring C-3 and *C*H_2CH_2OH), 22.7 (ring C-4) and 21.5 (Ar*C*H_3); *m/z* (EI) 297 (1%, M^+), 252 (34), 142 (9), 141 (6), 129 (8), 128 (100), 98 (6), 97 (32), 96 (23), 91 (18) and 84 (21) (Found: M^+, 297.1387. $C_{15}H_{23}NO_3S$ requires 297.1399).

(8R,8aR*)-8-[(4-Methylphenyl)sulfonyl]octahydroindolizine* **25** (150 mg, 75%) and *(8R*, 8aS*)-8-[(4-methylphenyl)*

sulfonyl]octahydroindolizine **26** (14.8 mg, 7%) were obtained by reducing 1,2,3,5,6,7-hexahydroindolizin-8-yl 4-methylphenyl sulfone **20** (200 mg, 0.72 mmol) in methanol (10 cm^3) with sodium borohydride (34 mg, 0.90 mmol) for 24 h. After work-up and chromatography on silica gel with EtOAc–MeOH (10 : 1) as eluent, the major product **25** was isolated as colourless needles, mp 101–102 °C; characterisation as described above. The minor product **27** was a clear oil; R_f 0.38 (EtOAc); ν_{max} (film)/cm^{-1} 2965 (m), 1710 (m), 1597 (m), 1376 (m), 1300 (s), 1150 (s), 1088 (m) and 1036 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.75 (2H, d, *J* 8.2, Ar 2-H/6-H), 7.35 (2H, d, *J* 8.2, Ar 3-H/5-H), 3.06–3.01 (2H, m, C*H*SO_2 and 8a-H), 2.94 (1H, ddd, *J* 12.8, 9.5 and 3.3, 3-H_{eq}?), 2.46 (3H, s, ArCH_3), 2.24–1.91 and 1.80–1.55 (2 × 5H, clusters of m, ring CH_2) and 1.43 (1H, qd, *J* 12.8 and 4.3, 7-H_{ax}?); δ_C (50 MHz; $CDCl_3$; Me_4Si) 144.6 and 135.1 (Ar*C*), 129.6 and 128.7 (Ar*C*H), 66.6 (C-8), 62.5 (C-8a), 53.4 (C-5), 51.6 (C-3), 29.9 (C-1), 25.6, 24.5, 21.5 (Ar*C*H_3) and 20.7; *m/z* (EI) 279 (14%, M^+), 278 (62), 277 (11), 172 (16), 149 (17), 124 (39), 123 (100), 122 (46), 97 (30), 96 (36) and 91 (43) (Found: M^+, 279.1289. $C_{15}H_{21}NO_2S$ requires 279.1293).

(7R,8R*,8aR*)-8-[(4-Methylphenyl)sulfonyl]octahydroindolizin-7-ol* **27** (130 mg, 64%) was obtained by reducing 8-[(4-methylphenyl)sulfonyl]-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **21** (200 mg, 0.69 mmol) in MeOH–$CHCl_3$ (1 : 1; 10 cm^3) with sodium borohydride (39 mg, 1.03 mmol) for 1 h. After work-up and chromatography on silica gel with EtOAc as eluent, the product, a single diastereomer, was isolated as a clear oil; R_f 0.53 (EtOAc); ν_{max} (film)/cm^{-1} 3420 (br m), 2970 (m), 1635 (m), 1570 (m), 1461 (m), 1366 (m), 1300 (m), 1144 (s), 1081 (m) and 666 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.79 (2H, d, *J* 8.3, Ar 2-H/6-H), 7.37 (2H, d, *J* 8.3, Ar 3-H/5-H), 4.16 (1H, d?, *J ca.* 2?, C*H*OH), *ca.* 3.45 (1H, br s, O*H*), 3.07–2.98 (2H, m, 8-H and 8a-H), 2.84–2.74 (2H, m, 3-H_{eq} and 5-H_{eq}), 2.55 (1H, td, *J* 11.9 and 2.8, 3-H_{ax}), 2.46 (3H, s, ArCH_3), 2.23 (1H, br quintet, *J ca.* 9.1, 5-H_{ax}), 2.22–2.04, *ca.* 1.89 and 1.87–1.51 (1H + 1H + 4H, clusters of m, ring CH_2); δ_C (100 MHz; $CDCl_3$; Me_4Si) 145.1 and 135.8 (Ar*C*), 129.9 and 128.3 (Ar*C*H), 70.1 (C-8), 63.6 (C-7), 56.5 (C-8a), 52.9 (C-3), 45.7 (C-5), 32.4, 29.6, 21.6 and 20.8 (Ar*C*H_3); *m/z* (EI) 295 (4%, M^+), 278 (6), 266 (14), 265 (40), 264 (16), 140 (30), 139 (78), 138 (25), 137 (46), 123 (10), 122 (100), 97 (42), 96 (31) and 91 (11) (Found: M^+, 295.1241. $C_{15}H_{21}NO_3S$ requires 295.1242).

Attempted oxidative desulfonylation of (8*R**,8a*R**)-8-[(4-methylphenyl)sulfonyl]octahydroindolizine 25

n-Butyllithium (1.28 M in hexane; 2.0 cm^3, 2.56 mmol) was added by syringe to a solution of the title compound **25** (0.25 g, 0.89 mmol) in dry THF (10 cm^3), cooled under nitrogen to −78 °C. The resulting yellow solution was stirred for 15 min before the addition of neat bis(trimethylsilyl) peroxide (0.19 g, 1.07 mmol). The reaction mixture was stirred overnight at ambient temperature before being quenched with ice-cold aq. saturated $NaHCO_3$ solution (20 cm^3). After extraction with diethyl ether (2 × 30 cm^3), the combined organic fractions were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil. After column chromatography on silica gel with EtOAc–hexane (1 : 1) as eluent, *(8R*,8aS*)-8-[(4-methylphenyl)sulfonyl]octahydroindolizine* **26** (0.21 g, 84%) was isolated as a clear oil; characterisation as described above.

Reductive desulfonylation of vinylogous sulfonamides: general procedure

Sodium amalgam (6%) was prepared by carefully heating a mixture of sodium (1.50 g) and mercury (25.0 g) over an open flame until there was an ignition. The amalgam was stored under nitrogen until required. The amalgam (excess; *ca.* 2 g) was added to a solution of vinylogous sulfonamide (0.5–1 mmol scale) in THF–MeOH (1 : 1; 10–20 cm^3) containing a suspension of Na_2HPO_4 (3 equiv.), and the mixture was stirred at ambient temperature under nitrogen until TLC indicated consumption of the reactant. After removal of solids by filtration, the filtrate was evaporated *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered and purified where necessary. The following results were recorded.

Ethyl (2E)-(1-methylpyrrolidin-2-ylidene)acetate **28** (90 mg, 86%) was obtained by treating ethyl [(4-methylphenyl)sulfonyl](1-methypyrrolidin-2-ylidene)acetate **10** (200 mg, 0.62 mmol) with sodium amalgam (6%; 2.0 g) and Na_2HPO_4 (280 mg, 1.97 mmol) in THF–MeOH (1 : 1; 10 cm^3) for 14 h. The product, a clear oil, was chromatographically pure. R_f 0.41 (EtOAc–hexane 3:7); ν_{max} (film)/cm^{-1} 2978 (m), 2943 (m), 1686 (s), 1595 (s), 1410 (m) and 1377 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.46 (1H, s, =C*H*), 4.09 (2H, q, *J* 7.2, OCH_2CH_3), 3.39 (2H, t, *J* 7.0, NCH_2), 3.13 (2H, t, *J* 7.8, CH_2C=), 2.80 (3H, s, NCH_3), 1.95 (2H, br quintet, *J ca.* 7.3, $CH_2CH_2CH_2$) and 1.25 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$; Me_4Si) 169.1 (*C*=O), 165.3 (N*C*=CH), 77.4 (NC=*C*H), 57.8 (OCH_2CH_3), 54.0 (NCH_2), 32.8 (CH_2C=), 32.1 (NCH_3), 20.7 ($CH_2CH_2CH_2$) and 14.4 (OCH_2CH_3). Data accord with those published elsewhere in the literature.[27] Picrate salt: mp 87.5–88.5 °C (from EtOAc) (Found: C, 45.5; H, 4.4; N, 14.6. $C_9H_{15}NO_2 \cdot C_6H_3N_3O_7$ requires C, 45.2; H, 4.55; N, 14.1%).

2,3,5,6-Tetrahydroindolizin-7(1H)-one **29** (73 mg, 77%) was obtained by treating 8-[(4-methylphenyl)sulfonyl]-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **21** (200 mg, 0.69 mmol) with sodium amalgam (2.0 g) and Na_2HPO_4 (200 mg, 1.41 mmol) in THF–MeOH (1 : 1; 20cm^3) for 14 h. The product, a clear oil, was chromatographically pure. R_f 0.29 (EtOAc–MeOH 10 : 1); ν_{max} (film)/cm^{-1} 2964 (m), 2870 (m), 1616 (m), 1568 (s), 1506 (m), 1369 (m) and 1319 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.97 (1H, s, 8-H), 3.48 (2H, t, *J* 7.9, 5-H), 3.42 (2H, t, *J* 6.9, 3-H), 2.70 (2H, t, *J* 7.7, 1-H), 2.50 (2H, t, *J* 7.9, 6-H) and 2.08 (2H, quintet, *J ca.* 7.3, 2-H); δ_C (50 MHz; $CDCl_3$; Me_4Si) 190.4 (C-7), 169.0 (C-8a), 92.5 (C-8), 52.9 (C-3), 44.8 (C-5), 34.6 (C-6), 31.5 (C-1) and 20.9 (C-2). Data accord with those published elsewhere in the literature.[28]

Ethyl (2E)-1-[(3-hydroxypropyl)pyrrolidin-2-ylidene]acetate **30** (91 mg, 87%) was obtained by treating ethyl [1-(3-acetoxypropyl)pyrrolidin-2-ylidene][(4-methylphenyl)sulfonyl]acetate **11** (200 mg, 0.49 mmol) with sodium amalgam (6%; 2.0 g) and Na_2HPO_4 (210 mg, 1.48 mmol) in THF–MeOH (1 : 1; 10cm^3) for 14 h. The product, purified by chromatography on silica gel with EtOAc as eluent, was obtained as a yellow oil (lit.,[4] mp 62–63 °C); R_f 0.45 (EtOAc); ν_{max} (film)/cm^{-1} 3419 (br m), 2977 (m), 2945 (w), 2874 (w), 1658 (m), 1586 (s), 1148 (m) and 1067 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.54 (1H, s, =C*H*), 4.07 (2H, q, *J* 7.1, OCH_2CH_3), 3.65 (2H, t, *J* 6.0, CH_2OH), 3.41 (3H, overlapping br s and t, *J* 7.1, O*H* and chain NCH_2), 3.31 (2H, t, *J* 7.2, ring NCH_2), 3.13 (2H, t, *J* 7.7, CH_2C=), 1.94 (2H, quintet, *J ca.* 7.4, ring $CH_2CH_2CH_2$), 1.81 (2H, quintet, *J ca.* 6.7, CH_2CH_2OH) and 1.24 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$; Me_4Si) 169.6 (*C*=O), 164.9 (N*C*=CH), 77.0 (NC=*C*H), 59.4 and 58.0 (CH_2OH, OCH_2CH_3), 52.5 (ring NCH_2), 42.9 (chain NCH_2), 32.5 (CH_2C=), 28.7 (CH_2CH_2OH), 20.7 (ring C-4) and 14.4 (OCH_2CH_3); *m/z* (EI) 213 (37%, M^+), 196 (15), 182 (15), 170 (10), 169 (100), 168 (83), 155 (13), 154 (9), 126 (23), 125 (12), 110 (26), 108 (13), 97 (80), 96 (87) and 80 (9) (Found: M^+, 213.1369. $C_{11}H_{19}NO_3$ requires 213.1365). Data accord with those published elsewhere in the literature.[4]

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