Convenient route to γ-nitro-α-amino acids: conjugate addition of nitroalkanes to dehydroalanine derivatives

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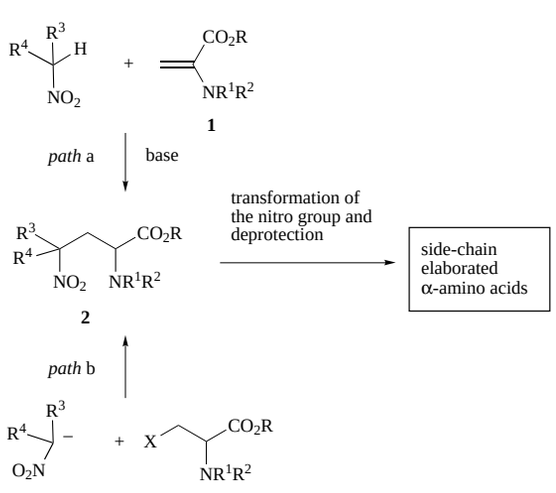
γ-Nitro-α-amino acid derivatives are obtained in good yield from the base-catalysed conjugate addition of nitroalkanes to *N*-protected dehydroalanine esters (methyl 2-amidoacrylates). The outcome of the reaction is dependent on the *N*-protecting group (the ease of the product formation correlates with the electron-withdrawing ability and hence stabilising effect on the adduct α-anion of the 2-substituent in the order phthalimido > benzyloxycarbonylamino > acetamido), the nitroalkane, and on the reaction conditions. Conditions were established in reactions of methyl 2-phthalimidoacrylate 4 with nitromethane for selectively obtaining 1 : 1-, 2 : 1- or 3 : 1-adducts. Good yields of the 1 : 1-adducts are obtained when the reaction is carried out with an excess of nitroalkane. Restricting the amount of nitromethane gives rise to the higher adducts. Similarly, reactions of 4 with nitroethane can be adjusted to give 1 : 1- or 2 : 1-adducts selectively. These reactions occur with little or no diastereoselectivity. As a model for a dehydroalanine residue in a peptide chain, the diamide *N*-cyclohexyl-2-acetamidoacrylamide 7 has been prepared. This dehydroalanine reacts with 2-nitropropane and with nitromethane in refluxing *tert*-butyl alcohol to give reasonable yields of 1 : 1-adducts. As the nitro group of the resultant γ-nitro-α-amino acid derivatives can be transformed into a variety of other functionalities, the methodology described in this paper offers a versatile entry to a range of γ-substituted α-amino acids.

Introduction

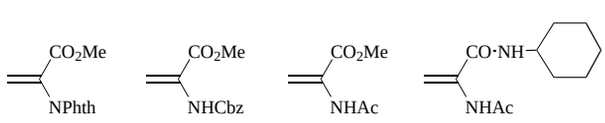
In the course of work on the synthesis of γ-lactam analogues of β-lactam antibiotics,[1] we required a convenient synthesis of open-chain precursors, in the form of γ-aza-α-amino acids. It was clear to us that the corresponding γ-nitro-α-amino acids would be an even more useful synthetic objective as not only would the desired γ-aza-α-amino acids be readily available by reduction of the nitro group but other transformations of the nitro group[2–5] would provide a convenient synthesis of a range of side-chain modified α-amino acids. Schöllkopf and his colleagues have reported a synthesis of γ-nitro-α-amino acids that involves a Michael addition of titanated bis-lactam ethers of cyclo(-L-Val-Gly-) to nitroalkenes as the first step.[6] We required a more general synthesis, however, that would allow elaboration at the γ-position of the amino acid.

There appeared to be two possibilities for short syntheses of such nitro compounds **2**; conjugate additions of nitroalkanes to dehydroalanine derivatives **1**, (*path* a, Scheme 1), or displacement reactions using 'β-cation' synthetic equivalents, β-halo-α-amino acids **3** (X = Cl or I) and related activated serine derivatives **3** (*e.g.* X = OTs) (*path* b, Scheme 1), with an alkylnitronate as the nucleophile. The second approach appears to offer the possibility of synthesis of single amino acid enantiomers without the need for the chiral induction that is required by the first approach and follows a biomimetic strategy in that the enzymic synthesis of non-protein β-substituted alanines in plants utilises *O*-acetyl-L-serine.[7] While there are reports of the use of β-iodoalanine and related activated serine derivatives in reactions with nucleophiles,[8–12] these compounds show a pronounced tendency to undergo elimination under basic conditions to form the corresponding dehydroalanines **1** *in situ*.[8–16] The use of cyclic 'β-cation' synthetic equivalents can overcome such elimination.[15,17]



Scheme 1

In 1957, Wieland *et al.*[18] reported the only previous example of the first approach, (*path* a, Scheme 1), a synthesis of methyl 4-methyl-4-nitro-2-phenylacetamidopentanoate by a conjugate addition of 2-nitropropane to methyl 2-phenylacetamidoacrylate. We have investigated this approach further as a number of appropriately protected dehydroalanines **1** were readily available from any of the corresponding serine,[13,18–21] alanine[22] or cysteine[23,24] derivatives, and a range of more complex, 3-substituted derivatives were also available.[9,25–27] We now report in full that primary and secondary nitroalkanes undergo conjugate addition to dehydroalanine derivatives **4**–**7** to give



4 **5** **6** **7**

γ-nitro-α-amino acid derivatives in a general process that is efficiently catalysed by base. We have previously communicated a stereoselective conversion of L-alanine into L-leucine[28] and the synthesis of γ-lactam analogues of monobactams[1] using such a nitroalkane conjugate addition as the key step in each case.

Results and discussion

The dehydroalanines derivatives **4**–**7** used as acceptors in this

study differ in their substituent on the amino nitrogen; typical *N*-protecting groups in amino acid chemistry were chosen to cover a range of different substituent electronic effects. Methyl 2-phthalimidoacrylate **4** and methyl 2-(benzyloxycarbonylamino)acrylate **5** were prepared in good yield from the corresponding serine derivatives by dehydration using diethyl azodicarboxylate–PPh_3.[19] Cyclisation of *N*-acylserine esters to 4,5-dihydrooxazolines under these dehydration conditions has been reported but were found not to be significant in the preparation of **4** or **5**.[20] Synthesis of *N*-Cbz-L-alanyl-dehydroalanine benzyl ester and benzyl 2-(trifluoroacetylamino)acrylate from the corresponding serine derivatives in other work required the use of disuccinimido carbonate in the presence of triethylamine to avoid this complication.[29] Methyl 2-acetamidoacrylate **6** was prepared from alanine.[22] *N*-Cyclohexyl-2-acetamidoacrylamide **7** was prepared in 64% yield by a sequence in which 2-acetamidoacrylic acid, obtained by hydrolysis of the methyl ester,[22] and cyclohexylamine were coupled using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline in dry tetrahydrofuran. Use of the ethyl chloroformate mixed anhydride method of coupling was less successful yielding the diamide **7** in 28% yield. Attempted syntheses of *N*-benzyl- and *N*-*tert*-butyl-2-acetamidoacrylamide from 2-acetamidoacrylic acid by way of the acid chloride gave only low yields of products. Dehydroalanine derivatives† **4**–**7** were used soon after their isolation as they were all found to be labile compounds which polymerised on prolonged standing.

Nitromethane, nitroethane, 2-nitropropane, nitrocyclohexane and 2-nitroacetic acid esters were used to examine addition to the dehydroalanines. In other work involving specific synthetic targets we have considerably extended the range of nitro compounds used.

A number of sets of reaction conditions were investigated. Use of dry toluene as solvent with fluoride ion, in the form of tetrabutylammonium fluoride, as base was found to be a system in which reactions of the more active acrylates **4** and **5** generally proceeded well and which could be easily monitored. The use of KF-silica reagent[30] failed to catalyse the reaction. Reactions on the less reactive compounds did not occur in toluene but did proceed at reasonable rates in *tert*-butyl alcohol or dioxan using *N*-benzyltrimethylammonium hydroxide as base.

Addition of nitroalkanes to *N*-protected dehydroalanine methyl esters

Base-catalysed conjugate addition of nitroalkanes to the *N*-phthalimido protected dehydroalanine **4** was found to be facile (Scheme 2). Thus treatment of methyl 2-phthalimidoacrylate **4** with excess 2-nitropropane in toluene catalysed by the base tetrabutylammonium fluoride (TBAF) gave the adduct methyl 4-methyl-4-nitro-2-phthalimidopentanoate **13** in 93% yield. Similar reaction of **4** with nitrocyclohexane gave methyl-3-(1′-nitrocyclohexyl)-2-phthalimidopropanoate **14** in 82% yield (Scheme 2).

The ease of reaction of methyl 2-phthalimidoacrylate **4** with nitromethane and with nitroethane, however, led to the formation of higher adducts as well as the 1:1-adducts. To obtain 1:1-adducts selectively, it was found that a considerable excess of the nitroalkane had to be used. Using nitromethane (in 100-fold excess) as both the reagent and the solvent for the reaction with **4** yielded the 1:1-adduct, methyl 4-nitro-2-phthalimidobutanoate **8**, in 80% yield when 1 equiv. of KF was used as base in a reaction heated at reflux for 1.5 h (Scheme 2).

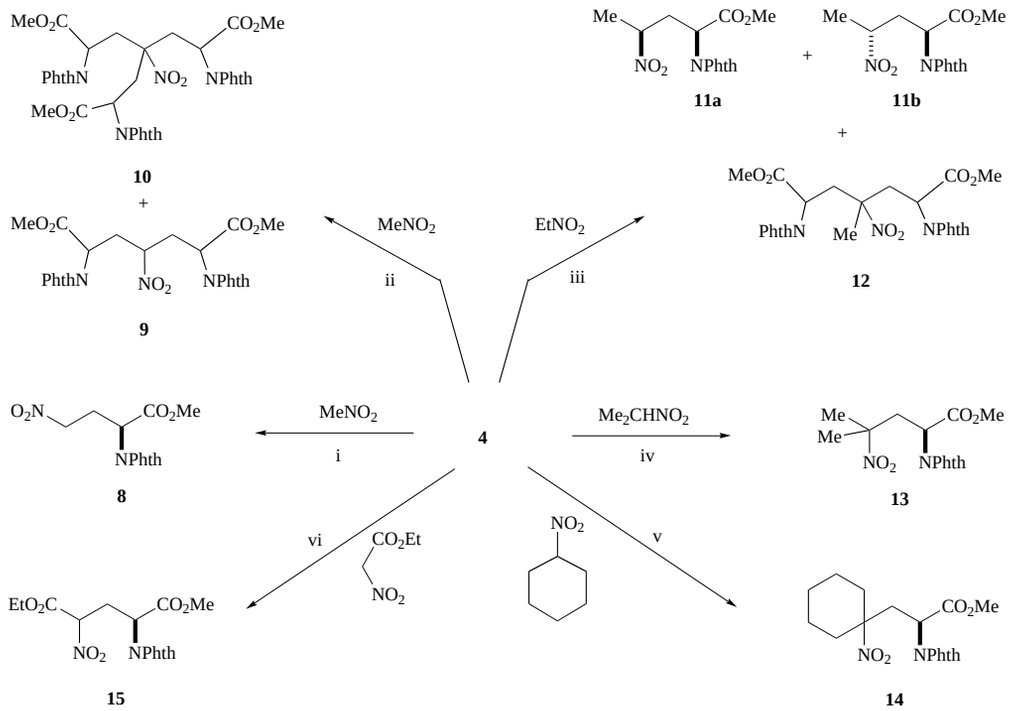
Reaction of methyl 2-phthalimidoacrylate **4** with nitromethane (5 equiv.) in toluene with TBAF (0.2 equiv.) at room temperature for 2 h gave the 2:1-adduct, dimethyl 4-nitro-2,6-diphthalimidoheptane-1,7-dioate **9**, in 79% yield and the 3:1-adduct, dimethyl 4-(2′-phthalimido-3′-methoxy-3′-oxopropyl)-4-nitro-2,6-diphthalimidoheptane-1,7-dioate **10**, in 10% yield: no 1:1-adduct was obtained. Use of just 1 equiv. of nitromethane led to an increase in the yield to 41% of 3:1-adduct **10** with a consequent decrease in the yield to 51% of 2:1-adduct **9**. Such higher adducts are also seen in the reaction of methyl 2-phthalimidoacrylate **4** with nitroethane but they are not seen in the reactions of the other dehydroalanines used in this study. An explanation for this difference is given later.

Reaction of the phthalimidoacrylate **4** with nitroethane (5 equiv.) and TBAF (0.2 equiv.) in dry toluene at 25 °C for 45 min and work-up that included column chromatography over silica gave a 3:2 mixture of the diastereomeric 1:1-adducts, methyl (2*RS*,4*RS*)-4-nitro-2-phthalimidopentanoate **11a** and methyl (2*RS*,4*SR*)-4-nitro-2-phthalimidopentanoate **11b**, in 65% yield and the 2:1-adduct, dimethyl 4-methyl-4-nitro-2,6-diphthalimidoheptane-1,7-dioate **12**, in 29% yield (Scheme 2). The diastereomers **11a** and **11b** were separated by preparative HPLC. Structure determination of the less polar, major diastereomer by single crystal X-ray crystallography showed it to be methyl (2*RS*,4*RS*)-4-nitro-2-phthalimidopentanoate **11a**; details of this structure and that of a related compound will be published elsewhere. Examination of the 400 MHz ^{1}H NMR spectrum of **11a** shows that in $CDCl_3$ solution the compound adopts a very similar conformation on average to that seen in the solid state structure in which the carbon backbone C1–C2–C3–C4–C5 has a saw-tooth arrangement. This conformation in the (2*R*,4*R*)-enantiomer of **11a** is depicted in Fig. 1a. In this conformer there is a strong charge-dipole interaction between the nitro group and a carbonyl of the phthalimide. The ^3J coupling constants between the methylene protons at C–3 and the methine protons at C–2 and C–4 is particularly informative. The *pro-S* proton (δ 2.88) at C–3 of **11a** (Fig. 1) is anti-periplanar to both H–2 and H–4 and this is reflected in relative large coupling constants ($^3J_{2,3}$ 9.0 Hz, $^3J_{3,4}$ 7.8 Hz) while the *pro-R* proton (δ 2.75) is in a gauche arrangement to both H–2 and H–4 ($^3J_{2,3}$ 5.8 Hz, $^3J_{3,4}$ 5.8 Hz). Examination of the 400 MHz ^{1}H NMR spectrum of the diastereomer **11b** shows that this compound in $CDCl_3$ solution adopts a very different conformation on average (Fig. 1b) to that of **11a**; in particular, steric interactions are minimised and the nitro group is too far from the carbonyls of either the phthalimido or the ester groups for intramolecular interaction. The *pro-S* proton (δ 3.02) at C–3 of **11b** (Fig. 1b) is anti-periplanar to H–4 but in a gauche arrangement with H–2 ($^3J_{2,3}$ 4.5 Hz, $^3J_{3,4}$ 10.0 Hz) while the *pro-R* proton (δ 2.72) is anti-periplanar to H–2 but in a gauche arrangement with H–4 ($^3J_{2,3}$ 11.1 Hz, $^3J_{3,4}$ 3.3 Hz).

When each of the diastereomers **11a** and **11b** was treated separately with TBAF in toluene the same 3:2 equilibrium mixture of the two diastereomers, **11a** and **11b**, was obtained. The small thermodynamic preference for the (2*RS*,4*RS*)-isomer **11a** suggests that in toluene the favourable charge-dipole interaction between the nitro group and a phthalimido carbonyl group is worth more than the energy penalty due to steric effects associated with this conformation. The steric energy penalty to achieve the charge-dipole interaction between the nitro group and a phthalimido carbonyl group would be higher in the other diastereomer, **11b**, due to the introduction of a steric interaction between the C–5 methyl and the phthalimido group. The different effects dominating the two conformations (charge-dipole *versus* steric effects) suggests that there should be a solvent effect on the position of the equilibrium between **11a** and **11b** under equilibrating conditions although this has not been investigated.

The formation of 2:1- and 3:1-adducts in the reactions of methyl 2-phthalimidoacrylate **4** is a consequence of the ability of the phthalimido group, compared with the other *N*-protecting groups used in this study, to stabilise α-anion addition intermediates thereby shifting the position of the

† As achiral dehydroalanines, **4**–**7** have been used as the Michael acceptor in this work; the resultant products are necessarily racemic although for simplicity only one of the enantiomers is shown in the Schemes.



Scheme 2 *Reagents and conditions*: i, KF, heat, 1.5 h; ii, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 2.5 h; iii, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 45 min; iv, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 21 h; v, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 90 min; vi, $Bu_4NF{\cdot}3H_2O$, toluene, room temp., 1 h

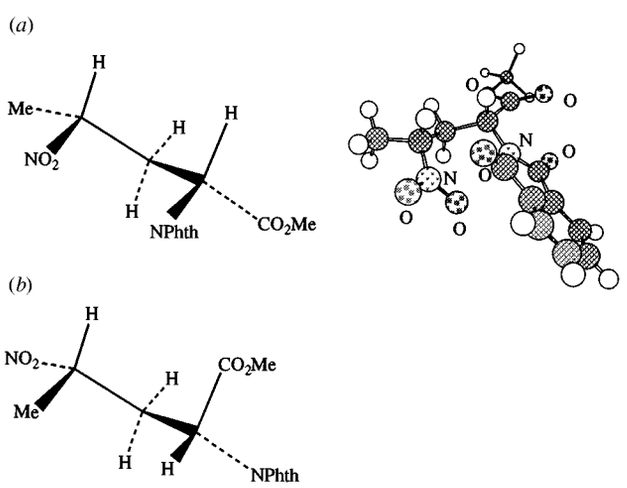


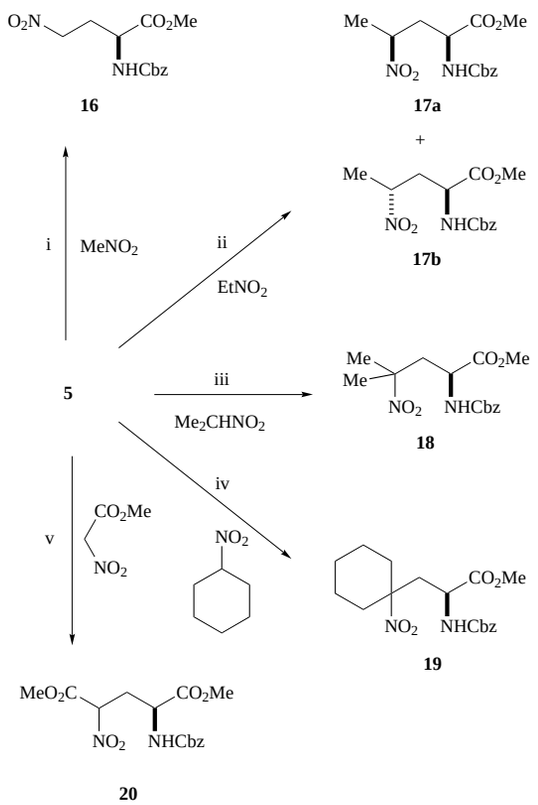
Fig. 1 Minimum energy conformers (from AM1 calculations) of: (*a*) methyl (2*R*,4*R*)-4-nitro-2-phthalimidopentanoate **11a** and (*b*) methyl (2*R*,4*S*)-4-nitro-2-phthalimidopentanoate **11b**

equilibrium in the addition towards the product and is also because of the relative acidities of the starting and product nitroalkanes. In a number of different solvents, measurements have shown that 2-nitropropane is about 1 pK_a unit more acidic than nitroethane which in turn is about 2 pK_a units more acidic than nitromethane.[31] Hence, the 1 : 1-adduct **8** should be readily formed and, being a primary nitroalkane, should be sufficiently more acidic than nitromethane to compete for reaction with base to generate the nitronate of this 1 : 1-adduct. Reaction of this nitronate with methyl 2-phthalimidoacrylate **4** results in an α-anionic addition intermediate which again is stabilised by the phthalimido group, evidently sufficiently so as to counteract the better leaving group ability of the nitronate of the 1 : 1-adduct, compared with the nitronate of nitromethane; this is probably not the case with the other acrylates used in this study. The double Michael addition is known to occur between primary nitroalkanes and 2 equiv. of electron-deficient olefins.[32]

The protected γ-nitro-α-amino esters, 5-ethyl 1-methyl 4-nitro-2-phthalimidopentane-1,5-dioates **15**, were obtained as a 1:1 mixture of diastereomers in a 70% yield from the conjugate addition of ethyl nitroacetate to methyl 2-phthalimidoacrylate **4** (Scheme 2). Attempts to separate the diastereomers **15** by semi-preparative normal phase HPLC proved to be futile as the diastereomers readily epimerised to give back an equal mixture of compounds. The lability of the C–4 hydrogen arises from its acidity as the resultant anion is stabilised by the nitro and ester groups attached to C–4. The ^{1}H NMR spectrum of the mixture of diastereomers **15** was able to be fully assigned by COSY NMR but which isomer belonged to which set of carbon assignments could not be determined even using HETCOR studies.

The *N*-Cbz protected dehydroalanine **5** was found to be less reactive than the *N*-phthaloyl analogue **4** and higher adducts were not observed in reactions with nitromethane or nitroethane. The 1 : 1-adduct methyl 2-(benzyloxycarbonylamino)-4-nitrobutanoate **16** was obtained in 71% yield by reaction at 50 °C in dioxan for 2 h of **5** with the nitronate from nitromethane, generated using *N*-benzyltrimethylammonium hydroxide as base, followed by acidification with ice-cold aqueous HCl (Scheme 3). Using nitromethane (in 150-fold excess) as both the reagent and the solvent for the reaction yielded methyl 2-(benzyloxycarbonylamino)-4-nitrobutanoate **16** in 84% yield when **1** equiv. of KF was used as base in a reaction heated at reflux for 14 h.

Reaction of **5** with nitroethane using sodium methoxide as base in dioxan at 50 °C overnight yielded a 1 : 1 diastereomeric mixture in methyl 2-(benzyloxycarbonylamino)-4-nitropentanoates **17** in 80% yield following acidification with ice-cold aqueous HCl; care has to be exercised in this work-up to avoid formation of the corresponding 4-oxopentanoate by a Nef oxidation. These two diastereomers were separated and purified by HPLC. The less polar isomer was assigned as methyl (2*RS*,4*RS*)-2-(benzyloxycarbonylamino)-4-nitropentanoate **17a** on the basis of the similarity (pattern of chemical shifts and coupling constants) of its 400 MHz ^{1}H NMR spectrum to that of (2*RS*,4*RS*)-2-phthalimido-4-nitropentanoate **11a** suggesting that they have similar average conformations which implies that there is also a charge-dipole interaction between the nitro group



Scheme 3 *Reagents and conditions*: i, *N*-benzyltrimethylammonium hydroxide, dioxan, N_2, heat at 50 °C, 2 h; ii, 8.87% sodium methoxide in methanol, dioxan, N_2, stirred at 40–50 °C, overnight; iii, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 22 h; iv, KF, 18-crown-6, toluene, heat, 5 h; v, *N*-benzyltrimethylammonium hydroxide, dioxan, N_2, stirred overnight at 40–50 °C, then acidified HCl (3 mol dm^{-3})

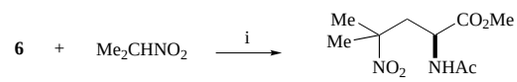
and the carbonyl of the Cbz group of **17a**. The other isomer, therefore, is methyl (2*RS*,4*SR*)-2-(benzyloxycarbonylamino)-4-nitropentanoate **17b** and it has a similar (pattern of chemical shifts and coupling constants) 400 MHz ^{1}H NMR spectrum to that of (2*RS*,4*SR*)-2-phthalimido-4-nitropentanoate **11b** further supporting these assignments. A 1:1 mixture (65% yield) of these diastereomers was also obtained from prolonged reaction of **5** and nitroethane in toluene using TBAF as base while a 3:2 mixture was obtained in 97% yield when reaction took place in the more polar nitroethane with KF as base.

Reaction of **5** and 2-nitropropane in toluene with TBAF as catalyst for 22 h afforded methyl 2-(benzyloxycarbonylamino)-4-methyl-4-nitropentanoate **18** in 85% yield (Scheme 3). When the optically active base, quinine, was used methyl 2-(benzyloxycarbonylamino)-4-methyl-4-nitropentanoate **18** was obtained in 63% yield after 24 h and as the product possessed little optical activity, chiral induction of the reaction was minimal.

Methyl 2-(benzyloxycarbonylamino)-3-(1′-nitrocyclohexyl)-propanoate **19** was obtained in 77% yield by conjugate addition of nitrocyclohexane to methyl 2-(benzyloxycarbonylamino)-acrylate **5** in toluene; the reaction was catalysed by KF solubilised by addition of 18-crown-6 (Scheme 3).

The nitronate derived from methyl nitroacetate by treatment with *N*-benzyltrimethylammonium hydroxide was allowed to react with the acrylate **5** in anhydrous dioxan–methanol at 45 °C for 16 h to give dimethyl 2-(benzyloxycarbonylamino)-4-nitropentane-1,5-dioates **20**, as a 1:1 mixture of diastereomers (Scheme 3). When 1 equiv. of methyl nitroacetate was used, the yield of **20** was 75%. It was observed that in order for the reaction to proceed to completion, a stoichiometric amount of the hydroxide base was essential. Tetrabutylammonium fluoride was also employed, in place of *N*-benzyltrimethylammonium hydroxide, as a base catalyst when toluene was used as the solvent. In this case the mixture had to be heated at reflux to drive the reaction to completion and the yield of **20** was 61%. The mixture of diastereomers **20** was separated into the individual diastereomers by HPLC but each of these compounds readily equilibrated to an equal mixture of diastereomers, like the corresponding phthalimido-protected analogues **15**.

The *N*-acetyl protected dehydroalanine **6** was found to be considerably less reactive than either the *N*-phthaloyl or *N*-Cbz protected analogues **4** and **5** and did not form an adduct on heating for several days in nitromethane with KF as catalyst. Reaction of **6** with 2-nitropropane in toluene with TBAF under the standard conditions required a reaction time of 66 h for the complete disappearance of starting dehydroalanine and work-up of the reaction gave methyl 2-acetamido-4-methyl-4-nitropentanoate **21** in 76% yield (Scheme 4). In another otherwise



Scheme 4 *Reagents and conditions*: i, $Bu_4NF{\cdot}3H_2O$, toluene, stir at room temp., 66 h

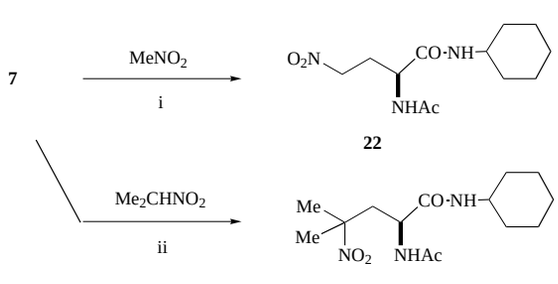
identical reaction which was worked up after 41.5 h, **21** was obtained in 54% yield and the starting dehydroalanine derivative **6** was recovered in 25% yield.

Addition of nitroalkanes to *N*-cyclohexyl-2-acetamidoacrylamide 7

The diamide *N*-cyclohexyl-2-acetamidoacrylamide, **7**, was chosen as a model of a dehydroalanine residue incorporated in a peptide chain. Reactions of alkylnitronates with *N*-cyclohexyl-2-acetamidoacrylamide **7** were much slower than corresponding reactions on the acrylates **4**–**6**.

Reaction of **7** with 2-nitropropane, chosen first to avoid side-product complications, showed that the standard conditions used for other dehydroalanines were not applicable. Thus treatment of **7** with 2-nitropropane (5 equiv.) in toluene using TBAF as catalyst at room temperature failed to yield any of the adduct *N*-cyclohexyl-2-acetamido-4-methyl-4-nitropentanamide **23** after 24 h, and gave only 11% of **23** along with 50% of recovered alkene **7** when the reaction mixture was heated at reflux for 21.5 h.

The use of a polar protic solvent was found to be beneficial. Heating a mixture of the diamide, *N*-cyclohexyl-2-acetamidoacrylamide **7** with excess 2-nitropropane (5.7 equiv.) and the base *N*-benzyltrimethylammonium hydroxide (1.5 equiv.) in dry *tert*-butyl alcohol for 6 h gave **23** in nearly quantitative yield (84% yield after recrystallisation of the product) (Scheme 5).



Scheme 5 *Reagents and conditions*: i, *N*-benzyltrimethylammonium hydroxide, *tert*-butyl alcohol, N_2, heat, 30 min; ii, *N*-benzyltrimethylammonium hydroxide, *tert*-butyl alcohol, N_2, heat, 6 h

Reaction in *tert*-butyl alcohol at room temperature for 18 h returned starting materials. Thus elevated temperatures, an alternate proton source for efficient trapping of the adduct and the use of a hindered base all favoured the formation of the addition product.

These conditions were used for the reaction of the diamide, *N*-cyclohexyl-2-acetamidoacrylamide **7**, with nitromethane and gave the 1:1-adduct *N*-cyclohexyl-2-acetamido-4-nitrobutanamide **22** in moderate yield (Scheme 5). Thus, heating a mixture of the diamide **7** with excess nitromethane (5.4 equiv.) and base *N*-benzyltrimethylammonium hydroxide (1.25 equiv.) in dry *tert*-butyl alcohol for 30 min gave **22** in 42% yield; use of a longer reaction time (1.5 h) resulted in a lower yield of **22** (18%) and the formation of additional products. Once again no reaction occurred in toluene at room temperature for 18 h when TBAF was used as base.

Conclusion

γ-Nitro-α-amino acid derivatives are obtained in good yield from the base-catalysed conjugate addition of primary and secondary nitroalkanes to *N*-protected dehydroalanine esters (methyl 2-amidoacrylates) and the addition reaction can even be extended to 2-amidoacrylamides which serve as a model of a dehydroalanine residue incorporated in a peptide chain. While simple nitroalkanes were used in this study, more elaborate nitroalkanes have been used in other work directed at specific synthetic targets. The γ-nitro-α-amino acids may be of interest as substrates for 'mechanism-based' inhibition of enzymes,[33] and the reduced compounds may be of interest as GABA (γ-aminobutyric acid) analogues. As the starting materials used in this study are achiral and stereogenic centres are generated in the reaction, the products are necessarily racemic. This limitation can be overcome by using a chiral dehydroalanine derivative such as (2*S*)-3-benzoyl-2-(*tert*-butyl)-4-methylidene-1,3-oxazolidin-5-one as the acceptor.[28,34,35] In other work we have transformed γ-nitro-α-amino acids, derived by conjugate addition of nitroalkanes to dehydroalanines, into γ-amido-, γ-amino-, γ-chloro-, γ-hydroxy-, γ-oxo- and γ-acetoxy-α-amino acids and into γ-lactam analogues of β-lactam antibiotics. The following paper reports some of this work.[36]

Experimental

Melting points were recorded on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed by the Australian Mineral and Development Laboratories, Melbourne and by the Microanalytical unit of the School of Chemistry, University of New South Wales. Infrared spectra were either obtained on a Perkin-Elmer 710B or a Perkin-Elmer 1600 FTIR spectrophotometer from the neat liquid film (sodium chloride plates) or as chloroform solutions as indicated. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz), Varian XL-100 (100 MHz) or Bruker WH-400 (400 MHz) instrument and are quoted in ppm relative to tetramethylsilane ($SiMe_4$) as internal standard; *J* values are given in Hz. ^{13}C NMR spectra were acquired on a Bruker WH-400 (100 MHz) spectrometer and are reported as the fully decoupled spectra assigned with the aid of DEPT analysis. Electron impact (EI) mass spectra were recorded on a Kratos/AEI MS 9 spectrometer at 70 eV, which was connected to a DS 30 data handling system when high resolution spectra were required. Chemical ionisation (CI) mass spectra were recorded on a Hewlett-Packard HP 5989A 'engine' quadrapole mass spectrometer, which was connected to the HP Chemstation data system, with methane as the ionising gas.

Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh). Solvents for chromatography were distilled before use. Analytical high performance liquid chromatography (HPLC) was carried out on a system consisting of a Waters model 6000A pump, U6K injector, a Waters model 440 ultraviolet detector (set at a wavelength of 254 nm) and a Waters model R401 refractive index detector. Preparative HPLC was performed with a Waters model 510EF pump, U6K injector, a Waters model 481 ultraviolet detector (set at a wavelength of 254 nm) and a Waters model R403 refractive index detector. The columns used were Waters μ-Porasil (semi-preparative) 7.8 mm ID × 30 cm, Whatman Partisil 5 (analytical) 4.6 mm ID × 25 cm, Whatman Partisil M9 10/50 (semi-preparative) 9.4 mm ID × 50 cm and Whatman Partisil 10 (preparative) 22.0 mm ID × 50 cm.

Solvents were purified and dried as necessary by standard methods. Light petroleum refers to that fraction of bp 60–80 °C. Nitromethane, nitroethane and 2-nitropropane were distilled and passed down a short column of Activity I alumina immediately prior to use. Tetrabutylammonium fluoride trihydrate ($Bu_4NF{\cdot}3H_2O$) was used as supplied (Aldrich). Ether refers to diethyl ether. All reactions involving organic solvents were performed under a static atmosphere of dry nitrogen. Organic extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate.

Preparation of dehydroalanines

Methyl 2-phthalimidoacrylate **4** and methyl 2-(benzyloxycarbonylamino)acrylate **5** were prepared in high yield from the corresponding serine derivatives by dehydration using diethyl azodicarboxylate–PPh_3.[19] Methyl 2-acetamidoacrylate **6** was prepared from alanine according to a published procedure.[22] 2-Acetamidoacrylic acid was obtained by hydrolysis of the methyl ester **6**.[22]

***N*-Cyclohexyl-2-acetamidoacrylamide 7.** To 2-acetamidoacrylic acid (1.73 g, 13.4 mmol) and cyclohexylamine (1.33 g, 13.4 mmol) in dry tetrahydrofuran (60 cm^3) was added 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (3.74 g, 15.1 mmol). The solution was heated at reflux for 1 h and allowed to cool and then evaporated to dryness to yield a colourless solid, which was chromatographed over silica (ethyl acetate–light petroleum; 1:1) to give N-*cyclohexyl*-2-*acetamidoacrylamide* **7** (1.79 g, 64%) as colourless prisms; mp 133–134 °C (from benzene) (Found: C, 62.8; H, 8.8; N, 13.4. $C_{11}H_{18}N_2O_2$ requires C, 62.8; H, 8.6; N, 13.3%); $\nu_{max}(CHCl_3)$/cm^{-1} 3450, 3390m, 1700m, 1660s and 1640s; δ_H(90 MHz; $CDCl_3$) 2.10 (3 H, s, CH_3), 1.10–2.15 (10 H, m, 5 × CH_2), 3.75 (1 H, m, methine), 5.10 (1 H, s, vinyl), 5.95 (1 H, br s, NH), 6.36 (1 H, s, vinyl) and 8.05 (1 H, br s, NH); *m*/*z* (EI) 210 (M^+, 58%), 112 (67), 111 (20), 98 (83) and 87 (43).

Conjugate additions of nitroalkanes to methyl 2-phthalimidoacrylate 4

Formation of a 1:1-adduct with nitromethane: synthesis of methyl 4-nitro-2-phthalimidobutanoate 8. A solution of methyl 2-phthalimidoacrylate **4** (700 mg, 3.03 mmol) in nitromethane (25 cm^3) was treated with potassium fluoride (210 mg, 3.6 mmol) and heated under reflux for 1.5 h. The reaction mixture was allowed to cool to room temperature and then partitioned between water (30 cm^3) and dichloromethane (20 cm^3). The organic layer was separated, washed with water (30 cm^3), dried and concentrated under reduced pressure to leave a yellow oil, which was purified by chromatography over silica (ether–light petroleum; 1:1) to give *methyl* 4-*nitro*-2-*phthalimidobutanoate* **8** (710 mg, 80%) as a colourless crystalline solid; mp 77.5–78.5 °C (from dichloromethane–hexane) (Found: C, 53.6; H, 4.2; N, 9.9. $C_{13}H_{12}N_2O_6$ requires C, 53.4; H, 4.1; N, 9.6%); $\nu_{max}(CHCl_3)$/cm^{-1} 1780 (C=O phthalimide), 1745 (C=O ester), 1720 (C=O phthalimide), 1555 (NO_2) and 1380 (NO_2); δ_H(90 MHz; $CDCl_3$) 2.40–3.20 (2 H, m, 3-H), 3.74 (3 H, s, OCH_3), 4.52 (2 H, t, *J* 6.0, 4-H), 4.99 (1 H, dd, *J* 9.0 and 5.0, 2-H) and 7.60–7.93 (4 H, m, ArH); *m*/*z* (EI) 268 ($M^+ - NO_2$, 27%), 233 (3) and 186 (100).

Formation of 2:1- and 3:1-adducts with nitromethane: synthesis of dimethyl 4-nitro-2,6-diphthalimidoheptane-1,7-dioate 9 and dimethyl 4-(2′-phthalimido-3′-methoxy-3′-oxopropyl)-4-nitro-2,6-diphthalimidoheptane-1,7-dioate 10. A solution of methyl 2-phthalimidoacrylate **4** (500 mg, 2.2 mmol) and nitromethane (660 mg, 11 mmol) in dry toluene (25 cm^3) was

treated with $Bu_4NF·3H_2O$ (140 mg, 0.43 mmol) and stirred at room temperature for 2.5 h. The reaction mixture was then washed with water (2×10 cm^3) and concentrated under reduced pressure to leave a yellow oil which was chromatographed over silica (ether then followed with ethyl acetate). The ether fraction yielded *dimethyl* 4-*nitro*-2,6-*diphthalimidoheptane*-1,7-*dioate* **9** (452 mg, 79%) as colourless crystals; mp 173–176 °C (from chloroform–light petroleum) (Found: C, 57.3; H, 4.0; N, 7.8. $C_{25}H_{21}N_3O_{10}$ requires C, 57.4; H, 4.0; N, 8.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785 (C=O phthalimide), 1760 (C=O ester), 1730 (C=O phthalimide), 1560 (NO_2) and 1390 (NO_2); δ_H(90 MHz; $CDCl_3$) 3.21–3.65 (4 H, m, 3- and 5-H), 3.70 (6 H, m, diastereotopic OCH_3), 4.33–4.67 (1 H, m, 4-H), 4.69–4.98 (2 H, m, 2- and 6-H) and 7.58–7.93 (8 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 32.53 (CH_2), 48.83 (CH), 53.11 (OCH_3), 81.16 (CH), 123.69 (ArC), 131.55 (*ipso* ArC), 134.34 (ArC), 167.00 (C=O), 167.32 (C=O) and 168.17 (C=O); *m*/*z* (EI) 477 ($M^+ - NO_2$, 8%), 464 (13) and 417 (30).

The ethyl acetate fraction yielded the 3:1-adduct dimethyl 4-(2′-phthalimido-3′-methoxy-3′-oxopropyl)-4-nitro-2,6-diphthalimidoheptane-1,7-dioate **10** (60 mg, 10%) as colourless crystals; mp 214.5–215.5 °C (from chloroform–light petroleum) (Found: C, 58.4; H, 4.0; N, 7.4. $C_{37}H_{30}N_4O_{14}$ requires C, 58.9; H, 4.0; N, 7.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (C=O phthalimide), 1750 (C=O ester), 1720 (C=O phthalimide) and 1540 (NO_2); δ_H(90 MHz; $CDCl_3$) 2.98–3.45 (6 H, m, CH_2), 3.24, 3.62 and 3.67 (9 H, 3 × s, OCH_3), 4.74–5.21 (3 H, m, 2-H) and 7.48–7.92 (12 H, m, ArH); *m*/*z* (EI) 708 ($M^+ - NO_2$, 18%), 695 (1.5), 675 (5), 648 (22) and 104 (100).

Formation of 1:1- and 2:1-adducts with nitroethane: synthesis of methyl (2*RS*,4*RS*)-4-nitro-2-phthalimidopentanoate 11a, methyl (2*RS*,4*SR*)-4-nitro-2-phthalimidopentanoate 11b and dimethyl 4-methyl-4-nitro-2,6-diphthalimidoheptane-1,7-dioate 12. A solution of methyl 2-phthalimidoacrylate **4** (1.50 g, 6.5 mmol) and nitroethane (2.44 g, 33 mmol) in dry toluene (20 cm^3) was treated with $Bu_4NF·3H_2O$ (600 mg, 1.9 mmol) at room temperature. After 45 min, the reaction mixture was then washed with water (20 cm^3). The organic layer was diluted with ether (30 cm^3) and passed down a short column of silica (ether). The effluent from this column was concentrated under reduced pressure and rechromatographed over silica in a 'gravity flow column' to afford two fractions.

The first fraction was obtained by elution of the column with ether–hexane (1:1) and it yielded *methyl* 4-*nitro*-2-*phthalimidopentanoate* **11** (1.30 g, 65%); mp 90–92 °C (from chloroform–hexane) as a 3:2 mixture of two diastereomers. A portion (127 mg) of this mixture was further separated by preparative HPLC (Whatman Partisil 10, 20% ethyl acetate–light petroleum, flow rate 9.0 cm^3 min^{-1}). The first-eluted compound (t_R 66.0 min, 68 mg) was the major isomer and it was shown by single crystal X-ray crystallography to be *methyl* (2RS,4RS)-4-*nitro*-2-*phthalimidopentanoate* **11a** obtained as colourless orthorhomboids; mp 119–120 °C (from chloroform–light petroleum) (Found: C, 55.1; H, 4.9; N, 9.1. $C_{14}H_{14}N_2O_6$ requires C, 54.9; H, 4.6; N, 9.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 (C=O phthalimide), 1740 (C=O ester), 1710 (C=O phthalimide), 1540 (NO_2) and 1380 (NO_2); δ_H(400 MHz; $CDCl_3$) 1.63 (3 H, d, *J* 6.6, CH_3), 2.75 (1 H, ddd, *J* 14.8, 5.8 and 5.8, 3-H), 2.88 (1 H, ddd, *J* 14.8, 9.0 and 7.8, 3-H), 3.75 (3 H, s, OCH_3), 4.67–4.77 (1 H, m, 4-H), 4.93 (1 H, dd, *J* 9.0 and 5.8, 2-H), 7.75–7.81 (2 H, m, ArH) and 7.86–7.95 (2 H, m, ArH); *m*/*z* (EI) 260 ($M^+ - NO_2$, 3%), 247 (18), 217 (52) and 200 (100).

Further elution yielded the minor diastereomer, *methyl* (2RS,4SR)-4-*nitro*-2-*phthalimidopentanoate* **11b** (t_R 73.2 min, 46 mg) as colourless crystals; mp 105–107 °C (from chloroform–light petroleum) (Found: C, 55.0; H, 4.8; N, 9.1. $C_{14}H_{14}N_2O_6$ requires C, 54.9; H, 4.6; N, 9.2%) [Found: $(M - NO_2)^+$, 260.0918. $C_{14}H_{18}N_2O_6 - NO_2$ requires 260.0923]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 (C=O phthalimide), 1740 (C=O ester), 1710 (C=O phthalimide), 1540 (NO_2) and 1380 (NO_2); δ_H(400 MHz; $CDCl_3$) 1.60 (3 H, d, *J* 6.8, CH_3), 2.72 (1 H, ddd, *J* 15.3, 11.1 and 3.3, 3-H), 3.02 (1 H, ddd, *J* 15.3, 10.0 and 4.5, 3-H), 3.76 (3 H, s, OCH_3), 4.55 (1 H, ddq, *J* 10.0, 3.3 and 6.8, 4-H), 4.93 (1 H, dd, *J* 11.1 and 4.5, 2-H), 7.75–7.81 (2 H, m, ArH) and 7.84–7.94 (2 H, m, ArH); *m*/*z* (EI) 305 ($M^+ - 1$, 1%), 274 (0.7), 260 (3), 247 (9), 217 (40), 200 (100), 182 (13), 130 (23), 104 (33), 83 (90) and 76 (36).

Further elution of the 'gravity flow column' with ether gave the 2:1-adduct, *dimethyl* 4-*methyl*-4-*nitro*-2,6-*diphthalimidoheptane*-1,7-*dioate* **12** (510 mg, 29%) as colourless crystals; mp 140–142 °C (from aqueous ethanol) (Found: C, 56.6; H, 4.8; N, 7.5. $C_{26}H_{23}N_3O_{10} + H_2O$ requires C, 56.2; H, 4.5; N, 7.6%) [Found: $(M - NO_2)^+$, 491.1453. $C_{26}H_{23}N_3O_{10} - NO_2$ requires 491.1454]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (C=O phthalimide), 1750 (C=O ester), 1720 (C=O phthalimide) and 1540 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.81 (3 H, s, CH_3), 2.73 (2 H, dd, *J* 15.0 and 4.0, 3- and 5-H), 3.24 (2 H, dd, *J* 15.0 and 11.0, 3- and 5-H), 3.70 (6 H, s, OCH_3), 5.00 (2 H, dd, *J* 11.0 and 4.0, 2- and 6-H) and 7.50–7.90 (8 H, m, ArH); *m*/*z* (EI) 491 ($M^+ - NO_2$, 23%), 431 (67), 252 (100), 224 (67), 214 (38), 187 (20), 160 (23), 130 (41), 104 (39) and 76 (21); *m*/*z* (CI, CH_4) 538 ($M^+ + 1$, 13%).

Formation of a 1:1-adduct with 2-nitropropane: synthesis of methyl 4-methyl-4-nitro-2-phthalimidopentanoate 13. A solution of methyl 2-phthalimidoacrylate **4** (410 mg, 1.77 mmol) and 2-nitropropane (790 mg, 8.85 mmol) in dry toluene (18 cm^3) was treated with $Bu_4NF·3H_2O$ (150 mg, 0.47 mmol) and allowed to stand at room temperature for 21 h. The reaction mixture was then washed with water (20 cm^3) and concentrated under reduced pressure to leave a solid which was recrystallised to give *methyl* 4-*methyl*-4-*nitro*-2-*phthalimidopentanoate* **13** (530 mg, 93%) as colourless crystals; mp 165–167 °C (from aqueous ethanol) (Found: C, 54.9; H, 5.3; N, 8.3. $C_{15}H_{16}N_2O_6 + 0.5\ H_2O$ requires C, 54.7; H, 5.2; N, 8.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (C=O phthalimide), 1750 (C=O ester), 1720 (C=O phthalimide) and 1540 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.61 and 1.67 (6 H, 2 × s, diastereotopic CH_3), 2.88 (1 H, dd, *J* 16.0 and 3.0, 3-H), 3.12 (1 H, dd, *J* 16.0 and 10.0, 3-H), 3.70 (3 H, s, OCH_3), 4.98 (1 H, dd, *J* 10.0 and 3.0, 2-H) and 7.53–7.90 (4 H, m, ArH); *m*/*z* 274 ($M^+ - NO_2$, 15%), 261 (18) and 214 (100).

Formation of a 1:1-adduct with nitrocyclohexane: synthesis of methyl 3-(1′-nitrocyclohexyl)-2-phthalimidopropanoate 14. A solution of methyl 2-phthalimidoacrylate **4** (460 mg, 1.99 mmol) and nitrocyclohexane (1.28 g, 9.95 mmol) in dry toluene (20 cm^3) was treated with $Bu_4NF·3H_2O$ (120 mg, 0.38 mmol) and stirred at room temperature for 90 min. The reaction mixture was then washed with water (2×20 cm^3) and concentrated under reduced pressure to leave a yellow oil, which was chromatographed over silica (dichloromethane) to give a colourless oil which crystallised on standing. The solid was recrystallised to give *methyl* 3-(1′-*nitrocyclohexyl*)-2-*phthalimidopropanoate* **14** (590 mg, 82%) as colourless prisms; mp 114–116 °C (from chloroform–hexane) (Found: C, 59.8; H, 5.8; N, 7.8. $C_{18}H_{20}N_2O_6$ requires C, 60.0; H, 5.6; N, 7.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (C=O phthalimide), 1740 (C=O ester), 1715 (C=O phthalimide), 1540 (NO_2) and 1380 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.00–2.00 (8 H, m, cyclohexyl H), 2.20–2.70 (2 H, m, 2′- and 6′-H), 2.90 (2 H, ddd, *J* 15.0, 10.0 and 3.0, 3-H), 3.70 (3 H, s, OCH_3), 5.02 (1 H, dd, *J* 10.0 and 3.0, 2-H) and 7.60–7.97 (4 H, m, ArH); *m*/*z* (EI) 314 ($M^+ - NO_2$, 4%), 301 (75), 254 (7) and 200 (100).

Formation of a 1:1-adduct with ethyl nitroacetate: synthesis of 5-ethyl 1-methyl 4-nitro-2-phthalimidopentane-1,5-dioates 15. A solution of methyl 2-phthalimidoacrylate **4** (400 mg, 1.73 mmol) in dry toluene (20 cm^3) was treated with ethyl nitroacetate (689 mg, 5.18 mmol, 3 equiv.) and $Bu_4NF·H_2O$ (53.0 mg, 0.203 mmol). The reaction mixture was stirred at room temperature for 1 h, then washed with water (3×20 cm^3), dried and concentrated under reduced pressure to a yellow oil. The excess ethyl nitroacetate was removed by distillation (100 °C/1 mm Hg, 2 h) to yield 5-*ethyl* 1-*methyl* 4-*nitro*-2-*phthalimido*-

pentane-1,5-*dioates* **15** (458 mg, 70%) as an orange viscous oil (Found: C, 52.9; H, 4.6; N, 7.9. $C_{16}H_{16}N_2O_8$ requires C, 52.7; H, 4.4; N, 7.7%); ν_{max}(liquid film)/cm^{-1} 3484 (NH), 2991 (CH), 2955 (CH), 1778, 1749, 1720 br (C=O ester), 1561 (NO_2) and 1385 (NO_2); δ_H(400 MHz; $CDCl_3$) Isomer 1: 1.27 or 1.30 (3 H, t, *J* 7.0, CH_3), 2.98–3.09 (1 H, m, 3-H_a), 3.20–3.32 (1 H, m, 3-H_b), 3.80 (3 H, s, OCH_3), 4.20–4.28 or 4.27–4.35 (2 H, m, OCH_2), 5.03 (1 H, dd, *J* 9.0 and 6.0, 2-H), 5.36 (1 H, dd, *J* 8.0 and 6.0, 4-H), 7.76–7.82 (2 H, m, ArH) and 7.86–7.93 (2 H, m, ArH); Isomer 2: 1.27 or 1.30 (3 H, t, *J* 7.0, CH_3), 2.94–3.04 (1 H, m, 3-H_a), 3.25–3.36 (1 H, m, 3-H_b), 3.80 (3 H, s, OCH_3), 4.20–4.28 or 4.27–4.35 (2 H, m, OCH_2), 4.98 (1 H, dd, *J* 9.0 and 6.0, 2-H), 5.20 (1 H, dd, *J* 8.0 and 6.0, 4-H), 7.76–7.82 (2 H, m, ArH) and 7.86–7.93 (2 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 14.41 (CH_3), 30.51 (CH_2), 30.78 (CH_2), 48.98 (CH), 49.12 (CH), 53.89 (OCH_3), 64.13 (OCH_2), 85.28 ($CHNO_2$), 86.06 ($CHNO_2$), 124.50 (ArC), 124.54 (ArC), 132.16 (*ipso* ArC), 135.23 (ArC), 135.26 (ArC), 164.23 (CO), 164.45 (CO), 167.76 (CO), 167.87 (CO), 168.74 (CO) and 168.86 (CO); *m*/*z* (EI) 334 ($M^+ - NO$, 3.6%), 318 ($M^+ - NO_2$, 3.5), 305 ($M^+ - CO_2CH_3$, 19), 276 (15), 275 (100), 259 (20), 258 (79), 244 (12), 230 (63), 212 (15), 200 (19), 199 (49), 190 (13), 187 (15), 186 (33), 184 (29), 174 (13), 163 (25), 160 (17), 148 (39), 147 (25), 130 (36), 105 (16), 104 (72), 83 (43), 77 (19), 76 (59) and 55 (19).

Analytical normal phase HPLC [Whatman Partisil 5, ethyl acetate–light petroleum (1:3), flow rate 1.35 cm^3 min^{-1}] showed the presence of two diastereomers in the ratio of 1:1 with retention times of 11.2 and 12.4 min, respectively. Attempts to separate the diastereomers by semi-preparative normal phase HPLC [Whatman Partisil M9 10/50, ethyl acetate–light petroleum (1:3), flow rate 3.0 cm^3 min^{-1} failed because of facile epimerisation at C–4.

Reactions of methyl 2-(benzyloxycarbonylamino)acrylate 5

Formation of a 1:1-adduct with nitromethane: synthesis of methyl 2-(benzyloxycarbonylamino)-4-nitrobutanoate 16. Method 1. A solution of *N*-benzyltrimethylammonium hydroxide in methanol (40% w/v, 0.425 cm^3, 1.02 mmol) was added to a stirred solution of nitromethane (175 mg, 2.87 mmol) in anhydrous dioxan (2 cm^3) under nitrogen. After 10 min, methyl 2-(benzyloxycarbonylamino)acrylate **5** (207 mg, 0.88 mmol) in dioxan (2 cm^3) was added dropwise under nitrogen to the vigorously stirred mixture. The reaction mixture was then heated at 50 °C for 2 h, allowed to cool and ice-cold aqueous HCl (10%; 3 cm^3) was added, followed by water (20 cm^3). The mixture was extracted with chloroform (2 × 20 cm^3). The combined extracts were washed three times with water, dried and evaporated to dryness. The crude product was purified by flash chromatography (ethyl acetate–light petroleum; 3:7) to give *methyl* 2-(*benzyloxycarbonylamino*)-4-*nitrobutanoate* **16** (185 mg, 71%) as a pale yellow oil (Found: C, 52.8; H, 5.3; N, 9.9. $C_{13}H_{16}N_2O_6$ requires C, 52.7; H, 5.4; N, 9.5%); ν_{max}($CHCl_3$)/cm^{-1} 3410 (NH), 1720 (C=O ester) and 1550 (NO_2); δ_H(400 MHz; $CDCl_3$) 2.30–2.43 (1 H, m, 3-H), 2.58–2.71 (1 H, m, 3-H), 3.78 (3 H, s, OCH_3), 4.40–4.55 (3 H, m, 2- and 4-H), 5.12 (2 H, s, CH_2Ar), 5.47 (1 H, br d, *J* 6.9, NH) and 7.29–7.40 (5 H, m, ArH); *m*/*z* 296 (M^+, 0.4%), 146 (6), 142 (13), 108 (42), 107 (18), 91 (100) and 65 (10).

Method 2. A solution of methyl 2-(benzyloxycarbonylamino)acrylate **5** (560 mg, 2.38 mmol) in nitromethane (20 cm^3) was treated with anhydrous potassium fluoride (180 mg) and heated under reflux for 14 h. The reaction mixture was then cooled and partitioned between water (50 cm^3) and ether (50 cm^3). The organic layer was separated and washed with water (30 cm^3), dried and evaporated to leave a yellow oil. Chromatography of the product over silica (ether–light petroleum; 1:1) gave methyl 2-(benzyloxycarbonylamino)-4-nitrobutanoate **16** (592 mg, 84%) as an oil. This compound co-chromatographed with and had identical spectroscopic data to the product prepared by Method 1.

Formation of 1:1-adducts with nitroethane: synthesis of methyl (2*RS*,4*RS*)-2-(benzyloxycarbonylamino)-4-nitropentanoate 17a and methyl (2*RS*,4*SR*)-2-(benzyloxycarbonylamino)-4-nitropentanoate 17b. Method 1. A stirred solution of nitroethane (14.0 g, 0.187 mol) in anhydrous dioxan (10 cm^3) under nitrogen was treated with 8.87% sodium methoxide in methanol (0.98 g, 18.1 mmol). A thick white precipitate was formed. After 10 min, methyl 2-(benzyloxycarbonylamino)acrylate **5** (4.25 g, 18.1 mmol) in dioxan (10 cm^3) was added dropwise under nitrogen to the vigorously stirred mixture. The reaction mixture was then stirred at 40–50 °C overnight. It was allowed to cool and acidified with aqueous HCl (3 mol dm^{-3}). The solution was diluted with water (100 cm^3) and extracted twice with chloroform. The combined extracts were washed five times with water, dried and evaporated to leave a brownish oil, which was purified by chromatography over silica (ethyl acetate–light petroleum; 2:3) to give a 1:1 diastereomeric mixture of *methyl* 2-(*benzyloxycarbonylamino*)-4-*nitropentanoates* **17** (4.49 g, 80%) as a colourless oil (Found: C, 54.4; H, 6.0; N, 9.1. $C_{14}H_{18}N_2O_6$ requires C, 54.2; H, 5.9; N, 9.0%). These two diastereomers were further separated and purified by HPLC (Waters μ-Porasil, 30% ethyl acetate–light petroleum, flow rate 6.0 cm^3 min^{-1}).

The first fraction (t_R 9.8 min) yielded *methyl* (2RS,4RS)-2-(*benzyloxycarbonylamino*)-4-*nitropentanoate* **17a** as a colourless oil (Found: M^+, 310.1166. $C_{14}H_{18}N_2O_6$ requires *M*, 310.1165); ν_{max}($CHCl_3$)/cm^{-1} 3417 (NH), 1741 (C=O ester), 1723 (C=O urethane), 1555 (NO_2) and 1350 (NO_2); δ_H(400 MHz; $CDCl_3$) 1.61 (3 H, d, *J* 6.8, CH_3), 2.30 (1 H, ddd, *J* 14.6, 7.0 and 4.9, 3-H), 2.45 (1 H, ddd, *J* 14.6, 8.6 and 7.1, 3-H), 3.76 (3 H, s, OCH_3), 4.47 (1 H, ddd, *J* 8.6, 8.0 and 4.9, 2-H), 4.66 (1 H, ddq, *J* 7.1, 7.0 and 6.8, 4-H), 5.12 (2 H, s, CH_2Ar), 5.44 (1 H, br d, *J* 8.0, NH) and 7.36 (5 H, m, ArH); *m*/*z* (EI) 310 (M^+, 0.6%), 156 (12), 108 (27), 107 (15) and 91 (100).

The second fraction (t_R 11.8 min) yielded *methyl* (2RS,4SR)-2-(*benzyloxycarbonylamino*)-4-*nitropentanoate* **17b** as a colourless oil (Found: M^+, 310.1166. $C_{14}H_{18}N_2O_6$ requires *M*, 310.1165); ν_{max}($CHCl_3$)/cm^{-1} 3427 (NH), 1740 (C=O ester), 1724 (C=O urethane), 1555 (NO_2) and 1351 (NO_2); δ_H(400 MHz; $CDCl_3$) 1.57 (3 H, d, *J* 6.8, CH_3), 2.05 (1 H, ddd, *J* 14.3, 10.0 and 3.9, 3-H), 2.67 (1 H, ddd, *J* 14.3, 9.1 and 5.2, 3-H), 3.76 (3 H, s, OCH_3), 4.22–4.36 (1 H, m, 2-H), 4.70 (1 H, ddq, *J* 9.1, 3.9 and 6.8, 4-H), 5.11 (2 H, s, CH_2Ar), 5.45 (1 H, br d, *J* 6.0, NH) and 7.35 (5 H, m, ArH); *m*/*z* (EI) 310 (M^+, 2%), 264 (0.4), 156 (12), 108 (25), 107 (13) and 91 (100).

Method 2. A solution of methyl 2-(benzyloxycarbonylamino)acrylate **5** (160 mg, 0.7 mmol) in nitroethane (15 cm^3) was treated with anhydrous potassium fluoride (160 mg, 3 mmol), stirred at room temperature for 15 h and was then heated under reflux for 4.5 h. The reaction mixture was worked up to give a 3:2 mixture (by HPLC — Waters μ-Porasil, 25% ethyl acetate–light petroleum, flow rate 6.0 cm^3 min^{-1}) of the diastereomeric methyl 2-(benzyloxycarbonylamino)-4-nitropentanoates **17a** and **17b** (195 mg, 97%) as a yellow oil. The products were separated by preparative HPLC as above and both compounds co-chromatographed with and had identical spectroscopic properties to the corresponding compounds obtained by Method 1.

Method 3. A solution of methyl 2-(benzyloxycarbonylamino)acrylate **5** (1.00 g, 4.25 mmol) and nitroethane (1.60 g, 21 mmol) in dry toluene (20 cm^3) was treated with $Bu_4NF\cdot 3H_2O$ (270 mg, 0.85 mmol) and allowed to stand for 24 h at room temperature. The reaction mixture was then warmed to 35–40 °C for 8 h, cooled and allowed to stand for a further 36 h. The reaction mixture was worked up and chromatographed to give a 1:1 mixture of methyl 2-(benzyloxycarbonylamino)-4-nitropentanoates **17** (850 mg, 65%), that co-chromatographed with and had an NMR spectrum identical to that of the product obtained by Method 1.

Formation of a 1:1-adduct with 2-nitropropane: synthesis of methyl 2-(benzyloxycarbonylamino)-4-methyl-4-nitropentanoate 18. A solution of methyl 2-(benzyloxycarbonylamino)acrylate **5** (900 mg, 3.8 mmol) in dry toluene (20 cm^3) was treated with 2-nitropropane (1.78 g, 20 mmol) and $Bu_4NF·3H_2O$ (350 mg, 1.1 mmol). This mixture was allowed to stand for 22 h at room temperature. It was then washed with water (20 cm^3) and evaporated to leave a pale yellow oil, which yielded two products on chromatography over silica (ether–hexane; 1:1). The first eluted fraction gave starting material **5** (95 mg, 11%). The second fraction afforded *methyl* 2-(*benzyloxycarbonylamino*)-4-*methyl*-4-*nitropentanoate* **18** (1.06 g, 85%) as a colourless oil (Found: M^+, 324.1320. $C_{15}H_{20}N_2O_6$ requires *M*, 324.1320); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH), 1720 (C=O ester), 1695 (C=O urethane) and 1540 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.63 (6 H, s, CH_3), 2.42 (2 H, d, *J* 7.0, 3-H), 3.65 (3 H, s, OCH_3), 4.50 (1 H, dt, *J* 9.0 and 7.0, 2-H), 5.08 (2 H, s, CH_2Ar), 5.30 (1 H, d, *J* 9.0, NH) and 7.30 (5 H, s, ArH); *m*/*z* (EI) 324 (M^+, 1%), 278 (2.5), 265 (3.9), 218 (9.2) and 91 (100).

Formation of a 1:1-adduct with nitrocyclohexane: synthesis of methyl 2-(benzyloxycarbonylamino)-3-(1′-nitrocyclohexyl)-propanoate 19. Methyl 2-(benzyloxycarbonylamino)acrylate **5** (330 mg, 1.4 mmol) in dry toluene (20 cm^3) was treated with nitrocyclohexane (400 mg, 3.1 mmol), anhydrous potassium fluoride (220 mg, 3.78 mmol) and 18-crown-6 (1.00 g, 3.78 mmol) and heated at reflux for 5 h. The reaction mixture was then cooled, washed with water (3 × 20 cm^3) and brine (20 cm^3), dried and concentrated under reduced pressure to a dark yellow oil, which was purified by chromatography over silica using ether–light petroleum (1:1) as eluent to give *methyl* 2-(*benzyloxycarbonylamino*)-3-(1′-*nitrocyclohexyl*)*propanoate* **19** (391 mg, 77%) as a colourless oil (Found: M^+, 364.1664. $C_{18}H_{24}N_2O_6$ requires *M*, 364.1633); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH), 1710 (C=O ester) and 1540 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.20–1.80 (8 H, m, cyclohexyl H), 2.00–2.60 (4 H, m, 3-, 2′- and 6′-H), 3.64 (3 H, s, OCH_3), 4.20–4.60 (1 H, m, 2-H), 5.06 (2 H, s, CH_2Ar), 5.43 (1 H, d, *J* 10.0, NH) and 7.28 (5 H, s, ArH); *m*/*z* (EI) 364 (M^+, 0.8%), 318 (15), 305 (6) and 107 (100).

Formation of a 1:1-adduct with methyl nitroacetate: synthesis of dimethyl 2-(benzyloxycarbonylamino)-4-nitropentane-1,5-dioates 20. Method 1. *N*-Benzyltrimethylammonium hydroxide as base catalyst. To a stirred solution of methyl nitroacetate (9.70 g, 9.06 mmol) in anhydrous dioxan (30 cm^3) under nitrogen was added *N*-benzyltrimethylammonium hydroxide in methanol (40% w/v; 46 cm^3, 0.11 mol). After 10 min, methyl 2-(benzyloxycarbonylamino)acrylate **5** (21.3 g, 9.06 mmol) in dioxan (30 cm^3) was added dropwise under nitrogen to the vigorously stirred mixture. The reaction mixture was stirred overnight at 40–50 °C and then allowed to cool and acidified with aqueous HCl (3 mol dm^{-3}) which caused the solution to turn green. Water was then added to the solution and the mixture was extracted with chloroform. The combined extracts were washed with water, then dried, filtered, and concentrated under reduced pressure to yield crude product as a brownish oil (26.9 g). A sample of the crude product (1.57 g) was purified by flash chromatography (light petroleum–ethyl acetate; 3:2) to give a 1:1 diastereomeric mixture of *dimethyl* 2-(*benzyloxycarbonylamino*)-4-*nitropentane*-1,5-*dioates* **20** (1.41 g, 75%) as a colourless oil (Found: C, 51.0; H, 5.0; N, 7.9. $C_{15}H_{18}N_2O_8$ requires C, 50.8; H, 5.1; N, 7.9%) (Found: M^+, 354.1069. $C_{15}H_{18}N_2O_8$ requires *M*, 354.1063); $\nu_{max}(CHCl_3)/cm^{-1}$ 3425w, 2950w, 1753s, 1734s, 1725s, 1569s, 1506m, 1439m, 1348m and 1323m; δ_H(400 MHz; $CDCl_3$) Isomer 1: 2.30–2.51 (1 H, m, 3-H), 2.64 (1 H, ddd, *J* 14.8, 8.2 and 7.6, 3′-H), 3.77 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.40–4.52 (1 H, m, 2-H), 5.12 (2 H, s, CH_2Ar), 5.32 (1 H, dd, *J* 8.2 and 4.0, 4-H), 5.40–5.49 (1 H, br s, NH) and 7.31–7.41 (5 H, m, ArH); Isomer 2: 2.81–3.01 (2 H, m, 3- and 3′-H), 3.77 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.53–4.63 (1 H, m, 2-H), 5.12 (2 H, s, CH_2Ar), 5.39–5.50 (2 H, m, NH and 4-H) and 7.31–7.41 (5 H, m, ArH); *m*/*z* (EI) 354 (M^+, 0.38%), 295 (<1), 264 (<1), 251 (<1), 231 (2), 205 (5), 200 (10), 108 (32), 107 (15), 92 (12), 91 (100) and 65 (9).

The diastereomeric mixture of dimethyl 2-(benzyloxycarbonylamino)-4-nitropentane-1,5-dioates **20** was further separated and purified by HPLC [μ-Porasil column, light petroleum–ethyl acetate (7:3), flow rate 3.0 cm^3 min^{-1}]; however, each isomer epimerised very quickly, even at low temperature, back to an equal mixture of both isomers. The NMR spectral assignments to the individual isomers were made by consideration of the spectrum of a sample enriched with isomer 1.

Method 2. $Bu_4NF·3H_2O$ as base catalyst. Methyl nitroacetate (720 mg, 6.73 mmol) was added to a stirred solution of methyl 2-(benzyloxycarbonylamino)acrylate **5** (545 mg, 2.32 mmol) in anhydrous toluene (10 cm^3), followed by $Bu_4NF·3H_2O$ (70 mg, 0.22 mmol) at room temperature. The mixture was stoppered and stirred overnight. The reaction mixture was then heated at reflux for 7 h, allowed to cool, and washed with water, dried, filtered, then concentrated under reduced pressure. The crude product was purified as above to give dimethyl (2-benzyloxycarbonylamino)-4-nitropentane-1,5-dioates **20** (500 mg, 61%) as a yellow oil, that co-chromatographed with and had an NMR spectrum identical to that of the product obtained by Method 1 above.

Addition to methyl 2-acetamidoacrylate 6

Formation of a 1:1-adduct with 2-nitropropane: synthesis of methyl 2-acetamido-4-methyl-4-nitropentanoate 21. A solution of methyl 2-acetamidoacrylate **6** (1.06 g, 7.44 mmol) in dry toluene (20 cm^3) was treated with 2-nitropropane (3.15 g, 35.3 mmol) and $Bu_4NF·3H_2O$ (554 mg, 1.79 mmol) and stirred at room temperature for 66 h. The reaction was then washed with water (3 cm^3) and the organic layer was separated, dried and concentrated under reduced pressure to leave a gum. Chromatography over silica (ethyl acetate–light petroleum; 3:1) as eluent gave *methyl* 2-*acetamido*-4-*methyl*-4-*nitropentanoate* **21** (1.31 g, 76%) as a colourless gum which crystallised on standing to give prisms, mp 53–55 °C (from ether) (Found: C, 46.7; H, 6.8; N, 12.3. $C_9H_{16}N_2O_5$ requires C, 46.6; H, 6.9; N, 12.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (NH), 1760 (C=O ester), 1690 (C=O amide) and 1560 (NO_2); δ_H(90 MHz; $CDCl_3$) 1.75 and 1.77 [6 H, 2 × s, $C(CH_3)_2$], 2.06 (3 H, s, $COCH_3$), 2.56 (2 H, m, 3-H), 3.80 (3 H, s, OCH_3), 4.89 (1 H, m, 2-H) and 6.06 (1 H, br s, NH); *m*/*z* (EI) 201 (25%), 173 (41), 127 (25), 126 (55), 88 (69) and 84 (94).

Additions to *N*-cyclohexyl-2-acetamidoacrylamide 7

Formation of a 1:1-adduct with nitromethane: synthesis of *N*-cyclohexyl-2-acetamido-4-nitrobutanamide 22. To *N*-cyclohexyl-2-acetamidoacrylamide **7** (171 mg, 0.81 mmol) and nitromethane (329 mg, 5.4 mmol) in dry *tert*-butyl alcohol (5 cm^3) was added a solution of *N*-benzyltrimethylammonium hydroxide in methanol (40% w/v, 0.425 cm^3, 1.02 mmol) under nitrogen. The solution was heated at reflux for 30 min, then allowed to cool and aqueous HCl (3 mol dm^{-3}; 2 cm^3) was added, followed by water (10 cm^3). The solution was extracted with dichloromethane (3 × 10 cm^3). The combined extracts were washed with water, dried and evaporated to give a yellow residue (193 mg) which was purified by flash chromatography over silica (ethyl acetate) to give N-*cyclohexyl*-2-*acetamido*-4-*nitrobutanamide* **22** (93 mg, 42%) as colourless needles; mp 175–178 °C (from ethanol) [Found: $(M - NO_2)^+$, 225.1609. $C_{12}H_{21}N_3O_4 - NO_2$ requires 225.1603]; δ_H(400 MHz; $CDCl_3$) 1.12 (10 H, m, cyclohexyl CH_2), 2.03 (3 H, s, NHCOCH_3), 2.31 (1 H, m, 3-H), 2.46 (1 H, m, 3-H), 3.72 (1 H, m, cyclohexyl methine), 4.46 (2 H, m, 4-H), 4.63 (1 H, m, 2-H) and 6.81 (1 H, br d, NH); *m*/*z* (EI) 272 ($M^+ + 1$, 2.45%), 225 (10.4), 190 (23), 173 (32), 155 (24), 146 (42), 116 (45), 103 (44), 98 (57), 86 (51), 83 (50), 74 (39), 73 (41), 60 (71), 56 (100) and 43 (90); *m*/*z* (CI, CH_4) 272 ($M^+ + 1$, 100%), 254 (46), 238 (66), 225 (17), 181 (10), 179 (11) and 100 (31).

Formation of a 1:1-adduct with 2-nitropropane: synthesis of *N*-cyclohexyl-2-acetamido-4-methyl-4-nitropentanamide 23. To *N*-cyclohexyl-2-acetamidoacrylamide **7** (178 mg, 0.86 mmol) and 2-nitropropane (438 mg, 5.7 equiv.) in dry *tert*-butyl alcohol (5 cm^3) was added a solution of *N*-benzyltrimethylammonium hydroxide in methanol (40% w/v, 0.485 cm^3, 1.3 mmol) under nitrogen. The solution was heated at reflux for 6 h and then allowed to cool and aqueous HCl (3 mol dm^{-3}; 2 cm^3) was added, followed by water (10 cm^3). The solution was extracted with dichloromethane (3 × 10 cm^3), and the combined extracts were washed with water, dried and evaporated under reduced pressure to give a pale yellow solid (248 mg), mp 162–164 °C, which was purified by recrystallisation from ethyl acetate–light petroleum to give N-*cyclohexyl*-2-*acetamido*-4-*methyl*-4-*nitropentanamide* **23** (214 mg, 84%) as colourless needles; mp 164–165 °C (Found: C, 56.4; H, 8.4; N, 14.2. $C_{14}H_{25}N_3O_4$ requires C, 56.2; H, 8.4; N, 14.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3414w, 3296w, 2990w, 2932m, 2849w, 1659s, 1541s (NO_2), 1374w and 1348w; δ_H(400 MHz; $CDCl_3$) 1.60 and 1.62 [3 H, each, 2 × s, $C(CH_3)_2NO_2$], 1.96 (3 H, s, $NHCOCH_3$), 1.09–2.18 (10 H, m, cyclohexyl CH_2), 2.35 (1 H, dd, *J* 15.0 and 4.4, 3-H), 2.50 (1 H, dd, *J* 15.0 and 9.2, 3-H), 3.69 (1 H, m, cyclohexyl methine), 4.64 (1 H, m, 2-H), 6.53 (1 H, br s, NH) and 6.67 (1 H, br s, NH); *m/z* (EI) 300 ($M^+ + 1$, 0.3%), 126 (64), 112 (13), 98 (11), 88 (28), 86 (28), 85 (41), 84 (100), 70 (35), 60 (79) and 55 (44).

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References

1 M. J. Crossley, R. L. Crumbie, Y. M. Fung, J. J. Potter and M. A. Pegler, *Tetrahedron Lett.*, 1987, **28**, 2883.
2 R. C. Coombes, *Comprehensive Organic Chemistry*, Pergamon Press, Oxford, 1979, vol. 2, ch. 7.
3 N. Ono, H. Miyake, R. Tamura and A. Kaji, *Tetrahedron Lett.*, 1981, **22**, 1705.
4 N. Ono, A. Kamimura, H. Miyake, I. Hamamoto and A. Kaji, *J. Org. Chem.*, 1985, **50**, 3692.
5 N. Ono, *Nitro Compounds*; *Recent Advances in Synthesis and Chemistry*, VCH, New York, 1990, ch. 1.
6 K. Busch, U. M. Groth, W. Kühnle and U. Schöllkopf, *Tetrahedron*, 1992, **48**, 5607.
7 F. Ikegami and I. Murakoshi, *Phytochemistry*, 1994, **35**, 1089.
8 G. C. Lancini, A. Diena and E. Lazzari, *Tetrahedron Lett.*, 1966, 1769.
9 U. Schmidt, J. Häusler, E. Öhler and H. Poisel, *Fortschr. Chem. Org. Naturst.*, 1979, **37**, 251.
10 A. Bernardini, A. E. Hallaoui, R. Jacquier, C. Pigiére, P. Viallefont and J. A. Bajgrowicz, *Tetrahedron Lett.*, 1983, **24**, 3717.
11 J. A. Bajgrowicz, A. E. Hallaoui, R. Jacquier, C. Pigiére and P. Viallefont, *Tetrahedron Lett.*, 1984, **25**, 2759.
12 J. A. Bajgrowicz, A. E. Hallaoui, R. Jacquier, C. Pigiére and P. Viallefont, *Tetrahedron*, 1985, **41**, 1833.
13 I. Photaki, *J. Am. Chem. Soc.*, 1963, **85**, 1123.
14 A. Srinivasan, R. W. Stephenson and R. K. Olsen, *J. Org. Chem.*, 1977, **42**, 2253.
15 L. D. Arnold, R. G. May and J. C. Vederas, *J. Am. Chem. Soc.*, 1988, **110**, 2237.
16 M. J. Crossley, R. C. Reid and A. W. Stamford, unpublished results.
17 J. E. Baldwin, A. C. Spivey, C. J. Schofield and J. B. Sweeney, *Tetrahedron*, 1993, **49**, 6309.
18 T. Wieland, G. Ohnacker and W. Ziegler, *Chem. Ber.*, 1957, **90**, 194.
19 H. Wojciechowska, R. Pawlowicz, R. Andruszkiewicz and J. Grzybowska, *Tetrahedron Lett.*, 1978, 4063.
20 H. Ogura, O. Sato and K. Takeda, *Tetrahedron Lett.*, 1981, **22**, 4817.
21 R. Andruszkiewicz and A. Czerwinski, *Synthesis*, 1982, 968.
22 A. J. Kolar and R. K. Olsen, *Synthesis*, 1977, 457.
23 M. Sokolovsky, T. Sadeh and A. Patchornik, *J. Am. Chem. Soc.*, 1964, **86**, 1212.
24 D. H. Rich, J. P. Tam, P. Mathiaparanam, J. A. Grant and C. Mabuni, *J. Chem. Soc.*, *Chem. Commun.*, 1974, 897.
25 O. Pieroni, G. Montagnoli, A. Fissi, S. Merlino and F. Ciardelli, *J. Am. Chem. Soc.*, 1975, **97**, 6820.
26 H. Poisel and U. Schmidt, *Angew. Chem.*, *Int. Ed. Engl.*, 1976, **15**, 294.
27 A. Srinivasan, R. W. Stephenson and R. K. Olsen, *J. Org. Chem.*, 1977, **42**, 2256.
28 M. J. Crossley and C. W. Tansey, *Aust. J. Chem.*, 1992, **45**, 479.
29 M. J. Crossley and A. W. Stamford, *Aust. J. Chem.*, 1994, **47**, 1695.
30 J. H. Clark, *J. Chem. Soc.*, *Chem. Commun.*, 1978, 789.
31 R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439.
32 O. Von Schickh, H. G. Padeken and A. Segnitz, in *Houben-Weyl*, '*Methoden der Organischen Chemie*', 4th edn., ed. E. Muller, Georg Thieme Verlag, Stuttgart, 1971, vol. X/1, p. 182.
33 T. A. Alston, D. J. T. Porter and H. J. Bright, *Acc. Chem. Res.*, 1983, **16**, 418.
34 J. Zimmermann and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1104.
35 A. L. J. Beckwith and C. L. L. Chai, *J. Chem. Soc.*, *Chem. Commun.*, 1990, 1087.
36 M. J. Crossley, Y. M. Fung, E. Kyriakopoulos and J. J. Potter, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1123.

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