Asymmetric induction α to nitrogen in pyrrolidines and piperidines *via* radical chemistry

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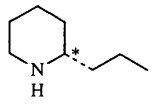
Attempts to control the stereochemistry of radical reactions at the 2-position of pyrrolidines and piperidines carrying chiral auxiliaries on the nitrogen are presented.

Introduction

The synthesis of natural products such as the alkaloids poses many problems, one of which is the control of stereochemistry to give the natural stereoisomer. A variety of stereogenic centres is found in alkaloids but a particularly common structural feature is the presence of a chiral centre adjacent to nitrogen in a ring. From simple alkaloids such as coniine **1**[1] with one chiral



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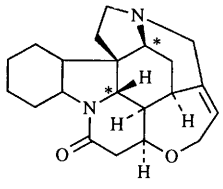

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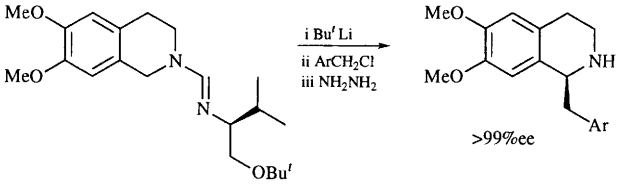
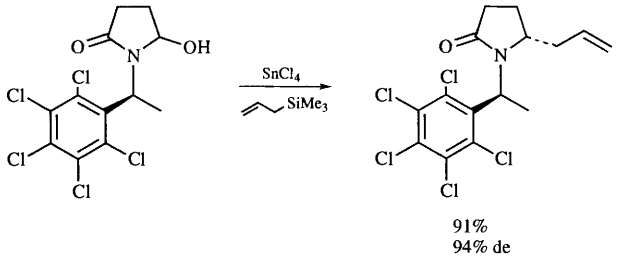
centre adjacent to nitrogen in a piperidine ring to complex alkaloids such as strychnine **2**[2] with a number of such centres embedded in their skeleton, it is vital that the synthetic chemist addresses the problem of stereocontrol at these centres. Groups that have tackled this challenge have adopted anion methodology such as Meyers (Scheme 1)[3] or cation methodology such as Polniaszek (Scheme 2).[4]



Scheme 1

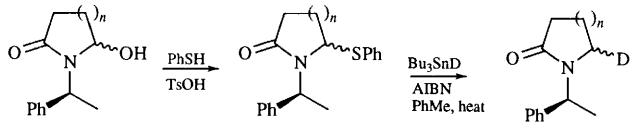


Scheme 2

In the last ten years radical reactions have come to the fore in organic synthesis,[5] achieving transformations which are impossible *via* traditional methods. Recently, radical reactions have been accomplished with a high degree of diastereoselectivity,[6] using a chiral auxiliary to control stereochemistry, and two reports have shown a radical reaction proceeding with a high degree of diastereoselectivity α to nitrogen.[7] We now report our approach to this problem using radical chemistry and employing a chiral auxiliary on the nitrogen atom in a similar manner to Meyers and Polniaszek. At the outset of this work, we anticipated that the use of a different reaction manifold would complement their work.

Discussion

Initially the *N*-(α-methylbenzyl) chiral auxiliary used by Polniaszek was investigated. The 5- and 6-membered ring hydroxy lactams **3a,b**[4] were converted into their phenylsulfanyl-derivatives **4a,b** by reaction with thiophenol and catalytic toluene-*p*-sulfonic acid. Although the phenylsulfanyl group is a relatively poor radical precursor, Hart[8] has shown the utility of this group in similar systems as the carbon radical produced is stabilised by the adjacent nitrogen atom. The first radical reaction attempted on **4a,b** involved reaction with Bu_3SnD and azoisobutyronitrile (AIBN) in toluene heated at 80 °C (Scheme 3).



3a *n* = 1
b *n* = 2

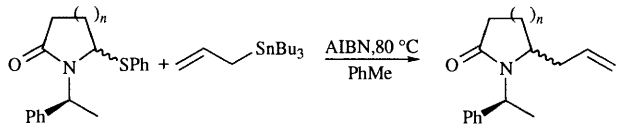
4a *n* = 1 92%
b *n* = 2 41%

5a *n* = 1 53% de = 36%
b *n* = 2 100% de = 40%

Scheme 3

The stereochemical outcome in each case was assessed by ^1H and ^2H NMR studies. Although the yields of the deuterio-compounds **5a,b** were reasonable (53 and 100%, respectively), the diastereoselectivities were poor (36 and 40%, respectively). The results are disappointing in the light of Hamon's deuteriation of glycine carrying a chiral group.[9] In order to confirm the diastereoselectivity in the case of the piperidine system, the reaction sequence was reversed starting with reduction of the glutarimide with lithium triethylborodeuteride and ending with reaction using tributyltin hydride–AIBN. As expected, this gave a 7:3 mixture of diastereoisomers, favouring the diastereoisomer which had been the minor product in the reaction of **4b** with tributyltin deuteride. Another factor which has been shown to affect stereoselectivity is the reaction temperature.[10] The reaction of **4b** with tributyltin deuteride using triethylborane–oxygen as the initiator[11] was investigated and found to be extremely slow at −20 °C. At 20 °C the reaction proceeded at a reasonable rate and gave **5b** in 85% yield but with no increase in the diastereoselectivity.

In terms of alkaloid synthesis, we were more interested in C–C bond forming reactions and to this end, we reacted phenylsulfanyllactams **4a,b** with allyltributylstannane and



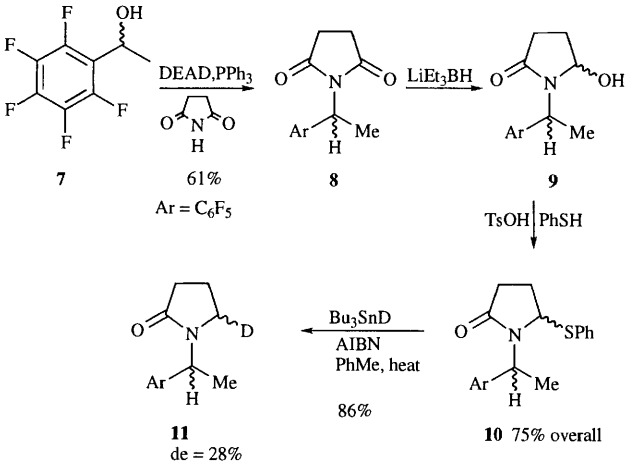
4a $n = 1$
b $n = 2$

6a $n = 1$ 8% de = 6%
b $n = 2$ 38% de = 8%

Scheme 4

AIBN. We were surprised to find that not only were the yields of allylated products poor but the diastereoselectivities as judged by NMR were very small indeed (Scheme 4). Further investigation of these reactions showed firstly that AIBN is required in order to observe allylation, confirming the radical nature of the reaction, and secondly a major by-product is elimination of thiophenol to generate the cyclic enamide. This reaction pathway is particularly prominent for the pyrrolidinone system and presumably arises *via* a Lewis acid-assisted elimination involving a tin species as the Lewis acid. Such acid and radical pathways involving neutral tin species have been reported previously.[12]

Polniaszek suggested that the diastereoselectivities observed in his acyliminium ion chemistry arose from an electronic effect favouring a particular conformation. By adding electron withdrawing groups to the phenyl ring, Polniaszek argued that there is a greater interaction between the σ* orbital of the benzylic bond and the π* orbital of the acyliminium ion, leading to a preference for one conformation over another and so greater diastereoselectivity.[4] Experimentally, this was supported by changing to the pentachlorophenethyl chiral auxiliary which led to a diasteroisomeric excess of 94% favouring the other isomer.[4] We decided to explore whether this electronic effect operates in the radical reaction manifold by introducing electron-withdrawing groups on the aromatic ring. Given the weakness of the C–Cl bond under radical conditions, we settled on the pentafluorophenyl group to explore any possible electronic effect. A Mitsunobu reaction[13] on pentafluorophenethyl alcohol **7** using succinimide gave the *N*-substituted succinimide **8** in 61% yield (Scheme 5). Reduction of



7 **8** **9**

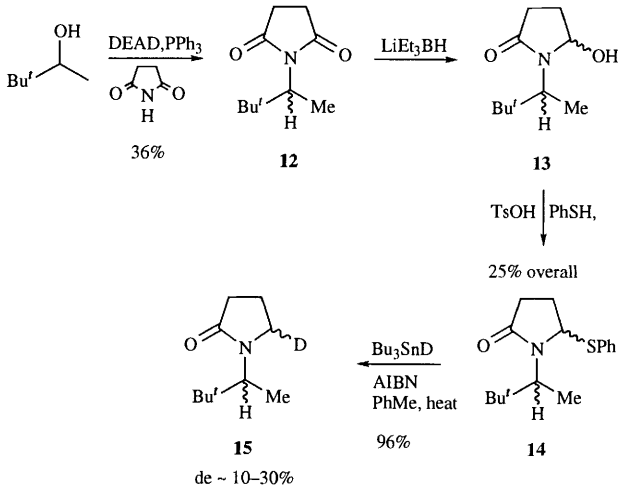
11 de = 28%

10 75% overall

Scheme 5

one of the carbonyl groups to a hydroxy group **9** and reaction as above with thiophenol and toluene-*p*-sulfonic acid gave radical precursor **10** in 75% overall yield. Although this reaction sequence was carried out starting with the racemic alcohol, it was felt that the well known stereospecificity of the Mitsunobu reaction would allow access to the optically pure series if the optically pure alcohol was available. Reaction of **10** with Bu_3SnD and AIBN in toluene as before yielded the deuterio-derivative **11** in good yield (86%) but with slightly lower diastereoselectivity (28%) than for **4a**. We conclude that any electronic effect observed in the cationic reaction manifold is not found in the radical manifold. One clear difference between the two reaction pathways is the absence of a good Lewis acid in the radical series. Thus the possibility of chelation between the Lewis acid and the aromatic ring substituted with atoms carrying lone pairs acting in a manner so as to fix the conformation is not possible.

Failure to change the diastereoselectivity of the reaction by changing the electronic nature of the chiral auxiliary led us to explore the possibility of a simple steric effect on the stereochemical course of the reaction. To this end, we decided to replace the benzene ring in our chiral auxiliary with a *tert*-butyl group. Based on the relative *A*-values, the *tert*-butyl group is considerably larger than the phenyl group.[14] The synthesis of radical precursor **14** follows that of **10** and is summarised in Scheme 6. Reaction of **14** with Bu_3SnD and



12 **13**

15 **14**

Scheme 6

AIBN in toluene at 80 °C yielded the deuterio-derivative **15** in good yield (96%) but, again. with relatively poor diastereoselectivity. In this case, it was difficult to ascertain the diastereoisomeric excess by NMR owing to overlapping signals and in spite of trying a number of approaches to obtain a more accurate figure, we feel it is only possible to record an upper (30%) and a lower (10%) limit to the diastereoselectivity.

In conclusion, a range of chiral auxiliaries has been tried in order to control the stereochemical outcome of the reaction. However, although the chiral auxiliaries differed in their electronic and steric properties, little change was noticed in the diastereoselectivities of the radical reactions α to nitrogen. The main problem with controlling the diastereoselectivity of radical reactions is the nature of the transition states involved. Owing to the inherently high reactivity of radicals, the transition state tends to be early when the radical and reactant are at some considerable distance. This means that steric effects are a relatively weak influence on the stereochemical outcome of the reaction. Further work in this area will probably concentrate on captodative radicals[15] which, being more stable, involve reactions through later transition states. In this context, it is instructive to note that the example of Hamon potentially involves just such a radical intermediate.[9] The use of chiral auxiliaries with the ability to coordinate to Lewis acids is an intriguing possibility.[16]

Experimental

General

All reactions were carried out under argon and solutions dried with magnesium sulfate. Petrol refers to light petroleum (bp 40–60 °C), which was redistilled prior to use. Column chromatography was performed with silica gel (Merck 7734) using the flash chromatography technique. Thin layer chromatographic analysis was performed using plastic-backed silica plates

(Merck 5735). Components were visualised by either UV or phosphomolybdic acid dip. Melting points were recorded on a Gallenkamp heating block and are uncorrected. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl immediately before use. Infrared spectra were recorded on a Perkin-Elmer 983G spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AM360 spectrometer operating at 360 MHz for proton and 90 MHz for carbon. Tetramethylsilane was adopted as the internal standard for ^{1}H NMR spectra, and the solvent peaks for ^{13}C NMR spectra. Chemical shifts (δ_H and δ_C) are quoted as downfield from tetramethylsilane. *J* Values are given in Hz. High resolution mass spectra were performed at the Chemistry Department, King's College, London University. Elemental analyses of compounds were carried out at the Chemistry Department, University College, London University.

N-[(*S*)-1′-Phenylethyl]-5-phenylsulfanylpyrrolidin-2-one 4a

N-[(*S*)-1′-Phenylethyl-5-hydroxypyrrolidin-2-one[4] (567 mg, 2.77 mmol) was dissolved in thiophenol (10 cm^3) and toluene-*p*-sulfonic acid (20 mg, 0.11 mmol) was added. After stirring for 3 h at room temperature, the reaction was diluted with dichloromethane (30 cm^3) and washed with NaOH solution (2 mol dm^{-3}; 3 × 50 cm^3) and water (50 cm^3). The organic layer was then dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–petrol, 1:1) to yield *pyrrolidinone* **4a** (754 mg, 92%) as a viscous clear oil as a 1:1 mixture of diastereoisomers; R_f 0.5 (ethyl acetate–petrol, 1:1) (Found: [M + H]$^+$, 298.1269. $C_{18}H_{19}NOS$ requires *M* + *H* 298.1266); ν_{max}(neat)/cm^{-1} 1695 (OC–N); δ_H($CDCl_3$) 1.83 (1.5 H, d, *J* 7.1, CH_3), 1.84 (1.5 H, d, *J* 7.2, CH_3), 2.03–2.39 [4 H, m, C(3 + 4)H_2], 4.48 [0.6 H, dd. *J* 6.4, 1.6, C(5)H], 4.91 [0.4 H, dd, *J* 7.4, 1.6, C(5)H], 5.10 (0.4 H, q, *J* 7.3, PhCH), 5.44 (0.6 H. q, *J* 7.2, PhCH) and 7.23–7.47 (10 H, m, PhH); δ_C($CDCl_3$) 17.79, 18.08 (CH_3), 27.60, 28.18, 29.30, 29.96 [C(3 + 4)], 51.39, 52.97 [C(1′)], 66.09, 67.91 [C(5)], 127.40–129.07 (PhC), 133.63, 134.10 (SPhC), 139.12 (PhC), 141.23 (SPhC), 174.56 and 174.91 [C(2)]; *m*/*z* [EI] 298.1 [(M + H)$^+$, 0.4%], 188.1 [(M − SPh)$^+$, 55.7] and 105.1 [(PhCHCH$_3$)$^+$, 100.0].

N-[(*S*)-1′-Phenylethyl][5-^{2}H$_1$]pyrrolidin-2-one 5a

Tributyltin deuteride (922 mg, 3.17 mmol) was added to a solution of *N*-[(*S*)-1′-phenylethyl]-5-phenylsulfanylpyrrolidin-2-one **4a** (472 mg, 1.52 mmol) in toluene (1 cm^3) and heated to 80 °C. AIBN was added (37 mg, 0.23 mmol) and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling the crude product was purified by column chromatography (ethyl acetate–petrol, 1:1) to yield the *pyrrolidinone* **5a** (160 mg, 53%) as a clear oil; R_f 0.18 (ethyl acetate–petrol, 1:1) (Found: M$^+$, 190.1215. $C_{12}H_{14}DNO$ requires *M*, 190.1216); ν_{max}(neat)/cm^{-1} 1675 (OC–N); δ_H($CDCl_3$) 1.51 (3 H, d, *J* 7.1, CH_3), 1.79–1.99 and 2.33–2.48 [4 H, m, C(3 + 4)H_2], 2.96 [0.66 H, dd, *J* 8.4 and 5.4, C(5)H], 3.30 [0.33 H, dd, *J* 7.7 and 6.7 Hz, C(5)H), 5.49 (1 H, q, *J* 7.1, PhCH) and 7.23–7.36 (5 H, m, PhH); δ_C($CDCl_3$) 15.88 (CH_3), 17.40, 31.06 [C(3 + 4)], 41.63 [t, J_{C-D} 21.7, C(5)], 48.58 [C(1′)], 126.67, 127.07, 128.16, 139.89, (PhC) and 174.14 [C(2)]; *m*/*z* 190.1 [M$^+$, 100%], 175.1 [(M − CH_3)$^+$, 59.4] and 105.1 [(PhCHCH$_3$)$^+$, 27.3].

N-[(*S*)-1′-Phenylethyl]-5-prop-2″-enylpyrrolidin-2-one 6a

Allyltributyltin (1.166 g, 3.53 mmol) was added to a solution of *N*-[(*S*)-1′-phenylethyl]-5-phenylsulfanylpyrrolidin-2-one **4a** (351 mg, 1.13 mmol) in toluene (1 cm^3) and heated to 80 °C. AIBN was added (28 mg, 0.17 mmol) and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling, the crude product was purifid by column chromatography (ethyl acetate–petrol, 1:1) to yield the piperidinone **6a** (21 mg, 8%) as a clear oil (Found: M$^+$, 229.1485. $C_{15}H_{19}NO$ requires *M*, 229.1467); ν_{max}(neat)/cm^{-1} 1680 (OC–N); δ_H($CDCl_3$) 1.64 ($\frac{3}{2}$ H, d *J* 7.3, CH_3), 1.65 ($\frac{3}{2}$ H, d, *J* 7.3, CH_3), 1.67–2.53 [6 H, m, C(3 + 4 + 1″)H_2], 3.27–3.34 [0.4 H, m, C(5)H], 3.73–3.79 [0.6 H, m, C(5)H], 4.85–5.07 [2 H, m, C(3″)H_2], 5.38–5.65 [2 H, m, C(2″ + 1′)H] and 7.23–7.40 (5 H, m, PhH); δ_C($CDCl_3$) 16.19, 18.28 (CH_3), 23.65, 23.89, 30.21, 30.25 [C(3 + 4)], 38.73. 39.55 [C(1″)], 49.39, 50.56 [C(1′)], 56.16, 56.44 [C(5)], 118.11, 118.41 [C(3″)], 126.92, 127.12, 127.30, 127.42, 127.48, 127.51, 128.32, 128.49 (PhC), 133.15, 133.28 [C(2″)], 139.59, 141.79 (PhC) and 175.34 [C(2)]; *m*/*z* 229.1 [M$^+$, 0.1%], 188.1 [M$^+$ − CH_2-CH=CH_2, 34] and 105.1 [PhCHCH$_3$$^+$, 100].

N-[(*S*)-1′-Phenylethyl]-6-phenylsulfanyl-2-piperidone 4b

N-[(*S*)-1′-Phenylethyl]-6-hydroxy-2-piperidone[4] (577 mg, 2.63 mmol) was dissolved in thiophenol (10 cm^3) and toluene-*p*-sulfonic acid (20 mg, 0.11 mmol) was added. After stirring for 3 h at room temperature, the reaction was diluted with CH_2Cl_2 (30 cm^3) and washed with NaOH (2 mol dm^{-3}; 3 × 50 cm^3) and water (50 cm^3). The organic layer was then dried and the solvent removed. The crude product was purified by column chromatography (ethyl acetate–petrol, 3:7) to yield the *piperidinone* **4b** (337 mg, 41%) as a viscous clear oil and 3:2 mixture of diastereoisomers; R_f 0.5 (ethyl acetate–petrol, 1:1) (Found: M$^+$, 311.1349. $C_{19}H_{21}NOS$ requires *M*, 311.1344); ν_{max}(neat)/cm^{-1} 1647 (O=C–N); δ_H($CDCl_3$) 1.52–1.60 [1 H, m, C(5)H_2], 1.77 (1.5 H, d, *J* 7.1, CH_3), 1.78 (1.5 H, d, *J* 7.2, CH_3), 1.82–2.03 [1 H, m, C(5)H_2], 2.33–2.68 [4 H, m, C(3 + 4)H_2], 4.47 [0.5 H, t, *J* 3.5, C(6)H], 4.85 [0.5 H, t, *J* 3.5, C(6)H], 5.24 (0.5 H, q, *J* 7.0, PhCH), 5.92 (0.5 H, q, *J* 7.1, PhCH) and 7.20–7.41 (10 H, m, PhH + SPh); *m*/*z* [EI] 312 [M$^+$ + H, 19.5%], 311 [M$^+$, 1.0] and 202 [M$^+$ − SPh, 100].

N-[(*S*)-1′-Phenylethyl][6-^{2}H$_1$]-2-piperidone 5b

A solution of *N*-[(*S*)-1′-phenylethyl]-6-phenylsulfanyl-2-piperidone **4b** (160 mg, 0.51 mmol) in toluene (1 cm^3) was heated to 80 °C whilst tributyltin deuteride (300 mg, 1.03 mmol) and AIBN (13 mg, 0.08 mmol) was added and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling, toluene was removed under reduced pressure and the residue taken up in dichloromethane (30 cm^3) which was then washed with 20% aq. ammonia (5 × 30 cm^3) and water (30 cm^3), dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–petrol, 1:1) to yield the *piperidinone* **5b** (105 mg, 100%) as a white crystalline solid, mp 65 °C; R_f 0.15 (ethyl acetate–petrol, 1:1) (Found: C, 76.0; H, 8.3; N, 6.6. $C_{13}H_{16}DNO$ requires C, 76.4; H, 8.39; N, 6.86%) (Found: M$^+$, 204.1409. $C_{13}H_{16}DNO$ requires *M*, 204.1388); ν_{max}(Nujol)/cm^{-1} 1630 (OC–N); δ_H($CDCl_3$) 1.50 (3 H, d, *J* 7.1, CH_3), 1.53–1.78 [4 H, m, C(4 + 5)H_2], 2.47 [2 H, t, *J* 6.7, C(3)H_2], 2.76, [0.75 H, t, *J* 4.8, C(6)H], 3.06–3.13 [0.25 H, m, C(6)H], 6.15 (1 H, q, *J* 7.1, PhCH_3) and 7.23–7.35 (5 H, m, PhH); δ_C($CDCl_3$) 15.21 (CH_3), 20.99 [C(5)], 22.93 [C(4)], 32.38 [C(3)], 40.98 [t, J_{H-D} 21.1, C(6)], 49.47 (Ph–C), 127.04. 127.20. 128.25 (Ph–H), 140.36 (Ph–C) and 169.45 [C(2)]; *m*/*z* 204.1 [M$^+$, 100%], 189.1 [M$^+$ − CH_3, 46.8] and 113.0 [M$^+$PhCHCH$_3$, 44.6].

N-[(*S*)-1′-Phenylethyl]-6-prop-2″-enyl-2-piperidone 6b

Allyltributyltin (980 mg, 2.97 mmol) was added to a solution of *N*-[(*S*)-1′-phenylethyl]-6-phenylsulfanyl-2-piperidone **4b** (230 mg, 0.74 mmol) in toluene (1 cm^3) and heated to 80 °C. AIBN was added (18 mg, 0.11 mmol) and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling, toluene was removed under reduced pressure and the residue taken up in dichloromethane (30 cm^3) which was then washed with 20% aq. ammonia (5 × 30 cm^3) and water (30 cm^3), dried and evaporated to dryness. The crude product was purified by column chromatography (ethyl acetate–petrol, 2:3) to yield the *piperidinone* **6b** (69 mg, 38%) as a clear oil; R_f 0.26 (ethyl acetate–petrol, 1:1) (Found: M$^+$, 243.1626. $C_{16}H_{21}NO$ requires *M*, 243.1623); ν_{max}(neat)/cm^{-1} 1630 (OC–N); δ_H($CDCl_3$) 1.46–1.98

[7 H, m, C(4 + 5)H_2 + C(2′)H_3], 2.27–2.52 [4 H, m, C(3)H_2 + C(1″)H_2], 3.13–3.17 [0.5 H, m, C(6)H], 3.45–3.48 [0.5, m, C(6)H], 4.69–5.07 [2 H, m, C(3″)H_2], 5.34–5.46 [0.5 H, m, C(2″)H], 5.51–5.63 [0.5 H, m, C(2″)H], 5.81 [0.5 H, q, *J* 7.1, C(1′)H], 5.94 [0.5 H, q, *J* 7.1, C(1′)H] and 7.24–7.40 (5 H, m, PhH); δ_C($CDCl_3$) 16.22, 17.47 [C(2′)], 25.29, 25.61 [C(5)], 30.92, 31.02 [C(4)], 37.30, 38.52 [C(1″)] 51.95, 52.00, 52.19, 52.83 [C(6) + C(1′)], 117.33, 117.51 [C(3″)], 127.23, 127.35, 127.39, 127.81, 128.32 [PhC–H], 134.20, 134.32 [C(2″)], 140.50, 140.82 (PhC–C), 169.94 and 170.32 [C(2)]; *m*/*z* 243.1 [M^+, 4.4%], 202.1 [(M − allyl)$^+$, 47.9] and 98.1, [(M − $PhCHCH_3$ − allyl − H)$^+$, 100].

N-[(±)-1′-(2″,3″,4″,5″,6″-Pentafluorophenyl)ethyl]succinimide 8

A solution of triphenylphosphine (4.452 g, 16.97 mmol) in THF (60 cm^3) was added to a 38% solution of diethyl azodicarboxylate in toluene (6.93 cm^3, 16.91 mmol) under argon and with stirring at −5 °C. The reaction mixture was then cooled to −10 °C, succinimide (1.752 g, 17.68 mmol) was added and the reaction mixture stirred for 5 min at 0 °C. 1-(Pentafluorophenyl)ethanol **7** (3.000 g, 14.14 mmol) was then added dropwise at 0 °C and the reaction mixture was stirred for 60 h at room temperature, during which time the solution turned red. The reaction mixture was then quenched with brine (100 cm^3) and the two layers separated, the aqueous layer being further extracted with dichloromethane. The combined organic layers were dried and solvent was removed. The crude product was first recrystallised from dichloromethane–petrol and the mother liquor purified by column chromatography (ethyl acetate–petrol, 1 : 1) followed by further recrystallisation from petrol to yield the *succinimide* **8** (2.712 g, 66%) as a white crystalline solid, mp 72–75 °C; R_f 0.5 (ethyl acetate–petrol, 1 : 1) (Found: M^+, 293.0478. $C_{12}H_8F_5NO_2$ requires *M*, 293.0475) (Found: C, 49.0; H, 2.6; N, 5.0%. $C_{12}H_8F_5NO_2$ requires C, 49.16; H, 2.75; N, 4.78%); ν_{max}(Nujol)/cm^{-1} 1779 and 1706 (O=C–N–C=O); δ_H($CDCl_3$) 1.82 (3 H, dt, *J* 7.4 and 2.2, CH_3), 2.73 [4 H, s, C(3 + 4)H_2] and 5.64 (1 H, q, *J* 7.3, PhCH); δ_C($CDCl_3$) 16.58 (CH_3), 27.81 [C(3 + 4)], 42.23 (PhCH), 111.9 (t, J_{C-F} 14, *ipso*-phenyl C), 137.25 (ddt, J_{C-F} 260, 20 and 16, *ortho*-phenyl C), 140.6 (d,† J_{C-F} 252, *para*-phenyl C), 145.8 (dtd, J_{C-F} 260, 10 and 5, *meta*-phenyl C) and 175.75 [C(2 + 5)]; *m*/*z* [EI] 293.0 M^+, 100.0%], 273.0, [M^+ − HF, 13.8], 222.0 [$ArCHNCO^+$, 27.0] and 196.0 [$ArCH_2CH_3^+$, 20.2].

N-[(*S*)-1′-(2″,3″,4″,5″,6″-Pentafluorophenyl)ethyl]-5-hydroxypyrrolidin-2-one 9

A solution of lithium triethylborohydride in THF (1 mol dm^{-3}; 1.06 cm^3, 1.06 mmol) was added dropwise to a solution of *N*-[(*S*)-1′-(2″,3″,4″,5″,6″-pentafluorophenyl)ethyl]succinimide **8** (208 mg, 0.71 mmol) in THF (15 cm^3) under argon with stirring at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched with $NaHCO_3$ (5 cm^3), and 30% hydrogen peroxide in water (1 cm^3) was added at 0 °C and the mixture stirred for 20 min. Solvent was removed under reduced pressure and the aqueous residue extracted with dichloromethane (2 × 30 cm^3). The combined organic layers were dried and the solvent was removed. The crude product was purified by column chromatography (ethyl acetate) to yield the *pyrrolidinone* **9** (137 mg, 66%) as a white solid, mp 90–95 °C; R_f 0.38 (ethyl acetate) (Found: M^+, 295.0633. $C_{12}H_{10}F_5NO_2$ requires *M*, 295.0632); ν_{max}(CH_2Cl_2)/cm^{-1} 3242, (O–H) and 1698 (OC–N); δ_H($CDCl_3$) 1.77 (3 H, d, *J* 7.3 , CH_3), 1.90–2.76 (4 H, m, 2 CH_2), 4.97–5.16 (1 H, m, OH) and 5.40–5.52 [2 H, m, ArCH + C(6)H]; δ_C($CDCl_3$) 16.95 (CH_3), 28.15, 28.37, 28.69, 29.07 [C(3 + 4) of both diastereoisomers], 42.28, 43.02 (ArCH), 81.96, 82.41 [C(5)], 113† (*ipso*-phenyl), 115.80 (t, J_{C-F} 13.3, *ipso*-phenyl), 130 (d,† J_{C-F} 280, aromatic-C), 137.2 (d,† J_{C-F} 240, aromatic-C), 142.2 (d,† J_{C-F} 250, aromatic-C), 144.8 (d,† J_{C-F} 250, aromatic-C), 174.71 and 175.98 [C(2)]; *m*/*z* [EI] 295.1 [M^+, 100.0%], 277.1 [M^+ − H_2O, 16.4] and 234.0 [(M − CO − H_2O − CH_3)$^+$, 20.1].

N-[(±)-1′-(2″,3″,4″,5″,6″-Pentafluorophenyl)ethyl]-5-phenylsulfanylpyrrolidin-2-one 10

N-[(*S*)-1′-(2″,3″,4″,5″,6″-Pentafluorophenyl)ethyl]-5-hydroxypyrrolidin-2-one **9** (450) mg, 1.53 mmol) was dissolved in thiophenol (10 cm^3) and toluene-*p*-sulfonic acid (20 mg, 0.11 mmol) was added. After stirring for 3 h at room temperature, the reaction was diluted with dichloromethane (30 cm^3) and washed with NaOH (2 mol dm^{-3}; 3 × 50 cm^3) and water (50 cm^3). The organic layer was then dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–petrol, 1 : 1) to yield the *pyrrolidinone* **10** (384 mg, 67%) as a viscous clear oil and a mixture of diastereoisomers; R_f 0.67 + 0.56 (ethyl acetate–petrol, 1 : 1) (Found: M^+ + H, 388.0817. $C_{18}H_{15}F_5NOS$ requires *M* + H, 388.0795); ν_{max}(neat)/cm^{-1} 1705 (O=C–N); δ_H($CDCl_3$) 1.94 (3 H, d, *J* 7.4, CH_3), 2.07–2.12 [2 H, m, C(4)H_2], 2.24–2.40 [2 H, m, C(3)H_2], 5.15 [1 H, d, *J* 6.4, C(5)H], 5.52 (1 H, q, *J* 7.4, ArCH), 7.35–7.39 (3 H, m, PhH) and 7.47–7.51 (2 H, m, Ph); δ_C($CDCl_3$)‡ 17.39, 17.65 (CH_3), 28.95 [C(4)], 28.89, 29.06 [C(3)], 43.58, 44.08 (Ar–C), 66.42, 67.08 [C(5)], 128.57, 128.86, 129.24, 129.46, 130.82, 131.69, 134.1, 131.47 (Ph), 174.14 and 174.94 [C(2)]; *m*/*z* 388.1 [(M + H)$^+$, 0.2%], 278.1 [M^+ − SPh, 80.4] 109.0 [(SPh)$^+$, 18.2%], 84 [M^+ − $ArCHCH_3$ − SPh + H, 100].

N-[(±)-1′-(2″,3″,4″,5″,6″-Pentafluorophenyl)ethyl][5-$^2H_1$]pyrrolidin-2-one 11

Tributyltin deuteride (124 mg, 0.42 mmol) was added to a solution of pyrrolidinone **10** (80 mg, 0.21 mmol) in toluene (0.5 cm^3) and heated to 80 °C. AIBN was added (5 mg, 0.03 mmol) and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling the crude product was purified by column chromatography (ethyl acetate–petrol, 1 : 1) to yield the *pyrrolidinone* **11** (47 mg, 81%) as a clear oil; R_f 0.33 (ethyl acetate–petrol, 1 : 1) (Found: M^+, 280.0750. $C_{12}H_9DF_5NO$ requires *M*, 208.0745); ν_{max}(neat)/cm^{-1} 1672 (OC–N); δ_H($CDCl_3$) 1.60 [3 H, d, *J* 7.4 C(2′)H_3], 1.97–2.07 + 2.29–2.43 [4 H, m, C(3 + 4)H_2] 3.58 [0.7 H, t, *J* 6.7, C(5)H], 3.74 [0.3 H, t, *J* 7.3, C(5)H], 5.83 (1 H, q, *J* 7.4, ArCH); δ_C($CDCl_3$) 23.70 [C(2′)], 30.69 [C(4)], 40.80 [C(3)], 42.27 [C(1′)], 43.38 [t, J_{C-D} 20.2, C(5)], 114.5, 136.05, 138.84, 138.98 and 146.46 (aromatic-C†) and 175.09 [C(2)]; *m*/*z* 280.1 [M^+, 86.9%] and 237.1 [(M − CO − CH_3)$^+$, 14].

N-[(±)-3′,3′-Dimethyl-2′-butyl]succinimide 12

A solution of triphenylphosphine (12.614 g, 48.09 mmol) in THF (150 cm^3) was added to a 38% solution of diethyl azodicarboxylate in toluene (16.4 cm^3, 40.02 mmol) under argon with stirring at −5 °C. The reaction mixture was then cooled to −10 °C, succinimide (4.964 g, 50.01 mmol) was added and the reaction mixture stirred for 5 min at 0 °C. 3,3-Dimethylbutan-2-ol (4.095 g, 40.08 mmol) was then added dropwise at 0 °C and the reaction mixture was stirred for 60 h at room temperature during which time the solution turned red. The reaction mixture was then quenched with brine (100 cm^3) and the two layers separated, the aqueous layer being further extracted with dichloromethane. The combined organic layers were dried and solvent removed. The crude product was first recrystallised from dichloromethane–petrol and the mother liquor purified by column chromatography (ethyl acetate–petrol, 1 : 1) followed by further recrystallisation from di-

† Signal too weak to observe all/any C–F coupling.

‡ Signals from C_6F_5 too weak to observe.

chloromethane–petrol to remove a white solid impurity to yield the *succinimide* **12** (2.675 g, 36%) as a clear oil; R_f 0.45 (1:1, ethyl acetate–petrol) (Found: M^+, 183.1238. $C_{10}H_{17}NO_2$ requires *M*, 183.1259); ν_{max}(neat)/cm^{-1} 1769 and 1706 (O=C–N–C=O); δ_H($CDCl_3$) 0.94 [9 H, s, 3C(4′)H_3], 1.41 [3 H, d, *J* 7.3, C(1′)H_3], 2.60–2.76 [4 H, m, C(3 + 4)H_2] and 4.05 [1 H, q, *J* 7.3 C(2′)H]; δ_C($CDCl_3$) 11.98 [C(1′)], 27.07 [C(4′)], 27.54 and 27.58 [C(3 + 4)], 35.47 [C(3′)], 55.98 [C(2′)] and 177.66 and 177.72 [C(2 + 5)]; *m*/*z* 183.1 [(M^+, 1.6%], 168.1 [(M − CH_3)$^+$, 14.9] and 127.1 [(M − Bu^t + H)$^+$, 100].

N-[(±)-3′,3′-Dimethyl-2′-butyl]-5-hydroxypyrrolidin-2-one 13

A solution of lithium triethylborohydride in THF (1 mol dm^{-3}; 9.1 cm^3, 9.1 mmol) was added dropwise to a solution of *N*-[(±)-3′,3′-dimethyl-2′-butyl]succinimide **12** (1.100 g, 6.01 mmol) in THF (70 cm^3) under argon with stirring at −78 °C. After stirring for 40 min at −78 °C, the reaction was quenched with saturated $NaHCO_3$ solution (20 cm^3) and 30% hydrogen peroxide in water (2.5 cm^3) was added to it at 0 °C and the mixture stirred for 20 min. The quenched reaction mixture was extracted with dichloromethane (2 × 100 cm^3) and the combined organic layers were dried and the solvent was removed. The crude product was purified by column chromatography (ethyl acetate) to yield the *pyrrolidinone* **13** (641 mg, 58%) as a 2:1 mixture of diastereoisomers and a white solid, mp 90–95 °C; R_f 0.3 (ethyl acetate) (Found: M^+, 185.1467. $C_{10}H_{19}NO_2$ requires *M*, 185.1416); ν_{max}(CH_2Cl_2)/cm^{-1} 3280 (O–H) and 1685 (OC–N); δ_H($CDCl_3$) 0.92 [3 H, s, 3C(4′)H_3], 0.97 [6 H, s, 3C(4′)H_3], 1.28 [1 H, d, *J* 7.4, C(1′)H_3], 1.29 [2 H, d, *J* 7.3, C(1′)H_3], 1.91–1.97, 2.13–2.55 and 2.60–2.70 [5 H, m, C(3)H_2 + C(4)H_2 + OH], 4.03 [0.6 H, q, *J* 7.31, C(2′)H], 4.30 [0.4 H, q, *J* 7.3, C(2′)H], 5.16 [0.4 H, br s, C(5)H] and 5.50 [0.6 H, bs, C(5)H]; δ_C($CDCl_3$) 13.29 and 14.48 [C(1′)], 27.36 [C(4′)], 28.37 and 29.17 [C(3 + 4)], 35.88 [C(3′)], 54.72 [C(2′)], 83.27 [C(5)] and 176.151 and 176.23 [C(2)]; *m*/*z* 185.1 [(M^+), 2.9%], 128.1 [(M − Bu^t)$^+$, 100] and 110.1 [(M − Bu^tH_2O)$^+$, 26].

N-[(±)-3′,3′-Dimethyl-2′-butyl]-5-phenylsulfanylpyrrolidin-2-one 14

N-[(±)-3′,3′-Dimethyl-2′-butyl]-5-hydroxypyrrolidin-2-one **13** (2.96 g, 16.0 mmol) was dissolved in thiophenol (25 cm^3) and toluene-*p*-sulfonic acid (20 mg, 0.11 mmol) was added. After stirring for 3 h at room temperature, the reaction was diluted with dichloromethane (30 cm^3) and washed with NaOH solution (2 mol dm^{-3}; 3 × 50 cm^3) and water (50 cm^3). The organic layer was then dried and the solvent removed. The crude product was purified by column chromatography (ethyl acetate–petrol, 1:1) to yield the *pyrrolidinone* **14** (920 mg, 25%) as a viscous clear oil as a mixture of diastereoisomers: R_f 0.51 (ethyl acetate–petrol, 1:1) (Found: M^+ + H, 278.1591. $C_{16}H_{23}NOS$ requires *M* + H, 278.1579); ν_{max}(neat)/cm^{-1} 1700 (O=C–N); δ_H($CDCl_3$) 0.97 + 0.98 [9 H, s, 3C(4′)H_3], 1.44 [3 H, d, *J* 7.3, C(1′)H_3], 1.53 [3 H, d, *J* 7.1, C(1′)H_3], 2.13–2.49 [4 H, m, C(3 + 4)H_2], 3.31 [1 H, q, *J* 7.1, C(2′)H], 4.20 [1 H, q, *J* 7.3, C(2′)H], 4.88 [1 H, d, *J* 5.6, C(5)H], 5.19 [1 H, d, *J* 5.7, C(5)H], 7.30–7.38 (3 H, m, PhH) and 7.43–7.51 (2 H, m, PhH); δ_C($CDCl_3$) 14.61 [C(1′)], 27.58 [C(4′)], 28.53 and 28.69 [C(3 + 4)], 35.68 [C(3′)], 55.47 [C(2′)], 67.60 [C(5)], 128.13 129.25, 133.38 and 133.59 (Ph) and 175.89 [C(2)]; *m*/*z* 278.2 [(M + H)$^+$, 4.7%], 220.1 [(M − Bu^t)$^+$, 6.2] and 168.1 [(M − SPh)$^+$, 82.3].

N-[(±)-3′,3′-Dimethyl-2′-butyl][5-$^2H_1$]pyrrolidin-2-one 15

Tributyltin deuteride (430 mg, 1.47 mmol) was added to a solution of *N*-[(±)-3′,3′-dimethyl-2-butyl]-5-phenylsulfanyl-pyrrolidin-2-one **14** (204 mg, 0.74 mmol) in toluene (1.0 cm^3) and heated to 80 °C. AIBN was added (18 mg, 0.11 mmol) and the reaction mixture stirred at 80 °C for 16 h under argon. After cooling the crude product was purified by column chromatography (ethyl acetate–petrol, 1:1) to yield the *pyrrolidinone* **15** (120 mg, 96%) as a clear oil; R_f 0.24 (ethyl acetate–petrol, 1:1) (Found: M^+ + H, 171.1654. $C_{10}H_{19}DNO$ requires *M*, 171.1603); ν_{max}(neat)/cm^{-1} 1663 (O=C–N); δ_H($CDCl_3$) 0.93 [9 H, s, 3C(4′)H_3], 1.11 [3 H, d, *J* 7.1, C(1′)H_3], 1.91–2.04 and 2.28–2.45 [4 H, m, C(3)H_2 + C(4)H_2], 3.38–3.43 [1 H, m, C(5)H] and 4.04 [1 H, q, *J* 7.1, C(2′)H]; δ_C($CDCl_3$) 12.40 [C(1′)], 18.45 [C(4)], 27.04 [C(4′)], 30.94 [C(3)], 35.16 [C(3′)], 44.24 [t, *J* 21.7, C(5)], 54.14 [C(2′)] and 175.11 [C(2)]; *m*/*z* 171.2 [(M^+ + H)$^+$, 9.3%], 113.1 [(M − Bu^t)$^+$, 100], 99.1 [(M − CO − 2CH_2 − CHD)$^+$, 2.17].

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