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Diastereoselective protonation of extended pyrrol-3-en-2-one enolates: an attempted 'de-epimerisation'

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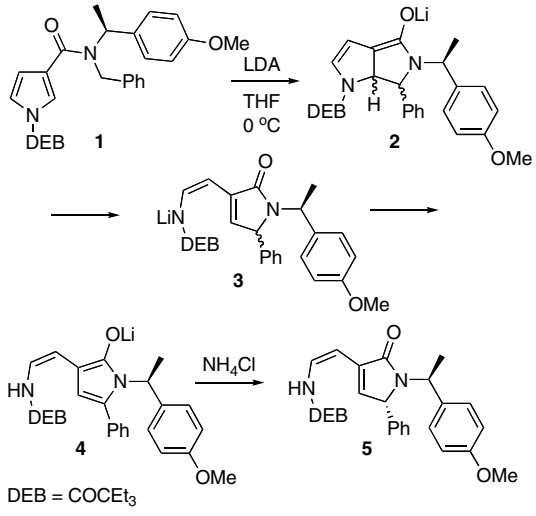
Abstract—The extended cyclic enolate derived from a simple pyrrol-3-en-2-one (butenolactam) was deuterated at the 5-position with very high diastereoselectivity if the nitrogen atom carries an α-methyl-*p*-methoxybenzyl group. A similar diastereoselective protonation was observed in a pyrrol-3-en-2-one formed by dearomatising cyclisation of a pyrrole. Protonation of an *N*-α-methyl-*p*-methoxybenzyl dihydroisoindolone lacked stereoselectivity.

1. Introduction

N-Benzyl-*N*-α-methylbenzyl amides and carbamates can be deprotonated diastereoselectively: the stereochemistry of the resulting benzylic organolithium can be used as a means of making, diastereoselectively, some *meso* amines.[1] Recent work in connection with a dearomatising cyclisation reaction[2,3] suggests that an α-methyl-*p*-methoxybenzyl substituent[4] is able to govern the facial selectivity of reprotonation. Pyrrol-3-en-2-one **5** is formed from **1** as a single diastereoisomer[5] on treatment with base, a result which can be explained only if extended butenolactam enolate **4**, formed by fragmentation of the dearomatising anionic cyclisation product **2**, is reprotonated diastereoselectively (Scheme 1).[2] Recent developments in enantioselective protonation[6] have demonstrated its potential in asymmetric synthesis by 'de-racemising' a chiral starting material: we hoped that this comparable diastereoselective protonation could be developed into means of 'de-epimerising' a mixture of diastereoisomers, imposing uniform stereochemistry at the site of protonation and hence, after deprotection of the nitrogen atom, allowing an enantioselective synthesis of pyrrol-3-en-2-ones.[7] Many compounds in this class are biologically active.[8]



Scheme 1. Cyclisation, ring opening and reprotonation of pyrrole.

2. Results and discussion

We started by stripping away the complexities of butenolactam **3** to reveal the simple parent structure **8**. Butenolactam **8** was made by allylation of acrylamide **6** followed by ring closing metathesis[9] with the 'first-generation' ruthenium based catalyst of Grubbs. Formation of the extended enolate and alkylation with methyl iodide led to α-methylated lactam **9** (Scheme 2). With

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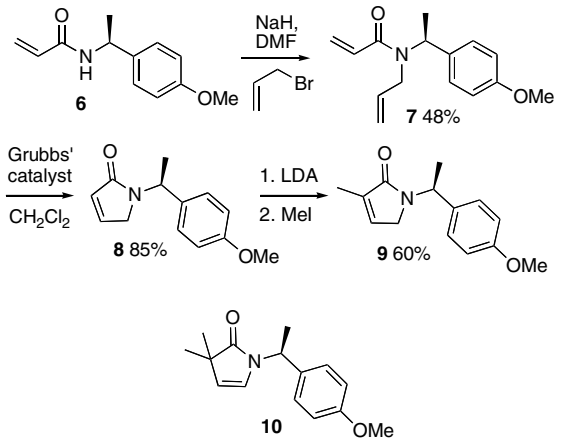
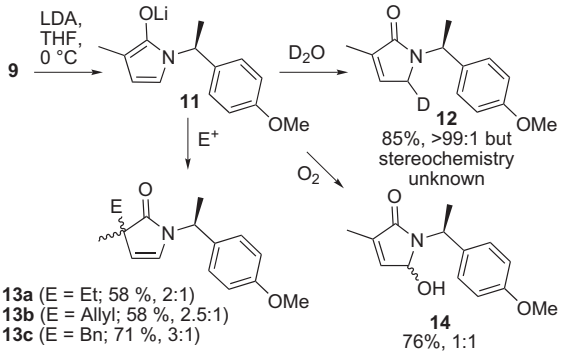


Scheme 2. Synthesis and alkylation of a simple chiral butenolactam.

excess LDA, however, **10** was formed as a by-product. With 3 equiv LDA, **10** was formed in 66% yield.

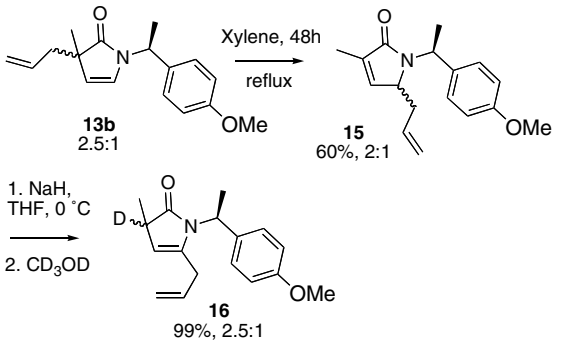
Lactam **9** was converted to the extended lithium enolate (lithioxypyrrole) **11** by thorough degassing and treatment with LDA in THF. Deuteration of the enolate gave, as hoped, a single diastereoisomer (by NMR) of the deuterated lactam **12**,[10] suggesting that diastereoselective protonation may be a general feature of these chiral enolates (Scheme 3). Unless the reaction was degassed, the major product was a mixture of hydroxylated lactams **14**.[11]



Scheme 3. Diastereoselectivity in deuteration, alkylation and oxidation of the chiral lactam **9**.

The diastereoselectivity of this protonation is in accordance with the diastereoselective protonation of enolate **4**, and gave us confidence that it may be possible similarly to reprotonate a range of pyrrol-3-en-2-ones diastereoselectively. However, the synthesis of pyrrol-3-en-2-ones bearing a substituent at the 5-position, required for the diastereoselective formation of a stereogenic centre, turns out to be complicated by the fact that alkylation, unlike deuteration, takes place invariably at the α-position of enolate **11** and its congeners, leading to mixtures of diastereoisomers of lactams **13** (Scheme 3).[12]

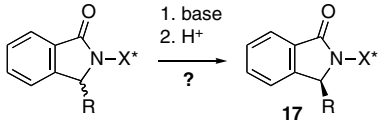
We therefore turned to a [3,3]-sigmatropic rearrangement of **13b** as a means to make 5-substituted lactam



Scheme 4. A 5-substituted pyrrol-3-en-2-one by [3,3]-sigmatropic rearrangement, and its deuteration.

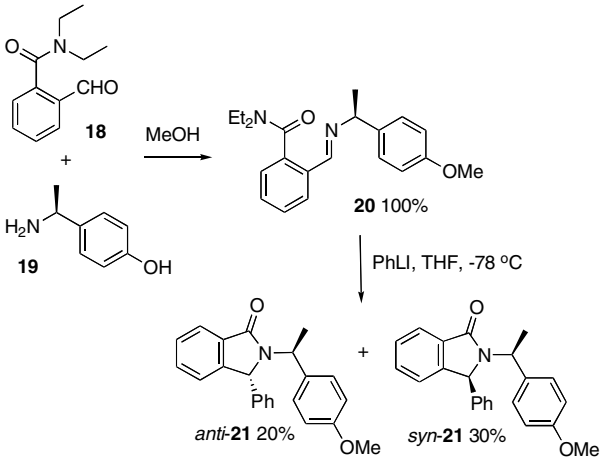
15 (Scheme 4). 5-Allylbutenolactam **15** was successfully formed from **13b** on heating to reflux in xylene for 48 h, but with poor diastereoselectivity, presumably due to stereospecific transformation of the 2.5:1 mixture of α-allylated diastereoisomers. Deprotonation with sodium hydride (deprotonation with LDA failed) gave an enolate, which was however unfortunately deuterated α-, rather than γ-, to the carbonyl group, and with modest diastereoselectivity, to yield **16**. Steric hindrance from the allyl group presumably diverts deuteration to the α-position, in contrast with protonation of **4**, while the increased distance from the stereocontrolling influence of the α-methyl-*p*-methoxybenzyl group results in modest diastereoselectivity.

A further structural modification was therefore made. Chiral 3-substituted dihydroisoindolones are important building blocks for several classes of alkaloid natural products,[13] and can be seen simply as benzo-fused analogues of **8**. Chiral dihydroisoindolones **17** have been made enantioselectively,[14] but we attempted the application of the diastereoselective deuteration reaction to their synthesis by 'de-epimerisation' of an initial mixture of diastereoisomers formed without selectivity, by deprotonation and reprotonation (Scheme 5).



Scheme 5. Proposed 'de-epimerisation' of a dihydroisoindolinone.

Condensation of chiral amine **19** with *N*,*N*-diethyl-2-formylbenzamide **18**[15] gave imine **20**, which on treatment with phenyllithium, afforded the dihydroisoindolones[16] *anti*-**21** and *syn*-**21** in a ratio of 1:1.5 (Scheme 6). The stereochemistry of *syn*-**21** was confirmed by an X-ray crystal structure determination (Fig. 1). However, treatment of either *syn*-**21** or a mixture of *anti*- and *syn*-**21** with NaH followed by aqueous quench returned only the same 1:1.5 mixture of diastereoisomers formed by the addition of PhLi to the imine. Presumably, this ratio represents the diastereoselectivity of reprotonation in this system: further reactions with dihydroisoindolinones were not pursued.



Scheme 6. Formation of a chiral dihydroisoindolinone.

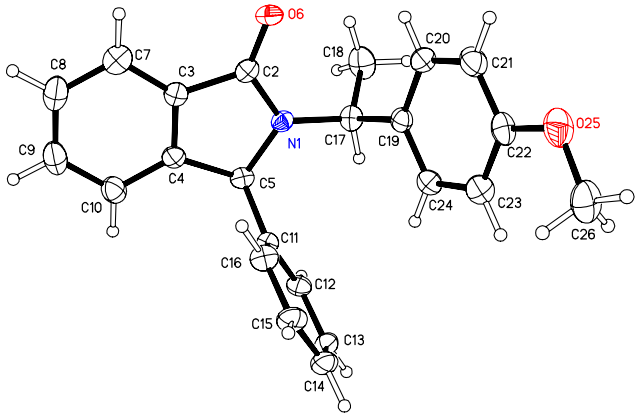


Figure 1. X-ray crystal structure of *syn*-**21**.

3. Conclusion

In conclusion, it is possible to protonate or deuterate pyrrol-3-en-2-ones, such as **3** and **9**, with remarkably high diastereoselectivity. However changing the structure of the pyrrol-3-en-2-ones by the introduction of a 5-substituent or by ring fusion leads to a change in the regioselectivity of protonation and/or loss of diastereoselectivity, preventing the development of a synthetically useful 'de-epimerisation' procedure for such 5-substituted pyrrol-3-en-2-ones.

4. Experimental

Melting points (mp) were measured using a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter using a cell with a path length of 0.25 dm. Concentrations (*c*) are given in grams per 100 mL.

Infra-red spectra were recorded on a Perkin–Elmer 1710 Fourier transform spectrometer (225–4400 cm^{-1}). The samples were prepared as evaporated films on sodium chloride disks. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 Spectrometer operating at ambient probe temperature using an internal deuterium lock (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). Chemical shifts are reported in parts per million (δ) at lower frequencies relative to tetramethylsilane (TMS). They are reported as; position, multiplicity, coupling constant (Hz) and assignment. Standard abbreviations are used throughout (s–singlet, d–doublet, dd–doublet of doublets, t–triplet, q–quartet, m–multiplet and br–broad).

Mass spectra, including chemical ionisation (CI) and electron impact (EI), were recorded on a Micromass VG Trio 2000 quadrupole mass spectrometer. Accurate mass measurements were recorded on a Kratos Concept-1S mass spectrometer and are correct to ±0.001.

The solvents used were either distilled over appropriate drying agents, or of analytical grade. Petrol refers to the fraction of light petroleum ether boiling between 40 and 60 °C. All other commercially available reagents were purified as necessary following standard procedures.

Flash chromatography[17] was performed using Apollo silica gel (40–63 μm). Analytical thin layer chromatography (TLC) was carried out using ALUGRAM® SIL G/UV_{254} plates with visualisation using either UV light or alkaline potassium permanganate.

4.1. Method A: Amide formation

Triethylamine (6.0 mmol, 2.0 equiv), amine (6.1 mmol, 2.2 equiv) and DMAP (0.3 mmol, 0.1 equiv) in CH_2Cl_2 (10 mL) were stirred at 0 °C under a nitrogen atmosphere for 15 min. A solution of the acryloyl chloride (3.0 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C over 10 min and the solution stirred at room temperature for 14 h. HCl (2 M) was added and the layers separated. The organic layer was washed with 2 M HCl and water, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product.

4.2. Method B: Allylation

The amide (1.9 mmol, 1.0 equiv) in DMF (2 mL) was added dropwise to a suspension of sodium hydride (2.9 mmol, 1.5 equiv of a 60% suspension in oil) in DMF (2 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 30 min and a solution of the appropriate allyl bromide (2.4 mmol, 1.2 equiv) in DMF (2 mL) added dropwise at 0 °C. The solution was stirred at room temperature for 1 h and quenched by the addition of water. The mixture was extracted with EtOAc and the combined organic fractions washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product.

4.3. Method C: Deprotonation and enolate quench

n-Butyllithium (0.69 mmol, 1.0 equiv of a 2.4 M solution in hexane) was added dropwise to a solution of diisopropylamine (0.69 mmol, 1.0 equiv) in THF (2.5 mL) at 0 °C under a nitrogen atmosphere. The LDA solution was stirred at 0 °C for 20 min and a solution of the 1,5-dihydropyrrol-2-one (0.69 mmol, 1.0 equiv) in THF (2.5 mL) added dropwise. The solution was degassed and stirred at 0 °C for 3 h and then quenched by the addition of the electrophile (1.4 mmol, 2.0 equiv). The mixture was allowed to warm to room temperature for 30 min and water added. The mixture was extracted with EtOAc and the combined organic layers washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product.

4.4. *N*-[1-(4-Methoxyphenyl)ethyl]acrylamide 6

(*S*)-(−)-1-(4-Methoxyphenyl)ethylamine (10.0 g, 66.2 mmol, 2.2 equiv) was treated according to **Method A** to afford the *title compound* (6.06 g, 98%) as needles: mp 107.5 °C; $[\alpha]_D^{22} = -159.7$ (*c* 0.12, $CHCl_3$); R_f (5:1 petrol–EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 3270 (NH), 2971 (CH), 1657 (C=O); δ_H (300 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.5, Ar*H*), 6.83 (2H, d, *J* 8.5, Ar*H*), 6.24 (1H, dd, *J* 17.5 and 1.5, C*H*$_A$H$_B$CH), 6.10 (2H, m, *J* 10.0, N*H* and CH_2CH), 5.60 (1H, dd, *J* 10.0 and 1.5, CH$_A$*H*$_B$CH), 5.15 (1H, q, *J* 7.0, C*H*CH_3), 3.78 (3H, s, OCH_3), 1.50 (3H, d, *J* 7.0, CHCH_3); δ_C (75 MHz, $CDCl_3$) 164.5, 158.7, 135.2, 130.9, 127.4, 126.4, 113.9, 109.9, 55.3, 48.2, 21.5; *m*/*z* (CI) 206 (100%, M+H$^+$). Found: M$^+$, 205.1104. $C_{12}H_{15}NO_2$ requires 205.1103.

4.5. *N*-Allyl-*N*-[1-(4-methoxyphenyl)ethyl]acrylamide 7

N-[1-(4-Methoxyphenyl)ethyl]acrylamide **6** (0.25 g, 1.22 mmol, 1.0 equiv) was treated according to **Method B**. Purification by flash column chromatography (SiO_2; 15:1 petrol–EtOAc) afforded the *title compound* (0.142 g, 48%) as a clear oil: $[\alpha]_D^{22} = -86.0$ (*c* 0.02, $CHCl_3$); R_f (5:1 petrol–EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 2971 (CH), 1676 (C=O); δ_H (300 MHz, DMSO, 100 °C) 7.22 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, dd, *J* 16.5 and 10.5, C*H*CH_2), 6.18 (1H, dd, *J* 16.5 and 2.5, CHC*H*$_A$H$_B$), 5.60–5.70 (3H, m, C*H*CH_3 and CH_2CHCH_2), 5.0 (2H, m, CHCH$_A$*H*$_B$ and CH_2CHCH_2), 3.75 (3H, s, OCH_3), 3.60–4.0 (2H, m, C*H*$_2$CHCH$_2$), 1.48 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 158.5, 136.1, 133.0, 129.4, 128.6, 128.2, 115.9, 113.7, 55.1, 50.3, 44.8, 38.7, 16.9; *m*/*z* (CI) 246 (100%, M+H$^+$). Found: M$^+$, 245.1420. $C_{15}H_{19}NO_2$ requires 245.1416.

4.6. 1-[1-(4-Methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one 8

Grubbs' catalyst[9] (0.05 g, 0.061 mmol, 0.1 equiv) was added portion wise to a solution of *N*-allyl-*N*-[1-(4-methoxyphenyl)ethyl]acrylamide **7** (0.15 g, 0.61 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at room temperature under a nitrogen atmosphere. The solution was heated under reflux for 12 h and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 1:1 petrol–EtOAc) afforded the *title compound* (0.11 g, 85%) as a yellow oil: $[\alpha]_D^{22} = -122.0$ (*c* 0.15, $CHCl_3$); R_f (5:1 petrol–EtOAc) 0.20; ν_{max} ($CHCl_3$)/cm^{-1} 2934 (CH), 1687 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 7.02 (1H, dd, *J* 6.0 and 1.5, CH_2CHCH), 6.85 (2H, d, *J* 8.5, Ar*H*), 6.18 (1H, dd, *J* 6.0 and 1.5, CH_2CHCH), 5.55 (1H, q, *J* 7.0, C*H*CH_3), 3.80 (3H, s, OCH_3), 3.58–4.0 (2H, dd, *J* 18.5 and 1.5, NCH_2), 1.60 (3H, d, *J* 7.5, CHCH_3); δ_C (75 MHz, $CDCl_3$) 171.2, 159.1, 143.0, 133.3, 128.4, 128.2, 114.2, 55.5, 48.8, 48.6, 18.4; *m*/*z* (CI) 218 (100%, M+H$^+$). Found: M$^+$, 217.1102. $C_{13}H_{15}NO_2$ requires 217.1103.

4.7. 1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 9

1-[1-(4-Methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one **8** (0.15 g, 0.7 mmol, 1.0 equiv) and iodomethane (0.10 mL, 1.4 mmol, 2.0 equiv) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 15:1 petrol–EtOAc) afforded the *title compound* (0.09 g, 60%) as a yellow oil: $[\alpha]_D^{22} = -124.2$ (*c* 0.15, $CHCl_3$); R_f (1:1 petrol–EtOAc) 0.60; ν_{max} ($CHCl_3$)/cm^{-1} 2972 (CH), 1658 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.62 (1H, d, *J* 1.0, NCH_2CH), 5.55 (1H, q, *J* 7.0, C*H*CH_3), 3.82 (3H, s, OCH_3), 3.75 (1H, dd, 18.5 and 1.5, NC*H*$_A$H$_B$CH), 3.45 (1H, dd, *J* 18.5 and 1.5, NCH$_A$*H*$_B$CH), 1.95 (3H, s, CH_3), 1.60 (3H, d, *J* 7.0, CHCH_3); δ_C (75 MHz, $CDCl_3$) 171.8, 159.1, 135.8, 135.4, 133.6, 129.2, 128.4, 114.1, 55.5, 49.1, 46.6, 18.1, 11.6; *m*/*z* (CI) 232 (100%, M+H$^+$). Found: M$^+$, 231.1266. $C_{14}H_{17}NO_2$ requires 231.1259.

4.8. 1-[1-(4-Methoxyphenyl)ethyl]-3,3-dimethyl-1,3-dihydropyrrol-2-one 10

n-Butyllithium (1.04 mL of a 2.0 M solution in hexane, 2.1 mmol, 3.0 equiv) was added dropwise to a solution of diisopropylamine (0.29 mL, 2.1 mmol, 3.0 equiv) in THF (2.5 mL) at 0 °C, under a nitrogen atmosphere. The LDA solution was stirred at 0 °C for 20 min and a solution of 1-[1-(4-methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one **9** (0.15 g, 0.69 mmol, 1.0 equiv) in THF (2.5 mL) added dropwise. The solution was stirred at 0 °C for 3 h and quenched by the addition of iodomethane (0.26 mL, 4.14 mmol, 6.0 equiv). The mixture was warmed to room temperature for 30 min and water (5 mL) added. The mixture was extracted with EtOAc (4 × 5 mL) and the combined organic layers washed with water (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 5:1 petrol–EtOAc) afforded the *title compound* (0.11 g, 66%) as a yellow oil: $[\alpha]_D^{22} = -126.4$ (*c* 0.15, $CHCl_3$); R_f (5:1 petrol–EtOAc) 0.25; ν_{max} ($CHCl_3$)/cm^{-1} 2967 (CH), 1695 (C=O); δ_H (300 MHz, $CDCl_3$) 7.18 (2H, d, *J* 8.5, Ar*H*), 6.85 (2H, d, *J* 8.5, Ar*H*), 6.26 (1H, d, *J* 5.5, NC*H*CH), 5.35 (1H, q, *J* 7.0, C*H*CH_3), 5.30 (1H, d, *J* 5.5, NCHC*H*), 3.80 (3H, s, OCH_3), 1.55 (3H, d, *J* 7.0, CHCH_3), 1.20 (3H, s, CH_3), 1.17 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 182.3, 159.1, 133.3, 129.0, 128.7, 127.9, 126.8, 117.9, 114.2,

55.5, 48.7, 46.9, 26.1, 23.4, 18.9; *m/z* (CI) 246 (100%, M+H$^+$). Found: M$^+$, 245.1412. $C_{15}H_{19}NO_2$ requires 245.1416.

4.9. 1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-5-deutero-1,5-dihydropyrrol-2-one 12

1-[1-(4-Methoxyphenyl)ethyl]- 3-methyl-1,5-dihydropyrrol-2-one **11** (0.15 g, 0.65 mmol, 1.0 equiv) and deuterium oxide (0.5 mL) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 10:1 petrol–EtOAc) afforded the *title compound* (0.11 g, 85%) as a colourless oil: $[\alpha]_D^{22} = -95.1$ (*c* 0.10, $CHCl_3$); R_f (3:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2973 (CH), 1668 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, d, *J* 2.0, NCDC*H*), 5.55 (1H, q, *J* 7.0, C*H*CH$_3$), 3.80 (3H, s, OC*H*$_3$), 3.65 (1H, d, *J* 8.5, NC*D*CH), 1.95 (3H, s, C*H*$_3$), 1.60 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 171.9, 159.2, 136.1, 135.5, 135.4, 133.7, 128.5, 114.2, 55.6, 49.2, 46.2 (t), 18.2, 11.7; *m/z* (CI) 233 (100%, M+H$^+$). Found: M$^+$, 232.1314. $C_{14}H_{16}NO_2D$ requires 232.1317.

4.10. 3-Ethyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 13a

1-[1-(4-Methoxyphenyl)ethyl]- 3-methyl-1,5-dihydropyrrol-2-one **11** (0.10 g, 0.43 mmol, 1.0 equiv) and iodoethane (0.05 mL, 0.52 mmol, 1.2 equiv) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 50:1 petrol–EtOAc) afforded the *title compound* (0.065 g, 58%) as a yellow oil in a 2:1 ratio of diastereoisomers: R_f (5:1 petrol–EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 2935 (CH), 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.92 (2H, d, *J* 8.5, Ar*H*), 6.35 (1H, d, *J* 5.0, NC*H*CH), 5.45 (1H, q, *J* 7.0, C*H*CH$_3$), 5.28 (1H, d, *J* 5.0, NCHC*H*), 3.85 (3H, s, OC*H*$_3$), 1.75 (2H, q, *J* 7.5, C*H*$_2$CH$_3$), 1.62 (3H, d, *J* 7.0, CHC*H*$_3$), 1.25 (3H, s, C*H*$_3$), 0.82 (3H, t, *J* 7.5, CH$_2$C*H*$_3$), 0.75 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 181.9, 159.3, 133.4, 129.2, 128.9, 128.3, 128.2, 127.8, 115.8, 114.6, 114.3, 114.2, 55.6, 51.7, 48.9, 48.8, 31.6, 30.4, 22.6, 22.4, 19.2, 19.1, 9.5, 9.3; *m/z* (CI) 260 (100%, M+H$^+$). Found: M$^+$, 259.1563. $C_{16}H_{21}NO_2$ requires 259.1567.

4.11. 3-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 13b

1-[1-(4-Methoxyphenyl)-ethyl]-3-methyl-1,5-dihydropyrrol-2-one **11** (0.15 g, 0.65 mmol, 1.0 equiv) and allyl bromide (0.08 mL, 0.97 mmol, 1.5 equiv) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 30:1 petrol–EtOAc) afforded the *title compound* (0.065 g, 58%) as a colourless oil in a 2.5:1 ratio: R_f (5:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2968 (CH), 1698 (C=O); δ_H (300 MHz, $CDCl_3$) 7.22 (2H, d, *J* 7.0, Ar*H*), 6.90 (2H, d, *J* 7.0, Ar*H*), 6.30 (1H, d, *J* 4.97, NC*H*CH), 5.65–5.66 (1H, m, CH$_2$C*H*CH$_2$), 5.40 (1H, q, *J* 7.02, C*H*CH$_3$), 5.28 (1H, d, *J* 5.0, NCHC*H*), 5.03–5.05 (2H, m, CH$_2$CHC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 2.35–2.36 (2H, m, C*H*$_2$CHCH$_2$), 1.58 (3H, d, *J* 7.0, CHC*H*$_3$), 1.20 (3H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 181.2, 159.2, 133.7, 133.1, 128.5, 128.4, 127.7, 121.7, 115.4, 55.5, 50.8, 48.7, 41.7, 21.8, 19.1, 18.9; *m/z* (CI) 272 (100%, M+H$^+$). Found: M$^+$, 271.1560. $C_{17}H_{21}NO_2$ requires 271.1572.

4.12. 3-Benzyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 13c

1-[1-(4-Methoxyphenyl)-ethyl]-3-methyl-1,5-dihydropyrrol-2-one **11** (0.10 g, 0.43 mmol, 1.0 equiv) and benzyl bromide (0.06 mL, 0.52 mmol, 1.2 equiv) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 25:1 petrol–EtOAc) afforded the *title compound* (0.098 g, 71%) as a yellow oil in a 3:1 ratio of diastereoisomers: R_f (1:1 petrol–EtOAc) 0.85; ν_{max} ($CHCl_3$)/cm^{-1} 2968 (CH), 1688 (C=O); δ_H (300 MHz, $CDCl_3$) 7.10–7.30 (7H, m, Ar*H*), 6.82 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, d, *J* 5.0, NC*H*CH$_{major}$), 6.55 (1H, d, *J* 5.0, NC*H*CH$_{minor}$), 6.05 (1H, d, *J* 5.0, NCHC*H*$_{major}$) 6.0 (1H, d, *J* 5.0, NCHC*H*$_{minor}$), 5.25 (1H, q, *J* 7.0, C*H*CH$_3$), 3.80 (3H, s, OC*H*$_3$), 3.02 (1H, dd, *J* 13.0 and 3.5, C*H*$_A$H$_B$Ph), 2.78 (1H, d, *J* 13.0 and 4.0, CH$_A$*H*$_B$Ph), 1.25 (3H, s, C*H*$_3$), 1.15 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 181.0, 159.2, 137.4, 133.2, 130.5, 130.4, 128.2, 128.1, 128.0, 127.8, 127.6, 126.8, 115.3, 114.3, 114.1, 55.6, 52.6, 52.5, 48.6, 48.5, 43.9, 43.6, 23.2, 22.3, 19.2, 18.5; *m/z* (CI) 322 (100%, M+H$^+$). Found: M$^+$, 321.1722. $C_{21}H_{23}NO_2$ requires 321.1723.

4.13. 5-Hydroxy-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 14

1-[1-(4-Methoxyphenyl)- ethyl]-3-methyl-1,5-dihydropyrrol-2-one **11** (0.10 g, 0.43 mmol, 1.0 equiv) was treated according to **Method C** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 25:1 petrol–EtOAc) afforded the *title compound* (0.08 g, 76%) as a yellow oil in a 1:1 ratio of diastereoisomers: R_f (1:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3376 (OH), 2935 (CH), 1678 (C=O); δ_H (300 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.5, ArH_A), 7.32 (2H, d, *J* 8.5, ArH_B), 6.90 (2H, d, *J* 8.5, ArH_A), 6.85 (2H, d, *J* 8.5, ArH_B), 6.48 (1H, t, *J* 2.0, C*H*C(H)OH$_A$), 6.40 (1H, t, *J* 2.0, C*H*C(H)OH$_B$), 5.48 (1H, d, *J* 9.0, CHC(*H*)OH$_A$), 5.40 (1H, q, *J* 7.0, C*H*CH$_{3A}$), 5.22 (1H, q, *J* 7.0, C*H*CH$_{3B}$), 5.04 (1H, d, *J* 9.0, CHC(*H*)OH$_B$), 3.78 (6H, s, 2 × OC*H*$_{3A+B}$), 1.88 (6H, s, 2 × C*H*$_{3A+B}$), 1.74 (3H, d, *J* 7.0, CHC*H*$_{3A}$), 1.68 (3H, d, *J* 7.0, CHC*H*$_{3B}$); δ_C (75 MHz, $CDCl_3$) 170.6, 170.5, 159.3, 159.2, 138.5, 138.2, 137.7, 137.2, 134.7, 133.2, 129.2, 128.8, 114.5, 114.2, 81.6, 81.2, 55.7, 50.4, 50.3, 19.3, 18.4, 11.3, 11.2, 0.4; *m/z* (CI) 248 (100%, M+H$^+$). Found: M$^+$, 247.1201. $C_{14}H_{17}NO_3$ requires 247.1203.

4.14. 5-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 15

3-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one **13b** (0.11 g, 0.41 mmol, 1.0 equiv) in

xylene (7 mL) was heated under reflux for 48 h and the mixture concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 25:1 petrol–EtOAc) afforded the *title compound* (0.06 g, 60%) as a colourless oil in a 2:1 mixture of diastereoisomers: $[\alpha]_D^{22} = -113.7$ (*c* 0.15, $CHCl_3$); R_f (10:1 petrol–EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 2924 (CH), 1680 (C=O); δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.55 (1H, t, *J* 2.0, C*H*CHCH$_2$), 5.53–5.55 (1H, m, CH$_2$C*H*CH$_2$), 5.45–5.46 (2H, m, CH$_2$CHC*H*$_2$), 5.06–5.08 (2H, m, C*H*$_2$CHCH$_2$), 5.02 (1H, d, *J* 2.0, CHC*H*CH$_2$), 3.80 (3H, s, OC*H*$_3$), 1.94 (3H, s, C*H*$_3$), 1.70 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 172.6, 159.0, 140.4, 134.9, 132.9, 132.8, 128.6, 118.6, 118.5, 113.9, 59.6, 55.5, 50.7, 36.8, 18.8, 11.5; *m*/*z* (CI) 272 (100%, M+H$^+$). Found: M$^+$, 271.1567. $C_{17}H_{21}NO_2$ requires 271.1572.

4.15. 5-Allyl-5-deutero-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrolo-2-one 16

5-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **15** (0.13 g, 0.48 mmol, 1.0 equiv) in THF (5 mL) was added dropwise to a suspension of sodium hydride (0.04 g, 0.72 mmol, 1.5 equiv) in THF (5 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at 0 °C for 3 h after which CD_3OD (1 mL) was added dropwise. The mixture was allowed to warm to room temperature and then extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 1:1 petrol–EtOAc) afforded the *title compound* (0.13 g, 99%) as a colourless oil in a 2.5:1 ratio of diastereoisomers: R_f (1:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2926 (CH), 1684 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 7.05 (1H, d, *J* 1.5, C*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 5.57–5.59 (1H, m, CH$_2$C*H*CH$_2$), 5.39–5.41 (2H, m, CH$_2$CHC*H*$_2$), 5.09–5.10 (2H, m, C*H*$_2$CHCH$_2$), 4.82 (1H, q, *J* 7.0, C*H*CH$_3$), 3.80 (3H, s, OC*H*$_3$), 1.94 (3H, s, C*H*$_3$), 1.70 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.4, 161.2, 134.8, 132.0, 128.5, 128.1, 115.9, 113.4, 113.1, 105.2, 59.8, 48.5, 39.7, 36.4, 21.3, 19.7; *m*/*z* (CI) 273 (100%, M−H$^+$). Found: M$^+$, 272.1638. $C_{17}H_{20}NO_2D$ requires 272.1635.

4.16. *N*,*N*-Diethyl-2-{[1-(4-methoxyphenyl)ethylimino]-methyl}benzamide 20

A mixture of *N*,*N*-diethyl-2-formylbenzamide **18** (0.50 g, 2.4 mmol, 1.0 equiv) and (*S*)-1-(4-methoxyphenyl)ethylamine (0.36 g, 2.4 mmol, 1.0 equiv) in methanol (15 mL) was stirred at room temperature, under a nitrogen atmosphere, over 4 Å sieves for 12 h. The sieves were removed by filtration and washed with EtOAc (10 mL). Combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford the *title compound* (0.83 g, 100%) as a clear oil: $[\alpha]_D^{22} = +236.0$ (*c* 0.12, $CHCl_3$); R_f (1:1 petrol–EtOAc) 0.55; ν_{max} ($CHCl_3$)/cm^{-1} 2971 (CH), 1667 (C=O), 1632 (C=N); δ_H (300 MHz, $CDCl_3$) 8.40 (1H, s, *H*C=N), 8.05–8.06 (1H, m, Ar*H*), 7.26–7.42 (5H, m, Ar*H*), 6.88 (2H, d, *J* 6.5, Ar*H*), 4.49 (1H, q, *J* 6.5, C*H*CH$_3$), 3.82 (3H, s, OC*H*$_3$), 3.60 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 3.08 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 1.56 (3H, d, *J* 6.5, CHC*H*$_3$), 1.26 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 0.98 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.0, 158.7, 156.8, 138.1, 137.2, 132.8, 130.5, 129.0, 127.9, 126.9, 126.3, 114.0, 69.4, 55.5, 43.3, 39.3, 24.8, 14.1, 13.2; *m*/*z* (CI) 339 (100%, M+H$^+$). Found: M$^+$, 338.1994. $C_{21}H_{26}N_2O_2$ requires 338.1994.

4.17. 2-[1-(4-Methoxyphenyl)ethyl]-3-phenyl-2,3-dihydroisoindol-1-one *syn*-21

Phenyllithium (0.82 mL of a 2.0 M solution in dibutyl ether, 1.62 mmol, 1.2 equiv) was added dropwise to a solution of *N*,*N*-diethyl-2-{[1-(4-methoxyphenyl)ethylimino]methyl}benzamide **20** (0.46 g, 1.35 mmol, 1.0 equiv) in THF (15 mL) at −78 °C under a nitrogen atmosphere. The solution was stirred at −78 °C for 3 h, quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature over 12 h. Water (5 mL) was added and the mixture extracted with EtOAc (4 × 10 mL). Combined organics were washed with water (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 50:1 petrol–EtOAc) afforded the *title compound* (0.080 g, 30%) as a yellow oil: $[\alpha]_D^{22} = -193.3$ (*c* 0.10, $CHCl_3$); R_f (10:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2924 (CH), 1687 (C=O); δ_H (300 MHz, $CDCl_3$) 7.88 (1H, dd, *J* 5.5 and 2.5, Ar*H*), 7.40–7.45 (2H, m, Ar*H*), 7.18–7.22 (5H, m, Ar*H*), 7.04 (1H, d, *J* 6.0, Ar*H*), 6.98 (2H, d, *J* 6.0, Ar*H*), 6.68 (2H, d, *J* 8.5, Ar*H*), 5.45 (1H, s, C*H*Ph), 5.05 (1H, q, *J* 7.5, C*H*CH$_3$), 3.72 (3H, s, OC*H*$_3$), 1.85 (3H, d, *J* 7.5, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.5, 158.9, 146.9, 138.0, 134.3, 132.5, 132.1, 129.1, 128.9, 128.6, 128.1, 123.8, 123.3, 113.9, 65.1, 55.6, 52.7, 30.1, 19.0, 0.4; *m*/*z* (CI) 344 (100%, M+H$^+$). Found: M$^+$, 343.1567. $C_{23}H_{21}NO_2$ requires 343.1572.

Also obtained was 2-[1-(4-methoxyphenyl)ethyl]-3-phenyl-2,3-dihydroisoindol-1-one *anti*-**21** (0.070 g, 20%) as a yellow oil: $[\alpha]_D^{22} = +171.9$ (*c* 0.08, $CHCl_3$); R_f (10:1 petrol–EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2932 (CH), 1686 (C=O); δ_H (300 MHz, $CDCl_3$) 7.90 (1H, dd, *J* 6.5 and 1.5, Ar*H*), 7.38–7.44 (3H, m, Ar*H*), 7.28–7.30 (2H, m, Ar*H*), 7.12 (2H, d, *J* 8.5, Ar*H*), 7.0 (2H, dd, *J* 7.5 and 1.5, Ar*H*), 6.95 (1H, d, *J* 7.5, Ar*H*), 6.85 (2H, d, *J* 8.5, ArH), 5.75 (1H, q, *J* 7.5, C*H*CH$_3$), 5.05 (1H, s, C*H*Ph), 3.85 (3H, s, OC*H*$_3$), 1.20 (3H, d, *J* 7.5, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 168.2, 158.2, 146.4, 138.1, 131.7, 131.0, 129.5, 128.2, 127.9, 127.7, 127.4, 127.3, 122.8, 122.2, 112.9, 62.4, 54.5, 49.6, 17.3, 0.5; *m*/*z* (CI) 344 (100%, M+H$^+$). Found: M$^+$, 343.1566. $C_{23}H_{21}NO_2$ requires 343.1572.

The data for the X-ray crystal structure of *syn*-**21** have been deposited with the Cambridge X-ray crystallographic database, deposition number CCDC 268131.

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