Azabicyclo[3.2.0]heptan-7-ones (carbapenams) from pyrrole

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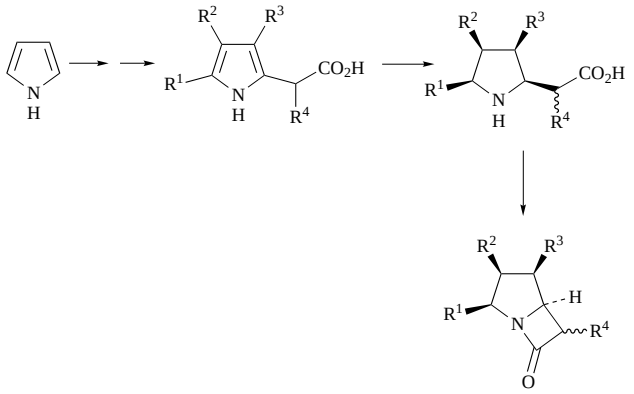
The azabicyclo[3.2.0]heptan-7-ones 4, 10, 16 and 24 have been prepared from pyrrole. The same general approach has been used for all these derivatives; namely, substitution of pyrrole at the 2- and 5-carbon atoms, catalytic hydrogenation to produce pyrrolidine-2-acetic acid derivatives, and cyclisation using tris(1,3-dihydro-2-oxobenzoxazol-3-yl)phosphine oxide 6. The catalytic hydrogenation of 2,5-disubstituted pyrroles gives only the corresponding *cis*-2,5-disubstituted pyrrolidines. The hydrogenation proceeds more easily when the nitrogen atom bears a *tert*-butoxycarbonyl substituent. The *N*-*tert*-butoxycarbonylpyrroles 8 and 21 bearing an α-substituent in the acetate side chain were hydrogenated with a high degree of facial stereoselectivity. This allowed the 6-phthalimidoazabicyclo-[3.2.0]heptan-7-one 24 to be isolated as a single diastereoisomer. The X-ray crystal structure of a precursor, the triester, 22a, has been obtained.

The aim of this work was to explore the possibility of preparing new azabicyclo[3.2.0]heptan-7-one (carbapenam) derivatives starting from pyrrole. Pyrrole is known to undergo a wide range of high yielding and predictable electrophilic substitution reactions and the intention was to exploit this reactivity to introduce a range of substituents on to the five membered ring. The carbapenam ring system could then be constructed by reduction followed by a cyclodehydration of an appropriate side chain carboxylic acid. This general approach is outlined in Scheme 1.

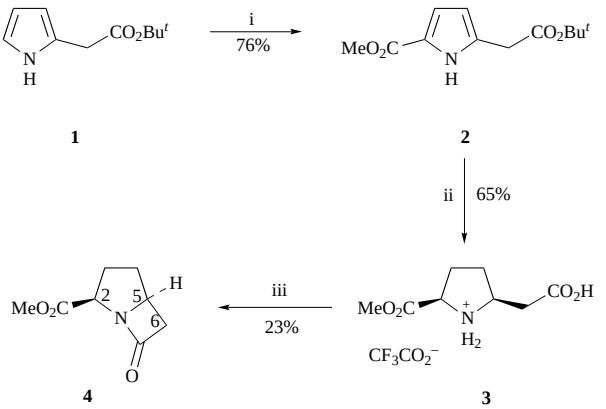


Scheme 1

The sequence has been used once before, to prepare the parent azabicyclo[3.2.0]heptan-7-one.[1] Ethyl pyrrole-2-acetate was prepared from pyrrole and ethyl diazoacetate. The ester was converted into the corresponding pyrrolidine by catalytic hydrogenation and the azetidinone was obtained from this in unspecified yield. There are several other literature examples of the preparation of the ring system by cyclisation of pyrrolidine-2-acetic acids. These syntheses start from glutamic acid derivatives[2,3] or from proline[4] and can thus be directed to producing chiral non-racemic products.

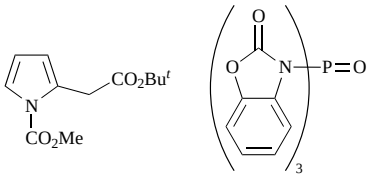
The stereochemistry of products obtained by the route outlined in Scheme 1 will be determined in the reduction step. Pyrroles can be catalytically hydrogenated to pyrrolidines and literature precedents indicate that this leads to *cis* substituted products.[5,6] From the literature examples there was no indication whether any control could be exercised over substituents located in a side chain (*e.g.* R^4 in Scheme 1). The experiments reported here have been confined to pyrrole-2-acetic acid derivatives bearing a hydrogen or a methoxycarbonyl substituent at C-5 (R^1 = H, CO_2Me) but unsubstituted at C-3 and C-4 ($R^2 = R^3$ = H). Pyrroles have been prepared in which hydrogen, methyl and phthalimido groups have been present as the side chain substituent R^4.

The carbapenam **4** was prepared by the route shown in Scheme 2. Pyrrole was first converted into *tert*-butyl pyrrole-2-



Scheme 2 *Reagents and conditions:* i, $(CCl_3CO)_2CO$, 110 °C, then MeOH, room temp.; ii, H_2 (13.5 atm), Rh–Al_2O_3, TFA, room temp.; iii, **6**, NEt_3, MeCN, 80 °C

acetate **1**. Three methods were investigated for carrying out this reaction. *tert*-Butyl diazoacetate[7] and pyrrole gave the ester **1** in moderate yield (52%) when heated together at 80 °C in the presence of copper bronze. However, the reaction mixture became dark and viscous and the ester **1** showed a tendency to decompose when it was being isolated by vacuum distillation. The method of Baciocchi *et al.*,[8] involving the substitution of pyrrole by alkoxycarbonylmethyl radicals generated from alkyl iodoacetates, was also investigated. *tert*-Butyl iodoacetate (prepared from *tert*-butyl bromoacetate and sodium iodide) was stirred with a large excess of pyrrole in aqueous DMSO in the presence of iron(II) sulfate and hydrogen peroxide. The pyrrole had to be removed by distillation and, even when pyrrole was used in large excess, some 2,5-disubstitution occurred. The best method proved to be that recently described by Schloemer *et al.* by which the ester **1** is produced from *N*-pyrrolylmagnesium chloride and *tert*-butyl bromoacetate.[9] This gave the ester **1** cleanly and in good yield. The diester **2** was prepared from this in 76% yield by reaction with triphosgene and methanol. A minor by-product, the *N*-methoxycarbonylpyrrole **5**, was removed by column chromatography.

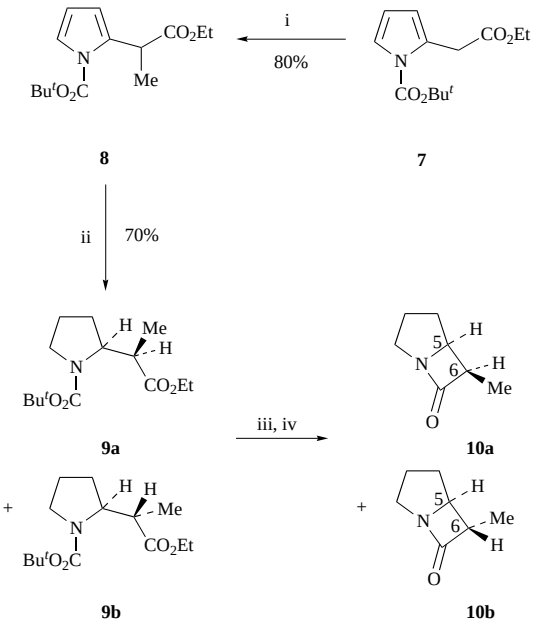


5 **6**

The catalytic hydrogenation of the diester **2** could be achieved only in an acidic medium. The reaction was carried out over a rhodium catalyst[6] and under a pressure of hydrogen of 13 atm. There was no reaction in ethanol containing a small amount of acetic acid and the reduction took place slowly in neat acetic acid as solvent. The hydrogenation was much more rapid in trifluoroacetic acid and this had the advantage of hydrolysing the *tert*-butyl ester at the same time. The pyrrolidine monoester was isolated as its trifluoroacetate salt **3** in 65% yield after recrystallisation; there was no evidence (by NMR) of the presence of another isomer in the crude reaction mixture.

Tris (1,3-dihydro-2-oxobenzoxazolin-3-yl)phosphine oxide **6** was used to bring about the cyclisation of the amino acid **3**. This and some closely related phosphine oxides were first described by Kunieda and co-workers[10] and were shown to be effective reagents for the cyclisation of β-amino acids to β-lactams. In particular, they were superior to some other commonly used dehydrating agents for the preparation of bicyclic β-lactams. The reagent **6** is a crystalline solid that is easily prepared from inexpensive starting materials. The azetidinone **4** was isolated in 23% yield as a colourless oil. The relative stereochemistry at C-2 and C-6 was established from the ^{1}H NMR spectrum, which is closely similar to that of the corresponding *p*-nitrobenzoate ester reported by Bycroft *et al.*[11] The signal for H-2† appears near δ 3.9 in these two esters but at δ 4.42 in the epimeric ester in which H-2 and H-5 are *trans*.[3] The ester **4** was previously reported only as a mixture with its epimer.[12] This route produced the azetidinone ester **4** as a racemate but the catalytic hydrogenation step is stereoselective. The next objective was to determine whether the method could be adapted to the preparation of azabicyclo[3.2.0]heptan-7-ones bearing a substituent at C-6 with any degree of control of stereochemistry. In order to explore this possibility the 6-methyl derivatives **10a** and **10b** were prepared by the route shown in Scheme 3. Ethyl pyrrole-2-acetate was first protected on nitrogen by reaction with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine (DMAP). The diester **7** was then methylated in the side chain in good yield by reaction with potassium hexamethyldisilazide (KHMDS) and iodomethane and the resulting diester **8** was hydrogenated over rhodium in ethanol containing acetic acid. The hydrogenation of the ester **8** was easier than that of the ester **2** because of the activating effect of the 1-*tert*-butoxycarbonyl substituent, as Kaiser and Muchowski found.[6] The product of the hydrogenation was a mixture of the pyrrolidine diesters **9a** and **9b**. The hydrogenation proceeded with a surprisingly high degree of diastereoselectivity. The ratio of the two esters was estimated as 8 : 1 from the NMR spectrum of the mixture, but it was not possible at this stage to determine which was the major component. The mixture was hydrolysed, and the protecting group removed, by reaction with hydrochloric acid and the resulting mixture of amino acids was cyclised to the azetidinones **10a** and **10b** by using the phosphine oxide **6**. The mixture of azetidinones could not be isolated completely free from dihydrobenzoxazolone, a contaminant derived from the cyclising agent, by column chromatography. The two isomers were identified from the

† The numbering system is based on systematic nomenclature and differs from that often used in the literature for carbapenems and related compounds.



8 **7** **9a** **10a** **9b** **10b**

Scheme 3 *Reagents and conditions:* i, KHMDS then MeI, −78 °C; ii, H_2 (13.5 atm), Rh–Al_2O_3, TFA, room temp.; iii, HCl, room temp.; iv, **6**, NEt_3, MeCN, 80 °C

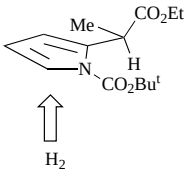
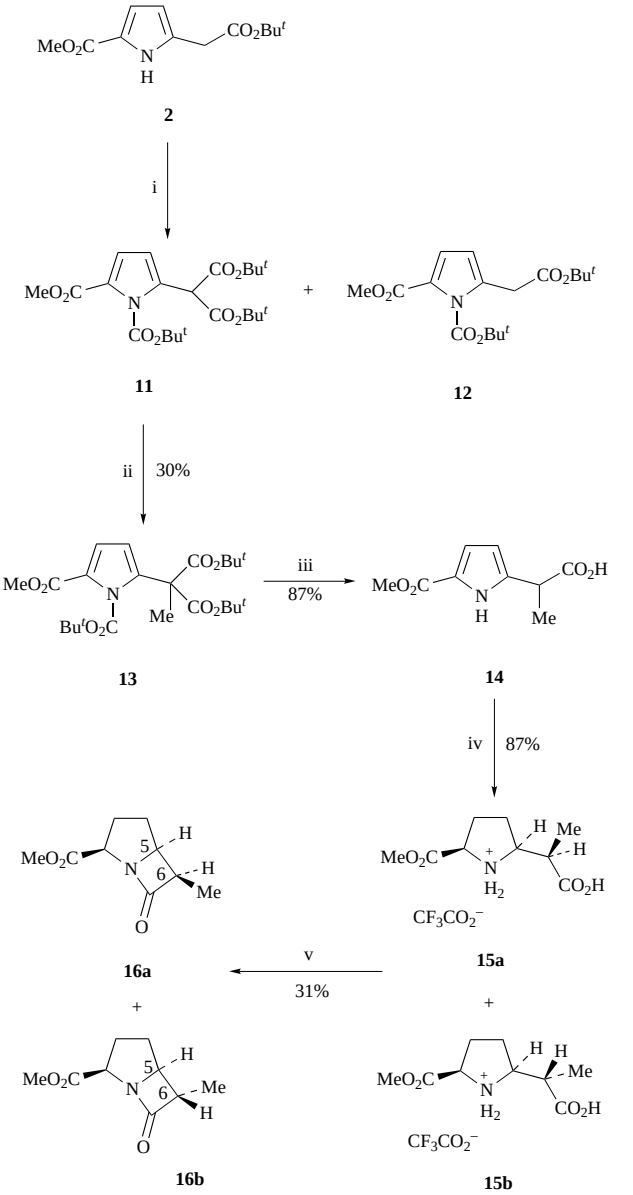


Fig. 1 A conformation of the diester **8** that will lead to preferential formation of the pyrrolidine **9a**

mass spectrum and the ^{1}H NMR spectrum of the mixture. A decoupling experiment allowed the H-5 to H-6 coupling constant of the major isomer to be determined. The value of 5.2 Hz indicates a *cis* arrangement of the two hydrogens and thus the structure **10a** for the major isomer. Hence, the major product of hydrogenation of the pyrrole diester **8** is the pyrrolidine **9a**. The selectivity of the hydrogenation is consistent with a reduction that takes place through a conformation of the ester **8** in which the methyl group of the side chain lies in the same plane as the pyrrole ring. Hydrogenation would then take place preferentially from the less hindered face (Fig. 1). Molecular modelling calculations carried out on analogous indole diesters, which show the same facial selectivity when hydrogenated, indicate that this is likely to be a minimum energy conformation.[13]

An analogous route to the azetidinone esters **16a** and **16b** was devised, starting from the pyrrole diester **2**. All our attempts to introduce the Boc protecting group cleanly were unsuccessful. There was a competitive substitution of the side chain methylene group and, with one equivalent of di-*tert*-butyl dicarbonate, a mixture of the starting ester **2**, the required triester **12** and the tetraester **11** was produced. The triester **12** was unchanged when treated with more di-*tert*-butyl dicarbonate and so it is not an intermediate in the formation of the tetraester **11**. A mixture of **11** and **12** was methylated and from the resulting reaction mixture the tetraester **13** was isolated in low yield (Scheme 4). When this was treated with TFA at room temperature the α-methylpyrrole-2-acetic acid **14** was formed; this was isolated in good yield as a crystalline solid.

The ester **14** was hydrogenated in TFA and the trifluoroacetate salts **15a** and **15b** were isolated. In this case the hydrogenation was unselective, the ratio of **15a** to **15b** being 1 : 1. Evidently the *tert*-butoxycarbonyl substituent on nitrogen is

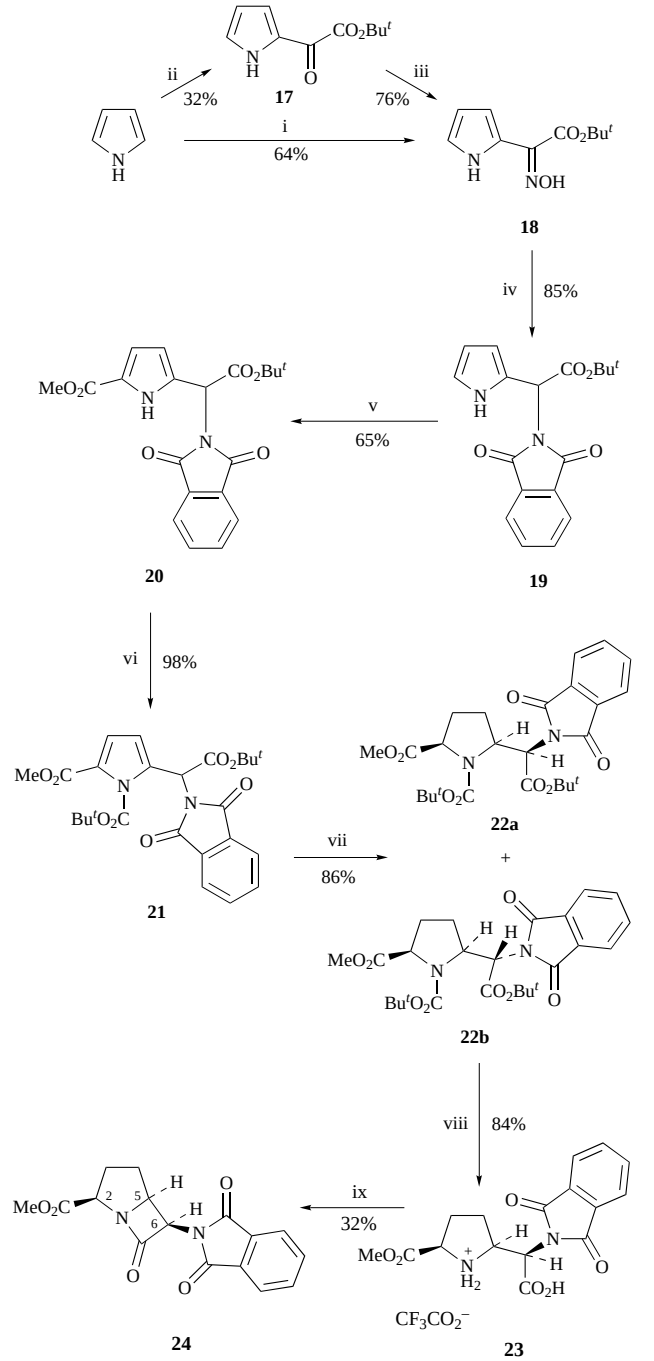


Scheme 4 *Reagents and conditions:* i, $(Bu^tO_2C)_2O$, DMAP, room temp.; ii, KHMDS then MeI, −78 °C; iii, TFA, room temp.; iv, H_2 (13.5 atm), Rh–Al_2O_3, TFA, room temp.; v, **6**, NEt_3, MeCN, 80 °C

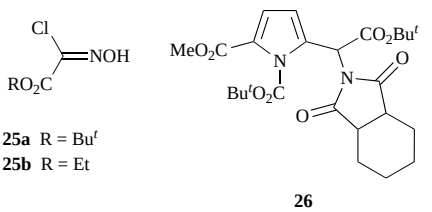
important in enforcing a conformational preference on the pyrrole for the hydrogenation step. The mixture of salts **15a** and **15b** was cyclised, as before, to give the corresponding β-lactams **16a** and **16b** (1 : 1) in 31% yield. The mixture was not separated but it was possible to assign signals corresponding to each isomer in the NMR spectrum.

An alternative approach to 6-substituted azabicyclo-[3.2.0]heptan-7-ones of this type is to replace the acetate side chain with one containing an appropriate functional group in the first step of the reaction sequence. This approach was adopted in order to prepare derivatives bearing a protected amino group (Scheme 5). Pyrrole was first converted into the hydroxyimino ester **18**. This reaction was achieved in one step by using the chlorooxime **25a** as an electrophile; we have previously reported an analogous reaction with the corresponding ethyl ester **25b**.[14] The chlorooxime **25a**, which is a new compound, was prepared from *tert*-butyl glycine. A method of preparation of the oxime **18** that proved to be easier to scale up was a two step sequence by way of the oxo ester **17**. This ester was prepared in modest yield from pyrrole, oxalyl chloride and *tert*-butyl alcohol.

The oxime **18** was reduced to the corresponding amine using aluminium amalgam and this was directly converted into the



Scheme 5 *Reagents and conditions:* i, **25a**, Na_2CO_3, room temp.; ii, $(COCl)_2$, pyridine, −78 °C then Bu^tOH; iii, $HONH_3^+Cl^-$, pyridine, 80 °C; iv, Al–Hg then *N*-ethoxycarbonylphthalimide, NEt_3, room temp.; v, $(Cl_3CO)_2CO$, 110 °C, then MeOH, room temp.; vi, $(Bu^tO_2C)_2O$, DMAP, room temp.; vii, H_2 (13.5 atm), Pt–C, room temp.; viii, TFA, room temp.; ix, **6**, NEt, MeCN, 80 °C



25a R = Bu^t
25b R = Et

26

phthalimide **19**. The remaining steps of the reaction sequence are analogous to those in Scheme 3. The methoxycarbonyl group was introduced at C-5 using triphosgene and the pyrrole nitrogen of the diester **20** was protected (in this case without complications) as its *tert*-butoxycarbonyl derivative **21**. When this compound was hydrogenated over rhodium the only prod-

uct detected was a tetrahydro derivative **26** in which the benzene ring has been reduced in preference to the pyrrole ring. In contrast, hydrogenation over platinum took place selectively at the pyrrole ring. A 4:1 mixture of isomers **22a** and **22b** was obtained, from which the major component **22a** was isolated in 62% yield. An X-ray crystal structure of the triester **22a** was obtained and this clearly established the relative stereochemistry at C-α, C-2 and C-5.‡ The hydrogenation of the diester **21** thus shows the same facial stereoselectivity as that of the diester **8**. The presence of the *tert*-butoxycarbonyl substituent on nitrogen is apparently more important in determining this selectivity than the nature of the substituent in the side chain. The diester was hydrolysed with TFA to give the trifluoroacetate salt **23**. This was cyclised to the azetidinone **24**, which was isolated in 32% yield as a crystalline solid. Its structure was established from the ^{1}H NMR spectrum. The coupling constant of 5.2 Hz between H-5 and H-6 is consistent with a *cis* relationship of the two hydrogens. The signal for H-6 is also coupled to H-2 (*J* 1.0 Hz). This long range coupling and the chemical shift of the signal for H-2 (4.1 ppm) are indicative of the all *cis* structure **24**.

In summary, the methodology is quite flexible in terms of the types of substituent that can be incorporated into the final products. It could probably be extended to pyrroles containing additional substituents at the 3- and 4-positions of the pyrrole ring. The predictable *cis* hydrogenation of pyrroles, together with the unexpected diastereoselectivity observed in the hydrogenation of the *N*-*tert*-butoxycarbonylpyrroles, allows some degree of stereochemical control in the formation of the azetidinones. The yields of azetidinones are moderate, probably because of incomplete conversion of the amino acids, but longer reaction times did not result in an increase in the yields.

Experimental

General

^{1}H NMR spectra were recorded either on a Bruker AC 200 (200 MHz) or on a Bruker AMX 400 (400 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). *J* Values are in Hz. Infrared spectra were recorded either on a Perkin-Elmer 298 or on a Perkin-Elmer 1720-X FTIR spectrometer. Solid samples were run as KBr discs unless indicated otherwise, and liquids as thin films. Mass spectra were recorded on a VG micromass 7070E as electron impact or chemical ionisation spectra. Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. Melting points (mp) were determined on a Kofler block. Flash column chromatography was carried out using Mackerey Nagel MN-Kieselgel 60 and hand bellows or an air line to supply the pressure to the column. Thin layer chromatography (TLC) was carried out on Merck 10 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}. Ether refers to diethyl ether.

tert-Butyl pyrrole-2-acetate 1 [8]

Methylmagnesium chloride (13.90 ml, 41.8 mmol; 3.0 M in THF) was added dropwise by means of a cannula over 15 min to a stirred solution of pyrrole (2.97 g, 44.3 mmol) in dry THF (66 ml) at −20 °C. The solution was stirred at −20 °C for 30 min, then at room temp. for 30 min. The pale green solution was cooled to −10 °C then *tert*-butyl bromoacetate (1.95 g, 1.6 ml, 10 mmol) was added rapidly and the solution was stirred and allowed to reach room temp. over 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was washed with ether. The combined organic extracts were washed with aqueous saturated ammonium chloride, dried ($MgSO_4$) and evaporated to a dark oil. The excess of pyrrole was removed by distillation. The product was distilled at 125 °C and 0.05 mmHg to yield *tert*-butyl pyrrole-2-acetate **1** as a yellow oil (1.24 g, 68%) (Found: M^+, 181.110. Calc. for $C_{10}H_{15}NO_2$: *M*, 181.110); ν_{max}(film)/cm^{-1} 3388, 1720, 1369, 1148 and 717; δ_H(400 MHz) 1.46 (9 H, s), 3.58 (2 H, s), 5.99 (1 H, m, H-3), 6.14 (1 H, m, H-4), 6.74 (1 H, m, H-5) and 8.76 (1 H, br s, NH).

tert-Butyl 5-methoxycarbonylpyrrole-2-acetate 2

Triphosgene (1.64 g, 5.5 mmol) was added to a solution of *tert*-butyl pyrrole-2-acetate **1** (1.00 g, 5.5 mmol) in dry toluene (50 ml). The solution was heated under reflux for 1.5 h. The solution was allowed to cool, then dry methanol (20 ml) was added and the solution was stirred at room temp. for a further 1.5 h. After this time an excess of triethylamine (5.0 ml) was added and the solution was stirred for 15 min. The solvent was removed, ether was added and the solid residue was filtered off. The ether fractions were decolourised with charcoal then evaporated to leave a red crystalline solid. Column chromatography (1:2 ether–light petroleum, bp 40–60 °C) gave the diester **2** (1.0 g, 76%) as a colourless solid, mp 75 °C (Found: C, 60.6; H, 7.3; N, 5.65. $C_{12}H_{17}NO_4$ requires C, 60.2; H, 7.2; N, 5.85%); ν_{max}(Nujol)/cm^{-1} 3270, 1731, 1687, 1286, 1121, 1002 and 770; δ_H(200 MHz) 1.48 (9 H, s), 3.60 (2 H, s, CH_2CO), 3.84 (3 H, s), 6.03 (1 H, dd, $J_{2,3}$ 2.7, $J_{3,4}$ 3.8, H-3), 6.83 (1 H, dd, $J_{1,4}$ 2.7, $J_{3,4}$ 3.8, H-4) and 9.54 (1 H, br s, NH); *m*/*z* 239 (M^+, 19%), 183 (37), 138 (100), 106 (51) and 57 (62).

A by-product that was isolated as an oil in low yield by column chromatography was tentatively identified as the diester **5**, ν_{max}(film)/cm^{-1} 1742, 1442, 1333, 1156 and 721; δ_H(200 MHz) 1.45 (9 H, s, CMe_3), 3.78 (2 H, s, CH_2CO), 3.90 (3 H, s, Me), 6.08–6.15 (2 H, m, H-3 and H-4) and 7.25 (1 H, m, H-5); *m*/*z* 239 (M^+, 7%), 138 (84) and 57 (100).

5-Methoxycarbonylpyrrolidinium-2-acetic acid trifluoroacetate 3

The diester **2** (1.67 g, 7.0 mmol) was placed in a hydrogenation bomb with rhodium on alumina (0.20 g) and trifluoroacetic acid (4 ml). The bomb was pressurised to 13.5 atm and the contents were stirred vigorously for 12 h. A further portion (0.10 g) of catalyst was added, the bomb was repressurised and the contents stirred for 12 h. The catalyst was filtered off and the filtrate was evaporated to leave the salt **3** as an oil which crystallised on standing. Recrystallisation gave the salt **3** (1.37 g, 65%), mp 108 °C (from dichloromethane–ether) (Found: C, 39.3; H, 4.7; N, 4.4. $C_{10}H_{14}F_3NO_6$ requires C, 39.7; H, 5.0; N, 4.6%); ν_{max}(Nujol)/cm^{-1} 2923, 1729, 1706, 1332, 1197, 797 and 720; δ_H(TFA with C_6D_6 capillary; 400 MHz) 2.00 (1 H, m, H-4), 2.52 (2 H, m, H-3 and H-3′), 2.71 (1 H, m, H-4′), 3.24 (2 H, m, CH_2CO), 4.04 (3 H, s, Me), 4.34 (1 H, unresolved m, H-2), 4.82 (1 H, m, H-5), 7.78 (2 H, br s, NH) and 8.47 (1 H, br s, OH); *m*/*z* (FAB) 188 (M^+, 100%) and 128 (49).

Methyl 7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate 4

A solution of the salt **3** (0.40 g, 1.3 mmol), the phosphine oxide **6** (0.59 g, 1.3 mmol) and triethylamine (0.63 ml, 0.46 g, 4.5 mmol) in dry acetonitrile (50 ml) was heated under reflux under nitrogen for 6 h. The solution was evaporated to a solid, then subjected to column chromatography (ether) under nitrogen. The faster running fractions yielded benzoxazolinone, while the lower fractions gave the azetidinone **4** as a colourless oil (0.05 g, 23%) (Found: M^+, 169.074. $C_8H_{11}NO_3$ requires *M*, 169.074); δ_H(200 MHz) 1.71–1.91 (1 H, m, H-4′), 2.08–2.43 (3 H, m, H-3, H-3′ and H-4), 2.78 (1 H, dd, $J_{6,6'}$ 15.9, $J_{5,6'}$ 2.7, H-6′), 3.12 (1 H, ddd, $J_{6,6'}$ 15.9, $J_{5,6}$ 4.9, $J_{2,6}$ 1.6, H-6), 3.65–3.76 (1 H, m, H-5), 3.77 (3 H, s, Me) and 3.90 (1 H, m, H-2); *m*/*z* 169 (M^+, 37%), 141 (66), 110 (100) and 68 (38).

‡ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/136.

Tris(2,3-dihydro-2-oxobenzoxazol-3-yl)phosphine oxide 6
Phosphorus oxychloride (1.15 ml, 1.89 g, 12.3 mmol) was added under nitrogen to a solution of 2,3-dihydrobenzoxazol-2-one (5.0 g, 37 mmol) in dry dichloromethane (50 ml) at 0 °C. Triethylamine (5.57 ml, 4.05 g, 40 mmol) was then added dropwise and the mixture was stirred at 0 °C for 1 h, then at room temp. for 12 h. The solid was filtered off and washed well with dichloromethane. The dichloromethane layers were combined and evaporated to leave an off-white solid. This material was purified by column chromatography (dichloromethane) under nitrogen, and a colourless solid was isolated (4.0 g, 72%), mp 250 °C (lit.,[10] mp 252 °C) (Found: C, 56.15; H, 2.7; N, 9.3. Calc. for $C_{21}H_{12}N_3O_7P$: C, 56.1; H, 2.7; N, 9.35%); ν_{max}/cm^{-1} 1804, 1478, 1251, 1132, 967 and 755; δ_H(200 MHz) 7.20–7.30 (9 H, m) and 7.68–7.73 (3 H, m); *m*/*z* 449 (M$^+$, 21%), 315 (100), 134 (63.84) and 106 (48).

Ethyl 1-*tert*-butoxycarbonylpyrrole-2-acetate 7
To a solution of ethyl pyrrole-2-acetate (2.00 g, 13 mmol) in dichloromethane (100 ml) was added DMAP (1.59 g, 13 mmol) followed by di-*tert*-butyl dicarbonate (4.19 g, 19.2 mmol). The solution was stirred at room temp. for 3 h, when TLC showed that all of the starting material had reacted. The solution was evaporated to leave a yellow solid. After column chromatography (dichloromethane) the diester **7** was isolated as a yellow oil (3.20 g, 97%) (Found: C, 61.5; H, 7.7; N, 5.8. $C_{13}H_{19}NO_4$ requires C, 61.6; H, 7.6; N, 5.5%); ν_{max}(film)/cm^{-1} 1740, 1319, 1180, 1128 and 728; δ_H(200 MHz) 1.30 (3 H, t, *J* 7.15, CH_2CH_3), 1.62 (9 H, s, CMe_3), 3.91 (2 H, s), 4.16–4.33 (2 H, q, *J* 7.15, CH_2CH_3), 6.12–6.17 (2 H, m, H-3 and H-4 of pyrrole) and 7.28–7.30 (1 H, m, H-5 of pyrrole); *m*/*z* (CI) 271 (M$^+$ + NH_4, 10%), 254 (21), 168 (100), 154 (100), 136 (60) and 68 (77).

Ethyl 1-*tert*-butoxycarbonyl-α-methylpyrrole-2-acetate 8
The ester **7** (1.00 g, 4 mmol) in dry THF (2 ml) was cooled to −78 °C under nitrogen. A solution of potassium bis(trimethylsilyl)amide (12 ml, 6 mmol, 1.5 equiv.; 0.5 M in toluene) and dry THF (2 ml) was added dropwise. The solution became deep red. After 1 h iodomethane (0.45 ml, 0.85 g, 8 mmol) in dry THF (3 ml) was added dropwise at −78 °C. An exothermic reaction occurred. The mixture was stirred for 1.5 h then quenched with saturated aqueous ammonium chloride. The solution was extracted with ether (3 × 20 ml), then the combined ether layers were washed with brine and water, dried ($MgSO_4$) and evaporated to a red oil. Column chromatography (dichloromethane) yielded the ester **8** as an oil (0.85 g, 80%) (Found: C, 63.0; H, 8.0; N, 5.6. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%); ν_{max}(film)/cm^{-1} 1738, 1331, 1178, 1132 and 724; δ_H(200 MHz) 1.22 (3 H, t, *J* 7.1, CH_2CH_3), 1.55 (12 H, br s, CMe_3 and CH*Me*), 4.14 (2 H, q, *J* 7.1, CH_2CH_3), 4.24 (1 H, q, *J* 7.7, C*H*Me), 6.10–6.13 (2 H, m, H-3 and H-4) and 7.21–7.26 (1 H, m, H-5); *m*/*z* 267 (M$^+$, 0.3%), 167 (20), 94 (100) and 57 (91).

Ethyl 1-*tert*-butoxycarbonyl-α-methylpyrrolidine-2-acetate 9a and 9b
Rhodium on alumina catalyst (0.02 g; 5% by weight) was added to a solution of pyrrole ester **8** (0.27 g, 1 mmol) in ethanol (5.0 ml) and acetic acid (1.0 ml) in a 25 ml pressure hydrogenation apparatus. The bomb was pressurised to 13.5 atm and the contents were stirred for 12 h. The catalyst was filtered off and the filtrate was evaporated to a small volume. Ether (5.0 ml) was added and the solution was stirred with solid sodium carbonate for 1 h. The mixture was filtered and the filtrate was evaporated to leave **9a** and **9b** as a yellow oil (0.19 g, 70%) (Found: M$^+$, 271.179. $C_{14}H_{25}NO_4$ requires *M*, 271.178); ν_{max}(film)/cm^{-1} 1729, 1693, 1169 and 773; δ_H(200 MHz) 1.03 (0.3 H, d, *J* 7.15, CH*Me* of **9b**), 1.13 (2.7 H, d, *J* 7.1, CH*Me* of **9a**), 1.25 (3 H, 2 × t, *J* 7.1, CH_2CH_3), 1.48 (9 H), 1.70–2.0 (4 H, m, H-3, H-3′, H-4 and H-4′), 3.13–3.25 (2 H, m, H-5 and H-5′), 3.40–3.53 (1 H, unresolved m, C*H*Me), 3.90–4.00 (1 H, unresolved m, H-2) and 4.11 (2 H, 2 × q, *J* 7.1, CH_2CH_3); *m*/*z* 271 (M$^+$, 0.5%), 170 (18), 114 (59), 70 (100) and 57 (67).

6-Methyl-1-azabicyclo[3.2.0]heptan-7-ones 10a and 10b
Conc. hydrochloric acid (10.0 ml) was added to the esters **9** (0.30 g, 1.1 mmol). The solution was stirred at room temp. for 1 h then diluted with water and stirred for a further 12 h. The solution was evaporated to leave the corresponding carboxylic acid hydrochlorides as a red oil (0.17 g, 86%); δ_H(200 MHz, D_2O) 1.29 (0.3 H, d, *J* 7.3), 1.32 (2.7 H, d, *J* 7.3), 1.65–1.85 (1 H, m, H-3), 1.93–2.10 (2 H, m, H-4 and H-4′), 2.19–2.34 (1 H, m, H-3′), 2.90 (1 H, m), 3.5 (2 H, m, H-5 and H-5′) and 3.68–3.80 (1 H, m, H-2′); *m*/*z* (FAB) 144 (M$^+$, 100%), 98 (16) and 70 (53).

A solution of the hydrochlorides (0.30 g, 1.68 mmol) and tris(1,3-dihydro-2-oxo-benzoxazol-3-yl)phosphine oxide **6** (0.76 g, 1.68 mmol) in dry acetonitrile (100 ml) was heated under reflux with triethylamine (0.60 g, 0.80 ml, 6.00 mmol) for 6 h. The solution was allowed to cool then evaporated to leave a crystalline solid. Column chromatography under nitrogen (3:2 dichloromethane–ethyl acetate) yielded a solid which NMR showed to be a mixture of the β-lactams **10a** and **10b** and dihydrobenzoxazolone (Found: M$^+$, 125.084. $C_7H_{11}NO$ requires *M*, 125.084); δ_H(200 MHz) 0.82 (1 H, m, H-4), 1.09 (2.6 H, d, *J* 7.4, CH*Me* of **10a**), 1.36 (0.4 H, d, *J* 7.4, CH*Me* of **10b**), 1.78–1.90 (1 H, m, H-4′), 1.90–2.08 (2 H, m, H-3 and H-3′), 2.73–2.86 (1 H, m, H-2), 3.33–3.46 (1 H, m, H-6), 3.46–3.58 (1 H, m, H-2′) and 3.69–3.79 (1 H, m, H-5); *m*/*z* 125 (M$^+$, 25%), 67 (100) and 41 (41).

***tert*-Butyl 1-*tert*-butoxycarbonyl-5-methoxycarbonylpyrrole-2-acetate 12 and di-*tert*-butyl 1-*tert*-butoxycarbonyl-5-methoxycarbonylpyrrole-2-malonate 11**
To a solution of the pyrrole diester **2** (4.50 g, 18.8 mmol) in dichloromethane (100 ml) at room temp. was added DMAP (2.48 g, 20.3 mmol) and di-*tert*-butyl dicarbonate (6.50 g, 29.8 mmol). After 3 h the solvent was removed. Column chromatography of the residue (ether–light petroleum 1:2) gave an oil (1.95 g) that crystallised on standing, *m*/*z* 339 (M$^+$ of **12**, 0.2%), 239 (5), 138 (51) and 57 (100). The solid was a mixture of the esters **12** and **11** by NMR. **12**: δ_H(200 MHz) 1.44 (9 H, s, CMe_3), 1.55 (9 H, s, CMe_3), 3.80 (2 H, s, CH_2CO), 3.82 (3 H, s, MeO), 6.02 (1 H, d, *J* 3.8, H-3) and 6.78 (1 H, m, H-4). **11**: δ_H(200 MHz) 1.48 (18 H, s, 2 × CMe_3), 1.57 (9 H, s, CMe_3), 3.82 (3 H, s, MeO), 5.07 (1 H, s, α-CH), 6.19 (1 H, d, *J* 2.8, H-3) and 6.78 (1 H, m, H-4).

Di-*tert*-butyl 1-*tert*-butoxycarbonyl-5-methoxycarbonyl-α-methylpyrrole-2-malonate 13
A solution of the esters **12** and **11** (1.63 g) in dry THF (50 ml) was cooled to −78 °C under nitrogen. A solution of KHMDS (14.4 ml of 0.5 M solution in toluene, 7.2 mmol) in dry THF (10 ml) was added dropwise. The solution gradually became deep red. After 30 min freshly distilled iodomethane (2 ml, 4.56 g, 32 mmol) was added dropwise. The solution was stirred at −78 °C for 1 h then allowed to warm to room temp. during 1 h. Saturated aqueous ammonium chloride was added and the product was extracted with ether (3 × 40 ml). Column chromatography (ether–light petroleum 2:1) yielded the ester **13** (0.50 g) as a pale yellow crystalline solid, mp 124–126 °C (from hexane) (Found: C, 60.8; H, 7.8; N, 3.1. $C_{23}H_{35}NO_8$ requires C, 60.9; H, 7.8; N, 3.1%); ν_{max}/cm^{-1} 1764, 1732, 1368, 1230, 1160, 844 and 756; δ_H(200 MHz) 1.48 (18 H, s, 2 × CMe_3), 1.53 (9 H, s, CMe_3), 1.89 (3 H, s, Me), 3.81 (3 H, s, MeO), 5.94 (1 H, d, *J* 3.85, H-3) and 6.72 (1 H, d, *J* 3.85, H-4); *m*/*z* 453 (M$^+$, 0.3%), 353 (6), 252 (52), 196 (100), 138 (48) and 57 (100).

5-Methoxycarbonyl-α-methylpyrrole-2-acetic acid 14
TFA (3 ml) was added dropwise to a solution of the malonate ester **13** (0.525 g, 1.16 mmol) in dichloromethane (3 ml) at room

temp. After 2 h the solution was evaporated to leave a pale pink oil which crystallised on standing (0.20 g, 87%), mp 114–116 °C (colourless crystals from dichloromethane–hexane) (Found: M^+, 197.069. $C_9H_{11}NO_4$ requires *M*, 197.069); ν_{max}(Nujol)/cm^{-1} 3297, 1674, 1457, 1215 and 768; δ_H(200 MHz) 1.58 (3 H, d, *J* 7.7, CH*Me*), 3.82–3.90 (1 H, q, *J* 7.7, C*H*Me), 3.84 (3 H, s, MeO), 6.13 (1 H, dd, $J_{3,4}$ 3.8, $J_{1,3}$ 2.7, H-3), 6.86 (1 H, dd, $J_{3,4}$ 3.8, $J_{1,4}$ 2.7, H-4), 9.00 (1 H, br s, NH) and 10.25 (1 H, br s, OH); *m*/*z* 197 (M^+, 36%), 152 (97), 138 (55), 120 (100), 106 (61), 69 (65) and 57 (59).

5-Methoxycarbonyl-α-methylpyrrolidinium-2-acetic acid trifluoroacetates 15a and 15b

A solution of the acid **14** (0.20 g, 1.02 mmol) in TFA (5 ml) was placed in a hydrogenation bomb with rhodium on alumina catalyst (0.20 g; 10% by weight). The bomb was pressurised to 13.5 atm and the contents were stirred vigorously for 12 h. A further portion of catalyst (0.01 g) was added, the bomb was repressurised and the contents were stirred for a further 12 h. The catalyst was filtered off and the filtrate was evaporated to leave a colourless oil (0.28 g, 87%) (Found: M^+, 202.108. $C_9H_{16}NO_4$ requires *M*, 202.108); ν_{max}/cm^{-1} 3381, 1682, 1459, 1203 and 724; δ_H(200 MHz; TFA with C_6D_6 capilliary) 1.90 (3 H, 2 × d, *J* 7.15, CH*Me* of **15a** and **15b**), 2.20–2.52 (1 H, m, H-3′), 2.75–2.95 (2 H, m, H-4 and H-4′), 3.00–3.15 (1 H, m, H-3), 3.59–3.93 (1 H, m, C*H*Me), 4.40 (3 H, s, MeO), 4.55–4.65 (1 H, m, H-2) and 5.10–5.25 (1 H, m, H-5); *m*/*z* (FAB) 202 (M^+, 100%), 128 (72), 68 (35) and 57 (27).

Methyl 6-methyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylates 16a and 16b

A solution of the salts **15a** and **15b** (0.28 g, 0.89 mmol), the phosphine oxide **6** (0.39 g, 0.89 mmol) and triethylamine (0.43 ml, 0.31 g, 3.07 mmol) in dry acetonitrile (35 ml) was heated under reflux under nitrogen for 6 h. The solvent was removed and column chromatography (ether) of the residue gave a 1:1 mixture (by NMR) of **16a** and **16b** as a colourless oil (0.05 g, 31%) (Found: M^+, 183.090. $C_9H_{13}NO_3$ requires *M*, 183.090); *m*/*z* 183 (M^+, 16%), 124 (36), 115 (41) and 40 (100). **15a**: δ_H(200 MHz) 1.22 (3 H, d, *J* 7.7, CH*Me*), 1.75–2.39 (4 H, m, H-3, H-3′, H-4 and H-4′), 3.30 (1 H, m, H-6), 3.74 (3 H, s, MeO), 3.75–3.84 (1 H, m, H-5) and 3.86–3.94 (1 H, m, H-2). **15b**: δ_H(200 MHz) 1.34 (3 H, d, *J* 7.2, CH*Me*), 1.75–2.39 (4 H, m, H-3, H-3′, H-4 and H-4′), 3.00 (1 H, dq, $J_{5,6}$ 2.2, $J_{6\text{-Me}}$ 7.2, H-6), 3.34–3.45 (1 H, m, H-5), 3.75 (3 H, s, MeO) and 3.84–3.94 (1 H, m, H-2).

tert-Butyl α-oxopyrrole-2-acetate 17

Oxalyl chloride (3.6 ml, 5.24 g, 41 mmol) was added dropwise under nitrogen to dichloromethane (200 ml) at −78 °C containing pyridine (3.00 ml, 2.94 g, 37 mmol), freshly distilled pyrrole (2.95 ml, 3.05 g, 45.5 mmol) and sodium carbonate (10 g). The dark green reaction mixture was stored at −20 °C overnight. *tert*-Butyl alcohol was added and the mixture was allowed to reach room temperature, then heated under reflux for 1 h. The sodium carbonate was filtered off and the solution was evaporated to leave a black oil. Column chromatography [dichloromethane–ethyl acetate (3:1)] gave a red crystalline solid. Recrystallisation gave the pyrrole **17** (2.56 g, 32%), mp 74–78 °C (from dichloromethane–hexane) (Found: C, 61.9; H, 6.9; N, 7.1. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.1%); ν_{max}(Nujol)/cm^{-1} 3391, 1731, 1632, 1250, 1056 and 777; δ_H(200 MHz) 1.66 (9 H, s), 6.31–6.38 (1 H, m, H-4), 7.14–7.21 (1 H, m, H-3), 7.29–7.35 (1 H, m, H-5) and 10.17 (1 H, br s, NH); *m*/*z* 195 (M^+, 3%), 94 (83) and 57 (100).

tert-Butyl α-hydroxyiminopyrrole-2-acetate 18

(i) From the oxo ester 17. A solution of the keto ester **17** (5.0 g, 25.6 mmol), hydroxylamine hydrochloride (5.0 g, 72 mmol) and pyridine (5.0 ml, 4.9 g, 62 mmol) in ethanol (50 ml) was heated under reflux for 1 h. The ethanol was removed by evaporation and water (50 ml) was added to the cooled residue. The flask was cooled in an ice bath and stirred until the product crystallised. The solid was filtered off then dissolved in ether and washed with dilute hydrochloric acid until the washings were neutral. The ether layer was dried ($MgSO_4$) and evaporated to dryness leaving the oxime **18** (4.1 g, 76%), mp 124 °C (from dichloromethane–hexane) (Found: C, 57.1; H, 6.7; N, 13.4. $C_{10}H_{14}N_2O_3$ requires C, 57.1; H, 6.7; N, 13.3%); ν_{max}(Nujol)/cm^{-1} 3382, 3169, 1715, 1271, 1107 and 996; δ_H(200 MHz) 1.62 (9 H, s), 6.31–6.35 (1 H, m, H-4), 6.98–6.99 (1 H, m, H-3), 7.29–7.31 (1 H, m, H-5) and 10.65 (1 H, br s, NH); *m*/*z* 210 (M^+, 6%), 154 (57), 106 (45), 93 (61), 92 (100) and 57 (54).

(ii) From the chlorooxime 25a. Pyrrole (14.70 ml, 212.0 mmol) in dichloromethane (120 ml) with sodium carbonate (17.0 g, 170.0 mmol) and the chlorooxime **25a** [(3.81 g, 21.2 mmol) added in one portion] gave, after distillation of the excess of pyrrole and recrystallisation of the solid residue, the oxime **18** (3.03 g, 64%).

tert-Butyl α-phthalimidopyrrole-2-acetate 19

The hydroxyimino ester **18** (5.1 g, 15.6 mmol) in aqueous tetrahydrofuran (1:10; 120 ml) was reduced by reaction with aluminium amalgam prepared from aluminium foil.[14] The reaction was monitored by TLC until the starting material had been consumed (1.5 h). The mixture was then filtered through Celite, the filter pad washed well with tetrahydrofuran, and the combined filtrate and washings were reduced in volume (to *ca.* 40–50 ml). To the solution was added triethylamine (2.4 ml, 17.3 mmol) followed by *N*-ethoxycarbonylphthalimide (3.80 g, 17.3 mmol) and the mixture was stirred for 2.5 h. Then the solvent was removed and the crude product was dissolved in dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and concentrated. Flash chromatography [dichloromethane–hexane (7.5:1)] of the residue gave the ester **19** as a colourless solid (6.75 g, 85%), mp 128–130 °C (from dichloromethane–hexane) (Found: C, 66.3; H, 5.6; N, 8.6; M^+, 326.126. $C_{18}H_{18}N_2O_4$ requires C, 66.25; H, 5.6; N, 8.6%; *M*, 326.127); ν_{max}/cm^{-1} 1771, 1736, 1392, 1250, 1158, 1109 and 731; δ_H(400 MHz) 1.41 (9 H, s), 6.00 (1 H, s), 6.13 (1 H, dd, *J* 6.0 and 2.7, H-3), 6.26–6.28 (1 H, m, H-4), 6.79–6.81 (1 H, m, H-5), 7.70–7.75 (2 H, m), 7.84–7.88 (2 H, m) and 9.29 (1 H, br, NH); *m*/*z* 326 (M^+, 2%), 270 (10), 225 (100), 198 (13), 104 (13), 76 (14) and 57 (25).

tert-Butyl 5-methoxycarbonyl-α-phthalimidopyrrole-2-acetate 20

To a solution of the pyrrole **19** (1.0 g, 3.06 mmol) in dry toluene (25 ml) under nitrogen was added triphosgene (0.91 g, 3.06 mmol) and the solution was heated under reflux. The reaction was monitored by direct phase HPLC [silica column, mobile phase: dichloromethane–isopropyl alcohol (98:2), flux 1.25 ml min^{-1}] which showed the gradual disappearance of the starting material. After 1.5 h the solution was cooled to room temperature and methanol (10 ml) was added. The mixture was stirred for a further 1.5 h then triethylamine was added in slight excess. Evaporation of the solvent followed by flash chromatography [dichloromethane–ethyl acetate (20:1)] afforded the diester **20** (0.76 g, 65%), mp 127–128 °C (colourless prisms from dichloromethane–hexane) (Found: C, 62.6; H, 5.2; N, 7.3; *m*/*z* 384.132. $C_{20}H_{20}N_2O_6$ requires C, 62.5; H, 5.2; N, 7.3%; *M*, 384.132); ν_{max}(Nujol)/cm^{-1} 3341, 1751, 1698, 1392, 1221 and 767; δ_H(400 MHz) 1.49 (9 H, s), 3.85 (3 H, s), 5.99 (1 H, s), 6.26 (1 H, dd, $J_{3,4}$ 3.7, $J_{3,1}$ 2.5, H-3), 6.83 (1 H, d, $J_{3,4}$ 3.7, H-4), 7.74–7.78 (2 H, m), 7.87–7.92 (2 H, m) and 9.96 (1 H, br s); *m*/*z* 384 (M^+, 1%), 328 (8), 310 (8), 283 (100), 251 (44), 104 (23) and 57 (30).

tert-Butyl 1-*tert*-butoxycarbonyl-5-methoxycarbonyl-α-phthalimidopyrrole-2-acetate 21

To a stirred solution of the diester **20** (1.72 g, 4.48 mmol) in dry dichloromethane (30 ml) was added DMAP (0.55 g, 4.48

mmol) followed by di-*tert*-butyl dicarbonate (1.46 g, 6.72 mmol). After 45 min the reaction was complete (TLC). Evaporation of the solvent followed by flash chromatography [dichloromethane–hexane (20:1)] gave the triester **21** (2.13 g, 98%), mp 111–112 °C (colourless crystals from dichloromethane–hexane) (Found: C, 62.1; H, 5.8; N, 5.8. $C_{23}H_{24}N_2O_8$ requires C, 62.0; H, 5.8; N, 5.8%); ν_{max}(Nujol)/cm^{-1} 1777, 1751, 1387, 1328, 1230 and 1153; δ_H(400 MHz) 1.41 (9 H, s, 2-CMe_3), 1.57 (9 H, s, 1-CMe_3), 3.81 (3 H, s), 6.13 (1 H, d, *J* 4.1, H-3), 6.57 (1 H, s), 6.75 (1 H, d, *J* 4.1, H-4), 7.73–7.78 (2 H, m) and 7.87–7.91 (2 H, m); *m*/*z* (CI) 502 $(M + NH_4)^+$ (85), 402 (100), 346 (100) and 283 (100).

tert-Butyl 1-*tert*-butoxycarbonyl-5-methoxycarbonyl-α-phthalimidopyrrolidine-2-acetates 22a and 22b

A solution of the triester **21** (2.35 g, 4.85 mmol) in acetic acid–methanol (4:1) (35 ml) containing a suspension of 5% platinum on carbon (0.47 g; 20%) was stirred under hydrogen at atmospheric pressure and room temperature. After 32 h more catalyst (0.23 g, 10%) was added and after 16 h the reaction was complete. The mixture was filtered, first through filter paper and then through a Celite pad, both filter paper and Celite pad being well washed with methanol. Evaporation of the solvent gave a colourless oil (2.03 g, 86%) which crystallised on standing, δ_H(200 MHz) 0.99 (9 H, br s), 1.26 (approx. 2 H, s, CMe_3 of **22b**), 1.36 (approx. 7 H, s, CMe_3 of **22a**), 2.10–2.34 (4 H, m, H-3, H-3′, H-4 and H-4′ of **22a** and **22b**), 3.69 (0.75 H, s, MeO of **22b**), 3.71 (2.25 H, s, MeO of **22a**), 4.21 (1 H, unresolved m, H-2 of **22a** and **22b**), 4.42 (0.25 H, d, *J* 10.3, α-CH of **22b**), 4.65 (0.75 H, d, *J* 10.1, α-CH of **22a**), 4.78 (1 H, unresolved m, H-5 of **22a** and **22b**), 7.67 (2 H, unresolved m) and 7.81–7.85 (2 H, m). Recrystallisation gave the ester **22a** (1.46 g, 62%), mp 131–132 °C (from dichloromethane–hexane) (Found: C, 61.7; H, 6.6; N, 5.7. $C_{25}H_{32}N_2O_8$ requires C, 61.5; H, 6.6; N, 5.7%); ν_{max}/cm^{-1} 1746 and 1708; δ_H(400 MHz) 1.01 (9 H, br s), 1.42 (9 H, s), 2.11–2.32 (4 H, m, H-3, H-3′, H-4 and H-4′), 3.76 (3 H, s), 4.21 (1 H, unresolved m, H-2), 4.70 (1 H, d, *J* 10.1, α-C*H*), 4.85 (1 H, unresolved m, H-5), 7.68 (2 H, unresolved m) and 7.86–7.89 (2 H, m); *m*/*z* (CI) 489 [$(M + H)^+$, 89%], 390 (64), 389 (100), 333 (58) and 128 (49).

5-Methoxycarbonyl-α-phthalimidopyrrolidinium-2-acetic acid trifluoroacetate 23

The ester **22a** (0.60 g, 1.23 mmol) in dichloromethane–trifluoroacetic acid (1:1) (4 ml) was stirred at room temperature for 2 h. Evaporation of the solvent left an oil which was dissolved in dichloromethane (1 ml) and upon the addition of ether gave the trifluoroacetate salt **23** as a colourless solid (0.46 g, 84%), mp 151–153 °C (Found: C, 48.3; H, 3.9; N, 6.1. $C_{18}H_{17}F_3N_2O_8$ requires C, 48.4; H, 3.8; N, 6.3%); ν_{max}/cm^{-1} 1778 and 1718; δ_H(400 MHz, D_2O) 1.68–1.78 (1 H, m), 2.12–2.34 (3 H, m), 3.62 (3 H, s), 4.35–4.40 (1 H, m, H-2), 4.44 (1 H, approx. dd, *J* 9.3 and 4.7, H-5), 5.16 (1 H, d, *J* 5.0, α-C*H*), 7.76–7.79 (2 H, m) and 7.84–7.87 (2 H, m); *m*/*z* (FAB) 333 (M^+, 67%), 128 (59), 43 (89) and 41 (100).

Methyl 6-phthalimido-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate 24

A solution of the salt **23** (37 mg, 0.08 mmol), the phosphine oxide **6** (37 mg, 0.08 mmol) and triethylamine (0.04 ml, 0.03 g, 0.28 mmol) in dry acetonitrile (30 ml) was heated under reflux under nitrogen for 6 h. The solution was allowed to cool then evaporated to dryness. Column chromatography (ether) yielded the bicyclic β-lactam **24** (8 mg, 32%), mp 122–124 °C (from ether) (Found: M^+, 314.090. $C_{16}H_{14}N_2O_5$ requires *M*, 314.090); ν_{max}/cm^{-1} 1786, 1769 and 1723; δ_H(400 MHz) 1.85–2.32 (4 H, m, H-3, H-3′, H-4 and H-4′), 3.90 (3 H, s), 4.10 (2 H, m, H-2 and H-5), 5.55 (1 H, dd, $J_{5,6}$ 5.2, $J_{2,6}$ 1.0, H-6), 7.74–7.78 (2 H, m) and 7.85–7.91 (2 H, m); *m*/*z* 314 (M^+, 46%), 200 (53), 128 (100), 104 (68) and 80 (37).

tert-Butyl chloro(hydroxyimino)acetate 25a

Glycine *tert*-butyl ester phosphite was prepared in two steps from *tert*-butyl chloroacetate by the method described by Moore and Rydon.[15] Glycine *tert*-butyl ester phosphite (26.2 g, 122 mmol) was dissolved in water (100 ml) and hydrochloric acid (density 1.19 g cm^{-3}; 10.2 ml, 122 mmol) was added. The mixture was cooled to 5 °C and sodium nitrite (8.42 g, 122 mmol) in water (30 ml) was added dropwise, but rapidly. A second equivalent of hydrochloric acid and a second equivalent of sodium nitrite were added rapidly in the same manner and then the reaction mixture was extracted with ether. The extracts were dried over magnesium sulfate and concentrated to give a pale-green oil which solidified on standing. Recrystallisation gave the chlorooxime **25a** as colourless crystals (9.62 g, 54%), mp 90–91 °C (from dichloromethane–hexane) (Found: C, 40.3; H, 5.6; N, 7.8. $C_6H_{10}NO_3$ requires C, 40.5; H, 5.6; N. 7.8%); ν_{max}(Nujol)/cm^{-1} 3317, 1698, 1423, 1074 and 1023; δ_H(400 MHz) 1.57 (9 H, s) and 9.65 (1 H, br s, OH); *m*/*z* (CI) 199 (13%) and 197 [$(M + NH_4)^+$, 42%], 163 (21), 147 (24), 74 (38) and 52 (100).

tert-Butyl 1-*tert*-butoxycarbonyl-α-(hexahydrophthalimido)-5-methoxycarbonylpyrrole-2-acetate 26

The pyrrole **21** (3.29 g, 68 mmol) in methanol (20 ml) was stirred under hydrogen at atmospheric pressure and room temperature with 5% rhodium on alumina (0.03 g, 10%). After 18 h, TLC showed the presence of the starting pyrrole and a new component. Filtration and evaporation of the solvent gave a colourless oil which upon flash chromatography [dichloromethane–ethyl acetate (7.5:1)] gave the pyrrole ester **26** (0.17 g, 52%), mp 147–149 °C (from dichloromethane–hexane) (Found: C, 61.4; H, 7.0; N, 5.7. $C_{25}H_{34}N_2O_8$ requires C, 61.2; H, 7.0; N, 5.7%); ν_{max}/cm^{-1} 1757 and 1741; δ_H(400 MHz) 1.42 (9 H, s), 1.47 (4 H, unresolved m), 1.58 (9 H, s), 1.88 (4 H, unresolved m), 2.91–2.98 (2 H, m), 3.82 (3 H, s), 6.05 (1 H, dd, *J* 3.8 and 0.7, H-3), 6.38 (1 H, s, α-CH) and 6.74 (1 H, dd, *J* 3.3 and 0.4, H-4); *m*/*z* (CI) 508 [$(M + NH_4)^+$, 16%], 408 (100) and 352 (100).

Crystal data for 22a

$C_{25}H_{32}N_2O_8$, $M = 488.54$. Monoclinic, $a = 12.862(8)$, $b = 9.629(7)$, $c = 22.560(7)$ Å, $\beta = 102.37(3)°$, $V = 1625(2)$ Å^3 (by least-squares refinement on diffractometer angles for 20 centred reflections with $6.96 < 2\theta < 11.26°$, $\lambda = 0.710\ 69$ Å, $T = 297$ K), space group $P2_1/c$ (#14), $Z = 4$, $D_c = 1.189$ g cm^{-3}, clear prism, 0.300 × 0.200 × 0.350 mm, μ(Mo-Kα) = 0.83 cm^{-1}.

Data collection and processing

Rigaku AF6S diffractometer, graphite-monochromated Mo-Kα radiation, ω–2θ scans to a maximum 2θ value of 50.0° with ω scan width $(1.1 + 0.30 \tan \theta)°$; 5376 reflections collected of which 5132 were unique ($R_{int} = 0.034$). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection; no decay correction was applied. 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 data were corrected for Lorenz and polarisation effects.

Structure solution and refinement

Automatic direct methods[16] (all non-H atoms). Non-H atoms were refined either anisotropically or isotropically. The final cycle of full-matrix least-squares refinement was based on 1887 observed reflections [$I > 3.00\ \sigma(I)$] and 191 variable parameters and converged (largest parameter shift was 0.06 times its esd) with weighted and unweighted agreement factors as shown in eqns. (1) and (2).

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.101 \quad (1)$$

$$R_w = \{[\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]\}^{1/2} = 0.099 \quad (2)$$

The standard deviation of an observation of unit weight was 7.73. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.52 and −0.40 e Å^{-3}, respectively. All calculations were performed using the TEXSAN crystallographic structure package of the Molecular Structure Corporation.[17]

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