Annulation of dihydroimidazoles: a 1,3-dipolar cycloaddition route to pyrrolo[1,2-*a*]imidazoles, pyrrolidines and pyrroles

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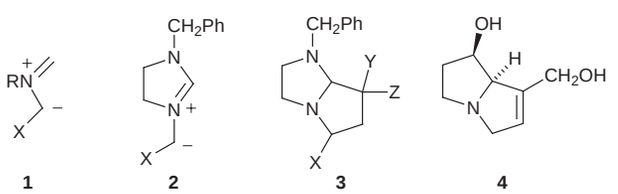
4,5-Dihydroimidazolium ylides, formed by *N*-alkylation of 4,5-dihydroimidazoles, undergo diastereoselective *endo* 1,3-dipolar cycloaddition with electron-deficient alkene dipolarophiles to afford hexahydropyrrolo[1,2-*a*]imidazoles; reduction of the aminal functionality in the cycloadducts leads to substituted pyrrolidines. Cycloaddition using 2-chloropropenonitrile, followed by base treatment, affords pyrroles.

Introduction

The use of azomethine ylides **1** as 1,3-dipoles in cycloaddition reactions to form five-membered nitrogen-containing rings has been the focus of considerable attention.[1] Our long-standing interest in the chemistry of 4,5-dihydroimidazoles (2-imidazolines),[2] including their annulation,[3] and the limited reports of the use of amidines as sources of azomethine ylides,[4] prompted us to investigate the generation and reactions of 4,5-dihydroimidazolium ylides **2**. In our preliminary reports,[5] ylides **2** have been shown to undergo diastereoselective cycloaddition reactions to produce novel hexahydropyrrolo[1,2-*a*]imidazoles **3**, of interest (i) as aza-analogues of naturally occurring pyrrolizidines, *e.g.* retronecine **4**, the heterocyclic sub-unit of



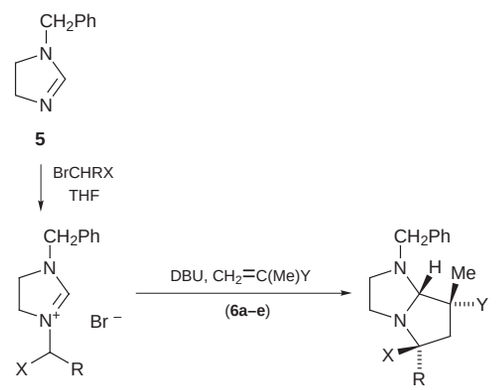
1 **2** **3** **4**

many of the hepatotoxic pyrrolizidine alkaloids,[6] and (ii) because hexahydropyrrolo[1,2-*a*]imidazoles have been reported to have antiinflammatory properties.[7] Furthermore, reduction or elimination leads to the formation of pyrrolidines and pyrroles respectively. We now report in full the results of our investigations in this area.[5]

Results and discussion

Our strategy for generation of the ylides **2** was the *N*-alkylation of a 2-unsubstituted 4,5-dihydroimidazole followed by *C*-deprotonation. Initial investigations focussed on stabilised azomethine ylides, that is those bearing an electron withdrawing group on the formally negative end of the dipole. In our early protocol,[5a] later revised to a one-pot procedure,[5b] a quaternary salt of the dihydroimidazole was formed and isolated before being subjected to the deprotonation–cycloaddition step.

Thus, 1-benzyl-4,5-dihydroimidazole **5** was easily prepared by treatment of *N*-benzyl-1,2-diaminoethane with excess triethyl orthoformate under acidic catalysis. Dihydroimidazole **5** was smoothly *N*-alkylated to form the quaternary salts **6a**–**g** using, respectively, the α-bromo esters methyl, ethyl and *tert*-butyl bromoacetate, as well as ethyl 2-bromopropionate, 2-bromoacetophenone, bromoacetonitrile, and 4-nitrobenzyl bromide by dropwise addition of the bromide to a stirred solution of the imidazoline in THF under nitrogen (Scheme 1). Isolation by simple filtration or evaporation afforded hygroscopic solids or semi-solids which were not fully characterized and were used immediately.



6a; R = H, X = CO_2Me
6b; R = H, X = CO_2Et
6c; R = H, X = CO_2Bu^t
6d; R = Me, X = CO_2Et
6e; R = H, X = COPh
6f; R = H, X = CN
6g; R = H, X = 4-$O_2NC_6H_4$

7a; R = H, X = Y = CO_2Me
7b; R = H, X = CO_2Et, Y = CO_2Me
7c; R = H, X = CO_2Bu^t, Y = CO_2Me
7d; R = H, X = COPh, Y = CO_2Me
7e; R = H, X = CO_2Me, Y = CN
7f; R = H, X = CO_2Et, Y = CN
7g; R = H, X = CO_2Bu^t, Y = CN
7h; R = Me, X = CO_2Et, Y = CN
7i; R = H, X = COPh, Y = CN

Scheme 1

Selecting as a test reaction 1-benzyl-3-ethoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide **6b** as dipole precursor, and methyl 2-methylpropenoate as dipolarophile, a range of bases was examined for ylide formation by deprotonation of the dihydroimidazolium salt. *n*-Butyllithium in THF at −78 °C failed to yield any cycloaddition product, as did triethylamine or diisopropylethylamine at room temperature in the absence of solvent, or a number of the phosphazene bases in THF.[8] Success finally came with the use of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) at room temperature without solvent, affording cycloadduct **7b** which was isolated as a 10 : 1 mixture of stereoisomers after chromatography, although in a disappointingly low yield of 6%. After extensive investigation it was found that the yield of this test reaction could be raised to 34%, and yields between 29–69% obtained for the range of cycloadditions examined, with considerable improvement in the stereoisomer ratio, using one of two protocols: *Protocol A*: Dropwise addition of DBU over 10 minutes to a slurry of freshly prepared quaternary salt in excess dipolarophile; and

Table 1 Cycloaddition of azomethine ylides derived from salts **6a**–**e** (Scheme 1)

Entry	Salt	R	X	Y	Cycloadduct	Yield (%)	Protocol
1	**6a**	H	CO_2Me	CO_2Me	**7a**	29 (64)	A (C)
2	**6b**	H	CO_2Et	CO_2Me	**7b**	34	A
3	**6c**	H	CO_2Bu^t	CO_2Me	**7c**	52 (71)	B (C)
4	**6e**	H	COPh	CO_2Me	**7d**	50	B
5	**6a**	H	CO_2Me	CN	**7e**	42 (46)	B (C)
6	**6b**	H	CO_2Et	CN	**7f**	42	B
7	**6c**	H	CO_2Bu^t	CN	**7g**	69	B
8	**6d**	Me	CO_2Et	CN	**7h**	63	B
9	**6e**	H	COPh	CN	**7i**	46	B

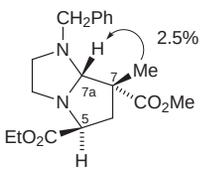
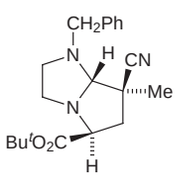


Fig. 1

Protocol B: Addition of DBU by syringe pump over 4 hours to a solution of the quaternary salt and excess dipolarophile in THF at reflux.

In later experiments it was found unnecessary to isolate the quaternary salt, and the final preferred protocol,[5b] *Protocol C*, consisted of *in situ* formation of the quaternary salt by addition of the bromo compound to a solution of imidazoline **5** in THF at reflux, followed immediately by addition of excess dipolarophile and then addition of DBU by syringe pump over 4 hours.

Cycloaddition using the salts **6a**–**c**, derived from methyl, ethyl and *tert*-butyl bromoacetates, respectively, proceeded smoothly with both methyl 2-methylpropenoate and 2-methylpropenonitrile as dipolarophile, affording *endo* adducts **7a–c** and **7e–g**, respectively (Scheme 1, Table 1). In some early, low-yielding preparations of **7g** performed at room temperature, significant proportions of a second stereoisomer **8** were



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observed. This allowed for the separation of **7g** and **8** and the characterisation of the latter as the *exo* adduct, supporting our postulate that any trace stereoisomer seen in the other cycloadditions is indeed the *exo* cycloadduct. The quaternary salt **6d**, derived from alkylation of **5** by ethyl 2-bromopropionate, afforded a 63% yield of cycloadduct **7h** with 2-methylpropenonitrile. Using the quaternary salts **6f** and **6g**, from alkylation of **5** with bromoacetonitrile or 4-nitrobenzyl bromide, respectively, cycloaddition products could not be isolated, although the benzoylmethyl salt **6e** did undergo reaction. Using methyl 2-methylpropenoate and 2-methylpropenonitrile, cycloadducts **7d** and **7i** were isolated in 50 and 46% yield, respectively.

The relative stereochemistry of the cycloadducts was secured by ^{1}H NOE difference spectroscopy. For example in cycloadduct **7b**, as shown in Fig. 1, observation of an enhancement of the signal for the bridgehead proton at C-7a on irradiation of the C-7 methyl group protons confirms that they are on the same face of the molecule, consistent with an *endo* approach of the dipolarophile to the azomethine ylide dipole. Failure to observe an enhancement at the C-5(H) on irradiation of the C-7 methyl group provides tentative evidence that they are on opposite faces of the molecule, an observation in agreement with later findings[9] and consistent with an *anti* dipole geometry.

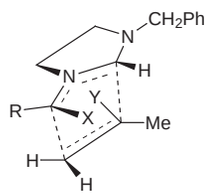
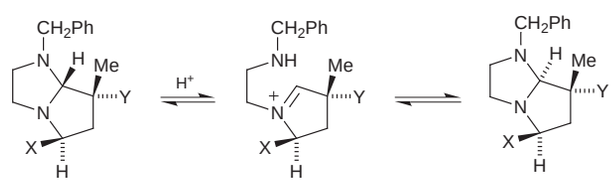


Fig. 2

The proposed transition state is summarised in Fig. 2, and is consistent with other results involving azomethine ylides generated from iminium salts.[10]

The observed regiochemistry of cycloaddition is as expected for a stabilised azomethine ylide with an electron-deficient dipolarophile, with HOMO-dipole/LUMO-dipolarophile orbital control;[11] there was no evidence of products with the alternative possible regiochemistry.

When the pyrroloimidazoles **7** were analysed by ^{1}H NMR spectroscopy immediately after chromatography on silica gel using ethyl acetate–hexane as eluent, they were found to consist of a single diastereoisomer. On storage, however, or if chromatography was performed with a basic eluent (dichloromethane–ethanol–aqueous ammonia or ethyl acetate–triethylamine), then varying amounts of a new stereoisomer were encountered, consistent with C-7a epimerisation of the primary cycloadduct; a plausible rationalization is shown in Scheme 2.



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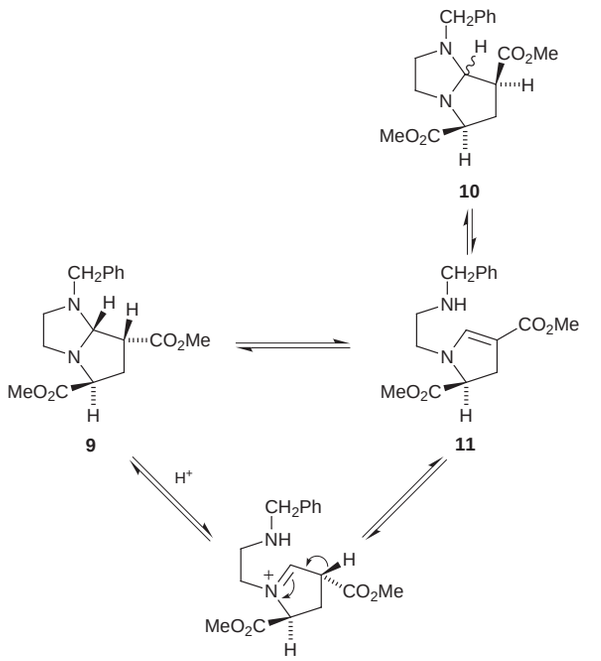
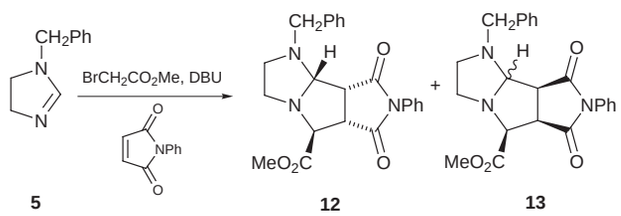
Scheme 2

Extending our studies to α-unsubstituted dipolarophiles, using *Protocol C*, treatment of dihydroimidazole **5** with methyl bromoacetate and three equivalents of methyl propenoate, followed by addition of DBU *via* syringe pump, afforded, after column chromatography, a 52% yield of cycloadduct as a 2.3 : 1 ratio of stereoisomers which could not be separated. Spectral data are consistent with the stereoisomers being epimers at C-7, *i.e.* **9** and **10**, and considering the stereoselectivity of the earlier examples, this ratio is unlikely to reflect the *endo* : *exo* preference of the reaction, rather to be a result of the chromatography. Cycloadducts **9** and **10** could also not be fully separated from a much more polar material, tentatively postulated to be enamino ester **11**, although there was no firm evidence of this in the ^{1}H or ^{13}C NMR spectra, suggesting that if **11** is present, it is in trace amounts or forms only under the acidic conditions of silica gel (Scheme 3).

Using *Protocol C*, and methyl bromoacetate to alkylate dihydroimidazole **5**, cycloaddition of *N*-phenylmaleimide afforded a 6 : 1 mixture of *endo* : *exo* adducts **12** and **13**, respect-



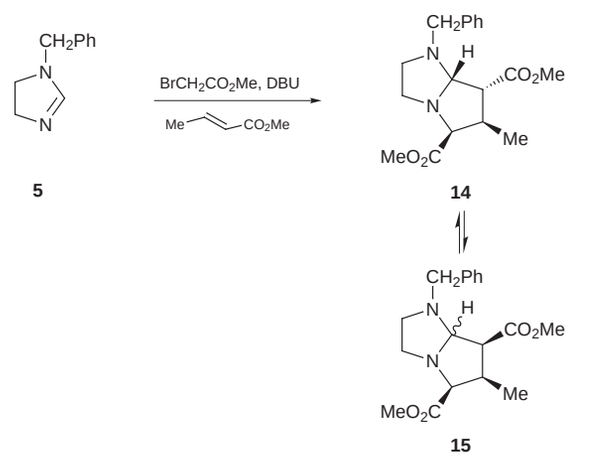
Scheme 3



Scheme 4

ively, in a combined yield of 31% (Scheme 4). Repeated column chromatography allowed for their separation, although with significant loss of material, affording only 8% of **12** and 4% of **13**.

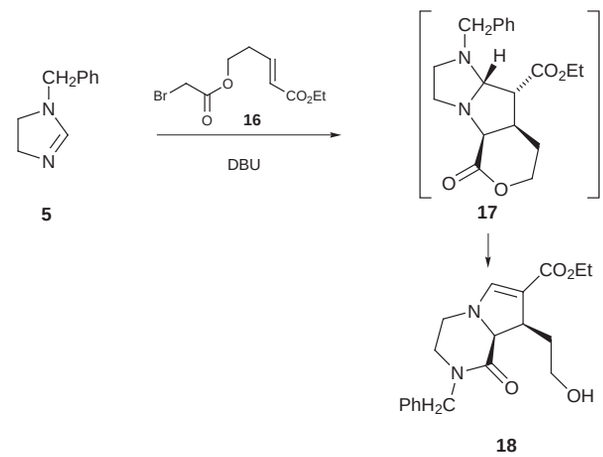
Again employing *Protocol C* and alkylating with methyl bromoacetate, cycloaddition of methyl (*E*)-but-2-enoate afforded a 22% yield of **14** as a single diastereoisomer, but this epimerised at C-7 on standing (Scheme 5) to afford **15**. Con-



Scheme 5

firmation of stereochemistry in the adducts **12** and **14** came from ^{1}H NOE difference experiments, but a combination of insufficient material and overlapping signals did not permit rigorous configurational assignment at C-7a in **13** and **15**.

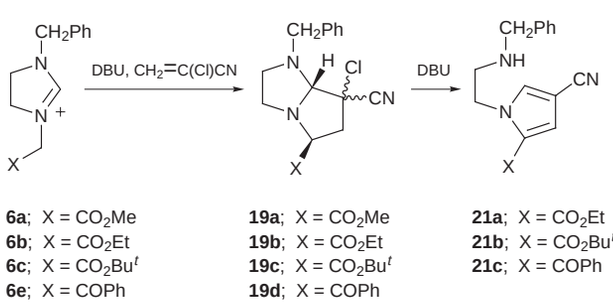
We wished to examine an intramolecular variant of the cycloaddition, to which end the bromo ester ethyl 5-(bromoacetoxy)pent-2-enoate **16** was prepared using the sequence that we have previously outlined.[12] Hydration of propenal and *in situ* Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane afforded ethyl 5-hydroxypent-2-enoate, and reaction with bromoacetyl bromide led to the dienophile **16**, which was not stable on storage and had to be used directly. Treatment of the dihydroimidazole **5** in THF at reflux with one equivalent of bromo ester **16** followed by addition of DBU *via* syringe pump over 4 hours afforded, after chromatography over silica gel, not the expected cycloadduct **17**, but rather lactam **18**. Evidence for the structure of **18**, postulated to be formed as shown in Scheme 6 *via* collapse of **17** involving elimination (*cf.*



Scheme 6

Scheme 3) and lactam formation, came from the ^{1}H and ^{13}C NMR spectra, in particular signals at δ_H 7.08 and δ_C 148.10 (methine), and from infrared absorptions at ν_{max} 3376 (br, OH), 1710 (enamino ester C=O), 1657 (lactam C=O) and 1629 (C=C) cm^{-1}.

Of interest for the potential access to aza-analogues of retronecine, the cycloaddition using alkynes such as methyl propynoate as dipolarophiles was investigated, but it was found that base-catalysed polymerisation processes intervened and none of the cycloadduct was isolated. An alternative approach, circumventing the use of alkynes, would be to synthesise 7-halo-substituted cycloadducts which could undergo hydrogen halide elimination on base treatment to introduce the desired C-6,7 unsaturation. To this end, the commercially available 2-chloropropenonitrile was found to add to quaternary salts **6a**–**c** and **6e** (*Protocol B*) to produce cycloadducts **19a**–**d**, respectively, as a 1:1 mixture of stereoisomers in all cases (Scheme 7). Elimination was effected by treatment of the



6a; X = CO_2Me
6b; X = CO_2Et
6c; X = CO_2Bu^t
6e; X = COPh

19a; X = CO_2Me
19b; X = CO_2Et
19c; X = CO_2Bu^t
19d; X = COPh

21a; X = CO_2Et
21b; X = CO_2Bu^t
21c; X = COPh

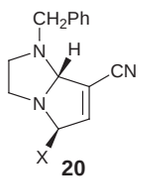
Scheme 7

chloro-cycloadducts with DBU in DMSO at 100 °C, but it did not prove possible to isolate the desired dihydropyrroles **20** which instead underwent a second elimination to form the *N*-substituted pyrroles, **18b**–**d** affording **21a**–**c**, respectively.

Also of interest was the cycloaddition of unstabilised ylides, conveniently prepared by the fluoride-mediated desilylation protocol developed by Vedejs.[13] Quaternary salt **22** was pre-

Table 2 Reduction of cycloadducts with sodium cyanoborohydride (Scheme 9)

Entry	R^1	R^2	X	Y	Cycloadduct	Pyrrolidine	Yield (%)
1	H	Me	CO_2Et	CO_2Me	**7b**	**24a**	68
2	H	Me	CO_2Et	CN	**7f**	**24b**	99
3	H	Me	CO_2Bu^t	CN	**7g**	**24c**	86
4	Me	Me	CO_2Et	CN	**7h**	**24d**	71
5	H	Cl	CO_2Bu^t	CN	**19c**	**24e**	86
6	H	Me	H	CO_2Me	**23b**	**24f**	82



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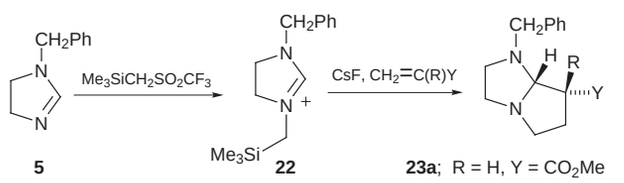
pared by alkylating the dihydroimidazole **5** as a solution in diethyl ether with trimethylsilylmethyl trifluoromethanesulfonate; solvent evaporation afforded **22** as a solid. The salt was taken up in diglyme and added by cannula to a slurry of caesium fluoride and the dipolarophile in diglyme, and the mixture stirred at room temperature for 20 h. After chromatography adducts **23a**–**c** were isolated, using methyl propenoate, methyl 2-methylpropenoate and 2-methylpropenonitrile, respectively, in yields of 43, 47, and 60% (Scheme 8). Adducts **23a** and **23b**



5 **22**

23a; R = H, Y = CO_2Me
23b; R = Me, Y = CO_2Me
23c; R = Me, Y = CN

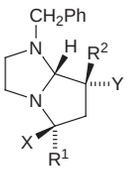
Scheme 8

were each obtained as a 1 : 1 mixture of diastereoisomers, and **23c** as a 2 : 1 mixture.

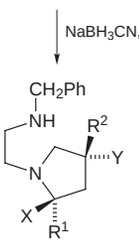
A number of fruitless attempts were made to extend the scope of the cycloaddition to less electron-poor alkenes. For example, use of 4-nitro- and 4-cyano-phenylethene, or phenylethene itself as dipolarophiles met with no success.

Treatment of an acidic solution of the cycloadducts **7** with $NaBH_3CN$ smoothly effected aminal cleavage, resulting in good yields of *N*-substituted pyrrolidines (Scheme 9, Table 2). Thus **7b** and **7f**–**h** were reduced to afford pyrrolidines **24a**–**d** in yields of 68, 99, 86 and 71%, respectively. 2-Chloropropenonitrile adduct **19c** was similarly reduced in 86% yield to **24e**, whilst 5-unsubstituted adduct **23b** was reduced to **24f** (82%). All of the pyrrolidines **24** were obtained as a single diastereoisomer after chromatography, except for chloropyrrolidine **24e** which was obtained as a 1 : 1 mixture of epimers at C-4, reflecting the composition of stereoisomers in the precursor cycloadduct **19c**. Whilst *tert*-butyloxycarbonylpyrrolidines **24c** and **24e** were stable towards lactamisation, the ethyl esters **24a**, **24b** and **24d** were found to lactamise slowly on standing. In contrast, reduction of methyl ester **9** resulted in an extremely facile cyclisation to afford lactam **25** (45% over 2 steps from **5** *via Protocol C*) as the sole product in an unchanged epimer ratio of 2.3 : 1. Chromatography allowed for the separation of pure *trans* lactam (10%), although with a considerable accompanying loss of material; the minor *cis* isomer could not be isolated in a pure form.

Reduction need not necessarily lead to ring opening. Thus, treatment of **7c** with $LiAlH_4$ in Et_2O afforded an 87% yield of diol **26a**, whilst similar treatment of **23b** gave alcohol **26b** in 98% yield (Scheme 10).

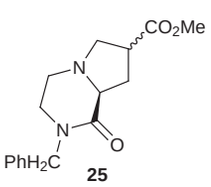


7b; R^1 = H, R^2 = Me, X = CO_2Et, Y = CO_2Me
7f; R^1 = H, R^2 = Me, X = CO_2Et, Y = CN
7g; R^1 = H, R^2 = Me, X = CO_2Bu^t, Y = CN
7h; R^1 = R^2 = Me, X = CO_2Et, Y = CN
19c; R^1 = H, R^2 = Cl, X = CO_2Bu^t, Y = CN
23b; R^1 = X = H, R^2 = Me, Y = CO_2Me



24a; R^1 = H, R^2 = Me, X = CO_2Et, Y = CO_2Me
24b; R^1 = H, R^2 = Me, X = CO_2Et, Y = CN
24c; R^1 = H, R^2 = Me, X = CO_2Bu^t, Y = CN
24d; R^1 = R^2 = Me, X = CO_2Et, Y = CN
24e; R^1 = H, R^2 = Cl, X = CO_2Bu^t, Y = CN
24f; R^1 = X = H, R^2 = Me, Y = CO_2Me

Scheme 9



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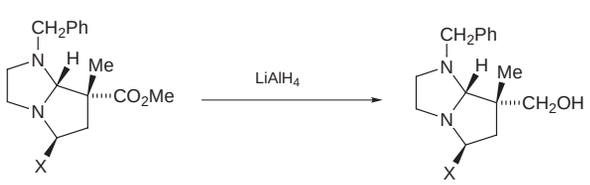

7c; X = CO_2Bu^t
23b; X = H

26a; X = CH_2OH
26b; X = H

Scheme 10

We have thus demonstrated the formation of 4,5-dihydroimidazolium ylides and their diasteroselective 1,3-dipolar cycloadditions with a variety of electron-deficient dipolarophiles to form pyrrolo[1,2-*a*]imidazoles and thence, by reduction or elimination, pyrrolidines and pyrroles. The extension of this methodology into asymmetric synthesis of the important pyrrolidine ring system has subsequently been accomplished.[9,12]

Experimental

Melting points were obtained on a Gallenkamp capillary or a Reichert hot stage and are uncorrected. IR spectra were recorded using Pye Unicam SP1000, Pye Unicam SP3-100 or

Perkin-Elmer 1720X FT spectrometers. Mass spectra were recorded using AEI MS902 or VG 7070E spectrometers. ^{1}H NMR spectra were obtained using the following spectrometers: Perkin-Elmer R32 or JEOL FX90Q at 90 MHz; Bruker WM200 at 200 MHz; Bruker WM250 at 250 MHz; Bruker AM400 or JEOL EX400 at 400MHz. ^{13}C NMR spectra were recorded using the following instruments: JEOL FX90Q spectrometer at 22.7 MHz; Bruker WM200 at 50.3 MHz; Bruker WM250 at 62.9 MHz; JEOL EX270 at 68 MHz; Bruker AM400 or JEOL EX400 at 100.6 or 100.4 MHz, respectively. ^{1}H NMR spectra were determined in deuteriochloroform solution unless indicated, and chemical shifts are quoted in parts per million (ppm) from tetramethylsilane as internal standard; coupling constants are quoted in Hz. ^{13}C NMR spectra were determined in deuteriochloroform solution and chemical shifts quoted in ppm from tetramethylsilane as internal standard or from tetramethylsilane using $CDCl_3$ as internal standard. Column chromatography was carried out at medium pressure using Merck Kieselgel 60 (Art. 9385). Thin layer chromatography (TLC) was carried out on silica plates (Kieselgel 60, F_{254}, Merck Art. 5554). Solvent extracts were dried over anhydrous magnesium sulfate or sodium sulfate for at least 10 min. Ether refers to diethyl ether and light petroleum corresponds to the fraction with bp 40–60 °C. Tetrahydrofuran (THF) and ether were distilled from lithium aluminium hydride or potassium immediately prior to use. Other dry solvents were prepared as described in Perrin *et al.*[14]

1-Benzyl-4,5-dihydroimidazole 5

N-Benzyl-1,2-diaminoethane[15] (70 g, 0.467 mol), triethyl orthoformate (4.0 mol equiv., 276 g, 1.86 mol) and toluene-4-sulfonic acid (catalytic, 4.0 g, 23 mmol) were heated together under gentle reflux for 20 h. The resulting solution was cooled, basified by the addition of aqueous NaOH (5% w/v, 50 cm^3) and extracted with chloroform (2 × 250 cm^3). The combined organic extracts were dried and concentrated *in vacuo*. Fractional distillation of the resulting liquor gave the *title compound* **5** (53.61 g, 72%), bp 120 °C at 2 mmHg (Found: M^+, 160.0987; $C_{10}H_{12}N_2$ requires *M*, 160.1000); ν_{max}(film)/cm^{-1} 3205, 2835, 2800, 1681, 1614, 1591, 1357 and 980; δ_H(80 MHz) 3.13 and 3.82 (each 2H, t, *J* 9.9, NCH_2CH_2N), 4.28 (2H, s, PhCH_2), 6.97 (1H, s, CH) and 7.31 (5H, s, Ar-H); δ_C(100.6 MHz) 47.92 and 51.49 (NCH_2CH_2N), 54.91 (PhCH_2), 127.40, 127.53 and 128.48 (Ar-CH), 136.78 (Ar-C) and 157.27 (C-2); *m*/*z* 160 (M^+, 75%), 159 (5), 120 (7), 92 (26), 91 (100), 69 (25) and 65 (16). Compound **5** solidified on standing and a portion was recrystallised from cyclohexane–hexane to yield a colourless hygroscopic solid, mp 46 °C.

Preparation of imidazolium bromides 6a–g

1-Benzyl-3-methoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 6a. Methyl bromoacetate (0.60 cm^3, 6.36 mmol) was added dropwise to a stirred solution of 1-benzyl-4,5-dihydroimidazole **5** (970 mg, 6.06 mmol) in dry THF (30 cm^3) under an atmosphere of nitrogen. The mixture was stirred for a further 30 min and the resulting liquor was then concentrated *in vacuo* yielding the title compound **6a** (1.89 g, 100%) as a viscous hygroscopic colourless oil which was used without further purification; ν_{max}(film)/cm^{-1} 3420, 3070, 2900, 1740, 1640, 1425, 1295, 1220, 1125 and 705; δ_H(90 MHz) 3.76 (3H, s, CH_3), 4.07 (4H, m, NCH_2CH_2N), 4.75 (2H, s, CH_2CO_2), 4.88 (2H, s, PhCH_2), 7.40 (5H, m, Ar-H) and 10.05 (1H, s, CH).

1-Benzyl-3-ethoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 6b. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (520 mg, 3.25 mmol) by the method described above for the preparation of **6a** but using ethyl bromoacetate (0.40 cm^3, 3.57 mmol). This yielded the title compound **6b** (1.17 g, >100%) as a hygroscopic semi-solid which was used without further purification; ν_{max}(film)/cm^{-1} 3450, 2950, 1745, 1650, 1210, 1030 and 710; δ_H(90 MHz) 1.30 (3H, t, *J* 7, CH_2CH_3), 4.15 (6H, m, NCH_2CH_2N and OCH_2), 4.75 (2H, s, CH_2CO_2), 4.95 (2H, s, PhCH_2), 7.50 (5H, m, Ar-H) and 10.00 (1H, s, CH).

1-Benzyl-3-*tert*-butoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 6c. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (460 mg, 2.87 mmol) by the method described above for the preparation of **6a** but using *tert*-butyl bromoacetate (0.48 cm^3, 3.02 mmol). This yielded the title compound **6c** (990 mg, 97%) as a hygroscopic solid which was used without further purification; ν_{max}(film)/cm^{-1} 3420, 2980, 1740, 1640, 1380, 1160 and 710; δ_H(90 MHz) 1.50 (9H, s, 3 × CH_3), 4.10 (4H, m, NCH_2CH_2N), 4.55 (2H, s, CH_2CO_2), 4.95 (2H, s, PhCH_2), 7.50 (5H, m, Ar-H) and 10.05 (1H, s, CH).

1-Benzyl-3-(1-ethoxycarbonylethyl)-4,5-dihydro-1*H*-imidazol-3-ium bromide 6d. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (840 mg, 5.25 mmol) by the method described above for the preparation of **6a** but using ethyl 2-bromopropionate (0.68 cm^3, 5.25 mmol). This yielded the title compound **6d** (1.79 g, >100%) as a colourless hygroscopic oil which was used without further purification; δ_H(60 MHz) 1.30 (3H, t, *J* 7.2, CH_2CH_3), 1.75 (3H, d, *J* 7.2, $CHCH_3$), 4.0 (4H, m, NCH_2CH_2N), 4.25 (2H, q, *J* 7.2, OCH_2), 5.00 (3H, m, PhCH_2 and CHCO), 7.40 (5H, m, Ar-H) and 10.10 (1H, s, 2-H).

3-Benzoylmethyl-1-benzyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 6e. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (800 mg, 5.0 mmol) by the method described above for the preparation of **6a** but using 2-bromoacetophenone (1.04 g, 5.25 mmol) in dry THF (5 cm^3). This yielded the title compound **6e** (1.87 g, >100%) as a pale yellow hygroscopic solid which was used without further purification; δ_H(60 MHz) 4.00 (4H, m, NCH_2CH_2N), 4.80 (2H, s, PhCH_2), 5.50 (2H, s, CH_2CO_2), 7.50 (8H, m, Ar-H), 8.00 (2H, m, Ar-H) and 9.90 (1H, s, CH).

1-Benzyl-3-cyanomethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 6f. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (980 mg, 6.12 mmol) by the method described above for the preparation of **6a** but using bromoacetonitrile (0.45 cm^3, 6.43 mmol). This yielded the title compound **6f** (1.69 g, 99%) as a colourless hygroscopic solid which was used without further purification; ν_{max}(KBr)/cm^{-1} 3400, 2920, 2280, 1640, 1300, 1220, 750 and 700; δ_H(90 MHz) 3.95 (4H, m, NCH_2CH_2N), 4.86 (2H, s, PhCH_2), 5.32 (2H, s, CH_2CN), 7.38 (5H, m, Ar-H) and 9.90 (1H, s, CH); δ_C(22.7 MHz) 37.39, 48.33, 48.98 and 52.34 (CH_2), 113.78 (CN), 128.73 and 129.05 (Ar-CH), 131.65 (Ar-C) and 158.58 (C-2).

1-Benzyl-3-(*p*-nitrobenzyl)-4,5-dihydro-1*H*-imidazol-3-ium bromide 6g. This was prepared from 1-benzyl-4,5-dihydroimidazole **5** (1.0 g, 6.25 mmol) by the method described above for the preparation of **6a** but using 4-nitrobenzyl bromide (1.48 g, 6.875 mmol) in dry THF (5 cm^3). This yielded the title compound **6g** (2.53 g, >100%) as a colourless hygroscopic solid which was used without further purification; ν_{max}(film)/cm^{-1} 2900, 1640, 1510, 1350, 1210, 800 and 730; δ_H(90 MHz) 3.85 (4H, m, NCH_2CH_2N), 4.90 (2H, s, PhCH_2), 5.20 (2H, s, $CH_2C_6H_4NO_2$), 7.40 (5H, m, Ar-H), 7.80 and 8.30 (each 2H, d, *J* 9, Ar-H) and 10.50 (1H, s, CH).

1-Benzyl-5,7-bis(methoxycarbonyl)-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7a *via* cycloaddition Protocol A

To 1-benzyl-3-methoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide **6a**, prepared from 1-benzyl-4,5-dihydroimidazole **5** (970 mg, 6.06 mmol) and methyl bromoacetate (0.60 cm^3, 6.36 mmol), was added methyl 2-methylpropenoate (0.97 cm^3, 9.09 mmol) and the mixture stirred for 5 min to produce a slurry. DBU (1.01 cm^3, 6.67 mmol) was then added dropwise over 10 min and the resulting mixture stirred for a further 16 h. After concentration *in vacuo* and partitioning between chloroform (2 × 30 cm^3) and water (30 cm^3), the combined organic extracts were dried and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with dichloromethane–ethanol–conc. aq. ammonia

(400 : 8 : 1 v/v/v) to afford the *title compound* **7a** (580 mg, 29%) as a colourless oil (Found: M^+, 332.1742; $C_{18}H_{24}N_2O_4$ requires *M*, 332.1736); ν_{max}(film)/cm^{-1} 2949, 2842, 2802, 1730, 1453, 1435, 1202, 1159, 1137 and 701; δ_H(400 MHz) 1.42 (3H, s, CH_3), 2.10 (1H, dd, *J* 13.2 and 10.1, CHC*H*H), 2.57 (1H, m, NCH*H*-CH_2N), 2.77 (2H, m, NCH_2CHHN and CHCH*H*), 3.00 (1H, m, NC*H*HCH_2N), 3.20 (1H, m, NCH_2CHHN), 3.25 (1H, d, *J* 12.8, PhC*H*H), 3.72 and 3.74 (6H, 2 × s, 2 × CH_3), 4.04 (3H, m, 7a-H, PhCH*H* and $CHCO_2$) and 7.27 (5H, m, Ar-H); δ_C(100.6 MHz) 23.10 (CH_3), 42.59 (CH*C*H$_2$), 51.68 and 51.96 (OCH_3), 52.69 (quaternary C), 53.07 and 54.70 (NCH_2CH_2N), 58.55 (Ph*C*H$_2$), 67.72 (*C*HCO), 95.09 (C-7a), 126.87, 128.19 and 128.53 (Ar-CH), 138.72 (Ar-C), 174.29 and 174.86 (CO); *m*/*z* 332 (M^+, 2%), 301 (6), 273 (8), 232 (100), 141 (89), 114 (13) and 91 (58). A portion of the title compound was converted to the *oxalate salt*, m.p. 64–66 °C, and recrystallised from ethanol–ether (Found: C, 54.6; H, 6.4; N, 6.1%; $C_{20}H_{26}N_2O_8\cdot H_2O$ requires C, 54.5; H, 6.4; N, 6.4%).

1-Benzyl-5-ethoxycarbonyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7b. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (740 mg, 4.625 mmol) by the method described above for the preparation of **7a** *via* Protocol A but using ethyl bromoacetate (810 mg, 4.85 mmol), methyl 2-methylpropenoate (1.0 cm^3, 9.25 mmol) and DBU (0.86 cm^3, 5.78 mmol). The crude product was purified by column chromatography eluting with dichloromethane–ethanol–conc. aq. ammonia (400 : 8 : 1 v/v/v) to yield the *title compound* **7b** (537 mg, 33.5%) as a colourless oil (Found: M^+, 346.1882; $C_{19}H_{26}N_2O_4$ requires *M*, 346.1892); ν_{max}(film)/cm^{-1} 2980, 2810, 1730, 1450, 1200, 1040, 750 and 700; δ_H(250 MHz) 1.28 (3H, t, *J* 7.1, CH_2CH_3), 1.42 (3H, s, CH_3), 2.10 (1H, dd, *J* 10.2 and 13.2, CHC*H*H), 2.57 (1H, m, NCH_2CHHN), 2.77 (2H, m, NCH_2CHHN and CHCH*H*), 3.01 and 3.22 (each 1H, m, NCH_2CH_2N), 3.24 (1H, d, *J* 12.8, PhC*H*H), 3.72 (3H, s, OCH_3), 4.02 (3H, m, 7a-H, PhCH*H* and $CHCO_2$), 4.20 (2H, dq, *J* 2.4 and 7.1, OCH_2) and 7.25 (5H, m, Ar-H); δ_C(22.7 MHz) 14.15 (CH_2CH_3), 23.14 (CCH_3), 42.37 (CH*C*H$_2$), 51.47 (OCH_3), 52.67 (quaternary C), 52.94 and 54.56 (NCH_2CH_2N), 58.57 (Ph*C*H$_2$), 60.52 (OCH_2), 67.62 (*C*HCO), 95.14 (C-7a), 126.78, 127.97 and 128.46 (Ar-CH), 138.75 (Ar-C), 173.58 and 174.72 (CO); *m*/*z* 346 (M^+, 2%), 315 (6), 273 (10), 246 (100), 174 (26), 155 (65), 100 (11) and 91 (69).

1-Benzyl-5-*tert*-butoxycarbonyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7c *via* cycloaddition Protocol B

1-Benzyl-3-*tert*-butoxycarbonylmethyl-4,5-dihydro-1*H*-imidazol-3-ium bromide **6c**, prepared from 1-benzyl-4,5-dihydroimidazole **5** (820 mg, 5.125 mmol) and *tert*-butyl bromoacetate (0.83 cm^3, 5.125 mmol), was taken up in dry THF (30 cm^3), heated to reflux and methyl 2-methylpropenoate (1.54 g, 15.37 mmol) added in one portion. DBU (0.77 cm^3, 5.125 mmol) was then added dropwise to the refluxing mixture over a period of 4 h. After a further 20 h of heating at reflux the reaction was cooled, concentrated *in vacuo* and partitioned between chloroform (2 × 30 cm^3) and water (30 cm^3). The combined organic extracts were dried and concentrated *in vacuo*, and the crude product was purified by column chromatography eluting with hexane–ethyl acetate (1 : 3 v/v) to yield the *title compound* **7c** (993 mg, 52%) as a colourless oil (Found: M^+, 374.2202; $C_{21}H_{30}N_2O_4$ requires *M*, 374.2206); ν_{max}(film)/cm^{-1} 2980, 2800, 1730, 1450, 1370, 1150, 750 and 705; δ_H(250 MHz) 1.41 (3H, s, CH_3), 1.47 [9H, s, $C(CH_3)_3$], 2.04 (1H, dd, *J* 13.2 and 10.0, CHC*H*H), 2.55 (1H, m, NC*H*HCH_2N), 2.72 (1H, dd, *J* 13.3 and 7.1, CHCH*H*), 2.79 (1H, m, NCH*H*CH_2N), 3.00 and 3.17 (each 1H, m, NCH_2CH_2N), 3.22 (1H, d, *J* 12.8, PhC*H*H), 3.71 (3H, s, OCH_3), 3.88 (1H, dd, *J* 10.0 and 7.0, $CHCO_2$), 4.01 (1H, s, 7a-H), 4.05 (1H, d, *J* 12.8, PhCH*H*) and 7.28 (5H, m, Ar-H); *m*/*z* 374 (M^+, 1%), 274 (48), 218 (100), 186 (9), 140 (6), 127 (60) and 91 (62).

5-Benzoyl-1-benzyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7d. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (800 mg, 5.0 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using 2-bromoacetophenone (1.04 g, 5.25 mmol), methyl 2-methylpropenoate (2.0 g, 20.0 mmol) and DBU (800 mg, 5.25 mmol) and heating the mixture under reflux for 1 h. Column chromatography eluting with ether–hexane (3 : 1 v/v) afforded the *title compound* **7d** (947 mg, 50%) as a colourless oil (Found: M^+, 378.1917; $C_{23}H_{26}N_2O_3$ requires *M*, 378.1943); ν_{max}(film)/cm^{-1} 3020, 2940, 2800, 1725, 1685, 1450, 1205, 1140 and 705; δ_H(250 MHz) 1.42 (3H, s, CH_3), 2.00 (1H, dd, *J* 12.9 and 10.7, CHC*H*H), 2.61 and 2.77 (each 1H, m, NCH_2CH_2N), 2.92 (1H, dd, *J* 12.9 and 6.5, CHCH*H*), 3.12 (2H, m, NC*H*$_2$$CH_2$N), 3.29 (1H, d, *J* 13.0, PhC*H*H), 3.78 (3H, s, OCH_3), 4.13 (2H, m, PhCH*H* and 7a-H), 4.99 (1H, dd, *J* 10.6 and 6.5, CHCO), 7.39 (8H, m, Ar-H) and 8.06 (2H, m, Ar-H); δ_C(22.7 MHz) 22.93 (CH_3), 43.68 (CH*C*H$_2$), 51.53 (CH_3O), 52.40 (NCH_2-*C*H$_2$N), 52.83 (quaternary C), 54.51 (N*C*H$_2$$CH_2$N), 58.52 (Ph*C*H$_2$), 70.92 (*C*HCO), 95.14 (C-7a), 126.62, 127.92, 128.24 and 132.74 (Ar-CH), 135.99 and 138.70 (Ar-C), 174.94 (ester CO) and 199.26 (ketone CO); *m*/*z* 378 (M^+, 0.5%), 376 (3), 317 (8), 278 (100), 273 (14), 187 (63), 161 (11), 105 (33) and 91 (89).

1-Benzyl-7-cyano-5-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7e. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (660 mg, 4.125 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using methyl bromoacetate (0.63 g, 4.125 mmol), 2-methylpropenonitrile (1.04 cm^3, 12.37 mmol) and DBU (0.62 cm^3, 4.125 mmol). Column chromatography eluting with ethyl acetate–hexane (1 : 1 v/v) afforded the *title compound* **7e** (519 mg, 42%) as a colourless oil (Found M^+, 299.1569; $C_{17}H_{21}N_3O_2$ requires *M*, 299.1634); ν_{max}(film)/cm^{-1} 2960, 2820, 2255, 1740, 1450, 1200, 760 and 705; δ_H(250 MHz) 1.35 (3H, s, CH_3), 2.23 (1H, dd, *J* 10.9 and 13.1, CHC*H*H), 2.75 (2H, m, NCH_2CHHN and CHCH*H*), 2.91 (1H, m, NCH_2CHHN), 3.27 (2H, m, NC*H*$_2$$CH_2$N), 3.52 (1H, d, *J* 12.9 PhC*H*H), 3.76 (3H, s, OCH_3), 3.80 (1H, dd, *J* 10.9 and 5.9, $CHCO_2$), 3.91 (1H, s, 7a-H), 4.00 (1H, d, *J* 12.9, PhCH*H*), 7.30 (3H, m, Ar-H) and 7.45 (2H, m, Ar-H); δ_C(22.7 MHz) 22.55 (CH_3), 43.62 (CH*C*H$_2$), 44.11 (quaternary C), 52.29 (OCH_3), 53.05 and 54.67 (NCH_2CH_2N), 58.84 (Ph*C*H$_2$), 66.10 (*C*HCO), 93.08 (C-7a), 122.06 (CN), 127.43, 128.46 and 129.00 (Ar-CH), 138.48 (Ar-C) and 172.66 (CO); *m*/*z* 299 (M^+, 1%), 298 (2), 232 (83), 173 (17), 141 (100), 114 (22) and 91 (84). A portion of the title compound was converted to the *oxalate salt* and recrystallised from ethanol–ether (Found: C, 56.4; H, 6.4; N, 10.2%; $C_{19}H_{23}N_3O_6\cdot H_2O$ requires C, 56.0; H, 6.2; N, 10.3%).

1-Benzyl-7-cyano-5-ethoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7f. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (750 mg, 4.69 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using ethyl bromoacetate (0.52 cm^3, 4.69 mmol), 2-methylpropenonitrile (1.18 cm^3, 14.06 mmol) and DBU (0.70 cm^3, 4.69 mmol). Column chromatography eluting with ethyl acetate–hexane (1 : 1 v/v) afforded the *title compound* **7f** (621 mg, 42%) as a colourless oil (Found: M^+, 313.1786; $C_{18}H_{23}N_3O_2$ requires *M*, 313.1790); ν_{max}(film)/cm^{-1} 2990, 2820, 2240, 1740, 1450, 1190, 750 and 700; δ_H(400 MHz) 1.28 (3H, t, *J* 7.1, CH_2CH_3), 1.35 (3H, s, CH_3), 2.25 (1H, dd, *J* 10.8 and 13.0, CHCH*H*), 2.73 (2H, m, NCH_2CHHN and CHC*H*H), 2.91 (1H, m, NCH_2-CH*H*N), 3.26 (2H, m, NC*H*$_2$$CH_2$N), 3.50 (1H, d, *J* 12.9, PhC*H*H), 3.77 (1H, dd, *J* 10.8 and 5.9, $CHCO_2$), 3.90 (1H, s, 7a-H), 4.00 (1H, d, *J* 12.9, PhCH*H*), 4.20 (2H, q, *J* 7.1, OCH_2), 7.30 (3H, m, Ar-H) and 7.48 (2H, m, Ar-H); δ_C(22.7 MHz) 14.10 (CH_2CH_3), 22.44 (CH_3), 43.41 (CH*C*H$_2$), 43.89 (quaternary C), 52.83 and 54.46 (NCH_2CH_2N), 58.63 (Ph*C*H$_2$), 61.01 (OCH_2), 66.05 (*C*HCO), 92.86 (C-7a), 121.96 (CN), 127.21, 128.29 and 128.84 (Ar-CH), 138.37 (Ar-C) and 171.96 (CO);

m/*z* 313 (M^+, 3%), 246 (85), 240 (13), 174 (26), 155 (92), 100 (18) and 91 (100).

1-Benzyl-5-*tert*-butoxycarbonyl-7-cyano-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7g. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (790 mg, 4.944 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using *tert*-butyl bromoacetate (0.80 cm^3, 4.94 mmol), 2-methylpropenonitrile (1.24 cm^3, 14.81 mmol) and DBU (0.74 cm^3, 4.94 mmol). Column chromatography eluting with ethyl acetate–hexane (1:2 v/v) afforded the *title compound* **7g** (1.17 g, 69%), mp 73–77 °C, as a colourless solid (Found: C, 70.5; H, 8.2; N, 12.4%; M^+, 341.2075: $C_{20}H_{27}N_3O_2$ requires C, 70.35; H, 8.0; N, 12.3%; *M*, 341.2103); ν_{max}(KBr)/cm^{-1} 2980, 2940, 2810, 2240, 1735, 1455, 1370, 1150 and 700; δ_H(400 MHz) 1.35 (3H, s, CH_3), 1.47 [9H, s, $C(CH_3)_3$], 2.17 (1H, dd, *J* 13.0 and 10.8, CHC*H*H), 2.67 (1H, dd, *J* 13.0 and 5.8, CHCH*H*), 2.75 and 2.90 (each 1H, m, NCH_2CH_2N), 3.25 (2H, m, NCH_2CH_2N), 3.50 (1H, d, *J* 12.9, PhC*H*H), 3.68 (1H, dd, *J* 10.8 and 5.8, $CHCO_2$), 3.88 (1H, s, 7a-H), 4.00 (1H, d, *J* 12.9, PhCH*H*), 7.27 (1H, m, Ar-H), 7.33 and 7.46 (each 2H, m, Ar-H); δ_C(22.7 MHz) 22.55 (CH_3), 28.02 [$C(CH_3)_3$], 43.51 ($CHCH_2$), 43.89 (*C*CN), 52.83 and 54.51 (NCH_2CH_2N), 58.63 ($PhCH_2$), 66.75 ($CHCO_2$), 81.38 (CMe_3), 92.92 (C-7a), 122.17 (CN), 127.27, 128.29 and 128.89 (Ar-CH), 138.48 (Ar-C) and 171.20 (CO); *m*/*z* 341 (M^+, 8%), 274 (51), 240 (27), 218 (100), 186 (8), 173 (11), 127 (62) and 91 (63). Also isolated from some experiments was *exo isomer* **8**: δ_H(250 MHz) 1.42 (3H, s, CH_3), 1.49 [9H, s, $C(CH_3)_3$], 2.39 (1H, dd, *J* 12.9 and 6.1, CHC*H*H), 2.72 (3H, m, NC*H*HC*H*HN and CHCH*H*), 3.17 (1H, m, NCH_2CHHN), 3.25 (1H, m, $NCHHCH_2N$), 3.40 (1H, dd, *J* 10.9 and 6.1, $CHCO_2$), 3.47 and 4.04 (each 1H, d, *J* 13.3, $PhCH_2$), 4.43 (1H, s, 7a-H) and 7.33 (5H, m, Ar-H); δ_C(22.7 MHz) 19.95 (CH_3), 28.17 [$C(CH_3)_3$], 38.37 (*C*CN), 43.03 ($CHCH_2$), 53.64 and 55.11 (NCH_2CH_2N), 57.98 ($PhCH_2$), 65.78 ($CHCO_2$), 81.65 (CMe_3), 91.02 (C-7a), 123.42 (CN), 127.37, 128.51 and 128.67 (Ar-CH), 137.99 (Ar-C) and 171.26 (CO).

1-Benzyl-7-cyano-5-ethoxycarbonyl-5,7-dimethylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 7h. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (750 mg, 4.69 mmol) by the method described above for the preparation of **7c** *via* Protocol A but using ethyl 2-bromopropionate (0.64 cm^3, 4.57 mmol), 2-methylpropenonitrile (1.0 cm^3, 11.72 mmol) and DBU (0.68 cm^3, 4.57 mmol). Column chromatography eluting with hexane–ethyl acetate (7:3 v/v) afforded the *title compound* **7h** (960 mg, 63%) as a colourless oil (Found: M^+, 327.1917; $C_{19}H_{25}N_3O_2$ requires *M*, 327.1946); ν_{max}(film)/cm^{-1} 2980, 2930, 2805, 2240, 1730, 1455, 1150, 1030, 750 and 705; δ_H(250 MHz) 1.28 (6H, m, 2 × CH_3), 1.59 (3H, s, CH_3), 2.53 (2H, s, CCH_2), 2.69 and 3.00 (each 1H, m, NCH_2CH_2N), 3.19 (2H, m, NCH_2CH_2N), 3.50 (1H, d, *J* 12.6, PhC*H*H), 3.87 (1H, s, 7a-H), 4.06 (1H, d, *J* 12.6, PhCH*H*), 4.17 (2H, q, *J* 7.1, OCH_2), 7.31 (3H, m, Ar-H) and 7.48 (2H, m, Ar-H); δ_C(22.7 MHz) 14.21 (CH_2CH_3), 20.81 and 24.50 (2 × CH_3), 42.65 (*C*CN), 45.68 (CCH_2C), 49.42 and 54.56 (NCH_2CH_2N), 59.17 ($PhCH_2$), 61.34 (OCH_2), 67.13 (CCO_2), 93.35 (C-7a), 123.80 (CN), 127.37, 128.46 and 129.22 (Ar-CH), 138.64 (Ar-C) and 174.83 (CO); *m*/*z* 327 (M^+, 2%), 261 (21), 260 (90), 254 (14), 187 (25), 169 (100), 120 (11) and 91 (82). A portion of the title compound was converted to the *oxalate salt*, m.p. 86–87 C and recrystallised from ethanol–ether (Found: C, 57.9; H, 6.85; N, 9.4%: $C_{21}H_{27}N_3O_6{\cdot}H_2O$ requires C, 57.9; H, 6.7; N, 9.6%).

5-Benzoyl-1-benzyl-7-cyano-7-methylhexahydro-1*H*-pyrrolo-[1,2-*a*]imidazole 7i. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (940 mg, 5.875 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using 2-bromoacetophenone (1.23 g, 6.17 mmol), 2-methylpropenonitrile (1.57 g, 23.50 mmol) and DBU (980 mg, 6.46 mmol) and heating the mixture under reflux for 1 h. Column chromatography eluting with ether–hexane (1:1 v/v) afforded the *title compound* **7i** (930 mg, 46%) as a pale yellow oil (Found: M^+, 345.1784; $C_{22}H_{23}N_3O$ requires *M*, 345.1841); ν_{max}(film)/cm^{-1} 3050, 3020, 2980, 2940, 2840, 2240, 1685, 1445, 1225, 740 and 700; δ_H(400 MHz) 1.34 (3H, s, CH_3), 2.23 (1H, dd, *J* 10.7 and 13.1, CHC*H*H), 2.77 (2H, m, NCH_2CHHN and CHCH*H*), 2.92 (1H, m, NCH_2CHHN), 3.22 and 3.30 (each 1H, m, NCH_2CH_2N), 3.52 (1H, d, *J* 12.8, PhC*H*H), 3.97 (1H, s, 7a-H), 4.03 (1H, d, *J* 12.8, PhCH*H*), 4.73 (1H, dd, *J* 10.7 and 5.8, CHCO), 7.42 (8H, m, Ar-H) and 7.98 (2H, m, Ar-H); δ_C(22.7 MHz) 22.22 (CH_3), 43.95 ($CHCH_2$), 44.16 (quaternary C), 52.61 and 54.62 (NCH_2CH_2N), 58.52 ($PhCH_2$), 68.54 (*C*HCO), 92.81 (C-7a), 122.28 (CN), 127.10, 128.19, 128.51, 128.67 and 133.17 (Ar-CH), 135.77 and 138.32 (Ar-C) and 197.53 (CO); *m*/*z* 345 (M^+, 2%), 343 (6), 278 (100), 240 (11), 187 (56), 173 (16), 161 (10), 105 (18) and 91 (72).

1-Benzyl-5,7-bis(methoxycarbonyl)hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole stereoisomers 9 and 10 *via* cycloaddition Protocol C

To a solution of 1-benzyl-4,5-dihydroimidazole **5** (1.00 g, 6.25 mmol) stirred at reflux under an atmosphere of nitrogen in THF (30 cm^3) was added methyl bromoacetate (956 mg, 6.25 mmol) followed by methyl propenoate (1.613 g, 18.75 mmol). DBU (950 mg, 6.25 mmol) was then added dropwise (syringe pump) to the refluxing mixture over a period of 4 h. The solution was heated at reflux for a further 2 h, after which it was cooled to room temperature and partitioned between chloroform (3 × 30 cm^3) and water (30 cm^3). The combined organic phase was dried, evaporated under reduced pressure, and the residue purified by column chromatography eluting with ethyl acetate to yield the *title compounds* **9** and **10** as a colourless oil (1.04 g, 52%) identified as a 2.3:1 mixture of epimers at C-7 (Found: M^+, 318.1580. $C_{17}H_{22}N_2O_4$requires *M*, 318.1579); ν_{max}(film)/cm^{-1} 2951, 2843, 1738, 1680, 1601, 1453, 1438, 1199 and 1169; δ_H(400 MHz) 2.23 (1H, dt, *J* 7.2 and 13.2, CHCH*H*), 2.56 (2H, m, $NCHHCH_2N$ and CHC*H*H), 2.74 (0.3H, dt, *J* 6.4 and 6.8, NCH_2CHHN), 2.81 (0.7H, dt, *J* 6.0 and 5.6, NCH_2CHHN), 2.95 (0.3H, m, 7-H), 3.06 (1H, m, $NCHHCH_2N$), 3.23 (0.7H, m, 7-H), 3.25 (1H, m, NCH_2CHHN), 3.30 (1H, d, *J* 13.2, PhC*H*H), 3.61 (0.3H, m, 5-H), 3.66 (0.9H, s, CH_3), 3.69 (2.1H, s, CH_3), 3.74 (3H, s, CH_3), 3.97 (0.7H, m, 5-H), 4.03 (1H, d, *J* 13.2, PhCH*H*), 4.17 (0.3H, d, *J* 3.6, 7a-H), 4.42 (0.7H, d, *J* 6.4, 7a- H) and 7.20 (5H, m, Ar-H); δ_C(100.4 MHz) 32.52 (C-6, major isomer), 33.51 (C-6, minor isomer), 46.98 (C-7, major isomer), 48.45 (C-7, minor isomer), 51.52, 51.65, 51.70 (3 × CH_3O), 52.03 (NCH_2CH_2N, minor isomer), 52.58 (NCH_2CH_2N, major isomer), 53.28 (NCH_2CH_2N, minor isomer), 53.95 (NCH_2CH_2N, major isomer), 56.37 ($PhCH_2$, minor isomer), 57.96 ($PhCH_2$, major isomer), 66.30 (C-5, major isomer), 68.02 (C-5, minor isomer), 87.24 (C-7a, major isomer), 88.17 (C-7a, minor isomer), 126.43, 126.59, 128.02, 128.20, 128.33, 128.44 (Ar-CH), 138.04 (Ar-C, minor isomer), 138.31 (Ar-C, major isomer), 172.46, 172.73 and 173.67 (CO); *m*/*z* 318 (M^+, 3%), 317 (7), 287 (11), 259 (8), 233 (13), 232 (85), 141 (93), 114 (22) and 91 (100).

Cycloadducts with *N*-phenylmaleimide, 12 and 13. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (2.0 g, 12.5 mmol) by the method described above for the preparation of **9** and **10** *via* Protocol C but using methyl bromoacetate (1.92 g, 1.18 cm^3, 12.5 mmol), *N*-phenylmaleimide (6.50 g, 37.5 mmol) and DBU (1.90 g, 1.86 cm^3, 12.5 mmol). Column chromatography eluting with toluene–ether (3:2 v/v) followed by ether afforded the *title compound* **12** as an off-white solid (190 mg, 8%), mp 52–55 °C (Found: $M^+ - H$, 404.1558. $C_{23}H_{23}N_3O_4$ requires *M* − H, 404.1610); ν_{max}(film)/cm^{-1} 3028, 2951, 2846, 1777, 1713, 1496, 1377, 1186 and 694; δ_H(250 MHz) 2.57 (1H, m, $NCHHCH_2N$), 2.89 (2H, m, $NCHHCH_2N$ and NCH_2CHHN), 3.24 (1H, m, NCH_2CHHN), 3.31 (1H, d, *J* 12.3, PhC*H*H), 3.78 (5H, m, COCHCHCO and OCH_3), 4.27 (1H, d, *J* 12.3, PhCH*H*), 4.32 (1H, d, J 1.3, NC*H*CO), 4.61 (1H, d, *J* 6.3, NCHN), 7.26 (7H, m, Ar-H) and 7.41 (3H, m, Ar-H); δ_C(68 MHz) 50.28 and 50.86 (CO*C*H*C*HCO), 51.97 (NCH_2CH_2N), 52.42 (OCH_3), 52.58

(NCH_2CH_2N), 58.55 ($PhCH_2$), 66.85 (NCHCO), 87.08 (NCHN), 126.49, 126.90, 127.81, 128.45, 128.82 and 128.97 (Ar-CH), 131.82 and 137.81 (Ar-C), 171.77, 174.29 and 174.86 (CO); *m*/*z* 404 ($M^+ - H$ 6%), 232 (86), 141 (79) and 91 (100); and the *exo* adduct **13** as a colourless solid (90 mg, 4%); δ_H(400 MHz) 2.43 (1H, m, $NCHHCH_2N$), 2.84 (1H, m, NCH_2CHHN), 3.22 (1H, m, $NCHHCH_2N$), 3.31 (1H, m, NCH_2CHHN), 3.41 (1H, d, *J* 8.3, CHCONPh), 3.51 (1H, d, *J* 12.3, PhCHH), 3.82 (4H, m, CHCONPh and OCH_3), 4.09 (2H, m, NCHN and PhCHH), 4.18 (1H, d, *J* 7.8, NCHCO) and 7.37 (10H, m, Ar-H); δ_C(68 MHz) 47.80 and 48.45 (COCHCHCO), 50.06 and 51.48 (NCH_2CH_2N), 52.33 (OCH_3), 55.81 ($PhCH_2$), 69.44 (NCHCO), 88.45 (NCHN), 126.27, 127.31, 128.43, 128.54, 128.61 and 128.99 (Ar-CH), 131.48 and 137.46 (Ar-C), 170.44, 174.59 and 174.82 (CO).

1-Benzyl-5,7-bis(methoxycarbonyl)-6-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 14. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (1.0 g, 6.25 mmol) by the method described above for the preparation of **9** and **10** *via* Protocol C but using methyl bromoacetate (0.96 g, 0.59 cm^3, 6.25 mmol), methyl (*E*)-but-2-enoate (1.87 g, 1.99 cm^3, 18.75 mmol) and DBU (0.95 g, 0.93 cm^3, 6.25 mmol). Column chromatography eluting with light petroleum–ethyl acetate (1:1 v/v) yielded the *title compound* **14** as a pale yellow sticky solid (0.450 g, 22%) (Found: M^+, 332.1737. $C_{18}H_{24}N_2O_4$ requires *M*, 332.1736); ν_{max}(film)/cm^{-1} 3027, 2950, 2843, 1738, 1436, 1198, 1170 and 701; δ_H(400 MHz; C_6D_6) 0.99 (3H, d, *J* 6.9, CH_3), 2.17 (1H, m, CHH-CH_2N), 2.48 (1H, m, CH_2CHHN), 2.76 (1H, m, $CHHCH_2N$), 2.95 (1H, m, CH_2CHHN), 3.01 (2H, m, PhCHH and $CHCH_3$), 3.10 (1H, dd, *J* 6.5 and 7.7, $CHCHCO_2Me$), 3.31 and 3.34 (each 3H, s, OCH_3), 3.81 (1H, d, *J* 7.2, NCHCO), 3.96 (1H, d, *J* 13.3, PhCHH), 4.47 (1H, d, *J* 6.5, 7a-H) and 7.18 (5H, m, Ar-H); δ_C(68 MHz; C_6D_6) 14.70 (CH_3), 36.67 ($CHCH_3$), 51.32 and 51.41 (2 × OCH_3), 52.99 and 53.64 (NCH_2CH_2N), 54.58 ($CHCHCO_2Me$), 58.53 ($PhCH_2$), 71.48 (NCHCO), 86.63 (C-7a), 126.67, 128.00 and 128.07 (Ar-CH), 138.71 (Ar-C), 172.02 and 172.90 (CO); *m*/*z* 332 (M^+, 2%), 232 (55), 213 (15), 154 (24), 141 (50), 120 (29) and 91 (100).

Ethyl (*E*)-5-(Bromoacetoxy)pent-2-enoate 16

Propenal (50 cm^3, 0.66 mol), sulfuric acid (1.5 M, 66 cm^3) and water (120 cm^3) were heated together at 45–60 °C for 2 h before the solution was cooled to 0 °C and brought to pH 8 by the addition of sodium carbonate. Ethoxycarbonylmethylenetriphenylphosphorane (83.3 g, 0.195 mol) and water (50 cm^3) were added, followed by portionwise addition of sodium carbonate (37.1 g, 0.35 mol) with stirring over 2 h. After stirring for a further 0.5 h, the solution was extracted with ether (3 × 300 cm^3), the combined organic extract dried and evaporated under reduced pressure, and the residue purified by column chromatography eluting with light petroleum–ethyl acetate (3:1 v/v) to yield ethyl (*E*)-5-hydroxypent-2-enoate as a colourless oil (10.94 g, 39%) that was used directly; δ_H(400 MHz) 1.29 (3H, t, *J* 7.2, CH_2CH_3), 2.48 (2H, m, CH_2CH), 3.55 (2H, t, *J* 6.4, CH_2OH), 4.19 (2H, q, *J* 7.2, CH_2CH_3), 4.2 (1H, br s, OH), 5.89 (1H, d, *J* 15.6, CH=CHCO) and 6.96 (1H, dt, *J* 15.6 and 6.8, CH=CHCO). To ethyl (*E*)-5-hydroxypent-2-enoate (2 g, 13.9 mmol) in dry dichloromethane (40 cm^3) at −10 °C (ice–salt bath) were added with stirring triethylamine (4.2 g, 41.7 mmol) followed dropwise by bromoacetyl bromide (8.4 g, 41.7 mmol). The solution was allowed to warm to 20 °C and stirred for a further 10 min before the addition of saturated aqueous sodium hydrogen carbonate (50 cm^3). The mixture was stirred for 30 min, the layers separated, and the aqueous phase extracted with dichloromethane (3 × 50 cm^3). The combined organic phases were dried, evaporated under reduced pressure and the residue was distilled (Kugelrohr apparatus, 3 mmHg, oven temp. 200 °C) to afford the title compound **16** as a colourless oil (2.5 g, 68%), bp 110 °C at 0.05 mmHg, that deteriorated on storage and was used directly, without further characterization, in the cycloaddition reaction, see below; δ_H(400 MHz) 1.29 (3H, t, *J* 7.2, CH_2CH_3), 2.59 (2H, m, CH_2CH), 3.84 (2H, s, CH_2Br), 4.20 (2H, q, *J* 7.2, CH_2CH_3), 4.30 (2H, t, *J* 6.6, CH_2OCOCH_2Br), 5.92 (1H, d, *J* 16.0, CH=CHCO) and 6.91 (1H, dt, *J* 16.0 and 7.0, CH=CHCO).

2-Benzyl-7-ethoxycarbonyl-8-(2-hydroxyethyl)-1,2,3,4,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-1-one 18. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (302 mg, 1.89 mmol) by the method described above for the preparation of **9** and **10** *via* Protocol C but using ethyl (*E*)-5-(bromoacetoxy)pent-2-enoate **16** (500 mg, 1.89 mmol) and DBU (287 mg, 1.89 mmol). Column chromatography eluting with ethyl acetate afforded the *title compound* **18** (100 mg, 15%) as a colourless oil (Found: M^+, 344.1736. $C_{19}H_{24}N_2O_4$requires *M*, 344.1736); ν_{max}($CDCl_3$)/cm^{-1} 3376 (br), 2983, 2933, 2876, 1710, 1657, 1629, 1554, 1455, 1441, 1351, 1254, 1088, 1055 and 1029; δ_H(400 MHz) 1.25 (3H, t, *J* 7.2, CH_3), 1.68 and 2.03 (each 1H, m, CH_2CH_2OH), 3.1–3.7 (7H, m, CH_2OH, NCH_2CH_2N, NCHCH), 4.15 (2H, m, CH_2CH_3), 4.48 (1H, d, *J* 10, NCHCH), 4.65 (2H, dd, *J* 14.8, 13.2, $PhCH_2$), 7.08 (1H, s, NCH=C) and 7.30 (5H, m, Ar-H); δ_C(100.4 MHz) 14.36 (CH_3), 31.79 (CH_2CH_2OH), 40.59 (NCHCH), 43.68 (NCH_2CH_2N), 46.84 (NCH_2CH_2N), 50.12 ($PhCH_2$), 59.70 (CH_2CH_3), 60.27 (CH_2OH), 67.16 (NCHCH), 106.43 (CH=*C*), 127.73, 128.04 and 128.68 (Ar-CH), 135.70 (Ar-C), 148.10 (*C*H=C), 166.32 and 166.81 (CO); *m*/*z* 344 (M^+, 4%), 253 (1) and 91 (100).

1-Benzyl-7-chloro-7-cyano-5-methoxycarbonylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 19a. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (890 mg, 5.56 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using methyl bromoacetate (890 mg, 5.84 mmol), 2-chloropropenonitrile (1.95 g, 22.25 mmol) and DBU (930 mg, 6.12 mmol) and heating the resulting mixture under reflux for 1 h. Column chromatography eluting with ethyl acetate–hexane (1:2 v/v) afforded the *title compound* **19a** (582 mg, 33%) as a pale yellow oil identified as a 1:1 mixture of diastereoisomers (Found: M^+, 319.1099; $C_{16}H_{18}{}^{35}ClN_3O_2$ requires *M*, 319.1088); ν_{max}(film)/cm^{-1} 3020, 2960, 2860, 2250, 1740, 1440, 1200, 740 and 700; δ_H(400 MHz) 2.87 (3.5H, m, NCH_2CH_2N, CHCHH and CHCHH), 3.12 (0.5H, dd, *J* 13.4 and 6.4, CHCHH), 3.21 (0.5H, m, $NCHHCH_2N$), 3.30 (1.5H, m, $NCHHCH_2N$ and $NCHHCH_2N$), 3.55 (0.5H, d, *J* 13.1, PhCHH), 3.67 (0.5H, d, *J* 13.3, PhCHH), 3.78 (4H, m, OCH_3 and $CHCO_2$), 4.13 (0.5H, d, *J* 13.3, PhCHH), 4.30 (0.5H, d, *J* 13.1, PhCHH), 4.39 and 4.59 (each 0.5H, s, 7a-H) and 7.35 (5H, m, Ar-H); δ_C(22.7 MHz) 45.14, 53.16, 53.70, 53.81, 54.62, 57.49 and 57.87 (CH_2), 52.29 (OCH_3), 59.98 and 60.79 (quaternary C), 64.37 and 64.86 ($CHCO_2$), 91.78 and 94.06 (C-7a), 116.92 and 117.03 (CN), 127.21, 128.24, 128.56 and 128.67 (Ar-CH), 137.40 (Ar-C), 171.09 and 171.53 (CO); *m*/*z* 319 (M^+, 3%), 260 (7), 232 (100), 173 (13), 114 (14) and 91 (93).

1-Benzyl-7-chloro-7-cyano-5-ethoxycarbonylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 19b. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (880 mg, 5.50 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using ethyl bromoacetate (960 mg, 5.77 mmol), 2-chloropropenonitrile (1.32 cm^3, 16.5 mmol) and DBU (880 mg, 5.77 mmol) and heating the resulting mixture at reflux for 1 h. Column chromatography eluting with ethyl acetate–hexane (1:1 v/v) afforded the *title compound* **19b** (709 mg, 39%) as a yellow oil identified as a 1:1 mixture of diastereoisomers (Found: M^+, 333.1194, 335.1240; $C_{17}H_{20}{}^{35,37}ClN_3O_2$ requires *M*, 333.1244, 335.1215); ν_{max}(film)/cm^{-1} 2980, 2830, 2250, 1730, 1190, 1030, 760, 760 and 705; δ_H(400 MHz) 1.30 (3H, t, *J* 7.2, CH_3), 2.85 (3.5H, m, NCH_2CH_2N, CHCHH and CHCHH), 3.12 (0.5H, dd, *J* 13.4 and 6.4, CHCHH), 3.21 (0.5H, m, $NCHHCH_2N$), 3.30 (1.5H, m, $NCHHCH_2N$ and $NCHHCCH_2N$), 3.55 (0.5H, d, *J* 13.1, PhCHH), 3.67 (0.5H, d, *J* 13.2, PhCHH), 3.76 (1H, dd, *J* 9.8 and 6.6, $CHCO_2$), 4.13 (0.5H, d, *J* 13.2, PhCHH), 4.23 (2H, m, OCH_2), 4.30 (0.5H, d, *J* 13.1,

PhCH*H*), 4.39 and 4.59 (each 0.5H, s, 7a-H) and 7.35 (5H, m, Ar-H); δ_C(22.7 MHz) 14.15 (CH_3), 45.41, 53.37, 53.91, 54.08, 54.84, 57.71 and 58.09 (CH_2), 60.25 and 61.01 (quaternary C), 61.50 (CH_2), 64.75 and 65.18 (CH), 92.00 and 94.27 (C-7a), 117.19 and 117.30 (CN), 127.43, 128.46, 128.78 and 128.89 (Ar-CH), 137.67 (Ar-C), 170.82 and 171.26 (CO); *m*/*z* 335 and 333 (M^+, 0.2 and 1%), 297 (5), 246 (57), 174 (17), 155 (63), 120 (8) and 91 (100).

1-Benzyl-5-*tert*-butoxycarbonyl-7-chloro-7-cyanohexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 19c. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (1.43 g, 8.94 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using *tert*-butyl bromoacetate (1.51 cm^3, 9.38 mmol), 2-chloropropenonitrile (2.85 cm^3, 35.75 mmol) and DBU (1.40 cm^3, 9.38 mmol) and heating the resulting mixture at reflux for 1 h. Column chromatography eluting with ether–hexane (4 : 1 v/v) afforded the *title compound* **19c** (1.76 g, 55%) as a pale yellow oil, identified as a 1 : 1 mixture of diastereoisomers (Found: M^+, 361.1530; $C_{19}H_{24}{}^{35}ClN_3O_2$ requires *M*, 361.1557); ν_{max}(film)/cm^{-1} 2990, 2850, 2250, 1730, 1460, 1370, 1160 and 710; δ_H(400 MHz) 1.47 [9H, s, $C(CH_3)_3$], 2.82 (3H, m, NCH_2-CH*H*N, NCH_2CHHN, CHCH*H* and CHC*H*H), 2.95 (0.5H, m, NCH_2CHHN), 3.07 (0.5H, dd, *J* 13.4 and 6.3, CHCH*H*), 3.20 (0.5H, m, NCH*H*CH_2N), 3.29 (1.5H, m, NCH*H*CH_2N and NC*H*HCH_2N), 3.54 (0.5H, d, *J* 13.1, PhC*H*H), 3.67 (1.5H, m, PhC*H*H and $CHCO_2$), 4.13 (0.5H, d, *J* 13.4, PhCH*H*), 4.28 (0.5H, d, *J* 13.1, PhCH*H*), 4.38 and 4.58 (each 0.5H, s, 7a-H) and 7.36 (5H, m, Ar-H); δ_C(22.7 MHz) 28.02 [$C(CH_3)_3$], 45.52 (CH_2), 53.32, 53.86, 54.08 and 54.84 (NCH_2CH_2N), 57.71, 58.09 (PhCH_2), 60.31 and 61.12 (quaternary C), 65.45 and 65.83 (CH), 82.03 and 82.14 (CMe_3), 92.00 and 94.33 (C-7a), 117.30 and 117.41 (CN), 127.37, 128.40, 128.78 and 128.89 (Ar-CH), 137.78 (Ar-C), 169.90 and 170.44 (CO); *m*/*z* 363 and 361 (M^+, 0.6 and 2%), 274 (31), 262 (8), 260 (22), 218 (100), 173 (9), 127 (74) and 91 (94).

5-Benzoyl-1-benzyl-7-chloro-7-cyanohexahydro-1*H*-pyrrolo-[1,2-*a*]imidazole 19d. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (660 mg, 4.125 mmol) by the method described above for the preparation of **7c** *via* Protocol B but using 2-bromoacetophenone (860 mg, 4.33 mmol), 2-chloropropenonitrile (1.08 cm^3, 13.6 mmol) and DBU (0.63 g, 4.125 mmol) and heating the resulting mixture under reflux for 1 h. Column chromatography eluting with ether–hexane (1 : 1 v/v) afforded the *title compound* **19d** (536 mg, 36%) as a yellow oil identified as a 1 : 1 mixture of diastereoisomers that was used directly in the preparation of pyrrole **21c** (see below); ν_{max}(film)/cm^{-1} 3050, 3025, 2940, 2840, 2250, 1690, 1600, 1450, 1270, 910 and 740; δ_H(60 MHz) 3.10 (6H, m, NCH_2CH_2N and CHCH_2), 3.60 (0.5H, d, *J* 6.0, PhC*H*H), 3.75 (0.5H, d, *J* 6.0, PhC*H*H), 4.45 (3H, m, PhCH*H*, 7a-H and CHCO), 7.55 (8H, m, Ar-H) and 8.05 (2H, m, Ar-H); δ_C(22.7 MHz) 45.52 (CHCH_2), 53.25, 53.75, 54.28 and 54.83 (NCH_2CH_2N), 57.87 and 58.19 (PhCH_2), 60.69 and 61.66 (quaternary C), 66.48 and 67.24 (*C*HCO), 92.16 and 94.33 (C-7a), 117.24 and 117.57 (CN), 127.32, 128.35, 128.46, 128.78 and 133.55 (Ar-CH), 135.55, 135.88 and 137.67 (Ar-C), 196.12 and 196.45 (CO); *m*/*z* (M^+ not observed) 327 (3%), 221 (61), 220 (54), 192 (20), 126 (20), 91 (100) and 77 (46).

Preparation of pyrroles 21a–c

1-(2-Benzylaminoethyl)-4-cyano-2-ethoxycarbonylpyrrole 21a. To 1-benzyl-7-chloro-7-cyano-5-ethoxycarbonylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **19b** (165.7 mg, 0.497 mmol) in dry DMSO (10 cm^3) stirred at 100 °C was added DBU (83.2 mg, 0.547 mmol). The mixture was maintained at this temperature for 3 h, then allowed to cool and the liquor partitioned between chloroform (2 × 30 cm^3) and water (30 cm^3). The combined organic extract was washed with water (5 × 30 cm^3), dried and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with ethyl acetate–hexane (1 : 1 v/v) to yield the *title compound* **21a** (108 mg, 73%) as a colourless oil (Found: M^+, 297.1485; $C_{17}H_{19}N_3O_2$ requires *M*, 297.1477); ν_{max}(film)/cm^{-1} 3350, 3125, 2980, 2230, 1710, 1550, 1490, 1400, 1270, 1205, 1100 and 740; δ_H(250 MHz) 1.34 (3H, t, *J* 7.2, CH_3), 1.43 (1H, br s, NH), 2.97 (2H, t, *J* 5.9, NCH_2-CH_2N), 3.75 (2H, s, PhCH_2), 4.27 (2H, q, *J* 7.1, OCH_2), 4.43 (2H, t, *J* 5.9, NCH_2CH_2N) and 7.26 (7H, m, Ar-H); δ_C(22.7 MHz) 14.32 (CH_3), 49.25 and 50.07 (NCH_2CH_2N), 53.59 (PhCH_2), 60.69 (OCH_2), 92.76 (Ar-C), 115.35 (CN), 120.66 (Ar-CH), 123.58 (Ar-C), 127.16, 127.97, 128.51 and 133.98 (Ar-CH), 140.00 (Ar-C) and 160.10 (CO); *m*/*z* 297 (M^+, 6%), 251 (5), 147 (5), 121 (9), 120 (100), 106 (5) and 92 (97).

1-(2-Benzylaminoethyl)-2-*tert*-butoxycarbonyl-4-cyanopyrrole 21b. Prepared from 1-benzyl-5-*tert*-butoxycarbonyl-7-chloro-7-cyanohexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **19c** (508.6 mg, 1.41 mmol) by the method described above for the preparation of **21a** but using DBU (0.23 cm^3, 1.55 mmol). Column chromatography eluting with ether afforded the *title compound* **21b** (272 mg, 59%) as a yellow oil (Found: $M^+ - C_4H_9OH$, 251.1081; $C_{19}H_{23}N_3O_2 - C_4H_{10}O$ requires *M*, 251.1059); ν_{max}(film)/cm^{-1} 3320, 3010, 2975, 2230, 1710, 1550, 1490, 1400, 1280, 1170, 1140 and 1100; δ_H(60 MHz) 1.45 (1H, br, s, NH), 1.55 [9H, s, $C(CH_3)_3$], 2.95 (2H, t, *J* 4.0, NCH_2CH_2N), 3.75 (2H, s, PhCH_2), 4.40 (2H, t, *J* 4.0, NCH_2CH_2N), 7.10 (1H, d, *J* 1.7, Ar-H) and 7.30 (6H, m, Ar-H); δ_C(22.7 MHz) 28.18 [$C(CH_3)_3$], 49.15 and 49.90 (NCH_2CH_2N), 53.48 (PhCH_2), 81.70 (CMe_3), 92.27 (Ar-C), 115.46 (CN), 120.28 (Ar-CH), 124.77 (Ar-C), 126.99, 127.92, 128.40 and 133.55 (Ar-CH), 139.94 (Ar-C) and 159.34 (CO); *m*/*z* (M^+ not observed) 251 ($M^+ - C_4H_9OH$, 7%), 120 (66), 91 (100) and 41 (13).

2-Benzoyl-1-(2-benzylaminoethyl)-4-cyanopyrrole 21c. Prepared from 5-benzoyl-1-benzyl-7-chloro-7-cyanohexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **19d** (539.3 mg, 1.47 mmol) by the method described above for the preparation of **21a** but using DBU (0.24 cm^3, 1.62 mmol). Column chromatography eluting with ethyl acetate–triethylamine (99.5 : 0.5 v/v) afforded the *title compound* **21c** (242 mg, 50%) as a yellow oil (Found: M^+, 329.1505; $C_{21}H_{19}N_3O$ requires *M*, 329.1528); ν_{max}(film)/cm^{-1} 3350, 3130, 3070, 2850, 2240, 1640, 1400, 1280, 1140, 910, 740 and 700; δ_H(60 MHz) 1.65 (1H, br s, NH), 3.05 (2H, t, *J* 4.0, NCH_2CH_2N), 3.80 (2H, s, PhCH_2), 4.55 (2H, t, *J* 4.0, NCH_2-CH_2N), 7.00 (1H, m, Ar-H), 7.35 (5H, m, Ar-H), 7.60 (4H, m, Ar-H) and 7.85 (2H, m, Ar- H); δ_C(22.7 MHz) 49.31 and 50.07 (NCH_2CH_2N), 53.43 (PhCH_2), 92.65 (Ar-C), 115.14 (CN), 124.29, 126.99, 127.86, 128.35 and 129.16 (Ar-CH), 130.57 (Ar-C), 132.36 and 135.34 (Ar-CH), 138.53 and 139.94 (Ar-C) and 185.94 (CO); *m*/*z* 329 (M^+, 2%), 327 (5), 311 (25), 234 (26), 220 (16), 219 (11), 120 (28) and 91 (100).

1-Benzyl-3-(trimethylsilylmethyl)-4,5-dihydro-1*H*-imidazol-3-ium trifluoromethanesulfonate 22

Trimethylsilylmethyl trifluoromethanesulfonate (0.465 cm^3, 2.33 mmol) was added dropwise to a stirred solution of 1-benzyl-4,5-dihydroimidazole **5** (340 mg, 2.12 mmol) in dry acetonitrile (10 cm^3) under an atmosphere of nitrogen. After 2 h the liquor was concentrated *in vacuo* and on standing yielded the title compound **22** as a colourless hygroscopic solid (760 mg, 98%) which was used without further purification; ν_{max}-(film)/cm^{-1} 3060, 2950, 1650, 1260, 1150, 1030 and 850; δ_H(400 MHz) 0.13 (9H, s, 3 × CH_3), 3.10 (2H, s, CH_2Si), 3.78 and 3.88 (each 2H, m, NCH_2CH_2N), 4.60 (2H, s, PhCH_2), 7.33 (5H, m, Ar-H) and 8.38 (1H, s, 2-H); *m*/*z* (FAB +ve) 643 [$(2M - OTf)^+$, 2%], 247 (100), 155 (20), 130 (15), 91 (95), 73 (95) and 59 (85).

Preparation of pyrroloimidazoles 23a–c

1-Benzyl-7-methoxycarbonylhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole 23a. 1-Benzyl-3-(trimethylsilylmethyl)-4,5-dihydro-1*H*-imidazol-3-ium trifluoromethanesulfonate **22**, prepared (see above) from 1-benzyl-4,5-dihydroimidazole **5** (505 mg, 3.18 mmol) and trimethylsilylmethyl trifluoromethanesulfonate

(0.66 cm^3, 3.32 mmol), was taken up in dry diglyme (15 cm^3) and added by cannula to a slurry of caesium fluoride (2.40 g, 15.79 mmol) and methyl propenoate (285 mg, 3.32 mmol) in dry diglyme (20 cm^3) under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 5 h and then concentrated *in vacuo.* The semi-solid was partitioned between chloroform (2 × 40 cm^3) and water (40 cm^3), and the combined organic extracts were dried and concentrated *in vacuo*. Column chromatography of the crude product eluting with chloroform–isopropylamine (99.5:0.5 v/v) yielded the *title compound* **23a** (351 mg, 43%) as a colourless oil identified as a 1:1 mixture of diastereoisomers; ν_{max}(film)/cm^{-1} 2950, 2820, 1730, 1670, 1600, 1160, 750 and 700; δ_H(200 MHz) 2.20 and 2.66 (each 2.5H, m), 3.12 (5H, m), 3.57 and 3.61 (3H, 2 × s, OCH_3), 3.70 (1H, m), 3.84 (0.5H, d, *J* 15.6, PhCH*H*), 3.95 (0.5H, d, *J* 5.0, 7a-H) and 7.19 (5H, m, Ar-H); δ_C(62.9 MHz) 29.54 and 34.75 (CH*C*H_2), 41.40 and 44.41 (*C*HCO_2), 49.61 and 51.70 (OCH_3), 52.71, 53.15, 53.52, 54.01, 55.16, 57.36, 57.70 and 58.40 (4 × CH_2), 85.62 and 88.82 (C-7a), 127.95, 128.14, 128.63 and 128.91 (Ar-CH), 138.68 (Ar-C), 173.94 and 174.38 (CO); *m*/*z* 261 (M^+ + H, 20%), 260 (M^+, 30), 259 (45), 229 (10), 201 (8), 174 (42), 91 (100) and 83 (65). A small portion of the title compound was converted to the *bis*(*oxalate*) *salt* (Found: C, 51.7; H, 5.8; N, 6.7%; $C_{19}H_{24}N_2O_{10}$ requires C, 51.8; H, 5.5; N, 6.3%).

1-Benzyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo-[1,2-*a*]imidazole 23b. Prepared according to the method described above for the preparation of **23a** but using 1-benzyl-3-(trimethylsilylmethyl)-4,5-dihydro-1*H*-imidazol-3-ium trifluoromethanesulfonate **22** prepared from 1-benzyl-4,5-dihydroimidazole **5** (720 mg, 4.50 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (1.12 g, 4.725 mmol) in dry diglyme (15 cm^3), caesium fluoride (2.05 g, 13.5 mmol) and methyl 2-methylpropenoate (900 mg, 9.0 mmol) in dry diglyme (40 cm^3), and stirring for 20 h at room temperature before concentration *in vacuo*. The resulting semi-solid was partitioned between chloroform (2 × 50 cm^3) and water (50 cm^3), and the combined organic extracts were dried and concentrated *in vacuo*. Column chromatography of the crude product eluting with ethyl acetate–triethylamine (99.5:0.5 v/v) afforded the *title compound* **23b** (575 mg, 47%) as a colourless oil identified as a 1:1 mixture of diastereoisomers (Found: M^+, 274.1660; $C_{16}H_{22}N_2O_2$ requires *M*, 274.1681); ν_{max}(film)/cm^{-1} 2950, 2820, 1730, 1450, 1270, 1140 and 1090; δ_H(200 MHz) 1.37 and 1.39 (3H, 2 × s, CH_3), 1.72 and 1.88 (each 0.5H, m, CH*H*CO_2), 2.64 and 3.07 (each 3.5H, m), 3.28 and 3.36 (each 0.5H, d *J* 10.8, PhC*H*H), 3.68 and 3.70 (3H, 2 × s, OCH_3), 3.90 (0.5H, s, C-7a H), 4.03 and 4.09 (each 0.5H, d, *J* 10.8, PhCH*H*), 4.25 (0.5H, s, 7a-H) and 7.25 (5H, m, Ar-H); δ_C(50.3 MHz) 18.90 and 23.11 (CH_3), 36.24 and 38.15 (CH_3C*C*H_2), 51.45, 51.52, 51.82, 52.46, 52.88, 53.31, 53.62, 53.71 and 54.74 (C), 58.34 and 59.35 (Ph*C*H_2), 90.18 and 95.34 (C-7a), 126.63, 126.74, 128.03, 128.11, 128.23 and 128.38 (Ar-CH), 139.22 and 139.42 (Ar-C), 175.24 and 176.81 (CO); *m*/*z* 274 (M^+, 13%), 174 (57), 96 (10), 91 (32) and 83 (100).

1-Benzyl-7-cyano-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole 23c. Prepared from 1-benzyl-4,5-dihydroimidazole **5** (750 mg, 4.68 mmol) by the method described above for the preparation of **23a** but using trimethylsilylmethyl trifluoromethanesulfonate (1.16 g, 4.92 mmol), caesium fluoride (2.14 g, 14.06 mmol) and 2-methylpropenonitrile (470 mg, 7.03 mmol). Column chromatography eluting with dichloromethane–ethanol–conc. aq. ammonia (800:8:1 v/v/v) afforded the *title compound* **23c** (680 mg, 60%) as a colourless oil identified as a 2:1 mixture of diastereoisomers (Found: M^+, 241.1576; $C_{15}H_{19}N_3$ requires *M*, 241.1579); ν_{max}(film)/cm^{-1} 3025, 2925, 2840, 2250, 1500, 1450, 750 and 700; δ_H(250 MHz) 1.40 and 1.45 (3H, 2 × s, CH_3), 1.95 (0.66H, m, CH*H*CCN), 2.05 (0.33H, m, CH*H*CCN), 2.40, 2.60, 2.75 and 2.85 (each 1H, m), 3.15 (3H, m), 3.43 (1H, m, PhC*H*H), 3.70 (0.66H, s, 7a-H), 4.04 (0.33H, d, *J* 13.4, PhCH*H*), 4.12 (0.66H, d, *J* 12.7, PhCH*H*), 4.22 (0.33H, s, 7a-H) and 7.30 (5H, m, Ar-H); δ_C(22.7 MHz) 19.40 and 22.93 (CH_3), 38.80 and 39.23 (*C*H_2CCN), 39.56 and 43.30 (*C*CN), 51.58, 52.72, 53.10, 53.70, 54.08 and 54.51 (CH_2), 58.52 and 58.95 (Ph*C*H_2), 91.19 and 93.08 (C-7a), 122.93 (CN), 127.21, 128.29, 128.46 and 129.00 (Ar-CH), 138.21 and 138.53 (Ar-C); *m*/*z* 241 (M^+, 22%), 174 (80), 91 (89), 83 (100) and 56 (59).

Synthesis of tetrahydropyrroles 24a–f

1-(2-Benzylaminoethyl)-2-ethoxycarbonyl-4-methoxycarbonyl-4-methyltetrahydropyrrole 24a. A solution of 1-benzyl-5-ethoxycarbonyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **7b** (347.1 mg, 1.0 mmol) in dry ethanol (20 cm^3) was made acidic to methyl green indicator by the dropwise addition of hydrochloric acid (2 M). Sodium cyanoborohydride (69 mg, 1.10 mmol) was added portionwise while maintaining the acidic pH. The resulting mixture was stirred at room temperature for 3 h, made basic by the addition of solid potassium hydrogen carbonate and partitioned between chloroform (2 × 50 cm^3) and water (50 cm^3). The combined organic extract was dried, concentrated *in vacuo*, and the crude product purified by column chromatography eluting with ethyl acetate–triethylamine (99.5:0.5 v/v) to yield the *title compound* **24a** (237 mg, 68%) as a colourless oil (Found: M^+, 348.2024; $C_{19}H_{28}N_2O_4$ requires *M*, 348.2039); ν_{max}(film)/cm^{-1} 3320, 2950, 2810, 1730, 1460, 1180 and 750; δ_H(250 MHz) 1.25 (3H, t, *J* 7.1, CH_2CH_3), 1.40 (3H, s, CH_3), 1.78 (1H, dd, *J* 13.2 and 7.0, CHC*H*H), 2.05 (1H, br s, NH), 2.70 (5H, m, NCH_2-CH_2N and CHCH*H*), 2.87 and 2.95 (each 1H, d, *J* 9.3, N*C*H_2-CCO_2), 3.37 (1H, dd, *J* 9.0 and 7.0, $CHCO_2$), 3.66 (3H, s, OCH_3), 3.73 and 3.83 (each 1H, d, *J* 13.2, PhCH_2), 4.15 (2H, q, *J* 7.1, OCH_2) and 7.30 (5H, m, Ar-H); δ_C(22.7 MHz) 14.10 (CH_2CH_3), 24.23 (CH_3), 40.43 (CH*C*H_2), 47.41 (N*C*H_2CH_2N), 47.85 (quaternary C), 51.96 (OCH_3), 53.70 (NCH_2*C*H_2N), 53.81 (Ph*C*H_2), 60.47 (NCH_2), 62.69 (OCH_2), 65.62 (CH), 126.67, 128.02 and 128.19 (Ar-CH), 140.59 (Ar-C), 173.58 and 176.73 (CO); *m*/*z* 348 (M^+, 9%), 302 (21), 273 (16), 229 (16), 228 (100), 211 (33), 174 (15), 156 (44) and 91 (55).

1-(2-Benzylaminoethyl)-4-cyano-2-ethoxycarbonyl-4-methyltetrahydropyrrole 24b. Prepared from 1-benzyl-7-cyano-5-ethoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **7f** (295.2 mg, 0.943 mmol) by the method described above for the preparation of **24a** but using sodium cyanoborohydride (65 mg, 1.04 mmol). Column chromatography eluting with ethyl acetate–triethylamine (99.5:0.5 v/v) afforded the *title compound* **24b** (295 mg, 99%) as a colourless oil (Found: $M^+ - C_2H_5OH$, 269.1495; $C_{18}H_{25}N_3O_2 - C_2H_6O$ requires *M*, 269.1528); ν_{max}(film)/cm^{-1} 3320, 2980, 2950, 2820, 2240, 1730, 1450, 1190, 740 and 700; δ_H(250 MHz) 1.25 (3H, t, *J* 7.1, CH_2CH_3), 1.50 (3H, s, CH_3), 1.97 (1H, dd, *J* 13.7 and 6.4, CHC*H*H), 2.05 (1H, br s, NH), 2.70 (5H, m, NCH_2CH_2N and CHCH*H*), 2.94 and 3.02 (each 1H, d, *J* 9.4, N*C*H_2CCO_2), 3.54 (1H, dd, *J* 9.4 and 6.4, $CHCO_2$), 3.72 and 3.82 (each 1H, d, *J* 13.7, PhCH_2), 4.13 (2H, q, *J* 7.2, OCH_2) and 7.30 (5H, m, Ar-H); *m*/*z* (M^+ not observed), 269 ($M^+ - C_2H_5OH$, 46%), 240 (32), 202 (17), 178 (79), 174 (41), 136 (20), 122 (19) and 91 (100).

1-(2-Benzylaminoethyl)-2-*tert*-butoxycarbonyl-4-cyano-4-methyltetrahydropyrrole 24c. Prepared from 1-benzyl-5-*tert*-butoxycarbonyl-7-cyano-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole **7g** (241 mg, 0.71 mmol) by the method described above for the preparation of **24a** but using sodium cyanoborohydride (45 mg, 0.706 mmol). Column chromatography eluting with chloroform–isopropylamine (99.5:0.5 v/v) afforded the *title compound* **24c** (208 mg, 86%) as a colourless oil (Found: M^+, 343.2251; $C_{20}H_{29}N_3O_2$ requires *M*, 343.2260); ν_{max}(film)/cm^{-1} 3280, 2975, 2820, 2230, 1730, 1450, 1360, 1150 and 750; δ_H(250 MHz) 1.45 [9H, s, C$(CH_3)_3$], 1.50 (3H, s, CH_3), 1.93 (1H, dd, *J* 13.3 and 6.2, CHC*H*H), 2.07 (1H, br s, NH), 2.75 (5H, m, NCH_2CH_2N and CHCH*H*), 2.93 and 3.00 (each 1H, d, *J* 9.6,

NCH_2CCN), 3.42 (1H, dd, *J* 8.9 and 6.3, $CHCO_2$), 3.72 and 3.82 (each 1H, d, *J* 13.2, PhCH_2) and 7.30 (5H, m, Ar-H); δ_C(22.7 MHz) 24.17 (CH_3), 28.07 [$C(CH_3)_3$], 35.82 (quaternary C), 42.11 ($CHCH_2$), 47.30 and 53.21 (NCH_2CH_2N), 53.86 (PhCH_2), 63.45 (NCH_2), 65.40 (CH), 81.43 (CMe_3), 124.50 (CN), 126.83, 128.13 and 128.35 (Ar-CH), 140.54 (Ar-C) and 172.01 (CO); *m*/*z* 343 (M^+, 5%), 242 (34), 167 (70), 134 (18), 123 (43), 120 (36), 109 (10) and 91 (100).

1-(2-Benzylaminoethyl)-4-cyano-2-ethoxycarbonyl-2,4-dimethyltetrahydropyrrole 24d. Prepared from 1-benzyl-7-cyano-5-ethoxycarbonyl-5,7-dimethylhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole **7h** (303.5 mg, 0.93 mmol) by the method described above for the preparation of **24a** but using sodium cyanoborohydride (64.2 mg, 1.03 mmol). Column chromatography eluting with ethyl acetate–triethylamine (99.5 : 0.5 v/v) afforded the *title compound* **24d** (217 mg, 71%) as a colourless oil (Found: M^+, 329.2097; $C_{19}H_{27}N_3O_2$ requires *M*, 329.2103); ν_{max}(film)/cm^{-1} 3320, 2980, 2840, 2250, 1730, 1460, 1200, 1150 and 750; δ_H(250 MHz) 1.23 (3H, t, *J* 7.1, CH_2CH_3), 1.41 and 1.45 (each 3H, s, CH_3), 2.08 (1H, br s, NH), 2.26 and 2.32 (each 1H, d, *J* 13.8, CCH_2C), 2.60 (4H, m, NC*H*HCH_2N and NC*H*HCCN), 2.85 (1H, m, NCH*H*CH_2N), 3.21 (1H, d, *J* 9.4, NCH*H*CCN), 3.75 and 3.85 (each 1H, d, *J* 13.4, PhCH_2), 4.12 (2H, q, *J* 7.1, OCH_2) and 7.25 (5H, m, Ar-H); δ_C(22.7 MHz) 14.10 (CH_2CH_3), 22.49 and 22.92 (CH_3), 35.01 (quaternary C), 46.60, 47.25, 49.58, 53.42, 60.47 and 61.28 (CH_2), 67.19 (quaternary C), 125.37 (CN), 126.56, 127.81 and 128.13 (Ar-CH), 140.21 (Ar-C) and 173.58 (CO); *m*/*z* 329 (M^+, 2%), 256 (13), 209 (96), 183 (10), 181 (18), 137 (64), 120 (53) and 91 (100).

1-(2-Benzylaminoethyl)-2-*tert*-butoxycarbonyl-4-chloro-4-cyanotetrahydropyrrole 24e. Prepared from 1-benzyl-5-*tert*-butoxycarbonyl-7-chloro-7-cyanohexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole **19c** (249 mg, 0.69 mmol) by the method described above for the preparation of **24a** but using sodium cyanoborohydride (43 mg, 0.69 mmol). Column chromatography eluting with chloroform–isopropylamine (99.5 : 0.5 v/v) afforded *the title compound* **24e** (208 mg, 86%) as a yellow oil identified as a 1 : 1 mixture of diastereoisomers (Found M^+, 363.1721; $C_{19}H_{26}{}^{35}ClN_3O_2$ requires *M*, 363.1713); ν_{max}(film)/cm^{-1} 3320, 2980, 2250, 1725, 1455, 1370, 1150 and 750; δ_H(60 MHz) 1.45 [9H, s, $C(CH_3)_3$], 2.10 (1H, br s, NH), 3.20 (9H, m), 3.80 (2H, s, PhCH_2) and 7.35 (5H, m, Ar-H); δ_C(22.7 MHz) 28.02 (CH_3), 45.63, 45.79, 47.20, 47.58 and 52.94 (CH_2), 53.42 (quaternary C), 53.86 and 54.46 (CH_2), 55.05 (quaternary C), 64.21 and 65.13 (CH), 65.72 and 66.70 (NCH_2), 82.14 and 82.25 (CMe_3), 117.95 and 119.09 (CN), 126.89, 128.13 and 128.40 (Ar-CH), 140.38 (Ar-C) and 170.71 (CO); *m*/*z* 363 (M^+, 1%), 264 (3), 262 (8), 226 (13), 187 (10), 152 (17), 120 (80) and 91 (100).

1-(2-Benzylaminoethyl)-3-methoxycarbonyl-3-methyltetrahydropyrrole 24f. Prepared from 1-benzyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **23b** (155.4 mg, 0.567 mmol) by the method described above for the preparation of **24a** but using sodium cyanoborohydride (37 mg, 0.595 mmol). Column chromatography eluting with ethyl acetate–triethylamine (99.5 : 0.5 v/v) afforded the *title compound* **24f** (128 mg, 82%) as a colourless oil (Found: M^+, 276.1875; $C_{16}H_{24}N_2O_2$ requires *M*, 276.1838); ν_{max}(film)/cm^{-1} 3310, 2950, 2800, 1725, 1450, 1200, 1125, 740 and 700; δ_H(250 MHz) 1.33 (3H, s, CH_3), 1.64 (1H, m, CH_2CHH), 1.95 (1H, br s, NH), 2.37 (2H, m, NC*H*HCCO_2 and CH_2CHHC), 2.65 (6H, m, NCH_2-CH_2NCH_2), 2.95 (1H, d, *J* 9.2, NCH*H*CCO_2), 3.70 (3H, s, OCH_3), 3.83 (2H, s, PhCH_2) and 7.30 (5H, m, Ar-H); δ_C(22.7 MHz) 25.36 (CH_3), 36.09 (CH_2CH_2C), 47.58 (CH_2), 48.39 (quaternary C), 51.96 (OCH_3), 53.81, 54.08, 55.38 and 64.21 (CH_2), 126.83, 128.08 and 128.35 (Ar-CH), 140.70 (Ar-C) and 177.76 (CO); *m*/*z* 276 (M^+, 1%), 273 (2), 156 (100) and 91 (37).

2-Benzyl-7-methoxycarbonyloctahydropyrrolo[1,2-*a*]pyrazin-1-one 25

Pyrroloimidazole stereoisomer mixture **9** and **10** was prepared as described above from 1-benzyl-4,5-dihydroimidazole **5** (1.00 g, 6.25 mmol) but using methyl bromoacetate (0.96 g, 0.59 cm^3, 6.25 mmol), methyl propenoate (1.61 g, 1.69 cm^3, 18.75 mmol) and DBU (0.95 g, 0.93 cm^3, 6.25 mmol). The solvent was removed *in vacuo* and the residue partitioned between chloroform (3 × 30 cm^3) and water (30 cm^3). The combined organic phase was dried and evaporated *in vacuo*, and the residue taken up in ethanol (20 cm^3) and made acidic to methyl green indicator by the dropwise addition of 2 M hydrochloric acid. Sodium cyanoborohydride (0.43 g, 6.88 mmol) was added portionwise and stirring at room temperature was continued for 16 h. The mixture was basified to pH 8 by the portionwise addition of solid potassium hydrogen carbonate and partitioned between dichloromethane (3 × 20 cm^3) and water (50 cm^3). The organic phase was dried, concentrated *in vacuo*, and the residue purified by column chromatography eluting with ethyl acetate–triethylamine (95 : 5 v/v) to yield the *title compound* **25** (183 mg, 10%) as a pale yellow oil (Found: M^+, 288.1460. $C_{16}H_{20}N_2O_3$ requires *M*, 288.1474); ν_{max}(film)/cm^{-1} 3028, 2951, 1732, 1650, 1494, 1452, 1356, 1203, 1175 and 703; δ_H(400 MHz) 2.30 and 2.57 (each 1H, m, $CHCH_2CH$), 2.79 (1H, m, NC*H*HCH_2N), 2.88 (1H, dd, *J* 10.1 and 7.1, NC*H*HCH), 2.95 (1H, m, NCH*H*-CH_2N), 3.10 (1H, m, C*H*CO_2Me), 3.20 (2H, m, NCH_2CHHN and NCH*H*CH), 3.37 (1H, m, NCH_2CHHN), 3.45 (1H, t, *J* 8.4, NCHCO), 3.71 (3H, s, OCH_3), 4.52 and 4.65 (each 1H, d, *J* 14.6, PhCH_2) and 7.29 (5H, m, Ar-H); δ_C(68 MHz) 30.73 ($CHCH_2CH$), 40.15 ($CHCO_2Me$), 44.76 and 46.24 (CH_2CH_2), 48.97 (PhCH_2), 51.61 (OCH_3), 55.58 (NCH_2CH), 63.38 (N*C*HCO), 127.08, 127.60 and 128.23 (Ar-CH), 136.28 (Ar-C), 169.11 (NCO) and 171.97 (CO_2Me); *m*/*z* 288 (M^+, 28%), 259 (33), 197 (81), 174 (25), 137 (18) and 91 (100).

1-Benzyl-5,7-bis(hydroxymethyl)-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole 26a

1-Benzyl-5-*tert*-butoxycarbonyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **7c** (479 mg, 1.28 mmol) in dry ether (10 cm^3) was added to a slurry of lithium aluminium hydride (107 mg, 2.82 mmol) in dry ether (20 cm^3). The resulting slurry was stirred for a further 2 h, quenched by the addition of ethyl acetate and partitioned between chloroform (2 × 40 cm^3) and water (40 cm^3). The combined organic extract was dried, concentrated *in vacuo* and the crude product purified by column chromatography eluting with chloroform–isopropylamine (99.5 : 0.5 v/v) to yield the *title compound* **26a** (308 mg, 87%) as a pale yellow viscous oil (Found: M^+, 276.1834; $C_{16}H_{24}N_2O_2$ requires *M*, 276.1838); ν_{max}(film)/cm^{-1} 3400, 2930, 2870, 1460, 1050, 770 and 700; δ_H(250 MHz) 1.15 (3H, s, CH_3), 1.80 (1H, dd, *J* 13.0 and 10.3, CHC*H*HC), 1.95 (1H, dd, *J* 6.5 and 13.0, CHCH*H*C), 2.61 and 2.81 (each 1H, m, NCH_2-CH_2N), 3.10 (3H, m, NCH_2CH_2N and $CHCH_2OH$), 3.37 (2H, m, CHC*H*HOH and PhC*H*H), 3.58 (1H, dd, *J* 10.8 and 3.8, CHCH*H*OH), 3.63 and 3.65 [each 1H, d, *J* 11.8, $C(CH_3)$-CH_2OH], 3.90 (1H, s, 7a-H), 4.00 (1H, d, *J* 12.6, PhCH*H*) and 7.32 (5H, m, Ar-H); δ_C(22.7 MHz) 23.79 (CH_3), 41.51, 44.43, 51.42, 54.08, 60.14, 63.88, 66.16 and 69.68 (C), 95.74 (C-7a), 127.54, 128.62 and 128.89 (Ar-CH) and 137.83 (Ar-C); *m*/*z* 276 (M^+, 2%), 275 (2), 246 (15), 245 (26), 204 (25), 187 (100), 126 (12), 113 (14) and 91 (94).

1-Benzyl-7-hydroxymethyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole 26b

This compound was prepared from 1-benzyl-7-methoxycarbonyl-7-methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **23b** (1.72 g, 6.28 mmol) by the method described above for the preparation of **26a** but using lithium aluminium hydride (286 mg, 7.54 mmol). Column chromatography eluting with chloroform–isopropylamine (99.5 : 0.5 v/v) afforded the *title compound* **26b** (1.52 g, 98%) as a yellow gum identified as a 1 : 1 mixture of diastereoisomers (Found: M^+, 246.1738; $C_{15}H_{22}N_2O$ requires *M*, 246.1732); ν_{max}(film)/cm^{-1} 3350, 3020, 2950, 2860, 2820,

1460, 1350, 1050 and 750; δ_H(250 MHz) 1.10 and 1.12 (3H, 2 × s, CH_3), 1.55, 2.00, 2.20 and 2.40 (each 0.5H, m), 3.20 (12H, br m) and 7.45 (5H, m, Ar-H); *m/z* 246 (M^+, 11%), 245 (26), 216 (18), 215 (36), 174 (47), 91 (67) and 83 (100).

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