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Synthesis of Side-chain Functionalized Amino Acid Derivatives Through Reaction of Alkyl Nitronates with α-Bromoglycine Derivatives

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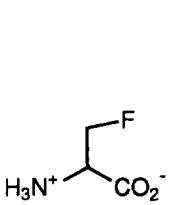
Abstract: Reactions of alkyl nitronates with α-bromoglycine derivatives provide access to a variety of halo-, β-nitro- and α,β-dehydro-α-amino acid derivatives, including β-functionalized α,β-dehydro-amino acid derivatives. The hydrochloride salts of free β-nitro-α-amino acids can also be prepared using this approach.

INTRODUCTION

Interest in the synthesis of halogenated and, in particular, fluorinated amino acid derivatives stems from their activity as enzyme inhibitors and potential as pharmaceutical agents.[1-4] For example, β-fluoroalanine **1** and the dopa analogue **2** have been studied as inhibitors of bacterial alanine racemase[2] and dopa decarboxylase,[3] respectively, while the methotrexate derivative **3** has been investigated for use in anticancer therapy.[4] β-Nitro-[5] and α,β-dehydro-[6] amino acids have also been studied as enzyme inhibitors and used to investigate structure-activity relationships. β-Functionalized α,β-dehydro-amino acid derivatives are of interest in synthesis because they have been shown to undergo addition-elimination reactions, with net substitution of the β-functional group, to give novel dehydro-amino acid derivatives.[7] Several years ago we reported[8] the synthesis of the β-nitro-amino acid derivatives **6a-d** through reaction of *N*-benzoyl-2-bromoglycine methyl ester **4** with the anions of the corresponding nitroalkanes **5a-d** (Scheme 1). We have now applied this procedure to the synthesis of α,β-dehydro-, δ- and ε-halo-β-nitro-, δ- and ε-halo-α,β-dehydro-, δ- and ε-halo-, β-halo-β-nitro-, α,β-dehydro-β-nitro- and α,β-dehydro-β-halo-amino acid derivatives. During the present work we determined that the procedure[8] for the synthesis of the β-nitro-amino acid derivatives **6a-d** was of limited utility in the synthesis of the corresponding free amino acids **7a-d**, however, these compounds have now been obtained using a variation of that method.



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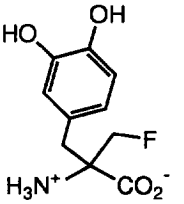

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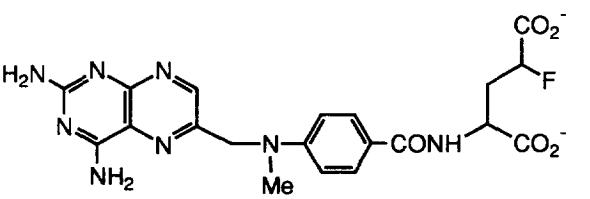
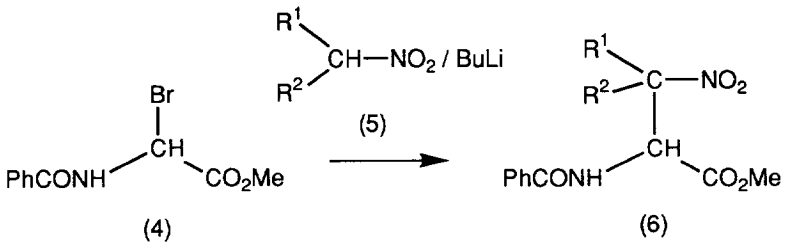


(3)

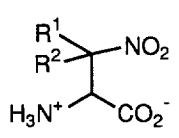
RESULTS AND DISCUSSION

The δ- and ε-halo-β-nitro-amino acid derivatives **6f-h** were prepared as outlined in Scheme 1, by incorporating the halogen into the nitroalkane. 3-Fluoro-1-nitropropane **5f** and 4-fluoro-1-nitrobutane **5g** were synthesized using the method of Pattison and coworkers,[9] by treatment of the corresponding 1-fluoro-ω-iodoalkanes with silver nitrite. 3-Chloro-1-nitropropane **5h** was prepared in a similar manner, by treating the corresponding chloroiodoalkane with silver nitrite. Treatment of the nitronate salt of 3-fluoro-1-nitropropane **5f** with 0.5 mole equivalents of the α-bromoglycine derivative **4**, in tetrahydrofuran/hexamethylphosphoramide (5:1) at -78 °C,[8] afforded the 5-fluoro-3-nitropentanoic acid derivative **6f**, in 64% yield as a 1.5:1 mixture of diastereomers. The diastereomers were separated by chromatography of the mixture on silica and subsequently crystallized from ethyl acetate/light petroleum, in yields of 35% and 23%. Similar treatment of the nitronate salt



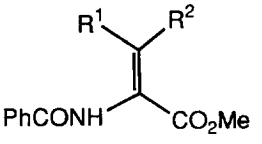
a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = Ph$, $R^2 = H$
d) $R^1 = R^2 = Me$
e) $R^1 = Et$, $R^2 = Me$
f) $R^1 = CH_2CH_2F$, $R^2 = H$
g) $R^1 = CH_2CH_2CH_2F$, $R^2 = H$
h) $R^1 = CH_2CH_2Cl$, $R^2 = H$
i) $R^1 = Cl$, $R^2 = H$
j) $R^1 = Cl$, $R^2 = Me$
k) $R^1 = Br$, $R^2 = Me$

Scheme 1



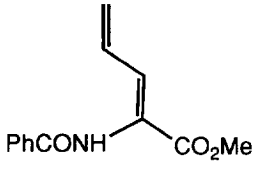
(7)

a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = Ph$, $R^2 = H$
d) $R^1 = R^2 = Me$
e) $R^1 = Et$, $R^2 = Me$



(8)

a) $R^1 = CH_2CH_2F$, $R^2 = H$
b) $R^1 = CH_2CH_2CH_2F$, $R^2 = H$
c) $R^1 = NO_2$, $R^2 = H$
d) $R^1 = NO_2$, $R^2 = Me$
e) $R^1 = Cl$, $R^2 = Me$



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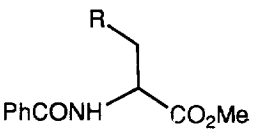


(10)

a) $R = CH_2CH_2F$
b) $R = CH_2CH_2CH_2F$

of 4-fluoro-1-nitrobutane **5g** with the bromide **4** gave methyl 2-benzamido-6-fluoro-3-nitrohexanoate **6g**, as a 5:1 mixture of diastereomers, in 72% yield. The major diastereomer was isolated in 41% yield and the minor diastereomer in 7% yield, after chromatography of the mixture on silica and crystallization from ethyl acetate/light petroleum. Reaction of the nitronate salt of 4-chloro-1-nitropropane **5h** with the α-bromoglycine derivative **4** afforded a 3:1 mixture of the diastereomers of the δ-chloro-β-nitro-amino acid derivative **6h**. The diastereomers were separated by chromatography of the mixture on silica and crystallization from ethyl acetate/light petroleum, and isolated in yields of 49% and 14%.

The δ- and ε-fluoro-β-nitro-amino acid derivatives **6f** and **6g** were efficiently converted to the corresponding α,β-dehydro-amino acid derivatives **8a** and **8b**. Treatment of each of the diastereomers of methyl 2-benzamido-5-fluoro-3-nitropentanoate **6f** with one equivalent of di-*iso*-propylamine, in chloroform at room temperature for 16 h, gave methyl (*Z*)-2-benzamido-5-fluoropent-2-enoate **8a** as a colourless oil, in 80% yield in each case. The stereochemistry of the alkene **8a** was assigned on the basis of the ease of interconversion of *E*- and *Z*-dehydro-amino acid derivatives and the greater stability of the *Z*-isomers.[10] The observation that each diastereomer of the nitro-amino acid derivative **6f** gave the same alkene **8a** may reflect either interconversion of the diastereomers of the starting material **6f**, prior to elimination, or isomerization of the product.[10] When treated with a ten-fold excess of di-*iso*-propylamine, the fluoride **6f** afforded the α,β,γ,δ-didehydro-amino acid derivative **9**, as the sole product. Reaction of the major diastereomer of methyl 2-benzamido-6-fluoro-3-nitrohexanoate **6g** with one equivalent of di-*iso*-propylamine gave the α,β-dehydro-amino acid derivative **8b** in 83% yield. The diene **9** and the monoene **8b** are each assumed to have the *Z*-configuration, by analogy with related compounds.[10]

Hydrogenation of methyl (*Z*)-2-benzamido-5-fluoropent-2-enoate **8a** over 10% palladium on carbon gave methyl 2-benzamido-5-fluoropentanoate **10a**, as a colourless solid, in 98% yield. Similar treatment of methyl (*Z*)-2-benzamido-6-fluorohex-2-enoate **8b** afforded the fluoride **10b**, in 94% yield. It is thus evident that β-nitro-amino acid derivatives can be used in the synthesis of α,β-dehydro-amino acid derivatives and the saturated analogues, with retention of fluorine at either the δ- or ε-position. Through asymmetric hydrogenation of α,β-dehydro-amino acid derivatives in the presence of chiral catalysts,[11] this approach should be suitable for the synthesis of the individual enantiomers of the corresponding amino acid derivatives.

In order to prepare β-functionalized α,β-dehydro-amino acid derivatives, reactions of α-halonitroalkanes were investigated. Chloronitromethane **5i** was prepared from nitromethane **5a** and *tert*-butyl hypochlorite, in the presence of styrene, as described by Heasley and coworkers.[12] α-Chloronitroethane **5j** was prepared using the method outlined by Levering,[13] which involved the chlorination of nitroethane **5b**. In a similar manner, α-bromonitroethane **5k** was prepared from nitroethane **5b**. Reaction of the bromoglycine derivative **4** with the nitronate salt of chloronitromethane **5i** gave *N*-benzoyl-β-nitro-α,β-dehydroalanine methyl ester **8c**, as a yellow solid in 42% yield. The structure of the amino acid derivative **8c** was determined using X-ray crystallographic analysis (Figure 1).[14] Similar treatment of the nitronate salt of 1-chloronitroethane **5j** with the bromide **4** gave a 1.4:1 mixture of the diastereomers of the β-chloro-β-nitro-amino acid derivative **6j**, in 48% yield. The β-nitro-α,β-dehydro-amino acid derivative **8d** was also isolated, in 9% yield, and its structure was determined using X-ray crystallographic analysis (Figure 2).[14] The diastereomers of the β-chloro-β-nitro-amino acid derivative **6j** were separated by chromatography on silica. Treatment of the major diastereomer with di-*iso*-propylamine gave a 2:1 mixture of the β-nitro-α,β-dehydro-amino acid derivative **8d** and the β-chloro-α,β-dehydro-amino acid derivative **8e**. The products **8d** and **8e** were separated by

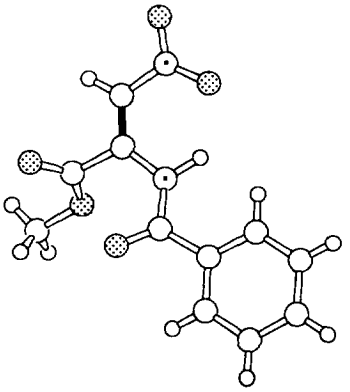


Figure 1. Molecular structure of **8c**.

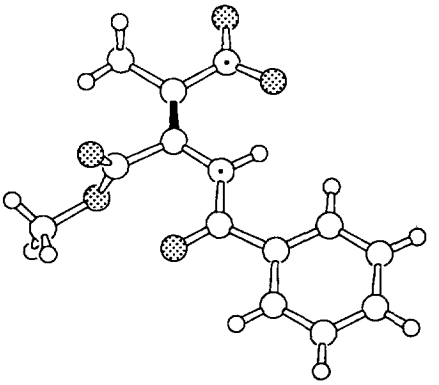


Figure 2. Molecular structure of **8d**.

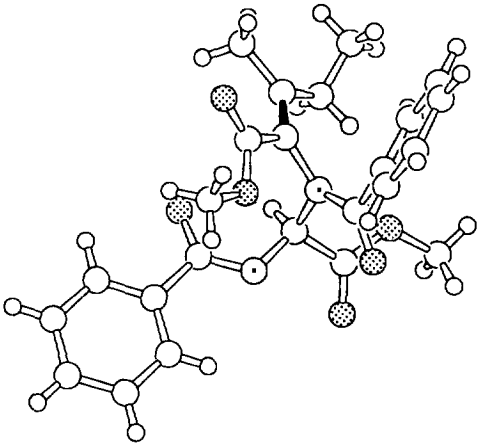


Figure 3. Molecular structure of **11**.

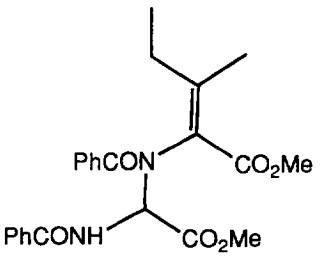
chromatography of the mixture on silica and isolated in yields of 39% and 17%, respectively. Reaction of the minor diastereomer of the β-chloro-β-nitro-amino acid derivative **6j** with di-*iso*-propylamine gave a 1:2 mixture of the nitro-amino acid derivative **8d** and the chloride **8e**. The Z-stereochemistry of the chloride **8e** is assumed by analogy with that of the nitroalkene **8d**.

When α-bromonitroethane **5k** was treated with butyllithium (1 equivalent) and subsequently with 0.5 mole equivalents of the α-bromoglycine derivative **4**, reaction gave a 2:1 mixture of the diastereomers of methyl 2-benzamido-3-nitrobutanoate **6b**.[8] This outcome can be attributed to *trans*-metallation of α-bromonitroethane **5k** having afforded the lithium salt of nitroethane **5b**, which reacted with the α-bromoglycine derivative **4**. Based on an estimation of the relative pK_a values of nitroethane **5b** and α-bromonitroethane **5k**, it was anticipated that the anion of nitroethane **5b** would react with an excess of α-bromonitroethane **5k** to produce the nitronate salt of the latter. Accordingly, reaction of a ten-fold excess of α-bromonitroethane **5k** with

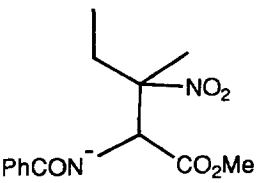
butyllithium, followed by reaction with the α-bromoglycine derivative **4**, afforded t ıe β-bromo-β-nitro-amino acid derivative **6k**, as a single diastereomer in 58% yield. The β-nitro-α,β-dehydr(-amino acid derivative **8d** was also isolated, in 6% yield, while the nitrobutanoate **6b** was obtained as a 1:1 m xture of diastereomers, in 13% yield. Treatment of the bromide **6k** with di-*iso*-propylamine gave the β-nitr(-α,β-dehydro-amino acid derivative **8d** in 81% yield.

In order to exploit reactions of bromoglycine derivatives with alkyl nitronate in the synthesis of free β-nitro-amino acids, we examined the deprotection of the amino acid derivatives **6a e**. The nitroalkanes **6a-d** were prepared as reported previously.[8] In an analogous manner, 2-nitrobutane **5e**, p epared by oxidation of 2-aminobutane with *m*-chloroperbenzoic acid,[15] was treated with butyllithium (1 eq ivalent) and subsequently with 0.5 mole equivalents of the α-bromoglycine derivative **4**, to give *N*-benzoyl-3-n troisoleucine methyl ester **6e**, in 70% yield as a 1:1.25 mixture of diastereomers. Small samples of each o the diastereomers of the isoleucine derivative **6e** were obtained by normal phase preparative HPLC of the mi ture. A by-product of the reaction of the nitronate salt of 2-nitrobutane **5e** with the bromide **4** was the α,β-deh ydro-isoleucine derivative **11**, the structure of which was determined using X-ray crystallographic analysis (igure 3).[14] Based on the mechanism proposed for reactions of alkyl nitronates with the bromide **4**,[8] formatio ı of the by-product **11** can be attributed to addition of the amide anion **12** to the imine **13**, followed by eliminati n.

Treatment of *N*-benzoyl-3-nitrovaline methyl ester **6d** with 6N HCl a reflux for 1 h gave the hydrochloride salt of β-nitrovaline **7d**, in 84% yield, which was converted to the cor sponding free amino acid **7d** by precipitation from a solution of ethanol and aniline (10:1 v/v).[16] The amino a(id **7d** was found to be less stable than the corresponding hydrochloride salt, consequently the β-nitro-amin o acids **7a-e** prepared as



(11)



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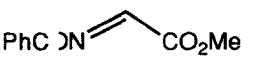

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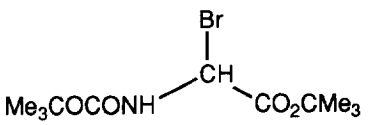
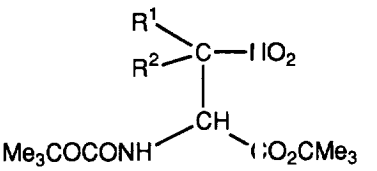


(14)



(15)

a) $R^1 = R^2 =$ 1
b) R^1 = Me, R^2 = H
c) R^1 = Ph, R^2 = H

described herein were stored and characterized as their hydrochloride salts. Each of the diastereomers of *N*-benzoyl-3-nitroisoleucine methyl ester **6e** reacted with 6N HCl to give the corresponding diastereomer of the hydrochloride salt of β-nitroisoleucine **7e**. There was no evidence of interconversion between the diastereomers of either the starting material **6e** or the product **7e** under the reaction conditions.

The amino acid derivatives **6d** and **6e** were the only ones amenable to deprotection with 6N HCl, however, similar treatment of the analogues **6a-c** giving only decomposition products. The different outcomes may be attributed to the fact that the amino acid derivatives **6a-c** are primary or secondary nitroalkanes, which are known to be susceptible to acid catalysed decomposition.[17] By contrast, tertiary nitroalkanes are not acid labile, explaining why the nitroalkanes **6d** and **6e** hydrolysed without decomposition. In order to obtain the hydrochloride salts of the β-nitro amino acids **7a-c** it was therefore necessary to use amino acid derivatives susceptible to deprotection under less vigorous conditions. Steglich and coworkers[18] reported that the carbamate **14** is suitable for the synthesis of free amino acids. After introduction of the side chain, both the protecting groups are easily removed by treatment with trifluoroacetic acid in chloroform. Consequently, the bromide **14** was prepared[18,19] and used in reactions with alkyl nitronates. Reaction of the bromide **14** with the salt of nitromethane **5a** gave the β-nitroalanine derivative **15a**, in 63% yield. The corresponding reaction using nitroethane **5b** gave a 2:1 mixture of the diastereomers of the β-nitro-α-amino acid derivative **15b**. The diastereomers were separated by chromatography of the mixture on silica. The major diastereomer crystallized from light petroleum as a colourless solid in 34% yield, while the minor diastereomer was isolated as an oil in 17% yield. Reaction of the bromide **14** with the salt of α-nitrotoluene **5c** gave the β-nitrophenylalanine derivative **15c** in 71% yield, as a 1:1 mixture of diastereomers. The diastereomers crystallized from dichloromethane/light petroleum with different shapes, one as spars and the other as clusters, thus enabling partial separation of the diastereomers by mechanical means.

The amino acid derivatives **15a-c** were used to prepare the hydrochloride salts of the corresponding free amino acids **7a-c**. Accordingly, treatment of the β-nitroalanine derivative **15a** with a solution of trifluoroacetic acid in chloroform, at reflux for 0.25 h, followed by treatment with HCl during work-up, gave the salt of β-nitroalanine **7a**, in 63% yield. Each of the diastereomers of the nitrobutanoate derivative **15b** was treated with trifluoroacetic acid, then HCl, to give the corresponding diastereomer of the hydrochloride salt of the amino acid **7b**. Similar reaction of a 1:1 mixture of the diastereomers of the β-nitrophenylalanine derivative **15c** afforded a 1:1 mixture of the diastereomers of the hydrochloride salt of β-nitrophenylalanine **7c**.

It is evident from the synthesis of the β-nitro-amino acid derivatives **7a-e** described above that reaction of alkyl nitronates with α-bromoglycine derivatives is a viable method for the synthesis of the corresponding free amino acids. The reported[5] method for the synthesis of β-nitroalanine **7a** is unsuitable for the preparation of secondary and tertiary nitroalkane analogues. Access to these compounds should provide the opportunity to probe novel aspects of enzyme inhibition, particularly with the tertiary derivatives because they are neither able to form the corresponding alkyl nitronates nor particulary susceptible to elimination, whereas those reaction modes are associated with enzyme inhibition by the alanine derivative **7a**.[5]

EXPERIMENTAL

General. ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on either a Bruker ACP-300 or a Bruker CXP-300 spectrometer, in $CDCl_3$ for protected amino acid

derivatives or D_2O for the free amino acids. With the ^1H and ^{13}C NMR spectra, tetramethylsilane and *tert*-butanol were used as internal standards for the spectra recorded in $CDCl_3$ and D_2O, respectively. Trifluoroacetic acid was used as the internal standard for the ^{19}F NMR spectra. Infrared spectra were recorded on a Jasco IRA-1 spectrometer, as nujol mulls for solids and thin films for oils. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Microanalyses were performed by the Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada.

N-Benzoyl-2-bromoglycine methyl ester **4**,[8] 2-nitrobutane **5e**,[15] 3-fluoro-1-nitropropane **5f**,[9] 4-fluoro-1-nitrobutane **5g**,[9] 3-chloro-1-nitropropane **5h**,[9] chloronitromethane **5i**,[12] 1-chloro-1-nitroethane **5j**,[13] 1-bromo-1-nitroethane **5k**,[13] the β-nitro-amino acid derivatives **6a-d**[8] and 2-bromo-*N*-*tert*-butoxycarbonylglycine *tert*-butyl ester **14**[18] were prepared using literature procedures, and they had physical and spectral properties consistent with those reported previously.

Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM) and HPLC on a Waters μ-Porasil Radial-Pak Cartridge (10 cm x 8 mm), each using ethyl acetate and light petroleum (bp 66-68 °C) as eluants.

General Procedure for Reactions of the α-Bromoglycine Derivative 4 with the Anions of the Nitroalkanes 5e-k. A solution of butyllithium (2.5 M in hexane, 0.42 ml, 1.05 mmol) was added dropwise to a solution of the nitroalkane **5e-k** (1.04 mmol) in tetrahydrofuran (5 ml) and hexamethylphosphoramide (1 ml) maintained at -78 °C. A solution of *N*-benzoyl-2-bromoglycine methyl ester **4** (0.52 mmol) in tetrahydrofuran (2 ml) was then added at -78 °C and, after 4 h at that temperature, acetic acid (3 ml) was added. The reaction mixture was allowed to warm slowly to room temperature and was then concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (25 ml) and the organic solution was washed with water (3 x 10 ml), then concentrated under reduced pressure to give the crude product.

Methyl 2-Benzamido-3-methyl-3-nitropentanoate 6e and Methyl (*Z*)-3-Aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate 11: Reaction of the bromide **4** with the anion of 2-nitrobutane **5e** gave a crude product which was chromatographed to give methyl 2-benzamido-3-methyl-3-nitropentanoate **6e** as a 1.25:1 mixture of diastereomers in 70% yield. A sample of each of the diastereomers was obtained by HPLC of the mixture. The minor diastereomer had: ^1H NMR δ 1.01 (3H, t, *J* = 7.5 Hz), 1.60 (3H, s), 2.07 (1H, qd, *J* = 7.5 and 15 Hz), 2.42 (1H, qd, *J* = 7.5 and 15 Hz), 3.80 (3H, s), 5.51 (1H, d, *J* = 9 Hz), 6.90 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 8.3, 19.2, 30.2, 53.2, 56.8, 93.5, 127.2, 128.8, 132.4, 133.1, 167.5, 168.9; υ_{max} 3443, 1746, 1671, 1549 cm^{-1}; MS (ei) *m/e* 294 (M^+), 247, 234, 215, 105; MS (ei) *m/e* 294.122 (M^+). Calc. for $C_{14}H_{18}N_2O_5$: *m/e* 294.122. The major diastereomer had: ^1H NMR δ 0.95 (3H, t, *J* = 7.5 Hz), 1.80 (3H, s), 1.93 (1H, qd, *J* = 7.5 and 15 Hz), 2.20 (1H, qd, *J* = 7.5 and 15 Hz), 3.77 (3H, s), 5.31 (1H, d, *J* = 10 Hz), 7.24 (1H, br d, *J* = 10 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 7.9, 20.1, 30.8, 53.1, 57.2, 92.2, 127.2, 128.8, 132.3, 133.0, 167.2, 168.8; υ_{max} 3445, 1744, 1673, 1549 cm^{-1}; MS (ei) *m/e* 294 (M^+), 248, 234, 105; MS (ei) *m/e* 294.122 (M^+). Calc. for $C_{14}H_{18}N_2O_5$: *m/e* 294.122. Continued chromatography of the crude reaction product also afforded a 1.5:1 mixture of methyl (*Z*)-3-aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate **11** and the

corresponding *E*-isomer, in 7% yield, from which a small sample of the *Z*-isomer **11** was obtained by crystallization of the mixture from ethyl acetate/light petroleum. The *Z*-isomer **11** had: mp 134-135 °C; ^{1}H NMR δ 1.19 (3H, t, *J* = 7.5), 2.12 (3H, s), 2.69 (1H, qd, *J* = 7.5 and 13.5 Hz), 2.97 (1H, qd, *J* = 7.5 and 13.5 Hz), 3.32 (3H, s), 3.87 (3H, s), 5.97 (1H, d, *J* = 9.5 Hz), 7.55 (11H, m); υ_{max} 3332, 1760, 1740, 1650, 1630, 1526 cm^{-1}; MS (ei) *m/e* 439 (M+H$^+$), 379, 247, 215, 142, 105; MS (ei) *m/e* 439.188 (M+H$^+$). Calc. for $C_{24}H_{27}N_2O_6$: *m/e* 439.187. The stereochemistry of the *Z*-isomer **11** was confirmed through X-ray crystallographic analysis (Figure 3).[14] The ^{1}H NMR spectrum of the mixture of methyl (*Z*)-3-aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate **11** and the corresponding *E*-isomer showed peaks for the *E*-isomer at δ 1.03 (3H, t, *J* = 7.5 Hz), 2.30 (3H, s), 2.36 (1H, qd, *J* = 7.5 and 12.5 Hz), 2.72 (1H, qd, *J* = 7.5 and 12.5 Hz), 3.30 (3H, s), 3.86 (3H, s), 5.99 (1H, d, *J* = 9.5 Hz), 7.55 (11H, m).

Methyl 2-Benzamido-5-fluoro-3-nitropentanoate 6f: Reaction of the bromide **4** with the anion of 3-fluoro-1-nitropropane gave the title compound **6f** in 64% yield as a 1.5:1 mixture of diastereomers. The diastereomers were separated by chromatography. The minor diastereomer eluted first and crystallized from ethyl acetate/light petroleum: 23%; mp 99-101 °C; ^{1}H NMR δ 2.32 (1H, m), 2.55 (1H, m), 3.84 (3H, s), 4.66 (2H, m, J_F = 46 Hz), 5.44 (2H, m), 7.07 (1H, br d, *J* = 9 Hz), 7.4-7.8 (5H, m); ^{13}C NMR δ 31.9 (d, *J* = 20 Hz), 53.3, 54.3, 80.2 (d, *J* = 167 Hz), 84.5 (d, *J* = 3 Hz), 127.9, 129.4, 133.2, 168.7, 169.4; ^{19}F NMR δ -147.6; υ_{max} 3345, 1754, 1670, 1550 cm^{-1}; MS (ei) *m/e* 298 (M$^+$), 251, 238, 191, 105; MS (ei) *m/e* 298.098 (M$^+$). Calc. for $C_{13}H_{15}FN_2O_5$: *m/e* 298.097. Continued elution gave the major diastereomer which crystallized from ethyl acetate/light petroleum: 35%; mp 112-114 °C; ^{1}H NMR δ 2.58 (2H, m), 3.85 (3H, s), 4.60 (2H, m, J_F = 47 Hz), 5.19 (1H, dt, *J* = 4.5 and 9 Hz), 5.28 (1H, dd, *J* = 4.5 and 7.5 Hz), 7.25 (1H, br d, *J* = 7.5 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 32.0 (d, *J* = 20 Hz), 54.1, 54.9, 80.6 (d, *J* = 168 Hz), 85.4 (d, *J* = 3 Hz), 127.9, 129.3, 133.1, 133.2, 168.0, 169.0; ^{19}F NMR δ -146.5; υ_{max} 3450, 1746, 1658, 1564 cm^{-1}; MS (ei) *m/e* 298 (M$^+$), 251, 238, 191, 105; MS (ei) *m/e* 298.097 (M$^+$). Calc. for $C_{13}H_{15}FN_2O_5$: *m/e* 298.097.

Methyl 2-Benzamido-6-fluoro-3-nitrohexanoate 6g: Reaction of the bromide **4** with the anion of 4-fluoro-1-nitrobutane gave the title compound **6g** as a 5:1 mixture of diastereomers in 72% yield. The diastereomers were partially separated by chromatography, and further purified by fractional crystallization from ethyl acetate/light petroleum. The minor diastereomer was the first to elute from the silica: 7%; mp 119-121 °C; ^{1}H NMR δ 1.88 (2H, m), 2.33 (2H, m), 3.83 (3H, s), 4.52 (2H, m, J_F = 47 Hz), 5.26 (1H, dt, *J* = 3 and 7.5 Hz), 5.43 (1H, dd, *J* = 3 and 9.5 Hz), 7.03 (1H, br d, 9.5 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 26.8 (d, *J* = 21 Hz), 26.9 (d, *J* = 4 Hz), 52.6, 53.5, 82.8 (d, *J* = 167 Hz), 87.2, 127.2, 128.8, 132.4, 132.8, 167.9, 169.0; ^{19}F NMR δ -145.0; υ_{max} 3450, 1753, 1670, 1542 cm^{-1}; MS (ei) *m/e* 313 (M+H$^+$), 266, 253, 205, 160, 121, 105, 77; MS (ei) *m/e* 313.119 (M+H$^+$). Calc. for $C_{14}H_{18}FN_2O_5$: *m/e* 313.120. The major diastereomer was the second to elute from the silica: 41%; mp 120-121 °C; ^{1}H NMR δ 1.88 (2H, m), 2.22 (1H, m), 2.43 (1H, m), 3.89 (3H, s), 4.52 (2H, m, J_F = 47 Hz), 5.04 (1H, dt, *J* = 4.5 and 9 Hz), 5.17 (1H, dd, *J* = 4.5 and 7 Hz), 7.08 (1H, br d, 7 Hz), 7.4-7.8 (5H, m); ^{13}C NMR δ 26.8 (d, *J* = 5 Hz), 27.2 (d, *J* = 20 Hz), 53.5, 54.2, 82.6 (d, *J* = 166 Hz), 88.4, 127.2, 128.8, 132.5, 132.7, 167.2, 168.4; ^{19}F NMR δ -145.6; υ_{max} 3375, 1748, 1652, 1565 cm^{-1}; MS (ei) *m/e* 313 (M+H$^+$), 266, 253, 205, 160, 121, 105, 77; MS (ei) *m/e* 313.120 (M+H$^+$). Calc. for $C_{14}H_{18}FN_2O_5$: *m/e* 313.120.

Methyl 2-Benzamido-5-chloro-3-nitropentanoate 6h: Reaction of the bromide **4** with the anion of 3-chloro-1-nitropropane gave the title compound **6h** as a 3:1 mixture of diastereomers, in 73% yield. The diastereomers were separated by chromatography. The major diastereomer eluted first and crystallized from ethyl acetate/light petroleum: 49%; mp 109-111 °C; ^{1}H NMR δ 2.46 (1H, m), 2.85 (1H, m), 3.63 (1H, ddd, *J* = 5, 9 and 12 Hz), 3.76 (1H, td, *J* = 6 and 12 Hz), 3.89 (3H, s), 5.23 (2H, m), 7.06 (1H, br d, *J* = 6.5 Hz), 7.5-7.9 (5H, m); ^{13}C NMR δ 33.3, 40.4, 53.6, 54.2, 85.5, 127.2, 128.8, 132.5, 132.6, 167.2, 168.3; υ_{max} 3300, 1760, 1650, 1560, 1540 cm^{-1}; MS (ei) *m/e* 316 and 314 (M^+), 270, 268, 256, 254, 207, 105; MS (ei) *m/e* 314.066 (M^+). Calc. for $C_{13}H_{15}{}^{35}ClN_2O_5$: *m/e* 314.067. The minor diastereomer was the second to elute and crystallized from ethyl acetate/light petroleum: 14%; mp 102-107 °C; ^{1}H NMR δ 2.37 (1H, dtd, *J* = 5, 7 and 15 Hz), 2.63 (1H, dtd, *J* = 5, 7 and 15 Hz), 3.72 (1H, ddd, *J* = 5, 7 and 12 Hz), 3.84 (1H, ddd, *J* = 5, 7 and 12 Hz), 3.86 (3H, s), 5.40 (1H, dd, *J* = 3 and 9 Hz), 5.54 (1H, dt, *J* = 3 and 7 Hz), 7.00 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 32.8, 40.3, 52.4, 53.6, 84.6, 127.3, 128.9, 132.5, 132.6, 168.0, 168.7; υ_{max} 3295, 1765, 1650, 1560, 1535 cm^{-1}; MS (ei) *m/e* 316 and 314 (M^+), 270, 268, 256, 254, 207, 105; MS (ei) *m/e* 314.066 (M^+). Calc. for $C_{13}H_{15}{}^{35}ClN_2O_5$: *m/e* 314.067.

Methyl (*Z*)-2-Benzamido-3-nitroprop-2-enoate 8c: Reaction of the bromide **4** with the anion of chloronitromethane **5i** gave the title compound **8c**: 42%; mp 93-95 °C; ^{1}H NMR δ 3.96 (3H, s), 6.91 (1H, s), 7.4-7.9 (5H, m), 11.17 (1H, br s); MS (ei) *m/e* 205 ($[M+H-NO_2]^+$), 163, 105; MS (ei) *m/e* 205.075 ($[M+H-NO_2]^+$). Calc. for $C_{11}H_{11}NO_3$: *m/e* 205.074. The structure of the dehydro-amino acid derivative **8c** was confirmed through X-ray crystallographic analysis (Figure 1).[14]

Methyl 2-Benzamido-3-chloro-3-nitrobutanoate 6j and Methyl (*Z*)-2-Benzamido-3-nitrobut-2-enoate 8d: Reaction of the bromide **4** with the anion of 1-chloro-1-nitroethane **5j** gave a crude product which was chromatographed to give methyl 2-benzamido-3-chloro-3-nitrobutanoate **6j** as a 1.4:1 mixture of diastereomers in 48% yield. The diastereomers were separated by further chromatography. The major diastereomer was isolated in 28% yield and had: ^{1}H NMR δ 2.21 (3H, s), 3.80 (3H, s), 6.10 (1H, d, *J* = 9 Hz, 1H), 7.11 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); υ_{max} 3268, 1746, 1654, 1578, 1522 cm^{-1}; MS (ei) *m/e* 302 and 300 (M^+), 269, 267, 256, 254, 243, 241, 219, 192, 105; MS (ei) *m/e* 300.052 (M^+). Calc. for $C_{12}H_{13}{}^{35}ClN_2O_5$: *m/e* 300.051. The minor diastereomer was isolated in 14% yield and had: ^{1}H NMR δ 2.28 (3H, s), 3.83 (3H, s), 5.87 (1H, d, *J* = 9.5 Hz, 1H), 7.15 (1H, br d, *J* = 9.5 Hz), 7.4-7.9 (5H, m); υ_{max} 3274, 1742, 1656, 1578, 1530 cm^{-1}; MS (ei) *m/e* 302 and 300 (M^+), 269, 267, 256, 254, 243, 241, 219, 192, 105; MS (ei) *m/e* 300.051 (M^+). Calc. for $C_{12}H_{13}{}^{35}ClN_2O_5$: *m/e* 300.051. Continued chromatography of the crude reaction product also afforded methyl (*Z*)-2-benzamido-3-nitrobut-2-enoate **8d** as a yellow solid in 9% yield: mp 91-92 °C; ^{1}H NMR δ 2.07 (3H, s), 4.04 (3H, s), 7.4-8.0 (5H, m), 11.86 (1H, br s); υ_{max} 3500, 1750, 1700, 1624, 1520 cm^{-1}; MS (ei) *m/e* 264 (M^+), 233, 218, 105; MS (ei) *m/e* 264.075 (M^+). Calc. for $C_{12}H_{12}N_2O_5$: *m/e* 264.075. Anal. Calc. for $C_{12}H_{12}N_2O_5$: C, 54.5; H, 4.6; N, 10.6. Found: C, 54.3; H, 4.8; N, 10.6. The structure of the alkene **8d** was confirmed through X-ray crystallographic analysis (Figure 2).[14]

Methyl 2-Benzamido-3-bromo-3-nitrobutanoate 6k: Reaction of the bromide **4** with the anion of 1-bromo-1-nitroethane **5k**, generated by treating 1-bromo-1-nitroethane with 0.1 mole equivalents of butyllithium, gave a crude product mixture which was chromatographed to give the title compound **6k** as a

single diastereomer: 58%; mp 97-98 °C; ^{1}H NMR δ 2.45 (3H, s), 3.86 (3H, s), 5.88 (1H, d, J = 9.5 Hz), 7.04 (1H, br d, J = 9.5 Hz), 7.4-8.0 (5H, m); υ_{max} 3272, 1740, 1648, 1562 cm^{-1}; MS (ei) *m/e* 346 and 344 (M$^+$), 300, 298, 286, 284, 192, 105, 77; MS (ei) *m/e* 345.999 (M$^+$). Calc. for $C_{12}H_{13}{}^{81}BrN_2O_5$: *m/e* 345.999. Continued chromatography of the crude reaction product also afforded methyl (*Z*)-2-benzamido-3-nitrobut-2-enoate **8d** in 6% yield, identical in all respects to the sample obtained as described above, and a 1:1 mixture of the diastereomers of methyl 2-benzamido-3-nitrobutanoate **6b** in 13% yield, identical in all respects to the sample obtained previously.[8]

Methyl (*Z*)-2-Benzamido-5-fluoropent-2-enoate 8a. Di-*iso*-propylamine (6.8 mg, 0.07 mmol) was added to solution of the major diastereomer of methyl 2-benzamido-5-fluoro-3-nitropentanoate **6f** (20 mg, 0.07mmol) in chloroform (1 ml), and the mixture was stirred at room temperature for 18 h, then it was diluted with chloroform (5 ml), washed with water (2 x 3 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue afforded the title compound **8a** as an oil in 80% yield: ^{1}H NMR δ 2.66 (2H, tdd, J = 6, 7 and 28 Hz), 3.83 (3H, s), 4.62 (2H, td, J = 6 and 47 Hz), 6.83 (1H, t, J = 7 Hz), 7.4-7.6 (3H, m), 7.75 (1H, br s), 7.8-7.9 (2H, m); υ_{max} 3700, 3680, 1720, 1600, 1580, 1490 cm^{-1}; MS (ei) *m/e* 251 (M$^+$), 105, 77; MS (ei) *m/e* 251.097 (M$^+$). Calc. for $C_{13}H_{14}NO_3$: *m/e* 251.096. Treatment of the minor diastereomer of the pentanoate **6f** with di-*iso*-propylamine under analogous conditions also gave the alkene **8a** in 80% yield.

Methyl (*Z*)-2-Benzamido-6-fluorohex-2-enoate 8b. Treatment of the major diastereomer of the hexanoate **6g** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave the title compound **8b** in 83% yield: mp 89-90 °C; ^{1}H NMR δ 1.92 (2H, pd, J = 7.5 and 26 Hz), 2.40 (2H, q, J = 7.5 Hz), 3.82 (3H, s), 4.50 (2H, td, J = 7.5 and 47 Hz), 6.78 (1H, t, J = 7.5 Hz), 7.4-7.6 (3H, m), 7.75 (1H, br s), 7.8-7.9 (2H, m); ^{13}C NMR δ 24.7 (d, J = 5 Hz), 28.7 (d, J = 20 Hz), 52.4, 83.2 (d, J = 165 Hz), 125.9, 127.3, 128.5, 132.0, 133.5, 136.6, 164.9, 165.7; ^{19}F NMR δ -145.6; υ_{max} 3680, 3600, 1730, 1610, 1585, 1490 cm^{-1}; MS (ei) *m/e* 266 (M+H$^+$), 206, 160, 105, 77; MS (ei) *m/e* 266.120 (M+H$^+$). Calc. for $C_{14}H_{17}FNO_3$: *m/e* 266.119.

Reaction of Methyl 2-Benzamido-3-bromo-3-nitrobutanoate 6k with Di-*iso*-propylamine. Treatment of the butanoate **6k** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave the alkene **8d** in 81% yield, identical in all respects to the sample obtained as described above.

Reaction of Methyl 2-Benzamido-3-chloro-3-nitrobutanoate 6j with Di-*iso*-propylamine. Treatment of the major diastereomer of the butanoate **6j** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave a 2:1 mixture of the alkene **8d** and methyl (*Z*)-2-benzamido-3-chlorobut-2-enoate **8e**. Chromatography of the mixture afforded **8d** in 39% yield, identical in all respects to the sample obtained as described above, and the chloride **8e** in 17% yield: mp 130-132 °C; ^{1}H NMR δ 2.45 (3H, s), 3.85 (3H, s), 7.4-7.6 (3H, m), 7.66 (1H, br s), 7.8-8.0 (2H, m); υ_{max} 3650, 1745, 1620, 1578, 1480 cm^{-1}; MS (ei) *m/e* 255 and 253 (M$^+$), 224, 222, 218, 186, 105; MS (ei) *m/e* 253.051 (M$^+$). Calc. for $C_{12}H_{12}{}^{35}ClNO_3$: *m/e* 253.051. The analogous reaction of the minor diastereomer of

the butanoate **6j** gave a 63% yield of a 1:2 mixture of the alkenes **8d** and **8e**, from which the components were separated by chromatography in yields of 17% and 33%, respectively.

Methyl (Z)-2-Benzamidopenta-2,4-dienoate 9. A mixture of the major diastereomer of methyl (Z)-2-benzamido-5-fluoro-3-nitropentanoate **6f** (40 mg, 0.13 mmol), di-*iso*-propylamine (1 ml) and chloroform (2 ml) was stirred at room temperature for 18 h, then it was diluted with chloroform (10 ml), washed with water (3 x 10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue afforded the title compound **9** (26 mg, 87%) as a colourless oil: ^{1}H NMR δ 3.82 (3H, s), 5.43 (1H, d, *J* = 10.5 Hz), 5.57 (1H, d, *J* = 16.5 Hz), 6.49 (1H, ddd, *J* = 10.5, 11.5 and 16.5 Hz), 7.06 (1H, d, *J* = 11.5 Hz), 7.4-7.6 (3H, m), 7.85 (1H, br s), 7.8-7.9 (2H, m); υ_{max} 3400, 1760, 1730, 1690, 1520, 1500 cm^{-1}; MS (ei) *m/e* 231 (M^+), 105, 77; MS (ei) *m/e* 231.090 (M^+). Calc. for $C_{13}H_{13}NO_3$: *m/e* 231.090.

Methyl 2-Benzamido-5-fluoropentanoate 10a. A mixture of the alkene **8a** (9.3 mg, 0.04 mmol), 10% palladium on activated carbon (7 mg) and ethyl acetate (5 ml) was stirred under hydrogen (25 psi) for 3 h, then it was filtered through celite and the filtrate was concentrated under reduced pressure. Chromatography of the residual oil gave the title compound **10a** (9.2 mg, 98%): mp 53-56 °C, ^{1}H NMR δ 1.83 (2H, m), 2.04 (2H, m), 3.81 (3H, s), 4.49 (2H, td, *J* = 5.5 and 47 Hz), 4.88 (1H, dt, *J* = 5 and 7.5 Hz), 6.77 (1H, br d, *J* = 7.5H), 7.4-7.6 (3H, m), 7.8-7.9 (2H, m); ^{13}C NMR δ 26.4 (d, *J* = 23 Hz), 28.8 (d, *J* = 5 Hz), 52.0, 52.6, 83.2 (d, *J* = 166 Hz), 127.0, 128.6, 131.9, 133.7, 167.1, 172.8; ^{19}F NMR δ -144.4; υ_{max} 3444, 1739, 1666, 1580, 1516 cm^{-1}; MS (ei) *m/e* 254 ($M+H^+$), 253, 194, 105, 77; MS (ei) *m/e* 253.112 (M^+). Calc. for $C_{13}H_{16}FNO_3$: *m/e* 253.111.

Methyl 2-Benzamido-6-fluorohexanoate 10b. Hydrogenation of the alkene **8b** as described above for the preparation of the pentanoate **10a** gave the title compound **10b** in 94% yield, as colourless needles from dichloromethane/light petroleum: mp 73-74 °C; ^{1}H NMR δ 1.7 (6H, m), 3.71 (3H, s), 4.36 (2H, td, *J* = 6 and 47 Hz), 4.77 (1H, dt, *J* = 5.5 and 7.5 Hz), 6.75 (1H, br d, *J* = 7.5 Hz), 7.3-7.5 (3H, m), 7.7-7.8 (2H, m); ^{19}F NMR δ -144.0; υ_{max} 3300, 1746, 1632, 1578, 1532 cm^{-1}; MS (ei) *m/e* 267 (M^+), 208, 193, 161, 105, 77; MS (ei) *m/e* 267.127 (M^+). Calc. for $C_{14}H_{18}FNO_3$: *m/e* 267.127. Anal. Calc. for $C_{14}H_{18}FNO_3$: C, 62.9; H, 6.8; N, 5.2. Found: C, 62.9; H, 6.9; N, 5.2.

3-Nitrovaline 7d. A suspension of the nitrovaline derivative **6d** (0.30 g, 1.0 mmol) in 6N HCl (30 ml) was heated at reflux for 2 h, then it was cooled and concentrated under reduced pressure. The residue dissolved in water and that aqueous solution was washed with ethyl acetate, then concentrated under reduced pressure to give the hydrochloride salt of the title compound **7d** (0.14 g, 70%): mp 143-145 °C; ^{1}H NMR δ 1.79 (3H, s), 1.86 (3H, s), 4.71 (1H, s); ^{13}C NMR δ 25.2, 25.6, 60.4, 89.2, 170.1; υ_{max} 1666, 1601, 1552, 1508 cm^{-1}; MS (fab) *m/e* 163 ($M-Cl^+$), 116, 72, 70.

A solution of the hydrochloride salt of 3-nitrovaline **7d** (0.30 g, 1.5 mmol) in ethanol (30 ml) and aniline (3 ml) was allowed to stand at room temperature for 18 h. The precipitate that formed was collected by filtration and washed with ethanol to give the title compound **7d** (0.11 g, 46%): mp 145-147 °C; ^{1}H NMR δ 1.74 (3H, s), 1.79 (3H, s), 4.34 (1H, s); ^{13}C NMR δ 24.9, 25.9, 62.1, 89.6, 171.6; MS (fab) *m/e* 163 ($M+H^+$), 116, 72, 70.

3-Nitro-*iso*-leucine 7e Hydrochloride Salt. Treatment of the major diastereomer of the *iso*-leucine derivative **6e** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitrovaline **7d** gave the title compound in 70% yield as a single diastereomer: mp 132-133 °C (dec.); ^{1}H NMR δ 0.94 (3H, t, *J* = 7 Hz), 1.75 (3H, s), 2.08 (1H, qd, *J* = 7 and 14 Hz), 2.19 (1H, qd, *J* = 7 and 14 Hz), 4.47 (1H, s); ^{13}C NMR δ 9.3, 20.7, 33.1, 61.2, 93.5, 171.1; υ_{max} 1642, 1601, 1539, 1495 cm^{-1}; MS (fab) *m/e* 177 (M-Cl$^+$), 130, 86, 84. Treatment of the minor diastereomer of the *iso*-leucine derivative **6e** with 6N HCl under analogous conditions afforded the other diastereomer of the title compound in 64% yield: mp 132-135 °C (dec.); ^{1}H NMR δ 0.92 (3H, t, *J* = 7 Hz), 1.63 (3H, s), 2.20 (1H, qd, *J* = 7 and 14 Hz), 2.22 (1H, qd, *J* = 7 and 14 Hz), 4.72 (1H, s); ^{13}C NMR δ 9.2, 19.6, 32.2, 59.9, 93.0, 170.1; υ_{max} 1647, 1608, 1549, 1506 cm^{-1}; MS (fab) *m/e* 177 (M-Cl$^+$), 130, 86, 84.

***N-tert*-Butoxycarbonyl-3-nitroalanine *tert*-Butyl Ester 15a.** Treatment of the bromide **14** with the anion of nitromethane **5a**, as described above for the reactions of the bromide **4**, gave the title compound **15a** in 63% yield: mp 99-100 °C; ^{1}H NMR δ 1.45 (9H, s), 1.48 (9H, s), 4.61 (1H, td, *J* = 3.5 and 7 Hz), 4.82 (1H, dd, *J* = 3.5 and 15 Hz), 4.95 (1H, dd, *J* = 3.5 and 15 Hz), 5.52 (1H, br d, *J* = 7 Hz); ^{13}C NMR δ 27.5, 28.2, 51.8, 75.7, 80.8, 84.0, 155.2, 167.0; υ_{max} 3436, 1760, 1712, 1562, 1498 cm^{-1}; MS (ei) *m/e* 290 (M$^+$), 234, 178; MS (ei) *m/e* 290.149 (M$^+$). Calc. for $C_{12}H_{22}N_2O_6$: *m/e* 290.148. Anal. Calc. for $C_{12}H_{22}N_2O_6$: C, 49.6; H, 7.6; N, 9.7. Found: C, 49.5; H, 7.8; N, 9.4.

***N-tert*-Butoxycarbonyl-3-methyl-3-nitroalanine *tert*-Butyl Ester 15b.** Treatment of the bromide **14** with the anion of nitroethane **5b**, as described above for the reactions of the bromide **4**, gave the title compound **15b** in 60% yield as a 2:1 mixture of diastereomers. Chromatography of the mixture gave the major diastereomer in 34% yield, as needles from light petroleum: mp 65-66 °C; ^{1}H NMR δ 1.45 (9H, s), 1.49 (9H, s), 1.66 (3H, d, *J* = 7 Hz), 4.66 (1H, dd, *J* = 4 and 8 Hz), 4.89 (1H, dq, *J* = 4 and 7 Hz), 5.42 (1H, br d, *J* = 8 Hz); ^{13}C NMR δ 15.6, 27.7, 28.1, 56.3, 80.5, 80.7, 83.5, 155.1, 167.0; υ_{max} 3420, 1720, 1550 cm^{-1}; MS (ei) *m/e* 304 (M$^+$), 248, 232, 202, 192, 102; Anal. Calc. for $C_{13}H_{24}N_2O_6$: C, 51.3; H, 8.0; N, 9.2. Found: C, 51.6; H, 8.3; N, 9.0. Continued chromatography gave the minor diastereomer as an oil in 17% yield: ^{1}H NMR δ 1.49 (18H, s), 1.65 (3H, d, *J* = 7 Hz), 4.64 (1H, dd, *J* = 3 and 9 Hz), 5.70 (1H, dq, *J* = 3 and 7 Hz), 5.94 (1H, br d, *J* = 9 Hz); ^{13}C NMR δ 15.7, 27.7, 28.2, 55.9, 80.6, 82.8, 83.7, 156.0, 167.5; υ_{max} 3420, 1740, 1560 cm^{-1}; MS (ei) *m/e* 305 (M+H$^+$), 249, 232, 202, 192, 102; MS (ei) *m/e* 249.108 (M-$C_4H_7^+$). Calc. for $C_9H_{17}N_2O_6$: *m/e* 249.109.

***N-tert*-Butoxycarbonyl-3-nitrophenylalanine *tert*-Butyl Ester 15c.** Treatment of the bromide **14** with the anion of α-nitrotoluene **5c**, as described above for the reactions of the bromide **4**, gave the title compound **15c** in 71% yield as a 1:1 mixture of diastereomers. Crystallization of the mixture from dichloromethane/light petroleum resulted in the formation of two distinct crystal types, which were partially separated by sorting. One diastereomer of the title compound **15c** crystallized as spars: mp 167-169 °C; ^{1}H NMR δ 1.35 (9H, s), 1.42 (9H, s), 4.99 (1H, t, *J* = 8 Hz), 5.08 (1H, br d, *J* = 8 Hz), 6.00 (1H, d, *J* = 8 Hz), 7.4 (5H, m); υ_{max} 3430, 1740, 1570, 1515 cm^{-1}; MS (ei) *m/e* 367 (M+H$^+$), 311, 255, 230, 219, 208, 175, 164, 163; MS (ei) *m/e* 367.186 (M+H$^+$). Calc. for $C_{18}H_{27}N_2O_6$: *m/e* 367.187. The other diasteromer of the title compound **15c** crystallized as needle clusters: mp 163-166 °C; ^{1}H NMR δ 1.33 (9H, s), 1.39 (9H, s),

4.95 (1H, dd, J = 5.5 and 9.5 Hz), 5.49 (1H, br d, J = 9.5 Hz), 6.03 (1H, d, J = 5.5 Hz), 7.3-7.5 (5H, m); υ_{max} 3410, 1735, 1540, 1505 cm^{-1}; MS (ei) *m/e* 367 ($M+H^+$), 311, 255, 230, 219, 175, 164, 163; MS (ei) *m/e* 367.188 ($M+H^+$). Calc. for $C_{18}H_{27}N_2O_6$: *m/e* 367.187.

3-Nitroalanine 7a Hydrochloride Salt. A solution of the ester **15a** (150 mg, 0.41 mmol) in trifluoroacetic acid (10 ml) and chloroform (10 ml) was heated at reflux for 0.25 h, then it was cooled and concentrated under reduced pressure. The residue was dissolved in 0.1 N HCl, and the solution was washed with ethyl acetate then concentrated under reduced pressure, to give the title compound (34 mg, 63%): mp 125-127 °C; ^1H NMR δ 4.55 (1H, dd, J = 3 and 5.5 Hz), 5.06 (1H, dd, J = 3 and 17 Hz), 5.16 (1H, dd, J = 5.5 and 17 Hz); υ_{max} 1606, 1540 cm^{-1}; ^{13}C NMR δ 53.1, 75.1, 171.1; MS (fab) *m/e* 135 ($M+H^+$), 108, 91, 75.

3-Methyl-3-nitroalanine 7b Hydrochloride Salt. Treatment of the major diastereomer of the β-methylalanine derivative **15b** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitroalanine **7a** gave the title compound in 56% yield as a single diastereomer: ^1H NMR δ 1.63 (3H, d, J = 7 Hz), 4.68 (1H, d, J = 2.5 Hz), 5.23 (1H, dq, J = 2.5 and 7 Hz); ^{13}C NMR δ 16.0, 57.3, 82.6, 170.5; MS (fab) *m/e* 149 ($M+H^+$), 110, 108, 103, 102. Treatment of the minor diastereomer of the methylalanine derivative **15b** with 6N HCl under analogous conditions afforded the other diastereomer of the title compound in 61% yield: ^1H NMR δ 1.79 (3H, d, J = 7.5 Hz), 4.64 (1H, d, J = 4 Hz), 5.35 (1H, dq, J = 4 and 7.5 Hz); ^{13}C NMR δ 16.9, 56.7, 82.0, 170.0; MS (fab) 149 ($M+H^+$), 110, 108, 103, 102.

3-Nitrophenylalanine 7c Hydrochloride Salt. Treatment of a 1:1 mixture of the diastereomers of the phenylalanine derivative **15c** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitroalanine **7a** gave the title compound in 45% yield as a 1:1 mixture of diastereomers: ^1H NMR δ 4.68 (0.5H, d, J = 5.5 Hz), 5.02 (0.5H, d, J = 5 Hz), 6.41 (0.5H, d, J = 5 Hz), 6.53 (0.5 H, d, J = 5.5 Hz), 7.3-7.5 (5H, m); υ_{max} 1652, 1604, 1560 cm^{-1}; MS (fab) *m/e* 211 ($M+H^+$), 164, 148, 120.

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