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PAPER

Chemoselective reduction of 2-acyl-*N*-sulfonylpyrroles: Synthesis of 3-pyrrolines and 2-alkylpyrroles†

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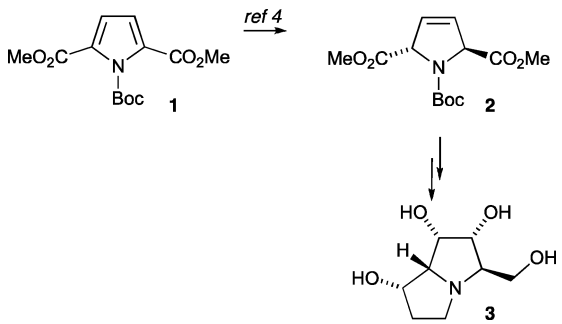
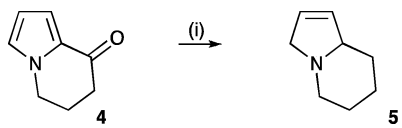
The partial reduction of pyrroles is not a common practice even though it offers a potential route to pyrroline building blocks, commonly used for synthesis. We have investigated the reduction of 2-acyl-*N*-sulfonylpyrroles and by varying the hydride source and solvent, achieved a chemoselective reduction, leading to 3-pyrrolines and alkyl pyrroles in high yield.

The dearomatisation of aromatic and heteroaromatic rings is an important source of functional building blocks for synthetic chemistry.[1,2] While most of these derivatives can be reduced by classical conditions such as the Birch reaction, pyrroles are typically inert due to the high electron density of this heterocyclic system. Recently Donohoe has demonstrated that reducing the electron density by the addition of at least two electron withdrawing groups, pyrrolic derivatives can be dearomatised to give the corresponding 3-pyrroline derivatives.[3] This methodology has been exploited as a key step in the synthesis of the polyhydroxylated pyrrolizidine 1-epiaustraline (**3**, Scheme 1).[4]



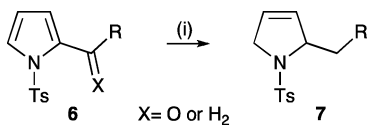
Scheme 1 Synthesis of (±)-1-epiaustraline from a 3-pyrroline building block.

It was demonstrated over a century ago by Knorr and Rabe that the electron rich pyrroles can be reduced to 3-pyrrolines by the action of zinc powder in 5 M hydrochloric acid.[5] The mechanism is assumed to proceed by protonation of pyrrole at C-2 to form an iminium species which is then reduced. Recently we reported an adaption of this method for the reduction of bicyclic 2-acylpyrroles (**4**) for the synthesis of indolizidine derivatives (Scheme 2).[6] While the reaction is rapid and high yielding, the harsh conditions required, zinc powder in refluxing methanol with conc. hydrochloric acid, means that this method is incompatible with many functional groups and thus milder reaction conditions would be desirable.



Scheme 2 Reduction of 2-acylpyrroles to pyrrolines; (i) Zn, HCl (conc), EtOH, reflux.

A potential alternative to these methods was reported by Ketcha, who demonstrated that the less electron rich *N*-phenylsulfonylpyrroles possessing alkyl or acyl groups at C-2 or C-3 could be reduced to the corresponding 3-pyrrolines by the action of sodium cyanoborohydride in trifluoroacetic acid (TFA) (Scheme 3).[7] Since this report there has been no application of this methodology possibly due to the reported potential for minor explosions during the addition. Herein we report our investigation into the reduction of *N*-sulfonylpyrroles and the potential application of this methodology to the synthesis of pyrrolidine alkaloids.



Scheme 3 *Reagents and conditions*: (i) $NaBH_3CN$, TFA, rt.

The initial focus was to investigate the reaction conditions reported by Ketcha for the reduction of *N*-tosylpyrrole to identify modifications that could be made to reduce the large excess of sodium cyanoborohydride as well as the volume of trifluoroacetic acid used as the solvent. The use of a co-solvent such as ethanol or acetic acid had a dramatic effect in that no reaction occurred at

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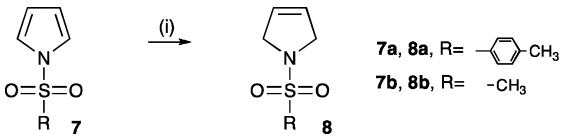
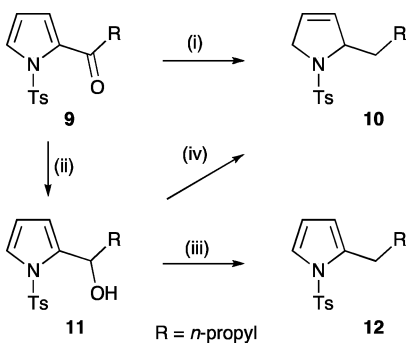
all and neither could sodium cyanoborohydride be replaced with sodium borohydride. However, we did find that for the simple *N*-tosyl and *N*-methanesulfonylpyrroles the volume of trifluoroacetic acid reported[7] could be reduced by one third and only three equivalents of reducing agent were required (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) $NaBH_3CN$, TFA, rt.

These conditions were also effective for the reduction of 2-acyl derivatives such as **9** and it was found that dichloromethane could be used as a co-solvent for these substrates giving the corresponding 3-pyrroline **10** (R = *n*-propyl) in an 81% isolated yield (Scheme 5). However, there was no reaction when acetic acid was used as the proton source. The synthesis of 2-acyl pyrrole derivatives can be readily achieved by the reaction of the *N*-sulfonylpyrroles with the appropriate carboxylic acid and trifluoroacetic anhydride (TFAA).[8] As for the reduction of the unsubstituted derivative **7a**, the combination of sodium cyanoborohydride in acetic acid gave no reaction and we hypothesised that the initial reduction of the carbonyl to the alcohol was the limiting step. Protonation of the carbonyl is most likely required for reduction with sodium cyanoborohydride which is hindered due to the decreased electron donation from the *N*-sulfonylpyrrole. An IR spectrum indicates the carbonyl has vinylogous amide character with the carbonyl showing a stretch at 1670 cm^{-1} instead of a more typical aromatic ketone of 1690 cm^{-1}. Hence a stronger acid source is required for the initial reduction to occur. Therefore, we hypothesised that initial reduction to an α-hydroxy derivative might be more effective. Therefore **9** was reacted with sodium borohydride in ethanol to give the stable α-hydroxy derivative **11** in quantitative yield. When **11** was subjected to sodium cyanoborohydride in acetic acid/dichloromethane the corresponding 2-alkyl pyrrole **12** was formed in 90% yield. This indicated that the reduction of the carbonyl group is in fact the rate limiting step in these reactions. While the reduction of keto groups attached to pyrroles to the corresponding alkanes is well known,[9] this method constitutes a practical two step sequence. In fact, we also found that the reaction can be carried out in the one flask by removal of the solvent after borohydride reaction and addition of acetic acid/sodium

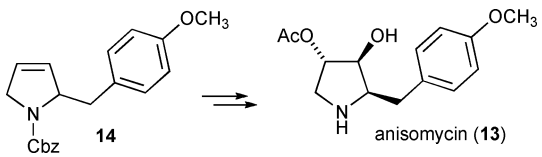


Scheme 5 *Reagents and conditions*: (i) $NaBH_3CN$, TFA, CH_2Cl_2; (ii) $NaBH_4$, EtOH; (iii) $NaBH_3CN$, AcOH, CH_2Cl_2; (iv) $NaBH_4$, TFA, CH_2Cl_2.

cyanoborohydride to give **12** in 91%. Therefore the reduction of acyl pyrroles to alkyl derivatives can now be carried out in a practical one-pot procedure.

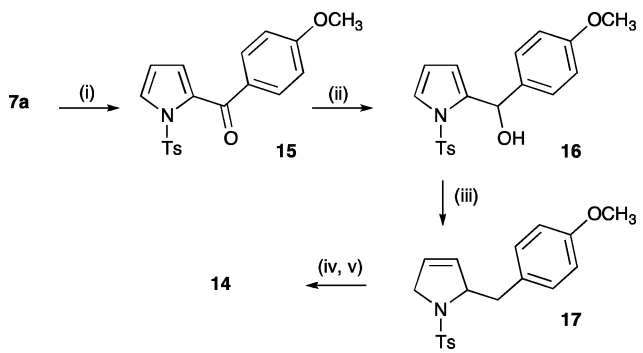
When the hydride source was changed to sodium borohyride no reaction of the alcohol **11** was observed, however, changing the acid to trifluoroacetic acid had a dramatic effect, forming the 3-pyrroline **10** in good yield (Scheme 5). This reaction was the first example of the formation of a 3-pyrroline with a hydride source other than sodium cyanoborohydride. This reaction represents an effective alternative protocol to that reported by Ketcha[7] and by choice of solvent and hydride source, highly chemoselective reductions of 2-acyl-*N*-sulfonylpyrroles can be achieved.

We chose to apply this methodology to the synthesis of the pyrrolidine alkaloid anisomycin (**13**) as the benzyloxycarbonyl protected 3-pyrroline **14** is the key intermediate in the majority of syntheses (Scheme 6).[10]



Scheme 6 Key intermediate (**14**) in the synthesis of anisomycin.

The reaction of *N*-tosylpyrrole **7a** with anisic acid in the presence of trifluoroacetic anhydride provided the carbon skeleton **15** in one step, but reduction of **15** to the 3-pyrroline **17** under the standard conditions resulted in no reaction (Scheme 7). The carbonyl in this instance is also conjugated to the aromatic ring which hinders the first reduction step. Therefore, the ketone was reduced to the alcohol **16** with sodium borohydride and then this was subjected to the reduction conditions to give the desired 3-pyrroline **17** as a 2 : 1 mixture with the fully reduced pyrrolidine in a combined 88% yield over two steps. While this intermediate could be converted directly to anisomycin[11] we decide to confirm the structure by conversion to the common intermediate **14**. Typically *N*-tosylamines are difficult to deprotect but reaction with magnesium metal in methanol under sonication[12] gave the crude amine that was transformed to the protected 3-pyrroline **14** in 74% yield, therefore completing a relatively short formal synthesis of the natural product.



Scheme 7 *Reagents and conditions*: (i) anisic acid, TFAA, CH_2Cl_2; (ii) $NaBH_4$, EtOH; (iii) $NaBH_3CN$, TFA, CH_2Cl_2; (iv) Mg, CH_3OH, sonication; (v) CbzCl, toluene, 2 M NaOH.

To compare this result with our zinc reduction methodology[6] we prepared the 2-aroylpyrrole **19**, by reaction of the magnesium salt

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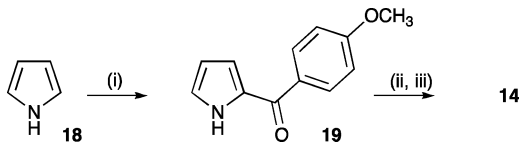
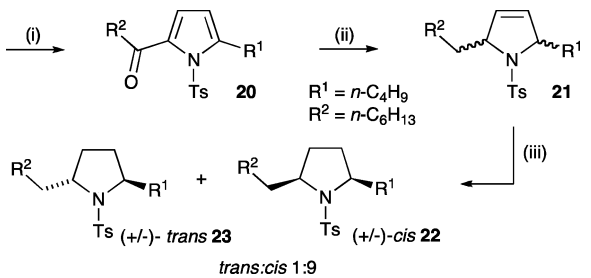
of pyrrole with the corresponding acid chloride, and subjected it to the standard conditions (Scheme 8). The initial reduction showed numerous products as well as the desired pyrroline by ^{1}H NMR, therefore the crude mixture was treated with benzyl chloroformate to give the protected pyrroline **14** in a 45% yield over two steps. Therefore the hydride reaction methodology is the preferred synthetic route to intermediates of this type as the reactions and products are much cleaner.



Scheme 8 *Reagents and conditions*: (i) EtMgBr, THF 0 °C, then anisic chloride (ii) Zn, HCl (conc), EtOH, reflux; (iii) CbzCl, toluene, 2 M NaOH.

We also investigated the synthesis of the toxin pyrrolidine 197, which comes from the poison arrow frogs *Dendrobates histrionicus*,[13] as a platform to investigate the viability and stereochemical outcome of the reduction of 2,5-disubstituted-*N*-sulfonylpyrroles (Scheme 9). Acylation of 2-butylpyrrole **12**, prepared earlier, with heptanoic acid gave the desired carbon skeleton of the target compound **20** in 73% yield. Reduction of **20** with sodium cyanoborohydride in trifluroacetic acid occurs to give the 3-pyrroline **21** and the saturated pyrrolidine in an ~ 2 : 1 ratio by ^{1}H NMR. The compounds could not be separated by coloumn chromotography therefore, the crude product was subjected to catalytic hydrogenation to yield the known *N*-tosylpyrrolidines **22** and **23**[14] as an ~ 9 : 1 mixture of diastereoisomers as identified by ^{1}H and ^{13}C NMR. The major isomer was found to the *cis* derivative **22** as determined by comparison with the literature.[13] It is not unexpected that the *cis*-diastereomer is favoured as hydride is delivered preferentially from the least hindered face away from the second substituent. This is in contrast to the zinc reduction chemistry which normally yields the *trans* derivatives.[5,6] Therefore the hydride methodology is complementary to the zinc reduction chemistry as either diastereomer of 3-pyrrolines could be synthesised from a common intermediate.



Scheme 9 *Reagents and conditions*: (i) Heptanoic acid, TFAA, CH_2Cl_2; (ii) $NaBH_3CN$, TFA, CH_2Cl_2; (iii) H_2, Pd/C, EtOH.

Conclusions

In conclusion, we have demonstrated that 2-acyl-*N*-sulfonylpyrroles are useful synthetic building blocks and that their reduction can be controlled to generate alkylpyrroles and 3-pyrrolines in good yield. The methodology has been used as the platform for the formal synthesis of the anti-biotic natural product anisomycin and can have application in the synthesis of *cis*-2,5-disubstituted pyrrolidines.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Varian Mercury 2000 spectrometer. Spectra were run in $CDCl_3$ unless otherwise stated. Chemical shifts are measured in ppm and referenced internally to residual $CHCl_3$ for ^{1}H NMR (δ 7.26) and the central peak of $CDCl_3$ for ^{13}C NMR (δ 77.04). Coupling constants, *J* are recorded in Hz.

Infrared spectra were recorded on a Shimadzu FTIR 8400 s spectrometer as thins flims on NaCl plates unless otherwise stated. Mass spectroscopy was performed on a Kratos Concept ISQ mass instrument.

A Unisonics Australia FXP12D ultrasonic bath was used for reactions involving sonication. Flash chromatography was performed according to the method of Still and co-workers using silica gel 60 (32–63 μm).[15] Solvents and reagents were obtained from Aldrich, AJAX or BDH chemicals and used as supplied or purified by standard laboratory methods if required. *N*-Sulfonylpyrroles **7a**[16] and **7b**[17] were prepared by literature methods.

1-(*p*-Toluenesulfonyl)-2,5-dihydropyrrole (8a)

To a stirred solution of **7a** (0.210 g, 0.95 mmol) in trifluoroacetic acid (5 mL) at room temp was added sodium cyanoborohydride (0.21 g, 3.0 mmol), slowly in small portions and the mixture stirred for 1 h. The solvent was removed under reduced pressure before solid Na_2CO_3 was added to neutralize residual acid, water (10 mL) added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through silica gel and the solvent removed under reduced pressure yielding the desired product **8a** (0.20 g, 94%), as a pale yellow oil that crystallised on standing. The spectroscopic data was consistent with the literature.[18] δ_H (300 MHz, $CDCl_3$) 2.35 (3H, s), 4.03 (4H, s), 5.58 (2H, s), 7.24 (2H, d, *J* 8.1), 7.63 (2H, d, *J* 8.1).

1-Methanesulfonyl-2,5-dihydropyrrole (8b)

The above method was used to reduce **7b** yielding **8b** (80% yield) as a colourless oil that solidified on standing. The spectroscopic data was consistent with the literature.[19] δ_H (300 MHz, $CDCl_3$) 2.80 (3H, s), 4.14 (4H, s), 5.78 (2H, s); δ_C (75 MHz, $CDCl_3$) 34.3, 54.8, 125.6.

1-[1-(*p*-Toluenesulfonyl)pyrrol-2-yl]butan-1-one (9)

n-Butyric acid (0.5 mL, 7.2 mmol) was added to a solution of *N*-tosylpyrrole **7a** (0.798 g, 3.6 mmol) in trifluoroacetic anhydride (5 mL) and dichloromethane (10 mL) and the resulting solution stirred overnight at room temp. The volatiles were removed under reduced pressure, water (10 mL) added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with saturated sodium carbonate and saturated brine solutions, dried and filtered through a plug of silica gel eluting with ethyl acetate/hexane (20 : 80) yielding the desired product **9** (1.05 g, 97%) as a yellow oil which crystallized on standing. The product

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was used without further purification. ν_{max}/cm^{-1} (film) 3152, 2964, 2875, 1677, 1596, 1440, 1123, 1090, 1063, 669; (300 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.5), 1.61 (2H, sextet, *J* 7.5), 2.38 (3H, s), 2.62 (2H, t, *J* 7.5), 6.29 (1H, at, *J* 3.3), 7.00 (1H, m), 7.27(2H, d, *J* 8.2), 7.76 (1H, m), 7.86 (2H, d, *J* 8.2); δ_C (75 MHz, $CDCl_3$) 13.8, 18.5, 21.8, 41.5, 110.4, 123.4, 128.4, 129.5, 130.2, 133.6, 136.2, 144.8, 189.2; *m*/*z* (EI) 291.09269 (M^+ $C_{15}H_{17}NO_3S$ requires 291.09291), 291 (3%), 248 (65), 155 (75) 91 (100).

2-Butyl-1-(*p*-toluenesulfonyl)-2,5-dihydropyrrole (10)

Sodium cyanoborohydride (88 mg, 1.40 mmol) was added slowly in small portions to a solution of pyrrole **9** (0.135 g, 0.465 mmol) in dichloromethane (6 mL) and trifluoroacetic acid (3 mL) at 0 °C. The mixture was stirred for 1 h before another portion of sodium cyanoborohydride (88 mg, 1.40 mmol) was added and the reaction mixture stirred overnight at room temp. The volatiles were removed under reduced pressure, water (10 mL) added and the pH adjusted to ~8–9 by the addition of solid sodium carbonate. The solution was extracted with dichloromethane (3 × 10 mL), and the extracts combined and dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the pyrroline **10** (0.105 g, 81%) as a pale yellow oil. ν_{max}/cm^{-1} (film) 2956, 2929, 2860, 1725, 1461, 1346, 1288, 1163, 1091, 667; δ_H (300 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9), 1.27–1.76 (6H, m), 2.41 (3H, s), 4.10 (2H, apparent d, *J* 3.6), 4.45 (1H, m), 5.58 (2H, bs), 7.28 (2H, d, *J* 8.4), 7.70 (2H, d, *J* 8.4); δ_C (75 MHz, $CDCl_3$) 14.3, 21.7, 22.9, 26.9, 36.1, 55.8, 67.6, 124.8, 127.6, 129.9, 130.1, 135.1, 143.5; *m*/*z* (EI) 279.12831 (M^+ $C_{15}H_{21}NO_2S$ requires 279.12930), 279 (14%), 222 (30), 167 (41), 149 (100).

1-[1-(*p*-Toluenesulfonyl)pyrrol-2-yl]butan-1-ol (11)

Sodium borohydride (1.17 g, 30.1 mmol) was added to a solution of pyrrole **9** (2.96 g, 10.2 mmol) in ethanol (37 mL) and dichloromethane (13 mL) at 0 °C and the mixture stirred for 2 h at room temp. The volatiles were removed under reduced pressure, water added (130 mL) and extracted with dichloromethane (3 × 50 mL). The extracts were combined dried on $MgSO_4$ and filtered and evaporated to afford the alcohol **11** (2.76 g, 93%) as colourless oil. ν_{max}/cm^{-1} (film) 3568, 3527, 2959, 2872, 1363, 1152, 1088, 1057, 672; δ_H (300 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.2), 1.36 (2H, m), 1.73 (2H, m), 2.40 (3H, s), 2.78 (1H, br s), 4.82 (1H, dd, *J* 7.9 5.7), 6.24 (2H, m), 7.29 (3H, m), 7.67 (2H, d, *J* 8.7); δ_C (75 MHz, $CDCl_3$) 13.9, 19.5, 21.8, 37.3, 65.1, 111.8, 112.4, 123.6, 126.8, 130.3, 136.5, 138.5, 145.4; *m*/*z* (EI) 293.10856 (M^+ $C_{15}H_{19}NO_3S$ requires 293.10856), 293 (5%), 275 (10), 250 (100), 155 (75), 91 (50).

2-Butyl-1-(*p*-toluenesulfonyl)pyrrole (12)

Sodium cyanoborohydride (163 mg, 2.6 mmol) was added carefully to a solution of alcohol **11** (255 mg, 0.87 mmol) in dichloromethane (1.5 mL) and acetic acid (4.5 mL) at 0 °C and the mixture allowed to warm to room temp over 5 h. The volatiles wer removed under reduced pressure, water (10 mL) added and the pH adjusted to ~8–9 by the addition of solid sodium carbonate. The solution was extracted with dichloromethane (3 × 10 mL), and the extracts combined and dried with $MgSO_4$, filtered and evaporated to afford the pyrrole **12** (216 mg, 90%) as a pale yellow oil. ν_{max}/cm^{-1} (film) 3153, 2957, 2862, 1366, 1189, 1175, 1155, 1091, 668; δ_H (300 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.7), 1.34 (2H, sext., *J* 7.7), 1.52 (2H, quint., *J* 7.7), 2.40 (3H, s), 2.65 (2H, t, *J* 7.7), 5.97 (1H, m), 6.19 (1H, at, *J* 3.6), 7.26 (3H, m), 7.62 (2H, d, *J* 8.1); δ_C (75 MHz, $CDCl_3$) 14.0, 21.8, 22.5, 27.0, 30.9, 111.4, 111.9, 122.3, 126.9, 130.1, 136.2, 136.7, 144.9; *m*/*z* (EI) 277.11366 (M^+ $C_{15}H_{19}NO_2S$ requires 277.11365) 277 (12%), 234 (25), 155 (50), 91 (100).

1-(*p*-Toluenesulfonyl)-2-(*p*-methoxybenzoyl)pyrrole (15)

N-Tosylpyrrole **7a** was reacted with anisic acid (1.5 *equiv*.) by the method described for compound **9** to give the desired product **15** as a white solid (90%). ν_{max}/cm^{-1} (film) 2954, 2923, 2853, 1742, 1461, 1377, 722; δ_H (300 MHz, $CDCl_3$) 2.42 (3H, s), 3.84 (3H, s), 6.32 (1H, at, *J* 3.3), 6.66 (1H, m), 6.90 (2H, d, *J* 8.4 Hz), 7.34 (2H, d, *J* 8.1), 7.71 (m, 1H), 7.82 (2H, d, *J* 8.7), 8.00 (2H, d, *J* 8.4).

(4-Methoxyphenyl)-[1-(p-toluenesulfonyl)pyrrol-2-yl]methanol (16)

Sodium borohydride (82 mg, 2.17 mmol) was added slowly to a solution of pyrrole **15** (255 mg, 0.717 mmol) in ethanol (20 mL) at 0 °C. The reaction was warmed slowly to room temp and stirred for 18 h. Further sodium borohydride (90 mg, 2.37 mmol) was added and the reaction stirred for a further 18 h. The volatiles were removed under reduced pressure and the residue taken up in water (30 mL) and extracted with dichloromethane (3 × 10 mL). The organic extracts were washed with water (20 mL), dried on magnesium sulphate, filtered and the solvent removed under reduced pressure, yielding the *title compound* **16** (234 mg, 91%) as an oil that solidified on standing. ν_{max}/cm^{-1} (film) 3386, 2955, 2934, 1512, 1362, 1172; δ_H (300 MHz, $CDCl_3$) 2.41 (3H, s), 3.15 (1H, d, *J* 4.6), 3.79 (3H, s), 5.82–5.86 (1H, m), 6.02 (1H, d, *J* 4.5), 6.18 (1H, at, *J* 3.3), 6.80 (2H, d, *J* 8.7), 7.16 (2H, d, *J* 8.7), 7.25 (2H, d, *J* 7.0), 7.30 (1H, dd, *J* = 3.3, 1.7), 7.59 (2H, d, *J* 8.3 Hz); δ_C (75 MHz, $CDCl_3$) 21.9, 55.5, 68.0, 111.7, 113.7, 115.5, 124.1, 126.9, 128.1, 130.2, 133.2, 136.3, 138.5, 139.9, 159.3; *m*/*z* (EI) 357.10289 (M^+ $C_{19}H_{19}NO_4S$ requires 357.10348) 357 (15%), 201 (100), 170 (83), 155 (20), 135 (78), 91 (81).

2-[(4-Methoxyphenyl)methyl]-1-(p-toluenesulfonyl)-2,5-dihydropyrrole (17)

Using the method described above for the reduction of **10**, sodium cyanoborohydride (494 mg, 7.86 mmol) was reacted with pyrrole **16** (234 mg, 0.654 mmol) in dichloromethane (12 mL)/trifluoroacetic acid (12 mL). The product was purified by column chromatography on silica gel (eluent: dichloromethane) to yield the pyrroline **17** and the saturated pyrroline as an inseparable 2 : 1 mixture (218 mg, 97%) as a colourless solid. Compound **17** ν_{max}/cm^{-1} (film) 2954, 1611, 1512, 1336, 1247, 1161, 665; δ_H (300 MHz, $CDCl_3$) 2.41 (3H, s), 2.90 (1H, dd, *J* 13.2 8.7), 3.07–3.30 (1H, m), 3.78 (3H, s), 3.83–4.16 (2H, m), 4.55–4.65 (1H, m), 5.42–5.57 (2H, m), 6.80–6.86 (2H, m), 7.12–7.17 (2H, m), 7.25–7.32 (2H, m), 7.71–7.78 (2H, m); δ_C (75 MHz, $CDCl_3$) 21.8, 42.4, 55.4, 56.0, 68.8, 113.8, 114.0, 125.3, 127.7, 129.4, 130.0, 131.1, 134.9, 143.7, 158.4; *m*/*z* (EI) 343.12368 (M^+ $C_{19}H_{21}NO_3S$ requires 343.12421), 343 (2%), 222 (100), 155 (95), 121 (40), 91 (97)

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Benzyl 2-[(4-methoxyphenyl)methyl]-2,5-dihydropyrrole-1-carboxylate (14)

Method 1. Zinc dust (102 mg, 1.59 mmol) then concentrated HCl (3 mL) were added in five portions to a hot solution of **19** (30.0 mg, 0.149 mmol) such that reflux was maintained. After the reaction had ceased the mixture was cooled and the zinc salts dissolved using concentrated ammonia, before extraction with dichloromethane (3 × 10 mL). The organic extracts were dried with sodium sulphate, filtered and the solvent removed under reduced pressure. Without further characterisation the crude pyrroline was immediately dissolved in toluene (5 mL)/triethylamine (0.1 mL), chilled to 0 °C and benzyl chloroformate (50 µL) added. After 3 h the reaction mixture was washed with water, and the organic layer dried and the solvent removed under reduced pressure. The title compound was purified by column chromatography on silica gel (eluent ethyl acetate/hexanes, 1 : 4), to give carbamate **14** (20 mg, 42%) as a colourless oil. The spectral properties were consistent with that previously reported.[10]

Method 2. Magnesium turnings (310 mg, 12.75 mmol) were added to a solution of pyrroline **19** (218 gm, 0.634 mmol) in dry methanol (10 mL) under a nitrogen atmosphere and sonicated for 4.5 h. The solvent was removed under reduced pressure and ethyl acetate (15 mL) added to the residue. The resulting suspension was stirred for 5 min. then filtered through a plug of celite and the solvent removed under reduced pressure yielding the intermediate 2-[(4-methoxyphenyl)methyl]-2,5-dihydro-(1*H*)-pyrrole as a colourless oil. The intermediate was immediately dissolved in toluene (15 mL)/2 M sodium hydroxide (15 mL), chilled to 0° C and benzyl chloroformate (0.275 mL, 1.902 mmol) added. After 2 h the organic phase was separated and the aqueous extracted with ethyl acetate (10 mL). The combined organic extracts were washed with water, dried and the solvent removed under reduce pressure. The title compound was purified by column chromatography on silica gel (eluent ethyl acetate/hexanes, 1 : 4), to give carbamate **14** (152 mg, 74%) as a colourless oil. The spectroscopic data was consistent with the literature.[10] ν_{max}/cm^{-1} (film) 3032, 2933, 1696, 1512, 1412, 1247, 1103, 698; δ_H (300 MHz, $CDCl_3$) 2.75–2.94 (1H, m), 2.99–3.17 (1H, m), 3.38–3.45 (1H, m), 3.77 (3H, s), 4.12–4.24 (1H, m), 4.71–4.82 (1H, m), 5.16–5.31 (2H, m), 5.63–5.73 (2H, m), 6.75–6.80 (2H, m), 6.93 (1H d, *J* 8.4), 7.03 (1H, d, *J* 8.4), 7.30–7.50 (5H, m); *m*/*z* (EI) 323.1505 (M^+ $C_{20}H_{21}NO_3$ requires 323.1524), 323 (1%), 202 (10), 158 (13), 121 (22), 91 (100).

2-(*p*-Methoxybenzoyl)pyrrole (19)

Pyrrole (0.110 mL, 1.59 mmol) was added drop wise to a chilled (0 °C) solution of 3.0 M methylmagnesium bromide (0.56 mL, 1.68 mmol) in anhydrous toluene (30 mL) before heating at 60 °C for 1 h. After cooling to 0 °C, a solution of 4-methoxybenzoyl chloride (217 mg, 1.27 mmol) in anhydrous toluene (15 mL) was added drop wise and the reaction stirred at room temp for 18 h. The reaction was quenched with saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were washed with water (15 mL), 2 M sodium carbonate (15 ml), dried and the solvent removed under reduced pressure yielding the title compound (232 mg, 90%) as a pale solid. ν_{max}/cm^{-1} (film) 3275, 2965, 1600, 1423, 1398, 1336, 1256, 1169, 1029, 892; δ_H (300 MHz, $CDCl_3$) 3.88 (3H, s), 6.25–6.35 (1H, m), 6.88–6.91 (1H, m), 6.95–7.00 (1H, m), 7.12–7.14 (2H, m), 7.91–7.96 (2H, m), 10.05 (1H, bs); δ_C (75 MHz, $CDCl_3$) 55.7, 111.1, 113.8, 119.0, 119.4, 125.1, 131.1, 131.4, 163.0, 184.0; *m*/*z* (EI) 201.07893 (M^+ $C_{12}H_{11}NO_2$ requires 201.07898) 201 (100%), 170 (23), 135 (46), 94 (33).

1-[5-Butyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]heptan-1-one (20)

n-Heptanoic acid (0.240 mL, 1.67 mmol) was added to a solution of pyrrole **12** (0.232 g, 0.84 mmol) in dichloromethane (5 mL) and trifluoroacetic anhydride (0.48 mL). The resulting mixture was treated as described for **9**, yielding the title compound (quantitative) as a colourless oil. ν_{max}/cm^{-1} (film) 2925, 1704, 1669, 1368, 1173, 1091, 1042; δ_H (300 MHz, $CDCl_3$) 0.88 (6H, m), 1.23–1.68 (12H, m), 2.42 (3H, s), 2.74 (2H, t, *J* 7.5), 2.88 (2H, t, *J* 7.8), 6.00 (1H, d, *J* 3.6), 6.75 (1H d, *J* 3.6), 7.30 (2H, d, *J* 7.8), 7.92 (2H, d, *J* 8.4); δ_C (75 MHz, $CDCl_3$) 14.1, 14.3, 21.9, 22.7 (2C), 25.2, 28.7, 29.1, 31.2, 31.8, 41.4, 111.1, 120.9, 127.7, 129.7, 136.8, 137.1, 144.8, 145.6, 192.3; *m*/*z* (EI) 389.20241 (M^+ $C_{22}H_{31}NO_3S$ requires 389.20246), 389 (8%), 304 (70), 255 (79), 234 (100), 150 (83), 91 (93).

***cis*-2-Butyl-5-heptyl-1-(p-toluenesulfonyl)-2,5-dihydropyrrole (21)**

The procedure described for the reduction of pyrrole **10** was carried out on pyrrole **20** to give an ~ 2 : 1 mixture of the pyrroline **21** and the saturated pyrrolidine **22** as a pale-yellow oil (58% yield) that was used in the next reaction without further purification. Compound **21** δ_H (300 MHz, $CDCl_3$) 0.88 (6H, m), 1.16–1.85 (18H, m), 2.39 (3H, s), 4.28 (2H, dd, *J* 4.5, 8.1), 5.56 (2H, br s), 7.27 (2H, d, *J* 8.4), 7.67 (2H, d, *J* 8.4); δ_C (75 MHz, $CDCl_3$) 14.2, 14.3, 22.9, 25.8, 27.9, 29.4, 29.5, 29.7, 29.8, 32.0, 37.6, 37.9, 68.11, 68.13, 127.7, 129.1, 129.7, 129.7, 135.0, 143.4.

***cis*-2-Butyl-5-heptyl-1-(p-tolylsulfonyl)pyrrolidine (22)**

To a solution of crude pyrroline **21** (0.1964 g, 0.56 mmol) in methanol (10 mL) was added Pd/C (10% w/w, 50 mg) and then hydrogenated under an atmosphere of hydrogen (40psi) on a Parr shaker hydrogenator for 3.5 h. The reaction mixture was filtered through a plug of Celite, the solvent removed under reduced pressure and purified by column chromatography on silica gel (dichloromethane) to afford a 9 : 1 mixture of pyrrolidines **22** and **23**[13] (178 mg, 91%) as a colourless oil. Compound **22** δ_H (300 MHz, $CDCl_3$) 0.87 (6H, m), 1.28–1.86 (22H, m), 2.41 (3H, s), 3.54 (2H, m), 7.27 (2H, d, *J* 8.3), 7.68 (2H, d, *J* 8.3); δ_C (75 MHz, $CDCl_3$) 14.28, 14.31, 21.7, 22.8, 22.9, 26.5, 28.7, 29.5, 29.7, 29.8 (2C), 32.0, 37.2, 37.5, 61.8, 61.9, 127.7, 129.7, 135.5, 143.2; *m*/*z* (APCI) 380 (100%), EI+ 322 (22), 280 (32), 155 (65), 91 (100).

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