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Studies towards the enantioselective synthesis of 5,6,8-trisubstituted amphibian indolizidine alkaloids *via* enaminone intermediates

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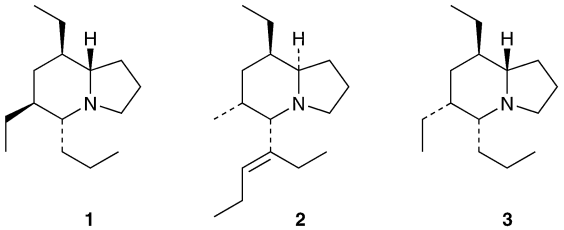
Investigations aimed at the enantioselective total synthesis of indolizidine 223A, a recently described 5,6,8-trisubstituted indolizidine alkaloid from a dendrobatid frog, are described. *tert*-Butyl (2*R*,3*R*)-3-amino-2-ethylhexanoate and its (2*S*,3*R*)-diastereomer, prepared in several steps from lithium *N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amide and *tert*-butyl (2*E*)-hex-2-enoate by the Davies protocol, served as chiral building blocks from which two complementary suites of diastereomeric intermediates were made *en route* to pivotal *tert*-butyl 3-[2-(alkoxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoate intermediates **20** and **21**. Cyclisation of these enaminones, achieved by acid hydrolysis of the *tert*-butyl esters and activation of the liberated carboxylic acids as mixed anhydrides, afforded 6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate esters **28** and **29**. Several further transformations of these potential scaffolds for the synthesis of the target alkaloidal systems are also reported.

Introduction

Over 500 alkaloids belonging to a variety of structural classes have been isolated from the skins of amphibians.[1,2] Among the most numerous are the indolizidine alkaloids,[3] which appear to be sequestered by the animals from dietary sources, especially arthropods.[4] This group of alkaloids includes relatively simple 3,5- and 5,8-disubstituted indolizidines as well as the structurally and stereochemically more complex pumiliotoxins and allopumiliotoxins. Indolizidine 223A, the first naturally occurring 5,6,8-trisubstituted indolizidine alkaloid, was reported in 1997 as a major component of skin extracts from a Panamanian population of the frog *Dendrobates pumilio*.[5] Enough material was isolated for quite extensive FTIR, EIMS and ^{1}H NMR spectroscopic studies, on the strength of which the structure and relative stereochemistry shown in **1** were proposed, although the optical rotation was not measured and the absolute stereochemistry was not determined. Toyooka *et al.* set out to confirm the structure of indolizidine 223A by synthesis, and succeeded in preparing the dextrorotatory enantiomer *ent*-**1**.[6] However, the spectra obtained did not match those of the natural product, which aroused the suspicion that the alkaloid was probably a diastereomer of **1**. In the interim, another trisubstituted indolizidine, alkaloid 249H, had been thoroughly characterised, and was shown to possess a *cis*-arrangement of substituents at C-5 and C-6, as shown in **2**.[7] The synthetic route was thus modified to produce the 5,6-*cis*-disubstituted analogue of **1**.[6] The product, (5*R*,6*R*,8*R*,8a*S*)-(−)-**3**, was identical in all spectroscopic respects to the natural product, thereby necessitating a structural revision of indolizidine 223A. While the absolute configuration of the alkaloid still remains unknown, the structure shown as (−)-**3** appears to be highly probable since it ties in with that unambiguously ascertained for better-known 5,8-disubstituted indolizidine alkaloids such as (−)-indolizidine 207A **4** and (−)-indolizidine 209B **5**. Racemic 6-*epi*-indolizidine 223A, (±)-**1**, has subsequently been synthesised by Harris and Padwa;[8] while Pu and Ma have reported syntheses of both (−)-6-*epi*-indolizidine 223A and (−)-indolizidine 223A.[9] Additional 5,6,8-trisubstituted indolizidine alkaloids have been detected in trace amounts in amphibian skin extracts, but only tentative structures have been proposed at this stage.[2,5]



Our continuing investigations into the use of β-acylated enamines ('enaminones' in general) and related compounds as intermediates in alkaloid synthesis[10,11] take advantage of their ability to function either as ambident nucleophiles or as ambident electrophiles depending on the synthetic strategy envisaged. These readily prepared compounds are easily incorporated into structures that contain the gross skeletal features found in many alkaloidal systems, and they also offer ample opportunity for controlling diastereoselectivity and enantioselectivity. A case in point is our reported enantioselective synthesis[12] of (−)-indolizidine 209B **5**, the key steps in which are shown in Scheme 1. The chiral amine (*R*)-(−)-**6**, prepared from lithium *N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amide and *tert*-butyl (2*E*)-oct-2-enoate by the powerful Davies protocol,[13] was converted in three steps into the pyrrolidine-2-thione (+)-**7**, from which the enaminone (+)-**8** (a vinylogous urethane) was readily prepared by the Eschenmoser sulfide contraction.[14] Chemoselective reduction of the saturated ester to the alcohol (−)-**9** followed by cyclisation *via* the corresponding iodide produced the hexahydroindolizine (+)-**10**, which is itself an enaminone. Diastereoselective reduction of **10** yielded (−)-**11**, which was converted by standard methods into the target alkaloid (−)-**5**. We envisaged that this route could be adapted for the enantioselective synthesis of 5,6,8-trisubstituted indolizidines such as **1** and **3**. However,

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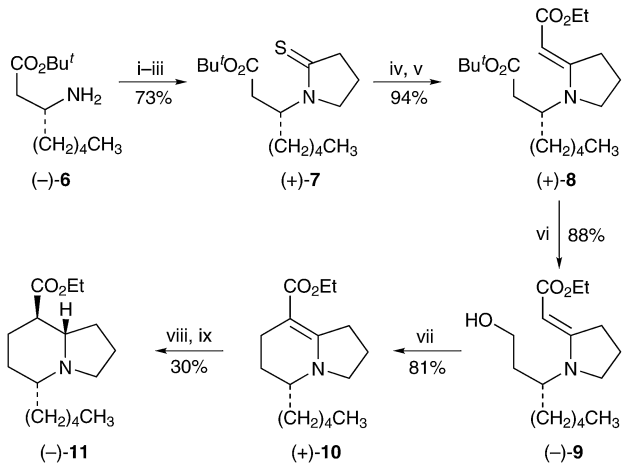
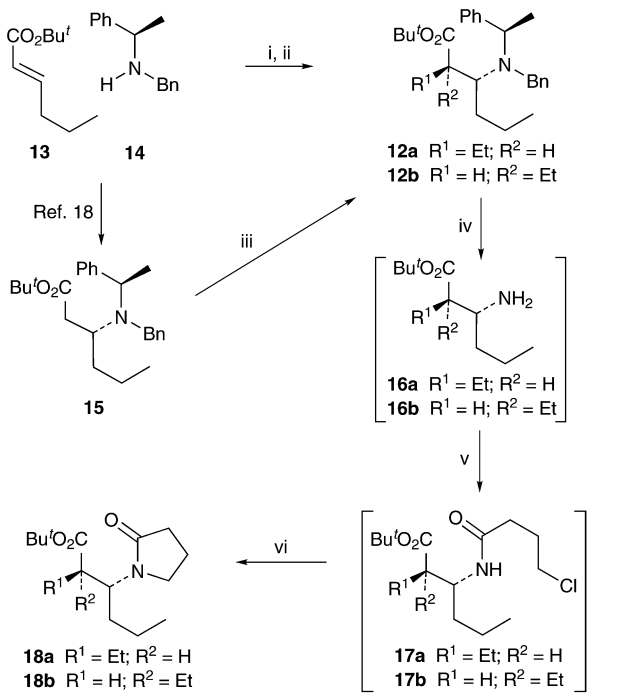


Scheme 1 *Reagents and conditions*: i, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, reflux; ii, $KOBu^t$, Bu^tOH, rt; iii, Lawesson's reagent, PhMe, reflux (73% over 3 steps); iv, $BrCH_2CO_2Et$, MeCN, rt; v, Ph_3P, Et_3N, MeCN, rt (94% over 2 steps); vi, $LiAlH_4$, THF, rt (88%); vii, I_2, imidazole, Ph_3P, PhMe, 110 °C (81%); viii, H_2 (1 atm), PtO_2, AcOH, rt; ix, NaOEt (cat.), EtOH, reflux (30% over 2 steps).

two important additional features would need to be addressed. Firstly, instead of the chiral amine **6**, a chiral α-alkyl β-amino ester **12** containing two contiguous stereocentres of known absolute configuration would be required from the outset. Secondly, manipulation of the ethoxycarbonyl substituent in late intermediates such as **11** becomes necessary in order to elaborate the alkyl substituent at C-8. The extent to which our expectations were realised is described in this paper.



Scheme 2 *Reagents and conditions*: i, **14** + *n*-BuLi, THF, −78 °C, 30 min, then add **13**, 3 h; ii, EtI, −78 °C to rt, 18 h (**12a** + **12b**, 58 : 42, 36% over 2 steps); iii, LDA, THF, −78 °C, 1 h, then EtI, −78 °C, 1h, −78 °C to rt, 18 h (**12a** + **12b**, 56 : 44, 88%); iv, H_2 (7 atm), 10% Pd/C, AcOH, rt, 72 h; v, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, rt, 18 h; vi, Bu^tOK, Bu^tOH, rt, 36 h, then separation by chromatography (**18a**, 39% over 3 steps; **18b**, 24% over 3 steps).

Results and discussion

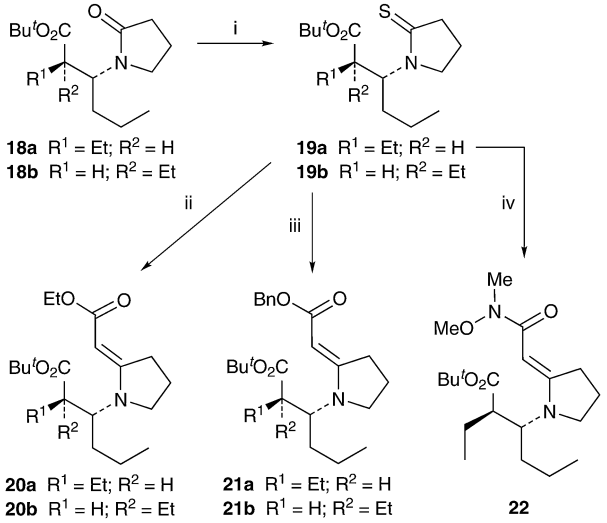
The Davies group has achieved the stereocontrolled synthesis of chiral α-alkyl β-amino esters by three modifications of their basic strategy: using a trisubstituted alkenoate of defined geometry in place of the *trans*-disubstituted alkenoate; trapping the intermediate enolate formed in the conjugate addition to *trans*-disubstituted alkenoates *in situ* with suitable electrophiles (the tandem approach); or treating ester enolates generated from pre-formed chiral β-amino esters with electrophiles (the consecutive approach). The first strategy has been applied to cycloalkene-1-carboxylates, where the amine and ester end up *syn* to each other on the ring;[15] and to (*E*)-2-alkylalk-2-enoates, in which case the amine and 2-alkyl substituents are preferentially *syn*.[16] The tandem and consecutive approaches give yields and diastereoselectivities that depend quite substantially on the reaction conditions, substrate structure and steric effects of the alkylating agent, although in general there is a preference for an *anti* orientation of the 2-alkyl and amine substituents.[17] Because the commencement of our investigations, like those of Padwa and Ma, antedated the structural revision of indolizidine 223A, we believed that we required the *anti* α-alkyl β-amino ester **12a**. We accordingly chose to investigate tandem and consecutive approaches to **12** with *tert*-butyl (2*E*)-hex-2-enoate[18] **13** and (+)-*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amine **14** as precursors.

The tandem method entailed adding the alkenoate over 30 min to the amide anion, generated by treating the parent amine **14** with *n*-butyllithium in THF at −78 °C (Scheme 2). After 3 h, an excess of iodoethane was added, and the reaction mixture was allowed to stand at ambient temperature for 18 h. An inseparable mixture of two diastereomers **12a**,**b** in a ratio of about 58 : 42 (established both by NMR spectroscopy and by HPLC) was isolated in a poor yield of 36%, a result consistent with similar findings by Davies and Walters.[17b] In the consecutive approach, when pre-formed (+)-*tert*-butyl (3*R*)-3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]aminohexanoate[9,18] **15** was treated with LDA in THF at −78 °C followed by the addition of excess iodoethane, the isolated yield of **12a**,**b** was improved to 88%, although the ratio of diastereomers was essentially the same (56 : 44). The identity of the major isomer could not be established at this stage, but later results (*vide infra*) proved that it was indeed the expected *anti* product. It is worth noting that Pu and Ma were able to prepare the *syn*-adduct **12b** in 67% yield and 98% diastereomeric excess from the (*R*)-(+)-amine **14** and *tert*-butyl (2*E*)-2-ethylhex-2-enoate.[9] The ^{13}C NMR spectrum reported for this diastereomer corresponds quite closely with that of our minor diastereomer.

Debenzylating the diastereomeric mixture **12a**,**b** to give the primary amines **16a**,**b** was accomplished by hydrogenolysis under pressure (7 atm) over palladium catalysts (Scheme 2). When a solution of isomers **12** in methanol was hydrogenated over Pearlman's catalyst (20% palladium hydroxide on charcoal), the primary amines **16** could be isolated after work-up, but attempted purification resulted in drastically diminished yields as reaction with atmospheric carbon dioxide rapidly resulted in the formation of solid products, presumably carbonate and/or carbamate salts.[19] Hydrogenolysis in acetic acid over 10% palladium on charcoal was more successful, since the amines could be preserved in solution in protonated form until required. However, even after prompt neutralisation and purification, the isolated yield of primary amines was 47% at best. The ratio of diastereomers (56 : 44) was similar to that in the precursors. Since speedy conversion into more robust intermediates was clearly advisable at this stage, the mixture of primary amines **16** was acylated with 4-chlorobutanoyl chloride to give amides **17a** and **17b**, which could be separated by column chromatography on silica gel. However, even these compounds were found to decompose rather rapidly. In the end, our most successful strategy involved a sequential procedure in which the crude primary amines formed by hydrogenolysis in acetic acid were immediately treated with 4-chlorobutanoyl chloride, after which the unpurified mixture of amide diastereomers **17** was cyclised by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol to give the separable lactams **18a** and **18b** in variable yields (*ca.* 65% overall). Once again, unambiguous confirmation of the

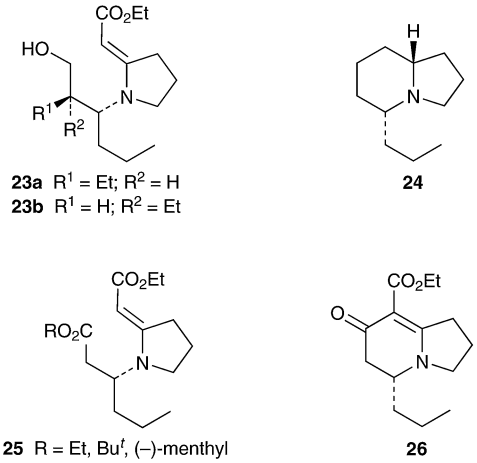
relative stereochemistry of these two products was not possible, but was inferred with hindsight from products formed later in the reaction sequence. The ^{1}H and ^{13}C NMR spectra of the two isomers were very similar, but the specific rotations had opposite signs. (In general in these investigations, compounds of the *anti* series proved to be dextrotatory, while those of the *syn* series were laevorotatory.) A noteworthy observation is that the strongly basic conditions required for cyclisation effected a degree of epimerisation at the enolisable α-position. This was confirmed by subjecting the individual uncyclised amides **17a** and **17b** to the basic cyclisation conditions; in either case, a mixture of diastereomeric lactams was formed, with the *anti* product **18a** again being dominant. Davies *et al.* have reported similar base-induced epimerisation with 2-aminocycloalkanecarboxylates.[15a]

Thionation of lactams **18a** and **18b**, accomplished with Lawesson's reagent in boiling toluene, produced the thiolactams **19a** and **19b** in yields of 81 and 95%, respectively, thereby opening the way to forming the pivotal enaminone intermediates by the Eschenmoser sulfide contraction procedure (Scheme 3). Reaction between each thiolactam and ethyl bromoacetate or benzyl bromoacetate in acetonitrile smoothly produced *S*-alkyl salts, from which the desired vinylogous urethanes **20** and **21** were generated by treatment with triphenylphosphine and triethylamine. The ethyl esters **20a** and **20b** were isolated in better than 96% yield, while the yields of benzyl esters **21a** and **21b** were somewhat lower (90 and 81%, respectively). In all cases the (*E*)-geometry of the newly formed double bond was inferred from the through-space deshielding of the methylene protons on C-3 by the carbonyl group[14a] (δ_H >3.0). No useful products were obtained when bromoacetone was used as the alkylating agent – an unfortunate failure, since this reactant would have introduced a carbon chain of the correct length for the 8-ethylindolizidine target. We also considered Weinreb amides[20] as possible candidates for late-stage chain extension, and to this end performed the sulfide contraction between the major thione **19a** and *N*-methoxy-*N*-methyl-2-bromoacetamide [21] to give the vinylogous urea **22** in 91% yield. This appears to be only the second time in which an enaminone incorporating a Weinreb amide has been reported.[21]

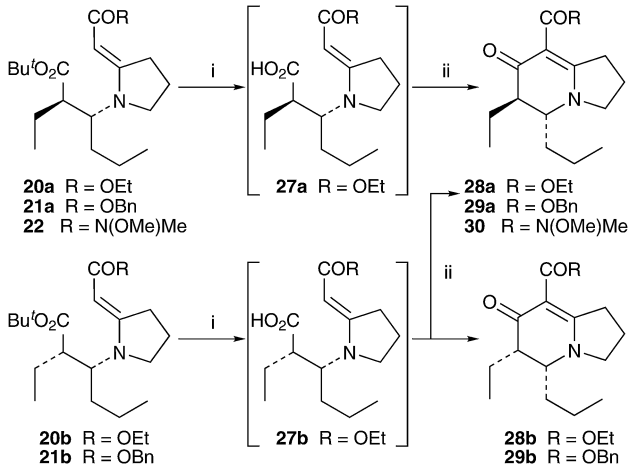


Scheme 3 *Reagents and conditions*: i, Lawesson's reagent, toluene, reflux, 18 h (**19a**, 81%; **19b**, 95%); ii, $BrCH_2CO_2Et$, MeCN, rt, 76 h, then PPh_3, NEt_3, rt, 3–5 h (**20a**, 97%; **20b**, 96%); iii, $BrCH_2CO_2Bn$, MeCN, rt, 18 h, then PPh_3, NEt_3, rt, 3–5 h (**21a**, 90%; **21b**, 81%); iv, $BrCH_2CON(OMe)Me$, MeCN, rt, 40 h, then PPh_3, NEt_3, rt, 3–5 h (**22**, 91%).

Following the precedent established in our synthesis of indolizidine 209B (*cf.* **8** → **9**, Scheme 1), the next step to be carried out was the chemoselective reduction of the saturated *tert*-butyl ester in the enaminone intermediates **20** with lithium aluminium hydride in THF to give alcohols **23**, the precursors for alkylative cyclisation to create the indolizidine core. To our consternation, repeated attempts to achieve this transformation with the ethyl esters **20** failed, no matter how we varied the solvent, temperature or reductant. The quality of the reagent and solvent was not at fault since, when we repeated the reported transformation **8** → **9** in parallel with the attempted reductions of **20** using exactly the same batch of reactant and solvent, the former proceeded smoothly while the latter returned only the starting material. It appears that the additional ethyl substituent α to the *tert*-butyl ester in **20** increases steric hindrance at the carbonyl group to such an extent that reduction cannot proceed. At this stage a change in strategy was indicated. We reasoned that, if we could hydrolyse the *tert*-butyl esters in compounds **20** to the corresponding carboxylic acids, we should be able to carry out an acylative cyclisation to form 2,3,5,6-tetrahydroindolizin-7(1*H*)-ones, which could then be deoxygenated at a later stage. The reason for our optimism lay in our reported synthesis of the simple alkaloid indolizidine 167B **24**, among others, one step of which entailed acid- or base-induced hydrolysis of ethyl, *tert*-butyl or (−)-menthyl esters **25** and cyclisation of the carboxylic acid intermediate *via* a mixed anhydride to yield the product **26** in overall yields of up to 89%.[18,22]



In the event, when solutions of **20a** and **20b** in trifluoroacetic acid were maintained at ambient temperature for 3 h before neutralisation and work-up, (2*R*,3*R*)-3-[(2*E*)-(2-ethoxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoic acid **27a** and its (2*S*,3*R*)-isomer **27b** could be isolated and characterised (Scheme 4), although attempts at purification



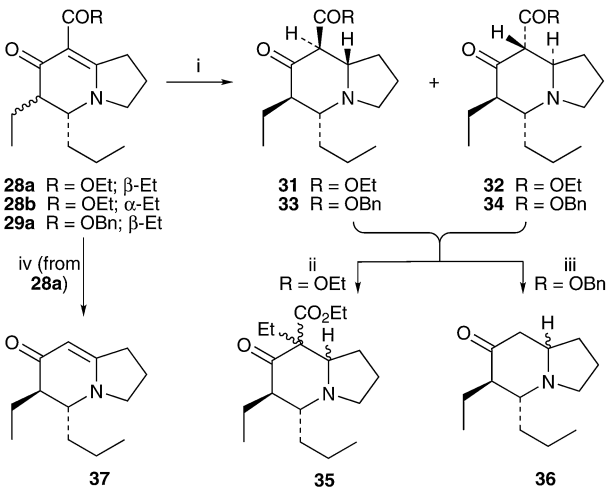
Scheme 4 *Reagents and conditions*: i, CF_3CO_2H, rt, 3 h; ii, Ac_2O, K_2CO_3, MeCN, rt, 18 h, then reflux, 3 h. [Yields from (2*R*,3*R*)-precursors: **28a**, 85% over 2 steps; **29a**, 80% over 2 steps; **30**, 83% over 2 steps. Yields from (2*S*,3*R*)-precursors: **28a** + **28b**, 52%, *ca.* 3 : 1, over 2 steps; **29a** + **29b** + mixed fraction, 32% + 12% + 9% over 2 steps.]

resulted in poor recovery of products. In general, it was not necessary to purify these acids; simply evaporating the trifluoroacetic acid and then treating the crude product with acetic anhydride and potassium carbonate in dry acetonitrile yielded ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylates. However, in this case the two diastereomeric precursors showed an unexpected difference in behaviour, with reaction temperature also playing a crucial role. The vinylogous urethane **20a** consistently produced the expected 5,6-*trans*-disubstituted product, ethyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28a**, in 85% yield after 24 h of stirring at room temperature, followed by 3 h of heating under reflux. By contrast, the vinylogous urethane **20b** produced a mixture of the 5,6-*trans*- and *cis*-disubstituted products **28a** and **28b** in about 52% overall yield when warmed at 50 °C for the same period. If we started with the purified (2*S*,3*R*)-carboxylic acid **27b** and heated the cyclisation reaction mixture under reflux for 18 h, the sole product isolated, in about the same modest yield, was the 5,6-*trans*-disubstituted product **28a**. In other words, under these conditions, the ethyl group in the (2*S*,3*R*)-series undergoes epimerisation at the enolisable position during or after the cyclisation, no doubt induced by the base present in the reaction medium (either potassium carbonate, or the potassium acetate generated). Since the isolated products maintained optical activity, alternative explanations for the stereochemical inversion involving retro-Mannich or retro-Michael ring opening/ring closing equilibria[23] seem not to be tenable, as both would also have led to racemisation. The relative stereochemistry of the cyclised product **28a** was confirmed by NOESY spectroscopy, which showed no interaction between the *trans*-disposed protons at C-5 and C-6, but a clear interaction between 5-H and both sets of protons on the ethyl substituent attached to C-6. This result also supports the relative stereochemistry assigned to all precursors leading up to these products.

To confirm that the isomerisation of the C-6 ethyl group was indeed occurring, we repeated the two-step hydrolysis/intramolecular acylation sequence with the benzyl esters **21a** and **21b**. Following room-temperature cleavage of the *tert*-butyl group with trifluoroacetic acid, the unpurified carboxylic acid intermediates were heated under reflux in acetonitrile containing acetic anhydride and potassium carbonate for 18 h. From the (2*R*,3*R*)-precursor **21a**, benzyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29a** was isolated as the sole isomer in 80% yield. Its NMR spectra matched those obtained for the corresponding ethyl ester **28a**. The diastereomeric vinylogous urethane **21b**, on the other hand, produced the epimerised product **29a** as the major isomer in 32% isolated yield, together with a mixed fraction (9%) and 12% of the minor isomer, benzyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29b**. Finally, hydrolysis and cyclisation of the (2*R*,3*R*)-vinylogous urea **22** produced only the expected indolizinone **30** in 83% yield, without apparent deleterious effect on the Weinreb amide.

A fortuitous consequence of the cyclisation studies is that the problem we encountered right at the outset of the synthesis, *viz.* the formation of diastereomers, was no longer of any consequence, since in principle *the cyclisation step allows the two diastereomers to converge*, *forming a single*, *thermodynamically stable product* – unfortunately, the wrong one for ultimate conversion into indolizidine 223A. However, the structure of the natural product had not yet been revised when we obtained these results, and so we were encouraged to proceed with the synthesis. With two of the putative target's stereogenic centres in place, the next objective was to introduce the remaining two by a stereoselective reduction of the carbon–carbon double bond of the enaminone unit, a task for which we had established ample precedent in a variety of previous syntheses.[12,18,22,24] Our experience has been that steric factors favour the preferential delivery of hydride reductants to the bridgehead position C-8a on the face of the double bond *anti* to the substituent at C-5 (the *re* face in this case); isomeric mixtures may be formed at C-8, but base-mediated epimerisation facilitates conversion into the isomer containing the equatorial C-8 substituent. Catalytic hydrogenation also occurs on the face of the double bond opposite to the C-5 substituent, with the expected *cis*-stereocontrol at both C-8 and C-8a. In the present case, however, the additional substituent at C-6 lies within the same topos as the incoming reductant, thereby introducing a further steric factor whose effect on the stereochemical outcome of the double bond reduction is likely to be significant.

Our normally successful conditions for catalytic hydrogenation with acetic acid as solvent and platinum dioxide as catalyst failed to reduce the double bond of **28a**. However, following a good precedent for the stereoselective reduction of the alkene bond in bicyclic β-keto esters similar to **28a**,[25] we achieved a chemoselective reduction of the double bond with lithium aluminium hydride in tetrahydrofuran at −78 °C (Scheme 5). Two isomeric octahydroindolizinones were obtained in a ratio of 3 : 1 and an overall yield of 79%. ^{13}C NMR spectroscopic signals for the saturated ketone and ester groups in the major isomer at δ 205.7 and 168.6 (δ 208.5 and 169.0 in the minor isomer), respectively, attested to the preservation of both carbonyl groups under the reaction conditions. Spectroscopic evidence points to structure **31**, *i.e.* ethyl (5*R*,6*R*,8*S*,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate, as the major isomer. Support for a *cis*-relationship of the hydrogen atoms at positions C-5 and C-8a was provided by a strong Bohlmann band[26] at 2801 cm^{-1} in the FTIR spectrum, a feature that arises from the antiperiplanar alignment of these hydrogen atoms with the lone pair on nitrogen, and which also implies a *trans*-fused indolizidine ring system. Most importantly, diagnostic new signals for the methine protons at C-8 and C-8a in the ^{1}H NMR spectrum also support the proposed stereochemistry. The signal for 8-H, a doublet at δ 3.31, shows a coupling constant of 11 Hz, which suggests a *trans*-diaxial relationship with its neighbour, and an equatorial disposition of the ester substituent. The matching coupling constant of 11 Hz for 8a-H is found in the double double doublet signal at δ 2.73. The identity of the minor isomer is less certain because most of its signals in the ^{1}H NMR spectrum were obscured by those of the major isomer. However, two well-separated signals – a doublet ($J \approx 10.3$ Hz) at δ 3.29 and a broad doublet ($J \approx 11$ Hz) with unresolved fine coupling at δ 2.98 – appear to be due to 8-H and 8a-H, respectively. If these assignments are correct and 8-H



Scheme 5 *Reagents and conditions*: i, $LiAlH_4$, THF, −78 °C, 2.5 h, then work-up (yield from **28a**: **31** + **32**, *ca.* 3 : 1, 79%; yield from **28b** :**31** + **32**, *ca.* 4 : 1, 65%; yield from **29a**: **33** + **34**, *ca.* 3 : 1, 73%); ii, NaH, THF, 0 °C, 1.5 h, then EtI, rt, 7 d (**35**, *ca.* 4 : 1 mixture of isomers, 35%); iii, H_2 (1 atm), 10% Pd/C, EtOH, rt, 18 h (**36**, mixture of isomers, 52%); iv, aq. NaOH (1 M), reflux, 1.5 h, then conc. HCl, reflux, 30 min (**37**, 84%).

and 8a-H are also *trans* to each other, then the minor isomer is likely to have the (5*R*,6*R*,8*R*,8a*R*) configuration as shown in **32**, and the ring fusion in the indolizidine system can only be *cis*, with the lone pair and 8a-H *cis* to each other. In this case, hydride must be delivered to C-8a from the *si* face of the double bond, probably as a result of steric hindrance to the *re* face by the C-6 ethyl substituent. Remarkably, when the hydride reduction was repeated with ethyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28b** (that is, the minor isomer of the bicyclic vinylogous urethane, with the C-5 and C-6 substituents *cis* to each other), exactly the same pair of indolizidine isomers was obtained in 65% yield and a ratio of 4 : 1. In other words, the ethyl substituent at the enolisable C-6 position appears to have epimerised once again under the basic reaction (or work-up) conditions. For comparison, the (5*R*,6*R*)-benzyl ester **29a** was also reduced under comparable conditions. Two principal inseparable isomers (ratio 3 : 1, by NMR spectroscopy) were obtained in an overall yield of 73%. Since the spectroscopic properties paralleled those of the ethyl esters, structures **33** and **34** are tentatively proposed. Attempted reduction of the hexahydroindolizinone **30** incorporating the Weinreb amide yielded unidentifiable products.

If the route described thus far is to be generally suitable for making natural or unnatural 5,6,8-trialkyl indolizidines, then a final suite of transformations must still be explored: introduction of an alkyl substituent at C-8, and defunctionalisation of the carbonyl group at C-7. Attempts to achieve the first of these tasks met with mixed success. Although the ester group of **31** might be viewed as the obvious forerunner of the two-carbon chain in the desired target alkaloids (*e.g.* by reduction and chain extension), several operationally simpler, more direct approaches were selected for initial investigation. Firstly, since compounds **31**–**34** are β-keto esters, we explored the feasibility of α-alkylation followed by ester hydrolysis and decarboxylation. We found that the isomer mixture **31**/**32** was readily deprotonated with sodium hydride in THF, but subsequent reaction with iodoethane was inefficient, producing a mixture of isomeric products **35** in modest yield (30–40%; *ca.* 4 : 1 by NMR spectroscopy). Apart from obvious NMR spectroscopic signals for the additional ethyl substituent and the loss of the signal for 8-H, the only other notable spectroscopic feature was a Bohlmann band at 2796 cm^{-1} in the infrared spectrum, which suggests the retention of a *trans*-fused ring junction in the product. Unfortunately, all attempts to hydrolyse and decarboxylate the ester group in this crowded system under a variety of conditions (including boiling with 1 M aqueous sodium hydroxide or 48% hydrobromic acid, or with sodium chloride in DMSO) failed. Ethylation of the mixture of benzyl esters **33**/**34** was even poorer; moreover, subsequent attempts to cleave the benzyl ester by hydrogenolysis over palladium on carbon left the ethylated intermediate untouched. Changing the order of the steps also proved to be futile; while the benzyl ester could be removed from the isomer mixture **33**/**34** by hydrogenolysis over palladium on carbon followed by decarboxylation, attempts to generate and ethylate an enolate from the resulting unstable product **36** under kinetic conditions (LDA, THF, −78 °C) failed dismally. Finally, the bicyclic vinylogous urethane **28a** could be hydrolysed and decarboxylated quite readily to give the enaminone **37** in good yield (84%). However, attempts to alkylate this nucleophilic intermediate exclusively on the enamine carbon atom gave inconclusive results.

In the final analysis, the synthetic approach adopted in this work was scuppered by a more serious problem: the inability to remove the carbonyl group at C-7. All attempts to prepare suitable derivatives of **31** for defunctionalisation, including the 1,3-dithiane and *p*-toluenesulfonylhydrazone, were fruitless. Since we have previously been able to form derivatives of related 5-alkylindolizidin-7-ones unsubstituted at C-6,[18,22,27] it seems that the additional substituent at this site in **31** once again provides a formidable steric check to further reaction, as it did in the attempted reduction of **20** to **23**. The electrophilic carbonyl group of **20** is effectively the Trojan horse in our approach: while the acylative cyclisation **20** → **28** was excellent for creating the indolizidine nucleus, it necessarily resulted in the formation of a ketone buttressed on both sides, and therefore far less susceptible to attack by nucleophiles.

In conclusion, although the strategy described in this paper was ultimately unsuitable for the synthesis of indolizidine 223A itself, the results obtained provide valuable insights into the synthesis and reactivity of multiply-substituted indolizidin-7-ones. Furthermore, our original plan of proceeding by way of an alkylative cyclisation, which would avoid the troublesome carbonyl group at C-7, still presents tantalising prospects for future investigations provided that we can devise viable alternative routes to cyclisation precursors such as the alcohols **23**. We are currently exploring routes involving the preparation of stereochemically unambiguous enaminone intermediates related to **23** from derivatives of homochiral 3-amino-2-ethylhexan-1-ols.[28]

Experimental

All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) was distilled from Na/benzophenone; dichloromethane, acetonitrile and triethylamine from CaH_2; and toluene from Na metal. 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 Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C), Bruker 300 (300.139 MHz for ^{1}H, 75.035 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. Optical rotations were measured on a Jasco DIP-370 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

tert-Butyl (2*R*,3*R*)-3-{*N*-Benzyl-*N*-[(1*R*)-1-phenylethyl]amino}-2-ethylhexanoate 12a and its (2*S*,3*R*) epimer 12b

(a) Tandem approach. A solution of (1*R*)-*N*-benzyl-α-methylbenzylamine **14** (Aldrich; 0.30 cm^3, 300 mg, 1.42 mmol) in dry THF (6 cm^3) in a flame-dried, nitrogen-purged 3-necked flask was cooled to −78 °C. *n*-BuLi (1.45 M in hexane, 0.89 cm^3, 1.29 mmol) was added dropwise, and the deep purple solution obtained was stirred for 30 min. *tert*-Butyl (2*E*)-hex-2-enoate[18] **13** (203 mg, 1.19 mmol) in THF (1 cm^3) was added dropwise over 30 min, and the resulting solution was left to react for 3 h at −78 °C. Iodoethane (0.42 cm^3, 819 mg, 5.25 mmol) was added by syringe. The mixture was kept at −78 °C for 30 min, then allowed to warm to rt over 18 h, affording a deep yellow solution. Saturated aq. NH_4Cl solution (10 cm^3) was added dropwise, and the organic components were extracted with Et_2O, then CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield a yellow oil. Column chromatography on silica gel with EtOAc–hexane (1 : 200 to 1 : 50) as mobile phase yielded an inseparable mixture (*ca.* 58 : 42, by NMR spectroscopy and HPLC) of tert-*butyl* (2*R*,3*R*)-3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]amino-2-ethylhexanoate **12a** and its (2*S*,3*R*)-epimer **12b** (174 mg, 36% over two steps) as a light yellow oil, R_f 0.56 (EtOAc–hexane, 1 : 20); ν_{max}(film)/cm^{-1} 3062 (w), 3028 (w), 2965 (s), 2873 (s), 1725 (s), 1456 (m), 1368 (m), 1254 (m), 1151 (s), 752 (m) and 700 (m); *m*/*z* (EI) 409 (M^+,

≪1%), 267 (21), 266 (100), 206 (13), 163 (10), 162 (86), 160 (11), 105 (82), 104 (19) and 103 (10) [found: PrCHN(CHMePh)Bn^+, 266.1908. $C_{19}H_{24}N$ requires 266.1909]. The signals due to the individual isomers were distinguishable by NMR spectroscopy. *Major isomer* **12a**: δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.60–7.40 (10H, m, Ar*H*), 3.98 (1H, q, *J* 6.9, NC*H*MePh), 3.91 and 3.78 (2H, AB system, *J* 15.0, NCH_2Ph), 2.97 (1H, br q, *J ca.* 5.9, NC*H*Pr), 2.28 (1H, ddd, *J* 10.8, 5.9 and 3.8, C*H*CO_2Bu^t), 1.43 (9H, s, OCMe_3), 1.26 (3H, d, *J* 6.8, NCH*Me*Ph), 1.58–1.21 (6H, m, remaining CH_2), 0.79 and 0.69 (6H, 2 × t, *J* 7.2 and 7.4, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 174.8 (*C*=O), 144.7 and 142.5 (Ar*C*), 128.3, 128.1, 127.9, 127.7, 126.5 and 126.3 (Ar*C*H), 79.8 (O*C*Me_3), 60.2 and 59.4 (N*C*HPh and N*C*HPr), 51.3 and 50.8 (N*C*H_2Ph and *C*HCO_2Bu^t), 32.0 (NCH*C*H_2Et), 28.1 (OC*Me*$_3$), 22.5 and 21.2 (remaining *C*H_2), 18.3 (NCH*Me*Ph), 14.3 and 12.2 (2 × *Me*). *Minor isomer* **12b**: δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.60–7.40 (10H, m, Ar*H*), 3.99 (1H, q, *J* 6.8, NC*H*MePh), 3.82 and 3.75 (2H, AB system, *J* 15.0, NCH_2Ph), 2.76 (1H, ddd, *J* 8.0, 6.4 and 4.0, NC*H*Pr), 2.18 (1H, ddd, *J* 10.9, 6.6 and 4.2, C*H*CO_2Bu^t), 1.41 (9H, s, OCMe_3), 1.27 (3H, d, *J* 6.8, NCH*Me*Ph), 1.58–1.21 (6H, m, remaining CH_2), 0.82 and 0.74 (6H, 2 × t, *J* 6.9 and 7.3, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 175.1 (*C*=O), 144.9 and 142.7 (Ar*C*), 128.5, 128.1, 128.0, 127.8, 126.7 and 126.3 (Ar*C*), 79.9 (O*C*Me_3), 60.2 and 59.3 (N*C*HPh and N*C*HPr), 51.8 and 51.2 (N*C*H_2Ph and *C*HCO_2Bu^t), 32.9 (NCH*C*H_2Et), 28.0 (OC*Me*$_3$), 25.0 and 21.1 (remaining *C*H_2), 20.0 (NCH*Me*Ph), 14.3 and 11.9 (2 × *Me*).

(b) Consecutive approach. *n*-BuLi (1.25 M in hexane, 11.6 cm^3, 14.5 mmol) was added dropwise to a solution of diisopropylamine (2.03 cm^3, 1.47 g, 14.5 mmol) in dry THF (50 cm^3) under an atmosphere of N_2 at −78 °C. After 15 min, (+)-*tert*-butyl (3*R*)-3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]aminohexanoate[9,18] **15** (3.69 g, 9.67 mmol) in dry THF (30 cm^3) was added dropwise over 30 min, and the reaction mixture was stirred for a further 1 h. A solution of iodoethane (3.55 cm^3, 6.92 g, 44.4 mmol) in THF (30 cm^3) was then added. The temperature was maintained at −78 °C for 1 h, after which the mixture was allowed to warm to rt over 18 h. Saturated aq. NH_4Cl solution (20 cm^3) was added dropwise. After 1 h, the reaction mixture was extracted with CH_2Cl_2. After drying ($MgSO_4$) and removal of solvent *in vacuo*, the yellow oil obtained was purified by column chromatography on silica gel as described above to yield an inseparable mixture (*ca.* 56 : 44, by NMR spectroscopy) of *tert*-butyl (2*R*,3*R*)-3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]amino-2-ethylhexanoate **12a** and its (2*S*,3*R*)-epimer **12b** (3.49 g, 88%); characterisation as described above.

tert-Butyl (2*R*,3*R*)-3-amino-2-ethylhexanoate 16a and its (2*S*,3*R*) epimer 16b

A solution of *tert*-butyl 3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]-amino-2-ethylhexanoate diastereomers **12a** and **12b** (188 mg, 0.46 mmol) in glacial acetic acid (5 cm^3) containing a suspension of 10% palladium on charcoal (56 mg) was placed in an autoclave. The sealed vessel was purged four times with H_2 (1 atm), and then left to stir under H_2 (7 atm) for 72 h at rt. The catalyst was removed by filtration over celite, the plug washed with MeOH, and the filtrate reduced in volume. The resulting concentrated solution was made basic with aq. $NaHCO_3$ solution (10%), and the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated to yield a yellow oil. Silica column chromatography with MeOH–EtOAc (1 : 200) afforded an inseparable mixture (56 : 44) of *tert*-butyl (2*R*,3*R*)-3-amino-2-ethylhexanoate **16a** and its (2*S*,3*R*)-epimer **16b** (47 mg, 47%) as a yellow oil; R_f 0.19 (EtOAc). The unstable free amines were rapidly converted into solids on exposure to the atmosphere, but the following spectroscopic data could be obtained: ν_{max}(film)/cm^{-1} 3400–3200 (w, br), 2963 (s), 2933 (s), 2874 (s), 1725 (s), 1460 (m), 1368 (m), 1254 (m) and 1155 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.90–2.85 and 2.85–2.78 (1H, 2 × m, C*H*NH_2 of minor and major isomers, respectively), 2.18–2.13 and 2.13–2.07 (H, 2 × m, C*H*CO_2Bu^t of major and minor isomers, respectively), 1.72–1.30, 1.47 and 1.46 (17H, m and 2 × s, remaining CH_2 and NH_2 with OCMe_3 of major and minor isomers, respectively) and 0.92 (6H, br t, *J ca.* 7.3, 2 × *Me*); *m*/*z* (EI) 215 (M^+, 0.17%), 158 (4), 116 (26), 98 (7) and 72 (100) (found: M^+, 215.1878. $C_{12}H_{15}NO_2$ requires 215.1885). The signals due to the individual isomers were distinguishable by ^{13}C NMR spectroscopy. *Major isomer* **16a**: δ_C (100 MHz; $CDCl_3$) 174.4 (*C*=O), 80.2 (O*C*Me_3), 54.3 and 52.7 (N*C*H and *C*HCO_2Bu^t), 37.9 (NCH*C*H_2Et), 28.1 (OC*Me*$_3$), 22.7 and 19.3 (remaining *C*H_2), 14.0 and 11.9 (2 × *Me*). *Minor isomer* **16b**: δ_C (100 MHz; $CDCl_3$) 174.5 (*C*=O), 80.1 (O*C*Me_3), 55.0 and 52.7 (N*C*H and *C*HCO_2Bu^t), 37.6 (NCH*C*H_2Et), 28.0 (OC*Me*$_3$), 20.9 and 19.4 (remaining *C*H_2), 14.0 and 12.0 (2 × *Me*).

tert-Butyl (−)-(2*R*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate 18a and *tert*-butyl (+)-(2*S*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate 18b

(a) A solution of *tert*-butyl 3-[*N*-benzyl-*N*-(1*R*)-1-phenylethyl]-amino-2-ethylhexanoate diastereomers **12a** and **12b** (1.00 g, 2.44 mmol) in glacial acetic acid (25 cm^3) containing a suspension of 10% palladium on charcoal (200 mg) was hydrogenated in an autoclave (7 atm) as described above. The catalyst was removed by filtration through celite, the plug washed with EtOH, and all solvent removed under vacuum to afford amines **16** as a yellow oil. The oil was purged with N_2, and dissolved in $CHCl_3$ (25 cm^3). $NaHCO_3$ (623 mg, 7.42 mmol) and 4-chlorobutyryl chloride (1.07 cm^3, 1.35 g, 9.57 mmol) were added, and the resulting mixture was stirred at rt for 18 h. Inorganic solids were removed by filtration and washed with $CHCl_3$. The filtrate and washings were concentrated under vacuum to yield a mixture of the crude amides **17a** and **17b** (*vide infra*) as a brown oil. This oil was purged with N_2, then dissolved in dry Bu^tOH (10 cm^3) under an atmosphere of N_2. Bu^tOK (542 mg, 4.83 mmol) was added, giving a salmon-pink suspension. The mixture was stirred at rt for 18 h before being neutralised with glacial acetic acid, diluted with water (10 cm^3) and extracted with CH_2Cl_2. As the reaction appeared to be incomplete, the organic extracts were dried ($MgSO_4$) and evaporated to dryness. The resulting orange oil was dissolved in fresh Bu^tOH (10 cm^3) containing Bu^tOK (539 mg, 4.80 mmol), and stirred at rt for a further 18 h. Work-up as described before yielded an orange oil, which was purified by flash chromatography on silica gel with EtOAc–hexane (1 : 5) as mobile phase to yield two oils, (+)-*tert*-butyl (2*R*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate **18a** (165 mg, 24%), and (−)-*tert*-butyl (2*S*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate **18b** (270 mg, 39%), as well as a mixed fraction (17 mg, 2.5%).

18a: R_f 0.50 (EtOAc–hexane, 1 : 2); $[\alpha]_D^{19}$ +52.7 (*c* 1.35, EtOH); ν_{max}(film)/cm^{-1} 2966 (s), 2875 (s), 1725 (s), 1692 (s), 1461 (m), 1423 (m), 1367 (m), 1287 (m) and 1158 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.21 (1H, td, *J* 10.7 and 3.7, NC*H*Pr), 3.48 (1H, dt, *J* 9.3 and 6.6, NCH_aH_b), 3.20 (1H, td, *J* 9.3 and 7.3, NCH$_a$$H_b$), 2.39–2.31 (3H, m, C*H*CO_2Bu^t and ring COCH_2), 1.96 (2H, quintet, *J ca.* 7.6, ring NCH$_2$CH_2), 1.62–1.51 and 1.58 (3H, overlapping m and t, *J* 7.4, chain NCHCH_2 and COCHC$H_a$$H_b$), 1.45–1.35 and 1.40 (10H, overlapping m and s, COCHCH$_a$$H_b$ and OCMe_3), 1.26–1.16 (2H, m, remaining CH_2), 0.92 and 0.91 (6H, 2 × t, *J ca.* 7.3, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 174.7 and 172.7 (2 × *C*=O), 80.3 (O*C*Me_3), 52.6 and 52.5 (N*C*H and *C*HCO_2Bu^t), 42.6 (N*C*H_2), 31.6 and 31.1 (NCH*C*H_2Et and CO*C*H_2), 27.6 (OC*Me*$_3$), 22.8, 19.0 and 18.2 (remaining *C*H_2), 13.7 and 11.5 (2 × *Me*); *m*/*z* (EI) 283 (M^+, 1.1%), 227 (4), 210 (8), 184 (4), 141 (13), 140 (100), 98 (13), 86 (9) and 57 (10) (found: M^+, 283.2157. $C_{16}H_{29}NO_3$ requires 283.2147).

18b: R_f 0.42 (EtOAc–hexane, 1 : 2); $[\alpha]_D^{19}$ −16.8 (*c* 1.43, EtOH); ν_{max}(film)/cm^{-1} 2965 (s), 2875 (s), 1727 (s), 1690 (s), 1461

(m), 1423 (m), 1369 (m), 1266 (m) and 1150 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.22 (1H, td, *J* 11.0 and 3.1, NC*H*Pr), 3.24 (1H, dt, *J* 9.6 and 7.0, NCH_aH_b), 3.15 (1H, dt, *J* 9.6 and 6.9, NCH$_a$$H_b$), 2.41 (2H, t, *J* 8.0, ring COCH_2), 2.28 (1H, td, *J* 10.6 and 3.8, C*H*CO_2Bu^t), 2.00 (2H, quintet, *J ca.* 7.5, ring NCH$_2$CH_2), 1.59–1.50 (2H, m, chain NCHCH_2), 1.47 (9H, s, OC*Me*$_3$), 1.42–1.30 and 1.28–1.17 (2 × 2H, 2 × m, remaining CH_2), 0.90 and 0.88 (6H, 2 × t, *J ca.* 7.4, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 175.5 and 173.1 (2 × *C*=O), 80.7 (O*C*Me$_3$), 52.4 and 51.7 (N*C*H and *C*HCO_2Bu^t), 42.4 (NCH_2), 32.1 and 31.3 (NCH*C*H$_2$Et and CO*C*H$_2$), 28.0 (OC*Me*$_3$), 23.0, 19.2 and 18.4 (remaining *C*H$_2$), 13.7 and 11.4 (2 × *Me*); *m/z* (EI) 283 (M^+, 1.1%), 227 (4), 210 (8), 184 (4), 141 (12), 140 (100), 98 (11), 86 (8) and 57 (9) (found: M^+, 283.2139. $C_{16}H_{29}NO_3$ requires 283.2147).

(b) In a separate experiment, the unstable intermediate amides **17** were separated for characterisation by flash chromatography on silica gel with EtOAc–hexane (1 : 5) as the mobile phase. The following data were recorded.

(+)-*tert*-Butyl (3*R*)-3-[*N*-(4-chloro-1-oxo)butyl]amino-(2*R*)-2-ethylhexanoate **17a**: beige oil, R_f 0.43 (EtOAc–hexane, 1 : 5); $[\alpha]_D^{21}$ +228 (*c* 0.14, hexane); ν_{max}(film)/cm^{-1} 3308 (m, br), 2964 (s), 2934 (s), 2874 (s), 1726 (s), 1651 (s), 1517 (m), 1460 (m), 1369 (m), 1252 (m) and 1155 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.48 (1H, br d, *J ca.* 9.3, N*H*), 4.15–4.11 (1H, m, NC*H*Pr), 3.60 (2H, t, *J* 6.3, CH_2Cl), 2.38 and 2.37–2.32 (3H, overlapping t, *J* 7.4, and m, NHCOCH_2 and C*H*CO_2Bu^t), 2.12 (2H, quintet, *J ca* 6.7, CH_2CH$_2$Cl), 1.68–1.60 (1H, m, CHCH_aH$_b$), 1.53–1.32 and 1.50 (14H, overlapping m and s, remaining CH_2 and OC*Me*$_3$), 0.94 and 0.91 (6H, 2 × t, *J* 7.5 and 7.1, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 175.2 and 171.2 (2 × *C*=O), 81.3 (O*C*Me$_3$), 50.3 and 49.2 (N*C*H and *C*HCO_2Bu^t), 44.4 (*C*H$_2$Cl), 36.6 and 33.5 (NCH*C*H$_2$Et and NHCO*C*H$_2$), 28.2 (*C*H$_2$CH$_2$Cl), 28.1 (OC*Me*$_3$), 23.6 and 19.4 (remaining *C*H$_2$), 13.9 and 11.9 (2 × *Me*); *m/z* (EI) 319 (M^+, <1%), 276 (9), 246 (14), 222 (13), 220 (38), 178 (15), 177 (11), 176 (46), 140 (12), 116 (75), 72 (100) and 57 (34) (found: M^+, 319.1924. $C_{16}H_{30}ClNO_3$ requires 319.1914).

(−)-*tert*-Butyl (3*R*)-3-[*N*-(4-chloro-1-oxo)butyl]amino-(2*S*)-2-ethylhexanoate **17b**: beige oil, R_f 0.32 (EtOAc–hexane, 1 : 5); $[\alpha]_D^{21}$ −246 (*c* 0.06, hexane); ν_{max}(film)/cm^{-1} 3290 (m), 2965 (s), 2874 (s), 1726 (s), 1646 (s), 1548 (m), 1459 (m), 1369 (m), 1257 (m), 1156 (s) and 756 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 5.68 (1H, br d, *J ca.* 7.6, N*H*), 4.22–4.10 (1H, m, NC*H*Pr), 3.61 (2H, t, *J* 6.1, CH_2Cl), 2.36 (2H, t, *J* 7.1, NHCOCH_2), 2.27 (1H, ddd, *J* 9.9, 6.1 and 4.8, C*H*CO_2Bu^t), 2.12 (2H, quintet, *J ca.* 6.6, CH_2CH$_2$Cl), 1.69–1.63 (1H, m, CHCH_aH$_b$), 1.51–1.26 and 1.47 (14H, overlapping m and s, remaining CH_2 and OC*Me*$_3$), 0.93 and 0.91 (6H, 2 × t, *J* 7.4 and 7.1, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 173.1 and 171.1 (2 × *C*=O), 80.9 (O*C*Me$_3$), 52.8 and 50.0 (N*C*H and *C*HCO_2Bu^t), 44.5 (*C*H$_2$Cl), 34.0 and 33.5 (NCH*C*H$_2$Et and NHCO*C*H$_2$), 28.2 (*C*H$_2$CH$_2$Cl), 28.1 (OC*Me*$_3$), 22.0 and 19.4 (remaining *C*H$_2$), 13.8 and 12.1 (2 × *Me*); *m/z* (EI) 319 (M^+, <1%), 246 (11), 220 (9), 178 (16), 176 (50), 140 (10), 116 (24), 72 (100) and 57 (31) (found: M^+, 319.1913. $C_{16}H_{30}ClNO_3$ requires 319.1914).

tert-Butyl 3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate isomers 19a,b

(a) (+)-*tert*-Butyl (2*R*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19a**. A solution of *tert*-butyl (+)-(2*R*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate **18a** (500 mg, 1.76 mmol) in dry toluene (25 cm^3) containing fresh, dry Lawesson's reagent (430 mg, 1.06 mmol) was heated at reflux under an atmosphere of N_2 for 18 h. The mixture was then concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel with hexane–CH_2Cl_2 to remove Lawesson's reagent residues, followed by EtOAc–hexane (3 : 7). (+)-*tert*-Butyl (2*R*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19a** (429 mg, 81%) was obtained as a yellow oil; R_f 0.56 (EtOAc–hexane, 3 : 7); $[\alpha]_D^{19}$ +80.1 (*c* 1.36, EtOH); ν_{max}(film)/cm^{-1} 2965 (s), 2875 (s), 1721 (s), 1642 (s), 1455 (m), 1291 (m), 1196 (m) and 755 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.19 (1H, br t, *J ca.* 7.1, NC*H*Pr), 3.84 (1H, dt, *J* 10.8 and 6.8, NCH_aH_b), 3.48 (1H, dt, *J* 10.8 and 7.5, NCH$_a$$H_b$), 2.97 (2H, t, *J* 7.8, CSCH_2), 2.41 (1H, br q, *J ca.* 9.6, C*H*CO_2Bu^t), 1.99 (2H, quintet, *J ca.* 7.6, ring NCH$_2$CH_2), 1.80–1.52 and 1.65 (3H, overlapping m and t, *J* 7.4, COCHCH_aH_b and chain NCHCH_2), 1.52–1.10 and 1.43 (12H, overlapping m and s, remaining CH_2 and OC*Me*$_3$), 0.94 and 0.92 (6H, 2 × t, *J* 7.4 and 7.1 2 × *Me*); δ_C (50 MHz; $CDCl_3$) 202.4 (*C*=S), 172.2 (ester *C*=O), 81.0 (O*C*Me$_3$), 57.3 (N*C*HPr), 53.0 (*C*HCO_2Bu^t), 49.3 (br, N*C*H$_2$), 45.1 (*C*H$_2$C=S), 32.7 (NCH*C*H$_2$Et), 27.7 (OC*Me*$_3$), 22.8, 20.1 and 19.0 (remaining *C*H$_2$), 14.1 and 11.6 (2 × *Me*); *m/z* (EI) 300 (14%), 299 (M^+, 71), 266 (10), 243 (16), 242 (67), 226 (35), 214 (12), 210 (62), 198 (30), 157 (51), 156 (53), 125 (29), 124 (32), 115 (55), 102 (100), 101 (12), 85 (18), 57 (28) and 55 (35) (found: M^+, 299.1916. $C_{16}H_{29}NO_2S$ requires 299.1919).

(b) (−)-*tert*-Butyl (2*S*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19b**. The above procedure was repeated with (−)-*tert*-butyl (2*S*,3*R*)-3-(2-oxopyrrolidin-1-yl)-2-ethylhexanoate **18b** (370 mg, 1.31 mmol) and Lawesson's reagent (340 mg, 0.84 mmol) in dry toluene (25 cm^3). After column chromatography, *thiolactam* **19b** was obtained as a chromatographically pure reddish solid (373 mg, 95%), R_f 0.52 (EtOAc–hexane, 3 : 7). Subsequent recrystallisation afforded colourless needles, mp 116–117.5 °C (from EtOH–H_2O) (found: C, 64.64; H, 9.90; N, 4.67; S, 11.22. $C_{16}H_{29}NO_2S$ requires C, 64.17; H, 9.76; N, 4.68; S, 10.71%); $[\alpha]_D^{19}$ −139.0 (*c* 0.26, abs. EtOH); ν_{max}(film)/cm^{-1} 2963 (s), 2928 (m), 2872 (m), 1724 (s), 1499 (m), 1451 (m), 1320 (m), 1282 (m) and 1163 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 5.25 (1H, br s, NC*H*Pr), 3.55 (1H, dt, *J* 10.9 and 7.3, NCH_aH_b), 3.47 (1H, dt, *J* 10.9 and 7.1, NCH$_a$$H_b$), 3.04 (2H, t, *J* 7.8, CSCH_2), 2.37 (1H, br s, C*H*CO_2Bu^t), 2.05 (2H, quintet, *J ca.* 7.5, ring NCH$_2$CH_2), 1.70–1.60 (2H, m, chain NCHCH_2), 1.49 (9H, s, OC*Me*$_3$), 1.37–1.31 and 1.31–1.16 (2 × 2H, 2 × m, remaining CH_2), 0.92 and 0.89 (6H, 2 × t, *J* 7.3 and 7.4, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 203.2 (*C*=S), 172.5 (ester *C*=O), 80.9 (O*C*Me$_3$), 56.9 (br, N*C*HPr), 51.9 (*C*HCO_2Bu^t), 48.8 (br, N*C*H$_2$), 45.0 (*C*H$_2$C=S), 32.3 (NCH*C*H$_2$Et), 27.9 (OC*Me*$_3$), 22.8, 20.2 and 19.0 (remaining *C*H$_2$), 13.8 and 11.5 (2 × *Me*).

General procedure for sulfide contractions

Solutions of the thiolactams **19a** or **19b** in MeCN (0.25 M) were stirred at rt with the appropriate alkylating agent (ethyl bromoacetate, benzyl bromoacetate or *N*-methoxy-*N*-methyl-2-bromoacetamide, 1.7–1.8 equiv.) under N_2 for the stipulated period. The solvent and excess alkylating agent were removed *in vacuo*, and the residue was dissolved in fresh MeCN (0.25 M solution). PPh_3 (1.5 equiv.) and then NEt_3 (1.5 equiv.) were added in that order, the reaction usually generating an exotherm. The mixture was stirred at rt for 3–5 h. Precipitated solids were removed by filtration through celite and washed with EtOAc–hexane (1 : 1). The filtrate was evaporated *in vacuo*. Column chromatography of the crude product mixture on silica gel was performed with CH_2Cl_2 phosphorus-containing compounds, after which the desired product was eluted with EtOAc–hexane mixtures. The following results were recorded.

(+)-*tert*-Butyl (2*R*,3*R*)-3-[(2*E*)-2-(ethoxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoate **20a** (506 mg, 97%) was obtained as a yellow oil from (+)-*tert*-butyl (2*R*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19a** (444 mg, 1.48 mmol) and ethyl bromoacetate (0.28 cm^3, 407 mg, 2.43 mmol) stirred in MeCN (6 cm^3) for 76 h, followed by evaporation, dissolution in fresh MeCN (5 cm^3), and treatment with PPh_3 (592 mg, 2.26 mmol) and NEt_3 (0.31 cm^3, 224 mg, 2.21 mmol); yellow oil, R_f 0.17 (EtOAc–hexane, 1 : 19); $[\alpha]_D^{23}$ +49.2 (*c* 1.93, EtOH); ν_{max}(film)/cm^{-1} 2970 (m), 2877 (m), 1727 (s), *ca.* 1680 (m, shoulder), 1459 (m), 1370 (m), 1257 (m) and 1158 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.69 (1H, s, =C*H*), 4.11 and 4.03 (2H, AB system, J_{AB} 10.8, further split into q, *J* 7.1,

OCH_2Me), 3.74 (1H, br td, *J* 10.5 and 3.7, NC*H*Pr), 3.39 (1H, ddd, *J* 9.3, 7.7 and 5.2, NCH_aH$_b$), 3.30–3.10 (2H, m, NCH$_a$$H_b$ and =CCH_aH$_b$), 3.06 (1H, *ca.* dt, *J ca.* 17.2 and 8.5, =CCH$_a$$H_b$), 2.39 (1H, br td, *J ca.* 9.6 and 3.9, C*H*CO$_2$Bu^t), 1.95–1.80 (2H, m, ring NCH$_2$CH_2), 1.61–1.40 (4H, 2 × m, NCHCH_2Et and COCHCH_2Me), 1.40 (9H, s, OCMe_3), 1.30–1.15 and 1.24 (6H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH$_2$CH_3), 0.94 and 0.91 (6H, 2 × t, *J* 7.3 and 7.4, 2 × *Me*); δ_C (100 MHz; CDCl$_3$) 172.2 and 169.6 (2 × *C*=O), 165.5 (N*C*=CH), 80.7 (O*C*Me$_3$), 79.3 (NC=*C*H), 57.9 (O*C*H$_2$Me), 55.9 (N*C*HPr), 53.0 (*C*HCO$_2$Bu^t), 45.7 (br, N*C*H$_2$), 32.4 and 32.1 (=C*C*H$_2$ and chain NCH*C*H$_2$Et), 27.7 (OC*Me*$_3$), 23.1, 21.1 and 19.2 (remaining *C*H$_2$), 14.7 (OCH$_2$*C*H$_3$), 14.0 and 11.5 (2 × *Me*); *m/z* (EI) 353 (M$^+$, 13%), 308 (20), 280 (18), 266 (19), 252 (19), 211 (44), 210 (100), 182 (27), 156 (69), 110 (23), 57 (18) and 55 (14) (found: M$^+$, 353.2562. $C_{20}H_{35}NO_4$ requires 353.2566).

(−)-*tert*-Butyl (2*S*,3*R*)-3-[(2*E*)-(2-ethoxycarbonyl)methylenepyrrolidin-1-yl]-2-ethylhexanoate **20b** (345 mg, 96%) was obtained from (−)-*tert*-butyl (2*S*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19b** (304 mg, 1.02 mmol) and ethyl bromoacetate (0.19 cm^3, 286 mg, 1.71 mmol) stirred in MeCN (4 cm^3) for 77 h, followed by evaporation, dissolution in fresh MeCN (5 cm^3), and treatment with PPh$_3$ (391 mg, 1.49 mmol) and NEt$_3$ (0.21 cm^3, 152 mg, 1.50 mmol); yellow oil, R_f 0.17 (EtOAc–hexane, 1 : 19); $[\alpha]_D$ [23] −35.52 (*c* 0.70, EtOH); ν_{max}(film)/cm^{-1} 2970 (s), 2874 (s), 1725 (s), 1684 (s), 1590 (s), 1377 (m), 1267 (m), 1138 (m) and 1061 (m); δ_H (200 MHz; CDCl$_3$; Me$_4$Si) 4.70 (1H, s, =C*H*), 4.08 (2H, q, *J* 7.1, OCH_2Me), 3.75 (1H, br t, *J ca.* 10.4, NC*H*Pr), 3.30–3.10 and 3.20 (4H, m and br t, *J ca.* 7.7, NCH_2 and =CCH_2), 2.34 [1H, br m (t?), C*H*CO$_2$Bu^t], 1.91 (2H, quintet, *J* 7.4, ring NCH$_2$CH_2), 1.70–1.32 and 1.48 (12H, overlapping m and s, NCHCH_2Et, COCHCH_2Me and OCMe_3), 1.32–1.14 and 1.26 (6H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH$_2$CH_3), 0.88 and 0.87 (6H, 2 × t, *J* 7.1 and 7.4, 2 × *Me*); δ_C (50 MHz; CDCl$_3$) 173.2 and 169.8 (2 × *C*=O), 166.8 (N*C*=CH), 80.8 (O*C*Me$_3$), 79.6 (NC=*C*H), 58.2 (O*C*H$_2$Me), 55.4 (br, N*C*HPr), 52.0 (*C*HCO$_2$Bu^t), 45.4 (br, N*C*H$_2$), 32.7 and 32.6 (=C*C*H$_2$ and chain NCH*C*H$_2$Et), 28.0 (OC*Me*$_3$), 23.0, 21.1 and 19.2 (remaining *C*H$_2$), 14.6 (OCH$_2$*C*H$_3$), 13.8 and 11.5 (2 × *Me*); *m/z* (EI) 353 (M$^+$, 10%), 308 (15), 266 (17), 252 (16), 211 (34), 210 (100), 182 (19), 156 (72), 110 (23), 57 (24) and 55 (20) (found: M$^+$, 353.2587. $C_{20}H_{35}NO_4$ requires 353.2566).

(+)-*tert*-Butyl (2*R*,3*R*)-3-[(2*E*)-2-(benzyloxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoate **21a** (195 mg, 90%) was obtained from (+)-*tert*-butyl (2*R*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19a** (157 mg, 0.52 mmol) and benzyl bromoacetate (0.15 cm^3, 217 mg, 0.95 mmol) stirred in MeCN (2.6 cm^3) for 18 h, followed by evaporation, dissolution in fresh MeCN (2.6 cm^3), and treatment with PPh$_3$ (210 mg, 0.80 mmol) and NEt$_3$ (0.11 cm^3, 80 mg, 0.79 mmol); yellow oil, R_f 0.64 (EtOAc–hexane, 3 : 7); $[\alpha]_D$ [22] +56.7 (*c* 1.22, EtOH); ν_{max}(film)/cm^{-1} 3065 (w), 3031 (w), 2965 (m), 2934 (m), 2874 (m), 1721 (s), 1687 (s), 1579 (s), 1457 (m), 1390 (m), 1367 (m), 1258 (m), 1125 (m) and 1052 (m); δ_H (300 MHz; CDCl$_3$; Me$_4$Si) 7.51–7.21 (5H, m, Ar*H*), 5.15 and 5.02 (2 × 1H, AB system, *J* 12.6, PhCH_2), 4.77 (1H, s, =C*H*), 3.73 (1H, br t, *J ca.* 10.6, NC*H*Pr), 3.40 (1H, ddd, *J* 9.3, 8.0 and 5.1, NCH_aH$_b$), 3.26–3.10 (2H, m, NCH$_a$$H_b$ and =CCH_aH$_b$), 3.07 (2H, dt, *J* 17.8 and 8.7, =CCH$_a$$H_b$), 2.45–2.28 [1H, br m (t?), C*H*CO$_2$Bu^t], 1.95–1.82 (2H, m, ring NCHCH_2), 1.65–1.40 (4H, m, CHCH_2Et and COCHCH_2Me), 1.36 (9H, s, OCMe_3), 1.19 (2H, sextet, *J* 7.7, NCHCH_2Me), 0.92 and 0.89 (6H, 2 × t, *J* 7.4 and 7.5, 2 × *Me*); δ_C (75 MHz; CDCl$_3$) 172.3 and 169.4 (2 × *C*=O), 166.0 (N*C*=CH), 138.0 (Ar*C*), 128.3, 127.9 and 127.4 (Ar*C*H), 80.8 (O*C*Me$_3$), 79.0 (NC=*C*H), 64.2 (O*C*H$_2$Ph), 56.2 (br, N*C*HPr), 53.1 (*C*HCO$_2$Bu^t), *ca* 46.0 (br, N*C*H$_2$), 32.6 and 32.2 (=C*C*H$_2$ and chain NCH*C*H$_2$Et), 27.8 (OC*Me*$_3$), 23.2, 21.1 and 19.2 (remaining *C*H$_2$), 14.0 and 11.6 (2 × *Me*); *m/z* (EI) 415 (M$^+$, 123%), 342 (9), 314 (12), 308 (8), 273 (49), 272 (77), 266 (28), 252 (10), 244 (18), 218 (57), 210 (12), 138 (15), 110 (17), 91 (100), 83 (12), 57 (26) and 55 (17) (found: M$^+$, 415.2721. $C_{25}H_{37}NO_4$ requires 415.2723).

(−)-*tert*-Butyl (2*S*,3*R*)-3-[(2*E*)-2-(benzyloxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoate **21b** (174 mg, 81%) was obtained from (−)-*tert*-butyl (2*S*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19b** (157 mg, 0.52 mmol) and benzyl bromoacetate (0.15 cm^3, 217 mg, 0.95 mmol) stirred in MeCN (3 cm^3) for 18 h, followed by evaporation, dissolution in fresh MeCN (3 cm^3), and treatment with PPh$_3$ (210 mg, 0.80 mmol) and NEt$_3$ (0.11 cm^3, 80 mg, 0.79 mmol); yellow oil, R_f 0.58 (EtOAc–hexane, 3 : 7); $[\alpha]_D$ [22] −38.5 (*c* 1.21 in ethanol); ν_{max}(film)/cm^{-1} 3087 (w), 3065 (w), 3031 (w), 2964 (m), 2934 (m), 2874 (m), 1721, 1687 (s), 1580 (s), 1459 (m), 1422 (m), 1389 (m), 1367 (m), 1126 (m) and 1052 (m); δ_H (400 MHz; CDCl$_3$; Me$_4$Si; assignments verified by HETCORR) 7.45–7.20 (5H, m, Ar*H*), 5.09 (2H, s, PhCH_2), 4.77 (1H, s, =C*H*), 3.74 (1H, br t, *J ca.* 9.4, NC*H*Pr), 3.25–3.10 and 3.21 (4H, overlapping m and td, *J* 7.7 and 1.4, NCH_2 and =CCH_2), 2.31 (1H, br m, C*H*COBu^t), 1.90 (2H, quintet, *J* 7.3, ring NCH$_2$CH_2), 1.65–1.45 (2H, m, COCHCH_aH$_b$Me and NCHCH_aH$_b$Et), 1.47 (9H, s, OCMe_3), 1.40–1.30 (2H, m, COCHCH$_a$$H_b$Me and NCHCH$_a$$H_b$Et), 1.30–1.10 (2H, m, NCHCH$_2$CH_2Me), 0.87 and 0.86 (6H, 2 × t, *J* 7.1 and 7.4, 2 × *Me*); δ_C (100 MHz; CDCl$_3$; assignments verified by HETCORR) 173.2 and 169.4 (2 × *C*=O), 166.7 (br, N*C*=CH), 137.8 (Ar*C*), 128.3, 127.9 and 127.4 (Ar*C*H), 80.9 (O*C*Me$_3$), 79.3 (NC=*C*H), 64.3 (O*C*H$_2$Ph), 55.7 (br, N*C*HPr), 52.0 (br, *C*HCO$_2$Bu^t), 45.6 (br, N*C*H$_2$), 32.7 (overlapping =C*C*H$_2$ and chain NCH*C*H$_2$Et), 28.0 (OC*Me*$_3$), 23.1 (COCH*C*H$_2$Me), 21.1 (ring NCH$_2$*C*H$_2$), 19.3 (NCHCH$_2$*C*H$_2$Me), 13.8 and 11.5 (2 × *Me*); *m/z* (EI) 415 (M$^+$, 13%), 342 (7), 314 (14), 308 (12), 273 (50), 272 (100), 266 (39), 252 (11), 244 (18), 218 (66), 210 (17), 138 (12), 110 (15), 91 (85), 83 (10), 57 (18) and 55 (13) (found: M$^+$, 415.2720. $C_{25}H_{37}NO_4$ requires 415.2723).

(+)-*tert*-Butyl (2*R*,3*R*)-2-ethyl-3-{(2*E*)-[2-(*N*-methoxy-*N*-methylaminocarbonyl)methylene]pyrrolidin-1-yl}hexanoate **22** (316 mg, 91%) was obtained from (+)-*tert*-butyl (2*R*,3*R*)-3-(2-thioxopyrrolidin-1-yl)-2-ethylhexanoate **19a** (282 mg, 0.94 mmol) and *N*-methoxy-*N*-methyl-2-bromoacetamide[21] (343 mg, 1.88 mmol), stirred in MeCN (2 cm^3) for 40 h, followed by evaporation, dissolution in fresh MeCN (2 cm^3), and treatment with PPh$_3$ (373 mg, 1.42 mmol) and NEt$_3$ (0.17 cm^3, 123 mg, 1.22 mmol); yellow oil, R_f 0.24 (EtOAc–hexane, 1 : 1); $[\alpha]_D$ [19] +148.6 (*c* 1.26, EtOH); ν_{max}(film)/cm^{-1} 2967 (m), 2875 (m), 1723 (s), 1637 (s), 1573 (s), 1455 (m), 1409 (m), 1370 (m), 1253 (m), 1159 (m) and 1099 (m); δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 5.25 (1H, s, =C*H*), 3.81 (1H, br td, *J* 10.6 and 3.0, NC*H*Pr), 3.68 (3H, s, O*Me*), 3.40 (1H, ddd, *J* 9.3, 8.0 and 4.9, NCH_aH$_b$), 3.27 (1H, dddd, *J* 17.8, 8.8, 5.5 and 1.0, =CCH_aH$_b$), 3.15, 3.14 and 3.10 [5H, overlapping br q? (*J ca.* 7.6?), s and br dd (*J ca.* 17.8 and 8.8), NCH$_a$$H_b$, N*Me* and, =CCH$_a$$H_b$], 2.43 (1H, br q, *J ca.* 8.2, C*H*CO$_2$Bu^t), 1.95–1.75 (2H, m, ring NCH$_2$CH_2), 1.65–1.50 (4H, m, 2 × CH_2), 1.38 (9H, s, OCMe_3], 1.29–1.11 (2H, m, CH_2), 0.93 and 0.91 (6H, 2 × t, *J* 7.4 and 7.3, 2 × *Me*); δ_C (100 MHz; CDCl$_3$) 172.5 and 172.1 (2 × *C*=O), 165.1 (N*C*=CH), 80.5 (O*C*Me$_3$), 78.0 (NC=*C*H), 60.7 (O*C*Me$_3$), 55.9 (N*C*HPr), 52.5 (*C*HCO$_2$Bu^t), 45.5 (br, N*C*H$_2$), 33.0 (N*C*H$_3$), 32.5 and 31.9 (=C*C*H$_2$ and chain NCH*C*H$_2$), 27.8 (OC*Me*$_3$), 23.0, 21.2 and 19.2 (remaining *C*H$_2$), 13.9 and 11.6 (2 × *Me*); *m/z* (EI) 368 (M$^+$, absent), 309 (15), 308 (72), 295 (6), 253 (16), 252 (100), 225 (5), 182 (5), 164 (4), 136 (7), 110 (22), 57 (9) and 55 (10) [found: M$^+$ − N(OMe)Me, 308.2232. $C_{18}H_{30}NO_3$ requires 308.2226. M$^+$ − OBu^t, 295.2019. $C_{16}H_{27}N_2O_3$ requires 295.2022].

(+)-Ethyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 28a

(a) A solution of (+)-*tert*-butyl (2*R*,3*R*)-3-[(2*E*)-(2-ethoxycarbonyl)methylenepyrrolidin-1-yl]amino-2-ethylhexanoate **20a**

(478 mg, 1.35 mmol) in trifluoroacetic acid (2.70 cm^3) was stirred for 3 h at rt. Removal of the solvent *in vacuo* gave crude (2*R*,3*R*)-3-[(2*E*)-(2-ethoxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoic acid **27a** as an orange oil, R_f 0.16 (EtOAc–hexane, 3 : 7); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.6–6.2 (1H, br s, CO_2H), 4.66 (1H, s, =C*H*), 4.04 [2H, overlapping q (= incipient AB system, J_{AB} *ca.* 3.7), *J* 7.1, OCH_2CH_3], 3.78 (1H, br td, *J* 9.9 and 3.5, NC*H*Pr), 3.40 (1H, ddd, *J* 9.2, 7.6 and 5.5, NCH_aH_b), 3.20–2.90 (3H, m, CH_aH_bN and $=CCH_2$), 2.49 (1H, br dt, *J ca.* 8.5 and 7.7, C*H*CO_2H), 1.95–1.80 (2H, m, ring NCH_2CH_2), 1.80–1.40 (4H, m, $NCHCH_2Et$ and $COCHCH_2Me$), 1.32–1.00 and 1.23 (5H, overlapping m and t, *J* 7.1, CH_2CH_2Me and OCH_2CH_3), 0.92 and 0.89 (6H, 2 × t, *J* 6.9 and 7.4, 2 × *Me*); δ_C (50 MHz; $CDCl_3$) 177.9 (*C*O_2H), 170.3 (*C*O_2Et), 166.1 (N*C*=CH), 78.7 (NC=*C*H), 58.4 (OCH_2CH_3), 56.3 (N*C*HPr), 51.2 (*C*HCO_2H), *ca.* 45 (missing or v br, NCH_2), 32.7 and 31.9 ($=CCH_2$ and chain $NCHCH_2Et$), 22.7, 21.2 and 19.3 (remaining CH_2), 14.6 (OCH_2CH_3), 13.9 and 11.8 (C-6) (2 × *Me*).

(b) The unpurified acid **27a** was dissolved in MeCN (7.0 cm^3) containing K_2CO_3 (564 mg, 4.08 mmol) and acetic anhydride (0.51 cm^3, 551 mg, 5.40 mmol). The solution was stirred at rt under an atmosphere of N_2 for 18 h, by which stage a thick crystalline suspension had formed. The mixture was heated under reflux for 3 h, then cooled to rt. The solids were removed by filtration, and the filtrate was added to a saturated aq. $KHCO_3$ solution. Extraction with CH_2Cl_2, drying ($MgSO_4$), evaporation and chromatography on silica gel with EtOAc followed by MeOH–EtOAc (1 : 19) yielded (+)-ethyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28a** (321 mg, 85%); as a pale yellow oil, R_f 0.46 (MeOH–EtOAc, 1 : 9); $[a]_D^{19}$ +50.5 (*c* 1.76, EtOH); ν_{max}(film)/cm^{-1} 2961 (m), 2939 (m), 2876 (m), 1699 (m), 1653 (mO), 1559 (s), 1458 (m), 1381 (m), 1306 (m), 1236 (m), 1155 (m) and 1101 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si; assignments unambiguous by COSY, COLOC, NOESY and HETCORR) 4.22 [2H, overlapping q (= incipient AB system), *J* 7.1, OCH_2CH_3], 3.75 (1H, dt, *J* 10.3 and 7.8, 3-H_{eq}), 3.51 (1H, ddd, *J* 10.3, 8.5 and 5.3, 3-H_{ax}), 3.36 (1H, t, *J* 7.1, 5-H), 3.31 (1H, t?, *J ca.* 8.6, 1-H_a), 3.26 (1H, ddd, *J* 18.6, 8.4 and 5.9, 1-H_b), 2.20–2.04 (3H, m, 6-H and 2-H), 1.69–1.55 and 1.59 [3H, m and sextet?, *J* 7.6?, C(6)CH_aH_bMe and C(5)CH_2Et], 1.48–1.35 [2H, m (= *ca.* septet, *J ca.* 7.5), C(6)CH_aH_bMe and C(5)$CH_2CH_aH_b$Me], 1.33–1.20 and 1.31 [4H, m and t, *J* 7.1, C(5)$CH_2CH_aH_b$Me and OCH_2CH_3], 0.96 [3H, t, *J* 7.5, C(6)CH_2Me] and 0.90 [3H, t, *J* 7.3, C(5)CH_2CH_2Me]; δ_C (100 MHz; $CDCl_3$; assignments unambiguous by COSY, COLOC and HETCORR) 190.9 (C-7), 170.1 (C-8a), 166.4 (ester *C*=O), 95.8 (C-8), 59.3 (OCH_2CH_3), 58.2 (C-5), 53.8 (C-3), 50.9 (C-6), 34.8 (C-1), 31.8 [C(5)*C*H_2Et], 24.6 [C(6)*C*H_2Me], 21.1 (C-2), 18.7 [C(5)CH_2CH_2Me], 14.5 (OCH_2CH_3), 13.7 [C(5)CH_2CH_2Me] and 11.5 [C(6)CH_2Me]; *m*/*z* (EI) 280 (MH^+, 8%), 279 (M^+, 41), 250 (6), 239 (10), 238 (69), 237 (8), 236 (23), 234 (49), 209 (13), 208 (100), 207 (10), 192 (11), 190 (52), 164 (36), 162 (26), 124 (23) and 55 (15) (found: M^+, 279.1843. $C_{16}H_{25}NO_3$ requires 279.1834).

(+)-Ethyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 28b

(a) A solution of (−)-*tert*-butyl (2*S*,3*R*)-3-[(2*E*)-(2-ethoxycarbonyl)methylenepyrrolidin-1-yl]amino-2-ethylhexanoate **20b** (96 mg, 0.27 mmol) in trifluoroacetic acid (0.45 cm^3) was stirred for 3 h at rt. Removal of the solvent *in vacuo* gave crude (2*S*,3*R*)-3-[(2*E*)-(2-ethoxycarbonylmethylene)pyrrolidin-1-yl]-2-ethylhexanoic acid **27b** as an orange oil, R_f 0.20 (EtOAc–hexane, 3 : 7); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.5–7.5 (1H, br s, CO_2H), 4.74 (1H, s, =C*H*), 4.09 (2H, q, OCH_2CH_3, *J* 7.1), 3.84 (1H, br t, NC*H*, *J* 8.7), 3.35–3.00 (4H, br t, NCH_2 and $=CCH_2$), 2.50 [1H, br m (t?), C*H*CO_2H], 1.93 (2H, quintet, *J* 7.2, ring NCH_2CH_2), 1.71–1.30 (4H, m, $NCHCH_2Et$ and $COCHCH_2Me$), 1.30–1.10 and 1.26 (5H, overlapping m and t, *J* 7.1, CH_2CH_2Me and OCH_2CH_3), 0.91 and 0.88 (6H, 2 × t, *J* 7.1 and 7.3, 2 × CH_3); δ_C (50 MHz; $CDCl_3$) 179.0 (*C*O_2H), 170.1 (*C*O_2Et), 166.6 (N*C*=CH), 79.0 (NC=*C*H), 58.5 (OCH_2CH_3), 55.4 (N*C*HPr), 51.3 (*C*HCO_2H), 45.7 (NCH_2), 32.9 and 32.7 ($=CCH_2$ and chain $NCHCH_2Et$), 22.9, 21.2 and 19.4 (remaining CH_2), 14.7 (OCH_2CH_3), 13.8 and 11.7 (2 × *Me*); *m*/*z* (EI) 297 (M^+, 10%), 252 (31), 211 (28), 210 (100), 182 (28), 156 (46), 136 (10), 110 (35) 102 (10) and 55 (23) (found: M^+, 297.1945. $C_{16}H_{27}NO_4$ requires 297.1940).

(b) The unpurified acid **27b** was dissolved in MeCN (5.0 cm^3) containing K_2CO_3 (75 mg, 0.54 mmol, 2.0 equiv.) and acetic anhydride (0.05 cm^3, 54 mg, 0.53 mmol). The mixture was stirred at 50 °C under N_2 for 24 h, by which stage a thick crystalline suspension had formed. A further portion of acetic anhydride (0.05 cm^3, 54 mg, 0.53 mmol) was added, and heating was maintained for 12 h. The mixture was concentrated *in vacuo*, then partitioned between H_2O (5.0 cm^3) and CH_2Cl_2. The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting orange oil was purified by column chromatography on silica gel with EtOAc as eluent. A mixture of **28a** and (+)-ethyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28b** (39 mg, 52%; *ca.* 3 : 1) was isolated as yellow oil. Careful flash chromatography afforded a small quantity of pure **28b** for characterisation; R_f 0.53 (MeOH–EtOAc, 1 : 9); $[a]_D^{19}$ +38.1 (*c* 0.85, EtOH); ν_{max}(film)/cm^{-1} 2962 (m), 2935 (m), 2876 (m), 1707 (m), 1647 (m), 1568 (s), 1462 (m), 1380 (m), 1307 (m), 1235 (m), 1154 (m) and 1103 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si; assignments confirmed by HETCORR) 4.20 [2H, overlapping q (= incipient AB system), *J* 7.1, OCH_2CH_3], 3.75 (1H, dt, *J* 10.3 and 7.3, 3-H_{eq}), 3.67–3.57 (2H, m, 3-H_{ax} and 5-H), 3.37 (1H, dt, *J* 18.6 and 8.1, 1-H_a), 3.21 (1H, dt, *J* 18.6 and 7.6, 1-H_b), 2.48 (1H, dt, *J* 7.1 and 5.8, 6-H), 2.10 (2H, quintet, *J* 7.5, 2-H), 1.93 [1H, *ca.* septet, *J ca.* 7.2, C(6)CH_aH_bMe], 1.71–1.57 [1H, m, C(5)CH_aH_bEt], 1.56–1.42 [1H, m, C(5)CH_aH_bEt], 1.42–1.20 and 1.32 [6H, overlapping m and t, *J* 7.1, C(6)CH_aH_bMe, $C(5)CH_2CH_2$Me and OCH_2CH_3], 0.96 and 0.91 (6H, 2 × t, *J* 7.5 and 7.2, 2 × *Me*); δ_C (100 MHz; $CDCl_3$; assignments confirmed by DEPT and HETCORR) 190.1 (C-7), 171.4 (C-8a), 166.4 (ester *C*=O), 97.3 (C-8), 59.2 (OCH_2CH_3), 57.2 (C-5), 53.6 (C-3), 48.8 (C-6), 34.6 (C-1), 29.0 [C(5)*C*H_2Et], 21.0 (C-2), 19.5 [C(5)CH_2CH_2Me], 17.8 [C(6)*C*H_2Me], 14.4 (OCH_2CH_3), 14.0 [C(5)CH_2CH_2Me] and 12.0 [C(6)CH_2Me]; *m*/*z* (EI) 279 (M^+, 8%), 248 (11), 234 (8), 222 (59), 208 (18), 204 (15), 196 (20), 140 (100) and 98 (16) (found: M^+, 279.1835. $C_{16}H_{25}NO_3$ requires 279.1834).

(+)-Benzyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 29a

A solution of (+)-*tert*-butyl (2*R*,3*R*)-3-[(2*E*)-(2-benzyloxycarbonyl)methylenepyrrolidin-1-yl]amino-2-ethylhexanoate **21a** (174 mg, 0.42 mmol) in trifluoroacetic acid (2 cm^3) was stirred for 3 h at rt, followed by concentration *in vacuo*. The intermediate carboxylic acid, obtained as an orange oil, was immediately dissolved in MeCN (5 cm^3), to which K_2CO_3 (173 mg, 1.25 mmol) was added, followed by acetic anhydride (0.16 cm^3, 173 mg, 1.69 mmol). The mixture was heated under reflux for 18 h in an atmosphere of N_2, affording a thick crystalline suspension. Work-up as described above followed by flash chromatography on silica gel (EtOAc, then MeOH–EtOAc, 1 : 19) yielded (+)-benzyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29a** (114 mg, 80%) as a pale yellow oil; R_f 0.38 (MeOH–EtOAc, 1 : 9); $[a]_D^{22}$ +25.8 (*c* 0.66, EtOH); ν_{max}(film)/cm^{-1} 2960 (m), 2932 (m), 2874 (m), 1711 (m), 1676 (s), 1648 (s), 1566 (s), 1458 (m), 1384 (m), 1307 (m), 1232 (m), 1152 (m) and 1102 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.50–7.40 (2H, m, Ar*H*), 7.35–7.20 (3H, m, Ar*H*), 5.23

(2H, s, OCH_2Ph), 3.74 (1H, dt, *J* 10.4 and 7.9, 3-H_{eq}), 3.49 (1H, ddd, *J* 10.5, 7.7 and 6.0, 3-H_{ax}), 3.36 (1H, t, *J* 7.0, 5-H), 3.28 (1H, *ca.* t, *J ca.* 8.5, 1-H_a), 3.25 [1H, m (= dd?, *J ca.* 8.4 and 6.9), 1-H_b], 2.25–2.00 [3H, m (including dt? *J ca.* 17.6 and 8.0?), 6-H and 2-H], 1.80–1.55 [3H, m (including sextet?, *J ca.* 7.2), C(6)CH_aH_bMe and C(5)CH_2Et], 1.55–1.20 (3H, m, C(6)CH_aH_bMe and C(5)CH_2CH_2Me], 0.97 and 0.90 (6H, 2 × t, *J ca.* 7.0, 2 × *Me*); δ_C (50 MHz; $CDCl_3$) 190.7 (C-7), 170.0 (C-8a), 165.8 (ester *C*=O), 137.1 (Ar*C*), 128.0, 127.3 and 127.1 (Ar*C*H), 95.2 (C-8), 64.7 (O*C*H_2Ph), 58.2 (C-5), 53.7 (C-3), 50.7 (C-6), 34.6 (C-1), 31.7 [C(5)*C*H_2Et], 24.5 [C(6)*C*H_2Me], 20.9 (C-2), 18.5 [C(5)CH$_2$*C*H_2Me], 13.5 [C(5)CH_2CH_2*Me*] and 11.3 [C(6)CH_2*Me*]; *m*/*z* (EI) 341 (M^+, 23%), 298 (6), 270 (31), 248 (11), 235 (19), 234 (90), 207 (36), 190 (15), 164 (23), 136 (17), 91 (100) and 55 (16) (found: M^+, 341.2003. $C_{21}H_{27}NO_3$ requires 341.1991).

Benzyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 29b

A solution of (−)-*tert*-butyl (2*S*,3*R*)-3-[(2*E*)-(2-benzyloxycarbonyl)methylenepyrrolidin-1-yl]amino-2-ethylhexanoate (**21b**) (308 mg, 0.74 mmol) in trifluoroacetic acid (2.5 cm^3) was stirred for 3 h at rt, followed by concentration *in vacuo*. The intermediate carboxylic acid, obtained as an orange oil, was immediately dissolved in MeCN (3.7 cm^3), to which K_2CO_3 (321 mg, 2.32 mmol) was added, followed by acetic anhydride (0.28 cm^3, 302 mg, 2.96 mmol). The mixture was heated under reflux for 18 h in an atmosphere of N_2. Work-up as described above followed by flash chromatography on silica gel (EtOAc, then MeOH–EtOAc, 1 : 19) yielded three fractions: (+)-benzyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29a** (81 mg, 32%) as a pale yellow oil, R_f 0.38 (MeOH–EtOAc, 1 : 9); characterisation as described above; a mixed fraction (22 mg, 9%); and benzyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29b** (31 mg, 12%) as a pale yellow oil; R_f 0.34 (MeOH–EtOAc, 1 : 9); ν_{max}(film)/cm^{-1} 2960 (m), 2933 (m), 2874 (m), 1710 (m), 1653 (m), 1647 (m), 1559 (s), 1458 (m), 1387 (m) and 1129 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.45–7.10 (5H, m, Ar*H*), 5.16 (2H, s, OCH_2Ph), 3.66 (1H, dt, *J* 10.2 and 7.4, 3-H_{eq}), 3.60–3.45 (2H, m, 3-H_{ax} and 5-H), 3.26 (1H, dt, *J* 18.7 and 8.2, 1-H_a), 3.11 (1H, dt, *J* 18.6 and 7.7, 1-H_b), 2.42 (1H, dt, *J* 7.2 and 5.6, 6-H), 1.99 (2H, quintet, *J* 7.6, 2-H), 1.84 [1H, *ca.* septet, *J ca.* 5.9, C(6)CH_aH_bMe], 1.70–1.00 (5H, m, remaining CH_2), 0.88 and 0.84 (6H, 2 × t, *J* 7.5 and 7.0, 2 × *Me*); δ_C (50 MHz; $CDCl_3$) 190.2 (C-7), 171.7 (C-8a), 166.2 (ester *C*=O), 137.4 (Ar*C*), 128.3, 127.6 and 127.3 (Ar*C*H), 97.2 (C-8), 65.0 (O*C*H_2Ph), 57.4 (C-5), 53.7 (C-3), 49.0 (C-6), 34.7 (C-1), 29.2 [C(5)*C*H_2Et], 21.1 (C-2), 19.6 [C(5)CH$_2$*C*H_2Me], 17.9 [C(6)*C*H_2Me], 14.1 [C(5)CH_2CH_2*Me*] and 12.0 [C(6)CH_2*Me*]; *m*/*z* (EI) 341 (M^+, 19%), 339 (14), 284 (9), 270 (20), 249 (21), 248 (61), 235 (11), 234 (61), 231 (21), 207 (22), 164 (12), 140 (71), 136 (9), 91 (100) and 55 (15) (found: M^+, 341.1998. $C_{21}H_{27}NO_3$ requires 341.1991).

(+)-(5*R*,6*R*)-6-Ethyl-*N*-methoxy-*N*-methyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide 30

A solution of (+)-*tert*-butyl (2*R*,3*R*)-2-ethyl-3-{(2*E*)-[2-(*N*-methoxy-*N*-methylaminocarbonyl)methylene]pyrrolidin-1-yl}-hexanoate **22** (145 mg, 0.39 mmol) in trifluoroacetic acid (1.0 cm^3) was stirred for 3 h at rt, followed by concentration *in vacuo*. The intermediate carboxylic acid, obtained as a brown oil, was immediately dissolved in MeCN (2.0 cm^3), to which K_2CO_3 (170 mg, 1.23 mmol) was added, followed by acetic anhydride (0.15 cm^3, 162 mg, 1.59 mmol). The mixture was heated under reflux for 18 h in an atmosphere of N_2. Work-up as described above followed by chromatography on silica gel (MeOH–EtOAc, 1 : 9) yielded (+)-(5*R*,6*R*)-6-ethyl-*N*-methoxy-*N*-methyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-acetamide **30** (96 mg, 83%) as a yellow oil; R_f 0.29 (MeOH–EtOAc, 1 : 9); $[\alpha]_D^{18}$ +103.1 (*c* 0.74, EtOH); ν_{max}(film)/cm^{-1} 2961 (m), 2934 (m), 2877 (m), 1724 (w), 1616 (s), 1576 (s), 1466 (m), 1385 (m), 1276 (m), 1081 (m) and 1014 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.69 (3H, s, O*Me*), 3.69 (1H, dt, *J* 10.2 and 7.5, 3-H_{eq}), 3.48 (1H, ddd, *J* 10.2, 7.4 and 6.0, 3-H_{ax}), 3.38 (1H, br t, *J* 6.6, 5-H), 3.21 (3H, s, N*Me*), 3.10–2.90 (2H, m, 1-H), 2.21–2.00 (3H, m, 2-H and 6-H), 1.80–1.15 [6H, m, C(5)CH_2CH_2Me, C(6)CH_2Me], 0.98 [3H, t, *J* 7.4, C(6)CH$_2$*Me*] and 0.92 [3H, t, *J* 7.2, C(5)CH_2CH_2*Me*]; δ_C (50 MHz; $CDCl_3$) 188.8 (C-7), 166.1 (amide *C*=O), 99.1 (C-8), 60.7 (O*Me*), 58.2 (C-5), 53.0 (C-3), 50.2 (C-6), 34.5 (br, N*Me*), 32.0 (C-1), 31.8 [C(5)*C*H_2Et], 24.8 [C(6)*C*H_2Me], 21.3 (C-2), 18.7 [C(5)CH$_2$*C*H_2Me], 13.8 [C(5)CH_2CH_2*Me*] and 11.5 [C(6)CH_2*Me*], signal for C-8a missing or obscured; *m*/*z* (EI) M^+ absent, 279 (M^+ − Me, 32%), 250 (4.6, M^+ − CH_3CH_2), 236 (18), 234 (43), 222 (9), 209 (13), 208 (100), 207 (10), 191 (9), 190 (59), 164 (37), 162 (34), 136 (14), 109 (9) and 55 (17) [found: M^+ − N(OMe)Me, 234.1493. $C_{14}H_{20}NO_2$ requires 234.1494].

Ethyl (5*R*,6*R*,8*S*,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate 31 and its (5*R*,6*R*,8*R*,8a*R*) isomer 32

(a) $LiAlH_4$ (49 mg, 1.29 mmol) was added to a solution of (+)-ethyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28a** (199 mg, 0.71 mmol) in dry THF (8.5 cm^3) in a flame-dried flask under an atmosphere of N_2 at −78 °C. The mixture was stirred at this temperature for 2.5 h, allowed to warm to room temperature, then treated sequentially with water (50 μl), aqueous NaOH solution (15%; 50 μl) and water (150 μl). The granular precipitate was filtered off through celite, the solids were washed with acetone, and the filtrate was evaporated *in vacuo*. Column chromatography of the crude product on silica gel with EtOAc–hexane (1 : 9) eluent yielded an inseparable mixture of ethyl (5*R*,6*R*,8S,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate **31** and a *minor isomer* **32** with putative (5*R*,6*R*,8*R*,8a*R*)-stereochemistry (158 mg, 79%; ratio 3 : 1 by NMR spectroscopy) as a yellow oil; R_f 0.26 (EtOAc–hexane, 1 : 9); ν_{max}(film)/cm^{-1} 2961 (s), 2934 (s), 2876 (s), 2801 (m, Bohlmann band), 1744 (s), 1717 (s), 1566 (s), 1462 (m), 1378 (m), 1335 (m), 1303 (m), 1258 (m), 1204 (m), 1174 (m), 1151 (m), 1098 (m) and 1026 (m); *m*/*z* (EI) 281 (M^+, 8%), 252 (17), 239 (14), 238 (100), 222 (27), 208 (32), 192 (17), 170 (13), 140 (12), 138 (27), 124 (38), 70 (15) and 55 (24) (found: M^+, 281.1953. $C_{16}H_{27}NO_3$ requires 281.1991). Most of the signals due to the individual isomers were distinguishable by NMR spectroscopy. *Major isomer* **31**: δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.22 [2H, overlapping q (= incipient AB system), *J* 7.2, OCH_2CH$_3$], 3.31 (1H, d, *J* 11.0, 8-H), 3.15 (1H, td, *J* 8.7 and 2.8, 3-H_{eq}), 2.73 (1H, ddd, *J* 11.0, 8.8 and 6.2, 8a-H), 2.35 (1H, br m, 5-H), 2.20 (1H, q?, *J ca.* 8.8, 6-H), 2.10–1.95 (1H, m, 3-H_{ax}), 1.95–1.70 (3H, m, 1-H and 2-H_a), 1.67–1.55 [4H, m, 2-H_b, C(5)CH_2Et and C(5)CH$_2$CH_aH$_b$Me], 1.55–1.42 [2H, m, C(5)CH$_2$CH$_a$$H_b$Me and C(6)C$H_aH_b$Me], 1.42–1.25 and 1.28 [4H, overlapping m and t, *J* 7.2, C(6)CH$_a$$H_b$Me and OCH$_2CH_3$], 0.94 and 0.91 (6H, 2 × t, *J* 7.1 and 7.4, 2 × *Me*); δ_C (100 MHz; $CDCl_3$) 205.7 (C-7), 168.6 (ester *C*=O), 65.3 (C-8a), 64.0 (C-5), 62.7 (C-8), 60.8 (O*C*H$_2$CH$_3$), 52.3 (C-6), 49.8 (C-3), 33.2 [C(5)*C*H$_2$Et], 29.8 (C-1), 21.3 (C-2), 17.9 and 16.2 (remaining *C*H$_2$), 14.1 (OCH$_2$*C*H$_3$), 14.4 and 11.6 (2 × *Me*). Discernible signals for *minor isomer* **32**: δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.29 (d, *J* 10.3, 8-H), 2.98 (br d, *J ca.* 11.0, 8a-H), 2.87 (td, *J* 8.4 and 3.7, 3-H_{eq}), 1.28 (t, *J* 7.2, OCH$_2$CH_3) and 0.91 (t, *J* 7.6, remaining *Me*); δ_C (100 MHz; $CDCl_3$) 208.5 (C-7), 169.0 (ester *C*=O), 60.6 (O*C*H$_2$CH$_3$), 59.3, 57.6, 56.1, 48.6, 31.1, 27.7, 24.8, 22.3, 20.1, 14.0 and 12.1; two signals obscured by major isomer.

(b) When the above procedure was repeated with ethyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28b** (388 mg, 1.39 mmol) and $LiAlH_4$ (91 mg, 2.40 mmol) in THF (15 cm^3) under the conditions described

above, the same mixture of isomers **31** and **32** (254 mg, 65%; ratio 4 : 1 by NMR spectroscopy) was obtained as a yellow oil; characterisation as described in (a).

Benzyl (5*R*,6*R*,8*S*,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate 33 and its (5*R*,6*R*,8*R*,8a*R*) isomer 34

When the above procedure was repeated with (+)-benzyl (5*R*,6*S*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **29a** (134 mg, 0.39 mmol) and $LiAlH_4$ (22 mg, 0.58 mmol) in THF (3.9 cm^3) under the conditions described above, an inseparable mixture of benzyl (5*R*,6*R*,8*S*,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate **33** and a *minor isomer*, probably (5*R*,6*R*,8*R*,8a*R*)-**34** (99 mg, 73%; ratio 3 : 1 by NMR spectroscopy) was obtained as a pale yellow oil after purification by chromatography on silica gel with EtOAc–hexane (1 : 9) as eluent; R_f 0.70 (MeOH–EtOAc, 1 : 9); ν_{max}(film)/cm^{-1} 3066 (w), 3033 (w), 2960 (m), 2934 (m), 2874 (m), 2801 (m, Bohlmann band), 1744 (s), 1713 (s), 1458 (m), 1382 (m), 1337 (m), 1302 (m), 1259 (m), 1146 (m), 749 (m) and 697 (m); *m*/*z* (EI) 343 (M^+, 7%), 301 (11), 300 (51), 234 (8), 222 (13), 192 (7), 140 (19), 124 (24), 91 (100) and 55 (13) (found: M^+, 343.2131. $C_{21}H_{29}NO_3$ requires 343.2147). Most of the signals due to the *major isomer* **33**: were distinguishable by NMR spectroscopy: δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.40–7.20 (5H, m, aryl H), 5.20 (2H, distorted AB system, J_{AB} *ca.* 12.4, OCH_2Ph), 3.38 (1H, d, *J* 11.1, 8-H), 3.13 (1H, td, *J* 8.3 and 3.2, 3-H-3$_{eq}$), 2.75 (1H, ddd, *J* 11.1, 8.8 and 6.3, 8a-H), 2.30–2.40 (1H, br m, 5-H), 2.19 (1H, *ca.* q, *J ca.* 8.7, 6-H), 2.10–1.85 (1H, m, 3-H_{ax}), 1.85–1.70, 1.70–1.50 and 1.50–1.10 (3H + 6H + 1H, clusters of m, remaining CH_2), 0.93 and 0.90 (6H, 2 × t, 7.1 and 7.4, 2 × *Me*); δ_C (50 MHz; $CDCl_3$) 205.4 (C-7), 168.5 (ester *C*=O), 135.7 (Ar*C*), 128.4, 128.1 and 128.0 (Ar*C*H), 66.6 (O*C*H_2Ph), 65.3 (C-8a), 64.0 (C-5), 62.8 (C-8), 52.3 (C-6), 49.7 (C-3), 33.2 [C(5)*C*H_2Et], 29.8 (C-1), 21.3 (C-2), 17.9 and 16.2 (remaining *C*H_2), 14.4 and 11.6 (2 × *Me*). Discernible signals for *minor isomer* **34**: δ_H 3.36 (d, *J* 10.3); δ_C 63.7, 60.7, 59.4, 56.1, 48.6, 31.1, 30.8, 22.6, 20.1, 18.4, 14.0 and 12.1.

Ethyl 6,8-diethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate isomers 35

NaH (19 mg, 0.79 mmol) was added in a single portion to a solution of ethyl (5*R*,6*R*,8*S*,8a*S*)-6-ethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate **31** and its (5*R*,6*R*,8*R*,8a*R*) isomer **32** (113 mg, 0.40 mmol) in THF (2.0 cm^3) under an atmosphere of N_2 at 0 °C. The solution changed colour from purple to deep green over 1.5 h. Iodoethane (0.04 cm^3, 78 mg, 0.50 mmol) was then added, and the mixture was left to react at rt for 7 d. After addition of saturated aqueous NH_4Cl (2.0 cm^3) solution, the mixture was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Chromatography of the crude orange oil on silica gel with EtOAc–hexane (1 : 19) as eluent yielded a mixture of isomers of ethyl 6,8-diethyl-7-oxo-5-propyloctahydroindolizine-8-carboxylate **35** (43 mg, 35%; 4 : 1 by NMR spectroscopy) as a pale yellow oil; R_f 0.34 (EtOAc–hexane, 1 : 19); ν_{max}(film)/cm^{-1} 2961 (m), 2876 (m), 2796 (w, Bohlmann band), 1734 (s), 1711 (s), 1458 (m), 1374 (m), 1310 (w), 1239 (m), 1184 (w), 1125 (m) and 1026 (w); *m*/*z* (EI) 309 (M^+, 10), 294 (10), 267 (17), 266 (100), 236 (9), 166 (11), 140 (49), 125 (13), 124 (39), 97 (10), 70 (23), 69 (11), 57 (11) and 55 (21) (found: M^+, 309.2307. $C_{18}H_{31}NO_3$ requires 309.2304). Discernible signals for *major isomer*, tentatively assigned as (5*R*,6*R*,8*R*,8a*S*): δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.27–4.12 [2H, overlapping q (= incipient AB system), *J* 7.1, OCH_2CH$_3$], 3.18 (1H,br td, *J ca.* 8.6 and 2.9, 3-H_{eq}), 2.85 (1H, t, *J* 8.3, 8a-H), 2.31 (1H, ddd, *J* 10.6, 7.3 and 2.8, 6-H?), 2.24 and 2.17 [2H, br m and q?, *J ca.* 7.6, 5-H and C(8)CH_aH$_b$CH$_3$?], 2.07 [1H, br q, *J ca.* 8.8, 3-H_{ax}?], 1.99 [1H, *ca.* quintet, *J ca.* 7.2, C(8)CH$_a$$H_bCH_3$?], 1.90–1.70 and 1.70–1.50 (9H, 2 × m, CH_2), 1.35–1.20 and 1.27 [4H, overlapping m and t, *J* 7.1, C(5)CH$_2$CH$_a$$H_b$Me and OCH$_2CH_3$], 0.94, 0.92 and 0.91 (9H, 3 × t, *J* 7.2, 7.5 and 7.4, 3 × *Me*); δ_C (100 MHz, $CDCl_3$) 208.9 (C-7), 171.5 (ester *C*=O), 68.5 (C-8a), 65.8 (C-8), 64.7 (C-5), 60.6 (O*C*H$_2$CH$_3$), 51.1 (C-6), 49.9 (C-3), 33.0 [C(5)*C*H$_2$Et], 24.2 (C-1), 21.6 (C-2), 20.9, 17.8 and 15.5 (remaining *C*H$_2$), 14.1 (OCH$_2$*C*H$_3$), 14.5, 11.9 and 9.2 (3 × *Me*). Discernible signals for minor isomer: δ_H 1.26 (t, *J* 7.1); δ_C 65.8, 60.4, 52.1, 51.5, 33.5, 25.0, 24.9, 22.3, 18.4, 15.6, 11.9 and 9.4.

(+)-(5*R*,6*R*)-6-Ethyl-5-propyl-2,3,5,6-tetrahydroindolizin-7(1*H*)-one 37

A suspension of (+)-ethyl (5*R*,6*R*)-6-ethyl-7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **28a** (245 mg, 0.88 mmol) in aqueous NaOH solution (1 M, 5 cm^3) was heated under reflux for 1.5 h. The hot homogeneous solution was then made acidic with conc. HCl, and heating was continued for 30 min. The solution was cooled to room temperature and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*, and the resulting yellow oil was purified by column chromatography on silica gel with EtOAc–hexane (1 : 2) as eluent to give (+)-(5R,6R)-6-ethyl-5-propyl-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **37** (153 mg, 84%) as a pale yellow oil, R_f 0.36 (EtOAc–hexane, 1 : 2); $[\alpha]_D$ ^{22} +210.01 (*c* 1.49, EtOH); ν_{max}(film)/cm^{-1} 2960 (m), 2933 (m), 2873 (m), 1626 (m), 1576 (s), 11506 (w), 1472 (w), 1241 (w), 1186 (w), 1151 (w) and 1080 (w); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.84 (1H, d, *J* 0.7, 8-H), 3.60 (1H, dt, *J* 9.8 and 7.4, 3-H_a), 3.42 and 3.35 [2H, overlapping dt (*J* 9.8 and 6.5) and br td (*J ca* 5.1 and 1.4), 5-H and 3-H_b], 2.68 (2H, br t, *J ca.* 7.5, 1-H), 2.07 and 2.06 (3H, *ca.* t and quintet, *J ca.* 7.6, 6-H and 2-H), 1.80–1.15 (6H, m, remaining CH_2), 0.97 and 0.91 (6H, 2 × t, *J* 7.4 and 7.1, 2 × *Me*); δ_C (50 MHz, $CDCl_3$) 193.8 (C-7), 165.0 (C-8a), 89.8 (C-8), 58.1 (C-5), 51.8 (C-3), 50.0 (C-6), 31.9 (C-1), 30.8 [C(5)*C*H$_2$Et], 25.1 [C(6)*C*H$_2$Me], 21.4 (C-2), 18.6 [C(5)CH$_2$*C*H$_2$Me], 13.8 [C(5)CH$_2$CH$_2$*Me*] and 11.4 [C(6)CH$_2$*Me*]; *m*/*z* (EI) 207 (M^+, 31%), 192 (5), 178 (7), 165 (12), 164 (53), 140 (9), 137 (10), 136 (100), 110 (22) and 55 (10) (found: M^+, 207.1630. $C_{13}H_{21}NO$ requires 207.1623).

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References

1 J. W. Daly, H. M. Garraffo and T. F. Spande, in *The Alkaloids. Chemistry and Pharmacology*, G. A. Cordell, ed., Academic Press, San Diego, 1993, vol. 43, pp. 185–288.
2 J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*, S. W. Pelletier, ed., Pergamon Press, Amsterdam, 1999, vol. 13, pp. 1–161.
3 A. S. Howard and J. P. Michael, in *The Alkaloids. Chemistry and Pharmacology*, A. Brossi, ed., Academic Press, New York, 1986, vol. 28, pp. 183–308; J. P. Michael, in *The Alkaloids. Chemistry and Biology*, G. A. Cordell, ed., Academic Press, New York, 2001, vol. 55, pp. 91–258. For annual reports on progress in the chemistry of indolizidine and quinolizidine alkaloids, see:; J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 625–649 and earlier reviews in this series.
4 J. W. Daly, in *The Alkaloids. Chemistry and Biology*, G. A. Cordell, ed., Academic Press, San Diego, 1998, vol. 50, pp. 141–169.; J. W. Daly, T. Kaneko, J. Wilham, H. M. Garraffo, T. F. Spande, A. Espinosa and M. A. Donnelly, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 13 996–14 001; J. W. Daly, *J. Med. Chem.*, 2003, **46**, 445–452; R. A. Saporito, H. M. Garraffo, M. A. Donnelly, A. L. Edwards, J. T. Longino and J. W. Daly, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 8045–8050.
5 H. M. Garraffo, P. Jain, T. F. Spande and J. W. Daly, *J. Nat. Prod.*, 1997, **60**, 2–5.

6 N. Toyooka, A. Fukutome, H. Nemoto, J. W. Daly, T. F. Spande, H. M. Garraffo and T. Kaneko, *Org. Lett.*, 2002, **4**, 1715–1717; N. Toyooka, A. Fukutome, H. Shinoda and H. Nemoto, *Tetrahedron*, 2004, **60**, 6197–6216.
7 T. Tokuyama, A. Shimada, H. M. Garraffo, T. F. Spande and J. W. Daly, *Heterocycles*, 1998, **49**, 427–436.
8 J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371–4381.
9 X. Pu and D. Ma, *J. Org. Chem.*, 2003, **68**, 4400–4405.
10 J. P. Michael, C. B. de Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly and T. V. Stanbury, *Pure Appl. Chem.*, 1999, **71**, 979–988.
11 J. P. Michael, C. B. de Koning, T. J. Malefetse and I. Yillah, *Org. Biomol. Chem.*, 2004, 3510–3517 and refs. cited therein.
12 J. P. Michael and D. Gravestock, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1919–1928.
13 S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183–186; J. F. Costello, S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1994, **5**, 1999–2008.
14 (*a*) M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710–734; (*b*) K. Shiosaki, in *Comprehensive Organic Synthesis*, B. M. Trost, ed., Pergamon Press, Oxford, 1991, vol. 2, pp. 865–892.
15 (*a*) S. G. Davies, O. Ichihara, I. Lenoir and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1411–1415; (*b*) S. G. Davies and D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2629–2634; (*c*) M. E. Bunning, A. M. Chippindale, S. G. Davies, R. M. Parkin, A. D. Smith and J. M. Withey, *Org. Biomol. Chem.*, 2003, **1**, 3698–3707; (*d*) S. G. Davies, D. Diez, M. M. El Hammouni, A. C. Garner, N. M. Garrido, M. J. C. Long, R. M. Morrison, A. D. Smith, M. J. Sweet and J. M. Withey, *Chem. Commun.*, 2003, 2410–2411.
16 S. G. Davies, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1141–1147; S. G. Davies, O. Ichihara and I. A. S. Walters, *Synlett*, 1994, 117–118.
17 (*a*) S. G. Davies, N. M. Garrido, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Chem. Commun.*, 1993, 1153–1155; (*b*) S. G. Davies and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1129–1139; (*c*) For related studies with carboxamides, see: S. G. Davies, A. J. Edwards and I. A. S. Walters, *Recl. Trav. Chim.*, 1995, **114**, 175–183.
18 J. P. Michael and D. Gravestock, *S. Afr. J. Chem.*, 1998, **51**, 146–157.
19 H. B. Wright and M. B. Moore, *J. Am. Chem. Soc.*, 1948, **70**, 3865–3866.
20 J. Singh, N. Satyamurthi and I. S. Aidhen, *J. Prakt. Chem.*, 2000, **342**, 340–347.
21 M. F. Mechelke and A. I. Meyers, *Tetrahedron Lett.*, 2000, **41**, 4339–4342.
22 J. P. Michael and D. Gravestock, *Eur. J. Org. Chem.*, 1998, 865–870.
23 P. Slosse and C. Hootelé, *Tetrahedron*, 1981, **37**, 4287–4294.
24 J. P. Michael, C. B. de Koning, C. San Fat and G. L. Nattrass, *Arkivoc*, 2002, **ix**, 62–77.
25 H. Takahata, K. Yamabe, T. Suzuki and T. Yamazaki, *Heterocycles*, 1986, **24**, 37–39.
26 F. Bohlmann, *Chem. Ber.*, 1985, **91**, 2157–2167.
27 In a more closely related example, (±)-ethyl (5*R**,8*S**,8a*S**)-7-oxo-5-pentylindolizidine-8-carboxylate was readily converted into its 1,3-dithiane derivative in 87% yield upon treatment with propane-1,3-dithiol and boron trifluoride etherate in trifluoroacetic acid at ambient temperature: J. P. Michael and D. Gravestock, unpublished results.
28 A further synthetic approach to indolizidine 223A and congeners was reported after this manuscript was submitted: R. Kumareswaran, J. Gallucci and T. V. RajanBabu, *J. Org. Chem.*, 2004, **69**, 9151–9158.