Synthesis of Side-Chain Functionalized Amino Acids

A Thesis

Submitted Towards the

Degree of

Doctor of Philosophy

by

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B. Sc. (Hons.)

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My family have always played a big role in all of my endeavours, and this was no exception. Mum, Dave, Helen, and Anni, thankyou. As for my surrogate Mother Winks, thank-you very much, particularly during my last two weeks in Adelaide.

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STATEMENT

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other institution and, to the best of my knowledge and belief, contains no material previously published or writtten by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan or photocopying.

Peter Roselt (B.Sc. Hons.) 20/2/93

PUBLICATIONS

Some of the work described in this thesis has been reported in the following publication:

Synthesis and Molecular Structure of Stable Derivatives of (*E*)- and (*Z*)-Dehydrophenylalanine.

Christopher J. Easton, Craig A. Hutton, Peter D. Roselt and Edward R. T. Tiekink, *Aust. J. Chem.*, 1991, **44**, 687-694.

ABSTRACT

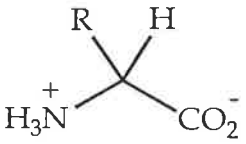
Reactions of *N*-phthaloyl-protected α-amino acids with *N*-bromosuccinimide have established that side-chain functionalization can be achieved without protection of the carboxyl group. Side-chain halogenated *N*-phthaloylamino acids, obtained using this procedure, have proven to be suitable for the synthesis of γ-butyrolactones.

β-Functionalized *N*-phthaloylamino acid ester and amide derivatives, obtained by halogenation of the corresponding proteinogenic amino acid derivatives, have been shown to be useful in the synthesis, including stereoselective synthesis, of α,β-dehydroamino acid derivatives. γ-Functionalized *N*-phthaloylamino acid derivatives, obtained using the same approach, have been found to be suitable for the synthesis of α,β-methano- and γ-fluoro-amino acid derivatives. Optimal conditions for the synthesis of the fluorides have been developed.

The condensation of unsubstituted, α-halo and ω-halo nitroalkanes with α-bromoglycine derivatives has been shown to be a viable method for the synthesis of a vast array of compounds including β-nitro-, α,β-dehydro-, ω-halo-β-nitro-, ω-halo-α,β-dehydro-, ω-halo-, β-halo-β-nitro-, β-nitro-α,β-dehydro- and β-halo-α,β-dehydro-amino acid derivatives. The utility of this condensation reaction is extended by the successful deprotection of the β-nitroamino acid derivatives to afford the corresponding free novel amino acids.

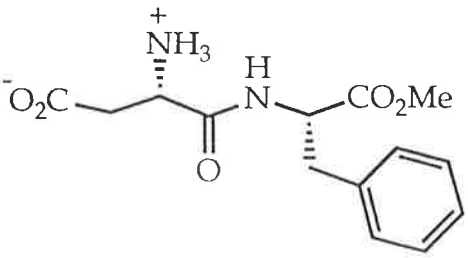
INTRODUCTION

It was over 150 years ago that glycine, the first naturally occurring amino acid to be discovered, was isolated from gelatin hydrolysates.[1] Today, more than 500 naturally occurring amino acids have been identified, of which approximately 240 occur free in nature.[2-4] They occur in nature as the monomeric building blocks of all proteins, peptides, and many other natural products. A particular class of amino acids, the monosubstituted α-amino acids (1) contain a chiral α-carbon about which is arranged the amino and carboxyl groups, the α-hydrogen and the side chain (R). It is the side chain which endows each α-amino acid with its unique properties. Those α-amino acids of natural origin are almost invariably homochiral.



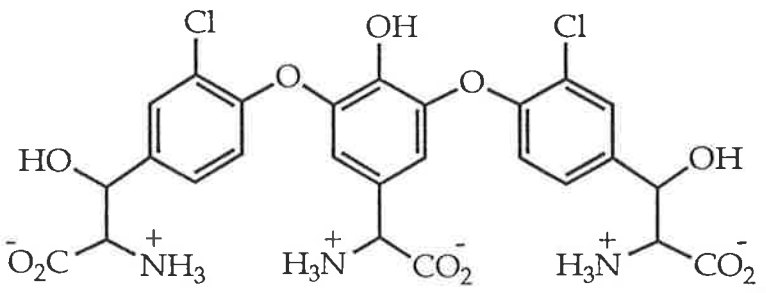
(1)

α-Amino acids, either in their free form or as components of peptides, are used extensively as food additives,[5] agrochemicals[6] and pharmaceuticals.[7] A food additive of particular note is the artificial sweetener known as aspartame (2), a dipeptide which has been found to be about 160 times sweeter than sucrose.[8]



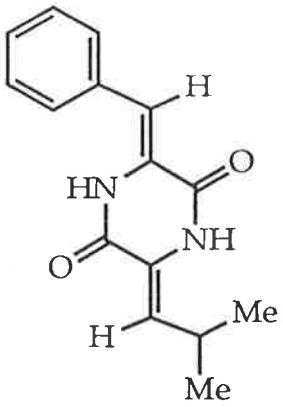
(2)

In 1956, the first glycopeptide antibiotic, vancomycin, was discovered.[9-11] From *Amycolatposis orientalis* (previously designated as *Streptomyces orientalis*), vancomycin is bacteriacidal against Gram-positive bacteria. It contains as a structural unit the unusual vancomycinic acid (3) which itself contains chloro-substituted β-hydroxytyrosine units. Incidentally, vancomycin owes much of its importance to the emergence of pathogenic strains of Gram-positive bacteria that have proven resistant to penicillin and cephlasporin therapies.



(3)

Another much studied pharmacologically active α-amino acid derivative is albonoursin (4). This asymmetrically substituted cyclic dipeptide derivative has been isolated from *Streptomyces noursei*,[12] *Streptomyces albus* var. *fungatus*[13] and *Actinomyces tumemacerance*.[14] Naturally occurring, albonoursin (4) has been found to exhibit antibacterial activity and to inhibit the growth of transplantable solid brain tumors in mice.[14]

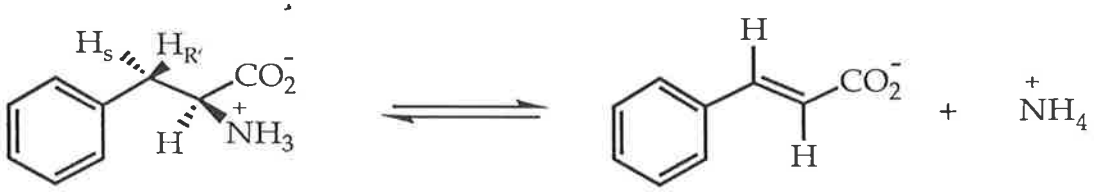


(4)

Given their natural occurrence and obviously broad-spectrum physiological activity, intense interest has focussed on the synthesis of α-amino acids, compounds which are sometimes unavailable from natural sources in quantities sufficient for thorough structural and biological testing. Often it is only through the synthesis of these physiologically important compounds that it becomes possible to confirm both their structure and function. Along with their increased availability through synthesis is an increase in the potential for their phamacological use. Their production also opens routes to the synthesis of unnatural analogues. Analogues of naturally occurring amino acids have played a vital role in studies of the function of their natural counterparts. Biochemical labelling studies,[15,16] the development of enzyme inhibitors[17-20] and conformational restriction studies[21-23] are but three areas where the synthesis of unnatural amino acid analogues has provided insight into the function of naturally occurring amino acids.

To obtain a proper understanding of the mechanism of a biochemical transformation, a precise knowledge of the chemistry of each discrete step is demanded. With the aid of analogues of natural amino acids it becomes possible to follow their biochemical fate and consequently gain insight to

reaction mechanisms. Take the example of aromatic amino acids. They are transformed into a wide variety of primary and secondary metabolites,[24] and it has been with the aid of synthetic analogues that their metabolic paths have been plotted.[15,16] By way of illustration, the (*S*)-phenylalanine derivatives (7) and (8), each stereoselectively labelled at the β-centre with deuterium, have been used to study the stereochemical course of the elimination catalysed by phenylalanine ammonia lyase (PAL).[15,16] This enzyme catalyzes the elimination of a proton and ammonia from (*S*)-phenylalanine (5) to give *trans*-cinnamate (6) (Scheme 1). Taking advantage of the prochiral nature of



(5) (6)

Scheme 1

(7) (8)

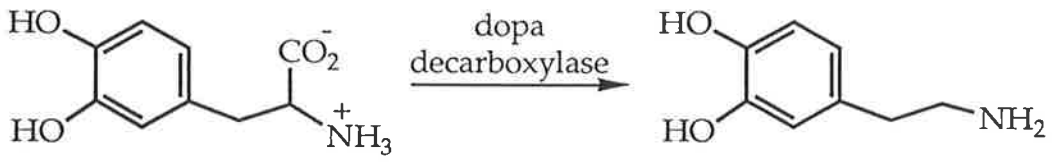
phenylalanine (5) at the β-centre, the problem of whether the enzyme-catalysed elimination reaction is stereospecific was solved by utilizing the stereoselectively labelled phenylalanine analogues (7) and (8) and testing for the presence of deuterium incorporated in the product. From this study it was

determined that PAL removed the *pro-S* hydrogen in the elimination reaction.[15,16]

Another area where analogues of naturally occurring amino acids have played a vital role is in the characterization of the active centres of enzymes and even enzyme-substrate complexes. Understanding the active site of an enzyme increases the likelihood that an effective enzyme inhibitor can be designed.[25,26] Organofluorine compounds have played a significant role in the understanding of enzyme mechanisms and in the synthesis of enzyme inhibitors.[27,28] Fluorine is not a sterically demanding substituent, with its small van der Waals radius (1.35 Å) closely resembling that of hydrogen (1.20 Å).[29] Fluorine also possesses the greatest electronegativity of all the elements.[29] As a result, substituting fluorine for hydrogen in a molecule can have profound effects on the electron distribution in that molecule, affecting the basicity or acidity of neighbouring groups, dipole moments in the molecule and the overall reactivity of the molecule. Fluorine can also participate in hydrogen bonding owing to its increased electron density. This fact, combined with the comparable carbon-oxygen and carbon-fluorine bond lengths (C-F = 1.39 Å and C-O = 1.43 Å) clearly indicates the potential for fluorine to replace hydroxyl in physiologically interesting compounds.[28] It is also worth noting that the unique magnetic properties of the ^{19}F nucleus have been utilized in ^{19}F n.m.r. spectroscopic investigations of receptor and metabolic phenomena of a number of systems, without interference from other nuclei.[29]

Consequently the development of synthetic methods for the convenient introduction of fluorine into specific positions of physiologically important amino acids has gained much attention. Owing to their potential medicinal utility as irreversible or suicide inhibitors of certain amino acid decarboxylases

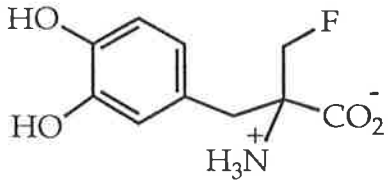
of physiological importance, a great deal of interest has been shown in β-fluoro amino acids.[17] Dopamine (10) is one example typical of a physiologically important amine produced by decarboxylation (Scheme 2).[18]



(9) (10)

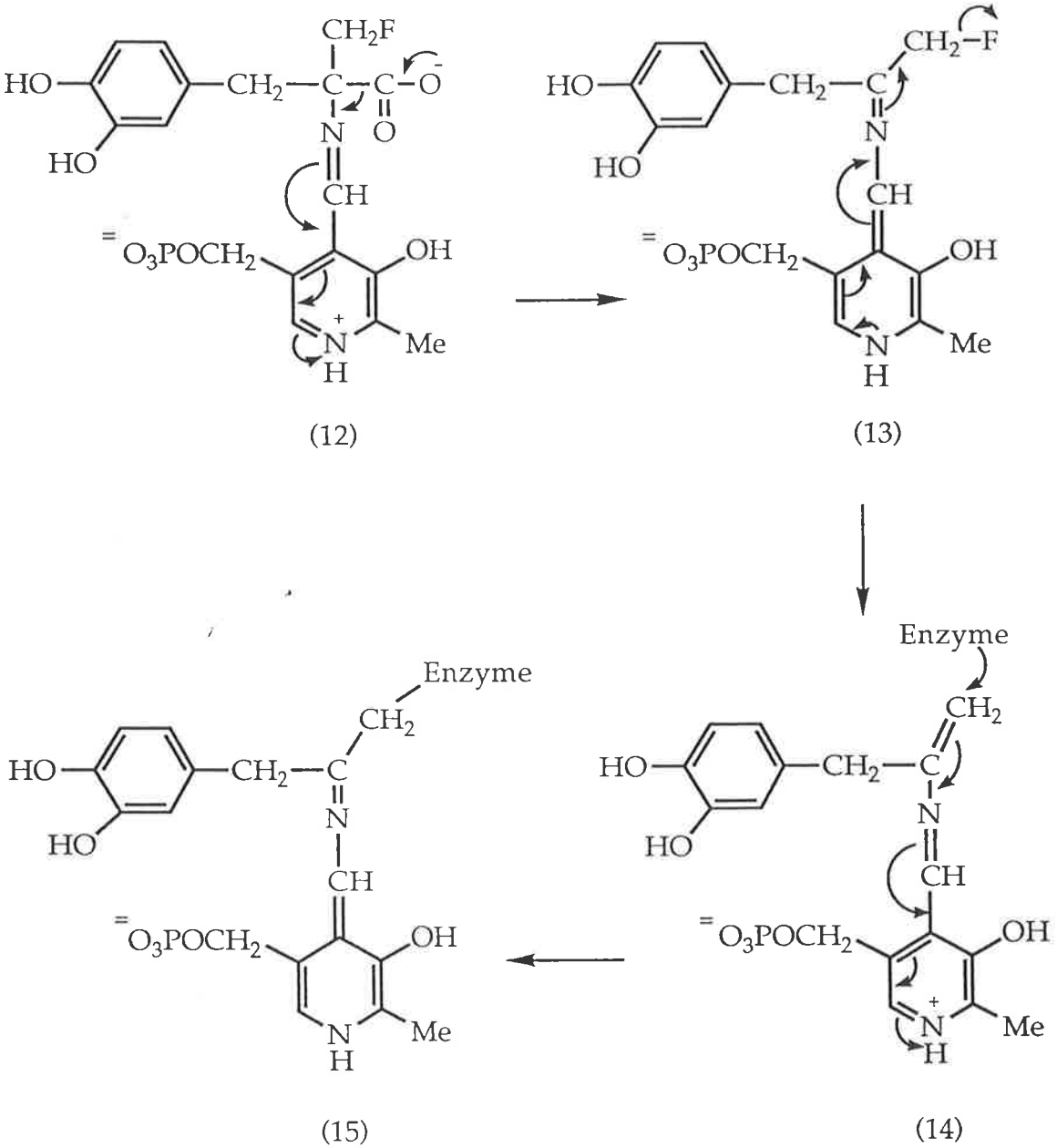
Scheme 2

A β-fluoro amino acid recognized as a potent suicide inhibitor of dopa decarboxylase, the enzyme responsible for the production of dopamine (10), is the fluoromethylated dopa (11).[17] The metabolic fate of the fluorinated substrate (11) is depicted in Scheme 3.



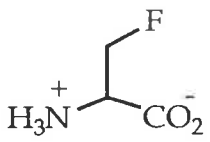
(11)

Enzyme inactivation is dependent upon loss of fluoride from the intermediate Schiff base (13), formed between pyridoxal phosphate and the fluorinated amino acid (11) after the loss of carbon dioxide. Loss of fluoride generates the reactive Michael-type acceptor (14) which can add an enzyme-bound nucleophile. This renders the enzyme inactive.



Scheme 3

A range of synthetic β-substituted amino acids has been prepared as suicide or mechanism-based inhibitiors for a wide variety of pyridoxal-phosphate dependent enzymes.[19] The paradigmatic β-fluoroalanine (16) first synthesized by Kollonitsch and colleagues[20] at Merck in 1975 illustrates the strategy of mechanism-based enzyme inhibition in the inactivation of bacterial alanine racemase. The molecular action of the fluorinated amino acid (16) is outlined in Scheme 4.[20]



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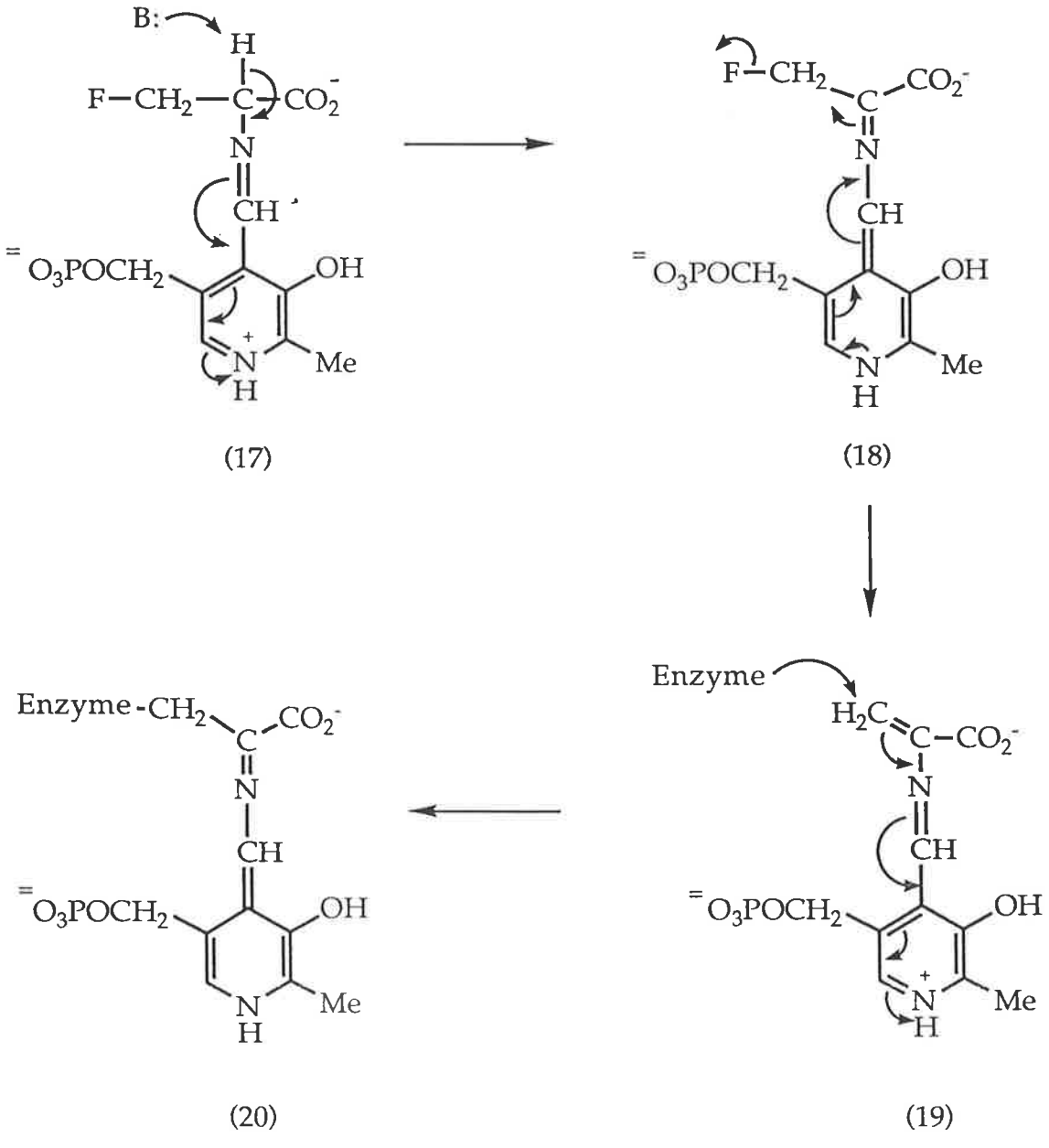
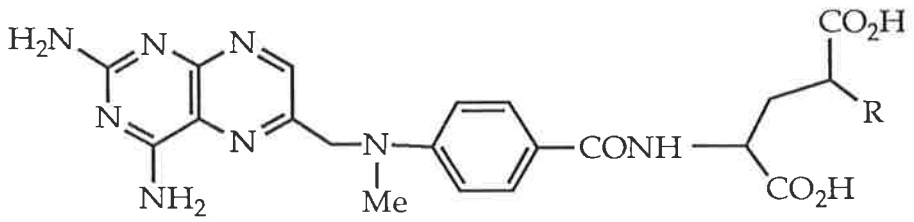


(17) (18) (19) (20)

Scheme 4

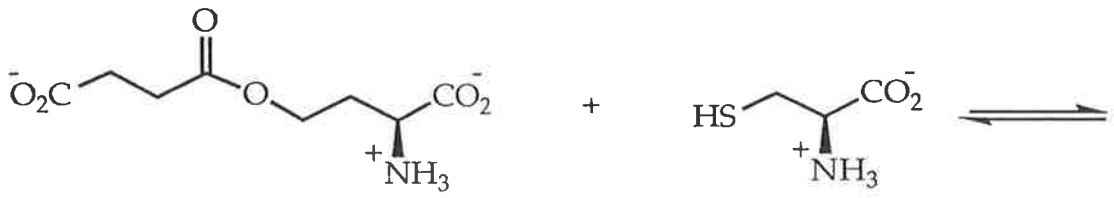
Also gaining attention as physiologically active variants of naturally occurring amino acids are γ-fluoro amino acids. Chemical modification of the antitumor agent methotrexate (MTX) (21) is just one means of discovering clinically useful analogues to treat those patients who display resistance to MTX (21).[30] Recent approaches to the development of analogues of MTX (21) have targeted the synthesis of γ-fluoroglutamic acid which was incorporated into the methotrexate analogue (22).[31] The fluoride (22) possesses some interesting and promising features for high dose treatment of cancers that show resistance to MTX (21).[30]



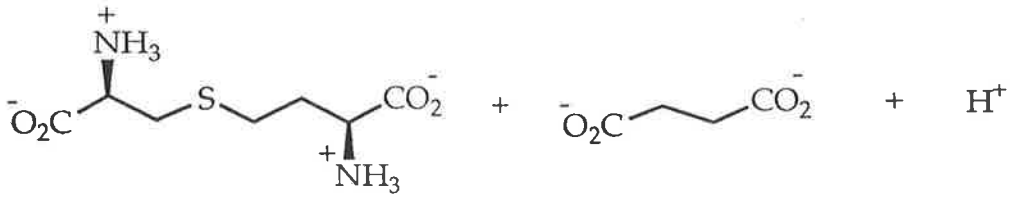
(21) R = H
(22) R = F

Another proven application of γ-substituted α-amino acids is in the study of the reaction catalyzed by the enzyme cystathione γ-synthase from *Escherichia coli*.[27] This enzyme catalyzes the pyridoxal-phosphate dependent synthesis of cystathionine (25) from *O*-succinyl-(*S*)-homoserine (23) and (*S*)-cysteine (24) *via* a substitution reaction (Scheme 5a). In the absence of (*S*)-cysteine (24), *O*-succinyl-(*S*)-homoserine (23) undergoes an enzyme catalyzed reaction to form succinate (26), α-ketobutyrate (27) and ammonia (Scheme 5b).[32] Recent studies

have provided evidence for the pyridoxamine derivative of vinylglyoxalate (32) as an intermediate (otherwise known as the partitioning intermediate) in the reactions catalysed by cystathione γ-synthase.[33] A generalized mechanism for these reactions is outlined in Scheme 6.

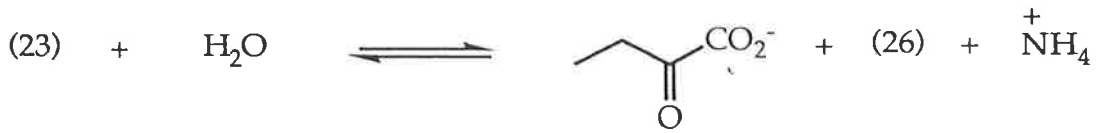


(23) (24)



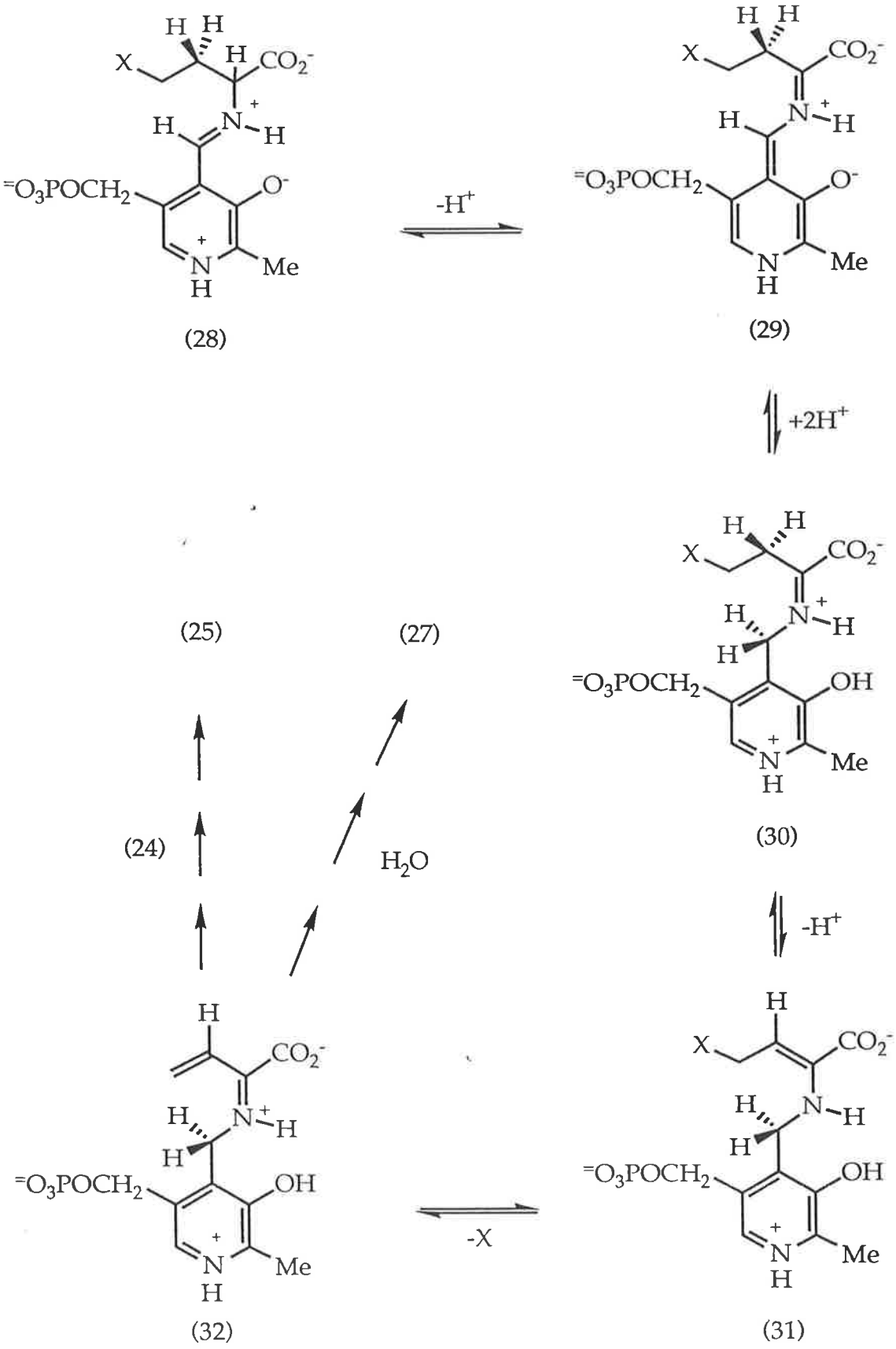
(25) (26)

Scheme 5a



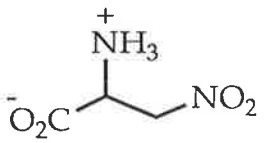
(27)

Scheme 5b



Scheme 6

Not as developed as the fluoroamino acid derivatives but still subject to similar types of investigation are the nitro-analogues of physiologically active compounds. Enzyme inhibition by nitro-substituted amino acids has been reported.[29,34] Bright and coworkers[34] have found β-nitro-α-amino acids to serve as potent reversible inhibitors. This is particularly the case where the ionizable nitro-substituted amino acids appear to function as transition state analogues. A comparison of the nitronate group with the carboxylate group reveals some interesting similarities with respect to geometry, polarity, and charge. This explains why the nitronate (34) binds 1600 times more tightly than aspartate (35) binds to aspartase.[35] In accord with the enzyme activity of β-fluoro-α-amino acids as suicide substrates, β-nitroalanine (33) was found to inactivate alanine and aspartate aminotransferases, probably by a mechanism analogous to that of the reaction of β-fluoroalanine,[36] whereby elimination of nitrite yields a reactive intermediate which then binds covalently and irreversibly to the enzyme.



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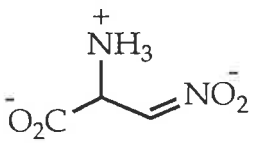

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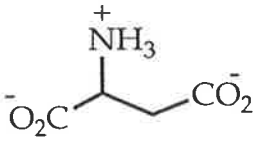
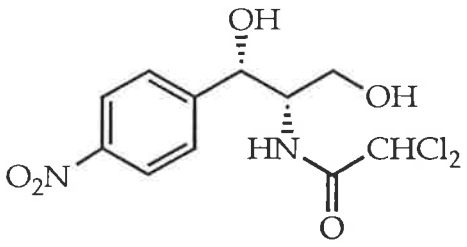


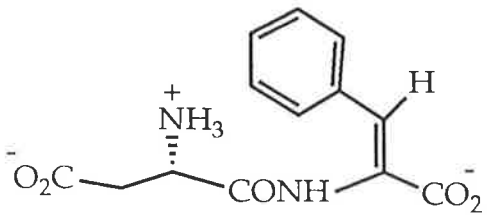
(35)

Although nitro-substituted compounds such as chloramphenicol (36) are valuable phamaceuticals,[37] no drugs yet exploit the analogy of the nitro group to the carboxylate group, but in the future this and other features of the nitro group may permit the rational design of pharmacologically valuable enzyme inhibitors.



(36)

α,β-Dehydroamino acid derivatives are important in a number of diverse areas.[38,39] By way of illustration, consider the α,β-dehydrophenylalanine derivatives. They have been found to occur widely in nature as constituents of peptides, many of which have interesting physiological properties.[40] They are also of interest in the synthesis of other phenylalanine derivatives, particularly through asymmetric hydrogenation,[41-44] and have been used extensively as structural variants to probe structure-activity relationships in peptides.[45,46] Peptides synthesized incorporating α,β-dehydrophenylalanine residues include analogues of aspartame (2),[47] bradykinin[48] and thyrotropin-releasing hormone.[49] Analogues of bradykinin and thyrotropin-releasing hormone showed enhanced activity, while the analogue of aspartame (37) was not sweet.



(37)

Since their discovery in 1975[50] enkephalins have stimulated a large number of conformational studies aimed at elucidation of the structure that elicits opioid activity.[51] Insight into the receptor-bound conformation can be gained by introducing peptide backbone modifications which restrict the conformational freedom of the peptide, providing the rigid analogue maintains bioactivity. Incorporation of dehydroamino acid residues into the enkephalins has led to the development of hormone analogues possessing enhanced activity, enhanced opiate receptor selectivity, and greater resistance to degradation.[52] The (Z)-dehydrophenylalanine (Δ^zPhe) containing enkephalinamide (39), a structural variant of the methionine enkephalin (38), has proved to be the most potent analogue tested thus far, being five times more potent than the parent saturated structure.[53]

Tyr-Gly-Gly-Phe-Met-OH

(38)

Tyr-(*R*)-Ala-Gly-Δ^zPhe-Met-NH_2

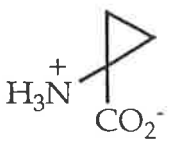
(39)

In general, a dehydroamino acid residue may alter the activity of a peptide by virtue of an increased receptor binding affinity, by its ability to react irreversibly with a nucleophile on the receptor surface, or by increasing resistance to enzymic degradation.[53]

It is interesting to note that in all cases where dehydroamino acid residues have replaced the saturated analogue, the (Z)-isomer was used in the modification. Although a number of procedures have been reported for the synthesis of α,β-dehydrophenylalanine derivatives,[40] many afford the (Z)-

isomer exclusively and significant quantities of the (*E*)-isomer have been produced only in a limited number of cases.[40,43,54] Even in those cases the (*E*)-isomer has often proved unstable and isomerized to give the more stable (*Z*)-isomer.[43,54]

Other interesting synthetic targets have been the cyclopropylamino acids.[55] Naturally occurring cyclopropylamino acids include 1-aminocyclopropanecarboxylic acid (40), coronamic acid (41) and carnosidine (42). The cyclopropylamino acid (40) was first isolated from cider apples and perry pears.[56] Subsequent studies established its central role as an intermediate in the biosynthesis of ethylene from methionine in plants.[57] Coronamic acid (41) is just one component of a toxin, produced by *Pseudomonas coronafacience*, known to induce chlorosis in Italian ryegrass.[58] Carnosadine (42) is a naturally occurring cyclopropylamino acid isolated from the red alga *Grateloupia carnosa*.[59]



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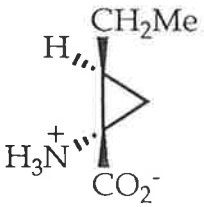

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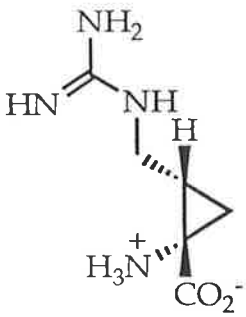
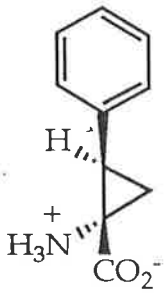


(42)

Both natural and synthetic cyclopropylamino acids, otherwise referred to as 2,3-methanoamino acids, have generated a great deal of interest as probes into structure-activity relationships.[45] The diastereomers of the cyclopropylamino acid 2,3-methanophenylalanine (43) and (44) have been incorporated into

enkephalin analogues to investigate structure-activity relationships.[21,22] In particular, (Z)-2,3-methanophenylalanine containing enkephalins showed reduced activity and a strong receptor preference, while the (*E*)-2,3-methanophenylalanine containing enkephalins showed a marked difference in their activity.[60] The modified peptides were also found to be resitant to degradation, being stable to hydrolysis by both chymotrypsin and carboxypeptidase *in vitro*.



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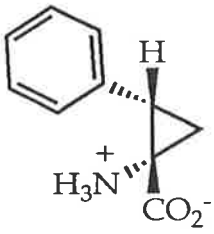


(44)

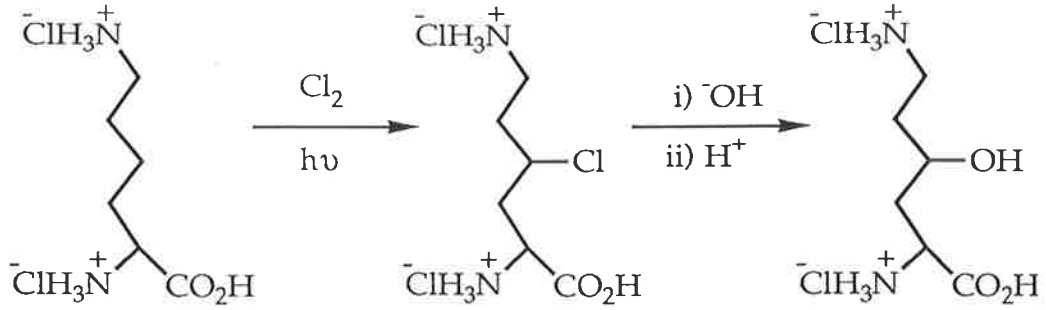
The cyclopropane ring of a methanoamino acid is known to restrict rotation about the C_α-C_β bond so that the β-functionality is fixed in space with respect to the two proximal peptide bonds, as is the case with α,β-dehydroamino acid derivatives. The unsaturated character of the cyclopropane ring favours certain conformations of the residue itself, as indeed is seen with α,β-dehydroamino acid derivatives. Conjugation of the benzene ring with the carbonyl function is observed in the ultraviolet spectra of the isomers of methanophenylalanine, with the (Z)-isomer showing the greater effect. This is probably due to the *trans* arrangement of the affected groups.[55] A cyclopropylamino acid incorporated into a peptide renders the side chain

effectively frozen in a fixed conformation. A result of the steric constraints introduced by the cyclopropyl moiety has been a gain in insight into the orientation of the side chains in receptor bound states.[23]

α-Amino acids have also been used in organic synthesis as a source of chiral raw materials and as constituents for reagents and/or catalysts in asymmetric synthesis. The obvious importance of amino acids has therefore prompted the development of a multitude of methods for their racemic and asymmetric synthesis.[61]

One approach to the synthesis of rare and unnatural α-amino acids involves the elaboration of proteinogenic α-amino acids through side chain modification. This method often involves the elaboration of a pre-existing functionality. Examples include utilizing the β-hydroxy group of serine[62-64] and modification of aspartic and glutamic acid through the Barton decarboxylation technique.[65,66] These procedures utilize the important fact that proteinogenic amino acids are a cheap and readily available source of enantiomerically pure starting materials.

Complementary to the side chain modification of amino acids through the manipulation of pre-existing functionality is the regioselective free radical modification of proteinogenic amino acids. Free radical reactions have the advantage of direct introduction of a functional group to the amino acid side chain. This approach is exemplified by the γ-chlorination and subsequent elaboration of lysine (45), as described by Kollonitsch and coworkers (Scheme 7).[67-69] The chlorination procedure involved ultraviolet irradiation of a concentrated hydrochloric acid solution of lysine (45), at 70°C with the concurrent introduction of chlorine gas.



Scheme 7

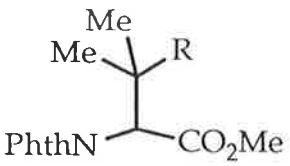
In radical reactions where a hydrogen is replaced by a functional group, the regioselectivity is determined in the hydrogen atom transfer step and is affected by a number of factors.[70] They include radical stability, steric effects and polar effects. Radical stabilizing effects are important when there is extensive C-H bond breaking and consequently, significant development of radical character in the transition state. Steric factors can influence the regioselectivity of the hydrogen abstraction either by hindering the approach of the hydrogen abstractor and/or by reducing the stability of the product radical by constraining its conformation. Polar effects refer to activating-deactivating effects brought on by the partial charge stabilizing factors in the transition state of the hydrogen abstraction step.[70,71]

Polar effects were proposed to be responsible for the regioselectivity seen with the free radical chlorination of lysine (45).[67-69] It was considered that under the reaction conditions described, the electron withdrawing aminium and

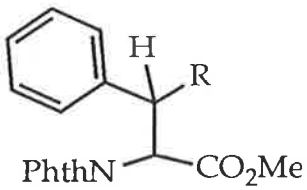
carboxyl groups deactivate adjacent positions to attack by the electrophilic chlorine atom. The range of this inductive or polar effect is such that reaction occurs at the position farthest away from both the α-substituents and the ε-aminium substituent.

The widespread application of radical reactions to the functionalization of amino acids is limited by the insolubility of amino acids in the organic solvents commonly used in such processes. This problem can be overcome by suitable protection of the amino acids, however such changes to the amino acids have been shown to affect the regioselectivity of the reactions. Whereas Kollonitsch[67-69] utilized the instability of the α-centred radical to affect side chain functionalization of lysine (45), hydrogen atom transfer reactions of *N*-acyl-α-amino acid derivatives generally favor formation of the corresponding α-carbon centred radicals.[72,73] Stabilization of a radical of this type results from overlap of the semi-occupied p-orbital of the radical with the π-orbitals of the electron-releasing amido substituent and the electron-withdrawing carboxy substituent. This type of radical has been referred to as captodative,[74] merostabilized[75] or push-pull stabilized.[76] It is therefore apparent that this type of amino acid protection is not suitable when considering side chain functionalization.

In contrast to *N*-acyl-protected amino acid derivatives, *N,N*-diacyl-protected amino acid derivatives undergo hydrogen atom transfer reactions of their side chains. For example, the free radical bromination of the *N*-phthaloyl-protected derivatives of valine (48a) and phenylalanine (49a) resulted in regioselective formation of the bromides (48b) and (49b), respectively.[77]

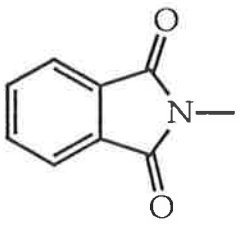


(48)



(49)

a) R = H
b) R = Br



= PhthN-

This contrast in regioselectivity can be explained by considering the stability of the resulting α-centred radicals. Whereas *N*-acylamino-substituted α-carbon-centred radicals are stabilized by resonance, there is less delocalization of the unpaired spin density by a phthalimido substituent. In addition, in planar conformations where there is maximum resonance stabilization, non-bonding interactions are considerably greater with phthalimido- and carboxyl-substituted radicals than with acylamino- and carboxyl-substituted radicals (Figure 1).[78,79]

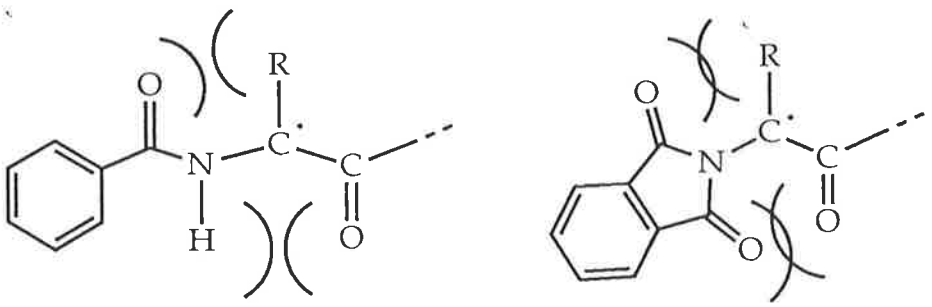
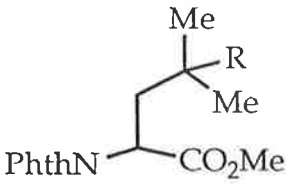
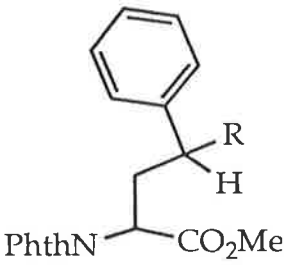


Figure 1. Nonbonding interactions associated with planar conformations of benzamido- and phthalimido-substituted radicals.

This deactivating effect of the phthaloyl substituent has also been utilized to affect γ-functionalization of *N*-phthaloylleucine methyl ester (50a) and *N*-phthaloylhomophenylalanine methyl ester (51a). Hydrogen abstraction from the benzylic and tertiary centres takes place in preference to hydrogen abstraction from the α-centre of the phthaloyl-protected amino acid derivatives. Subsequent bromine transfer to the γ-centres yielded the bromides (50b) and (51b).[80,81]



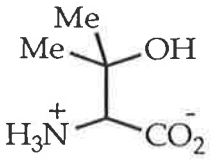
(50)



(51)

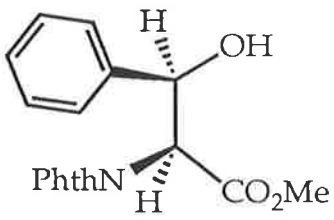
a) R = H
b) R = Br

It is evident from the free radical reactions of the *N*-phthaloyl-protected amino acid derivatives (48a)-(51a) that side chain functionalization of *N*-phthaloyl-substituted amino acids takes place *via* the most stable side-chain radical. This type of regioselectivity is also observed in biological systems. For example, β-hydroxyvaline (52) is a naturally occurring amino acid thought to result from the enzymatic oxidation of valine. Evidence exists for the oxidation being radical in nature and it is possible that the observed regioselectivity is a reflection of polar effects.[82]

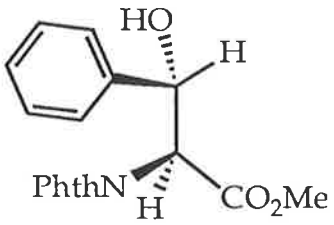


(52)

An obvious advantage of using radical reactions for amino acid side-chain functionalization is that the stereochemistry of the starting α-amino acids is retained in the products. This is exemplified by the stereocontrolled synthesis of the homochiral β-hydroxyphenylalanine derivatives (53) and (54) from the diastereomers of the β-bromophenylalanine derivative (49a).[80]



(53)



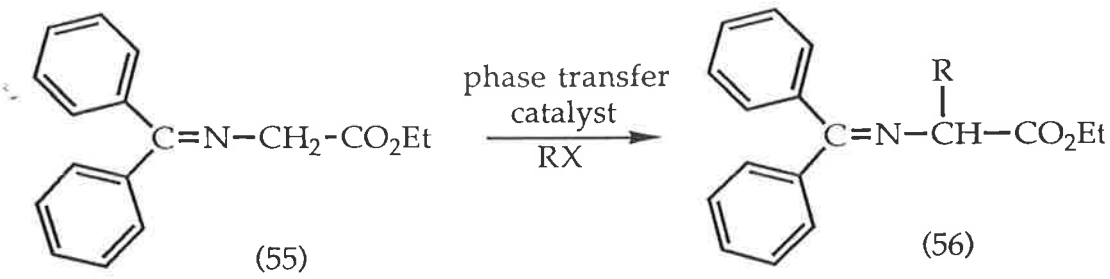
(54)

Functional group protection of any type is undesirable as it leads to additional steps in a synthetic pathway. The protection of an amino acid as its *N*-phthaloyl-substituted derivative is important in order to achieve side-chain functionalization. The necessity to protect the carboxyl group was uncertain, however, at the outset of the work described in this thesis. This and other

aspects of the scope and limitations of the bromination of *N*-phthaloyl-protected amino acid derivatives are the subject of the investigation described in Chapter One of the Results and Discussion of this thesis.

The amenability of halogenated amino acid derivatives to further elaboration is well documented. Such an example already mentioned is the stereocontrolled synthesis of homochiral β-hydroxyphenylalanine.[80] Another example is the elimination of hydrogen chloride from β-chloro-α-amino acid derivatives to afford α,β-dehydroamino acid derivatives,[82] whilst the synthesis of γ-hydroxylysine has also been highlighted.[67-69] The side chain functionalization of proteinogenic amino acid derivatives and subsequent manipulation of the introduced functionality is thus a powerful approach to the synthesis of rare and unnatural amino acids. The amenability of side chain halogenated amino acids derivatives, prepared as described in Chapter One of the Results and Discussion of this thesis, to elaboration is the subject of the studies described in Chapters Two and Three of the Results and Discussion of this thesis. In Chapter Two, the use of β-brominated amino acid derivatives in the stereocontrolled synthesis of α,β-dehydroamino acid derivatives is examined, while in Chapter Three, the focus of attention is on the scope and limitations of using γ-brominated amino acid derivatives in the synthesis of 2,3-methano and γ-fluorinated amino acid derivatives.

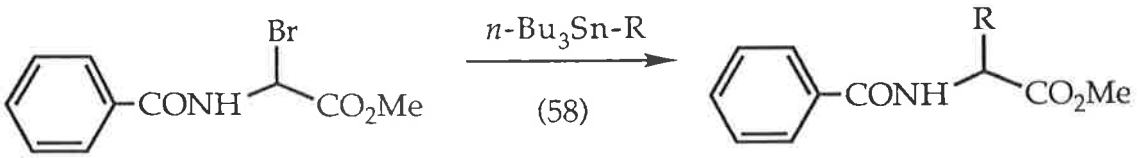
Alternative methods for the preparation of α-amino acid derivatives include the elaboration of various glycine derivatives. O'Donnell and coworkers[83,84] have developed a general synthesis of amino acids based on the catalytic phase-transfer alkylation of the benzophenone imine of glycine ethyl ester (55) (Scheme 8).



(55) (56)

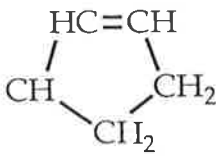
Scheme 8

Elaboration of the α-bromoamino acid derivative (57) by reaction with allylic stannanes (58), *via* radical carbon-carbon bond formation, has been reported to afford a number of interesting allylic glycine derivatives (59) (Scheme 9).[85-87]



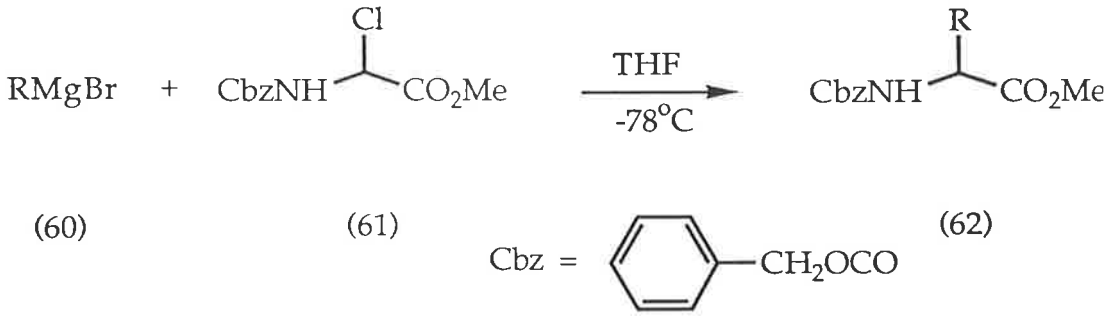
(57) (59)

a) R = CH_2-CH=CH_2
b) R = CH_2-CMe=CH_2

c) R = 

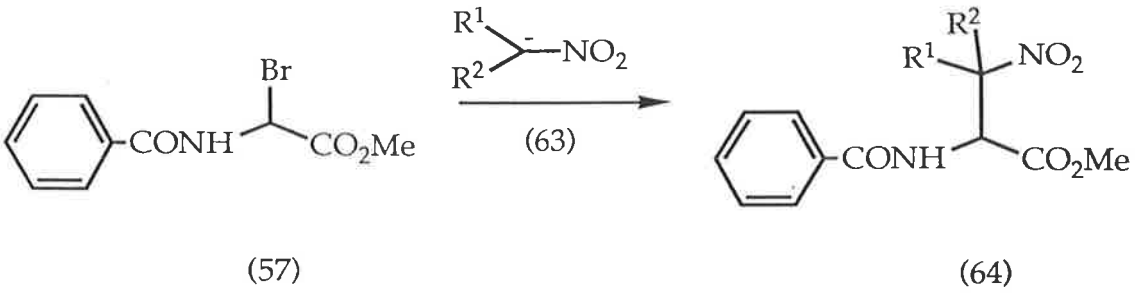
Scheme 9

The synthesis of α-amino acids involving cationic glycine equivalents has gained considerable popularity as a result of its evident diversity. Derivatives of α-haloamino acids have been utilized as facile electrophilic glycine templates susceptible toward a diverse range of nucleophiles, including Grignard reagents,[88,89] alkyl malonates,[90] and mixed cuprates.[91,92] An example worthy of note is the reaction of Grignard reagents with cationic glycine equivalents. Castelhano and coworkers[89] have utilized the α-chloroglycine methyl ester (61) in reactions with vinylic Grignard reagents (60) to yield a vast array of vinylglycine derivatives (62) in good to excellent yields (Scheme 10).



Scheme 10

A complementary method for the synthesis of α-amino acid derivatives is through reaction of the α-bromoglycine derivative (57) with the alkyl nitronates (63a-e) (Scheme 11), considered to proceed *via* an electron transfer mechanism.[93]



(57) (64)

	R^1	R^2
a)	H	H
b)	Me	Me
c)	Me	H
d)	CO_2Me	H
e)		H

Scheme 11

The product β-nitro amino acid derivatives (64a-e) proved useful in the synthesis of α,β-dehydroamino acid derivatives, through reaction with di-*iso*-propylamine.[93]

Though there are many synthetic methods for the synthesis of α,β-dehydroamino acid derivatives, there are only a few that are effective for the synthesis of derivatives with additional functionality.[94] The extent to which additional functionality could be incorporated into an α,β-dehydroamino acid derivative was investigated using an extension of the alkyl nitronate approach to amino acid derivatives. In particular, remotely

and β-functionalized amino acid derivatives were targeted. That work is described in Chapter Four of the Results and Discussion of this thesis.

The utility of the above described procedures depends on the ease of deprotection of the derived amino acid derivatives. This is a particular limitation with compounds containing functional groups which are known to be susceptible to harsh hydrolytic conditions. In the work described in Chapter Five of the Results and Discussion of this thesis, the application of the techniques described in Chapter Four to the preparation of free amino acids is discussed.

RESULTS AND DISCUSSION: CHAPTER ONE

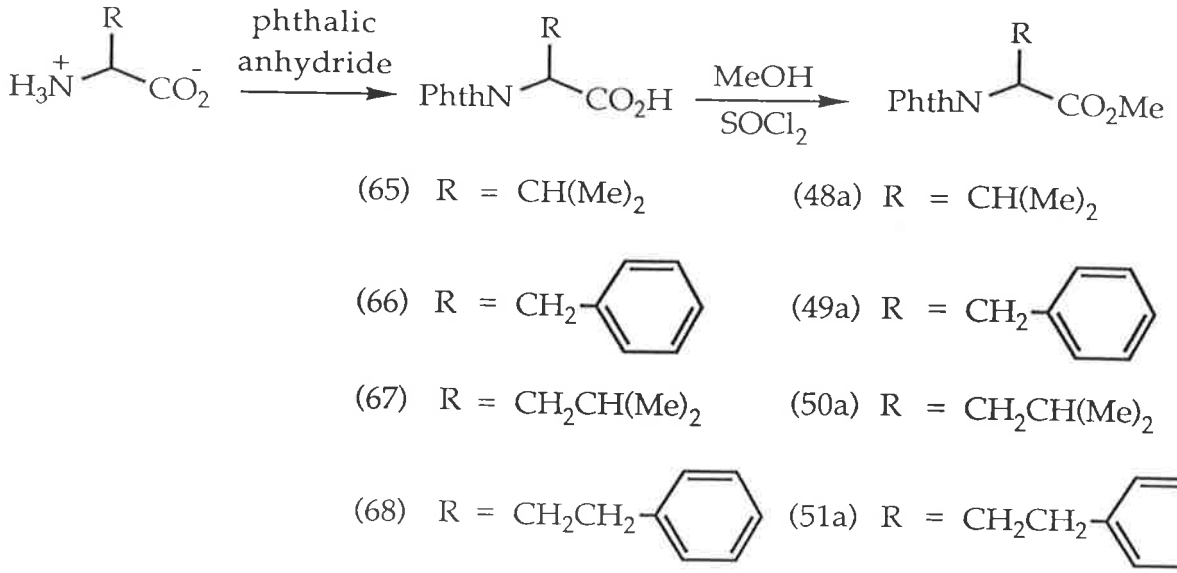
Side-Chain Functionalization of *N*-Phthaloyl-protected α-Amino Acid Derivatives

As outlined in the Introduction, the aim of the work described in this Chapter was to examine the scope and limitations of bromination as a method for side-chain functionalization of *N*-phthaloyl-α-amino acid derivatives.

Preparation of *N*-Phthaloyl-α-amino Acid Derivatives

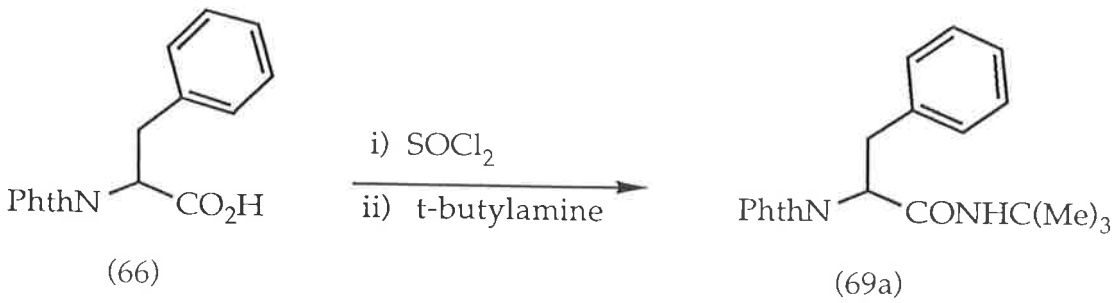
The *N*-phthaloylamino acid ester derivatives (48a) - (51a), required for the work described in this Chapter, were obtained as described below (Scheme 12). The *N*-phthaloylamino acids (65) - (68) were prepared from valine, phenylalanine, leucine, and homophenylalanine, respectively. The procedure, as described by Reese,[95] involved heating an intimate mixture of equimolar amounts of phthalic anhydride and the appropriate amino acid to form a melt (150°C). Discolouration of the mixture was avoided by ensuring that the temperature was maintained below 160°C. The melt was stirred vigorously for 15-30 minutes at this temperature.

The methyl esters (48a) - (51a) were prepared by treating the corresponding *N*-phthaloylamino acids (65) - (68) with a methanolic solution of hydrogen chloride, which had been prepared by the dropwise addition of thionyl chloride to a cooled solution of dry distilled methanol.



Scheme 12

The *tert*-butylamide (69a), also required for the work described in this Chapter, was prepared by treating *N*-phthaloylphenylalanine (66) with thionyl chloride to produce the intermediate acid chloride, which was then treated with *tert*-butylamine (Scheme 13). All substrates used in the work described in this Chapter had spectroscopic and physical data consistent with that previously reported.[77,80,81]



(66) (69a)

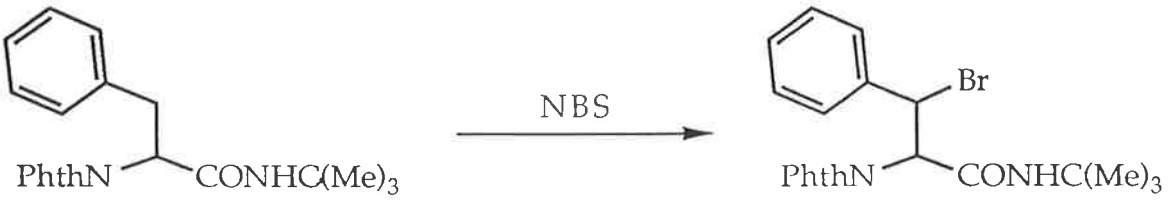
Scheme 13

Reactions of *N*-Phthaloyl-α-amino Acid Derivatives

The *N*-phthaloylamino acid derivatives (48a) - (51a) and (69a) were treated with *N*-bromosuccinimide as previously reported,[77,80,81] to give the bromides (48b) - (51b) and (69b). Accordingly, the *N*-phthaloylamino acid derivatives (48a) - (51a) and (69a) were each treated with one mole equivalent of *N*-bromosuccinimide in a refluxing solution of carbon tetrachloride or, as was the case for the phenylalanine derivatives (49a) and (69a), in a solution of carbon tetrachloride/dichloromethane (1:1). The reactions were initiated by irradiating the solutions with a 300 watt mercury lamp and they were carried out under an inert atmosphere of nitrogen for 2 h. The bromides (48b) - (51b) obtained in this manner had spectroscopic and physical data consistent with that previously reported.[77,80,81]

The reaction of the *N*-phthaloylphenylalanine derivative (69a) gave a 1:1 mixture of the diastereomers of the β-bromophenylalanine derivative (69b) (Scheme 14). Attempts to separate the diastereomers by fractional crystallization or by chromatography on silica were only partly successful. However, recrystallization of the mixture from a solution of light petroleum/propanol-2-ol (1:1) resulted in the formation of crystals of two distinct sizes and shapes. After separation of the crystal types on 0.25 mm and 0.60 mm mesh sieves, the small colourless crytals recrystallized from light petroleum/propan-2-ol to give the (2*RS*,3*RS*)-diastereomer (69bi) in 41% yield, while recrystallization of the pale yellow granules gave the (2*RS*,3*SR*)-diastereomer (69bii) in 39% yield. The ^{1}H n.m.r spectrum of the (2*RS*,3*RS*)-diastereomer (69bi) showed two doublet resonances, one at δ 5.28 (J = 11.8 Hz) and the other at δ 6.25 (J = 11.8 Hz). These resonances were attributed to the α- and β-protons respectively. The α- and β-protons of the (2*RS*,3*SR*)-diastereomer (69bii) resonated in the ^{1}H n.m.r. spectrum at δ 5.32 (J = 11.5 Hz)

and 6.04 (J = 11.5 Hz) respectively. The mass spectrum of each diastereomer of the bromide (69b) showed a pair of isotopic molecular ions at m/z 430 and 428. Microanalytical data for the bromide (69b) is consistent with the proposed composition. The relative stereochemistry of the diastereomers (69bi) and (69bii) was determined from elimination reactions that are discussed in Chapter Two of the Results and Discussion of this thesis.



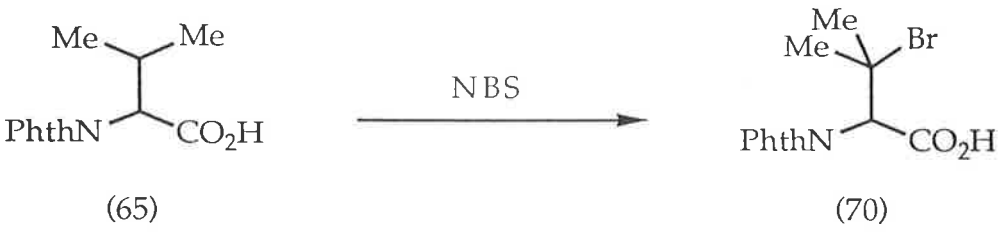
(69a) (69b)

Scheme 14

The treatment of *N*-phthaloylphenylalanine methyl ester (49a) with *N*-bromosuccinimide resulted in the production of a 1:1 mixture of the diastereomers of the bromide (49b). Separation of the diastereomers of the bromide (49b) was affected by fractional crystallization from a dilute solution of ethyl acetate/light petroleum. The (2*RS*,3*RS*)-diastereomer (49bi) crystallized first as fine needles, which recrystallized from ethyl acetate/light petroleum in 41% yield. The (2*RS*,3*SR*)-diastereomer (49bii) crystallized second as granules and subsequent recrystallization from ethyl acetate/light petroleum gave that diastereomer in 43% yield. Both the spectral and physical characteristics of the diastereomers of the bromide (49b) corresponded to those already reported.[77] In particular, the ^{1}H n.m.r. spectrum of the (2*RS*,3*RS*)-diastereomer (49bi) showed a doublet resonance at δ 5.55 (J = 11.2 Hz) attributed to the α-proton, while the doublet resonance at δ 6.06 (J = 11.2 Hz) was attributed to the β-

proton. The ^{1}H n.m.r. spectrum of the (2*RS*,3*SR*)-diastereomer (49bii) showed two doublet resonances, one at δ 5.62 (J = 10.4 Hz) and the other at 5.95 (J = 10.4 Hz), corresponding to the α- and β-protons, respectively. The assignment of the relative stereochemistry of the diastereomers (49bi) and (49bii) was determined from elimination reactions that are discussed in Chapter Two of the Results and Discussion of this thesis.

While the esters (48a) - (51a) and the amide (69a) thus afford the corresponding bromides (48b) - (51b) and (69b), it was of interest to determine if the acids (65) - (68) would react with *N*-bromosuccinimide in an analogous manner, and in the process avoid protection of the carboxyl group. In a fashion similar to that employed for the bromination of the esters (48a) - (51a) and the amide (69a), *N*-phthaloylvaline (65) was treated with *N*-bromosuccinimide to give 3-bromo-*N*-phthaloylvaline (70) as an oil, which crystallized from dichloromethane/light petroleum in 89% yield (Scheme 15).



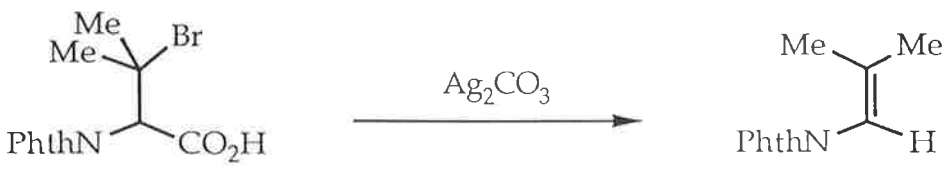
(65) (70)

Scheme 15

Strong evidence in support of the structure of the bromide (70) was obtained from the ^{1}H n.m.r. spectrum. Singlet resonances at δ 2.02 and 2.17 were attributed to the protons of the methyl substituents. A singlet resonance assigned to the α-proton was at δ 5.27. Low resolution mass spectroscopic analysis of the bromide (70) gave peaks at *m/z* 326 and 328 of equal abundance,

corresponding to the protonated molecular ion. These peaks were of insufficient intensity for high resolution mass spectral analysis. Consequently high resolution mass spectral analysis was carried out on a fragment ion at *m/z* 201.079. This was consistent with the ion $[M\text{-}CO_2HBr]^+$, which had the theoretical value of *m/z* 201.078. Satisfactory microanalytical data was not obtained for the bromide (70). This may reflect the propensity of the bromide (70) to undergo a decarboxylative-elimination.[96] The bromide (70) was therefore characterized as its corresponding enimide derivative (71).

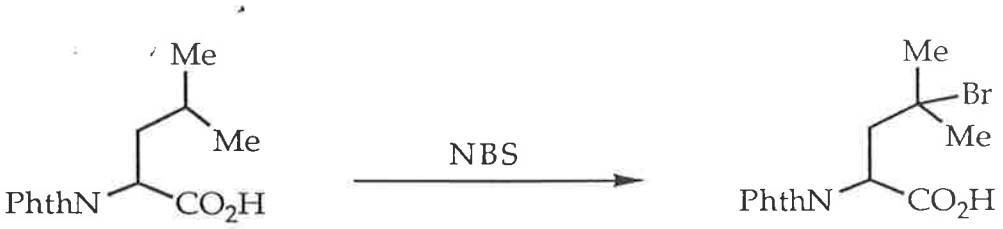
Treatment of 3-bromo-*N*-phthaloylvaline (70) with 0.5 equivalents of silver carbonate in acetonitrile and water, whilst shielding the reaction mixture from light, gave the enimide (71) in 72% yield (Scheme 16). The ^1H n.m.r. spectrum of the enimide (71) showed a multiplet centred at δ 5.90 corresponding to the vinylic proton coupled through long range coupling to the two β-methyl groups. Two doublet resonances at δ 1.67 (J = 1.0 Hz) and 1.93 (J = 1.0 Hz) were attributed to the β-methyl groups. High resolution mass spectral analysis of the enimide (71) showed a peak in the spectrum at *m/z* 201.079 for the molecular ion. The composition of (71) was substantiated by elemental analysis.



(70) (71)

Scheme 16

Having established that the acid (65), as for the ester (48a), reacted with *N*-bromosuccinimide by side-chain functionalization, in order to determine the generality of the bromination of free acids, the reaction of *N*-phthaloylleucine (67) with *N*-bromosuccinimide was investigated. Reaction of the acid (67) with *N*-bromosuccinimide in an analogous fashion to that described above, and recrystallization of the product from a dilute solution of dichloromethane/light petroleum, gave the bromide (72), as fine needles, in 84% yield (Scheme 17). The structure of the γ-bromide (72) was assigned on the

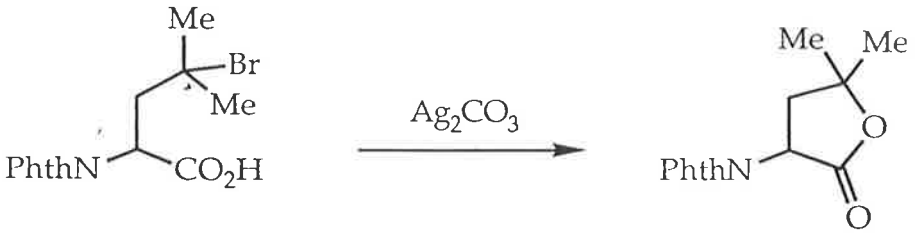


(67) (72)

Scheme 17

basis of spectral data. The ^{1}H n.m.r. spectrum showed singlet resonances at δ 1.75 and 1.83, due to the methyl substituents. The resonances centred at δ 2.78 (J = 3.1 and 15.8 Hz) and 2.88 (J = 9.1 and 15.8 Hz) were in accordance with the geminally coupled β-protons, which were further coupled to the α-proton. The α-proton was seen as a doublet of doublets in the spectrum at δ 5.12 (J = 3.1 and 9.1 Hz). Peaks in the mass spectrum at m/z 294 and 296 were consistent with the isotopic fragment ions of $C_{13}H_{13}NO_2Br$, which resulted from the loss of CO_2H from the molecular ion. Microanalytical data confirmed the composition of the bromide (72).

Additional evidence in support of formation of the γ-bromide (72) was obtained through its conversion to the γ-lactone derivative (73). Treatment of 4-bromo-*N*-phthaloylleucine (72) with 0.5 equivalents of silver carbonate in acetonitrile, with vigorous stirring for 2 h, gave 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) in 80% yield (Scheme 18). Conclusive structure determination was afforded by comparison of the spectral



(72) (73)

Scheme 18

and physical data with that of an authentic sample.[80] The ^{1}H n.m.r. spectrum of the γ-lactone (73) showed two singlets, each with intensity corresponding to three protons, at δ 1.51 and 1.64, attributable to the protons of the γ-methyl substituents. The spectrum also showed an ABX splitting pattern, with resonances at δ 2.44 (J = 9.7 and 12.1 Hz) and 2.60 (J = 11.5 and 12.1 Hz) attributable to the geminally coupled β-protons. A doublet of doublets at δ 5.24 (J = 9.7 and 11.5 Hz) corresponds to the vicinally coupled α-proton.

In order to examine the application of side-chain bromination to aryl amino acid derivatives, the reactions of *N*-phthaloylphenylalanine (66) and *N*-phthaloylhomophenylalanine (68) with *N*-bromosuccinimide were investigated. Accordingly, the *N*-phthaloylarylamino acid derivatives (66) and

(68) were each treated with *N*-bromosuccinimide under similar conditions to those described in the previous two examples. The reaction of *N*-phthaloyl-phenylalanine (66) with *N*-bromosuccinimide gave a 1:1 mixture of diastereomers of the bromide (74) (Scheme 19). The ratio of diastereomers was determined from the ^1H n.m.r. spectrum of the crude reaction mixture,

(66) (74)

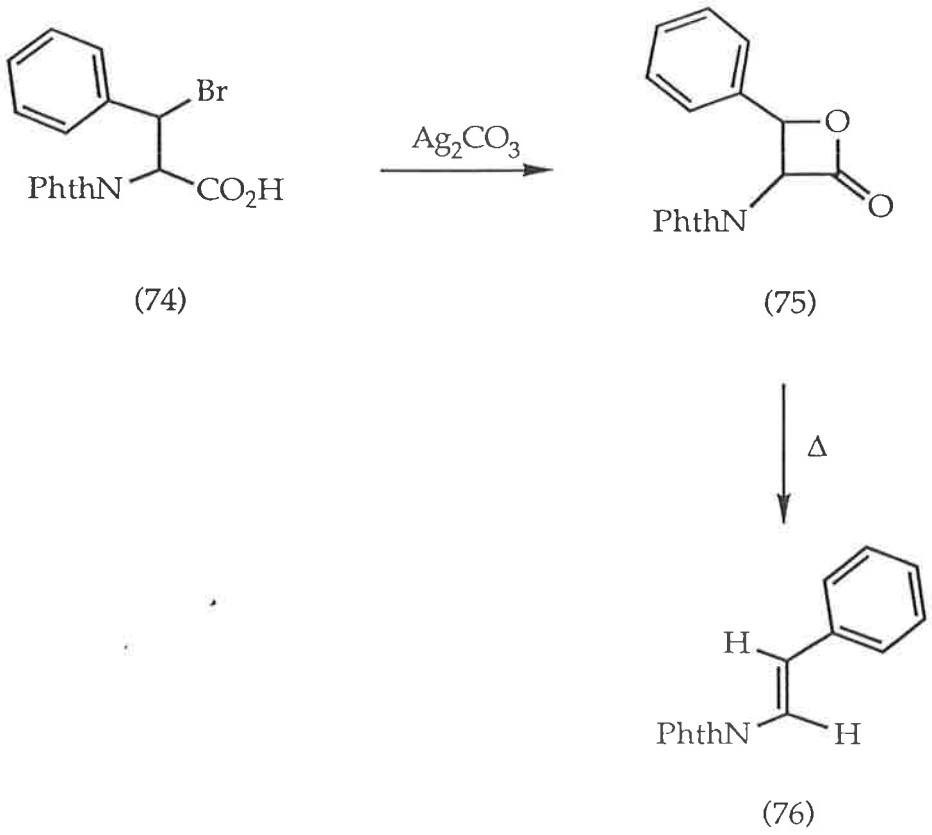
Scheme 19

which showed single proton doublet resonances at δ 5.64 (J = 10.4 Hz) and 5.86 (J = 10.4 Hz), corresponding to the α- and β-protons of one diastereomer, and single proton doublet resonances at δ 5.55 (J = 11.2 Hz) and 5.97 (J = 11.2 Hz), corresponding to the α- and β-protons of the other diastereomer. The bromide (74) crystallized from dichloromethane/light petroleum as a 1:1 mixture of the diastereomers, in 77% yield. The mass spectrum of the bromide (74) showed peaks at m/z 373 and 375 of equal abundance due to the isotopic molecular ions. Accurate mass analysis of the molecular ions was not obtained owing to their low intensity in the spectrum. However, accurate mass analysis was performed on the base peak in the spectrum at m/z 249.078. This peak was attributed to the fragment ion $[M\text{-}CO_2HBr]^+$ resulting from decarboxylative

elimination of the molecular ion. Consistent microanalytical data was not obtained for the bromide (74). This probably reflects the tendency of the bromide (74) to undergo decarboxylative elimination in a similar fashion to the β-bromovaline derivative (70). As a result, the bromide (74) was characterized as its corresponding enimide (76).

Treatment of a 1:1 mixture of the diastereomers of 3-bromo-*N*-phthaloylphenylalanine (74) with silver carbonate at room temperature, under conditions identical to those described above for reaction of the bromovaline derivative (70), afforded the enimide (76) as a single geometric isomer in 83% yield. Evidence for the enimide (76) was gained from the physical and spectral data. In particular, the ^{1}H n.m.r. spectrum showed doublet resonances at δ 7.36 and 7.65 with a coupling constant of J = 15.2 Hz, the magnitude of which is as expected for the *trans*-isomer.[97] The mass spectrum showed a peak at m/z 249.079 corresponding to the molecular ion. The composition of the enimide (76) was confirmed by microanalysis.

When the reaction of the bromide (74) with silver carbonate was carried out between 0-5°, the product composition altered quite considerably (Scheme 20). Analysis of the crude reaction mixture using ^{1}H n.m.r. spectroscopy strongly indicated the presence of the *cis*-isomer of the lactone (75a), a trace amount of the *trans*-isomer of the lactone (75b) and the enimide (76). The presence of the *cis*-isomer of the lactone (75a) was evident from doublet resonances at δ 6.33 (J = 9.1 Hz) and 6.70 (J = 9.1 Hz) attributable to the C(3) and C(4) protons. The C(3) and C(4) protons of the *trans*-isomer of the lactone (75b) gave rise to doublet resonances in the spectrum at δ 5.92 (J = 4.5 Hz) and 6.67 (J = 4.5 Hz). Following chromatography of the reaction mixture on silica, the *cis*-isomer of the lactone (75a) was isolated as a pale yellow solid in 13% yield, the enimide (76) was isolated in 67% yield but the *trans*-isomer of the lactone (75b) was not isolated.



(74) (75) (76)

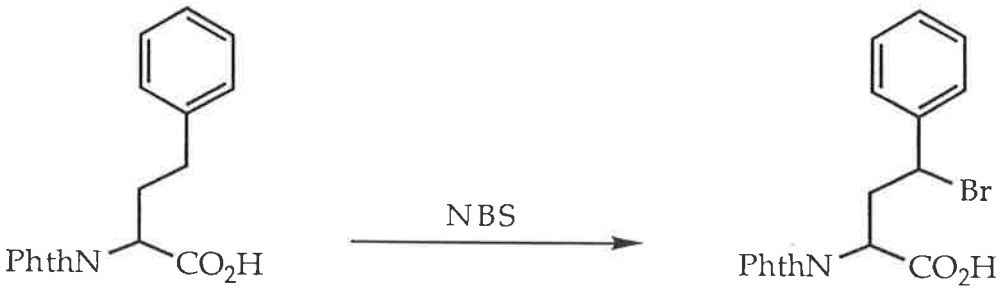
Scheme 20

It would appear from these results that formation of the enimide (76) proceeds *via* the lactone (75). The lactone (75) would result from cyclization of the carboxylate salt of the bromide (74).[98] The lactone (75) is obviously unstable to heat and undergoes decarboxylation to afford the enimide (76). It has been well established that upon heating β-lactones undergo facile cycloreversions to generate the corresponding alkenes and carbon dioxide.[99]

Initial attempts to crystallize the bromide (74) from ethanol/water resulted in the conversion of one of the diastereomers (74i) to the enimide (76), which precipitated from solution. Filtration of the solution and concentration of the

mother liquor yielded the other diastereomer (74ii) as a pale green solid, which was assigned the (2*RS*,3*SR*)-stereochemistry based on the similarity of its ^{1}H n.m.r. spectral data with that of the (2*RS*,3*SR*)-diastereomer of the corresponding ester (49aii). The selective conversion of the (2*RS*,3*RS*)-diastereomer of the acid (74i) to the enimide (76) can be attributed to a preferred conformation where the carboxylate is *anti* to bromine. The corresponding conformer of the other diastereomer (74ii) is disfavoured by steric interactions between the phthalimido and phenyl substituents.

The reaction of *N*-phthaloylhomophenylalanine (68) with *N*-bromo-succinimide gave a 1.2:1 mixture of diastereomers of the bromide (77). The structure of the bromide (77) and the ratio of diastereomers was deduced from



(68) (77)

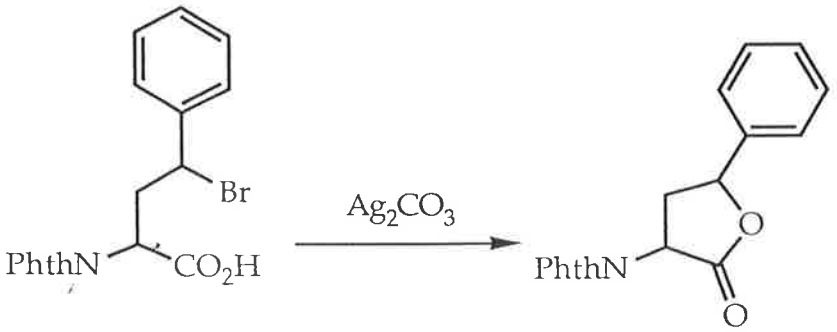
Scheme 21

spectral data. In the ^{1}H n.m.r. spectrum there was a triplet resonance at δ 5.25 (J = 7.4 Hz), due to the α-proton of the major diastereomer, while a triplet resonance at δ 5.09 (J = 7.5 Hz) corresponded to the α-proton of the minor diastereomer. The mass spectrum of the bromide (77) showed peaks at m/z 389 and 387, corresponding to the isotopic molecular ions. Accurate mass

measurement of the molecular ion at *m/z* 387.012 was in good accord with the calculated value of *m/z* 387.011. Attempts to crystallize the bromide (77) were unsuccessful owing to the propensity of the material to form the γ-lactone (78). This made it possible, however, to characterize the bromide (77) as the γ-lactone derivative (78).

Reaction of 4-bromo-*N*-phthaloylhomophenylalanine (77) with silver carbonate under conditions similar to those described above, gave a 1:1 mixture of diastereomers of the γ-lactone (78), in 67% yield (Scheme 22). The ratio of diastereomers was determined from the ^{1}H n.m.r. spectrum. Attempts to separate the diastereomers by chromatography on silica were unsuccessful, however, crystallization of the mixture from dichloromethane/light petroleum resulted in the formation of crystals of different shapes, enabling partial separation of the diastereomers by mechanical means. The ^{1}H n.m.r spectrum of the diastereomer (78i), which crystallized as spars, showed resonances at δ 5.31 (*J* = 9.2 and 12.1 Hz) and 5.50 (*J* = 6.2 and 10.7 Hz), corresponding to the γ- and α-protons, respectively. An ABMX splitting system centred at δ 2.89 (*J* = 10.7, 12.1, and 12.5 Hz) and δ 2.91 (*J* = 6.2, 9.2 and *J* = 12.5 Hz) was indicative of the diastereotopic nature of the β-protons. Elemental analysis confirmed the composition of the diastereomer of the γ-lactone (78i). The ^{1}H n.m.r. spectrum of the diastereomer (78ii), isolated as colourless clusters of crystals, showed peaks in the spectrum at δ 5.16 (triplet, *J* = 9.7 Hz) and 5.92 (*J* = 3.4 and 9.7 Hz) corresponding to the γ- and α-protons, respectively. The diasterotopic β-protons gave rise to resonances at δ 2.64 (*J* = 3.4, 9.7 and *J* = 13.0 Hz) and 3.11 (*J* = 9.7 and 13.0 Hz). The mass spectrum of the γ-lactone (78) showed a peak at *m/z* 307 attributable to the molecular ion. High resolution mass spectral analysis of the molecular ion showed a peak at m/z 307.083. This is in good accord with the theoretical

value of *m*/z 307.085. Altman and Ben-Ishai[100] have found that in related 2,4-disubstituted butyrolactones the chemical shift difference between the geminal protons is larger for the *cis*-isomer. On this basis the lactones (78i) and (78ii) can be assigned the *trans*- and *cis*-stereochemistry, respectively.



(77) (78)

Scheme 22

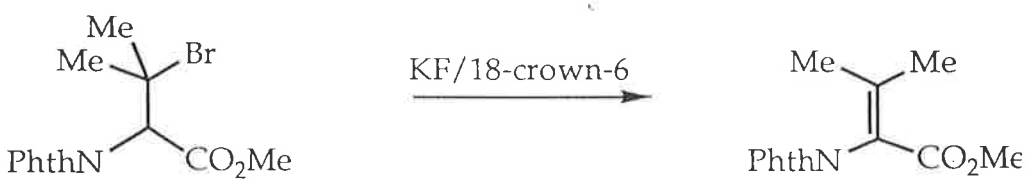
The above reactions of the acids (65a) - (68a) to give the corresponding bromides (65b) - (68b) establish that side-chain functionalization of *N*-phthaloylamino acids can be achieved without protection of the carboxyl group. In addition, lactones such as the derivatives of leucine (73) and homophenylalanine (78) are accessible using this approach. Amino acid lactones have attracted attention as strychnine antagonists[101] and as synthetically useful derivatives of those amino acid derivatives. The latter criterion stems from the amenability of incorporating the amino acid residues directly into a peptide using the lactone form.[102]

RESULTS AND DISCUSSION: CHAPTER TWO

Synthesis of α,β-Dehydroamino Acid Derivatives

Access to the β-brominated amino acid derivatives (48b), (49b) and (69b) as described in Chapter One of the Results and Discussion, prompted a study of their utility in the stereoselective synthesis of α,β-dehydroamino acid derivatives.

Treatment of 3-bromo-*N*-phthaloylvaline methyl ester (48b) with the 18-crown-6 complex of potassium fluoride in acetonitrile[103] at reflux for 2 h afforded *N*-phthaloyl-α,β-dehydrovaline methyl ester (79) in 77% yield, after chromatography on silica and recrystallization from ethyl acetate/light petroleum (Sheme 23). The spectral and physical characteristics of the α,β-dehydrovaline derivative (79) were consistent with those previously reported.[104,105] In particular, the ^{1}H n.m.r. spectrum showed a peak at δ 3.68 corresponding to the methyl ester protons, while the singlet resonances at δ 1.88 and 2.43 were attributed to the protons of the vinylic methyl groups.



(48b) (79)

Scheme 23

Analysis of the *N*-phthaloyl-α,β-dehydrovaline derivative (79) using X-ray crystallography (Appendix 1) revealed some interesting details about the conformation of the molecule (Figure 2). The C(1)-C(2) and C(2)-C(3) bond lengths of 1.481(4)Å and 1.343(4)Å, respectively, coupled with the torsion angle -25.1° for C(3)-C(2)-C(1)-O(1) and the relative disposition of the substituents indicate that there is no extended conjugation in this molecule. In addition, the *N*-phthaloyl group adopts an orientation perpendicular to the plane of C(1)-C(2)-C(3).

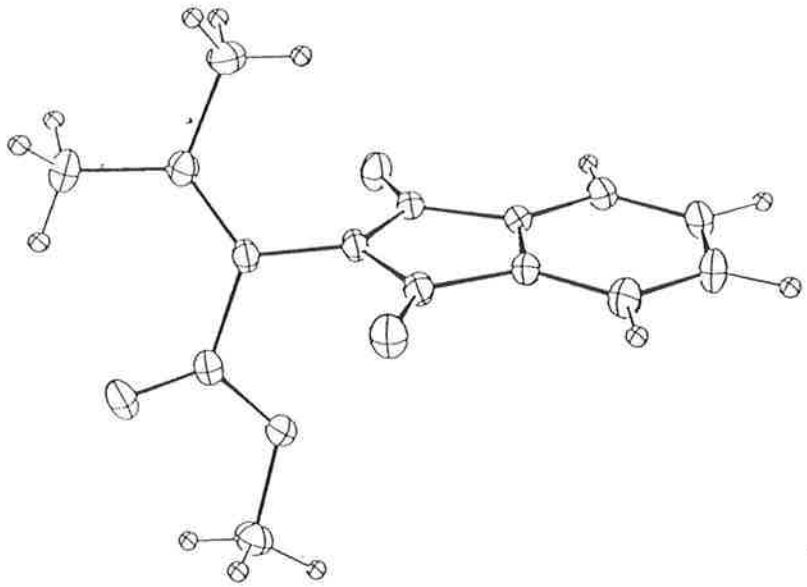
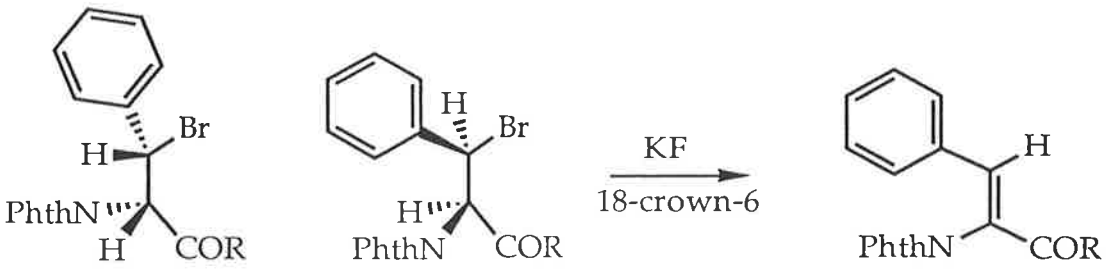


Figure 2. Crystal structure of *N*-phthaloyl-α,β-dehydrovaline methyl ester (79).

Treatment of the (2*RS*,3*RS*)-diastereomer of the β-bromophenylalaninamide (69bi) with the 18-crown-6 complex of potassium fluoride in acetonitrile at reflux for 0.5 h gave the (*Z*)-dehydrophenylalanine derivative (80), in 84% yield (Scheme 24). The structure of the product was deduced from the spectral and X-ray crystallographic data (Appendix 2). The ^{1}H n.m.r. spectrum showed a singlet peak at δ 7.59 corresponding to the vinylic proton. A broad singlet peak at δ 5.97 was attributed to the amide proton. Accurate mass analysis of a

peak in the mass spectrum at *m*/z 348.149 was in good accord with the theoretical value for the molecular ion. Elemental analysis was consistent with the composition of the dehydrophenylalanine derivative (80).



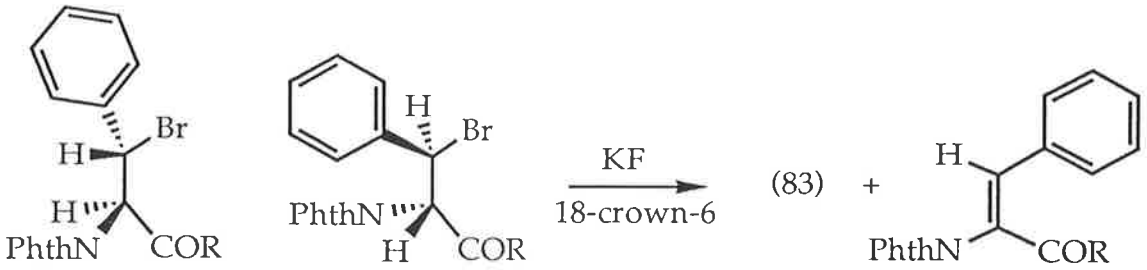
(69bi) (80)

R = $NHC(Me)_3$

Scheme 24

Similar treatment of the (2*RS*,3*SR*)-diastereomer of the bromide (69bii) with the 18-crown-6 complex of potassium fluoride gave a 5:1 mixture of the (*E*)- and (*Z*)-dehydrophenylalanine derivatives (81) and (80), respectively (Scheme 25). This was evident from the ^1H n.m.r. spectrum of the crude reaction mixture which showed two singlet resonances at δ 1.22, due to the protons of the *tert*-butyl group of the (*E*)-isomer (81), and at δ 1.40, due to the protons of the *tert*-butyl group of the (*Z*)-isomer (80). The (*E*)-isomer (81) and the (*Z*)-isomer (80) were separated by fractional crystallization from ethyl acetate/light petroleum, with the (*E*)-isomer (81) crystallizing in 57% yield, while the (*Z*)-isomer (80) was obtained in 10% yield. Other characteristic resonances in the ^1H n.m.r. spectrum of the (*E*)-dehydrophenylalanine derivative (81) were a singlet resonance at δ 7.05, due to the vinylic proton, and a broad singlet resonance at δ 5.50, attributable to the amide proton. The mass spectrum gave rise to a peak at *m*/z 348.147 which corresponded with the theoretical value for the molecular ion. The composition of the (*E*)-isomer

(81) was confirmed by elemental and X-ray crystallographic analysis (Appendix 3).

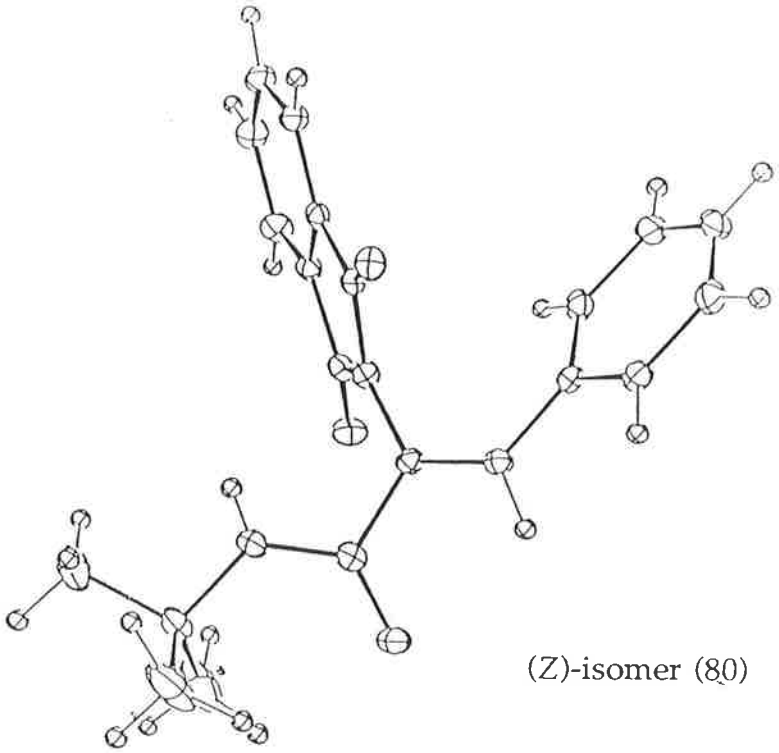


(69bii) (81)

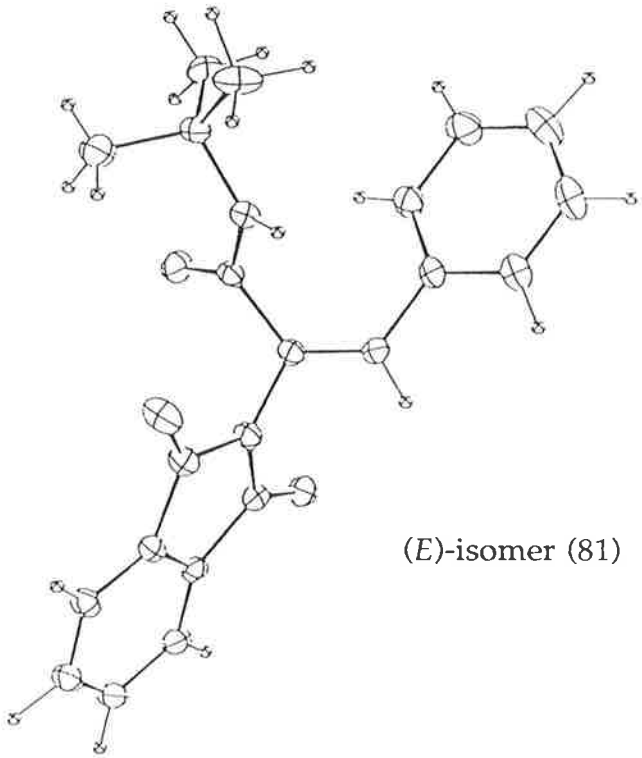
R = $NHC(Me)_3$

Scheme 25

The reactions of the diastereomers of the β-bromophenylalanine derivative (69b) with potassium fluoride are stereoselective and most probably favour *anti*-elimination. It is on this basis that the bromide (69bi) which affords solely the (*Z*)-dehydrophenylalanine derivative (80) was assigned the (2*RS*,3*RS*)-stereochemistry, while the bromide (69bii) that gave mainly the (*E*)-dehydrophenylalanine derivative (81) was determined to have the (2*RS*,3*SR*)-stereochemistry. Formation of the (*Z*)-dehydrophenylalanine derivative (80) as a minor product in the reaction of the bromide (69bii) can be explained by deprotonation of the bromide at the α-centre, followed by rotation about the C(2)-C(3) bond, with subsequent elimination of bromide ion. By submitting the (*E*)-isomer (81) to the reaction conditions for a further 2 h and observing no isomerization to the (*Z*)-isomer (80), it was possible to rule out an alternative explanation of Michael-type addition of base to the β-carbon of the double bond in the (*E*)-isomer (81), followed by rotation about the C(2)-C(3) bond and elimination of base.



(Z)-isomer (80)



(*E*)-isomer (81)

Figure 3. Crystal structures of the α,β-dehydrophenylalanine derivatives (80) and (81).

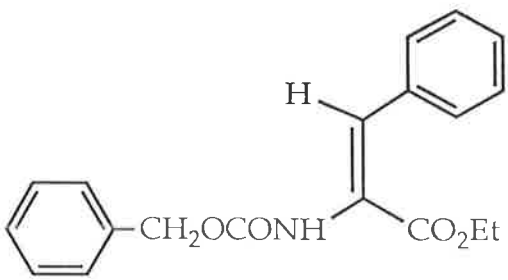
The molecular structures of the dehydrophenylalanine derivatives (80) and (81), as determined by X-ray crystallographic analysis, are illustrated in Figure 3, and selected bond lengths and bond angles are listed in Table 1. The structures are truly molecular, there being no significant intermolecular interactions in either crystal lattice. As can be seen from Table 1 there are no significant differences in bond lengths describing the two isomers.

Bond lengths (Å)			Bond angles (degrees)		
Atoms	(80)	(81)	Atoms	(80)	(81)
C(1)-O(1)	1.236(3)	1.216(4)	O(1)-C(1)-N(3)	124.2(2)	124.9(3)
C(1)-N(3)	1.337(3)	1.340(5)	O(1)-C(1)-C(2)	120.1(2)	119.8(3)
C(1)-C(2)	1.502(3)	1.505(5)	N(3)-C(1)-C(2)	115.7(2)	115.3(3)
C(2)-N(2)	1.431(3)	1.428(4)	C(1)-C(2)-N(2)	117.1(2)	113.5(3)
C(2)-C(3)	1.336(3)	1.331(5)	C(1)-C(2)-C(3)	120.3(2)	126.8(3)
N(3)-C(4)	1.408(3)	1.467(5)	N(2)-C(2)-C(3)	122.5(2)	119.5(3)
C(3)-C(31)	1.475(5)	1.475(5)	C(2)-C(3)-C(31)	129.8(2)	127.3(4)
			C(2)-C(3)-H(3)	116(1)	119(2)
			C(31)-C(3)-H(3)	114(1)	114(2)

Table 1. Selected interatomic parameters for (*Z*)-*N*-*tert*-butyl-N^{α}-phthaloyl-α,β-dehydrophenylalaninamide (80) and (*E*)-*N*-*tert*-butyl-N^{α}-phthaloyl-α,β-dehydrophenylalaninamide (81).

There are some significant differences in bond angles, however, notably the angles about C(2). The C(1)-C(2)-C(3) angle of 126.8(3)° in the (*E*)-isomer (81) is greater than the comparable angle of 120.3(2)° in the (*Z*)-isomer (80) owing to the proximity of the phenyl group to the *N*-*tert*-butylamido residue; the remaining angles about C(2) are contracted in the (*E*)-isomer (81) to accommodate the expansion in the C(1)-C(2)-C(3) angle. The lack of coplanarity of the four critical residues around C(2)-C(3) indicates that there is little if any extended conjugation in either of the dehydrophenylalanine derivatives (80) or (81). In summary, on the basis of the results of the X-ray crystallographic analysis the only apparent differences defining the two molecules may be explained in terms of steric effects.

The crystal structures of several other dehydrophenylalanine derivatives have been reported.[44,106-113] Interestingly in all but one example[106] the compounds were found to have the (*Z*)-configuration and showed little or no extended conjugation. In the case of the *N*-benzyloxycarbamate-protected derivative (82), the single (*E*)-dehydrophenylalanine derivative hitherto reported, there was found to be substantial conjugation between the carbamate residue and C(2)-C(3). This difference probably arises from the relative facility of the carbamate residue to reorganize the π-electron density in the (*E*)-dehydrophenylalanine derivative (82), compared to the amido substituents in each of the (*Z*)-dehydrophenylalanine derivatives.



(82)

There are no molecular structure data for the (Z)-isomer corresponding to the carbamate (82), and the isomers (80) and (81) structurally characterized in this study are the first such pair available. The data for the (*E*)-isomer (81) establishes that extended conjugation is not a prerequisite for the synthesis of (*E*)-dehydrophenylalanine derivatives. The steric effects evident from a comparison of the isomers (80) and (81) may reflect why the (*Z*)-isomers of dehydrophenylalanine derivatives seem to predominate, but the extent of this correlation is not clear.

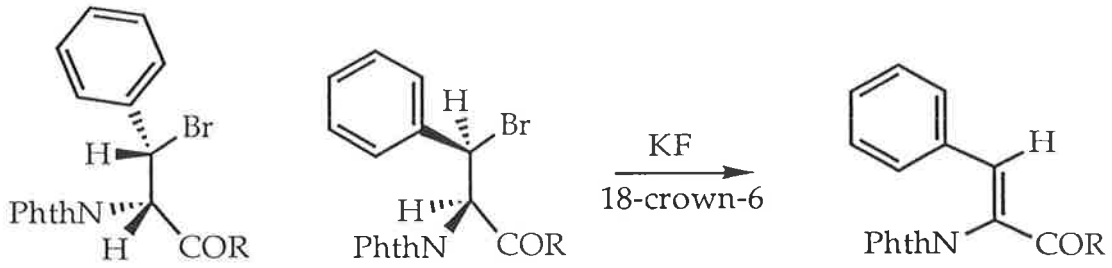
There has been a number of reports of the isomerization of dehydrophenylalanine derivatives under neutral and acidic conditions.[106,114-116] For example, the (*E*)-dehydrophenylalanine derivative (82) isomerized to the corresponding (*Z*)-isomer on heating in chloroform and, more rapidly, on standing in neat trifluoroacetic acid.[106] In contrast both the phthalimides (80) and (81) were stable under these conditions. Their stability to acid presumably reflects the lack of extended conjugation and the steric hindrance to direct protonation of the double bond in each molecule.

A number of empirical spectroscopic rules have been developed for the determination of the configuration of dehydrophenylalanine derivatives. Srinivasan, Richards and Olsen[116] reported that in compounds with the (Z)-configuration, the ^{1}H n.m.r. chemical shift of the vinyl proton shows a downfield shift when the solvent is changed from chloroform to trifluoro-acetic acid, whereas the converse is observed with (*E*)-isomers. In accord with this observation, the ^{1}H n.m.r. chemical shift of the vinyl proton in the (Z) isomer (80) moves 0.15 ppm downfield from δ 7.59 in chloroform to δ 7.74

in trifluoroacetic acid, whereas that of the (*E*)-isomer (81) moves 0.17 ppm upfield from δ 7.05 in chloroform to δ 6.88 in trifluoroacetic acid.

Prokof'ev and Karpeiskaya[117] reported the use of the $^3J_{C_1,H_\beta}$ vicinal coupling constant between the carbonyl carbon and the vinyl proton in the proton coupled ^{13}C n.m.r. spectrum to distinguish between the (*E*)- and (*Z*)-isomers of related unsaturated azlactones and the corresponding carboxylic acids. They found 12.5 and 10.0 Hz coupling constants for (*E*)-isomers and 5.5 and 5.0 Hz coupling constants for (*Z*)-isomers of azlactones and acids, respectively. In the proton-decoupled spectra, the carbonyl carbon of the (*E*)-isomer (81) had a chemical shift of δ 161.9 and that of the (*Z*)-isomer (80) had a chemical shift of δ 162.9. In the proton-coupled spectra, coupling $^3J_{C_1,H_\beta}$ of 9.6 Hz for the (*E*)-isomer (81) and 3.5 Hz for the (*Z*)-isomer (80) was observed, thus confirming the earlier correlation.

Reactions of the ester (49b), an analogue of the amide (69b), were also investigated. Treatment of (2*RS*,3*RS*)-3-bromo-*N*-phthaloylphenylalanine methyl ester (49bi) with the 18-crown-6 complex of potassium fluoride under similar conditions to those described above, gave the (*Z*)-dehydrophenylalanine derivative (83) in 88% yield (Scheme 26). The structure of the dehydrophenylalanine derivative (83) was confirmed on the basis of spectral data. The ^1H n.m.r. spectrum showed a singlet resonance at δ 3.82 corresponding to the ester methyl group. The vinylic proton resonated as a singlet at δ 8.12. A peak at *m/z* 307.085 in the mass spectrum corresponded to the molecular ion of the dehydroamino acid derivative (83) and microanalytical data was consistent with the composition.

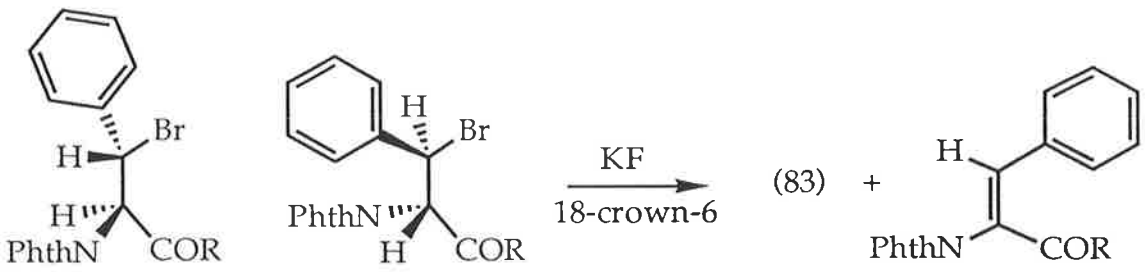


(49bi) (83)

R = OMe

Scheme 26

Reaction of the diastereomeric bromide (49bii) with potassium fluoride under similar conditions to those described for the preparation of the (*Z*)-isomer (83) resulted in the production of a 2:1 mixture of the (*Z*)- and (*E*)-dehydroamino acid derivatives (83) and (84), respectively (Scheme 27). The ratio of geometric isomers was determined from the ^{1}H n.m.r. spectrum of the crude reaction mixture. The spectrum showed singlet resonances at δ 3.74 and 3.82 due to the protons of the methyl ester of the (*E*)-isomer (84) and the (*Z*)-isomer (83), respectively. The two isomers were found to be inseparable by chromatography on silica. Consequently, they were isolated as a mixture in 88% yield. The two isomers proved to be partially separable by fractional crystallization from ethyl acetate/light petroleum. The (*Z*)-isomer (83) was obtained pure in this manner, but the (*E*)-isomer (84) was contaminated with residual (*Z*)-isomer (83). The ^{1}H n.m.r spectrum of a 5:1 mixture of the (*E*)- and (*Z*)-isomers (84) and (83) showed a singlet resonance at δ 7.23 due to the vinylic proton of the (*E*)-isomer (84).



(49bii) (84)

R = OMe

Scheme 27

The relative lack of stereoselectivity in the reaction of the ester (49bii) compared to the amide (69bii) can be attributed to the greater acidity of the α-hydrogen of the ester (49bii), such that formation of the α-anion and rotation about the C(2)-C(3) bond, prior to elimination of bromide, proceeds to a greater extent.

The molecular structure of the (Z)-dehydrophenylalanine methyl ester derivative (83), as determined using X-ray crystallography, is illustrated in Figure 4. There are two molecules in the unit cell. Although the torsion angles O(1)-C(1)-C(2)-C(3) of -1.0 and -3.5° in these molecules indicate the possibility of interaction between orbitals of the ester and alkene moieties in each molecule, the C(1)-C(2) and C(2)-C(3) bond distances indicate a lack of conjugation (Appendix 4).

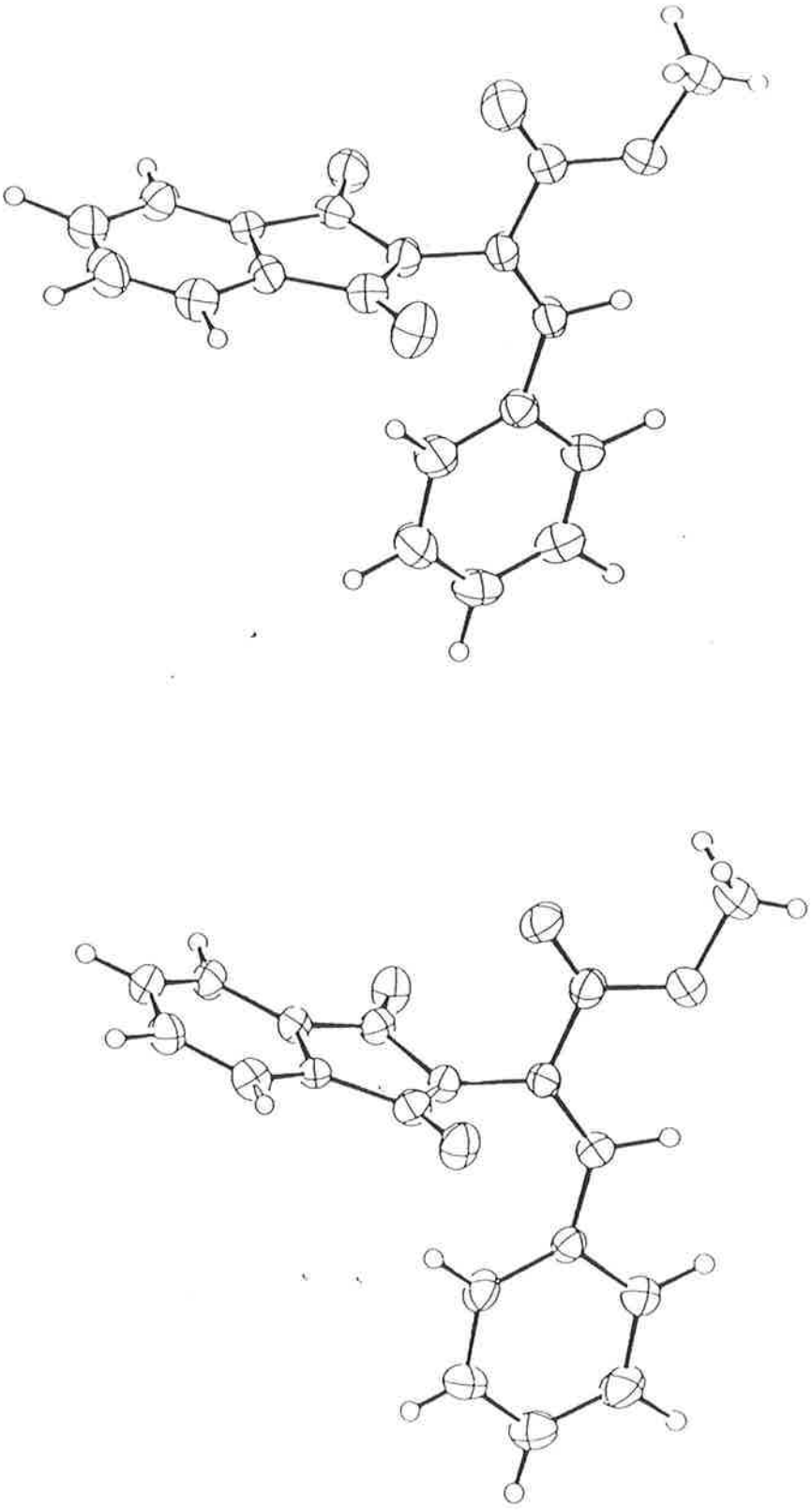


Figure 4. Crystal structures of the (Z)-dehydrophenylalanine methyl ester derivative (84).

In the broad-band proton-decoupled ^{13}C n.m.r. spectra, the carbonyl carbon of the (*E*)-isomer (84) had a chemical shift of δ 163.7, and that of the (*Z*)-isomer (83) had a chemical shift of δ 163.8. In the proton-coupled spectra, coupling $^{3}J_{C_1,H_\beta}$ of 15.0 Hz for the (*E*)-isomer (84) and 3.9 Hz for the (*Z*)-isomer (83) was observed. The larger coupling constant for the (*E*)-isomer (84) is in accord with the above observations made for the *N-tert*-butylamide derivatives (80) and (81), and the correlation proposed by Prokof'ev and Karpeiskaya.[117]

In the ^{1}H n.m.r. spectrum the chemical shift of the vinyl proton of the (*Z*)-isomer (83) moves 0.21 ppm downfield from δ 8.12 in chloroform to δ 8.33 in trifluoroacetic acid, consistent with the correlation discussed above for the amides (80) and (81). However, in contrast to that correlation, the chemical shift of the vinylic proton for the (*E*)-isomer (84) moves 0.04 ppm downfield from δ 7.23 in chloroform to δ 7.27 in trifluoroacetic acid. Thus the empirical rule proposed by Srinivasan, Richards and Olsen,[116] does not always hold.

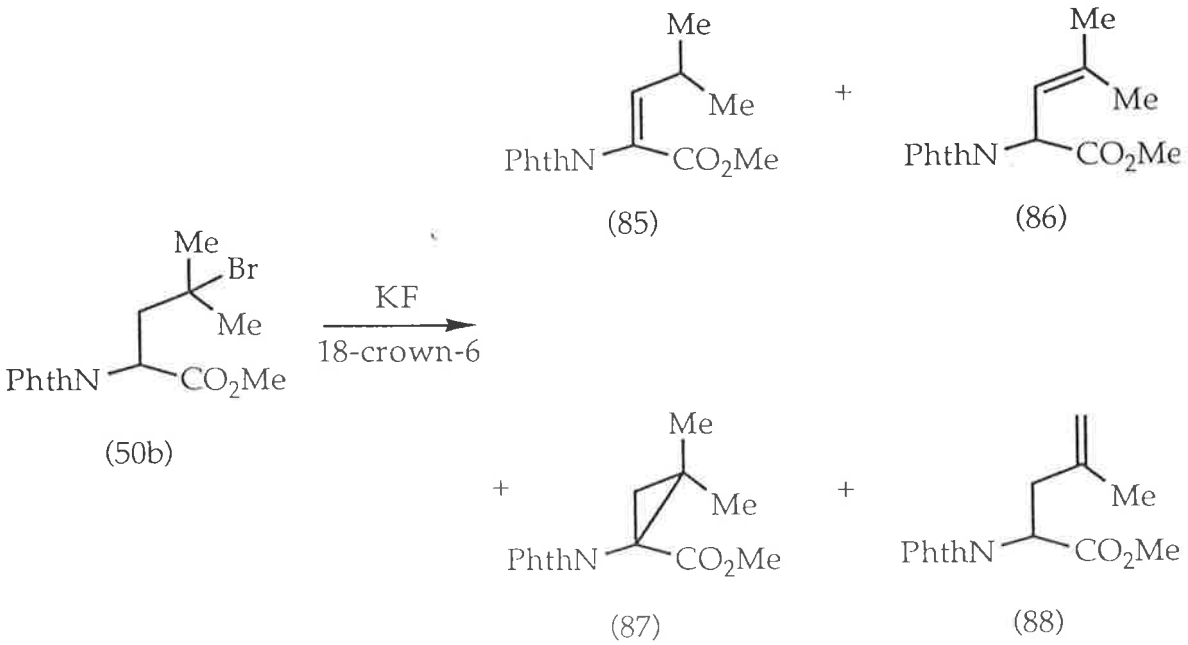
The reaction of the ester (49b) to give the dehydrophenylalanine derivatives (83) and (84), combined with the above reactions of the bromides (48b) and (69b) to give the corresponding dehydroamino acid derivatives (79)-(81), indicate the utility of side-chain functionalization of amino acid derivatives, followed by elimination, as a method for the stereoselective synthesis of α,β-dehydroamino acid derivatives.

RESULTS AND DISCUSSION: CHAPTER THREE

Elaboration of γ-Brominated *N*-Phthaloyl-α-amino Acid Derivatives

The work described in this Chapter was aimed at the synthesis of non-proteinogenic α-amino acid derivatives through elaboration of the γ-bromides (50b) and (51b), prepared as described in Chapter One of the Results and Discussion of this thesis. α,β-Methano- and γ-fluoro-amino acid derivatives were of particular interest as a result of their proven physiological activity.[30,31,55]

4-Bromo-*N*-phthaloylleucine methyl ester (50b) was treated with the 18-crown-6 complex of potassium fluoride in acetonitrile at reflux for 5 h. Following work-up, a mixture of four products was isolated. From the ^{1}H n.m.r. spectrum of this mixture, it was possible to tentatively identify the components as the α,β-dehydroleucine derivative (85), the β,γ-dehydroleucine derivative (86), the α,β-methanovaline derivative (87) and the γ,δ-dehydroleucine derivative (88), in the ratio 2.25 : 2.0 : 1.75 : 1.0 (Scheme 28).



(50b) (85) (86) (87) (88)

Scheme 28

The identity of *N*-phthaloyl-α,β-methanovaline methyl ester (87) was confirmed by comparison of its ^{1}H n.m.r. spectral data with that of an authentic sample, prepared by stirring the bromide (50b) with sodium hydride in tetrahydrofuran.[81] The ^{1}H n.m.r. spectra showed two singlet resonances, each with intensity equivalent to three protons, at δ 1.20 and 1.51, attributable to the protons of the γ-methyl substituents. Doublet resonances at δ 1.52 (J = 5.9 Hz) and 1.89 (J = 5.9 Hz) were attributed to the diastereotopic β-protons.

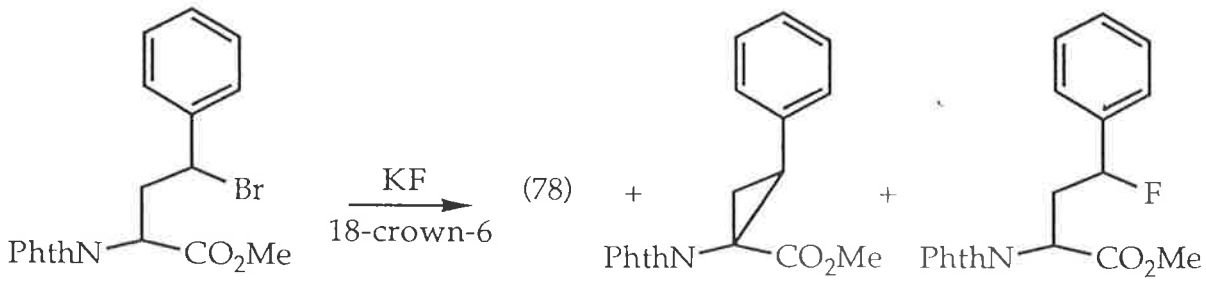
Evidence for the structure of *N*-phthaloyl-α,β-dehydroleucine methyl ester (85) was a doublet resonance at δ 7.16 (J = 10.7 Hz) in the ^{1}H n.m.r. spectrum corresponding to the vinylic β-proton, coupled to the γ-proton. The γ-proton gave rise to a septet of doublets resonance centred at δ 2.48 (J = 6.6 and 10.7 Hz). The protons of the γ-methyl substituents resonated in the spectrum as a doublet at δ 1.09 (J = 6.6 Hz). Only one isomer of the alkene (85) was detected. This is presumed to be the (*Z*)-isomer, based on the relative stability of (*E*)- and (*Z*)-dehydroamino acid derivatives.[106,114,115]

Evidence for *N*-phthaloyl-β,γ-dehydroleucine methyl ester (86) in the ^{1}H n.m.r spectrum was a septet of doublets resonance centred at δ 5.82 (J =1.4 and 9.1 Hz), corresponding to the vinylic proton coupled to the α-proton (δ 5.65, J = 9.1 Hz) and to the vinylic methyl substituents through long range coupling. The resonances attributable to the protons of the γ-methyl substituents appeared in the spectrum as two doublets at δ 1.78 (J = 1.4 Hz) and 1.79 (J = 1.4 Hz).

The ^{1}H n.m.r. spectrum of the mixture also showed broad singlets at δ 4.66 and 4.69, attributable to the vinylic protons of *N*-phthaloyl-γ,δ-dehydroleucine methyl ester (88). Doublets of doublets at δ 2.86 (J = 4.2 and 14.2 Hz) and 3.11 (J = 12.2 and 14.2 Hz) were attributable to the geminally coupled β-protons.

Formation of the β,γ-dehydroleucine derivative (86), the 2,3-methanovaline derivative (87) and the γ,δ-dehydroleucine derivative (88) can be attributed to direct elimination of the elements of hydrogen bromide from the bromide (50b). The α,β-dehydroleucine derivative (85) probably forms through fluoride-catalysed deprotonation/protonation of its isomer (86), which contains an acidic α-hydrogen.

In a similar fashion to that described above for reaction of the leucine derivative (50b), a 4:1 mixture of the diastereomers of 4-bromo-*N*-phthaloyl-homophenylalanine methyl ester (51b) was treated with 2 equivalents of potassium fluoride. The reaction afforded a complex mixture of products, with the components being difficult to separate. Following repeated chromatography on silica, a mixture comprising a 4:1 mixture of the (*Z*)- and (*E*)-diastereomers of *N*-phthaloyl-α,β-methanophenylalanine methyl ester (89), and a 1:1 mixture of the diasteromers of 4-fluoro *N*-phthaloylhomo-phenylalanine methyl ester (90) was isolated. A 1:1 mixture of the diastereomers of the 5-phenyl-3-phthalimido-γ-butyrolactone (78) was also obtained, in 25% yield (Scheme 29).



(51b) (89) (90)

Scheme 29

The lactone (78) was identified by comparison with an authentic sample obtained as described above. The identity of the α,β-methanophenylalanine derivative (89) was confirmed by comparison of its ^{1}H n.m.r. spectral data with that of an authentic sample, prepared by treating the bromide (51b) with sodium hydride.[81] Using this method, the α,β-methanophenylalanine derivative (89) was obtained as a 25:1 mixture of the (*Z*)- and (*E*)-diastereomers. The ^{1}H n.m.r. spectrum showed doublets of doublets at δ 2.27 (*J* = 6.6 and 9.9 Hz) and 2.43 (*J* = 6.6 and 8.5 Hz) which were attributed to the geminally coupled Cβ'-protons of the (*Z*)-diastereomer. A doublet of doublets at δ 3.38 (*J* = 8.5 and 9.9 Hz) was attributed to the benzylic Cβ-proton of the same diastereomer. The ^{1}H n.m.r spectrum of the (*E*)-diastereomer showed doublets of doublets at δ 1.90 (*J* = 6.2 and 9.9 Hz) and 2.50 (*J* = 6.2 and 9.1 Hz), which can be attributed to the Cβ'-protons. The benzylic Cβ-proton resonated as an apparent triplet at δ 3.17 (*J* = 9.5 Hz).

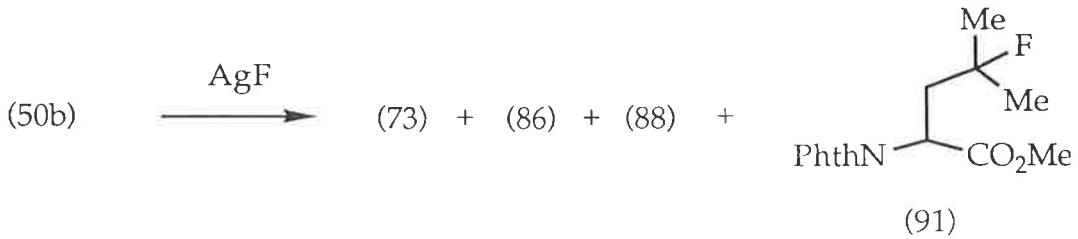
The γ-fluorohomophenylalanine derivative (90) was analysed by n.m.r and mass spectrometry. The ^{1}H n.m.r spectrum showed a doublet of doublets of doublets centred at δ 5.73 (*J* = 4.4, 7.7 and 47.9 Hz) corresponding to the γ-proton of one diastereomer. The largest coupling constant is characteristic of geminal fluorine-proton coupling.[97] The γ-proton of the other diastereomer resonated at δ 5.40 (*J* = 5.5, 9.0 and 48.1 Hz). The ^{19}F n.m.r. spectrum of the mixture showed two peaks at δ -102.0 and -105.4. The high resolution mass spectrum showed a peak at *m/z* 341.107, due to the molecular ion, which is in good accord with the theoretical value of *m/z* 341.106.

Evidently, in the reaction of the bromide (51b) with potassium fluoride, elimination to give the α,β-methanophenylalanine derivative (89) competes with nucleophilic substitution to give the fluoride (90). Production of the

lactone (78) can be attributed to a nucleophilic substitution reaction of the bromide (51b) with adventitious water, followed by cyclization.

A potentially useful product of the reaction of the bromide (51b) is the fluoride (90). In an attempt to improve the yield of this material and to obtain the leucine analogue (91), reactions of the bromides (50b) and (51b) with other sources of fluoride ion were studied. Initially silver fluoride was chosen. It is a popular fluorinating reagent as a result of its high selectivity and, because of its low basicity compared to alkali metal fluorides, it is more prone to react by nucleophilic substitution than by elimination.[118]

4-Bromo-*N*-phthaloylleucine methyl ester (50b), when treated with silver fluoride in anhydrous acetonitrile, afforded a complex product mixture from which 4-fluoro-*N*-phthaloylleucine methyl ester (91) was isolated as a low melting point solid in 15% yield. *N*-Phthaloyl-β,γ-dehydroleucine methyl ester (86) and *N*-phthaloyl-γ,δ-dehydroleucine methyl ester (88) were isolated in 42% yield as a 1:2 mixture of isomers, respectively. 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) was also isolated, in 14% yield (Scheme 30).



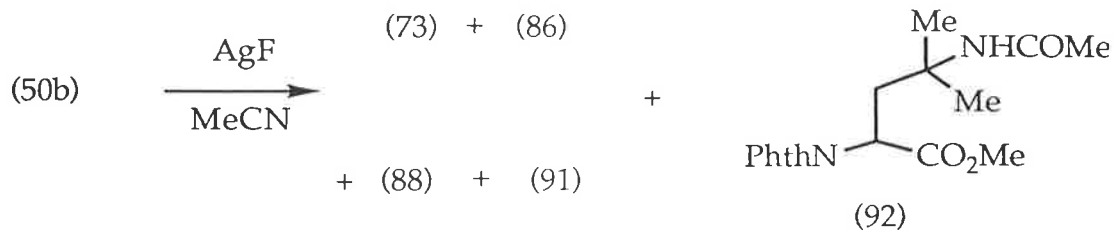
Scheme 30

The structure of 4-fluoro-*N*-phthaloylleucine methyl ester (91) was confirmed on the basis its physical and spectral data. In particular, the ^{1}H n.m.r. spectrum showed doublets at δ 1.38 (J = 21.43 Hz) and 1.47 (J = 21.16 Hz) corresponding to the protons of the γ-methyl substituents coupled to fluorine. The α-proton of the fluoride (91) resonated in the spectrum as a doublet of doublets at δ 5.18 (J = 2.8 and 11.0 Hz). The mass spectrum showed no molecular ion, however, fragment ions at *m/z* 278 $[M\text{-}OCH_3]^+$ and 234 $[M\text{-}CO_2CH_3]^+$ were present in the spectrum. The composition of the γ-fluoride (91) was confirmed by elemental analysis.

The contrast between the reaction of the bromide (50b) with potassium fluoride and silver fluoride is consistent with the greater nucleophilicity of the silver salt and basicity of the potassium salt. As discussed above, with potassium fluoride the production of the α,β-methanovaline derivative (87) and the α,β-dehydroleucine derivative (85) involved fluoride acting as a base, whereas these products were not seen in the reaction using silver fluoride. Conversely, the fluoride (91) results from nucleophilic substitution of the bromide (50b) and is only seen in the reaction using silver fluoride.

In an attempt to improve the yield of the γ-fluoride (91), the reaction conditions were modified by the addition of water. Efficient fluorination has been achieved using wet silver fluoride.[119] Treatment of the 4-bromo-*N*-phthaloylleucine derivative (50b) with excess silver fluoride in moist acetonitrile gave the γ-fluoroleucine derivative (91) in 16% yield. A 1:2 mixture of the β,γ- and γ,δ-dehydroleucine derivatives (86) and (88) was isolated from the reaction mixture, in 39% yield. The lactone (73) was also isolated, in 11% yield. An

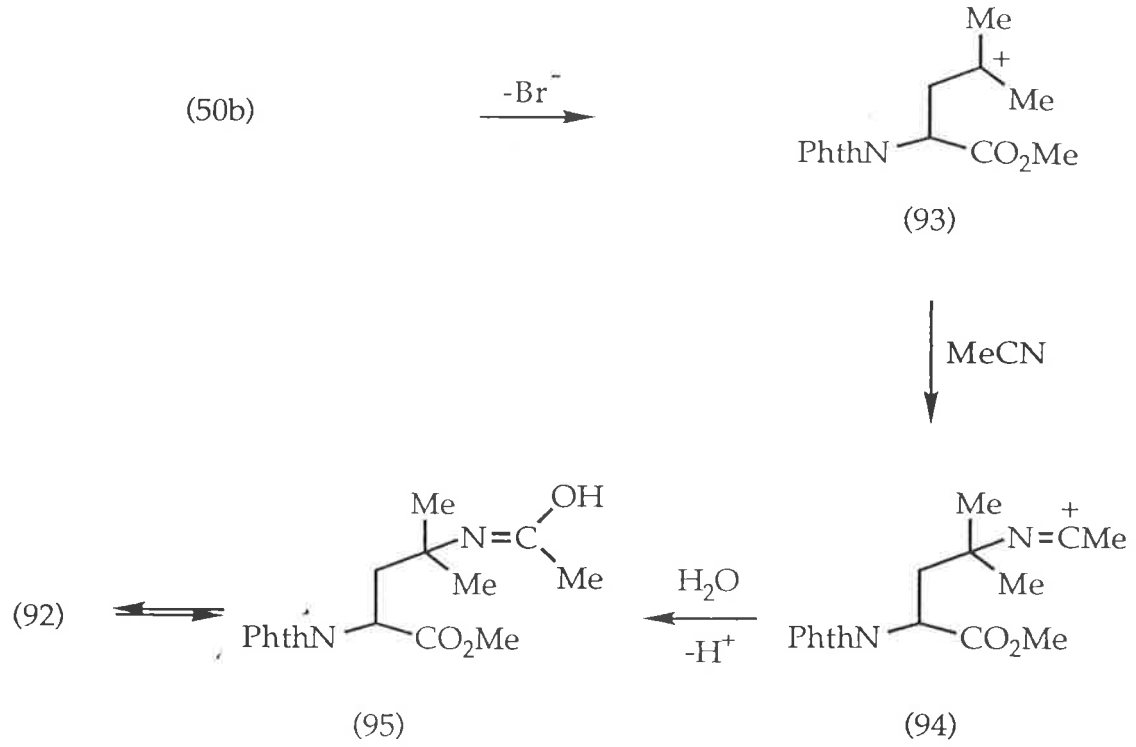
unusual product to come from this reaction was 4-acetamido-*N*-phthaloyl-leucine methyl ester (92), which was isolated in 14% yield (Scheme 31).



Scheme 31

The ^{1}H n.m.r. spectrum of the acetamide (92) showed a doublet of doublets at δ 4.92 (J = 4.0 and 7.7 Hz) attributable to the α-proton which was vicinally coupled to the diastereotopic β-protons. The β-protons resonated in the spectrum as doublets of doublets at δ 2.67 (J = 4.0 and 15.2 Hz) and δ 2.75 (J = 7.7 and 15.2 Hz). A broad singlet at δ 5.59 was due to the amide proton. The high resolution mass spectrum showed a peak at m/z 332.138, due to molecular ion, which is in good accord with the theoretical value of m/z 332.137.

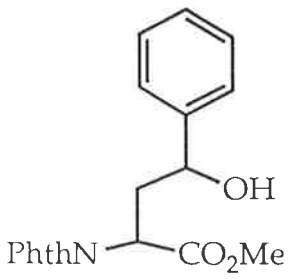
The acetamide (92) may result from what amounts to a modification of the Ritter reaction,[120,121] whereby the bromide (50b) is first converted to the carbocation (93). Acetonitrile then adds to the carbocation (93) generating the charged intermediate (94), which reacts with water to form the acetamide (92) *via* the tautomer (95) (Scheme 32).



Scheme 32

Silver fluoride supported on calcium fluoride has also received attention as a fluorinating agent with increased nucleophilicity.[122] Silver fluoride is supported on calcium fluoride by concentrating an aqueous mixture of silver carbonate, hydrogen fluoride and calcium fluoride. The 4-bromo-*N*-phthaloyl-leucine derivative (50b) was stirred in the dark with 2 mole equivalents of silver fluoride supported on calcium fluoride, in acetonitrile for 7 h at room temperature. Following work-up, the ^{1}H n.m.r. spectrum showed the major product of the reaction to be the γ-fluoride (91) which was subsequently isolated in 24% yield. The β,γ- and γ,δ-dehydroleucine derivatives (86) and (88) were isolated as a 1:2 mixture, in 32% yield. The ubiquitous γ-butyrolactone (73) was also isolated, in 14% yield.

Each of the procedures used to obtain the γ-fluoroleucine derivative (91) was also applied to the synthesis of 4-fluoro-*N*-phthaloylhomophenylalanine methyl ester (90), with best results being obtained using moist acetonitrile. Stirring one diastereomer of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) with silver fluoride in moist acetonitrile for 7 h afforded 4-fluoro-*N*-phthaloylhomophenylalanine methyl ester (90) in 24% yield as a 4:1 mixture of the diastereomers. The γ-lactone (78) was also obtained, as a 1:1 mixture of diastereomers in 11% yield. The major product isolated from the complex reaction mixture was a 33% yield of a 2:1 mixture of the diastereomers of 4-hydroxy-*N*-phthaloylhomophenyalanine methyl ester (96). The ^{1}H n.m.r. spectrum of this material showed a broad doublet of doublets at δ 4.57 (J = 4.2 and 8.8 Hz) attributable to the γ-proton of the minor diastereomer. A broad doublet of doublets resonance at δ 4.92 (J = 5.2 and 6.5 Hz) corresponded to the γ-proton of the major diastereomer. Doublet of doublets resonances at δ 5.08 (J = 5.3 and 8.8 Hz) and 5.25 (J = 4.7 and 10.4 Hz) were attributable to the α-proton of the major and minor diastereomers, respectively. The mass spectrum of the mixture of diastereomers showed a molecular ion at m/z 339.



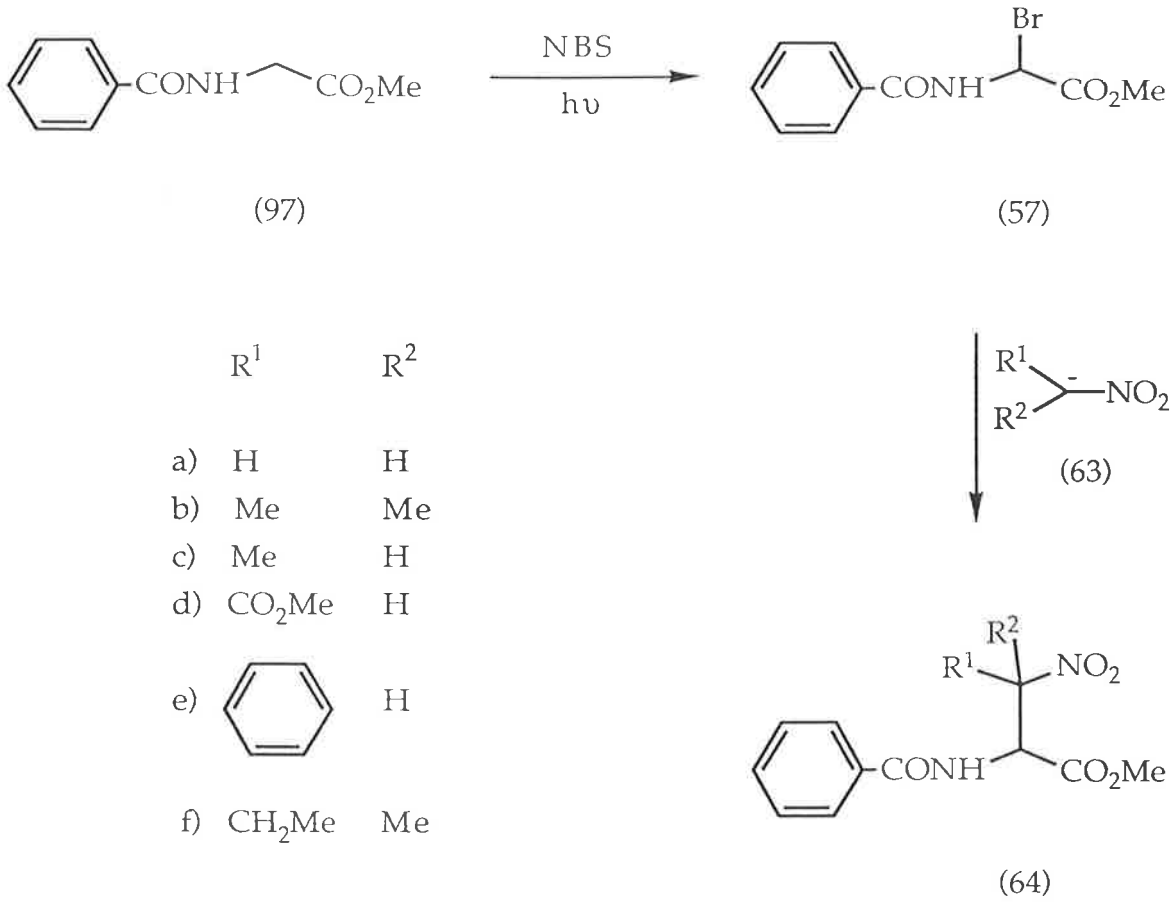
(96)

While the above reactions of the bromides (50b) and (51b) give complex mixtures of products, with silver fluoride the corresponding γ-fluoroamino acid derivatives (91) and (90) were obtained. Consequently, side-chain functionalization of proteinogenic amino acid derivatives followed by nucleophilic substitution with silver fluoride appears to be a viable complementary method for the synthesis of compounds of this type.

RESULTS AND DISCUSSION: CHAPTER FOUR

Synthesis of Amino Acid Derivatives Using Alkyl Nitronates

As an alternative method for the synthesis of amino acid derivatives, the scope and limitations of reaction of the α-bromoglycine derivative (57) with alkyl nitronates were investigated. In accordance with the literature procedure of Burgess and Easton,[93] treatment of *N*-benzoyl-2-bromoglycine methyl ester (57) with the alkyl nitronates (63a-e) gave the corresponding β-nitroamino acid derivatives (64a-e) in yields ranging from 61 to 84% (Scheme 33). The butanoic acid derivative (64c) was isolated as a 2:1 mixture of diastereomers in 61% yield, while the phenylalanine derivative (64e) was isolated as a 1:1 mixture of diastereomers in 66% yield. Conditions for the synthesis of the β-nitroalanine derivative (64a) were typical. A solution of *n*-butyllithium in hexanes (2.5 M) was added to a solution of nitromethane in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) (5:1) at -78°, under an atmosphere of nitrogen. *N*-Benzoyl-2-bromoglycine methyl ester (57), prepared immediately before use by the treatment of *N*-benzoylglycine methyl ester (97) with *N*-bromosuccinimide under ultraviolet photolysis (300 watt mercury lamp), was added in a dropwise fashion as a THF solution. The reaction mixture was maintained at -78° for 4 h, at which point the reaction was quenched with acetic acid. Work-up involved chromatography on silica with the product crystallizing from ethyl acetate/light petroleum. *N*-Benzoyl-3-nitroalanine methyl ester (64a) was isolated in 63% yield and possessed spectral and physical properties consistent with those reported.[93]



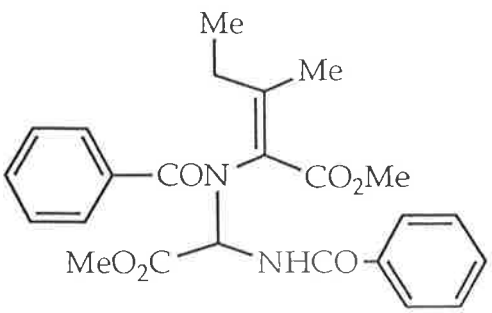
Scheme 33

A β-nitroamino acid derivative not previously prepared was *N*-benzoyl-3-nitro-*iso*-leucine methyl ester (64f). 2-Nitrobutane, the nitroalkane used to produce the β-nitro-*iso*-leucine derivative (64f), was prepared by oxidation of the primary amino group of *sec*-butylamine.[123] The method as outlined by Gilbert and Borden[123] involved refluxing *sec*-butylamine with *m*-chloro-perbenzoic acid in 1,2-dichloroethane for 4 h. 2-Nitrobutane was purified by distillation and isolated in 43% yield, and had physical and spectral properties consistent with those reported.[123]

Treatment of the α-bromoglycine derivative (57) with the nitronate salt (63f) of 2 nitrobutane, under conditions identical to those outlined for the synthesis of

the β-nitroalanine derivative (64a), afforded *N*-benzoyl-3-nitro-*iso*-leucine methyl ester (64f) in 70% yield as a 1:1.25 mixture of diastereomers. A small sample of this mixture was subjected to preparative h.p.l.c. on silica to separate the diastereomers, thus enabling n.m.r. spectral analysis of the individual isomers. The ^{1}H n.m.r. spectrum of the minor diastereomer showed a doublet resonance at δ 5.31 (J = 9.83 Hz) attributable to the α-proton. The diastereotopic γ-methylene protons appeared as quartets of doublets at δ 2.07 (J = 7.4 and 14.8 Hz) and 2.42 (J = 7.4 and 14.8 Hz). Analysis of the minor diastereomer using ^{13}C n.m.r. spectroscopy showed a peak at δ 92.2 of low intensity, clearly indicating the presence of a tertiary β-nitro substituent. F.t.i.r. spectral analysis of the minor diastereomer of the β-nitro-*iso*-leucine derivative (64f) showed two peaks in the spectrum at 1386 and 1549 cm^{-1} due to the asymmetrical and symmetrical stretching modes of the β-nitro group. The ^{1}H n.m.r. spectrum of the major diastereomer showed a doublet resonance at δ 5.31 (J = 9.9 Hz) attributable to the α-proton. The α-proton was coupled to the amide proton which appeared as a broad doublet in the spectrum at δ 7.24 (J = 9.9 Hz). The diastereotopic γ-methylene protons appeared in the spectrum as quartets of doublets at δ 1.93 (J = 7.3 and 14.6 Hz) and 2.20 (J = 7.3 and 14.6 Hz). The ^{13}C n.m.r. spectrum of the major diastereomer showed a low intensity peak at δ 92.2, characteristic of a tertiary carbon bearing a nitro group. F.t.i.r. spectral analysis of the major diastereomer of the β-nitroamino acid derivative (64f) showed peaks characteristic of the nitro moiety at 1394 and 1549 cm^{-1}. The mass spectrum of the mixture of diastereomers of the *iso*-leucine derivative (64f) displayed characteristic peaks at m/z 294 and 248, corresponding to the molecular ion and the fragment ion $[M\text{-}NO_2]^+$, respectively. Accurate mass analysis of the peak at m/z 294.122 corresponded to the calculated value of m/z 294.122.

An interesting by-product of the reaction of the nitronate salt (63f) of 2-nitrobutane with *N*-benzoyl-2-bromoglycine methyl ester (57) was the α,β-dehydro-*iso*-leucine derivative (98). Tentative structural assignment was based on ^{1}H n.m.r. and mass spectral data. The mass spectrum showed peaks at *m/z* 439 and 379, corresponding to the protonated molecular ion and the fragment ion $[M\text{-}CO_2CH_3]^+$, respectively. High resolution mass spectral analysis of the protonated molecular ion at *m/z* 439.188 was in good accord with the calculated value of *m/z* 439.187. From the ^{1}H n.m.r. spectrum of the α,β-dehydro-*iso*-leucine derivative (98) it was deduced that the product was a single geometric isomer existing in two conformations. Doublet resonances in the spectrum at δ 5.97 (*J* = 9.4 Hz) and 5.99 (*J* = 9.3 Hz) corresponded to the diamido-substituted methine proton in the major and minor conformers, respectively. Resonances attributable to the diastereotopic methylene protons of the major conformer appeared at δ 2.69 (*J* = 7.5 and 13.5 Hz) and 2.97 (*J* = 7.5 and 13.5 Hz). The analogous protons of the minor conformer resonated in the spectrum at δ 2.36 (*J* = 7.5 and 12.4Hz) and 2.72 (*J* = 7.4 and 12.4Hz). At 50°, the maximum operating temperature of the spectrometer, partial coalescence of the ^{1}H n.m.r. signals was observed. Confirmation of the structure of the product (98) was on the basis of X-ray crystallographic analysis of a single crystal (Appendix 5). The crystal structure is illustrated in Figure 5.



(98)

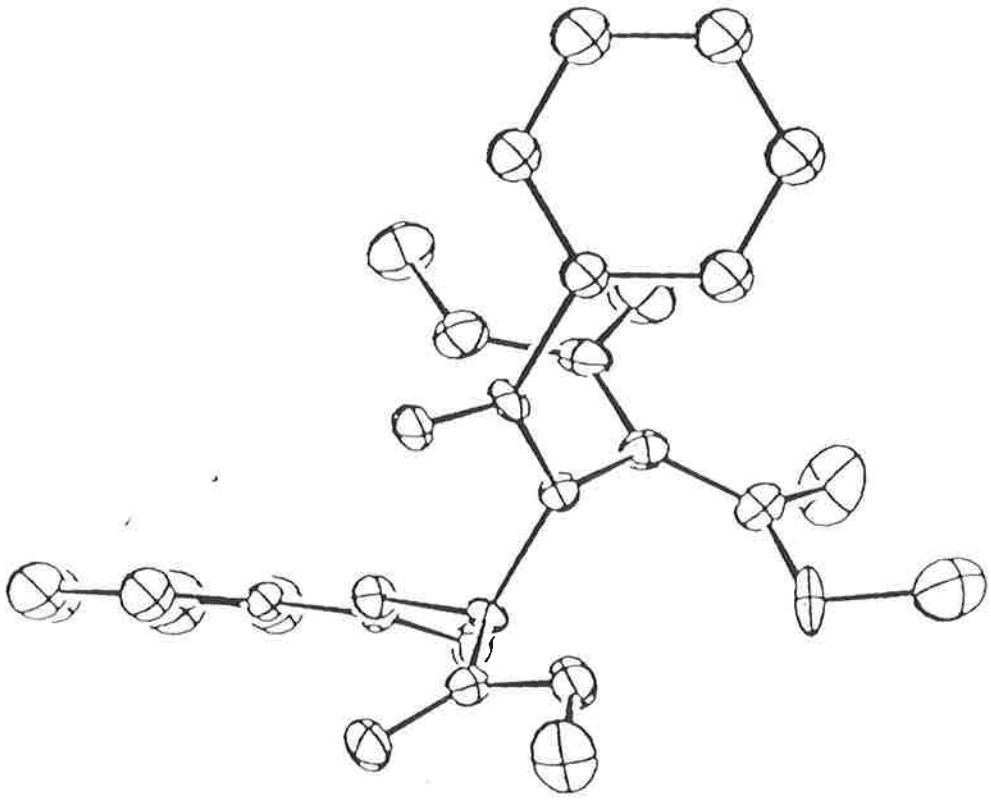
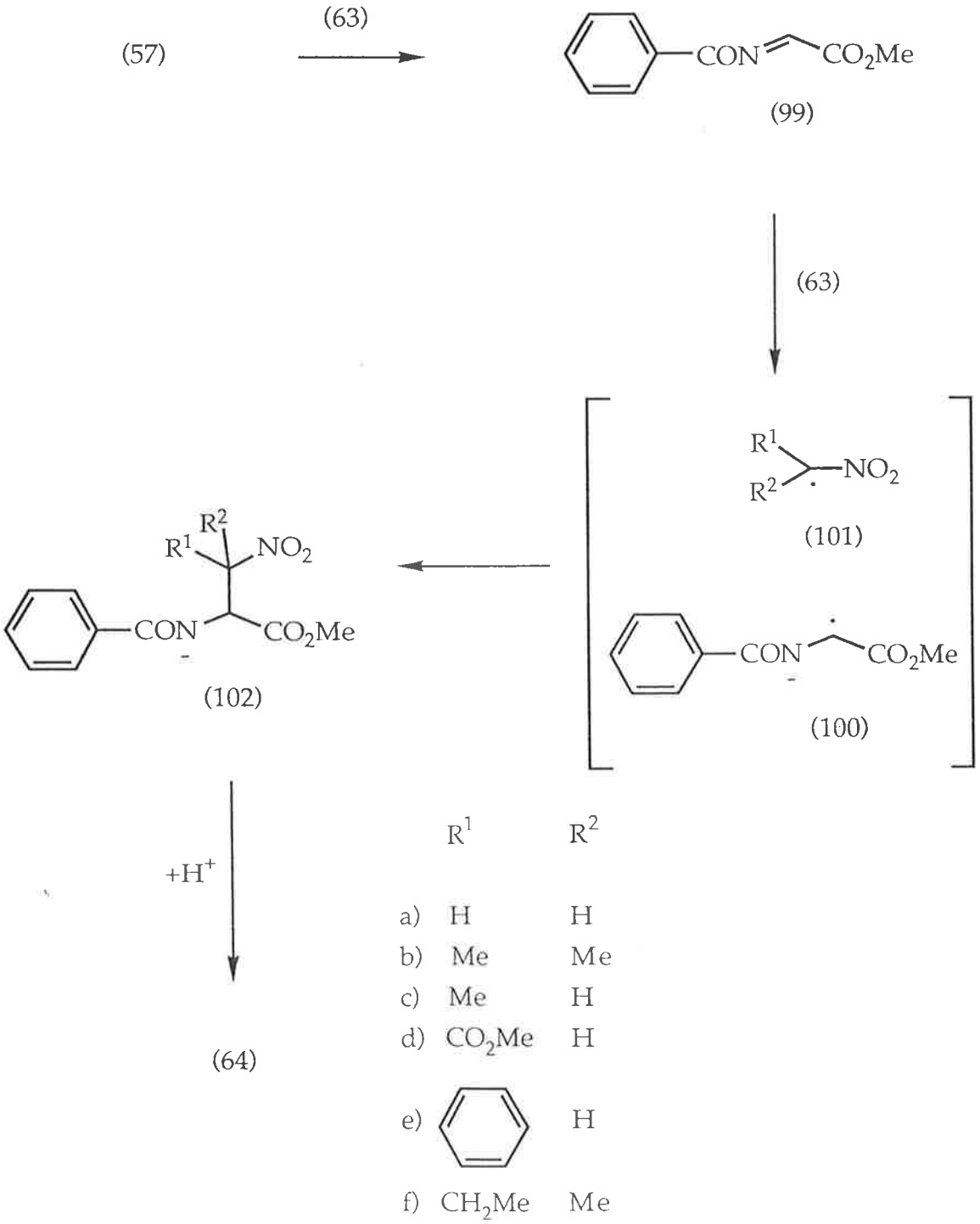


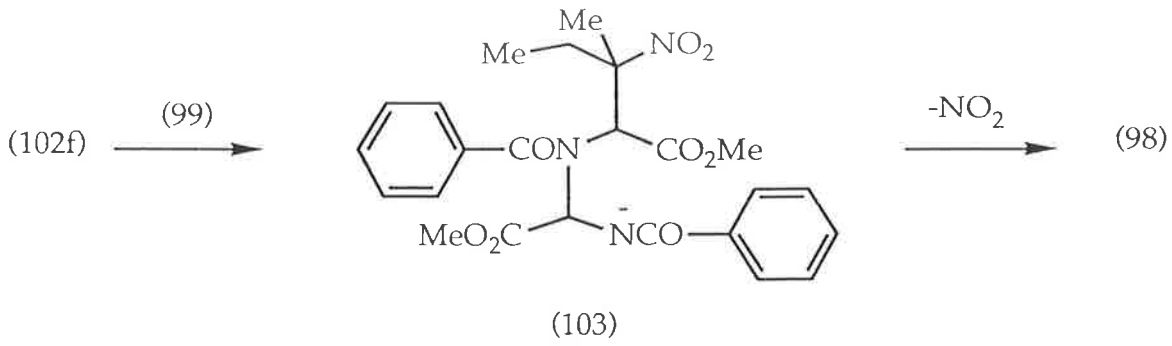
Figure 5. Crystal structure of the dehydro-*iso*-leucine derivative (98).

The proposed[93] mechanism of formation of the β-nitroamino acid derivatives (64) is shown in Scheme 34. Initially, one equivalent of the alkylnitronate (63) serves as a base, eliminating the elements of hydrogen bromide from the glycine derivative (57), to afford the reactive imine intermediate (99). Subsequent electron transfer from a second equivalent of the nitronate (63) to the imine (99) gives the radical anion (100) and the radical (101), which then combine to give the anionic species (102). In turn this is protonated to yield the β-nitroamino acid derivative (64). Isolation of the dehydro-*iso*-leucine

derivative (98) as a by-product of the reaction of the alkyl nitronate (63f) provides good evidence in support of this mechanism. Its formation can be attributed to reaction of the anion (102f) with the imine (99) (Scheme 35), thus confirming the presence of these species in the reaction mixture.



Scheme 34



(103)

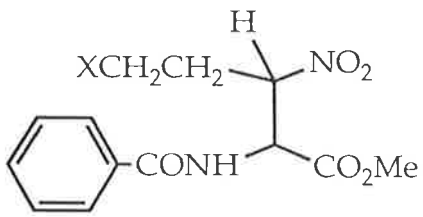
Scheme 35

As described in the Introduction, side-chain fluorinated and other halogenated amino acid derivatives are particularly important. It was therefore of interest to determine if compounds of this type could be prepared by condensation of halogenated alkyl nitronates with the α-bromoglycine derivative (57).

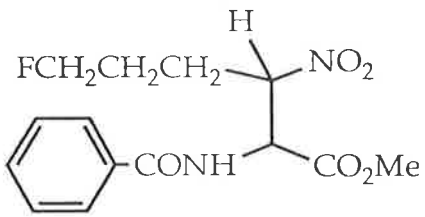
The fluoronitroalkanes, 3-fluoro-1-nitropropane and 4-fluoro-1-nitrobutane, chosen for this study, were synthesized using the method of Pattison and coworkers.[124] They were prepared by vigorously stirring the corresponding 1-fluoro-ω-iodoalkanes with silver nitrite in anhydrous diethyl ether at room temperature for 18 h. 3-Chloro-1-nitropropane, also used in this study, was prepared by treating the corresponding chloroiodoalkane with silver nitrite in diethyl ether. These halonitroalkanes had spectral and physical characteristics consistent with those previously reported.[125-127]

Treatment of the α-bromoglycine derivative (57) with the nitronate salt of 3-fluoro-1-nitropropane under similar conditions to those described above for the synthesis of the β-nitroalanine derivative (64a), afforded the 5-fluoro-3-nitropentanoic acid derivative (104a), in 64% yield as a 1.5:1 mixture of diastereomers. The diastereomers were separated by chromatography on silica and subsequently crystallized from ethyl acetate/light petroleum in yields of 35% and 23%. Each diastereomer was characterized on the basis of its spectral

data. The ^{1}H n.m.r. spectrum of the major diastereomer showed a doublet of doublets at δ 5.28 (J = 4.4 and 7.3 Hz) and a doublet of triplets at δ 5.19 (J = 4.4 and 9.0 Hz) corresponding to the α- and β-protons, respectively. The protons geminal to fluorine appeared as a multiplet centred at δ 4.61. The ^{1}H n.m.r. spectrum of the minor diastereomer showed a two proton multiplet resonance centred at δ 5.44, attributable to both the α- and β-protons. The protons geminal to fluorine resonated in the spectrum as a multiplet centred at δ 4.60, with fluorine-proton coupling of J = 47 Hz. Analysis of the diastereomers using ^{19}F n.m.r. spectroscopy showed a peak in the spectrum of the major diastereomer at δ -146.5, and a peak in the spectrum of the minor diastereomer at δ -147.6. Mass spectral analysis of each of the diastereomers of the fluoride (104a) gave a molecular ion at m/z 298, while high resolution mass spectral analysis of this peak was in good accord with the theoretical value.



(104)



(105)

a) X = F

b) X = Cl

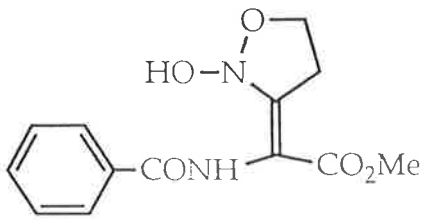
Similar treatment of the nitronate salt of 4-fluoro-1-nitrobutane with *N*-benzoyl-2-bromoglycine methyl ester (57) gave methyl 2-benzamido-6-fluoro-3-nitrohexanoate (105), as a 5:1 mixture of diastereomers, in 72% yield. The diastereomers were partially separated by chromatography on silica, with further separation being achieved by fractional crystallization from ethyl

acetate/light petroleum. The major diastereomer was isolated in 41% yield, while the minor diastereomer was isolated only in low yield. The ^{1}H n.m.r. spectrum of the minor diastereomer showed a doublet of triplets resonance at δ 5.26 (J = 4.4 and 8.9 Hz), attributable to the β-proton. The doublet of doublets resonance at δ 5.43 (J = 3.2 and 9.4 Hz) was attributable to the α-proton coupled to the amide proton, which resonated as a broad doublet at δ 7.03 (J = 9.4 Hz). The multiplet resonance centred at δ 4.52 was attributable to the protons geminal to fluorine, with a fluorine-proton coupling constant J = 47 Hz. The ^{1}H n.m.r. spectrum of the major diastereomer showed a doublet of triplets at δ 5.04 (J = 4.4 and 8.9 Hz), due to the β-proton, and a doublet of doublets at δ 5.17 (J = 4.4 and 7.0 Hz), due to the α-proton. The multiplet resonance centred at δ 4.52 was attributable to the protons geminal to fluorine with a fluorine-proton coupling constant J = 47 Hz. The ^{19}F n.m.r. spectrum of the minor diastereomer showed a peak at δ -145.0, whilst that of the major diastereomer showed a peak at δ -145.6. The mass spectrum of each diastereomer showed a peak at m/z 313 corresponding to the molecular ion.

When the nitronate salt of 4-chloro-1-nitropropane was treated with the α-bromoglycine derivative (57) under similar conditions to those described for the synthesis of the fluorides (104a) and (105), the reaction afforded a 3:1 mixture of the diastereomers of the δ-chloro-β-nitroamino acid derivative (104b). The diastereomers were separated by chromatography on silica with further purification being achieved by crystallization of the individual diastereomers from ethyl acetate/light petroleum. The major diastereomer was isolated in 49% yield and the minor diastereomer in 14% yield. Characteristic signals in the ^{1}H n.m.r. spectrum of the minor diastereomer were a doublet of triplets resonance at δ 5.54 (J = 3.0 and 7.2 Hz), which was attributed to the β-proton, and a doublet of doublets resonance due to the α-proton, which appeared at δ 5.40 (J = 3.0 and 9.0 Hz). The ^{1}H n.m.r. spectrum

of the major diastereomer showed a multiplet at δ 5.23 due to the α- and β-protons. The diastereotopic δ-protons resonated as a doublet of doublets of doublets at δ 3.63 (J = 5.1, 8.9 and 11.7 Hz) and a triplet of doublets at δ 3.76 (J = 5.9 and 11.7 Hz). Mass spectral analysis of each diastereomer showed peaks at m/z 314 and 316 in a 3:1 ratio, due to the isotopic molecular ions. High resolution mass spectral analysis of the major isotopic molecular ion in each case revealed a peak at m/z 314.066, which was in good accord with the calculated value of m/z 314.067.

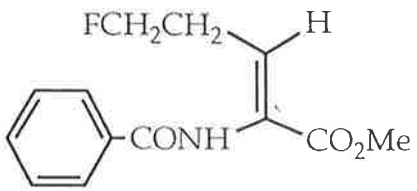
A product isolated from the reaction of the nitronate salt of 3-chloro-1-nitropropane with the α-bromoglycine derivative (57) was tentatively assigned the cyclic structure (106). The ^{1}H n.m.r. spectrum of this product (106) showed doublets of doublets of doublets at δ 2.93 (J = 6.5, 8.5 and 17.5 Hz) and 3.29 (J = 5.5, 8.5 and 17.5 Hz) due to the γ-protons. Triplets of doublets resonances at δ 4.35 (J = 5.5 and 8.5 Hz) and 4.61 (J = 6.5 and 8.5 Hz) were attributed to the δ-protons. The geminal coupling constants lie at the limits expected for five-membered ring systems.[97] The high resolution mass spectrum of the dehydroamino acid derivative (106) showed a peak at m/z 279.097, attributable to the protonated molecular ion. Formation of the azafuran (106) can be attributed to intramolecular substitution of chloride, with O-alkylation, in the salt of the β-nitroamino acid derivative (104b).



(106)

Having established that the side-chain halogenated β-nitroamino acid derivatives (104a), (104b) and (105) could be prepared, procedures to remove the nitro group while retaining the halogen were investigated. It was envisaged that this could be achieved by elimination, with subsequent hydrogenation.

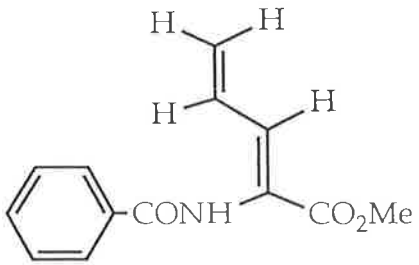
Treatment of each of the diastereomers of methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a) with one equivalent of di-*iso*-propylamine in chloroform at room temperature overnight gave methyl (Z)-2-benzamido-5-fluoropent-2-enoate (107) as a colourless oil, in 80% yield. The ^{1}H n.m.r. spectrum of the fluoride (107) showed a triplet of doublets at δ 4.62 (J = 5.8 and 47 Hz) due to the δ-protons. The larger coupling constant is consistent with geminal fluorine-proton coupling.[97] A triplet resonance at δ 6.83 (J = 7.2 Hz) was attributed to the vinylic proton. The mass spectrum of the α,β-dehydroamino acid derivative (107) showed a peak at *m/z* 251.097 due to the molecular ion. The observation of only the (Z)-pent-2-enoate (107) can be attributed to the greater stability of this isomer and the ease of interconversion of (*E*)- and (*Z*)-dehydroamino acid derivatives.[106]



(107)

When treated with a ten fold excess of di-*iso*-propylamine, the fluoride (104a) afforded the α,β,γ,δ-tetradehydroamino acid derivative (108) as the sole

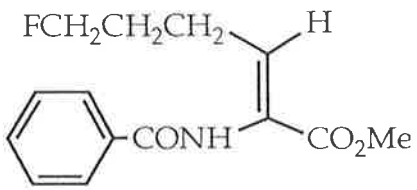
product. The ^{1}H n.m.r. spectrum of the diene (108) showed, in addition to a singlet resonance at δ 3.82 due to the protons of the methyl ester moiety, four sets of vinylic proton resonances. Doublet resonances at δ 5.43 (J_{cis} = 10.7 Hz) and 5.57 (J_{trans} = 16.5 Hz) were attributable to the terminal vinylic protons. A doublet of doublets of doublets at δ 6.49 (J = 10.7, 11.3 and 16.5 Hz) was due to the γ-proton with a further doublet resonance at δ 7.06 (J = 11.3 Hz) attributable to the β-proton. The mass spectrum of the diene (108) showed a peak at m/z 231.089, corresponding to the molecular ion. The diene (108) is assumed to have the (Z)-configuration by analogy with related compounds discussed above.



(108)

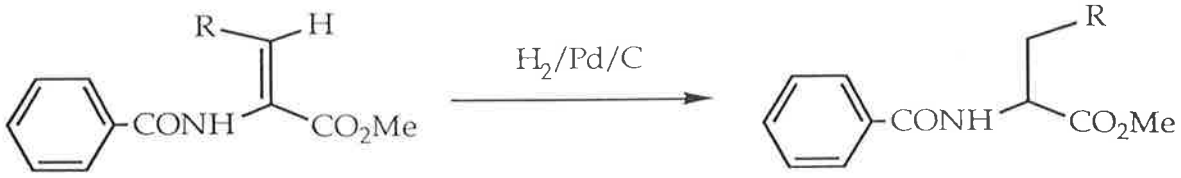
Reaction of the major diastereomer of methyl 2-benzamido-6-fluoro-3-nitrohexanoate (105) with one equivalent of di-*iso*-propylamine at room temperature gave the α,β-dehydroamino acid derivative (109) in 83% yield. The ^{1}H n.m.r. spectrum of the hexenoate (109) showed a triplet of doublets at δ 4.50 (J = 5.9 and 47 Hz) attributable to the protons geminally coupled to fluorine. A triplet resonance at δ 6.78 (J = 7.4 Hz) corresponded to the vinylic proton. The high resolution mass spectrum of the fluoride (109) showed a

peak at *m/z* 266.120 which corresponded to the theoretical value for the protonated molecular ion of *m/z* 266.119. The hexenoate (109) is presumed to have the (*Z*)-geometry. While the ^{1}H n.m.r. spectrum of the crude reaction mixture showed the presence of the corresponding (*E*)-isomer, with a triplet of doublets at δ 4.51 (*J* = 5.9 and 47.1 Hz) due to the protons geminally coupled to fluorine and a triplet at δ 7.24 (*J* = 7.6 Hz) attributable to the vinylic proton, it was not isolated. Presumably it isomerized to the (*Z*)-hex-2-enoate (109) during workup.



(109)

Hydrogenation of methyl (*Z*)-2-benzamido-5-fluoropent-2-enoate (107) at 25 p.s.i. of hydrogen over 10% palladium on activated carbon gave methyl 2-benzamido-5-fluoropentanoate (110), as a colourless solid, in 98% yield (Scheme 36). The ^{1}H n.m.r. spectrum of the fluoride (110) showed a triplet of doublets at δ 4.49 (*J* = 5.6 and 47.0 Hz) attributable to the δ-methylene protons which were coupled to the γ-protons and to fluorine. A doublet of triplets resonance in the spectrum at δ 4.88 (*J* = 5.2 and 7.5 Hz) was attributable to the α-proton. The ^{19}F n.m.r. spectrum of the fluoride (110) showed a single peak at δ -144.41. The mass spectrum of the fluoride showed peaks at *m/z* 253 and 254 due to the molecular ion and the protonated molecular ion, respectively. The high resolution mass spectrum of the peak at *m/z* 253.112 corresponded to the theoretical value of *m/z* 253.111.



(107) R = CH_2CH_2F

(109) R = $CH_2CH_2CH_2F$

(110) R = CH_2CH_2F

(111) R = $CH_2CH_2CH_2F$

Scheme 36

Similar treatment of methyl (Z)-2-benzamido-6-fluorohex-2-enoate (109) with hydrogen over 10% palladium on activated carbon yielded the fluoride (111), which crystallized from dichloromethane/light petroleum as needles, in 94% yield. The ^1H n.m.r. spectrum of the fluoroamino acid derivative (111) showed a triplet of doublets at δ 4.77 (J = 5.4 and 7.5 Hz) attributable to the α-proton coupled to the amide proton, which resonated as a broad doublet at δ 6.75 (J = 7.5 Hz), and the β-protons, which resonated as a multiplet at δ 1.69. Elemental analysis of the fluoride (111) is consistent with the assigned composition.

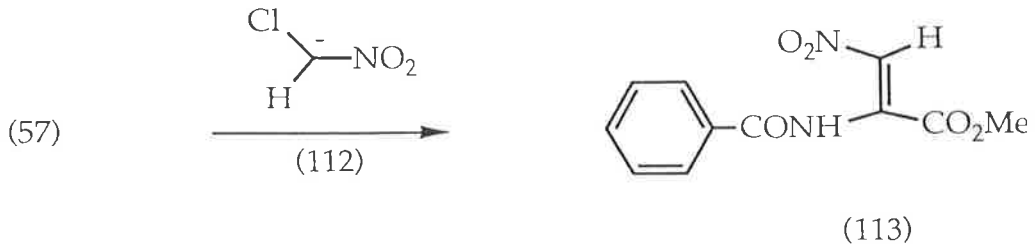
It is thus evident that the nitro substituent can be removed from ω-halo-β-nitroamino acid derivatives, with retention of the halogen. Through asymmetric hydrogenation with chiral catalysts,[128] this process can be expected to be amenable to the synthesis of chiral side-chain halogenated amino acids.

In the reactions of the β-nitroamino acid derivatives (104a) and (105) to give the corresponding α,β-dehydroamino acid derivatives (107) and (109), the nitro functionality is lost. In order to prepare α,β-dehydroamino acid derivatives with retention of vinylic functionality, reactions of the nitronate salts of

α-halonitroalkanes with the α-bromoglycine derivative (57) were investigated. β-Functionalized α,β-dehydroamino acid derivatives are of interest in synthesis because they undergo addition-elimination reactions, with net substitution of the β-functional group, to give novel dehydroamino acid derivatives.[129-131]

The α-halonitroalkanes used in this study were prepared using two different methods. Chloronitromethane was prepared from nitromethane and *tert*-butyl hypochlorite, in the presence of styrene, as described by Heasley and coworkers.[132] α-Choronitroethane was prepared using the method outlined by Levering,[133] which involved the chlorination of nitroethane. In a similar manner, α-bromonitroethane was prepared from nitroethane.

Treatment of *N*-benzoyl-2-bromoglycine methyl ester (57) with the nitronate salt (112) of chloronitromethane, under reaction conditions identical to those described for the synthesis of the β-nitroalanine derivative (64a), yielded *N*-benzoyl-β-nitro-α,β-dehydroalanine methyl ester (113) (Scheme 37) as a yellow solid, in 42% yield. The crystal structure of the β-nitro-α,β-dehydroamino acid derivative was determined using X-ray crystallographic analysis (Appendix 6) and is shown in Figure 6. The ^{1}H n.m.r. spectrum showed a singlet at δ 6.91, due to the vinylic proton, and a broad singlet



Scheme 37

at δ 11.17, attributable to the amide proton. The chemical shift of the amide proton is consistent with hydrogen bonding to the nitro group, as seen in the crystal structure.

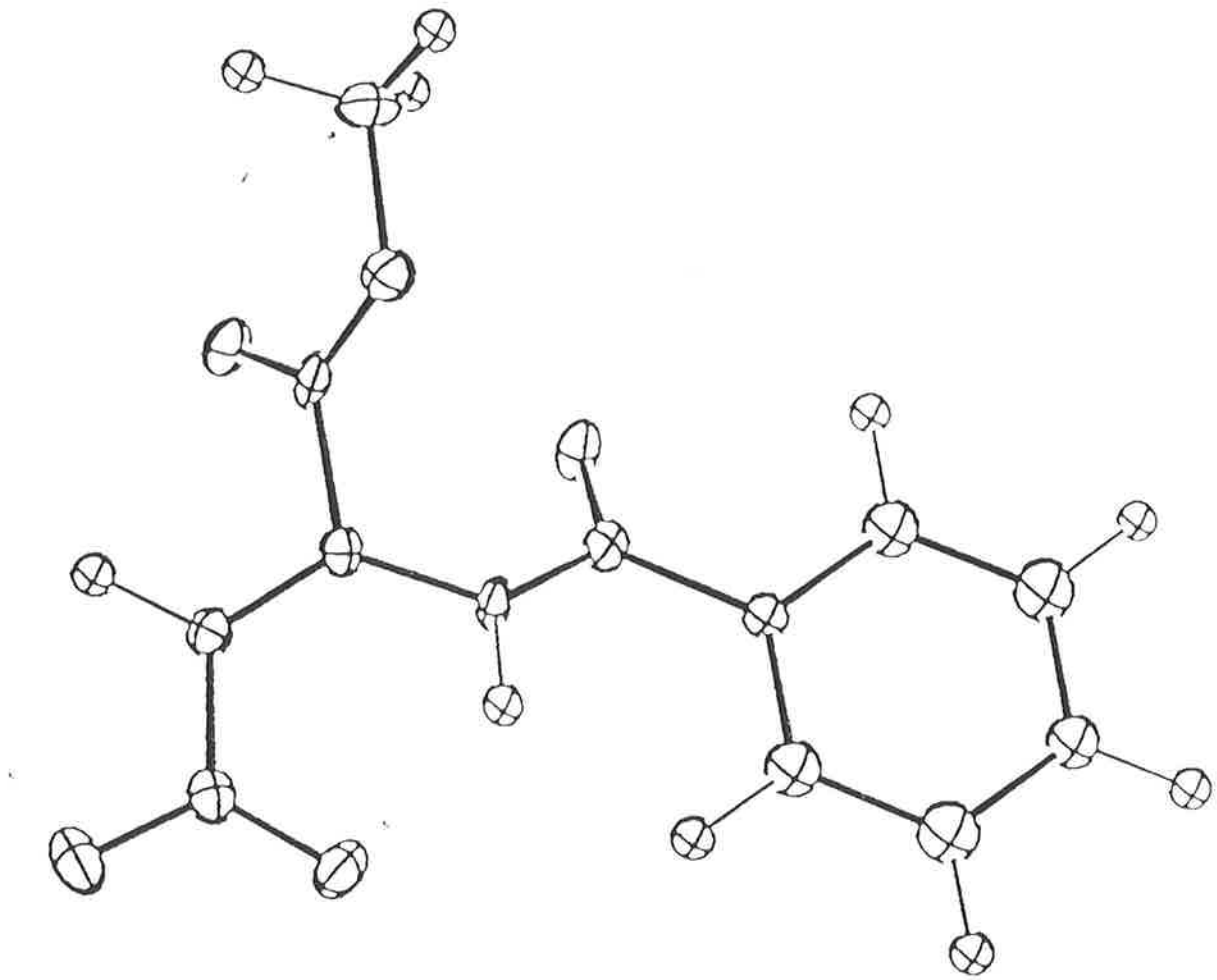
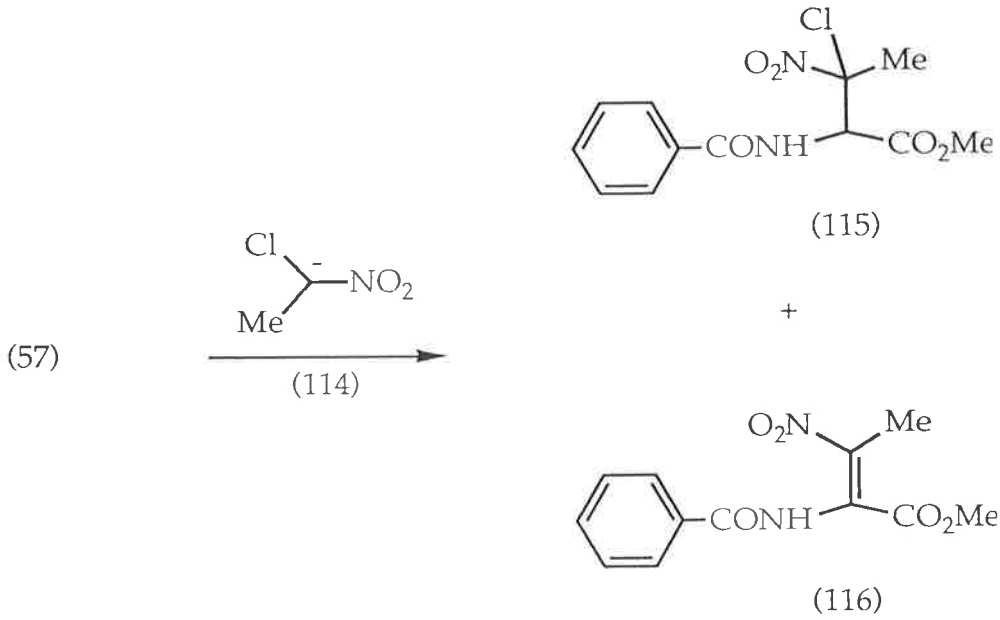


Figure 6: Crystal structure of the β-nitro-α,β-dehydroalanine derivative (113).

Similar treatment of the nitronate salt (114) of 1-chloronitroethane with the α-bromoglycine derivative (57) gave a 1.4:1 mixture of the diastereomers of the β-chloro-β-nitroamino acid derivative (115), in 48% yield. The β-nitro-α,β-dehydroamino acid derivative (116) was also isolated, in 9% yield, as a single isomer (Scheme 38).



Scheme 38

The diastereomers of the β-chloro-β-nitroamino acid derivative (115) were separable using chromatography on silica. The ^{1}H n.m.r. spectrum of the major diastereomer showed a doublet at δ 6.10 (J = 9.0 Hz) due to the α-proton, while that of the minor diastereomer showed a doublet at δ 5.87 (J = 9.7 Hz) also attributable to the α-proton. The mass spectrum of each diastereomer displayed peaks at m/z 269 and 267 due to the isotopic molecular ions.

The structure of the β-nitro-α,β-dehydroamino acid derivative (116) was determined on the basis of spectral and X-ray crystallographic data

(Appendix 7). As was the case with the β-nitroalanine derivative (113), the ^{1}H n.m.r. spectrum of the analogue (116) showed a broad singlet at low field (δ 11.86) due to the amide proton and the chemical shift of this proton is consistent with hydrogen bonding to the nitro group, as indicated in the crystal structure (Figure 7).

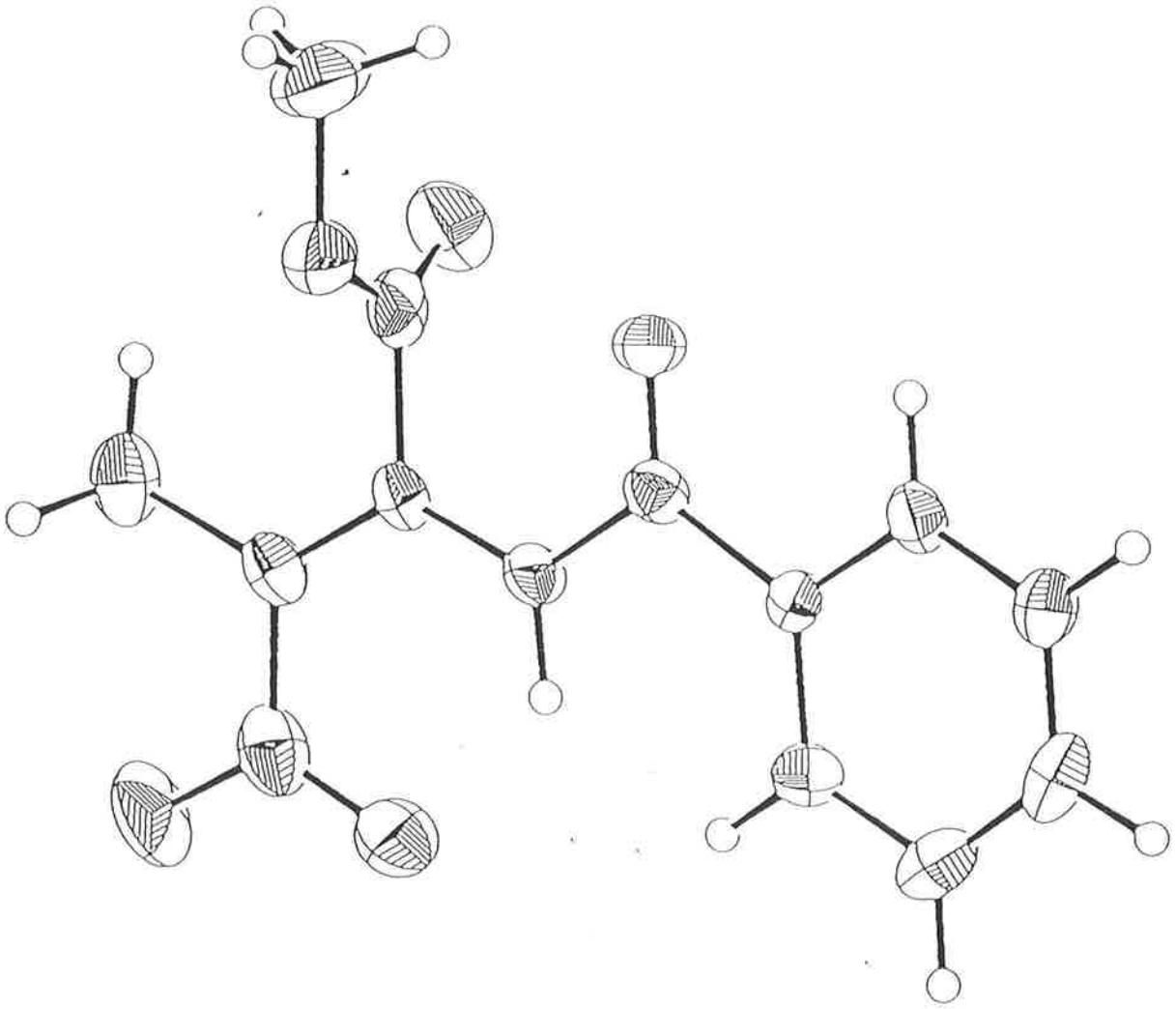
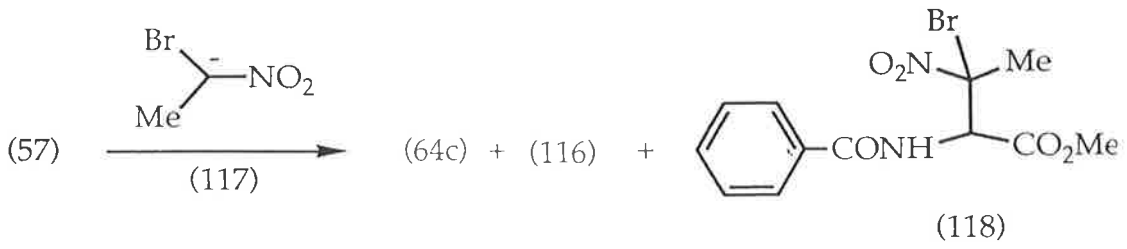


Figure 7. Crystal structure of the β-nitro-α,β-dehydroamino acid derivative (116).

When α-bromonitroethane was treated with *n*-butyllithium (1 equivalent) and subsequently with the α-bromoglycine derivative (57) (0.5 equivalents), the only product isolated from the reaction was a 2:1 mixture of the diastereomers of methyl 2-benzamido-3-nitrobutanoate (64c). The structure of this product was confirmed by the comparison of its spectral data with that of an authentic sample. Presumably the β-nitroamino acid derivative (64c) results from *trans*-metallation of α-bromonitroethane to give lithium ethyl nitronate, which reacts with the α-bromoglycine derivative (57). Based on an estimation of the relative pK_a values of nitroethane and α-bromonitroethane, it was anticipated that lithium ethyl nitronate would react with an excess of α-bromonitroethane to produce the nitronate salt (117). Accordingly, reaction of a ten-fold excess of α-bromonitroethane with *n*-butyllithium, followed by reaction with the α-bromoglycine derivative (57), afforded the β-bromo-β-nitroamino acid derivative (118), as a single diastereomer in 58% yield. The β-nitro-α,β-dehydroamino acid derivative (116) was also isolated, in 6% yield, while the product of *trans*-metallation (64c) was isolated as a 1:1 mixture of diastereomers, in 13% yield (Scheme 39).



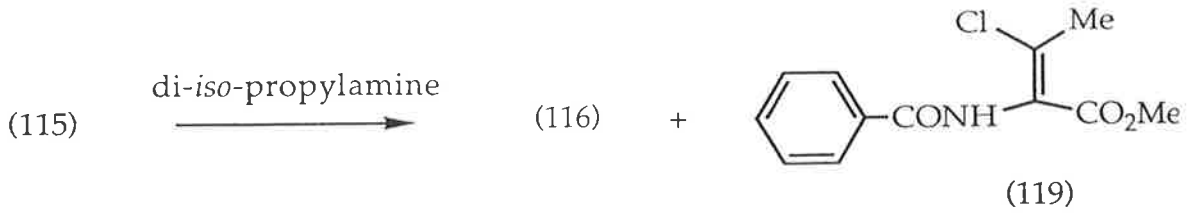
Scheme 39

The ^{1}H n.m.r. spectrum of the bromide (118) displayed a doublet resonance at δ 5.88 (J = 9.5 Hz) due to the α-proton. A broad doublet at δ 7.04 (J = 9.5 Hz) was

attributable to the amide proton coupled to the α-proton. The high resolution mass spectrum showed a peak at *m/z* 345.999 which corresponded to the calculated value of *m/z* 345.999 for the molecular ion of the ^{81}Br isotope.

The reactions of the α-bromoglycine derivative (57) with the nitronate salts (112), (114) and (117) gave the β-halo-β-nitroamino acid derivatives with spontaneous elimination of the halide, at least in part, to afford the β-nitro-α,β-dehydroamino acid derivatives (113) and (116). In order to improve the yield of the β-nitro-α,β-dehydroamino acid derivative (116), the reaction of the β-bromo-β-nitroamino acid derivative (118) with base was investigated. Treatment of the β-bromide (118) with di-*iso*-propylamine as described above for the synthesis of ω-fluoro-α,β-dehydroamino acid derivatives, gave the β-nitro-α,β-dehydroamino acid derivative (116) in 81% yield.

This reaction was repeated with each of the diastereomers of the β-chloro-β-nitroamino acid derivative (115). Treatment of the major diastereomer of the β-chloride (115) with di-*iso*-propylamine gave a 2:1 mixture of the β-nitro-α,β-dehydroamino acid derivative (116) and the β-chloro-α,β-dehydroamino acid derivative (119), in 72% yield (Scheme 40). The two products were separated by chromatography on silica, with the β-nitro amino acid derivative (116) isolated in 39%, and the β-chloroamino acid derivative isolated in 17% yield. The ^{1}H n.m.r. spectrum of the β-chloroamino acid derivative showed a singlet resonance at δ 2.54 attributable to the protons of the β-methyl substituent. A singlet at δ 3.85 was attributable to the protons of the methyl ester moiety. The mass spectrum of the chloride (119) showed peaks at *m/z* 253 and 255 due to the isotopic molecular ion.



Scheme 40

Reaction of the minor diastereomer of the β-chloro-β-nitro amino acid derivative (115) with di-*iso*-propylamine gave a 2:1 mixture of the β-chloride (119) and the β-nitroamino acid derivative (116). The ratios of the β-chloride (119) and the β-nitrite (116) in the reactions of the diastereomers of the chloronitroamino acid derivative (115) presumably reflect a preference for *anti*-elimination. The minor product in each case probably results from rotation about the C(2)-C(3) bond, prior to loss of the β-substituent, in the anion derived from the starting material (115).

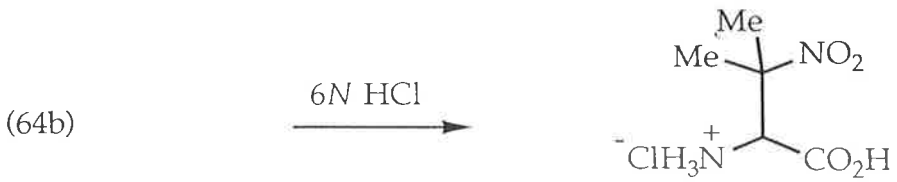
These results establish that reactions of alkyl nitronates with α-haloglycine derivatives are suitable for the preparation of α,β-dehydroamino acid derivatives with β-vinylic functionality. Combined with the other results described herein, it is clear that the approach is amenable to the synthesis of a vast array of compounds including β-nitro-, α,β-dehydro-, ω-halo-β-nitro-, ω-halo-α,β-dehydro-, ω-halo-, β-halo-β-nitro-, β-nitro-α,β-dehydro and β-halo-α,β-dehydro-amino acid derivatives.

RESULTS AND DISCUSSION: CHAPTER FIVE

Synthesis of β-Nitro-α-amino Acids

While it is clear from the work described in the previous Chapter that a large range of β-nitroamino acid derivatives can be prepared, the procedure is of limited utility unless it is applicable to the synthesis of free amino acids. Consequently, the deprotection of the amino acid derivatives (64a-f) was investigated.

Treatment of *N*-benzoyl-3-nitrovaline methyl ester (64b) with 6N HCl under reflux for 1 h gave β-nitrovaline as its hydrochloride salt (120), in 84% yield (Scheme 41). The ^{1}H n.m.r spectrum of the salt (120) showed peaks at δ 1.79 and 1.86 corresponding to the β-methyl protons. A singlet resonance at δ 4.71 was attributable to the α-proton. The ^{13}C n.m.r. spectrum showed a peak at δ 89.2 corresponding to the carbon bearing the nitro group. Fast atom bombardment (f.a.b.) mass spectral analysis showed a peak at *m/z* 163, corresponding to the protonated amino acid, and a peak at *m/z* 116, corresponding to loss of the nitro substituent.

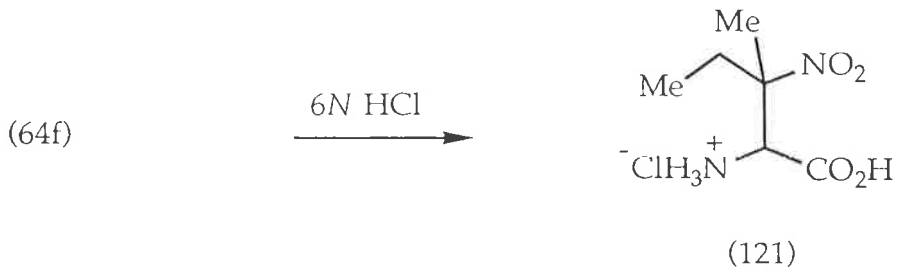


(120)

Scheme 41

The β-nitrovaline hydrochloride salt (120) was converted to the corresponding free amino acid by precipitation from a solution of ethanol and aniline (10:1 v/v).[134] The free amino acid was less stable than the salt (120) and, consequently, the amino acids prepared as described below were stored and characterized as their hydrochloride salts.

Treatment of each of the diastereomers of *N*-benzoyl-3-nitro-*iso*-leucine methyl ester (64f) with 6N HCl gave the corresponding isomer of the β-nitro-*iso*-leucine hydrochloride salt (121) (Scheme 42). There was no evidence of interconversion between the diastereomers of either the starting material (64f) or the product (121) under the reaction conditions. The ^{1}H n.m.r. spectrum of the minor diastereomer of the salt (121) showed a singlet resonance at δ 4.72 characteristic of the α-proton. Quartets of doublets resonances at δ 2.20 (J = 7.0 and 14.0 Hz) and 2.22 (J = 7.0 and 14.0 Hz) were attributable to the diastereotopic methylene protons. The ^{1}H n.m.r. spectrum of the major diastereomer of the salt (121) showed similar resonances, with a singlet at δ 4.47 attributable to the α-proton, and quartet of doublets resonances at δ 2.08 (J = 7.0 and 14.0 Hz) and 2.19 (J = 7.0 and 14.0 Hz) due to the diastereotopic methylene protons. F.a.b. mass spectra of each diastereomer of the salt (121) showed peaks at *m/z* 177 and 130, corresponding to the protonated amino acid and loss of nitrite from the amino acid, respectively.



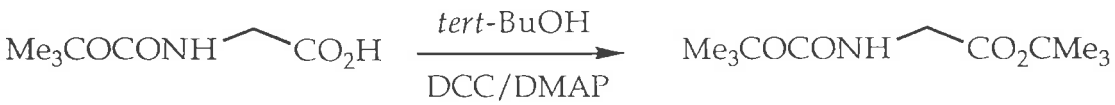
(121)

Scheme 42

Treatment of the β-nitroamino acid derivatives (64a), (64c), (64d) and (64e) with hydrochloric acid resulted in decomposition. These compounds are primary or secondary nitroalkanes which are known to be susceptible to acid catalysed decomposition.[135] By contrast, tertiary nitroalkanes are not acid labile, explaining why the nitrites (64b) and (64f) hydrolyzed without decomposition.

Clearly an alternative method for the synthesis of primary and secondary β-nitro-α-amino acids was in order. Steglich and coworkers[91] discovered that the carbamate (124) was an α-bromoglycine derivative of choice for the synthesis of free amino acids. Both the *tert*-butyl ester and *tert*-butoxycarbonyl protecting groups are easily removed by treatment with trifluoroacetic acid in chloroform. Consequently, the use of the bromide (124) for the synthesis of β-nitroamino acids was investigated.

The protected glycine derivative (123) was prepared using the method outlined by Hassner and Alexanian (Scheme 43).[136] Accordingly, a solution of the carboxylic acid (122), *N*,*N*-dicyclohexylcarbodiimide (DCC), *t*-butyl alcohol and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in ether was stirred at room temperature for 18 h. Following work-up and chromatography on silica, the *t*ert-butyl ester (123) was isolated in 89% yield. The spectral characteristics of the glycine derivative (123) are consistent with those previously reported.[91]



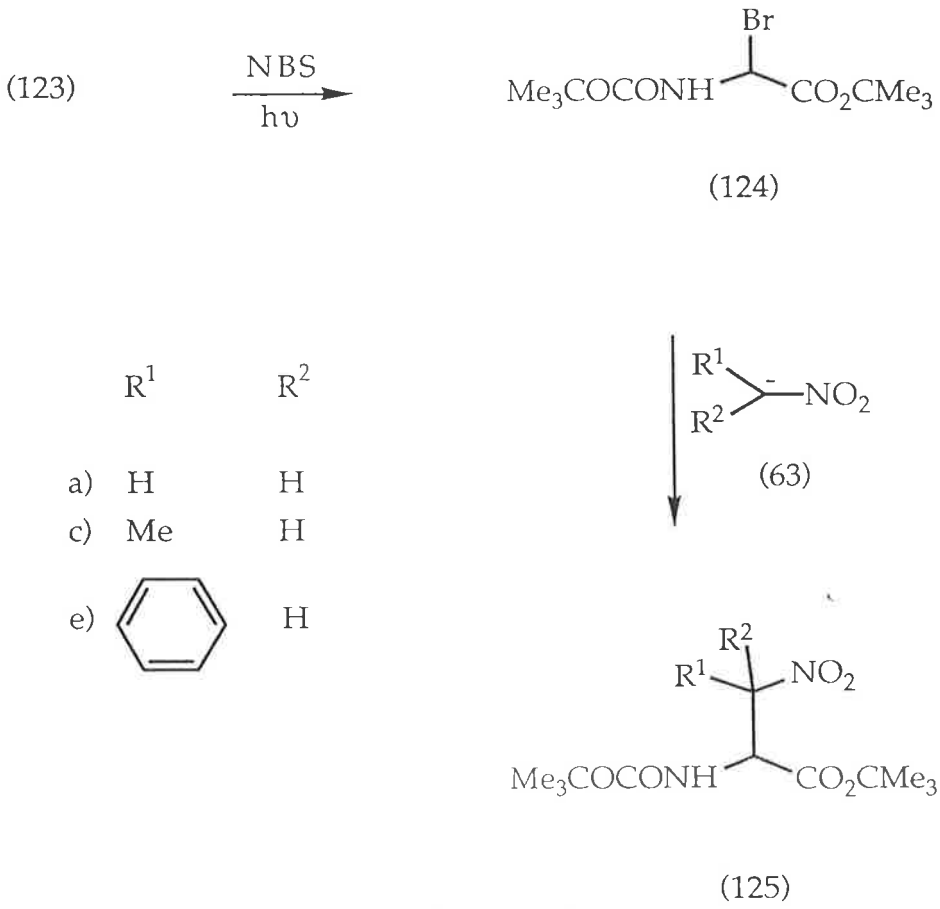
(122) (123)

Scheme 43

Photobromination (300 watt mercury lamp) of the glycine derivative (123) was carried out with *N*-bromosuccinimide in dry carbon tetrachloride, to afford the

bromide (124) as a yellow oil. The ^1H n.m.r. spectrum of the product (124) showed a doublet at δ 5.93 attributable to the α-proton.

The conditions used for the synthesis of the *N*-benzoyl-β-nitroamino acid derivatives (64a-f) were applied with the bromide (124) (Scheme 44). Under these conditions, methyl nitronate (63a) gave the β-nitroalanine derivative (125a) in 63% yield, which was characterized on the basis of its physical and spectral data. The ^1H n.m.r. spectrum showed a doublet of triplets at δ 4.60 (J = 7.2 and 3.6 Hz) for the α-proton. The amide proton resonated as a broad doublet at δ 5.52 (J = 7.2 Hz). The expected ABX pattern due to the β-protons appeared in the spectrum at δ 4.80 (J = 3.6 and 14.8 Hz) and 4.95 (J = 3.6 and 14.8 Hz). The compostion of the β-nitroamino acid derivative (125a) was confirmed by elemental analysis.

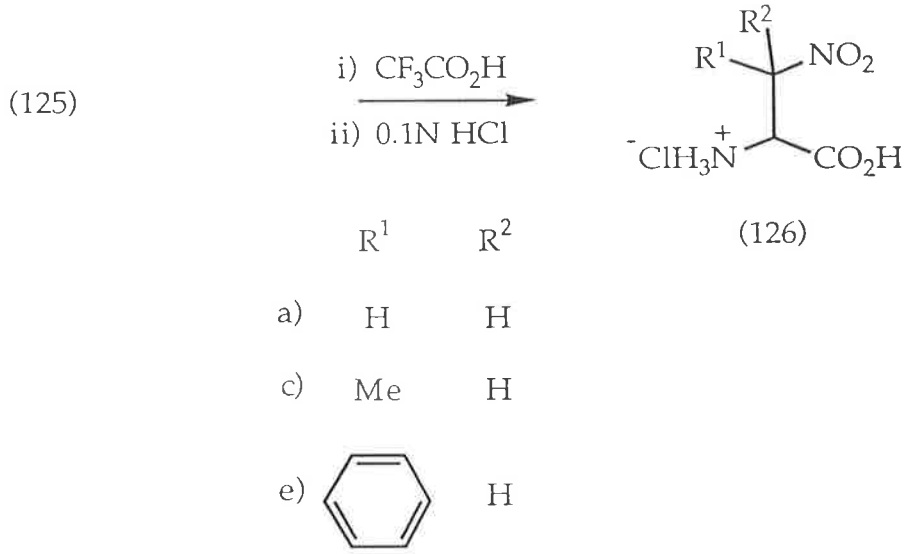


Scheme 44

Treatment of the bromide (124) with two equivalents of ethyl nitronate (63c) gave a 2:1 mixture of the diastereomers of the β-nitro-α-amino acid derivative (125c), which were separated by chromatography on silica. The major diastereomer crystallized from light petroleum as a colourless solid in 34% yield, whilst the minor diastereomer was isolated as an oil in 17% yield. The ^{1}H n.m.r spectrum of the major diastereomer showed a doublet of doublets at δ 4.66 (J = 3.8 and 7.8 Hz) due to the α-proton. The amide proton resonated in the spectrum as a broad doublet centred at δ 5.42 (J = 7.8 Hz). The doublet of quartets pattern centred at δ 4.89 (J = 3.8 and 7.0 Hz) was attributable to the β-proton. Consistent with this assignment was the doublet resonance at δ 1.66 (J = 7.0 Hz) due to the γ-methyl substituent. The ^{1}H n.m.r. spectrum of the minor diastereomer showed a doublet of doublets at δ 4.64 (J = 3.2 and 9.2 Hz) due to the α-proton. The amide proton resonated as a doublet at δ 5.94 (J = 9.2 Hz) and the β-proton resonated as a doublet of quartets at δ 5.70 (J = 3.2 and 7.0 Hz). High resolution mass spectral analysis and elemental analysis of the major diasteromer is consistent with the expected values, whilst high resolution mass spectral data of the minor diastereomer is in good accord with the expected results.

Reaction of the bromide (124) with benzyl nitronate (63e) gave the β-nitrophenylalanine derivative (125e) in 71% yield, as a 1:1 mixture of diastereomers. The diastereomers crystallized from dichloromethane/light petroleum with different shapes, thus enabling partial separation of the diastereomers by mechanical means. One diastereomer crystallized as spars and its ^{1}H n.m.r. spectrum showed a triplet resonance at δ 4.99 (J = 8.0 Hz) due to the α-proton, coupled to both the amide proton and the β-proton. A broad doublet resonance at δ 5.08 (J = 8.0 Hz) was attributable to the amide proton while a doublet resonance at δ 6.00 (J = 8.0 Hz) was characteristic of the β-proton. The ^{1}H n.m.r. spectrum of the other diastereomer, which

crystallized as clusters, showed a doublet of doublets centred at δ 4.95 (J = 5.4 and 9.6 Hz) which was attributable to the α-proton. A broad doublet resonance at δ 5.49 (J = 9.6 Hz) was attributable to the amide proton and a doublet resonance at δ 6.03 (J = 5.4 Hz) corresponded to the β-proton. High resolution mass spectral analysis of each of the diasteromers of the β-nitrophenylalanine derivative (125f) was in good accord with the theoretical value.



Scheme 45

Treatment of the β-nitroalanine derivative (125a) with a solution of trifluoroacetic acid in chloroform, followed by workup which included taking the reaction mixture up into 0.1N HCl and washing with water, gave the corresponding water soluble hydrochloride salt (126a) in 63% yield (Scheme 45). The ^1H n.m.r. spectrum of the β-nitroalanine salt (126a) showed a doublet of doublets resonance at δ 4.55 (J = 2.9 and 5.4 Hz) attributable to the α-proton. Doublet of doublets resonances at δ 5.06 (J = 2.9 and 16.8 Hz) and 5.16 (J = 5.4 and 16.8 Hz) were due to the diasterotopic β-protons. The ^{13}C n.m.r. spectrum showed peaks at δ 53.1, 75.1 and 171.1, due to the α-, β- and carboxyl-carbons,

respectively. F.a.b. mass spectral analysis of the salt (126a) showed a peak at *m/z* 135 due to the protonated amino acid.

Each of the diastereomers of the nitrobutanoate derivative (125c) was treated with trifluoroacetic acid, in an identical fashion to that described for the β-nitroalanine derivative (125a). Each gave the corresponding hydrochloride salt (126c) as a single diastereomer, without isomerization. The ^{1}H n.m.r. spectrum of one diastereomer showed a doublet resonance at δ 1.63 (J = 7.2 Hz) attributable to the methyl substituent. A doublet resonance at δ 4.68 (J = 2.3 Hz) was due to the α-proton, and a doublet of quartets resonance at δ 5.23 (J = 2.3 and 7.2 Hz) was attributable to the β-proton. The ^{1}H n.m.r. spectrum of the other diastereomer displayed a doublet at δ 1.79 (J = 7.3 Hz) due to the protons of the methyl subtituent. A doublet resonance at δ 4.64 (J = 3.8 Hz) was attributable to the α-proton, while a doublet of quartets at δ 5.35 (J = 3.8 and 7.3 Hz) was due to the β-proton. The mass spectrum of each diastereomer of (126c) showed a peak at *m/z* 149 due to the protonated amino acid.

Similar reaction of a 1:1 mixture of the diastereomers of the β-nitrophenylalanine derivative (125f) with trifluoroacetic acid afforded a 1:1 mixture of the diastereomers of the β-nitrophenylalanine hydrochloride salt (126f). The f.a.b. mass spectrum of the mixture of diastereomers showed peaks at *m/z* 233 and 211 due to the amino acid plus sodium ion and the protonated amino acid, respectively. The ^{1}H n.m.r. spectrum showed doublets at δ 4.68 (J = 5.6 Hz) and 5.02 (J = 5.1Hz) due to the α-proton of each diastereomer, and doublets at δ 6.41 (J = 5.1 Hz) and 6.53 (J = 5.6 Hz) due to the corresponding β-protons.

It is evident from the effective deprotection of the β-nitroamino acid derivatives (125a), (125c) and (125e) using trifluoroacetic acid, that this approach to the synthesis of free β-nitroamino acids is a viable one. Thus the

procedure described above is suitable for the preparation of amino acids of primary, secondary and tertiary nitroalkanes. The reported[35] method for the synthesis of the primary nitroalkane, β-nitroalanine (33), is unsuitable for the preparation of the secondary and tertiary 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 alkylnitronates nor particulary susceptible to elimination, whereas those reaction modes are associated with enzyme inhibition by the alanine derivative (33).[35]

CONCLUSION

The work described in this thesis has shown that side-chain functionalization of *N*-phthaloyl-protected α-amino acids can be achieved without protection of the carboxyl group. The halogenated amino acid derivatives obtained in this manner have been found to be suitable for the synthesis of γ-butyrolactones, compounds that are of interest in the synthesis of novel peptides and due to their inherent physiological activity.

Side chain halogenated *N*-phthaloylamino acid ester and amide derivatives, accessible using the same approach, have proved to be versatile intermediates in the synthesis of α,β-dehydro-, α,β-methano- and γ-fluoro-α-amino acid derivatives. The stereocontrol exhibited in the synthesis of the α,β-dehydroamino acid derivatives is of special interest because these compounds are particularly useful in the study of conformationally restricted peptides. Fluoroamino acids are of interest as enzyme inhibitors and the procedures described above provide a complementary route for the synthesis of compounds of this type.

Reactions of haloalkylnitronates with α-bromoglycine derivatives have been used in the synthesis of a wide variety of saturated and unsaturated α-amino acid derivatives, substituted at various positions with halo and nitro substituents. Halo and nitro substituted amino acids are of interest in probing enzyme-catalysed reactions and unsaturated amino acid derivatives allow for the synthesis of chiral amino acids, through asymmeytric hydrogenation.

Consequently, the procedures developed in the work described in this thesis provide access to a range of classes of amino acids and their derivatives, which

are likely to be useful in diverse studies of the chemistry, biochemistry, physiology and pharmacology of amino acids.

EXPERIMENTAL

General

Melting points were determined on a Kofler hot-stage under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada and the Chemical and Micro Analytical Services Pty. Ltd., Victoria, Australia.

Chromatography was carried out on either a Chromatatron 7924T (Harrison Research, Palo Alto/TC research, Norwich) using Merck silica gel 60 PF_{254}, or by flash chromatography[137] using Merck Kieselgel 60 (230-400 mesh ASTM).

High perfomance liquid chromatography (h.p.l.c.) was carried out using a Waters 6000A solvent pump, a Waters U6K injector and a Waters Model 441 Absorbance Detector operating at 254 nm, in conjunction with an I.C.I. DP-700 data station. A Waters Radial Pak normal phase 10 μm silica column (8 mm) was used.

Infrared spectra were recorded on a Hitachi 270-30 spectrometer or a Jasco A-102 spectrophotometer using the 1603 cm^{-1} band of polystyrene as a reference.

Carbon nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded on either a Bruker CXP300 or ACP300 spectrometer operating at 75.5 MHz. Spectra were either recorded in deuterated chloroform using undeuterated solvent as the internal standard, or recorded in deuterium oxide using *tert*-butanol as an external standard. Chemical shifts are reported as δ in parts per million.

Fluorine nuclear magnetic resonance (^{19}F n.m.r.) spectra were recorded on a Bruker CXP300 spectrometer operating at 282 MHz. Spectra were recorded in the solvent indicated using trifluoroacetic acid as an external standard. Chemical shifts are quoted as δ in parts per million.

Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded on either a Bruker ACP300 or CXP300 spectrometer operating at 300 MHz. Spectra were recorded in the solvents indicated using either tetramethylsilane ($CDCl_3$) as an internal standard or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (D_2O) as an external standard. Chemical shifts are quoted as δ in parts per million. Multiplicities are abbreviated to:- s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Electron impact (e.i.) mass spectra were recorded with an AEI MS-30 double focussing spectrometer operating at 70 eV. Only the major fragments are given. Fast atom bombardment (f.a.b.) mass spectra were recorded on a Vacuum Generators ZAB 2HF spectrometer.

All solvents were distilled before use. Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from benzophenone ketyl. Drying and purification of other solvents and reagents was accomplished by standard laboratory procedures. [138,139]

N-Phthaloylphenylalanine (66)

A mixture of phenylalanine (10.0 g, 60 mmol) and finely ground phthalic anhydride (8.9 g, 60 mmol) was heated on an oil bath at 150° for 30 minutes. The mixture was allowed to cool to room temperature when it was dissolved in dichloromethane and washed with water. The organic layer was then dried over $MgSO_4$ and concentrated to yield the *title compound* (66) as an oil which solidified on standing (quantitative yield): m.p. 177-179° (lit.[140] 178°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.59 (d, *J* = 8.5 Hz, 2H), 3.23 (t, *J* = 8.5 Hz, 1H), 7.16 (s, 5H, ArH), 7.62-7.77 (m, 4H, PhthH), 10.68 (br s, 1H, CO_2H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 34.3, 53.0, 123.5, 126.9, 128.5, 128.7, 131.3, 134.1, 136.3, 167.4, 174.6; IR (nujol) 1774, 1738, 1712, 1614, 1500 cm^{-1}; MS (e.i.) *m/z* 295 $[M]^+$, 251, 250, 232, 204, 249, 148 {100}.

N-Phthaloylphenylalanine methyl ester (49a)

N-Phthaloylphenylalanine (49a) (17.7 g, 60 mmol) was dissolved in dry methanol (200 ml) which had been pre-treated with thionyl chloride (10.8 g, 90 mmol). The solution was stirred under nitrogen for 18 h at room temperature and the solvent was then removed under reduced pressure. The residue was diluted with dichloromethane and washed with 10% Na_2CO_3, water, and then concentrated under reduced pressure. The concentrate was recrystallized from ethyl acetate/light petroleum to give the *title compound* (49a) in (16.9 g, 91%). The ^{1}H n.m.r. spectral data was consistent with that previously reported[141] : m.p. 83-85° (lit[104] 73-75°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 10.9 and 14.3 Hz, 1H), 3.64 (dd, *J* = 5.6 and 14.3 Hz, 1H), 3.80 (s, 3H), 5.20 (dd, *J* = 5.6 and 10.9 Hz, 1H), 7.18 (s, 5H, ArH), 7.68-7.72 (m, 2H, PhthH), 7.77-7.81 (m, 2H,

PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 33.7, 51.9, 52.3, 122.5, 125.8, 127.5, 127.8, 130.6, 133.1, 135.7, 166.4, 168.3.

N-Phthaloylvaline (65)

Treatment of valine (12.6 g, 85 mmol) with finely ground phthalic anhydride (10.0 g, 85 mmol), as described for the synthesis of *N*-phthaloylphenylalanine (66) from phenylalanine, gave the *title compound* (65) as a white solid (18.0 g, 86%): m.p. 99-101° (lit.[95] 101.5-102°); ^1H n.m.r. (300 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H), 2.77 (m, 1H), 4.65 (d, *J* = 8.3 Hz, 1H), 7.74-7.90 (m, 4H, PhthH), 10.68 (br s, 1H, CO_2H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 19.4, 20.9, 28.3, 57.4, 123.6, 131.5, 134.2, 167.7, 174.5; IR (nujol) 3224, 1760, 1696, 1610 cm^{-1}.

N-Phthaloylvaline methyl ester (48a)

Treatment of *N*-phthaloylvaline (65) (10.0 g, 40 mmol) with methanol (150 ml) which had been pre-treated with thionyl chloride (5.6 g, 45 mmol) as described above for the synthesis of *N*-phthaloyphenylalanine methyl ester (49a) from *N*-phthaloylphenylalanine (66) gave the *title compound* (48a) as a viscous oil (8.6 g, 83 %): ^1H n.m.r. (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 2.77 (m, 1H), 3.72 (s, 3H), 4.58 (d, *J* = 8.3 Hz, 1H), 7.76-7.90 (m, 4H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 19.3, 20.8 , 28.5, 52.4, 57.4, 123.5, 131.6, 134.8, 167.7, 169.2.

N-Phthaloylleucine (67)

Treatment of leucine (5.0 g, 38 mmol) with finely ground phthalic anhydride (5.6 g, 38 mmol) as described for the synthesis of *N*-phthaloylphenylalanine (66) from phenylalanine, gave the *title compound* (67) as a white solid (9.0 g, 91%): m.p. 104-106° (lit.[140]110°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.50-1.55 (m, 1H), 1.91-2.01 (m, 1H), 2.34-2.44 (m, 1H), 5.02 (dd, *J* = 4.2 and 11.5 Hz, 1H), 7.74-7.77 (m, 2H, PhthH), 7.87-7.90 (m, 2H, PhthH), 9.64 (br s, 1H, CO_2H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 20.9, 23.0, 25.0, 36.9, 50.4, 123.6, 131.6, 134.2, 167.7, 175.9.

N-Phthaloylleucine methyl ester (50a)

Treatment of *N*-phthaloylleucine (67) (5.0 g, 19 mmol) with methanol (150 ml) which had been pre-treated with thionyl chloride (2.72 g, 22 mmol) as described for the synthesis of *N*-phthaloylphenylalanine (66) from phenylalanine, gave the *title compound* (50a) as a clear viscous oil which crystallized on long standing: m.p. 43-45°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 1H), 1.40 (m, 1H), 1.92 (ddd, *J* = 4.4, 10.3 and 14.4 Hz, 1H), 2.30 (ddd, *J* = 4.0, 11.7 and 14.4 Hz, 1H), 3.69 (s, 3H), 4.92 (dd, *J* = 4.4 and 11.7 Hz, 1H), 7.70-7.73 (m, 2H, PhthH), 7.80-7.84 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 20.9, 23.0, 24.9, 37.1, 50.4, 52.6, 123.3, 131.7, 134.0, 167.6, 170.1.

N-*tert*-Butyl-N$^{\alpha}$-phthaloylphenylalaninamide (69a)

To a stirred suspension of *N*-phthaloylphenylalanine (66) (8.85 g, 30 mmol) in carbon tetrachloride (120 ml) was added thionyl chloride (3.6 g, 33 mmol). The mixture was heated to reflux until no suspension remained. The solution was

then cooled to room temperature and concentrated under reduced pressure. Pyridine (2.6 ml, 33 mmol) and *tert*-butylamine (3.46 ml, 33 mmol) were then added in a dropwise fashion to the on going concentrate which had been redissolved in carbon tetrachloride (100 ml). The mixture was stirred for 3 h, at which point the mixture was concentrated under reduced pressure. The concentrate was dissolved in chloroform, washed with 10% HCl, saturated Na_2CO_3, and water. After concentration and crystallization from carbon tetrachloride, the *title compound* (69a) was isolated as a crystalline solid (7.48 g, 71%): m.p. 194-195°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 3.48 (dd, *J* = 10.0 and 14.1 Hz, 1H), 3.56 (dd, *J* = 6.7 and 14.1 Hz, 1H), 4.99 (dd, *J* = 6.7 and 10.0 Hz, 1H), 5.62 (br s, 1H, NH), 7.18 (s, 5H, ArH), 7.68-7.80 (m, 4H, ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 28.4, 35.0, 51.5, 56.5, 123.3, 126.8, 128.6, 128.7, 131.2, 134.0, 136.8, 167.3, 167.9; IR (nujol) 3300, 2950, 1720, 1660, 1510, 1380, 720 cm^{-1}; MS (e.i.) *m/z* 350 $[M]^+$; Analysis calc'd for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.3; N, 8.0; found: C, 72.0; H, 6.3; N, 8.1.

N-Phthaloylhomophenylalanine (68)

A mixture of homophenylalanine (1.0 g, 5.6 mmol) and finely ground phthalic anhydride (0.9 g, 6.0 mmol) was heated in an oil bath for 30 minutes. The melt was then allowed to cool to room temperature. The viscous oil was dissolved in dichloromethane and washed with water. The organic layer was concentrated to give the *title compound* (68) as a white solid (1.55 g, 90%): m.p. 144-145° (lit.mp 145°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.56-2.77 (m, 4H), 4.93 (m, 1H), 7.09-7.29 (m, 5H, ArH), 7.73-7.77 (m, 2H, PhthH), 7.84-7.88 (m, 2H, PhthH), 9.03 (br s, 1H, CO_2H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 29.6, 32.6, 51.6, 123.5, 126.0, 128.3, 128.4, 131.6, 134.2, 140.0, 167.6, 175.0.

N-Phthaloylhomophenylalanine methyl ester (51a)

N-Phthaloylhomophenylalanine (68) (1.0 g, 5.5 mmol) was dissolved in dry methanol (50 ml) which had been pre-treated with thionyl chloride (0.5 ml, 7.0 mmol). The solution was stirred at room temperature under an atmosphere of nitrogen for 18 h. The solution was then concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with 10% Na_2CO_3, water, and then concentrated under reduced pressure to give the *title compound* (51a) as a colourless oil (0.88 g, 85 %). The spectral data for this compound was consistent with that previously reported[81]: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.55-2.71 (m, 4H), 3.72 (s, 3H), 4.88 (m, 1H), 7.08-7.22 (m, 5H, Ar**H**), 7.72-7.76 (m, 2H, Phth**H**), 7.82-7.86 (m, 2H, Phth**H**); IR (nujol) 1794, 1744, 1720, 1388, 1098, 708 cm^{-1}; MS (e.i.) *m/z* 323 $[M]^+$.

3-Bromo-*N*-phthaloylvaline methyl ester (48b)

N-Phthaloylvaline methyl ester (48a) (1.0 g, 4.4 mmol) was dissolved in refluxing carbon tetrachloride (100 ml) under nitrogen. *N*-bromosuccinimide (0.78 g, 4.4 mmol) was added and the refluxing mixture was irradiated with a 300 watt mercury lamp for 2 h. The solution was cooled, washed with water, and concentrated under reduced pressure to afford 3-bromo-*N*-phthaloylvaline methyl ester (48b). The residue was chromatographed on silica to afford the *title compound* (48b) as an oil which crystallized from dichloromethane/light petroleum as colourless crystals (1.06 g, 71%): m.p. 131-132° (lit.[77] 131-132°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.15 (s, 3H), 3.71 (s, 3H), 5.17 (s, 1H), 7.81 (m, 2H, Phth**H**), 7.92 (m, 2H, Phth**H**); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 31.6, 32.5, 52.5, 59.8, 64.3, 123.7, 131.3, 134.4, 165.9, 167.2.

4-Bromo-*N*-phthaloylleucine methyl ester (50b)

Treatment of *N*-phthaloylleucine methyl ester (50a) (3.0 g, 11 mmol) with *N*-bromosuccinimide (2.0 g, 11 mmol) as described for the preparation of 3-bromo-*N*-phthaloylvaline methyl ester (48a), gave 4-bromo-*N*-phthaloylleucine methyl ester (50b) as an oil. Chromatography on silica and crystallization from dichloromethane/light petroleum afforded the *title compound* (50b) as a crystalline solid (2.65 g, 68%): m.p. 63-64° (lit.[104] 63-64°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.76 (s, 3H), 1.84 (s, 3H), 2.85 (m, 2H), 3.75 (s, 3H), 5.25 (dd, *J* = 4.2 and 8.2 Hz, 1H), 7.76 (m, 2H, PhthH), 7.89 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 33.8, 34.8, 44.3, 50.1, 53.2, 63.6, 123.6, 131.9, 134.3, 167.6, 169.6.

(2RS,3RS)-3-Bromo-N-*t*-butyl-N$^\alpha$-phthaloylphenylalaninamide (69bi) and (2RS,3SR)-3-Bromo-N-*t*-butyl-N$^\alpha$-phthaloylphenylalaninamide (69bii)

N-*t*-Butyl-*N*$^\alpha$-Phthaloyl-(*R,S*)-phenylalaninamide (69a) (20 g, 57 mmol) was dissolved in dichloromethane/carbon tetrachloride (1:1, 200 ml). *N*-Bromosuccinimide (12.0 g, 67.5 mmol) was added and the mixture was heated at reflux for 2 h while it was irradiated with a 300 watt mercury lamp. The resultant solution was cooled, then filtered. The filtrate was washed with water, then dried and concentrated under reduced pressure to give a 1:1 mixture of (2*RS*,3*RS*)-3-bromo-*N*-*t*-butyl-*N*$^\alpha$-phthaloyl-phenylalaninamide (69bi) and (2*RS*,3*SR*)-3-bromo-*N*-*t*-butyl-*N*$^\alpha$-phthaloyl-phenylalaninamide (69bii) (24.5 g, 100%). A sample of the mixture (15.0 g) was recrystallized from light petroleum/propan-2-ol (1:1, 500ml) to give two types of crystals. These were separated according to size by using 0.25 and 0.60 mm mesh sieves. The smaller, colourless, needle-shaped crystals were recrystallized from light

petroleum/propan-2-ol to give (2*RS*, 3*RS*)-3-bromo-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (69bi) (6.10 g, 41%): m.p. 199-200°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 5.28 (d, *J* = 11.8 Hz, 1H), 5.85 (br s, 1H), 6.25 (d, *J* = 11.8 Hz, 1H), 7.60 (m, 5H, ArH), 7.95 (m, 4H, PhthH); IR (nujol) 3375, 1775, 1705, 1530 cm^{-1}; MS (e.i.) *m*/*z* 430, 428[M]$^{+}$; Analysis calc'd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5; found: C, 58.8; H, 4.9; N, 6.6. The larger, pale yellow, granular crystals were recrystallized from light petroleum/propan-2-ol to give (2*RS*,3*SR*)-3-bromo-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (69bii) (5.84 g, 39%): m.p. 213-213.5°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 5.32 (d, *J* = 11.5 Hz, 1H), 6.04 (d, *J* = 11.5 Hz, 1H), 6.50 (br s, 1H), 7.40 (m, 5H, ArH), 7.75 (m, 4H, PhthH); IR (nujol) 3350, 1700, 1530 cm^{-1}; MS (e.i.) *m*/*z* 430/428 [M]$^{+}$; Analysis calc'd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5; found: C, 58.5; H, 5.0; N, 6.8.

(2*RS*,3*RS*)-3-Bromo-*N*-Phthaloylphenylalanine methyl ester (49bi) and (2*RS*,3*SR*)-3-Bromo-*N*-Phthaloylphenylalanine methyl ester (49bii)

N-Phthaloylphenylalanine methyl ester (49a) (5.0 g, 16 mmol) was dissolved in a refluxing mixture of carbon tetrachloride and dichloromethane (4:1, 100 ml). *N*-Bromosuccinimide (2.9 g, 16 mmol) was added and the resulting refluxing mixture was irradiated with a 300 watt mercury lamp for 2h. The solution was allowed to cool, then washed with water and concentrated under reduced pressure to give a 1:1 mixture of the diastereomers of 3-bromo-*N*-phthaloylphenylalanine methyl ester (49b) (5.5 g, 88%). The diastereomers were fractionally crystallized from a dilute solution in ethyl acetate/light petroleum. (2*RS*, 3*SR*)-3-bromo-*N*-Phthaloylphenylalanine methyl ester (49bi) crystallized first as needles: m.p. 144-145° (lit.[80] 135-136°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.58 (s, 3H), 5.55 (d, *J* = 11.2 Hz, 1H), 6.06 (d, *J* = 11.2 Hz, 1H), 7.41 (m, 3H, ArH), 7.63 (m, 2H, ArH), 7.84 (m, 2H, PhthH), 7.99 (m, 2H, PhthH); ^{13}C

n.m.r. (75.5 MHz, $CDCl_3$) δ 50.7, 52.9, 56.7, 123.9, 128.1, 129.0, 131.5, 134.5, 139.1, 166.3, 167.1; IR (nujol) 1755, 1709, 708 cm^{-1}; MS (e.i.) *m/z* 389/387[M]$^+$, 330, 328, 308, 276 {100}, 249, 248, 218, 190. (2*RS*, 3*RS*)-3-bromo-*N*-Phthaloyl-phenylalanine methyl ester (49bii) crystallized second as granular crystals m.p. 127-128° (lit.[80] 122-123°); ^1H n.m.r. (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.62 (d, *J* = 10.4 Hz, 1H), 5.95 (d, *J* = 10.4 Hz, 1H), 7.19 (m, 3H, ArH), 7.37 (m, 2H, ArH), 7.66 (m, 4H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 47.6, 53.1, 57.0, 123.6, 128.1, 128.6, 128.9, 130.9, 134.3, 137.1, 166.3, 167.2; IR (nujol) 1774, 1758, 1718, 727 cm^{-1}; MS (e.i.) *m/z* 389/387[M]$^+$, 330, 328, 308, 276, 249, 248 {100}, 218, 190.

4-Bromo-*N*-phthaloylhomophenylalanine methyl ester (51b)

Treatment of *N*-phthaloylhomophenylalanine methyl ester (51a) (1.00 g, 3.1 mmol) with *N*-bromosuccinimide as described above for the preparation of 3-bromo-*N*-phthaloylvaline methyl ester (48b) (0.56 g, 3.1 mmol), gave a 1:1 mixture of the diastereomers of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b). The diastereomers of the bromide (51b) were crystallized from dichloromethane/light petroleum to give diastereomeric mixtures of the bromide (51b) as colourless crystals (0.86 g, 69%). *c*. 5:1 mixture of diastereomers: m.p. 109-111°C (lit.[81] m.p. 112-118°C, 5:1 mixture of diastereomers). ^1H n.m.r. (300 MHz, $CDCl_3$) one diastereomer: δ 2.99-3.31 (m, 2H), 3.75 (s, 3H), 4.91 (t, *J* = 7.6 Hz, 1H), 5.21 (dd, *J* =5.9 and 9.2 Hz, 1H), 7.05-7.38 (m, 5H, ArH), 7.70-7.88 (m, 4H, PhthH): other diastereomer: δ 2.99-3.31 (m, 2H), 3.73 (s, 3H), 4.91 (t, *J* = 7.6 Hz, 1H), 5.10 (t, *J* = 7.5 Hz, 1H), 7.05-7.38 (m, 5H, ArH), 7.70-7.88 (m, 4H, PhthH); IR (nujol) 1775, 1744, 1716, 706 cm^{-1}, MS (e.i.) *m/z* 322 [M-Br]$^+$.

3-Bromo-*N*-phthaloylvaline (70)

N-Phthaloylvaline (65) (2.0g, 8.7 mmol) was dissolved in refluxing carbon tetrachloride. *N*-bromosucinimide (1.55g, 8.7 mmol) was added and the resulting solution was stirred at reflux and irradiated with a 300 watt mercury lamp for 2h. The resulting solution was then cooled to room temperature and partitioned with water. The organic phase was concentrated under reduced pressure to yield crude 3-bromo-*N*-phthaloylvaline (70) which crystallized from dichloromethane/light petroleum (2.38g, 89%): m.p. 160-162°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.17 (s, 3H), 5.27 (s, 1H), 7.4 (br s, 1H), 7.82 (m, 2H, PhthH), 7.94 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 31.9, 32.8, 60.2, 63.6, 124.0, 131.4, 134.6, 167.3, 170.4; IR (nujol) 3200 (br), 1775, 1752, 1712, 1192, 1168, 1098, 1085, 928, 898, 720 cm^{-1}; MS (e.i.) calc'd for $C_{12}H_{11}NO_2Br$: *m/z* 201.078, found 201.079; 328/326 $[M]^+$, 246, 201 {100}; Analysis calc'd for $C_{13}H_{12}NO_4Br$: C, 47.87; H, 3.71; N, 4.29; found: C, 46.13; H, 3.64; N, 3.83.

4-Bromo-*N*-phthaloylleucine (72)

Reaction of the *N*-phthaloylleucine (67) with *N*-bromosuccinimide as described above for the preparation of 3-bromo-N-phthaloylvaline (70) from N-phthaloylvaline (65), gave the *title compound* (72) which recrystallized from dichloromethane/light petroleum as colourless needles in 84% yield: m.p. 129-130°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.83 (s, 3H), 2.78 (dd, *J* = 3.1, 15.8 Hz, 1H), 2.88 (dd, *J* = 9.1, 15.8 Hz, 1H), 5.29 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.75 (m, 2H, PhthH), 7.87 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 33.9, 34.7, 44.2, 49.9, 63.4, 123.7, 131.8, 134.3, 167.5, 174.2; IR (nujol) 3416 br, 1780, 1714, 1320, 1205, 1180, 1130, 1076, 1040, 880 cm^{-1}; MS (e.i.) calc'd for $C_{14}H_{14}NO_4$: *m/z*

260.092, found 260.093; 296/294 $[M]^+$, 260 {100}; Analysis calc'd for $C_{14}H_{14}NO_4Br$: C, 49.4; H, 4.2; N, 4.1; found: C, 49.8; H, 4.4; N, 4.2.

3-Bromo-*N*-phthaloylphenylalanine (74)

N-Phthaloylphenylalanine (66) was treated with *N*-bromosuccinimide as described above for the preparation of 3-bromo-*N*-phthaloylvaline (70) from *N*-phthaloylvaline (65), to afford a 1:1 mixture of the diastereomers of 3-bromo-*N*-phthaloylphenylalanine (74) which fractionally recrystallized from dichloromethane/light petroleum in 77% yield. One diastereomer: m.p. 152-155°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 5.64 (d, *J* = 10.4 Hz, 1H), 5.86 (d, *J* = 10.4 Hz, 1H), 7.10-7.37 (m, 5H, ArH), 7.61-7.80 (m, 4H, PhthH), 8.03 (br s, 1H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 47.0, 56.9, 123.7, 128.1, 128.6, 129.0, 130.8, 143.4, 137.0, 166.3, 171.6. Other diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 5.55 (d, *J* = 11.2 Hz, 1H), 5.97 (d, *J* = 11.2 Hz, 1H), 6.64 (br s, 1H, CO_2H), 7.10-7.55 (m, 5H, ArH), 7.76-7.95 (m, 4H, PhthH); ^{13}C n.m.r. (75.7 MHz, $CDCl_3$) δ 50.36, 56.34, 124.03, 128.11, 128.85, 129.02, 131.44, 134.58, 138.90, 167.03, 170.29; IR (nujol) 3450 br, 1798, 1718, 1608, 1168, 1104, 924, 868 cm^{-1}; MS (e.i.) calc'd for $C_{16}H_{11}NO_2$: *m/z* 249.079, found 249.078; 375/373 $[M]^+$, 249 {100}, 232, 220, 204; Analysis calc'd for $C_{17}H_{12}NO_4Br$: C, 54.6; H, 3.2; N, 3.7; found: C, 52.8; H, 3.2; N, 3.5.

4-Bromo-*N*-phthaloylhomophenylalanine (77)

Reaction of *N*-phthaloylhomophenylalanine (68) with *N*-bromosuccinimide as described above for the preparation of 3-bromo-*N*-phthaloylvaline (70) from *N*-phthaloylvaline (65), afforded the *title compound* (77) as a 1.2:1 mixture of diastereomers which was not purified further owing to its lability: m.p. 59-65°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) major diastereomer, δ 3.00-3.29 (m, 2H), 5.25 (t, *J* =

7.5 Hz, 1H), 4.96 (dd, J = 7.5 and 5.8 Hz, 1H), 6.70-7.37 (m, 5H, ArH), 7.70-7.89 (m, 4H, PhthH), minor diastereomer, δ 3.00-3.29 (m, 2H), 4.90 (t, J = 7.5 Hz, 1H), 5.09 (t, J = 7.5 Hz, 1H), 6.70-7.37 (m, 5H, ArH), 7.70-7.89 (m, 4H, PhthH); IR ($CDCl_3$) 3152, 1778, 1724, 1614, 1470, 1388, 1264, 1172, 1096, 886 cm^{-1}; MS (e.i.) calc'd for $C_{18}H_{14}NO_4Br$: m/z 387.011, found 387. 012; 389/387 $[M]^+$, 308/307, 265 {100}.

2-Methyl-1-phthalimidopropene (71)

3-Bromo-*N*-phthaloylvaline (70) (0.25g, 0.73 mmol) was dissolved in acetonitrile/water (2:1, 15 ml). Silver carbonate (0.10 g, 0.37 mmol) was added to the solution and the mixture was stirred in the dark for 1 h. The reaction mixture was then filtered through a bed of celite and the filtrate concentrated under reduced pressure. The concentrate was triturated with chloroform, filtered through celite, and concentrated to afford an oil which crystallized from dichloromethane/light petroleum as pale green crystalline solid (0.11 g, 72%): m.p. 90°; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.67 (d, J = 1.0 Hz, 3H), 1.93 (d, J = 1.0 Hz, 3H), 5.90 (m, 1H), 7.71-7.77 (m, 2H, PhthH), 7.85 (m, 2H, PhthH); IR ($CDCl_3$) 1786, 1768, 1718, 1614, 1394, 1264 cm^{-1}; MS (e.i.) calc'd for $C_{12}H_{11}NO_2$: m/z 201.079, found 201.079; 201 $[M]^+${100}, 186, 182, 130, 76; Analysis calc'd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0; found: C, 71.3; H, 5.3; N, 6.8.

(*E*)-2-Phthalimidostyrene (76)

Procedure A:

Reaction of a 1:1 mixture of the diastereomers of 3-bromo-*N*-phthaloylphenylalanine (74) with silver carbonate under conditions identical to those described for the synthesis of 2-methyl-1-phthalimidopropene (71)

from 3-bromo-N-phthaloylvaline (70), yielded (*E*)-2-phthalimidostyrene (76) as a yellow crystalline solid in 83% yield: m.p. 185-187°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 7.36, (d, *J*=15.2 Hz, 1H), 7.36-7.38 (m, 3H, ArH), 7.46-7.49 (m, 2H, ArH), 7.65 (d, *J* = 15.2 Hz, 1H), 7.74-7.93 (m, 4H, PhthH); IR ($CDCl_3$) 1790, 1760, 1705, 1640 cm^{-1}; MS (e.i.) calc'd for $C_{16}H_{11}NO_2$: m/z 249.079, found 249.079; 249 [M-CO_2]$^+$ {100}, 232, 220, 204, 104, 102; Analysis calc'd for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.5; N, 5.6; found: C, 77.3; H, 4.4; N, 5.7.

Procedure B:

When the above reaction was carried out at 0°, and care was taken not to overheat the reaction mixture upon concentration under reduced pressure, the product composition changed quite considerably. In addition to the (*E*)-2-phthalimidostyrene (76) which is isolated in 67% yield, *cis*-4-phenyl-3-phthalimido-γ-propiolactone (75) is isolated in 13% yield with the separation of the two products being achieved by chromatography on silica using ethyl acetate and light petroleum as eluants: *cis*-4-phenyl-3-phthalimido-γ-propiolactone (75): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 6.33 (d, *J* = 9.1 Hz, 1H), 6.70 (d, *J* = 9.1 Hz, 1H), 7.19-7.26 (m, 5H, ArH), 7.22-7.77 (m, 2H, PhthH), 7.83-7.92 (m, 2H, PhthH); IR ($CDCl_3$) 3050, 1840, 1780, 1760 cm^{-1}; MS (e.i.) 249 [M-CO_2]$^+$ {100}, 232, 220, 204, 104, 102.

Evidence for the *trans*-4-phenyl-3-phthalimido-γ-propiolactone: ^{1}H n.m.r. spectrum of the crude reaction mixture, however this product is not isolated: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 5.67 (d, *J* = 4.5 Hz, 1H), 5.92 (d, *J* = 4.5 Hz, 1H), 7.19-7.26 (m, 5H, ArH), 7.22-7.77 (m, 2H, PhthH), 7.83-7.92 (m, 2H, PhthH).

5,5-Dimethyl-3-phthalimido-γ-butyrolactone (73)

3-Bromo-*N*-phthaloylleucine (72) (2.0 g, 7.7 mmol) was dissolved in acetonitrile (100 ml). Silver carbonate (1.1 g, 3.9 mmol) was added to the stirred solution and the reaction mixture was shielded from the light. The reaction mixture was stirred for 24 h, at which point it was filtered through a bed of celite and the filtrate concentrated under reduced pressure. The concentrate was triturated with chloroform and again filtered through a bed of celite. The filtrate was concentrated to yield 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) which was crystallized from dichloromethane/light petroleum (1.6 g, 80%): m.p. 126-128° (lit.mp 131°) ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.52 (s, 3H), 1.64 (s, 3H), 2.44 (dd, *J* = 12.1 and 9.7 Hz, 1H), 2.60 (dd, *J* = 12.1 and 11.5 Hz, 1H), 5.24 (dd, *J* = 9.7 and 11.5 Hz, 1H), 7.77 (m, 2H, Phth**H**), 7.88 (m, 2H, Phth**H**); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 27.6, 29.0, 38.5, 40.6, 82.4, 123.7, 131.7, 134.5, 167.0, 171.5.

5-Phenyl-3-phthalimido-γ-butyrolactone (78)

Treatment of crude 4-bromo-*N*-phthaloylhomophenylalanine (77) (0.6 g, 1.6 mmol) with silver carbonate (0.22 g, 0.8 mmol) under identical conditions to those described for the synthesis of 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) from 3-Bromo-*N*-phthaloylleucine (72) resulted in the production of a 1:1 mixture of the diastereomers of 5-phenyl-3-phthalimido-γ-butyrolactone (78). Crystallization from dichloromethane/light petroleum gave crystals of different shapes. Small quantities of each diastereomer of the lactone (78) were isolated by mechanical means. Spar shaped crystals, *trans*-isomer (78i): m.p. 143-144°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.89 (ddd, *J* = 12.1, 12.5 and 10.7 Hz, 1H), 2.92 (ddd, *J* = 9.2, 6.2 and 12.5 Hz, 1H), 5.31 (dd, *J* =

12.1 and 9.2 Hz, 1H), 5.50 (dd, J = 10.7 and 6.2 Hz, 1H), 7.32-7.56 (m, 5H, ArH), 7.77 (m, 2H, PhthH), 7.91 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 35.3, 48.9, 79.0, 123.8, 126.4, 128.9, 129.2, 131.6, 134.5, 137.9, 166.9, 171.5; IR ($CDCl_3$) 3000, 1795, 1780, 1730, 1390, 1095 cm^{-1}; MS (e.i.) calc'd for $C_{18}H_{13}NO_4$: m/z 307.085, found 307.083; 307 $[M]^+$, 245, 148, 116 {100}; Analysis calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.3; N, 4.6; found: C, 70.2; H, 4.2; N, 4.6. Cluster shaped crystals, *cis*-isomer (78ii): m.p. 140-143°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.64 (ddd, J = 9.0, 3.4 and 13.0 Hz, 1H), 3.11 (dt, J = 13.0 and 9.0 Hz, 1H,), 5.16 (t, J = 9.0 Hz, 1H), 5.92 (dd, J = 3.4 and 9.0 Hz, 1H), 7.33-7.54 (m, 5H, ArH), 7.76 (m, 2H, PhthH), 7.88 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 29.7, 46.4, 78.5, 123.8, 125.0, 128.6, 129.1, 131.60, 134.5, 138.9, 166.9, 172.2; IR ($CDCl_3$) 3005, 1790, 1780, 1730, 1720, 1395 cm^{-1};MS (e.i.) calc'd for $C_{18}H_{14}NO_4$: m/z 308.092, found 308.092; 308 $[M+1]^+$, 245, 239, 148, 116 {100}

N-Phthaloyl-α,β-dehydrovaline methyl ester (79)

A solution of 18-crown-6 in acetonitrile (1.15 M, 25 ml) was treated with anhydrous potassium fluoride (0.10 g, 2.0 mmol), and stirred vigorously at reflux for 0.5 h. 3-Bromo-N-phthaloylvaline methyl ester (48b) (0.30 g, 0.9 mmol) was then added. The mixture was stirred at reflux for a further 1 h, then it was cooled and concentrated under reduced pressure. The residue was suspended in ethyl acetate, and the suspension was washed with water, then dried and concentrated under reduced pressure to leave an oil. Crystallization of the oil from ethyl acetate/light petroleum afforded N-phthaloyl-α,β-dehydrovaline methyl ester (79) as colourless crystals (0.18 g, 77%): m.p. 81-82° (lit.[104] 66-72°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2 43 (s, 3H), 3.68 (s, 3H), 7.80 (m, 2H), 7.92 (m, 2H); IR (nujol) 1728, 1227, 720 cm^{-1}; MS (e.i.) m/z 259

$[M]^+$, 227, 132, 104 {100}, 76; Analysis calc'd for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.1; N, 5.4; found: C, 64.7; H, 5.1; N, 5.4.

(*Z*)-*N*-*t*-Butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (80)

A solution of 18-crown-6 in acetonitrile (1.15 M, 25 ml) was treated with anhydrous potassium fluoride (0.11g, 2.3 mmol), and stirred vigorously at reflux for 0.5 h. (2*RS*,3*RS*)-3-Bromo-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloyl-phenylalaninamide (69bi) (0.50 g, 1.2 mmol) was then added; the mixture was stirred at reflux for a further 0.5 h, then it was cooled and concentrated under reduced pressure. The residue was suspended in ethyl acetate; the suspension was washed with water, then dried and concentrated under reduced pressure. Recrystallization of the solid from ethyl acetate/light petroleum afforded the *title compound* (80) (0.36 g, 84%) as colourless crystals: m.p. 215-215°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 5.97 (br s, 1H, NH), 7.25 (m, 5H, ArH), 7.59 (s, 1H), 7.85 (m, 4H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 28.6, 52.0, 124.0, 125.3, 128.5, 128.8, 129.5, 131.9, 133.1, 134.5, 135.6, 162.9, 166.7; IR (nujol) 3350, 1780, 1720, 1660, 1630, 1525 cm^{-1}; MS (e.i.) calc'd for $C_{21}H_{20}N_2O_3$: *m/z* 348.147, found 348.149; 348 $[M]^+$; Analysis calc'd for $C_{21}H_{20}N_2O_3$: C, 72.4; H, 5.8; N, 8.0; found: C, 72.6; H, 5.8; N, 8.0.

(*E*)-*N*-*t*-Butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (81)

Treatment of (2*RS*,3*SR*)-3-bromo-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (69bii) with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described above for the preparation of (*Z*)-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloyl-dehydrophenylalaninamide (80), afforded a 5:1 mixture of the (*E*)- and (*Z*)-*N*-*t*-Butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (81) and (80). The

isomers (80) and (81) were separated from a dilute solution of ethyl acetate/light petroleum. (*E*)-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloyl-dehydrophenylalaninamide (81) was isolated as colourless crystals in 57% yield, while the *Z*-isomer (80) was isolated in 9% yield. *E*-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloyl-dehydrophenylalaninamide (81) : m.p. 185-186°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 5.50 (br s, 1H, NH), 7.05 (s, 1H), 7.40 (m, 5H, ArH), 7.85 (m, 4H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 28.0, 51.7, 123.6, 123.8, 128.5, 128.92, 129.1, 131.8, 132.2, 133.2, 134.4, 161.9, 166.9; IR (nujol) 3420, 1715, 1660, 1510 cm^{-1}; MS (e.i.) calc'd for $C_{21}H_{20}N_2O_3$: *m/z* 348.147, found 348.147; Analysis calc'd for $C_{21}H_{20}N_2O_3$: C, 72.4; H, 5.8; N, 8.0; found: C, 72.5; H, 5.8; N, 8.0.

(Z)-*N*-Phthaloyl-α,β-dehydrophenylalanine methyl ester (83)

Treatment of (2*RS*,3*RS*)-3-bromo-*N*-phthaloylphenylalanine methyl ester (49bi) with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described above for the preparation of (*Z*)-*N*-*t*-Butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (80) from (2*RS*,3*RS*)-3-Bromo-*N*-*t*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (69bi), afforded (*Z*)-*N*-Phthaloyl-α,β-dehydrophenylalanine methyl ester (83) as a colourless crystalline solid in 88% yield: m.p. 136-137°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 7.26-7.42 (m, 5H, ArH), 7.78 (m, 2H, PhthH), 7.90 (m, 2H, PhthH), 8.12 (s, 1H); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 52.7, 119.8, 123.9, 128.8, 129.3, 130.5, 131.9, 132.1, 134.4, 142.9, 163.8, 166.7; IR ($CDCl_3$) 1780, 1720, 1640, 1600 cm^{-1}; MS (e.i.) calc'd for $C_{18}H_{13}NO_4$: *m/z* 307.085, found 307.085; 307[M]$^{+}${100}, 279, 248, 247; Analysis calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.3; N, 4.6; found: C, 70.6; H, 4.2; N, 4.4.

(*E*)-*N*-Phthaloyl-α,β-dehydrophenylalanine methyl ester (84)

Treatment of (2*RS*,3*SR*)-3-bromo-*N*-phthaloylphenylalanine methyl ester (49bii) with the 18-crown-6 complex of potassium fluoride in acetonitrile as described above for the preparation of (*Z*)-*N*-*t*-Butyl-*N*α-phthaloyl-α,β-dehydrophenylalaninamide (80) from (2*RS*,3*RS*)-3-Bromo-*N*-*t*-butyl-*N*α-phthaloylphenylalaninamide (69bi), afforded a 2:1 mixture of (*Z*)- and (*E*)-*N*-phthaloyl-α,β-dehydrophenylalanine methyl ester (83) and (84) as an oil in 88% yield. Recrystallization of the mixture from ethyl acetate/light petroleum afforded the *Z*-isomer (83) in 34% yield, however the *E*-isomer was isolated as an oil as a 5:1 mixture of the (*E*)- and (*Z*)-isomers (84) and (83). (*E*)-isomer (84): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 7.23 (s, 1H), 7.29-7.49 (m, 5H, ArH), 7.80 (m, 2H, PhthH), 7.93 (m, 2H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 52.3, 120.7, 123.8, 128.1, 129.3, 130.5, 131.6, 133.0, 134.5, 139.7, 163.7, 166.6. IR($CDCl_3$) 1780, 1724, 1645, 1600, 1560 cm-1; MS (e.i): *m/z* 307 $[M]^+$ {100}, 279, 248, 247 .

Reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with the 18-crown-6 complex of potassium fluoride in acetonitrile.

A solution of 18-crown-6 in acetonitrile (1.15 M, 20 ml) was treated with anhydrous potassium fluoride (70 mg, 1.4 mmol) and stirred vigorously at reflux for 30 minutes. 4-Bromo-*N*-phthaloylleucine methyl ester (50b) (0.25 g, 0.7 mmol) was then added and the mixture was stirred at reflux for a further 5 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was suspended in ethyl acetate; the suspension was washed with water, then dried and concentrated under reduced pressure to leave an oil. Chromatography on silica afforded a

mixture of *N*-Phthaloyl-α,β-dehydroleucine methyl ester (85), *N*-Phthaloyl-β,γ-dehydroleucine methyl ester (86), *N*-Phthaloyl-α,β-methanovaline methyl ester (87) and *N*-Phthaloyl-γ,δ-dehydroleucine methyl ester (88) in the ratio 2.25 : 2.0 : 1.75: 1.0. (150 mg, 88%).

N-Phthaloyl-α,β-dehydroleucine methyl ester (85): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.6 Hz, 6H), 2.48 (septet of doublets , *J* = 6.6 and 10.7 Hz, 1H), 3.77 (s, 3H), 7.16 (d, *J* = 10.7 Hz, 1H), 7.73-7.93 (m, 4H, PhthH).

N-Phthaloyl-β,γ-dehydroleucine methyl ester (86): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.78 (d, *J* = 1.4 Hz, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 3.74 (s, 3H), 5.65 (d, *J* = 9.1 Hz, 1H), 5.82 (septet of doublets, *J* = 1.4 and 9.1 Hz, 1H), 7.73-7.93 (m, 4H, PhthH).

N-Phthaloyl-α,β-methanovaline methyl ester (87): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.51 (s, 3H), 1.52 (d, *J* = 5.9 Hz, 1H), 1.89 (d, *J* = 5.9 Hz, 1H), 3.65 (s, 3H), 7.76 (m, 2H, PhthH), 7.88 (m, 2H, PhthH).

N-Phthaloyl-γ,δ-dehydroleucine methyl ester (88): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.76 (s, 3H), 2.86 (dd, *J* = 4.2 and 14.2 Hz, 1H), 3.11 (dd, *J* = 12.2 and 14.2 Hz, 1H), 3.74 (s, 3H), 4.66 (br s, 1H), 4.69 (br s, 1H), 5.10 (dd, *J* = 4.2 and 12.2 Hz, 1H), 7.73-7.93 (m, 4H, PhthH);

IR($CDCl_3$) 3000, 2990, 1775, 1745, 1714, 1650, 1615, 1440, 1400 cm^{-1}; MS (e.i.) m/z 273 $[M]^+$, 257, 241, 132.

N-Phthaloyl-α,β-methanovaline methyl ester (87)

A stirred solution of 4-bromo-*N*-phthaloylleucine methyl ester (50b) (2.1 g, 6.0 mmol) in dry tetrahydrofuran (100 ml) was treated with sodium hydride (70% in parrafin oil, 0.40 g, 11 mmol), which was added portion wise under an atmosphere of nitrogen. After stirring vigorously for 24 h, the mixture was

filtered through a bed of celite and the filtrate concentrated under reduced pressure to afford a residue which was dissolved in dichloromethane. The dichloromethane solution was washed with water, dried, filtered, and then concentrated under reduced pressure to afford an oil. This oil was chromatographed on silica using ethyl acetate and light petroleum as eluants, and crystallized from dichloromethane/light petroleum (1.20 g, 73%): m.p. 89-92°(lit.[81]95-97°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.51 (s, 3H), 1.52 (d, *J* = 5.9 Hz, 1H), 1.89 (d, *J* = 5.9 Hz, 1H), 3.65 (s, 3H), 7.76 (m, 2H, PhthH), 7.88 (m, 2H, PhthH); IR($CDCl_3$) 1770, 1734, 1440, 720 cm^{-1}; ^{13}C n.m.r. (300 MHz, $CDCl_3$) δ 19.2, 23.3, 28.4, 29.8, 41.0, 52.6, 123.4, 129.3, 134.1, 168.4, 170.4; MS (e.i.) *m/z* 273 $[M]^+$.

Reaction of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) with the 18-crown-6 complex of potassium fluoride in acetonitrile.

Treatment of a 4:1 mixture of the diastereomers of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) (0.25 g, 0.64 mmol) with the 18-crown-6 complex of potassium fluoride (75 mg, 1.25 mmol) in acetonitrile as described for the reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with the 18-crown-6 complex of potassium fluoride, afforded a complex mixture of products. Chromatography on silica yielded a mixture of the diastereomers of *N*-phthaloyl-α,β-methanophenylalanine methyl ester (89) in a 4:1 ratio and the diastereomers of 4-fluoro-*N*-phthaloylhomophenylalanine methyl ester (90) in a 1:1 ratio (150 mgs). 5-Phenyl-3-phthalimido-γ-butyrolactone (78) was isolated as a 1:1 mixture of diasteromers (50 mg, 25%) and had spectral characteristics identical to those reported in Chapter One of the Results and Discussion of this thesis.

N-Phthaloyl-α,β-methanophenylalanine methyl ester, (89) major (*Z*)-isomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.27 (dd, *J* = 6.6 and 9.9 Hz, 1H), 2.43 (dd, *J* = 6.6 and 8.5 Hz, 1H), 3.38 (dd, *J* = 8.5 and 9.9 Hz, 1H), 3.72 (s, 3H), 7.07-7.17 (m, 5H, ArH), 7.60-7.85 (m, 4H, PhthH), minor (*E*)-isomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.90 (dd, *J* = 6.2 and 9.9 Hz, 1H), 2.50 (dd, *J* = 6.2 and 9.1 Hz, 1H), 3.17 (apparent t, *J* = 9.5 Hz, 1H), 3.72 (s, 3H), 7.07-7.17 (m, 5H, ArH); MS (e.i.) *m*/z 321 $[M]^+$.

4-Fluoro-*N*-phthaloylhomophenylalanine methyl ester (90), one diasteromer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.77-2.94 (m, 2H), 3.75 (s, 3H), 5.15 (dd, *J* = 5.7 and 8.6 Hz, 1H), 5.73 (ddd, *J* = 4.4, 7.7 and 47.9 Hz, 1H), 7.19-7.30 (m, 5H, ArH), 7.71-7.81 (m, 4H, PhthH); ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -105.4, other diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.72-2.94 (m, 2H), 3.75 (s, 3H), 5.20 (dd, *J* = 4.8 and 10.8 Hz, 1H), 5.40 (ddd, *J* = 5.5, 9.0 and 48.1 Hz, 1H), 7.13-7.19 (m, 5H, ArH), 7.71-7.87 (m, 4H, PhthH); ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -102.0; IR ($CDCl_3$) 1780, 1750, 1720, 1390, 1260, 1120 cm^{-1}; MS (e.i.) calc'd for $C_{19}H_{16}FNO_4$: m/z 341.106, found 341.107; 341 $[M]^+$, 322, 321, 282, 262, 219 {100}, 187.

N-Phthaloyl-α,β-methanophenylalanine methyl ester (89).

Treatment of a 1:1 mixture of the diastereomers of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) with sodium hydride in dry tetrahydrofuran, as described above for the preparation of *N*-phthaloyl-α,β-methanovaline (87) from 4-bromo-*N*-phthaloylleucine methyl ester (50b), gave *N*-phthaloyl-α,β-methanophenylalanine (89) as an oil in 35% yield and as a mixture of diastereomers *c*. 25:1. The spectral characteristics of this compound were identical to those recorded above for *N*-phthaloyl-α,β-methanophenylalanine methyl ester (89).

Reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with AgF in anhydrous acetonitrile.

A mixture of 4-bromo-*N*-phthaloylleucine methy ester (50b) (0.21 g, 0.6 mmol) and silver fluoride (0.15 g, 1.2 mmol) in dry acetonitrile was stirred vigorously in the dark and under anhydrous conditions for 5 h at room temperature. The mixture was then filtered through a bed of celite and the filtrate concentrated under reduced pressure. The concentrate was diluted with chloroform and the resulting suspension was filtered through celite. The filtrate was concentrated under reduced pressure and the residue chromatographed on silica using ethtyl acetate and light petroleum as eluants to afford 4-fluoro-*N*-phthaloylleucine methyl ester (91) (26 mg, 15%), 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) (22 mg, 14%) and a 1:2 mixture of *N*-phthaloyl-β,γ-dehydroleucine methyl ester (86) and *N*-phthaloyl-γ,δ-dehydroleucine methyl ester (88) (69 mg, 42%).

4-Fluoro-*N*-phthaloylleucine methyl ester (91): m.p. 71-72°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.38 (d, *J* = 21.43 Hz, 3H), 1.47 (d, *J* = 21.16 Hz, 3H), 2.51 (ddd, *J* = 2.8, 15.5 and 29.3 Hz, 1H), 2.81 (ddd, *J* = 11.0, 15.5 and 13.6 Hz, 1H), 3.76 (s, 3H), 5.18 (dd, *J* = 2.8 and 11.0 Hz, 1H), 7.74-7.78 (m, 2H, PhthH), 7.85-7.90 (m, 2H, PhthH); ^{13}C n.m.r. (300MHz, $CDCl_3$) δ 25.45 (d, *J* = 25.4 Hz), 28.0 (d, *J* = 24.4 Hz), 38.57 (d, *J* = 20.8 Hz), 48.3, 53.0, 94.5 (d, *J* = 167.4 Hz), 123.5, 131.4, 134.1, 167.6, 169.8; IR ($CDCl_3$) 3000, 1750, 1720; MS (e.i.) calc'd for $C_{13}H_{13}FNO_2$: *m/z* 234.093, found 234.094; 278, 273, 234, 214{100}; Analysis calc'd for $C_{15}H_{16}FNO_4$: C, 61.4; H, 5.5; N, 4.8; found: C, 61.4; H, 5.4; N, 4.7.

Reaction of 4-bromo-*N*-phthaloylleucine methyl ester with silver fluoride in moist acetonitrile.

4-Bromo-*N*-phthaloylleucine methyl ester (50b) (0.3 g, 0.84 mmol) was stirred with silver fluoride (1.08 g, 8.5 mmol) in a solution of acetonitrile (25 ml) and water (0.5 ml) for 5 h. The mixture was shielded from light for the duration of the reaction. Work-up identical to that described for the reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with silver fluoride in dry acetonitrile afforded 4-fluoro-*N*-phthaloylleucine methyl ester (91) in 16% yield, a 1:2 mixture of *N*-phthaloyl-β,γ-dehydroleucine methyl ester (86) and *N*-phthaloyl-γ,δ-dehydroleucine methyl ester (88) in 39% yield, 5,5-dimethy-3-phthalimido-γ-butyrolactone (73) in 11% yield and 4-acetamido-*N*-phthaloylleucine methyl ester (92) in 14% yield.

4-Acetamido-*N*-phthaloylleucine methyl ester (92): m.p. 123-124°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.36 (s, 3H), 1.71 (s, 3H), 2.67 (dd, *J* = 4.0 and 15.2 Hz, 1H), 2.75 (dd, *J* = 7.7 and 15.2 Hz, 1H), 3.73 (s, 3H), 4.92 (dd, *J* = 4.0 and 7.7 Hz, 1H), 5.59 (br s, 1H, NH), 7.74-7.77 (m, 2H, PhthH), 7.86-7.89 (m, 2H, PhthH); ^{13}C (300 MHz, $CDCl_3$) δ 24.1, 27.0, 27.7, 38.2, 48.5, 52.7, 53.1, 123.6, 131.8, 134.3, 167.5, 169.8, 170.4; IR (nujol) 3330, 1780, 1760, 1730, 1650, 1560 cm^{-1}; MS (e.i.) calc'd for $C_{17}H_{20}N_2O_5$: m/z 332.137, found 332.138; 332 $[M]^+$, 274, 213, 57 {100}.

Preparation of silver fluoride supported on calcium fluoride.[122]

A mixture of silver carbonate (5.0g) dissolved in water (6 ml), 48% aqueous hydrogen fluoride (2.0 g) and calcium fluoride (20.0 g) was slowly evaporated to dryness at 50° in the dark. The final reagent was a grey free flowing granular powder.

Reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with silver fluoride supported on calcium fluoride in acetonitrile.

4-Bromo-*N*-phthaloylleucine methyl ester (50b) (0.20 g, 0.56 mmol) was stirred vigorously with silver fluoride supported on calcium fluoride (0.71 g, 20% AgF, 1.12 mmol) in the dark, in dry acetonitrile (20 ml), for 5 h at room temperature. The reaction mixture was filtered through a bed of celite and the filtrate concentrated under reduced pressure. The concentrate was diluted with chloroform and the resulting suspension was filtered through a bed of celite. The filtrate was concentrated to give a residue which was chromatographed on silica using ethyl acetate and light petroleum as eluants to afford 4-fluoro-*N*-phthaloylleucine methyl ester (91) (24%), a 1:2 mixture of *N*-phthaloyl-β,γ-dehydroleucine methyl ester (86) and *N*-phthaloyl-γ,δ-dehydroleucine methyl ester (88) (32%), and 5,5-dimethyl-3-phthalimido-γ-butyrolactone (73) (14 %).

Reaction of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) with silver fluoride in moist acetonitrile.

Reaction of a single diastereomer of 4-bromo-*N*-phthaloylhomophenylalanine methyl ester (51b) (0.25 g, 0.62 mmol) with silver fluoride (0.16 g, 1.25 mmol) in moist acetonitrile (20 ml), as described for the reaction of 4-bromo-*N*-phthaloylleucine methyl ester (50b) with silver fluoride in moist acetonitrile, afforded a 2:1 mixture of the diastereomers of 4-hydoxy-*N*-phthaloylhomophenylalanine methyl ester (96) (70 mg, 33%), a 4:1 mixture of the diastereomers of 4-fluoro-*N*-phthaloylhomophenylalanine methyl ester (90) (50 mg, 24%) and a 1:1 mixture of the diastereomers of 5-phenyl-3-

phthalimido-γ-butyrolactone (78) (11 mg, 11%) as a 1:1 mixture of diastereomers.

4-Fluoro-*N*-phthaloylhomophenylalanine methyl ester (90), major diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.77-2.94 (m, 2H), 3.75 (s, 3H), 5.15 (dd, *J* = 5.7 and 8.6 Hz, 1H), 5.73 (ddd, *J* = 4.4, 7.7 and 47.9 Hz, 1H), 7.19-7.30 (m, 5H, ArH), 7.71-7.81 (m, 4H, PhthH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 36.1 (d, *J* = 24 Hz), 48.6 (d, *J* = 3 Hz), 53.0, 92.3 (d, *J* = 172 Hz), 123.4, 125.0 125.1, 128.3, 128.4, 131.7, 134.1, 138.8, 139.0, 167.3, 169.3; ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -105.4, minor diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.72-2.94 (m, 2H), 3.75 (s, 3H), 5.20 (dd, *J* = 4.8 and 10.8 Hz, 1H), 5.40 (ddd, *J* = 5.5, 9.0 and 48.1 Hz, 1H), 7.13-7.19 (m, 5H, ArH), 7.71-7.87 (m, 4H, PhthH); ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -102.0.

4-Hydroxy-*N*-phthaloylhomophenylalanine methyl ester, major diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.54-2.76 (m, 2H), 3.70 (s, 3H), 4.92 (br dd, *J* = 5.2 and 6.5 Hz, 1H), 5.08 (dd, *J* = 5.3 and 8.8 Hz, 1H), 7.11-7.32 (m, 5H, ArH), 7.67-7.97 (m, 4H, PhthH), minor diastereomer: δ 2.54-2.76 (m, 2H), 3.71 (s, 3H), 4.57 (br dd, *J* = 4.2 and 8.8 Hz, 1H), 5.25 (dd, *J* = 4.7 and 10.4 Hz, 1H), 7.11-7.32 (m, 5H, ArH), 7.71-7.85 (m, 4H, PhthH); I.R. ($CDCl_3$) 1780, 1730, 1714 cm^{-1}; MS (e.i.) 339 $[M]^+$, 322, 308, 219 {100}.

Chloronitromethane

A solution of *t*-butyl hypochlorite (5.0 g, 50 mmol) in dichloromethane was added in a dropwise fashion to a stirred solution of styrene (0.37 g, 3.6 mmol) and nitromethane (20 g, 330 mmol) which was maintained at 0°. The reaction mixture was stirred for 30 minutes at this temperature. The *title compound* was then isolated from the reaction mixture by fractional distillation (2.79 g, 61%): b.p. 121-122°/740 mm Hg (lit.[132] b.p. 122-123°)

1-Chloro-1-nitroethane

A solution of sodium hydroxide (4.0 g, 0.9 mol) in water (20 ml) was added to a stirred and cooled suspension (ice bath) of nitroethane (7.5 g, 0.1 mol) in water (30 ml). Once the nitroethane had dissolved, stirring of the solution was ceased and the temperature maintained between 0-5°. Chlorine gas (7.8 g, 0.11 mol) was bubbled through the cooled solution over 2 h, with no stirring . The product fell from solution and settled on the bottom of the reaction vessel as droplets. The essentially pure 1-chloro-1-nitroethane was periodically removed from the reaction mixture and distilled to give the *title compound* (6.7g, 61%). b.p. 120-123°, (lit.[133] 124-126°)

1-Bromo-1-nitroethane

Nitroethane (5.0 g, 67 mmol) was added to a vigorously stirred solution of sodium hydroxide dissolved in ethanol (100 ml). The resulting suspension was concentrated under reduced pressure to yield the sodium nitronate salt as a pale green solid. The salt was resuspended in carbon tetrachloride (100 ml) and cooled to 0°. Bromine (10.7 g, 67 mmol) in carbon tetrachloride (200 ml) was added in a dropwise fashion to the stirred suspension of the nitronate salt and allowed to react overnight. The mixture was then filtered through a bed of celite to remove insoluble sodium salts. The *title compound* was isolated from the product mixture by fractional distillation (2.7 g, 37%): b.p. 53°/15 mm Hg.

1-Chloro-4-fluorobutane

1,4-Dichlorobutane (50 g, 390 mmol) and anhydrous potassium fluoroide (32 g, 670 mmol) were vigorously stirred in diethylene glycol (150 g) in a round bottom flask fitted with a fractionating side-arm. The mixture was heated to 160° under reduced pressure (170 mm Hg) for 8 h. The *title compound* distilled form the reaction mixture as it formed. The crude distillate was redistilled to yield the *title compound* (15.3 g, 36%): b.p. 72-76°/170-180 mm Hg (lit.[126] b.p. 114-114.5°, 740mm Hg).

1-Fluoro-4-iodobutane

Sodium iodide (40.5 g, 270 mmol) was dissolved in boiling acetone (60 ml). 4-Fluoro-1-chorobutane (10.0 g, 91 mmol) was added dropwise to the heated solution and refluxed for 18 h. The mixture was cooled to room temperature, diluted with water (50 ml), and extracted with diethyl ether. The ethereal extract was washed with 10% sodium thiosulfate, water, dried over Na_2SO_4 and concentrated under reduced pressure. The concentrate was fractionally distilled to yield the *title compound*: (13.7 g, 75%) b.p. 88-90°/76 mm Hg (lit [127] b.p. 52.5-53.5° 13 mm Hg).

4-Fluoro-1-nitrobutane

Silver nitrite (10.7 g, 68 mmol) was vigorously stirred in diethyl ether (50 ml) under anhydrous conditions. 1-Fluoro-4-iodobutane (12.0 g, 59 mmol) was added in a dropwise fashion to the reaction mixture cooled over ice. The mixture warmed slowly to room temperature and was stirred for a further 48h. Silver salts were removed by filtering the reaction mixture through a bed of

celite. The *title compound* was isolated from the reaction mixture by fractional distillation (4.65 g, 65%): b.p. 88-90°/19-20 mm Hg (lit.[124] 78-79°, 15 mm Hg).

3-Chloropropylmethanesulfonate

Methanesulfonyl chloride (24.1 g, 21mmol) was added to a stirred solution of 3-chloropropanol (20.0 g, 21 mmol) and pyridine (22.0 g, 2.8 mmol) in dichloromethane, maintained at 0°. The solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was washed with dilute hydrochloric acid followed by water and then dried. Evaporation of the solvent yielded the *title compound* as a colourless oil (32.0 g, 86%): b.p. 250° /14 mm Hg (block).

1-Chloro-3-fluoropropane

3-Chloropropylmethanesulfonate (17.3 g, 100 mmol) and anhydrous potassium fluoride (11.6 g, 200 mmol) were stirred in diethylene glycol (200 g) at 100°, under reduced pressure. The *title compound* was removed by distillation from the reaction mixture as it was produced (1.29 g, 13 %): b.p. 78-80°/740 mm Hg (lit.[127] 80.5-81.3°/740 mm Hg).

3-Fluoro-1-iodopropane

Reaction of 3-chloro-1-fluoropropane (1.29 g, 14 mmol) with sodium iodide (2.35 g, 40 mmol) under the conditions described for the synthesis of 4-fluoro-1-iodobutane from 4-chloro-1-fluorobutane, yielded the *title compound* (0.5 g, 17%): b.p. 68-69°/95 mm Hg (lit.[127] b.p. 127.5-127.8°).

3-Fluoro-1-nitropropane

Treatment of 3-fluoro-1-iodopropane (0.50 g, 2.6 mmol) with silver nitrite (0.40 g, 2.6 mmol) under the conditions described for the synthesis of 4-fluoro-1-nitrobutane from 4-fluoro-1-nitrobutane afforded the *title compound* (0.18 g, 65%): b.p. 73-75°/20 mm Hg, (lit.[124] b.p. 69-70°/19 mm Hg).

2-Nitrobutane

m-Chloroperbenzoic acid (4.1g, 20 mmol, 85% pure) was dissolved in dichloroethane (30 ml) and stirred at reflux. A solution of *sec*-butylamine (5 mmol) in dichloroethane (5 ml) was added dropwise to the refluxing solution. The solution was refluxed for 3 h, the reaction mixture was cooled, filtered, washed with 1N NaOH (3 x 25 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product distilled (43%): b.p. 63-66°/70 mm Hg. (lit.[123] 65-66°C/70 mm Hg).

***N*-Benzoyl-2-bromoglycine methyl ester (57)**

A mixture of *N*-benzoylglycine methyl ester (97) (1.0g, 5.2 mmol) and *N*-bromosuccinimide (0.9g, 5.2 mmol) in carbon tetrachloride (100 ml) was irradiated for 15 minutes while refluxing under nitrogen. The reaction mixture was filtered under an atmosphere of nitrogen and the solvent removed under reduced pressure to afford *N*-benzoyl-2-bromoglycine methyl ester (57). The product was used immediately and in the crude state: The ^1H n.m.r. spectral data of this compound was consistent with that previously reported.[93] ^1H n.m.r. (300 MHz, $CDCl_3$) δ 4.03 (s, 3H), 6.74 (d, J = 10 Hz, 1H), 7.50-8.10 (m, 6H, ArH and NH).

N-Benzoyl-3-nitroalanine methyl ester (64a)

A solution of *n*-butyllithium (0.88 mls, 2.5 M in hexanes, 2.2 mmol) was added dropwise to a solution of nitromethane (135 mg, 2.2 mmol) in tetrahydrofuran (THF) (10 ml) and hexamethylphosphoramide (HMPA) (2 ml) maintained at -78°. A solution of *N*-benzoyl-2-bromoglycine methyl ester (64a) (1.1 mmol) in THF (2 ml) was then added at -78° and, after 4 h at that temperature, acetic acid (0.35 ml) was added. The mixture was concentrated, then diluted with ethyl acetate (50 ml), washed with water (2x25 ml), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica using ethyl acetate and light petroleum as eluants to give the *title compound* (64a) as a colourless solid from ethyl acetate/light petroleum (175mg, 63%): m.p. 119° (lit.[93] 118-119°); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.99 (dd, *J* = 4 and 16 Hz, 1H), 5.1 (dd, *J* = 4 and 16 Hz, 1H), 5.17 (td, *J* = 4 and 8 Hz, 1H), 7.1 (br d, *J* = 8 Hz, 1H, NH), 7.4-7.7 (m, 5H, ArH).

N-Benzoyl-3-nitrovaline methyl ester (64b)

Reaction of the glycine derivative (57) with the nitronate salt of 2-nitropropane (63b), as described above for the preparation of *N*-benzoyl-3-nitroalanine methyl ester (64a) from the methyl nitronate (63a), gave the *title compound* (64b) as an oil (1.13 84%). The ^{1}H n.m.r. data of *N*-Benzoyl-3-nitrovaline methyl ester (64b) was consistent with that previously reported.[93] ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.89 (s, 3H), 3.78 (s, 3H), 5.35 (d, *J* = 9 Hz, 1H), 7.13 (br d, *J* = 9 Hz, 1H, NH), 7.3-7.9 (m, 5H, ArH).

Methyl 2-benzamido-3-nitrobutanoate (64c)

Reaction of the bromoglycine derivative (57) with ethyl nitronate (63c), as described above for the preparation of *N*-benzoyl-3-nitroalanine methyl ester (64a) from methyl nitronate (63a), gave the *title compound* (64c) as a 2:1 mixture of diastereomers in 61% yield which were subsequently separated by chromatography on silica using ethyl acetate and light petroleum as eluants.

One diastereomer crystallized from ethyl acetate/light petroleum as colourless crystals: m.p. 86-88° (lit.[93] 89-90°); ^{1}Hn.m.r. (300 MHz, $CDCl_3$) δ 1.70 (d, *J* = 6 Hz, 3H), 3.83 (s, 3H), 5.34 (m, 2H), 6.96 (br d, *J* = 11 Hz, 1H, NH), 7.4-7.9 (m, 5H, ArH).

The other diastereomer was isolated as an oil: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.82 (d, *J* = 6 Hz, 3H), 3.87 (s, 3H), 5.06 (m, 1H), 5.16 (m, 1H), 7.14 (br d, *J* = 11 Hz, 1H, NH), 7.4-7.9 (m, 5H, ArH).

***N*-Benzoyl-3-nitroaspartic acid dimethyl diester (64d)**

Treatment of methyl nitroacetate with *n*-butyllithium (0.2 equivalents) and, subsequently with the α-bromoglycine derivative (57) (0.1 equivalents), using the conditions described for the preparation of *N*-benzoyl-3-nitroalanine methyl ester (64a) from methyl nitronate (63a), gave a 1:1 mixture of diastereomers of the *title compound* (64d) as an oil, in 66% yield. The ^{1}H n.m.r. spectral data for the *title compound* (64d) was consistent with that previously reported.[93] ^{1}H n.m.r. ($CDCl_3$) δ 3.82 (s, 3H), 3.87 (s, 0.5 x 3H), 3.94 (s, 0.5 x 3H), 5.64 (dd, *J* = 3.0 and 6.0 Hz, 0.5 x 1Hz), 5.80 (dd, *J* = 4.0 and 9.0 Hz, 0.5 x 0.5 Hz), 5.98 (d, *J* = 3 .0 Hz, 0.5 x 1H), 5.99 (dd, *J* = 4.0 Hz, 0.5 x 1H) , 7.20 (m, 1H), 7.40-7.90 (m, 5H, ArH)

N-Benzoyl-3-nitrophenylalanine methyl ester (64e)

Reaction of the glycine derivative (57) with benzyl nitronate (63e), as described above for the preparation of *N*-benzoyl-3-nitroalanine methyl ester (64a) from methyl nitronate (63a), gave the *title compound* (64e) which crystallized from chloroform/light petroleum as a 1:1 mixture of diastereomers, in 66% yield. m.p. 155-159° (lit[93] 160-165°)^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.63 (t, *J* = 9.0 Hz, 0.5 x 1H), 5.66 (dd, *J* = 6.0 and 9.0 Hz, 0.5 x 1H) , 6.26 (d, *J* = 9.0H, 0.5x1H), 6.34 (d, *J* = 6.0 Hz, 0.5x1H), 7.20-7.60 (m, 5H, ArH), 7.79 (br d, *J* = 9.0 Hz, 1H, NH).

N-Benzoyl-3-nitro-*iso*-leucine methyl ester (64f)

Reaction of the glycine derivative (57) with the nitronate salt of 2-nitrobutane (63f), as described above for the preparation of *N*-benzoyl-3-nitroalanine methyl ester (64a) from methyl nitronate (63a), gave the *title compound* (64f) as a 1:1.25 mixture of diastereomers (1.20 g, 70%). The diastereomers could be separated by h.p.l.c. on a Radialpak normal phase column using ethyl acetate and light petroleum as eluants.

Minor diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.80 (s, 3H), 2.07 (qd, *J*=7.4,14.8Hz,1H), 2.42 (qd, *J*=7.4, 14.8 Hz, 1H), 3.77 (s, 3H), 5.31 (d, *J* = 9.83 Hz, 1H), 7.23 (br d, *J* = 9.83 Hz, 1H), 7.67 (m, 5H, ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 8.0, 20.1, 30.9, 53.1, 57.3, 92.2, 127.2, 128.8, 132.4, 167.5, 168.9; IR ($CDCl_3$) 3443, 3156, 2900, 2854, 1794, 1746, 1671, 1618, 1603, 1549, 1508, 1482, 1451, 1438, 1394, 1341, 1288, 1261, 1221, 1183, 1097, 1012 cm^{-1}; MS (e.i.) calc'd for $C_{14}H_{18}N_2O_5$: m/z 294.122, found 294.122; 294 $[M]^+$, 247, 234, 215, 105{100}.

Major diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.80 (s, 3H), 1.93 (qd, *J* = 7.3, 14.6 Hz, 1H), 2.20 (qd, *J* = 7.3, 14.6 Hz, 1H), 3.77 (s, 3H),

5.31 (d, 9.9Hz, 1H), 7.24 (br d, J = 9.9 Hz, 1H, NH), 7.5-7.9 (m, 5H, ArH); ^{13}C n.m.r. (75 MHz, $CDCl_3$) 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; IR ($CHCl_3$) 3156, 2956, 1817, 1794, 1744, 1673, 1549, 1509, 1394 cm^{-1}; MS (e.i.) calc'd for $C_{14}H_{18}N_2O_5$: m/z 294.122, found 294.122; 294 $[M]^+$, 248, 234, 105 {100}.

Also isolated from the reaction in 7% yield was the *N*-(1-benzamido-1-methoxycarbonyl methyl)-*N*-benzoyl-α,β-dehydro-*iso*-leucine methyl ester (98). It was present as a single geometric isomer, which was a mixture of two conformers in a 3:2 ratio: m.p. 134-135°; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.03 (t, J = 7.5 Hz, 0.4x3H), 1.19 (t, J = 7.5 H, 0.6x3H), 2.12 (s, 0.6x3H), 2.30 (s, 0.4x3H), 2.36 (dq, J = 7.5 and 12.4 Hz, 0.4x1H), 2.69 (dq, J = 7.5 and 13.5 Hz, 0.6x1H), 2.72 (dq, J = 7.5 and 12.4 Hz, 0.4x1H), 2.97 (dq, J = 7.5 and 13.5 Hz, 0.6x1H), 3.30 (s, 0.4x3H), 3.32 (s, 0.6x3H), 3.86 (s, 0.4x3H), 3.87 (s, 0.6x3H), 5.97 (d, J = 9.4 Hz, 0.6x1H), 5.99 (d, J = 9.3 Hz, 0.4x1H), 7.28-7.86 (m, 6H); IR (nujol) 3332, 1760, 1740, 1650, 1630, 1526, 772, 720 cm^{-1}; MS (e.i.) calc'd for $C_{24}H_{27}N_2O_6$: m/z 439.187, found 439.188; 439 $[M+H]^+$, 379, 247, 215, 142, 105 {100}.

Methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a)

A solution of *n*-butyllithium (2.5 M, 0.56 ml, 1.04 mmol) was added dropwise to a solution of 3-fluoro-1-nitropropane (0.12 g, 1.04 mmol) in THF (5 ml) and HMPA (1 ml) maintained at -78°. A solution of *N*-benzoyl-2-bromoglycine methyl ester (57) (0.52 mmol) in THF (2 ml) was then added at -78° 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), washed with water (3x10 ml), then concentrated under reduced pressure. The residue was chromatographed on silica using ethyl acetate and light

petroleum as eluants. Chromatography on silica allowed for the separation of the diastereomers with subsequent crystallization of the diastereomers from ethyl acetate/light petroleum giving the major diastereomer in 35% yield (55 mg) and the minor diastereomer in 23% yield (35 mg).

Minor diastereomer: m.p. 99-101°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.22-2.42 (m, 1H), 2.46-2.65 (m, 1H), 3.84 (s, 3H), 4.47-4.83 (m, J_F = 47 Hz, 1H), 5.41-5.47 (m, 2H), 7.07 (br d, J = 8.9 Hz, 1H NH), 7.45-7.61 (m, 3H, ArH), 7.82-7.85 (m, 2H, ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 31.9 (d, J = 20 Hz), 53.3, 54.3, 8.2 (d, J = 167 Hz), 84.5 (d, J = 3 Hz), 127.9 , 129.4, 133.2, 168.7, 169.4; ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -147.6; MS (e.i) calc'd for $C_{13}H_{15}FN_2O_5$: *m/z* 298.097, found 298.098; 298 $[M]^+$, 251, 238, 191, 105 {100}.

Major diastereomer: m.p. 112-114°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.39-2.77 (m, 2H), 3.85 (s, 3H), 4.45-4.77 (m, 2H), 5.19 (dt, J = 4.4 and 9.0 Hz, 1H), 5.28 (dd, J = 4.4 and 7.3 Hz, 1H), 7.25 (br d, J = 7.3H, 1H NH), 7.42-7.58 (m, 3H ArH), 7.78-7.82 (m, 2H ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 32.0 (d, J = 20 Hz), 54.1, 54.9, 80.6 (d, J = 168 Hz), 85.4, 127.9, 129.3, 133.1, 133.2, 168.0, 169.0; ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -146.5; MS (e.i.) calc'd for $C_{13}H_{15}FN_2O_5$: m/z 298.097, found 298.097; 298 $[M]^+$, 251, 238, 191, 105 {100}.

Methyl 2-benzamido-6-fluoro-3-nitrohexanoate (105)

Reaction of the glycine derivative (57) with the nitronate salt of 4-fluoro-1-nitrobutane, as described above for the preparation of methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a) from the nitronate salt of 3-fluoro-1-nitropropane, gave the *title compound* (105) as a 5:1 mixture of diastereomers in 72% yield, which were partially separated by chromatography on silica using ethyl acetate and light petroleum as eluants and further purified by fractional

crystallization from ethyl acetate/light petroleum to afford the minor diastereomer in 7% yield and the major diastereomer in 41% yield.

Minor diastereomer: m.p. 119-121°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.79-1.97 (m, 2H), 2.17-2.28 (m, 1H), 2.36-2.50 (m, 1H), 3.83 (s, 3H), 4.40-4.64 (m, J_F = 47 Hz, 2H), 5.26 (dt, J = 4.4 and 8.9 Hz, 1H), 5.43 (dd, J = 3.2 and 9.4 Hz, 1H), 7.03 (br d, 9.4 Hz, 1H NH), 7.45-7.61 (m, 3H, ArH), 7.83-7.86 (m, 2H, ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 26.9 (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, 134.5, 132.8, 167.9, 169.0; ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -145.0; MS (e.i.) calc'd for $C_{14}H_{17}FN_2O_5$: *m/z* 313.120, found 313.119; 313 $[M+1]^+$, 266, 253, 205, 160, 121, 105 {100}, 77.

Major diastereomer (41%): m.p. 120-121°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.79-1.97 (m, 2H), 2.17-2.28 (m, 1H), 2.36-2.50 (m, 1H), 3.89 (s, 3H), 4.39-4.64 (m, J_F = 47 Hz, 2H), 5.04 (dt, J = 4.4 and 8.9 Hz, 1H), 5.17 (dd, J = 4.4 and 7.0 Hz, 1H), 7.08 (br d, 7.0 Hz, 1H, NH), 7.45-7.61 (m, 3H, ArH), 7.79-7.82 (m, 2H ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) 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 n.m.r. (282 MHz, $CDCl_3$) δ -145.6; MS (e.i.) calc'd for $C_{14}H_{17}FN_2O_5$: m/z 313.119, found 313.120; 313 $[M+1]^+$, 266, 253, 205, 160, 121, 105 {100}, 77.

Methyl 2-benzamido-3-chloro-5-nitropentanoate (104b)

Reaction of the glycine derivative (57) with the nitronate salt of 3-chloro-1-nitropropane, as described above for the preparation of methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a) from the nitronate salt of 3-fluoro-1-nitropropane, gave the *title compound* (105), as a 3:1 mixture of diastereomers, in 73% yield. Further chromatography on silica affected separation of the diastereomers with subsquent crystallization from ethyl

acetate/light petroleum yielding the major diastereomer in 49% yield and the minor diastereomer in 14% yield.

Minor diastereomer: m.p. 102-107°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.37 (ddt, *J* = 4.8,7.2 and 15.0 Hz, 1H), 2.63 (ddt, *J* = 4.9, 7.2 and 15.0 Hz, 1H), 3.72 (ddd, *J* = 4.9, 7.2 and 12.0 Hz, 1H), 3.84 (ddd, *J* = 4.8, 7.2 and 12.0 Hz, 1H), 3.86 (s, 3H), 5.40 (dd, *J* = 3.0 and 9.0 Hz, 1H), 5.54 (dd, *J* = 3.0 and 7.2 Hz, 1H), 7.00 (br d, *J* = 9.0 Hz, 1H NH), 7.47-7.62 (m, 3H ArH), 7.82-7.86 (m, 2H ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 32.8, 40.3, 52.4, 53.6, 84.6, 127.3, 128.9, 129.0, 132.6, 168.0, 168.7; IR($CDCl_3$) 3295, 1765, 1650, 1560, 1535, 1350; MS (e.i.) calc'd for $C_{13}H_{15}N_2O_5Cl$: *m/z* 314.067, found 314.066; 316/314 (1:3, $[M]^+$), 270, 268, 256, 254, 207, 105 {100}.

Major diastereomer: m.p. 109-111°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.51-2.42 (m, 1H), 2.89-2.80 (m, 1H), 3.63 (ddd, *J* = 5.1 8.9 and 11.7 Hz, 1H), 3.76 (td, *J* = 5.9 and 11.7 Hz, 1H), 3.89 (s, 3H), 5.23 (m, 2H), 7.06 (br d, *J* = 6.4 Hz, 1H NH), 7.45-7.60 (m, 1H ArH), 7.80-7.83 (m, 2H ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 33.3, 40.4, 53.6, 54.2, 85.5, 127.2, 128.8, 132.5, 132.6, 167.2, 168.3; IR($CDCl_3$) 3300, 1760, 1650, 1560, 1540, 1355, 970 cm^{-1}; MS (e.i.) calc'd for $C_{13}H_{15}N_2O_5Cl$: *m/z* 314.067, found 314.066; 316/314 (1:3 $[M]^+$), 270/268 (1:3), 256/254 (1:3), 207, 105 {100}.

Also isolated from the reaction mixture was 2-hydroxy-3-(1-benzamido-1-methoxycarbonyl methylene)-2-aza-1-oxacyclopentane (106), isolated in 6 % yield: m.p. 160-164°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.93 (ddd, *J* = 6.5, 8.5 and 17.5 Hz, 1H), 3.29 (ddd, *J* = 5.5, 8.5 and 17.5 Hz, 1H), 3.87 (s, 3H), 4.35 (td, *J* = 5.5 and 8.5 Hz, 1H), 4.61 (td, *J* = 6.5 and 8.5 Hz, 1H), 7.74-7.56 (m, 3H, ArH) 7.80-7.83 (m, 2H, ArH), 7.85 (s, 1H), 7.91 (br s, 1H); IR(nujol) 3360, 3226, 1750, 1650, 1540, 1080, 960, 940; MS (e.i.) calc'd for $C_{13}H_{15}N_2O_5$: *m/z* 279.098, found 279.097; 279$[M+1]^+$, 219, 158, 157, 105{100}, 77.

(Z)-Methyl 2-benzamido-5-fluoropent-2-enoate (107)

Di-*iso*-propylamine (6.8 mgs, 0.07 mmol) was added to solution of the each diastereomer of (Z)-methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a) (20 mg, 0.07mmol) in chloroform (1 ml) and stirred at room temperature for 18 h. The reaction mixture was diluted with chloroform (5 ml), washed with water (2x3 ml) and concentrated under reduced pressure. The residue was chromatographed on silica using ethyl acetate and light petroleum as eluants. (Z)-Methyl 2-benzamido-5-fluoropent-2-enoate (107) was isolated as an oil in 80% yield. ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.66 (ddt, *J* = 5.8 7.2 and 28 Hz, 2H), 3.83 (s, 3H), 4.62 (td, *J* = 5.8 and 47 Hz, 2H), 6.83 (t, *J* = 7.2 Hz, 1H), 7.45-7.51 (m, 1H ArH), 7.75 (br s, 1H, NH), 7.85-7.89 (m, 2H ArH); IR($CDCl_3$) 3680, 3700, 1720, 1600, 1580, 1490, 1220; MS (e.i.) calc'd for $C_{13}H_{14}NO_3$: *m/z* 251.096, found 251.097; 251[M]$^+$, 105{100}, 77.

Methyl 2-benzamidopenta-2,4-dienoate (108)

One diastereomer of (Z)-methyl-2-benzamido-3-nitro-5-fluoropentenoate (105) (40 mg, 0.13 mmol) was stirred at room temperature with an excess of di-*iso*-propylamine (1 ml) in chloroform (2 ml) overnight. This gave the *title compound* (108) in near quantitative yield, as a colourless oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.43 (d, *J* = 10.7 Hz, 1H), 5.57 (d, *J* = 16.5 Hz, 1H), 6.49 (ddd, *J* = 10.7, 11.3 and 16.5 Hz, 1H), 7.06 (d, *J* = 11.3 Hz, 1H), 7.45-7.58 (m, 3H, ArH), 7.85 (br s, 1H, NH), 7.88-7.90 (m, 2H, ArH); IR($CDCl_3$) 3400, 3010, 1760, 1730, 1690, 1520, 1500; MS (e.i.) calc'd for $C_{13}H_{13}NO_3$: *m/z* 231.090, found 231.090; 231 [M]$^+$, 105 {100}, 77.

(Z)-Methyl 2-benzamido-6-fluorohex-2-enoate (109)

Di-*iso*-propylamine (36 mgs, 0.32 mmol) was added to a solution of one diastereomer of methyl 2-benzamido-6-fluoro-3-nitropentanoate (105) (100 mg, 0.32mmol) in chloroform (5 ml) and stirred at room temperature for 18 h. The reaction mixture was diluted with chloroform (5 ml), washed with water (2x3 ml) and concentrated under reduced pressure. The residue was chromatographed on silica using ethyl acetate and light petroleum as eluants and gave the *title compound* (109) in 83% yield: m.p. 89-90°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.82-2.00 (pentet of doublets, *J* = 7.4 and 26 Hz, 2H), 2.40 (q, *J* = 7.4 Hz, 2H), 3.82 (s, 3H), 4.50 (td, *J* = 5.9 and 47 Hz, 2H), 6.78 (t, *J* = 7.4 Hz, 1H), 7.46-7.57 (m, 3H, ArH), 7.75 (br s, 1H, NH), 7.87-7.90 (m, 2H, ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) 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 n.m.r. (282 MHz, $CDCl_3$) δ -145.6; IR($CDCl_3$) 3680, 3600, 1730, 1610, 1585, 1490, 1220; MS (e.i.) calc'd for $C_{14}H_{17}NO_3F$: *m/z* 266.119, found 266.120; 266 $[M+1]^+$, 206, 160, 105 {100}, 77.

Evidence for the *(E)*-methyl 2-benzamido-6-fluorohex-2-enoate from the ^{1}H n.m.r. spectrum of the crude reaction mixture: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.82-2.00 (m, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 3.87 (s, 3H), 4.51 (td, *J* = 5.9 and 47.1 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.46-7.57 (m, 3H, ArH), 7.87-7.90(m, 2H, ArH), 8.24 (br s, 1H, NH). The *(E)*-isomer was not isolated from the crude reaction mixture.

Methyl 2-benzamido-5-fluoropentanoate (110)

A stirred solution of methyl 2-benzamido-5-fluoropent-2-enoate (107) (9.3 mgs, 0.04 mmol) and 10% palladium on activated carbon (7 mg) in ethyl acetate (5 ml) was placed under an atmosphere of hydrogen (25 p.s.i) for 3 h. The

reaction mixture was then filtered through a bed of celite and the filtrate concentrated under reduced pressure. The recovered oil was chromatographed on silica using ethyl acetate and light petroleum as eluants to afford methyl 2-benzamido-5-fluoropentanoate (110) as a low melting point solid (9.2 g, 98%): m.p. 53-56°, ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.68-1.97 (m, 3H), 2.05-2.14 (m, 1H), 3.81 (s, 3H), 4.49 (td, *J* = 5.6 and 47 Hz, 2H), 4.88 (dt, *J* = 5.2 and 7.5 Hz, 1H), 6.77 (br d, *J* = 7.5H, 1H NH), 7.43-7.56 (m, 3H ArH), 7.80-7.84 (m, 2H ArH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 26.4 (d, *J* = 23 Hz), 28.8 (d, *J* = 5 Hz), 52.0, 52.6, 83.2 (d, *J* = 166), 127.0, 128.6, 131.9, 133.7, 167.1, 172.8; ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -144.41; IR($CDCl_3$) 3444, 3008, 2960, 1739, 1666, 1580, 1516, 1360 cm^{-1}; MS (e.i.) calc'd for $C_{13}H_{16}NO_3F$: *m/z* 253.111, found 253.112; 254 $[M+1]^+$, 253 $[M]^+$, 194, 105 {100}, 77.

Methyl 2-benzamido-6-fluorohexanoate (111)

Methyl 2-benzamido-6-fluorohex-2-enoate (109) (0.5 g, 1.88 mmol) was treated with 10% palladium on activated carbon as described above for the preparation of methyl 2-benzamido-5-fluoropentanoate (111). The *title compound* (111) was recovered as colourless needles from dichloromethane/light petroleum in 94% yield: m.p. 73-74°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.40-1.98 (m, 6H), 3.71 (s, 3H), 4.77 (dt, *J* = 5.4 and 7.5 Hz, 1H), 6.75 (br d, *J* = 7.5H, 1H NH), 7.34-7.48 (m, 3H ArH), 7.72-7.75 (m, 2H ArH); ^{19}F n.m.r. (282 MHz, $CDCl_3$) δ -144.00; IR(nujol) 3300, 1746, 1632, 1578, 1532 cm^{-1}; Analysis calc'd for $C_{14}H_{18}NO_3F$: C, 62.9; H, 6.8; N, 5.2; found: C, 62.9; H, 6.9; N, 5.2; MS (e.i.) calc'd for $C_{14}H_{18}NO_3F$: *m/z* 267.127, found 267.127; 267 $[M]^+$, 208, 193, 161, 105 {100}, 77.

N-Benzoyl-3-nitro-α,β-dehydroalanine methyl ester (113)

A solution of *n*-butyllitium (2.5 M, 2.08 ml, 5.2 mmol) was added dropwise to a solution of chloronitromethane (0.49 g, 5.2 mmol) in THF (20 ml) and HMPA (5 ml) maintained at -78°. A solution of *N*-benzoyl-2-bromoglycine methyl ester (57) (2.59 mmol) in THF (5 ml) was added at -78° and after 4 h at that temperature, acetic acid was added. The reaction mixture was allowed to warm to room temperature and was then concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (50 ml) and washed with water (3x20 ml) then concentrated under reduced pressure. The residue was chromatographed on silica using ethyl acetate and light petroleum as eluants and yielded the *title compound* (113) as a yellow solid (0.27g, 42%): m.p. 93-95°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.91 (s, 1H), 7.52-7.96 (m, 3H, ArH), 7.92-7.95 (m, 2H, ArH), 11.17 (br s, 1H, NH); MS (e.i.) calc'd for $C_{11}H_{11}NO_3$: *m/z* 205.074, found 205.075; 220, 205, 163, 105 {100}.

Methyl 2-benzamido-3-chloro-3-nitrobutanoate (115)

Reaction of the α-bromoglycine derivative (57) with the nitronate salt of 1-chloro-1-nitroethane (114), as described above for the preparation of *N*-benzoyl-3-nitro-α,β-dehydroalanine methyl ester (113) from the nitronate salt (112) of chloronitromethane, afforded the *title compound* (115) as a 1.4:1 mixture of diastereomers in 48% yield. (Z)-Methyl 2-benzamido-3-nitrobut-2-enoate (116) was isolated as a yellow solid in 9% yield. The diastereomers of methyl 2-benzamido-3-chloro-3-nitrobutanoate (115) were separated by chromatography on silica using ethyl acetate and light petroleum. The minor diastereomer was isolated in 14% yield while the major diastereomer was isolated in 28% yield. methyl 2-benzamido-3-chloro-3-nitrobutanoate (115) major diastereomer : ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.80 (s, 3H), 6.10

(d, J = 9.0 Hz, 1H), 7.11 (br d, J = 9.0 Hz, 1H, NH), 7.48-7.61 (m, 3H, ArH), 7.87-7.90 (m, 2H, ArH); IR(nujol) 3268, 1746, 1656, 1578, 1522, 1390 cm^{-1}; MS (e.i.) 302/300 (1:3[M]$^+$), 269/267 (1:3), 256/254 (1:3), 243/241 (1:3), 219, 192, 105{100}. minor diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.83 (s, 3H), 5.87 (d, J = 9.7 Hz, 1H), 7.15 (br d, J = 9.7 Hz, 1H, NH), 7.44-7.56 (m, 3H, ArH), 7.79-7.82 (m, 2H, ArH); IR(nujol) 3274, 1742, 1656, 1578, 1530, 1376 cm^{-1} MS (e.i.) 302/300 (1:3[M]$^+$), 269/267 (1:3), 256/254 (1:3), 243/241 (1:3), 219, 192, 105 {100}.

(Z)-Methyl 2-benzamido-3-nitrobut-2-enoate (116): m.p. 69-71°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 4.04 (s, 3H), 7.53-7.67 (m, 3H ArH), 7.94-7.97 (m, 2H ArH), 11.86 (br s, 1H NH); IR($CDCl_3$) 3500, 1750, 1700, 1624, 1520; MS (e.i.) calc'd for $C_{14}H_{18}NO_3$: m/z 264.075, found 264.075; 264 [M]$^+$, 233, 218, 105 {100}; Analysis calc'd for : C, 54.54; H, 4.58; N, 10.60; found: C, 54.25; H, 4.84; N, 10.62.

Methyl 2-benzamido-3-bromo-3-nitrobutanoate (118)

Treatment of 1-bromo-1-nitroethane with n-butyllithium (0.2 equivalents) and, subsequently with the α-bromoglycine derivative (57), using the conditions described above for the preparation of *N*-benzoyl-3-nitro-α,β-dehydroalanine methyl ester (113) from the nitronate salt (112) of chloronitromethane (112), afforded the *title compound* (118) as a single diastereomer in 58% yield. Methyl 2-benzamido-3-bromo-3-nitrobutanoate (118): mp. 97-98°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.86 (s, 3H), 5.88 (d, J = 9.5 Hz, 1H), 7.04 (d, J = 9.5 Hz, 1H, NH), 7.45-7.63 (m, 3H, ArH), 7.83-7.86 (m, 2H, ArH); IR(nujol) 3272, 1740, 1648, 1562, 1330 cm^{-1}; MS (e.i.) calc'd for $C_{12}H_{13}N_2O_5Br$: m/z 345.999, found 345.999; 346/344 (1:3[M]$^+$), 300/298(1:1), 286/284(1:1), 192, 105 {100}, 77.

(Z)-Methyl 2-benzamido-3-nitrobut-2-enoate (116)

Treatment of the diastereomer of methyl 2-benzamido-3-bromo-3-nitrobutanoate (118) with di-*iso*-propylamine, as described for the synthesis of (Z)-methyl 2-benzamido-5-fluoropent-2-enoate (107) from (Z)-methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a), gave a (Z)-methyl 2-benzamido-3-nitrobut-2-enoate (116) in 81% yield.

Reaction of methyl 2-benzamido-3-chloro-3-nitrobutanoate (115) with di-*iso*-propylamine.

Treatment of the major diastereomer of methyl 2-benzamido-3-chloro-3-nitrobutanoate (113) with di-*iso*-propylamine, as described for the synthesis of (Z)-methyl 2-benzamido-5-fluoropent-2-enoate (107) from (Z)-methyl 2-benzamido-5-fluoro-3-nitropentanoate (104a), gave a 2:1 mixture of (Z)-methyl 2-benzamido-3-nitrobut-2-enoate (116) and methyl 2-benzamido-3-chlorobut-2-enoate (119). The products of this reaction were separated by chromatography on silica using ethyl acetate and light petroleum as eluants with (Z)-methyl 2-benzamido-3-nitrobut-2-enoate (116) being isolated in 39% yield and methyl 2-benzamido-3-chlorobut-2-enoate (116) being isolated in 17% yield. Methyl 2-benzamido-3-chlorobut-2-enoate (116): m.p. 130-132°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.85 (s, 3H), 7.47 (m, 3H, ArH), 7.66 (br s, 1H, NH), 7.84-7.87 (m, 2H ArH); MS (e.i.) calc'd for $C_{12}H_{12}NO_3Cl$: m/z 253.051, found 253.051; 255/253 (1:3, $[M]^+$), 224/222 (1:3), 218, 186, 105 {100}.

Similar reaction of the minor diastereomer of methyl 2-benzamido-3-chloro-3-nitrobutanoate (115) with di-*iso*-propylamine gave a 2:1 mixture of methyl 2-benzamido-3-chlorobut-2-enoate (119) and (Z)-methyl 2-benzamido-3-nitrobut-2-enoate (116), in 63 % yield. Methyl 2-benzamido-3-chlorobut-2-

enoate (119) and (Z)-methyl 2-benzamido-3-nitrobut-2-enoate (116) were separated by chromatography on silica using ethyl acetate and light petroleum as eluants in 33% and 17%, respectively..

3-Nitrovaline hydrochloride (120)

A suspension of *N*-benzoyl-3-nitrovaline methyl ester (0.30 g, 1.0 mmol) in 6N HCl (30 ml) was stirred vigorously at reflux for 2 h. The solution was then cooled and concentrated under reduced pressure. The concentrate was diluted with water and washed with ethyl acetate. The aqueous layer was then concentrated to yield 3-nitrovaline hydrochloride salt (120) (0.14 g, 70%): m.p. 143-145°; ^{1}H n.m.r. (300 MHz, D_2O) δ 1.79 (s, 3H), 1.86 (s, 3H), 4.71 (s, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 25.23, 25.57, 60.40, 89.22, 170.11; MS (f.a.b.) *m/z* 163 (M+1), 116 (100), 72, 70.

3-Nitrovaline .

3-Nitrovaline hydrochloride (120) (0.30 g, 1.5 mmol) was dissolved in ethanol (30 ml) and aniline (3 ml) and allowed to stand at room temperature for 18 h. Crystallized 3-nitrovaline was collected by filtration and washed with cold ethanol (0.11g, 46%): m.p. 145-147°; ^{1}H n.m.r. (300 MHz, D_2O) δ 1.74 (s, 3H), 1.79 (s, 3H), 4.34 (s, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 24.9, 25.9, 62.1, 89.6, 171.6; IR (nujol) 2922 (br), 1654, 1590, 1538, 1392, 1377, 1344 cm^{-1}; MS (f.a.b.) 163 $[M+1]^+$ {100}, 116, 72, 70.

3-Nitro-*iso*-leucine hydrochloride (121)

Treatment of the major diastereomer of *N*-benzoyl-3-nitro-*iso*-leucine methyl ester (64f) with 6N HCl, as described for the synthesis of 3-nitrovaline

hydrochloride (120) from *N*-benzoyl-3-nitrovaline methyl ester (64b), gave the *title compound* (121) in 70% yield, with no isomerization of the diastereomer observed using 1H n.m.r.. spectroscopy: 3-Nitro-*iso*-leucine hydrochloride (121) major diastereomer, m.p. 132-133° (dec); ^{1}H n.m.r. (300 MHz, D_2O) δ 0.94 (t, *J* = 7.0 Hz, 3H), 1.75 (s, 3H), 2.08 (qd, *J* = 7.0 and 14.0 Hz, 1H), 2.19 (qd, *J* = 7.0 and 14.0 Hz, 1H), 4.47 (s, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 9.3, 20.7, 33.1, 61.2, 61.2, 93.5, 171.1; MS (f.a.b.) *m/z* 177 $[M+1]^+$ {100}, 130, 86, 84;

Similar reaction of the minor diastereomer of *N*-benzoyl-3-nitro-*iso*-leucine methyl ester (64f) with 6N HCl, afforded the title compound (121), in 64% yield, with no isomerization of the diastereomer observed using ^{1}H n.m.r. spectroscopy. 3-Nitro-*iso*-leucine hydrochloride (121) minor diastereomer: m.p. 132-135° (dec); ^{1}H n.m.r. (300 MHz, D_2O) δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.63 (s, 3H), 2.20 (qd, *J* = 7.0 and 14.0 Hz, 1H), 2.22 (qd, *J* = 7.0 and 14.0 Hz, 1H), 4.72 (s, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 9.2, 19.6, 32.2, 59.9, 93.0, 170.1; MS (f.a.b.) *m/z* 177 $[M+1]^+$ {100}, 130, 86, 84.

N-*tert*-butoxycarbonylglycine *tert*-butyl ester (123)

A solution of *N*-*tert*-butoxycarbonylglycine (122) (0.75 g, 4.3 mmol), *N*,*N*-dicyclohexylcarbodimide (0.97 g, 4.7 mmol), *t*-butyl alcohol (2.0 g) and dimethylaminopyridine (0.1 g) in ether (100 ml) was allowed to stir at room temperature for 18h. The *N*,*N*-dicyclohexylurea was filtered from the reaction mixture and the filtrate washed with water, 5% acetic acid and again with water. The organic layer was concentrated under reduced pressure to give the *title compound* (123) as an oil, which was used without further purification (0.88g, 89%). The spectral data of this compound was consistent with that reported[91]: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.47 (s, 9H), 3.80 (d, *J* = 5.5 Hz, 1H), 5.00 (br s, 1H NH).

2-bromo-*N*-*tert*-butoxycarbonylglycine *tert*-butyl ester (124)

A mixture of *N*-*tert*-butoxycarbonylglycine *tert*-butyl ester (123) (0.24g, 1.04 mmol) and *N*-bromosuccinimide (0.185g, 1.04 mmol) in carbon tetrachloride (100ml) was irradiated for 15 minutes while refluxing under nitrogen. The reaction mixture was filitered under nitrogen to remove succinimide and the solvent was removed under reduced pressure with minimal heating to afford the *title compound* (124) which was used immediately. Conversion to the bromide was quantitative. The spectral data for this compound was consistent with that reported[91]: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.52 (s, 9H), 5.93 (br d, J = 11.0 Hz, 1H, NH), 6.23 (d, J = 11.0 Hz, 1H).

***N*-*tert*-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a)**

A solution of butyllithium (2.4 M in hexanes, 0.88 ml, 2.12 mmol) was added dropwise to a solution of nitromethane (0.12 g, 2.12 mmol) in THF (8 ml) and HMPA (2 ml) maintained at -78°. A solution of 2-bromo-*N*-*tert*-butoxycarbonylglycine *tert*-butyl ester (124) (1.04 mmol) in THF (ml) was then added at -78°, after 4h at that temperature, acetic acid (1.5 mmol) was added. The mixture was concentrated under vacuo then partitioned between ethyl acetate and water. The organic phase was concentrated under vacuo and the residue chromatographed on silica using ethyl acetate and light petroleum as eluants. The resulting oil was crystallized from dichloromethane/light petroleum to yield the title compound in 63% (185 mg): m.p. 99-100°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.48 (s, 9H), 4.6 (dt, J = 7.2 and 3.6 Hz, 1H), 4.8 (dd, J = 3.6 and 14.8 Hz, 1H), 4.95 (dd, J = 3.6 and 14.8 Hz, 1H), 5.52 (br d, J = 7.2 Hz, 1H, NH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 27.5, 28.2, 51.8, 75.7, 80.8, 84.0, 155.2, 167.0; IR ($CDCl_3$) 3436, 2984, 1760, 1712, 1562, 1498 cm^{-1}; MS (e.i.) calc'd for

$C_{12}H_{22}N_2O_6$: m/z 290.148, found 290.149; 290 $[M]^+$, 234, 178 {100}; Analysis calc'd 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.

tert-Butyl 2-(_tert_-butoxycarbonylamino)-3-nitrobutanoate (125c)

Reaction of the 2-bromo-*N*-*tert*-butoxycarbonylglycine *tert*-butyl ester (124) with ethyl nitronate (63c), as described above for the preparation of *N*-*tert*-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a) from methyl nitronate (63a), gave the title compound (125c) as a 2:1 mixture of diastereomers (190 mg, 60%), which were separated by chromatography on silica using diethyl ether/light petroleum as eluants. The major diastereomer crystallized from light petroleum as clusters of needles (105 mg, 34%), whereas the minor diastereomer was obtained as an oil (53 mg, 17%).

Major diastereomer: m.p. 65-66°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.49 (d, 9H), 1.66 (d, *J* = 7.0 Hz, 3H), 4.66 (dd, *J* = 3.8 and 7.8 Hz, 1H), 4.89 (dq, *J* = 3.8 and 7.0 Hz, 1H), 5.42 (br d, *J* = 7.8H, NH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 15.6, 27.7, 28.1, 56.3, 80.5, 80.7, 83.5, 155.1, 167.0; IR($CDCl_3$) 3420, 2990, 1720, 1550 cm^{-1}; MS (e.i.) calc'd for $C_9H_{16}N_2O_6$: *m*/z 248.101, found 248.102; 304 $[M]^+$, 248, 232, 202, 192, 102{100}; Analysis calc'd 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.

Minor diastereomer : ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.49 (s, 18H), 1.65 (d, *J* = 7.0 Hz, 3H), 4.64 (dd, *J* = 3.2 and 9.2 Hz, 1H), 5.70 (dq, *J* = 3.2 and 7.0 Hz, 1H), 5.94 (br d, *J* = 9.2Hz, NH); ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) δ 15.7, 27.7, 28.2, 55.9, 80.6, 82.8, 83.7, 156.0, 167.5; IR ($CDCl_3$) 3420, 1740, 1560 cm^{-1}; MS (e.i.) calc'd for $C_9H_{17}N_2O_6$: *m*/z 249.109, found 249.108; 305 $[M+1]^+$, 249, 232, 202, 192, 102 {100}.

N-*tert*-butoxycarbonyl-3-nitrophenylalanine *t*-butyl ester (125e)

Reaction of the 2-bromo-*N-tert*-butoxycarbonylglycine *tert*-butyl ester (124) with benzyl nitronate (63c), as described above for the preparation of *N-tert*-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a) from methyl nitronate (63a), gave the title compound (125e) as a 1:1 mixture of diastereoemers (270mg, 71%). Partial separation of the diastereomers was made possible by the diastereomers crystallizing from dichloromethane/light petroleum as crystals with different shapes.

One diastereomer crystallized as spars: m.p. 167-169°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.42 (s, 9H), 4.99 (t, *J* = 8.0 Hz, 1H), 5.08 (br d, *J* = 8.0 Hz, NH), 6.00 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 5H, ArH); IR ($CDCl_3$) 3420, 1740, 1570, 1515 cm^{-1}; MS (e.i.) calc'd for $C_{18}H_{27}N_2O_6$: m/z 367.1869, found 367.1862; 367 $[M+1]^+$, 311, 255{100}, 230, 219, 208, 175, 164, 163.

The other diasteromer crystallized as clusters: m.p. 163-166°; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.39 (s, 9H), 4.95 (dd, J = 5.4 and 9.6 Hz, 1H), 5.49 (br d, *J* = 9.6H, NH), 6.03 (d, *J* = 5.4 Hz, 1H), 7.33-7.46 (m, 5H, ArH); IR ($CDCl_3$) 3410, 1735, 1540, 1505 cm^{-1}; MS (e.i.) calc'd for $C_{18}H_{27}N_2O_6$: *m/z* 367.187, found 367.188; 367 $[M+1]^+$, 311, 255 {100}, 230, 219, 175, 164, 163.

3-nitroalanine hydrochloride (126a)

N-tert-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a) was refluxed for 15 minutes with trifluoroacetic acid/chlororform (1:1, 20ml). The solvent was evaporated to dryness under reduced pressure. The residue was redissolved in 0.1N HCl (10 ml) and extracted with ethyl acetate. The aqueous phase was concentrated to afford the *title compound* (126a) in 63% yield: m.p. 125-127°;

^{1}H n.m.r. (300 MHz, D_2O) δ 4.55 (dd, *J* = 2.9 and 5.4 Hz, 1H), 5.06 (dd, *J* = 2.9 and 16.8 Hz, 1H), 5.16 (dd, *J* = 5.4 and 16.8 Hz, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 53.1, 75.1, 171.1; IR(nujol) 2900 (br), 1750, 1540 cm^{-1}MS (f.a.b.) *m/z* 135 $[M+1]^+$, 108 {100}, 91, 75.

3-methyl-3-nitroalanine hydrochloride (126c).

Reaction of each of the major diastereomer of *tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-nitrobutanoate (125c) with trifluoroacetic acid/chloroform, as described for the synthesis of 3-nitroalanine hydrochloride (126a) from *N-tert*-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a), afforded 3-methyl-3-nitroalanine hydrochoride (126c), in 56% yield, with no isomerization of the diastereomers observed by ^{1}H n.m.r. spetroscopy. 3-methyl-3-nitroalanine hydrochloride (126c) major diasteromer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.63 (d, *J* = 7.2 Hz, 3H), 4.68 (d, *J* = 2.3 Hz, 1H), 5.23 (dq, *J* = 2.3 and 7.2 Hz, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 16.0, 57.3, 82.6, 170.5; MS (f.a.b.) 149 $[M+1]^+$ {100}, 110, 108, 103, 102;

Similar reaction of the minor diastereomer of *tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-nitrobutanoate (125c) with trifluoroacetic acid, yielded the *title compound* (126c) in 61% yield, with no isomerization of the diastereomer observed by 1H n.m.r. spectroscopy: 3-methyl-3-nitroalanine hydrochloride (126c) minor diastereomer: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.79 (d, *J* = 7.3 Hz, 3H), 4.64 (d, *J* = 3.8 Hz, 1H), 5.35 (dq, *J* = 3.8 and 7.3 Hz, 1H); ^{13}C n.m.r. (75.5 MHz, D_2O) δ 16.9, 56.7, 82.0, 170.0; MS (f.a.b.) 149 $[M+1]^+$ {100}, 110, 108, 103, 102.

3-nitrophenylalanine hydrochloride (126e)

Reaction of a 1:1 mixture of the diastereomers of *N-tert*-butoxycarbonyl-3-nitrophenylalanine *t*-butyl ester (125f) with trifluoroacetic acid/chlororform, as described for the synthesis of 3-nitroalanine hydrochloride (126a) from *N-tert*-butoxycarbonyl-3-nitroalanine *tert*-butyl ester (125a), afforded a 1:1 mixture of the diastereomers of 3-nitrophenylalanine hydrochloride (126f), in 45% yield: ^{1}H n.m.r. (300 MHz, D_2O) δ 4.68 (d, J = 5.6 Hz, 0.5 x 1H), 5.02 (d, J = 5.1 Hz, 0.5 x 1H), 6.41 (d, J = 5.1 Hz, 0.5 x 1H), 6.53 (d, J = 5.6 Hz, 0.5 x 1H), 7.38-7.40 (m, 0.5 x 5H, ArH), 7.49-7.51 (m, 0.5 x 5H, ArH); MS (f.a.b.) 233 $[M+23]^+$, 211 $[M+1]^+$, 164, 148, 120 {100}.

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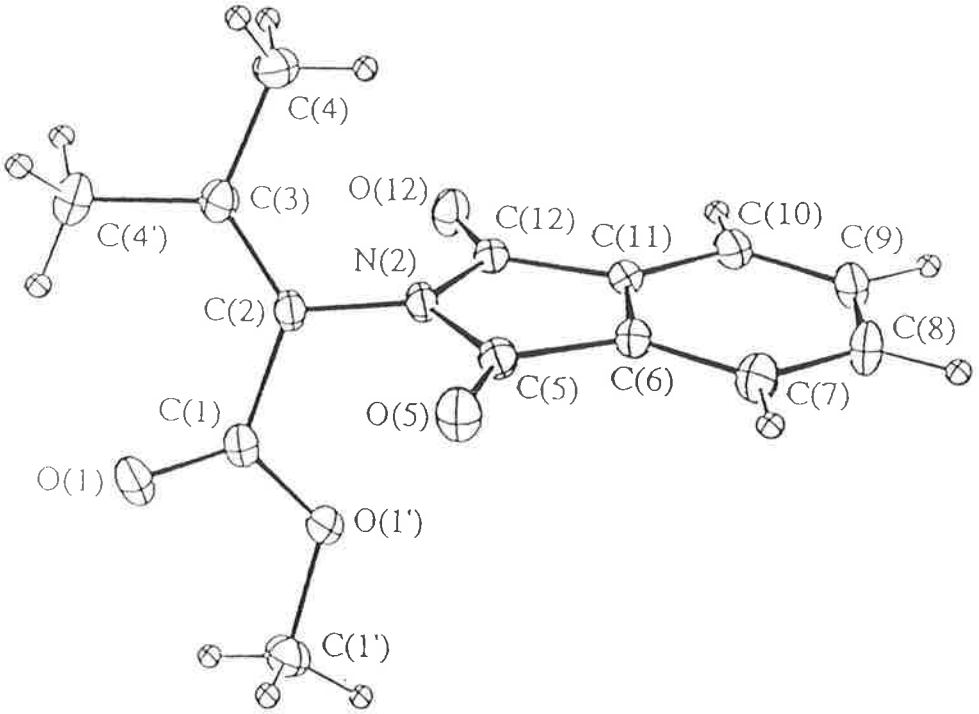
Appendix 1

Crystal structure of

N-phthaloyl-α,β-dehydrovaline methyl ester (79)



Bond distances (Å) for

N-phthaloyl-α,β-dehydrovaline methyl ester (79)

C(1)	---	O(1)	1.201(3)	C(1)	---	O(1')	1.339(3)
C(1')	---	O(1')	1.444(3)	C(5)	---	O(5)	1.202(3)
C(12)	---	O(12)	1.205(3)	C(2)	---	N(2)	1.431(3)
C(5)	---	N(2)	1.404(3)	C(12)	---	N(2)	1.401(3)
C(2)	---	C(1)	1.481(4)	H(11)	---	C(1')	0.969(41)
H(12)	---	C(1')	0.986(42)	H(13)	---	C(1')	0.961(43)
C(3)	---	C(2)	1.343(4)	C(4)	---	C(3)	1.491(4)
C(4')	---	C(3)	1.497(4)	H(41)	---	C(4)	0.992(39)
H(42)	---	C(4)	0.934(36)	H(43)	---	C(4)	0.966(33)
H(44)	---	C(4')	0.883(44)	H(45)	---	C(4')	0.932(46)
H(46)	---	C(4')	1.004(44)	C(6)	---	C(5)	1.485(3)
C(7)	---	C(6)	1.386(4)	C(11)	---	C(6)	1.373(3)
H(7)	---	C(7)	1.045(32)	C(8)	---	C(7)	1.386(5)
H(8)	---	C(8)	0.998(28)	C(9)	---	C(8)	1.370(5)
H(9)	---	C(9)	1.002(30)	C(10)	---	C(9)	1.397(5)
H(10)	---	C(10)	1.027(30)	C(11)	---	C(10)	1.386(4)
C(12)	---	C(11)	1.482(3)				

Bond angles (deg.) for

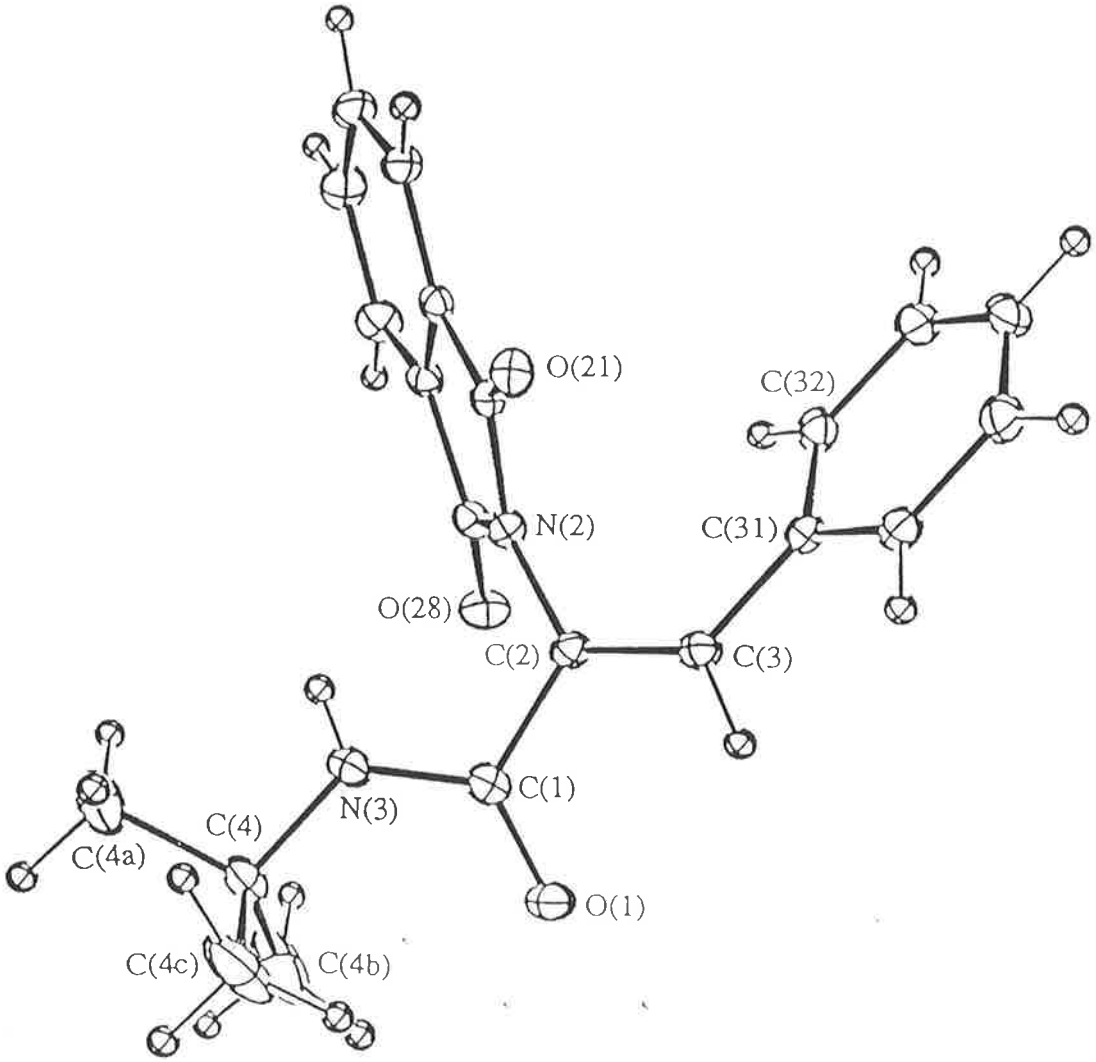
N-phthaloyl-α,β-dehydrovaline methyl ester (79)

C(1')	- O(1')	- C(1)	115.5(2)	C(5)	- N(2)	- C(2)	123.2(2)
C(12)	- N(2)	- C(2)	125.0(2)	C(12)	- N(2)	- C(5)	111.3(2)
O(1')	- C(1)	- O(1)	122.7(2)	C(2)	- C(1)	- O(1)	125.4(2)
C(2)	- C(1)	- O(1')	111.9(2)	H(11)	- C(1')	- O(1')	108.1(21)
H(12)	- C(1')	- O(1')	102.7(23)	H(12)	- C(1')	- H(11)	109.1(32)
H(13)	- C(1')	- O(1')	109.9(23)	H(13)	- C(1')	- H(11)	101.8(28)
H(13)	- C(1')	- H(12)	124.6(33)	C(1)	- C(2)	- N(2)	114.7(2)
C(3)	- C(2)	- N(2)	120.5(2)	C(3)	- C(2)	- C(1)	124.8(2)
C(4)	- C(3)	- C(2)	121.6(2)	C(4')	- C(3)	- C(2)	124.0(3)
C(4')	- C(3)	- C(4)	114.5(3)	H(41)	- C(4)	- C(3)	111.0(20)
H(42)	- C(4)	- C(3)	111.5(21)	H(42)	- C(4)	- H(41)	109.2(28)
H(43)	- C(4)	- C(3)	114.2(19)	H(43)	- C(4)	- H(41)	100.9(27)
H(43)	- C(4)	- H(42)	109.5(28)	H(44)	- C(4')	- C(3)	116.8(27)
H(45)	- C(4')	- C(3)	103.6(25)	H(45)	- C(4')	- H(44)	101.5(36)
H(46)	- C(4')	- C(3)	112.9(22)	H(46)	- C(4')	- H(44)	109.7(34)
H(46)	- C(4')	- H(45)	111.6(34)	N(2)	- C(5)	- O(5)	124.3(2)
C(6)	- C(5)	- O(5)	130.1(2)	C(6)	- C(5)	- N(2)	105.6(2)
C(7)	- C(6)	- C(5)	129.9(2)	C(11)	- C(6)	- C(5)	108.7(2)
C(11)	- C(6)	- C(7)	121.4(2)	H(7)	- C(7)	- C(6)	122.7(17)
C(8)	- C(7)	- C(6)	117.1(3)	C(8)	- C(7)	- H(7)	120.1(17)
H(8)	- C(8)	- C(7)	119.8(16)	C(9)	- C(8)	- C(7)	121.3(3)
C(9)	- C(8)	- H(8)	118.8(16)	H(9)	- C(9)	- C(8)	118.6(16)
C(10)	- C(9)	- C(8)	122.0(3)	C(10)	- C(9)	- H(9)	119.4(17)
H(10)	- C(10)	- C(9)	125.9(16)	C(11)	- C(10)	- C(9)	116.1(3)
C(11)	- C(10)	- H(10)	117.8(16)	C(10)	- C(11)	- C(6)	122.1(2)
C(12)	- C(11)	- C(6)	108.4(2)	C(12)	- C(11)	- C(10)	129.5(2)
N(2)	- C(12)	- O(12)	124.9(2)	C(11)	- C(12)	- O(12)	129.1(2)
C(11)	- C(12)	- N(2)	106.0(2)				

Appendix 2

Crystal structure of

(Z)-*N*-*tert*-butyl-N^{α}-phthaloyl-α,β-dehydrophenylalaninamide (80)



Bond distances (Å) for

(Z)-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (80)

C(1)	---	O(1)	1.236(3)	C(21)	---	O(21)	1.205(3)
C(28)	---	O(28)	1.211(3)	C(2)	---	N(2)	1.431(3)
C(21)	---	N(2)	1.415(3)	C(28)	---	N(2)	1.404(3)
C(1)	---	N(3)	1.337(3)	C(4)	---	N(3)	1.480(3)
H(3N)	---	N(3)	0.824(26)	C(2)	---	C(1)	1.502(3)
C(3)	---	C(2)	1.336(3)	C(31)	---	C(3)	1.462(3)
H(3)	---	C(3)	0.962(24)	C(4A)	---	C(4)	1.521(4)
C(4B)	---	C(4)	1.501(4)	C(4C)	---	C(4)	1.511(4)
H(41)	---	C(4A)	0.970	H(42)	---	C(4A)	0.970
H(43)	---	C(4A)	0.970	H(44)	---	C(4B)	0.970
H(45)	---	C(4B)	0.970	H(46)	---	C(4B)	0.970
H(47)	---	C(4C)	0.970	H(48)	---	C(4C)	0.970
H(49)	---	C(4C)	0.970	C(22)	---	C(21)	1.485(3)
C(23)	---	C(22)	1.386(3)	C(27)	---	C(22)	1.385(3)
C(24)	---	C(23)	1.385(4)	H(23)	---	C(23)	0.930(30)
C(25)	---	C(24)	1.383(4)	H(24)	---	C(24)	0.930(29)
C(26)	---	C(25)	1.390(4)	H(25)	---	C(25)	0.935(36)
C(27)	---	C(26)	1.383(3)	H(26)	---	C(26)	1.011(27)
C(28)	---	C(27)	1.486(3)	C(32)	---	C(31)	1.401(3)
C(36)	---	C(31)	1.390(3)	C(33)	---	C(32)	1.375(4)
H(32)	---	C(32)	0.927(26)	C(34)	---	C(33)	1.364(4)
H(33)	---	C(33)	0.933(32)	C(35)	---	C(34)	1.390(4)
H(34)	---	C(34)	0.960(31)	C(36)	---	C(35)	1.379(4)
H(35)	---	C(35)	1.019(29)	H(36)	---	C(36)	0.947(27)

Bond angles (deg.) for

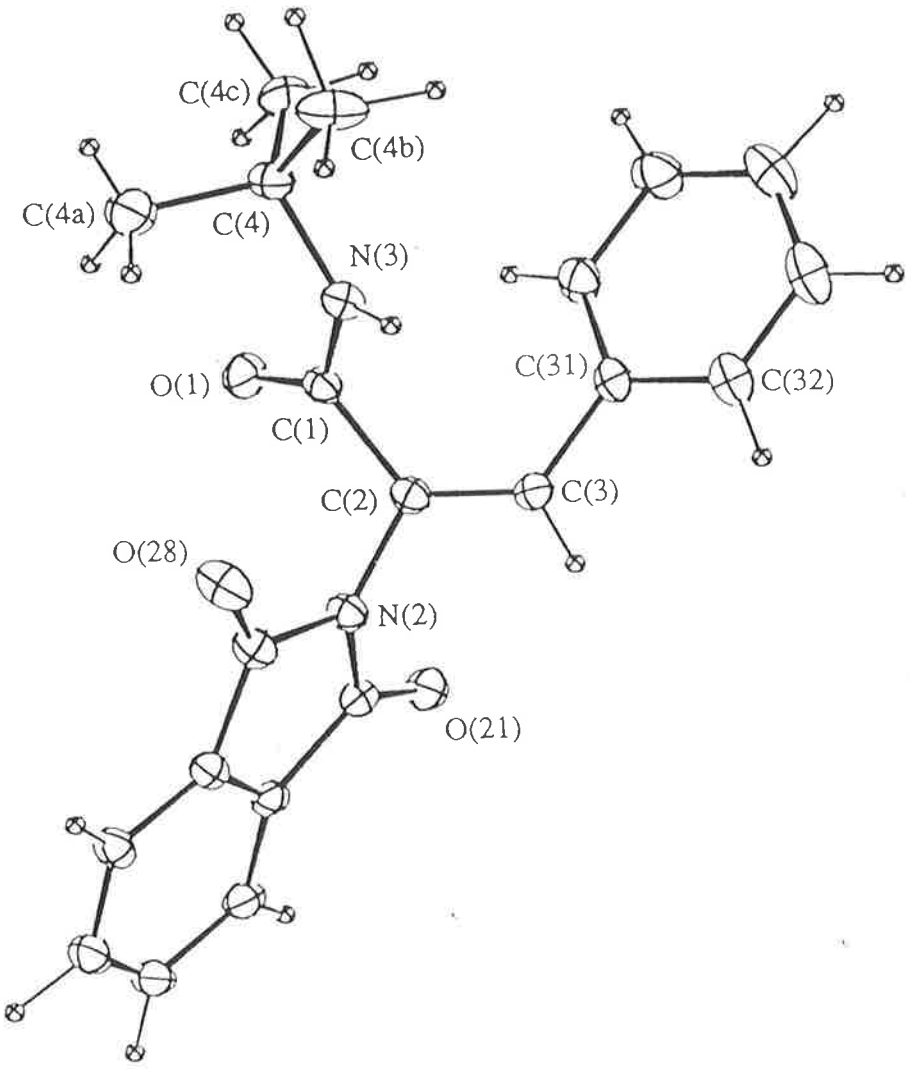
(Z)-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (80)

C(21)	- N(2)	- C(2)	125.6(2)	C(28)	- N(2)	- C(2)	122.3(2)
C(28)	- N(2)	- C(21)	111.6(2)	C(4)	- N(3)	- C(1)	126.9(2)
H(3N)	- N(3)	- C(1)	117.6(18)	H(3N)	- N(3)	- C(4)	115.3(18)
N(3)	- C(1)	- O(1)	124.2(2)	C(2)	- C(1)	- O(1)	120.1(2)
C(2)	- C(1)	- N(3)	115.7(2)	C(1)	- C(2)	- N(2)	117.1(2)
C(3)	- C(2)	- N(2)	122.5(2)	C(3)	- C(2)	- C(1)	120.3(2)
C(31)	- C(3)	- C(2)	129.8(2)	H(3)	- C(3)	- C(2)	116.0(14)
H(3)	- C(3)	- C(31)	114.2(14)	C(4A)	- C(4)	- N(3)	106.7(2)
C(4B)	- C(4)	- N(3)	110.3(2)	C(4B)	- C(4)	- C(4A)	108.5(3)
C(4C)	- C(4)	- N(3)	109.5(2)	C(4C)	- C(4)	- C(4A)	109.8(3)
C(4C)	- C(4)	- C(4B)	111.9(3)	H(41)	- C(4A)	- C(4)	109.5(2)
H(42)	- C(4A)	- C(4)	109.3(2)	H(42)	- C(4A)	- H(41)	109.5(-)
H(43)	- C(4A)	- C(4)	109.6(2)	H(43)	- C(4A)	- H(41)	109.5(-)
H(43)	- C(4A)	- H(42)	109.5(-)	H(44)	- C(4B)	- C(4)	109.6(2)
H(45)	- C(4B)	- C(4)	109.3(2)	H(45)	- C(4B)	- H(44)	109.5(-)
H(46)	- C(4B)	- C(4)	109.6(2)	H(46)	- C(4B)	- H(44)	109.5(-)
H(46)	- C(4B)	- H(45)	109.5(-)	H(47)	- C(4C)	- C(4)	109.5(2)
H(48)	- C(4C)	- C(4)	109.2(2)	H(48)	- C(4C)	- H(47)	109.5(-)
H(49)	- C(4C)	- C(4)	109.7(2)	H(49)	- C(4C)	- H(47)	109.5(-)
H(49)	- C(4C)	- H(48)	109.5(-)	N(2)	- C(21)	- O(21)	125.0(2)
C(22)	- C(21)	- O(21)	129.6(2)	C(22)	- C(21)	- N(2)	105.4(2)
C(23)	- C(22)	- C(21)	129.6(2)	C(27)	- C(22)	- C(21)	108.8(2)
C(27)	- C(22)	- C(23)	121.6(2)	C(24)	- C(23)	- C(22)	116.6(2)
H(23)	- C(23)	- C(22)	121.8(18)	H(23)	- C(23)	- C(24)	121.6(18)
C(25)	- C(24)	- C(23)	122.2(2)	H(24)	- C(24)	- C(23)	115.8(18)
H(24)	- C(24)	- C(25)	122.0(18)	C(26)	- C(25)	- C(24)	121.0(2)
H(25)	- C(25)	- C(24)	120.6(21)	H(25)	- C(25)	- C(26)	118.2(21)
C(27)	- C(26)	- C(25)	117.1(2)	H(26)	- C(26)	- C(25)	120.8(15)
H(26)	- C(26)	- C(27)	122.0(15)	C(26)	- C(27)	- C(22)	121.6(2)
C(28)	- C(27)	- C(22)	108.3(2)	C(28)	- C(27)	- C(26)	130.1(2)
N(2)	- C(28)	- O(28)	124.6(2)	C(27)	- C(28)	- O(28)	129.4(2)
C(27)	- C(28)	- N(2)	105.9(2)	C(32)	- C(31)	- C(3)	123.1(2)
C(36)	- C(31)	- C(3)	119.2(2)	C(36)	- C(31)	- C(32)	117.6(2)
C(33)	- C(32)	- C(31)	121.0(3)	H(32)	- C(32)	- C(31)	119.5(15)
H(32)	- C(32)	- C(33)	119.2(15)	C(34)	- C(33)	- C(32)	120.6(3)
H(33)	- C(33)	- C(32)	117.3(19)	H(33)	- C(33)	- C(34)	121.8(19)
C(35)	- C(34)	- C(33)	119.7(3)	H(34)	- C(34)	- C(33)	117.2(18)
H(34)	- C(34)	- C(35)	123.1(18)	C(36)	- C(35)	- C(34)	120.0(3)
H(35)	- C(35)	- C(34)	120.5(15)	H(35)	- C(35)	- C(36)	119.4(15)
C(35)	- C(36)	- C(31)	121.1(2)	[illegible]			
H(36)	- C(36)	- C(35)	119.8(15)				

Appendix 3

Crystal structure of

(*E*)-*N*-*tert*-butyl-N^{α}-phthaloyl-α,β-dehydrophenylalaninamide (81)



Bond distances (Å) for

(*E*)-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (81)

C(1)	---	O(1)	1.216(4)	C(21)	---	O(21)	1.205(4)
C(28)	---	O(28)	1.197(4)	C(2)	---	N(2)	1.428(4)
C(21)	---	N(2)	1.407(5)	C(28)	---	N(2)	1.406(4)
C(1)	---	N(3)	1.340(5)	C(4)	---	N(3)	1.467(5)
H(3N)	---	N(3)	0.854(49)	C(2)	---	C(1)	1.505(5)
C(3)	---	C(2)	1.331(5)	C(31)	---	C(3)	1.475(5)
H(3)	---	C(3)	0.886(33)	C(4A)	---	C(4)	1.521(6)
C(4B)	---	C(4)	1.520(6)	C(4C)	---	C(4)	1.515(5)
H(41)	---	C(4A)	1.046(71)	H(42)	---	C(4A)	0.805(68)
H(43)	---	C(4A)	1.040(64)	H(44)	---	C(4B)	0.909(53)
H(45)	---	C(4B)	1.105(63)	H(46)	---	C(4B)	1.002(50)
H(47)	---	C(4C)	1.008(43)	H(48)	---	C(4C)	0.966(45)
H(49)	---	C(4C)	0.926(59)	C(22)	---	C(21)	1.495(5)
C(23)	---	C(22)	1.376(5)	C(27)	---	C(22)	1.371(5)
C(24)	---	C(23)	1.399(6)	H(23)	---	C(23)	0.941(36)
C(25)	---	C(24)	1.372(6)	H(24)	---	C(24)	1.000(43)
C(26)	---	C(25)	1.375(5)	H(25)	---	C(25)	1.045(35)
C(27)	---	C(26)	1.392(4)	H(26)	---	C(26)	0.933(36)
C(28)	---	C(27)	1.486(5)	C(32)	---	C(31)	1.388(5)
C(36)	---	C(31)	1.381(5)	C(33)	---	C(32)	1.380(6)
H(32)	---	C(32)	1.007(50)	C(34)	---	C(33)	1.360(7)
H(33)	---	C(33)	0.953(47)	C(35)	---	C(34)	1.359(8)
H(34)	---	C(34)	0.983(52)	C(36)	---	C(35)	1.394(6)
H(35)	---	C(35)	0.925(45)	H(36)	---	C(36)	0.887(39)

Bond angles (deg.) for

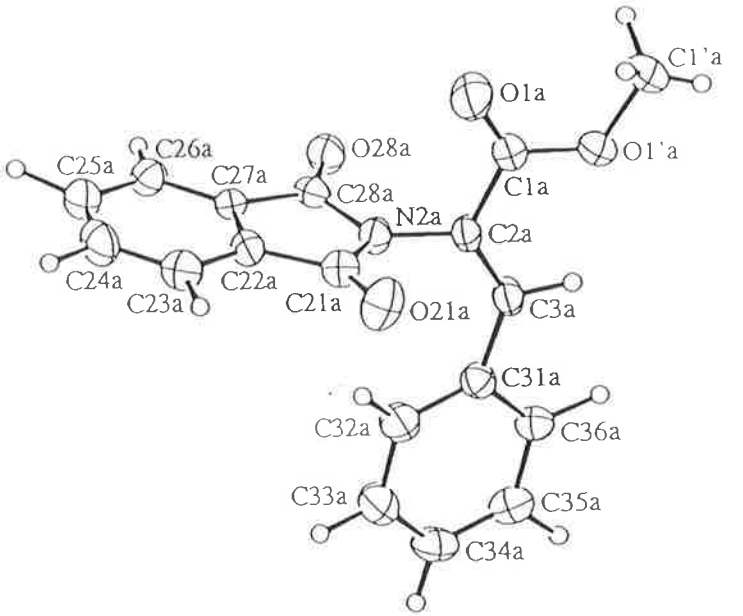
(*E*)-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-α,β-dehydrophenylalaninamide (81)

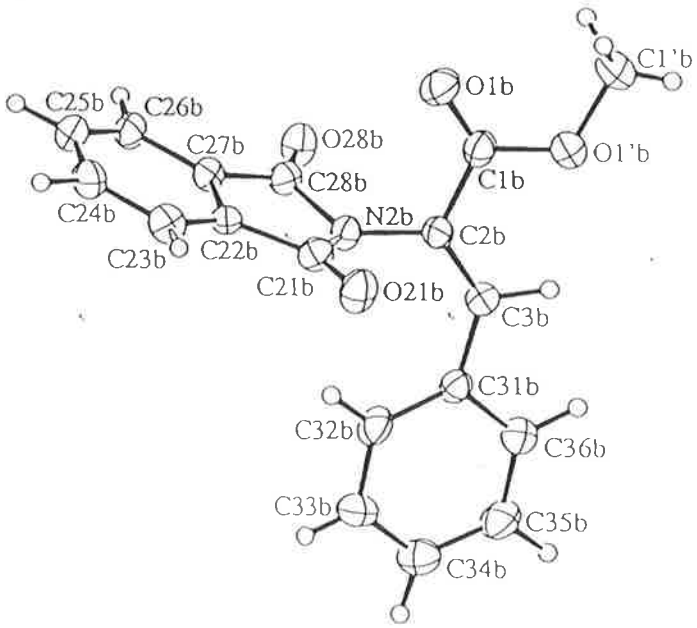
C(21)	- N(2)	- C(2)	125.9(3)	C(28)	- N(2)	- C(2)	121.7(3)
C(28)	- N(2)	- C(21)	112.1(3)	C(4)	- N(3)	- C(1)	126.1(4)
H(3N)	- N(3)	- C(1)	116.3(30)	H(3N)	- N(3)	- C(4)	115.8(31)
N(3)	- C(1)	- O(1)	124.9(3)	C(2)	- C(1)	- O(1)	119.8(3)
C(2)	- C(1)	- N(3)	115.3(3)	C(1)	- C(2)	- N(2)	113.5(3)
C(3)	- C(2)	- N(2)	119.5(3)	C(3)	- C(2)	- C(1)	126.8(3)
C(31)	- C(3)	- C(2)	127.3(4)	H(3)	- C(3)	- C(2)	118.5(17)
H(3)	- C(3)	- C(31)	114.2(17)	C(4A)	- C(4)	- N(3)	109.7(3)
C(4B)	- C(4)	- N(3)	106.2(4)	C(4B)	- C(4)	- C(4A)	111.3(5)
C(4C)	- C(4)	- N(3)	109.8(3)	C(4C)	- C(4)	- C(4A)	110.7(5)
C(4C)	- C(4)	- C(4B)	109.0(4)	H(41)	- C(4A)	- C(4)	112.6(36)
H(42)	- C(4A)	- C(4)	111.1(39)	H(42)	- C(4A)	- H(41)	110.9(58)
H(43)	- C(4A)	- C(4)	104.4(35)	H(43)	- C(4A)	- H(41)	106.3(49)
H(43)	- C(4A)	- H(42)	111.3(52)	H(44)	- C(4B)	- C(4)	104.0(32)
H(45)	- C(4B)	- C(4)	105.3(32)	H(45)	- C(4B)	- H(44)	114.2(47)
H(46)	- C(4B)	- C(4)	108.6(26)	H(46)	- C(4B)	- H(44)	122.3(42)
H(46)	- C(4B)	- H(45)	101.4(38)	H(47)	- C(4C)	- C(4)	110.8(21)
H(48)	- C(4C)	- C(4)	107.0(23)	H(48)	- C(4C)	- H(47)	100.6(34)
H(49)	- C(4C)	- C(4)	111.6(38)	H(49)	- C(4C)	- H(47)	119.0(40)
H(49)	- C(4C)	- H(48)	106.4(42)	N(2)	- C(21)	- O(21)	125.4(3)
C(22)	- C(21)	- O(21)	129.3(3)	C(22)	- C(21)	- N(2)	105.3(3)
C(23)	- C(22)	- C(21)	129.9(3)	C(27)	- C(22)	- C(21)	108.1(3)
C(27)	- C(22)	- C(23)	122.0(3)	C(24)	- C(23)	- C(22)	116.1(4)
H(23)	- C(23)	- C(22)	119.6(21)	H(23)	- C(23)	- C(24)	124.3(21)
C(25)	- C(24)	- C(23)	122.3(4)	H(24)	- C(24)	- C(23)	116.7(25)
H(24)	- C(24)	- C(25)	121.1(24)	C(26)	- C(25)	- C(24)	120.8(4)
H(25)	- C(25)	- C(24)	120.0(20)	H(25)	- C(25)	- C(26)	118.9(20)
C(27)	- C(26)	- C(25)	117.4(4)	H(26)	- C(26)	- C(25)	125.5(22)
H(26)	- C(26)	- C(27)	117.0(22)	C(26)	- C(27)	- C(22)	121.3(3)
C(28)	- C(27)	- C(22)	109.6(3)	C(28)	- C(27)	- C(26)	129.1(4)
N(2)	- C(28)	- O(28)	124.3(3)	C(27)	- C(28)	- O(28)	130.9(3)
C(27)	- C(28)	- N(2)	104.9(3)	C(32)	- C(31)	- C(3)	118.6(3)
C(36)	- C(31)	- C(3)	122.5(4)	C(36)	- C(31)	- C(32)	118.9(4)
C(33)	- C(32)	- C(31)	120.4(5)	H(32)	- C(32)	- C(31)	120.5(28)
H(32)	- C(32)	- C(33)	119.1(25)	C(34)	- C(33)	- C(32)	120.0(5)
H(33)	- C(33)	- C(32)	119.8(24)	H(33)	- C(33)	- C(34)	120.2(24)
C(35)	- C(34)	- C(33)	120.6(5)	H(34)	- C(34)	- C(33)	113.6(28)
H(34)	- C(34)	- C(35)	125.8(28)	C(36)	- C(35)	- C(34)	120.3(5)
H(35)	- C(35)	- C(34)	118.5(27)	H(36)	- C(36)	- C(35)	119.2(33)
C(35)	- C(36)	- C(31)	120.1(5)	[illegible]			

Appendix 4

Crystal structures of

(*Z*)-*N*-phthaloyl-α,β-dehydrophenylalanine methyl ester (84)





Bond distances (Å) for

(Z)-*N*-phthaloyl-α,β-dehydrophenylalanine methyl ester (84)

atom	atom	distance	atom	atom	distance	atom	atom	distance
O(1a)	C(1a)	1.176(6)	C(3b)	C(31b)	1.443(6)	C(27a)	C(28a)	1.466(6)
O(1'a)	C(1a)	1.315(5)	C(3b)	H(3b)	0.99(4)	C(27b)	C(28b)	1.465(6)
O(1'a)	C(1'a)	1.449(7)	C(3a)	C(31a)	1.443(6)	C(31a)	C(32a)	1.379(7)
O(1'b)	C(1b)	1.320(5)	C(3a)	H(3a)	0.98(3)	C(31a)	C(36a)	1.377(6)
O(1'b)	C(1'b)	1.441(7)	C(21a)	C(22a)	1.472(7)	C(31b)	C(32b)	1.375(6)
O(1b)	C(1b)	1.191(5)	C(21b)	C(22b)	1.472(6)	C(31b)	C(36b)	1.383(6)
O(21a)	C(21a)	1.187(5)	C(22b)	C(23b)	1.371(6)	C(32a)	C(33a)	1.373(8)
O(21b)	C(21b)	1.188(5)	C(22b)	C(27b)	1.374(6)	C(32a)	H(32a)	0.94(5)
O(28b)	C(28b)	1.188(5)	C(22a)	C(23a)	1.372(6)	C(32b)	C(33b)	1.365(7)
O(28a)	C(28a)	1.201(5)	C(22a)	C(27a)	1.356(6)	C(32b)	H(32b)	0.92(3)
N(2a)	C(2a)	1.412(5)	C(23a)	C(24a)	1.380(8)	C(33b)	C(34b)	1.356(7)
N(2a)	C(21a)	1.407(6)	C(23a)	H(23a)	0.95(5)	C(33b)	H(33b)	0.93(4)
N(2a)	C(28a)	1.379(6)	C(23b)	C(24b)	1.370(7)	C(33a)	C(34a)	1.352(8)
N(2b)	C(2b)	1.417(5)	C(23b)	H(23b)	0.91(4)	C(33a)	H(33a)	1.06(5)
N(2b)	C(21b)	1.394(5)	C(24b)	C(25b)	1.360(7)	C(34a)	C(35a)	1.341(7)
N(2b)	C(28b)	1.404(5)	C(24b)	H(24b)	1.02(4)	C(34a)	H(34a)	1.01(4)
C(1a)	C(2a)	1.465(6)	C(24a)	C(25a)	1.349(8)	C(34b)	C(35b)	1.356(7)
C(1'a)	H(1'a)	1.07(4)	C(24a)	H(24a)	0.98(4)	C(34b)	H(34b)	0.94(4)
C(1'a)	H(1'b)	1.07(6)	C(25a)	C(26a)	1.376(7)	C(35b)	C(36b)	1.361(7)
C(1'a)	H(1'c)	0.85(5)	C(25a)	H(25a)	1.13(5)	C(35b)	H(35b)	1.02(5)
C(1b)	C(2b)	1.472(6)	C(25b)	C(26b)	1.375(7)	C(35a)	C(36a)	1.375(7)
C(1'b)	H(1'd)	0.90(5)	C(25b)	H(25b)	0.95(4)	C(35a)	H(35a)	0.99(4)
C(1'b)	H(1'e)	1.05(5)	C(26b)	C(27b)	1.363(6)	C(36a)	H(36a)	1.08(4)
C(1'b)	H(1'f)	0.92(6)	C(26b)	H(26b)	0.95(4)	C(36b)	H(36b)	0.97(3)
C(2a)	C(3a)	1.311(6)	C(26a)	C(27a)	1.370(6)			
C(2b)	C(3b)	1.318(6)	C(26a)	H(26a)	0.99(4)			

Bond angles (deg.) for

(Z)-*N*-phthaloyl-α,β-dehydrophenylalanine methyl ester (84)

atom	atom	atom	angle
C(1a)	O(1'a)	C(1'a)	115.4(5)
C(1b)	O(1'b)	C(1'b)	115.5(4)
C(2a)	N(2a)	C(21a)	124.2(5)
C(2a)	N(2a)	C(28a)	123.6(5)
C(21a)	N(2a)	C(28a)	111.3(4)
C(2b)	N(2b)	C(21b)	120.9(4)
C(2b)	N(2b)	C(28b)	122.6(4)
C(21b)	N(2b)	C(28b)	111.0(4)
O(1a)	C(1a)	O(1'a)	124.1(6)
O(1a)	C(1a)	C(2a)	123.3(6)
O(1'a)	C(1a)	C(2a)	112.6(5)
O(1'a)	C(1'a)	H(1'a)	107(3)
O(1'a)	C(1'a)	H(1'b)	103(4)
O(1'a)	C(1'a)	H(1'c)	104(4)
H(1'a)	C(1'a)	H(1'b)	112(4)
H(1'a)	C(1'a)	H(1'c)	109(5)
H(1'b)	C(1'a)	H(1'c)	119(6)
O(1'b)	C(1b)	O(1b)	124.0(5)
O(1'b)	C(1b)	C(2b)	111.9(5)
O(1b)	C(1b)	C(2b)	124.1(5)
O(1'b)	C(1'b)	H(1'd)	103(4)
O(1'b)	C(1'b)	H(1'e)	107(3)
O(1'b)	C(1'b)	H(1'f)	117(5)
H(1'd)	C(1'b)	H(1'e)	111(5)
H(1'd)	C(1'b)	H(1'f)	121(6)
H(1'e)	C(1'b)	H(1'f)	97(5)
C(24a)	C(23a)	H(23a)	129(3)
C(22b)	C(23b)	C(24b)	117.8(5)
C(22b)	C(23b)	H(23b)	123(3)
C(24b)	C(23b)	H(23b)	118(3)
C(23b)	C(24b)	C(25b)	120.9(6)
C(23b)	C(24b)	H(24b)	121(2)
C(25b)	C(24b)	H(24b)	119(2)
C(23a)	C(24a)	C(25a)	122.6(6)
C(23a)	C(24a)	H(24a)	119(3)
C(25a)	C(24a)	H(24a)	118(3)
C(24a)	C(25a)	C(26a)	120.5(6)
C(24a)	C(25a)	H(25a)	127(3)
C(26a)	C(25a)	H(25a)	112(3)
C(24b)	C(25b)	C(26b)	121.7(5)
C(24b)	C(25b)	H(25b)	119(3)
C(26b)	C(25b)	H(25b)	119(3)
C(25b)	C(26b)	C(27b)	117.4(5)
C(25b)	C(26b)	H(26b)	122(3)
C(27b)	C(26b)	H(26b)	120(3)
C(25a)	C(26a)	C(27a)	117.0(6)
C(25a)	C(26a)	H(26a)	122(3)
C(27a)	C(26a)	H(26a)	121(3)
C(22a)	C(27a)	C(26a)	122.5(5)
C(22a)	C(27a)	C(28a)	108.0(5)
[illegible]			

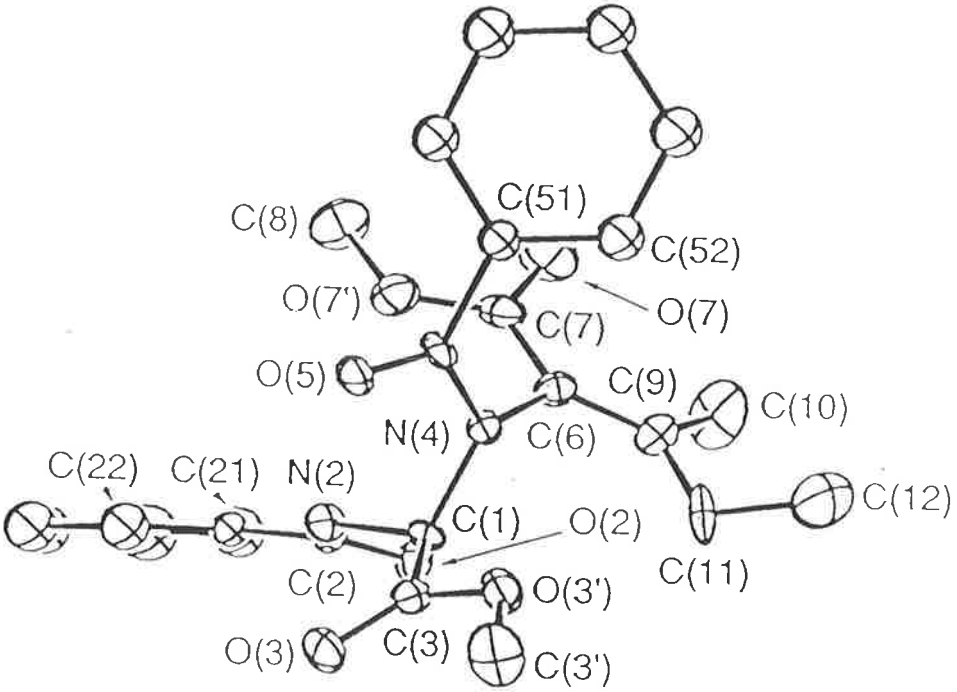
atom	atom	atom	angle
N(2a)	C(2a)	C(1a)	112.5(5)
N(2a)	C(2a)	C(3a)	123.6(5)
C(1a)	C(2a)	C(3a)	123.9(5)
N(2b)	C(2b)	C(1b)	112.1(4)
N(2b)	C(2b)	C(3b)	124.8(5)
C(1b)	C(2b)	C(3b)	123.2(5)
C(2b)	C(3b)	C(31b)	132.5(5)
C(2b)	C(3b)	H(3b)	114(2)
C(31b)	C(3b)	H(3b)	114(2)
C(2a)	C(3a)	C(31a)	131.9(5)
C(2a)	C(3a)	H(3a)	114(2)
C(31a)	C(3a)	H(3a)	114(2)
O(21a)	C(21a)	N(2a)	124.7(5)
O(21a)	C(21a)	C(22a)	130.7(6)
N(2a)	C(21a)	C(22a)	104.5(5)
O(21b)	C(21b)	N(2b)	124.7(5)
O(21b)	C(21b)	C(22b)	129.9(5)
N(2b)	C(21b)	C(22b)	105.4(4)
C(21b)	C(22b)	C(23b)	130.0(5)
C(21b)	C(22b)	C(27b)	108.9(5)
C(23b)	C(22b)	C(27b)	120.9(5)
C(21a)	C(22a)	C(23a)	129.7(6)
C(21a)	C(22a)	C(27a)	109.5(5)
C(23a)	C(22a)	C(27a)	120.8(5)
C(22a)	C(23a)	C(24a)	116.6(6)
C(22a)	C(23a)	H(23a)	114(3)
C(22b)	C(27b)	C(26b)	108.1(4)
C(26b)	C(27b)	C(26b)	130.6(5)
O(28a)	C(28a)	N(2a)	124.4(5)
O(28a)	C(28a)	C(27a)	129.2(6)
N(2a)	C(28a)	C(27a)	106.5(5)
O(28b)	C(28b)	N(2b)	123.3(5)
O(28b)	C(28b)	C(27b)	130.7(5)
N(2b)	C(28b)	C(27b)	106.0(4)
C(3a)	C(31a)	C(32a)	125.3(6)
C(3a)	C(31a)	C(36a)	117.2(5)
C(32a)	C(31a)	C(36a)	117.5(5)
C(3b)	C(31b)	C(32b)	126.2(5)
C(3b)	C(31b)	C(36b)	116.9(5)
C(32b)	C(31b)	C(36b)	116.8(5)
C(31a)	C(32a)	C(33a)	121.3(6)
C(31a)	C(32a)	H(32a)	119(3)
C(33a)	C(32a)	H(32a)	119(3)
C(31b)	C(32b)	C(33b)	121.4(5)
C(31b)	C(32b)	H(32b)	120(2)
C(33b)	C(32b)	H(32b)	119(2)
C(32b)	C(33b)	C(34b)	120.4(6)
C(32b)	C(33b)	H(33b)	117(3)
C(34b)	[illegible]		

atom	atom	atom	angle
C(11a)	C(34a)	H(34a)	119(2)
C(35a)	C(34a)	H(34a)	120(2)
C(33b)	C(34b)	C(35b)	119.6(6)
C(33b)	C(34b)	H(34b)	113(3)
C(35b)	C(34b)	H(34b)	127(3)
C(34b)	C(35b)	C(36b)	120.2(6)
C(34b)	C(35b)	H(35b)	120(3)
C(36b)	C(35b)	H(35b)	119(3)
C(34a)	C(35a)	C(36a)	120.2(6)
C(34a)	C(35a)	H(35a)	123(3)
C(36a)	C(35a)	H(35a)	116(3)
C(31a)	C(36a)	C(35a)	120.7(6)
C(31a)	C(36a)	H(36a)	120(2)
C(35a)	C(36a)	H(36a)	119(2)
C(31b)	C(36b)	C(35b)	121.5(6)
C(31b)	C(36b)	H(36b)	117(2)
C(35b)	C(36b)	H(36b)	121(2)

Appendix 5

Crystal structure of the

α,β-dehydro-*iso*-leucine methyl ester derivative (98)



Bond distances (Å) for the

α,β-dehydro-*iso*-leucine methyl ester derivative (98)

C(2)	---	C(2)	1.250(13)	C(3)	---	O(3)	1.227(14)
C(3)	---	O(3')	1.337(16)	C(3')	---	O(3')	1.447(13)
C(5)	---	O(5)	1.237(13)	C(7)	---	O(7)	1.235(16)
C(7)	---	O(7')	1.348(16)	C(8)	---	O(7')	1.418(14)
C(1)	---	N(2)	1.419(12)	C(2)	---	N(2)	1.322(15)
C(1)	---	N(4)	1.480(13)	C(5)	---	N(4)	1.353(13)
C(6)	---	N(4)	1.460(15)	C(3)	---	C(1)	1.512(16)
C(21)	---	C(2)	1.508(16)	C(51)	---	C(5)	1.487(15)
C(7)	---	C(6)	1.444(19)	C(9)	---	C(6)	1.342(17)
C(10)	---	C(9)	1.470(19)	C(11)	---	C(9)	1.425(19)
C(12)	---	C(11)	1.428(20)	C(23)	---	C(22)	1.395(-)
C(21)	---	C(22)	1.395(-)	C(24)	---	C(23)	1.395(-)
C(25)	---	C(24)	1.395(-)	C(26)	---	C(25)	1.395(-)
C(21)	---	C(26)	1.395(-)	C(53)	---	C(52)	1.395(-)
C(51)	---	C(52)	1.395(-)	C(54)	---	C(53)	1.395(-)
C(55)	---	C(54)	1.395(-)	C(56)	---	C(55)	1.395(-)
C(51)	---	C(56)	1.395(-)				

Bond angles (deg.) for the

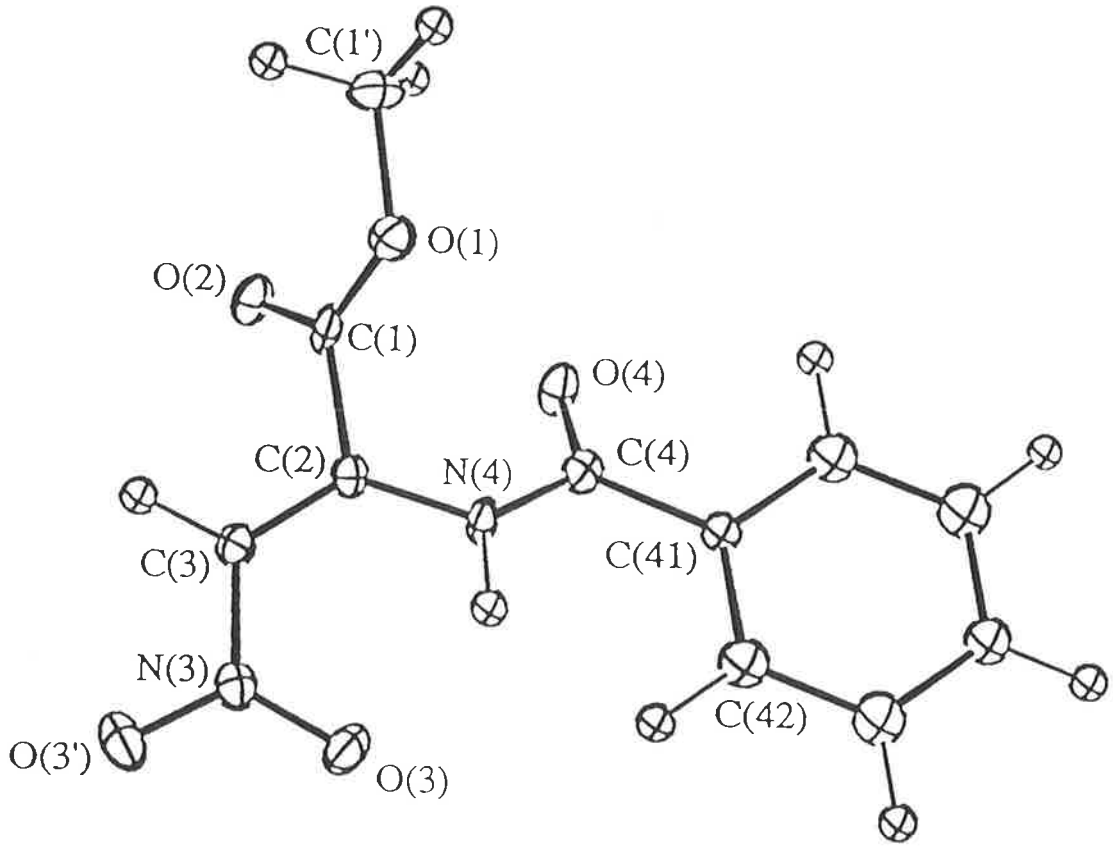
α,β-dehydro-*iso*-leucine methyl ester derivative (98)

C(3')	- O(3')	- C(3)	117.2(11)	C(8)	- O(7')	- C(7)	117.8(14)
C(2)	- N(2)	- C(1)	116.4(11)	C(5)	- N(4)	- C(1)	117.7(10)
C(6)	- N(4)	- C(1)	117.7(10)	C(6)	- N(4)	- C(5)	119.8(11)
N(4)	- C(1)	- N(2)	113.7(10)	C(3)	- C(1)	- N(2)	111.8(12)
C(3)	- C(1)	- N(4)	110.1(11)	N(2)	- C(2)	- O(2)	125.5(13)
C(21)	- C(2)	- O(2)	116.2(14)	C(21)	- C(2)	- N(2)	118.4(12)
O(3')	- C(3)	- O(3)	122.7(15)	C(1)	- C(3)	- O(3)	123.3(16)
C(1)	- C(3)	- O(3')	114.0(14)	N(4)	- C(5)	- O(5)	120.6(11)
C(51)	- C(5)	- O(5)	119.3(12)	C(51)	- C(5)	- N(4)	119.7(12)
C(7)	- C(6)	- N(4)	115.3(15)	C(9)	- C(6)	- N(4)	122.3(16)
C(9)	- C(6)	- C(7)	121.7(17)	O(7')	- C(7)	- O(7)	119.9(17)
C(6)	- C(7)	- O(7)	126.5(18)	C(6)	- C(7)	- O(7')	113.4(16)
C(10)	- C(9)	- C(6)	126.0(18)	C(11)	- C(9)	- C(6)	116.4(17)
C(11)	- C(9)	- C(10)	117.5(16)	C(12)	- C(11)	- C(9)	114.7(17)
C(21)	- C(22)	- C(23)	120.0(-)	C(24)	- C(23)	- C(22)	120.0(-)
C(25)	- C(24)	- C(23)	120.0(-)	C(26)	- C(25)	- C(24)	120.0(-)
C(21)	- C(26)	- C(25)	120.0(-)	C(22)	- C(21)	- C(2)	121.1(7)
C(26)	- C(21)	- C(2)	118.7(7)	C(26)	- C(21)	- C(22)	120.0(-)
C(51)	- C(52)	- C(53)	120.0(-)	C(54)	- C(53)	- C(52)	120.0(-)
C(55)	- C(54)	- C(53)	120.0(-)	C(56)	- C(55)	- C(54)	120.0(-)
C(51)	- C(56)	- C(55)	120.0(-)	C(52)	- C(51)	- C(5)	121.1(6)
C(56)	- C(51)	- C(5)	118.7(6)	C(56)	- C(51)	- C(52)	120.0(-)

Appendix 6

Crystal structure of

N-benzoyl-β-nitro-α,β-dehydroalanine methyl ester (113)



Bond distances (Å) for

N-benzoyl-β-nitro-α,β-dehydroalanine methyl ester (113)

C(1)	---	O(1)	1.326(8)
C(1)	---	O(2)	1.196(8)
N(3)	---	O(3')	1.217(7)
C(3)	---	N(3)	1.431(9)
C(4)	---	N(4)	1.382(8)
C(3)	---	C(2)	1.322(9)
C(1')	---	O(1)	1.452(8)
N(3)	---	O(3)	1.230(7)
C(4)	---	O(4)	1.219(8)
C(2)	---	N(4)	1.387(8)
C(2)	---	C(1)	1.508(10)
C(41)	---	C(4)	1.478(8)

Bond angles (deg.) for

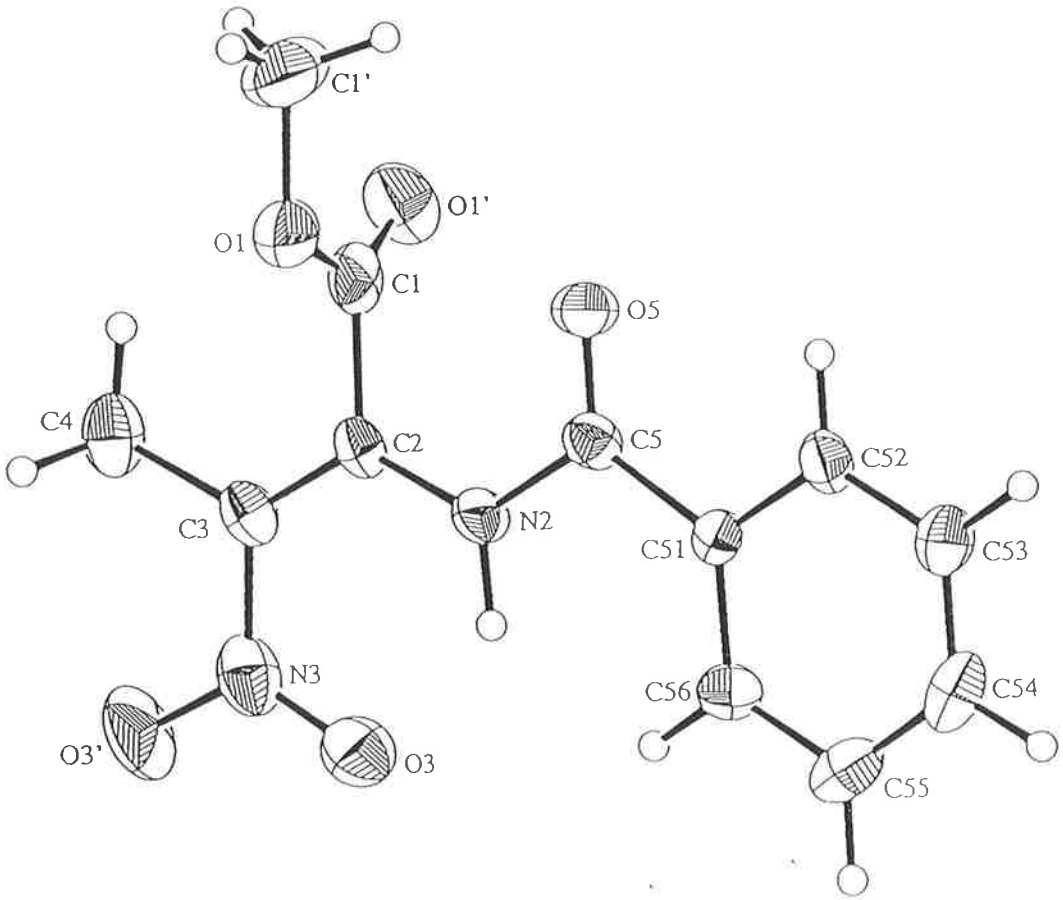
N-benzoyl-β-nitro-α,β-dehydroalanine methyl ester (113)

C(1')	-	O(1)	- C(1)	116.4(6)
C(3)	-	N(3)	- O(3)	121.0(6)
C(4)	-	N(4)	- C(2)	122.4(6)
C(2)	-	C(1)	- O(1)	110.6(7)
C(1)	-	C(2)	- N(4)	117.9(6)
C(3)		C(2)	C(1)	114.8(6)
N(4)	-	C(4)	- O(4)	119.9(6)
C(41)	-	C(4)	- N(4)	116.6(6)
C(42)	-	C(41)	- C(4)	122.5(4)
O(3')	-	N(3)	- O(3)	122.2(7)
C(3)	-	N(3)	- O(3')	116.8(7)
O(2)	-	C(1)	- O(1)	125.5(7)
C(2)	-	C(1)	- O(2)	123.7(8)
C(3)	-	C(2)	- N(4)	127.1(7)
C(2)	-	C(3)	- N(3)	123.6(7)
C(41)	-	C(4)	- O(4)	123.4(7)
C(46)	-	C(41)	- C(4)	117.4(4)

Appendix 7

Crystal structure of

Methyl (Z)-2-benzamido-3-nitrobut-2-enoate (116)



Bond distances (Å) for

Methyl (Z)-2-benzamido-3-nitrobut-2-enoate (116)

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.304(7)	C(2)	C(3)	1.321(6)
O(1)	C(1')	1.442(7)	C(3)	C(4)	1.480(6)
O(1')	C(1)	1.173(6)	C(5)	C(51)	1.473(6)
O(3)	N(3)	1.230(5)	C(51)	C(52)	1.378(5)
O(3')	N(3)	1.205(5)	C(51)	C(56)	1.370(6)
O(5)	C(5)	1.189(5)	C(52)	C(53)	1.356(6)
N(2)	C(2)	1.357(5)	C(53)	C(54)	1.343(7)
N(2)	C(5)	1.373(5)	C(54)	C(55)	1.368(7)
N(3)	C(3)	1.436(6)	C(55)	C(56)	1.359(6)
C(1)	C(2)	1.504(8)			

Bond angles (deg.) for

Methyl (Z)-2-benzamido-3-nitrobut-2-enoate (116)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(1)	C(1')	114.8(6)	C(2)	C(3)	C(4)	125.9(5)
C(2)	N(2)	C(5)	124.5(4)	O(5)	C(5)	N(2)	120.4(5)
O(3)	N(3)	O(3')	121.3(6)	O(5)	C(5)	C(51)	123.6(5)
O(3)	N(3)	C(3)	119.9(5)	N(2)	C(5)	C(51)	116.0(5)
O(3')	N(3)	C(3)	118.8(5)	C(5)	C(51)	C(52)	115.7(5)
O(1)	C(1)	O(1')	127.6(7)	C(5)	C(51)	C(56)	125.5(5)
O(1)	C(1)	C(2)	109.9(6)	C(52)	C(51)	C(56)	118.8(5)
O(1')	C(1)	C(2)	122.3(7)	C(51)	C(52)	C(53)	120.3(5)
N(2)	C(2)	C(1)	116.4(4)	C(52)	C(53)	C(54)	120.2(5)
N(2)	C(2)	C(3)	127.3(5)	C(53)	C(54)	C(55)	120.8(6)
C(1)	C(2)	C(3)	116.3(5)	C(54)	C(55)	C(56)	119.3(5)
N(3)	C(3)	C(2)	120.3(5)	C(51)	C(56)	C(55)	120.6(5)
N(3)	C(3)	C(4)	113.7(5)				