Hydrogenation of pyrrolizin-3-ones; new routes to pyrrolizidines†

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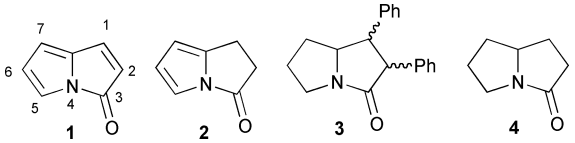
Pyrrolizin-3-ones (*e.g.* **1**) can be easily hydrogenated to their hexahydro (pyrrolizidin-3-one) derivatives in the presence of heterogeneous catalysts. Good diastereoselectivity (up to >97:3, depending on catalysts and solvent) can be achieved if the pyrrolizin-3-one is substituted at the 1- (or 7-) position(s), but the selectivity is reduced if both positions are substituted. Subsequent deoxygenation of the pyrrolizidin-3-ones provides concise, diastereoselective routes to the necine bases (±)-heliotridane **5**, (±)-isoretronecanol **6** and (±)retronecanol **7**.

Introduction

It has long been known that catalytic hydrogenation of pyrrolizin-3-ones (*e.g.* **1**) gives 1,2-dihydro-compounds **2** under mild conditions.[1–5] Isolated reports of further reduction to the hexahydropyrrolizin-3-one (pyrrolizidin-3-one) system have also appeared. For example, the 1,2-diphenylpyrrolizidinone(s) **3** were obtained by hydrogenation of the corresponding pyrrolizinone using Adam's catalyst in acetic acid. Pyrrolizidin-3-one itself **4** can also be made by hydrogenation of **2** in ethanol at atmospheric pressure in the presence of *ca.* 200% by weight of palladium/charcoal,[6a] and other examples are known.[6b] Reduction under such mild conditions is surprising because pyrroles in general require much more forcing conditions.[7] However, it is known that hydrogenation of pyrroles bearing electron withdrawing groups on nitrogen is facilitated by comparison with *N*-unsubstituted or *N*-alkyl analogues.[8]



Here, we report the results of a systematic study of pyrrolizin-3-one hydrogenation, including optimisation of the amount and nature of the catalyst and the solvent. This method complements the synthetic routes to pyrrolizidin-3-ones by ring synthesis, which we reviewed in 2000.[9] With the availability of a range of substituted pyrrolizin-3-ones by various thermal strategies,[10–12] the diastereoselectivity of hydrogenation of 1- and 7-substituted pyrrolizinones was studied. The major use of pyrrolizidin-3-ones[9] is their reduction to the necine base components of the important pyrrolizidine class of alkaloids,[13] and this strategy is applied here to (±)-heliotridane **5**, (±)-isoretronecanol **6** and (±)-retronecanol **7**.

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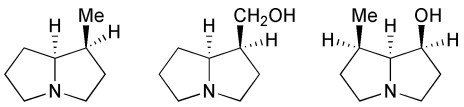
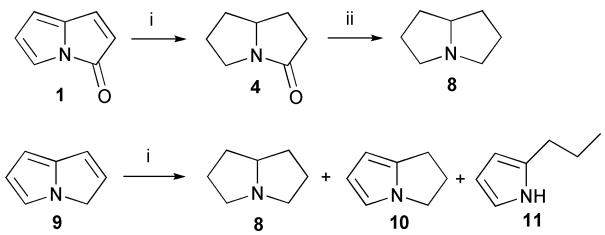


(Only one of the enantiomeric pairs is shown)

Results and discussion

We have discovered that hydrogenation of pyrrolizin-3-one[10] **1** in ethanol, using just 10% by weight of palladium/charcoal and an H_2 pressure of 45 psi, gives a 94% yield of the pyrrrolizidin-3-one **4** after 2 h at room temperature. Its NMR spectrum was almost completely resolved at 600 MHz and the analysis is shown in the ESI†.

Lithium aluminium hydride deoxygenation of pyrrolizidin-3-ones to pyrrolizidines is well known[14] and the parent compound **8** was isolated as the picrate salt in 51% yield by this procedure (Scheme 1). (The low yield was due to the volatility of the free base.) In contrast, direct catalytic hydrogenation of pyrrolizine **9** under our conditions[15] gave a mixture of **8**, dihydropyrrolizine **10** and 2-propylpyrrole **11** in a 20:45:35 ratio (Scheme 1). These preliminary results suggest that a pyrrolizinone route to pyrrolizidines may be more efficient than a method involving pyrrolizines.



Scheme 1 *Reagents and conditions:* (i) H_2, Pd/C, 45 psi; (ii) $LiAlH_4$, Et_2O/THF.

In order to develop a pyrrolizinone route to pyrrolizidines, the diasteroselectivity of hydrogenation of 1-methylpyrrolizin-3-one[11] **12** to the known[16] pyrrolizidinones **14** and **15**, and of 7-methylpyrrolizin-3-one[11] **16** to the known[17] pyrrolizidinones **18** and **19** was studied (Scheme 2). The pairs of perhydro-compounds were readily distinguished from the methyl signals in their

Table 1 Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **12** (45 psi, 2 h) to **14** and **15**

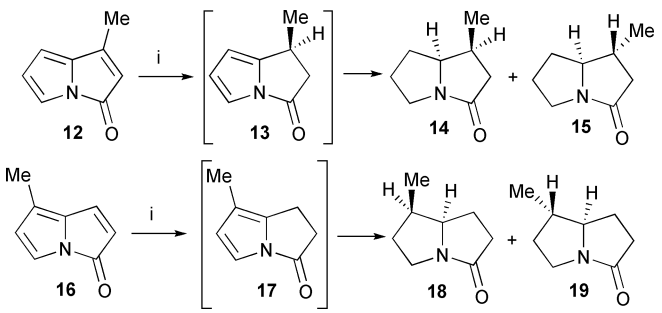
Catalyst	Solvent	Ratio **14**:**15**
5% Pd/C	Hexane	82:18
5% Pd/C	Ethyl acetate	74:26
5% Pd/C	Ethanol	76:24
5% Pd/C	DMF	Not formed[a]
5% Pd/C	*t*-Butanol	74:26
5% Pd/C	Acetic acid	69:31
5% Pd/$CaCO_3$	Hexane	89:11
5% Pd/$CaCO_3$	Ethyl acetate	87:13
Raney Ni	Hexane	93:7[a]
Raney Ni	Ethyl acetate	94:6[a]
Raney Ni	Ethanol	93:7[a]
PtO_2	Hexane	85:15
PtO_2	Acetic acid	78:22
Pt black	Hexane	85:15[a]
5% Rh/C	Hexane	89:11
5% Rh/C	Acetic acid	85:15
5% Rh/Al_2O_3	Hexane	88:12
5% Rh/Al_2O_3	Ethyl acetate	89:11
5% Rh/Al_2O_3	Ethanol	91:9
5% Rh/Al_2O_3	Ethanol	90:10[b]
5% Rh/Al_2O_3	Acetic acid	90:10
5% Ru/C	Water	33:67[a]

[a] Compound **13** present. [b] Hydrogenation at atmospheric pressure for 24 h.

Table 2 Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **16** (45 psi, 2 h) to **18** and **19**

Catalyst	Solvent	Ratio **18**:**19**
5% Pd/C	Ethanol	84:16
5% Pd/C	Acetic acid	86:14
5% Pd/$CaCO_3$	Hexane	92:8[a]
Raney Ni	Ethanol	96:4[a]
PtO_2	Hexane	93:7
5% Rh/C	Hexane	98:2
5% Rh/C	Hexane	98:2[b]
5% Rh/C	Ethyl acetate	98:2
5% Rh/Al_2O_3	Hexane	96:4
5% Rh/Al_2O_3	Acetic acid	96:4

[a] Compound **17** present. [b] Hydrogenation at atmospheric pressure for 48 h.



Scheme 2 *Reagents and conditions:* (i) H_2/catalyst, 45 psi, 20 °C. 2 h. Best method for **14**/**15**; 5% Rh/Al_2O_3, EtOH, yield 90%, dr 90:10. Best method for **18**/**19**; 5% Rh/C, hexane, yield 97%, dr 98:2. (For asymmetric compounds, only one of the enantiomeric pairs is shown.)

^{1}H NMR spectra (*cis*-isomer **14**: δ_H 0.98, ^3J 7.0 Hz; *trans*-isomer **15**: δ_H 1.16, ^3J 6.6 Hz[16]) and (*cis*-isomer **18**: δ_H 0.81, ^3J 7.3 Hz; *trans*-isomer **19**: δ_H 1.02, ^3J 6.1 Hz[17]), and results are shown in Tables 1 and 2. Ratios were measured from the ^{1}H NMR spectra of the crude hydrogenation mixtures. Evans and Fandrick report the formation of **14** and **15** in a 90:10 diastereomeric ratio, using Rh/Al_2O_3 in ethanol, in agreement with our results.[6b]

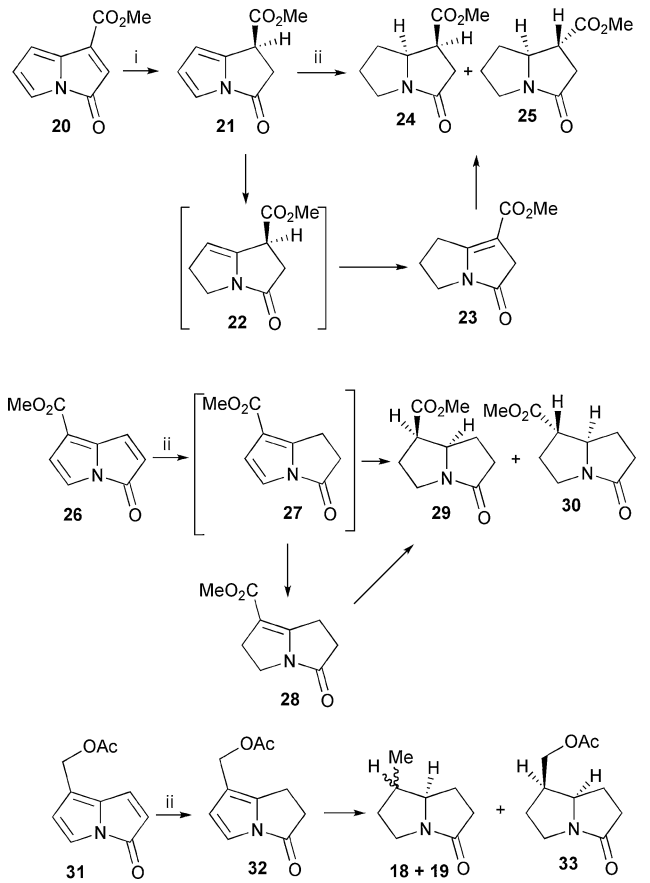
As with pyrrolizine hydrogenation,[15,18] control of further hydrogenation of the dihydro-compound **13** depends on the steric effect of the methyl group at the new asymmetric centre, which would be expected to lie preferentially away from the catalyst surface, leading to the *cis*-isomer **14**. Indeed, **14** is the major product under all but one of the hydrogenation conditions (Table 1) with diastereomeric ratios (dr) ranging from 2.2 (Pd/C/acetic acid) to 15.4 (Raney Ni/ethyl acetate). Both the nature of the catalyst and the solvent affect the dr, with the former proving to be the major influence. The highest selectivity was shown by Raney nickel, but the catalyst activity was low, with the dihydro-compound **13** the major product. 5% Rhodium/alumina (7% by weight of substrate) in ethanol was therefore used for a preparative-scale hydrogenation, and gave a 90% yield of **14** and **15** in a 90:10 ratio.

Hydrogenation of the 7-methyl isomer **16** occurred with much higher diastereoselectivity than that of the 1-methyl compound **12**, with again the *cis*-isomer **18** being the major product (Table 2). In this case, 5% rhodium/carbon (13% by weight) was used for the preparative-scale reaction; **18** was obtained in 94% yield, with a trace (*ca.* 3%) of the *trans*-isomer **19**. The very high diastereoselectivity observed in the hydrogenation of **16** (and other 7-substituted pyrrolizin-3-ones) is due to the *cis*-hydrogenation of the pyrrole ring in **17** (and related compounds), which leads to the hydrogen atoms at positions 7 and 7a to be *cis* to one another.

The synthesis of (±)heliotridane **5**, a common alkaloid degradation product,[19] was completed by reduction of the lactam using lithium aluminium hydride (*cf.* ref. 14). Heliotridane was isolated as its picrate salt and freed from the minor diasteromer by recrystallisation from ethanol to give **5** (70% from **14** + **15**; 79% from **18** + **19**). The overall (unoptimised) yield of **5** in 3 steps from 2-acetylpyrrole *via* **12** is 36% and in 3 steps from 3-methylpyrrole-2-carboxaldehyde *via* **16** is 53%.

In order to approach the synthesis of the necine base (±)-isoretronecanol[13,20] **6**, three pyrrolizinone precursors **20**, **26** and **30** were studied (Scheme 3). 1-Methoxycarbonylpyrrolizin-3-one **20** is an unusual compound because it spontaneously dimerises at the 1,2-double bond under normal conditions.[12] However, it was possible to isolate the stable 1,2-dihydro-compound **21** by carrying out the hydrogenation at –20 °C at atmospheric pressure. These conditions were not optimised and, unusually, some of the 2,5,6,7-tetrahydro compound[21] **23** was also isolated. This suggests that the 5,6-double bond of **21** may be the first pyrrole bond to be reduced, to provide the tetrahydro intermediate **22**, then the remaining double bond moves into conjugation. It is clear that these steps must all take place on the catalyst surface since no deuterium was incorporated into **23** when the hydrogenation was carried out in [^{2}H] methanol.

The known[22] *cis*- and *trans*-hexahydro-1-methoxycarbonyl-pyrrolizin-3-one **24** and **25** can be synthesised if the hydrogenation of **20** (Pd/C in methanol) is carried out in two steps (*viz.* atmospheric pressure H_2, –20 °C, 2 h, followed by 55 psi H_2, 20 °C, 24 h). The yield is 53% (for the two steps from the pyrolysis precursor) and **24** and **25** are obtained in a ratio of 91:9. The intermediate formation of **23** may be beneficial stereochemically, since its hydrogenation would be expected to provide



Scheme 3 *Reagents and conditions:* (i) H_2/Pd/C, 15 psi, –20 °C, 2 h. (ii) H_2/catalyst, 45 psi, 20 °C. 2 h. Best method for **24**/**25**; 5% Pd/C, MeOH, yield 53%, dr 91:9. Best method for **29**/**30**; 5% Rh/Al_2O_3, HOAc, yield 98%, dr >98:2. Best method for **33**; 5% Rh/C, EtOH, yield 84% (remainder **18**), dr >98:2. (For asymmetric compounds, only one of the enantiomeric pairs is shown.)

the *cis*-isomer **24** by *cis*-hydrogenation of the C(7a)–C(1) double bond.

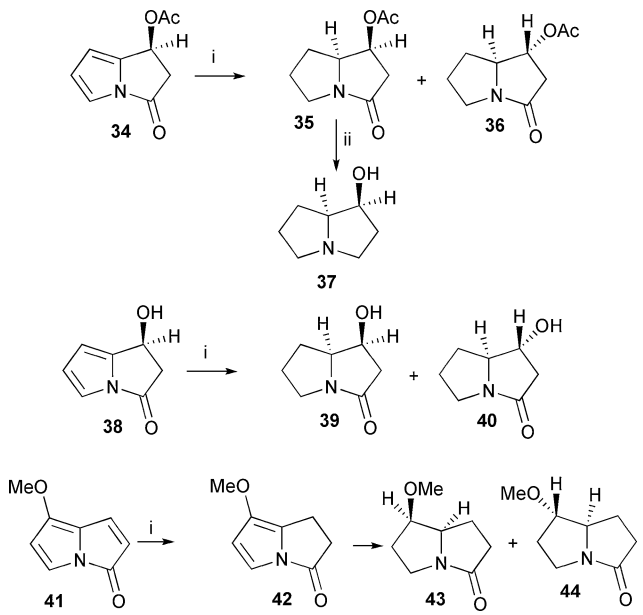
7-Methoxycarbonylpyrrolizin-3-one[11] **26** proved more resistant to complete hydrogenation, and only the dihydro-compound **27** was isolated under a variety of conditions. However, using rhodium-on-alumina catalyst in acetic acid, and with extended reaction times, the known[23] *cis*-hexahydropyrrolizinone **29** was obtained exclusively and in excellent yield; the *trans*-isomer **30** could not be detected. The high diastereoselectivity probably results from intermediate formation of the tetrahydro-intermediate **28**, which was tentatively identified in one case (by comparison with the ^{13}C NMR spectrum of the known[14] ethyl ester). Ring opening occurs if the hydrogenation is carried out over PtO_2 in ethanol (see Experimental section); alcohol solvents should be avoided when handling the ester **26**.

Hydrogenation of the acetoxy-compound[24] **31** also proved more complex than anticipated (see ESI†). Although the dihydro-compound **32** could be obtained, further reaction was complicated by hydrogenolysis to give the 7-methyl compounds **18** and **19**. Hydrogenolysis was minimised (totalling 16% of the mixture) when rhodium/carbon in ethanol was used as the catalyst. The diastereoselectivity was again high, with only the *cis*-isomers **18** and **33** detected under these conditions.

(±)-Isoretronecanol **6** was obtained in each case by lithium aluminium hydride reduction of the precursors **24** (+ 10% **25**), **29** and **33** (+ 16% **18**). The product was purified by bulb-to-bulb distillation and/or by isolation and recrystallisation of the picrate salt. In each case, the hydride performs the dual role of reducing the lactam and the ester functions. As might be expected, the best yield (83%) was obtained from the pure substrate **29**, representing an overall yield of 81% for the two steps from the pyrrolizinone **26**. For comparison, a recent SmI_2-mediated synthesis of (±)-isoretronecanol **6** required around 15 steps.[20]

Because many of the necine bases have alcohol groups at the 1(7)-position(s), preliminary studies were carried out to ascertain if the diasteroselectivity of hydrogenation was likely to be affected by oxygen-containing substituents at the these sites. Substrates **34** and **38** were prepared as previously described[24] by sequential hydrochlorination of pyrrrolizin-3-one **1** and quenching with acetate and with water, respectively. The methoxy-compound **41** was prepared by the standard Meldrum's acid pyrolysis route.[11]

Hydrogenation of the acetoxy-compound **34** provides the *cis*-isomer **35** with significantly better selectivity than the corresponding methyl derivative **12** (Scheme 4 and ESI†). The configuration of the product was confirmed by transformation to the known[25] pyrrolizidine **37**. The pattern of the ^{1}H NMR signal due to the 1-position was also characteristic of these compounds (*cis*-isomer **35**, apparent triplet, ^3J 5.0 Hz, due to equal coupling to H-7a and one of the protons on H-2; *trans*-isomer **36**, triplet of doublets J 8.2 and 4.9, due, respectively to equal coupling with both of the protons H-2 and with H-7a – *cf.* data for **4** shown in Fig. S1 in ESI†).

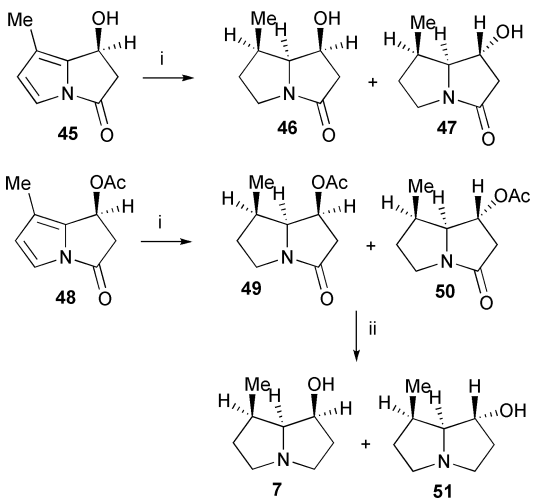


Scheme 4 *Reagents and conditions:* (i) H_2/catalyst, 45 psi, 20 °C. 2 h; Best method for **35**/**36**; 5% Pd/C, EtOH, yield 97%, dr 95:5. Best method for **39**/**40**; 5% Rh/Al_2O_3, EtOH, yield 93%, dr 90:10. Method for **43**/**44**; 5% Pd/C, EtOH, dr 86:14 (not optimised). (ii) $LiAlH_4$. (For asymmetric compounds, only one of the enantiomeric pairs is shown.)

The selectivity of hydrogenation of hydroxy-compounds may be affected by coordination to the catalyst surface.[26] In the case of the 1,2-dihydro-1-hydroxypyrrolizinone **38**, however, the major

product was again the known[27] *cis* isomer **39** (see ESI†). The diastereoselectivity was relatively insensitive to the nature of the catalyst and solvent (ratios of **39**:**40** vary from 83:17 using Pd/C in ethanol, to 90:10 using Rh/Al_2O_3 in ethanol). The presence of the 7-methoxy substituent in compound **41** similarly had little effect on the progress of the hydrogenation, with **43** and **44** obtained in a 86:14 ratio under standard conditions (Pd/C, ethanol).

With these results in place, the hydrogenation of the 1-substituted 7-methyl-1,2-dihydropyrrolizinones **45** and **48** was studied (Scheme 5). The starting materials were made, as before,[24] by sequential hydrochlorination and nucleophilic quenching of the parent pyrrolizinone (see ESI). In these cases, three new asymmetric centres are created in the hydrogenation, leading to four possible enantiomeric pairs of products. In practice, hydrogenation of **45** led to only two enantiomeric pairs **46** and **47**, but the selectivity relating these sets of isomers was poor, ranging from 67:33 (5% Rh/C in ethanol) to 40:60 (5% $Pd/CaCO_3$ in ethanol) (see ESI). Assuming that the pyrrole ring is hydrogenated in a *cis* manner (as observed for the other pyrrolizinones) the assignment of **46** and **47** was confirmed by the NOE measurements shown in Fig. S2† and the consistency of the coupling constants with related examples as reported in the Experimental section. (In particular *cis*-isomer **46**, H-1 is an apparent triplet, ^3J 4.0 Hz, due to equal coupling to H-7a and one of the protons on H-2; *trans*-isomer **47**, H-1 is a triplet of doublets ^3J 8.0 and 5.9, due, respectively to equal coupling with both of the protons H-2 and with H-7a.)

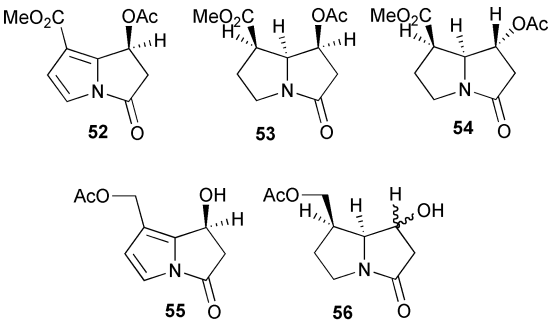


Scheme 5 *Reagents and conditions:* (i) H_2/catalyst, 45 psi, 20 °C. 2 h; Best method for **49**/**50**; 5% Rh/C, EtOAc, yield 96%, dr 86:14. (ii) $LiAlH_4$. (Only one of the enantiomeric pairs is shown.)

Conditions for more selective hydrogenation of the acetoxy-compound **48** were discovered using 5% Rh/C in ethyl acetate, which gave **49** and **50** in a 86:14 ratio (see ESI). This selectivity is nevertheless considerably lower than for the model compound **34**, owing to the increased steric hindrance on the 'inside' face of the pyrrolizidine. The structure of the two isomers was unequivocally elucidated by NMR spectroscopy. The key NOE enhancements which led to the assignment of stereochemistry are shown in the ESI, in particular the correlation between the 1-proton and the 7-methyl group in **50**.

Lithium aluminium hydride reduction of the 86:14 mixture of **49** and **50** gave an 88% overall yield of retronecanol **7** and its isomer **51**, which provided pure retronecanol (as its picrate salt) after recrystallisation of the picrate mixture from ethanol. The characterisation of the picrate salt is secure (see Experimental section) but our NMR spectra of retronecanol free base were not consistent with the only literature data from a previous synthesis.[28] Although retronecanol is most often obtained as an alkaloid degradation product, its *p*-methoxybenzoyl ester has been isolated from *Ehretia aspera* Willd.[29]

Some preliminary experiments were carried out to explore the robustness of the hydrogenation method to other groups in the 7-position, but results were disappointing. Thus hydrogenation of the ester **52** (see ESI) over Rh/alumina in glacial acetic acid gave two major products, **53** and **54**, in a 67:33 ratio. Stereochemistry was assigned by analysis of the pattern of the H-1 proton, as discussed above for **35**/**36** and **46**/**47**. Hydrogenation of the acetoxy-compound **55** (see ESI) was (as found for **31**) complicated by hydrogenolysis of the acetoxy group to provide **46** and **47**, as well as a mixture of acetoxy compounds **56**.



(Only one of the enantiomeric pairs is shown)

Conclusions

Hydrogenation of 1- or 7-substituted pyrolizin-3-ones to the hexahydro-compound(s) can proceed in excellent yield in the presence of small amounts (*ca.* 10%) of heterogeneous catalyst. By appropriate choice of catalyst and solvent, the diastereoselectivity can be optimised (and is often >90:10), with the major isomer being formed by addition of all hydrogen atoms to the face of the bicycle away from any sp^3-hybridised substituent. Due to steric hindrance on the inner face of the molecule, the diastereoselectivity of hydrogenation of 1,7-disubstituted pyrrolizin-3-ones is lower under similar conditions. These results have provided concise, diasterocontrolled routes to the necine bases (±)-heliotridane **5**, (±)-isoretronecanol **6** and (±)-retronecanol **7**.

Experimental

^1H and ^{13}C NMR spectra were recorded at 200 (or 250) and 50 (or 63) MHz respectively for solutions in [^2H]chloroform unless otherwise stated. Coupling constants are quoted in Hz. Mass spectra were recorded under electron impact conditions.

Hydrogenation of pyrrolizin-3-ones – general

The hydrogenations were performed at room temperature using hydrogen pressures of 45 to 60 psi in a Parr hydrogenation

apparatus. Preliminary hydrogenation experiments were carried out on a small scale as follows; a solution of the substrate (10–20 mg) in solvent (10–15 cm^3) was hydrogenated with the heterogeneous catalyst (*ca.* 5 mg) for the time stated. Filtration through Celite and removal of the solvent under vacuum afforded the hydrogenation products. Results are reported in Tables 1–2 and ESI†. Diastereomeric mixtures were generally not separated. On larger scales, the amount of catalyst was progressively lowered without further optimisation.

Hexahydropyrrolizin-3-one 4

A solution of pyrrolizin-3-one[10] **1** (337 mg, 2.8 mmol) in ethanol (20 cm^3) was hydrogenated at 45 psi over 5% Pd/C (30 mg) for 2 h at room temperature. After filtration through Celite, the solvent was removed to yield hexahydropyrrolizin-3-one **4** (332 mg, 94%) as a colourless liquid, bp 90–95 °C (12 Torr) [lit.,[30] 88–94 °C (8 Torr)]; δ_H (600 MHz) 3.80 (1H, m, H-7A), 3.43 (1H, ddd, ^2J 11.6, ^3J 7.8 and 7.8, H-5b), 2.95 (1H, dddd, ^2J 11.6, ^3J 9.1 and 3.8, ^4J 1.4, H-5a), 2.64 (1H, dddt, ^2J 16.6, ^3J 11.2 and 8.9, ^nJ 1.1, H-2a), 2.35 (1H, ddd, ^2J 16.6, ^3J 9.4 and 1.9, H-2b), 2.20 (1H, dddd, ^2J 12.6, ^3J 8.9, 6.8 and 1.9, H-1a), 2.02 (1H, m, H-6b), 1.89–1.99 (2H, m, H-6a and H-7a) 1.63 (1H, dddd, ^2J 12.6, ^3J 11.2, 9.4 and 7.8, H-1b) and 1.23 (1H, m, H-7b); δ_C 174.49 (C3), 61.84 (C7A), 40.62 (C5), 35.07 (C2), 31.82 (C7), 26.83 (C1) and 26.67 (C6).

Pyrrolizidinium picrate 8

To an ice-cooled solution of hexahydropyrrolizin-3-one **4** (121 mg, 1.0 mmol) in dry ether (5 cm^3) was added lithium aluminium hydride (1 M in tetrahydrofuran, 3 cm^3) and the mixture was stirred at reflux for 1 h. Wet ether (10 cm^3), water (5 cm^3) and a saturated aqueous solution of potassium sodium tartrate (5 cm^3) were added sequentially. After filtration through Celite, the solution was extracted with ether (2 × 20 cm^3), dried ($MgSO_4$) and concentrated. Picric acid (1.0 g) dissolved in acetone (1 cm^3) was added to a solution of the concentrate in ether (1 cm^3). Crystallisation of the salt was completed by addition of ether (10 cm^3). The solid was filtered off and washed thoroughly with ether to give pyrrolizidinium picrate **8** (167 mg, 51%), mp 244–261 °C (slow decomp.) (from ethanol) (lit.,[31] 254 °C); δ_H (picrate) 11.39 (1H, br s), 8.85 (2H, s), 4.38 (1H, br q, ^3J 7.0), 3.81 (2H, br sextet, ^3J 6.0), 2.98 (2H, s), 2.42–2.03 (6H, m) and 1.77 (2H, s); δ_C (picrate) 162.21 (quat), 141.48 (quat), 127.85 (quat), 126.45, 68.03, 55.51, 30.95 and 25.02.

Hydrogenation of 3*H*-pyrrolizine 9

A solution of 3*H*-pyrrolizine[32] **9** (196 mg, 1.9 mmol) in ethanol (20 cm^3) was hydrogenated at 55 psi over 5% Pd/C (205 mg) for 8 h at room temperature. After filtration through Celite, the solvent was removed to yield an oil (200 mg) containing 1,2-dihydro-3*H*-pyrrolizine, hexahydropyrrolizine and 2-propyl-1*H*-pyrrole in the respective ratios 45:20:35. Dry flash chromatography (using hexane and ethyl acetate as eluents) gave 1,2-dihydro-3*H*-pyrrolizine **10** (16 mg); δ_H 6.63 (1H, dd, ^3J 2.6, ^4J 1.1), 6.25 (1H, dd, ^3J 3.3 and 2.6), 5.83 (1H, dd, ^3J 3.3 and ^4J 1.1), 3.96 (2H, t, ^3J 7.2), 2.86 (2H, t, ^3J 7.2) and 2.59 (2H, quintet, ^3J 7.2); δ_C 137.03 (quat), 113.42, 111.93, 98.59, 45.94, 27.67 and 23.83 (consistent with literature data[33]) followed by 2-propyl-1*H*-pyrrole **11** (7 mg), bp 65–70 °C (50 Torr) [lit.,[34] 111 °C (80 Torr)]; δ_H 7.87 (1H, br, NH), 6.66 (1H, m), 6.13 (1H, m), 5.91 (1H, m), 2.57 (2H, t, ^3J 7.7), 1.66 (2H, tq, ^3J 7.7 and 7.3) and 0.96 (3H, t, ^3J 7.3); δ_C 132.57 (quat), 115.86, 108.14, 104.85, 29.71, 22.81 and 13.81. Hexahydropyrrolizine **8** was too volatile to be isolated; it was identified by comparing the ^1H and ^{13}C NMR spectra of the reaction mixture with those of the two isolated products; δ_H 3.56 (1H, quintet, *J* 6.8), 3.03–3.14 (2H, m) and 1.13–2.60 (10H, m); δ_C 64.19, 54.81, 32.23 and 25.75 (in agreement with literature data.[35])

Hydrogenation of 1-methylpyrrolizin-3-one 12

(i) The diasteroselectivity of the hydrogenation was studied on a small scale, varying the catalysts and solvents (Table 1).

(ii) A solution of 1-methylpyrrolizin-3-one[11] **12** (161 mg, 1.2 mmol) in ethanol (20 cm^3) was hydrogenated over 5% Rh/Al_2O_3 (11 mg) for 4 h at 45 psi. The usual work-up gave *cis*- and *trans*-hexahydro-1-methylpyrrolizin-3-one (151 mg, 90%) in a ratio of 90:10; *cis*-hexahydro-1-methylpyrrolizin-3-one **14**; δ_H 3.91 (1H, td, ^3J 9.6 and 6.4), 3.45 (1H, td, ^3J 11.6 and 7.8), 3.02 (1H, m), 2.84 (1H, ddt, ^2J 16.3, ^3J 8.0 and ^nJ 1.1), 2.49 (1H, m), 1.83–2.12 (2H, m; including 1H at 1.98 ppm, dd, ^2J 16.3 and ^nJ 2.7), 1.42–1.73 (2H, m) and 0.91 (3H, d, ^3J 7.2, Me); δ_C 174.12 (quat), 64.90, 42.95, 40.94, 29.44, 26.76, 24.86 and 15.74; *m/z* 139 (M^+, 66%), 138 (14), 124 (6), 111 (60), 97 (24), 83 (9), 70 (100), 69 (56), 68 (31), 56 (14), 55 (15), 42 (33), 41 (56) and 39 (26) (in agreement with literature data;[16]) *trans*-hexahydro-1-methylpyrrolizin-3-one **15**; δ_H 1.09 (3H, d, ^3J 6.5).

(iii) Hydrogenation on a small scale over 5% Pd/C in dimethyl formamide afforded 1,2-dihydro-1-methylpyrrolizin-3-one **13**, bp 50–55 °C (0.3 Torr) (Found: M^+, 135.0690. C_8H_9NO requires M, 135.0684); δ_H 6.96 (1H, d, ^3J 3.0), 6.42 (1H, t, ^3J 3.0), 5.94 (1H, d, ^3J 3.3), 3.35 (1H, m), 3.22 (1H, dd, ^2J 18.1 and ^3J 8.0), 2.57 (1H, dd, ^2J 18.1 and ^3J 3.3) and 1.34 (3H, d, ^3J 6.8, Me); δ_C 171.36 (quat), 145.28 (quat), 118.76, 110.44, 103.47, 43.31, 27.19 and 20.70; *m/z* 135 (M^+, 100%), 120 (11), 107 (30), 106 (67), 94 (61), 80 (18), 66 (14), 53 (22) and 39 (18).

Hydrogenation of 7-methylpyrrolizin-3-one 16

(i) The diasteroselectivity of the hydrogenation was studied on a small scale, varying the catalysts and solvents (Table 2).

(ii) A solution of 7-methylpyrrolizin-3-one[11] **16** (136 mg, 1.0 mmol) in hexane (40 cm^3) was hydrogenated over 5% Rh/C (18 mg) for 48 h at atmospheric pressure. The usual work-up gave *cis*-hexahydro-7-methylpyrrolizin-3-one **18** (133 mg, 94%); δ_H 3.97 (1H, dt, ^3J 5.3 and 7.4), 3.48 (1H, dt, ^3J 11.4 and 7.6), 3.02 (1H, m), 2.68 (1H, dt, ^2J 16.6 and ^3J 9.7), 2.40 (1H, ddd, ^2J 16.6, ^3J 9.6 and 2.9), 1.66–2.24 (5H, m) and 0.81 (3H, d, ^3J 7.3, Me) (in agreement with the literature data[17]); δ_C 174.67 (quat), 64.25, 39.00, 34.64, 34.38, 32.63, 20.52 and 13.11; *m/z* 139 (M^+, 67%), 138 (29), 137 (36), 97 (100), 84 (54), 69 (55) and 55 (42). A trace of *trans*-hexahydro-7-methylpyrrolizin-3-one **19** was present (<3%); δ_H 1.02 (3H, d, ^3J 6.1, Me).

(iii) Hydrogenation (on a small scale) over Raney nickel in ethanol for 2 h at 45 psi gave 1,2-dihydro-7-methylpyrrolizin-3-one **17** as white crystals, mp 78–80 °C (from hexane) (Found: C, 71.1; H, 7.0; N, 10.4. C_8H_9NO requires C, 71.1; H, 6.65; N, 10.35%); δ_H 6.95 (1H, d, ^3J 3.1), 6.27 (1H, d, ^3J 3.1), 2.95–3.01 (2H, m),

2.86–2.91 (2H, m) and 1.99 (3H, s); δ_C 171.79 (quat), 135.29 (quat), 121.08, 113.99 (quat), 110.48, 34.71, 18.09 and 10.22; *m/z* 135 (M^+, 100%), 134 (63), 120 (46), 107 (74), 106 (97), 94 (87), 83 (57), 81 (56), 80 (61), 79 (58), 66 (55), 53 (77), 52 (72) and 51 (62).

Heliotridane 5 – general $LiAlH_4$ reduction method

The hexahydropyrrolizin-3-one (1 mmol) was reduced with an excess of lithium aluminium hydride (LAH) in refluxing tetrahydrofuran (10 cm^3) overnight (unless otherwise stated), under anhydrous conditions. The mixture was then cooled in ice and wet ether (10 cm^3), water (5 cm^3) and a saturated aqueous solution of potassium sodium tartrate (5 cm^3) were added sequentially. After filtration through Celite the solution was extracted with ether (2 × 20 cm^3), the organic phase was dried ($MgSO_4$) and concentrated to yield the products.

(i) A 90:10 mixture of *cis*- to *trans*-hexahydro-1-methylpyrrolizin-3-ones **14** and **15** (105 mg, 0.8 mmol) was reduced with LAH (1 M in tetrahydrofuran, 3 cm^3): treatment of the products with picric acid followed by recrystallisation from ethanol gave heliotridane **5** as its picrate (188 mg, 70%), mp 240–244 °C (decomp.) (from ethanol) (lit.,[36] 240–243 °C); δ_H (picrate) 11.41 (1H, br s), 8.94 (2H, s), 4.28 (1H, m), 4.02 (1H, m), 3.67 (1H, m), 3.12 (1H, m), 2.90–2.51 (2H, m), 2.27–1.95 (4H, m), 1.88–1.60 (2H, m) and 1.13 (3H, d, ^3J 6.7, Me); δ_C (picrate) 160.05 (quat), 140.42 (quat), 130.29 (quat), 126.41, 70.92, 56.90, 54.58, 34.61, 30.44, 25.87, 25.70 and 13.32.

(ii) A 98:2 mixture of *cis*- to *trans*-hexahydro-7-methylpyrrolizin-3-ones **18** and **19** (86 mg, 0.6 mmol) was reduced with LAH (1 M in tetrahydrofuran, 2.5 cm^3). Treatment of the products with picric acid gave heliotridane **5** as its picrate (173 mg, 79%), mp 242–245 °C (decomp.) (after recrystallisation from ethanol); the NMR data were the same as those reported above.

Hydrogenation of 1-methoxycarbonylpyrrolizin-3-one 20

(i) A solution of 1-methoxycarbonylpyrrolizin-3-one **20** [from FVP of dimethyl pyrrol-2-ylbut-2-enedioate[12] (131 mg, 0.6 mmol), 700 °C, 90-100 °C, 0.004 Torr, 30 min] in methanol (60 cm^3) was hydrogenated over 5% Pd/C (80 mg) for 3 h at atmospheric pressure at *ca.* –20 °C. After filtration through Celite the solvent was removed under vacuum and the residue was purified by flash chromatography (using hexane/ethyl acetate as eluents) to give 1,2-dihydro-1-methoxycarbonylpyrrolizin-3-one **21** (37 mg, 33% over two steps), bp 115–120 °C (0.5 Torr) (Found: M^+, 179.0585. $C_9H_9NO_3$ requires *M*, 179.0582); δ_H 7.04 (1H, d, ^3J 3.0), 6.45 (1H, t, ^3J 3.0), 6.16 (1H, d, ^3J 3.0), 4.19 (1H, dd, ^3J 8.3 and 3.6), 3.77 (3H, s), 3.47 (1H, dd, ^2J 18.7 and ^3J 3.6) and 3.18 (1H, dd, ^2J 18.7 and ^3J 8.3); δ_C 170.40 (quat), 169.55 (quat), 135.80 (quat), 119.03, 111.90, 106.38, 52.85, 37.75 and 37.68; *m/z* 179 (M^+, 67%), 151 (13), 125 (54), 121 (64), 120 (100), 94 (74), 93 (79), 92 (91) and 91 (51) followed by 1-methoxycarbonyl-2,5,6,7-tetrahydropyrrolizin-3-one **23** (25 mg, 22%) as a light yellow solid mp 78–79 °C (from hexane/ethyl acetate) (lit.,[21] 80–81 °C); δ_H (360 MHz) 3.69 (3H, s), 3.54 (2H, t, ^3J 7.1, H-5), 3.49 (2H, t, ^5J 3.0, H-2), 2.89 (2H, tt, ^3J 7.7 and ^5J 3.0, H-7) and 2.37 (2H, tt, ^3J 7.7 and 7.1, H-6); δ_C 172.76 (quat), 163.98 (quat), 161.57 (quat), 98.50 (quat), 50.90, 41.41, 41.05, 26.46 and 25.43; *m/z* 181 (M^+, 81%), 150 (39), 123 (17), 122 (100), 95 (22), 94 (65) and 67 (25).

(ii) No deuterium was incorporated into the tetrahydo product **23** when the hydrogenation of 1,2-dihydro-1-methoxycarbonylpyrrolizin-3-one **21** was carried out in [^{2}H]methanol over 5% Pd/C at *ca.* –20 °C. Similarly, no resonance was observed by ^{2}H NMR spectroscopy when 1,2-dihydro- and 2,5,6,7-tetrahydro-1-methoxycarbonylpyrrolizin-3-one were set aside in [$^2H_4$]methanol, for 30 and 44 days respectively.

(iii) A solution of 1-methoxycarbonylpyrrolizin-3-one **20** [from FVP of dimethyl pyrrol-2-ylbut-2-enedioate[12] (174 mg, 0.8 mmol), 700 °C, 90 °C, 0.004 Torr, 40 min] in methanol (80 cm^3) was hydrogenated over 5% Pd/C (80 mg) for 2 h at atmospheric pressure at *ca.* –20 °C, at which point the solution was colourless. The hydrogen pressure was increased to 50 psi and the reaction mixture was hydrogenated for a total time of 27 h at room temperature. After filtration through Celite the solvent was removed to yield *cis*- and *trans*-hexahydro-1-methoxycarbonylpyrrolizin-3-one (81 mg, 53%) in a ratio 91:9 (by ^{13}C NMR); *cis*-hexahydro-1-methoxycarbonylpyrrolizin-3-one **24**; δ_H 4.09 (1H, ddd, ^nJ 10.1, 8.4 and 5.6), 3.70 (3H, s), 3.59 (1H, dt, ^nJ 11.5 and 8.0), 3.40 (1H, td, ^nJ 8.0 and 6.1), 3.04 (1H, ddd, ^nJ 11.8, 9.0 and 3.6), 2.80 (2H, m), 1.79–2.10 (3H, m) and 1.26 (1H, m); δ_C 173.95 (quat), 172.15 (quat), 62.58, 51.84, 41.57, 39.75, 35.98, 27.37 and 25.91 (in agreement with literature data[22]); *trans*-hexahydro-1-methoxycarbonylpyrrolizin-3-one **25**; δ_C (one quaternary signal not apparent) 172.34, 63.64, 52.18, 45.66, 41.06, 38.35, 31.48 and 26.57 (in agreement with literature data[22]).

(iv) Hydrogenation (on a small scale) over 5% Rh/Al_2O_3 at 55 psi for 5 h, in either ethyl acetate or a mixture of ethyl acetate and acetic acid (in a ratio of 94:6), gave a mixture of 1,2-dihydro-, 2,5,6,7-tetrahydro- and the *cis*- and *trans*-hexahydro-1-methoxycarbonylpyrrolizin-3-one **21** and **23–25**, identified by NMR spectroscopy. From the ^{13}C NMR spectra the amount of the *trans*-hexahydro **25** compound relative to its *cis*-isomer **24** was barely detectable (≤5%).

Hydrogenation of 7-methoxycarbonylpyrrolizin-3-one 26

(i) Small-scale hydrogenations of 7-methoxycarbonylpyrrolizin-3-one[11] **26** at 45 psi for 3-4 h using a range of different catalysts and solvents (5% Rh/C, ethyl acetate; 5% Rh/C, toluene; 5% Rh/Al_2O_3, toluene; 5% Rh/Al_2O_3, hexane; 5% Rh/C, hexane) gave 1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one **27** as colourless crystals, mp 85–86 °C (from hexane) (Found: C, 60.15; H, 4.95; N, 7.65. $C_9H_9NO_3$ requires C, 60.35; H, 5.05; N, 7.8%); ν_{max} (nujol) 1760 and 1706; δ_H 6.98 (1H, d, ^3J 3.3), 6.76 (1H, d, ^3J 3.3), 3.80 (3H, s), 3.20–3.26 (2H, m) and 3.00–3.06 (2H, m); δ_C 171.86 (quat), 164.17 (quat), 146.35 (quat), 118.08, 111.83 (quat), 111.63, 51.21, 33.70 and 20.62; *m/z* 179 (M^+, 93%), 164 (10), 151 (36), 148 (33), 120 (100), 119 (26), 92 (28) and 65 (28).

(ii) A solution of 7-methoxycarbonylpyrrolizin-3-one **26** (69 mg, 0.4 mmol) in glacial acetic acid (13 cm^3) was hydrogenated over 5% Rh/Al_2O_3 (39 mg) at 55 psi for 7 h. After filtration through Celite, acetic acid was neutralised with a saturated solution of sodium carbonate (60 cm^3), extracted with dichloromethane (2 × 50 cm^3) and washed with water (50 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed to give *cis*-hexahydro-7-methoxycarbonylpyrrolizin-3-one **29** (70 mg, 98%); δ_H 4.13 (1H, apparent q, ^3J 7.2), 3.77 (1H, dt, ^3J 11.3 and 7.9), 3.65 (3H, s), 2.93–3.09 (2H, m), 2.61 (1H, m), 2.07–2.41 (4H, m)

and 1.68 (1H, m); δ_C 175.29 (quat), 172.77 (quat), 62.96, 51.69, 45.14, 40.94, 33.74, 30.04 and 22.20 (in agreement with literature data[23]); *m/z* 183 (M^+, 36%), 168 (7), 155 (36), 152 (23), 97 (100), 69 (53), 58 (39), 55 (25), 43 (91) and 41 (33).

(iii) From the ^{13}C NMR spectrum of the product obtained by hydrogenation of **26** in ethanol over 5% Rh/Al_2O_3 (for 17 h at 45 psi), it was tentatively identified as 7-methoxycarbonyl-1,2,5,6-tetrahydropyrrolizin-3-one **28**; δ_C 172.00 (quat), 165.60 (quat), 160.05 (quat), 102.62 (quat), 50.94, 40.73, 33.56, 31.75 and 20.75 [by comparison with the data of the ethyl ester analogue previously reported;[14] δ_C 171.10 (quat), 164.35 (quat), 159.47 (quat), 101.33 (quat), 58.67, 40.02, 32.81, 31.12, 20.26 and 13.63].

(iv) Hydrogenation of **26** (on a small scale) over PtO_2 in ethanol for 3 h at 45 psi gave ethyl (3-methoxycarbonyl)pyrrol-2-ylpropanoate bp 110–115 °C (0.6 Torr) (Found: M^+, 225.1001. $C_{11}H_{15}NO_4$ requires M, 225.1001); δ_H 9.14 (1H, br s), 6.55 (1H, t, ^3J 2.9), 6.50 (1H, t, ^3J 2.9), 4.10 (2H, q, ^3J 7.1), 3.77 (3H, s), 3.24 (2H, t, ^3J 6.6), 2.66 (2H, t, ^3J 6.6,) and 1.21 (3H, t, ^3J 7.1); δ_C 174.41 (quat), 165.71 (quat), 137.90 (quat), 116.21, 111.00 (quat), 109.92, 60.66, 50.64, 33.46, 21.23 and 13.97; *m/z* 225 (M^+, 23%), 193 (21), 180 (30), 165 (52), 151 (85), 150 (20), 138 (71), 124 (20), 120 (100), 108 (20), 106 (51), 94 (23), 93 (23) and 65 (20).

Hydrogenation of 7-acetoxymethylpyrrolizin-3-one 31

(i) Hydrogenation (on a small scale) of 7-acetoxymethylpyrrolizin-3-one[24] **31** in ethyl acetate at 45 psi for 2-3 h over either 5% Pd/C, 5% $Pd/CaCO_3$, or 5% Rh/C, gave 7-acetoxymethyl-1,2-dihydropyrrolizin-3-one **32** as a brown oil, bp 140–145 °C (0.9 Torr) (Found: M^+, 193.0744. $C_{10}H_{11}NO_3$ requires *M*, 193.0739); δ_H 6.96 (1H, d, ^3J 3.1), 6.39 (1H, d, ^3J 3.1), 4.87 (2H, s), 2.97 (4H, br s) and 1.99 (3H, s); δ_C (two quaternaries not apparent) 171.73 (quat), 170.84 (quat), 119.37, 111.30, 58.17, 34.21, 20.84 and 18.47; *m/z* 193 (M^+, 32%), 179 (25), 173 (41), 145 (40), 138 (62), 134 (55), 133 (86), 120 (35), 106 (52), 105 (39), 97 (100), 79 (35), 69 (45) and 55 (53).

(ii) 7-Acetoxymethylpyrrolizin-3-one **31** (70 mg, 0.4 mmol) was hydrogenated over 5% Rh/C (18 mg) in ethanol for 2.5 h at 45 psi. The usual work-up gave a quantitative mixture of *cis*-hexahydro-7-methylpyrrolizin-3-one **18** (16%) and *cis*-7-acetoxymethylhexahydropyrrolizin-3-one **33** (84%); δ_H 3.95–4.12 (3H, m), 3.58 (1H, dt, *J* 11.7 and 7.6), 3.01 (1H, m), 2.66 (1H, m), 2.32–2.46 (2H, m), 2.04 (3H, s) and 1.77–2.27 (4H, m); δ_C 174.59 (quat), 170.74 (quat), 63.25, 62.65, 40.09, 37.63, 34.43, 30.27, 21.31 and 20.76 (in agreement with literature data[37]); the correct molecular ion was observed at *m/z* 197 (M^+, 1%), but breakdown peaks could not be assigned because the sample was contaminated with **18**.

(iii) *Cis*- and *trans*-hexahydro-7-methylpyrrolizin-3-ones **18** and **19** were obtained from small-scale hydrogenations at 45 psi for 3 h under the following conditions; 5% Pd/C, ethanol; PtO_2, ethyl acetate; 5% Rh/Al_2O_3, acetic acid; 5% Rh/Al_2O_3, ethanol.

Isoretronecanol 6

Isoretronecanol **6** was obtained by LAH reduction of various precursors (see below) using the general method outlined above for heliotridane, but with the following workup method. The solution was concentrated and ether (10 cm^3) was added, followed by water (typically 0.2 cm^3 per mmol of LAH). The resulting mixture was stirred for 5 h, then filtered. The filtrate was concentrated and purified by bulb-to-bulb distillation.

(i) From a 91:9 mixture of *cis*- to *trans*-hexahydro-1-methoxycarbonylpyrrolizin-3-ones **24** and **25** (81 mg, 0.5 mmol) and LAH (60 mg, 1.6 mmol), *cis*- and *trans*-hexahydro-1-hydroxymethylpyrrolizine (38 mg, 61%) were obtained in unchanged ratio. One recrystallisation of the picrate gave the picrate salt of isoretronecanol **6**, mp 186–188 °C (from ethanol) (lit.,[14] 192–194 °C); δ_C (picrate) ([$^2H_6$]acetone) 160.99 (quat), 141.21 (quat), 125.72 (quat), 124.57, 69.13, 59.60, 55.34, 53.55, 42.02, 25.18, 24.93 and 24.47.

(ii) From *cis*-hexahydro-7-methoxycarbonylpyrrolizin-3-one **29** (69 mg, 0.4 mmol) and LAH (46 mg, 1.2 mmol), isoretronecanol **6** (46 mg, 83%) was obtained as a colourless oil, bp 110–120 °C (0.4 Torr), mp 188–189 °C (picrate) (from ethanol) (lit.,[14] 192–194 °C). The free base has the following spectroscopic data: δ_H 4.54 (1H, br, OH), 3.62 (2H, dd, ^nJ 7.3 and 2.0), 3.43 (1H, td, ^nJ 6.9 and 9.9), 3.06 (1H, ddd, ^nJ 9.3, 6.5 and 3.5), 2.93 (1H, ddd, ^nJ 11.1, 9.2 and 6.4), 2.56 (1H, ddd, ^nJ 11.1, 7.7 and 3.4), 2.32–2.49 (2H, m) and 1.22–1.84 (5H, m); δ_C 66.05, 62.88, 55.47, 53.87, 44.20, 27.00, 26.31 and 25.76; *m/z* 141 (M^+, 26%), 140 (10), 124 (17), 110 (11), 97 (6), 84 (12), 83 (100), 82 (43), 70 (11) and 55 (32).

(iii) From a 84:16 mixture of *cis*-7-acetoxymethylhexahydropyrrolizin-3-one **33** to *cis*-hexahydro-7-methylpyrrolizin-3one **18** (70 mg, 0.4 mmol) and LAH (64 mg, 1.7 mmol), isoretronecanol **6** (30 mg, 56%) was obtained from the distillation (spectra identical with those above). No trace of heliotridane was observed in the ^1H NMR spectrum.

Hydrogenation of 1-acetoxy-1,2-dihydropyrrolizin-3-one 34

A solution of 1-acetoxy-1,2-dihydropyrrolizin-3-one[24] **34** (505 mg, 2.8 mmol) in ethanol (50 cm^3) was hydrogenated over 5% Pd/C (59 mg) for 3 h at 45 psi. The usual work-up gave a mixture of *cis*- and *trans*-1-acetoxyhexahydropyrrolizin-3-one (504 mg, 97%) in a ratio of 95:5; *cis*-1-acetoxyhexahydropyrrolizin-3-one **35** is a colourless liquid, bp 95–100 °C (0.3 Torr) (Found: M^+, 183.0901. $C_9H_{13}NO_3$ requires *M*, 183.0895); δ_H 5.29 (1H, t, ^3J 5.0, H-1), 4.07 (1H, ddd, ^3J 8.7, 6.8 and 4.8, H-7A), 3.53 (1H, dt, ^3J 11.2 and 7.7, H-5), 3.00 (1H, m, H-5), 2.97 (1H, ddt, ^2J 17.2, ^3J 5.6 and ^nJ 1.2, H-2), 2.40 (1H, d, ^2J 17.2, H-2), 1.95–2.08 (2H, m), 2.01 (3H, s) and 1.55–1.80 (2H, m); δ_C 171.75 (quat), 169.93 (quat), 69.79 (C1), 64.86 (C7A), 41.93 (C2), 41.06 (C5), 26.71, 24.07 and 20.54 (CH_3); *m/z* 183 (M^+, 4%), 140 (5), 125 (14), 123 (37), 112 (11), 97 (21), 95 (15), 86 (23), 84 (39) and 70 (100). The minor *trans*-isomer **36** has the following characteristic ^1H NMR signal: δ_H 4.95 (1H, td, *J* 8.2 and 4.9, H-1).

cis-Hexahydro-1-hydroxypyrrolizine 37

Using the general method outlined above for heliotridane, and the work-up for isoretronecanol, a 95:5 mixture of *cis*- and *trans*-1-acetoxyhexahydropyrrolizin-3-ones **35** and **36** (49 mg, 0.3 mmol) and LAH (40 mg, 1.0 mmol) gave *cis*-hexahydro-1-hydroxypyrrolizine **37** (30 mg, 87%) as a colourless liquid, bp 80–90 °C (15 Torr); mp 241–243 °C (picrate) (from ethanol) (lit.,[25] 243–245 °C). The free base has the following spectroscopic data: δ_H 4.20 (1H, dd, ^3J 7.0 and 4.4), 3.39–3.67 (3H, m), 2.91–3.10

(2H, m), 2.43–2.68 (2H, m) and 0.70–2.04 (5H, m); δ_C 71.38, 68.78, 55.35, 51.93, 36.78, 27.53 and 24.09.

Hydrogenation of 1,2-dihydro-1-hydroxypyrrolizin-3-one 38

A solution of 1,2-dihydro-1-hydroxypyrrolizin-3-one[24] **38** (882 mg, 6.4 mmol) in ethanol (55 cm^3) was hydrogenated over 5% Rh/Al_2O_3 (76 mg) for 6 h at 45 psi. The usual work-up gave a mixture of *cis*- and *trans*-hexahydro-1-hydroxypyrrolizin-3-one, which were partially separated by dry flash chromatography (using ethyl acetate as eluent). A first fraction gave a mixture of the two isomers (171 mg, 19%). The second fraction afforded *cis*-hexahydro-1-hydroxypyrrolizin-3-one **39** (671 mg, 74%) as a light yellow solid, mp 97–99 °C (from ethyl acetate); δ_H 4.33 (1H, t, ^3J 4.5, H-1), 3.92 (1H, m), 3.48 (1H, dt, ^3J 11.7 and 7.1), 2.97 (1H, m), 2.88 (1H, ddt, ^2J 16.7, ^3J 4.9, ^nJ 1.2, H-2), 2.34 (1H, d, ^2J 16.7, H-2), 1.94–2.12 (3H, m) and 1.71 (1H, m); δ_C 173.39 (quat), 67.77, 67.02, 45.46, 41.33, 27.04 and 22.79 (in agreement with the literature data[27]); *m/z* 141 (M^+, 82%), 113 (36), 112 (85), 70 (100), 69 (27) and 41 (28). *Trans*-hexahydro-1-hydroxypyrrolizin-3-one **40** has the following NMR data: δ_H 2.71 (1H, apparent d, ^3J 8.3, H-2); δ_C (one quaternary not apparent) 72.91, 69.13, 44.18, 41.37, 29.59 and 26.44 (in agreement with literature data[27]).

Hydrogenation of 7-methoxypyrrolizin-3-one 41

(i) Hydrogenation (on a small scale) of 7-methoxypyrrolizin-3-one[11] **41** over 5% Rh/C in hexane/ethyl acetate for 2.5 h at 45 psi gave 1,2-dihydro-7-methoxypyrrolizin-3-one **42** bp 50–55 °C (0.4 Torr) (Found: M^+, 151.0632. $C_8H_9NO_2$ requires *M*, 151.0633); δ_H 6.88 (1H, d, ^3J 3.4), 6.22 (1H, d, ^3J 3.4), 3.81 (3H, s), 3.06–3.14 (2H, m) and 2.93–3.00 (2H, m); δ_C 171.29 (quat), 142.19 (quat), 118.35, 110.95, 109.09, 58.39, 34.26 and 30.76 (1 quat not assigned); *m/z* 151 (M^+, 59%), 120 (100), 92 (42), 80 (45), 79 (33), 65 (25) and 52 (14).

(ii) Hydrogenation (on a small scale) of 7-methoxypyrrolizin-3-one **41** over 5% Pd/C in ethanol for 3 h at 45 psi gave a mixture of *cis*- and *trans*-hexahydro-7-methoxypyrrolizin-3-one in a 86:14 ratio; *cis*-isomer **43**, bp 95–100 °C (0.8 Torr) (Found: M^+, 155.0942. $C_8H_{13}NO_2$ requires *M*, 155.0946); δ_H 3.87 (1H, m, H-7A), 3.48–3.60 (2H, m, H-7 and H-5), 3.28 (3H, s, OMe), 3.06 (1H, br t, ^nJ 10.1, H-5), 2.62 (1H, m), 2.12–2.48 (2H, m) and 1.89–2.05 (3H, m); δ_C (one quaternary not apparent) 68.93, 66.40, 56.27, 39.18, 35.75, 34.29 and 17.80; *m/z* 155 (M^+, 37%), 97 (100), 86 (28), 84 (60), 69 (67), 55 (34) and 41 (50). *Trans*-isomer **44**; δ_H 3.34 (3H, s, OMe).

Hydrogenation of 1,2-dihydro-1-hydroxy-7-methylpyrrolizin-3-one 45

(i) Hydrogenation (on a small scale) of **45** (ESI†) in ethanol at 45 psi for 6 h over 5% Rh/C gave the hexahydro-1-hydroxy-7-methylpyrrolizin-3-one isomers **46** and **47** in a 67:33 ratio. (Found: M^+, 155.0948. $C_8H_{13}NO_2$ requires *M*, 155.0946); *m/z* 155 (M^+, 69%), 126 (100), 97 (62), 84 (100), 83 (31), 82 (41), 71 (43), 69 (32), 56 (80), 55 (39) and 41 (84). The two isomers were not separated; their NMR data were obtained by comparison of the spectra of the above reaction mixture and that of the 5% $Pd/CaCO_3$ reduction in which the major product was reversed (see below). Some of the proton signals of the two isomers were overlapping; a range of chemical shifts has been given in those cases: *cis*-7,7A-*cis*-7A,1-hexahydro-1-hydroxy-7-methylpyrrolizin-3-one **46** δ_H (360 MHz) 4.53 (1H, td, ^3J 4.0 and ^nJ 1.3, H-1), 3.77–3.85 (2H, m), 2.65–2.93 (2H, m), 2.30–2.43 (1H, m), 2.23 (1H, d, ^2J 16.8, H-2), 1.91 (1H, m), 1.60–1.69 (1H, m) and 1.25 (3H, d, ^3J 7.1, Me); δ_C 172.40 (quat), 71.74, 67.46, 44.41, 39.88, 34.49, 31.93 and 13.86; *cis*-7,7A-*trans*-7A,1-hexahydro-1-hydroxy-7-methylpyrrolizin-3-one **47**; δ_H (360 MHz) 4.35 (1H, td, ^3J 8.0 and 5.9, H-1), 3.77–3.85 (1H, m), 3.51 (1H, dt, ^3J 11.6 and 7.9), 3.02 (1H, m), 2.65–2.93 (2H, m), 2.30–2.43 (1H, m), 2.15 (1H, m), 1.60–1.69 (1H, m) and 0.90 (3H, d, ^3J 7.1, Me); δ_C 175.86 (quat), 71.34, 67.63, 45.15, 43.03, 34.79, 34.69 and 13.37.

(ii) Using ethanol as the solvent, the two products **46** and **47** were formed after hydrogenation for 5 h at 55 psi, in the ratios 64:36 using 5% Rh/Al_2O_3 and 40:60 using 5% $Pd/CaCO_3$ catalysts.

In some reaction mixtures a third isomer was observed: δ_H 0.80 (3H, ^3J 7.1, Me).

Hydrogenation of 1-acetoxy-1,2-dihydro-7-methylpyrrolizin-3-one 48

(i) A solution of 1-acetoxy-1,2-dihydro-7-methylpyrrolizin-3-one **48** (106 mg, 0.5 mmol) (see ESI†) in ethyl acetate (25 cm^3) was hydrogenated at 55 psi over 5% Rh/C (21 mg) for 4 h, at which point only 40% of the starting material had been converted. The mixture was rehydrogenated under the same conditions, but with a higher loading of catalyst (50 mg) for a total time of 15 h. The usual work-up gave a mixture of the 1-acetoxyhexahydro-7-methylpyrrolizin-3-one isomers **49** and **50** (104 mg, 96%) in a 86:14 ratio, which were not separated. (Found: M^+, 197.1050. $C_{10}H_{15}NO_3$ requires *M*, 197.1051); *m/z* 197 (M^+, 5%), 139 (62), 138 (36), 137 (84), 126 (21), 109 (35), 97 (100), 95 (33), 84 (96), 83 (24), 69 (58), 68 (30), 56 (36), 55 (52), 43 (91) and 41 (59). *Cis*-7,7A-*cis*-7A,1-1-acetoxyhexahydro-7-methylpyrrolizin-3-one **49**; δ_H (360 MHz) 5.40 (1H, ddd, ^3J 5.8, 5.0 and 2.5, H-1a), 4.00 (1H, dd, ^3J 7.4 and 5.0, H-7Aa), 3.82 (1H, ddd, ^3J 11.4, 7.6 and 4.6, H-5b), 2.96 (1H, m, H-5a), 2.91 (1H, dd, ^2J 17.2 and ^3J 5.8, H-2a), 2.38 (1H, dd, ^2J 17.2 and ^3J 2.5, H-2b), 2.35 (1H, m, H-7a), 2.05 (3H, s, OCOMe), 2.02 (1H, m, H-6a), 1.63 (1H, dq, ^3J 12.3 and 7.6, H-6b) and 1.04 (3H, d, ^3J 7.1, Me); δ_C 174.24 (quat), 170.05 (quat), 71.76, 65.89, 42.35, 41.37, 34.71, 34.34, 21.05 and 13.52. The *cis*-7,7A-*trans*-7A,1-isomer **50** was identified by comparison with the data obtained from the Pd/C reduction (see below).

(ii) Small-scale hydrogenations of **48** were carried out at 55 psi for 4–6 h. The catalysts, solvents and ratios of **49**:**50** are indicated; 5% Rh/C, ethyl acetate, 83:17; 5% Rh/Al_2O_3, ethyl acetate, 72:28; 5% Rh/C, ethanol, 79:21; 5% Pd/C, ethanol, 40:60. These latter conditions allowed the NMR characterisations, from the reaction mixture, of the following isomer: *cis*-7,7A-*trans*-7A,1-1-acetoxyhexahydro-7-methylpyrrolizin-3-one **50**; δ_H (360 MHz) 5.10 (1H, ddd, ^3J 8.7, 6.9 and 4.8, H-1b), 3.82 (1H, t, ^3J 4.8, H-7Aa), 3.50 (1H, dt, ^3J 11.7 and 8.5, H-5b), 3.07 (1H, m, H-5a), 2.87 (1H, dd, ^2J 17.3 and ^3J 8.7, H-2b), 2.77 (1H, dddd, ^2J 17.3, ^3J 6.9, ^nJ 1.4 and 1.0, H-2a), 2.33 (1H, m, H-7a), 2.15 (1H, m, H-6a), 2.07 (3H, s, O(CO)Me), 1.73 (1H, m, H-6b) and 0.88 (3H, d, ^3J 7.1, Me); δ_C 171.88 (quat), 170.50 (quat), 70.43, 68.38, 40.99, 39.47, 33.98, 32.37, 20.75 and 13.68.

In some reaction mixtures a third, minor, isomer was observed: δ_H 0.82 (3H, ^3J 7.4, Me).

Retronecanol 7

A 86:14 mixture of 1-acetoxyhexahydro-7-methylpyrrolizin-3-ones **49** and **50** (104 mg, 0.5 mmol)] was reduced by LAH (75 mg, 2.0 mmol) using the general method outlined above for heliotridane, and the workup method for isoretronecanol. The products were distilled at 100–110 °C (0.6 Torr) to give a mixture of the hexahydro-1-hydroxy-7-methyl-3*H*-pyrrolizines **7** and **51** (66 mg, 88%) in a 86:14 ratio; *cis*-7,7A-*cis*-7A,1-hexahydro-1-hydroxy-7-methyl-(3*H*)-pyrrolizine (retronecanol) **7** δ_H (360 MHz) 4.29 (1H, m, H-1), 3.50 (1H, m), 3.40 (1H, dd, ^3J 7.8 and 3.3, H-7A), 3.25 (1H, td, ^3J 7.0 and 4.0), 2.92 (1H, td, ^3J 10.9 and 6.8), 2.80 (1H, td, ^nJ 10.0 and 1.6), 2.34 (1H, m), 1.84–2.02 (3H, m), 1.75 (1H, m) and 1.26 (3H, d, ^3J 7.0, Me); δ_C 72.80, 72.58, 56.15, 54.35, 37.27, 35.48, 32.85 and 13.87 (^{13}C and ^{1}H NMR data disagree with values claimed in the literature,[28] but characterisation of the picrate salt is secure–see below); *m/z* 141 (M^+, 14%), 97 (58), 83 (21), 82 (100), 69 (19), 55 (26) and 41 (41); *cis*-7,7A-*trans*-7A,1-hexahydro-1-hydroxy-7-methyl-3H-pyrrolizine **51** showed characteristic signals at δ_H 4.53 (1H, m) and 1.08 (3H, d, ^3J 7.1, Me); δ_C 73.97, 71.56, 54.02, 53.23, 34.98, 32.57, 31.76 and 14.41. Purification of the mixture was achieved by synthesis of the picrates and recrystallisation from ethanol to give the picrate salt of retronecanol **7**, mp 208–211 °C (from ethanol) (lit.,[38] 210 °C); δ_H ([$^2H_6$]acetone) (picrate) 10.57 (1H, br), 8.77 (2H, s), 4.59 (1H, br s), 4.01–4.19 (2H, m), 3.76 (1H, m), 3.31–3.57 (2H, m), 2.65 (1H, m), 2.02–2.41 (3H, m) and 1.39 (3H, d, ^3J 6.9, Me); δ_C ([$^2H_6$]acetone) (picrate) 159.94 (quat), 140.68 (quat), 127.28 (quat), 124.61, 73.70, 70.31, 54.79, 54.22, 35.48, 33.97, 31.17 and 10.91. The picrate of the minor isomer **51** has the following characteristic NMR signals; δ_H ([$^2H_6$]acetone) (picrate) 1.26 (3H, d, ^3J 7.0, Me); δ_C ([$^2H_6$]acetone) (non-picrate signals) 74.12, 68.76, 53.65, 52.70, 33.48, 32.97, 30.22 and 11.57.

Hydrogenation of 1-acetoxy-1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one 52

A solution of 1-acetoxy-1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one **52** (see ESI†) in glacial acetic acid was hydrogenated (on a small scale) over 5% Rh/Al_2O_3 for 7 h at 55 psi. A mixture of perhydro compounds was produced, mainly composed of two compounds identified as the isomers of 1-acetoxyhexahydro-7-methoxycarbonylpyrrolizin-3-one **53** and **54** in a 67:33 ratio, (Found: M^+, 241.0966. $C_{11}H_{15}NO_5$ requires *M*, 241.0950); *m/z* 241 (26), 198 (10), 183 (54), 182 (31), 181 (88), 168 (66), 155 (65), 138 (68), 128 (80), 103 (86), 97 (90), 96 (55), 73 (74), 69 (100), 68 (73), 67 (55) and 55 (88). The following ^{1}H NMR data were characteristic: *cis*-7,7A-*cis*-7A,1-1-acetoxyhexahydro-7-methoxycarbonylpyrrolizin-3-one **53**; δ_H 5.45 (1H, td, ^nJ 5.0 and 1.3, H-1), 4.34 (1H, dd, ^nJ 9.1 and 4.6), 4.01 (1H, m), 3.64 (3H, s, CO_2Me) and 1.96 (3H, s, O(CO)Me); *cis*-7,7A-*trans*-7A,1-1-acetoxy-hexahydro-7-methoxycarbonylpyrrolizin-3-one **54**; δ_H 5.14 (1H, ddd, ^nJ 9.3, 5.9 and 3.8, H-1), 3.68 (3H, s, CO_2Me) and 2.08 (3H, s, O(CO)Me).

Hydrogenation of 1,2-dihydro-1-hydroxy-7-acetoxymethylpyrrolizin-3-one 55

A solution of 1,2-dihydro-1-hydroxy-7-acetoxymethylpyrrolizin-3-one **55** (see ESI†) in ethanol was hydrogenated (on a small scale) over 5% Rh/C for 3 h at 45 psi. A complex mixture of 4 major perhydro products was obtained; *cis*-7,7A-*cis*-7A,1- and *cis*-7,7A-*trans*-7A,1-hexahydro-1-hydroxy-7-methylpyrrolizin-3-one **46** and **47** were identified from their ^{13}C NMR resonances. The other two compounds were assigned as isomers of hexahydro-1-hydroxy-7-acetoxymethylpyrrolizin-3-one **56** from the ^{13}C NMR spectrum of the mixture; δ_C (one carbon signal not apparent) 175.33 (quat), 172.10 (quat), 170.87 (quat), 170.71 (quat), 69.72, 67.86, 65.99, 64.01 (CH_2), 63.36 (CH_2), 45.13, 43.61, 42.77, 40.70, 39.94, 37.10, 30.55, 30.07, 20.84 and 20.77.

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