Reduction of electron-deficient pyrroles using group I and II metals in ammonia

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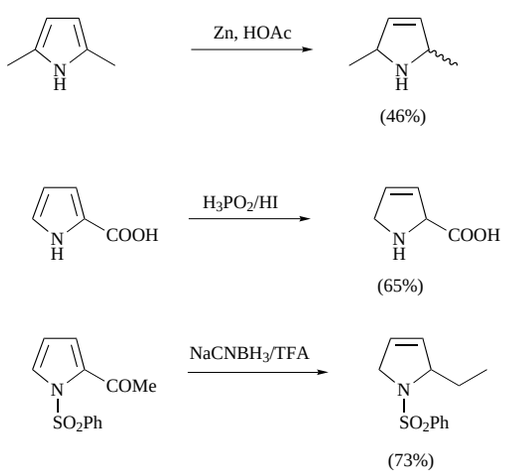
The preparation and Birch reduction of a series of electron-deficient pyrroles is described. This methodology allows the synthesis of a variety of C-2 substituted 3-pyrrolines‡ in good to excellent yields. The role of various activating groups (amide, ester, carbamate and urea) has been examined with regard to both stability under the Birch conditions and ease of deprotection after reduction. In addition, we discovered that the 3-pyrroline skeleton can be oxidised at C-5 with chromium trioxide–3,5-dimethylpyrazole to form the 3-pyrrolin-2-one nucleus. The identity of the Birch reduced products and also of the oxidised 3-pyrrolin-2-ones has been confirmed by X-ray crystallography on two derivatives.

Introduction

Development of new methods for the synthesis of substituted pyrroles has been a key element in the field of heterocyclic chemistry for many years. Extensive study into the reactivity pattern displayed by pyrrole has shown that it has a great propensity to act as a nucleophile in addition and substitution reactions. Correspondingly, chemistry which involves the pyrrole nucleus acting as an electron acceptor or electrophile is much less common. This is exemplified with redox chemistry: the oxidation of pyrroles has been the subject of much interesting and varied work,[1] while the reduction of pyrroles remains a relatively unexplored area.[2]

As part of a general programme directed towards the stereoselective reduction of aromatic heterocycles, we chose to investigate reduction of pyrrole to the pyrroline skeleton. Indeed, this synthetic transformation is precedented in the literature, being effected by the combination of a reducing agent (Zn, $NaBH_3CN$, H_3PO_2 *etc.*)[3–5] in the presence of acid, so as to activate the heterocycle (Scheme 1).

However, it appeared that a reduction protocol which did not involve acid as an activator was not known. The development of such a reaction would be useful in enabling the synthesis of substituted pyrrolines containing acid sensitive functionality and in addition, may enable functionalisation of the pyrrole ring by reductive alkylation procedures.



Scheme 1

The most obvious choice of reduction conditions with which to accomplish this goal were those developed by Birch and which have come to bear his name, *i.e.* (typically) sodium in liquid ammonia solvent with *tert*-butyl alcohol added as a proton source.[6] Although this reaction has been utilised extensively in the field of aromatic chemistry, its use in the reduction of pyrroles was unknown.[7] Consideration of the basic tenants of the reaction provided us with at least two good reasons why this might be the case. Firstly, the pyrrole nucleus is electron-rich (as attested to by its high nucleophilicity) and this factor is generally a disadvantage when one is considering the addition of electrons to the aromatic system. Secondly, the presence of an acidic hydrogen atom on the pyrrole nitrogen ($pK_a \approx 17$) may present the opportunity for deprotonation under the reducing conditions (by an alkoxide for example): the resulting anion would be extremely resistant to further reduction (a similar situation is arrived at if one attempts the reduction of phenols under Birch conditions). In order to circumvent such potential pitfalls we decided to synthesise some electron-deficient and N-protected pyrroles so as to investigate their reactivity under Birch conditions. Some of the work described in this paper has been the subject of preliminary communication and which we now wish to discuss in detail.[8]

Results and discussion

Compound **3** (Scheme 2) was chosen as our first target because it was easy to prepare and satisfied the criteria defined above: in addition, placing an electron withdrawing group in the 2-position of the pyrrole should control the regiochemistry of reduction and also provide an opportunity for reductive alkylation. Therefore, **3** was prepared from commercially available 2-trichloroacetylpyrrole (**1**) in two high yielding steps,[9] and was subsequently subjected to a Birch reductive alkylation with sodium metal in ammonia, quenching with methyl iodide (Scheme 2). To our delight, we succeeded in isolating pyrroline **4** from the reaction mixture in 20–30% yield: the ^1H NMR spectrum of this compound clearly indicated that a significant transformation of the aromatic ring had taken place and showed two multiplets at 5.8, 5.6 ppm (2H, C*H*=C*H*) and one at 3.7 ppm (2H, CH_2CH=CH). In addition a *N*-methyl resonance appeared as a singlet at 2.3 ppm and another methyl singlet was observed at 1.2 ppm. These features, together with ^{13}C NMR,

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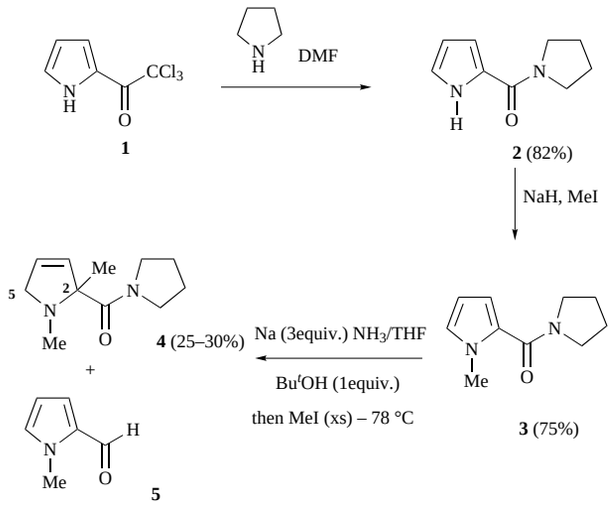
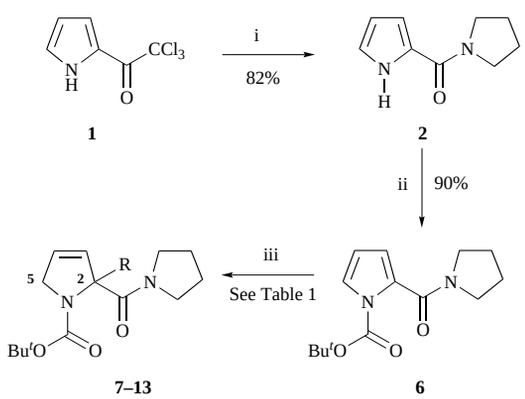
‡ The '3-' denotes the position of the double bond. They are more correctly referred to as dihydropyrroles.



Scheme 2

infra-red and mass spectra were all consonant with the proposed structure. Although we had achieved success in this reaction, we were dismayed to discover that the major product was in fact the volatile aldehyde **5**, which had resulted from amide reduction rather than pyrrole reduction.[10]

Unfortunately, the ratio of **4**:**5** could not be increased despite attempted reduction under a variety of conditions (which included variation of co-solvent, proton source and metal). Presumably, this failure is a consequence of a lack of regioselectivity in the site of protonation of the radical-anion resulting from the addition of an electron to the aromatic system (*vide infra*). It was reasoned that replacing the *N*-methyl group with a protecting group that was also capable of withdrawing electrons would alleviate this problem by promoting reduction of the aromatic portion of the molecule. Therefore, *N*-Boc pyrrole **6** was identified as a suitable substrate for reduction (Scheme 3). The target pyrrole was synthesised efficiently from



Scheme 3 *Reagents*: i, pyrrolidine, DMF; ii, NaH, $(Boc)_2O$; iii, Na (3 equiv.), NH_3/THF then RX (xs) −78 °C

1 (*via* compound **2**) and was then reduced under a variety of conditions. Success was achieved using a reductive alkylation protocol which did not involve the addition of an alcohol as a proton source (Scheme 3). Indeed, addition of a THF solution of **6** to a blue solution of sodium (3 equiv.) in ammonia at −78 °C resulted in rapid reduction: quenching of the reaction after 5 minutes with an electrophile dispersed the coloration and gave the α-alkylated material in good yield (Scheme 3). A range of primary alkyl halides were used as electrophiles and each reacted efficiently and regioselectively with the pyrroline enolate (Table 1). Unfortunately, quenching the reduction with isopropyl iodide gave only the protonated compound **13**, as a result of an elimination process; this compound could be

Table 1 Birch reduction of **6**

Entry	RX	R	Yield (%)	Compound
1	MeI	Me	85	**7**
2	BnBr	Bn	72	**8**
3	AllylBr	Allyl	71	**9**
4	EtI	Et	81	**10**
5	BuI	Bu	86	**11**
6	Bu^iI	Bu^i	79	**12**
7	NH_4Cl	H	71	**13**

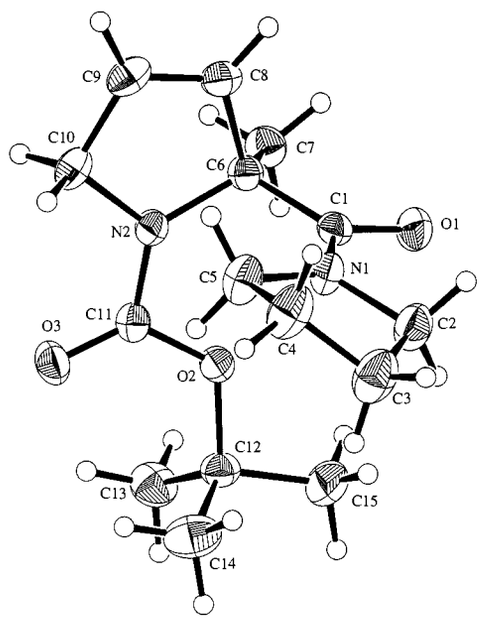
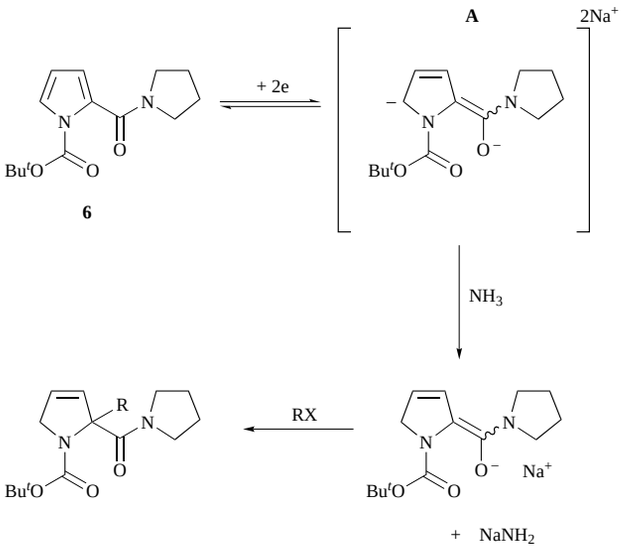


Fig. 1 X-Ray crystal structure of (*RS*)-**7**. X-Ray crystallographic numbering shown.

obtained more easily by quenching the reaction with an aqueous solution of ammonium chloride (entry 7, Table 1).

The identity of each of the Birch reduced compounds **7**–**13** was clarified by examination of their spectroscopic data. The ^1H NMR spectra of each of the reduced products showed the presence of two olefinic protons at 5–6 ppm, together with incorporation of resonances due to the alkyl group of the electrophile. In each case, the position of the double bond was confirmed by the observation of a 2H multiplet at 4–4.5 ppm which was assigned to the methylene protons attached to C-5. All of the reduced compounds exhibited doubling of resonances in their ^1H and ^{13}C NMR spectra, presumably as a consequence of hindered rotation. In each case, the situation was clarified by performing the data collection in 1,2-dichlorobenzene at 120–140 °C which gave rise to a single set of signals (albeit somewhat broad). Moreover, each compound gave a satisfactory mass spectrum and elemental analysis, and compound **7** was further characterised by X-ray crystallography (Fig. 1).

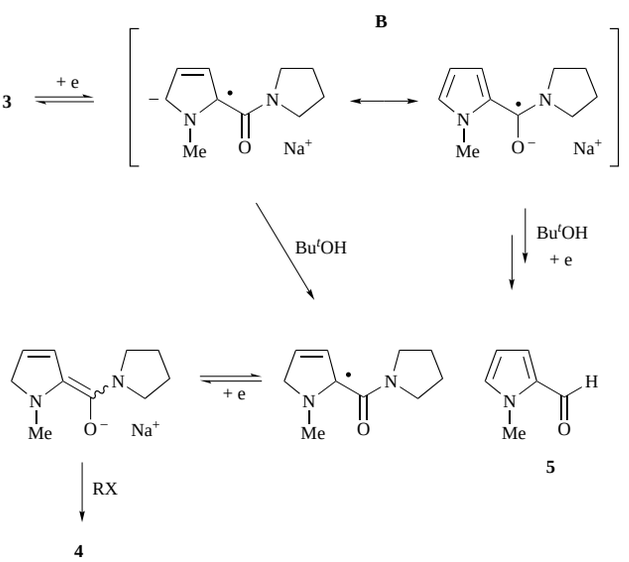
We find the selective reduction of compound **6** particularly striking and worthy of comment. Firstly, the requirement that reduction is performed without an alcohol as a proton source is interesting. This observation leads us to believe that reduction is occurring *via* a mechanism which involves the intermediacy of a dianion (**A**, Scheme 4), formed by the capture of two electrons by the pyrrole nucleus. This should be basic enough to deprotonate ammonia thus yielding an enolate.[11] Indeed, the pyrrole **6** is so electron-deficient that reduction occurs in less than 5 minutes at −78 °C. We made the observation that pyrrole **2** is a minor by-product (5–15%) in these reactions and speculate that it arises from nucleophilic attack of sodium amide (formed in the above mechanism) at the Boc carbonyl prior to reduction. In support of this, we found that **6** was



Scheme 4

resistant to Boc cleavage by liquid ammonia alone at −78 °C. In fact, rapid addition of substrate to the ammonia solution is a means of minimising (≤5%) the appearance of the unwanted compound **2**.

The second point of note regards the absence of aldehyde by-product in the reduction of **6**, which is especially interesting when compared to the non-selective reduction of **3**. It occurs to us that the reduction of **3** (as outlined in Scheme 2) proceeds *via* a more conventional pathway involving addition of an electron and protonation of the corresponding radical anion (**B**) by *tert*-butyl alcohol (Scheme 5). Addition of a second electron forms



Scheme 5

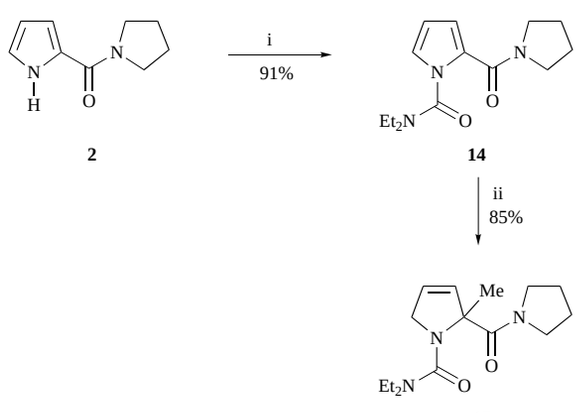
an enolate which awaits reaction with the electrophile. However, formation of the aldehyde by-product (**5**) can be explained by protonation of the radical anion **B** at the *carbonyl group* by *tert*-butyl alcohol. Subsequent addition of a second electron will form a hemiaminal species which presumably breaks down to the aldehyde upon quench and work-up.

Although the contrasting product distributions from reduction of **3** and **6** could be explained by the operation of two different mechanisms, we have some evidence that suggests otherwise. For example, we have performed the reduction of **3** under conditions which do not include addition of an alcohol (and which should, therefore, promote reaction *via* a dianion). This reaction resulted in a product mixture that was similar to that observed earlier with *tert*-butyl alcohol present (*i.e.* aldehyde **5** was the major compound formed). It is therefore more likely that the success of the Birch reduction of **6** is a consequence of a regioselective protonation of dianion **A** at C-5 rather than at the carbonyl group. We therefore have to ask why the dianion derived from **6** (**A**) should protonate so regioselectively while the radical anion (**B**) (or dianion) derived from **3** does not? In general terms it may be concluded that making the aromatic ring comparatively electron rich (compound **3**) discourages reduction of that portion of the molecule and conversely, reducing electron density within it (compound **6**) encourages arene reduction. This trend is in clear agreement with that observed during the Birch reduction of benzenoid systems. Assuming kinetic control we suggest that several factors may be responsible for the regiocontrol displayed by each radical anion (or dianion), and these would include: the total charge at each reactive position; the orbital coefficient of the HOMO of the radical-anion (or dianion) at each reactive position, and the steric hindrance at each possible site of protonation. Obviously it is not easy to assess quantitatively the difference that a change of nitrogen protecting group will have on each of these parameters and a more exacting explanation awaits further investigation of this system.

The effect of changing the reactive metal was next examined. The reductive alkylation of **6**→**7** was chosen as a representative example and was performed with three metals: in each case the reaction profile was identical and the isolated yields of **7** proved to be rather similar [Na (85%), Ca (75%), Li (71%)]. Clearly, the particular source of electrons and the nature of the cationic counterion is relatively unimportant to the success of this reaction. The success of lithium and calcium may have ramifications as far as the practicality of this reaction is concerned, as they are easier to handle than sodium.

Dialkylamides and isopropyl esters as activating groups for pyrrole

Alternative N-protecting and electron withdrawing groups for pyrrole were also examined for their stability during the Birch reduction. Thus, compound **14** was prepared from **2** *via* deprotonation and reaction with diethylcarbamoyl chloride (Scheme 6). This compound was then reduced under conditions



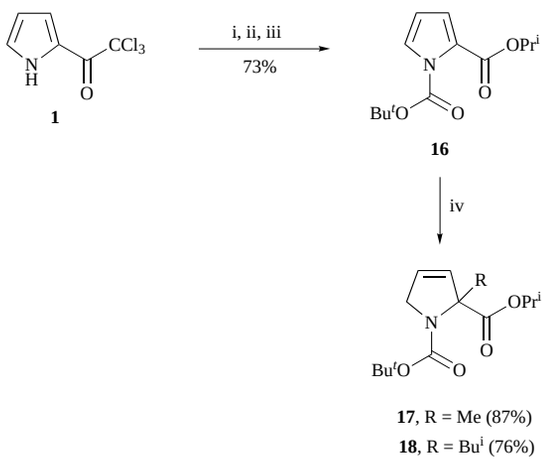
Scheme 6 *Reagents*: i, NaH, Et_2NCOCl; ii, Na (3 equiv.) NH_3/THF then MeI (xs) −78 °C

that had proven to be successful for the N-Boc amide derivative. Birch reduced urea **15** was obtained as the sole product of the reaction in high yield. In fact, deprotected pyrrole **2** was not detected in this reduction at all, presumably because the N-protecting group (amide) shows greater resistance towards nucleophilic attack by sodamide.

The success of this reaction illustrates that a variety of electron withdrawing groups can be tolerated on the pyrrole nitrogen. However, this reaction sequence was not pursued further

because of perceived difficulties in removing the urea group from the reduced product.

We also examined the reduction of *N*-Boc pyrroles substituted with an ester at C-2:[12] this functionality was chosen because of the relative ease and selectivity with which the ester group could be removed after reduction. Ester **16** was prepared from 2-trichloroacetylpyrrole **1** in three steps and in excellent overall yield (Scheme 7). Reductive alkylation of **16** under

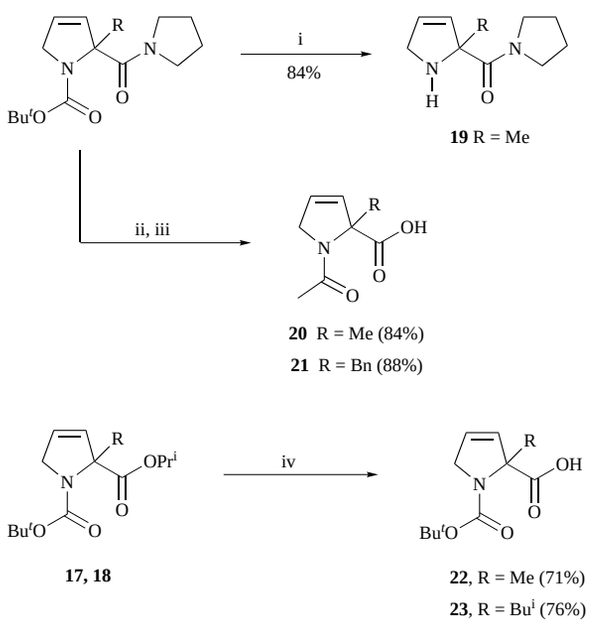


Scheme 7 *Reagents*: i, KOH; ii, $(COCl)_2$ then Pr^iOH; iii, NaH, $(BOC)_2O$; iv, Na (3 equiv.) NH_3/THF then RI (xs) −78 °C

standard conditions proceeded without complication and gave the two α-alkylated derivatives shown in the scheme. The two electrophiles that were chosen to quench the ester enolate illustrate that this activating group is equally useful for the synthesis of highly substituted pyrrolines as the amide group described earlier.

Although excellent yields of **17** and **18** were obtained from the reduction, it was discovered that the substrate must be added rapidly to the reaction mixture: slow addition resulted in the formation of C-2 amide derivatives of the two pyrrolines.

With the Birch reduced products in hand we next examined removal of the various activating and protecting groups to prove the utility of this chemistry in synthesis. For example, the Boc group could be conveniently removed from the amide substituted compounds by treatment with trifluoroacetic acid (**19**, Scheme 8). In addition, the amide functionality could be



Scheme 8 *Reagents*: i, TFA, DCM; ii, (aq.) HCl; reflux iii, Ac_2O, Py then (aq.) KOH; iv, (aq.) KOH, MeOH

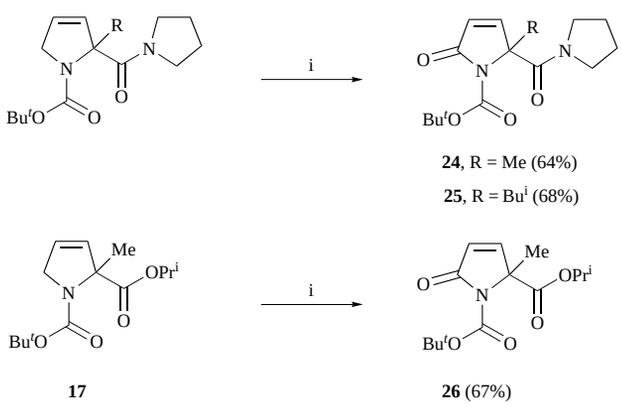
hydrolysed to the corresponding carboxylic acids in excellent yields by reaction with concentrated HCl (6 M) at reflux (Boc deprotection occurs first): the amino acids thus formed were conveniently purified as their *N*-acetyl derivatives. Migration of the double bond at C-3 into conjugation with the amine was not observed. Presumably, under such acidic conditions the amine functionality is protonated thus disfavouring further protonation of the olefin at C-3 (this is a prerequisite step for olefin migration under acidic conditions).

We also examined the saponification of **17** and **18** with potassium hydroxide and formed the *N*-Boc amino acids in good yields (Scheme 8). The advantages of carrying an ester through the reduction procedure revolve around the relative ease of deprotection to the acid without removal of the Boc group.

In addition, we coupled acid **22** with pyrrolidine [promoted by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)] to produce a sample of **7** that was identical with the material that was produced in the Birch reduction of amide **6** (and whose identity was confirmed by X-ray crystallography). This correlation confirms the nature of acid **22** and therefore ester **17** unambiguously.

Oxidation of the 3-pyrroline skeleton to form substituted 3-pyrrolin-2-ones

During an attempted recrystallisation of compound **7** from diethyl ether, we occasionally observed the formation of a new compound. Chromatography of the mother liquors on silica gel allowed the isolation of this compound, which was subsequently proven to be the γ-lactam **24** (Scheme 9). Presumably,



Scheme 9 *Reagents*: i, CrO_3, 3,5-dimethylpyrazole

this compound was formed by a free radical chain reaction involving atmospheric oxygen.[13] However, the yield of **24** proved to be rather low and unpredictable and so we sought a more reproducible method of achieving this oxidation. Eventually, we discovered that the chromium trioxide–3,5-dimethylpyrazole combination was the most reliable method for effecting this transformation, and gave yields of 64–68% on three different substrates (Scheme 9).[14]

The nature of the pyrrolin-2-ones (2,5-dihydropyrrol-2-ones) **24**, **25** and **26** was determined by examination of the corresponding NMR and IR spectra. In each case, ^1H NMR spectroscopy revealed that the two alkene methine resonances were shifted from δ 5–6 (pyrroline) to δ 6–7 ppm (pyrrolin-2-one). There was also an absence of the 2H multiplet at 4 ppm which was previously attributed to the methylene protons at C-5 of the pyrroline. ^{13}C NMR spectroscopy indicated the presence of three carbonyl groups and the IR spectrum of **24**, **25** and **26** exhibited several bands between 1600–1780 cm^{-1}. Compound **24** was further characterised by X-ray crystallography to rule out the possibility that a rearranged vinylogous amide (4-pyrrolin-3-one) was present (Fig. 2). We expect that the synthesis and reactivity pattern displayed by these substrates will be the basis of future work and that they could hold

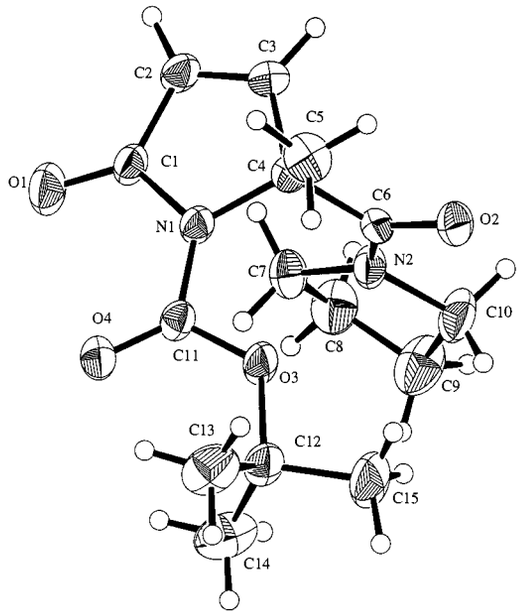


Fig. 2 X-Ray crystal structure of (*RS*)-**24**. X-Ray crystallographic numbering shown.

promise as intermediates in the synthesis of pyrrolidinone containing natural products.

To conclude, we have demonstrated that a series of electron deficient pyrroles are capable of undergoing Birch reduction and reductive alkylation procedures to give substituted 3-pyrrolines in good to excellent yields. Both the Boc and urea groups provide suitable protection for the pyrrole amine and also activate the heterocycle towards reduction. Introduction of an ester or amide at C-2 allowed a reductive alkylation protocol to be performed and ensured the regiochemical outcome of the reaction. Each of the two positions that require protection (C-2 carbonyl and the pyrrole nitrogen) can be blocked with groups that are mutually compatible and which can be removed orthogonally. In addition, a versatile and useful oxidation reaction which yields the 3-pyrrolin-2-one skeleton has also been discovered. Therefore, this methodology will prove to have use in the synthesis of biologically important molecules and further studies will be reported in due course.

Experimental

General details

Melting points were determined with an 'Electrothermal' capillary melting point apparatus and are uncorrected. IR spectra were measured with a ATI Mattison Genesis Series FTIR as KBr discs or neat oils as appropriate. The ^{1}H (500, 300 and 200 MHz) NMR and ^{13}C (125, 75 and 50 MHz) NMR spectra were obtained on a Varian Unity 500, Bruker AC300 and Varian Gemini 200 spectrometers. *J* Values are given in Hz. Elemental analyses were performed in-house. Mass spectra were obtained on a Kratos Concept Mass Spectrometer using the electron impact mode (70 eV) or chemical ionisation. GC studies were performed using a CP-Chirasil DEXCB column (25 m × 0.32 mm, 0.28 μ) controlled by a Shimadzu Cromatopac R4AX unit. Thin layer chromatography (TLC) was performed on Polygram 0.25 mm silica gel pre-coated plastic sheets and visualised with UV light (254 nm) and/or phosphomolybdic acid in ethanol, *p*-anisaldehyde in glacial acetic acid or basic potassium permanganate as appropriate. Chromatography was performed on silica gel (Merck 60). All solvents were purified by following standard literature methods. Ammonia was pre-dried over sodium and distilled into the reaction vessel under a nitrogen atmosphere. All the alkyl halides used were filtered through a plug of anhydrous potassium carbonate prior to use. Isoprene was distilled and stored over 4 Å molecular sieves under nitrogen. Petrol refers to the fraction of light petroleum which boils between 40 and 60 °C. All chiral compounds described in the Experimental are racemic.

2-(Pyrrolidin-1-ylcarbonyl)pyrrole 2

Freshly distilled pyrrolidine (4.4 cm^3, 52.0 mmol) was added dropwise to a solution of the trichloroacetylpyrrole **1** (5 g, 23.6 mmol) dissolved in DMF (15 cm^3). After 10 h, water (40 cm^3) was added, followed by 2 M HCl (20 cm^3). The mixture was then extracted with EtOAc (3 × 50 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the pyrrole amide **2** (3.17 g, 82%) as an off-white solid; mp 118–119 °C; ν_{max}(film)/cm^{-1} 3224, 2974, 2870, 1585, 1453 and 1416; δ_H(300 MHz; $CDCl_3$) 10.4 (1 H, br s, NH), 6.97–6.91 (1 H, m, ArH), 6.63–6.57 (1 H, m, ArH), 6.30–6.23 (1 H, m, ArH), 3.81–3.61 (4 H, m, 2 × NCH_2CH) and 2.08–1.82 (4 H, m, 2 × NCH$_2$CH_2); δ_C(75 MHz; $CDCl_3$) 160.5, 126.1, 121.1, 112.0, 109.6, 47.9, 47.0, 26.7 and 24.0; *m*/*z* (EI) 164 (M$^+$, 35%), 108 (20), 94 (70) and 70 (100); ($C_9H_{12}N_2O$ requires 164.0950. Found 164.0954).

2-(Pyrrolidin-1-ylcarbonyl)-*N*-methylpyrrole 3

A solution of the pyrrole amide **2** (5 g, 30.5 mmol) in THF (10 cm^3) was added to NaH (1.46 g, 60.9 mmol) in THF (10 cm^3) at room temperature. After 1 h, methyl iodide (4.75 cm^3, 76.3 mmol) was added and the reaction heated at 60 °C for 12 h. After cooling, the reaction mixture was washed with brine and extracted with EtOAc (3 × 20 cm^3) and dried (Na_2SO_4). Flash chromatography (eluting with petrol–EtOAc, 5:1) afforded the *N*-methylpyrrole **3** (4.1 g, 75%) as a yellow oil; ν_{max}(film)/cm^{-1} 2953, 2873, 1612, 1531, and 1433; δ_H(300 MHz; $CDCl_3$) 6.70–6.65 (1 H, m, ArH), 6.55–6.48 (1 H, m, ArH), 6.15–6.05 (1 H, m, ArH), 3.85 (3 H, s, NMe), 3.65 (4 H, br s, 2 × NCH$_2$) and 1.95–1.85 (4 H, m, 2 × NCH$_2$CH_2); δ_C(75 MHz; $CDCl_3$) 162.3, 127.0, 126.5, 113.9, 107.0, 49.8, 46.7, 36.9, 27.0 and 24.6; *m*/*z* (EI) 178 (M$^+$, 100%), 108 (100), 81 (40), and 70 (35); ($C_{10}H_{14}N_2O$ requires 178.1106. Found 178.1101).

1,2-Dimethyl-2-(pyrrolidin-1-ylcarbonyl)-2,5-dihydropyrrole 4

A solution of *N*-methylpyrrole amide **3** (320 mg, 1.8 mmol) in THF (10 cm^3) was added to a mixture of ammonia (100 cm^3), and sodium (124 mg, 5.4 mmol) at −78 °C. *tert*-Butyl alcohol (120 mg) was added and the reaction stirred for 1 h. Methyl iodide (1 cm^3) was then added followed by NH_4Cl (excess) after a further 2 h. The reaction mixture was diluted with brine, extracted with dichloromethane and dried (Na_2SO_4). Flash chromatography (eluting with petrol–EtOAc 1:1) gave the dihydropyrrole **4** (90 mg, 26%) as a yellow oil; ν_{max}(film)/cm^{-1} 2969, 1626, and 1413; δ_H(200 MHz; $CDCl_3$) 5.80 (1 H, dt, *J* 6.0 and 2.0, CH=CH), 5.63 (1 H, dt, *J* 6.0 and 2.0, CH=CH), 3.80–3.65 (2 H, m, NCH_2CH), 3.55–3.20 (4 H, m, 2 × NCH_2CH$_2$), 2.30 (3 H, s, NMe), 1.95–1.60 (4 H, m, 2 × NCH$_2$CH_2), and 1.20 (3 H, s, NCMe); δ_C(50 MHz; $CDCl_3$) 172.6, 134.7, 128.5, 74.4, 60.0, 48.3, 47.3, 34.8, 27.6, 23.8 and 17.6; *m*/*z* (CI) 195 (M$^+$ + 1, 95%), 193 (100) and 96 (25); ($C_{11}H_{19}N_2O$ requires 195.1497. Found 195.1500).

N-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrole 6

A solution of the pyrrole amide **2** (5 g, 30.5 mmol) in THF (15 cm^3) was added to NaH (1.46 g, 60.9 mmol) in THF (15 cm^3) at room temperature. After 30 min, di-*tert*-butyl dicarbonate (10.5 cm^3, 45.7 mmol) was added dropwise and the reaction was heated at 45 °C for 12 h. The reaction mixture was then diluted with water (10 cm^3), extracted with EtOAc (3 × 30 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (eluting with petrol–EtOAc 1:2) afforded the *N*-Boc pyrrole amide **6** (7.25 g, 90%) as a colourless solid; mp 102–103 °C (Found: C, 63.59; H, 7.72; N, 10.49. Calc. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60%); ν_{max}(film)/cm^{-1} 2976, 2876, 1744, 1640, 1555 and 1460; δ_H(300 MHz, $CDCl_3$) 7.23 (1 H, dd, *J* 1.6 and 3.6, Ar*H*), 6.30 (1 H, dd, *J* 1.6 and 3.6, Ar*H*), 6.17 (1 H, t, *J* 3.6, Ar*H*), 3.60 (2 H, t, *J* 6.6, NCH_2CH$_2$), 3.30 (2 H, t, *J* 6.6,

NCH_2CH_2), 2.00–1.80 (4 H, m, 2 × NCH_2CH_2), and 1.55 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 162.8, 148.3, 129.0, 121.6, 113.0, 110.6, 84.4, 48.3, 45.6, 27.8, 25.8 and 24.6; *m*/*z* (CI) 265 ($M^+ + 1$, 75%), 209 (100), 165 (25), 94 (10) and 70 (15); ($C_{14}H_{20}N_2O_3$ requires 264.1474. Found 264.1476).

N-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-methyl-2,5-dihydropyrrole 7

A solution of *N*-Boc-pyrrole amide **6** (500 mg, 1.9 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.7 mmol) at −78 °C. After 1 h, methyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. Brine was added and the product extracted with EtOAc (3 × 50 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **7** (451 mg, 85%) as a colourless solid; mp 95–98 °C (Found: C, 64.45; H, 8.54; N, 9.85. Calc. for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99%); ν_{max}(film)/cm^{-1} 2974, 2874, 1696, 1639 and 1391; δ_H(300 MHz, $CDCl_3$) 5.87, 5.81 (1 H, dt, *J* 6.2 and 1.9, C*H*=CH), 5.62 (1 H, dt, *J* 6.2 and 1.9, CH=C*H*), 4.30–4.08 (2 H, m, NCH_2CH), 3.57–3.00 (4 H, m, 2 × NCH_2CH_2), 2.00–1.65 (4 H, m, 2 × NCH_2CH_2), 1.63, 1.58 (3 H, s, NCMe), 1.45 and 1.42 (9 H, s, CMe_3); δ_H(300 MHz, $C_6H_4Cl_2$, 140 °C) 5.65–5.55 (1 H, m, C*H*=CH), 5.50–5.40 (1 H, m, CH=C*H*), 4.15–4.00 (2 H, m, NCH_2CH), 3.40–3.15 (4 H, m, 2 × NCH_2CH_2), 1.75–1.50 (7 H, m, 2 × NCH_2CH_2 and NCMe) and 1.38 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 168.9, 153.1, 132.0, 131.6, 125.4, 80.2, 72.3, 72.0, 53.3, 48.2, 45.0, 28.4, 27.3 and 23.4; *m*/*z* (CI) 281 ($M^+ + 1$, 100%), 225 (40), 181 (25) and 82 (40); ($C_{15}H_{24}N_2O_3$ requires 280.1787. Found 280.1775).

N-(*tert*-Butyloxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-benzyl-2,5-dihydropyrrole 8

A solution of *N*-Boc-pyrrole amide **6** (500 mg, 1.9 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.7 mmol) at −78 °C. After 1 h, isoprene (5 drops) was added followed by benzyl bromide (1 cm^3) and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **8** (485 mg, 72%) as a colourless solid; mp 152–153 °C (Found: C: 70.36; H, 7.75; N, 7.88. Calc. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86%); ν_{max}(film)/cm^{-1} 2973, 2874, 1696, 1640 and 1393; δ_H(300 MHz, $CDCl_3$) 7.25–7.00 (5 H, m, Ph*H*), 5.71, 5.64 (1 H, dt, *J* 6.4 and 2.0, C*H*=CH), 5.57 (1 H, dt, *J* 6.4 and 2.0, CH=C*H*), 3.99–3.00 (8 H, m, NCH_2CH, 2 × NCH_2CH_2, CH_2Ph), 2.0–1.65 (4 H, m, 2 × NCH_2CH_2) and 1.55, 1.50 (9 H, s, CMe_3); δ_H(300 MHz, $C_6H_4Cl_2$, 140 °C) 5.50–5.35 (2 H, m, CH=CH), 3.90–3.60 (2 H, m, NCH_2CH), 3.45–3.15 (6 H, m, 2 × NCH_2CH_2, CH_2Ph), 1.75–1.50 (4 H, m, 2 × NCH_2CH_2) and 1.45 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 168.9, 153.0, 137.3, 137.0, 131.2, 131.0, 129.3, 128.9, 127.7, 127.6, 127.3, 126.2, 126.0, 80.6, 79.7, 75.8, 75.7, 54.1, 48.4, 48.3, 45.0, 40.6, 39.4, 28.6, 28.4, 27.4, 27.3, 23.3 and 23.2; *m*/*z* (CI) 357 ($M^+ + 1$, 100%), 301 (65), 257 (15) and 158 (10) ($C_{21}H_{29}N_2O_3$ requires 357.2178. Found 357.2182).

N-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-allyl-2,5-dihydropyrrole 9

A solution of *N*-Boc-pyrrole amide **6** (433 mg, 1.64 mmol) in THF (20 cm^3) was added rapidly to a mixture of ammonia (200 cm^3), THF (30 cm^3) and sodium (113 mg, 4.91 mmol) at −78 °C. After 1 h, allyl bromide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–ethyl acetate 3:1) gave the dihydropyrrole **9** (357 mg, 71%) as a colourless solid (Found: C, 66.78; H, 8.62; N, 8.90. Calc. for $C_{17}H_{26}N_2O_3$; C, 66.64; H, 8.55; N, 9.14%); ν_{max}(film)/cm^{-1} 1696, 1627, and 1391; δ_H(300 MHz, $CDCl_3$) 5.96–5.84 (1 H, m, C*H*=CH), 5.64–5.48 (2 H, m, CH=C*H*), 5.06–4.96 (2 H, m, $CH=CH_2$), 4.13–3.98 (2 H, m, NCH_2CH), 3.62–3.34 (2 H, m, NCH_2CH_2), 3.30–3.16 (1 H, m, $CH_2CH=CH_2$), 3.08–2.98 (2 H, m, NCH_2CH_2), 2.78–2.68 (1 H, dd, *J* 4.0 and *J* 7.5, $CH_2CH=CH_2$), 1.94–1.50 (4 H, m, 2 × NCH_2CH_2) and 1.39, 1.38 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 168.9, 153.0, 133.2, 132.8, 129.5, 129.1, 126.8, 126.7, 118.9, 118.7, 80.2, 74.7, 54.7, 54.4, 48.2, 44.9, 39.6, 38.1, 28.2, 27.3 and 23.2; *m*/*z* (CI), 307 ($M^+ + 1$, 40%) and 207 (100); ($C_{17}H_{26}N_2O_3$ requires 306.1943. Found 306.1939).

N-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-ethyl-2,5-dihydropyrrole 10

A solution of *N*-Boc-pyrrole amide **6** (500 mg, 1.89 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.69 mmol) at −78 °C. After 1 h, ethyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **10** (451 mg, 81%) as a colourless oil (Found: C, 65.21; H, 8.76; N, 9.50. Calc. for $C_{16}H_{26}N_2O_3$: C: 65.28; H, 8.90; N, 9.52%); ν_{max}(film)/cm^{-1} 2970, 2876, 1692, 1641, 1476 and 1393; δ_H(300 MHz, $CDCl_3$) 5.98, 5.91 (1 H, dt, *J* 6.3 and 2.1, C*H*=CH), 5.43 (1 H, dt, *J* 6.3 and 2.1, CH=C*H*), 4.15, 4.09 (2 H, t, *J* 2.1, NCH_2CH), 3.55–2.95 (4 H, m, 2 × NCH_2CH_2), 2.60–1.55 (6 H, m, CH_2CH_3, 2 × NCH_2CH_2), 1.49, 1.38 (9 H, s, CMe_3) and 0.80, 0.70 (3 H, t, *J* 7.0, CH_2CH_3); δ_H(300 MHz, $C_6H_4Cl_2$, 140 °C) 5.80–5.70 (1 H, m, C*H*=CH), 5.35–5.25 (1 H, m, CH=C*H*), 4.10–4.05 (2 H, m, NCH_2CH), 3.45–3.30 (4 H, m, 2 × NCH_2CH_2), 2.60–2.40 (1 H, m, *H*CHCH$_3$), 2.15–2.05 (1 H, m, HC*H*CH$_3$), 1.75–1.55 (4 H, m, 2 × NCH_2CH_2), 1.40 (9 H, s, CMe_3) and 0.75–0.65 (3 H, m, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 169.3, 169.0, 153.2, 152.2, 129.6, 129.2, 126.9, 126.6, 80.1, 79.6, 75.7, 75.4, 55.0, 54.7, 48.2, 44.7, 28.3, 27.9, 27.3 and 23.3; *m*/*z* (CI) 295 ($M^+ + 1$, 100%), 239 (35), 195 (25) and 96 (50) ($C_{16}H_{26}N_2O_3$ requires 294.1943. Found 294.1941).

N-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-butyl-2,5-dihydropyrrole 11

A solution of *N*-Boc-pyrrole amide **6** (500 mg, 1.9 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.7 mmol) at −78 °C. After 1 h, butyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **11** (524 mg, 86%) as a colourless oil (Found: C, 66.78; H, 9.10; N, 8.65. Calc. for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69%); ν_{max}(film)/cm^{-1} 2963, 2872, 1694, 1641 and 1392; δ_H(300 MHz, $CDCl_3$) 5.96, 5.90 (1 H, dt, *J* 6.3 and 2.1, C*H*=CH), 5.49 (1 H, dt, *J* 6.3 and 2.1, CH=C*H*), 4.17, 4.10 (2 H, t, *J* 2.1, NCH_2CH), 3.55–3.0 (4 H, m, 2 × NCH_2CH_2), 2.50–1.60 [6 H, m, $CH_2(CH_2)_2CH_3$, 2 × NCH_2CH_2], 1.45, 1.42 (9 H, s, CMe_3), 1.40–0.95 [4 H, m, $CH_2(CH_2)_2CH_3$] and 0.89 (3 H, t, *J* 7.0, CH_2CH_3); δ_H(300 MHz, $C_6H_4Cl_2$, 140 °C) 5.70–5.60 (1 H, m, C*H*=CH), 5.35–5.25 (1 H, m, CH=C*H*), 4.10–4.00 (2 H, m, NCH_2CH), 3.35–3.15 (4 H, m, 2 × NCH_2CH_2), 2.50–2.30 (1 H, m, HC*H*CH$_2$), 2.10–1.95 (1 H, m, *H*CHCH$_2$), 1.70–1.45 (4 H, m, 2 × NCH_2CH_2), 1.35 (9 H, s, CMe_3), 1.30–0.90 (4 H, m, $CH_2CH_2CH_3$) and 0.80–0.70 (3 H, m, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 169.3, 169.0, 153.2, 152.1, 130.1, 129.7, 126.5, 126.3, 80.1, 79.5, 75.3, 75.0, 54.6, 48.2, 44.7, 34.7, 28.3, 28.1, 27.3, 24.9, 24.6, 23.2, 22.7, 22.6 and 14.1; *m*/*z*

(CI), 323 ($M^+ + 1$, 100%), 267 (55), 223 (35) and 124 (35) ($C_{18}H_{31}N_2O_3$ requires 323.2335. Found 323.2338).

***N*-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-isobutyl-2,5-dihydropyrrole 12**

A solution of *N*-Boc-pyrrole amide **6** (516 mg, 2.0 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (152 mg, 6.6 mmol) at −78 °C. After 1 h, isobutyl iodide (1 cm^3) was added and after a further 12 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **12** (482 mg, 79%) as a colourless solid; mp 82–86 °C (Found: C, 67.08; H, 9.52; N, 8.67. Calc. for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69%); ν_{max}(film)/cm^{-1} 2955, 2870, 1696, 1640 and 1394; δ_H(300 MHz, $CDCl_3$) 5.97, 5.89 (1 H, dt, *J* 6.3 and 2.0, C*H*=CH), 5.52 (1 H, dt, *J* 6.3 and 2.0, CH=C*H*), 4.20, 4.15 (2 H, t, *J* 2.0, NCH_2CH), 3.55–2.95 (4 H, m, 2 × NC$H_2$$CH_2$), 2.50–2.20 (1 H, m, C*H*Me_2), 2.10–1.50 (6 H, m, 2 × NCH_2CH_2, C$H_2$$CHMe_2$), 1.45, 1.40 (9 H, s, CMe_3), 0.90 (3 H, d, *J* 6.7, C$H_3$$CHCH_3$) and 0.88 (3 H, d, *J* 6.7, CH_3CHCH_3); δ_H(300 MHz, $C_6H_4Cl_2$, 140 °C) 5.75–5.65 (1 H, m, C*H*=CH), 5.45–5.35 (1 H, m, CH=C*H*), 4.15–4.05 (2 H, m, NCH_2CH), 3.40–3.20 (4 H, m, 2 × NC$H_2$$CH_2$), 2.50–2.35 (1 H, m, C*H*Me_2), 2.15–2.05 (1 H, m, HC*H*$CHMe_2$), 1.70–1.45 (5 H, m, 2 × NCH_2CH_2, *H*CH-$CHMe_2$), 1.40 (9 H, s, CMe_3) and 0.90–0.75 (6 H, m, CMe_2); δ_C(75 MHz, $CDCl_3$) 169.3, 153.2, 130.9, 130.4, 126.4, 80.2, 79.6, 75.6, 75.3, 54.7, 48.5, 44.7, 43.0, 28.4, 27.4, 25.3, 24.6, 23.2 and 23.0; *m*/*z* (CI), 323 ($M^+ + 1$, 100%), 267 (30), 223 (10) and 124 (25); ($C_{18}H_{31}N_2O_3$ requires 323.2335. Found 323.2339).

***N*-(*tert*-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2,5-dihydropyrrole 13**

A solution of the *N*-Boc-pyrrole amide **6** (500 mg, 1.9 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.7 mmol) at −78 °C. After 1 h, saturated NH_4Cl solution (5 cm^3) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydropyrrole **13** (358 mg, 71%) as a pale yellow oil (Found: C, 63.06; H, 8.45; N, 10.39. Calc. for $C_{14}H_{22}N_2O_4$: C, 63.17; H, 8.33; N, 10.53%); ν_{max}(film)/cm^{-1} 2974, 2875, 1704, 1659 and 1399; δ_H(300 MHz, $CDCl_3$) 6.04–5.92 (1 H, m, C*H*=CH), 5.74–5.64 (1 H, m, CH=C*H*), 5.24–5.09 (1 H, m, C*H*NBoc), 4.38–4.12 (2 H, m, NCH_2CH), 3.60–3.38 (4 H, m, 2 × NC$H_2$$CH_2$), 2.05–1.80 (4 H, m, 2 × NCH_2CH_2) and 1.47, 1.42 (9 H, s, CMe_3); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 6.12 (1 H, d, *J* 7.5, C*H*=CH), 5.94 (1 H, d, *J* 7.5, CH=C*H*), 5.50–5.44 (1 H, m, C*H*NBoc), 4.64–4.46 (2 H, m, NCH_2CH), 3.86–3.72 (4 H, m, 2 × NC$H_2$$CH_2$), 2.18–2.0 (4 H, m, 2 × NCH_2CH_2) and 1.80 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 168.3, 168.1, 153.8, 153.4, 129.1, 128.8, 124.5, 79.9, 79.7, 66.8, 65.7, 53.7, 53.4, 46.5, 46.2, 45.9, 45.6, 28.4, 28.3, 26.5, 26.2 and 23.9; *m*/*z* (CI), 267 ($M^+ + 1$, 100%), 211 (50), 167 (35) and 68 (30); ($C_{14}H_{22}N_2O_3$ requires 266.1630. Found 266.1634).

***N*-(*N*,*N*-Diethylcarbamoyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrole 14**

A solution of the pyrrole amide **2** (5 g, 30.5 mmol) in THF (15 cm^3) was added to NaH (1.46 g, 60.9 mmol) in THF (15 cm^3) at room temperature. After 30 min, *N*,*N*-diethylcarbamoyl chloride (5.8 cm^3, 45.8 mmol) was added slowly and the reaction was heated at 45 °C for 8 h. The reaction mixture was diluted with water (10 cm^3), extracted with EtOAc (3 × 30 cm^3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (eluting with petrol–EtOAc 1:2) afforded the *N*-diethylcarbamoylpyrrole amide **14** (7.3 g, 91%) as a colourless oil (Found: C, 63.66; H, 8.21; N, 15.73. Calc. for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96%); ν_{max}(film)/cm^{-1} 2971, 2876, 1705, 1622, 1534 and 1433; δ_H(300 MHz, $CDCl_3$) 6.85 (1 H, dd, *J* 2.9, 1.5, Ar*H*), 6.55 (1 H, dd, *J* 3.7, 1.5, Ar*H*), 6.20 (1 H, dd, *J* 3.7, 2.9, Ar*H*), 3.74–3.56 (4 H, m, 2 × NC$H_2$$CH_3$), 3.34 (4 H, br s, 2 × NC$H_2$$CH_2$), 1.92 (4 H, br s, 2 × NCH_2CH_2) and 1.20 (6 H, t, *J* 7, 2 × NCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 155.7, 149.6, 123.0, 118.2, 109.0, 104.4, 44.3, 41.9, 37.9, 22.0 and 19.6; *m*/*z* (EI), 263 (M^+, 50%), 100 (100), 94 (60), 72 (100), and 70 (90) ($C_{14}H_{21}N_3O_2$ requires 263.1634. Found 263.1631).

***N*-(*N*,*N*-Diethylcarbamoyl)-2-(pyrrolidin-1-ylcarbonyl)-2-methyl-2,5-dihydropyrrole 15**

A solution of pyrrole amide **14** (500 mg, 1.9 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (131 mg, 5.7 mmol) at −78 °C. After 2 h, methyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with toluene–acetone 5:1) gave the dihydropyrrole **15** (447 mg, 85%) as a colourless solid; mp 152–153 °C; ν_{max}(film)/cm^{-1} 2970, 2872, 1639, 1620, 1414 and 1349; δ_H(300 MHz, $CDCl_3$) 5.85 (1 H, dt, *J* 6.3, *J* 2.0, C*H*=CH), 5.64 (1 H, dt, *J* 6.3, *J* 2.0, CH=C*H*), 4.36 (1 H, dt, *J* 2.0, *J* 14.7, NCH_2CH), 4.09 (1 H, dt, *J* 2.0, *J* 14.7, NCH_2CH), 3.73–3.35 (4 H, m, 2 × NC$H_2$$CH_2$), 3.35–2.89 (4 H, m, 2 × NC$H_2$$CH_3$), 1.98–1.66 (4 H, m, 2 × NCH_2CH_2), 1.58 (3 H, s, CMe) and 1.11 (6 H, t, *J* 7.1, 2 × NCH_2CH_3); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 6.04 (1 H, d, *J* 6.0, C*H*=CH), 5.90 (1 H, d, *J* 6.0, CH=C*H*), 4.65 (1 H, d, J_{AB} 11.5, NCH_2CH), 4.47 (1 H, d, J_{AB} 11.5, NCH_2CH), 3.81–3.70 (4 H, m, 2 × NC$H_2$$CH_2$), 3.62–3.50 (2 H, m, NC$H_2$$CH_3$), 3.35–3.25 (2 H, m, NC$H_2$$CH_3$), 2.10–1.95 (7 H, m, 2 × NCH_2CH_2, C*M*e) and 1.45 (6 H, t, *J* 7.2, 2 × NCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 169.3, 159.4, 131.6, 125.0, 74.1, 54.6, 48.1, 44.5, 43.3, 27.2, 23.8, 23.1 and 14.0; *m*/*z* (CI), 280 ($M^+ + 1$, 30%), 209 (100), 181 (35), and 72 (25) ($C_{15}H_{23}N_3O_2$ requires 279.1946. Found 279.1945).

Isopropyl *N*-(*tert*-butoxycarbonyl)pyrrole-2-carboxylate 16

Trichloroacetyl pyrrole **1** (5 g, 23.7 mmol) was suspended in water (5 cm^3) and KOH (1.33 g, 23.7 mmol) was added. The reaction was heated at 80 °C for 12 h and excess water removed by azeotropic distillation with toluene. The potassium salt was dried under vacuum for 12 h and then suspended in dichloromethane (15 cm^3). Oxalyl chloride (3.1 cm^3, 35.5 mmol) was added dropwise to the mixture in an ice bath and after 30 min the reaction was refluxed for 3 h. Excess oxalyl chloride was removed *in vacuo* and the acid chloride was then dissolved in isopropyl alcohol (10 cm^3) and heated at reflux for 12 h. Excess isopropyl alcohol was evaporated to afford the pyrrole isopropyl ester (2.73 g, 75%) as a dark viscous oil.

A solution of the pyrrole isopropyl ester (2.5 g, 16.3 mmol) in THF (5 cm^3) was added to NaH (782 mg, 32.6 mmol) in THF (10 cm^3) at room temperature. After 30 min, di-*tert*-butyl dicarbonate (9.0 cm^3, 39.1 mmol) was added slowly and the reaction heated at 45 °C for 12 h. The reaction mixture was then diluted with water (10 cm^3), extracted with dichloromethane (3 × 30 cm^3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (eluting with petrol–EtOAc 5:1) afforded the *N*-Boc pyrrole isopropyl ester **16** (4.0 g, 97%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 2980, 2930, 1753, 1724 and 1450; δ_H(300 MHz, $CDCl_3$) 7.35 (1 H, dd, *J* 3.5, 1.8, Ar*H*), 6.85 (1 H, dd, *J* 3.5, 1.8, Ar*H*), 6.20 (1 H, t, *J* 3.5, Ar*H*), 5.20 (1 H, sp, *J* 6.3, C*H*Me_2) 1.65, 1.55 (9 H, s, CMe_3) and 1.09 (6 H, d, *J* 6.3, CMe_2); δ_C(75 MHz, $CDCl_3$) 213.5, 212.8, 160.4, 148.4, 126.5, 126.1, 110.0, 85.2, 84.6, 68.3, 27.7, 27.4 and 21.9; *m*/*z* (CI) 254 ($M^+ + 1$, 10%), 215 (55), 198 (100), 111 (35) and 94 (30) ($C_{13}H_{19}NO_4$ requires 253.1314. Found 253.1316).

N-(*tert*-Butoxycarbonyl)-2-(isopropoxycarbonyl)-2-methyl-2,5-dihydropyrrole 17

A solution of the *N*-Boc pyrrole isopropyl ester **16** (500 mg, 2.0 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (40 cm^3) and sodium (136 mg, 6.0 mmol) at −78 °C. After 5 min, methyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 9:1) afforded the dihydropyrrole **17** as a colourless oil (463 mg, 87%) (Found: C, 62.44; H, 8.68; N, 5.27. Calc. for $C_{14}H_{23}NO_4$: C, 62.51; H, 8.62; N, 5.21%); ν_{max}(film)/cm^{-1} 2977, 2927, 1740, 1707, 1456 and 1389; δ_H(300 MHz, $CDCl_3$) 5.91–5.78 (1 H, m, C*H*=CH), 5.60–5.50 (1 H, m, CH=C*H*), 5.04–4.82 (1 H, m, C*H*Me_2), 4.38–4.04 (2 H, m, NCH_2CH), 1.64, 1.58 (3 H, s, CMe), 1.44, 1.42 (9 H, s, CMe_3) and 1.25–1.14 (6 H, m, CH*Me*$_2$); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 5.45–5.35 (1 H, m, C*H*=CH), 5.25–5.15 (1 H, m, CH=C*H*), 4.70–4.60 (1 H, m, C*H*Me_2), 3.97 (1 H, d, J_{AB} 15.5, NCH_2CH), 3.84 (1 H, d, J_{AB} 15.5, NCH_2CH), 1.40 (3 H, s, CMe), 1.15 (9 H, s, CMe_3), 0.89 (3 H, d, *J* 6.4, *Me*CHMe) and 0.86 (3 H, d, *J* 6.4, MeCH*Me*); δ_C(75 MHz, $CDCl_3$) 171.9, 171.8, 153.5, 153.4, 131.8, 126.8, 80.2, 79.5, 72.2, 71.7, 68.8, 68.5, 54.5, 28.5, 28.4, 22.6, 21.8 and 21.7; *m*/*z* (CI) 270 (M^+ + 1, 100%), 214 (15), 170 (10) and 82 (15) ($C_{14}H_{24}NO_4$ requires 270.1705. Found 270.1712).

N-(*tert*-Butoxycarbonyl)-2-(isopropoxycarbonyl)-2-isobutyl-2,5-dihydropyrrole 18

A solution of the *N*-Boc pyrrole isopropyl ester **16** (500 mg, 2.0 mmol) in THF (10 cm^3) was added rapidly to a mixture of ammonia (150 cm^3), THF (30 cm^3) and sodium (136 mg, 6.0 mmol) at −78 °C. After 5 min, isobutyl iodide (1 cm^3) was added and after a further 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for **7**, flash chromatography (eluting with petrol–acetone 9:1) afforded the dihydropyrrole **18** as a colourless oil (473 mg, 76%) (Found: C, 65.62; H, 9.19; N, 4.62. Calc. for $C_{17}H_{29}NO_4$; C, 65.57; H, 9.39; N, 4.50%); ν_{max}(film)/cm^{-1} 2977, 2868, 1736, 1706, 1468 and 1390; δ_H(300 MHz, $CDCl_3$) 5.93–5.81 (1 H, m, C*H*=CH), 5.53–5.44 (1 H, m, CH=C*H*), 5.02–4.82 (1 H, m, OC*H*Me_2), 4.40–4.03 (2 H, m, NCH_2CH), 2.40–1.80 (2 H, m, CH_2CHMe_2), 1.55–1.45 (1 H, m, CH_2C*H*Me_2), 1.40, 1.45 (9 H, s, CMe_3), 1.25–1.10 (6 H, m, OCH*Me*$_2$) and 0.90–0.85 (6 H, m, CH_2CH*Me*$_2$); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 6.15–6.10 (1 H, m, C*H*=CH), 5.89–5.84 (1 H, m, CH=C*H*), 5.36–5.29 (1 H, m, OC*H*Me_2), 4.69 (1 H, d, *J* 15.5, NCH_2CH), 4.51 (1 H, d, *J* 15.5, NCH_2CH), 2.90–2.70 (1 H, m, *H*CH-CHMe_2), 2.40 (1 H, dd, *J* 15.2, *J* 5.8, HC*H*CHMe_2), 2.07–1.97 (1 H, m, CH_2C*H*Me_2), 1.85 (9 H, s, CMe_3), 1.57 (3 H, d, *J* 6.2, *Me*CMe), 1.54 (3 H, d, *J* 6.2, MeC*Me*) and 1.31–1.26 (6 H, m, CH_2CH*Me*$_2$); δ_C(75 MHz, $CDCl_3$) 171.9, 171.8, 153.5, 153.2, 131.0, 130.7, 127.3, 80.1, 79.3, 75.7, 75.2, 68.6, 68.3, 55.1, 55.0, 41.1, 39.9, 28.3, 24.7, 24.5, 24.0, 23.3, 21.7 and 21.5; *m*/*z* (CI) 312 (M^+ + 1, 10%), 256 (100), 212 (80) and 124 (50) ($C_{17}H_{29}NO_4$ requires 311.2096. Found 311.2099).

2-(Pyrrolidin-1-ylcarbonyl)-2-methyl-2,5-dihydropyrrole 19

A solution of the pyrroline **7** (60 mg, 0.21 mmol) in dichloromethane (10 cm^3) was cooled in an ice bath and treated with trifluoroacetic acid (0.5 cm^3). After 6 h at room temperature, the reaction mixture was poured into NaOH solution (0.5 M) and extracted with dichloromethane (3 × 10 cm^3). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the dihydropyrrole **19** (32.4 mg, 84%) as a colourless solid; mp 68–69 °C (Found: C, 66.60; H, 8.90; N, 15.50. Calc. for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54%); ν_{max}(film)/cm^{-1} 3338, 2966, 2875, 1605 and 1452; δ_H(200 MHz, $CDCl_3$) 5.90–5.80 (2 H, m, CH=CH), 3.76 (2 H, br s, NCH_2CH), 3.65–3.40 (4 H, m, 2 × NCH_2CH_2), 2.80 (1 H, br s, NH), 2.00–1.70 (4 H, m, 2 × NCH_2CH_2) and 1.44 (3 H, s, CMe); δ_C(300 MHz, $CDCl_3$) 173.3, 131.3, 129.6, 72.9, 53.0, 47.7, 47.1, 26.9, 26.3 and 23.3; *m*/*z* (CI) 181 (M^+ + 1, 100%) and 82 (45); ($C_{10}H_{17}N_2O$ requires 181.1341. Found 181.1339).

N-Acetyl-2-methyl-2,5-dihydropyrrole-2-carboxylic acid 20

A solution of the dihydropyrrole **7** (100 mg, 0.36 mmol) in 6 M HCl (5 cm^3) was heated at 120 °C for 6 h. Excess water was removed by azeotropic distillation *in vacuo* (using toluene) to afford a brown oil which was dissolved in pyridine–CH_2Cl_2 (1:1, 10 cm^3) and cooled to 0 °C under an atmosphere of nitrogen. Acetic anhydride (0.5 cm^3), was added dropwise and the reaction mixture stirred at room temperature for 12 h. The reaction was then evaporated *in vacuo* and treated with 3 M KOH–THF (1:1, 10 cm^3). After 12 h at room temperature the reaction was acidified with 2 M HCl and extracted with EtOAc (3 × 20 cm^3). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a brown oil. Trituration in diethyl ether–petrol (1:1) gave **20** (50 mg, 84%) as a brown solid; mp 145–149 °C (Found: C, 56.60; H, 6.53; N, 8.28. Calc. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28%); ν_{max}(film)/cm^{-1} 1731, 1635, 1598, 1462 and 1377; δ_H(200 MHz, D_2O) 6.05–5.95 (1 H, m, C*H*=CH), 5.80–5.70 (1 H, m, CH=C*H*), 4.45–4.35 (2 H, m, NCH_2CH), 2.06 (3 H, s, NCOMe) and 1.55 (3 H, s, CMe); δ_C(50 MHz, D_2O) 178.6, 175.0, 133.8, 130.0, 75.5, 58.1, 24.5 and 23.2; *m*/*z* (CI) 170 (M^+ + 1, 100%), 124 (10); ($C_8H_{12}NO_3$ requires 170.0817. Found 170.0820).

N-Acetyl-2-benzyl-2,5-dihydropyrrole-2-carboxylic acid 21

A solution of the dihydropyrrole **8** (80 mg, 0.22 mmol) in 6 M HCl (3 cm^3) was heated at 120 °C for 18 h. Excess water was removed by evaporation *in vacuo* to afford a brown oil which was dissolved in pyridine–CH_2Cl_2 (1:1, 2 cm^3) and cooled to 0 °C under an atmosphere of nitrogen. Acetic anhydride (0.5 cm^3) was added dropwise and the reaction mixture stirred at room temperature for 18 h. The reaction was then evaporated *in vacuo* and treated with 3 M KOH–THF (1:1, 10 cm^3). After 16 h at room temperature the reaction was acidified with 2 M HCl and extracted with EtOAc (3 × 20 cm^3). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a brown oil. Trituration in diethyl ether–petrol (1:1) gave the title compound (48 mg, 88%) as a brown solid; mp 175–178 °C (Found: C, 68.28; H, 6.05; N, 5.57. Calc. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%); ν_{max}(film)/cm^{-1} 1729, 1637 and 1601; δ_H(200 MHz, $CDCl_3$) 7.48–7.05 (5 H, m, Ph*H*), 5.97 (1 H, dt, *J* 6 and 2, C*H*=CH), 5.72 (1 H, dt, *J* 6 and 2, CH=C*H*), 4.10 (1 H, dt, *J* 14.5 and 2, NCH_2CH), 3.83 (1 H, d, *J* 14, PhCH_2), 3.45 (1 H, dt, *J* 14.5 and 2, NCH_2CH), 3.14 (1 H, d, *J* 14, PhCH_2) and 2.10 (3 H, s, NCOMe); δ_C(50 MHz, $CDCl_3$) 172.9, 172.2, 135.4, 130.4, 127.8, 126.8, 126.1, 78.3, 56.4, 38.1 and 22.9; *m*/*z* (CI) 246 (M^+ + 1, 100%); ($C_{14}H_{16}NO_3$ requires 246.1130. Found 246.1127).

N-(*tert*-Butoxycarbonyl)-2-methyl-2,5-dihydropyrrole-2-carboxylic acid 22

A solution of the dihydropyrrole **17** (200 mg, 0.74 mmol) in methanol (5 cm^3) was treated with concentrated KOH solution (5 cm^3) and the mixture heated at 40 °C for 3 h. The reaction mixture was then cooled in an ice bath, acidified (HCl, 2 M) to pH (6–5) and extracted with EtOAc (3 × 20 cm^3). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (eluting with petrol–acetone 9:1) afforded the dihydropyrrole carboxylic acid **22** (124 mg, 71%) as a colourless solid; mp 94–96 °C (Found: C, 57.86; H, 7.49; N, 6.04. Calc. for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16%);

ν_{max}(film)/cm^{-1} 3084, 2978, 1742, 1704, 1624 and 1393; δ_H(300 MHz, $CDCl_3$) 9.60 (1 H, br s, CO_2H), 5.92, 5.84 (1 H, dt, *J* 6.2 and 2.0, C*H*=CH), 5.72, 5.58 (1 H, dt, *J* 6.2 and 2.0, CH=C*H*), 4.44–4.08 (2 H, m, NCH_2CH), 1.71, 1.64 (3 H, s, CMe) and 1.50, 1.46 (9 H, s, CMe_3); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 6.10–6.00 (2 H, m, CH=CH), 4.60–4.45 (2 H, m, NCH_2CH), 2.05 (3 H, s, CMe) and 1.85 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 178.1, 176.3, 154.9, 153.6, 131.7, 131.1, 127.6, 81.2, 80.8, 71.7, 54.6, 28.4, 22.6 and 21.8; *m*/*z* (CI) 228 ($M^+ + 1$, 35%), 189 (100), 172 (70), 128 (20) and 82 (60); ($C_{11}H_{18}NO_4$ requires 228.1236. Found 228.1242).

N-(*tert*-Butoxycarbonyl)-2-isobutyl-2,5-dihydropyrrole-2-carboxylic acid 23

A solution of the dihydropyrrole **18** (103 mg, 0.74 mmol) in methanol (5 cm^3) was treated with concentrated KOH solution (3 cm^3) and the mixture heated at 60 °C for 48 h. The reaction mixture was then cooled in an ice bath, acidified (HCl, 2 M) to pH (6–5) and extracted with EtOAc (3 × 15 cm^3). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (eluting with petrol–acetone 6:1) afforded **22** (68 mg, 76%) as a colourless oil (Found: C, 62.67; H, 8.99; N, 5.11. Calc. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20%); ν_{max}(film)/cm^{-1} 3100, 1740, 1706 and 1625; δ_H(300 MHz, $CDCl_3$) 10.20 (1 H, br s, CO_2H), 5.95–5.44 (2 H, m, CH=CH), 4.37–4.05 (2 H, m, NCH_2CH), 2.28, 2.13 (1 H, dd, *J* 14 and 8, CH_2CHMe$_2$), 1.82 (1 H, dd, *J* 14 and 8, CH_2CHMe$_2$), 1.52–1.44 (1 H, m, C*H*Me$_2$), 1.41, 1.36 (9 H, s, CMe_3) and 0.83, 0.79 (6 H, d, *J* 7, CH*Me*$_2$); δ_H(500 MHz, $C_6H_4Cl_2$, 140 °C) 5.60–5.40 (2 H, m, CH=CH), 3.95–3.85 (2 H, m, NCH_2CH), 2.07 (1 H, ddd, *J* 15, 7.5 and 2.5, CH_2CHMe$_2$), 1.72 (1 H, br d, *J* 15, CH_2CHMe$_2$), 1.44–1.32 (1 H, m, C*H*Me$_2$), 1.25 (9 H, s, CMe_3) and 0.64 (6 H, br d, *J* 7.5, CMe$_2$); δ_C(75 MHz, $CDCl_3$) 178.1, 153.6, 130.5, 130.3, 128.1, 125.9, 80.6, 75.1, 55.2, 55.1, 41.2, 40.4, 28.3, 24.5, 24.1, 23.9 and 23.2; *m*/*z* (CI) 270 ($M^+ + 1$, 20%) and 214 (100); ($C_{14}H_{24}NO_4$ requires 270.1705. Found 270.1712).

N-(*tert*-Butoxycarbonyl)-5-(pyrrolidin-1-ylcarbonyl)-5-methyl-2,5-dihydropyrrol-2-one 24

The complex between chromium trioxide and 3,5-dimethylpyrazole was prepared at low temperature (−30 °C to −20 °C) by rapid addition of 3,5-dimethylpyrazole (686 mg, 7.14 mmol) to pre-dried chromium trioxide (714 mg, 7.14 mmol), suspended in dichloromethane (5 cm^3). After stirring for 30 min, the substrate **7** (100 mg, 0.357 mmol) was added and the temperature slowly raised to 0 °C. After 2 h the mixture was treated with (aq.) KOH (3 M, 3 cm^3), stirred for a further 1 h at room temperature and concentrated under reduced pressure. The red solid residue was dissolved in EtOAc (15 cm^3) and then washed with ice cold 2 M HCl (5 × 10 cm^3). The organic layer was then treated with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography, eluting with petrol–acetone (4:1) afforded **24** (67 mg, 64%) as an off-white solid; mp 130–135 °C (Found: C, 61.23; H, 7.35; N, 9.31. Calc. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52%); ν_{max}(film)/cm^{-1} 1777, 1742, 1717 and 1644; δ_H(200 MHz, $CDCl_3$) 7.05 (1 H, d, *J* 6, C*H*=CH), 6.19 (1 H, d, *J* 6, CH=C*H*), 3.55–3.00 (4 H, m, 2 × NCH_2CH$_2$), 1.86–1.62 (4 H, m, 2 × NCH$_2$CH_2), 1.72 (3 H, s, CMe) and 1.47 (9 H, s, CMe_3); δ_C(75 MHz, $CDCl_3$) 169.0, 164.8, 150.7, 148.2, 126.2, 83.7, 71.5, 48.9, 45.5, 27.9, 27.2, 23.6 and 23.1; *m*/*z* (CI) 295 ($M^+ + 1$, 5%) and 195 (100); ($C_{15}H_{23}N_2O_4$ requires 295.1658. Found 295.1661).

N-(*tert*-Butoxycarbonyl)-5-(pyrrolidin-1-ylcarbonyl)-5-isobutyl-2,5-dihydropyrrol-2-one 25

The complex between chromium trioxide and 3,5-dimethylpyrazole was prepared at low temperature (−30 °C to −20 °C) by rapid addition of 3,5-dimethylpyrazole (621 mg, 6.21 mmol) to pre-dried chromium trioxide (597 mg, 6.21 mmol), suspended in dry dichloromethane (5 cm^3). After stirring for 30 min, the substrate **12** (100 mg, 0.311 mmol) was added and the temperature slowly raised to 0 °C. After 2 h the mixture was treated with (aq.) KOH (3 M, 3 cm^3) and stirred for a further 1 h at room temperature and concentrated under reduced pressure. The red solid residue was then dissolved in EtOAc (15 cm^3) and washed with ice cold 2 M HCl (5 × 10 cm^3). The organic layer was then treated with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography, eluting with petrol–acetone (4:1) afforded **25** as a colourless oil (71 mg, 68%); ν_{max}(film)/cm^{-1} 1777, 1742, 1644 and 1312; δ_H(300 MHz, $CDCl_3$) 6.99 (1 H, d, *J* 6, C*H*=CH), 6.31 (1 H, d, *J* 6, CH=C*H*), 3.64–3.02 (4 H, m, 2 × NCH_2CH$_2$), 2.43 (1 H, dd, *J* 15 and 6, CH_2CHMe$_2$), 2.30 (1 H, dd, *J* 15 and 6, CH_2CHMe$_2$), 2.00–1.58 (4 H, m, 2 × NCH$_2$CH_2), 1.51 (9 H, s, CMe_3), 1.36–1.22 (1 H, m, C*H*Me$_2$) and 0.87 (6 H, d, *J* 7, CH*Me*$_2$); δ_C(75 MHz, $CDCl_3$) 169.5, 164.9, 149.4, 148.2, 127.0, 83.51, 74.3, 49.1, 45.3, 41.7, 27.9, 27.2, 25.0, 24.3, 22.9 and 22.3; *m*/*z* (FAB), 359 ($M^+ + 23$, 40%) and 259 (100), 237 (70); ($C_{18}H_{29}N_2O_4$ requires 337.2127. Found 337.2138).

N-(*tert*-Butoxycarbonyl)-5-(isopropoxycarbonyl)-5-methyl-2,5-dihydropyrrol-2-one 26

The complex between chromium trioxide and 3,5-dimethylpyrazole was prepared at low temperature (−30 °C to −20 °C) by rapid addition of 3,5-dimethylpyrazole (715 mg, 7.43 mmol) to pre-dried chromium trioxide (744 mg, 7.44 mmol), suspended in dry dichloromethane (5 cm^3). After stirring for 30 min, the substrate **17** (100 mg, 0.37 mmol) was added and the temperature slowly raised to 0 °C. After 2 h the mixture was treated with (aq.) KOH (3 M, 3 cm^3) and stirred for a further 1 h at room temperature and concentrated under reduced pressure. The red solid residue was then dissolved in EtOAc (15 cm^3) and washed with ice cold 2 M HCl (5 × 10 cm^3). The organic layer was then treated with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography, eluting with petrol–acetone (4:1) afforded **26** (70.5 mg, 67%) as a colourless oil (Found: C, 59.18; H, 7.42; N, 5.03. Calc. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94%); ν_{max}(film)/cm^{-1} 1782, 1739 (br) and 1607; δ_H(200 MHz, $CDCl_3$) 6.95 (1 H, d, *J* 6.9, C*H*=CH), 6.17 (1 H, d, *J* 6.9, CH=C*H*), 5.0 (1 H, sept, *J* 6.9, C*H*Me$_2$), 1.72 (3 H, s, CMe), 1.53 (9 H, s, CMe_3), 1.22 (3 H, d, *J* 6.9, *Me*CHMe) and 1.18 (3 H, d, *J* 6.9, MeCH*Me*); δ_C(75 MHz, $CDCl_3$) 168.6, 168.1, 150.0, 148.6, 126.8, 83.60, 70.25, 70.17, 28.00, 21.54, 21.49 and 20.52; *m*/*z* (CI) 284 ($M^+ + 1$, 10%) and 184 (100); ($C_{14}H_{22}NO_5$ requires 284.1498. Found 284.1498).

Crystal data: (*RS*)-7

$C_{15}H_{24}N_2O_3$, $M = 280.37$. Monoclinic, space group $P2_1/c$ (#14), crystal dimensions 0.18 × 0.25 × 0.37 mm, colourless prismatic crystal, $a = 8.388(2)$, $b = 13.930(3)$, $c = 13.570(3)$ Å, $\beta = 103.57(2)$, $U = 1541.4(6)$ Å^3 by least-squares refinement on diffractometer angles for 25 carefully centered reflections in the range $15.28 < 2\theta < 21.71°$, $Z = 4$, $D_c = 1.208$ g cm^{-1}, $F(000) = 608.00$.

Data collection and processing. Rigaku AFC5R diffractometer, graphite monochromated Mo-Kα radiation ($\lambda = 0.710\,69$ Å), μ(Mo-Kα) 0.79 cm^{-1}, 3054 reflections measured, maximum 2θ value of 50.1°, segment ($+h$, $+k$, $\pm l$), 2851 unique reflections measured ($R_{int} = 0.024$), 1728 of these with $I > 3.00\sigma(I)$ used in refinement. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.97 to 1.00. The intensities of three representative reflections measured after every 150 reflections showed no sign of decay.

Structure solution and refinement. Solution by direct methods,[15] hydrogen atoms included in idealised positions (C–H 0.95 Å) with isotropic thermal parameters 20% greater than the equivalent B value of the relevant carbon. The structure was refined by full-matrix least-squares refinement on F with all non-hydrogen atoms anisotropic and the hydrogen atoms fixed, $R = 0.041$, $R_\omega = 0.037$, $\omega = 1/[\sigma^2(F_o) + 0.00\,002F_o^2]$ for 181 refined parameters. Max/min peaks in final difference map 0.15/0.13.

Crystal data: (*RS*)-24

$C_{15}H_{22}N_2O_4$, $M = 294.35$. Orthorhombic, space group $Pna2_1$ (#33), crystal dimensions $0.50 \times 0.18 \times 0.18$ mm, colourless block crystal, $a = 16.585(3)$, $b = 8.566(2)$, $c = 11.409(3)$ Å, $U = 1620(1)$ Å^3 by least-squares refinement on diffractometer angles for 25 carefully centered reflections in the range $15.15 < 2\theta < 19.67°$, $Z = 4$, $D_c = 1.21$ g cm^{-1}, $F(000) = 632.00$.

Data collection and processing. Rigaku AFC5R diffractometer, graphite monochromated Mo-Kα radiation ($\lambda = 0.710\,69$ Å), μ(Mo-Kα) 0.9 cm^{-1}, 1676 unique reflections measured, maximum 2θ value of 50.0°, segment ($+h$, $+k$, $+l$), 1113 of these with $I > 3.00\,\sigma(I)$ used in refinement. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.96 to 1.00. The intensities of three representative reflections measured after every 150 reflections showed no sign of decay.

Structure solution and refinement. Solution by direct methods,[15] hydrogen atoms included in idealised positions (C–H 0.95 Å) with isotropic thermal parameters 20% greater than the equivalent B value of the relevant carbon. The structure was refined by full-matrix least-squares refinement on F with all non-hydrogen atoms anisotropic and the hydrogen atoms fixed, $R = 0.046$, $R_\omega = 0.035$, $\omega = 1/[\sigma^2(F_o)]$ for 190 refined parameters. Max/min peaks in final difference map $0.15/-0.15$. Calculations for both crystal structures were performed using TEXSAN.§[16]

§ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/178.

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References

1 For example see: A. Gossauer and P. Nesvadba, in *The Chemistry of Heterocyclic Compounds*: *Pyrroles*, J. Wiley, New York, 1990, vol. 48, Part 1.
2 G. W. Gribble, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol 8; T. J. Donohoe, R. Garg and C. A. Stevenson, *Tetrahedron*: *Asymmetry*, 1996, **7**, 317.
3 G. G. Evans, *J. Am. Chem. Soc.*, 1951, **73**, 5230; D. P. Schumacher and S. S. Hall, *J. Am. Chem. Soc.*, 1982, **104**, 6076; J. Cornforth and Minghui Dui, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 1463.
4 D. M. Ketcha, K. P. Carpenter and Q. Zhou, *J. Org. Chem.*, 1991, **56**, 1318.
5 J. W. Scott, A. Focella, U. O. Hengartner, D. R. Parrish and D. Valentine Jr., *Synth. Commun*, 1980, **10**, 529.
6 For general reviews of the Birch reduction see: (*a*) L. N. Mander, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol 8; (*b*) P. W. Rabideau and Z. Marcinow, *Org. React.*, 1992, **42**, 1; (*c*) P. W. Rabideau, *Tetrahedron*, 1989, **45**, 1579.
7 A. J. Birch and J. Slobbe, *Heterocycles*, 1976, **5**, 905.
8 T. J. Donohoe and P. M. Guyo, *J. Org. Chem.*, 1996, **61**, 7664.
9 Compound **1** can also be prepared conveniently from pyrrole and trichloroacetyl chloride: J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 3618; D. M. Wallace, S. H. Leung, M. S. O'Senge and K. Smith, *J. Org. Chem.*, 1993, **58**, 7245.
10 E. M. Kaiser, *Synthesis*, 1972, 391.
11 For example see: P. W. Rabideau and E. G. Burkholder, *J. Org. Chem.*, 1978, **43**, 4283.
12 J. M. Hook, L. N. Mander and M. Woolias, *Tetrahedron Lett.*, 1982, **23**, 4499; see also P. W. Rabideau, D. M. Wetzel and D. M. Young, *J. Org. Chem.*, 1984, **49**, 1544.
13 For a reference to autoxidation see: A. H. Haines, *Methods for the Oxidation of Organic Compounds*, Academic Press, London, 1985.
14 E. J. Corey and G. W. Fleet, *Tetrahedron Lett.*, 1973, 4499.
15 SIR92: A. Altomare, M. Cascarano, C. Giacovazzo and A. Guagliardi, *J. Appl. Cryst.*, 1993, **26**, 343.
16 TEXSAN, Structure analysis package, 1992, MSC, The Woodlands, TX 77 381, USA.

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