Regioselective Modification of Amino Acid Derivatives

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by

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Statement

To the best of my knowledge, this thesis contains no material previously submitted for a degree or diploma and contains no material previously published except where due reference is made.

Tan Eng Wui
Publications

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


Abstract

With the aim of developing procedures for the regioselective modification of amino acid derivatives, radical bromination and methods for enhancing regiocontrol of radical bromination of amino acid derivatives have been investigated. The selective bromination of glycine residues in N-benzoyldipeptide derivatives is reported. The selectivity of these reactions is governed by a balance of the inherent preference for reaction of glycine residues and a bias for reaction of N-terminal residues.

Regioselectivity complementary to that observed with N-benzoyldipeptide derivatives is exhibited in brominations of N-phthaloyldipeptide derivatives. The N-phthaloyl substituent disfavors reaction of the N-terminal residue to effect reaction at the C-terminal residue. The extent of the deactivating effect of the N-phthaloyl substituent is such that C-terminal non-glycine residues react preferentially to N-terminal glycine residues. The effect of the N-phthaloyl substituent extends to tripeptide derivatives where it permits selective bromination in substrates with multiple glycine residues.

α-Bromoglycine residues in peptide derivatives are amenable to, at least, some of the numerous techniques which have been developed elsewhere for the elaboration of α-halo-glycine derivatives. The synthesis of β-carboxyaspartic acid and allylglycine containing dipeptide derivatives is reported. An important factor worthy of consideration in modifications of residues in dipeptide derivatives is that of asymmetric induction.
A relationship between the position of the residue in the peptide, with regard to the pattern of intramolecular hydrogen-bonding, and diastereoselectivity of reaction is evident.

To discover the factors governing the contrasting effects of the N-benzoyl and N-phthaloyl substituents, the relative reactivity of the methyl esters of N-benzoylglycine, N-benzoyl-β-alanine, N-phthaloylglycine and N-phthaloyl-β-alanine was determined. It was concluded that the N-phthaloyl substituent is less activating than the N-benzoyl substituent and that non-bonding interactions within N-phthaloyl-α-amino acid derivatives give rise to additional deactivating influences.

Bromination of the position adjacent to nitrogen in the methyl esters of N-phthaloyl-β-alanine and N-phthaloylGABA is reported. The functionalized derivatives are susceptible to modifications and, as a consequence, are suitable synthons for the preparation of β- and γ-substituted β- and γ-amino acid derivatives, respectively.

The α-position of N-phthaloyl-α-amino acid derivatives is deactivated towards bromination to such an extent that reaction occurs at tertiary, benzylic, allylic and N-phthaloyl substituted positions on the side-chain.

The synthesis of derivatives of α,β-didehydrovaline, β,γ-didehydrovaline, α,β-methanovaline, the lactone of γ-hydroxyleucine and optically active derivatives of β-hydroxyvaline and γ-hydroxyleucine using the N-phthaloyl derivatives of β-bromovaline and γ-bromoleucine is reported.
Introduction

Amino acids\(^1,2\) play a vital role in biology being the components from which all peptides and proteins are assembled. At present more than 700 naturally occurring amino acids have been identified, of which approximately 240 are found free in nature\(^2,3\). Only about 20 out of this large class of natural products are constituents of proteins\(^2\). The remaining non-proteinogenic amino acids consist of rare and specialized forms, a majority of which possess important biological characteristics either as the free species or as residues in peptides. As a consequence of their wide ranging properties amino acids have found important applications in agriculture, pharmacy and the food industry. To meet the increasing requirement for these compounds the synthesis of amino acids has become an important endeavour in chemistry. In addition, studies of structure activity relationships and the mechanisms of chemical transformations of amino acids in biological processes have generated interest in the design and synthesis of biologically active unnatural amino acids which exhibit enzyme inhibitory, antibiotic, antimetabolite or conformational-inducing properties.

Free radical reactions of amino acids and their derivatives have been implicated in many biochemical processes. Some examples are the biosynthesis of penicillin and cephalosporin\(^4-8\), the cross-linking of protein to DNA\(^9-11\), and the yellowing of protein\(^12\). Radical reactions of amino acids and their derivatives have been
studied with the aim of investigating these biochemical processes\textsuperscript{6,13,14}, as well as to develop synthetic methods applicable to the modification of amino acid residues\textsuperscript{15-27}.

The free radicals detected by electron spin resonance spectroscopy, upon irradiation of proteins\textsuperscript{28,29}, have been divided into three groups:

(a) aromatic radicals
(b) sulfur radicals
(c) aliphatic radicals

The aromatic radicals are associated with reactions of aromatic moieties on the side-chains of amino acid residues such as phenylalanine, tyrosine, and tryptophan\textsuperscript{30}. Sulfur radicals are thought to be formed through the sensitization of sulfur containing side-chains by aromatic amino acid residues\textsuperscript{31-33}. The aliphatic radicals consist mostly of $\alpha$-carbon centered radicals (Figure 1). These radicals are of special interest because they are particular to amino acid systems. This being the case the present study is targetted at the formation, and the factors governing the formation, of $\alpha$-centered radicals of amino acid derivatives.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{aliphatic_radicals.png}
\caption{Aliphatic radicals formed by irradiation of proteins.}
\end{figure}
The α-carbon centered radicals 1, 2 and 3 have been detected in electron spin resonance spectroscopic studies of N-acetyl-glycine\textsuperscript{36-39}, N-acetylamino\textsubscript{36,39,40,42} and pyroglutamic acid\textsuperscript{42,43}, respectively. The radicals 4 and 5 were detected in similar studies with glycylglycine\textsuperscript{34,35,39-41} and glycylalanine\textsuperscript{41}, respectively.

These radicals are formed readily due to their inherent stability which arises from extensive delocalization of unpaired spin density through resonance. The electron spin resonance spectra of 1 and 4 show only 70-75\% of the unpaired spin density to be at the respective α-centers\textsuperscript{29,34,35,41}. The delocalization of unpaired spin density is also shown by molecular orbital calculations for the radical 1\textsuperscript{29}. These calculations show that the spin density is spread over the amido and carboxyl groups (Figure 2).
Figure 2. Distribution of the unpaired spin density in the radical produced by hydrogen atom transfer from N-acetylglycine. 

Radicals of the type 1 have been classified by Viehe et. al. as "capto-dative" radicals. The term capto-dative describes the combined resonance effect imparted by an electron withdrawing (capto) and an electron donating (dative) group on a radical center. In the case of 1, the "capto" and "dative" groups are the carboxyl and amido substituents, respectively. The theoretical basis of the stabilizing effect of an electron donor and an electron acceptor group was postulated by Dewar in 1952. Later, the principle was recognized by Balaban who presented several examples of radicals which were stabilized by what was referred to as "push-pull" resonance. Katritzky et. al. independently developed the concept and coined the term "merostabilization". The name "capto-dative", however, appears to have been generally accepted to describe stabilization of this nature. A controversy over the "capto-dative" concept is whether the overall stabilizing effect of an electron donating and an electron withdrawing group is greater than the sum of the individual group effects: Although the debate continues it is clear that the stabilization of the radical
stems from the combined, but not necessarily potentializing, action of both substituents.

The facility of formation of $\alpha$-centered radicals is also reflected in the products of radical reactions of amino acid derivatives. Elad et. al. have reported photoalkylation reactions of amino acid derivatives as a means of modifying peptides$^{61-67}$. These reactions are exemplified by alkylations of the glycylglycine derivative $6^{63}$ with but-1-ene and with toluene. Irradiation with ultraviolet light of a mixture of 6 and but-1-ene in acetone at room temperature gave 7a and 8a, in yields of 17 and 14%, respectively. By substituting toluene for but-1-ene as the alkylating agent, 7b and 8b were formed in 26 and 35% yield, respectively.

\[
\begin{align*}
\text{CF}_3\text{CONH} & \text{CH} \rightarrow \text{CONH} \rightarrow \text{CH} \rightarrow \text{CO}_2\text{Me} \\
\text{R} & \\
\text{CF}_3\text{CONH} & \text{CH} \rightarrow \text{CONH} \rightarrow \text{CH} \rightarrow \text{CO}_2\text{Me} \\
\text{R} & \\
\text{CF}_3\text{CONH} & \text{CH} \rightarrow \text{CONH} \rightarrow \text{CH} \rightarrow \text{CO}_2\text{Me} \\
\text{8} & 
\end{align*}
\]

a) $R = \text{CH}_2\text{CH}_2\text{CH}_2\text{Me}$  
b) $R = \text{CH}_2\text{Ph}$  
c) $R = \text{CH}_2\text{CH(}\text{CH}_2\text{Me})\text{CH}_2\text{CH}_2\text{CH}_2\text{Me}$

The proposed mechanism of photoalkylation is as shown in Scheme 1. Acetone, through absorption of ultraviolet light, forms the corresponding triplet ketone. This species abstracts a hydrogen atom to form an $\alpha$-centered radical. With but-1-ene, the $\alpha$-
centered radical reacts by addition to the terminal carbon of the double bond. Supporting this mechanism was the detection of low molecular weight telomers, such as 7c and 8c. In reaction with toluene, the α-centered radical reacts by coupling with a benzyl radical, formed by hydrogen abstraction from toluene. The formation of bibenzyl, from coupling of benzyl radical, is consistent with the mechanism. In the absence of an alkylating agent, dehydrodimers of the amino acid derivatives were produced, presumably, from the coupling of the α-centered radicals.

Scheme 1
In a variation of the procedure\textsuperscript{64,67} visible light was used in conjunction with an \(\alpha\)-diketone photosensitizer and a peroxide, such as camphorquinone and di-\textit{tert}-butyl peroxide, respectively. In this case the hydrogen abstracting species is, presumably, alkoxy radical produced from reaction of peroxide with triplet \(\alpha\)-diketone. This was suggested from the lack of reaction in the absence of a peroxide.

Obata and Niimura\textsuperscript{68} employed di-\textit{tert}-butyl peroxide with ultraviolet light as photoinitiator in the dimerization of methyl \(N\)-
acetylglycinate 9a and methyl pyroglutamate 9b to give the corresponding dehydrodimers 10a and 10b. The dimerization process presumably involves combination of α-centered radicals formed by hydrogen atom transfer to tert-butoxy radicals, as shown in Scheme 2.

\[
\text{Me}_3\text{COOCMe}_3 \xrightarrow{h\nu} 2\text{Me}_3\text{CO}^* \\
\text{Me}_3\text{CO}^* + \text{R}^1\text{CONH}-\text{CH}-\text{CO}_2\text{Me} \rightarrow \text{Me}_3\text{COH} + \text{R}^1\text{CONH}-\text{C}^*\text{CO}_2\text{Me}
\]

\[
\text{R}^1\text{CONH}-\text{C}^*\text{CO}_2\text{Me} \rightarrow \text{R}^1\text{CONH}-\text{C}-\text{CO}_2\text{Me}
\]

\[
\text{R}^1\text{CONH}-\text{C}^*\text{CO}_2\text{Me} \rightarrow \text{R}^1\text{CONH}-\text{C}-\text{CO}_2\text{Me}
\]

(a) \( R^1 = \text{Me}, R^2 = \text{H} \)
(b) \( R^1, R^2 = \text{CH}_2\text{CH}_2 \)

Scheme 2

Formation of α-centered radicals have also been inferred from products of brominations of amino acid derivatives with \( N \)-bromosuccinimide under free radical conditions\(^{3,69-77} \). For example, treatment of the glycine derivative 11 with \( N \)-bromosuccinimide, with benzoyl peroxide as radical initiator, in carbon tetrachloride gave the α-bromoglycine derivative 12\(^{70} \) (Scheme 3).
The mechanism of bromination of reactive substrates with \( N \)-bromosuccinimide, which has been generally accepted, is as shown in Scheme 4.

\[
\begin{align*}
\text{RH} + \text{Br}^* & \quad \rightarrow \quad \text{R}^* + \text{HBr} \\
\text{HBr} + \text{NBS} & \quad \rightarrow \quad \text{Br}_2 + \text{succinimide} \\
\text{R}^* + \text{Br}_2 & \quad \rightarrow \quad \text{RBr} + \text{Br}^*
\end{align*}
\]

Scheme 4

This mechanism was originally postulated by Goldfinger and co-workers in 1953\textsuperscript{78}. Hydrogen atom abstraction by bromine atom from the substrate forms hydrogen bromide and the substrate radical. Hydrogen bromide reacts with \( N \)-bromosuccinimide to supply a constant but low concentration of molecular bromine. Bromine atom transfer from molecular bromine to the substrate radical affords the brominated product and bromine atom. The latter propagates the chain. Although alternative mechanisms have been proposed for brominations with \( N \)-bromosuccinimide, the fact that the bromination of 11 can also be effected with bromine
instead of $N$-bromosuccinimide\textsuperscript{70,71} indicates that the mechanism depicted in Scheme 4 probably applies for amino acid derivatives.

A characteristic of radical reactions of amino acid derivatives is the selective reactions of glycine residues. Of the $\alpha$-centered radicals detected upon the irradiation of proteins, the majority are glycyl radicals\textsuperscript{29}. They were identified by their electron spin resonance spectra which show a doublet with hyperfine splitting analogous to that exhibited by radicals 1 and 4.

The selective reaction of glycine residues was also observed in the photoalkylation procedure developed by Elad et al.\textsuperscript{61-67}. The general trend can be represented by the reactions of the derivatives of glycylalanine 13 and alanyl glycine 14\textsuperscript{65}. On irradiation with ultraviolet light in the presence of acetone and toluene, the selectivity for alkylation of the glycine residue was 7:1 in 13 and 20:1 in 14. When the alkylating reagent was but-1-ene, instead of toluene, the selectivity was 10:1 for 13 and 7:1 for 14.

\[
\begin{align*}
\text{Me} & \quad \text{CF}_3\text{CONH} - \text{CH}_2 - \text{CONH} - \text{CH} - \text{CO}_2\text{Me} \\
13
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CF}_3\text{CONH} - \text{CH} - \text{CONH} - \text{CH}_2 - \text{CO}_2\text{Me} \\
14
\end{align*}
\]
The preference for reaction of glycine residues under free radical conditions does not follow the general expectation that tertiary radicals should be formed more readily than secondary ones\textsuperscript{79}. This is because \(\alpha\)-centered glycyl radicals are secondary whereas the \(\alpha\)-centered radicals of \(\alpha\)-substituted \(\alpha\)-amino acid residues, such as alanine and valine, are tertiary. The greater reactivity expected of tertiary positions takes into account the greater relief of steric compression on formation of a tertiary radical compared to on formation of a secondary radical, and the greater stabilization, through hyperconjugation, of a tertiary radical relative to a secondary radical.

The phenomenon of the selective reaction of glycine residues in radical reactions was investigated through examining the relative rates of reaction of various amino acid derivatives with \(N\)-bromo-succinimide\textsuperscript{80,81} and di-\textit{tert}-butyl peroxide\textsuperscript{81}. It was found that the relative rates of reaction of 15\(a\), 15\(b\) and 15\(c\) with \(N\)-bromo-succinimide were 23 : 7.7 : 1\textsuperscript{80}. As the rate determining step of the reactions was shown to be \(\alpha\)-hydrogen atom transfer, the figures obtained are a reflection of the ease of formation of the corresponding \(\alpha\)-centered radicals 16\(a\), 16\(b\) and 16\(c\). Here, the \(\alpha\)-centered glycyl radical 16\(a\) was observed to be formed with greatest facility. This order of reactivity was also reflected in reactions with di-\textit{tert}-butyl peroxide\textsuperscript{81} where hydrogen abstraction is by \textit{tert}-butoxy radicals.
It was proposed that 16a is formed preferentially because it is more stable than either 16b or 16c, as a consequence of resonance. The greater stabilization was attributed to the ready ability of 16a to assume a planar configuration (Figure 3). This geometry maximizes overlap of the semi-occupied $p$-orbital of the radical with the $\pi$-systems of the amido and methoxycarbonyl groups. In contrast, the radicals 16b and 16c would be distorted out of planarity, due to non-bonding interactions. This retreat from planarity would, in turn, reduce the extent of orbital overlap and, as a consequence, stabilization through resonance. The radical 16c is less stable than 16b due to more severe steric interactions arising from its more bulky iso-propyl $\alpha$-substituent. This rationale that the reactivity of an amino acid moiety is checked by geometrical aspects of the product radical was reinforced by the relative rates of reaction of the methyl esters of $N$-benzoylsarcosine 17, pyroglutamic acid 18 and $N$-benzoylproline 19, with $N$-bromosuccinimide and di-tert-butyl peroxide, which when similarly considered were found to obey the hypothesis proposed\textsuperscript{81}.
Figure 3. Nonbonding interactions in planar conformations of radicals 16a, 16b and 16c.
Other factors apart from the selective reaction of glycine residues have been observed to affect the selectivity of radical reactions in amino acid derivatives. The reactivity of amino acid residues in peptides has been observed to be dependent upon the position of the residue in the chain\textsuperscript{65}. It has also been proposed that the conformation of a peptide can influence the selectivity of reaction\textsuperscript{65}.

In addition, the substituents, or lack thereof, on the \textit{N}- and \textit{C}-termini of an amino acid, or an amino acid derivative, can have a significant effect on the rate of formation of the corresponding \(\alpha\)-centered radical. For example, electron spin resonance studies of unprotected dipeptides have detected only the \(\alpha\)-centered radicals of the \textit{C}-terminal residues\textsuperscript{36,39-41,82}. Thus, the radicals formed from glycylglycine and glycylalanine are 4 and 5, respectively, but not the alternative \(\alpha\)-centered radicals 20 and 21. The selectivity of radical formation in 4 and 5 was attributed to the deactivating effect imparted by the aminium substituent to disfavor radical formation at the \textit{N}-terminal residues\textsuperscript{38,40}.

\[
\begin{align*}
&\text{H}_3\text{N}^-\text{CH}^-\text{CONH}^-\text{CH}_2\text{CO}^- \quad \text{Me} \\
&20 \\
&\text{H}_3\text{N}^-\text{CH}^-\text{CONH}^-\text{CH}^-\text{CO}^- \\
&21
\end{align*}
\]

The deactivating effect of the aminium group is also reflected in the fact that \(\alpha\)-centered radicals have been most frequently observed in reactions of amino acid derivatives, rather than with the unprotected zwitterionic analogues. Only when the amino group is not protonated have the radicals 22, 23 and 24, formed
from glycine, alanine and β-alanine, respectively, been detected in electron spin resonance studies\textsuperscript{38,83,84}. In these cases the amino substituent stabilizes the radical formed at the adjacent position.

\[
\begin{align*}
22 & \quad \text{H}_2\text{N} \text{--CH--CH}_2 \text{--CO}_2^- \\
23 & \quad \text{H}_2\text{N} \text{--CH--CO}_2^- \\
24 & \quad \text{H}_2\text{N} \text{--CH--CH}_2 \text{--CO}_2^-
\end{align*}
\]

Another relative substituent effect has been observed in the brominations of the \textit{N}-benzoyl- and the \textit{N}-phthaloylvaline derivatives, 15c and 25, respectively. Treatment of 25 with \textit{N}-bromosuccinimide in carbon tetrachloride, with irradiation by a 250W ultraviolet lamp, gave the corresponding β-bromovaline derivative 27\textsuperscript{85}. Presumably, the process involves formation of the β-carbon centered radical 26 through abstraction of the β-valyl hydrogen by bromine atom (Scheme 5). Subsequent bromine atom transfer from bromine to the radical 26 affords the product 27. The formation of the \textit{N}-phthaloyl-β-valyl radical 26 is in contrast to the formation of the \textit{N}-benzoyl-α-valyl radical 16c in the reaction of 15c\textsuperscript{80,81,90}. The relative deactivation of the α-position by the \textit{N}-phthaloyl group is akin to that by the aminium group, described above.
One of the aims of the work described in this thesis was to investigate methods for the selective bromination of glycine residues in peptides. Thus, radical brominations of \(N\)-benzoyl and \(N\)-phthaloyl protected peptides were investigated. The motive for studying two different protecting groups was to observe the effects of these substituents on the selectivity of reaction. The added influence of protecting group effects was considered a possible means of enhancing regiocontrol of bromination. The study of radical brominations of \(N\)-benzoyl peptides is described in Chapter 1 in the Results and Discussion section of this thesis. The investigation with \(N\)-phthaloyl peptides is described in Chapter 2. Prior to this investigation only the selective bromination of the glycine residue in \(N\)-benzoylglucylvaline methyl ester 28a to give the corresponding bromide 28b (Scheme 6) had been reported\(^80\).
The purpose of the selective bromination of glycine residues, in synthesis, is to provide a means for the selective modification of glycine residues in peptides. Derivatives of \( \alpha \)-haloglycine have met with widespread application in the synthesis of \( \alpha \)-amino acids\(^{23,69-77,86-89}\). They are utilized as facile electrophilic glycine equivalents which have been shown to be accommodating towards a variety of nucleophiles. These have included enamines\(^{71}\), Grignard reagents\(^{86}\), thioacetates\(^{69}\), anions of nitroalkanes\(^{23}\) and alkyl malonates\(^{87,88}\), trialkyl phosphites and phosphines\(^{70}\), diazomethane\(^{89}\), mixed cuprates\(^{72}\) and numerous others\(^{3,72,73}\) used in conjunction with Lewis acids.

The selective elaboration of glycine residues within a peptide would enable the preparation of peptides which might otherwise be difficult to construct. For example, the assembly of peptides which contain aspartic and/or glutamic acid residues has to be approached with care, the reason being that both the \( \alpha \)- and \( \omega \)-carboxyl groups
of these amino acids are reactive in peptide coupling reactions. That being the case, precautions have to be taken to ensure that only the carboxyl substituent required for coupling reacts. If such residues with multiple functionality were incorporated through modification of glycine residues, however, the problem of selective coupling would be circumvented. In addition, selective modification of glycine residues in peptides could enable the synthesis of peptides which contain residues that are unstable in their free state and, consequently, are not amenable to coupling reactions. Such is the case with $\alpha,\beta$-didehydro amino acids. Conversion of $\alpha$-haloglycine derivatives to derivatives of aspartic acid$^{87}$ and $\alpha,\beta$-didehydro amino acids$^{23}$ have been reported.

Although the aim of the selective bromination of glycine residues in peptides echoes the selective photoalkylation work of Elad et. al.$^{61-67}$, the synthetic potential of the bromination procedure is greater. This is because the $\alpha$-bromoglycine residue in a peptide should be susceptible to some, if not all, of the numerous techniques which have been developed for the modification of $\alpha$-haloglycine derivatives. The utility in synthesis of the methods developed in the investigation of the selective bromination of glycine residues in peptides, described in Chapters 1 and 2, was explored. The findings are presented in Chapter 3.

An examination of the factors governing the contrasting influences of the $N$-benzoyl and $N$-phthaloyl protecting groups on the selectivity of bromination, as evident by the reactions of $15c$,$^{80,81,90}$ and $25$,$^{85}$, forms another part of the work described in
this thesis. The factors which are known to affect the selectivity of hydrogen atom abstraction from carbon\textsuperscript{79} include:

(a) radical stabilization;

(b) steric effects;

(c) 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 effects can influence the regioselectivity of hydrogen abstraction in two ways. They can hinder the approach of the hydrogen abstractor as well as reduce stabilization of the product radical by constraining its conformation, as discussed above to account for the selective reaction of glycine residues. Polar effects refer to activating-deactivating effects, brought on by inductive and partial-charge stabilizing factors\textsuperscript{79,91}, in the transition state of the hydrogen abstraction step.

An example of polar effects taking precedent in the regioselectivity of reaction of amino acid derivatives is illustrated by the chlorination of 15c\textsuperscript{13,92}. It was observed that treatment of 15c with sulfuryl chloride in either benzene or carbon tetrachloride gave mixtures of the $\beta$-chlorovaline derivative 29 and the diastereoisomers of the $\gamma$-chlorovaline derivative 30. The reaction mechanism proposed involves $\beta$- and $\gamma$-hydrogen abstraction from 15c to form the radicals 31 and 32, respectively, followed by chlorine atom incorporation (Scheme 7).
The selectivity of reaction is in contrast to the bromination of 15c with N-bromosuccinimide, described above, which proceeded via the $\alpha$-centered radical 16c. The different selectivity of chlorination and bromination of 15c was attributed to the extent of development of radical character in the transition state of the hydrogen abstraction step. In chlorination the hydrogen abstractor is highly reactive electrophilic chlorine atom, which reacts via a transition state of little radical character. Under these circumstances reaction at the $\alpha$-position of 15c is disfavored by the inductively electron withdrawing amido and methoxycarbonyl substituents. Thus, reaction occurred at the $\beta$- and $\gamma$-positions. In bromination, hydrogen abstraction by bromine atom is via a transition state of greater radical character and, hence, is more influenced by radical stabilizing effects. Thus, bromination of 15c was selective for the $\alpha$-position due to the resonance stabilization of 16c by the amido and methoxycarbonyl moieties.
Polar effects have also been proposed to be involved in the biosynthesis of penicillin (Scheme 8). The mechanism of formation of the thiazolidine ring has been suggested and supported by various studies, to proceed via the formation of a \( \beta \)-valyl radical such as 34. The formation of the \( \beta \)-valyl radical 34, in preference to the corresponding \( \alpha \)-centered radical 35, has been postulated to be the result of polar effects disfavoring reaction of 33 at the \( \alpha \)-position.

Scheme 8
β-Hydroxyvaline 36 is a naturally occurring amino acid\textsuperscript{93-95} which has been found in the acid hydrolysate of the antibiotic berninamycin A\textsuperscript{96}. It is likely that the biosynthesis of 36 involves enzymic hydroxylation at the β-position of a valine residue in a peptide. There is evidence that such biological oxidations are radical in nature and it is possible that the regioselective β-hydroxylation is a reflection of polar effects\textsuperscript{97-100}.

Chapter 4 of this thesis describes the competitive bromination of a series of substrates with the aim of ascertaining the factor, or combination of factors, contributing to the contrasting effects imparted by the N-benzoyl and N-phthaloyl substituents. Chapter 5 describes an investigation into the application in synthesis of some of the results described in Chapter 4.

The extent to which an N-phthaloyl substituent disfavors reaction at the α-position of an amino acid residue is the subject of the study described in Chapter 6. Concurrently, the utility of the effect of the N-phthaloyl substituent as a method for selective side-chain functionalization of amino acid derivatives was examined. Such methods provide a means for the modification of amino acid side-chains through manipulation of the introduced functionality.
The chlorination and subsequent elaboration of the side-chains of some amino acids was described by Kollonitsch et al.\textsuperscript{101-103}. They named the procedure "C-derivatization of amino acids". The methodology is exemplified by the γ-chlorination of lysine 37 to give γ-chlorolysine 38, and the subsequent conversion of 38 to γ-hydroxylysine 39 (Scheme 9).\textsuperscript{103} The chlorination procedure involved ultraviolet irradiation of a concentrated hydrochloric acid solution of 37, at 70°, with the concurrent introduction of chlorine gas. Without ultraviolet irradiation no reaction was observed, which suggested a radical reaction mechanism. It was proposed that the α-position is deactivated to attack by electrophilic chlorine atom, by the strongly electron withdrawing α-aminium group. The range of the inductive effect is such that reaction occurs at the position farthest away from the aminium substituents.

![Scheme 9](image-url)
The methodology for side-chain modification through the elaboration of introduced functionality is complementary to the several examples of side-chain manipulations through exploitation of preexisting functionality. These include reactions utilizing the β-hydroxy group in serine\textsuperscript{104-107}, the elaboration of the alkenyl side-chain of allylglycine\textsuperscript{108-112} and modifications of aspartic and glutamic acid through the Barton decarboxylation technique\textsuperscript{15-19,113}. The philosophy of side-chain manipulation in synthesis is that the original configuration at the α-carbon of the amino acid is preserved. Thus, enantiomerically pure amino acids, which in the case of the proteinogenic forms are readily and cheaply available, can be used as substrates in the synthesis of rare and unnatural homochiral amino acids.

An examination of the use in synthesis of the techniques developed in the investigation of side-chain functionalization described in Chapter 6 is presented in Chapter 7.
Results and Discussion: Chapter 1
Bromination of N-Benzoyldipeptide Methyl Esters

Synthesis of Substrates
The dipeptide derivatives 28a, 40a-47a required for this study were prepared by coupling of the individual appropriately substituted amino acid derivatives, 48 and 49, as shown in Scheme 10.

Hippuric acid 48a was used as the N-terminal component in the dipeptides 28a, 40a, 44a-47a. The N-benzoylamino acid derivatives 48b, 48c and 48f, required for the synthesis of 41a, 42a and 43a, were prepared by the addition of benzoyl chloride to solutions of valine, alanine and leucine, respectively, under basic conditions.

The hydrochloride salts of the amino acid esters 49 were prepared by esterification of the appropriate amino acids in methanol, which had been pretreated with thionyl chloride. The amino acid esters 49 were generated upon treatment of the salts with triethylamine.

The chosen coupling procedure involved the use of ethyl chloroformate. This procedure was selected for its simplicity, availability of reagents required and comparable literature yields to other methods. Reaction of ethyl chloroformate with the carboxyl group of 48 under basic conditions, presumably, forms the mixed anhydride 50. The methyl ester 49 was subsequently introduced to react with 50 to yield the corresponding dipeptide.
*N*-Benzoylglycine methyl ester 15a was prepared by addition of thionyl chloride to a methanolic solution of 48a.

\[
\begin{align*}
\text{PhCONH—CH—CO}_2\text{H} & \quad \text{Cl} \quad \text{H}_3\text{N—CH—CO}_2\text{Me} \\
48 & \quad \text{ClCO}_2\text{Et}, \\
& \quad \text{Et}_3\text{N} \\
\text{PhCONH—CH—CO}_2\text{CO}_2\text{Et} & \quad \text{H}_2\text{N—CH—CO}_2\text{Me} \\
50 & \\
\text{PhCONH—CH—CONH—CH—CO}_2\text{Me} & \\
48, 49 & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th></th>
<th>40a</th>
<th>41a</th>
<th>42a</th>
<th>43a</th>
<th>28a</th>
<th>44a</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^1)</td>
<td>H</td>
<td>CH(Me)(_2)</td>
<td>CH(_2)CH(Me)(_2)</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>(R^2)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH(Me)(_2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>45a</th>
<th>46a</th>
<th>47a</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^1)</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>(R^2)</td>
<td>CH(_2)Ph</td>
<td>CH(_2)CO(_2)Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>48, 49</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^1, R^2)</td>
<td>H</td>
<td>CH(Me)(_2)</td>
<td>CH(_2)CH(Me)(_2)</td>
<td>CH(_2)Ph</td>
<td>CH(_2)CO(_2)Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

Scheme 10
Reactions of Substrates

The N-benzoyldipeptide methyl esters 28a, 40a-47a were found to be only sparingly soluble in carbon tetrachloride, which is the solvent commonly used in N-bromosuccinimide bromination reactions. Alternative solvents, which suitably dissolved the peptides 28a, 40a-47a, were investigated using N-benzoylglycine methyl ester 15a. When 15a was treated with N-bromosuccinimide in refluxing dichloromethane, under nitrogen, with irradiation by a 250W mercury lamp for 15 minutes, the $^1$H NMR spectrum of the crude reaction mixture, after solvent evaporation, had resonances identical to that of an authentic sample of 51, prepared under similar reaction conditions in carbon tetrachloride. Both spectra had a characteristic doublet at $\delta 6.65$ ($J = 10$ Hz), attributed to the $\alpha$-proton of 51. Although dichloromethane can, in principle, react with N-bromosuccinimide, presumably the high rate of bromination of the substrate 15a overcame competing solvent reactions. This result was a good indication that dichloromethane was a suitable solvent for brominations of reactive amino acid derivatives.

\[
\begin{align*}
\text{PhCONH} & \quad \text{CH} \quad \text{CO}_2\text{Me} \\
\text{Br} & \\
\end{align*}
\]

\[51\]

$N$-Benzoylglycylglycine methyl ester 40a was treated with one mole equivalent of $N$-bromosuccinimide in refluxing
dichloromethane, under nitrogen, with irradiation by a 250W mercury lamp, for 15 minutes. Analysis of an evaporated aliquot of the crude reaction mixture, by $^1$H NMR spectroscopy, showed a doublet resonance, at $\delta$ 6.94 ($J = 10$ Hz), attributable to the $\alpha$-proton of an $\alpha$-bromoglycine residue. The product was, however, not sufficiently stable for isolation.

To determine which of the two glycine residues of 40a had been brominated and to gauge the extent of conversion to the product, 1.5 mole equivalents of tri-$n$-butylstannyl deuteride, prepared by reduction of tri-$n$-butylstannyl chloride with lithium aluminium deuteride$^{114}$ (98% deuterium content), was added directly to the crude reaction mixture after cooling to room temperature. The deuteriated product 40c was isolated, after chromatography and recrystallization, in 67% yield based on 40a. The $^1$H NMR spectrum of 40c showed two sets of doublet resonances in an approximately 1:2 ratio, at $\delta$ 4.30 ($J = 5$ Hz) and $\delta$ 4.07 ($J = 6$ Hz), corresponding to the $\alpha$-proton of the $N$-terminal glycine residue and the $\alpha$-protons of the $C$-terminal glycine residue.

$$\text{PhCONH} - \text{CH} = \text{CONH} - \text{CH} - \text{CO}_2\text{Me}$$

40c

The mechanism of tin deuteride reduction of bromides$^{115}$ is as shown in Scheme 11. Bromine atom transfer from the substrate bromide to stannyl radical forms the substrate radical and stannyl
bromide. Deuterium atom transfer from stannyl deuteride to the substrate radical affords the deuteriated product and stannyl radical, which propagates the chain.

\[
\begin{align*}
R-\text{Br} & \quad + \quad R'_3\text{Sn}^* & \quad \rightarrow & \quad R^* & \quad + \quad R'_3\text{Sn-Br} \\
R^* & \quad + \quad R'_3\text{Sn-D} & \quad \rightarrow & \quad R-D & \quad + \quad R'_3\text{Sn}^*
\end{align*}
\]

Scheme 11

The location of the deuterium in 40c was determined by mass spectrometry. From a comparison of the mass spectrum of 40c with that obtained from 40a, run under identical conditions, the fragments containing deuterium could be identified by their one extra mass unit. In addition, the deuterium incorporation, as a percentage, could be calculated. The mass spectrometry data for 40c is as shown in Table 1. Limits to the accuracy of calculation of \(^2\text{H}_1\) incorporation were dependent upon signal intensity and baseline noise. It can be seen in Table 1 that the fragment with \(m/z\) 135 is the smallest fragment to contain deuterium. This information in combination with the \(^1\text{H}\) NMR data of 40c locates the deuterium to be on the \(\alpha\)-carbon of the \(N\)-terminal glycine residue. Consequently, the precursor bromide was assigned the structure 40b.

\[
\text{PhCONH} \quad \text{H} \\
\text{CH} \quad \text{CONH} \quad \text{CH} \quad \text{CO}_2\text{Me}
\]

40b
Table 1  Mass Spectrometry Data for 40c

<table>
<thead>
<tr>
<th>fragment</th>
<th>m/z</th>
<th>% $^2$H$_1$ incorporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCONHCHDCONHCH$_2$CO$_2$Me$^+$</td>
<td>251</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>PhCONHCHDCONHCH$_2$CO$^+$-</td>
<td>220</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>PhCONHCHDCO$^+$-</td>
<td>163</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>PhCONHCHD$^+$</td>
<td>135</td>
<td>65 ± 3</td>
</tr>
<tr>
<td>PhCO$^+$</td>
<td>105</td>
<td>0 ± 2</td>
</tr>
</tbody>
</table>

The percentage deuterium incorporation in 40c is a lower limit of the extent of conversion of 40a to the bromide 40b. The reason for this is because reactions which involve transfer of deuterium are influenced by kinetic isotope effects$^{116-118}$. Through these effects hydrogen atom is transferred in preference to deuterium atom. Two kinetic isotope effects affect the percentage of deuterium transferred in the deuteriation of 40b. The first is in the synthesis of the tri-$n$-butylstannyl deuteride used for the procedure. The active deuterium content of this reagent could not be accurately determined because the largest fragment detected in its mass spectrum corresponded to M$^+$-H/D. The second kinetic
Isotope effect is in the deuterium atom transfer from stannyl deuteride to the α-centered glycy1 radical 52 in the course of the reduction of the bromide 40b (Scheme 12).

\[
\begin{align*}
40b &\xrightarrow{\text{Bu}_3\text{Sn}} \text{PhCONH-CH-CONH-CH-CO}_2\text{Me} & H \\
&\xrightarrow{\text{Bu}_3\text{SnD}} \quad 40c
\end{align*}
\]

Scheme 12

Addition of methanol directly to a crude reaction mixture of the bromide 40b afforded the corresponding methoxy substituted adduct 40d in 62% yield, based on 40a. In the \(^1\)H NMR spectrum of 40d the methoxy substituent was represented by a singlet resonance with intensity equivalent to 3 hydrogens at \(\delta 3.48\). A doublet resonance at \(\delta 5.83\) (\(J = 8\) Hz) was attributed to the α-proton of the α-methoxyglycine residue. The location of the methoxy substituent was shown to be at the N-terminal residue by a signal at \(m/z 192\) in the mass spectrum of 40d attributable to the \(N\)-benzoyl-α-methoxyglycyl fragment (PhCONHCH(OMe)CO\(^+\)).

\[
\begin{align*}
\text{PhCONH-CH-CONH-CH-CO}_2\text{Me}
\end{align*}
\]

40d

The proposed mechanisms of methanol substitution are as depicted in Scheme 13. In Route 1, the facile elimination of
hydrogen bromide from the α-bromoglycine moiety 53 forms the very reactive acylimine 54. Addition of methanol to 54 affords the relatively stable α-methoxyglycine moiety 55. A direct substitution pathway, Route 2, is also possible. However, considering the reactivity of 54 and the facility of hydrogen bromide elimination from 53, contribution from the direct route is expected to be small.

\[
\begin{align*}
\text{Br} & \quad \text{MeOH} & \quad \text{OMe} \\
\text{CONH-CH-CO-} & \quad \text{Route 2} & \quad \text{CONH-CH-CO-} \\
\text{53} & \quad & \text{55} \\
\text{Route 1} & \quad -HBr & \quad \text{MeOH} \\
\text{CON=CH-CO-} & \quad & \text{54}
\end{align*}
\]

Scheme 13

The methoxy derivative 40d offered further information about the extent of conversion of 40a into 40b, and the selectivity of reaction. From the \(^1\text{H} \) NMR spectrum of the crude reaction mixture containing 40d, it was apparent that a small amount of 40a and a minor product was also present in addition to succinimide byproduct. After workup and chromatography on silica, the minor product was isolated and tentatively identified, by \(^1\text{H} \) NMR spectroscopy, as a 1:1 mixture of the two diastereomers of the dimethoxy substituted compound 56 (8\% yield).
The minor reaction of the C-terminal glycine residue of 40a, shown by this methoxylolation experiment, was not detected by the deuterium study. This is not unexpected when it is considered that the signals corresponding to M+ and M+-OMe in the mass spectrum of the dipeptide derivatives 40a and 40c are of very low intensity, as reflected by the large errors in percentage $^2H_1$ calculations of these signals shown in Table 1. These signals would be the only indication of the presence of the dideuteriated derivative 57, corresponding to reaction of the C-terminal glycine residue of 40a. Assuming that 57 was present in approximately 10% yield, in analogy to the yield of the dimethoxy derivative 56, the respective signals corresponding to M+ and M+-OMe, at m/z 252 and 221, were obscured by baseline noise. Reaction at the C-terminal glycine residue of 40a was also not detected in the crude bromination mixture, presumably, owing to a low signal-to-noise ratio.
The conditions employed in the bromination of 40a and the deuteriation and methoxylation techniques used for the subsequent characterization of the bromide 40b, described above, were standardized and utilized in the investigation of the other dipeptide derivatives 28a, 41a-47a. The principles of the derivatization techniques discussed above also apply in the investigation of 28a, 41a-47a.

Brominations of the N-benzoyldipeptide methyl esters 28a, 41a-47a were investigated. Formation of the corresponding bromides 28b, 41b, 42b and 44b-47b was detected by 1H NMR spectroscopic analysis of crude reaction mixtures, after solvent removal. The resonances attributed to the α-protons of the respective brominated glycine residues are presented in Table 2. Each of the bromides 41b and 46b was detected as a 2:3 mixture of diastereomers. The 1H NMR spectrum of the crude reaction mixture of 43a, after solvent removal, was, however, highly complex and no resonance corresponding to the α-proton of an α-bromoglycine residue was apparent.
Table 2 $^1$H NMR Spectral Data for 28b, 41b, 42b, 44b-47b

<table>
<thead>
<tr>
<th>δ</th>
<th>41b 6.60 (0.4 H, d, $J = 10$ Hz), 6.62 (0.6 H, d, $J = 10$ Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42b 6.45 (1 H, d, $J = 10$ Hz)</td>
</tr>
<tr>
<td>28b</td>
<td>6.70 (1 H, d, $J = 9$ Hz)</td>
</tr>
<tr>
<td>44b</td>
<td>6.95 (1 H, d, $J = 9$ Hz)</td>
</tr>
<tr>
<td>45b</td>
<td>6.90 (1 H, d, $J = 10$ Hz)</td>
</tr>
<tr>
<td>46b</td>
<td>6.95 (0.4 H, d, $J = 10$ Hz), 6.92 (0.6 H, d, $J = 10$ Hz)</td>
</tr>
<tr>
<td>47b</td>
<td>6.90 (1 H, d, $J = 10$ Hz)</td>
</tr>
</tbody>
</table>

Crude reaction mixtures of 28b, 41b, 42b and 44b-47b were treated *in situ* with tri-$n$-butylstannyl deuteride to afford the corresponding deuteriated derivatives 28c, 41c, 42c and 44c-47c. The yields for the deuteriated derivatives 28c, 41c, 42c and 44c-47c, based on 28a, 41a, 42a and 44a-47a, respectively, are given in Tables 3 and 4, together with the mass spectrometry data for 28c, 41c, 42c and 44c-47c.
Table 3  Yields and Mass Spectrometry Data for 41c and 42c

<table>
<thead>
<tr>
<th></th>
<th>% yield</th>
<th>% $^2$H$_1$ incorporation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M$^+$</td>
<td>PhCONHCHCONHCHDCO$_2$Me$^+$</td>
</tr>
<tr>
<td>41c</td>
<td>53</td>
<td>72 ± 7</td>
<td>78 ± 3</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>42c</td>
<td>51</td>
<td>51 ± 9</td>
<td>58 ± 2</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

Table 4  Yields and Mass Spectrometry Data for 28c and 44c-47c

<table>
<thead>
<tr>
<th></th>
<th>% yield</th>
<th>% $^2$H$_1$ incorporation</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M$^+$</td>
<td>M$^+$-CO$_2$Me</td>
<td>PhCONHCHD$^+$</td>
</tr>
<tr>
<td>28c</td>
<td>54</td>
<td>77 ± 4</td>
<td>79 ± 3</td>
<td>78 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>44c</td>
<td>36</td>
<td>81 ± 7</td>
<td>79 ± 3</td>
<td>79 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>45c</td>
<td>50</td>
<td>74 ± 7</td>
<td>-</td>
<td>75 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>46c</td>
<td>37</td>
<td>79 ± 4</td>
<td>-</td>
<td>79 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>47c</td>
<td>11</td>
<td>-</td>
<td>41 ± 3</td>
<td>40 ± 2</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>
The bromides 28b, 41b and 47b were also converted to the corresponding methoxy substituted derivatives 28d, 41d and 47d. The $^1$H NMR spectra of crude reaction mixtures, after solvent removal, showed twinning of resonances indicating that each of the methoxy derivatives 28d, 41d and 47d was formed as a 1:1 mixture of diastereomers The yields of 28d, 41d and 47d, based on 28a, 41a and 47a, respectively, and the $^1$H NMR spectral resonances of the methoxy protons and the $\alpha$-protons of the $\alpha$-methoxyglycine residues of 28d, 41d and 47d are given in Table 5.

\[
\begin{array}{c|cc}
\text{R}^1 & \text{R}^2 \\
\mid \mid \mid \\
\text{PhCONH} & \text{CH} & \text{CONH} & \text{CH} & \text{CO}_2\text{Me} \\
\end{array}
\]

<table>
<thead>
<tr>
<th></th>
<th>28d</th>
<th>41d</th>
<th>47d</th>
</tr>
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<tbody>
<tr>
<td>R^1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH(Me)2</td>
<td>OMe</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>R^2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>CH(Me)2</td>
<td>Me</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Yields and $^1$H NMR Spectral Data for 28d, 41d and 47d

<table>
<thead>
<tr>
<th></th>
<th>% yield</th>
<th>$\delta$ (total 3 H)</th>
<th>$\delta$ (total 1 H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41d</td>
<td>65</td>
<td>3.34 (s), 3.44 (s)</td>
<td>5.50 (d, $J = 9$ Hz), 5.57 (d, $J = 9$ Hz)</td>
</tr>
<tr>
<td>28d</td>
<td>73</td>
<td>3.53 (s)</td>
<td>5.80 (d, $J = 8$ Hz), 5.90 (d, $J = 8$ Hz)</td>
</tr>
<tr>
<td>47d</td>
<td>56</td>
<td>3.49 (s), 3.48 (s)</td>
<td>5.72 (d, $J = 8.4$ Hz), 5.79 (d, $J = 8.6$ Hz)</td>
</tr>
</tbody>
</table>
The low yield and degree of deuterium incorporation of 47c (Table 3) can be attributed to the instability of the bromide 47b, which is such that decomposition of 47b competes with its reduction by tri-n-butylstannyl deuteride. This rationale is supported by the relatively higher yield of the methoxy derivative 47d (Table 5). In fact consistently higher yields were obtained from derivatization with methanol compared to with tri-n-butylstannyl deuteride. This is, presumably, due the greater reactivity of the former towards α-bromoglycine residues. This relative reactivity was reflected in the duration required for the reactions to reach completion. When the extent of reduction and methoxylation was monitored by thin layer chromatography and 1H NMR analysis, the reactions of the bromides 28b, 40b-42b and 44b-47b with methanol were found to be complete in approximately 30 minutes at room temperature. In comparison the reductions with tri-n-butylstannyl deuteride required at least 4 hours. It can be reasoned that a higher percentage is converted by reaction with methanol before significant decomposition of the bromides 28b, 40-42b and 44-47b occurs. In addition, methanol, can react with the acylimine form 54 (Scheme 13), which might predominate if a significant amount of HBr is lost from the reaction mixture over time. To date, however, no literature account exists which reports reductions of imines by stannyl hydrides.

There remains no definitive explanation for the selectivity of bromination of the glycylglycine derivative 40a. The result indicates that the α-centered radical of the N-terminal glycine
residue 52 is formed in preference to that of the C-terminal glycine residue 58.

\[
\begin{align*}
\text{H} & \\
\text{PhCONH—CH—CONH—CH—CO}_2\text{Me} & \\
\end{align*}
\]

58

It was mentioned in the Introduction that peptide conformations can affect the selectivity of reaction\(^6\). It is known\(^1^{19},\)\(^1^{20}\) that dipeptides adopt preferred conformations, due to intra-molecular hydrogen bonding, in non-polar solvents such as dichloromethane. Therefore, it is possible that the selectivity of reaction, observed in 40a, is due to a particular conformation adopted by the dipeptide in dichloromethane. This conformation could favor reaction at the N-terminal residue as a result of steric and/or electronic factors. Alternatively, the difference in the reactivities of the N- and C-terminal residues of 40a could be due to the two glycine residues having different amino and carboxyl substituents.

The N-terminal bias is overridden in certain cases by the preferential reaction of glycine residues, as evident by the selective bromination of the C-terminal residue in 41a. Presumably, bromination is selective for a C-terminal glycine residue only if the preference for reaction of glycine residues is sufficiently great to overcome the N-terminal bias. Considering the low preference for formation of α-glycyl over α-alanyl radicals in bromination reactions, as discussed in the Introduction, the complex mixture of
products from the bromination of 43a can be attributed to reaction of the alanine residue69,121,122. The expected product bromide 59, after the initial loss of hydrogen bromide, can continue to react by addition of bromine, as shown in Scheme 14. The dibromide product 60 is, in turn, also prone to elimination of hydrogen bromide. Thus, this continuing process of hydrogen bromide elimination followed by bromine addition leads to the formation of a complex mixture of products.

![Scheme 14](image_url)

The low degree of deuterium incorporation of 42c can be attributed to 42a exhibiting a selectivity of bromination mediating that of 41a and 43a. The reactivity of the α-position of leucine
residues, in radical bromination, is expected to be greater than that of valine residues. This expectation is based on the rationale used to explain the greater reactivity of 15b over 15c, discussed in the Introduction. In the case of leucine, the main bulk of the iso-butyl α-substituent is spatially separated from the carbonyl oxygen of the N-benzyol substituent and, hence, intramolecular non-bonding interactions (Figure 4) are reduced. Reaction of the leucine residue would result in the type of reaction depicted in Scheme 14. This process would deplete the supply of N-bromosuccinimide to result in incomplete bromination of the glycine residue.

\[
\text{Figure 4. Non-bonding interactions in the planar conformation of the α-centered radical derived from an N-benzyolleucine moiety}
\]

From the reactions of 41a, 42a and 43a it is evident that the selectivity for bromination of C-terminal glycine residues in N-benzyoyldipeptide methyl esters is restricted. However, in a dipeptide where the glycine residue is at the N-terminal, mutual reinforcement of the two major factors governing selectivity in this system, which are the N-terminal bias of bromination and the preferential reaction of glycine residues, results. This explains the
generality in the selectivity of bromination observed in 28a, 44a-47a. The procedure described above, for functionalization of N-terminal glycine residues in dipeptides, as demonstrated, is accommodating towards a variety of C-terminal amino acid residues. The reactions of 28a, 44a, 45a, 46a and 47a illustrate this point with the residues of valine, leucine, phenylalanine, aspartic acid and alanine, respectively.

This method for the preparation of dipeptides with an α-haloglycine residue at the N-terminus is complementary to that used by Shiono and Harada for the synthesis of dipeptides with an α-chloroglycine residue at the C-terminal. The example they reported involved condensation of N-benzyloxy carbonyl-L-alaninamide 61 with methylglyoxylate hemiacetal 62, to form the α-hydroxyglycine derivative 63 (Scheme 15). This product was chlorinated with thionyl chloride to afford N-benzyloxy carbonyl alanyl-α-chloroglycine methyl ester 64. This procedure was later used by Castelhano et al. in the preparation of N-benzyloxy carbonyl phenylalanyl-α-chloroglycine methyl ester 65. In this instance N-benzyloxy carbonyl phenylalaninamide was employed as the substrate.
The regioselective bromination of glycine residues in dipeptides, described in this section, is an attractive option for the incorporation of an α-haloglycine residues into a peptide. The generality of the procedure for the preparation of dipeptide derivatives incorporating an N-terminal α-bromoglycine residue has been shown. The simplicity of the technique and the relatively high conversion to product demonstrate the viability of the method in synthesis.
Results and Discussion: Chapter 2
Bromination of N-Phthaloyldipeptide Methyl Esters

Synthesis of Substrates

The dipeptide derivatives 66a, 67a, 68, and 69 required for the study described in this section were prepared as shown in Scheme 16.

\[
\begin{align*}
\text{Phth} - \text{CH} - \text{CO}_2\text{H} & \quad \xrightarrow{70} \quad \text{R}^1 \quad \begin{array}{c} \text{H} \\ \text{Me} \end{array} \\
\text{Phth} - \text{CH} - \text{CO}_2\text{CO}_2\text{Et} & + \quad \text{H}_2\text{N} - \text{CH} - \text{CO}_2\text{Me} \quad \text{49} \\
\text{Phth} - \text{CH} - \text{CONH} - \text{CH} - \text{CO}_2\text{Me} & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>66a</th>
<th>67a</th>
<th>68</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>R(^1)</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>R(^2)</td>
<td>H</td>
<td>H</td>
<td>CH(Me)(_2)</td>
</tr>
</tbody>
</table>

\[ \text{Phth} = \]

Scheme 16
The preparation of \( N\)-phthaloylalanine 70b, required for the synthesis of 67a, was conducted utilizing an established procedure\textsuperscript{123} which involved heating an intimate mixture of phthalic anhydride and alanine to 150-160 °C and stirring the resulting melt within that temperature range for 30 minutes.

The dipeptide derivatives 66a, 68 and 69 were synthesized by coupling commercially available \( N\)-phthaloylglycine 70a with 49a, 49b and 49e, respectively. The dipeptide derivative 67a was prepared by coupling 70b with the methyl ester of glycine 49a. The coupling procedure utilized was similar to that described in Chapter 1, which involved the use of ethyl chloroformate.

The tripeptides 71a and 72a were formed by coupling \( N\)-phthaloylglycine 70a with the methyl esters of glycylglycine 73a and glycylvaline 73b, respectively (Scheme 17). The
hydrochloride salts of the methyl esters of the dipeptides 73a and 73b were obtained by stirring the dipeptides in methanol, which had been pretreated with thionyl chloride. Coupling of 70a to 73a and 73b was through the procedure using ethyl chloroformate, described in Chapter 1.
Reactions of Substrates

The N-phthaloylglycylglycine and alanylglycine derivatives 66a and 67a, respectively, were each treated with one mole equivalent of N-bromosuccinimide in refluxing dichloromethane, under nitrogen, and the reactions initiated by irradiation with a 250W mercury lamp. Although 66b and 67b were not sufficiently stable for isolation, their formation was detected by 1H NMR spectroscopic analysis of crude reaction mixtures, after solvent evaporation. The spectra of 66b and 67b each showed a doublet resonance attributable to the α-proton of the brominated glycine residue, at δ 6.60 (J = 10 Hz) for 66b and δ 6.56 (J = 10 Hz) for 67b.

The bromides 66b and 67b were characterized by preparation of the corresponding deuterio derivatives, 66c and 67c, as well as the corresponding methoxy derivatives, 66d and 67d. The principles and methods of derivatization of the bromides 66b and 67b are analogous to those used in the investigation described in Chapter 1. Thus, addition of methanol to crude reaction mixtures containing 66b and 67b gave the corresponding methoxy derivatives 66d and 67d. Their respective yields, based on 66a and 67a, and 1H NMR spectral data are given in Table 6. Treatment of the crude reaction mixtures of 66b and 67b with tri- n-butylstannyl deuteride afforded the corresponding deuteriated derivatives 66c and 67c. The respective yields of 66c and 67c, based on 66a and 67a, and their mass spectrometry data are presented in Table 7.
<table>
<thead>
<tr>
<th>R¹</th>
<th>66b</th>
<th>67b</th>
<th>66c</th>
<th>67c</th>
<th>66d</th>
<th>67d</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
<td>D</td>
<td>D</td>
<td>OMe</td>
<td>OMe</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Yields and $^1$H NMR Spectral Data for 66d and 67d

<table>
<thead>
<tr>
<th>% yield</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MeO-</td>
</tr>
<tr>
<td>66d 74</td>
<td>3.47 (3 H, s)</td>
</tr>
<tr>
<td>67d 72</td>
<td>3.45 (1.5 H, s)</td>
</tr>
<tr>
<td></td>
<td>3.47 (1.5 H, s)</td>
</tr>
</tbody>
</table>

Table 7 Yields and Mass Spectrometry Data for 66c and 67c.

<table>
<thead>
<tr>
<th>% yield</th>
<th>% $^2$H$_1$ incorporation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M$^+$</td>
</tr>
<tr>
<td>66c 73</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>67c 70</td>
<td>90 ± 4</td>
</tr>
</tbody>
</table>
The N-phthaloyldipeptide methyl esters 68 and 69 were each treated with one mole equivalent of N-bromosuccinimide in refluxing carbon tetrachloride, under nitrogen, and the reactions initiated by irradiation with a 250W mercury lamp. Carbon tetrachloride was used as solvent because it was found that 68 and 69 could be suitably dissolved. The use of carbon tetrachloride, as opposed to dichloromethane, reduces the likelihood of solvent reactions competing with substrate reactions.

The $^1$H NMR spectrum of the crude reaction mixture of 68 was complex but resonances corresponding to unreacted 68 were apparent. For the purpose of effecting complete consumption of 68 the amount of N-bromosuccinimide used was increased to 3 mole equivalents. The $^1$H NMR spectrum of the crude reaction mixture obtained utilizing excess N-bromosuccinimide was also complex, which suggested that a number of compounds were present. This was confirmed by thin layer chromatography of the reaction mixture on silica, which showed several components with closely resembling retention. No discrete products could be isolated from the mixture.

The reaction of the N-phthaloylglycylaspartic acid derivative 69 afforded a single product, which was assigned the structure 74. The didehydro derivative 74 was isolated after work-up and recrystallization in 81% yield. The $^1$H NMR spectrum of 74 showed a singlet resonance, with intensity equivalent to 1 hydrogen, at $\delta$ 5.57 attributable to the $\beta$-vinyl proton of the aspartic acid residue. The mass spectrum of 74 showed a molecular ion at $m/z$ 346 and
Elemental analysis data was consistent with the structure 74. There is some ambiguity as to the configuration of the $\alpha,\beta$-didehydro aspartic acid moiety in 74. Presumably, only one isomer is present because only one $^1$H NMR resonance for the vinyl proton was detected. To the extent that the Z-configuration is favored by $\alpha,\beta$-didehydroamino acid derivatives$^{23,124-126}$, the structure of the product was assigned as the Z-isomer 74.

```
MeO

H

Phth—CH—CONH—C—CO₂Me
```

74

Extending on the investigations of the N-phthaloyl-dipeptide methyl esters 66a, 67a, 68, 69 described above, brominations of the N-phthaloyl-tripeptide methyl esters 71a and 72a were studied.

It was found that the low solubility of 71a, in refluxing dichloromethane, required large amounts of solvent to effect dissolution. This prevented the use of the usual bromination procedure which, when tried, resulted in incomplete reaction due, presumably, to significant competing reactions of dichloromethane. This was evident from the bromination of 71a with 3 mole equivalents of N-bromosuccinimide, followed by treatment with tri-$n$-butylstannyl deuteride, to give 71c in 55% yield but with only 43% deuterium incorporation at the non-terminal glycine residue and 21% at the C-terminal glycine residue. The relative extent of
deuterium incorporation at the non- and C-terminal glycine residues suggests that there may be a slight preference for reaction of the non-terminal residue over the C-terminal residue. However, as the selectivity for the non-terminal residue is too low for practical applications, a decision to investigate concurrent bromination of the non-terminal and C-terminal glycine residues was made.

$$\text{Phth}-\text{CH}-\text{CONH}-\text{CH}-\text{CONH}-\text{CH}-\text{CO}_2\text{Me}$$

$$\begin{array}{c}
71 \\
\text{R} \quad \text{b} \quad \text{c} \\
\text{R} \quad \text{Br} \quad \text{D}
\end{array}$$

A modification to the bromination procedure, which entailed the portionwise addition of 4 mole equivalents of \textit{N-bromo-}
succinimide into a suspension of 71a, in refluxing dichloromethane, under nitrogen with irradiation, was attempted. Treatment of the crude reaction mixture with 3 mole equivalents of tri-\textit{n-}
butylstannyl deuteride gave the deuteriated compound 71c which was isolated in an overall yield of 55%. The mass spectrometry data for 71c is shown in Table 8. Extrapolating from 71c, the precursor bromide was identified as 71b.

The glyclyglycylvaline derivative 72a was treated with 1 mole equivalent of \textit{N-bromosuccinimide} in refluxing dichloromethane, under nitrogen, and the reaction initiated by irradiation with a 250W mercury lamp. The reaction afforded the bromide 72b which, although not sufficiently stable for isolation, was detected by $^1\text{H}$ NMR spectroscopic analysis of the crude
Table 8 Mass Spectrometry Data for 71c

<table>
<thead>
<tr>
<th>fragment</th>
<th>m/z</th>
<th>% ²H incorporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhthCH₂CONHCHDCONHCHDCO₂Me⁺⁻</td>
<td>335</td>
<td>90 ± 5 (²H₂)</td>
</tr>
<tr>
<td>PhthCH₂CONHCHDCO⁺⁻</td>
<td>245</td>
<td>97 ± 2 (²H₁)</td>
</tr>
<tr>
<td>PhthCH₂CONHCHD⁺⁻</td>
<td>218</td>
<td>97 ± 1 (²H₁)</td>
</tr>
<tr>
<td>PhthCH₂CO⁺⁻</td>
<td>188</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>CONHCHDCONHCHDCO₂Me⁺⁻</td>
<td>175</td>
<td>90 ± 2 (²H₂)</td>
</tr>
<tr>
<td>PhthCH₂⁺⁻</td>
<td>160</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

reaction mixture after solvent evaporation. The spectrum showed a doublet resonance attributable to the α-proton of the non-terminal α-bromoglycine residue at δ 6.65 (J = 10 Hz). Derivatization of 72b with methanol as well as with tri-n-butylstannyl deuteride gave, respectively, the methoxy derivative 72d, as a 1:1 mixture of diastereomers in 73% overall yield, and the deuteriated derivative 72c in 69% overall yield. The 300 MHz ¹H NMR spectrum of 72d showed two doublet resonances in a 1:1 ratio at δ 5.51 (J = 8.3 Hz) and 5.57 (J = 8.5 Hz), attributable to the α-proton of the α-methoxyglycine residue in each of the diastereomers and two singlet resonances in a 1:1 ratio, at δ 3.45 and 3.47, attributable to the protons of the α-methoxy substituent in each diastereomer. The mass spectrometry data for 72c is given in Table 9.
The preference for bromination of the C-terminal glycine residue in the N-phthaloylglycylglycine derivative 66a is in stark contrast to the selective bromination of the N-terminal glycine residue in the N-benzoylglycylglycine derivative 40a, described in Chapter 1. Also noteworthy, is the selective bromination of the glycine residue in the N-phthaloylalanylglycine derivative 67a when compared to the complex mixture of products obtained from

Table 9  Mass Spectrometry Data for 72c.

<table>
<thead>
<tr>
<th>fragment</th>
<th>m/z</th>
<th>% $^2$H$_1$ incorporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhthCH$_2$CONHCHDCONHCH(CHMe$_2$)CO$_2$Me$^+$</td>
<td>376</td>
<td>89 ± 8</td>
</tr>
<tr>
<td>PhthCH$_2$CONHCHDCONHCH(CHMe$_2$)$^+$</td>
<td>317</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>PhthCH$_2$CONHCHDCO$^+$</td>
<td>246</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>PhthCH$_2$CONHCHD$^+$</td>
<td>218</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>PhthCH$_2$CO$^+$</td>
<td>187</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>PhthCH$_2$+</td>
<td>161</td>
<td>0 ± 2</td>
</tr>
</tbody>
</table>
the reaction of N-benzyolalanylglycine derivative 41a with N-bromosuccinimide, discussed in Chapter 1. The high yields of 66c, 66d, 67c, and 67d, and the high percentage of deuterium incorporation in 66d and 67d, indicate that the selectivity of bromination for the respective C-terminal glycine residues of 66a and 67a is considerable. The comparative yields of 66d and 67c, and of 67d and 67c, suggest that the corresponding precursor bromides 66b and 67b are more stable under stannyl hydride reduction conditions than the bromides of the N-benzyldipeptides described in Chapter 1, where it was observed that the yields of deuteriated derivatives were consistently lower than those of methoxylated derivatives. The trend of the reactions of 66a and 67a suggests that reaction at the N-terminal residue is relatively disfavored, presumably, due to the effect of the N-phthaloyl substituent.

The mixture of products obtained from the bromination of 68 can be attributed to the selective reaction of the valine residue in spite of the fact that it has been reported that reaction of the valine derivative 15c with excess N-bromosuccinimide affords the dibromide derivative 7590. The proposed mechanism of reaction of 15c is as shown in Scheme 18. Hydrogen atom transfer to bromine atom from 15c forms the α-centered radical 16c. Bromine atom transfer to 16c forms the unstable α-bromo derivative 76. Elimination of hydrogen bromide across the carbon-nitrogen bond produces the acylimine 77, which tautomerizes to the α,β-didehydrovaline derivative 78. Addition of bromine to 78 gives the dibromide 75. Although extrapolation of this mechanism would
suggest that the corresponding dibromo dipeptide derivative should

be produced from the reaction of the valine residue in 68 with N-
bromosuccinimide. 15c and 68 are too disparate for direct
comparison. With 68, the products of reaction corresponding to 76,
77, 78 and 75 in the reaction of 15c might react differently
leading to a complex mixture of products.

The mechanism of formation of the α,β-didehydroaspartic acid
residue of 74 is, presumably, similar to the mechanism of reaction
of 15c, shown in Scheme 18. The difference being that the reaction
of the aspartic acid residue in 74 stops after formation of the α,β-
didehydro moiety. Presumably, the didehydro derivative 74 is not
susceptible to bromine addition because its extended conjugated
system would be disrupted in the process.
The selective reaction of the valine and aspartic acid residues in 68 and 69, respectively, shows that the extent of the N-phthaloyl substituent to disfavor reaction at the N-terminal residue is such that preferential reaction of non-glycine residues was exacted. The selectivity of reaction in 68 and 69 is in contrast to that of their corresponding N-benzoyl counterparts 28a and 46a described in Chapter 1, where reaction was selective for glycine residues.

The selective reactions of the tripeptide derivatives 71a and 72a show that the relative deactivating effect of the N-phthaloyl substituent extends to tripeptide derivatives. In 72a, the effect of the N-phthaloyl substituent combined with the preference for reaction of glycine residues over valine residues resulted in the selective bromination of a tripeptide with multiple glycine residues.

A comparison of the results described above and the findings described in the Chapter 1 clearly show that the selectivity of reaction in N-phthaloyl and N-benzoyleptide derivatives is complementary. In terms of the utility of the bromination procedure in synthesis, the shortcoming of the N-benzoyl system, as discussed in Chapter 1, is overcome in the N-phthaloyl system. The studies with N-benzoyl and N-phthaloyl dipeptide derivatives have established some factors which can be manipulated to influence the selectivity of radical brominations in peptide derivatives, thereby increasing regiocontrol over reaction. As a consequence the synthetic potential of this methodology for the direct introduction of the versatile bromide functionality into small peptides is augmented.
Results and Discussion: Chapter 3
Modification of α-Bromoglycine Residues in Peptides

From the work described in Chapters 1 and 2 of this thesis it was established that glycine residues could be selectively brominated in several small peptide derivatives. The investigation described in this section was aimed at using the selective bromination of glycine residues discussed in those Chapters as the first step in the synthesis of some dipeptide derivatives.

The preparation of dipeptide derivatives incorporating β-carboxyaspartic acid (Asa) residues 79 through modification of α-bromoglycine residues was investigated. The Asa residue was of interest because of its occurrence in nature. Asa was first identified in the ribosomal proteins of E. coli.\textsuperscript{127}. Because of its multiple carboxyl groups, Asa is difficult to incorporate into peptides using standard coupling procedures.

\[ HO-C \quad C-OH \]
\[ CH \]
\[ \text{---NH--CH--CO---} 79 \]

Previously, reactions of α-haloglycine derivatives with dialkyl malonate anions have been utilized in the synthesis of Asa derivatives\textsuperscript{87,88}. Using that approach, 41b, obtained from bromination of 41a, was treated in situ with 1.2 mole equivalents
of the sodium salt of diethyl malonate. The reaction afforded the two diastereomers of 80, in a 1:3 ratio. The ratio of diastereomers was inferred from the $^1$H NMR spectrum of the crude reaction mixture after solvent evaporation, which showed the methyl ester resonance of each of the diastereomers, at $\delta$ 3.73 and 3.77, in a 1:3 ratio. Following work-up of the reaction mixture, chromatography on silica and recrystallization, 80 was obtained in an overall yield of 18% as a 1:3 mixture of diastereomers. The $^1$H NMR spectrum of 80 showed a doublet of doublets resonance, attributable to the $\alpha$-proton of the Asa residue, at $\delta$ 5.36 ($J = 4, 9$ Hz). The mass spectrum of 80 had a molecular ion at $m/z$ 450 and elemental analysis data for 80 was consistent with the structure assigned.

\[
\text{CH(Me)}_2 \quad \text{CH(CO}_2\text{Et})_2
\]
\[
\text{PhCONH—CH—CONH—CH—CO}_2\text{Me}
\]

80

To complement the reaction of 41b, the bromide 28b, obtained from the bromination of 28a, was also treated in situ with the sodium salt of diethyl malonate. The reaction gave the dipeptide derivative 81 as a 1:1 mixture of diastereomers. The diastereomeric ratio was clearly shown in the $^1$H NMR spectrum of the crude reaction mixture, after solvent removal, by two methyl ester singlet resonances, at $\delta$ 3.66 and 3.75, of equal intensity. After work-up of the reaction mixture, chromatography on silica and recrystallization, 81 was isolated in 18% yield as a 1:1 mixture of diastereomers. The diastereomeric ratio was determined by $^1$H
NMR spectroscopic and HPLC analysis of 81. The $^1$H NMR spectrum of 81 had a multiplet resonance at $\delta$ 5.40 attributable to the $\alpha$-proton of the Asa residue. The mass spectrum of 81 had a molecular ion at $m/z$ 450 and elemental analysis data was also consistent with the structure 81.

\[
\begin{align*}
\text{PhCONH} & \text{CH} & \text{CONH} & \text{CH} & \text{CO}_2\text{Me} \\
\text{CH(CO}_2\text{Et})_2 & & \text{CH(Me)}_2
\end{align*}
\]

81

In addition to 81, a minor product and unreacted 28a were obtained as a mixture from chromatography of the crude reaction mixture. From $^1$H NMR spectral data, the minor product was tentatively identified as 82. A doublet resonance at $\delta$ 6.76 ($J = 9$ Hz) and a singlet resonance at $\delta$ 2.73, in a 1:4 ratio, were consistent with the $\alpha$-proton of the $\alpha$-succinimidoglycine residue and the methylene protons on the succinimide ring, respectively. The minor product 82 was calculated to be in less than 1% yield.

\[
\begin{align*}
\text{PhCONH} & \text{CH} & \text{CONH} & \text{CH} & \text{CO}_2\text{Me} \\
\text{O} & & \text{O} & & \text{CH(Me)}_2
\end{align*}
\]

82

The mechanism of reaction of an $\alpha$-bromoglycine residue with the anion of diethyl malonate is, presumably, as shown in Scheme 19. Reaction of the $\alpha$-bromoglycine residue 53 with the anion of
diethyl malonate or 83, forms the acylimine 54. This reactive intermediate is subsequently attacked by the anion of diethyl malonate to give the sodium salt 83. Aqueous work-up affords the residue 84. Formation of the minor product 82 is presumably through reaction of the acylimine 54 with the anion of succinimide 85, formed by reaction of succinimide with the anion of diethyl malonate (Scheme 20). Succinimide is present in the reaction mixture as a byproduct of the N-bromosuccinimide reaction used to generate the bromide 28b.

Scheme 19

Scheme 20
During the course of this work a radical allylation technique involving the use of allylstannanes was shown to be amenable to \( \alpha \)-bromoglycine derivatives\(^{22,128,129}\). The general reaction mechanism proposed\(^{130}\) is as shown in Scheme 21.

\[
RBr + Bu_3Sn^* \rightarrow R^* + Bu_3SnBr
\]

\[
R^* \quad \text{SnBu}_3 \rightarrow \quad R - \text{allyl} + Bu_3Sn^*
\]

Scheme 21

Bromine atom transfer from the substrate bromide to stannyl radical forms the substrate radical. Allyl group transfer from allylstannane to the substrate radical affords the allylated product and stannyl radical, which propagates the chain. The allylation procedure was investigated to study the viablity of the technique for elaboration of \( \alpha \)-bromoglycine residues in peptides, and also because allylglycine derivatives are of interest as mechanism-based enzyme inhibitors.

The bromide 45b was treated \textit{in situ} with two mole equivalents of allyltributylstannane, with a catalytic amount of azobisisobutyronitrile (AIBN) as radical initiator. The reaction afforded the allylglycylphenylalanine derivative 86 as a 1:1 mixture of diastereoisomers. The diastereomeric ratio was determined from the \( ^1H \) NMR spectrum of the crude reaction mixture, after solvent removal. The spectrum showed two methyl ester singlet resonances of equal intensity at \( \delta \) 3.69 and 3.74, corresponding to the two
diastereomers of 86. After chromatography on silica and recrystallization, 86 was obtained as an equal mixture of diastereomers in 34% yield. The 1H NMR spectrum of 86 showed several resonances in the region δ 5.5-7.0 characteristic for vinylic protons. The mass spectrum of 86 had a molecular ion at m/z 380 and a fragment corresponding to the loss of the phenylalanine residue at m/z 202. Elemental analysis data was also consistent with the structure 86.

![Chemical structure](image)

To investigate elaboration of an α-bromoglycine residue in an N-phthaloyl peptide derivative, the glycyl-α-bromoglycine derivative 66b was treated in situ with 2 mole equivalents of allyltributylstannane. The corresponding allylated product 87 was isolated after chromatography and recrystallization in 71% yield. The 1H NMR spectrum of 87 had a pattern of resonances in the δ 5.5-7.0 region similar to those of the allylglycylphenylalanine derivative 86. The mass spectrum of 87 had a molecular ion at m/z 316. The higher yield of 87 compared to that of 86 is, presumably, due to the greater stability of 66b compared to 45b.
The allylations of 45b and 66b show that the elaboration procedure with allyltributylstannane is amenable to both N- and C-terminal α-bromoglycine residues. Both N-benzoyl and N-phthaloyl substituents are tolerated.

The reactions of 41b and 28b with the anion of diethyl malonate, described above, show that diastereoselectivity in reactions of α-bromoglycine residues is an important aspect to consider if a chiral amino acid residue is present in the substrate. It can be inferred from the diastereomeric excess of the corresponding adducts 80 and 81 that the reaction of 41b was sterically controlled whilst the reaction of 28b was not. Since the chiral residue in both 41b and 28b is that of valine, it appears that the position of the chiral amino acid residue relative to the residue to be elaborated affects the diastereoselectivity of reaction. This postulate is supported by a review of the diastereoselectivity observed in elaboration reactions of the α-bromoglycine residue in 41b and 28b, and in bromination of the comparable 41a and 28a.

As discussed in Chapter 1, the bromide 41b, from the bromination of 41a, was detected as a 2:3 mixture of diastereomers. Bromination of 28a gave the bromide 28b as a 1:1 mixture of diastereoisomers, as evident from the 1H NMR spectrum of 28b,
which had two methyl ester singlet resonances at δ 3.73 and 3.75, of equal intensity. The diastereomeric ratio of the the bromides 41b and 28b can be misleading with regard to the diastereoselectivity of reaction. The reason is that α-bromoglycine residues undergo the equilibration shown in Scheme 13 in Chapter 1. The diastereomeric ratio could be the result of asymmetric induction during this process or during bromine atom transfer to α-centered glycdyl radical. Diastereoselectivity in bromine atom transfer from bromine is less likely considering the high exothermicity of the transfer process. Nevertheless, an unequal ratio of diastereomers does reflect an asymmetric environment about the site of reaction, be it an acylimine or a radical.

Deuterium transfer in the reduction of 41b with tri-n-butylstannyl deuteride proceeded with asymmetric induction as evident from the doublet resonances of the diastereomeric α-protons of the α-deuteroglycine residue of 41c, in an approximately 1:3 ratio, at δ 3.95 (J = 5 Hz) and 4.13 (J = 6 Hz) in the 300 MHz 1H NMR spectrum. The α-protons of the glycine residue of 28a were not seen to be diastereotopic by 300 MHz 1H NMR spectroscopy, and as a consequence no conclusion about the diastereoselectivity of formation of 28c can be drawn.

In Chapter 1, it was discussed that both the methoxy derivatives 41d and 28d were obtained as a 1:1 mixture of diastereomers, from 41b and 28b, respectively, by reaction with methanol.
In a separate study it was found that allylation of the bromides 41b and 28b with allyltributylstannane afford 88 and 89, as 1:1 and 1:3 ratios of diastereomers, respectively.

\[
\begin{align*}
\text{PhCONH} - & \text{CH} - \text{CONH} - \text{CH} - \text{CO}_2\text{Me} \\
\text{CH(Me)}_2
\end{align*}
\]

88

\[
\begin{align*}
\text{PhCONH} - & \text{CH} - \text{CONH} - \text{CH} - \text{CO}_2\text{Me} \\
\text{CH(Me)}_2
\end{align*}
\]

89

With the exception of methanol substitution all the reactions of 41a, 41b, 28a and 28b follow the trend discussed above, regardless of the ionic or radical nature of the reaction. In the radical reactions an \( \alpha \)-centered glycyl radical intermediate is produced whilst in the ionic reactions an acylimine intermediate is formed. The configurations of the \( \alpha \)-centered glycyl radical and the acylimine moiety are comparable as shown in Figure 5. The radical, through resonance has partial double bond character across the N-C\( \alpha \) bond. As a consequence, the relative conformation of the acylimine and radical moieties would be expected to be similar. The resemblance in the conformations of the two intermediates is a possible explanation for the diastereoselective trend being reflected in radical as well as in ionic reactions.
Figure 5. Configurations of an acylimine
and an α-centered radical moiety

The stereochemistry at the α-position prior to the formation of the
radical or acylimine intermediate is unimportant to the
diastereomeric outcome of the reaction as it is lost in the formation
of the intermediate. Hence, asymmetric conditions about these
planar intermediates would be the prerequisite for diastereoselectivity.

An asymmetric environment can be the result of a preferred
conformation of the dipeptide structure. As discussed in Chapter 1,
conformations of peptides are dictated, primarily, by intramolecular
hydrogen-bonding\textsuperscript{119,120} which are normally between amide
hydrogens and amide oxygens. The relation of hydrogen-bonding to
diastereoselectivity of reaction is supported by the non-diastereo-
selective reaction of 41b with methanol. Methanol being a protic
species together with the presence of hydrogen bromide, which is a
byproduct bromination and the substitution reaction with methanol,
would disrupt any hydrogen-bonding within the peptide derivative.
Therefore, it is plausible that the particular patterns of hydrogen-
bonding in the reaction intermediates 90-93 produces an asymmetric environment about the C-terminal residues of 90 and 91 but not about the N-terminal residues of 92 and 93.

\[
\begin{align*}
90 & : \text{PhCONH--CH--CON--CH--CO}_2\text{Me} \\
91 & : \text{PhCONH--CH--CON--CH--CH}---\text{CO}_2\text{Me} \\
92 & : \text{PhCON--CH--CON--CH--CO}_2\text{Me} \\
93 & : \text{PhCON--CH--CON--CH--CO}_2\text{Me}
\end{align*}
\]

The trend that only elaborations of C-terminal residues occur with asymmetric induction appears to extend to some other dipeptide derivatives. As described above, the allylation of the N-terminal α-bromoglycine residue in 45b proceeded without asymmetric induction. The deuteriation of the N-benzyolleucyl-α-bromoglycine derivative 42b, however, is sterically influenced as shown by the doublet resonances of the diastereomeric α-protons of the α-deuteroglycine residue of 42c in an approximately 1:2 ratio, at δ 4.01 (\(J = 5.4\) Hz) and 4.04 (\(J = 5.6\) Hz) in the 300 MHz \(^1\)H NMR spectrum.

An exception to the trend discussed above is the bromide 46b and the deuterated derivative 46c, derived from the N-benzyol-
glycylaspartate substrate 46a. As described in Chapter 1, the bromide 46b consists of a mixture of diastereomers in a 2:3 ratio. In the 300 MHz 1H NMR spectrum of 46c the diastereomeric α-protons of the α-deuteroglycine residue appear as two doublet resonances, at δ 4.12 (J = 6.5 Hz) and δ 4.25 (J = 5.6 Hz), in a 1:2 ratio. The N-benzoylglycylaspartate case is contrary to the trend above, presumably, because of a different pattern of hydrogen bonding arising from the β-carboxyl substituent of the aspartic acid residue.

In summary, the α-bromoglycine residue in dipeptide derivatives can be modified using methods previously developed for elaboration of α-haloglycine derivatives. The incorporation of Asa residues in 80 and 81 shows that amino acid residues with multiple functionalities can be constructed within an existing peptide. An important aspect in elaboration reactions of α-bromoglycine residues is that of asymmetric induction. Steric control is dependent upon the position of the residue with regard to the pattern of intramolecular hydrogen-bonding in the peptide. The exploitation of diastereoselective elaborations of dipeptide derivatives in synthesis has already been demonstrated in a related system by Shiono and Harada in the asymmetric synthesis of aspartic acid (Scheme 22). The addition of dialkyl malonate anions to the chloro-substrate 64, followed by hydrolysis, gave aspartic acid with enantiomeric excesses ranging from 29-48% dependent upon the alkyl moieties on the malonate anion. It should be noted that the diastereoselectivity in the reaction of 41b with the sodium salt of diethyl malonate is greater than that in the similar reaction
of 64, where the diastereomeric ratio obtained was approximately 1:2.

\[
\begin{align*}
\text{64} & \xrightarrow{\text{Na}^+ \text{CH\(\text{CO}_2\text{Et})_2\}}} \xrightarrow{\text{6N-HCl reflux}} \text{aspartic acid} + \text{alanine}
\end{align*}
\]

Scheme 22
Results and Discussion: Chapter 4
Investigation of the Contrasting Effects of
N-Benzoyl and N-Phthaloyl Substituents

Synthesis of Substrates

Compounds 15c, 94-96 were required for the study described in this section.

The N-benzoylglycine derivative 15c was available from the work described in Chapter 1 and the N-benzoyl-β-alanine derivative 94 was the generous gift of Ms. G. Rositano131. The N-phthaloylglycine derivative 95 was prepared by stirring commercially available N-phthaloylglycine in methanol, which had been pretreated with thionyl chloride. N-Phthaloyl-β-alanine 97, the precursor of 96, was obtained through direct fusion of a mixture of phthalic anhydride and β-alanine at 150-160 °C (Scheme 23). Treatment of a dilute methanolic solution of 97 with thionyl chloride gave 96.
Scheme 23
Reactions of Substrates

In this investigation of the contrasting effects of \(N\)-phthaloyl and \(N\)-benzoyl substituents in bromination of \(\alpha\)-amino acid derivatives, the following question was asked. Does the disparity stem from a) only the different extents of activation imparted by each of the two substituents on an adjacent position; or b) the combined influence of each of the \(N\)-substituents with the \(C\)-terminal substituent of an amino acid residue; or c) the concerted action of the two aspects above? To answer this question the reactions of 15c and 94-96 with \(N\)-bromosuccinimide were investigated and compared. The \(\beta\)-alanine derivatives 94 and 96, which have the \(N\)- and \(C\)-terminal substituents spacially separated, were chosen to examine the relative effects of the \(N\)-substituents acting individually whilst the glycine derivatives 15c and 94 were selected to study the combined effects of the \(N\)-substituents with the methoxycarbonyl group.

As described in Chapter 1, the bromination of 15c, in carbon tetrachloride, gave the bromide 51. The mechanism of this reaction was described in the Introduction.

The \(N\)-phthaloylglycine derivative 95 was treated with 1 mole equivalent of \(N\)-bromosuccinimide in refluxing carbon tetrachloride, under nitrogen, and reaction initiated by irradiation with a 250W mercury lamp. After 2 h, the \(^1\)H NMR spectrum of an aliquot of the reaction mixture showed a singlet resonance of low intensity at \(\delta 6.57\), which was in the vicinity calculated for the resonance of the \(\alpha\)-proton of the \(\alpha\)-bromoglycine derivative 98,
along with the much more prevalent resonances corresponding to unreacted 95. Consequently, the duration of reaction and the amount of N-bromosuccinimide was increased. After 48 h, the 1H NMR spectrum of the reaction mixture showed that approximately 50% conversion to the material presumed to be the bromide 98 had occurred. As significant decomposition was suggested by the complexity of the spectrum, the reaction was stopped.

Work-up of the reaction mixture followed by chromatography on silica afforded a fraction which comprised a mixture of 98 and 95, owing to the very similar retention of the two compounds. The 1H NMR spectrum of this mixture indicated that the ratio of product to 98 was approximately 1:1. The bromide 98 was isolated through repeated fractional recrystallization. The mass spectrum of 98 showed fragments corresponding to loss of M+ - OMe− at m/z 266 and 268, of equal intensity. The twinned nature of the fragments is characteristic of a bromide functionality owing to the two common isotopes of bromine.

\[ 95 \xrightarrow{Br^\ast} 99 \xrightarrow{Br_2} 98 \]

Scheme 24
The proposed mechanism of reaction of 95 is as shown in Scheme 24. Hydrogen abstraction from 95 forms the α-centered radical 99. Bromine atom transfer to 99 from bromine affords the product 98.

Bromination of 96 with 1 mole equivalent of N-bromosuccinimide was performed under similar conditions to those described in the previous example. The reaction was followed by analyzing aliquots of the reaction mixture, at intervals, by 1H NMR spectroscopy. All starting material was consumed after 2 h. Work-up of the reaction followed by recrystallization afforded the bromide 100 in 84% yield. The 1H NMR spectrum of 100 showed a doublet of doublet resonance, at δ 6.59 (J = 7.1, 8.0 Hz), attributable to the β-proton. Compared to the chemical shift of the β-protons of the substrate 96 the chemical shift of the β-proton of 100 constitutes a down field shift of Δδ 2.4 ppm. The magnitude of the shift is typical for incorporation of a bromo substituent\(^{132}\). The mass spectrum of 100 showed two molecular ions at m/z 311 and 313, which agrees with the incorporation of bromine, and elemental analysis data for 100 was also consistent.

![Scheme 25](image-url)
The proposed mechanism of this reaction is as shown in Scheme 25. Hydrogen atom transfer from the β-position of 96, produces the intermediate β-centered radical 101. Transfer of a bromine atom, from molecular bromine to 101, affords the product 100.

In a separate investigation\textsuperscript{133} it had been established that treatment of 94 with 2 mole equivalents of \textit{N}-bromosuccinimide in refluxing carbon tetrachloride, under a nitrogen atmosphere and with reaction initiated by irradiation with a 250W mercury lamp, gave the \textit{E} - and \textit{Z} - isomers of 102, in a 1:1 ratio. With 1 mole equivalent of \textit{N}-bromosuccinimide most of the substrate 94 was consumed but another product, identified as 103, was present along with predominant 102.
To formulate the mechanism of reaction of 94 with N-bromosuccinimide it is pertinent to consider the relative rates of reaction of 94 and 96. The relative reactivity of 94 and 96 was established by conducting a competitive reaction between the two substrates. The progress of the reaction was easily and conveniently followed by analysing aliquots of crude reaction mixtures by $^1$H NMR spectroscopy. Chromatographic techniques were not used for product analysis because the brominated products 100 and 102 were anticipated to be unstable under either HPLC or GLC conditions. A 1:1:1 mixture of 94, 96 and N-bromosuccinimide in refluxing carbon tetrachloride, under nitrogen, was irradiated with a 250W mercury lamp. Analysis of the $^1$H NMR spectrum of the reaction mixture, after 20 min, indicated that the reaction was incomplete. Resonances corresponding to 102, 103, and to unreacted 94 and 96 were present in the spectrum. An additional one mole equivalent of N-bromosuccinimide was introduced to the reaction mixture and the reaction allowed to proceed for a further 20 minutes. The $^1$H NMR spectrum of the final mixture contained only signals corresponding to 102 and unreacted 96. The result establishes that 94 is much more reactive than 96.

With the result of the competitive reaction between 94 and 96 above, the mechanism of reaction of 94 with N-bromosuccinimide is postulated to be as shown in Scheme 26.
Bromination is selective for the β-position, via the radical 104, to produce the intermediate bromide 105. The greater reactivity of the β-position, relative to the α-position in 94, can be reasoned from the higher rate of reaction of 94, compared to 96, and the regioselectivity of bromination of 96. Since the only difference between 94 and 96 lies in the nature of their N-terminal substituents, the reaction of 94, logically, occurs at the β-position. Subsequently, the bromide 105 eliminates HBr to produce the imine 106, which tautomerises to the didehydro species 103. The elimination of HBr was postulated to occur across the nitrogen-carbon bond rather than the carbon-carbon bond because the bromide 100, which has no amide hydrogen, does not undergo elimination-addition reactions of this type. Molecular bromine
addition to 103 produces the dibromide intermediate 107. Elimination of HBr and subsequent tautomerism affords the two isomers of the product 102. The isolation of the didehydro intermediate 103, from reaction with one equivalent of $N$-bromosuccinimide, lends support to the proposed mechanism.

To ascertain an order of reactivity of the substrates 15c and 94-96, competitive reactions were conducted between pairs of the amino acid derivatives, as described for 94 and 96 above.

The competitive bromination between 15c and 94 was performed using a 1:1:1 mixture of each and $N$-bromosuccinimide in carbon tetrachloride under refluxing conditions. After 20 minutes, the $^1$H NMR spectrum of the reaction mixture only showed resonances corresponding to the $\alpha$-bromoglycine derivative 51 and unreacted 94. This result indicated that 15c had reacted preferentially to 94.

The competitive bromination of 96 and 95 was conducted as described for 15c and 94. After 90 minutes, the $^1$H NMR spectrum of the reaction mixture showed only the presence of 100 and unreacted 95. Hence, 96 is more reactive than 95.

Therefore, from competitive reactions the order of reactivity of 15c and 94-96 is 15c > 94 > 96 > 95. The relative reactivity of each adjacent pair in the sequence is at least equal to the maximum ratio measurable within the limits of detection by $^1$H NMR spectroscopy. This limit was very conservatively estimated to be 10:1. Hence, this puts the relative rates of reaction at greater than 1000:100:10:1 for 15c:94:96:95.
This scale reflects the relative rate of formation of the corresponding intermediate radicals, \textbf{16c}, \textbf{104}, \textbf{101} and \textbf{99}.

The relative rates of formation of \textbf{101} and \textbf{104} imply that the \textit{N}-benzoyl substituent is more activating than the \textit{N}-phthaloyl substituent. From the relative rates of formation of \textbf{16c} and \textbf{104}, it can be extrapolated that since the \textit{N}-benzoyl substituent is common to both radicals, the methoxycarbonyl moiety in \textbf{15c} is more \textit{activating} towards bromine atom abstraction than the methylene in \textbf{94}. The relative rates of formation of \textbf{99} and \textbf{101} imply that since the \textit{N}-phthaloyl substituent is common to both radicals, the methoxycarbonyl moiety in \textbf{95} is more \textit{deactivating} towards bromine atom abstraction than the methylene in \textbf{96}.

To evaluate these inferences, the interplay of radical stabilizing and polar effects in the transition state of hydrogen abstraction by bromine atom\textsuperscript{91} must be considered. Hydrogen atom transfer to bromine atom involves a transition state of substantial radical character. This being the case, radical stability effects are significant. In addition, because of the electrophilic nature of bromine atom, polar effects would also exert an important influence.

The balance of radical stabilization and polar effects in the transition state of hydrogen abstraction by bromine atom has been pictorially depicted as in Figure \textit{6}\textsuperscript{79,134}. Contributor (a) is pertinent when evaluating polar effects, contributor (c) shows the importance of radical stabilization, whilst (b) is the composite of the two extremes when the hydrogen abstracting species is electrophilic in
nature and the transition state involves substantial development of radical character.

\[ R-H \cdot Br \rightarrow \delta^+ \rightarrow R-H \rightarrow Br \rightarrow \delta^- \rightarrow R-H \cdot Br \]

**Figure 6.** Transition state of hydrogen atom abstraction by bromine atom

An indication of the significance of contributor (b)\textsuperscript{135,136} is shown by the relative rates of bromination of \( \alpha \)-substituted toluenes (\( \phi CH_2X \)) with \( N \)-bromosuccinimide\textsuperscript{134}, in carbon tetrachloride at 77 °C, which fall in the order \( X = OMe > S\phi > O\phi > Me > \phi > OCOMe > H > Cl > CO_2Me > CN > Br > NO_2 \). These reactions correlate better to Hammett \( \rho \sigma^+ \) than to \( \rho \sigma \), with \( \rho = -2.46 \). The relatively high value of \( \rho \) and the order of the substituents indicate that, in this particular system, polar effects dictate reactivity. The correlation to \( \sigma^+ \) is expected when there is a similarity of the transition state to 108\textsuperscript{137}.

Hence, it has been proposed that there is substantial contribution from structure (b) \( \text{(Figure 6)} \)\textsuperscript{135,136} in the transition state of hydrogen abstraction by bromine atom. In the following
discussions about factors governing the relative effects of the \( N \)-benzoyl and \( N \)-phthaloyl substituents consideration will be given to partial charge stabilization concerned with the transition state contributor (b).

Consider first the greater rate of reaction of 94 over 96. It is expected that the greater bulk of the \( N \)-phthaloyl substituent in 96 would be marginally more sterically hindering than the \( N \)-benzoyl substituent in 94. Thus, steric considerations favor, to a small degree, the formation of 104 over 101.

With regard to radical stabilization, the \( N \)-benzoyl substituent is expected to be more activating than the \( N \)-phthaloyl substituent. This expectation is based on the principle that stabilization of radicals by nitrogen substituents arises from the delocalization of unpaired spin density through donation of an electron from the lone pair on nitrogen\(^{138}\) (Figure 7).

\[
\begin{align*}
\text{N} & \quad \text{C} \\
\text{N}^+ & \quad \text{C}
\end{align*}
\]

Figure 7. Resonance stabilization of radicals by nitrogen\(^{138}\)

Comparing an acylamino radical, such as 104, against a diacylamino radical, such as 101, the lone pair of electrons on the amide nitrogen is more available for stabilization of 104 than those on the imide nitrogen in 101. This is because the electrons on the amide
nitrogen are involved in resonance with only one carbonyl group instead of two in the imide system (Figure 8). Moreover, on generation of the acylamino radical 104 the conjugation of the system is extended whilst on generation of the diacylamino radical 104 cross-conjugation results.

![Resonance stabilization of acylamino and diacylamino radicals](image)

**Figure 8.** Resonance stabilization of acylamino and diacylamino radicals

An example of the greater radical stabilizing ability of a benzamide group compared to a phthalamide group, is shown by the relative rates of hydrogen abstraction, on a per hydrogen basis, by phenyl radical from the methyl substituents of 108 and 109; which was found to be 13:8.5. The phenyl radical displays low
polar requirements\textsuperscript{139,140} and, hence, its reaction is controlled by radical stabilizing effects. The relative magnitudes of these reaction rates, then, is a measure of the relative radical stabilizing ability of the two groups. However, because phenyl radical is much more reactive\textsuperscript{79} than bromine atom and, consequently, shows significantly less discrimination, the relative stabilizing effects of the benzamido and phthalimido groups are expected to be expressed to a greater extent by the relative rate of hydrogen abstraction by bromine atom.

\begin{center}
\includegraphics[width=7cm]{molecule.png}
\end{center}

In terms of inductive polar effects, both the \textit{N}-benzoyl and \textit{N}-phthaloyl substituents, in 94 and 96, respectively, are deactivating because of the inductively electron withdrawing nature of nitrogen. However, the \textit{N}-phthaloyl group is more deactivating because of its greater electron demand which is, presumably, associated with its additional inductively electron withdrawing carbonyl group. The greater electron withdrawal by the \textit{N}-phthaloyl substituent can be inferred from a comparison of the \textsuperscript{1}H NMR spectra of 94 and 96. The $\beta$-protons in 96 are $\Delta\delta$ 0.37 ppm downfield from those of 94. The greater deshielding of the former reflects the greater inductive electron withdrawal by the \textit{N}-phthaloyl group.
With regard to stabilizing the partial positive charge in the transition state of hydrogen abstraction, the N-benzoyl group in 94 is expected to be have greater capacity than the N-phthaloyl in 96 because the more available unpaired electrons of the amide nitrogen, compared to the unpaired electrons of the imide nitrogen, can be more easily supplied (Figure 8).

From the comparison of N-benzoyl and N-phthaloyl groups discussed above, it can be seen that all the factors which affect reactivity favor the activation of 94 over 96, which rationalizes the significantly greater reactivity of 94 over 96.

A comparison of 15c and 94 is in effect a comparison of two α-substituted benzamides. In 15c and 94, the α-substituents are a methoxycarbonyl and a methylene, respectively. The greater reactivity of 15c over 94 would arise from contributions from these α-substituents.

Since 15c is more reactive than 94, the influence of steric effects cannot be a determining factor because, from a steric aspect, reaction of 94 is expected to be favored over reaction of 15c, which is the inverse of the relative reactivity observed. Steric effects are expected to favor reaction of 94 because of the greater bulk, and hence, greater steric hinderence, of the methoxycarbonyl substituent of 15c compared to the methylene of 94.

In terms of radical stabilization, it is expected that the methoxycarbonyl group in 15c would be considerably more stabilizing, through resonance, than the methylene in 94, through hyperconjugation. As discussed in the Introduction, radicals of the
type 15c enjoy enhanced stabilization owing to extensive delocalization of the unpaired electron.

From a polar aspect, the relative reactivity of 15c and 94 is contrary to expectation because the methoxycarbonyl group of 15c is more deactivating than the methylene of 94. The relative deactivation of the methoxycarbonyl group is shown by the order of reactivities of α-substituted tolenes, listed above, where Me, a close representative of a methylene, is seen to be more activating than CO2Me in a system where reactivity is dictated by polar effects. However, in the α-substituted N-methylbenzamide system of 15c and 94 contributions from polar effects are expected to be significantly lower. This expectation is based on the resemblance of the N-methylbenzamide system to the benzyl methyl ether system, MeOCH2C6H4X, in which ρ = -0.35 for bromine atom abstraction of ring substituted derivatives141. This is in comparison to ρ = -1.0 observed in the diphenylmethane system142, C6H5CH2C6H4X, which is comparable to the α-substituted toluene system discussed above. The small ρ value of the benzyl methyl ether system is indicative of the small part played by polar effects. The diminished polar control has been attributed to partial charge stabilization in the transition state through electron supply to the carbon radical from oxygen (Figure 9). This effect could, conceivably, be duplicated by the benzamide nitrogen.
It can be concluded, then, that the greater reactivity of 15c over 94 is the result of enhanced radical stabilization afforded by the methoxycarbonyl group in 15c which overshadows the diminished, unfavorable, polar effects and the marginally greater steric hinderence in 15c.

With regard to 95 being less reactive than 96, the deactivating influence of the methoxycarbonyl substituent in 95, relative to the methylene in 96, can be partially attributed to steric effects. From without, the α-position, of 95 appears to be more sterically hindered than the β-methylene of 96. This factor would contribute to the overall deactivation of 95. The dominant steric factor, however, is expected to be in effect from within the radical 99, which arises from the second carbonyl on the imide ring (Figure 10). As in the alanyl and valyl radicals 16b and 16c, respectively, described in the Introduction, this type of intramolecular non-bonding interactions would distort the radical 99 out of planarity and resonance stabilization would be reduced80,81.
The deactivating polar effects of the methoxycarbonyl group in 95 is not expected to be significantly reduced in the transition state of hydrogen atom abstraction, as in 15c, because the lone pair of electrons on the imide nitrogen in 95 is not as readily supplied as the electrons on the amide nitrogen in 15c, as discussed above. Accentuating this aspect is the non-planar conformation of the radical 99, discussed above, which would hinder the electron supply in the transition state of its formation because the forming $p$-orbital of the radical would be misaligned with the orbital of the lone pair of electrons on nitrogen.

Thus, the lesser activation of 95 compared to 96 can be attributed to deactivating polar and steric effects in 95 overriding the reduced resonance radical stabilizing effect of the methoxy-carbonyl group.

Through collating the conclusions reached from the comparisons of 15c and 94-96, discussed above, it can be seen that the contrasting effects of $N$-phthaloyl and $N$-benzoyl substituents in
brominations of α-amino acid derivatives are a result of the disparity of activation imparted by the individual N-substituents, in conjunction with the influence of each of the N-substituents in combination with the C-terminal substituent. The governing factors are a) that the N-phthaloyl substituent is less activating than the N-benzoyl substituent; and b) that non-bonding interactions arising from the second carbonyl of the N-phthaloyl substituent reduce radical stabilization and accentuates polar control, through reducing stabilization of partial-positive charge, in the transition state of hydrogen abstraction.
Results and Discussion: Chapter 5
Modification of β- and γ-Amino Acid Derivatives

In Chapter 4 it was discussed that reaction of the $N$-phthaloyl-$\beta$-alanine derivative 96 with $N$-bromosuccinimide afforded the $\beta$-bromo derivative 100. The aims of the study described in this section were (a) to investigate the utility of 100 as a synthon for the preparation of $\beta$-substituted $\beta$-amino acids, and (b) to extend the procedure of modification adjacent to an $N$-phthaloyl substituent to $\gamma$-amino acids.

\[
\begin{align*}
\text{H}_3\text{N} & \quad \text{CH} \quad \text{CH}_2 \quad \text{CO}^-
\end{align*}
\]

β-Amino acids\textsuperscript{143} are widely distributed in animals and plants, as metabolites or as constituents in peptide antibiotics. One example is β-phenylalanine 110 which has been found in a number of cyclic peptides. These include the cyclotetrapeptide roccanin isolated from \textit{Roccella canariensis}\textsuperscript{144,145}, a toxic pentapeptide\textsuperscript{146}, cyclochlorotine, and a toxic metabolite islanditoxin, isolated from \textit{Penicillium islandicum}\textsuperscript{147}. It is also found in hydrolysates of the peptide antibiotic edeine D\textsuperscript{148}. Unnatural β-amino acids have been investigated as replacement residues in pharmacologically active peptides with the aim of imparting increased resistance to enzymic degradation or potentiation of activity\textsuperscript{143}. This approach has met with considerable success. An example is the replacement of the 7-
proline residue of bradykinin with the unnatural β-amino acid β-homoproline 111. It was found that the modified peptide was more resistant to dipeptidylcarboxypeptidase in vitro and in vivo, but had the same activity as the natural peptide.

\[
\begin{align*}
\text{H}_2\text{N} & \text{CH} \quad \text{CO}_2^- \\
\text{N} & \text{CH}_2 \quad \text{CO}_2^- \\
\text{CH}_2 & \text{CO}_2^- \\
\text{H}_2 & \text{N}
\end{align*}
\]  

111  

112

γ-Amino acids have attracted interest due, primarily, to the important role played by the most simple form γ-aminobutyric acid 112, commonly known as GABA. GABA is a major inhibitory neurotransmitter in the central nervous system, and various neurological disorders have been attributed to deficiencies of brain GABA. The breakdown of GABA is catalyzed by the enzyme GABA-T (E. C. 2.6.1.19). It has been shown that inhibition of this enzyme raises the level of GABA150. A number of syntheses of substituted γ-aminobutyric acids have been targetted at producing inhibitors of GABA-T. Some examples which have been shown to act as mechanism based inhibitors are γ-substituted forms such as 113 and 114151.

\[
\begin{align*}
\text{H}_3\text{N} & \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CO}_2^- \\
\text{H}_3\text{N} & \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CO}_2^- \\
\text{H}_3\text{N} & \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CO}_2^- \\
\text{H}_3\text{N} & \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CO}_2^- \\
\end{align*}
\]  

114  

113
The bromide 100 was prepared in multi-gram scale, as described in Chapter 4, and stored dessicated in a freezer. Under these conditions it was stable for several months. To assess the utility of 100 in the synthesis of β-amino acids it was of interest to determine the scope of reactions which could be accommodated by 100. Thus, various reactions which can be applied to modify a bromo-functionality were investigated.

Treatment of 100 with an excess of methanol in dichloromethane afforded the corresponding β-methoxy derivative 115 (Scheme 27) in 92% yield. The product 115 was identified based on a methoxy singlet resonance, at δ 3.39, and an ABX splitting pattern corresponding to the α-protons and the β-proton at δ 3.23 ($J_{\text{vic}} = 6.4$ Hz, $J_{\text{gem}} = 16.6$ Hz), 3.44 ($J_{\text{vic}} = 7.2$ Hz, $J_{\text{gem}} = 16.6$ Hz) and 6.59 ($J_{\text{vic}} = 6.4, 7.2$ Hz), in its $^1$H NMR spectrum, and a molecular ion at $m/z$ 263 in its mass spectrum. In addition elemental analysis data was also consistent with the structure 115.

Treatment of 100 with triethylamine in dichloromethane gave the α,β-didehydro-β-alanine derivative 116 in 87% yield (Scheme 28). The $^1$H NMR spectrum of 116 had two doublet resonances
attributable to the α- and β-vinylic protons, at δ 6.97 (J = 14.9 Hz) and 7.94 (J = 14.9 Hz), respectively. The trans-configuration of the olefinic bond was assigned on the basis of the coupling constant of the two vinylic protons. A coupling constant of 14.9 Hz is typical for trans-alkenes\textsuperscript{132}. A molecular ion at \textit{m/z} 231 in the mass spectrum of \textit{116} and consistent elemental analysis data confirmed the identity of the product.

\[ \text{Et}_3\text{N} \xrightarrow{\text{CH}_2\text{Cl}_2} \]

\[ \text{H} \]

\[ \text{Phth} \]

\[ \text{C} \]

\[ \text{C} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{H} \]

Scheme 28

The bromide 100 in neat methanol gave a mixture of the methoxy derivative \textit{115} and the cis-α,β-didehydro derivative \textit{117}. Separation of the two products by chromatography on silica gave \textit{115} and \textit{117}, in 74 and 11% yield, respectively. The \textsuperscript{1}H NMR spectrum of \textit{117} had two doublet resonances, each with intensity equivalent to one hydrogen, at δ 5.75 (J = 11.3 Hz) and 6.56 (J = 11.3 Hz), attributable to the α- and β-vinylic protons respectively. The cis-configuration was assigned based on the coupling constant between the vinylic protons of 11.3 Hz, which is within the range expected for cis-coupling\textsuperscript{132}. The mass spectrum of \textit{117} had a molecular ion at \textit{m/z} 231 and a fragmentation pattern closely resembling that of \textit{116}. 
The proposed mechanism of reaction of 100 in methanol is as shown in Scheme 29. The major reaction is direct substitution on the bromide 100 by methanol to give the methoxy derivative 115. The minor reaction involves E1 elimination of the bromide 100, promoted by the polar solvent to afford both the \textit{cis}-isomer 117 and the \textit{trans}-isomer 116. Addition of methanol to 116 is faster than to 117, to afford the methoxy substituted derivative 115, leaving behind 117. The slow reaction of 117 can be attributed to non-bonding interactions, between the \textit{N}-phthaloyl and the methoxycarbonyl substituents, (Figure 11) which distort the system out of planarity thereby reducing activation of the olefin.
The bromide 100 was treated with allyltributylstannane to investigate the possibility of its elaboration via a radical reaction. In refluxing carbon tetrachloride, with AIBN as radical initiator, no reaction of 100 was observed after 24 h. When the reaction was conducted in refluxing benzene, all of the bromide 100 was consumed within 48 h. The product of reaction, 118 was separated from residual stannyl components by repeated chromatography on silica. The $^1$H NMR spectrum of 118 had a pattern of vinylic proton resonances in the range $\delta$ 5.5-7.0, similar to those of 86 and 87 discussed in Chapter 3, which is characteristic of an allyl substituent. The yield of 118 was 36%.
The lack of reaction of 100 in carbon tetrachloride can be attributed to competing reaction of the halogenated solvent. Whereas reactions of α-bromoglycine derivatives with allyltributylstannane can be conducted in chlorinated solvents, the reaction of 100 cannot, presumably, because formation of the radical 101, as discussed in Chapter 4, is relatively unfavorable.

\[
\begin{align*}
\text{ArH} & + \text{RCONH-CCH-CO}_2\text{H} & \xrightarrow{\text{H}_2\text{SO}_4} & \text{RCONH-CCH-CO}_2\text{H} \\
120 & & & 119
\end{align*}
\]

Scheme 30

Ben-Ishai et. al. reported the synthesis of arylglycine derivatives 119, through arylation of α-hydroxyglycine derivatives 120 with various aromatic compounds using concentrated sulfuric acid\(^{152}\), as depicted in Scheme 30. This methodology was applied to the bromide 100 using benzene as the aromatic component. Thus, 100 was dissolved in benzene and the solution treated with concentrated sulfuric acid. Upon work-up of the reaction followed by chromatography on silica, 121 was obtained in 45% yield. The \(^1\)H NMR spectrum of 121 had an ABX pattern consisting of three doublet of doublet resonances, at \(\delta\) 3.26 \((J_{\text{vic}} = 5.7 \text{ Hz}, J_{\text{gem}} = 16.5 \text{ Hz})\), 3.81 \((J_{\text{vic}} = 10.1 \text{ Hz}, J_{\text{gem}} = 16.5 \text{ Hz})\) and 5.84 \((J_{\text{vic}} = 5.7, 10.1 \text{ Hz})\), attributable to the α-protons and the β-proton, respectively. Also present in the spectrum was a multiplet with intensity equivalent to five protons, at \(\delta\) 7.46, corresponding to the
phenyl substituent. The mass spectrum of the product 121 had a molecular ion at m/z 309.

![Structure of compound 121](image)

121

A minor fraction, which consisted of a mixture of at least two products, was obtained from chromatography of the above reaction mixture. One of these products was identified as the cis-didehydro derivative 117 from a comparison of the 1H NMR spectrum of the fraction with that of the authentic sample of 117, obtained as described above. Judging from the intensities of the resonances in the 1H NMR spectrum of the fraction, 117 comprised about half of the mixture. The other component, or components, could not be conclusively identified. The yield of the fraction was estimated to be less than 5%.

The reactions of the bromide 100 described above show that it is susceptible to a range of reactions. The reaction with methanol shows that 100 is susceptible to weak nucleophiles. The reaction of 100 with benzene in the presence of sulfuric acid is an example of Friedel-Crafts alkylation. The reaction of 100 with triethylamine is an example of E2 elimination, whilst in neat methanol E1 elimination is suggested. Allylation with allyltributylstannane is indicative of the amenability of 100 towards radical reactions.
With the aim of extending the procedure for modification adjacent to a \( N \)-phthaloyl substituent to \( \gamma \)-amino acids the methyl ester of \( N \)-phthaloylGABA 122 was prepared as shown in Scheme 31. \( N \)-PhthaloylGABA 123 was prepared by direct fusion of phthalic anhydride with GABA 112. Esterification of 123 in methanol which had been pretreated with thionyl chloride gave 122.

![Scheme 31](image)

The \( N \)-phthaloylGABA derivative 122 was treated with one mole equivalent of \( N \)-bromosuccinimide in refluxing carbon tetrachloride, with irradiation to initiate the reaction. The reaction was followed by analysing aliquots of the reaction mixture by \( ^1 \)H NMR spectroscopy. The formation of the bromide 124 was indicated by a triplet resonance, attributable to the \( \gamma \)-proton, at \( \delta 6.18 \) (\( J = 7 \) Hz). After 2 h the extent of bromination was approximated to be 70\%. At this point the reaction was stopped because decomposition or competing reactions, or both, were evident by the presence of unanticipated resonances in the \( ^1 \)H NMR spectrum. As
the bromide 124 was insufficiently stable for isolation its elaboration had to be conducted \textit{in situ}.

Thus, treatment of the crude reaction mixture of 124 with methanol gave the corresponding methoxy substituted derivative 125. The overall yield of the reaction, based on 122, was 52%. The $^1$H NMR spectrum of 125 showed a doublet of doublets resonance attributable to the $\gamma$-proton, at $\delta 5.34$ ($J = 5.9, 7.9$ Hz), and a singlet resonance attributable to the methoxy protons, at $\delta 3.35$. The mass spectrum of 125 showed a molecular ion at $m/z$ 277 and elemental analysis was consistent with the structure.

The preparation of 125 illustrates the viability of the methodology for incorporation of substituents at the $\gamma$-position of GABA.

In summary, the activating effect of the \textit{N}-phthaloyl protecting group, which can be exploited to effect bromination $\alpha$ to nitrogen, is a useful tool for the elaboration of non-$\alpha$-amino acids. The examples described above show that it permits modification of $\beta$-alanine and GABA. The elaborations of 100 described above are by no means a comprehensive study of the types of reactions which can be accommodated, and as a consequence the full scope of elaborative possibilities open to 100 is probably much greater.
Results and Discussion: Chapter 6
Bromination of N-Phthaloyl-α-Amino Acid Derivatives

Synthesis of Substrates

The N-phthaloylamino acid derivatives 126-132 were required for the study described in this section.

\[
\begin{align*}
\text{Phth} & \quad \text{CO}_2\text{Me} \\
R & \quad \text{CH}_2\text{CH} (\text{Me})_2 \quad \text{CH}_2\text{Ph} \quad \text{CH}_2\text{CO}_2\text{Me} \quad \text{CH}_2\text{Me} \\
126 & \quad 127 \quad 128 \quad 129 \\
R & \quad (\text{CH}_2)_2\text{CO}_2\text{Me} \quad \text{CH}_2\text{CHCH}_2 \quad (\text{CH}_2)_4\text{Phth} \\
130 & \quad 131 \quad 132
\end{align*}
\]

The aspartic acid derivative 128 and α-aminobutyric acid derivatives 129 were the generous gifts of P. Singh and G. Riddell, respectively. The compounds 126, 127, 131 and 132 were synthesized, as shown in Scheme 32. The N-phthaloyl derivatives 133a-d were prepared from L-leucine, L-phenylalanine, allylglycine and lysine, respectively, utilizing an established procedure\textsuperscript{123}, which involved heating an intimate mixture of phthalic anhydride and the appropriate amino acid to 150-160°C and stirring the resulting melt within that temperature range for 30 minutes. For the synthesis of 133a-c an equimolar mixture of phthalic anhydride and the corresponding amino acid was used. The L-leucine derivative 133a had $[\alpha]^{23D}_{D} -25^\circ$ and the L-phenylalanine derivative 133b had $[\alpha]^{23D}_{D} -211^\circ$. These values of optical rotation were consistent with those reported in the literature for the respective enantiomerically pure compounds\textsuperscript{1}. In the synthesis of the lysine derivative 133d two mole equivalents of phthalic
anhydride were used to effect phthaloylation at both the α- and ε-amino groups. The N-phthaloyl amino acid derivatives 13a-d were esterified by treating a dilute methanolic solution of each with thionyl chloride. The L-configured derivatives 126 and 127 had [α]$$^{23}_D$$ -23° and -212°, respectively.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>133</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>CH$_2$CH(Me)$_2$</td>
<td>CH$_2$Ph</td>
<td>CH$_2$CHCH$_2$</td>
<td>(CH$_2$)$_4$Phth</td>
</tr>
</tbody>
</table>

MeOH/ SOCl$_2$

126, 127, 131, 132

Scheme 32

The L-glutamic acid derivative 130 was prepared using the procedure developed by Kidd and King$^{153,154}$, which involved the condensation of phthalic anhydride with the diester of glutamic acid, followed by ring closure of the phthalamic acid intermediate 134 through treatment with methanolic hydrogen chloride (Scheme 33).
Scheme 33

\[ (\text{CH}_2)_2\text{CO}_2\text{Me} \rightarrow \text{CONHCHCO}_2\text{Me} \]

Reagents: phthalic anhydride, MeOH/\(\text{SOCl}_2\)
Reactions of Substrates

With the aim of investigating the extent of deactivation of the α-position, of an N-phthaloyl α-amino acid derivative, reactions of 126-132 with N-bromosuccinimide were studied.

N-Phthaloyl-L-leucine methyl ester 126 was treated with one mole equivalent of N-bromosuccinimide in refluxing carbon tetrachloride, under nitrogen, with irradiation by a 250W mercury lamp for 2 h. After work-up of the reaction mixture followed by chromatography on silica, the γ-bromo derivative 135 was isolated in 82% yield. The 1H NMR spectrum of 135 showed two methyl singlet resonances at δ 1.84 and 1.76 attributable to the respective protons of the 2 methyl substituents at the γ-position. Mass spectroscopic analysis of 135 gave molecular ions at m/z 353 and 355 of equal abundance. The twinned pattern is characteristic for a bromide functionality. Consistent elemental analysis data confirmed the γ-bromoleucine structure 135. The product 135 had [α]$_{D}^{23}$ -26°.
The mechanism of formation of the bromide 135 is postulated to be as shown in Scheme 34. Hydrogen abstraction from the γ-tertiary position of 126 produces the radical 136. Bromine atom transfer to this radical affords 135. It should be noted that the tertiary radical 136 is formed preferentially over the α-centered radical 137. The result is consistent with the bromination of the N-phthaloylvaline derivative 25, described in the introduction, and shows that hydrogen abstraction by bromine atom is preferential for a tertiary alkyl position over the relatively deactivated α-position of the N-phthaloyl amino acid moiety.

The N-phthaloylphenylalanine derivative 127 was treated with one mole equivalent of N-bromosuccinimide under similar conditions as described in the previous example. The reaction gave the two diastereomers of the β-bromophenylalanine derivative 138 in equal ratio. The diastereomeric ratio was inferred from the 1H NMR spectrum of the crude reaction mixture, which showed two singlet resonances in a 1:1 ratio, at δ 3.50 and δ 3.80, each corresponding to the protons of the methyl ester substituent of one of the diastereomers. The diastereomers of 138 were readily
separated by fractional recrystallization and were independently characterized. The mass spectrum of each diastereomer gave molecular ions of $m/z$ 390 and 388 of equal intensity. The $^1$H NMR spectrum of each diastereomer showed two doublet resonances, which are attributable to the $\beta$-proton and the $\alpha$-proton; at $\delta$ 5.42 ($J = 10$ Hz) and 5.95 ($J = 10$ Hz), corresponding to the diastereomer with methyl ester resonance at $\delta$ 3.50; and at $\delta$ 5.55 ($J = 10$ Hz) and 5.92 ($J = 10$ Hz), corresponding to the diastereomer with methyl ester resonance at $\delta$ 3.80. The separated diastereoisomers were isolated in 43 ([\(\alpha\)]$_{23}^o$ -161°) and 40% ([\(\alpha\)]$_{23}^o$ -60°) yields, corresponding to the diastereoisomers with the methyl ester resonances at $\delta$ 3.50 and $\delta$ 3.80, respectively.

![Scheme 35](image)

Formation of 138 is presumed to be as shown in Scheme 35. Hydrogen abstraction by bromine atom from the benzylic position generates the radical 139. Bromine atom transfer from bromine to 139 occurs with equal facility from either face of the radical to give
the two diastereoisomers of the bromide 138. The lack of asymmetric induction in the bromine atom transfer step can be attributed to the extremely low activation energy of such halogen transfer reactions\(^9\).

The aspartic acid derivative 128 was treated with \(N\)-bromosuccinimide under the aforementioned conditions. The \(^1\)H NMR spectrum of the crude reaction mixture after 12 h showed only resonances corresponding to unreacted 128. Recovery of 128 from the reaction was quantitative.

The reaction of 129 with \(N\)-bromosuccinimide, under similar conditions to those described for 128, was exceedingly slow. After 24 h a substantial amount of starting material still remained, as detected by \(^1\)H NMR spectroscopy. The spectrum was also highly complex suggesting a number of products were present. This was confirmed by analysis of the reaction mixture by thin layer chromatography which showed several components with closely resembling retention. Chromatography on silica failed to separate any discrete products for identification.

Treatment of the glutamic acid derivative 130 with \(N\)-bromosuccinimide under the conditions described for the previous examples returned mostly starting material. Slight decomposition was inferred from complex resonances of low intensity in the spectrum.

The reaction of the \(N\)-phthaloylallylglycine derivative 131 with \(N\)-bromosuccinimide required 2 mole equivalents of the latter
to effect complete consumption of 131. The $^1$H NMR spectrum of the crude reaction mixture was complex indicating a number of products. However, upon work up and chromatography only the $\alpha,\beta,\gamma,\delta$-tetrahydro derivative 140 was isolated. The yield of 140 was 46%. The $^1$H NMR spectrum of 140 had four sets of vinylic proton resonances at $\delta$ 7.62 (d, $J = 11.2$ Hz), 6.35 (m), 5.83 (d, $J_{\text{trans}} = 11.3$ Hz) and 5.63 (d, $J_{\text{cis}} = 10.0$ Hz), attributable to the $\beta$-proton, the $\gamma$-proton and the two $\delta$-protons, respectively. The coupling between the $\delta$-proton resonances is, presumably, 0-Hz, which is within the range (0-3.5 Hz) expected for vinylic protons in a geminal relationship$^{132}$. The mass spectrum of 140 showed a molecular ion at $m/z$ 257. The Z-isomer of 140 is proposed because this configuration is generally favored by $\alpha,\beta$-didehydro amino acid derivatives.$^{124-126}$ The all transoid configuration of the extended conjugated system is assumed based on the preferred geometry of such systems and the inactivity of 140 towards maleic anhydride under Diels-Alder cycloaddition conditions, which requires the diene component to be in a cisoid configuration.

The moderate isolated yield of 140 can be attributed to the facility with which the product 140 polymerizes. Significant polymerization was responsible for the loss of a considerable amount of 140 during chromatography. Considering that 140 is an extensively conjugated ester, its tendency towards polymerization is not unexpected. Compound 140 resembles methyl acrylate 141, which is known to readily polymerize.
The initial observation of several products in the reaction mixture can be explained by considering the nature of allylic brominations. Hydrogen abstraction of a β-hydrogen from 131 produces the resonance stabilized radical 142, as shown in Scheme 36. Bromine atom transfer to 142 would afford four products. With regard to 142a, bromine atom transfer to the radical would form the two diastereoisomers of the β-bromoallylglycine derivative 143. Considering 142b and 142c, bromine atom transfer to the radical would give the corresponding trans- and cis-β,γ-didehydro derivatives 144 and 145. Elimination of hydrogen bromide from the brominated compounds 143, 144 and 145, which is expected to be facile, probably occurred upon work-up of the reaction. The driving force of the eliminations is, presumably, the formation of the extensively conjugated derivative 140.
Scheme 36
Bromination of the \( N_\alpha, N_\varepsilon \)-diphthaloyllysine derivative 132 was selective for the \( \varepsilon \)-position to give the bromide 146. Although this product was insufficiently stable for isolation its formation was detected by \( ^1\)H NMR spectroscopic analysis of the crude reaction mixture. A triplet resonance attributable to the \( \varepsilon \)-proton of 146 was at \( \delta \) 6.12 \((J = 7.5 \text{ Hz})\). The approximately \( \Delta \delta \) 2.5 ppm shift downfield, from \( \delta \) 3.65 \((J 6 \text{ Hz})\) of the \( \varepsilon \)-protons of 146, is characteristic for incorporation of a bromo substituent\(^{132}\).

\[
\begin{align*}
\text{Phth} & \quad \text{Phth} \\
\text{CH} & \quad \text{CH} \\
\text{Br} & \quad \text{OMe} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Scheme 37

The corresponding methoxy derivative 147 was prepared by treatment of the crude reaction mixture containing 146 with methanol. On work-up and purification by chromatography, 147 was isolated in 56\% yield as a 1:1 mixture of diastereomers. The \( ^1\)H NMR spectrum of 147 showed a triplet resonance with intensity equal to one proton, at \( \delta \) 5.23 \((J = 7.4 \text{ Hz})\), attributable to the \( \varepsilon \)-proton. By 300 MHz \( ^1\)H NMR spectroscopy, the methyl ester singlet
resonance of each of the diastereomers of 147 was just resolved, at δ 3.72 and at δ 3.73, in a 1:1 ratio.

From collation of the results discussed above it can be concluded that bromination of 126, 127 and 131, together with the bromination of 25, discussed in the Introduction, show that the extent to which the α-position of an N-phthaloyl amino acid derivative is deactivated permits selective bromination at tertiary, benzylic and allylic positions on the side-chain. As discussed in Chapter 4, the N-phthaloyl substituent, in isolation, is more activating than in combination with a methoxycarbonyl group. This is, again, illustrated in the selective bromination of the \(N_\alpha, N_\varepsilon\)-dipthaloylllysine derivative 132. The bromination of tertiary, benzylic and allylic positions, and positions α to nitrogen, mentioned above, do not give an indication of the full extent of deactivation afforded by the N-phthaloyl substituent because these features are relatively activated towards bromination.

With regard to the N-phthaloyl aspartic acid derivative 128, the β-position is deactivated towards hydrogen abstraction by bromine atom by the β-methoxycarbonyl substituent. The deactivating action of the methoxycarbonyl substituent is illustrated in the list of reactivities of α-substituted tolenues described in Chapter 4. The absence of reaction with 128 shows the extreme extent to which the α-position is deactivated. Whereas the N-phthaloylglycine derivative 95 reacted to a limited degree, as discussed in Chapter 4, 128 is effectively inert.
It can be suggested that α-substituents can add to the deactivation of the α-position of N-phthaloyl substituted amino acid derivatives. This proposal is based on the rationale used to explain the greater reactivity of the glycine derivative 15a compared to the valine and alanine derivatives 15b and 15c, respectively, discussed in the Introduction. The added non-bonding interactions of the α-substituent with a carbonyl oxygen of the N-phthaloyl substituent (Figure 12) would lead to greater distortion of the system out of planarity thereby accentuating the deactivating factors present in the N-phthaloyl system, discussed in Chapter 4.

![Figure 12. Non-bonding interactions in the planar conformation of the α-centered radical of an α-substituted N-phthaloyl-α-amino acid derivative.](image)

The distortion from planarity of a N-phthaloyl-α-amino acid derivative on formation of a sp2 hybridized α-carbon is shown by
the crystal structure of \( N \)-phthaloyl-\( \alpha,\beta \)-didehydrovaline methyl ester 148 (Figure 13). It can be speculated that the configuration adopted by 148 in crystal form is also assumed in solution. As can be seen, the \( N \)-phthaloyl substituent is almost perpendicular to the plane of the conjugated ester moiety. From the stability of 128 towards \( N \)-bromosuccinimide it can be reasoned that the \( \alpha \)-positions of \( N \)-phthaloyl-\( \alpha \)-substituted amino acid derivatives are inert under normal bromination conditions.

\[ \text{Me} \quad \text{Me} \]
\[ \text{Phth} \quad \text{CO}_2\text{Me} \]

148

For synthesis, refer Chapter 7. For bond-distances and bond-angles refer to the Appendix.
Extending this reasoning it can be suggested that the 
N-phthalooyl-α-aminobutyric acid derivative 129 reacts at the 
β-position rather than at the γ-position because a secondary position 
is expected to be more activated than a primary position, whilst the 
α-position is effectively inert. Nevertheless, a dialkyl substituted 
methylene is very unreactive towards bromine atoms. In carbon 
tetrachloride at 77 °C, in relation to atrialkyl substituted methine, 
such as the tertiary centers in 25 and 126, a methylene is 
approximately 90 times less reactive\textsuperscript{79}. That being the case, the 
complex mixture of products from the reaction is not entirely 
unexpected because (a) the slow rate of bromination of 129 could 
be matched by the rate of decomposition of the product bromide; 
and (b) the brominated product could be as, if not more, reactive 
than 129. The latter posssibility can be extrapolated from the 
relative selectivities for bromination of n-butyl bromide\textsuperscript{155}, which is 
shown in Figure 14. The markedly increased reactivity at C-2 has 
been proposed to be the result of the β-bromo substituent 
providing anchimeric assistance for hydrogen abstraction\textsuperscript{155}, as 
shown in Figure 15. Thus, if bromination of 129 occurred at the β-
position, the bromo substituent would activate the adjacent γ-
position toward reaction.

\[
\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{Br} \\
2.2 \quad 12.7 \quad 1.4
\]

**Figure 14.** Relative selectivities for 
bromination of n-butyl bromide.
Figure 15. Anchimeric assistance provided by a β-bromo substituent.

The N-phthaloylglutamic acid derivative 130 was unreactive towards N-bromosuccinimide because the β-position is secondary and the γ-position is deactivated by the γ-methoxycarbonyl substituent.

The work described in this section shows that, through the deactivation of the α-position of an amino acid moiety by a N-phthaloyl substituent, bromination at remote positions on the side-chain can be effected. With regard to the optically active bromides 135 and 138, the functionalized products have the potential to be used as chiral synthons.
Results and Discussion: Chapter 7
Modification of Brominated N-Phthaloyl-α-Amino Acid Derivatives

The study described in this section was aimed at synthesis of uncommon α-amino acid derivatives through elaboration of the brominated valine and leucine derivatives, 27 and 135, respectively. The bromoleucine derivative 135 was available from the study described in Chapter 6. The bromovaline derivative 27 was synthesized as shown in Scheme 38.

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \begin{array}{c}
\text{H}_3\text{N} \\
\text{CH} \\
\text{CO}_2
\end{array} \rightarrow \begin{array}{c}
\text{Phthalic anhydride} \\
\Delta
\end{array} \begin{array}{c}
\text{Me} \\
\text{CO}_2 \text{H}
\end{array} \]

\[ \text{MeOH} \rightarrow \text{25} \]
\[ \begin{array}{c}
\text{MeOH} \\
\text{SOCl}_2
\end{array} \rightarrow \begin{array}{c}
\text{NBS/} \text{hv}
\end{array} \]

Scheme 38

*N-Phthaloxyvaline* 149 was obtained by heating an intimate equimolar mixture of valine and phthalic anhydride to 140-150 °C and stirring the resulting melt within that temperature range for 30 minutes\(^{123}\). Esterification of 149 was effected by treating a methanolic solution of 149 with thionyl chloride. The methyl ester of *N*-phthaloxyvaline 25 was treated with *N*-bromosuccinimide in refluxing carbon tetrachloride for 2 h, under nitrogen, with irradiation by a 250W mercury lamp to afford the β-bromovaline derivative 27.
Treatment of 27 with sodium hydride in tetrahydrofuran afforded the α,β-didehydrovaline derivative 148 in 87% yield. The $^1$H NMR spectrum of 148 showed two singlet resonances, each with intensity equivalent to three hydrogens at δ 1.89 and 2.42, attributable to the respective protons of the two β-methyl substituents. The mass spectrum of 148 showed a molecular ion at $m/z$ 259 and elemental analysis data was consistent with the structure 148.

The mechanism of reaction is presumed to be as shown in Scheme 39. Hydride ion removes the more acidic α-hydrogen in preference to the γ-hydrogens. The mechanism of reaction could be concerted E2 elimination (Route 1) or stepwise ElcB (Route 2), the latter via the generation of the anion 150 followed by elimination of bromide. The synthesis of 148 is of interest because α,β-didehydroamino acid derivatives are inhibitors of pyridoxal phosphate-dependent enzymes.156
Treatment of 27 with sodium hydride in tetrahydrofuran afforded, after chromatography on silica, the \( \alpha,\beta \)-methanovaline derivative 151 in 67% yield. The \(^1\)H NMR spectrum of 151 had two singlet resonances, each with intensity equivalent to three hydrogens at \( \delta \) 1.20 and 1.51, attributable to the respective protons of the two \( \gamma \)-methyl substituents. The spectrum also showed two doublet resonances, at \( \delta \) 1.52 \((J = 5.9 \text{ Hz})\) and 1.89 \((J = 5.9 \text{ Hz})\), attributable to the two diastereotopic \( \beta \)-protons. The mass spectrum of the product 151 had a molecular ion at \( m/z \) 273.

At the outset of the process of identifying the product of reaction, two structures, 151 and 152, could be suggested based on \(^1\)H NMR and mass spectral data. The possible mechanisms of their formation are as shown in Scheme 40. Hydride removes the \( \alpha \)-proton to generate the anion 153. Considering the resonance contributors of the anion, 153a and 153b, either the \( \alpha \)-carbon or the carbonyl oxygen could have substituted on the tertiary \( \gamma \)-position affording 151 and 152, respectively.
In the $^1$H NMR spectrum of the product the different chemical shifts of the respective protons of the 2 methyl substituents indicate that the 2 methyl substituents are non-equivalent. When similarly considered, the $\beta$-protons are also disparate. The $^1$H NMR data is more in agreement with structure 151 than with structure 152. The reason is that the planarity of the 5-membered ring in 152 dictates that both facial aspects of the ring be equivalent, whilst the two facial aspects of the cyclopropane ring in 151 are not expected to be equivalent due to the chiral $\alpha$-position.

Conclusive structure determination was afforded by $^{13}$C NMR spectrometry. The features of interest on the two structures 151 and 152 were the carbon centers corresponding to the $\gamma$-carbon of the bromoleucine derivative 135. In structure 152 the $\gamma$-carbon is
oxygen substituted and tertiary, whereas in structure 151 the β-valyl carbon is quaternary. The $^{13}$C NMR spectral data of 151 is presented in Table 10. The chemical shift of the β-carbon of δ 29.9 shows that it is not oxygen substituted, which supports the structure 151.

### Table 10 $^{13}$C NMR Spectral Data of 151

<table>
<thead>
<tr>
<th>chemical shift, δ</th>
<th>splitting patterna</th>
<th>group</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.23</td>
<td>q</td>
<td>CH₃</td>
</tr>
<tr>
<td>23.37</td>
<td>q</td>
<td>CH₃</td>
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<td>OCH₃</td>
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</tr>
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<td>134.07</td>
<td>d</td>
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<td>O=O</td>
</tr>
<tr>
<td>170.04</td>
<td>s</td>
<td>O=O</td>
</tr>
</tbody>
</table>

a off resonance decoupling

Compound 151 is a derivative of the unnatural amino acid α,β-methanovaline 154, the synthesis of which was reported\textsuperscript{157} during the course of this work. α,β-Methano-derivatives of proteinogenic amino acids are of interest because of their potential as enzyme-inhibitors\textsuperscript{158,159}. It has been postulated that the cyclic substructure restricts movement about the α,β-carbon-carbon bond, thereby fixing the position of the β-substituent with respect to the
amino and acid termini of the amino acid moiety. The expected effect of this rigidity is that the carbonyl group of the acid terminus would be sterically hindered. Thus, the amide bond of an $\alpha$, $\beta$-methano-amino acid residue in a peptide is expected to exhibit relatively greater resistance toward enzymic hydrolysis$^{158}$. 

\[ \text{154} \]

The elimination reactions of 27 and 135, described above, proceed via the loss of the respective $\alpha$-hydrogens. That being the case the chirality at the $\alpha$-position of 27 and 135 was not utilized. To exploit the chirality of the bromides 27 and 135, their conversion to the corresponding $\beta$-hydroxyvaline and $\gamma$-hydroxyleucine derivatives were investigated.

The synthesis of optically active hydroxy amino acids is a field of research which has gained popularity owing to the importance of the target compounds in biological chemistry. Various hydroxy amino acids are essential components of biologically active peptides which include echinocandins$^{160-162}$, vancomycin$^{163}$ and cyclosporin A$^{164,165}$. They are also found in toxic peptides$^{166-170}$, peptidases$^{171}$, polyoxins$^{172}$ and are themselves of interest as enzyme inhibitors$^{173}$. $\beta$-Hydroxyvaline 36 was discussed in the introduction whilst $\gamma$-hydroxyleucine 155 is a rare
naturally occurring amino acid which is found in the mushroom toxin phalloine\textsuperscript{174}.

The bromide 27 and 1.5 mole equivalents of silver nitrate was stirred in a 1:1 mixture of acetone and water overnight. Work-up of the reaction followed by chromatography on silica gave compounds 148, 156 and 157. Their respective yields, after recrystallization of 148 and 157, were 8, 34 and 43\%. The $\alpha,\beta$-didehydrovaline derivative 148 was identified by comparison of the $^1$H NMR spectrum of the product with that of the authentic sample prepared as described above.

The $\beta,\gamma$-didehydrovaline derivative 156 was isolated as a viscous oil. The $^1$H NMR spectrum of 156 had a singlet resonance, with intensity equivalent to three hydrogens at $\delta 1.92$, attributable to the protons of the $\beta$-methyl substituent. The spectrum also
showed three singlet resonances, each equivalent to one hydrogen, at δ 5.11, 5.14 and 5.38 attributable to the α-proton and the two γ-vinyl protons. No attempt was made to assign these resonances to specific protons. The resonances of the γ-vinyl protons, presumably, do not couple as each shows up as a singlet. As mentioned in Chapter 6, a coupling constant of 0 Hz is within the range expected for vinylic protons in a geminal relationship. The mass spectrum of 156 showed a molecular ion at m/z 259.

The 1H NMR spectrum of the β-hydroxyvaline derivative 157 had two singlet resonances, each with intensity equal to three hydrogens at δ 1.31 and 1.53, attributable to the respective protons of the two β-methyl substituents. The spectrum also showed a singlet resonance at δ 4.91 attributable to the α-proton, and a broad singlet at δ 4.41 attributable to the proton of the hydroxy substituent. The mass spectrum of 157 showed a major fragment corresponding to loss of acetone which implicates the α-substituent. Elemental analysis data was consistent with the structure 157.

The mechanism of formation of 148, 156 and 157 is proposed to be as shown in Scheme 41. Silver being a strong halophile removes bromide from 27 produce the carbocation 158. The β-carbocation 158 reacts either by addition of water, enroute to the β-hydroxy derivative 157, or by elimination of an adjacent hydrogen, leading to the didehydro products 148 and 156. The overall reaction, then, can be considered as a competition between SN1 substitution and E1 elimination. The latter process
explains the formation of the $\beta,\gamma$-didehydro isomer 156, which is in contrast to the reaction of 27 with sodium hydride, described above, where 148 was exclusively produced.

![Chemical structure](attachment:image.png)

**Scheme 41**

The reaction of 27 with aqueous silver nitrate above establishes that the $\beta$-bromovaline derivative 27 can be elaborated to the corresponding $\beta$-hydroxyvaline derivative 157. To show that the method is amenable to racemic as well as optically active $\beta$-hydroxyvaline derivative, the synthesis of 157 was repeated starting with L-valine. The L-configured N-phthaloylvaline derivative 149, prepared using the method described above for the synthesis of racemic 149, had $[\alpha]^{23}_D -68^\circ$. The optically active valine derivative 149 was brominated and the crude bromide hydroxylated, as described above, to give optically active 157, which had $[\alpha]^{23}_D -33^\circ$.

With regard to the reaction mechanism depicted in Scheme 41, an investigation was conducted to see whether the ratio of E1
elimination to $S_N 1$ substitution could be adjusted in favor of the former by conducting the reaction in reagent grade acetone instead of in a 1:1 mixture of acetone/water. With this variation of the procedure 148, 156 and 157 were afforded in 14, 57 and 11% yield, respectively. The result showed that by reducing the amount of water in the reaction the E1 mechanism becomes predominant. This procedure is a viable synthesis of the $\beta,\gamma$-didehydrovaline derivative 156.

The optically active bromide 135 was treated with silver nitrate in a 1:1 mixture of acetone and water. Following work-up, chromatography on silica and recrystallization, compounds 159 and 160 were isolated in 7 and 67% yield, respectively. From chromatography of the reaction mixture a small fraction which consisted of a mixture of compounds was obtained. The identities of the compounds present were not obvious from the $^1H$ NMR spectrum of the fraction owing to overlapping resonances.

![Structures 159 and 160](image)

The $^1H$ NMR spectrum of the $\gamma$-hydroxyleucine lactone derivative 159 showed two singlet resonances, each with intensity equal to three protons at $\delta$ 1.49 and 1.62, attributable to the
respective protons of the two γ-methyl substituents. The spectrum also showed an ABX pattern consisting of resonances at δ 2.41 \( (J_{\text{vic}} = 9.7 \text{ Hz}, J_{\text{gem}} = 12.1 \text{ Hz}) \), 2.57 \( (J_{\text{vic}} = 11.6 \text{ Hz}, J_{\text{gem}} = 12.1 \text{ Hz}) \) and 5.21 \( (J_{\text{vic}} = 9.7, 11.6 \text{ Hz}) \) corresponding to the two diastereotopic β-protons and the α-proton. The mass spectrum of 159 showed a M+1 signal at \( m/z \) 260 and elemental analysis data was consistent with the structure 159.

The \(^1\)H NMR spectrum of the γ-hydroxyleucine derivative 160 showed two singlet resonances, each with intensity equivalent to three protons at δ 1.24 and 1.31, attributable to the respective protons of the two γ-methyl substituents. The spectrum also showed a broad singlet resonance, at δ 1.70, attributable to the proton of the hydroxy substituent. An ABX pattern consisting of resonances at δ 2.38 \( (J_{\text{vic}} = 8.8 \text{ Hz}, J_{\text{gem}} = 15.1 \text{ Hz}) \), 2.50 \( (J_{\text{vic}} = 3.9 \text{ Hz}, J_{\text{gem}} = 15.1 \text{ Hz}) \) and 5.15 \( (J_{\text{vic}} = 4.0, 8.8 \text{ Hz}) \) were attributed to the 2 diastereotopic β-protons and the α-proton. The mass spectrum of 160 had fragments corresponding to loss of methyl radical and acetone, presumably, due to cleavage of carbon-carbon bonds at the γ-carbon. Carbon-carbon bond fragmentations are expected of carbon centers bearing oxygen. Elemental analysis data was also in agreement with the structure 160. The γ-hydroxyleucine derivative 160 had \([\alpha]^{23}_D -22^\circ\).

The mechanism of reaction of 135 with aqueous silver nitrate is presumed to be as outlined in Scheme 42. The carbocation 161 is generated by removal of bromide by silver ion. Subsequent reactions of the intermediate 161 are expected to be related to the
reactions of the β-valyl cation 158 (Scheme 41). Addition of water to 161 affords the γ-hydroxy product whereas β-elimination would give the didehydro isomers 162 and 163. These isomers are likely to be the constituents of the unidentified minor fraction as they are expected to have closely matching retention on silica due to their structural similarity. The greater prominence of SN1 substitution over E1 elimination in this case, compared to in the β-bromo-Valine derivative 27 example discussed above, can be attributed to the γ-position of 135 being less hindered than the β-position of 27.

![Scheme 42](image)

The lactone 159 can be formed via two pathways, as shown in Scheme 43. Proceeding via Route 1, from 160, attack of the γ-hydroxyl group on the ester moiety results in the loss of methanol to produce 159. This mechanism is supported by the slow
conversion of 160 to 159 under conditions identical to those of the hydroxylation reaction. This type of intramolecular substitution has been attributed to the lability of the C-terminal peptide bond of γ-hydroxyleucine residues in peptides\textsuperscript{175,176}.

The mechanism depicted in Route 2 is that of intramolecular attack by the ester carbonyl oxygen on the γ-cationic center of 161. This process forms the stabilized carbocation 164 which can either (a) form 159 directly through substitution on the methoxy group, or (b) add water then lose methanol to give 159.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {160};
\node (b) at (2,0) {159};
\node (c) at (0,-2) {161};
\node (d) at (1,-2) {164};

\draw[->] (a) -- node[above] {-MeOH} (b);
\draw[->] (c) -- node[below] {Route 2} (d);
\draw[->] (d) -- node[below] {H\textsubscript{2}O} (b);
\draw[->] (c) -- node[below] {Route 2} (a);
\draw[->] (b) -- node[above] {-MeOH} (b);
\end{tikzpicture}
\end{center}

Scheme 43

This mechanism involving carbonyl oxygen substitution is supported by the quantitative conversion of 135 to 159 in dry \textsuperscript{2,2,2}-trifluoroethanol. Trifluoroethanol has high ionizing capacity yet low nucleophilicity\textsuperscript{177,178} which favors formation of carbocations. The
reaction of 135 in trifluoroethanol is a highly efficient synthesis of the γ-hydroxyleucine lactone derivative 159.

The hydroxylation, and variations of the hydroxylation, reaction described above establishes that 156, 157, 159 and 160 can be readily synthesized from valine and leucine. The didehydrovaline derivative 156 is significant because β,γ-amino acids are important as enzyme-inhibitors and antibiotics. Their action is that of mechanism-based alkylative inactivations of pyridoxal phosphate dependent enzymes. The γ-lactone 159 has attracted attention as a strychnine antagonist and is also a synthetically useful derivative of γ-hydroxyleucine. The latter criterion stems from the amenability of incorporating γ-hydroxyleucine residues directly into a peptide using the lactone form.

The synthetic procedures developed here for the preparation of 156, 157, 159 and 160 are significant because they allow the synthesis of optically active compounds from the corresponding optically active amino acids, which are readily and cheaply available. The efficiencies of conversion, especially considering the optically active nature of the products, range from high to very high in comparison to those of asymmetric syntheses and procedures which involve resolution of racemic mixtures.
In summary, the synthetic utility of side-chain brominated $\alpha$-amino acids is considerable. From only two side-chain functionalized amino acid derivatives several important amino acid derivatives were synthesized. The attractiveness of this method of amino acid synthesis is its simplicity, efficiency and, where applicable, the optical purity of the products. The full potential of the overall methodology of side-chain bromination, through exploitation of the effect of the $N$-phthaloyl substituent, followed by modification of the bromo functionality has only begun to be realized and should be a rich area for further investigation.
Conclusion

Selective radical bromination is a viable method for functionalizing glycine residues in small peptide derivatives. The attractiveness of the technique lies in its simplicity and the high to very high degree of conversion to product. Moreover, the selectivity of bromination can be influenced through the choice of either the N-benzoyl or N-phthaloyl substituent. Hence, to an extent the selectivity of reaction can be tailored to fit the requirement in synthesis.

The versatility in synthesis of the α-bromoglycine residue in small peptide derivatives appears to be comparable to that of other α-haloglycine derivatives, which is considerable. Hence, the overall methodology, of selective bromination followed by modification of the introduced bromide functionality, is a significant technique for the selective elaboration of small peptides.

From the discussion of the factors governing the contrasting effects of the N-benzoyl and N-phthaloyl substituents, it can be seen that partial charge stabilizing effects play a significant role in the determination of reactivity. With electrophilic radical abstractors, diminished polar control through partial charge stabilization in the transition state may contribute to the enhancement of reactivity in "capto-dative" systems as much as radical stabilizing effects. This interesting aspect should certainly be considered for further investigation.
The technique of bromination and subsequent modification of the β- and the γ-position of the β-alanine 96 and GABA 122 derivatives, respectively, has considerable potential as a method for the synthesis of β- and γ-substituted β- and γ-amino acid derivatives.

Bromination, followed by modification, of the side-chains of N-phthaloyl-α-amino acid derivatives permits the synthesis of various unnatural and rare amino acid derivatives. An important aspect of the procedure is that some products can be obtained optically pure. At the time of writing further investigations into the exploitation of this methodology was in progress.
Experimental

Melting points were measured using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada.

Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra were recorded on an AEI MS-3010 spectrometer and only major fragments are given with their relative abundances in parantheses.

$^1$H NMR spectra were recorded on either a Varian T-60, Jeol JNM-PMX60 or Bruker CXP300 spectrometer. Unless stated otherwise, NMR spectra were recorded as solutions in deuterochloroform with 1% tetramethyilsilane as an internal reference.

High performance liquid chromatographic analyses were conducted with a Waters Model 501 Solvent Delivery System, U6K Injector, Waters Model 481 absorbance detector (at 254 nm) and a Regis Pirkle Covalent (2S)-Phenylglycine column (25 cm × 4.6 mm).

$N$-Benzoylglycine methyl ester (15a)

Thionyl chloride (7.3 g, 61.4 mmol) was added dropwise to a cooled, and stirred, solution of hippuric acid 48a (10.0 g, 55.8 mmol) in methanol (100 ml) and the mixture left to stir
overnight under anhydrous conditions (CaCl₂ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness, under reduced pressure, to afford the crude product 15a. Recrystallization from dichloromethane/light petroleum gave 15a as colorless needles.

Yield 9.9 g, 92 %;
mp 81-83 °C (lit\textsuperscript{181}, 82-83 °C);
\(^1\)H NMR (60 MHz) \(\delta\) 3.90 (3 H, s), 4.32 (2 H, d, \(J = 4\) Hz), 6.84 (1 H, br. d, \(J = 4\) Hz), 7.3-8.0 (5 H, m).

**Tri-\(n\)-butylstannyl deuteride**

Tri-\(n\)-butylbutylstannyl deuteride was prepared according to the method described by Kuivila and Beumel, Jr.\textsuperscript{114} except that lithium aluminium deuteride (98% deuterium content) was used instead of lithium aluminium hydride.

**\(N\)-Benzoylamino acids (48)**

The appropriate amino acid (10 g) and potassium carbonate (1.1 mole equivalent) were added to water and ethyl acetate (1:1, 100 ml total) with stirring. Benzoyl chloride (1 mole equivalent) was introduced and the resulting mixture stirred for 2 h. The separated aqueous phase was washed with ethyl acetate and acidified (conc. hydrochloric acid) to give the corresponding \(N\)-benzoylamino acid. Recrystallization was effected in ethyl acetate/hexane.
Hydrochloride salts of amino acid methyl esters (49)

The appropriate amino acid (10 g) was added to methanol which had been pretreated with thionyl chloride (1.2 mole equivalents per carboxyl group) and the mixture left to stir overnight, under anhydrous conditions (CaCl₂ guard tube). Evaporation of the reaction mixture to dryness, under reduced pressure, afforded the corresponding hydrochloride salt of amino acid methyl ester.

Coupling Procedure for the Preparation of Dipeptide Derivatives

Ethyl chloroformate (1 mole equivalent) was added to a cooled (-10--5°) and stirred solution of the appropriate N-benzyloxymethyl amino acid 48 (5-10 g scale) in freshly distilled THF (100-150-ml) containing triethylamine (1 mole equivalent). After 20 minutes, a suspension of the hydrochloride salt of the amino acid methyl ester 49, in THF (75-100 ml) containing triethylamine (1.2 mole equivalent relative to the hydrochloride salt), was added and the resulting mixture left to stir at 0° for 2 hours and at room temperature overnight under a nitrogen atmosphere. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate and water. The organic phase was separated and partitioned successively with 5 % aqueous sodium bicarbonate (×2), 10% hydrochloric acid, water and dried over sodium sulfate. The dried solution was filtered, concentrated under reduced pressure
and diluted with light petroleum to effect crystallization of the peptide.

**N-Benzoylglycylglycine methyl ester (40a)**

The glycylglycine derivative 40a was prepared from hippuric acid 48a (5.0 g, 27.9 mmol) and the hydrochloride salt of glycine methyl ester 49a (3.5 g, 28.0 mmol) using the coupling procedure (p. 134) described above. Recrystallisation from dichloromethane/light petroleum gave 40a

Yield 2.65 g, 38%;
mp 81-82 °C (lit.182, 78-82 °C);
$^1$H NMR (60 MHz) δ 3.75 (3 H, s), 4.07 (2 H, d, J = 6 Hz), 4.30 (2 H, d, J = 5 Hz), 7.2-8.1, (7 H, m).

mass spectrum m/z 251 (M+1, 2), 250 (M+, 3), 219 (2), 218 (1), 162 (18), 135 (66), 134 (48), 105 (100), 77 (37).

**N-Benzoylvalylglycine methyl ester (41a)**

N-Benzoylvaline 48b [17.3 g, 92%; mp 129-131 °C (lit., 131 °C)] was prepared from valine by the general method described above. The valylglycine derivative 41a was prepared from N-benzoylvaline 48b (5.0 g, 22.6 mmol) and the hydrochloride salt of glycine methyl ester 49a (2.9 g, 23.2 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/light petroleum gave 41a as a white solid. The $^1$H NMR spectral data of 41a was consistent with that previously reported183.
Yield 5.9 g, 45 %;
mp 158-159 °C;

$^1$H NMR (300 MHz) $\delta$ 1.01 (3 H, d, $J = 7.2$ Hz), 1.04 (3 H, d, $J = 7.2$ Hz), 2.1-2.4 (1 H, m), 3.70 (3 H, s), 3.95 (1 H, dd, $J_{\text{vic}} = 6.0$ Hz, $J_{\text{gem}} = 16.8$ Hz), 4.13 (1 H, dd, $J_{\text{vic}} = 6.4$ Hz, $J_{\text{gem}} = 16.8$ Hz), 4.68 (1 H, dd, $J = 8.0$, 8.5 Hz), 7.2-7.7 (5 H, m), 7.84 (2 H, d, $J = 8.5$ Hz);
mass spectrum $m/z$ 292 (M+, 0.3), 291 (0.6), 260 (1.4), 249 (1.7), 204 (10.0), 175 (38.1), 176 (100.0), 105 (88.1), 77 (80.2).

$N$-Benzoylleucylglycine methyl ester (42a)

$N$-Benzoylleucine 48c (15.6 g, 87 %) was prepared from leucine by the general method described above. The leucylglycine derivative was prepared from $N$-benzoylleucine 48c (6 g, 25.5 mmol) and the hydrochloride salt of glycine methyl ester 49a (3.2 g, 25.6 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/hexane gave 42a as a white solid.

Yield 3.4 g, 43%;
mp 174-175 °C (lit$^{184,}$, 176 °C);

$^1$H NMR (300 MHz) $\delta$ 0.93 (3 H, d, $J = 6.0$ Hz), 0.95 (3 H, d, $J = 6.0$ Hz), 1.6-1.9 (1 H, m), 3.71 (3 H, s), 3.96 (1 H, dd, $J_{\text{vic}} = 5.4$ Hz, $J_{\text{gem}} = 18.1$ Hz), 4.07 (1 H, dd, $J_{\text{vic}} = 5.6$ Hz, $J_{\text{gem}} = 18.1$ Hz), 4.80 (1 H, m), 7.05 (1 H, br. dd, $J_{\text{vic}} = 5.4$, 5.6 Hz), 7.3-7.6 (3 H, m), 7.81 (1 H, d, $J = 8.7$ Hz), 7.81 (1 H, d, $J = 8.0$ Hz);
mass spectrum \( m/z \) 306 (M+, 0.6), 274 (13), 250 (7.9), 217 (10.9), 189 (76.9), 105 (100.0), 77 (66.4).

*N*-Benzoylalanylglucose methyl ester (43a)

*N*-Benzoylalanine 48f [18.6 g, 86%; mp 160-162 °C (lit., 163 °C)] was prepared from alanine by the method described above.

The alanylglucose derivative 43a was prepared from *N*-benzoylalanine 48f (5.0 g, 25.9 mmol) and the hydrochloride salt of glycine methyl ester 49a (3.3 g, 26.4 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/hexane gave 43a as colorless crystals.

Yield 2.8 g, 42% ;
mp 107-108 °C (lit184°, 110 °C);
\(^1\)H NMR (300 MHz) \( \delta \) 1.49 (3 H, d, \( J = 7.0 \) Hz), 3.71 (3 H, s), 4.03 (2 H, d, \( J = 5.0 \) Hz), 4.86 (1 H, dq, \( J_d = 7.0 \) Hz, \( J_q = 7.0 \) Hz), 7.2-7.7 (5 H, m), 7.82 (1 H, d, \( J = 8.5 \) Hz), 7.82 (1 H, d, \( J = 7.0 \) Hz);
mass spectrum \( m/z \) 265 (M+1, 1), 264 (M+, 1), 205 (8), 162 (15), 135 (44), 134 (50), 105 (100), 77 (71).

*N*-Benzoylglyclylvaline methyl ester (28a)

The glyclylvaline derivative 28a was prepared from hippuric acid 48a (10.0 g, 55.9 mmol) and the hydrochloride salt of valine methyl ester 49b (9.4 g, 56.3 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/light petroleum gave 28a as a white solid.
Yield 7.0 g, 38%;
mp 144-145 °C (lit\textsuperscript{185}, 145 °C);
$^1$H NMR (300 MHz) $\delta$ 0.95 (3 H, d, $J = 7.6$ Hz), 0.97 (3 Hz, d, $J = 7.9$ Hz), 2.0-2.6 (1 H, m), 3.74 (3 H, s), 4.27 (2 H, d, $J = 6.0$ Hz), 4.55 (1 H, dd, $J = 4.9$, 8.6 Hz), 7.2-7.7 (5 H, m), 7.85 (2 H, d, $J = 6.9$ Hz);
mass spectrum $m/z$ 293 (M$^+$+1, 9), 292 (M$^+$, 20), 233 (18), 162 (37), 135 (40), 134 (87), 105 (100), 77 (52).

**N-Benzoylglycylleucine methyl ester (44a)**

The glycylleucine derivative 44a was prepared from hippuric acid 48a (6.8 g, 38.0 mmol) and the hydrochloride salt of leucine methyl ester 49c (6.9 g, 38.1 mmol) using the coupling procedure (p. 134) described above. Recrystallization from ethyl acetate/light petroleum gave 44a as a white solid.

Yield 4.8 g, 41%;
mp 112-113 °C.
$^1$H NMR (300 MHz) $\delta$ 0.91 (6 H, d, $J = 6.4$ Hz), 1.4-2.0 (3 H, s), 4.23 (1 H, dd, $J_{\text{vic}} = 5.1$, $J_{\text{gem}} = 16.8$ Hz), 4.30 (1 H, dd, $J_{\text{vic}} = 5.1$, $J_{\text{gem}} = 16.8$ Hz), 4.60 (1 H, m), 7.3-7.7 (5 H, m), 7.84 (2 H, d, $J = 6.9$ Hz);
IR (NaCl, nujol) 1754, 1670, 1644, 1550 cm$^{-1}$;
mass spectrum $m/z$ 306 (M$^+$, 9), 250 (12), 247 (10), 162 (14), 135 (28), 134 (33), 105 (100), 77 (58).
Anal. Calcd for C$_{16}$H$_{22}$N$_2$O$_4$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.7; H, 7.2; N, 9.1.
N-Benzoylglycylphenylalanine methyl ester (45a)

The glycylphenylalanine derivative 45a was prepared from hippuric acid 48a (7.5 g, 41.9 mmol) and the hydrochloride salt of phenylalanine methyl ester 49d (9.0 g, 41.9 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/light petroleum gave 45a as a white solid.

Yield 5.1 g, 36%;
mp 112-114 °C.

1H NMR (300 MHz) δ 3.05 (1 H, dd, Jvic = 7.6 Hz, Jgem = 14.4 Hz), 3.15 (1 H, dd, Jvic = 7.6 Hz, Jgem = 14.4 Hz), 3.72 (3 H, s), 4.09 (2 H, d, J = 5.8 Hz), 4.87 (1 H, ddd, J = 7.6, 7.6, 7.6 Hz), 7.0-7.3 (6 H, m), 7.3-7.6 (4 H, m), 7.80 (1 H, d, J = 8.6 Hz), 7.80 (1 H, d, J = 7.1 Hz);

IR (NaCl, nujol) 3308, 1744, 1670, 1640, 1548, 1496, 1256, 700 cm⁻¹;

mass spectrum m/z 341 (M⁺+1, 3), 340 (M⁺, 7), 162 (100), 135 (7), 134 (34), 105 (64), 77 (36).

Anal. Calcd for C19H29N2O5: C, 67.0; H, 5.9; N, 8.2. Found: C, 66.8; H, 5.9; N, 8.2.

N-Benzoylglycylaspartic acid dimethyl ester (46a)

The glycylaspartic acid derivative 46a was prepared from hippuric acid 48a (5.0 g, 27.9 mmol) and the hydrochloride salt of aspartic acid dimethyl ester 49e (5.5 g, 27.9 mmol) using the
coupling procedure (p. 134) described above. Recrystallization from dichloromethane/light petroleum gave 46a as a white solid.

Yield 3.5 g, 39%;
mp 128-130 °C.

1H NMR (300 MHz) δ 2.85 (1 H, dd, J_{vic} = 4.8 Hz, J_{gem} = 16.4 Hz), 3.00 (1 H, dd, J_{vic} = 4.8 Hz, J_{gem} = 16.4 Hz), 3.64 (3 H, s), 3.73 (3 H, s), 4.12 (1 H, dd, J_{vic} = 6.5 Hz, J_{gem} = 18.2 Hz), 4.25 (1 H, dd, J_{vic} = 5.6 Hz, J_{gem} = 18.2 Hz) 4.88 (1 H, dt, J_t = 4.8 Hz, J_d = 8.4 Hz), 7.2-7.6 (5 H, m), 7.83 (2 H, d, J = 6.9 Hz);

IR (NaCl, nujol) 1732, 1610, 1638, 122 cm⁻¹;
mass spectrum m/z 322 (M⁺, 1.1), 291 (0.9), 290 (0.7), 162 (15.5), 135 (54.9), 134 (39.2), 105 (100), 77 (29.4).

m/z 322.1178 [(M⁺) calcd for C_{15}H_{18}N_{2}O_{6} 322.1165].

**N-Benzoylglycylalanine methyl ester (47a)**

The glycylalanine derivative 47a was prepared from hippuric acid 48a (10.0 g, 55.9 mmol) and the hydrochloride salt of alanine methyl ester 49f (7.8 g, 56.1 mmol) using the coupling procedure (p. 134) described above. Recrystallization from ethyl acetate/light petroleum gave 47a as colorless crystals.

Yield 5.6 g, 38 %;
mp 108-109 °C (lit^{186}, 110 °C);

1H NMR (300 MHz) δ 1.42 (3 H, d, J = 7.2 Hz), 3.72 (3 H, s), 4.20 (1 H, dd, J_{vic} = 4.7 Hz, J_{gem} = 16.5 Hz), 4.26 (1 H, dd, J_{vic} = 4.9 Hz, J_{gem} = 16.5 Hz), 4.57 (1 H, dq, J_d = 7.6 Hz, J_q = 7.6 Hz),
7.2-7.7 (5 H, m), 7.84 (1 H, d, $J = 8.6$ Hz), 7.84 (1 H, d, $J = 7.2$ Hz);
mass spectrum $m/z$ 205 (M$^+$-59, 8), 162 (15), 135 (44), 134 (50),
105 (100), 77 (71).

**Bromination of Peptide Derivatives**

A mixture of the peptide derivative (0.2 - 0.5 g) and $N$-bromosuccinimide (1 mole equivalent) in refluxing dichloromethane (25 ml), under nitrogen, was irradiated with a 250W mercury lamp for 20-30 minutes. $^1$H NMR spectroscopic analysis of the crude reaction mixture was performed after removal of the solvent under reduced pressure and the residue dissolved in deuterochloroform.

**Deuteration of Brominated Peptide Derivatives**

Tri-$n$-butylstannyl deuteride (1.5 mole equivalents) was added to the crude reaction mixture of the bromide at room temperature and the mixture left to stir overnight. The solvent was removed under reduced pressure and the residue dissolved in ether and water. The organic phase was separated, washed with water, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure. Chromatography on silica (PF$_{254}$, chromatotron) followed by recrystallization from dichloromethane/light petroleum gave the deuteriated product.

*N-Benzoyl-$\alpha$-deuteroglycylglycine methyl ester (40c)*
The glycylglycine derivative 40a (0.20 g, 0.80 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.134 g, 67 %; based on 40a, 63 % $^2$H$_1$ incorporation;
mp 79-81 °C;
$^1$H NMR (60 MHz) similar to that of 40a except $\delta$ 4.30 (-1.5 H, br. d, $J = 5$ Hz) instead of 4.30 (2 H, d, $J = 5$ Hz);
mass spectrum m/z 252 (M$^+$, 0.3), 251 (M$^+$, 0.5), 250 (0.3), 220 (0.6), 219 (0.5), 218 (0.2), 163 (7.0), 162 (4.5), 136 (34.0), 135 (40.4), 134 (12.8), 105 (100.0), 77 (40.0).

N-Benzoylvalyl-\(\alpha\)-deuteroglycine methyl ester (41c)

The valylglycine derivative 41a (0.20 g, 0.68 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.105 g, 53 %; based on 41a, 78 % $^2$H$_1$ incorporation;
mp 157-159 °C;
mass spectrum m/z 292 (M$^+$, 0.2), 291 (0.4), 290 (0.1), 261 (0.7) 260 (0.3), 250 (1), 249 (0.3), 204 (8.0), 175 (31.7), 176 (100.0), 105 (90.2), 77 (70.7).

N-Benzoylleucyl-\(\alpha\)-deuteroglycine methyl ester (42c)

The leucylglycine derivative 42a (0.20 g, 0.65 mmol) was brominated and deuteriated (p. 141) using the methods described above.
Yield 0.102 g, 51 %, based on 42a, 58 % $^2$H$_1$ incorporation; 
mp 173-174 °C;
mass spectrum m/z 307 (M+, 0.4), 306 (0.3), 275 (0.8), 274 (0.6), 
251 (4.4), 250 (3.3), 217 (10.5), 189 (83.7), 105 (100.0), 77 (88.4).

*N-Benzyol-α-deuteroglycylvaline methyl ester (28c)*

The glycylvaline derivative 28a (0.20 g, 0.68 mmol) was 
brominated and deuteriated (p. 141) using the methods described 
above.

Yield 0.107 g, 54 %, based on 28a, 78 % $^2$H$_1$ incorporation; 
mp 143-145 °C;
mass spectrum m/z 294 (M+1, 2), 293 (M+, 4), 292 (1), 234 (7), 
233 (2), 163 (15), 162 (4), 136 (33), 135 (44), 134 (13), 105 (100), 
77 (49)

*N-Benzyol-α-deuteroglycyleucine methyl ester (44c)*

The glycyleucine derivative 44a (0.20 g, 0.65 mmol) was 
brominated and deuteriated (p. 141) using the methods described 
above.

Yield 0.07 g, 36 %, based on 44a, 79 % $^2$H$_1$ incorporation; 
mp 112-113 °C;
mass spectrum m/z 307 (M+, 4), 306 (1), 251 (14), 250 (4), 248 
(10), 247 (3), 163 (28), 162 (11), 136 (71), 135 (98), 134 (26), 105 
(100), 77 (60).
N-Benzoyl-α-deuteroglycylphenylalanine methyl ester (45c)

The glycylphenylalanine derivative 45a (0.22 g, 0.65 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.111 g, 50 %, based on 45a, 75 % ²H₁ incorporation;
mp 112-114 °C;
mass spectrum m/z 342 (M⁺+1, 0.5), 341 (M⁺, 1.3), 340 (0.3), 163 (37.2), 162 (100.0), 136 (6.9), 135 (35.7), 134 (10.7), 105 (91.1), 77 (50.9).

N-Benzoyl-α-deuteroglycylaspartic acid dimethyl ester (46c)

The glycylaspartic acid derivative 46a (0.25 g, 0.78 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.093 g, 37 %, based on 46a, 79% ²H₁ incorporation;
mp 128-129 °C;
mass spectrum m/z 323 (M⁺, 4) 322 (1), 292 (4), 291 (5), 163 (34) 162 (11), 136 (64), 135 (66), 134 (14), 105 (100), 77 (32).

N-Benzoyl-α-deuteroglycylalanine methyl ester (47c)

The glycylalanine derivative 47a (0.30 g, 1.14 mmol) was brominated and deuteriated (p. 141) using the methods described above.
Yield 0.033 g, 11 %, based on 47a, 40 % 2H_1 incorporation; 
mp 108-110 °C; 
mass spectrum m/z 206 (M^+-59, 7), 205 (9), 163 (10), 162 (17), 
136 (68), 135 (50), 134 (50), 105 (100), 77 (59).

**Reaction of Brominated Peptide Derivatives with Methanol**

Methanol (0.5 ml, excess) was added directly to the crude reaction mixture of the bromide, at room temperature, and the mixture left to stir for 2 h (overnight reactions also gave satisfactory results). The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in ether and water. The organic phase was washed with water, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure.

**N-Benzoyl-α-methoxyglycylglycine methyl ester (40d)**

The glycylglycine derivative 40a (0.5 g, 2.0 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF_{254}, chromatotron) and recrystallized from dichloromethane/light petroleum to give 40d as a white solid.

Yield 0.35 g, 62 % based on 40a; 
mp 56-57 °C;
$^1$H NMR (60 MHz) $\delta$ 3.48 (3 H, s), 3.75 (3 H, s), 4.09 (1 H, d, $J = 6$ Hz), 5.83 (1 H, d, $J = 8$ Hz) and 7.20-8.17 (7 H, m);
IR (NaCl, nujol) 3474, 3320, 1728, 1674, 1528, 1230, 1090 cm$^{-1}$; mass spectrum $m/z$ 217 (M$^+$-63, 4), 192 (4), 164 (99), 105 (100), 77 (94).
$m/z$ 192.0669 [(M$^+$-NHCH$_2$CO$_2$Me) calcd for C$_{10}$H$_{10}$NO$_2$ 192.0661].

Minor product 56:
$^1$H NMR (60 MHz) $\delta$ 3.43 (6 H, s), 3.73 (3 H, s), 5.5-6.1 (2 H, m), 6.9-8.0 (7 H, m).

$N$-Benzoylvalyl-$\alpha$-methoxyglycine methyl ester (41d)

The valylglycine derivative 41a (0.5 g, 1.7 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF$_{254}$, chromatotron) and recrystallised from dichloromethane/light petroleum to give 41d as a white solid.

Yield 0.36 g, 65 % based on 41a, 1:1 mixture of diastereomers; mp 127-135 °C;
$^1$H NMR (60 MHz) $\delta$ 1.00 (6 H, d, $J = 8$ Hz, $J$), 2.15 (1 H, m), 3.34 (1.5 H, s), 3.44 (1.5 H, s), 3.63 (1.5 H, s), 3.73 (1.5 H, s), 4.79 (1 H, t, $J = 9$ Hz), 5.50 (0.5 H, d, $J = 9$ Hz), 5.57 (0.5 H, d, $J = 9$ Hz), and 7.20-8.20 (7 H, m).
IR (NaCl, nujol) 3252, 1756, 1630, 1534, 1466, 1218, 698 cm$^{-1}$; mass spectrum $m/z$ 322 (M$^+$, 2), 292 (4), 290 (3), 263 (10), 204 (85), 176 (83), 105 (100), 77 (75).
m/z 322.1518 [(M+)] calcd for C₁₆H₂₂N₂O₅ 322.1526.

N-Benzoyl-α-methoxyglycylvaline methyl ester (28d)

The glycylvaline derivative 28a (0.5 g, 1.7 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF₂₅₄, chromatotron) to give 28d as a viscous oil.

Yield 0.40 g, 73 % based on 28a, 1:1 mixture of diastereomers;

¹H NMR (60 MHz) δ 0.95 (6 H, d, J = 7 Hz), 2.20 (1 H, m), 3.53 (3 H, s), 3.97 (3 H, s), 4.60 (1 H, dd, J = 5, 9 Hz), 5.80 (0.5 H, d, J = 8 Hz), 5.90 (0.5 H, d, J = 8 Hz), and 7.20-8.20 (7 H, m);

IR (NaCl, nujol) 3296, 1744, 1690, 1640, 1528, 1492, 1154 cm⁻¹;

mass spectrum m/z 322 (M⁺, 1), 292 (3), 291 (2), 290 (2), 263 (2), 192 (3), 164 (77), 105 (100), 77 (78).

m/z 322.1534 [(M⁺)] calcd for C₁₆H₂₂N₂O₅ 322.1528

N-Benzoyl-α-methoxyglycylalanine methyl ester (47d)

The glycylalanine derivative 47a (0.5 g, 1.9 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF₂₅₄, chromatotron) to give 47d as a viscous oil.

Yield 0.29 g, 56 % based on 47a, 1:1 mixture of diastereomers;
\[ {^1}H\text{ NMR (300 MHz)} \delta 1.45 (3 \text{ H, d, } J = 7.3 \text{ Hz}), 3.48 (1.5 \text{ H, s}), 3.49 (1.5 \text{ H, s}), 3.74 (1.5 \text{ H, s}), 3.75 (1.5 \text{ H, s}), 4.61 (1 \text{ H, m}), 5.72 (0.5 \text{ H, d, } J = 8.4 \text{ Hz}), 5.79 (0.5 \text{ H, d, } J = 8.6 \text{ Hz}), 7.2-8.0 (7 \text{ H, m});\]

IR (NaCl, nujol) 3416, 1744, 1658, 1526, 1160, 1094 cm\(^{-1}\);

mass spectrum \(m/z\) 263 (M\(^{+}\)-31, 1), 164 (35), 105 (100), 77 (45).

\(m/z\) 263.10543 [(M\(^{+}\)-OMe) calcd for C\(_{13}\)H\(_{15}\)N\(_2\)O\(_4\) 263.1032].

**Preparation of \(N\)-Phthaloylamino Acids (70)**

An intimate mixture of the appropriate amino acid (6 g) and phthalic anhydride (1 mole equivalent) was heated to 150-165 °C (oil bath temperature) and the resulting melt was stirred within that temperature range for 30 minutes. After cooling to room temperature, the residue was dissolved in methanol (50 ml) and the solution triturated with water to effect crystallization of the corresponding \(N\)-phthaloylamino acid 70.

**\(N\)-Phthaloylglycylglycine methyl ester (66a)**

The glycylglycine derivative 66a was prepared from commercial \(N\)-phthaloylglycine 70a (6.0 g, 29.3 mmol) and the hydrochloride salt of glycine methyl ester 49a (3.7 g, 29.6 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/light petroleum gave 66a as colorless crystals.

Yield 4.2 g, 52 %;

mp 202-203 °C (lit\(^{187}\), 203-204 °C);
$^1$H NMR (60 MHz) $\delta$ 3.73 (3 H, s), 4.02 (2 H, d, $J = 5$ Hz), 4.43 (2 H, s), 7.5-8.2 (5 H, m);

mass spectrum $m/z$ 276 (5), 245 (1), 244 (2), 217 (5), 188 (10), 161 (100), 160 (76).

$N$-Phthaloylalanylglycine methyl ester (67a)

$N$-Phthaloylalanine 70b [13.7 g, 93 %; mp 159-161 °C (lit., 160-161 °C)] was prepared from alanine using the procedure described above. The alanylglycine derivative 67a was prepared from $N$-phthaloylalanine 70b (6.0 g, 27.4 mmol) and the hydrochloride salt of glycine methyl ester hydrochloride 49a (3.5 g, 28.0 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/hexane gave 67a as colorless crystals.

Yield 4.1 g, 51 %;

mp 145-146 °C (lit.);

$^1$H NMR (300 MHz) $\delta$ 1.73 (3 H, d, $J = 7.3$ Hz), 3.73 (3 H, s), 4.05 (2 H, d, $J = 5.1$ Hz), 4.98 (1 H, q, $J = 7.3$ Hz), 6.71 (1 H, br. d, $J = 5.1$ Hz), 7.74 (2 H, m), 7.85 (2 H, m);

IR (NaCl, nujol) 3276, 1756, 1718, 1650, 1548, 1212, 724 cm$^{-1}$;

mass spectrum $m/z$ 290 (0.2), 258 (0.3), 230 (0.2), 201 (3.1), 175 (100.0), 174 (30.6).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.9; H, 4.9; N, 9.7. Found: C, 58.0; H, 4.9; N, 9.7.

$N$-Phthaloylglycylvaline methyl ester (68)
The glycylvaline derivative 68 was prepared from commercial N-phthloylglycine 70a (5.0 g, 24.4 mmol) and the hydrochloride salt of valine methyl ester 49b (4.1 g, 24.6 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/hexane gave 68 as colorless crystals.

Yield 3.8 g, 49 %;
mp 195-196 °C (lit189, 196 °C);

$^1$H NMR (60 MHz) δ 0.92 (3 H, d, $J = 7$ Hz), 0.95 (3 H, d, $J = 7$ Hz), 1.9-2.5 (1 H, m), 3.76 (3 H, s), 4.43 (2 H, s), 4.59 (1 H, dd, $J = 4$, 8 Hz), 6.43 (1 H, br. d, $J = 8$ Hz), 7.5-8.2 (4 H, m).

$N$-Phthaloylglycylaspartic acid dimethyl ester (69)

The glycylaspartic acid derivative 69 was prepared from commercial $N$-phthloylglycine 70a (5.0 g, 24.4 mmol) and the hydrochloride salt of aspartic acid dimethyl ester 49e (4.8 g, 24.4 mmol) using the coupling procedure (p. 134) described above. Recrystallization from dichloromethane/hexane gave 69 as colorless crystals.

Yield 4.5 g, 53 %;
mp 177-178 °C;

$^1$H NMR ( MHz) δ 2.88 (1 H, dd, $J_{\text{vic}} = 4.2$, $J_{\text{gem}} = 17.4$ Hz), 3.06 (1 H, dd, $J_{\text{vic}} = 4.2$, $J_{\text{gem}} = 17.4$ Hz), 3.70 (3 H, s), 3.77 (3 H, s), 4.36 (1 H, d, $J = 16.1$ Hz), 4.45 (1 H, d, $J = 16.1$ Hz), 4.85 (1 H, dt, $J_t = 4.2$ Hz, $J_d = 8.4$ Hz), 6.83 (1 H, br. d, $J = 8.4$ Hz), 7.74 (2 H, m), 7.85 (2 H, m);
IR (NaCl, nujol) 3336, 1724 (br.), 16644, 1548, 1316, 1226, 1112, 952, 716 cm⁻¹;
mass spectrum m/z 288 (M⁺-60, 3), 188 (26), 161 (74), 160 (100).
Anal. Calcd for C₁₆H₁₆N₂O₇: C, 55.2; H, 4.6; N, 8.0. Found: C, 54.9; H, 4.6; N, 8.0.

N-Phthaloylglycylglycylglycine methyl ester (71a)

The compound 71a was prepared from commercial N-phthaloylglycine 70a (5.0 g, 24.4 mmol) and the hydrochloride salt of glycylglycine methyl ester 73a (4.5 g, 24.7 mmol) [prepared from glycylglycine using the methanol/thionyl chloride procedure described above (p. 13)] using the coupling procedure (p. 134) described above except that 73a was substituted for the amino acid methyl ester hydrochloride. Recrystallization from dichloromethane gave 71a as a white solid.

Yield 3.7 g, 46 %;
mp 231-232 °C;
¹H NMR (CDCl₃/DMSO) (60 MHz) δ 3.69 (3 H, s), 3.86 (2 H, d, J = 5 Hz), 3.90 (2 H, d, J = 6 Hz), 4.37 (2 H, s), 7.83 (4 H, br. s), 8.14 (1 H, br. t, J = 6 Hz), 8.51 (1 H, br. t, J = 5 Hz);
mass spectrum m/z 333 (M⁺, 0.9), 302 (0.8), 301 (1.8), 245 (27.9), 218 (87.5), 188 (36.0), 173 (32.4), 161 (88.2), 160 (100.0).

N-Phthaloylglycylglycylvaline methyl ester (72a)

The compound 72a was prepared from commercial N-phthaloylglycine 70a (5.0 g, 24.4 mmol) and the hydrochloride salt
of glycylvaline methyl ester 73b (5.5 g, 24.6 mmol) [prepared from glycylvaline using the methanol/thionyl chloride procedure described above (p. 145)] using the coupling procedure (p. 134) described above except that 73b was substituted for the amino acid methyl ester hydrochloride. Recrystallization from dichloromethane/light petroleum gave 72a as a white solid.

Yield 4.5 g, 49%;
mp 240-241 °C;
$^{1}$H NMR (300 MHz) δ;
IR (NaCl, nujol) 3298, 1728, 1644, 1557, 1467, 1422 cm$^{-1}$;
mass spectrum $m/z$ 375 (M$^+$, 3), 316 (17), 262 (10), 245 (14), 218 (19), 188 (19), 161 (37), 160 (100).
Anal. Calcd for C$_{18}$H$_{21}$N$_3$O$_6$: C, 57.58; H, 5.64; N, 11.20. Found: C, 57.51; H, 5.52; N, 11.09.

$N$-Phthaloylglycyl-$\alpha$-deuteroglycine methyl ester (66c)

The glycylglycine derivative 66a (0.20 g, 0.72 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.15 g, 73% based on 66a; 91% $^2$H$_1$ incorporation;
mp 201-203 °C;
$^{1}$H NMR (60 MHz) similar to that of 66a except δ 4.02 (1 H, br. d, $J = 5$ Hz) instead of 4.02 (2 H, d, $J = 5$ Hz);
mass spectrum $m/z$ 277 (M$^+$,13), 246 (3), 245 (3), 218 (6), 188 (12), 161 (100), 160 (64).
N-Phthaloylalanyl-α-deuteroglycine methyl ester (67c)

The alanylglycine derivative 67a (0.20 g, 0.69 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.14 g, 70 % based on 67a; 90% $^2$H$_1$ incorporation;
mp 145-146 °C;
$^1$H NMR (300 MHz) similar to that of 67a except δ 4.05 (1 H, br. d, $J$ = 5.1 Hz) instead of 4.05 (2 H, d, $J$ = 5.1 Hz);
mass spec $m/z$ 291 (M+,0.1), 259 (0.3), 231 (0.2), 201 (3.2), 175 (100.0), 174 (32.4).

N-Phthaloylglycyl-α-methoxyglycine methyl ester (66d)

The glycyglycine derivative 66a (0.2 g, 0.73 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF$_{254}$, chromatotron) and recrystallised from dichloromethane/light petroleum to give 66d as a white solid.

Yield 0.16 g, 74 % based on 66a;
mp 187-188 °C;
$^1$H NMR (60 MHz) δ 3.48 (3 H, s), 3.83 (3 H, s), 4.52 (2 H, s), 5.62 (1 H, d, $J$ = 10 Hz), 7.18 (1 H, d, $J$ = 10 Hz), and 7.67-8.13 (4 H, m);
IR (NaCl, nujol) 3260, 1772, 1670, 1414, 944, 712 cm$^{-1}$;
mass spectrum $m/z$ 247 (M$^+$-59, .41), 188 (14), 161 (23), 160 (100). $m/z$ 247.0712 [(M$^+$-CO$_2$Me), calcd for C$_{12}$H$_{11}$N$_2$O$_4$ 247.0719]
Anal. Calcd for C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}O\textsubscript{6}: C, 54.9; H, 4.6; N, 9.1. Found: C, 54.5; H, 4.6; N, 9.1.

\textit{N-Phthaloylalanyl-α-methoxyglycine methyl ester (67d)}

The alanylglycine derivative \textit{67a} (0.5 g, 1.7 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF\textsubscript{2}54, chromatotron) and recrystallized from dichloromethane/light petroleum to give \textit{67d} as a white solid.

Yield 0.38 g, 70 % based on \textit{67a}, 1:1 mixture of diastereomers;
mp 134-139 °C;
\textsuperscript{1}H NMR (300 MHz) \(\delta\) 1.72 (1.5 H, d, \(J = 7.4\) Hz), 1.74 (1.5 H, d, \(J = 7.5\) Hz), 3.45 (1.5 H, s), 3.47 (1.5 H, s), 3.78 (1.5 H, s), 3.79 (1.5 H, s), 5.00 (1 H, m), 5.56 (0.5 H, d, \(J = 9.1\) Hz), 5.58 (0.5 H, d, \(J = 9.2\) Hz), 6.93 (0.5 H, br. d, \(J = 9.2\) Hz), 6.98 (0.5 H, br. d, \(J = 9.1\) Hz), 7.75 (2 H, m), 7.87 (2 H, m);
IR (NaCl, nujol) 1750, 1718, 1670, 1466, 732 cm\textsuperscript{-1};
mass spectrum \textit{m/z} 261 (M\textsuperscript{+}-79, 76), 202 (87), 175 (73), 174 (100).

Anal. Calcd for C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{6}: C, 56.3; H, 5.0; N, 8.7. Found: C, 56.4; H, 5.0; N, 8.7.

\textit{N-Phthaloylglycyl-α-deuteroglycyl-α-deuteroglycine methyl ester (71c)}
The glycylglycylglycine derivative 71a (0.20 g, 0.60 mmol) was suspended in refluxing dichloromethane, (20 ml) under nitrogen, with irradiation with a 250W mercury lamp and treated with 3-4 ml of a solution of N-bromosuccinimide (0.43 g, 2.40 mmol) in dichloromethane (20 ml). After the bromine color had faded another 3-4 ml of the N-bromosuccinimide solution was added. This process was repeated until all the of the N-bromosuccinimide solution was used, which took approximately 1 hour. The reaction was allowed to proceed for another 20 minutes before irradiation was stopped and the reaction mixture cooled to room temperature. Tri-n-butylstannyl deuteride (0.53 g, 1.81 mmol) was added and the reaction mixture left to stir, under nitrogen, for 2 hours. Removal of solvent under reduced pressure followed by washing of the residue with water, and then hexane, gave the crude material which was recrystallised from dichloromethane to give 71c as a white solid.

Yield 0.11 g, 55 % based on 71a, 94 % 2H₂ incorporation;
mp 230-231 °C;

¹H NMR (300 MHz) similar to 71a except δ 3.86 (1 H, br. d, J = 5 Hz), 3.90 (1 H, br. d, J = 6 Hz), 8.14 (1 H, br. d, J = 6 Hz), 8.51 (1 H, br. d, J = 5 Hz) instead of 3.86 (2 H, d, J = 5 Hz), 3.90 (2 H, d, J = 6 Hz), 8.14 (1 H, br. t, J = 6 Hz), 8.51 (1 H, br. t, J = 5 Hz), respectively; mass spectrum m/z 335 (M⁺, 0.3), 304 (0.3), 303 (0.6), 246 (12), 219 (40), 188 (24), 175 (24), 161 (50), 160 (100).
N-Phthaloylglycyl-α-deuteroglycylvaline methyl ester (72c)

The glycylglycylvaline derivative 72a (0.20 g, 0.53 mmol) was brominated and deuteriated (p. 141) using the methods described above.

Yield 0.14 g, 69% based on 72a; 97% 2H\textsubscript{1} incorporation; mp 240-241 \degree C;

mass spectrum m/z 376 (M\textsuperscript{+}, 1), 317 (10), 263 (5), 246 (7), 219 (11), 188 (14), 161 (35), 160 (100).

N-Phthaloylglycyl-α-methoxyglycylvaline methyl ester (72d).

The glycylglycylvaline derivative 72a (0.2 g, 0.53 mmol) was brominated (p. 141) and the resulting bromide treated with methanol (p. 145) using the methods described above. The crude material was chromatographed on silica (PF\textsubscript{254}, chromatotron) and recrystallized from dichloromethane/light petroleum to give 72d as a white solid.

Yield 0.16 g, 73% based on 72a, 1:1 mixture of diastereomers;

mp 190-200 \degree C;

\textsuperscript{1}H NMR (60 MHz) δ 0.92 (6 H, m), 2.17 (1 H, m), 3.45 (1.5 H, s), 3.46 (1.5 H, s), 3.74 (1.5 H, s), 3.75 (1.5 H, s), 4.44 (3 H, m), 5.51 (0.5 H, d, \(J = 8.3\) Hz), 5.57 (0.5 H, d, \(J = 8.5\) Hz), 6.98 (2 H, m) and 7.73 (2 H, m), 7.88 (2 H, m);

IR (NaCl, nujol) 3280, 1728, 1658, 1582, 1420 cm\textsuperscript{-1};
mass spectrum *m/z* 373 (M⁺-32, 2), 247 (49), 188 (31), 161 (49), 160 (100).

Anal. Calcd for C₁₉H₂₃N₃O₇: C, 56.3; H, 5.7; N, 10.4. Found: C, 55.9; H, 5.7; N, 10.2.

**N-Phthaloylglycyl-α,β-dehydroaspartic acid dimethyl ester (74)**

The glycylaspartic acid derivative 69 (0.4 g, 1.15 mmol) was treated with *N*-bromosuccinimide using the procedure described above. The reaction mixture was concentrated to dryness and the residue was dissolved in chloroform/water. The organic phase was washed with water (×3), dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Recrystallization of the product from dichloromethane/hexane gave 74 as a white solid.

Yield 0.32 g, 81 %;

mp 175-176 °C;

¹H NMR (300 MHz) δ 3.73 (3 H, s), 3.79 (3 H, s), 4.50 (2 H, s), 5.57 (1 H, s), 7.73 (2 H, m), 7.87 (2 H, m), 10.50 (1 H, s);

IR (NaCl, nujol) 3296, 1730, 1710, 1684, 1660, 1514, 1418, 1292, 714 cm⁻¹;

mass spectrum *m/z* 346 (M⁺, 2), 345 (3), 314 (5), 287 (51), 186 (23), 161 (47), 160 (100).

Anal. Calcd for C₁₆H₁₄N₂O₇: C, 55.5; H, 4.1; N, 8.1. Found: C, 55.5; H, 4.0; N, 8.1.
N-Benzoylvalyl-α-(diethyl malonyl)glycine methyl ester (80)

The valylglycine derivative 41a (0.15 g, 0.51 mmol) was brominated (p. 141), using the procedure described above, and the reaction mixture was cooled to 0 °C. A solution of the sodium salt of diethyl malonate in THF, prepared by addition of sodium hydride (-80 % in oil) (0.02 g, 0.67 mmol) to diethyl malonate (0.10 g, 0.62 mmol) in THF, was added to the cooled reaction mixture of the bromide and the resulting solution stirred for 1 hour at 0 °C and then at room temperature for 0.5 h. The reaction mixture was concentrated to dryness at reduced pressure and the residue was dissolved in ether and water. The organic phase was washed with 5 % aqueous NH₄Cl, dried over sodium sulfate, filtered, concentrated and chromatographed on silica (PF₂₅₄, chromatotron). Recrystallization from dichloromethane/light petroleum gave the 80 as a white solid.

Yield 0.04 g, 18%, based on 41a, 3:1 mixture of diastereomers; mp 159-163 °C;

1H NMR (300 MHz) δ 1.00 (6 H, m), 1.19 (3 H, t, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz), 2.25 (1 H, m), 3.73 (0.75 H, s), 3.75 (1 H, m) 3.77 (2.25 H, s), 4.20 (4 H, m), 4.59 (1 H, t, J = 8 Hz), 5.36 (1 H, dd, J = 4, 9 Hz), 6.84 (1 H, br. d, J = 8 Hz), 7.02 (1 H, br. d, J = 9 Hz), 7.50-8.00 (5 H, m);

IR (NaCl, nujol) 3324, 1734, 1660, 1632 cm⁻¹;

mass spectrum m/z 451 (M⁺+1, 3), 450 (M⁺, 3), 408 (9), 405 (5), 329 (12), 248 (9), 204 (11), 177 (49), 176 (92), 105 (100), 77 (25).
$m/z$ 450.2028 [(M$^+$) calcd for C$_{22}$H$_{30}$N$_2$O$_8$ 450.2002].

$N$-Benzoyl-$\alpha$-(diethyl malonyl)glycylvaline methyl ester (81)

Compound 81 was synthesized using the procedure described for the preparation of 80 with the exception that the glycylvaline derivative 28a was used instead of the valylglycine derivative 41a. Recrystallization from dichloromethane/hexane gave 81 as a white solid.

Yield 0.04 g, 18 % based on 28a, 1:1 mixture of diastereomers; mp 119-127 °C;

$^1$H NMR (300 MHz) $\delta$ 0.95 (6 H, m), 1.22 (3 H, t, $J = 7$ Hz), 1.33 (3 H, m), 2.17 (1 H, m), 3.66 (1.5 H, s), 3.70 (1 H, m), 3.75 (1.5 H, s), 4.18 (4 H, m), 4.44 (1 H, m), 5.40 (1 H, m), 7.35 (1 H, br. d, $J = 8$ Hz), 7.5-7.9 (5 H, m), 8.03 (0.5 H, br. d, $J = 8$ Hz), 8.20 (0.5 H, br. d, $J = 8$ Hz);

IR (NaCl, nujol) 3280, 1742, 1668, 1644, 1550, 1468 cm$^{-1}$; mass spectrum $m/z$ 450 (M$^+$, 3), 405 (5), 320 (16), 293 (45), 292 (32), 139 (55), 105 (100), 77 (50).

$m/z$ 450.1989 [(M$^+$), calcd for C$_{22}$H$_{30}$N$_2$O$_8$ 450.2002].

Anal. Calcd for C$_{22}$H$_{30}$N$_2$O$_8$: C, 58.7; H, 6.7; N, 6.2. Found: C, 58.4; H, 6.5; N, 6.4.

$N$-Benzoylallylglycylphenylalanine methyl ester (86)

The glycylphenylalanine derivative 45a (0.5 g, 1.5 mmol) was brominated (p. 141) using the procedure described above and the reaction mixture was cooled to room temperature.
Allyltributylstannane (1.0 g, 3.0 mmol) and azobisisobutyronitrile (AIBN) (catalytic amount) was added and the mixture was stirred, under nitrogen, overnight. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in chloroform/water (1:1, total 60 ml). The organic phase was separated, dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF254, chromatotron). Recrystallization from dichloromethane/hexane gave 86 as a white solid.

Yield 0.2 g, 34 % based on 45a, 1:1 mixture of diastereomers; mp 109-110 °C;

$^1$H NMR (300 MHz) δ 2.54 (1 H, m), 3.08 (1 H, m), 3.69 (1.5 H, s), 3.74 (1 H, s), 4.74 (1 H, m), 4.87 (1 H m), 5.10 (2 H, m), 5.5-5.9 (1 H, m), 6.85 (2 H, m), 7.0-7.9 (10 H, m);

IR (NaCl, nujol) 3274, 1746, 1641, 1551, 1227, 699 cm$^{-1}$;

mass spectrum m/z 380 (M+, 2), 339 (10), 218 (12), 202 (27), 174 (93 ), 105 (100), 77 (80).

Anal. Calcd for C$_{22}$H$_{24}$N$_2$O$_4$: C, 69.5; H, 6.4; N, 7.4. Found: C, 69.3; H, 6.3; N, 7.4.

$N$-Phthaloylglycylallylglycine methyl ester (87)

Compound 87 was synthesized using the procedure described for the preparation of 86 with the exception that the $N$-phthlloylglycylglycine derivative 66a (0.4 g, 1.44 mmol) was used instead of the $N$-benzoylglycylphenylalanine derivative 45a.
Recrystallization from dichloromethane/hexane gave 87 as white needles.

Yield 0.32 g, 71% based on 66a;
mp 181-183 °C;
1H NMR (300 MHz) δ 2.4-2.7 (2 H, m), 3.75 (3 H, s), 4.38 (1 H, s), 4.40 (1 H, s), 4.69 (1 H, dt, J_d = 7.5 Hz, J_t = 5.6 Hz), 5.12 (1 H, d, J = 11.7 Hz), 5.13 (1 H, d, J = 14.8 Hz), 5.65 (1 H, m), 6.39 (1 H, br. d, J = 7.5 Hz), 7.74 (2 H, m), 7.88 (2 H, m);
IR (NaCl, nujol) 3280, 1728, 1665, 1467, 1425 cm⁻¹;
mass spectrum m/z 316 (M⁺, 2), 274 (3), 256 (5), 161 (22), 160 (100).

N-Phthaloyl-β-alanine methyl ester (96)

N-Phthaloyl-β-alanine 97 (12.8 g, 89%) was prepared from alanine using the procedure described above. The compound 97 (6.0 g, 27.4 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (3.3 g, 27.7 mmol), and the resulting solution was stirred overnight, under anhydrous conditions (CaCl₂ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol/water gave 96 as colorless crystals.

Yield 5.2 g, 82%;
mp 72-73 °C (lit²⁹, 72 °C);
\(^1\text{H} \text{NMR} \ (60 \text{ MHz}) \ \delta \ 2.80 \ (2 \text{ H, t, } J = 7 \text{ Hz}), \ 3.75 \ (3 \text{ H, s}), \ 4.07 \ (2 \text{ H, t, } J = 7 \text{ Hz}), \ 7.6-8.3 \ (4 \text{ H, m}).

\textbf{N-Phthaloylglycine methyl ester (95)}

\textit{N-Phthaloylglycine} \ 70\text{a} (6.0 g, 29.3 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (3.5 g, 29.4 mmol), and the resulting solution was stirred overnight, under anhydrous conditions (CaCl}_2 \text{ guard tube}). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol/water gave 95 as colorless crystals.

Yield 5.1 g, 79 %;

mp 116-117 °C (lit\textsuperscript{191}, 116 °C);

\(^1\text{H} \text{NMR} \ (60 \text{ MHz}) \ \delta \ 3.73 \ (3 \text{ H, s}), \ 4.39 \ (2\text{H, s}), \ 7.4-8.0 \ (4 \text{ H, m}).

\textbf{N-Phthaloyl-\(\alpha\)-bromoglycine methyl ester (98)}

A mixture of \textit{N}-phthaloylglycine \ 95 (0.30 g 1.4 mmol) and \textit{N}-bromosuccinimide(0.25 g, 1.4 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 2 h. Another portion of \textit{N}-bromosuccinimide (0.25 g, 1.4 mmol) was added and the reaction was allowed to continue under the original conditions for 48 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), washed with water (2\times 50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography of the
residue on silica (PF$_2$54, chromatotron) and repeated recrystallizations from dichloromethane/hexane gave 98 as colorless crystals.

Yield 0.11 g, 27 %;  
mp 116-118 °C;  
$^1$H NMR (300 MHz) δ 3.88 (3 H, s), 6.68 (1 H, s), 7.80 (2 H m), 7.94 (2 H, m);  
IR (NaCl, nujol) 1734, 1255, 738cm$^{-1}$;  
mass spectrum m/z 268 (M$^+$-31, 1), 266 (M$^+$-31, 1), 240 (10), 238 (10), 218 (100), 213 (8), 211 (8), 190 (13), 160 (29).  
m/z 237.9508 [(M$^+$-CO$_2$Me) calcd for C$_9$H$_5$NO$_2$Br 237.9504].

$N$-Phthaloyl(β-bromo)-β-alanine methyl ester (100)  
A mixture of $N$-phthaloyl-β-alanine methyl ester 96 (0.5 g, 2.1 mmol) and $N$-bromosuccinimide (0.38 g, 2.1 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 2 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The solution was triturated with hexane to effect crystallization of crude 100. Recrystallization from dichloromethane/hexane afforded 100 as fine white crystals.

Yield 0.56 g, 84 %;  
mp 95-97 °C ;
$^1$H NMR (300 MHz) δ 3.64 (1 H, dd, $J_{\text{vic}} = 7.1$ Hz, $J_{\text{gem}} = 17.2$ Hz), 3.70 (3 H, s), 3.89 (1 H, dd, $J_{\text{vic}} = 8.0$ Hz, $J_{\text{gem}} = 17.2$ Hz), 6.59 (1 H, dd, $J_{\text{vic}} = 7.1$, 8.0 Hz), 7.20 (2 H, m), 7.90 (2 H, m); IR (NaCl, nujol) 1740, 1719, 705 cm$^{-1}$; mass spectrum m/z 312, (M$^+$-1, 0.5), 310 (M$^+$-1, 0.6), 282 (4.4), 280 (5.1), 254 (1.4), 252 (1.4), 240 (2.0), 238 (2.0), 232 (71.8), 200 (100.0), 190 (46.5), 173 (73.2), 172 (57.7), 160 (35.2).

Anal. Calcd for C$_{12}$H$_{10}$O$_4$N: C, 46.2; H, 3.2; N, 4.5. Found: C, 46.4; H, 3.2; N, 4.6.

**Competitive Reaction between 94 and 96 with N-bromosuccinimide**

A mixture of the β-alanine derivatives 94 (0.20 g, 0.97 mmol) and 96 (0.22, 0.97 mmol) and N-bromosuccinimide (0.17 g, 0.97 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250 W mercury lamp for 20 minutes. An aliquot of the reaction mixture was filtered through a plug of glass wool and analysed by $^1$H NMR spectroscopy. Another portion of N-bromosuccinimide (0.17 g, 0.97 mmol) was added to the the reaction mixture and the reaction allowed to continue under the original conditions for a further 20 minutes. An aliquot of the reaction mixture was, again, filtered through a plug of glass wool and analysed by $^1$H NMR spectroscopy.

**Competitive Reaction between 15c and 94 with N-bromosuccinimide**
A mixture of the glycine derivative 15c (0.19 g, 0.91 mmol), the β-alanine derivative 94 (0.20, 0.97 mmol) and N-bromosuccinimide (0.17 g, 0.97 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250 W mercury lamp for 20 minutes. An aliquot of the reaction mixture was filtered through a plug of glass wool and analysed by 1H NMR spectroscopy.

Competitive Reaction between 95 and 96 with N-bromosuccinimide

A mixture of the glycine derivative 95 (0.20 g, 0.91 mmol), the β-alanine derivative 96 (0.21, 0.91 mmol) and N-bromosuccinimide (0.16 g, 0.91 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250 W mercury lamp for 90 minutes. An aliquot of the reaction mixture was filtered through a plug of glass wool and analysed by 1H NMR spectroscopy.

N-Phthaloyl-β-methoxy-β-alanine methyl ester (115)

To a stirred solution of the bromo-β-alanine derivative 100 (0.50 g, 1.60 mmol) in dichloromethane (40 ml) was added methanol (0.31 g, 9.68 mmol). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure and the residue was recrystallized from dichloromethane/hexane to afford 115 as colorless needles.

Yield 0.39 g, 92 %;
mp 118-120 °C;
$^1$H NMR (300 MHz) $\delta$ 3.23 (1 H, dd, $J_{\text{vic}} = 6.4$ Hz, $J_{\text{gem}} = 16.6$ Hz), 3.38 (3 H, s), 3.44 (1 H, dd, $J_{\text{vic}} = 7.2$ Hz, $J_{\text{gem}} = 16.6$ Hz), 3.68 (3 H, s), 6.59 (1 H, dd, $J_{\text{vic}} = 6.4$, 7.2 Hz), 7.76 (2 H, m), 7.89 (2 H, m); IR (NaCl, nujol) 1779, 1743, 1716, 1326, 1215, 726 cm$^{-1}$; mass spectrum $m/z$ 263 (M+, 3), 248 (21), 200 (100), 190 (98).

Anal. Calcd for C$_{13}$H$_{13}$NO$_5$: C, 59.3; H, 5.0; N, 5.3. Found: C, 58.9; H, 4.9; N, 5.3.

N-Phthaloyl-trans-$\alpha,\beta$-dehydro-$\beta$-alanine methyl ester (116)

To a stirred solution of the bromo-$\beta$-alanine derivative 100 (0.50 g, 1.60 mmol) in dichloromethane (40 ml) was added triethylamine (0.24 g, 2.40 mmol). After 1 h, the reaction mixture was extracted with 10 % hydrochloric acid (2×50 ml), then water (50 ml), and dried over sodium sulfate. The dried solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from dichloromethane/hexane to give 116 as light yellow crystals.

Yield 0.32 g, 87 %;
mp 125-127 °C;
$^1$H NMR (300 MHz) $\delta$ 3.80 (3 H, s), 6.97 (1 H, d, $J = 14.9$ Hz), 7.82 (2 H, m), 7.93 (2 H, m), 7.94 (1 H, d, $J = 14.9$ Hz);
IR (NaCl, nujol) 1788, 1743, 1710, 1638, 1317, 1299, 1263, 1221, 1194, 1176, 981, 711 cm$^{-1}$;
mass spectrum $m/z$ 231 (M+, 55), 201 (75), 200 (100), 172 (48), 171 (53).
Reaction of 100 in Methanol

The bromo-β-alanine derivative 100 (0.50 g, 1.60 mmol) was dissolved in methanol (30 ml) and the solution was stirred for 1 h. The reaction mixture was concentrated to dryness and the residue was chromatographed on silica (PF254, chromatotron) to give the methoxy-substituted compound 115 and the cis-α,β-dehydro-β-alanine derivative 117. Both products were recrystallized from dichloromethane/hexane to afford pure 115 (0.30 g, 71 %) and 117.

Data for 117:
yield 0.04 g, 11 %;
mp 148-150 °C;
$^1$H NMR (300 MHz) δ 3.90 (3 H, s), 5.75 (1 H, d, $J = 11.3$ Hz) and 6.56 (1 H, d, $J = 11.3$ Hz), 7.83 (2 H, m), 7.95 (2 H, m);
IR (NaCl, nujol) 1788, 1737, 1239, 1146, 723 cm$^{-1}$;
mass spectrum $m/z$ 231 (M+, 15), 200 (100), 172 (75).
$m/z$ 231.0529 [(M$^+$), calcd for C$_{12}$H$_9$NO$_4$ 231.0532]

N-Phthaloyl-β-allyl-β-alanine methyl ester (118)

The bromo-β-alanine derivative 118 (0.60 g, 1.92 mmol), allyltributylstannane (1.27 g, 3.83 mmol) and azobisisobutyronitrile (AIBN) (catalytic amount) in benzene (30 ml) was refluxed, under
nitrogen, for 48 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed (×3) on silica (PF$_{254}$, chromatotron) to afford 118 as a colorless oil.

Yield 0.19 g, 36 %;
$^1$H NMR (60 MHz) δ 2.4-3.3 (4 H, m), 3.63 (3 H, s), 4.4-5.4 (3 H, m), 5.5-6.2 (1 H, m), 7.5-8.0 (4 H, m);
IR (NaCl, nujol) 1776, 1743, 1713, 720 cm$^{-1}$;
mass spectrum $m/z$ 242 (M$^+$-31, 5), 232 (70), 200 (100).
$m/z$ 232.0616 [(M$^+$- CH$_2$CHCH$_2$), calcd for C$_{12}$H$_{10}$NO$_4$ 232.0609].

$N$-Phthaloyl-$\beta$-phenylalanine methyl ester (121)

A solution of the bromo-$\beta$-alanine derivative 100 (0.50 g, 1.60 mmol) in dry benzene (30 ml) was treated with concentrated sulfuric acid (5 ml). The mixture was vigorously stirred for 72 h under a nitrogen atmosphere, poured into ice (40 g) and extracted with ethyl acetate (4×20 ml). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_{254}$, chromatotron) to afford 121. Recrystallization of from dichloromethane/hexane gave 121 as colorless crystals.

Yield 0.23 g, 45 %;
mp 81-82 °C;
$^1$H NMR (300 MHz) δ 3.26 (1 H, dd, $J_{\nuic} = 5.7$ Hz, $J_{\text{gem}} = 16.5$ Hz), 3.63 (3 H, s), 3.81 (1 H, dd, $J_{\nuic} = 10.1$ Hz, $J_{\text{gem}} = 16.5$ Hz), 5.84 (1 H, dd, $J_{\nuic} = 5.7$, 10.1 Hz), 7.2-7.4 (3 H,m), 7.53 (2 H, d, $J = 6.7$ Hz), 7.69 (2 H, m), 7.80 (2 H, m);
IR (NaCl, nujol) 1740, 1707, 1332, 1176, 717 cm\(^{-1}\);
mass spectrum \(m/z\) 309 (M\(^+\), 28), 278 (6), 249 (100), 236 (70).
Anal. Calcd for C\(_{18}\)H\(_{15}\)NO\(_4\): C, 69.9; H, 4.9; N, 4.5. Found: C, 69.4; H, 4.9; N, 4.5.

\(N\text{-Phthaloyl-}\gamma\text{-aminobutyric acid methyl ester (122)}\)

\(N\text{-Phthaloyl-}\gamma\text{-aminobutyric acid (123)}\) (11.7 g, 86 %) was prepared from \(\gamma\text{-aminobutyric acid using the procedure described above.} The compound (6.0 g, 25.8 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (3.1 g, 26.1 mmol), and the resulting solution was stirred overnight, under anhydrous conditions (CaCl\(_2\) guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol/water gave 122 as colorless crystals.

Yield 5.0 g, 79 %;
mp 87-88 °C (lit\(^{190}\), 87 °C);
\(\text{H NMR (60 MHz) } \delta 1.8-2.7 \text{ (4 } \text{H, m), } 3.65 \text{ (3 } \text{H, s), } 3.73 \text{ (2 } \text{H, t, } J = 6 \text{ Hz), } 7.5-8.0 \text{ (4 } \text{H, m);}\)

\(N\text{-Phthaloyl-}\gamma\text{-methoxy-}\gamma\text{-aminobutyric acid methyl ester (125)}\)

The \(\gamma\text{-aminobutyric acid derivative (0.60 g, 2.43 mmol)}\) and \(N\text{-bromosuccinimide (0.43 g, 2.43 mmol)}\) in refluxing carbon tetrachloride (50 ml), under nitrogen, was irradiated with a 250W
mercury lamp for 2 h. After the reaction mixture had cooled to room temperature, methanol (0.4 g, excess) was added and the resulting mixture stirred for 2 h under nitrogen. The reaction mixture was concentrated to dryness under reduced pressure and the residue dissolved in chloroform/water (1:1, total 100 ml). The organic phase was separated, dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_2$54, chromatotron) to afford 125. Recrystallization from dichloromethane/hexane gave 125 as colorless needles.

Yield 0.35 g, 52 %;
mp 84-85 °C;
$^1$H NMR (300 MHz) δ 2.3-2.5 (3 H, m), 2.6-2.8 (1 H, m), 3.35 (3 H, s), 3.66 (3 H, m), 5.34 (1 H, dd, $J = 5.9, 7.9$ Hz), 7.75 (2 H, m), 7.90 (2 H, m);
IR (NaCl, nujol) 1734, 1713, 1326, 723 cm$^{-1}$;
mass spectrum $m/z$ 277 (M$^+$, 1), 262 (2), 246 (7), 190 (100), 186 (68).
Anal. Calcd for C$_{14}$H$_{15}$NO$_5$: C, 60.6; H, 5.5; N, 5.1. Found: C, 60.1; H, 5.3; N, 5.1.

$N$-Phthaloyl-L-leucine methyl ester (126)

$N$-Phthaloyl-L-leucine 133a [10.0 g, 84 %; mp 118-120 °C (lit., 118.5-119.5 °C); [α]$^{23}$D -25° (c 0.01, acetone) (lit., [α]$^{27}$D -24 ° (c 2.9, ethanol))] was prepared from L-leucine using the procedure described above. $N$-Phthaloyl-L-leucine 133a (7.0 g, 26.8 mmol)
was added to methanol (150 ml), which had been pretreated with thionyl chloride (3.2 g, 26.8 mmol), and the resulting solution was stirred overnight under anhydrous conditions (CaCl₂ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to a viscous oil. Bulb-to-bulb distillation of the residue (170 °C, 0.05 mm) gave 126 as a colorless oil.

Yield 6.3 g, 86 %;

1H NMR (300 MHz) δ 0.93 (3 H, d, J = 6.8 Hz), 0.96 (3 H, d, J = 6.6 Hz), 1.49 (1 H, m), 1.97 (1 H, ddd, J = 4.4, 10.3, 14.3 Hz), 2.34 (1 H, ddd, J = 4.1, 11.6, 14.3 Hz), 3.73 (3 H, s), 4.96 (1 H, dd, J = 4.4, 11.6 Hz), 7.75 (2 H, m), 7.87 (2 H, m);

\([\alpha]^{23}_D -23^\circ (c 0.01, \text{acetone}).\)

**N-Phthaloyl-L-phenylalanine methyl ester (127)**

*N*-Phthaloyl-L-phenylalanine 133b [9.9 g, 92 %; mp 183-184 °C (lit., 183-185 °C); \([\alpha]^{23}_D -211^\circ (c 0.01, \text{acetone})\) (lit., \([\alpha]_D -212^\circ (c 1.9, \text{ethanol}))\)] was prepared from L-phenylalanine using the procedure described above. *N*-Phthaloyl-L-phenylalanine 133b (6.5 g, 21.0 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (2.5 g, 21.0 mmol), and the resulting solution was stirred overnight under anhydrous conditions (CaCl₂ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from ethyl acetate/light petroleum gave 127 as
colorless crystals. $^1$H NMR spectral data was consistent with that previously reported$^{192}$.

Yield 5.7 g, 84 %;
mp 73-75 °C;
$^1$H NMR (60 MHz) δ 3.60 (1 H, d, J = 9 Hz), 3.65 (1 H, d, J = 7 Hz), 3.78 (3 H, s), 5.17 (1 H, dd, J = 7, 9 Hz), 7.13 (5 H, s), 7:5-8.1 (4 H, m);
$[\alpha]^{23}_D$ -212° (c 0.01, acetone).

N-Phthaloylallylglycine methyl ester (131)

N-Phthaloylallylglycine 133c (10.5 g, 82 %) was prepared from allylglycine using the procedure described above. N-Phthaloylallylglycine 133c (6.0 g, 24.5 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (2.9 g, 24.5 mmol), and the resulting solution was stirred overnight under anhydrous conditions (CaCl$_2$ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from dichloromethane/hexane gave 131 as colorless crystals.

Yield 5.1 g, 81 %;
mp 44-46 °C;
$^1$H NMR (300 MHz) δ 3.00 (2 H, m), 3.75 (3 H, s), 4.9-5.1 (3 H, m), 5.72 (1 H, m), 7.74 (2 H, m), 7.86 (2 H, m);
IR (NaCl, nujol) 1713, 1697, 1254, 1218, 717 cm$^{-1}$;
mass spectrum m/z 259 (M$^+$, 3), 227 (4), 218 (27), 200 (100).
$m/z$ 259.0852 [(M$^+$), calcd for C$_{14}$H$_{13}$NO$_4$ 259.0845]

$N_\alpha,N_\varepsilon$-Dipthaloyllysine methyl ester (132)

$N_\alpha,N_\varepsilon$-Dipthaloyllysine 133d (13.2 g, 79 %) was prepared using the procedure described above except that 2 mole equivalents of phthalic anhydride was used. $N_\alpha,N_\varepsilon$-Dipthaloyllysine 133d (6.0 g, 14.8 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (1.8 g, 15.1 mmol), and the resulting solution was stirred overnight under anhydrous conditions (CaCl$_2$ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and concentrated to dryness under reduced pressure. Recrystallization of the residue from dichloromethane/hexane gave 132 as colorless crystals. $^1$H NMR spectral data of 132 was consistent with that previously reported$^{193}$.

Yield 5.15 g, 83 %; 
mp 98-99 ºC; 
$^1$H NMR (300 MHz) δ 1.38 (2 H, m), 1.6-1.9 (2 H, m), 2.29 (2 H, q, $J$ = 7.9 Hz), 3.65 (2 H, t, $J$ = 7.2 Hz), 3.73 (3 H, s), (4.84 (1 H, t, $J$ = 7.8 Hz), 7.7-7.9 (8 H, m).

$N$-Phthaloyl-L-glutamic acid dimethyl ester (130)

L-Glutamic acid dimethyl ester hydrochloride (6.0 g, 28.4 mmol), synthesized from L-glutamic acid using the procedure for the preparation of amino acid methyl ester hydrochlorides described above, was treated in benzene (50 ml) with diethylamine
(4.2 g, 57.5 mmol). The mixture was stirred for 1 h, diluted with diethyl ether (100 ml), filtered and concentrated under reduced pressure to an oil. The residue was dissolved in diethyl ether, filtered, concentrated under reduced pressure and the residue dissolved in acetone. Phthalic anhydride (4.2 g, 28.4 mmol) was added and the resulting mixture was stirred for 2 h. This mixture was concentrated under reduced pressure and the residue dissolved in chloroform and extracted with 10% aqueous hydrochloric acid. The organic phase was dried over sodium sulfate, filtered and concentrated to a viscous oil under reduced pressure. The oil was dissolved in methanol and the solution was treated with thionyl chloride (4.0 g, excess), with cooling. The mixture was refluxed for 3 h, concentrated under reduced pressure, dissolved in chloroform, washed successively with 10% aqueous sodium bicarbonate and water, dried over sodium sulfate, filtered and concentrated to a viscous oil. Chromatography of the residue on silica (PF$_{254}$, chromatotron) gave 130 as a clear, colorless oil.

Yield 5.5 g, 64 % based on glutamic acid dimethyl ester hydrochloride;

$^1$H NMR (300 MHz) $\delta$ 2.3-2.7 (4 H, m), 3.62 (3 H, s), 3.75 (3 H, s), 4.94 (1 H, dd, $J = 4.8, 9.7$ Hz), 7.77 (2 H, m), 7.88 (2 H, m).

$N$-Phthaloyl-$\gamma$-bromo-L-leucine methyl ester (135)

A mixture of the L-leucine derivative 126 (0.50 g, 1.82 mmol) and $N$-bromosuccinimide (0.32 g, 1.82 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a
250W mercury lamp for 2 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (PF<sub>254</sub>, chromatotron) to afford crude 135 as a viscous oil. Crystallization of the oil was effected from dichloromethane/hexane, which gave 135 as colorless crystals.

Yield 0.53 g, 82 %;  
mp 63-64 °C;  
<sup>1</sup>H NMR (300 MHz) δ 1.76 (3 H, s), 1.84 (3 H, s), 2.85 (2 H, m), 3.74 (3 H, s), 5.25 (1 H, dd, J = 4.4, 8.0 Hz), 7.77 (2 H, m), 7.89 (2 H, m);  
IR (NaCl, nujol) 1719 (br.) 1269, 1230, 1134, 717 cm<sup>-1</sup>;  
mass spectrum <i>m/z</i> 296 (M<sup>+</sup>-59, 11), 294 (M<sup>+</sup>-59, 11), 274 (100), 214 (86);  
[α]<sup>23</sup><sub>D</sub> -26° (c 0.01, acetone).

Anal. Calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>4</sub>Br: C, 50.8; H, 4.6; N, 4.0. Found: C, 50.9; H, 4.6; N, 4.0.

**N-Phthaloyl-β-bromo-L-phenylalanine methyl ester (138)**

A mixture of the phenylalanine derivative 127 (0.50 g, 1.62 mmol) and N-bromosuccinimide (0.29 g, 1.62 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 2 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica
(PF$_{254}$, chromatotron) to afford crude 138 as a viscous oil. Recrystallization of the oil was effected from dichloromethane/hexane, to afford both diastereomers of 138 as colorless crystals.

Diastereomer which crystallized first:

yield 0.27 g, 43 %;
mp 135-136 °C;
$^1$H NMR (60 MHz) $\delta$ 3.50 (3 H, s), 5.42 (1 H, d, $J = 10$ Hz), 5.95 (1 H, d, $J = 10$ Hz), 7.0-7.9 (9 H, m);
IR (NaCl, nujol) 1755, 1709, 708 cm$^{-1}$;
mass spectrum m/z 389 (M$^+$, 5), 387 (M$^+$, 5), 330 (6), 328 (6), 308 (32), 276 (100), 249 (80), 248 (96), 218 (75), 190 (52);
m/z 389.0076 [(M$^+$), calcd for C$_{18}$H$_{14}$NO$_4$Br 389.0086];
$[\alpha]^{23}_D$ -167° (c 0.01, acetone).
Anal. Calcd for C$_{18}$H$_{14}$NO$_4$Br: C, 55.8; H, 3.7; N, 3.6. Found: C, 55.7; H, 3.7; N, 3.6.

Diastereomer which crystallized second:

yield 0.25 g, 40 %;
mp 122-123 °C;
$^1$H NMR (60 MHz) $\delta$ 3.80 (3 H, s) 5.55 (1 H, d, $J = 10$ Hz), 5.92 (1 H, d, $J = 10$ Hz) and 7.00-7.65 (9 H, m);
IR (NaCl, nujol) 1774, 1758, 1718, 727 cm$^{-1}$;
mass spectrum m/z 389 (M$^+$, 3), 387 (M$^+$, 3), 330 (5), 328 (5), 308 (32), 276 (70), 249 (100), 248 (96), 218 (80), 190 (47);
m/z 389.0091 [(M$^+$), calcd for C$_{18}$H$_{14}$NO$_4$Br 389.0086];
$[\alpha]^{23}_D$ -60° (c 0.01, acetone).
Anal. Calcd for C_{18}H_{14}NO_{4}Br: C, 55.8; H, 3.7; N, 3.6. Found: C, 56.2; H, 3.7; N, 3.7.

Treatment of *N*-phthaloyl-α-aminobutyric acid methyl ester (128) with *N*-bromosuccinimide

A mixture of the α-aminobutyric acid derivative 128 (0.50 g, 2.02 mmol) and *N*-bromosuccinimide (0.36 g, 2.02 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 24 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF_{254}, chromatotron). No discrete products could be isolated.

Treatment of *N*-phthaloylaspartic acid dimethyl ester (129) with *N*-bromosuccinimide

A mixture of the aspartic acid derivative 129 (0.50 g, 1.72 mmol) and *N*-bromosuccinimide (0.31 g, 1.74 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 12 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure to afford unreacted 129 in 100% yield.
Treatment of *N*-phthaloyl-*L*-glutamic acid dimethyl ester (130) with *N*-bromosuccinimide

A mixture of the glutamic acid derivative 130 (0.50 g, 1.64 mmol) and *N*-bromosuccinimide (0.29 g, 1.64 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 6 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. $^1$H NMR spectrum of the residue showed mostly unreacted 130.

*N*-Phthaloyl-α,β,γ,δ-tetrahydro-α-aminobutyric acid methyl ester (140)

A mixture of the allylglycine derivative 131 (0.50 g, 1.93 mmol) and *N*-bromosuccinimide (0.69 g, 3.86 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 2 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_{254}$, chromatotron). Recrystallization from dichloromethane/hexane afforded 131 as colorless crystals.

Yield 0.23 g, 46 %;
mp 123-124 °C;
1H NMR (300 MHz) δ 3.80 (3 H, s), 5.63 (1 H, d, J\textsubscript{cis} = 10.0 Hz), 5.83 (1 H, d, J\textsubscript{trans} = 11.3 Hz), 6.35 (1 H, m), 7.62 (1 H, d, J = 11.2 Hz), 7.79 (2 H, m), 7.94 (2 H, m);
IR (NaCl, nujol) 1719 (br.), 1305, 1251, 720 cm\textsuperscript{-1};
mass spectrum m/z 257 (M\textsuperscript{+}, 71), 198 (100).

$m/z$ 257.0680 [(M\textsuperscript{+}), calcd for C\textsubscript{14}H\textsubscript{11}NO\textsubscript{4} 257.0688]

**N\textsubscript{α},N\textsubscript{ε}-Diphthaloyl-ε-methoxylysine methyl ester (147)**

A mixture of the lysine derivative 132 (0.50 g, 1.19 mmol) and N-bromosuccinimide (0.21 g, 1.19 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 3 h and allowed to cool to room temperature. Methanol (0.5 g, excess) was added and the resulting mixture was stirred overnight under nitrogen. The solvent was evaporated under reduced pressure and the residue dissolved in chloroform and water. The organic phase was partitioned with water (2×50 ml), dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF\textsubscript{254}, chromatotron) to afford 147 as a light yellow oil.

Yield 0.3 g, 56 %;

1H NMR (300 MHz) δ 2.1-2.6 (6 H, m), 3.30 (3 H, s), 3.72 (1.5 H, s), 3.73 (3 H, s), 4.83 (1 H, m), 5.23 (1 H, t, J = 7.4 Hz);
IR (NaCl, nujol) 1713, 1326, 720 cm\textsuperscript{-1};
mass spectrum m/z 450 (M\textsuperscript{+}, 1), 419 (3), 190 (100), 187 (85).
$m/z$ 419.1232 [(M\textsuperscript{+}-OMe), calcd for C\textsubscript{23}H\textsubscript{13}N\textsubscript{2}O\textsubscript{6} 419.1243].
N-Phthaloyl-β-bromovaline methyl ester (27)

N-Phthaloylvaline 149 (11.3 g, 89 %; mp 101-102 °C (lit., 101.5-102 °C)) was prepared from valine using the procedure for synthesizing N-phthaloylamino acids described above. N-Phthaloyl-valine 149 (6.0 g, 24.3 mmol) was added to methanol (150 ml), which had been pretreated with thionyl chloride (2.9 g, 24.3 mmol), and the resulting solution was stirred overnight under anhydrous conditions (CaCl₂ guard tube). The reaction mixture was concentrated under reduced pressure, diluted with methanol and the solvent evaporated to afford N-phthaloylvaline methyl ester 25 as a viscous oil.

A mixture of N-phthaloylvaline methyl ester 25 (1.0 g, 3.83 mmol) was N-bromosuccinimide (0.68 g, 3.83 mmol) in refluxing carbon tetrachloride (30 ml), under nitrogen, was irradiated with a 250W mercury lamp for 2 h. The reaction mixture was diluted with carbon tetrachloride (30 ml), partitioned with water (2×50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (PF₂₅₄, chromatotron) to afford crude 27 as a viscous oil. Crystallization of the oil was effected from dichloromethane/hexane, which gave 27 as colorless crystals. ¹H NMR spectral data of 27 was consistent with that previously reported.

Yield 1.11 g, 85 %;
mp 131-132 °C (lit., 129-131 °C);
1H NMR (60 MHz) δ 1.98 (3 H, s), 2.15 (3 H, s), 3.72 (3 H, s), 5.17 (1 H, s), 7.4-8.1 (4 H, m).

N-Phthaloyl-α,β-dehydrovaline methyl ester (148)

A solution of the bromovaline derivative 27 (0.50 g, 1.47 mmol) in freshly distilled tetrahydrofuran (20 ml) was treated with sodium hydride (-80% in oil) (0.07 g, 2.33 mmol). After 0.5 h, the solvent was evaporated and the residue dissolved in ethyl acetate and water. The organic layer was partitioned with water, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Recrystallization of the residue from dichloromethane/hexane afforded 148 as colorless crystals.

Yield 0.33 g, 87 %;
mp 81-82 °C (lit194., 66-72 °C);
1H NMR (60 MHz) δ 1.88 (3 H, s), 2.43 (3 H, s), 3.68 (3 H, s), 7.4-8.1 (4 H, m);
IR (NaCl, nujol) 1728 (br.), 1227, 720 cm⁻¹;
mass spectrum m/z 259 (M⁺, 1), 227 (55), 132 (87), 104 (100), 76 (43).
Anal. Calcd for C₁₄H₁₃NO₄: C, 64.8; H, 5.1; N, 5.4. Found: C, 64.7; H, 5.1; N, 5.4.

N-Phthaloyl-2,3-methanovaline methyl ester (151)

A stirred solution of the bromoleucine derivative 135 (0.50 g, 1.41 mmol) in freshly distilled tetrahydrofuran (20 ml), under nitrogen, was treated with sodium hydride (-80% in oil) (in 4
portions over 6 h, total 0.07 g, 2.33 mmol). After 24 h, the solvent was evaporated and the residue dissolved in ethyl acetate and water. The organic layer was partitioned with water, dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_2$54, chromatotron) to afford 151 as a colorless, viscous oil.

Yield 0.26 g, 67%;

$^1$H NMR (300 MHz) 8 1.20 (3 H, s), 1.51 (3 H, s), 1.52 (1 H, d, $J = 5.9$ Hz), 1.89 (1 H, d, $J = 5.9$ Hz), 3.65 (3 H, s), 7.76 (2 H, m), 7.88 (2 H, m);

IR (NaCl, nujol) 1770, 1734, 1440, 1302, 1251, 1212, 1143, 1104, 720 cm$^{-1}$;

mass spectrum $m/z$ 273 (M$^+$, 1), 257 (2), 241 (56), 132 (100),

$m/z$ 241.07488 [(M$^+$-MeOH), calcd for C$_{14}$H$_{11}$NO$_3$ 241.0739].

Treatment of N-phthaloyl-$\beta$-bromovaline methyl ester (27) with silver nitrate in water/acetone

The bromovaline derivative 27 (0.60 g, 1.76 mmol) and silver nitrate (0.45 g, 2.65 mmol) was added to a 1:1 mixture of water and acetone (total 50 ml) and the resulting mixture was stirred overnight. The reaction mixture was filtered, concentrated under reduced pressure and extracted with diethyl ether (3×30 ml). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_2$54, chromatotron) to afford the dehydrovaline derivatives 148 and 156, and the $\beta$-hydroxyvaline derivative 157. The
Compounds 148 and 157 were recrystallized from dichloromethane/hexane to afford colorless crystals.

**Compound 148:**

yield 0.04 g, 8 %;

**Compound 156:**

yield 0.15 g, 34 %;

\(^1\text{H NMR (300 MHz)}\) δ 1.92 (3 H, s), 3.79 (3 H, s), 5.11 (1 H, s), 5.14 (1 H, s), 5.38 (1 H, s), 7.75 (2 H, m), 7.89 (2 H, m);

IR (neat) 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1338, 1293, 1245, 1203, 1113, 915, 117 cm\(^{-1}\);

mass spectrum m/z 259 (M\(^+\), 8), 227 (20), 200 (100);

m/z 259.0863 [(M\(^+\)), calcd for Cl\(_4\)H\(_9\)NO\(_2\), 259.0845]

**Compound 157:**

Yield 0.21 g, 43 %;

mp 86-87 °C;

\(^1\text{H NMR (300 MHz)}\) δ 1.31 (3 H, s), 1.53 (3 H, s), 3.77 (3 H, s), 4.41 (1 H, br. s), 4.91 (1 H, s), 7.80 (2 H, m), 7.91 (2 H, m);

IR (NaCl, nujol) 3544, 1767, 1725, 1275, 717 cm\(^{-1}\);

mass spectrum m/z 262 (M\(^+-15\), 10), 246 (5), 230 (28), 219 (100), 188 (74), 187 (98), 160 (74).

Anal. Calcd for C\(_{14}\)H\(_{13}\)NO\(_2\): C, 60.6; H, 5.5; N, 5.1. Found: C, 60.6; H, 5.5; N, 5.1.

**N-Phthaloyl-β-hydroxy-L-valine methyl ester (157)**

The optically active β-hydroxyvaline derivative 157 was synthesized using the same procedure as for the preparation of the
racemic compound, described above, except that L-valine was used at the outset. The *N*-phthaloyl-L-valine methyl ester (27) intermediate prepared had $[\alpha]^{23}_D -68^\circ \,(c \,0.01, \text{ acetone})$. *N*-Phthaloyl-β-hydroxy-L-valine methyl ester 157 was recrystallized from dichloromethane/hexane as colorless crystals.

Yield 0.22 g, 45 %; 
mp 79-80 °C; 
spectral data identical to racemic 157 presented above; 
$[\alpha]^{23}_D -33^\circ \,(c \,0.01, \text{ acetone})$.

**Treatment of *N*-phthaloyl-β-bromovaline methyl ester (27) with silver nitrate in acetone**

The bromovaline derivative 27 (0.60 g, 1.76 mmol) and silver nitrate (0.45 g, 2.65 mmol) was added to acetone (50 ml, reagent grade) and the resulting mixture was stirred overnight. The reaction mixture was filtered, the solvent evaporated under reduced pressure and the residue dissolved in diethyl ether and water (1:1, total 60 ml). The organic phase was separated, dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF$_{254}$, chromatotron) to afford the dehydrovaline derivatives 148 and 156, and the β-hydroxyvaline derivative 157 in 14, 57 and 11 % yield, respectively.

**Treatment of *N*-phthaloyl-γ-bromo-L-leucine methyl ester (135) with silver nitrate in water/acetone**
The bromo-L-leucine derivative 135 (0.60 g, 1.69 mmol) and silver nitrate (0.43 g, 2.54 mmol) was added to a 1:1 mixture of water and acetone (total 50 ml) and the resulting mixture was stirred overnight. The reaction mixture was filtered, concentrated under reduced pressure and extracted with diethyl ether (3×30 ml). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure and chromatographed on silica (PF254, chromatotron) to afford the γ-hydroxyleucine lactone derivative 159 and the β-hydroxyvaline derivative 160. Both 159 and 160 were recrystallized from dichloromethane/hexane to afford colorless crystals.

Compound 159:
Yield 0.03 g, 7 %;
mp 124-125 °C (lit190, 131 °C);
1H NMR (300 MHz) δ 1.49 (3 H, s), 1.61 (3 H, s), 2.41 (1 H, dd, Jvic = 9.7 Hz, Jgem = 12.1 Hz), 2.51 (1 H, dd, Jvic = 11.6 Hz, Jgem = 12.1 Hz), 5.21 (1 H, dd, Jvic = 9.7, 11.6 Hz), 7.74 (2 H, m), 7.85 (2 H, m);
IR (NaCl, nujol) 1767, 1725, 1215, 1111 cm⁻¹;
mass spectrum m/z 260 (M+1, 1), 215 (70), 200 (100), 160 (60).
m/z 260.0910 [(M+), calcd for C₁₄H₁₄NO₄ 260.0923].
Anal. Calcd for C₁₄H₁₄NO₄: C, 64.8; H, 5.1; N, 5.4. Found: C, 64.2; H, 5.1; N, 5.3.

Compound 160:
Yield 0.33 g, 67 %;
mp 71-72 °C;
$^1$H NMR (300 MHz) δ 1.24 (3 H, s), 1.31 (3 H, s), 1.70 (1 H, br. s), 2.38 (1 H, dd, $J_{vic} = 8.8$ Hz, $J_{gem} = 15.1$ Hz), 2.50 (1 H, dd, $J_{vic} = 3.9$ Hz, $J_{gem} = 15.1$ Hz), 3.73 (3 H, s), 5.15 (1 H, dd, $J_{vic} = 4.0$, 8.8 Hz), 7.74 (2 H, m), 7.86 (2 H, m);
IR (NaCl, nujol) 3514, 1770, 1743, 1707, 1272, 1230, 1161, 720 cm$^{-1}$;
mass spectrum m/z 276 (M$^+$-15, 7), 233 (17), 215 (30), 200 (40), 174 (100);
$[\alpha]^{23}_D$ -22° (c 0.01, acetone);
Anal. Calcd for C$_{15}$H$_{17}$NO$_5$: C, 61.8; H, 5.9; N, 4.8. Found: C, 61.8; H, 5.9; N, 4.80.

**N-Phthaloyl-γ-hydroxy-leucine lactone (159)**

The bromo-L-leucine derivative 135 (0.60 g, 1.69 mmol) was stored in dry trifluoroethanol for 36 h. Evaporation of the solvent under reduced pressure afforded 159 in quantitative yield.
References


131. Organic Chemistry Department, University of Adelaide.

133. Easton, C. J.; Rositano, G., unpublished observations.


Appendix

Bond Distances (Å) for

*N-Phthaloyl-α,β-Didehydrovaline Methyl Ester* 148

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### Bond Angles (deg.) for N-Phthaloyl-α,β-Didehydrovaline Methyl Ester

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