Supplementary Information: Despinoy and McNab

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

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Supporting Information

1,2-Dihydro-1-hydroxy-7-methylpyrrolizin-3-one 45

Reaction of a stirred solution of 7-methylpyrrolizin-3-one[1] **16** (284 mg, 2.1 mmol)) in dichloromethane (20 cm^3) with dry hydrogen chloride as previously reported[2] gave 1-chloro-1,2-dihydro-7-methylpyrrolizin-3-one as an orange oil (Found: M^+, 169.0307. C_8H_8ClNO requires *M*, 169.0294); δ_H 7.00 (1H, d, ^3J 3.1), 6.33 (1H, d, ^3J 3.1), 5.39 (1H, dd, ^3J 7.3 and 1.8), 3.63 (1H, dd, ^2J 19.0 and ^3J 7.3), 3.21 (1H, dd, ^2J 19.0 and ^3J 1.8) and 2.11 (3H, s); δ_C 167.54 (quat), 134.04 (quat), 121.92, 118.82 (quat), 112.25, 46.78, 45.72 and 10.18; *m/z* 171 (M^+, 42%), 169 (M^+, 62), 135 (47), 134 (87), 133 (72), 106 (78), 105 (61), 104 (75), 79 (66), 78 (60), 77 (56) and 52 (100).

The crude 1-chloro-1,2-dihydro-7-methylpyrrolizin-3-one obtained above was quenched with a mixture of water (15 cm^3) and acetone (4 cm^3) and stirred at room temperature for 35 min. After work-up[2] and dry flash chromatography gave unreacted 7-methylpyrrolizin-3-one **16** (66 mg, 23%), 1,2-dihydro-1-ethoxy-7-methylpyrrolizin-3-one formed fortuitously as a yellow liquid, (20 mg, 5%), bp 40-45 °C (0.2 Torr) (Found: M^+, 179.0946. $C_{10}H_{13}NO_2$ requires *M*, 179.0946); δ_H 6.97 (1H, d, ^3J 3.0), 6.30 (1H, dd, ^3J 3.0 and ^nJ 0.3), 4.93 (1H, ddd, ^3J 6.7 and 1.8, ^nJ 0.7), 3.45-3.63 (2H, two dq at 3.51 and 3.57, ^2J 8.8 and ^3J 7.0), 3.26 (1H, dd, ^2J 18.4 and ^3J 6.7), 2.91 (1H, dd, ^2J 18.4 and ^3J 1.8), 2.10 (3H, s) and 1.22 (3H, t, ^3J 7.0); δ_C 169.20 (quat), 135.11 (quat), 121.27, 117.85 (quat), 111.61, 68.47, 64.10, 43.11, 15.18 and 10.31; *m/z* 179 (M^+, 87%), 150 (43), 136 (37), 135 (62), 134 (100), 133 (65), 122 (47), 108 (74), 107 (62), 106 (78), 105 (61), 104 (70), 94 (51), 93 (71), 80 (59), 79 (68), 78 (61) and 77 (58) and 1,2-dihydro-1-hydroxy-7-methylpyrrolizin-3-one **45** (199 mg, 62%) as an orange oil, bp 165-170 °C (0.3 Torr) (Found: M^+, 151.0634. $C_8H_9NO_2$ requires *M*, 151.0633); δ_H 6.95 (1H, d, ^3J 3.1), 6.31 (1H, dd, ^3J 3.1 and ^nJ 0.4), 5.26 (1H, br d, ^3J 6.9), 3.37 (1H, dd, ^2J 18.7 and ^3J 6.9), 2.87 (1H, dd, ^2J 18.7 and ^3J 2.0), 2.36 (1H, br, OH) and 2.11 (3H, s); δ_C 169.18 (quat), 136.76 (quat), 121.50, 117.40 (quat), 111.47, 61.81, 46.01 and 10.31; *m/z* 151 (M^+, 58%), 134 (56), 108 (67), 104 (58), 80 (53) and 41 (100 %).

1-Acetoxy-1,2-dihydro-7-methylpyrrolizin-3-one 48

Quenching 1-chloro-1,2-dihydro-7-methylpyrrolizin-3-one [from 7-methylpyrrolizin-3-one **16** (257 mg, 1.9 mmol)] with sodium acetate (0.22 g, 2.7 mmol) in glacial acetic acid (20 cm^3) over 1 h gave, after workup[2b] and dry flash chromatography, unreacted 7-methylpyrrolizin-3-one **16** (28 mg, 11%) and 1-acetoxy-1,2-dihydro-7-methylpyrrolizin-3-one **48** (182 mg, 49%) as a colourless oil, bp 100-105 (0.3 Torr) (Found: M^+, 193.0741. $C_{10}H_{11}NO_3$ requires *M*, 193.0739); δ_H 7.02 (1H, d, ^3J 3.1), 6.33 (1H, d, ^3J 3.1), 6.12 (1H, br d, ^3J 7.3), 3.46 (1H, dd, ^2J 19.0 and ^3J 7.3), 2.90 (1H, dd, ^2J 19.0 and ^3J 1.8), 2.08 (3H, s) and 2.06 (3H, s); δ_C 170.45 (quat), 168.13 (quat), 132.78 (quat), 121.66, 118.81 (quat), 112.35, 63.17, 43.15, 20.75 and 10.27; *m/z* 193 (M^+, 35%), 135 (56), 134 (100), 133 (77), 109 (56), 108 (53), 106 (82), 105 (78), 104 (59), 80 (45), 79 (62), 78 (52) and 77 (53).

1-Acetoxy-1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one 52

As described above, hydrochlorination of 7-methoxycarbonylpyrrolizin-3-one **26** (over 2 days) gave 1-chloro-1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one as a yellow liquid, (Found: M^+, 213.0196. $C_9H_8ClNO_3$ requires *M*, 213.0193); δ_H 7.07 (1H, d, ^3J 3.2), 6.86 (1H, d, ^3J 3.2), 5.57 (1H, dd, ^3J 7.2 and 1.5), 3.86 (3H, s), 3.69 (1H, dd, ^2J 19.3 and ^3J 7.2) and 3.27 (1H, dd, ^2J 19.3 and ^3J 1.5); δ_C 167.82 (quat), 162.95 (quat), 142.91 (quat),

119.20, 114.32 (quat), 113.09, 51.67, 45.92 and 45.25; *m/z* 215 (M^+, 12%), 213 (M^+, 34), 179 (24), 178 (100), 177 (26), 147 (23), 146 (92), 119 (31), 118 (40) and 63 (43).
Quenching the chloro-compound [from **26** (207 mg, 1.2 mmol)] with sodium acetate (300 mg, 3.7 mmol) in glacial acetic acid (12 cm^3) for 30 h at room temperature followed by 4.5 h at 60 °C and work-up as previously described gave three major products after dry flash chromatography: unreacted 7-methoxycarbonylpyrrolizin-3-one **26** (46 mg, 22%), 1-acetoxy-1,2-dihydro-7-methoxycarbonylpyrrolizin-3-one **52** (53 mg, 19%) as a yellow solid, mp 93-94 °C (after sublimation) (Found: M^+, 237.0641. $C_{11}H_{11}NO_5$ requires *M*, 237.0637); δ_H 7.09 (1H, d, ^3J 3.3), 6.87 (1H, d, ^3J 3.3), 6.42 (1H, dd, ^3J 7.1 and 1.9), 3.80 (3H, s), 3.53 (1H, dd, ^2J 19.2 and ^3J 7.1), 2.92 (1H, dd, ^2J 19.2 and ^3J 1.9) and 2.10 (3H, s); δ_C 169.80 (quat), 168.36 (quat), 163.01 (quat), 141.25 (quat), 119.01, 114.57 (quat), 113.04, 62.54, 51.51, 42.29 and 20.55; *m/z* 237 (M^+, 11%), 195 (20), 194 (71), 178 (21), 177 (23), 164 (14), 163 (19), 162 (100), 146 (36), 134 (13), 118 (11), 103 (11) and 103 (11); 1,2-dihydro-1-hydroxy-7-methoxycarbonylpyrrolizin-3-one (14 mg, 6%) only partially separated from its 1-acetoxy analogue; identified by its ^{1}H NMR spectrum: δ_H 6.99 (1H, d, ^3J 3.3), 6.74 (1H, d, ^3J 3.3), 5.46 (1H, dd, ^3J 7.3 and 3.3), 3.88 (3H, s), 3.40 (1H, dd, ^2J 18.8 and ^3J 7.3) and 3.03 (1H, dd, ^2J 18.8 and ^3J 3.3).

7-Acetoxymethyl-1,2-dihydro-1-hydroxypyrrolizin-3-one 55
Our previous method,[2b] involving treatment of 7-acetoxymethylpyrrolizin-3-one[2] **31** (231 mg, 1.2 mmol) with dry HCl and quenching the resulting chloro-compound with a mixture of water (10 cm^3) and acetone (2.5 cm^3) over 30 min was scaled up, to allow full characterisation of the product. Standard work-up[2b] gave 7-acetoxymethyl-1,2-dihydro-1-hydroxypyrrolizin-3-one **55** as a colourless oil which crystallised on standing (233 mg, 92%), mp 59.5-60 °C (from hexane) (Found: C, 57.55; H, 5.25; N, 6.6. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.25; N, 6.7%); δ_H 6.95 (1H, d, ^3J 3.2), 6.42 (1H, d, ^3J 3.2), 5.30 (1H, dd, ^3J 6.9 and 1.9), 5.13 (1H, d, ^2J 12.5), 4.82 (1H, d, ^2J 12.5), 4.15 (1H, br s, OH), 3.29 (1H, dd, ^2J 18.7 and ^3J 6.9), 2.87 (1H, dd, ^2J 18.7 and ^3J 1.9) and 2.02 (3H, s); δ_C 171.91 (quat), 169.54 (quat), 140.31 (quat), 119.37, 115.48 (quat), 111.88, 60.98, 58.02, 44.62 and 20.89; *m/z* 209 (M^+, 17%), 191 (10), 150 (33), 149 (100), 121 (20), 108 (37), 104 (22), 93 (22), 79 (28), 53 (22) and 52 (22).

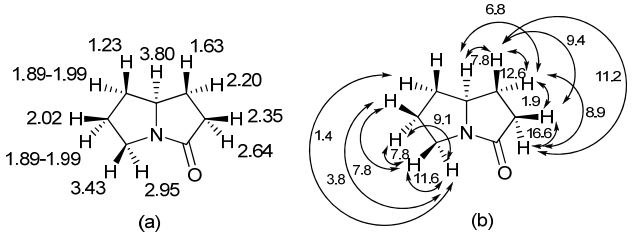


Fig. S1 (a) ^{1}H NMR chemical shifts of pyrrolizidin-3-one **4** ([^{2}H]chloroform); (b) assigned ^{1}H-^{1}H coupling constants of **4** (Hz)

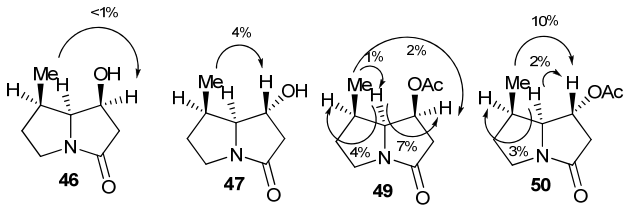
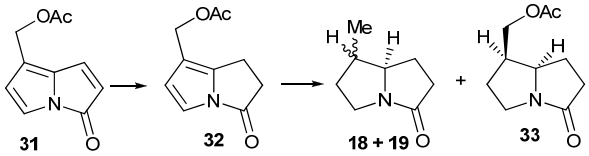


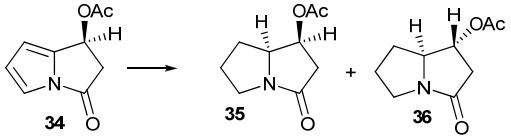
Fig. S2 NOE results for **46** and **47**, and for **49** and **50** (only one of the enantiomeric pairs is shown).

Table S1. Effect of catalysts and solvent on the hydrogenation of **31**.



Catalyst	Solvent	Products
5% Pd-C	ethyl acetate	**32**
5% Pd-C	ethanol	**18** and **19**
5% Pd-$CaCO_3$	ethyl acetate	**32**
PtO_2	ethyl acetate	**18** and **19**
5% Rh-C	ethyl acetate	**32**
5% Rh-C	ethanol	**33** and **18**
5% Rh-Al_2O_3	ethanol	**18** and **19**
5% Rl-Al_2O_3	acetic acid	**18** and **19**

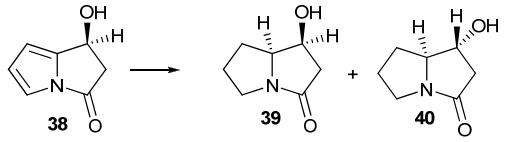
Table S2. Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **34** (45 psi, 2 h).



Catalyst	Solvent	Ratio 35 : 36
5% Pd/C	ethanol	93 : 7[a]
5% Pd/$CaCO_3$	ethanol	**35** only
PtO_2	ethanol	89 : 11
5% Rh/Al_2O_3	ethyl acetate	92 : 8
5% Rh/Al_2O_3	ethanol	92 : 8

[a]95 : 5 ratio obtained on scale-up

Table S3. Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **38** (45 psi, 2 h).



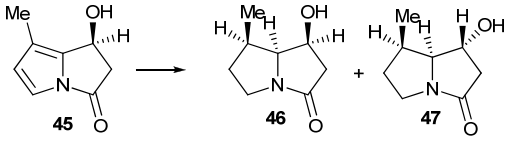
Catalyst	Solvent	Ratio 39 : 40
5% Pd-C	ethyl acetate	88 : 12
5% Pd-C	ethanol	83 : 17
5% Pd-$CaCO_3$	ethyl acetate	-[a]
5% Pd-$CaCO_3$	ethanol	90 : 10[b]
PtO_2	ethanol	88 : 12
5% Rh-C	ethanol	86 : 14
5% Rh-Al_2O_3	ethyl acetate	85 : 15
5% Rh-Al_2O_3	propan-2-ol	86 : 14
5% Rh-Al_2O_3	ethanol	90 : 10

[a]no reaction; [b]presence of remaining starting material

Table S4. Selected ^{1}H NMR data of *cis*-1-substituted pyrrolizidin-3-ones.

	H_{2a}			**H_{2b}**		
R_1	δ (ppm)	pattern	^nJ (Hz)	δ (ppm)	pattern	^nJ (Hz)
Me	2.84	ddt	16.3, 8.0, 1.1	1.98	dd	16.3, 2.7
OH	2.88	ddt	16.7, 4.9, 1.2	2.34	d	16.7
OAc	2.97	ddt	17.6, 5.6, 1.2	2.40	d	17.2

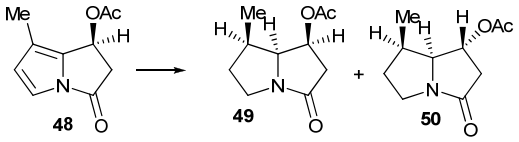
Table S5. Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **45**.



Catalyst	Solvent	46 : 47
5% Rh-C	ethanol	67 : 33[a]
5% Rh-C	ethyl acetate	-[b]
5% Rh-Al_2O_3	ethanol	64 : 36[a]
5% Pd-$CaCO_3$	ethanol	40 : 60

[a]presence of a third minor isomer; [b]no reaction

Table S6. Effect of catalysts and solvent on the diastereoselectivity of hydrogenation of **48**.



Catalyst	Solvent	49 : 50
5% Pd-C	ethanol	40 : 60[a]
5% Rh-Al_2O_3	ethyl acetate	72 : 28
5% Rh-C	ethyl acetate	83 : 17[a,b]
5% Rh-C	ethanol	79 : 21[a]

[a]presence of a third isomer; [b]86 : 14 ratio on a 106 mg scale

References

1 S. E. Campbell, M. C. Comer, P. A. Derbyshire, X. L. M. Despinoy, H. McNab, R. Morrison, C. C. Sommerville and C. Thornley, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2195-2202.

2 (a) H. McNab and C. Thornley, *J. Chem. Soc., Chem. Commun*., 1993, 1570-1571; (b) H. McNab and C. Thornley, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3584-3591.