Neighbouring Group Effects in Side Chain Reactions of Amino Acid Derivatives

by

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Last, but certainly not least, I am indebted to Lynne Wallace, for proof reading most of this thesis, for invaluable help in collating this thesis and for her continual support and friendship over the last year of my studies.
STATEMENT

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

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

Martin Merrett (B.Sc. Hons.) January 10, 1997
PUBLICATIONS

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


"Crystal Structure of (S)-3-Hydroxy-\text{-}N\text{-}tert\text{-}butyl\text{-}N\alpha\text{-}phthaloylvalinamide", C_{17}H_{22}N_{2}O_{4}, *Z. Krist.*, 1996, 211, 289 (Appendix 3).
ABSTRACT

Ionic chlorination of a β,γ-dehydrovaline derivative has been shown to occur regiospecifically at the γ-allylic position, which has been attributed to neighbouring group participation by the protected carboxy group.

anti-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative has been shown to occur stereoselectively, as a result of 1,2-asymmetric induction, to give diastereomers of a γ-functionalised valine derivative, which has been utilised in the stereocontrolled synthesis of a γ-hydroxyvaline diastereomer. This material was shown to be identical to the natural product, which was isolated from the plant species Kalanchoe daigremontiana.

1,4-Neighbouring group participation by a carboxy group has been discovered in hydrolysis reactions of N-phthaloyl β-bromophenylalanine, β-bromovaline and β-bromo-p-nitrophenylalanine derivatives using aqueous silver salts. The substitution process was enhanced when the carboxy group was protected as an amide rather than as an ester, which has been attributed to stabilisation of carbocation intermediates of reactions by the amido group, through a 1,4-interaction. The course of reactions of β-bromovaline and β-bromo-p-nitrophenylalanine derivatives is influenced by the neighbouring group effect of the protected carboxy group. Whereas elimination is the predominant reaction when the carboxy group is protected as an ester, substitution dominates when the carboxy group is protected as an amide. The effect of the neighbouring group to promote substitution over elimination has been exploited in the synthesis of a derivative of naturally occurring β-hydroxyvaline and a β-hydroxynitrophenylalanine derivative, which is a precursor to chloramphenicol.

The first example of 1,4-neighbouring group participation and anchimeric assistance in radical reactions has been discovered. The rates of bromination of
derivatives of N-phthaloyl-protected phenylalanine, tyrosine and nitrophenylalanine are enhanced when the carboxy group is protected as an amide rather than as an ester, which has been attributed to 1,4-neighbouring group participation and stabilisation of electron deficient transition states by the amido group. The stereoselectivity of hydrogen abstraction determined through investigation of bromination reactions of derivatives of N-phthaloyl-protected deuterophenylalanine is greater when the carboxy group is protected as an amide than when protected as an ester, consistent with neighbouring group participation by the amido moiety. The deuterium isotope effect measured from reactions of amide derivatives of deuterophenylalanine was lower than that in reactions of corresponding ester derivatives, consistent with neighbouring group participation and stabilisation of the reaction transition state. Stabilisation of electron deficient transition states by the amido group in the radical bromination reactions of phenylalanine derivatives has been shown to occur through direct interaction with the developing charge at the β-position, through investigation of reactions of derivatives of N-phthaloyl-p-methylphenylalanine.

A derivative of N-bromophenylalaninamide has been shown to react via an apparent 1,4-hydrogen shift, but further investigation revealed that the mechanism of reaction involves intermolecular electron transfer to an amidyl radical intermediate followed by intramolecular deprotonation at the β-benzylic position of an intermediate aryl radical cation species by the amido moiety. The stereoselectivity of hydrogen abstraction determined by investigating reactions of deuterated analogues of an N-bromophenylalaninamide derivative was shown to be consistent with an intramolecular reaction. A methylphenylalanine derived N-bromoamide has been shown to react with high regioselectivity at the β-position, consistent with an intramolecular reaction.
INTRODUCTION

Amino acids occur in nature as the fundamental constituents of proteins, peptides and many other species. To date, over five hundred naturally occurring amino acids have been reported, although only twenty occur commonly in proteins. A particular class of amino acids, the mono-substituted α-amino acids, possess a chiral α-carbon about which are arranged the amino and carboxy groups, the α-hydrogen and the side chain (R). It is the side chain which confers upon an amino acid its unique properties, which distinguish it physically, chemically and biologically. Biosynthesis of many of the non-proteinogenic amino acids is presumed to occur through functionalisation of the side chains of proteinogenic amino acids.

\[ \text{H}_3\text{N}^+\text{CO}_2^- \]

Amino acids have found importance as agrochemicals and pharmaceuticals, and in the food industry as flavours, taste enhancers and sweeteners. In addition, the use of analogues of natural amino acids has allowed a greater understanding of biochemical systems such as enzyme reaction mechanisms, protein conformations and regulatory interactions of peptides. As a result of their widespread natural occurrence, physiological activity and potential applications in biological systems, intense interest has been focussed on the synthesis of α-amino acids. α-Amino acids are sometimes unavailable from natural sources in quantities sufficient for thorough structural and biological testing and often it is only through the synthesis of these physiologically important compounds that it becomes possible to confirm both their structure and function.
Any synthesis of an α-amino acid should take into account the chirality at the α-carbon. One approach to the synthesis of unnatural amino acids involves the elaboration of proteinogenic α-amino acids through side chain modification. Complementary to the side chain modification of amino acids through the manipulation of pre-existing functionality is the regioselective free radical modification of proteinogenic amino acids. This latter approach is exemplified by the γ-chlorination and subsequent hydroxylation of lysine 2, as described by Kollonitsch et al. (Scheme 1), and has since been applied to the synthesis of the γ-hydroxyvaline diastereomers 3a and 3b (Scheme 2) and lactones of γ-hydroxy amino acids.

Scheme 1

Scheme 2
In halogenation reactions, regioselective hydrogen atom abstraction by halogen atom occurs as a result of several factors, which include product radical stability, steric effects and polar effects. Radical stability is important when there is substantial carbon–hydrogen bond cleavage in the transition state, that is, a relatively late transition state, and consequently the transition state species exhibits significant radical character. By hindering the approach of the abstracting species or by constraint of the conformation of the product radical, steric factors can also affect the regioselectivity of reaction. Polar effects refer to the activating and deactivating effects resulting from charge development in the reaction transition state. For example, polar effects were used to explain the regioselectivity observed in the chlorination of lysine, described above (Scheme 1). Since chlorine is more electronegative than carbon, hydrogen abstraction by chlorine atom occurs with separation of charge in the transition state and consequently a partial positive charge develops on the carbon from which the hydrogen atom is being abstracted. Hence, chlorine atom is considered to be electrophilic. The α- and ε-ammonium groups and the carboxy group are inductively electron withdrawing and therefore deactivate adjacent positions to attack by the electrophilic chlorine radical. Consequently, reaction occurs at the γ-position, the position most distant from both the α- and ε-positions.

Polar effects also play an important role in radical bromination reactions. N-Bromosuccinimide (NBS) is commonly employed in radical bromination reactions and can be used with a variety of substrates. For example, NBS is commonly used in the allylic bromination of alkenes, in benzylic bromination and, to a lesser extent, in the bromination of aliphatic substrates. Under standard conditions, which generally involve heating a solution of the substrate at reflux in carbon tetrachloride and initiation from either azobisisobutyronitrile (AIBN) decomposition or ultra-violet irradiation, the electrophilic bromine atom is the chain-carrying species. The most commonly accepted mechanism for reactions involving NBS is shown below (Scheme 3), in which the rate limiting step involves hydrogen abstraction by bromine atom from the substrate (RH).
Introduction

That is, the rate of reaction of a particular substrate reflects the ease with which hydrogen atom is abstracted from the substrate by bromine atom and hence reflects the rate of radical formation.

$$\text{Br}^\cdot + \text{RH} \rightarrow \text{HBr} + \text{R}^\cdot$$

$$\text{HBr} + \text{NBS} \rightarrow \text{succinimide} + \text{Br}_2$$

$$\text{Br}_2 + \text{R}^\cdot \rightarrow \text{RBr} + \text{Br}^\cdot$$

Polar effects have been used to explain the relative rates of reactions of substituted tolenes with NBS (Table 1).\(^{27,28}\) In these reactions a negative Hammett $\rho$ value was obtained, which indicates that hydrogen abstraction occurs with development of partial positive charge on the carbon from which the hydrogen is abstracted (Figure 1). As seen in the reactions involving hydrogen abstraction by chlorine radical, the development of a partial positive charge is disfavoured by electron withdrawing substituents and hence the rate of reaction is diminished in the presence of these groups. For example, the rate of hydrogen atom abstraction from toluene was determined to be twenty times that for reaction of the electron deficient $p$-nitrotoluene.\(^{27}\)

Figure 1. Polar transition state in hydrogen abstraction by bromine atom.
Table 1. Relative rates of reaction of substituted toluenes with NBS (per H) at 80 °C in carbon tetrachloride. 27

<table>
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<tr>
<th>Substituent</th>
<th>$k_{rel}$ (NBS)</th>
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<tr>
<td>$p$-OCH$_3$</td>
<td>11.7 ± 0.7</td>
</tr>
<tr>
<td>$p$-CH$_3$</td>
<td>2.56 ± 0.17</td>
</tr>
<tr>
<td>$p$-H (std)</td>
<td>1.00</td>
</tr>
<tr>
<td>$p$-Br</td>
<td>0.94 ± 0.03</td>
</tr>
<tr>
<td>$p$-NO$_2$</td>
<td>0.05</td>
</tr>
</tbody>
</table>

In comparison with reactions involving hydrogen abstraction by chlorine atom, those involving hydrogen abstraction by bromine atom are affected to a greater extent by product radical stability. For reaction involving hydrogen abstraction by bromine atom, a later transition state with more product radical character is involved. Consequently, bromine atom is a much more selective hydrogen abstracting species than chlorine atom. 26

Radical halogen abstraction reactions involving organotin reagents are also affected by product radical stability, steric effects and polar effects. 29 The mechanism of reactions involving organotin hydride reagents is shown in Scheme 4. The first irreversible step involving the organohalide is halogen abstraction by the stannyl radical ($R_3$Sn$^*$), which is a chain-carrying species in the process. The rate constant for the chain propagating reaction of an organotin radical with a substrate (R'Br) is dependent on the nature of R'. 30-32 Consequently, in a competitive experiment involving the substrates $R^1$Br and $R^2$Br, the relative rates of reaction with an organotin hydride reagent reflect the ease with which halogen is transferred from each substrate to the stannyl radical ($R_3$Sn$^*$), and hence reflect the relative rates of formation of the radicals $R^1*$ and $R^2*$. 
Introduction

Polar effects have been used to explain the relative rates of reactions of series of substituted benzyl bromides, benzyl chlorides\(^3\) and benzoyl chlorides\(^4\) with tributyltin hydride, in which positive Hammett \(p\) values were obtained. The positive Hammett \(p\) values indicate that halogen abstraction is facilitated by electron withdrawing substituents and that the reactions proceed with the development of a partial negative charge on carbon from which halogen is abstracted (Figure 2). This is in direct contrast to the trend observed in reactions involving hydrogen abstraction by halogen atoms, which proceed with the development of a partial positive charge on carbon bearing the hydrogen, and can be rationalised by considering the relative electronegativity of tin and carbon. Carbon is more electronegative than tin and therefore partial positive charge develops on the tin while the development of negative charge occurs on carbon. Hence, stannyl radicals are considered nucleophilic.

\[
\begin{align*}
R_3Sn^* + R'Br & \rightarrow R_3SnBr + R'^* \\
R_3SnH + R'^* & \rightarrow R'H + R_3Sn^*
\end{align*}
\]

Scheme 4

Figure 2. Polar transition state in bromine abstraction from benzyl bromides by tri-\(n\)-butyltin radical.
Introduction

The application of radical reactions in the functionalisation and elaboration of amino acids is limited by the virtual insolubility of the amino acids in the solvents typically used in such processes. This problem can be overcome by suitable protection of the amino acids, however such protection has been shown to markedly affect the regioselectivity of radical reactions. For example, whereas hydrogen atom abstraction by bromine atom from \( N \)-acyl-\( \alpha \)-amino acid derivatives generally favours formation of the corresponding \( \alpha \)-carbon centred radicals (Figure 3), \(^{35,36}\) formation of \( \alpha \)-carbon centred radicals is disfavoured in the chlorination of free amino acids, such as lysine 2 (Scheme 1), due to the strong deactivating effect of the protonated amino group.

![Figure 3. N-Acylamino acid \( \alpha \)-centred radicals.](image)

Stabilisation of an \( N \)-acylamino acid \( \alpha \)-centred radical occurs from overlap of the semi-occupied \( p \)-orbital of the radical with the \( \pi \)-orbitals of the electron donating (dative) amido and electron withdrawing (capto) carboxy substituents. Radicals of this type are extremely stable and are referred to either as captodative, \(^{37,38}\) merostabilised \(^{39}\) or push-pull stabilised radicals. \(^{40}\) The high stability of captodative radicals has been attributed to extended conjugation in the system. Extensive work in this area\(^ {41-50}\) has determined that the combined stabilisation provided by the substituents can be synergistic. As a result of the high stability and ease of formation of \( N \)-acylamino acid radicals, radical side chain functionalisation of \( N \)-acyl-protected \( \alpha \)-amino acid derivatives is limited since \( \alpha \)-centred
radical formation generally occurs in preference to side chain radical formation. This also destroys the chiral integrity at that position, leading to the formation of racemic products.

Maximum overlap of the semi-occupied $p$-orbital of the radical and the $\pi$-orbitals of the adjacent amido and carboxy substituents, and consequently maximum stability of the radical species, occurs when the $N$-acyl group and the carboxy group adopt a coplanar orientation. As the bulk of the side chain (R) increases, non-bonding interactions between this and the carboxy and amido groups also increase, resulting in the $\alpha$-carbon centred radical adopting a non-planar orientation such that maximum orbital overlap, and hence maximum radical stability, cannot be attained. An illustration of the effect of these non-bonding interactions on the stability of captodative radicals is seen in the radicals 4 - 6 (Figure 4). By examining the relative rates of reactions of the amino acid derivatives 7a - 9a with NBS to give the corresponding bromides 7b - 9b, Easton and Hay\textsuperscript{51}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Non-bonding interactions associated with planar conformation of the radicals 4 - 6.}
\end{figure}
showed that the rate of formation of the secondary radical 4 was greater than that of the tertiary radical 5, which in turn was greater than that of the tertiary radical 6. The relative rates of formation of these species were attributed to their relative stability.

The destabilising influence of steric interactions between substituents associated with planar conformations of N-acylamino acid α-centred radicals outweighs the normal thermodynamic preference for the production of tertiary radicals. Hence, treatment of the dipeptide derivative 10a with NBS results in the production of the bromide 10b in high yield.51,52

In comparison with N-acylamino acid derivatives, N-phthaloyl-protected amino acid derivatives undergo hydrogen atom transfer from the α-position much less readily, due to the steric and electronic effects imposed by the phthaloyl group. For example,
reaction of N-phthaloylglycine methyl ester 11a with NBS affords the bromide 11b considerably less efficiently than the reaction of N-benzoylglycine methyl ester 7a with NBS gives the bromide 7b, as determined through competitive experiments.\textsuperscript{53} Furthermore, whereas treatment of the N-benzoyl-protected dipeptide 12a with NBS affords the derivative 12b with incorporation of bromine onto the N-terminal glycyl moiety, bromine incorporation of the N-phthaloyl-protected derivative 13a occurred at the C-terminal glycine residue to give the bromide 13b.\textsuperscript{54}

Further investigation of the effect of the phthaloyl protecting group to limit \(\alpha\)-carbon centred radical formation showed that abstraction of the \(\alpha\)-hydrogen of \(N\)-phthaloylamino acid derivatives is disfavoured to the extent that reaction occurs regiospecifically on the side chains if suitably stabilised radicals can be formed.\textsuperscript{51,54-57}
Whereas treatment of the $N$-benzoyl-protected valine derivative 9a with NBS affords the dibromide 9b, with initial formation of the $\alpha$-centred radical 6, similar treatment of the $N$-phthaloylvaline derivative 14 with NBS affords the $\beta$-bromide 16 via the corresponding $\beta$-centred radical 15 (Scheme 5).

![Scheme 5](image)

The $N$-phthaloylphenylalanine derivatives 17 and 19 showed similar regioselectivity of reaction to that of the valine derivative 14 when treated with NBS. Treatment of the $N$-phthaloylphenylalanine derivative 17 with NBS afforded a 1:1 mixture of the $\beta$-bromide diastereomers 18a and 18b, via the $\beta$-centred side chain radical 21, while the amide 19 reacted to give a 1:1 mixture of the bromides 20a and 20b (Scheme 6), via the radical 22.

![Scheme 6](image)
In the reaction of the valine derivative 9a with NBS, the regioselectivity of hydrogen abstraction was determined through deuterium labelling experiments, by investigation of the relative rates of reactions of the deuterides 23a and 23b and the non-deuterated analogue 9a.\textsuperscript{51,55} Whereas the deuteride 23b reacted 3.7 times slower than the non-deuterated analogue 9a, the deuteride 23a reacted at the same rate. These relative rates of reaction establish that there is a deuterium isotope effect of 3.7 for \( \alpha \)-carbon–hydrogen bond cleavage, but there is no deuterium isotope effect for \( \beta \)-carbon–hydrogen bond cleavage. Hence, it was demonstrated that the bromination occurs via hydrogen atom abstraction from the \( \alpha \)-position of the valine derivative 9a and yields the dibromide 9b, the final product of the reaction with NBS.
In addition to determining the regioselectivity of hydrogen abstraction from reaction of the valine derivative 9a with NBS, the regioselectivity of hydrogen abstraction by chlorine atom was also investigated, by treatment of the deuterides 23a and 23b with sulfuryl chloride. In contrast to the reaction with NBS, hydrogen abstraction occurred mainly at the \( \beta \)-position to give the \( \beta \)-chloride 24, while no reaction at the \( \alpha \)-position was observed. A deuterium isotope effect of 1.3 for abstraction of the \( \beta \)-hydrogen was obtained in the reaction of the deuteride 23a.

Deuterium isotope effects arise due to the difference of nearly 6.3 kJ/mole between the zero-point energies of carbon-hydrogen and carbon-deuterium bonds, because of the effect of the larger mass of deuterium compared to hydrogen on stretching and bending frequencies. A portion of the energy associated with these stretching and bending frequencies can be lost in transition states during which these bonds are ruptured. In a symmetrical transition state, that is one in which there is an equal amount of bond breaking and bond making, most of this energy is lost and a large deuterium isotope effect will occur.
isotope effect will arise. If the transition state is not symmetrical, for example, if it possesses little bond breaking, only part of this energy is lost and a greatly reduced isotope effect will result. By way of illustration, consider hydrogen abstraction by bromine and chlorine atoms. Chlorine atom is a more reactive radical than bromine atom and hydrogen abstraction by the former involves an earlier transition state with less bond breaking, such that a lower deuterium isotope effect results.

The contrast in selectivity observed in the reactions of the N-benzoylvaline derivative 9a involving hydrogen abstraction by chlorine and bromine atom was interpreted in terms of the relative degrees of carbon–hydrogen bond homolysis in their transition states. The greater deuterium isotope effect of 3.7 for α-carbon–hydrogen bond cleavage in the reaction with NBS compared to the effect of 1.3 for β-carbon–hydrogen bond homolysis in the chlorination reaction indicates a greater degree of bond homolysis in the transition state in the former case. With little development of radical character in the transition state of the chlorination reaction, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups acting to retard attack at the adjacent α-position by the electrophilic chlorine atom. In the reaction involving NBS there is a greater degree of radical character in the transition state. Consequently, the reaction is more sensitive to radical stability and α-hydrogen abstraction occurs to give the captodative α-centred radical.

Brominated N-phthaloylamino acid derivatives have been used in the syntheses of a variety of side chain functionalised amino acid derivatives. For example, the stereoisomers 27 and 30 of [3-2H]-phenylalanine have been prepared, by treatment of the (S)-phenylalanine derived bromides 25 and 28 with deuterium gas over 5% palladium-on-carbon and hydrolysis of the resultant deuterides 26 and 29, respectively (Scheme 7).
Scheme 7

Under identical conditions to those described above, the deuterated phenylalaninamides 31a and 31b have also been prepared with retention of configuration at the β-position from the (S)-phenylalanine derived bromides 32a and 32b, respectively, by treatment with deuterium over 5% palladium-on-carbon.59
The deuterides 27 and 30 and the corresponding (2R)-isomers have been used to
determine the stereoselectivity of the hydrogen abstraction process in the reactions of (R)-
and (S)-phenylalanine with phenylalanine ammonia-lyase, an enzyme which catalyses the
elimination of ammonia and a proton from (S)-phenylalanine to give trans-cinnamic
acid.58

Brominated amino acid derivatives have also been utilised in syntheses of an
important class of amino acids, the hydroxy amino acids. For example, the
β-bromovaline derivative 33 derived from (S)-valine has been converted to the alcohol
34, a derivative of naturally occurring (S)-β-hydroxyvaline 35,60

![Scheme 8]

As a general procedure for the preparation of a wide variety of hydroxy amino
acids this method is limited, however, since the introduction of the functional group
occurs at the site of the most stable side chain radical, the position of which is determined
in the radical bromination reaction of the N-phthaloylamino acid derivative. Thus,
whereas the β-hydroxyvaline derivative 34 can be prepared from the corresponding
β-bromide 33, the derivatives 36a and 36b of the γ-hydroxyvaline isomers 3a and 3b
cannot be obtained directly using this approach, since formation of an unstable primary
radical would be required in the latter case. Therefore, an aim of the present work was to manipulate the regiospecifically functionalised bromide 33 in order to achieve relocation of the bromine functionality to the $\gamma$-position, a position removed from the site at which the most stable side chain radical is formed in the radical bromination with NBS, and to utilise this in the synthesis of naturally occurring $\gamma$-hydroxyvaline 37, of which the stereochemistry is unknown.

Three approaches were considered for this purpose, each of which involves initial elimination of hydrogen bromide from the $\beta$-bromide 33 to give the alkene 38, and subsequent elaboration to introduce functionality at the $\gamma$-position. In the first approach, it was thought that introduction of functionality at the $\gamma$-position could be achieved through allylic bromination of the alkene 38 to give the bromide 39. Following hydrolysis to the alcohol 40 and lactonisation, it was anticipated that hydrogenation would afford the lactone 42 (Scheme 9), from which the $\gamma$-hydroxyvaline diastereomers 3a and 3b could be obtained by hydrolysis. In addition to providing a route to $\gamma$-hydroxyvaline 37, the process is of further interest due to the possibility of stereoselectivity in the hydrogenolysis of the exocyclic double bond of the lactone 41. Therefore, the process could provide a stereocontrolled route to $\gamma$-hydroxyvaline 37.
The second approach considered for the synthesis of the γ-hydroxyvaline diastereomers 3a and 3b involves addition of molecular bromine to the alkene 38 and regioselective reduction at the tertiary position of the resultant dibromide 43 to give the γ-bromide isomers 44a and 44b (Scheme 10). Through hydrolysis of the γ-bromides 44a and 44b to the γ-alcohols 36a and 36b and deprotection, it was anticipated that the free amino acid diastereomers 3a and 3b could be obtained. Regioselective reduction of the dibromide 43 at the tertiary position using tri-n-butyltin hydride was expected. Following removal of a bromine to give the bridged radical 45, delivery of hydrogen atom to the more substituted end of the bridged intermediate\(^6\) should afford the γ-bromide diastereomers 44a and 44b.

![Scheme 9](image-url)
The third approach for introduction of functionality at the γ-position involves anti-Markovnikov addition of hydrogen bromide to the β,γ-alkene 38. Subsequent hydrolysis of the resultant γ-bromides 44a and 44b to the alcohols 36a and 36b and deprotection would thereby provide an alternative route to the γ-hydroxyvaline isomers 3a and 3b. Radical addition of hydrogen bromide to the alkene 38 was expected to occur regiospecifically to give the γ-bromides 44a and 44b, with delivery of hydrogen atom to the more substituted end of the bridged intermediate 45.

It was thought that both reduction of the dibromide 43 and addition of hydrogen bromide to the alkene 38 would proceed via the intermediate radical 45 to give the γ-bromides 44a and 44b. While it was envisaged that these reactions could be used to introduce bromine functionality at the γ-position, the reactions are of further interest due...
to the possibility of stereoselectivity, through 1,2-asymmetric induction. The radical 45 could adopt a preferred conformation due to minimisation of 1,3-allylic strain (A-strain) between the bulky phthalimido moiety and the adjacent side chain substituents such that delivery of hydrogen occurs in preference from the least hindered face of the molecule, thereby inducing stereoselectivity.

There have been many reports of 1,2-stereoinduction in radical reactions.\(^{62-81}\) The stereochemical outcome in these reactions is influenced by several factors, which include minimisation of 1,3-allylic strain,\(^{64-76}\) electronic effects\(^{69,77-80}\) and intramolecular hydrogen bonding.\(^{81}\) For example, the radical 47, produced from radical addition to the alkene 46, underwent hydrogen addition to give the adduct 48 in preference to the isomer 49 when the substituent R\(^2\) was larger than X, as a result of minimised strain between the carboxy oxygen and the substituents on the chiral centre (Scheme 11).\(^{65}\) As a result of conjugation between the radical centre and the ester group

![Scheme 11](image-url)
of the radical 47, the three carbons of the chiral centre, the radical centre and the carboxy group and the two oxygens of the ester lie almost in one plane. Allylic strain is smallest if the radical adopts a preferred conformation in which the carbon–hydrogen bond of the chiral centre points in the direction of the carbonyl oxygen (Figure 5). In this preferred conformation, the substituent X shields one face of the adjacent radical, while the substituent R² blocks the other. The bulk of these substituents controls the direction of attack. Hence, and by analogy, reduction of the dibromide 43 with tri-n-butyltin hydride and radical addition of hydrogen bromide to the alkene 38 have the potential to occur stereoselectively as a result of 1,2-stereoinduction.

Figure 5. Preferred conformation of the radical 47.

Thus, an aim of the present work was to manipulate the β-bromide 33 in order to relocate the bromine functionality to the adjacent γ-position and utilise this in the stereocontrolled synthesis of the γ-hydroxyvaline diastereomers 3a and 3b.

γ-Hydroxyvaline 37 was first recognised as a natural product when isolated in 1958 from the plant species Kalanchoe daigremontiana, in its leaves, stems and crowngall tumours. The relative stereochemistry of the natural product 37 has yet to be reported. Therefore, another aim of the present work was to isolate the natural product and determine its relative and absolute stereochemistry. Subsequent to its isolation in 1958,
γ-hydroxyvaline 37 was obtained as a degradation product of cephalosporin C, and has since been utilised to establish the infidelity of the proof-reading mechanism of the amino-acylation of tRNA by valyl-tRNA synthetases from *Saccharomyces cerevisiae* and *Escherichia coli*.

Few syntheses of γ-hydroxyvaline 37 have been described. A four step procedure beginning from hippuric acid 50 has been reported, however, the procedure required the separation of diastereomers and gave the racemic product 37 (Scheme 12). An alternative synthesis from α-keto-β-methyl-γ-butyrolactone 51 was neither diastereoselective nor enantioselective (Scheme 13).

Another approach involved free radical chlorination of (S)-valine, by treatment with either sulfuryl chloride or chlorine, followed by hydrolysis to give a mixture of the γ-hydroxyvaline diastereomers 3a and 3b (Scheme 2). The isomers were separated by crystallisation, affording the (2S,3S)-isomer 3a in 6% yield and the diastereomer 3b in 0.2% yield.

![Scheme 12](image-url)
Introduction

In summary, three approaches towards the stereocontrolled synthesis of the γ-hydroxyvaline diastereomers 3a and 3b investigated in the present work each involved elimination of hydrogen bromide from the β-bromide 33 to give the alkene 38. One procedure involved allylic bromination of the alkene 38 and conversion to the lactone 41, with subsequent asymmetric hydrogenation and deprotection to give the amino acids 3a and 3b. In addition, it was anticipated that the γ-bromides 44a and 44b could be obtained stereoselectively, through 1,2-stereoinduction, either by addition of bromine to the alkene 38 followed by regioselective reduction of the dibromide 43 at the tertiary position, or by anti-Markovnikov hydrobromination of the alkene 38. Hydrolysis of the γ-bromides 44a and 44b to the alcohols 36a and 36b and deprotection would then afford the free amino acids 3a and 3b. A further aim of this work was to isolate the natural γ-hydroxyvaline 37 and determine its relative and absolute stereochemistry. The results of these investigations are described in Chapter 1 of the Results and Discussion of this thesis.

Hydroxy amino acids are an important class of substituted amino acids. One particular type of hydroxy amino acids of interest are β-hydroxy amino acids, which are widespread in nature and play essential physiological roles. Examples of naturally occurring β-hydroxy amino acids include serine and threonine. β-Hydroxyphenylalanine
52a and β-hydroxytyrosine 52b have been implicated as precursors in the biosynthesis of the hypertensive agents adrenalin 53a and noradrenalin 53b,86 and of the antibiotic chloramphenicol 54,87-89 and as components of peptidases90 and esterases.5-7 They have been identified as components of biologically active cyclic peptides, such as vancomycin,91 lysobactin92,93 and bouvardin,94 and are themselves of interest as enzyme inhibitors.95

The conversion of brominated N-phthaloylamino acid derivatives into hydroxy amino acids and their derivatives has been investigated previously.60,96 Treatment of the bromoester 25 with aqueous silver nitrate in acetone afforded a 2:1 mixture of the alcohols 55 and 56, while the isomer 28 reacted to give the alcohol 55. Consistent with these results, a 1:1 mixture of the bromophenylalanine derivatives 25 and 28 afforded the corresponding alcohols 55 and 56 in the ratio 5:1 (Scheme 14).60
Introduction

Scheme 14

Similar treatment of a 1:1 mixture of the bromides 57a and 57b with aqueous silver nitrate afforded the alcohols 58 and 59 in the ratio 8:1 (Scheme 15), while a 1:1 mixture of the bromides 32a and 32b reacted to give solely the alcohol 60 (>99.9% d.e.) (Scheme 16).

Scheme 15

a) $R^1 = H$, $R^2 = Br$
b) $R^1 = Br$, $R^2 = H$
Silver salts were employed for the transformations of the brominated amino acid derivatives 25, 28, 32a, 32b, 57a, and 57b to the corresponding alcohols 55, 56, 58, 59, and 60, since mild, non-basic conditions were required due to the possibility of racemisation at the α-centre and elimination of hydrogen bromide, and also to avoid undesirable reactions of the phthalimido group due to its base-sensitivity. Using these conditions, no racemisation or unwanted side-reactions occurred. Silver ion induced reactions of organohalides have been shown to occur with graded SN1-SN2 character, the varying degree of which is dependent on the solvent, silver salt and bromide structure in each case, but that substitution of tertiary alkyl halides can normally be assumed to proceed via carbocation type intermediates. Given the graded nature of reactions involving aqueous silver salts, reactions involving their use are likely to proceed via electron deficient intermediates.

Subsequent deprotection of both the ester 55 and the amide 60 through acid catalysed hydrolysis afforded the free amino acid 61. Hence, reactions involving hydrolysis of brominated N-phthaloylamino acid derivatives to give corresponding hydroxylated amino acid derivatives have the potential to be used in syntheses of a variety of hydroxy amino acids.
The dramatic increase in the stereoselectivity of reaction of the bromoamides 32a and 32b compared to the bromoesters 25 and 28, and 57a and 57b, was attributed to neighbouring group participation by the amido substituent.96 The bromoamide 32b reacts with complete retention of configuration to give the alcohol 60, while the bromoamide 32a reacts with inversion of stereochemistry to give the same. Hence, it was postulated that the high stereoselectivity of reaction of the bromoamide 32b was due to greater stabilisation of the carbocation intermediate 62 by the amido group (Figure 6), than by the ester group in the reactions of the esters 25 and 28, and 57a and 57b. As a consequence of this stabilisation, the conformation of the carbocation was presumed to be locked, such that nucleophilic attack by water could only occur from the face opposite the amido group to give the alcohol 60.96

Figure 6. Stabilisation of the carbocation 62 by the amido group.
Introduction

Neighbouring group participation is a term which encompasses all reactions which involve non-electrostatic, through-space interactions between groups within the same molecule. This phenomenon occurs when a substituent within a molecule interacts with, or stabilises an intermediate or transition state by becoming bonded or partially bonded to the reaction centre. If the transition state of a rate-determining step is stabilised in this way, an increased reaction rate results and the neighbouring group participation is then said to provide anchimeric assistance. Reactions involving neighbouring group participation can be classified as 1,\(x\)-, where \(x\) is the number of ring atoms in the cyclic transition state structure. For example, for 1,4-neighbouring group participation, such as that shown in Figure 6, a 4-membered cyclic transition state structure is formed.

Many examples of neighbouring group participation involving a wide variety of functional groups have been described previously. One of the most commonly encountered forms of neighbouring group participation occurs in halogen addition to alkenes. The intermediate cation contains an electron-deficient carbonium ion carbon and a halogen with non-bonding electron pairs. Consequently, there is a tendency for overlap to produce a cyclic halonium ion (Figure 7). The existence of halonium ion species is evident from the \textit{trans}-addition of halogens to alkenes.

\[ \text{Figure 7. Formation of a cyclic halonium ion.} \]
The extent of interaction and neighbouring group participation by the halogen with the adjacent carbonium ion, and hence the symmetrical nature of the halonium ion intermediate decreases in the order I > Br > Cl, which is consistent with the known ease with which these elements increase their valency. Consequently, the bridged nature of iodonium and bromonium ions is greater than that of chloronium ions, such that the carbonium ion character of the chloronium ion is much greater than that of the corresponding bromonium and iodonium ions. Halonium ions have been proposed as intermediates in halolactonisation reactions of γ,δ-unsaturated carboxylic acids and ester derivatives.

Carbonyl compounds such as ketones and aldehydes can be involved in neighbouring group participation including the rare 1,4-participation. Solvolysis of the ketone 63 in trifluoroacetic acid occurs ca. $10^7$ times faster than the substitution of neopentyl tosylate 64, which was attributed to direct participation by the carbonyl group. In some cases, participation by a carbonyl group occurs through reaction of an adduct of the nucleophile and the carbonyl compound, such as an acetal, and not the carbonyl group itself (Scheme 17).

\[ \text{Me} \quad \text{Me} \]
\[ \text{O} \quad \text{O} \]
\[ \text{Ot} \quad \text{Ot} \]
\[ 63 \quad 64 \]
Ester and amide groups can also be involved in neighbouring group participation. The extent of neighbouring group participation and anchimeric assistance displayed by amides is known to be larger than that shown by esters. For example, Winstein et al. showed that the solvolysis of trans-2-benzamidocyclohexyl tosylate 65 in absolute ethanol proceeds 200 times faster than reaction of the corresponding trans-2-acetoxycyclohexyl tosylate 66 where neighbouring group participation had already been demonstrated. Consistent with this proposal, the oxygen of an amide is approximately $10^6$ times more basic than the oxygen of an ester.

1,5-Neighbouring group participation by a benzamido group has been demonstrated in the hydrolytic rearrangement of the diastereomeric benzamides 67, which was utilised in the stereocontrolled synthesis of chloramphenicol (Scheme 18).
The chemical and biochemical implications of amide participation in reactions of amino acid derivatives have attracted considerable attention.\textsuperscript{113,116-123} For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds,\textsuperscript{117-121} while amides derived from either the amino\textsuperscript{116,122} or carboxy group\textsuperscript{123} of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, mainly via 1,5-participation. Neighbouring group participation by an acetamido group has been identified in the hydrolysis reactions of the $N$-acylimidazole derivatives of $N$-acetylphenylalanine and $N$-acetylvaline 69 and 70, respectively, which reacted 100-250 fold faster than corresponding compounds which lacked an acetamido substituent.\textsuperscript{122}
Whereas 1,5-neighbouring group participation by amido groups is common. 1,4-participation by amides is extremely rare. In the reactions of the phenylalaninamides $32\text{a}$ and $32\text{b}$ to give the alcohol $60$, described above, 1,4-neighbouring group participation by the amido substituent was proposed to account for the high stereoselectivity compared to that of the reactions of the corresponding bromoesters $25$ and $28$. Not only can participation by a neighbouring group affect the stereoselectivity of reaction, it can also affect the rate of reaction. Many reactions have been shown to occur faster when substituted with an amido group rather than with an ester. Thus, it was envisaged that the effect of the neighbouring group to enhance the stereoselectivity of reaction of the phenylalanine derivatives $32\text{a}$ and $32\text{b}$ relative to the corresponding esters $28$ and $25$ could also affect the rates of the reactions. Hence, an aim of the present work was to investigate the effect of the carboxy protecting group on the rates of reactions of the phenylalanine derivatives $25$, $28$, $32\text{a}$ and $32\text{b}$ with aqueous silver salts in direct competitive experiments, in order to examine the importance of neighbouring group effects in these systems.

The reactions of the bromophenylalanine derivatives $25$, $28$, $32\text{a}$ and $32\text{b}$ are likely to proceed via electron deficient intermediates, due to the graded $S_N1$-$S_N2$ nature of reactions of organohalides involving silver ions. Therefore, in order to probe the electronic nature of the neighbouring group effect in these reactions, the nitrophenylalanine derivatives $71\text{a}$, $71\text{b}$, $72\text{a}$ and $72\text{b}$ were chosen as additional substrates for the investigation, since formation of electron deficient intermediates from reactions of these substrates would be disfavoured due to the destabilising influence of the electron withdrawing nitro-substituent on those intermediates. Hence, a further aim of the work was to investigate the relative rates of reactions of the nitrophenylalanine derivatives $71\text{a}$, $71\text{b}$, $72\text{a}$ and $72\text{b}$ in competitive experiments.
In addition to investigating the electronic nature of the neighbouring group effect, the generality of the process was also of interest. The phenylalanine-derived substrates 25, 28, 32a, 32b, 71a, 71b, 72a and 72b each contain an aromatic side chain. Therefore, in order to determine the influence of the aromatic group on the neighbouring group effect the bromovaline derivatives 33 and 73 were chosen for study, since these substrates contain a non-aromatic side chain. Hence, another aim of the work was to investigate the relative rate of reactions of the valine derivatives 33 and 73 in competitive experiments.

The relative stereochemistry of the alcohol 60 produced from reaction of the bromophenylalanine diastereomers 32a and 32b is identical to that of the natural product, chloramphenicol 54. By analogy with that system, it was anticipated that the hydrolysis reactions of the bromonitrophenylalanine derivatives 72a and 72b could occur with the same relative stereochemistry. Hence, a further aim of the work described...
here was to utilise the expected effect of the protected carboxy group to enhance the stereoselectivity of hydrolysis reactions of the (2S)-enantiomers of the bromides 72a and 72b in order to prepare the amino acid 74. The racemate of the amino acid 74 has previously been elaborated to chloramphenicol 54, and therefore an enantioselective synthesis of the alcohol 74 would provide a stereocontrolled route to chloramphenicol 54.

Chloramphenicol 54, which was isolated in 1974 from *Streptomyces venezuelae*, was one of the first broad spectrum antibiotics to be used medicinally and it is the only naturally occurring antibiotic which is economically produced on an industrial scale by synthesis rather than fermentation. Various syntheses of the natural product 54 have been reported. The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol but a disadvantage of that and other approaches is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide 75 has been reported. Alternatively, (S)-phenylalanine has been used to obtain the chloramphenicol precursor 68 in a multi-step synthesis, in which diastereocontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide 67 (Scheme 18).
In summary, it was envisaged that the nature of the neighbouring group effect used to explain the stereoselectivity of the hydrolysis reactions of the bromophenylalanine derivatives 25, 28, 32a and 32b could be examined through investigation of relative rates of reaction. The bromonitrophenylalanine derivatives 71a, 71b, 72a and 72b were thought to be suitable substrates to study the electronic nature of the intermediates of the reactions, while the reactions of the bromovaline derivatives 33 and 73 could be used to investigate the generality of the neighbouring group effect. Furthermore, it was anticipated that the stereoselectivity of hydrolysis of the phenylalaninamides 32a and 32b could be exploited with the (2S)-enantiomers of the nitrophenylalanine derivatives 72a and 72b and utilised in the stereocontrolled synthesis of the amino acid 74, a precursor to chloramphenicol 54. The results of these investigations are described in Chapter 2 of the Results and Discussion.

Although much less prevalent than in their ionic counterparts, neighbouring group participation is also seen in radical reactions. Anchimerically assisted bond homolyses of ortho-substituted aromatic peresters by neighbouring sulfide and thioether groups have been well documented. Neighbouring group participation has been proposed by Asmus et al., in which three electron bonded species occur as intermediates, for example, in the reaction of amino acids with hydroxyl radical [HO::NH2-CHRCO2-] and in the radical induced oxidation of sulfides [RR'S::OCOR']. Coordination of sulfur atom to bromine [R2S::Br] and chlorine [R2SO::Cl] has also been demonstrated, as has a three electron bond between sulfur and phosphorus and sulfur and the amino group of an amino acid.

Anchimeric assistance has been observed in hydrogen atom abstractions, in the vicinal bromination of alkyl bromides and in reactions of tert-butoxy radical with tetraethyl-silane, germaine and stannane. In the latter case, 1,3-participation in the hydrogen atom abstraction reaction occurs through stabilisation of the incipient radical in the transition state by the neighbouring organometallic group (MEt3) if attack by the
tert-butoxy radical occurs anti- to the MEt$_3$ group (Figure 8). Results of studies by Wilt et al.$^{148}$ have also been shown$^{147}$ to illustrate neighbouring group participation in halogen transfer reactions in a similar manner.

![Figure 8. Hydrogen abstraction by tert-butoxy radical with neighbouring group participation.](image)

**Figure 8.** Hydrogen abstraction by tert-butoxy radical with neighbouring group participation.

Of all the examples of neighbouring group participation in radical reactions, 1,3-participation by bromine is the most common. Radical formation adjacent to an electronegative group generally is disfavoured due to inductive deactivation. In the radical bromination of alkyl bromides, however, the position adjacent to the electronegative bromo-substituent is activated toward hydrogen abstraction. An illustration of this activation is seen in the free radical bromination of alkyl bromides, which gives a preponderance of vicinal dibromides.$^{61}$ For example, bromination of bromocyclopentane afforded *trans*-1,2-dibromocyclopentane in 90% yield, while bromocyclohexane gave *trans*-1,2-dibromocyclohexane in 94% yield.$^{146}$ The regioselectivity and stereoselectivity of bromination is due to bridging by the neighbouring bromine (Figure 9),$^{61}$ which is similar to that described above for halonium ion bridging. Attack on this bridged intermediate by bromine atom from the face opposite the bonded bromine results in formation of *trans*-products in each case.
Further evidence for bridged species in the vicinal bromination of alkyl bromides has been obtained from the isolation of optically active products, where racemic materials are expected in the absence of bridging, and from ESR studies.\textsuperscript{149-154}

In addition to influencing the regioselectivity and stereoselectivity of bromination, neighbouring group participation by bromine can also affect the rate of hydrogen abstraction from adjacent positions. For example, tertiary hydrogen abstraction from the bromobutane \textbf{76} by bromine atom occurs approximately 8 times faster than tertiary hydrogen abstraction from 2-methylbutane \textbf{77}.\textsuperscript{61}

In all the examples described above involving anchimeric assistance in hydrogen atom abstraction reactions, 1,3-neighbouring group participation was involved. The analogous 1,4-neighbouring group participation has not been observed. The bromination reactions of the phenylalanine, nitrophenylalanine and tyrosine\textsuperscript{96} derivatives \textbf{17} and \textbf{19}. 

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure9}
\caption{Bridged intermediate in the vicinal bromination of alkyl bromides.}
\end{figure}
Introduction

78a and 78b and 79a and 79b, respectively, could involve interaction of the carboxy protecting group with the electron deficient radical intermediates. Therefore, it was envisioned that these materials could be used to probe for possible neighbouring group participation in their radical bromination reactions. Furthermore, it was anticipated that the reverse transformations of the product bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b to the corresponding reduced materials 17, 19, 78a, 78b, 79a and 79b using triphenyltin hydride could be utilised to investigate the possibility of neighbouring group participation, since the radical intermediates of these reactions are identical to those of the bromination reactions. As part of this investigation, it was thought that the deuterides 26, 29, 31a and 31b\textsuperscript{58,59} could be used to determine the stereoselectivity of the hydrogen abstraction process. The results of these investigations are described in Chapter 3 of the Results and Discussion.

\begin{align*}
\text{p-NO}_2\text{-Ph} & \quad \text{p-AcO-Ph} \\
\begin{array}{c}
\text{PhthN}^\uparrow \text{COR} \\
\text{78} \\
a) R = \text{OMe} \\
b) R = \text{NHCMe}_3
\end{array} & \\
\begin{array}{c}
\text{PhthN}^\uparrow \text{COR} \\
\text{79} \\
a) R = \text{OMe} \\
b) R = \text{NHCMe}_3
\end{array}
\end{align*}

\begin{align*}
\text{p-AcOPh} & \\
\text{PhthN} \quad \text{CO}_2\text{Me} \\
\text{80} & \\
a) R^1 = \text{H}, R^2 = \text{Br} \\
b) R^1 = \text{Br}, R^2 = \text{H}
\end{align*}

\begin{align*}
\text{p-AcOPh} & \\
\text{PhthN} \quad \text{CONHCMe}_3 \\
\text{81} & \\
a) R^1 = \text{H}, R^2 = \text{Br} \\
b) R^1 = \text{Br}, R^2 = \text{H}
\end{align*}
The work described in Chapter 3 of the Results and Discussion involves an investigation of the possibility of neighbouring group participation in intermolecular atom abstractions. In addition to the possibility of participation in intermolecular reactions, it was thought that the amido group could also be involved in intramolecular 1,4-hydrogen abstraction from the benzylic position, through reaction of the corresponding amidyl radical 82 to give the radical 22 (Scheme 19).

Scheme 19

Intramolecular atom or group transfer in radical reactions can be considered to be another type of neighbouring group participation, of which many examples have been examined previously. The most commonly encountered group transfers involve 1,2-shifts, where a group such as phenyl migrates onto an adjacent atom. Hydrogen atom can also migrate, although 1,2-shifts of hydrogen appear to be unknown. For intramolecular hydrogen abstraction to occur, an approximately colinear arrangement of the bond being broken and the bond being formed in the transition state is required. Thus, reactions in which the transition state deviates farthest from linearity are either unknown, such as 1,2-migration, or are extremely uncommon, such as 1,3- and 1,4-migration. 1,5-Hydrogen transfers predominate these rearrangements. Although a linear transition state can be attained in 1,6-hydrogen transfers, these occur to a much lesser extent due to entropic factors.
1,4-Hydrogen shifts are uncommon in solution$^{157-171}$ and do not occur unless the isomerisation is strongly exothermic. A 1,4-hydrogen shift occurs upon photolysis or treatment with benzoyl peroxide of the N-chloroamide 83 (Scheme 20).$^{157}$ In this case, the amidyl radical 84 undergoes hydrogen migration to give the primary radical 85, which abstracts chlorine atom to afford the β-chloride 86. The unfavourable 1,4-shift is preferred over abstraction of hydrogen from the solvent, presumably due to steric hindrance of the amidyl radical 84.$^{157}$

Scheme 20

1,4-Hydrogen shifts have been proposed following addition of thiyl radicals to alkenes$^{158-160}$ or alkynes.$^{161}$ The driving force in these cases has been attributed to the exothermicity of the reactions, together with the stability of the product radicals. A 1,4-shift of hydrogen has been observed in reaction of 2,4,6-tri-tert-butylphenyl 87,$^{164,165}$ which involves quantum-mechanical tunnelling to give the radical 88. In this case, unusually large deuterium kinetic isotope effects have been observed.
The processes by which rearrangements of this type occur are often more complicated than the apparent overall shift. The 1,4-hydrogen shift from reaction of the radical $87$, which involves quantum mechanical tunnelling, is one such example.$^{164,165}$ Another example in which the overall structural change in the substrate molecule belies the complexity of the process is seen in the photochemistry of phthalimides.$^{172}$ Photolysis of the phenylalanine derivative $89$ in acetonitrile affords phthalimide $90$ and the cinnamate ester $91$, with reaction via an apparent 1,5-hydrogen transfer. The process by which this occurs involves electron transfer from the phenyl substituent to the phthalimido group followed by 1,5-proton transfer, with subsequent 2,3-bond cleavage (Scheme 21).$^{172}$

In order to investigate the possibility of intramolecular 1,4-hydrogen abstraction by the amidyl radical, the $N$-bromoamide $92$ was chosen for study, anticipating that photolysis of this material would give the amidyl radical $82$, which could then undergo hydrogen abstraction, either inter- or intramolecularly, to give the $\beta$-bromide diastereomers $20a$ and $20b$. The results of this investigation are described in Chapter 4 of the Results and Discussion of this thesis.
In the work described in Chapter 3 of the Results and Discussion of this thesis, the possibility of direct interaction of the amido group with the radical centre in radical bromination reactions of phenylalanine derivatives using NBS was investigated. In addition to the possibility of direct interaction, there is also a possibility of interaction of the carboxy protecting group with the aromatic amino acid side chain in these bromination reactions. In order to investigate this possibility, the p-methylphenylalanine derivatives
93 and 94 and the valine derivatives 95 and 96 were thought to be suitable substrates. The valine derivatives 95 and 96 provide the opportunity to probe for neighbouring group participation in their side chain bromination reactions in the absence of an aromatic side chain substituent. Since these derivatives do not contain an aromatic side chain, it is obvious that interaction of the carboxy protecting group with a side chain π-system cannot occur. The p-methylphenylalanine derivatives 93 and 94 contain two benzylic positions at which reaction could take place, at the β-position and at the p-methyl substituent. Therefore, the p-methyl substituent provides an internal standard within each molecule with which to probe the bromination reactions at each of these centres. Hence, an aim of the work described was to investigate the bromination reactions by carrying out competitive reactions, in order to determine the relative rates of reaction at the β-positions of the valine derivatives 95 and 96, and at each of the benzylic positions of the methylphenylalanine derivatives 93 and 94.

![Structures](image-url)
While the methylphenylalanine derivatives 93 and 94 could be used to investigate the possibility of interaction of the carboxy substituent in the bromination reactions using NBS, the amide 94 is of additional interest since it could be used to further investigate the possible intramolecular 1,4-hydrogen shift in the reaction of the N-bromophenylalanine derivative 92. The β-benzylc position of the methylphenylalanine derivative 94 lies within four atoms of the amido hetero-atoms, while the p-methyl group is situated nine atoms distant. Direct interaction of the carboxy protecting group with these centres requires a close spatial relationship, and given their position within the molecule, any such direct interaction is likely to be much greater at the β-carbon than at the p-methyl group, at which an intramolecular interaction cannot occur. Hence, the p-methyl substituents of the methylphenylalanine derivatives 93 and 94 provide internal standards within the molecules to probe for possible neighbouring group effects at both benzylc positions, and they allow further investigation into the possibility of interaction between the amido group and the aromatic moiety in the bromination processes using NBS. The results of these investigations are described in Chapter 5 of the Results and Discussion.
RESULTS AND DISCUSSION: CHAPTER 1

Stereoselective Synthesis of (2S,3S)-γ-Hydroxyvaline

As mentioned in the Introduction of this thesis, three routes for the synthesis of the γ-hydroxyvaline diastereomers 3a and 3b from (S)-valine were considered (Schemes 9 and 10), each of which involve reaction of the (R)-β-bromovaline derivative 33 to give the alkene 38. The β-bromide 33 was synthesised from (S)-valine as described below (Scheme 1.1). (S)-Valine was protected as the N-phthaloyl derivative 97 by treatment with phthalic anhydride at ca. 150 °C, then esterified by treatment with acidified methanol. In the initial phthaloylation reaction temperature control was important, as it has been reported that racemisation can occur at temperatures above 180 °C. The bromide 33 was prepared as reported previously, in high yield by heating a mixture of (S)-N-phthaloylvaline methyl ester 95 and NBS at reflux in carbon tetrachloride and irradiating with a 300 W sunlamp. The

\[
\text{(S)-Valine} \xrightarrow{\text{phthalic anhydride}} \text{PhthN} \text{CO}_2\text{H}
\]

\[
\text{PhthN} \text{CO}_2\text{Me} \xrightarrow{\text{SOCl}_2, \text{MeOH}} \text{PhthN} \text{CO}_2\text{Me}
\]

\[
\text{PhthN} \text{CO}_2\text{H} \xrightarrow{\text{NBS, hv}} \text{PhthN} \text{CO}_2\text{Me}
\]

Scheme 1.1
regiospecificity of bromine incorporation was determined using $^1$H NMR spectroscopy, which showed singlet resonances at $\delta$ 5.16, 2.15 and 1.99 corresponding to the $\alpha$- and diastereotopic methyl protons, consistent with substitution at the $\beta$-position.

One procedure for the preparation of the alkene 38 involves treatment of the $\beta$-bromide 33 with silver nitrate in aqueous acetone (Scheme 1.2).\(^{174}\) However, this procedure is limited since the $\beta$-hydroxyvaline derivative 34 is a major byproduct of the reaction, which was isolated in 43% yield. The $\alpha,\beta$-alkene 98 was also produced under these conditions. In order to avoid formation of the alcohol 34, the reaction was carried out under anhydrous conditions, by treatment of the bromide 33 with silver nitrate in dry methanol. The crude product was analysed by $^1$H NMR spectroscopy, which showed the $\beta,\gamma$-alkene 38 and the $\alpha,\beta$-alkene 98 present in the ratio ca. 5:1. After repeated chromatography of a portion of this mixture, the $\beta,\gamma$-dehydrovaline derivative 38 was isolated in 42% yield. The synthesis of the alkene 38 from the bromide 33, described above, is complementary to that reported by Griesbeck et al.,\(^{175,176}\) in which the alkene 38 was obtained by photolysis of the valine derivative 95, followed by oxidation (Scheme 1.3). This method is limited, however, since the photochemical reaction of the valine derivative 95 requires a stoichiometric amount of light, that is, the reaction is not catalytic, and therefore a large scale reaction of this type becomes impractical and inefficient.

![Scheme 1.2](image-url)
Results and Discussion Chapter 1

One approach considered for the stereocontrolled synthesis of the \( \gamma \)-hydroxyvaline diastereomers 3a and 3b involved asymmetric hydrogenation of the exocyclic methylene unit of the \( \beta \)-methylene-\( \gamma \)-lactone 41, followed by deprotection of the resultant lactones 42a and 42b (Scheme 1.4). In this case, it was thought that the hydrogenation would occur from the least hindered face of the exocyclic alkene 41, thus resulting in stereoselective formation of the lactones 42a and 42b.

\[
\text{Scheme 1.4}
\]

In order to test this hypothesis, preparation of the lactone 41 was attempted using the sequence shown below (Scheme 1.5). Treatment of the alkene 38 with NBS under photolytic conditions afforded the allylic bromide 39, in 80% yield after
purification by chromatography on silica. The regioselectivity of reaction was determined using $^1$H NMR spectroscopy, which showed singlet resonances at $\delta$ 5.72, 5.62 and 5.41, corresponding to the $\alpha$- and vinylic hydrogens, and doublet resonances at $\delta$ 4.28 ($J$ 10.8 Hz) and 4.13 ($J$ 10.8 Hz), corresponding to the diastereotopic allylic $\gamma$-hydrogens, consistent with substitution at the allylic $\gamma$-position.

Scheme 1.5

Hydrolysis of the allylic bromide 39 using aqueous silver nitrate in acetone afforded a crude product which was tentatively assigned as the allylic alcohol 40, using mass spectrometry, which showed a peak at $m/z$ 274 corresponding to the molecular ion minus hydrogen, and using $^1$H NMR spectroscopy. In the $^1$H NMR spectrum, singlet resonances occurred at $\delta$ 5.61, 5.44 and 5.30, corresponding to the $\alpha$- and vinylic protons, and a multiplet occurred between $\delta$ 4.38-4.20, corresponding to the two diastereotopic $\gamma$-hydrogens. From this data it is evident that isomerisation of the double bond to give an $\alpha,\beta$-unsaturated system did not occur during the reaction. Purification of the alcohol 40 was attempted using chromatography on silica, however only the lactone 99 was eluted. It was established that lactone formation had occurred by analysis of the product using mass spectrometry, which showed a peak at $m/z$ 243 corresponding to the molecular ion. Isomerisation to the $\alpha,\beta$-unsaturated system was determined using $^1$H NMR spectroscopy, which showed singlet resonances at $\delta$ 4.95...
and 2.13, corresponding to the methylene and methyl protons, respectively, consistent with a non-terminal alkene moiety. Consistent with this observation, an absence of peaks in the region \( \text{ca.} \delta 5.0-6.0 \) indicated that there were no \( \alpha- \) or vinylic protons present in the molecule, and consequently none of the lactone 41. Presumably, the alcohol 40 lactonised and isomerised during chromatography due to the acidic conditions on silica.

In an attempt to avoid lactonisation of the alcohol 40 during chromatography, less acidic conditions were used. The chromatographic process was repeated using 1% and then 5% triethylamine in the eluant, however, in each case the lactone 99 was isolated and neither the alcohol 40 nor exocyclic alkene 41 were detected. Thus, since none of the exocyclic alkene 41 was detected in the crude products from the reactions nor isolated following chromatography using these conditions, it appears that isomerisation of the double bond occurs immediately upon lactonisation of the alcohol 40. In addition to using triethylamine in the eluant to reduce the acidity of the chromatography conditions, purification of the alcohol 40 using basic alumina was also attempted. Under these conditions decomposition occurred and neither the alcohol 40 nor the lactones 41 and 99 were isolated. Therefore, given the difficulties encountered in the purification of the alcohol 40 and isolation of the lactone 41, the synthesis of the \( \gamma \)-hydroxyvaline isomers 3a and 3b using this procedure was not continued.
A second approach considered for the synthesis of the \( \gamma \)-hydroxyvaline isomers 3a and 3b involves reduction of the dibromide 43 using tri-\( n \)-butyltin hydride to give the \( \gamma \)-bromides 44a and 44b, which could be hydrolysed to the corresponding alcohols 36a and 36b and deprotected (Scheme 1.6). In addition, since the reduction of the dibromide 43 is likely to proceed \textit{via} the radical 45, it was thought that delivery of hydrogen to the radical 45 could occur stereoselectively due to 1,2-stereinduction, thus providing a stereocontrolled route to the \( \gamma \)-hydroxyvaline isomers 3a and 3b.

![Scheme 1.6](image)

In order to test this hypothesis, synthesis of the dibromide 43 was required. It was anticipated that electrophilic addition of bromine to the alkene 38 would give the dibromide 43. Hence, the alkene 38 was treated with a solution of bromine in carbon tetrachloride. Under these conditions, a crude product was obtained which was tentatively identified as a \textit{ca}. 3:1 mixture of diastereomers of the dibromide 43 (Scheme 1.7). Formation of a dibromide species from the reaction was determined from the mass spectrum of the crude product, which showed peaks at \( m/z \) 418, 420 and 422 in the ratio 1:2:1 corresponding to the molecular ion, whilst the regioselectivity of reaction was determined using \( ^1 \text{H} \) NMR spectroscopy. Singlet resonances at \( \delta \) 5.49 and 2.02
were attributed to the $\alpha$- and methyl protons, while peaks at $\delta$ 4.73 (d, $J$ 10.7 Hz) and 3.91 (d, $J$ 10.7 Hz) were attributed to the diastereotopic $\gamma$-hydrogens of the major isomer of the dibromide 43. Similarly, signals corresponding to the $\alpha$- and methyl protons were observed at $\delta$ 5.61 and 2.13, whilst peaks at $\delta$ 4.63 (d, $J$ 10.7 Hz) and 3.98 (d, $J$ 10.7 Hz) were attributed to the diastereotopic $\gamma$-hydrogens of the minor isomer of the dibromide 43. The dibromide 43 was unstable and was therefore used in the subsequent reaction without further purification and characterisation. Treatment of the crude dibromide 43 with tri-n-butyltin hydride afforded the alkene 38 as the major product (Scheme 1.7). There were no peaks in the $^1$H NMR spectrum of the crude material attributable to formation of the $\gamma$-bromides 44a and 44b. Presumably the alkene 38 was produced by displacement of bromine from the intermediate radical 45, which suggests that this process occurs much faster than delivery of hydrogen from tri-n-butyltin hydride to the radical 45.

**Scheme 1.7**

\[
\begin{align*}
\text{PhthN} & \quad \text{Br}_2 / \text{CCl}_4 \\
\text{CO}_2\text{Me} & \quad \left\uparrow \rightleftharpoons \\
38 & \quad \text{Bu}_3\text{SnH} \\
\text{PhthN} & \quad \text{Br}_2 \\
\text{CO}_2\text{Me} & \quad 43
\end{align*}
\]
As a method for introducing functionality at the γ-position, reduction of the dibromide 43 was unsuccessful. Hence, a variation of this approach was considered. It was anticipated that chlorine functionality could be introduced at the γ-position, by reduction of the dichloride 100 with tri-n-butyltin hydride to give the γ-chloride 102 via the radical 101 (Scheme 1.8). Given the greater strength of the chlorine–carbon bond relative to that of the bromine–carbon bond, it was anticipated that cleavage of the former bond would be less likely to occur and therefore addition of hydrogen to the radical 101 to give the γ-chlorides 102a and 102b (Scheme 1.8) would occur in preference to cleavage of this bond. In addition to allowing the introduction of functionality at the γ-position, this approach is of further interest due to the possibility of stereoselectivity as a result of 1,2-stereoinduction, using the same reasoning as described above for the reaction of the dibromide 43 with tri-n-butyltin hydride. Hydrolysis of the γ-chlorides 102a and 102b to the alcohols 36a and 36b followed by deprotection could therefore provide a stereocontrolled synthesis of the γ-hydroxyvaline isomers 3a and 3b.

\[
\begin{align*}
100 & \xrightarrow{ Bu_3SnH } 101 & 102a, 102b & \rightarrow 3a, 3b \\
& & a) R^1 = H, R^2 = Me \\
& & b) R^1 = Me, R^2 = H
\end{align*}
\]

Scheme 1.8
In order to investigate this hypothesis, synthesis of the dichloride 100 was required. It was envisioned that the dichloride 100 could be produced in an analogous manner to that used to prepare the dibromide 43, by treatment of the alkene 38 with a solution of chlorine in carbon tetrachloride. However, treatment of the alkene 38 with chlorine in carbon tetrachloride afforded the allylic chloride 103, which was isolated in 54% yield after chromatography on silica (Scheme 1.9). The regioselectivity of chlorination was determined using $^1$H NMR spectroscopy, which showed singlet resonances at $\delta$ 5.68, 5.59 and 5.42, corresponding to the $\alpha$- and vinylic hydrogens, respectively, and doublets at $\delta$ 4.37 ($J$ 12.1 Hz) and 4.22 ($J$ 12.1 Hz), corresponding to the diastereotopic $\gamma$-protons, consistent with substitution at the allylic $\gamma$-position. There were no peaks in the $^1$H NMR spectrum of the crude material attributable to formation of the dichloride 100 or the allylic chloride isomer 104. Since the dichloride 100 was not produced, synthesis of the $\gamma$-hydroxyvaline diastereomers 3a and 3b using this method was not pursued further.

Scheme 1.9

The regioselectivity of chlorination of the alkene 38 is identical to that seen in the bromination of the alkene 38 using NBS (Scheme 1.5), which suggested that the allylic chloride 103 is produced by a radical mechanism. In comparison, ionic bromination of the alkene 38 using molecular bromine occurs to give the dibromide 43.
(Scheme 1.7). While the addition of a halogen such as bromine to an unsaturated system generally occurs via an ionic mechanism, radical addition can occur in the presence of a radical initiator such as light. Although an initiator was not used in the reaction of the alkene 38 with chlorine, initiation of a radical process could occur with ambient light. To investigate this possibility, the reaction was carried out in the dark and in the presence of hydroquinone, a radical scavenger, since a radical reaction under these conditions would be unlikely to occur. Using these conditions the allylic chloride 103 was produced in identical proportions as in the previous reaction, as determined through analysis of the crude product using $^1$H NMR spectroscopy. This result suggests that the allylic chloride 103 is produced via an ionic mechanism.

One possible mechanism to account for the regioselectivity of reaction involves addition of chlorine to the alkene 38 to give the dichloride 100, which then undergoes elimination of hydrogen chloride to give the allylic chloride 103. However, it has already been shown that the alkene 38 reacts with bromine to give the dibromide 43. This material is likely to be more susceptible to elimination of the halogen than the dichloride 100 due to the greater leaving group ability of bromide to chloride ion, and on this basis formation of the allylic chloride 103 via elimination of hydrogen chloride from the dichloride 100 was discounted.

Another possible explanation of the regioselectivity of reaction involves deprotonation at the γ-position of an initially formed ionic species. Ionic additions of halogens such as iodine or bromine to unsaturated systems are known to occur via bridged halonium ions (Figure 7). In comparison with reactions of iodine and bromine, halonium ion formation from chlorine addition to alkenes occurs to a lesser extent, such that the more substituted end of the ion possesses much greater carbonium ion character. As a consequence of unsymmetrical bridging in the chloronium ion system, hydrogens on carbons adjacent to the carbonium ion centre are likely to be more acidic than those adjacent to a bridged halonium ion species. Therefore, it is
likely that the intermediate in the reaction of the alkene 38 with chlorine resembles the non-bridged tertiary carbocation 106, rather than the bridged species 105, from which deprotonation is likely to occur readily.

One species present in the reaction which could act as a base to remove a proton from the γ-position of the intermediate 106 is chloride ion. Statistically, a 1:3 ratio of the α,β-alkene 104 and the allylic chloride 103 would be expected, since removal of the α-hydrogen or one of the three methyl protons could occur. However, in the 1H NMR spectrum of the crude reaction mixture the allylic chloride 104 was not detected. Although steric hindrance by the bulky phthaloyl and methoxycarbonyl substituents to approach of chloride ion to the α-proton could affect reaction at this site, removal of the α-proton would still be expected to occur. Hence, this result suggests that the regioselectivity of reaction is not due to deprotonation at the γ-position by chloride ion.

Alternatively, the methoxycarbonyl substituent could act as an intramolecular base to remove a γ-proton (Scheme 1.10). Reaction in this manner would account for the regioselectivity of reaction and the absence of the chloride 104. In this process a favourable six-membered transition state is involved. Presumably, the analogous process involving removal of the α-hydrogen by the ester group, resulting in formation
of the chloride 104, does not occur since this would involve the less favourable four
membered transition state. Hence, the regioselectivity of reaction together with an
absence of the chloride isomer 104 is consistent with a mechanism involving
intramolecular deprotonation by the carboxy group.

\[
\text{Cl} \quad \text{PhthN} \quad \text{PhthN} \quad \text{CO}_2\text{Me}
\]

Scheme 1.10

Intramolecular reaction of the carboxy group in the chlorination reaction of the
alkene 38 is similar to that in halolactonisation reactions. Halolactonisation generally
involves the conversion of a β,γ- or γ,δ-unsaturated carboxylic acid into a halolactone,
although derivatives such as esters are also known to react in this manner.3,104,177-182
Halolactonisation occurs with intramolecular nucleophilic attack at an intermediate
halonium ion by a carboxy group, an example of which is shown in Scheme
1.11.177,178 For the analogous process to occur in the reaction of the alkene 38 with
chlorine, nucleophilic attack at the tertiary centre by the carboxy group is required.
This would produce a strained four membered ring, which is unfavourable, and
therefore deprotonation at the γ-position to give affording the allyl chloride 103
prevails.
In summary, the alkene 38 reacts with chlorine to give the allylic chloride 103 via an ionic mechanism. The regioselectivity of reaction and absence of the isomer 104 in the crude mixture is consistent with neighbouring group participation by the carboxy group to deprotonate the intermediate 106 at the γ-position.

Given that the attempts to prepare the γ-bromides 44a and 44b and the γ-chlorides 102a and 102b from the corresponding dihalides 43 and 100 were unsuccessful, synthesis of the γ-hydroxyvaline diastereomers 3a and 3b via an alternative route was investigated. The third approach considered for the synthesis of the γ-hydroxyvaline isomers 3a and 3b involved anti-Markovnikov radical addition of hydrogen bromide to the alkene 38, followed by hydrolysis. In addition to introducing bromine functionality at the less hindered end of the alkene moiety, anti-Markovnikov addition of hydrogen bromide to the alkene 38 is of further interest due to the possibility of 1,2-stereoisomerisation, as outlined previously.

The addition of hydrogen bromide to the alkene 38 was initially attempted by passing a dry stream of the gas through a solution of the alkene 38 in carbon tetrachloride for 10 mins, then heating the solution for 2 h at reflux and irradiating with a 300 W sunlamp. Analysis of the crude product using 1H NMR spectroscopy showed that decomposition had occurred, presumably due to the vigorous conditions used in the
Therefore, it was anticipated that decomposition could be minimised by carrying out the reaction under milder conditions. Accordingly, upon repeating the reaction, the temperature was maintained at approximately 5 °C, and the solution was irradiated for 30 mins. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy showed the presence of the diastereomeric $\gamma$-bromides 44a and 44b, in a 2.2:1 ratio (Scheme 1.12). The regioselectivity of hydrogen bromide addition to the alkene 38 was determined from the $^1$H NMR spectrum of the isomeric mixture. Doublet resonances occurred at $\delta$ 5.02 (J 8.4 Hz) and 1.03 (J 6.9 Hz), which correspond to the $\alpha$- and methyl hydrogens, respectively, while doublet of doublet resonances at $\delta$ 3.90 (J 5.1 and 10.2 Hz) and 3.66 (J 3.9 and 10.2 Hz) correspond to the diastereotopic $\gamma$-hydrogens of the major diastereomer 44a. In addition, doublets occurred at $\delta$ 4.91 (J 7.4 Hz) and 1.30 (J 6.6 Hz), corresponding to the $\alpha$- and methyl hydrogens, respectively, while doublet of doublet resonances occurred at $\delta$ 3.65 (J 3.7 and 10.3 Hz) and 3.25 (J 6.8 and 10.3 Hz), which correspond to the diastereotopic $\gamma$-protons of the minor isomer 44b. The $^1$H NMR spectral data are consistent with substitution at the $\gamma$-position. The diastereomers 44a and 44b were inseparable using chromatography on silica and the crude mixture was therefore used without purification.

\[
\text{PhthN} \text{CO}_2\text{Me} \xrightleftharpoons{\text{HBr}}^{hv} \text{PhthN} \text{CO}_2\text{Me} \text{HBr} \xrightarrow{\text{hv}} \text{PhthN} \text{CO}_2\text{Me} \quad \text{Br}
\]

\[
38 \quad 44 \quad a) R^1 = H, R^2 = \text{Me} \quad b) R^1 = \text{Me}, R^2 = H
\]

Scheme 1.12
Hydrolysis of the bromides 44a and 44b to the corresponding alcohols 36a and 36b was attempted initially by treatment with aqueous silver nitrate in acetone both at room temperature and at reflux but no reaction occurred. Given the lack of reactivity in this system, alternative methods to facilitate the substitution process were considered. It was anticipated that the use of a more powerful nucleophile or a better leaving group would favour the substitution process. The most obvious choice of a nucleophile more powerful than water is hydroxide ion, however, the sensitivity of the molecule to basic conditions precluded this treatment. Hence, conversion of the bromo-substituent to a better leaving group was envisioned.

Iodide ion is a better leaving group than bromide ion, hence conversion of the bromides 44a and 44b to the corresponding iodides 107a and 107b was performed. Accordingly, the bromides 44a and 44b were treated with sodium iodide in acetone at reflux. Under these conditions, the corresponding iodides 107a and 107b were produced (Scheme 1.13). Iodo substitution was confirmed from the 1H NMR spectrum, which contained doublet of doublets at δ 3.63 (J 5.4 and 10.2 Hz) and 3.50 (J 3.9 and 10.2 Hz) corresponding to the diastereotopic γ-hydrogens of the major isomer 107a, and doublet of doublets at δ 3.47 (J 3.8 and 10.2 Hz) and 3.01 (J 7.8 and 10.2 Hz) corresponding to the diastereotopic γ-hydrogens of the minor isomer 107b. The average chemical shift of the signals corresponding to the diastereotopic protons of the iodide diastereomers 107a and 107b is δ 3.40, while the average chemical shift of the signals corresponding to the diastereotopic protons of the γ-bromide isomers 44a and 44b is δ 3.62. That is, substitution of bromine for iodine results in an upfield shift of 0.22 ppm, which is consistent with the literature value of 0.3 ppm expected for such a transformation. The iodides 107a and 107b were unstable and therefore the crude product was used in the subsequent reaction without further purification.
Hydrolysis of the crude iodides 107a and 107b was achieved by treatment with silver nitrate in aqueous acetone, which gave a mixture containing the lactone 42a and the alcohols 36a and 36b. Acidic hydrolysis of the mixture, followed by purification by ion exchange chromatography, gave a 3:1 mixture of the γ-hydroxyvaline diastereomers 3a and 3b, in 60% yield from the γ-bromides 44a and 44b (Scheme 1.13). The 1H NMR spectral data for the diastereomers 3a and 3b are consistent with literature values. The major isomer 3a was separated from this mixture by fractional crystallisation.

Scheme 1.13

The relative stereochemistry of the γ-hydroxyvaline diastereomers 3a and 3b is apparent from comparison of their 1H NMR spectral data with literature values. In the 1H NMR spectrum of the mixture of isomers 3a and 3b, doublet resonances occur at δ 0.94 (J 7.2 Hz) and 1.02 (J 7.0 Hz), which correspond to the methyl protons of the major isomer 3a and the minor isomer 3b, respectively. The chemical shifts of the signals corresponding to the methyl groups of the isomers 3a and 3b are in close agreement with literature data, in which that signal of the (2S,3S)-isomer 3a occurred at δ 0.97, and at δ 1.04 for the (2S,3R)-diastereomer 3b. The absolute stereochemistry
of the alcohols 3a and 3b was confirmed by the optical rotation of the diastereomer 3a. The literature values for the specific rotation of the (2S,3S)-isomer 3a and the (2S,3R)-diastereomer 3b are +23.3° and +26.4°, respectively, while those of the corresponding (2R,3R)- and the (2R,3S)-enantiomers of 3a and 3b are -22.7° and -26.9°. The specific rotation obtained for the synthesised material in this work was +24.0°, which indicates that this material contains (2S)-stereochemistry, and is in close agreement with the value reported for the (2S,3S)-diastereomer 3a.

Repeated reactions of the iodides 107a and 107b with aqueous silver nitrate afforded various mixtures of the lactones 42a and 42b and the alcohols 36a and 36b (Scheme 1.13), which were difficult to separate due to incomplete lactonisation of the alcohols 36a and 36b. For this reason, crude mixtures were used directly to synthesise the free amino acids 3a and 3b. On one occasion, a crude mixture from reaction of the iodides 107a and 107b was chromatographed on silica giving a ca. 6:1 mixture of the lactones 42a and 42b, in 67% yield.

The relative stereochemistry of the lactone diastereomers 42a and 42b was determined using a nuclear Overhauser experiment. In the 1H NMR spectrum, signals due to the H3, H4, H5 and H5' protons of the lactone 42b occur at δ 5.01 (d, J 10.0 Hz), 3.06-2.90 (m), 4.66 (dd, J 8.4 and 8.7 Hz) and 4.26 (dd, J 8.0 and 8.7 Hz), respectively. Irradiation of the resonance centred at δ 2.98 affected the signals at δ 5.01 by +27%, at δ 4.66 by +0.2% and at δ 4.26 by -4.0%. The H3 and H5 protons of the lactone 42a give rise to a multiplet at δ 4.66, while the H4 and H5' proton signals of that compound occur at δ 3.27-3.11 (m) and 3.98 (dd, J 9.2 and 10.3 Hz), respectively. Irradiation of the resonance centred at δ 3.19 affected the signals at δ 4.66 by +5.5% and at δ 3.98 by -1.7%. These values indicate that interactions between the adjacent H3 and H4 protons of the (3S,4R)-isomer 42b are larger than for the (3S,4S)-isomer 42a, and can be attributed to a syn-relationship between the H3 and H4 protons of the isomer 42b.
Presumably, the production of the 6:1 mixture of the lactones \(42a\) and \(42b\) from reaction of a 2.2:1 mixture of the iodides \(107a\) and \(107b\) is a consequence of selective lactonisation of the alcohol \(36a\). This is in accord with the relative stereochemistry of the alcohols \(36a\) and \(36b\). In the eclipsed conformation required for lactonisation, unfavourable steric interactions exist between the phthalimido and methyl substituents of the (2S,3S)-isomer \(36b\) (Figure 1.1). In contrast, these unfavourable interactions are not present for the (2S,3R)-isomer \(36a\) (Figure 1.1), and therefore lactonisation of the (2S,3S)-alcohol \(36a\) occurs in preference to reaction of the (2S,3R)-isomer \(36b\).

![Figure 1.1](image)

**Figure 1.1.** Eclipsed conformations of the alcohols \(36a\) and \(36b\) required for lactonisation.

To determine the stereochemistry of the major isomer of the \(\gamma\)-bromides \(44a\) and \(44b\), the mass balance of the reactions of the bromides \(44a\) and \(44b\) to give the free amino acids \(3a\) and \(3b\), via the iodides \(107a\) and \(107b\) and the lactones \(42a\) and \(42b\), was considered. In the 2.2:1 mixture of the diastereomers of the bromides \(44a\) and \(44b\) used in the initial reaction, there was ca. 1.91 mmol of the major isomer and ca. 0.87 mmol of the minor isomer present. Using this mixture, the maximum theoretical yield of the free amino acid isomers \(3a\) and \(3b\) is 1.91 mmol (254 mg) and 0.87 mmol (115 mg), respectively. The free amino acids \(3a\) and \(3b\) (223 mg, 1.68 mmol) were isolated as a 3:1 mixture, which corresponds to 1.26 mmol (167 mg) of the isomer \(3a\).
and 0.42 mmol (56 mg) of the isomer 3b. Therefore, since the amount of the isomer 3a in this mixture is greater than the maximum theoretical yield of the minor isomer 3b, it is clear that the major isomer 3a is produced from the bromide 44a. Similarly, it is clear that the major iodide 107a is derived from the predominant bromide 44a, and it is the iodide 107a which affords the lactone 42a. As expected, therefore, the stereochemistry of the lactone 42a corresponds to that of the \( \gamma \)-hydroxyvaline isomer 3a. Using the same reasoning, the stereochemistry of the bromides 44a and 44b and the iodides 107a and 107b may be inferred from that of the alcohols 3a and 3b.

The stereoselectivity which arises in the anti-Markovnikov hydrobromination of the alkene 38 can be attributed to delivery of hydrogen atom to the less hindered face of the intermediate radical 45. Presumably, on the basis of minimisation of A-strain, steric interactions between the bulky phthalimido and methoxycarbonyl groups and the adjacent bromomethyl moiety are minimised such that the \( \alpha \)-carbon-hydrogen bond, the \( \beta \)-carbon and the bromomethyl substituent are approximately coplanar (Figure 1.2). In this configuration, delivery of hydrogen atom to the least hindered face of the radical 45, opposite to the bulky phthalimido moiety, results in formation of the (2S,3S)-bromide 44a. Stereoselective formation of the (2S,3S)-bromide 44a is consistent with the stereochemistry of the major isomer of the lactone 42a and the amino acid 3a which also possess the (2S,3S)-stereochemistry.

![Preferred conformation of the radical 45.](image)

\[ \text{Figure 1.2. Preferred conformation of the radical 45.} \]
In order to determine the absolute stereochemistry of the natural product, γ-hydroxyvaline was isolated from the plant species *Kalanchoe daigremontiana* using the procedure of Pollard *et al.*, which is outlined below. The lyophilised leaves and stems of the plant were stirred vigorously in water for 48 h, then the mixture was filtered. The filtrate was then washed with chloroform and evaporated to dryness, and the residue was purified by ion exchange chromatography using Amberlite IR-120 (NH₄⁺). The crude material was recrystallised from acetone and water, then analysed using ¹H NMR spectroscopy. By comparison of the ¹H NMR spectral data of the isolated material with that of the synthesised isomers 3a and 3b and by spiking with a sample of a 3:1 mixture of the isomers 3a and 3b of the synthetic material, the natural product was determined to be identical to the synthetic (2S,3S)-isomer 3a. In the spiking experiment, a sample of the natural product was added to the synthetic material and an enhancement of the signals corresponding to the major isomer 3a was observed. The relative and absolute stereochemistry of the natural product was confirmed by X-ray crystallographic analysis (Appendix 4), from which the (2S,3S)-stereochemistry was apparent. Consequently the synthesis described involving anti-Markovnikov hydrobromination of the alkene 38 constitutes a stereoselective synthesis of the natural isomer 3a.

In summary, as part of an attempted synthesis of the γ-hydroxyvaline diastereomers 3a and 3b, the reaction of the alkene 38 with chlorine resulted in formation of the allylic chloride 103. The mechanism of formation of this species was investigated, in which neighbouring group participation by the carboxy protecting group was implicated. It is proposed that the carboxy group acts as a base to remove a proton from the intermediate ion 106 (Scheme 1.10).

In addition, the γ-hydroxyvaline isomers 3a and 3b have been prepared stereoselectively from (S)-valine. The stereoselectivity in this process was achieved via 1,2-asymmetric induction, as a result of minimised A-strain by the intermediate radical
45, in the anti-Markovnikov radical hydrobromination of the $\beta$-$\gamma$-dehydrovaline derivative 38. The relative and absolute stereochemistry of the $\gamma$-hydroxyvaline isomers 3a and 3b was determined using a variety of methods, including a nuclear Overhauser enhancement experiment with the diastereomeric lactones 42a and 42b. The synthetic material 3a was shown to be identical to the natural product, which was isolated from the plant species *Kalanchoe daigremontiana*. The structure of the natural product was confirmed through X-ray crystallographic analysis (Appendix 4). This approach has the potential to be applied to the stereocontrolled synthesis of a variety of hydroxy amino acids.
RESULTS AND DISCUSSION: CHAPTER 2

Neighbouring Group Effects in Side Chain Substitution Reactions of Amino Acid Derivatives: A Stereocontrolled Route to Chloramphenicol

In the previous Chapter, the reaction of the dehydrovaline derivative 38 with chlorine to give the allylic chloride 103 was discussed, in which a mechanism involving neighbouring group participation by the carboxy group acting as a base to deprotonate the intermediate 106 was proposed to account for the regioselectivity of reaction. The effect of the neighbouring carboxy group to influence the regiochemistry of reaction in this manner is complementary to that proposed in the reactions of the bromophenylalanine derivatives 25 and 28, and 32a and 32b to give the alcohols 55 and 56, and 60, respectively, in which the stereoselectivity of reaction was markedly affected by the nature of that group. The apparent effect of the neighbouring carboxy group on the stereoselectivity of these reactions prompted an investigation into the rates of reactions, through competitive experiments, which are the subject of discussion in this Chapter. In order to investigate the generality of the neighbouring group effect and the dependence on the nature of the amino acid side chain, the valine derivatives 33 and 73 and the nitrophenylalanine derivatives 71a and 71b, and 72a and 72b were chosen for study. In these studies, the effect of the carboxy group on the rates and course of reactions was investigated. In addition, it was anticipated that the influence of the neighbouring carboxy group on the stereoselectivity of reactions of bromophenylalanine derivatives could be exploited in the synthesis of the β-hydroxy-nitrophenylalanine derivative 74, a precursor to chloramphenicol 54.

In the present work, the racemic analogues 18a and 18b, and 20a and 20b of the (S)-phenylalanine derived bromides 25 and 28, and 32a and 32b were used for convenience. The racemic bromides 18a and 18b, and 20a and 20b were prepared using standard procedures as described below. The bromovaline derivative 33 was
Results and Discussion Chapter 2

prepared as described in the previous Chapter, while the synthesis of the amide 73 is described herein. The (R)-nitrophenylalanine derived bromides 71a and 71b, and 72a and 72b were prepared using standard procedures, as were the corresponding racemic and (S)-nitrophenylalanine derived analogues. The amino acid derivatives referred to herein are racemic unless otherwise indicated.

(8)

(stereochemical descriptors show relative stereochemistry only)

Scheme 2.1

Preparation of amides 33 and 73 was achieved by the same method that led to amides 18 and 20, prepared from the amides 19a and 19b by treatment with NBS under photolytic conditions (Scheme 2.3).
Treatment of phenylalanine with phthalic anhydride gave N-phthaloylphenylalanine 108, in 90% yield (Scheme 2.1). N-Phthaloylphenylalanine methyl ester 17 was prepared in 90% yield from the acid 108, by treatment with acidified methanol. The racemic bromoesters 18a and 18b were prepared as a 1:1 mixture, by treatment of the ester 17 with NBS for 2 h in carbon tetrachloride and irradiation from a 300 W sunlamp, and isolated in quantitative yield (Scheme 2.1).

\[
\text{(RS)-phenylalanine} \xrightarrow{\text{phthalic anhydride}} \text{Ph} \xrightarrow{\text{SOCl}_2} \text{PhthN} \xrightarrow{\text{MeOH}} \text{CO}_2\text{H} \xrightarrow{\text{NBS}} \text{hv} \underline{18a} + \underline{18b}
\]

Scheme 2.1

Preparation of the amide 19 was achieved by treating N-phthaloylphenylalanine 108 with triethylamine and ethyl chloroformate, then tert-butylamine. The racemic bromoamides 20a and 20b were prepared from the amide 19 in a similar manner to that described above for the preparation of the bromoesters 18a and 18b, by treatment with NBS under photolytic conditions (Scheme 2.2).

\[
\text{i) NEt}_3 \xrightarrow{\text{ii) ClCO}_2\text{Et}} \xrightarrow{\text{iii) t-BuNH}_2} \text{Ph} \xrightarrow{\text{NBS}} \text{hv} \underline{20a} + \underline{20b}
\]

Scheme 2.2
The relative stereochemistry of the bromoesters 18a and 18b and the bromoamides 20a and 20b is apparent from their $^1$H NMR spectral data. The $^1$H NMR spectral data for these materials are identical to those reported for the corresponding (2R,3R)- and (2R,3S)-bromides 25 and 32b, and 28 and 32a,\textsuperscript{59} which show a general trend.\textsuperscript{59,96}

The valinamide 96 was prepared from (S)-N-phthaloylvaline 97 using an identical procedure to that described above for the preparation of the phenylalaninamide 19 from N-phthaloylphenylalanine 108, by treatment with triethylamine, ethyl chloroformate and then tert-butylamine. Reaction of the amide 96 with NBS in carbon tetrachloride under photolytic conditions gave (R)-3-bromo-\textit{N}-tert-butyl-\textit{N}$^\alpha$-phthaloylvalinamide 73 in 92% yield (Scheme 2.3). [Note that the Cahn-Ingold-Prelog designation at the $\alpha$-carbon of the bromides 18a, 18b, 20a, 20b, 33, 71a, 71b, 72a, 72b and 73 is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives 17, 19, 78a, 78b, 95 and 96, due to the change in priority of the substituents.] The regiochemistry of reaction was determined from the $^1$H NMR spectrum, which contained singlet resonances at $\delta$ 5.28, 2.07 and 1.86, corresponding to the $\alpha$-proton and the two diastereotopic methyl groups, respectively, consistent with substitution at the $\beta$-position.

\begin{center}
\textbf{Scheme 2.3}
\end{center}

\begin{align*}
\text{PhthN} & \text{CO}_2\text{H} & \text{PhthN} & \text{CONHCH}_3\\
97 & \text{i) NEt}_3 & 96 & \text{NBS} \\
& \text{ii) CICO}_2\text{Et} & & \text{hv} \\
& \text{iii) t-BuNH}_2 & & 73
\end{align*}
(R)-N-Phthaloyl-p-nitrophenylalanine 110 was prepared in 97% yield using a literature procedure,184 by heating a mixture of (R)-p-nitrophenylalanine 109 monohydrate, triethylamine and phthalic anhydride in toluene at reflux for 3 h in a flask which was fitted with a Dean-Stark apparatus. Treatment of this material with acidified methanol gave the ester 78a in 86% yield after recrystallisation of the crude product from a mixture of dichloromethane and light petroleum. Treatment of the ester 78a with NBS in carbon tetrachloride for 4 h gave a 1:1 mixture of the (2S,3S)- and (2S,3R)-bromides 71a and 71b, respectively, in quantitative yield (Scheme 2.4).

\[ \text{Scheme 2.4} \]

The nitrophenylalaninamide derivative 78b was prepared from the corresponding acid 110 in 54% yield, by treatment with triethylamine, ethyl chloroformate and then tert-butylamine. The (2S,3S)- and (2S,3R)-bromides 72a and 72b, respectively, were prepared as a 1:1 mixture from the amide 78b, by photolysis with NBS in a 4:1 mixture of carbon tetrachloride and dichloromethane for 3 h, and isolated in 98% yield (Scheme 2.5).
The stereochemistry of the bromides 71a and 71b was determined through X-ray crystallographic analysis of the (2S,3R)-isomer 71b (Appendix 5), whilst the stereochemistry of the bromoamides 72a and 72b was determined by comparison of spectral properties of the (2S,3R)-isomer 72b with that of a racemic sample. That sample was prepared from (RS)-p-nitrophenylalanine using the procedure described above for the preparation of the (2S,3R)- and (2S,3S)-bromides 72b and 72a, respectively, and separated from its diastereomer by fractional crystallisation. Its structure was determined through X-ray crystallographic analysis (Appendix 6).

The relative stereochemistry of the bromides 71a and 71b, and 72a and 72b is also apparent from their 1H NMR spectral data, which follow the same trends previously observed with the corresponding bromophenylalanine derivatives 25 and 28, and 32a and 32b (Table 2.1). The signals corresponding to the carboxy protecting groups occur at lower chemical shift for the diastereomers 71a and 72a than for the corresponding diastereomers 71b and 72b, while the diastereomers 71a and 72a exhibit the β-proton signal at higher chemical shift, the α-proton signal at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding diastereomers 71b and 72b.
Table 2.1. ¹H NMR spectral data for the bromides 18a, 18b, 20a, 20b, 25, 28, 32a, 32b, 71a, 71b, 72a and 72b.

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>J_{α,β}</th>
<th>R²</th>
<th></th>
<th>α</th>
<th>β</th>
<th>J_{α,β}</th>
<th>R²</th>
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<tbody>
<tr>
<td>18b</td>
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<td>11.2</td>
<td>3.55</td>
<td>18a</td>
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<td>5.91</td>
<td>10.5</td>
<td>3.82</td>
</tr>
<tr>
<td>20b</td>
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<td>11.8</td>
<td>1.02</td>
<td>20a</td>
<td>5.32</td>
<td>6.05</td>
<td>11.4</td>
<td>1.40</td>
</tr>
<tr>
<td>25b</td>
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<td>11.2</td>
<td>3.55</td>
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<td>5.91</td>
<td>10.5</td>
<td>3.82</td>
</tr>
<tr>
<td>32b</td>
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<td>32a</td>
<td>5.32</td>
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</tr>
<tr>
<td>71a</td>
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<td>6.02</td>
<td>11.2</td>
<td>3.59</td>
<td>71b</td>
<td>5.59</td>
<td>5.97</td>
<td>10.3</td>
<td>3.83</td>
</tr>
<tr>
<td>72a</td>
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<td>6.20</td>
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<td>1.11</td>
<td>72b</td>
<td>5.29</td>
<td>6.18</td>
<td>11.4</td>
<td>1.41</td>
</tr>
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</table>

² R values correspond to the signals of the carboxy protecting group.

Data from reference 59.

Under comparable conditions to those used in the preparation of the bromophenylalanine derivatives 18a, 18b, 20a, 20b, 25, 28, 32a, 32b, 71a, 71b, 72a and 72b, the nitro-substituted analogues 78a and 78b required longer to react. The rate of reaction of each substrate with NBS reflects the ease with which hydrogen is transferred from that substrate to bromine atom and is consistent with the transition state proposed for radical bromination in which hydrogen transfer to electrophilic bromine atom occurs with the development of a partial positive charge at the site of hydrogen abstraction (Figure 1). In the reactions of the nitrophenylalanine derivatives 78a and 78b, radical formation occurs with the development of a partial positive charge adjacent to the electron deficient nitro-aromatic moiety, which is unfavourable. Consequently, the nitrophenylalanine derivatives 78a and 78b require longer to react than the corresponding phenylalanine derivatives 17 and 19.
Results and Discussion Chapter 2

As described in the Introduction of this thesis, reaction of a 1:1 mixture of the bromophenylalanine derivatives 25 and 28 with aqueous silver nitrate affords the alcohols 55 and 56 in a 5:1 ratio (Scheme 14). In separate experiments, the bromoester 25 reacted to give a 2:1 mixture of the alcohols 55 and 56, with retention of stereochemistry being the dominant process, while the isomer 28 gave only the inverted alcohol 55. By comparison, under identical conditions to those used in the reactions of the bromoesters 25 and 28, each of the bromoamides 32a and 32b reacts to give only the alcohol 60 (Scheme 16).

By comparison with the bromophenylalanine derivatives 25 and 28, and 32a and 32b, which react solely by substitution, the reaction of the bromovaline derivative 33 with aqueous silver nitrate in acetone occurs with competing substitution and elimination. Thus, under these conditions the bromide 33 reacted to give a crude product containing the $\beta$-hydroxyvaline derivative 34 and the dehydrovaline derivatives 98 and 38 (Scheme 1.2), in the ratio ca. 3.5 : 1 : 3.5. Chromatography of the mixture afforded the alcohol 34 in 43% yield, and the alkenes 98 and 38, in yields of 8 and 34%, respectively. In comparison, when treated with aqueous silver nitrate under identical conditions, the bromoamide 73 reacted to give a ca. 2:1 mixture of the alcohol 111 and the alkene 112, from which the components were isolated in 63% and 26% yield, respectively (Scheme 2.6). The $^1$H NMR spectrum of the crude product of the reaction of the valinamide 73 showed no indication of formation of the $\alpha,\beta$-alkene 113.

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

34

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

38

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

98
Hydrolysis of the bromides 71a and 71b was initially attempted using the same conditions as used in the hydrolysis reactions of the β-bromophenylalanine derivatives 25 and 28, and 32a and 32b, however, under these conditions no reaction occurred. The lack of reactivity of the bromides 71a and 71b under these conditions is attributable to the destabilising influence of the electron withdrawing nitro-substituent to limit formation of an electron deficient centre at the benzylic position. Thus, in order to facilitate the substitution process, more vigorous conditions were employed. On one occasion, treatment of the bromoester 71b with aqueous silver nitrate at 65 °C for 48 h gave the alcohol 114 in 63% yield, with the dehydrophenylalanine derivatives 115 and 116 also being isolated as a 2:3 mixture in 25% yield (Scheme 2.7). Repeated experiments afforded the alcohol 114 in only 10-30% yield, with the alkenes 115 and 116 making up the remainder of the products. Under similar conditions, the bromide 71a gave only the alkene 115, in 84% yield, and neither the alcohol 114 nor the alkene 116 was detected in the crude product. Thus, reaction of the nitrophenylalanine derived bromoesters 71a and 71b to give mainly elimination products is in contrast to the reactions of the bromophenylalanine derivatives 25 and 28, and 32a and 32b, which react exclusively by substitution.
Treatment of a 1:1 mixture of the bromoamides 72a and 72b with aqueous silver nitrate under similar conditions to those used in the reactions of the bromoesters 71a and 71b afforded a crude product which was chromatographed on silica to give the (2R,3S)-alcohol 117 in 54% yield and a second product in 19% yield, which was tentatively identified as the nitrate 118 (Scheme 2.8). Neither the (2R,3R)-alcohol 119 nor the alkenes 120 and 121 was isolated from the reaction or identified in the $^1$H NMR spectrum of the crude material. Formation of the alcohol 117 was determined using infra-red spectroscopy, which showed a broad absorbance at 3400 cm$^{-1}$ characteristic of an alcohol, and using $^1$H NMR spectroscopy. In the $^1$H NMR spectrum resonances occurred at $\delta$ 5.17 (d, $J$ 4.9 Hz), 5.68 (dd, $J$ 4.9 and 8.3 Hz) and 1.37 (s), corresponding to the $\alpha$-, $\beta$- and tert-butyl protons, respectively. The assignment of peaks due to the $\alpha$- and $\beta$-protons was based on comparison of the spectra of the bromides 72a and 72b with that of the alcohol 117. Substitution of bromine for a hydroxyl moiety is reported to cause an upfield shift of the adjacent methine proton of 0.4 ppm.$^{183}$ Since the signals corresponding to the $\beta$-protons of the bromides 72a and 72b occur at $\delta$ 6.20 and 6.18, respectively, the $\beta$-hydrogen resonance of the alcohol 117 would be expected to occur at ca. $\delta$ 5.8. This value is in close agreement with the observed value of $\delta$ 5.68, and therefore the signal at $\delta$ 5.68 was attributed to the $\beta$-proton of the alcohol 117.
The absolute configuration at the α-carbon of the alcohols 114 and 117 is predetermined by that of the starting amino acid. (R)-Nitrophenylalanine was used in the initial reaction, and therefore the alcohols 114 and 117 contain the (2R)-stereochemistry. The relative stereochemistry of the alcohols 114 and 117 is apparent from their ¹H NMR spectra, from comparison with those of the β-hydroxyphenylalanine derivatives 55 and 56, and 60 and 122 and the β-hydroxytyrosine derivatives 123, 124 and 125 (Table 2.2). The ¹H NMR spectrum of the hydroxyester 114 shows a much closer correlation with that of the β-hydroxyphenylalanine derivative 55 and the β-hydroxytyrosine derivative 123 than the diastereomers 56 and 124, and indicates that the alcohol 114 has the (2R,3S)-stereochemistry. Similarly, the ¹H NMR spectrum of the hydroxy amide 117 shows a much closer correlation with that of the β-hydroxyphenylalanine derivative 60 and the β-hydroxytyrosine derivative 125 than with the alcohol 122, and indicates that the alcohol 117 has the (2R,3S)-configuration.
Table 2.2. $^1$H NMR spectral data of the alcohols 55, 56, 60, 114, 117 and 122 - 125.

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$J_{\alpha,\beta}$</th>
<th>R$^a$</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$J_{\alpha,\beta}$</th>
<th>R$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>55$^b$</td>
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<td>5.71</td>
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<td>56$^b$</td>
<td>4.95</td>
<td>5.46</td>
<td>8.4</td>
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<tr>
<td>123$^b$</td>
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<td>5.0</td>
<td>3.78</td>
<td>124$^b$</td>
<td>5.02</td>
<td>5.54</td>
<td>8.2</td>
</tr>
<tr>
<td>114</td>
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<td>5.79</td>
<td>4.4</td>
<td>3.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>60$^b$</td>
<td>5.11</td>
<td>5.63</td>
<td>6.2</td>
<td>1.30</td>
<td>122$^b$</td>
<td>4.61</td>
<td>5.39</td>
<td>8.3</td>
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<td>125$^b$</td>
<td>5.08</td>
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<td></td>
<td></td>
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<td>1.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ R values correspond to the signals of the carboxy protecting group.

$^b$ Data from reference 96.

The nitrate 118 was identified by comparison of the spectral properties with those of a racemic sample. That sample was prepared from the racemates of the bromides 72a and 72b, by treatment with silver nitrate in aqueous acetone, as described above for the reaction of the (2S,3S)- and (2S,3R)- bromides 72a and 72b. The mass spectrum of the racemate of the nitrate 118 contained a peak at m/z 457, corresponding to the protonated molecular ion, while the $^1$H NMR spectrum contained doublet resonances at $\delta$ 4.90 ($J$...
10.7 Hz) and 7.19 (J 10.7 Hz), corresponding to the α- and β-protons, respectively, consistent with β-substitution. The signal corresponding to the β-proton of the nitrate 118 occurs 1.51 ppm downfield from the signal corresponding to the β-proton of the (2R,3R)-alcohol 117. This downfield shift is similar to that observed for the signals corresponding to the protons attached to the carbons bearing the alcohol and nitrate moieties of the alcohols 127a - 127d and the corresponding nitrates 126a - 126d,188 in which those signals are shifted downfield by ca. 0.9 – 1.3 ppm. On this basis, therefore, the nitrate 118 was identified. Presumably, formation of the nitrate 118 in this reaction occurs in a manner similar to that of the alcohol 117, by nucleophilic substitution of bromine by nitrate anion. Therefore, by analogy with the alcohol 117, the nitrate 118 is likely to contain the same relative stereochemistry as the alcohol 117.

\[ \text{PhCONH} \text{H}_2\text{CO}_2\text{Me} \]
\[ \text{PhCONH} \text{Me}_2\text{CO}_2\text{Me} \]
\[ \text{PhCONH} \text{Ph}_2\text{CO}_2\text{Me} \]
\[ \text{PhCONH} \text{H}_2\text{CO}_2\text{Me} \]

In order to avoid formation of the nitrate 118 in the reaction of the bromides 72a and 72b, it was envisaged that a silver salt containing a non-nucleophilic counterion could be used in place of silver nitrate. Silver sulfate was chosen for this purpose. Accordingly, a 1:1 mixture of the bromoamides 72a and 72b was treated with silver sulfate in aqueous acetone at 65 °C for 3 days. Under these conditions a crude product was obtained which was chromatographed, affording the (2R,3S)-alcohol 117 in 63% yield. Neither the (2R,3R)-alcohol 119 nor the alkenes 120 and 121 was obtained following chromatography or identified in the \(^1\)H NMR spectrum of the crude product.
In order to make a comparison between the hydrolysis reactions of the nitrophenylalanine bromoesters 71a and 71b with those of the bromoamides 72a and 72b, a 1:1 mixture of the racemates of the bromoesters 71b and 71a was treated with silver sulfate under the same conditions as described above for the amides 72a and 72b. Under these conditions mainly the alkene 115 and less than 5% of either the (E)-isomer 116 or the racemate of the alcohol 114 were produced. The outcome of this reaction is similar to that of the reactions involving silver nitrate, which on most occasions resulted in elimination to give the alkenes 115 and 116.

In summary, it can clearly be seen that, under comparable reaction conditions, the bromoesters 71a and 71b react mainly by elimination, whereas the bromoamides 72a and 72b react solely by substitution. Hence, in the reactions of the nitrophenylalanine derivatives 71a and 71b and 72a and 72b with aqueous silver salts, the effect of the neighbouring carboxy group, when protected as an amide rather than an ester, is to promote substitution over elimination. The amide can stabilise electron deficient intermediates in the substitution reactions. In the absence of that stabilisation, substitution is disfavoured and elimination becomes the dominant process.

As described previously, an aim of the work was to investigate the effect of the neighbouring carboxy group on the relative rates of reactions of the amino acid derivatives 18a, 18b, 20a, 20b, 33, 71a, 71b, 72a, 72b and 73 by carrying out competitive experiments. The competitive reactions of the phenylalanine derivatives 18a, 18b, 20a and 20b and the valine derivatives 33 and 73 were carried out by treating approximately 1-2 molar equivalents of each substrate and ca. 0.1-0.5 molar equivalents of an internal standard with aqueous silver nitrate in acetone in the dark at room temperature for 16 h. The reactions of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b were carried out in an oil bath at 65 °C for 16 h, in the dark using silver...
sulfate. The internal standard chosen for use in these reactions was tert-butylbenzamide. The results obtained from a typical experiment in each case are shown in Tables 2.3, 2.4 and 2.5.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( k_{rel} (\text{Ag}^+/\text{H}_2\text{O}) )</th>
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<td>18b</td>
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</tr>
<tr>
<td>18a</td>
<td>2.6</td>
</tr>
<tr>
<td>20b</td>
<td>17</td>
</tr>
<tr>
<td>20a</td>
<td>16</td>
</tr>
</tbody>
</table>

† Assigned as unity within table.

**Table 2.3.** Relative rates of reaction of the bromophenylalanine derivatives 18a and 18b, and 20a and 20b with aqueous silver nitrate.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( k_{rel} (\text{Ag}^+/\text{H}_2\text{O}) )</th>
</tr>
</thead>
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<tr>
<td>33</td>
<td>1.0†</td>
</tr>
<tr>
<td>73</td>
<td>6.2</td>
</tr>
</tbody>
</table>

† Assigned as unity within table.

**Table 2.4.** Relative rates of reaction of the bromovaline derivatives 33 and 73 with aqueous silver nitrate.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( k_{rel} (\text{Ag}^+/\text{H}_2\text{O}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>71a</td>
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</tr>
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<td>71b</td>
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</tr>
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<tr>
<td>72b</td>
<td>1.0†</td>
</tr>
</tbody>
</table>

† Assigned as unity within table.

**Table 2.5.** Relative rates of reaction of the bromonitrophenylalanine derivatives 71a and 71b, and 72a and 72b with aqueous silver sulfate.
The relative reaction rates were determined using $^1$H NMR spectroscopy, by measuring the relative rates of consumption of each substrate relative to the internal standard. Integration of peaks characteristic of the residual bromides and the internal standard, and comparison with the starting mixtures, were used to determine the percentage of each substrate remaining. From these values the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction.

An indication of the reproducibility of the results was established in duplicate experiments, in which the values obtained varied by less than 20% in the reactions of the valine derivatives 33 and 73. In the reactions of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b, the relative rate of reaction of the bromoamides 72a and 72b varied by less than 10%, while the rate of reaction of the bromoester 71a ranged from 3.6 to 5.2 times greater than that of the isomer 71b. The rate of reaction of the bromoester 71b ranged from 1.2 times slower to 1.3 times faster than that of the bromoamide 72b. In the reactions of the phenylalanine derivatives 18a, 18b, 20a and 20b, the rate of reaction of the bromoester 18a ranged between 1.7 and 2.6 times faster than that of the bromide 18b, while the relative rates of reaction of the bromoamides 20a and 20b varied by less than 20%. The rates of reaction of the bromoamides 20a and 20b ranged between 10-20 times faster than those of the bromoester 18b. The variation of the rates of reaction of the amides 20a and 20b relative to those of the esters 18a and 18b can be attributed to the low extent of reaction of the bromoesters 18a and 18b and the high extent of reaction of the bromoamides 20a and 20b, due to the much greater reactivity of the amides 20a and 20b compared to that of the esters 18a and 18b. Using this method of relative reaction rate calculation, small differences in the percentage of reaction of each substrate present in the mixtures have a marked affect on the relative rates when the relative rates of reaction vary widely.
An indication of the reliability of the rates shown was determined by analysis of the mass balances of the reactions. In the reactions of the bromophenylalanine derivatives 18a, 18b, 20a and 20b, the starting materials and the racemates of the alcohols 55, 56 and 60 comprised greater than 90% of the material present. In the reactions of the valine derivatives 33 and 73 the starting materials, the corresponding alcohols 34 and 111 and the alkenes 38, 98 and 112 comprised approximately 90% of the material present, while in the reactions of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b, greater than ca. 70% of the ester- and amide-derived materials could be accounted for.

When treated under comparable conditions the nitrophenylalanine derivatives 71a, 71b, 72a and 72b were much less reactive than the phenylalanine derivatives 18a, 18b, 20a and 20b, however, the difference was too great to quantify accurately through competitive experiments. Presumably the lower reactivity of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b relative to that of the corresponding phenylalanine derivatives 18a, 18b, 20a and 20b is due to the electron withdrawing effect of the nitro substituent to limit formation of electron deficient intermediates in the reactions.

In an SN1 process, the stereochemical outcome of reaction could vary from complete retention of stereochemistry to complete inversion of configuration, whereas for an SN2 process, only inversion of configuration results. The reaction of the bromoester 18a to give the racemate of the alcohol 55 occurs with inversion of configuration, while there is a 2:1 preference for retention of stereochemistry in the reaction of the bromoester 18b. The logical interpretation of these results is that the bromoester 18a reacts via an SN2 process whereas an SN1 mechanism prevails in the reaction of the bromoester 18b. The modest stereoselectivity in the latter case can be attributed to a facial selectivity in the approach of the nucleophile to the intermediate carbocation 128 (Figure 2.1).
Results and Discussion Chapter 2

The results obtained in this study show a consistent trend for the reaction of the bromide 18a. The structure and electronic effects of the substituents on the carbon-bromine bond play a significant role in the reaction mechanism. The reaction of the bromoester 18b proceeds via an S_N1 type mechanism, where the silver ion coordinates to the bromine and assists in breaking the carbon-bromine bond as water attacks from the opposite face, to give the racemate of the alcohol 55 (Scheme 2.9).

By comparison, for reaction of the bromide 18a, removal of bromine to give the preferred conformation of the carbocation 128 occurs less readily than in the reaction of the bromoester 18b since rotation about the C2-C3 bond is required, and this would cause steric crowding between the ester moiety and the dissociating bromine. In contrast, attack of water from behind the breaking carbon-bromine bond is not hindered. Hence it is presumed that the reaction of the bromide 18a occurs via an S_N2 type mechanism, where the silver ion coordinates to the bromine and assists in breaking the carbon-bromine bond as water attacks from the opposite face, to give the racemate of the alcohol 55 (Scheme 2.9).
The racemic bromoamide \(20b\) reacts with retention of configuration to give the racemate of the alcohol \(60\), presumably in an \(S_N1\) process. The faster rate and enhanced stereoselectivity of this reaction compared to that of the bromoester \(18b\) is convincing evidence of anchimeric assistance and 1,4-neighbouring group participation by the amido substituent (Figure 2.2), to facilitate formation of the racemate of the intermediate carbocation \(62\) and effectively block one face of that species to reaction with the incoming nucleophile. Presumably, direct interaction of the amido substituent with the benzylic carbocation locks the conformation of the intermediate \(62\) such that the incoming nucleophile can only approach from the face of the intermediate species \(62\) opposite the amido moiety (Figure 2.2) to afford only the racemate of the alcohol \(60\).

![Figure 2.2. Stabilisation of the carbocation 62 by the amido substituent.](image)

The bromoester \(18a\) reacts with inversion of configuration to give only the racemate of the alcohol \(55\), presumably in an \(S_N2\) process. The racemic broamoamide \(20a\) also reacts with inversion of configuration to give the racemate of the alcohol \(60\), however, the reaction proceeds much faster than the reaction of the bromoester \(18a\) and at approximately the same rate as that of the broamoamide \(20b\) (Table 2.3). The enhanced rate of reaction of the broamoamide \(20a\) compared to that of the corresponding bromoester \(18a\) is inconsistent with simple \(S_N2\) displacement of bromine, as the amide \(20a\) would
then be expected to react slower than the ester 18a due to hindrance to approach of the incoming nucleophile by the bulky amido substituent. One interpretation of this result is that the amido substituent, being approximately $10^6$ times more basic than the ester moiety, facilitates the second order reaction by acting as a base to promote the nucleophilicity of water (Figure 2.3).

![Diagram showing relative stereochemistry](image)

**Figure 2.3.** Second order reaction of the bromoamide 20a.

In order to check this possibility, it was envisaged that a competitive reaction of the bromoamides 20a and 20b using deuterated water could be used. The second order reaction of the bromoamide 20a with aqueous silver nitrate involves cleavage of a hydrogen–oxygen bond of water (Figure 2.3). In comparison, the first order reaction of the bromoamide 20b does not involve cleavage of a hydrogen–oxygen bond in the transition state of the reaction. Therefore, only the rate of reaction of the bromide 20a using deuterium oxide is likely to be affected by a deuterium isotope effect associated with cleavage of the deuterium–oxygen bond, and hence a slower reaction rate than that of the bromide 20b in a competitive experiment under these conditions would be expected. Therefore, this experiment could be used to distinguish between a first and second order process in the reaction of the bromoamide 20a. Hence, an approximately 1:1 mixture of the bromoamides 20a and 20b was treated with silver nitrate in deuterium
oxide and acetone in a competitive experiment, using the procedure described above, and the relative rates of reaction were determined.

Using these conditions, the rate of reaction of the bromoamide 20b was determined to be 1.1 times faster than that of the bromoamide 20a. Differences in the solvation of both the silver ion and the substrates and intermediates by deuterium oxide compared to water could affect the reaction. Taking into consideration these factors as well as the experimental error associated with determination of the relative reaction rates using this method, it appears that the reactions of the bromoamides 20a and 20b are not affected by a deuterium isotope effect. Hence, this result suggests that the reaction of the bromide 20a does not involve cleavage of a deuterium–oxygen bond in the transition state, and on this basis, reaction of the bromoamide 20a via a second order process was discounted.

An alternative explanation to account for the enhanced rate of reaction of the bromoamide 20a compared to that of the bromoester 18a involves facilitation of a first order process by the amido substituent of the amide 20a. In the orientation of the bromoamide 20a required for neighbouring group participation by the amido substituent, carbocation formation occurs such that the bulky phenyl substituent is in close proximity to the phthalimido moiety (Scheme 2.10), which is unfavourable due to steric crowding. Relief of these unfavourable steric interactions occurs through rotation about the C2-C3 bond of the racemate of the carbocation 62 in the initially formed conformation, which is shown in Scheme 2.10, to give the most stable orientation (Figure 2.2). Approach of the nucleophile from the face opposite to the amido moiety of the carbocation 62 in the conformation shown in Scheme 2.10 would afford the racemate of the alcohol 122, with retention of configuration. Presumably, since none of the alcohol 122 is produced in the reaction, rotation about the C2-C3 bond occurs to give the racemate of the carbocation 62 in its preferred orientation (Figure 2.2) much faster than reaction in its initial orientation (shown in Scheme 2.10) with water.
Another mechanism considered which could account for the stereochemical outcome of the reaction of the bromoamide 20a and the enhanced rate of reaction compared to that of the corresponding ester 18a involved displacement of bromine by the amido moiety to give the formally bonded species 129 similar to the stabilised intermediate 62, followed by nucleophilic attack by water at the carboxy carbon and ring opening (Scheme 2.11). This mechanism involving 1,4-neighbouring group participation and anchimeric assistance by the amido group could account for the faster rate of reaction of the amide 20a compared to that of the ester 18a, however, it does not account for the high stereoselectivity of reaction. Nucleophilic attack at the $\beta$-carbon of the intermediate 129 from the face opposite to the amido moiety to give the alcohol 122 could occur in addition to reaction at the carboxy carbon, and since none of the alcohol 122 was produced, formation of racemic alcohol 60 via this mechanism is considered unlikely.
Several other explanations for the results obtained in the hydrolysis reactions of the phenylalanine derivatives 18a, 18b, 20a and 20b were considered, however, these do not account for the kinetic effects and the stereochemical outcome of the reactions. One possible explanation which could account for the high stereoselectivity of reaction of the phenylalanine derivative 20b compared to that from reaction of the corresponding ester 18b, is that the greater bulk of the tert-butyl amide group results in a greater conformational preference of the intermediate racemic carbocation 62 than for the racemic carbocation 128, such that approach of the nucleophile only occurs from the least hindered face of the molecule, opposite to the carboxy group. However, this explanation was discounted since it has been shown that the stereoselectivity of formation of the alcohols 58 and 59 from reaction of the tert-butyl esters 57a and 57b (Scheme 15) was only 8:1 despite the very similar size of the tert-butyl ester and tert-butyl amide moieties. Hence, this indicates that the effect of the amido group to dramatically increase the rate and stereoselectivity of reaction of the amide 20b compared to the ester 18b is not due to steric influences.
In summary, the stereoselectivity and enhanced rate of reaction of the bromoamides 20a and 20b compared to those of the corresponding bromoesters 18a and 18b is convincing evidence of anchimeric assistance and 1,4-neighbouring group participation by the amido substituent to facilitate formation of the racemic carbocation 62 and lock that species in its preferred conformation such that one face of the molecule is effectively blocked to approach of the incoming nucleophile (Figure 2.2).

The reactions of the bromovaline derivatives 33 and 73 with aqueous silver nitrate occur with competing substitution and elimination. The bromoester 33 reacts to give the alcohol 34 and the alkenes 98 and 38 (Scheme 1.2), in the ratio ca. 3.5 : 1 : 3.5. In comparison, the bromoamide 73 affords the alcohol 111 and the alkene 112 (Scheme 2.6) in the ratio ca. 2 : 1 and the reaction occurs approximately six times faster than the corresponding reaction of the bromoester 33 (Table 2.4). That is, not only does substitution occur to a greater extent in the reaction of the bromoamide 73 than in the reaction of the bromoester 33, the reaction also proceeds much faster. Therefore, the effect of the carboxy group, when protected as an amide rather than an ester, is to enhance the substitution process, to the extent that substitution is favoured over elimination.

In the absence of stabilisation by the amido group, elimination is the dominant process. Through stabilisation of the carbocation intermediate 130 by the amido group in the reaction of the valinamide 73, substitution competes more effectively with elimination, to the extent that substitution is favoured over elimination. Presumably, the substitution process is enhanced by the amido substituent in the reaction of the bromovaline derivative 73 in an analogous manner to that in the reactions of the bromophenylalanine derivatives 20a and 20b, through direct interaction and stabilisation of the carbocation intermediate 130 (Figure 2.4). Hence, the reaction of the
bromide 73, as a consequence of neighbouring group participation by the amido substituent to stabilise the intermediate carbocation 130, provides an efficient route to the alcohol 111, a derivative of the naturally occurring β-hydroxyvaline 35.

![Diagram](image)

**Figure 2.4.** Stabilisation of the carbocation 130 by the amido moiety.

The neighbouring group effect of the aminocarbonyl substituent to promote substitution over elimination is also seen in the reactions of the nitrophenylalanine derivatives 71a and 71b, and 72a and 72b with silver sulfate. By comparison with the bromophenylalanine derivatives 18a and 18b, 20a and 20b which react solely by substitution, the bromoesters 71a and 71b react mainly by elimination. Therefore, the effect of the nitro substituent in the hydrolysis reactions of the esters 71a and 71b is to destabilise electron deficient intermediates to the extent that elimination is favoured over substitution. In the reactions of the amides 72a and 72b, however, the dominant reaction is substitution. Hence, the effect of the amido group in these reactions is to diminish the destabilising influence of the nitro-aromatic substituent such that substitution becomes the dominant process.

In the competitive experiments involving the bromides 71a, 71b, 72a and 72b, the bromoesters 71a and 71b reacted to give less than 5% of the alcohol 114, whereas
the amides 72a and 72b reacted by substitution and at a very similar rate to that of the bromoester 71b. That is, substitution occurs to a much greater extent in the reactions of the bromoamides 72a and 72b and proceeds much faster than in the reactions of the bromoesters 71a and 71b. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination due to crowding with the phthalimido group, since the rate of substitution is greater in the reactions of the bromoamides 72a and 72b than in the reaction of the bromoester 71b.

The enhanced rate and greater extent of substitution in the reactions of the bromoamides 72a and 72b compared to the reactions of the esters 71a and 71b is consistent with 1,4-neighbouring group participation by the amido substituent to stabilise electron deficient intermediates of reaction. Presumably the origin of the effects seen in the reactions of the nitrophenylalanine derivatives 72a and 72b is analogous to that described above for the reactions of the corresponding phenylalanine derivatives 20a and 20b. The bromoamide 72a reacts with inversion of configuration to give the alcohol 117, whereas the bromide 72b reacts with retention of configuration to give the same. By analogy with the reactions of the bromoamides 20a and 20b, the bromides 72a and 72b react via $S_N 1$ processes facilitated by direct 1,4-participation by the amido substituent with the carbocation centre of the intermediate 131 (Figure 2.5).

![Figure 2.5](image)

**Figure 2.5.** Stabilisation of the carbocation 131 by the amido group.
In summary, the effect of the amido substituent in the reactions of the phenylalanine derivatives 20a and 20b is to enhance the rate and stereoselectivity of substitution compared to the reactions of the corresponding esters 18a and 18b, through direct interaction with the electron deficient benzylic carbocation 62. In a similar manner, the amido substituent facilitates reaction of the valinamide 73 through 1,4-neighbouring group participation by interacting directly with the electron deficient carbocation centre of the intermediate 130, such that substitution is enhanced to the extent that substitution is favoured over elimination. The effect of the amido substituent to promote substitution over elimination is also seen in the reactions of the nitrophenylalanine derivatives 72a and 72b. Whereas elimination is the dominant process in the reactions of the esters 71a and 71b, the amides 72a and 72b react solely by substitution, as a consequence of direct 1,4-neighbouring group participation by the amido substituent, through interaction with the electron deficient carbocation 131.

As mentioned previously, it was envisaged that the effect of the protected carboxy group to influence the stereoselectivity of reactions of the bromophenylalanine derivatives 25, 28, 32a and 32b could be exploited in the stereocontrolled synthesis of the chloramphenicol precursor 74, by hydrolysis of the (2S,3R)-alcohol 132. Previously the racemate of the alcohol 74 has been elaborated to chloramphenicol 54,124 and the process would therefore provide a stereocontrolled route to the natural product 54. Hence, the racemate and the (2S,3R)-enantiomer 132 of the β-hydroxy-p-nitrophenylalanine derivative 117 were synthesised from (RS)- and (S)-p-nitrophenylalanine, respectively, using the procedure outlined above for the preparation of the (2R,3S)-isomer 117.
In order to obtain the free amino acid 133, the (2R,3S)-alcohol 117 was deprotected using standard conditions by treatment with a mixture of 6N hydrochloric acid and acetic acid, and the (2R,3S)-amino acid 133 was isolated in 69% yield. The procedure used to prepare the (2R,3S)-amino acid 133 from the (2R,3S)-alcohol 117 was repeated using the racemate and the (2S,3R)-enantiomer 132 of the (2R,3S)-alcohol 117, from which the (2S,3R)-enantiomer 74 and the racemate of the amino acid 74 were obtained.

![Scheme 2.12](image.png)

The relative stereochemistry of the amino acids 74 and 133 was determined using ¹H NMR spectroscopy, which showed doublets at δ 5.77 (J 3.9 Hz) and 4.70 (J 3.9 Hz) corresponding to the β- and α-protons, respectively, by comparison with literature values. The absolute stereochemistry and optical purity was determined from the specific rotations of the (2S,3R)-enantiomer 74 and the (2R,3S)-isomer 133. The values obtained were +35.3° for the (2R,3S)-isomer 133 and −36.4° for the corresponding (2S,3R)-enantiomer 74, which are similar to the literature rotations of +27° for the (2R,3S)-isomer 133 and −33.8° for the corresponding (2S,3R)-enantiomer 74. Hence, this result further supports the assignment of stereochemistry of the alcohol 117, since it is the alcohol 117 which affords the free...
amino acid 133. Now stereocontrolled access to the (2S,3R)-amino acid 74, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic 54.
RESULTS AND DISCUSSION: CHAPTER 3

Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives

Neighbouring group participation in ionic reactions is very common, although the incidence of 1,4-participation is limited. In the previous Chapter, the hydrolysis reactions of the bromophenylalanine derivatives 18a, 18b, 20a and 20b, the nitrophenylalanine derivatives 71a, 71b, 72a and 72b and the valine derivatives 33 and 73 were examined. The rate and in some cases the stereoselectivity of substitution were dramatically affected by the nature of the protected carboxy group, which was attributed to 1,4-neighbouring group participation by the carboxy group, when protected as an amide rather than as an ester, through direct interaction with electron deficient carbocation intermediates. In contrast to their ionic counterparts, the incidence of neighbouring group participation in radical reactions is rare, particularly examples of 1,4-participation, which appear to be extremely uncommon. The effect of the carboxy substituent, when protected as an amide, to exert 1,4-neighbouring group participation in the hydrolysis reactions of the brominated amino acid derivatives 20a, 20b, 72a, 72b and 73 prompted the investigation into the possibility of 1,4-neighbouring group participation in side chain radical reactions of amino acid derivatives, which will be the topic of discussion in this Chapter.

The phenylalanine derivatives 17 and 19 and the nitrophenylalanine derivatives 78a and 78b, which were prepared in the previous Chapter, and the tyrosine derivatives 79a and 79b were thought to be suitable substrates to investigate the possibility of neighbouring group participation in their side chain bromination reactions. These reactions may be assumed to proceed via hydrogen abstraction by bromine atom to give the corresponding intermediate radicals 21, 22, 134a, 134b, 135a and 135b, which are similar to the carbocation intermediates 62 and 128 of the hydrolysis reactions of the
bromides 25, 32a and 32b, since the radicals 21, 22, 134a, 134b, 135a and 135b are electron deficient and sp²-hybridised at the β-carbon. By analogy with the hydrolysis reactions described in the previous Chapter, it was thought that the bromination reactions could involve interaction between the carboxy group and the radical centre, and hence they provide the opportunity to probe for neighbouring group participation in the side chain radical bromination processes.

In addition to the bromination reactions mentioned above, it was anticipated that the reverse transformations of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b to the corresponding reduced materials 17, 19, 78a, 78b, 79a and 79b using triphenyltin hydride could be used to probe for neighbouring group participation in side chain radical reactions, since these processes are also likely to proceed via the radical intermediates 21, 22, 134a, 134b, 135a and 135b.
Furthermore, as a result of the contrasting polar nature of the processes involving NBS and triphenyltin hydride, an insight into the nature of the reaction transition states could also be gleaned. Therefore, an aim of the work described in this Chapter was to investigate the possibility of neighbouring group participation in side chain radical bromination reactions of the amino acid derivatives 17, 19, 78a, 78b, 79a and 79b with NBS and in the reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride.

\[
\begin{align*}
\text{PhthN} & \quad \text{CO}_2\text{Me} \\
\text{R}^1 & \quad \text{R}^2
\end{align*}
\]

18

\[
\begin{align*}
\text{PhthN} & \quad \text{CONHCMe}_3 \\
\text{R}^1 & \quad \text{R}^2
\end{align*}
\]

20

(stereochemical descriptors show relative stereochemistry only)

\[
\begin{align*}
\text{p-NO}_2\text{-Ph} & \quad \text{R}^2 \\
\text{PhthN} & \quad \text{CO}_2\text{Me} \\
\text{R}^1
\end{align*}
\]

71

\[
\begin{align*}
\text{p-NO}_2\text{-Ph} & \quad \text{R}^2 \\
\text{PhthN} & \quad \text{CONHCMe}_3 \\
\text{R}^1
\end{align*}
\]

72

\[
\begin{align*}
\text{p-AcO-Ph} & \quad \text{R}^2 \\
\text{PhthN} & \quad \text{CO}_2\text{Me} \\
\text{R}^1
\end{align*}
\]

80

\[
\begin{align*}
\text{p-AcO-Ph} & \quad \text{R}^2 \\
\text{PhthN} & \quad \text{CONHCMe}_3 \\
\text{R}^1
\end{align*}
\]

81

a) \( R^1 = \text{H}, \ R^2 = \text{Br} \)
b) \( R^1 = \text{Br}, \ R^2 = \text{H} \)
The phenylalanine derivatives 17, 18a, 18b, 19, 20a and 20b and the nitrophenylalanine derivatives 71a, 71b, 72a, 72b, 78a and 78b used in this investigation were prepared as described in the previous Chapter. The N-phthaloyltyrosine derivative 136 and the corresponding ester 79a were available for use. The bromoesters 80a and 80b, the amide 79b and the bromoamides 81a and 81b were prepared as described previously. Accordingly, treatment of O-acetyl-N-phthaloyltyrosine 136 with triethylamine, ethyl chloroformate and then tert-butylamine afforded the tyrosinamide 79b in 75% yield. Bromination of the amide 79b under the standard conditions using NBS gave the isomers 81a and 81b in high yield, as a 1:1 mixture (Scheme 3.1). Similarly, treatment of the ester 79a with NBS gave a 1:1 mixture of the diastereomers 80a and 80b in high yield.

Scheme 3.1

With the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b in hand, their reactions with triphenyltin hydride were investigated. Thus, treatment of a ca. 1:1 mixture of the bromophenylalanine derivatives 18a and 18b with triphenyltin hydride in benzene under nitrogen, with irradiation from a 300 W sunlamp, afforded the corresponding phenylalanine ester derivative 17 in good yield. Under identical conditions, a mixture of the bromoamides 20a and 20b reacted with triphenyltin hydride to give the corresponding phenylalanine derivative 19, also in good yield.
similar conditions the nitrophenylalanine bromoesters 71a and 71b reacted with triphenyltin hydride to give the ester 78a, while the bromoamides 72a and 72b reacted to give the amide 78b. However, analysis of the crude products from these reactions using $^1$H NMR spectroscopy showed that some decomposition had occurred. Treatment of the bromotyrosinamides 81a and 81b and the tyrosine bromoesters 80a and 80b with triphenyltin hydride afforded the reduced analogues 79b and 79a, respectively. As with the reactions of the nitrophenylalanine derivatives 71a and 71b, and 72a and 72b, analysis of the crude products of these reactions using $^1$H NMR spectroscopy showed that some decomposition had occurred under the reaction conditions.

Participation by the neighbouring carboxy protecting group in the reactions of the phenylalanine, tyrosine and nitrophenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b with NBS has the potential to result in stereoselective formation of the corresponding bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b or to enhance the rates of reaction. Previously it has been shown$^{54,60}$ that 1:1 mixtures of the diastereomers of the bromides 25, 28, 32a, 32b, 80a, 80b, 81a and 81b are produced in the brominations. Similarly, the nitrophenylalanine derivatives 78a and 78b reacted with NBS to give 1:1 mixtures of the diastereomers of the bromides 71a and 71b, and 72a and 72b, respectively. The lack of stereoselectivity in these reactions indicates that the bromination reactions are not affected by steric constraints imposed by the bulky phthaloyl moiety, carboxy protecting group and phenyl substituent in the delivery of bromine to the (2S)-enantiomers of the intermediate benzylic radicals, and can be attributed to the low energy of activation of such halogen atom transfer processes.$^{25}$

In order to investigate the effect of the neighbouring carboxy group on the rates of the radical brominations, various mixtures of the amino acid derivatives 17, 19, 78a, 78b, 79a and 79b were treated with approximately one molar equivalent of NBS in competitive experiments. In these reactions, solutions of the substrates and tert-butyl
Results and Discussion Chapter 3

benzamide, an internal standard, in carbon tetrachloride were heated at reflux under an atmosphere of nitrogen, with initiation from irradiation by a 300 W sunlamp, and the crude mixtures were analysed using $^1$H NMR spectroscopy.

The relative rates of reaction were determined using $^1$H NMR spectroscopy in a manner identical to that described in Chapter 2 of the Results and Discussion of this thesis for the reactions of the bromides $18a$, $18b$, $20a$, $20b$, $33$, $71a$, $71b$, $72a$, $72b$ and $73$ with silver salts, by measuring the relative rates of consumption of the substrates $17$, $19$, $78a$, $78b$, $79a$ and $79b$ relative to the internal standard. In duplicate experiments the relative rates determined varied by less than 20%. An indication of the reliability of the rates shown (Table 3.1) was determined by analysis of the mass balance of the starting materials and products in the reactions. In most cases, the starting materials and the product comprised greater than 80% of the material present and the extent of reaction was between 20-80%. The results of these experiments are summarised in Table 3.1.

<table>
<thead>
<tr>
<th>substrate</th>
<th>$k_{rel}$ (NBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>79a</td>
<td>9</td>
</tr>
<tr>
<td>79b</td>
<td>34</td>
</tr>
<tr>
<td>78a</td>
<td>1†</td>
</tr>
<tr>
<td>78b</td>
<td>5</td>
</tr>
</tbody>
</table>

† Assigned as unity within column.

Table 3.1. Relative rates of reactions of the amino acid derivatives 17, 19, 78a, 78b, 79a and 79b with NBS.
As described above, another aim of the work was to investigate the possibility of neighbouring group participation in the reduction reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b using triphenyltin hydride, by determining the effect of the carboxy substituent on the relative rates of reaction. Hence, the relative rates of reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b were determined in competitive experiments. In these competitive experiments, various mixtures of approximately equimolar amounts of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b and tert-butylbenzamide in benzene were treated with less than one molar equivalent of triphenyltin hydride with initiation from irradiation by a 300 W sunlamp. The relative rates were determined from the ratios of products in the reaction mixtures, which were corrected to allow for the initial ratios of substrates in the mixtures, and confirmed through duplicate experiments. The relative rates determined from the duplicate experiments using this method varied by less than 20% in most cases, except in reactions involving the nitrophenylalanine derivatives 71a, 71b, 72a and 72b which were complicated by competing decomposition. The results of these experiments are summarised in Table 3.2.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>$k_{rel}(\text{Ph}_3\text{SnH})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a and 18b</td>
<td>1†</td>
</tr>
<tr>
<td>20a and 20b</td>
<td>1</td>
</tr>
<tr>
<td>80a and 80b</td>
<td>1.2</td>
</tr>
<tr>
<td>81a and 81b</td>
<td>1.4</td>
</tr>
<tr>
<td>71a and 71b</td>
<td>4</td>
</tr>
<tr>
<td>72a and 72b</td>
<td>4</td>
</tr>
</tbody>
</table>

† Assigned as unity within table.

Table 3.2. Relative rates of reaction of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride, as determined from product ratios.
The relative rates of reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b could also be determined by measuring their relative rates of consumption from mixtures, relative to the internal standard, as described above for the reactions involving NBS. However, calculation of the relative rates of reaction using this method was complicated in some cases due to decomposition under the reaction conditions, as determined by analysis of the material balance of the reactions. In most cases, the brominated substrate and the reduced product comprised greater than ca. 80% of the material present. In the reactions involving the nitrophenylalanine derivatives 71a, 71b, 72a and 72b, however, a significant amount of the material could not be accounted for, presumably due to decomposition under the reaction conditions. For example, in several of the experiments involving the nitrophenylalanine derivatives 71a, 71b, 72a and 72b, these bromides and the corresponding reduced materials 78a and 78b comprised less than 50% of the material identified in the crude product. In addition, decomposition of these materials also affected the reduction of other substrates. Hence, determination of the relative rates using this method was found to be unreliable. The results of these experiments are summarised in Table 3.3. The data used to compile this table were obtained from single experiments in which the mass balance was considered reliable (generally greater than 80% of the material accounted for) and where most of the bromides consumed afforded reduced materials.

In the reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride, there is a possibility of stereoselectivity. To examine this possibility in the reactions of the bromides 18a and 18b, a ca. 1:1 mixture of the bromophenylalanine derivatives 18a and 18b was treated with triphenyltin hydride as described above for the competitive experiments. Under these conditions, the stereoselectivity was less than 1.1. In a similar manner, reactions of the bromoamides 20a and 20b were examined for the possibility of stereoselectivity, and in this case, no stereoselectivity was observed.
Table 3.3. Relative rates of reactions of the bromides 18b, 20b, 71a, 72a, 80b and 81b, based on their rates of consumption from mixtures.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$k_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18b</td>
<td>1†</td>
</tr>
<tr>
<td>20b</td>
<td>1</td>
</tr>
<tr>
<td>80b</td>
<td>1.1</td>
</tr>
<tr>
<td>81b</td>
<td>1.3</td>
</tr>
<tr>
<td>71a</td>
<td>6</td>
</tr>
<tr>
<td>72a</td>
<td>6</td>
</tr>
</tbody>
</table>

† Assigned as unity within table.

The stereoselectivity of reaction of the bromides 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b was determined from the competitive reactions between the substrates. In the reactions of the nitrophenylalanine derivatives 71a and 71b, the diastereomer 71a reacted approximately 1.6 times faster than the bromide 71b, however, the ratio of the reduced material 78a to consumed bromides 71a and 71b was low, and approximately 50% of the material could not be accounted for, presumably due to decomposition. Consequently, it is not clear whether the observed diastereoselectivity of 1.6:1 is real or mainly due to decomposition. The bromoamide 72a reacted less than 1.4 times faster than the diastereomer 72b. As with the reaction of the esters 71a and 71b, the ratio of the reduced material 78b to consumed bromides 72a and 72b was low and approximately 50% of the material could not be accounted for in these reactions. Hence, this selectivity could also be due mainly to decomposition.

The bromotyrosine derivatives 80a and 80b reacted with a stereoselectivity which varied between 1:1.1 and 1:1.5, while the bromoamides 81a and 81b reacted with a stereoselectivity of less than 1.4:1. In the reactions of the esters 80a and 80b, the ratio of reduced material 79a to consumed bromides 80a and 80b was low and approximately
20% of the material could not be accounted for. Hence, the stereoselectivity of less than 1:1.5 could be a result of selective decomposition of the (2R,3S)-isomer 80a.

In summary, the reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride proceed with little stereoselectivity, most of which could be due to selective decomposition of one isomer under the reaction conditions. The relative rates of reactions were determined by measuring the relative rates of production of the reduced materials, from their ratio in the crude mixtures, or from the rates of consumption of bromides from the mixtures. As a result of decomposition during some reactions, the relative rates determined from the product ratios are likely to be the most reliable.

In the competitive experiments described above involving NBS, the phenylalanine derivatives 17 and 19 and the tyrosine derivatives 79a and 79b reacted much faster than the corresponding nitro-substituted analogues 78a and 78b, respectively (Table 3.1). For example, the phenylalanine derivatives 17 and 19 reacted approximately eight times faster than the corresponding nitro-substituted analogues 78a and 78b. From this data, using the Hammett equation and a $\sigma_p(\text{NO}_2)^+$ constant of 0.79, a rho ($\rho$) value of ca. -1.1 was obtained. The effect of the aromatic ring substituents in these reactions is similar to that previously reported for radical bromination of series of substituted toluene derivatives, in which a $\rho$ value of -1.4 was obtained and is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient centre at the site of hydrogen abstraction (Figure 1). Thus, as a result of positive charge development in the transition state, radical formation adjacent to the electron deficient nitro substituted aromatic moiety is disfavoured, such that the nitrophenylalanine derivatives 78a and 78b react slower than the corresponding phenylalanine and tyrosine derivatives 17, 19, 79a and 79b.
In the processes involving triphenyltin hydride, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds 71a and 71b, and 72a and 72b reacting faster than the corresponding phenylalanine and tyrosine derivatives 18a and 18b, 20a and 20b, 80a and 80b, and 81a and 81b, respectively (Table 3.2). For example, the nitro-substituted analogues 71a, 71b, 72a and 72b reacted approximately four times faster than the corresponding phenylalanine derivatives 18a, 18b, 20a and 20b (Table 3.2), which corresponds to a \( \rho \) value of ca. +0.47 (using the \( \sigma_{p(N02)}^- \) constant of 1.27). The relative reactivity of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b is to be expected, since the transition state for a reaction of this type involves transfer of halogen to the nucleophilic stannyl radical with the development of an electron rich centre at the site of halogen abstraction (Figure 2). Favorable delocalisation of the developing negative charge over the electron deficient nitro-aromatic system can occur in the reactions of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b, and therefore radical formation proceeds more readily than in the reactions of the corresponding bromophenylalanine and bromotyrosine derivatives 18a, 18b, 20a, 20b, 80a, 80b, 81a and 81b. Consequently, the nitrophenylalanine derivatives 71a, 71b, 72a and 72b react faster than the bromophenylalanine and bromotyrosine derivatives 18a, 18b, 20a and 20b, and 80a, 80b, 81a and 81b.

Whether the carboxy group is protected as an ester or an amide has little effect on the relative rates of reaction of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride, yet in the reactions with NBS, each of the amides 19, 78b, and 79b reacted approximately five times faster than the corresponding ester 17, 78a or 79a. These effects are not consistent with relief of steric constraints between the phthalimido and carboxy protecting groups in the reactions of the amides 19, 78b, and 79b with NBS, resulting from the greater bulk of the amido substituent relative to the ester group, as such factors would be expected to be at least as
severe in the reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b, where the large bromine atom is transferred to the bulky triphenyltin radical. The most obvious interpretation of the results is that the amido substituent of 19, 78b, and 79b, being more electron rich than the ester group of 17, 78a and 79a, facilitates reaction by interacting with the electron deficient benzylic radical centre in the bromination transition state (Figure 3.1). Consistent with this proposal, the extent of anchimeric assistance displayed by amides in ionic reactions is known to be larger than that shown by esters, as discussed in the previous Chapter.

![Figure 3.1](image.png)

**Figure 3.1.** Neighbouring group participation by the amido group in the reactions with NBS to give the radicals 22, 134b and 135b.

The effect of the amido group to delocalise the developing charge in the reaction transition state, as seen in the reactions of the phenylalanine derivatives 19, 78b and 79b with NBS, would not be expected in the reactions of the bromides 20a, 20b, 72a, 72b, 81a and 81b with triphenyltin hydride, since any interaction between the carboxy group and the electron rich centre developing in the transition state would be unfavourable and would therefore be avoided (Figure 3.2).
Figure 3.2. Transition state for the reactions with triphenyltin hydride to give the radicals 22, 134b and 135b.

In the reactions involving NBS, the low stereoselectivity of formation of the brominated products was attributed to the low energy of activation of the halogen transfer process involved, and indicated that the reactions are little affected by steric constraints imposed by the bulky phthaloyl moiety, carboxy protecting group and aromatic side chain substituent. Consistent with this interpretation, there was little stereoselectivity in the reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride, which indicates these processes are also little affected by steric interactions between substituents.

Several alternative explanations which could account for the enhanced reaction rates of the amides 19, 78b and 79b with NBS compared to those of the esters 17, 78a and 79a (Table 3.1) were considered. While stabilisation of the developing radicals could occur through hyperconjugation with the α-carbon–carboxy carbon (C1-C2) bond, it was thought that this effect would be similar for both an ester and an amide substituent. In any case, whether the carboxy group is protected as an ester or an amide has little effect on the relative rates of reductions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b using triphenyltin hydride, reactions in which hyperconjugative stabilisation of the developing radicals could also occur. On this basis,
the explanation of the greater reactivity of the amides 19, 78b and 79b with NBS compared to that of the esters 17, 78a and 79a resulting from hyperconjugative stabilisation of the incipient radicals was discounted.

Another explanation which could account for the greater reactivity of the amides 19, 78b and 79b compared to that of the esters 17, 78a and 79a with NBS was considered which involves destabilisation of the developing partial positive charge at the benzylic position due to the inductive electron withdrawing effect of the carboxy group. Since the carboxy carbon of the ester group is more electron deficient than that of the amido substituent, it was thought that the ester moiety could destabilise the developing positive charge at the β-position in the transition state to a greater extent than the amide, thereby resulting in the greater rates of reactions of the amides 19, 78b and 79b compared to those of the esters 17, 78a and 79a. However, the nature of the carboxy protecting group has little effect on the rates of reactions of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with triphenyltin hydride. In these reactions, the inductive effect of the carboxy protecting group would be to stabilise the developing negative charge at the β-carbon, which is opposite to the inductive effect expected in the reactions involving NBS, and therefore the esters 18a, 18b, 71a, 71b, 80a and 80b would be expected to react faster than the corresponding amides 20a, 20b, 72a, 72b, 81a and 81b. On this basis, the inductive effect of the carboxy group to account for the enhanced reaction rates of the amides 19, 78b and 79b compared to those of the esters 17, 78a and 79a with NBS was discounted.

Another rationalisation considered which might account for the greater reactivity of the amides 19, 78b and 79b compared to those of the esters 17, 78a and 79a in the reactions with NBS involved coordination of bromine atom to the amido substituent of the amides 19, 78b and 79b, thereby aiding in the approach of the bromine atom to the reaction site and facilitating reaction (Figure 3.3). Similar three-electron-bonded species have been proposed as intermediates, for example, in the reactions of amino acids with
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Figure 3.3. Bromine coordination to the amido substituent of the amides 19, 78b and 79b.

Evidence which precludes the involvement of bromine coordination to the amido substituent of the amides 19, 78b and 79b in the reactions with NBS is apparent from the stereoselectivity of hydrogen abstraction in the bromination reactions, which is discussed below.
One other explanation was considered which could account for the reactivity of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b with NBS. In principal, the phthalimido group could be involved in neighbouring group participation in the reactions with NBS, although this effect would be expected to be similar for both the esters 17, 78a and 79a and the amides 19, 78b and 79b. Hence, participation by the phthalimido group to account for the enhanced rates of reactions of the amides 19, 78b and 79b compared to those of the esters 17, 78a and 79a was discounted. Further evidence precluding the involvement of the phthalimido group in the hydrogen atom transfer process is obtained from the stereoselectivity of hydrogen abstraction, which is described below.

In the bromination reactions of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b, there was the possibility of stereoselective hydrogen abstraction. To examine this possibility, it was anticipated that the bromination reactions of the deuterated analogues 26 and 29, and 31a and 31b of the phenylalanine derivatives 17 and 19 could be employed. By measuring the deuterium content of the bromides 137a and 137b, and 138a and 138b, produced from reaction of each of the deuterides 26, 29, 31a and 31b with NBS it was anticipated that the stereoselectivity of the hydrogen abstraction process could be determined. The deuterides 26, 29, 31a and 31b were already available.58,59 Thus, the deuterides 26, 29, 31a and 31b were treated with NBS using standard bromination conditions and the percentage deuterium content determined, using 1H NMR spectroscopy and mass spectrometry. In the 1H NMR spectra, the deuterium content was determined from each diastereomeric bromide 137a and 137b, and 138a and 138b. In comparison, the deuterium content of the bromides 137a and 137b, and 138a and 138b was determined using mass spectrometry for the mixtures of diastereomers. The results of these experiments are shown in Table 3.4.
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### Table 3.4

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Table 3.4. Values of percentage deuterium content (%D), deuterium isotope effect (DIE) and selectivity (S) of hydrogen abstraction from reactions of the deuterides 26, 29, 31a and 31b.
The percentage deuterium content of the product bromides 137a and 137b and 138a and 138b was determined using $^1$H NMR spectroscopy, from the ratio of the integrals of the peaks corresponding to the $\alpha$- and $\beta$-hydrogens. The signals corresponding to the $\beta$-protons of the products are diminished relative to those of the corresponding non-deuterated analogues when those protons are replaced with deuterium and hence the integral of the $\beta$-proton signal relative to that corresponding to the $\alpha$-proton is reduced, in proportion to the amount of deuterium present at that position.

The percentage deuterium content of the product bromides 137a and 137b, and 138a and 138b, was also calculated using mass spectrometry, by comparison of the mass spectra of the product mixtures with those of authentic samples of the corresponding non-deuterated analogues 18a and 18b, and 20a and 20b. In the mass spectra of the non-deuterated bromides 18a and 18b, and 20a and 20b, peaks corresponding to both the molecular ion (MH) and the protonated molecular ion (MH$\pm$H) are present for both the $^{79}$Br and $^{81}$Br isotopes. Only the peaks corresponding to ions containing the $^{79}$Br isotope were used in these calculations. The mass spectra of the deuterated bromides 137a and 137b, and 138a and 138b contain peaks corresponding to the non-deuterated molecular ion (MH), the molecular ion plus hydrogen (MH$\pm$H) and the deuterated molecular ion (MD), among others. The peak corresponding to the deuterated molecular ion (MD) is coincident with the peak corresponding to the non-deuterated molecular ion plus hydrogen (MH$\pm$H). Therefore, in order to determine the deuterium content of the products a correction for the MH$\pm$H contribution of the peak corresponding to the deuterated ion (MD) must be made.

The intensities of the MH peaks relative to those of the protonated molecular ions (MH$\pm$H) of the non-deuterated materials 18a and 18b, and 20a and 20b were measured, and using these values the corrected deuterated ion (MD) intensity can be
calculated. From the ratio of the intensities of the peaks corresponding to the $M_D$ and $M_H$ ions the deuterium content of the product bromides 137a and 137b, and 138a and 138b is calculated.

Using the values of the percentage deuterium content determined from the $^1$H NMR and mass spectra, the deuterium isotope effects and the stereoselectivity of hydrogen abstraction for reaction of the deuterides 26, 29, 31a and 31b were calculated (Table 3.4). In order to calculate the stereoselectivity of hydrogen abstraction from the data obtained in these reactions a necessary assumption is made that the deuterium isotope effects for abstraction of the pro-$R$ and pro-$S$ deuteriums from the deuterides 25 and 26, and 31a and 31b are identical, which in the absence of neighbouring group effects, is a reasonable assumption.

The percentage deuterium content of the bromophenylalanine derivatives 137a, 137b, 138a and 138b measured from the $^1$H NMR and mass spectra (Table 3.4) varies by less than 5% in each case. This variation can be attributed to several factors. Using $^1$H NMR spectroscopy, errors can arise from the measurement of the integrals from which the deuterium content is determined. Errors associated with these values using this method of determination could occur from incomplete relaxation of the $\alpha$- and $\beta$-protons whilst acquiring the spectral data, from measurement of the integrals of those peaks from the spectra and also from uncertainties due to baseline noise. The measurement of the integrals from the spectra is likely to be the major source of error in this case.

Uncertainties also occur in the measurement of deuterium content using mass spectroscopy. In this case, values for the deuterium content are determined from comparison of the mass spectrum of the reaction mixture with that of a non-deuterated sample. These calculations are made based on the assumption that the intensity of the molecular ion is not affected by replacing hydrogen for a deuterium. In addition, errors arise due to baseline noise, isotope peaks and in the corrections which need to be made for protonated molecular ion peaks (M+H). Furthermore, uncertainty arises as a result of
the measurement of the peak intensities from the spectra and due to variation in the operating conditions of the mass spectrometer between analysis of each sample. Therefore, given the possible sources of error in the measurement of deuterium content using these methods, the difference of less than 5% are of little significance.

The observed selectivity ($S_{obs}$) of the reactions of the deuterides 26, 29, 31a and 31b is dependent on the actual selectivity ($S$) of the hydrogen abstraction process (for reaction of non-deuterated analogues) and the deuterium isotope effect associated with cleavage of the carbon–deuterium bond. The deuterium isotope effect and actual selectivity of the hydrogen abstraction process were calculated using Equation 3.1. An example of these calculations is shown below for the reactions of the deuterides 31a and 31b.

Using the value of deuterium content of the bromide 138a of 65% from reaction of the deuteride 31b (where $H_R = D$), the observed selectivity ($S_{obs}(H_R/H_S)$) of hydrogen abstraction is 0.5385, whereas the value of 79% deuterium content for the bromide 138a from reaction of the deuteride 31a (where $H_S = D$) corresponds to an observed selectivity of 3.7619.

Equation 3.1

$$S = S_{obs} \text{(138a from 31b)} \times \text{DIE} = S_{obs} \text{(138a from 31a)} + \text{DIE}$$

$$\therefore \text{DIE}^2 = \frac{S_{obs} \text{(138a from 31a)}}{S_{obs} \text{(138a from 31b)}}$$

$$\text{DIE}^2 = 6.986, \text{ therefore } \text{DIE} = \text{ca. } 2.64$$

Substituting DIE into Equation 3.1, the actual selectivity ($S$) = 1.42 for abstraction of the pro-$R$ hydrogen.
The deuterium isotope effect of approximately 3 for the reactions of the deuterides 31a and 31b is much less than the isotope effect of approximately 5 for the reactions of the esters 26 and 29 and is consistent with the proposed mechanism involving interaction of the amido substituent with the radical centre in the reaction transition state. Stabilisation of the transition state by the amido group in the reactions of the amides 31a and 31b and hence lowering of the energy of the transition state species relative to that in the reaction of the esters 26 and 29 results in a decrease in the difference between the zero point energies of the carbon-hydrogen and carbon-deuterium bonds and a diminished deuterium isotope effect for reaction of the amides 31a and 31b. Since radical hydrogen abstraction processes occur with relatively little bond cleavage in the transition state, the difference in the deuterium isotope effects for the reactions of the esters 26 and 29 and the amides 31a and 31b can be rationalised in terms of the relative extent of bond cleavage in the reaction transition states for each of the processes. The reactions of the amides 31a and 31b involve a lower isotope effect than those of the esters 26 and 29, which indicates that the former reactions occur with less bond cleavage at the transition state, consistent with neighbouring group participation by the amido substituent.

The experiments described above involving the deuterides 26, 29, 31a and 31b indicate that the stereoselectivity of hydrogen abstraction in the reaction of the amide 19 is greater than that in the reaction of the ester 17, which is consistent with neighbouring group participation by the amido substituent in the reaction of the amide 19 to facilitate hydrogen abstraction and radical formation, as shown in Figure 3.1. Considering the conformations B and C of 19 which have the correct orientation to undergo hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient centre, unfavourable steric interactions between the bulky phenyl and phthaloyl substituents are present in the conformation C. Consequently, the conformer B is likely to be preferred on steric grounds, and in this orientation stereoselective loss of the pro-R hydrogen would be expected.
The pro-$R$ selectivity of hydrogen abstraction in the reaction of the phenylalaninamide 19 is not simply a result of steric effects. The $^1$H n.m.r. spectra of the amides 31a and 31b, and the respective coupling constants, $J_{\alpha,\beta}$, of 9.8 and 5.8 Hz, indicate that the preferred conformation of the (S)-enantiomer of 19 is A. This is the only staggered conformation which will give rise to the large coupling constant between the $\alpha$-proton and the pro-$R$ $\beta$-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-$S$ hydrogen, as this site is the least hindered to approach of bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups.

Participation by the phthaloyl group in the hydrogen atom transfer process would be expected to result in stereoselective loss of the pro-$S$ hydrogen. This would occur from the conformer A, whereas loss of the pro-$R$ hydrogen would involve the conformer C. Not only is the conformer C of much higher ground state energy, but reaction via that conformer would also involve the development of additional steric interactions between
the phenyl and phthaloyl substituents in the transition state. Hence, the selectivity for abstraction of the pro-\(R\) hydrogen in the reaction of the amide 19 is inconsistent with neighbouring group participation by the phthalimido group and therefore precludes the involvement of the phthalimido group to account for the greater reactivity of the amides 19, 78b and 79b compared to that of the corresponding esters 17, 78a and 79a with NBS.

As mentioned above, one explanation that was considered which could account for the greater reactivity of the amides 19, 78b and 79b compared to that of the corresponding esters 17, 78a and 79a with NBS involved coordination of bromine atom to the amido substituent of the amides 19, 78b and 79b. Coordination of bromine atom and subsequent reaction with the amide 19 in the conformation C (Figure 3.5) is unlikely due to unfavourable steric crowding between the phenyl and phthaloyl substituents. Hence, reaction of coordinated bromine is most likely to occur in the conformers A and B. In the conformer A, abstraction of either the pro-\(R\) or pro-\(S\) hydrogen by coordinated bromine appears equally likely, whilst abstraction of only the pro-\(S\) hydrogen could occur in the conformation B. Therefore, coordination of bromine atom to the amido group would be expected to result in preferential abstraction of the pro-\(S\) hydrogen. However, preferential removal of the pro-\(S\) hydrogen is opposite to the stereoselectivity of hydrogen abstraction in the reaction of the amide 19, determined from the reactions of the deuterides 31a and 31b with NBS, and suggests that the reactions involving NBS do not occur with coordination of bromine to the amido group.

In conclusion, all of the above evidence indicates that the reactions of the phenylalanine derivatives 19, 78b and 79b with NBS involve anchimeric assistance in hydrogen atom abstraction by bromine atom, through neighbouring group participation by the adjacent protected carboxy group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously.61,144-148 While 1,3-participation occurs in reactions involving either
hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, neighbouring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilisation of electron deficient reaction transition states.
RESULTS AND DISCUSSION: CHAPTER 4

1,4-Hydrogen Transfer Reaction of an N-Bromophenylalaninamide Derivative

In the previous Chapter, side chain bromination reactions of the amino acid derivatives 17, 19, 78a, 78b, 79a and 79b were investigated. In these reactions, the rate of hydrogen atom transfer was enhanced when the carboxy group was protected as an amide, rather than an ester, which was attributed to neighbouring group participation by the amido substituent, through direct interaction with the radical centre. As part of that investigation, the remote possibility of reaction via an amidyl radical was considered, which had to be checked. For example, in the reaction of the phenylalanine derivative 19, it was thought that the amidyl radical species 82 could undergo an intramolecular 1,4-hydrogen transfer from the benzylic position to give the benzylic radical 22, which could then abstract bromine to afford the bromides 20a and 20b (Scheme 4.1). In this manner it was thought that the reactions of the amides 19, 78b and 79b could be accelerated relative to those of the corresponding esters 17, 78a and 79a, thereby accounting for the observed kinetic effects. The amidyl radical 82 of the phenylalanine derivative 19 was chosen as the substrate to investigate this possibility. Therefore, an aim of the work described in this Chapter was to investigate the possible involvement of amidyl radicals as intermediates in the reactions of the phenylalanine derived amides 19, 78b and 79b with NBS.

![Scheme 4.1](image-url)
It was envisaged that the amidyl radical 82 chosen for study could be obtained from photolysis of the N-bromoamide 92, which in turn could be prepared from the amide 19 (Scheme 4.2). Hence, synthesis of the N-bromoamide 92 was required.

Scheme 4.2

Few methods for the synthesis of N-bromoamides from the corresponding amide precursors have been reported.\textsuperscript{193-195} One procedure involves treating a solution of an amide in acetic acid with aqueous sodium bromite,\textsuperscript{194} while other methods involve treatment of an amide with tert-butyl hypobromite\textsuperscript{193,196} or molecular bromine and aqueous potassium hydroxide.\textsuperscript{195}

Initially, preparation of the N-bromoamide 92 was attempted using the procedure involving bromine.\textsuperscript{195} Accordingly, the amide 19 was dissolved in neat bromine and the solution was cooled to 0 °C, then aqueous potassium hydroxide was added. Following workup of the reaction mixture, analysis of the crude product using \textsuperscript{1}H NMR spectroscopy showed that the phenylalaninamide 19 had reacted to give mainly the p-bromophenylalanine derivative 139 (Scheme 4.3). The N-bromoamide 92 was not detected in the \textsuperscript{1}H NMR spectrum of the crude product. Purification of the bromide 139 was attempted using chromatography on silica, however, during this process some decomposition occurred. Consequently, the bromide 139 was not purified or characterised further. The regioselectivity of reaction was determined from the \textsuperscript{1}H NMR spectrum of the crude material, which contained doublet resonances at
8 7.31 (J 8.4 Hz), 7.05 (J 8.4 Hz) and 3.49 (J 8.5 Hz), and a triplet at δ 4.96 (J 8.5 Hz) corresponding to the two pairs of aromatic hydrogens of the substituted phenyl substituent and the β- and α-hydrogens, respectively, consistent with aromatic substitution at the para-position.

\[
\text{Scheme 4.3}
\]

Presumably, the bromide 139 is produced in the reaction by electrophilic aromatic substitution of the amide 19. In general, the use of elevated temperature, strongly acidic conditions or a Lewis acid catalyst is required to achieve electrophilic aromatic substitution in non-activated aromatic systems. In this case, however, the reaction was carried out in the absence of a Lewis acid catalyst, at 0 °C and in a basic medium, conditions in which electrophilic aromatic substitution of a non-activated substrate would not be expected to occur. One possible mechanism which could account for the ease of substitution involves neighbouring group participation by the amido group, through stabilisation of the arenium ion intermediate. While not pursued in the current work, it was anticipated that further investigation into this system would explain the ease of aromatic substitution.

Given that preparation of the N-bromoamide 92 using molecular bromine was unsuccessful, an alternative procedure involving tert-butyl hypobromite was investigated. Accordingly, the phenylalaninamide 19 was treated with a solution of tert-butyl hypobromite, which was prepared using literature procedures, at room
temperature for 16 h in the dark. Analysis of the crude product using $^1$H NMR spectroscopy showed that the $N$-bromoamide $92$ was present in high yield. Formation of the $N$-bromoamide $92$ in the reaction was established from the infrared spectrum of the crude product, in which the absorbance due to the NH stretching frequency of the amide $19$ was absent, and from the $^1$H NMR spectrum. In the $^1$H NMR spectrum, doublet of doublet resonances occurred at $\delta$ 5.69 ($J$ 5.4 and 10.5 Hz), 3.59 ($J$ 10.5 and 14.4 Hz) and 3.52 ($J$ 5.4 and 14.4 Hz), corresponding to the $\alpha$-, $\beta$- and $\beta'$-protons, respectively. The signal corresponding to the amide proton of the phenylalaninamide $19$ was absent, consistent with replacement of the amide proton in the reaction. The signal corresponding to the $\alpha$-proton is shifted downfield by ca. 0.7 ppm relative to that of the corresponding amide $19$, presumably due to the inductive electron withdrawing effect of the bromine attached to the amide nitrogen. This material was used in the subsequent photolysis reactions without purification or further characterisation.

With the $N$-bromoamide $92$ in hand, its photolysis reaction was investigated. Accordingly, a solution of the $N$-bromophenylalaninamide $92$ in carbon tetrachloride was heated at reflux under nitrogen for 5 mins whilst being irradiated with a 300 W sunlamp. Analysis of the crude product using $^1$H NMR spectroscopy showed that the $N$-bromoamide $92$ had reacted to give mainly a 1:1 mixture of the $\beta$-bromophenylalanine derivatives $20a$ and $20b$. The phenylalanine derivative $19$ comprised the remainder of the material present. Thus, since photolysis of the $N$-bromoamide $92$ results in formation of the bromide diastereomers $20a$ and $20b$, the mechanism of reaction of the $N$-bromoamide $92$, and hence the amidyl radical $82$, could be investigated.

As described previously, an aim of the work in this Chapter was to investigate the possibility of involvement of amidyl radicals in the bromination reactions using NBS, which are described in the previous Chapter. In that work, the stereoselectivity of hydrogen abstraction from the phenylalanine derivative $19$ was determined, through
investigation of the reactions of the deuterides $31a$ and $31b$ with NBS. In a similar manner it was anticipated that the stereoselectivity of hydrogen abstraction in the reaction of the $N$-bromoamide $92$ could be determined, by investigation of the photolysis reactions of the deuterides $140a$ and $140b$. If the reactions of the deuterides $31a$ and $31b$ with NBS proceed via amidyl radicals, then the stereoselectivity of hydrogen abstraction from reaction of the $N$-bromoamide derivatives $140a$ and $140b$ and of the deuterides $31a$ and $31b$ with NBS is likely to be the same. On the other hand, if the reactions of the deuterides $31a$ and $31b$ do not involve amidyl radical intermediates, then the stereoselectivity would be expected to be different. In order to investigate this hypothesis, preparation of the $N$-bromoamides $140a$ and $140b$ was required.

The deuterides $140a$ and $140b$ were prepared using an identical procedure to that described above for the preparation of the $N$-bromoamide $92$, by treatment of each of the deuterides $31a$ and $31b$, in separate experiments, with tert-butyl hypobromite. From these experiments, the corresponding $N$-bromoamides $140a$ and $140b$ were afforded in approximately 95 and 60% yields, respectively, and each with approximately 98% deuterium content as determined through $^1$H NMR spectroscopic analysis of the crude mixtures. In each case only a single diastereomer was detected in
the $^1$H NMR spectrum of the crude product, which suggests that no loss of chiral integrity occurs at either the α-carbon or the benzylic position during reaction. On this basis, the deuterium content of the $N$-bromoamides $140a$ and $140b$ is assumed to be identical to that of the starting deuterides $31a$ and $31b$. The deuterides $140a$ and $140b$ were used in the subsequent photolyses without further purification or characterisation.

Accordingly, a dilute carbon tetrachloride solution of each of the deuterides $140a$ and $140b$, at a concentration of approximately 2.3 and 1.5 mM, respectively, was heated at reflux under nitrogen for 5 mins, with irradiation using a 300 W sunlamp. Analysis of the crude reaction mixtures using $^1$H NMR spectroscopy showed that in each case the $\beta$-bromides $138a$ and $138b$ were produced as a 1:1 mixture of diastereomers.

![Chemical structure of 138](image)

The percentage deuterium in the bromides $138a$ and $138b$ produced from each reaction of the deuterides $140a$ and $140b$ was determined in a manner identical to that described in the previous Chapter for the reactions of the deuterides $31a$ and $31b$ with NBS, using $^1$H NMR spectroscopy and mass spectrometry. Using $^1$H NMR spectroscopy, the deuterium content was determined from the ratio of the integrals of the peaks corresponding to the α- and β-protons, while comparison of the mass spectrum of the bromides $138a$ and $138b$ with that of an authentic sample of the non-deuterated analogues $20a$ and $20b$ was used to calculate the deuterium content using...
mass spectrometry. From these values, the deuterium isotope effect (DIE) and the
selectivity of hydrogen abstraction were calculated, as described in the previous
Chapter. Again, an assumption is made that the deuterium isotope effects associated
with abstraction of the pro-R and pro-S deuteriums are identical. The results of these
experiments are summarised in Table 4.1.

<table>
<thead>
<tr>
<th></th>
<th>%D</th>
<th>DIE</th>
<th>selectivity (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMR</td>
<td>MS</td>
<td>NMR</td>
</tr>
<tr>
<td>comp.</td>
<td>138a</td>
<td>138b</td>
<td>138a</td>
</tr>
<tr>
<td>140a</td>
<td>23</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>140b</td>
<td>88</td>
<td>93</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 4.1. Percentage of deuterium retention (%D), deuterium isotope effect (DIE)
and selectivity (S) of hydrogen abstraction in the reactions of the
N-bromoamides 140a and 140b.

The percentage deuterium content of the bromides 138a and 138b calculated
using 1H NMR spectroscopy and mass spectrometry differed by up to 8% for the
reaction of the deuteride 140b and 5% for the reaction of the deuteride 140a,
presumably due to errors associated with the measurement of the deuterium content
from the spectra, as discussed in the previous Chapter for the reactions of the deuterides
26, 29, 31a and 31b with NBS. Although the differences in these values are large, they
are of little importance since it can clearly be seen that the stereoselectivity for loss of
the pro-S hydrogen in these reactions is opposite to that in the reactions of the
deuterides 31a and 31b, in which stereoselective loss of the pro-R hydrogen occurs.
Hence, these results indicate that different hydrogen abstracting species are involved in
each case, and that amidyl radicals are not involved in the reaction of the amide 19 with
NBS. By inference, therefore, amidyl radicals are not involved in the reactions of the amides 78b and 79b with NBS.

The deuterium isotope effect of approximately 1.6 obtained in the photolysis reactions of the deuterides 140a and 140b is significantly less than the value of approximately 2.6 obtained from the reactions of the deuterides 31a and 31b with NBS. A logical interpretation of this result is that the hydrogen abstracting species involved in the reactions of the N-bromoamides 140a and 140b is more reactive than that involved in the reactions with NBS, since it implies that there is less bond breaking at the transition state in the former case. However, despite the greater reactivity of the hydrogen abstracting species in the reactions of the N-bromides 140a and 140b, hydrogen abstraction occurs with greater stereoselectivity than that in the reactions of the deuterides 31a and 31b with NBS.

The stereoselectivity of 3.9 for removal of the pro-S hydrogen in the reactions of the N-bromoamides 140a and 140b is opposite to that obtained in the reactions of the deuterides 31a and 31b with NBS and is consistent with an intramolecular process. For intramolecular abstraction of hydrogen by the amidyl radical to occur, an eclipsed conformation of the radical species 82 is required such that the hydrogen to be abstracted and the amidyl radical centre are in close proximity. The two possible eclipsed conformations A and B in which intramolecular hydrogen abstraction by the amidyl radical can occur are shown in Figure 4.1. The preferred orientation of the radical 82 is likely to be conformation A, since this conformer does not involve severe steric crowding between the bulky phenyl and phthaloyl substituents present for conformer B. In conformer A, intramolecular hydrogen abstraction by the amidyl radical would result in preferential removal of the pro-S hydrogen, since this hydrogen is much closer to the amidyl radical centre. Hence, the stereoselectivity of hydrogen abstraction in these reactions is consistent with reaction via a rare intramolecular 1,4-hydrogen atom transfer.
**Figure 4.1.** Eclipsed conformations of the radical 82 required for intramolecular hydrogen transfer.

While the stereoselectivity of hydrogen abstraction in the reactions of the deuterides 140a and 140b is consistent with an intramolecular reaction, it does not unambiguously establish such a process. By photolysis of mixtures of the N-bromoamide 92 and a competitive substrate at series of concentrations of each substrate, it was anticipated that an insight into the inter- or intramolecular mechanism of reaction of the N-bromoamide 92 could be gleaned, since variation in the ratio of products at different concentrations of each material will be depend upon the mechanism of reaction of the N-bromoamide 92. *p*-tert-Butyltoluene was chosen as the competitive substrate in these reactions, due to the relatively low volatility and simple $^1$H NMR spectra of that material and of the product of its bromination reaction, *p*-tert-butylbenzyl bromide.

In order to compare the reactivity of the hydrogen abstracting species involved in the reaction of the N-bromoamide with that in the NBS reactions, an estimate of the relative reactivity of *p*-tert-butyltoluene and the phenylalanine derivative 19 toward hydrogen abstraction by bromine atom was determined in a competitive experiment. Accordingly, an approximately equimolar amount of the phenylalanine derivative 19 and *p*-tert-butyltoluene was treated with NBS, using standard radical bromination
conditions. Analysis of the crude product of the reaction using $^1$H NMR spectroscopy showed a 1:1 mixture of the $\beta$-bromides $20a$ and $20b$ and $p$-tert-butylbenzyl bromide to be present in the ratio ca. 1:4. An estimate of the relative rate of reaction of 

_tern_-butylytoluene and the phenylalanine derivative $19$ can be obtained from the extent of reaction of each substrate and hence the ratio of the products from reaction of each substrate. Therefore, the ratio of 1:4 of $\beta$-bromides $20a$ and $20b$ and $p$-tert-butylbenzyl bromide indicates that the rate of reaction of _tern_-butylytoluene is approximately four times that of the phenylalanine derivative $19$ (Table 4.2).

<table>
<thead>
<tr>
<th>substrate</th>
<th>$k_{rel}$ (NBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$19$</td>
<td>1$^\dagger$</td>
</tr>
<tr>
<td>$p$-MePhCMe$_3$</td>
<td>4</td>
</tr>
</tbody>
</table>

$^\dagger$ Assigned as unity within column.

**Table 4.2.** Relative rates of reaction of the phenylalanine derivative $19$ and _tern_-butyltoluene ($p$-MePhCMe$_3$) with NBS.

The greater reactivity of _tern_-butyltoluene toward hydrogen abstraction by bromine atom than the phenylalanine derivative $19$ presumably is due to stereoelectronic effects.$^{24}$ For benzylic hydrogen abstraction, maximum radical stabilisation occurs when the carbon-hydrogen bond being cleaved is perpendicular to the aromatic ring, such that delocalisation of the developing radical with the aromatic $\pi$-system occurs. As the steric bulk of the substituents at the benzylic position increases, the perpendicular orientation of the carbon-hydrogen bond to be cleaved and the aromatic ring cannot be attained and a slower rate of radical formation results.$^{24}$ The benzylic substituent of the phenylalanine derivative $19$ is much larger than the
hydrogens of tert-butyltoluene. Consequently, maximum delocalisation of the incipient
benzylic radical onto the side chain $\pi$-system of the phenylalanine derivative 19 cannot
be attained, and hence tert-butyltoluene reacts faster.

Having established the relative reactivity of $p$-tert-butyltoluene and the
phenylalanine derivative 19 towards NBS, the photolysis reactions of the
$N$-bromoamide 92 in the presence of tert-butyltoluene at a series of concentrations of
each starting material were carried out. The sample of the $N$-bromoamide 92 used in
these experiments was freshly prepared and contained approximately 20% of the amide
19. Portions of this material were taken for use in each experiment and dissolved in
solutions of tert-butyltoluene in carbon tetrachloride, then photolysed for 5 mins. The
crude mixtures were analysed using $^1$H NMR spectroscopy and from the $^1$H NMR
spectra the ratio of the products of reaction of each starting material was measured from
the integrals of peaks characteristic of those products. The results of these experiments
are shown in Table 4.3.

<table>
<thead>
<tr>
<th>[tert-butyltoluene]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[92] 0.92 mM</td>
</tr>
<tr>
<td>0.65 mM</td>
</tr>
<tr>
<td>1.30 mM</td>
</tr>
<tr>
<td>2.60 mM</td>
</tr>
</tbody>
</table>

Table 4.3. Ratio of the bromophenylalaninamides 20a and 20b to $p$-tert-butylbenzyl
bromide from photolysis of mixtures of the $N$-bromoamide 92 and
tert-butyltoluene at varying concentrations.
In each of these experiments, the N-bromoamide 92 reacted to give mainly the β-bromides 20a and 20b, which is in direct contrast to the reaction of the phenylalaninamide 19 and tert-butyltoluene with NBS, described above. In that reaction, tert-butylbenzyl bromide was the major product of the reaction. Hence, this result indicates that the β-position of the N-bromoamide 92 is much more reactive toward hydrogen abstraction than the β-position of the phenylalanine derivative 19 in the reaction with NBS, consistent with an intramolecular process. In addition, this result provides further evidence precluding the involvement of amidyl radicals in the bromination reactions using NBS.

The data shown in Table 4.3 display two general trends. Firstly, at low concentration of the N-bromoamide 92, (see first row of Table 4.3) the amount of tert-butylbenzyl bromide produced in the reactions increases in approximate proportion to the increase in the concentration of tert-butyltoluene, consistent with formation of this material by an intermolecular process. A similar trend is apparent at higher concentrations of the N-bromoamide 92 (rows 2 and 3 of Table 4.3), although in these cases the increase in the amount of tert-butylbenzyl bromide produced is not in proportion to its increase in concentration. Secondly, as the concentration of the N-bromoamide 92 is increased (down each column), the ratio of the bromoamides 20a and 20b to tert-butylbenzyl bromide also increases. However, the increase in the amount of tert-butylbenzyl bromide in the mixtures is not in proportion to the increase in the N-bromoamide 92 concentration. Hence, this result indicates that the bromides 20a and 20b are formed from reaction of the N-bromoamide 92 via a mechanism involving both intermolecular and intramolecular components.

In summary, the greater reactivity of the benzylic hydrogens of the N-bromoamide 92 compared to those of tert-butyltoluene in the concentration experiments described above is consistent with an intramolecular process. In addition, the stereoselectivity of hydrogen abstraction determined from the photolysis reactions
of the deuterides 140a and 140b is consistent with an intramolecular reaction. However, the concentration experiments indicate that the N-bromoamide 92 reacts to give the bromides 20a and 20b via a mechanism which comprises both intermolecular and intramolecular components.

To account for these results, it is proposed that intermolecular electron transfer from the aromatic phenyl substituent to the amidyl radical (amidyl-N·) occurs with intramolecular deprotonation at the benzylic position by the basic amido group (Scheme 4.4).

The electron transfer component of the proposed mechanism of reaction of the N-bromoamide 92 (Scheme 4.4) is consistent with the mechanism of side chain oxidation of alkylbenzenes, in which electron transfer processes can play an important role. The key step in these processes generally involves cleavage of a benzylic
carbon-hydrogen bond, with formation of a benzylic radical (Scheme 4.5) [where X\* is a generic one-electron reactant].\textsuperscript{200} However, competition can occur between hydrogen atom transfer and a two step mechanism involving first an electron transfer resulting in the formation of a radical cation, which is then deprotonated in the second step (Scheme 4.6).\textsuperscript{200-202} Aryl radical cations are known to be efficient sources of benzylic radicals, for example, from the photoelectron transfer reactions of phthalimides.\textsuperscript{203,204} Hence, aryl radical cations are highly acidic species. The competition between hydrogen atom transfer (Scheme 4.4) and the process involving electron transfer (Scheme 4.5) will be determined mainly by the relative redox potential of ArCH$_3$ and X\*, as well as by the strength of the HX bond and by the solvent, although the reorganisation energy associated with the electron transfer step can also play an important role.\textsuperscript{200}

\[
\text{ArCH}_3 + X^* \rightarrow \text{ArCH}_2^* + \text{HX}
\]

\textbf{Scheme 4.5}

\[
\begin{align*}
\text{PhCH}_3 & \rightarrow [\text{PhCH}_3]^{**} & \text{B} & \rightarrow \text{BH}^+ & \rightarrow \text{PhCH}_2^*
\end{align*}
\]

\textbf{Scheme 4.6}

Electrophilic radicals may be specifically solvated by formation of complexes with electron rich solvents.\textsuperscript{205,206} A common example of this phenomenon involves complexation of chlorine atom to benzene (Figure 4.2) or carbon disulfide. The bonding of chlorine atoms to aromatic solvents probably has the character of a charge-transfer complex,\textsuperscript{206} with the chlorine atom acting as the acceptor and the solvent acting as a donor (Figure 4.2).
Similarly, complexation of aminyl radical cations to aromatic systems has also been proposed, in the homolytic amination of aromatic substrates. As with complexes formed between an aromatic solvent and chlorine atom, an intermediate in this process similar to a charge-transfer complex has been ascribed (Figure 4.3).

Thus, presumably coordination of the amyl radical to the phenyl substituent in the reaction of the N-bromoamide occurs in a similar manner to complexation of chlorine atom and aminyl radical cations with aromatic systems, with subsequent electron transfer resulting in the development of positive charge on the aromatic moiety. A consequence of this charge development in the reaction of the N-bromoamide is that the side chain β-hydrogens become more acidic, thereby facilitating deprotonation at the benzylic position by the basic amido group (Scheme 4.4). Hence, complexation and electron transfer between the amyl radical and the phenyl substituent of the side chain would account for the intermolecular component of
the reaction, whilst deprotonation by the basic amido group would account for the
intramolecular component of the process.

Given that the proposed mechanism of reaction of the N-bromoamide 92
involves development of positive charge in the aromatic system, the process is likely to
be disfavoured by an electron withdrawing aromatic substituent, due to the destabilising
influence of that substituent on the developing charge in that system. An illustration of
the dependence of similar electron transfer processes involving development of partial
positive charge on the nature of the donor aromatic system was shown by Griesbeck et al.172
in the photochemistry of various phthalimides. In that work, investigation of
reactions of the phenylalanine, tyrosine and dihydroxyphenylalanine (DOPA)
derivatives 89, 141 and 142, respectively, revealed that electron transfer occurred much
more readily in the activated aromatic systems of the tyrosine and DOPA derivatives
141 and 142, respectively, than in the non-activated phenylalanine derivative 89.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{PhthN} & \quad \text{PhthN} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

Given the influence of the nature of the side chain aromatic substituent on the
electron transfer processes reported by Griesbeck et al.,172 it was anticipated that the
electron transfer process in the reaction of the N-bromoamide 92 could also be affected
by side chain aromatic substituents. In order to investigate this possibility, the
nitrophenylalanine derived N-bromoamide 143 was chosen for study, due to the
presence of the electron withdrawing nitro substituent. Hence, the N-bromoamide 143
was prepared from the nitrophenylalanine derivative \textbf{78b} (Scheme 4.7) by treatment with \textit{tert}-butyl hypobromite, using the procedure described above, and identified from the \textsuperscript{1}H NMR spectrum of the crude product of reaction. In the \textsuperscript{1}H NMR spectrum, a doublet of doublet resonance occurred at $\delta$ 5.66 ($J$ 6.6 and 9.3 Hz), corresponding to the $\alpha$-proton, which is very similar to the chemical shifts of the signals corresponding to the $\alpha$-protons of the $N$-bromoamides \textbf{92}, \textbf{140a} and \textbf{140b}, described above. Consistent with formation of the $N$-bromoamide \textbf{143}, the signal corresponding to the amide proton of the derivative \textbf{78b} was absent from the \textsuperscript{1}H NMR spectrum of the crude material. This material was used in the subsequent photolysis without purification or further characterisation.

\[
\begin{align*}
\text{PhthN}^+ & \text{CONHCMe}_3 \\
\text{p-NO}_2\text{-Ph} & \quad \text{t-BuOBr} \\
\text{78b} & \quad \text{PhthN}^+ & \text{CONBrCMe}_3 \\
\text{p-NO}_2\text{-Ph} & \quad \text{143}
\end{align*}
\]

\textbf{Scheme 4.7}

A solution of the $N$-bromoamide \textbf{143}, at a concentration of approximately 1.5 mM, and \textit{ca.} 1.3 molar equivalents of \textit{tert}-butyltoluene, in the ratio \textit{ca.} 1:1.3, was photolysed using the conditions described above for the reactions of the $N$-bromoamide \textbf{92}. Analysis of the crude product using \textsuperscript{1}H NMR spectroscopy showed that a 1:1 mixture of the bromides \textbf{72a} and \textbf{72b} and $p$-\textit{tert}-butylbenzyl bromide were present in the ratio 6.6:1. From this ratio, an estimate of the relative rate of formation of the products of the reaction of the $N$-bromoamide \textbf{143} and \textit{tert}-butyltoluene was
determined. Hence, allowing for the excess of tert-butyltoluene in the initial mixture, the rate of formation of the bromides 72a and 72b is estimated at approximately 8.6 times that of tert-butylbenzyl bromide.

The nitro-substituted N-bromoamide 143 reacted to give the corresponding bromides 72a and 72b considerably less efficiently than the reaction of the N-bromophenylalanine derivative 92 to give the β-bromides 20a and 20b, presumably due to the electron withdrawing influence of the nitro-aromatic substituent. For example, whereas photolysis of the N-bromoamide 92 and tert-butyltoluene, in the ratio 1:1.4, afforded a 1:1 mixture of the bromides 20a and 20b and tert-butylbenzyl bromide in the ratio 15.6:1 (Table 4.3), the nitrophenylalanine derivative 143 reacted with 1.3 molar equivalents of tert-butyltoluene to give the corresponding bromides 72a and 72b and tert-butylbenzyl bromide in the ratio 6.6:1. Hence, it can clearly be seen that reaction at the β-position of the nitrophenylalanine derived material in the reaction of the N-bromoamide 143 is diminished in comparison with that in the reaction of the phenylalanine derived N-bromoamide 92.

The deactivating effect of the nitro substituent at the β-position in the reaction of the N-bromoamide 143 is consistent with that seen in the bromination reactions described in the previous Chapter, in which the nitro substituted derivatives 78a and 78b reacted slower than the corresponding phenylalanine derivatives 17 and 19. In addition, the deactivating influence of the nitro group is consistent with the mechanism proposed for reaction of the N-bromoamide 92 (Scheme 4.4) involving electron transfer to electrophilic amidyl radical with positive charge development in the aromatic side chain substituent.

In conclusion, the involvement of amidyl radicals as intermediates in the reactions of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b with NBS has been precluded, through investigation of the reactions of the N-bromophenylalanine derivatives 92, 140a and 140b, in which the stereoselectivity of hydrogen abstraction
was opposite to that in the reactions of the phenylalanine derivatives 31a and 31b. The N-bromophenylalaninamide derivative 92 was determined to react via a process involving intermolecular and intramolecular components. A mechanism involving intermolecular electron transfer followed by intramolecular proton abstraction by the basic amido group was proposed to account for these results.

The rates of the nitro radical substitution reactions of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b discussed in Chapter 3 of the Results and Discussion of this chapter were dramatically affected by the nature of the carboxylic protecting group. The amides 19, 78b and 79b reacted approximately 4 times faster than the corresponding esters 17, 78a and 79a, which was attributed to direct interaction of the amido substituents with the developing benzylic radical centre in the electron deficient carboxylic esters. In the previous chapter, the phenylation reaction of the N-bromosuccinimide 92 was examined in order to check the possibility of involvement of amido radicals as intermediates in the bromination reactions described in Chapter 3. In that work, the N-bromosuccinimide 92 was determined to react via a mechanism involving electron transfer on the aromatic side chain substituent, which promoted the amide investigation into the possible involvement of the aromatic side chain substitution in the radical bromination reactions described in Chapter 3.

It was envisaged that the amido substitution would approximately 10 times more basic than an ester, could stabilize the charge developing in the benzylic system through interaction directly with the π-system as shown in Figure 5.1. In this manner it was thought that the amide substituent could facilitate the bromination reactions. Therefore, derivatives 98 and 96 and the N-methylphenylalanine derivatives 93 and 94 were chosen as substrates to investigate this possibility.
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p-Methylphenylalanine Derivatives as Probes to Investigate Neighbouring Group Participation in Side Chain Bromination Reactions of Amino Acid Derivatives

The rates of the side chain radical bromination reactions of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b discussed in Chapter 3 of the Results and Discussion of this thesis were dramatically affected by the nature of the carboxy protecting group. The amides 19, 78b and 79b reacted approximately 5 times faster than the corresponding esters 17, 78a and 79a, which was attributed to direct interaction of the amido substituents with the developing benzylic radical centres in the electron deficient transition states. In the previous Chapter, the photolysis reaction of the N-bromoamide 92 was examined in order to check the possibility of involvement of amidyl radicals as intermediates in the bromination reactions described in Chapter 3. In that work, the N-bromoamide 92 was determined to react via a mechanism involving electron transfer on the aromatic side chain substituent, which prompted the current investigation into the possible involvement of the aromatic side chain substituent in the radical bromination reactions described in Chapter 3.

It was envisaged that the amido substituent, being approximately $10^6$ times more basic than an ester, could stabilise the charge developing in the benzylic system through interaction directly with the $\pi$-system as shown in Figure 5.1. In this manner it was thought that the amido substituent could facilitate the bromination reactions. The valine derivatives 95 and 96 and the $p$-methylphenylalanine derivatives 93 and 94 were chosen as substrates to investigate this possibility.
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Figure 5.1. Neighbouring group participation by the amido group in the reactions to give the radicals 22, 134b and 135b.

The valine derivatives 95 and 96 were chosen for study since they provide the opportunity to probe for neighbouring group participation in side chain radical bromination reactions in the absence of an aromatic side chain substituent, while the methylphenylalanine derivatives 93 and 94 were chosen since the p-methyl-substituent could be exploited for use as an internal standard in the reactions. For radical bromination of the p-methylphenylalanine derivative 94 with interaction of the amido group with the aromatic side chain, both the β-hydrogens and the p-methyl-hydrogens would be expected to be activated towards hydrogen atom abstraction by bromine atom relative to those of the ester 93, and should therefore react faster. In comparison, for reaction of the amide 94 with direct interaction by the amido substituent at the benzylic position, reaction at the β-position would be expected to occur faster than that of the β-position of the ester 93, whereas the rates of reactions at the p-methyl-substituents would be unaffected by the nature of the carboxy group.
In addition to using the methylphenylalanine derivative 94 to investigate the bromination reactions involving NBS, it was envisaged that the amide 94 could be utilised to examine the role of the aromatic side chain substituent in the reaction of the N-bromoamide 92, through reaction of the methylphenylalanine derived N-bromoamide 144. In this case, the p-methyl substituent provides a probe to examine the reactivity of the β-hydrogens relative to that of the p-methyl hydrogens. In order to investigate these hypotheses, the valine derivatives 95 and 96 and the p-methylphenylalanine derivatives 93 and 94 were required.

The valine derivatives 95 and 96 and the corresponding bromides 33 and 73 were prepared as described in Chapters 1 and 2 of this thesis. It was anticipated that the p-methylphenylalanine derivatives 93 and 94 could be prepared from the bromoglycine derivative 7b as shown in Scheme 5.1.
It was expected that the N-benzoylmethylphenylalanine derivative 145 could be prepared from the bromoglycine derivative 7b by the addition of p-methylbenzylmagnesium bromide. A similar procedure has been used to prepare a variety of aliphatic and unsaturated amino acid derivatives, by treatment of bromoglycine derivatives with various Grignard reagents. Accordingly, the bromoglycine derivative 7b was synthesised from N-benzoylglycine methyl ester 7a, by treatment with NBS under photolytic conditions using a standard procedure. Treatment of the bromide 7b with p-methylbenzylmagnesium bromide, which was prepared from two equivalents of p-methylbenzyl bromide and magnesium turnings, afforded the N-benzoyl-p-methylphenylalanine derivative 145 in 23% yield, after chromatography on silica. Optimisation of the yield in this reaction was not attempted, but the most likely cause of the low yield is coupling of p-methylbenzyl bromide with p-methylbenzylmagnesium bromide, since coupling of benzyl Grignard reagents with corresponding benzyl halides.

Scheme 5.1

93) R = OMe
94) R = NHCMe₃
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is common in this type of reaction.\textsuperscript{209} Formation of the product 145 from coupling of \( p \)-methylbenzylmagnesium bromide to the bromoglycine derivative 7b was confirmed from the \( ^1 \text{H} \) NMR spectral data. In the \( ^1 \text{H} \) NMR spectrum, a multiplet occurred at \( \delta 5.06 \) and doublet of doublet resonances occurred at 3.25 (\( J 5.9 \) and 13.9 Hz) and 3.17 (\( J 5.7 \) and 13.9 Hz), corresponding to the \( \alpha \)- and diastereotopic \( \beta \)-protons of the derivative 145.

Acidic hydrolysis of the methylphenylalanine derivative 145 followed by crystallisation from ethanol and aniline afforded the free amino acid 146 as a white solid in 51\% yield. Treatment of the amino acid 146 with a mixture of phthalic anhydride and triethylamine in refluxing toluene for 4 h, with continual removal of water during the course of the reaction using a Dean-Stark apparatus, gave \( N \)-phthaloyl-\( p \)-methylphenylalanine 147 as a white solid in 97\% yield. This material was identified using \( ^1 \text{H} \) NMR spectroscopy and mass spectrometry, the latter showing a peak at \( m/z \) 309 corresponding to the molecular ion. In the \( ^1 \text{H} \) NMR spectrum, peaks characteristic of a phthaloyl substituent occurred between \( \delta 7.80-7.67 \), whilst a triplet occurred at \( \delta 5.20 \) (\( J 8.3 \) Hz) and a doublet at \( \delta 3.56 \) (\( J 8.3 \) Hz), corresponding to the \( \alpha \)- and \( \beta \)-protons of the derivative 147. From the acid 147, the ester 93 was prepared in 88\% yield by treatment with acidified methanol. The amide 94 was prepared in 97\% yield by treatment of the acid 147 with thionyl chloride, and then tert-butylamine.

With both the ester 93 and amide 94 in hand, their reactions with NBS were investigated. Since there is a possibility of multiple bromination of either of these substrates in the reactions with NBS, less than one molar equivalent of this reagent was used. Thus, treatment of the ester 93 with NBS under standard radical bromination conditions gave a crude product containing the \( p \)-bromomethyl compound 149, a 1:1 mixture of the \( \beta \)-bromide diastereomers 148a and 148b and the ester 93. Analysis of the crude product of the reaction using \( ^1 \text{H} \) NMR spectroscopy showed the bromide 149, the \( \beta \)-bromides 148a and 148b and the ester 93 were present in the ratio
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7.3 : 1 : 9.4. Following chromatography of the mixture on silica, the bromide 149 was isolated as a colourless oil in 30% yield.

![Scheme 5.2](image)

**Scheme 5.2**

The regiochemistry of bromine incorporation in the product bromides 148a and 148b, and 149 was determined using $^1$H NMR spectroscopy. In the $^1$H NMR spectrum of the $p$-bromomethyl derivative 149, a singlet resonance occurred at $\delta$ 4.39 corresponding to the bromomethyl moiety, while signals at $\delta$ 5.13 (dd, $J$ 5.7 and 10.8 Hz) and 3.57 (m) correspond to the $\alpha$- and $\beta$-protons, respectively. The peaks in the $^1$H NMR spectrum of the ester 149 corresponding to the $p$-bromomethyl protons and the $\alpha$- and $\beta$-protons were assigned by comparison with the $^1$H NMR spectral data of the non-brominated compound 93. The chemical shifts and splitting patterns of the signals corresponding to the $\alpha$- and $\beta$-protons of the ester 149 correlate closely with those corresponding to the $\alpha$- and $\beta$-protons of the starting material 93, which is consistent with substitution at the $p$-methyl substituent. Substitution of a methyl proton with bromine is reported to cause a downfield shift of 2.2 ppm.$^{183}$ The signal corresponding to the $p$-bromomethyl group is 2.18 ppm downfield from the signal
corresponding to the p-methyl group of the starting amide 93, which is in close agreement with the expected value of 2.2 ppm, and thus confirms the assignment of the peak at δ 4.39. Incorporation of a single bromine atom was apparent from the mass spectrum, which showed peaks of equal abundance at m/z 402 and 400, corresponding to the deprotonated molecular ion.

In the reaction of the ester 93 with NBS, the minor products were the β-bromides 148a and 148b. Approximately 0.7 molar equivalents of NBS were used in order to avoid multiple bromination, and as a consequence the yields of the bromides 148a and 148b were low. Therefore, the bromides 148a and 148b were not isolated, and were identified only from the 1H NMR spectrum of the crude product, by comparison of the spectrum with spectral data of the corresponding bromophenylalanine derivatives 18a and 18b, and 25 and 28 (Table 5.1). In the 1H NMR spectrum, doublets occurred at δ 5.50 (J 10.8 Hz) and 6.01 (J 10.8 Hz), which correspond to the α- and β-protons of the diastereomer 148a. In addition, doublets occur at δ 5.59 (J 10.5 Hz) and 5.93 (J 10.5 Hz), which correspond to the α- and β-protons of the diastereomer 148b. The 1H NMR spectral data of the bromide 148a correlate very closely with those of the bromophenylalanine derivatives 18b and 25, while those of the bromoester 148b are almost identical to those of the bromides 18a and 28, and on this basis the bromides 148a and 148b were identified.

Under identical conditions to those used in the reaction of the ester 93, the amide 94 reacted with NBS to give the β-bromide diastereomers 150a and 150b and the bromide 151 (Scheme 5.3). Analysis of the crude product using 1H NMR spectroscopy showed the bromide 151, a 1:1 mixture of the bromide diastereomers 150a and 150b, and the amide 94 in the ratio 1.4 : 1 : 4.5. Since the extent of reaction of the amide 94 was low, the yield of each of the bromides 150a, 150b and 151 was also low. Furthermore, the regioisomeric bromides 150a and 150b, and 151 were inseparable using chromatography on silica, and consequently were identified from the 1H NMR
Results and Discussion Chapter 5

spectral data obtained from the crude reaction mixture, by comparison with the corresponding bromophenylalanine derivatives 20a, 20b, 32a and 32b, and the p-bromomethyl derivative 149, as described below.

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>Jα,β</th>
<th>R</th>
<th>α</th>
<th>β</th>
<th>Jα,β</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>18b</td>
<td>5.52</td>
<td>6.02</td>
<td>11.2</td>
<td>3.55</td>
<td>18a</td>
<td>5.59</td>
<td>5.91</td>
<td>10.5</td>
</tr>
<tr>
<td>25b</td>
<td>5.52</td>
<td>6.02</td>
<td>11.2</td>
<td>3.55</td>
<td>28b</td>
<td>5.59</td>
<td>5.91</td>
<td>10.5</td>
</tr>
<tr>
<td>148a</td>
<td>5.50</td>
<td>6.01</td>
<td>10.8</td>
<td>3.56</td>
<td>148b</td>
<td>5.59</td>
<td>5.93</td>
<td>10.5</td>
</tr>
<tr>
<td>20b</td>
<td>5.22</td>
<td>6.17</td>
<td>11.8</td>
<td>1.02</td>
<td>20a</td>
<td>5.32</td>
<td>6.05</td>
<td>11.4</td>
</tr>
<tr>
<td>32b</td>
<td>5.22</td>
<td>6.17</td>
<td>11.8</td>
<td>1.02</td>
<td>32a</td>
<td>5.32</td>
<td>6.05</td>
<td>11.4</td>
</tr>
<tr>
<td>150a</td>
<td>5.22</td>
<td>6.17</td>
<td>11.4</td>
<td>1.03</td>
<td>150b</td>
<td>5.31</td>
<td>6.05</td>
<td>11.4</td>
</tr>
</tbody>
</table>

a R values correspond to the signals of the carboxy protecting group.
b Data from reference 59.

Table 5.1. 1H NMR spectral data of the bromophenylalanine derivatives 18a, 18b, 20a, 20b, 25, 28, 32a and 32b and the β-bromomethylphenylalanine derivatives 148a, 148b, 150a and 150b.

Scheme 5.3
The regiochemistry of bromine incorporation in the bromides 150a and 150b, and 151 is apparent from their $^1$H NMR spectral data. A singlet resonance at $\delta$ 4.38 corresponds to the $p$-bromomethyl moiety, while doublet of doublet resonances at $\delta$ 4.96 ($J$ 6.6 and 9.9 Hz), 3.57 ($J$ 6.6 and 14.7 Hz) and 3.43 ($J$ 9.9 and 14.7 Hz) correspond to the $\alpha$-proton and each of the diastereotopic $\beta$-protons, respectively, of the bromide 151. The assignment of the peak due to the $p$-bromomethyl group was based on comparison of the $^1$H NMR spectral data of the starting amide 94, in an identical manner to that described above for the ester 149. The signal corresponding to the $p$-bromomethyl group occurs 2.15 ppm downfield from the signal corresponding to the $p$-methyl group of the amide 94, which is in close agreement with the expected value of 2.2 ppm, and thus confirms the assignment of the peak at $\delta$ 4.38. In addition, the chemical shifts and coupling constants of the signals corresponding to the $\alpha$- and diastereotopic $\beta$-protons are very similar to those of the amide 94, consistent with substitution at the $p$-methyl substituent. Hence, on these bases, the bromide 151 was identified.

In a similar manner to that described above for the $\beta$-bromides 148a and 148b, the $\beta$-bromide diastereomers 150a and 150b were identified from the $^1$H NMR spectrum of the crude product, by comparison of the spectrum with spectral data of the corresponding bromophenylalanine derivatives 20a, 20b, 32a and 32b. In the $^1$H NMR spectrum, doublets occurred at $\delta$ 5.22 ($J$ 11.4 Hz) and 6.17 ($J$ 11.4 Hz), which correspond to the $\alpha$- and $\beta$-protons of the bromide diastereomer 150a. In addition, peaks present at $\delta$ 5.31 ($J$ 11.4 Hz) and 6.05 ($J$ 11.4 Hz) correspond to the $\alpha$- and $\beta$-protons of the bromoamide 150b (Table 5.1). These data for the bromide 150a correlate closely to those of the bromophenylalaninamides 20b and 32b, while those of the bromide 150b are almost identical to those of the bromophenylalanine derivatives 20a and 32a, and on this basis the bromides 150a and 150b were identified.
The relative rates of reaction of the valine derivatives 95 and 96 with NBS were determined in a competitive experiment in an identical manner to that described in Chapter 3 of the Results and Discussion of this thesis for the competitive reactions of the phenylalanine analogues 17, 19, 78a, 78b, 79a and 79b, by treating an approximately equimolar amount of each substrate 95 and 96 and tert-butylbenzamide with NBS and measuring the relative rates of consumption from the mixture. The relative rates obtained from this experiment were confirmed in duplicate experiments, and varied by less than 20%. In these experiments, the valine derivatives 95 and 96 reacted at the same rate.

An indication of the reliability of the relative rates was determined by analysis of the mass balance of the reactions. In all cases the starting materials 95 and 96 and the corresponding brominated products 33 and 73 comprised greater than 85% of the material present.

An estimate of the relative rates of reaction at the β-positions and the p-methyl substituents of the p-methylphenylalanine derivatives 93 and 94 can be obtained from the ratios of products in the crude reaction mixtures. The ratio of the β-bromides 148a and 148b to p-bromomethyl derivative 149 present in the crude mixture from reaction of the ester 93 was 1 : 7.3, whereas the ratio of the β-bromides 150a and 150b to the p-bromomethyl derivative 151 from reaction of the amide 94 was 1 : 1.4. Hence, these values indicate that the hydrogens of the p-methyl group of the ester 93 are ca. 7.3 times more reactive towards hydrogen abstraction by bromine atom than those at the β-position, whereas the hydrogens of the p-methyl group of the amide 94 are ca. 1.4 times more reactive than those at the β-position. From these data, it can be seen that the β-hydrogens of the amide 94 are approximately five times more reactive than those of the ester 93 relative to the corresponding p-methyl substituents, consistent with the relative rates of reaction of the amides 19, 78b and 79b and the esters 17, 78a and 79a, discussed in Chapter 3.
Although the product ratios allow an estimate of the relative reactivity of the \( \beta \)- and \( p \)-methyl hydrogens of the ester 93 and the amide 94 to be made, a comparison of the relative reactivity of the \( p \)-methyl substituents of the ester 93 and the amide 94 cannot be obtained from these data. In order to make this comparison, the ester 93 and the amide 94 were reacted with NBS in separate experiments in the presence of the competitive substrate \( \text{tert} \)-butyltoluene and the relative reaction rates were determined, as described previously. The results of a typical experiment in each case are shown in Table 5.2. In these cases, the relative rates of product formation from reactions of each substrate are shown. An indication of the reliability of the results was determined by analysis of the mass balance of the reactions. In all cases the starting materials and the brominated products comprised greater than 85% of the material present, and the extent of reaction of each substrate in these experiments was between 30-65%. By maintaining a low extent of reaction, the formation of unwanted products from multiple bromination was minimised.

<table>
<thead>
<tr>
<th>substrate</th>
<th>( k_{\text{rel}} (\beta-H) )</th>
<th>( k_{\text{rel}} (p-\text{Me}) )</th>
<th>( k_{\text{rel}} (\text{MePhCMe}_3) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>0.10</td>
<td>1.00</td>
<td>2.20</td>
</tr>
<tr>
<td>94</td>
<td>0.55</td>
<td>1.02</td>
<td>2.20</td>
</tr>
</tbody>
</table>

\( a \) Arbitrarily assigned within table.

\( b \) Refers to relative rate of product formation.

Table 5.2. Relative rates of reaction of the methylphenylalanine derivatives 93 and 94 (at the \( \beta \)-position and the \( p \)-methyl substituent) and \( \text{tert} \)-butyltoluene with NBS.
In a duplicate experiment involving the amide 94, the relative rates of reaction varied by less than 10% from those shown (Table 5.2). In a duplicate experiment involving the ester 93, the relative rates of formation of the bromide 149 and $p$-tert-butylbenzyl bromide varied by less than 10%, while the rate of formation of the $\beta$-bromides 148a and 148b relative to that of $p$-tert-butylbenzyl bromide varied by less than a factor of two. In the latter case, the large variation in the relative rate of formation can be attributed to the small amount of the bromides 148a and 148b produced, such that the errors associated with measurement of the integrals of the peaks characteristic of those bromides 148a and 148b were large.

In the competitive reactions of the $p$-methylphenylalanine derivatives 93 and 94 and tert-butyltoluene with NBS, the rates of reaction at the $p$-methyl substituent of the ester 93 and the amide 94 were approximately half that of tert-butyltoluene. Presumably, the lower rate of reaction of the $p$-methyl substituents of the ester 93 and the amide 94 compared to that of tert-butyltoluene is due to hindrance of the approach of bromine atom to the $p$-methyl substituent by the bulky phthaloyl and carboxy protecting groups. In addition, the hydrogens at the $\beta$-position were less reactive than those of the corresponding $p$-methyl substituent (Table 5.2), which is consistent with deactivation due to stereoelectronic effects, as described in the previous Chapter. However, it can clearly be seen that the deactivating stereoelectronic effect at the $\beta$-position is diminished by a factor of approximately 5 in the reaction of the amide 94 relative to that in the reaction of the ester 93, consistent with neighbouring group participation by the amido substituent to stabilise the developing positive charge in the transition state at that position.

In summary, the results obtained from the reactions of the $p$-methylphenylalanine derivative 93 and 94 indicate that the greater reactivity of the amides 19, 78b and 79b compared to that of the esters 17, 78a and 79a, which is described in Chapter 3, results
from neighbouring group participation by the amido substituent through direct interaction with the developing positive charge at the β-position and not through interaction with the aromatic π-system.

The valinamide 96 reacted at the same rate as the ester 95 in the competitive experiments described above, indicating that the neighbouring group effect of the amido substituent to enhance the rate of bromination on the side chains of amino acid derivatives is influenced by the nature of the side chain. The neighbouring group effect in the reactions of the phenylalanine derivatives 19, 78b and 79b occurs through stabilisation of the developing charge in the transition state by the amido substituent. Reactions involving benzylic hydrogen abstraction by a halogen atom such as bromine are affected by the polar nature of the processes, of which many examples have been described.25 In these processes, the reactions occur with the development of partial positive charge at the benzylic position, which is delocalised onto the aromatic system. By comparison, bromination reactions of aliphatic substrates are influenced by polar effects to a much lesser extent than benzylic bromination reactions, such that radical stability is the dominant factor in determining the regioselectivity of the process, as seen in the relative selectivity of gas phase bromination of butane and methyl pentanoate, shown below (Table 5.3).25,210,211 In the reaction of methyl pentanoate, bromination at C1, adjacent to the inductively electron withdrawing, resonance stabilising methoxycarbonyl substituent, occurs to a greater extent than in the reaction of butane, indicating that the stability of the product radical is the predominant factor affecting the bromination.

In contrast to the bromination of aliphatic substrates, in which radical stability is the dominant factor affecting the reactions, polar effects control benzylic bromination. For example, although the same substituents are adjacent to the reaction centre as in the reactions of butane and methyl pentanoate, the reaction of toluene with NBS occurs
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Relative selectivities

<table>
<thead>
<tr>
<th>X</th>
<th>X−CH₂−CH₂−CH₂−CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>H—</td>
<td>1.0 82 82 1.0†</td>
</tr>
<tr>
<td>CH₃OCO—</td>
<td>41 35 71 1.0†</td>
</tr>
</tbody>
</table>

† C-4 assigned as unity for each compound.

Table 5.3. Relative selectivities of gas phase bromination of butane and methyl pentanoate.

approximately four times faster than that of methyl phenylacetate (Table 5.4). That is, the benzylic position is deactivated towards hydrogen abstraction by bromine atom indicating that polar effects influence the hydrogen abstraction process to a greater extent than does radical stability.

<table>
<thead>
<tr>
<th>substrate</th>
<th>$k_{rel} (NBS)$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>H−CH₂Ph</td>
<td>1.0</td>
</tr>
<tr>
<td>CH₃OCO−CH₂Ph</td>
<td>0.27</td>
</tr>
</tbody>
</table>

† Relative reactivity per hydrogen.

Table 5.4. Relative rate of reaction of toluene and methyl phenylacetate with NBS.

Hence, and by analogy with the reactions of butane and methyl pentanoate, the reactions of the valine derivatives 95 and 96 with NBS occur with very little charge development at the β-position in the reaction transition state. Since the effect of the neighbouring amido substituent in the reactions of the phenylalanine derivatives 19, 78b...
and 79b is to stabilise the developing partial positive charge in the transition state, the analogous effect would not be expected in the reactions of the valine derivatives 95 and 96. Thus, this result is consistent with the neighbouring group effect of the amido substituent to stabilise the charge developing in the transition state in the reactions of the amides 19, 78b and 79b through direct interaction with the radical centre.

In Chapter 3 of the Results and Discussion of this thesis, several alternative explanations were considered which could account for the greater reactivity of the amides 19, 78b and 79b compared to that of the esters 17, 78a and 79a, including hyperconjugative stabilisation of the developing radical by the C1-C2 bond and coordination of bromine atom to the amido group of the amides 19, 78b and 79b. The valine derivatives 95 and 96 react with NBS at the same rate, which provides further evidence to preclude the involvement of hyperconjugation and bromine coordination to the amido moiety to account for the kinetic effects, since these effects would be expected to result in a greater reactivity of the amide 96 compared to that of the ester 95.

As mentioned above, another aim of the work described in this Chapter was to utilise the N-bromo-p-methylphenylalaninamide 144 to investigate the mechanism of reaction of the N-bromophenylalaninamide 92, which reacts via electron transfer to the amidyl radical and intramolecular deprotonation at the benzylic position by the amido group (Scheme 4.4). Given the structural limitations of the molecule (Figure 5.2), it was anticipated that β-bromination should predominate over p-methyl bromination in the reaction of the N-bromoamide 144, since intramolecular deprotonation by the amido group can only occur at the β-position.

In order to test this hypothesis the N-bromoamide 144 was required, which was synthesised from the amide 94 using the procedure described in the previous Chapter for the preparation of the N-bromoamides 92, 140a and 140b. This material was identified
Figure 5.2. Spatial proximity of the amido group to the β- and p-methyl hydrogens of the p-methylphenylalanine derivative 94.

from the $^1$H NMR spectrum of the crude product, which contained a doublet of doublets resonance at $\delta$ 5.66 ($J$ 5.0 and 10.8 Hz) corresponding to the α-hydrogen, consistent with that of the N-bromophenylalaninamide derivative 92.

With the N-bromoamide 144 in hand, its photolysis reaction was investigated. The reaction was carried out in the presence of tert-butyltoluene in order to make a comparison between the reactivity of the non-activated benzylic hydrogens of tert-butyltoluene with that of the p-methyl hydrogens of the methylphenylalanine derivative 144. Accordingly, a mixture of the N-bromoamide 144 (1.6 mM) and tert-butyltoluene, in the ratio ca. 1 : 1.4, was photolysed for 5 mins in carbon tetrachloride
at reflux under an atmosphere of nitrogen. Analysis of the crude product using $^1$H NMR spectroscopy showed the \( \beta \)-bromides 150a and 150b, the bromide 151 and \textit{tert}-butylbenzyl bromide were present in the ratio \( \text{ca. } 44 : 1 : 3.5 \).

The \textit{ca. } 12.6:1 ratio of \( \beta \)-bromides 150a and 150b to \textit{tert}-butylbenzyl bromide from this reaction indicates that the \( \beta \)-hydrogens of the \( N \)-bromoamide 144 are approximately 18 times more reactive than those of \textit{tert}-butyltoluene, despite deactivation at the \( \beta \)-position of the \( N \)-bromoamide 144 due to stereoelectronic effects. Consistent with this result, the hydrogens at the \( \beta \)-position of the \( N \)-bromoamide 92 were determined to be between 12 and 26 times more reactive than those of \textit{tert}-butyltoluene, based on the ratio of products of reaction of each substrate (Table 4.3) and allowing for the ratio of starting materials in the initial mixture.

The greater reactivity of the \( \beta \)-hydrogens of the \( N \)-bromoamide 144 compared to those of \textit{tert}-butyltoluene is consistent with reaction of the \( N \)-bromoamide 144 via the mechanism proposed in the previous Chapter for reaction of the \( N \)-bromoamide 92 involving intramolecular deprotonation at the \( \beta \)-position by the basic amido group. Presumably, due to the structural limitations of the molecule, intramolecular deprotonation at the \( p \)-methyl substituent by the amido group cannot occur, and as a consequence, reaction at the \( \beta \)-position occurs to a much greater extent than at the \( p \)-methyl substituent.

In conclusion, through investigation of the reactions of the valine derivatives 95 and 96 and the \( p \)-methylphenylalanine derivatives 93 and 94, it has been shown that the rates of reaction of the phenylalanine derived amides 19, 78b and 79b with NBS are enhanced relative to those of the corresponding esters 17, 78a and 79a, through stabilisation of the developing positive charge in the transition state by direct interaction of the amido group with the developing \( \beta \)-centred radicals. Furthermore, the regioselectivity of reaction of the \( N \)-bromo-\( p \)-methylphenylalanine derivative 144 has
provided convincing evidence in support of the mechanism proposed in Chapter 4 for reaction of the N-bromoamide 92 involving 1,4-neighbouring group participation by the amido moiety to deprotonate at the β-position.

A procedure involving asymmetric anti-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative has been developed for the stereoselective synthesis of a γ-hydroxy-valine precursor which could potentially be utilized in stereocontrolled syntheses of a variety of substituted amino acid derivatives.

1,4-Neighbouring group participation has been discovered in side chain hydrobromination reactions of derivatives of phenylalanine, norephendehylamine and tyrosine, and has been shown to occur through direct stabilisation of positive charge at the β-position in the reaction transition state by the amido substituent. The rates of radical bromination of N-phthaloyl derivatives of phenylalanine, tyrosine and norephendehylamine are enhanced when the carboxy group was protected as an amide rather than as an ester.
CONCLUSION

The work described in this thesis has demonstrated the importance of neighbouring group participation in a variety of reactions. 1,4-Neighbouring group participation by an amido substituent has been discovered in hydrolysis reactions of N-phthaloyl-protected phenylalanine, nitrophenylalanine and valine derivatives, and has been shown to occur through stabilisation of electron deficient carbocation intermediates of reactions. The effect of the neighbouring group effect in these hydrolysis reactions was to enhance the rates of the substitution processes and influence the course of the reactions and the stereochemical outcome in some cases. In reactions of valine and nitrophenylalanine derivatives, elimination is the predominant reaction when the carboxy group is protected as an ester, whereas substitution dominates when the carboxy group is protected as an amide. The effect of the neighbouring group to promote substitution over elimination has been exploited in the synthesis of a derivative of naturally occurring β-hydroxyvaline and a β-hydroxynitrophenylalanine derivative, which is a precursor to chloramphenicol, and has the potential to be utilised in syntheses of a variety of substituted amino acid derivatives.

A procedure involving asymmetric anti-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative has been developed for the stereoselective synthesis of a γ-hydroxyvaline diastereomer which could potentially be utilised in stereocontrolled syntheses of a variety of substituted amino acids.

1,4-Neighbouring group participation has been discovered in side chain radical bromination reactions of derivatives of phenylalanine, nitrophenylalanine and tyrosine, and has been shown to occur through direct stabilisation of positive charge at the β-position in the reaction transition states by the amido substituent. The rates of radical bromination of N-phthaloyl derivatives of phenylalanine, tyrosine and nitrophenylalanine are enhanced when the carboxy group was protected as an amide rather than as an ester.
which indicates that neighbouring group participation in radical reactions is of greater significance than previously recognised.

In summary, the various examples of neighbouring group participation by the protected carboxy group in the side chain reactions of amino acid derivatives discovered in the present work appear to be due to steric interactions between substituents within the molecules which move the carboxy oxygen in close proximity to the β-position, such that interaction with electron deficient centres of reactions can occur. These discoveries could be of great importance in the understanding of reactions of amino acids in peptides, such as in peptide secondary metabolism, in the auto-oxidation of amino acids and enzyme reaction mechanisms.
EXPERIMENTAL

General. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 or a Perkin Elmer 683 infrared spectrophotometer, calibrated against polystyrene film, as nujol mulls between sodium chloride plates unless stated otherwise. $^1$H NMR (300 MHz) and $^{13}$C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 or a Bruker ACP-300 spectrophotometer, in deuterochloroform with tetramethylsilane (TMS) as the internal standard or in deuterium oxide (D$_2$O) using sodium [2,2,3,3-2H$_4$]3-(trimethylsilyl)propionate (TSP) as an internal standard. Chemical shifts are quoted as $\delta$ in parts per million downfield from the internal standard. Multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; br, broad. Electron impact mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia or by the Microanalytical Services Unit of the Research School of Chemistry, Australian National University. Analytical thin layer chromatography was performed using Merck Keiselgel 60 F$_{254}$ silica on aluminium backing plates. Silica chromatography was performed by positive pressure flash chromatography on Merck-Keiselgel 60 (230-400 mesh ASTM), using between 20-50% ethyl acetate in light petroleum (b.p. 66-68 °C) as eluant, unless otherwise stated. Alumina chromatography was performed on Merck basic aluminium oxide 90 (70-230 mesh ASTM). All solvents were distilled before use. Anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Drying and purification of other reagents was performed using standard laboratory procedures. Organic solutions were dried by the addition of anhydrous Na$_2$SO$_4$. 
A Phillips MLU 300 W (220-240 V) sunlamp was used as the light source to initiate radical addition, bromination and reduction reactions, at a distance of between 5-10 cm from the reaction vessel. (S)-O-Acetyl-Nα-phthaloyltyrosine, (S)-O-acetyl-Nα-phthaloyltyrosine methyl ester, (2S,3R)-3-deutero-N-phthaloylphenylalanine methyl ester, (2S,3S)-3-deutero-N-phthaloylphenylalanine methyl ester, (2S,3R)-3-deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide, (2S,3S)-3-deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide, N-benzoylglycine methyl ester, and N-tert-butybenzamide were available for use.

(S)-Valine, (S)-, (R)- and (RS)-p-nitrophenylalanine and (RS)-phenylalanine were purchased from Sigma chemical company.
(S)-N-Phthaloylvaline Methyl Ester 95

A mixture of (S)-valine (6.12 g, 52 mmol) and phthalic anhydride (7.74 g, 52 mmol) was heated for 40 mins at 150 °C. After cooling to room temperature, the resultant oil was dissolved in methanol (150 ml) then thionyl chloride (0.5 ml) was added dropwise. The solution was stirred overnight at room temperature, then was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed twice with saturated sodium carbonate solution and then water. The solution was dried, then concentrated under reduced pressure, affording the title compound 95 as a colourless oil (11.28 g, 83%). $\delta_H$ 7.90-7.73 (m, 4 H, Phth), 4.58 (d, $J$ 8.3 Hz, 1 H, $\alpha$-H), 3.71 (s, 3 H, OMe), 2.77 (m, 1 H, $\beta$-H), 1.17 (d, $J$ 6.7 Hz, 3 H, $\beta$-Me), 0.91 (d, $J$ 6.8 Hz, 3 H, $\beta'$-Me); $m/z$ (%) 261 (M$^{+*}$, 10%), 202 (100), 187 (20); $m/z$ 261.101 (M$^{+*}$) [Calc. for C$_{14}$H$_{15}$NO$_4$ (M$^{+*}$) $m/z$ 261.100]. The spectral data for this material are consistent with literature values. 215

(R)-3-Bromo-N-phthaloylvaline Methyl Ester 33

A mixture of (S)-N-phthaloylvaline methyl ester 95 (10.48 g, 40.2 mmol) and NBS (7.15 g, 40.2 mmol) was heated at reflux for 2 h in carbon tetrachloride (150 ml) while being irradiated with a 300 W sunlamp. The mixture was cooled in an ice bath, filtered, then washed twice with water. The solution was dried, then was concentrated and the resultant oil was crystallised from a mixture of ether, light petroleum and dichloromethane, to give the title compound 33 as a fine white crystalline solid (11.46 g, 84%), m.p. 133-135°C (Lit.$^{54}$ 129-131°C). $\delta_H$ 7.94-7.78 (m, 4 H, ArH), 5.16 (s, 1 H, $\alpha$-H), 3.71 (s, 3 H, OMe), 2.15 (s, 3 H, $\beta$-Me), 1.99 (s, 3 H, $\beta'$-Me). The spectral data obtained for this compound are consistent with literature values.$^{54}$
Experimental

(S)-N-Phthaloyl-3,4-dehydrovaline Methyl Ester 38

Silver nitrate (8.19 g, 48 mmol) was added to a solution of the bromovaline derivative 33 (10.85 g, 32 mmol) in dry methanol (100 ml) over activated 4 Å sieves. The mixture was stirred at room temperature for 36 h in the dark, then saturated brine was added and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water, and the organic layer was separated, dried and concentrated. Analysis of the crude product using 1H-NMR spectroscopy showed the β,γ-alkene 38 and the corresponding α,β-alkene were present in the ratio ca. 5:1. A portion of this material was chromatographed on silica to give the alkene 38 as a colourless oil (3.46 g, 42%). δH 7.92-7.75 (m, 4 H), 5.38 (s, 1 H), 5.14 (s, 1 H), 5.11 (s, 1 H), 3.79 (s, 3 H, OMe), 1.92 (s, 3 H, β-Me). The 1H NMR spectral data for this compound are consistent with that reported.175,176

(S)-4-Bromo-N-phthaloyl-3,4'-dehydrovaline Methyl Ester 39

To a solution of the alkene 38 (1.05 g, 4.1 mmol) in carbon tetrachloride (40 ml) under a nitrogen atmosphere was added NBS (0.76 g, 4.3 mmol) and the resultant mixture was heated at reflux for 2 h with irradiation from a 300 W sunlamp. The mixture was cooled, then filtered and the filtrate was washed with water and dried. The solution was then concentrated under reduced pressure and the crude product was chromatographed on silica, affording the title compound 39 as a yellow oil (1.09 g, 80%). νmax(neat)/cm⁻¹ 3492, 2952, 1776, 1722, 1614, 1470, 1438, 1382, 1340, 1304, 1256, 1212, 1108, 1088, 1028, 960, 912, 792, 720, 700, 668; δH 7.92-7.88 (m, 2 H, ArH), 7.80-7.76 (m, 2 H, ArH), 5.72 (s, 1 H), 5.62 (s, 1 H), 5.41 (s, 1 H), 4.28 (d, J 10.8 Hz, 1 H, γ-H), 4.13 (d, J 10.8 Hz, 1 H, γ'-H), 3.79 (s, 3 H, OMe); δC 167.2, 166.5, 137.9, 134.2, 131.3, 123.3, 121.2, 53.3, 52.6, 33.4; m/z (%) 339 (M⁺, 20%),
Experimental

(S)-4-Hydroxy-N-phthaloyl-3,4'-dehydrovaline Methyl Ester 40

To a solution of (S)-4-bromo-N-phthaloyl-3,4'-dehydrovaline methyl ester 39 (120 mg, 0.4 mmol) in acetone (10 ml) was added a solution of silver nitrate (124 mg, 0.7 mmol) in water (10 ml) and the resultant mixture was stirred at room temperature for 16 h. Saturated brine was added and the mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude product was analysed using 1H NMR spectroscopy, which showed (S)-4-hydroxy-N-phthaloyl-3,4'-dehydrovaline methyl ester 40 as the major product from the reaction. $\nu_{\text{max (neat)/cm}^{-1}}$ 3500, 3020, 2960, 2920, 2775, 1750, 1720, 1640, 1470, 1430, 1380, 1340, 1220, 1110, 1090, 1030, 920, 760, 720, 670; $\delta_{\text{H}}$ 7.91-7.86 (m, 2 H, ArH), 7.79-7.73 (m, 2 H, ArH), 5.61 (s, 1 H), 5.44 (s, 1 H), 5.30 (s, 1 H), 4.38-4.20 (m, 2 H, CH2), 3.78 (s, 3 H, OMe), 2.62 (br s, 1 H, OH); $\delta_{\text{C}}$ 168.3, 167.3, 141.9, 134.3, 131.5, 123.6, 118.0, 64.2, 53.7, 52.9; $m/z$ (%) 274 (M-H, 35%), 243 (100), 216 (53), 199 (33), 160 (15), 130 (43); $m/z$ 274.072 (M-H) [Calc. for C14H12NO5 (M-H) $m/z$ 274.072]. Purification of this material was attempted using chromatography on silica, however, the lactone 99 was the sole product isolated. $\nu_{\text{max (neat)/cm}^{-1}}$ 3020, 2930, 1790, 1780, 1760, 1740, 1680, 1610, 1470, 1450, 1410, 1380, 1340, 1300, 1215, 1150, 1130, 1080, 1050, 1000, 880, 750, 680; $\delta_{\text{H}}$ 7.98-7.93 (m, 2 H, ArH), 7.83-7.79 (m, 2 H, ArH), 4.95 (s, 2 H, CH2), 2.13 (s, 3 H, Me); $\delta_{\text{C}}$ 165.5, 160.7, 134.6, 131.8, 124.0, 119.1, 110.7, 71.8, 29.2; $m/z$ (%) 243 (M**, 100%), 214 (17), 198 (19), 186 (61), 132 (30), 104 (87), 76 (57). Further attempts to purify this material using chromatography on silica with 1% and then 5% triethylamine in the eluant were unsuccessful, with only the lactone 99 isolated. Neither the alcohol 40 nor the lactone 41 were detected following
chromatography. Attempted purification using chromatography on basic alumina resulted in decomposition and neither the alcohol 40 nor the lactones 41 and 99 were isolated.

(R)-3,4-Dibromo-N-phthaloylvaline Methyl Ester 43

To a solution of (S)-N-phthaloyl-3,4-dehydrovaline methyl ester 38 (119 mg, 0.46 mmol) in carbon tetrachloride (40 ml) was added a solution of bromine in carbon tetrachloride (6 ml, 0.13 M). The solution was stirred at room temperature for 16 h, then was concentrated under reduced pressure. The crude product was analysed using $^1$H NMR spectroscopy, which showed a ca. 3:1 mixture of diastereomers of (R)-3,4-dibromo-N-phthaloylvaline methyl ester 43. (major diastereomer) $\delta_H$ 7.95-7.78 (m, 4 H, ArH), 5.49 (s, 1 H, $\alpha$-H), 4.73 (d, $J$ 10.7 Hz, 1 H, $\gamma$-H), 3.91 (d, $J$ 10.7 Hz, 1 H, $\gamma'$-H), 3.75 (s, 3 H, OMe), 2.02 (s, 3 H, Me); (minor isomer) $\delta_H$ 7.95-7.78 (m, 4 H, ArH), 5.61 (s, 1 H, $\alpha$-H), 4.63 (d, $J$ 10.7 Hz, 1 H, $\gamma$-H), 3.98 (d, $J$ 10.7 Hz, 1 H, $\gamma'$-H), 3.71 (s, 3 H, OMe), 2.13 (s, 3 H, Me); m/z (%) 422 (MH, 10%), 420 (MH, 20), 418 (MH, 10), 362 (10), 360 (20), 358 (10), 340 (80), 338 (80), 308 (20), 306 (20), 280 (80), 278 (80), 250 (68), 248 (75), 218 (100), 200 (100), 190 (65), 130 (75), 104 (80); m/z 416.922 (M$$^{+}$) [Calc. for $C_{14}H_{13}NO_{4}$Br$_2$ (M$$^{+}$) m/z 416.921].

This material was unstable and was therefore used without purification or further characterisation.
Treatment of the Dibromide 43 with Tri-n-butyltin Hydride.

To a solution of the crude dibromide 43 (189 mg, 0.45 mmol) in benzene (10 ml) was added tributyltin hydride (120 µl, 0.45 mmol) and a catalytic amount of AIBN. The solution was stirred for 16 h at room temperature, then concentrated and the residue was taken up in ether (20 ml). The ether solution was washed twice with aqueous saturated potassium fluoride solution, then filtered and the solution was concentrated under reduced pressure. Analysis of the crude product using $^1$H NMR spectroscopy showed that the dibromide 43 had reacted to give the alkene 38. There were no peaks in the $^1$H NMR spectrum that could be attributed to the $\gamma$-bromide diastereomers 44a and 44b.

Treatment of (S)-N-Phthaloyl-3,4-dehydrovaline Methyl Ester 38 with Chlorine in Carbon Tetrachloride

To a solution of the $\beta,\gamma$-alkene 38 (79 mg, 0.3 mmol) in carbon tetrachloride (10 ml) was added a solution of chlorine in carbon tetrachloride (0.4 ml, 2.4 M). The solution was stirred for 16 h at room temperature, then was concentrated under reduced pressure. The crude product was chromatographed on silica affording (S)-4-chloro-N-phthaloyl-3,4'-dehydrovaline methyl ester 103 as a colourless oil (48 mg, 54%).

$v_{\text{max (neat)/cm}}$ 3040, 2960, 1780, 1750, 1720, 1620, 1475, 1440, 1390, 1340, 1300, 1230, 1120, 1095, 1030 and 920; $\delta_H$ 7.98-7.75 (m, 4 H, ArH), 5.68 (s, 1 H), 5.59 (s, 1 H), 5.42 (s, 1 H), 4.37 (d, $J$ 12.1 Hz, 1 H, $\gamma$-H), 4.22 (d, $J$ 12.1 Hz, 1 H, $\gamma'$-H), 3.80 (s, 3 H, OMe); $m/z$ (%) 295 (M$^{**}$, 1%), 293 (M$^{**}$, 3), 258 (100), 236 (10), 234 (25), 200 (10), 199 (10), 198 (10), 160 (20), 130 (20), 104 (25); $m/z$ 258.078 (M-Cl) [Calc. for C$_{14}$H$_{12}$NO$_4$ (M-Cl) $m/z$ 258.077]; (Found: C, 57.2; H, 4.2; N, 4.7. Calc. for C$_{14}$H$_{12}$NO$_4$Cl: C, 57.2; H, 4.1; N, 4.8%).
Experimental

Treatmen of (S)-N-Phthaloyl-3,4-dehydrovaline Methyl Ester 38 with Chlorine in the Presence of a Radical Inhibitor.

The alkene 38 was treated with a solution of chlorine in carbon tetrachloride using the procedure described above for the preparation of the chloride 103 except that hydroquinone was added and the reaction was stirred for 16 h in the dark. The solution was concentrated under reduced pressure then the crude material was analysed using $^1$H NMR spectroscopy. This material was identical to that produced in the reaction described above for the reaction of the alkene 38 with chlorine.

(2S,3S)-4-Bromo-N-phthaloylvaline Methyl Ester 44a and (2S,3R)-4-Bromo-N-phthaloylvaline Methyl Ester 44b

Through a solution of the $\beta,\gamma$-dehydrovaline derivative 38 (819 mg, 3.2 mmol) in carbon tetrachloride (50 ml), in an ice-water bath, was passed a dry stream of hydrogen bromide, for 5 mins. During this time, and for a further 40 mins, the solution was irradiated with a 300 W sunlamp. The resultant solution was washed twice with water, then it was dried and concentrated under reduced pressure to afford a crude product as a colourless oil. Analysis of this material using $^1$H NMR spectroscopy, showed a 2.2:1 mixture of the bromides 44a and 44b (944 mg, 88%). 44a $\delta_H$ 7.94-7.78 (m, 4 H, ArH), 5.02 (d, $J$ 8.4 Hz, 1 H, $\alpha$-H), 3.90 (dd, $J$ 5.1, 10.2 Hz, 1 H, $\gamma$-H), 3.66 (dd, $J$ 3.9, 10.2 Hz, 1 H, $\gamma'$-H), 3.73 (s, 3 H, OMe), 3.01 (m, 1 H, $\beta$-H), 1.03 (d, $J$ 6.9 Hz, 3 H, $\beta$-Me); $\delta_C$ 168.2, 167.3, 134.2, 131.4, 123.5, 53.9, 52.5, 38.7, 34.8, 15.9; 44b $\delta_H$ 7.94-7.78 (m, 4 H, ArH), 4.91 (d, $J$ 7.4 Hz, 1 H, $\alpha$-H), 3.74 (s, 3 H, OMe), 3.65 (dd, $J$ 3.7, 10.3 Hz, 1 H, $\gamma$-H), 3.25 (dd, $J$ 6.8, 10.3 Hz, 1 H, $\gamma'$-H), 3.01 (m, 1 H, $\beta$-H), 1.30 (d, $J$ 6.6 Hz, 3 H, $\beta$-Me); $\delta_C$ 168.5, 167.2, 134.0, 131.3, 123.7, 54.7, 52.3, 36.9, 35.3, 16.7; $m/z$ (%) 341 (M$^{++}$, 1%), 339 (M$^{++}$, 1), 281 (20), 279 (20), 219 (50), 201 (100), 199 (100); $m/z$ 339.009 (M$^{++}$) [Calc. for C$_{14}$H$_{14}$BrNO$_4$ (M$^{++}$) $m/z$ 339.016].
(2S,3S)-4-Iodo-N-phthaloylvaline Methyl Ester 107a and (2S,3R)-4-Iodo-N-phthaloylvaline Methyl Ester 107b

A solution of a 2.2:1 mixture of the bromides 44a and 44b (944 mg, 2.8 mmol) and sodium iodide (1.28 g, 8.5 mmol) in acetone (40 ml) was heated at reflux for 2 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed with aqueous sodium metabisulfite solution, then water, and then it was dried and concentrated under reduced pressure, to give a 2.2:1 mixture of the iodides 107a and 107b as a yellow oil. 107a $\delta_H$ 7.97-7.76 (m, 4 H, ArH), 4.89 (d, $J$ 8.3 Hz, 1 H, $\alpha$-H), 3.74 (s, 3 H, OMe), 3.63 (dd, $J$ 5.4, 10.2 Hz, 1 H, $\gamma$-H), 3.50 (dd, $J$ 3.9, 10.2 Hz, 1 H, $\gamma'$-H), 2.59 (m, 1 H, $\beta$-H), 0.99 (d, $J$ 6.7 Hz, 3 H, $\beta$-Me); 107b $\delta_H$ 7.97-7.76 (m, 4 H, ArH), 4.83 (d, $J$ 7.3 Hz, 1 H, $\alpha$-H), 3.74 (s, 3 H, OMe), 3.47 (dd, $J$ 3.8, 10.2 Hz, 1 H, $\gamma$-H), 3.01 (dd, $J$ 7.8, 10.2 Hz, 1 H, $\gamma'$-H), 2.79 (m, 1 H, $\beta$-H), 1.25 (d, $J$ 6.5 Hz, 3 H, $\beta$-Me). The unstable iodides 107a and 107b were not purified and were used in the following reaction without further characterisation.

(2S,3S)-4-Hydroxyvaline 3a

To a stirred solution of the crude iodides 107a and 107b in aqueous acetone (30 ml) was added silver nitrate (711 mg, 4.2 mmol). The mixture was stirred at room temperature in darkness for 60 h, then brine was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with brine, then dried and concentrated under reduced pressure. The crude product was analysed using $^1$H NMR spectroscopy, which showed a mixture of the (2S,3S)-lactone 42a and the alcohols 36a and 36b. 42a $\delta_H$ 7.92-7.78 (m, 4 H, ArH), 4.70 (d, $J$ 11.5 Hz, 1 H, $\alpha$-H), 4.66
Experimental

(dd, J 8.4, 10.3 Hz, 1 H, γ-H), 3.98 (dd, J 9.2, 10.3 Hz, 1 H, γ'-H), 3.27-3.11 (m, 1 H, β-H), 1.23 (d, J 6.6 Hz, 3 H, Me); 36a δ$_{H}$ 7.93-7.72 (m, 4 H, ArH), 5.05 (d, J 5.4 Hz, 1 H, α-H), 3.74 (s, 3 H, OMe), 3.68 (dd, J 4.8, 11.8 Hz, 1 H, γ-H), 3.39 (dd, J 8.3, 11.8 Hz, 1 H, γ'-H), 2.82 (m, 1 H, β-H), 0.93 (d, J 6.6 Hz, 3 H, β-Me); 36b δ$_{H}$ 7.93-7.72 (m, 4 H, ArH), 4.91 (d, J 6.3 Hz, 1 H, α-H), 3.75 (s, 3 H, OMe), 3.57 (dd, J 5.0, 12.0 Hz, 1 H, γ-H), 3.51 (dd, J 6.6, 12.0 Hz, 1 H, γ'-H), 2.79 (m, 1 H, β-H), 1.10 (d, J 7.2 Hz, 3 H, β-Me).

The mixture containing the lactone 42a and alcohols 36a and 36b dissolved in a 2:1 mixture of 6 N hydrochloric and glacial acetic acid (25 ml), and the solution was heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was taken up in water and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in water, then the solution was applied to a column of Amberlite IR 120 cation exchange resin (NH$_4^+$ form). The column was washed with water (1 L), then eluted with aqueous ammonia solution (1 L). The eluate was boiled until no ammonia could be detected, then concentrated under reduced pressure affording a 3:1 mixture of the diastereomers 3a and 3b (223 mg, 60%). 3a δ$_{H}$ (D$_2$O) 3.85 (d, J 3.2 Hz, 1 H, α-H), 3.69 (dd, J 5.2, 11.4 Hz, 1 H, γ-H), 3.57 (dd, J 6.9, 11.4 Hz, 1 H, γ'-H), 2.33 (m, 1 H, β-H), 0.94 (d, J 7.2 Hz, 3 H, Me); 3b δ$_{H}$ (D$_2$O) 3.74 (d, J 4.4 Hz, 1 H, α-H), 3.64 (d, J 5.6 Hz, 2 H, CH$_2$O), 2.17 (m, 1 H, β-H), 1.02 (d, J 7.0 Hz, 3 H, Me).

Fractional crystallisation of this mixture from acetone and water afforded the (2S,3S)-isomer 3a (94 mg, 25%), m.p. 219-221 °C (dec.) (Lit. 22 212-214 °C (dec.)); δ$_C$ (D$_2$O) 176.9, 67.0, 60.2, 38.4, 13.5; [$\alpha$]$_{D5}$ $^{24}$ +24.0° (c, 0.2 in H$_2$O) (Lit. 22 (2S,3S)-isomer 3a $^{23}$+23.3°; (2S,3R)-isomer 3b $^{24}$+26.4°); (Found: C, 45.0; H, 8.4; N, 10.5. Calc for C$_5$H$_{11}$NO$_3$: C, 45.1; H, 8.3; N, 10.5%).
Experimental

(3S,4S)-4-Methyl-3-phthalimido-γ-butyrolactone 42a and (3S,4R)-4-Methyl-3-phthalimido-γ-butyrolactone 42b

The title compounds 42a and 42b were synthesised from a mixture of the iodides 107a and 107b by treatment with aqueous silver nitrate, using the procedure described above. In this case, however, the crude mixture was chromatographed on silica affording a ca. 6:1 mixture of the lactone diastereomers 42a and 42b as a colourless oil (607 mg, 67% from the bromides 44a and 44b). νmax(neat)/cm⁻¹ 3490, 2970, 1770, 1720, 1620, 1470, 1390, 1340, 1200, 1010; (3S,4R)-diastereomer 42b δH 7.92-7.78 (m, 4 H, ArH), 5.01 (d, J 10.0 Hz, 1 H, α-H), 4.66 (dd, J 8.4, 8.7 Hz, 1 H, γ-H), 4.26 (dd, J 8.0, 8.7 Hz, 1 H, γ'-H), 3.06-2.90 (m, 1 H, β-H), 1.02 (d, J 7.1 Hz, 3 H, Me); m/z (%) 245 (M⁺, 5%), 201 (25), 186 (100); m/z 245.070 (M⁺) [Calc. for C₁₃H₁₁N0₄ (M⁺) m/z 245.069]; (Found: C, 63.5; H, 5.0; N, 5.4. Calc. for C₁₃H₁₁NO₄: C, 63.7; H, 4.5; N 5.7%). The ¹H NMR spectral data for the (3S,4S)-lactone 42a is given above.

Extraction of γ-Hydroxyvaline from Kalanchoe daigremontiana

The leaves and stems of Kalanchoe daigremontiana were freeze-dried (20 g dry weight) and the residue was partitioned between chloroform and water. The mixture was separated and the aqueous phase was washed with chloroform. The solution was acidified to pH 1 with concentrated hydrochloric acid then stirred for 16 h at room temperature, then was filtered and the filtrate was concentrated to afford a crude extract. The crude extract was dissolved in water, then chromatographed on Amberlite IR 120 ion exchange resin using the procedure outlined by Pollard et al. to afford the natural product which was then recrystallised from acetone and water (43 mg, 0.2%), m.p. 208-214 °C (Lit. 212-214 °C). [α]D²⁰ +22.0° (c, 0.44 in H₂O) (Lit. 22 (2S,3S)-isomer 3a +23.3°; (2S,3R)-isomer 3b +26.4°). The ¹H NMR spectral data for this material are
identical to those given above for the synthesised (2S,3S)-isomer 3a. The relative stereochemistry of this material was confirmed through X-ray crystallographic analysis (Appendix 4).

**N-Phthaloylphenylalanine 108**

A mixture of phenylalanine (11.23 g, 68.0 mmol) and finely ground phthalic anhydride (10.06 g, 68.0 mmol) was heated at 150 °C for 40 mins. The resultant yellow gum was taken up in dichloromethane then washed with water and dried, then concentrated under reduced pressure, affording the title compound 108 as a white crystalline solid (17.98 g, 90%), m.p. 177-178 °C (Lit.161 178 °C). δH 10.68 (br s, 1 H, CO2H), 7.80-7.74 (m, 2 H, ArH), 7.71-7.66 (m, 2 H, ArH), 7.23-7.10 (m, 5 H, Ph), 5.23 (t, J 8.5 Hz, 1 H, α-H), 3.59 (d, J 8.5 Hz, 2 H, β-H). The spectral data for this material are consistent with that previously reported.59

**N-Phthaloylphenylalanine Methyl Ester 17**

The title compound 17 was prepared as described above for the preparation of the valine derivative 95, by treatment of N-phthaloylphenylalanine 108 (6.13 g, 20.8 mmol) with methanol which had been treated with thionyl chloride, and isolated as a colourless crystalline solid (5.79 g, 90%), m.p. 89-91 °C (Lit.174 73-75 °C). δH 7.79-7.75 (m, 2 H, ArH), 7.71-7.66 (m, 2 H, ArH), 7.22-7.12 (m, 5 H, Ph), 5.16 (dd, J 5.5, 11.0 Hz, 1 H, α-H), 3.78 (s, 3 H, OMe), 3.62 (dd, J 5.5, 14.4 Hz, 1 H, β-H), 3.54 (dd, J 11.0, 14.4 Hz, 1 H, β'-H). The spectral data for this material are consistent with those previously reported.59
**N-tert-Butyl-Nα-phthaloylphenylalaninamide 19**

To a suspension of N-phthaloylphenylalanine 108 (619 mg, 2.1 mmol) in dichloromethane (10 ml) was added triethylamine (0.29 ml, 2.1 mmol). The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.20 ml, 2.1 mmol) was added. That mixture was stirred for 10 min, then tert-butylamine (0.22 ml, 2.1 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound 19, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (392 mg, 53%), 192-194 °C (Lit.59 194-195 °C). δH 7.80-7.66 (m, 4 H, ArH), 7.17 (m, 5 H, Ph), 5.86 (br s, 1 H, NH), 4.98 (dd, J 6.7, 10.0 Hz, 1 H, α-H), 3.56 (dd, J 6.7, 14.1 Hz, 1 H, β-H), 3.47 (dd, J 10.0, 14.1 Hz, 1 H, β'-H), 1.30 (s, 9 H, CMe3). The spectral data for this compound are consistent with those reported.59

**3-Bromo-N-phthaloylphenylalanine Methyl Ester 18b and 3-Bromo-N-phthaloylphenylalanine Methyl Ester 18a**

A mixture of N-phthaloylphenylalanine methyl ester 17 (4.66 g, 15.1 mmol) and NBS (2.68 g, 15.1 mmol) in carbon tetrachloride (100 ml) was heated at reflux for 2 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, then filtered and the filtrate was washed with water, then dried. Concentration of the resultant solution afforded the title compounds 18a and 18b as a 1:1 mixture (5.80 g, 99%). 18b δH 7.97-7.94 (m, 2 H, ArH), 7.82-7.78 (m, 2 H, ArH), 7.59 (m, 2 H, Ph), 7.43-7.33 (m, 3 H, Ph), 6.02 (d, J 11.2 Hz, 1 H, β-H), 5.52 (d, J 11.2 Hz, 1 H, α-H), 3.55 (s, 3 H, OMe); 18a δH 7.72-7.62 (m, 6 H,
Experimental

ArH and Ph), 7.23-7.13 (m, 3 H, Ph), 5.91 (d, J 10.5 Hz, 1 H, β-H), 5.59 (d, J 10.5 Hz, 1 H, α-H), 3.82 (s, 3 H, OMe). The ^1H NMR spectral data for this material were consistent with literature values.54

(2RS,3RS)-3-Bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 20b and (2RS,3SR)-3-Bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 20a

The title compounds 20a and 20b were prepared as a 1:1 mixture of diastereomers from N-tert-butyl-Nα-phthaloylphenylalaninamide 19 by treatment with NBS, as described above for the preparation of the bromoesters 18a and 18b, and isolated in quantitative yield. 20b δH 7.96-7.77 (m, 4 H, ArH), 7.62-7.34 (m, 5 H, Ph), 6.17 (d, J 11.8 Hz, 1 H, β-H), 5.76 (br s, 1 H, NH), 5.22 (d, J 11.8 Hz, 1 H, α-H), 1.02 (s, 9 H, CMe3); 20a δH 7.72-7.62 (m, 4 H, ArH), 7.38-7.11 (m, 5 H, Ph), 6.41 (br s, 1 H, NH), 6.05 (d, J 11.4 Hz, 1 H, β-H), 5.32 (d, J 11.4 Hz, 1 H, α-H), 1.40 (s, 9 H, CMe3). The ^1H NMR spectral data for these materials were consistent with literature values.53,59,96

(S)-N-tert-Butyl-Nα-phthaloylvalinamide 96

To a suspension of (S)-N-phthaloylvaline 97 (15.57 g, 63 mmol) in dichloromethane (60 ml) was added triethylamine (6.37 g, 63 mmol). The resulting solution was cooled to 0 °C, then ethyl chloroformate (6.87 g, 63 mmol) was added and the mixture was stirred for 15 min. tert-Butylamine (4.60 g, 63 mmol) was added and the mixture was allowed to warm to room temperature and was stirred for a further 40 min. The mixture was filtered and the filtrate was washed with water, then it was dried and concentrated under reduced pressure. A portion (ca. 4.6 g, 25%) of the residue was chromatographed, to give the title compound 96 as a colourless crystalline solid (2.60 g).
Experimental

m.p. 144-147 °C; \( [\alpha]_D^{21} +32.3^\circ \) (c, 8.7 in CHCl₃); \( \nu_{\max} \text{cm}^{-1} \) 3400, 3365, 2920, 2850, 1760, 1710, 1680, 1550, 1530, 1470, 1400, 1070, 715; \( \delta_H \) 7.91-7.81 (m, 4 H, Phth), 7.13 (br s, 1 H, NH), 4.35 (d, \( J \) 11.3 Hz, 1 H, \( \alpha \)-H), 2.88 (m, 1 H, \( \beta \)-H), 1.39 (s, 9 H, CMe₃), 1.15 (d, \( J \) 6.7 Hz, 3 H, Me), 0.87 (d, \( J \) 6.5 Hz, 3 H, Me'); \( \delta_C \) 170.5, 169.9, 136.3, 133.4, 125.6, 66.7, 53.3, 30.6, 29.8, 21.7, 21.6; \( m/z \) (%) 303 (M+H⁺, 1%), 275 (1), 260 (5), 202 (100); (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for C₁₇H₂₂N₂O₃: C, 67.5; H, 7.3; N, 9.3%).

\( (R) \)-3-Bromo-N-tert-butyl-Nα-phthaloylvalinamide 73

A mixture of NBS (1.18 g, 6.6 mmol) and the valinamide 96 (1.33 g, 4.4 mmol) in carbon tetrachloride (60 ml) was heated at reflux for 2 h, whilst being irradiated with a 300 W sunlamp, then was cooled to and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound 73 as fine colourless needles, after recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; \( [\alpha]_D^{20} +11.6^\circ \) (c, 3.03 in CHCl₃); \( \nu_{\max} \text{cm}^{-1} \) 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080, 720; \( \delta_H \) 7.67 (m, 4 H, Phth), 5.28 (s, 1 H, \( \alpha \)-H), 2.07 (s, 3 H, Me), 1.86 (s, 3 H, Me'), 1.30 (s, 9 H, CMe₃); \( \delta_C \) 168.0, 163.8, 134.4, 131.2, 123.7, 65.9, 65.6, 51.9, 33.3, 32.8 and 28.4; \( m/z \) (%) 383 (MH, 5%), 382 (M, 7), 381 (MH and M–H, 10), 380 (M, 7), 379 (M–H, 5), 367 (15), 365 (15), 327 (30), 325 (30), 310 (30), 308 (30), 301 (100), 282 (100), 280 (100); (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for C₁₇H₂₁BrN₂O₃: C, 53.6; H, 5.6; N, 7.3%).
(R)-N-Phthaloyl-p-nitrophenylalanine 110

A mixture of (R)-p-nitrophenylalanine 109 monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 ml, 7.95 mmol) was heated at reflux in toluene (60 ml) for 3 h, during which time water was continuously removed using a Dean-Stark apparatus. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound 110 as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; [α]$_{578}^25$ $+234.5$° (c, 0.31 in MeOH); δ$_H$ 8.09 (d, $J$ 8.7 Hz, 2 H, ArH), 7.83-7.72 (m, 4 H, Phth), 7.36 (d, $J$ 8.7 Hz, 2 H, ArH), 5.26 (dd, $J$ 7.3, 9.2 Hz, 1 H, α-H), 3.72 (m, 2 H, β-H).

(RS)-N-Phthaloyl-p-nitrophenylalanine

This compound was prepared from (RS)-p-nitrophenylalanine, as described above for the synthesis of the corresponding (R)-isomer 110, and obtained in 93% yield, m.p. 185-187 °C.

(S)-N-Phthaloyl-p-nitrophenylalanine

This compound was prepared from (S)-p-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (R)-enantiomer 110, and obtained in 57% yield, m.p. 200-202 °C (Lit.$^{217}$ 204.7 °C); [α]$^{19}_{578}$ $-230.2$° (c, 0.086 in MeOH) (Lit.$^{217}$ $-232.5$° (c, 1.55 in MeOH)).
(R)-N-Phthaloyl-p-nitrophenylalanine Methyl Ester 78a

(R)-N-Phthaloyl-p-nitrophenylalanine 110 (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 ml) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound 78a as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; ν_max/cm\(^{-1}\) 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860, 720; δ_H 8.06 (d, J 8.6 Hz, 2 H, ArH), 7.82-7.72 (m, 4 H, Phth), 7.45 (d, J 8.6 Hz, 2 H, ArH), 5.31 (dd, J 5.5, 10.9 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 3.77 (dd, J 5.5, 14.3 Hz, 1 H, β-H), 3.71 (dd, J 10.9, 14.3 Hz, 1 H, β'-H); m/z (%) 354 (M\(^{+}\), 12%), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17), 76 (21).

(2S,3S)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester 71a and (2S,3R)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester 71b

To a solution of (R)-N-phthaloyl-p-nitrophenylalanine methyl ester 78a (2.20 g, 6.21 mmol) in carbon tetrachloride (40 ml), NBS (1.20 g, 6.74 mmol) was added and the mixture was heated at reflux for 4 h, whilst being irradiated with a 300 W sunlamp. The mixture was then allowed to cool, then it was filtered. The filtrate was washed with water, then dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds 71a and 71b as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2S,3S)-bromide 71a (1.17 g, 43%), m.p. 198-201 °C; ν_max/cm\(^{-1}\) 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820, 715; δ_H 8.27 (d, J 8.8 Hz,
2 H, ArH), 7.99-7.82 (m, 4 H, Phth), 7.78 (d, J 8.8 Hz, 2 H, ArH), 6.02 (d, J 11.2 Hz, 1 H, β-H), 5.51 (d, J 11.2 Hz, 1 H, α-H), 3.59 (s, 3 H, OMe); m/z (%) 434 (M**, 2%), 432 (M**, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40), 76 (37); (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for C_{18}H_{13}BrN_{2}O_{6}: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2S,3R)-bromide 71b (1.07 g, 40%), m.p. 195-197 °C; ν_{max}/cm^{-1} 1775, 1755, 1605, 1525, 1390, 1350, 855, 720; δ_{H} 8.07 (d, J 8.7 Hz, 2 H, ArH), 7.76-7.68 (m, 4 H, Phth), 7.56 (d, J 8.7 Hz, 2 H, ArH), 5.97 (d, J 10.3 Hz, 1 H, β-H), 5.59 (d, J 10.3 Hz, 1 H, α-H), 3.83 (s, 3 H, OMe); m/z (%) 434 (M**, 1%), 432 (M**, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28), 76 (26); (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for C_{18}H_{13}BrN_{2}O_{6}: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide 71b was confirmed through X-ray crystallographic analysis (Appendix 5).

**(RS)**-N-tert-Butyl-N^α-phthaloyl-p-nitrophenylalaninamide

To a suspension of (RS)-N-phthaloyl-p-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 ml), triethylamine (0.81 ml, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 ml, 5.86 mmol) was added. That mixture was stirred for 10 min, then tert-butylamine (0.61 ml, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C. ν_{max}/cm^{-1} 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1382, 1344, 1220, 1088, 1016, 888, 874,
Experimental

766, 726; δH 8.03 (d, J 8.6 Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, Phth), 7.33 (d, J 8.6 Hz, 2 H, ArH), 5.93 (br s, 1 H, NH), 5.02 (t, J 8.4 Hz, 1 H, α-H), 3.65 (d, J 8.4 Hz, 2 H, β-H), 1.33 (s, 9 H, CMe3); δC 168.3, 167.1, 147.4, 145.4, 135.1, 131.6, 130.3, 124.3, 124.2, 56.4, 52.4, 35.2, 29.1; m/z (%) 395 (M+, 5%), 352 (5), 341 (10), 256 (20), 236 (5), 213 (10); (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for C21H21N3O5: C, 63.8; H, 5.3; N, 10.6%).

(R)-N-tert-Butyl-Nα-phthaloyl-p-nitrophenylalaninamide 78b

This compound was prepared from (R)-N-phthaloyl-p-nitrophenylalanine 110, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); [α]D25 +117.0° (c, 0.227 in CHCl3).

(S)-N-tert-Butyl-Nα-phthaloyl-p-nitrophenylalaninamide

This compound was prepared from (S)-N-phthaloyl-p-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); [α]D21 -120.8° (c, 0.418 in CHCl3).

(2RS,3RS)-3-Bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide and (2RS,3SR)-3-Bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide

To a solution of (RS)-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50 ml), NBS (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h, whilst being irradiated with a 300 W sunlamp. The mixture was then allowed to cool to room temperature, then it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C. vmax/cm⁻¹ 3380,
Experimental

3350, 2950, 2920, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720, 700; \( m/z \) (FAB) (%) 476 (MH\(^+\), 40%), 474 (MH\(^+\), 40%), 420 (20), 418 (20), 295 (30), 154 (100), 136 (90); (Found: C, 53.1; H, 4.2; N, 8.9. Calc. for \( \text{C}_{21}\text{H}_{20}\text{BrN}_{3}\text{O}_{5} \): C, 53.2; H, 4.3; N, 8.9%). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2RS,3SR)-3-bromo-N-tert-butyl-\(N^\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide; \( \delta_H \) 8.08 (d, \( J \) 8.9 Hz, 2 H, ArH), 7.79-7.64 (m, 4 H, Phth), 7.56 (d, \( J \) 8.9 Hz, 2 H, ArH), 6.23 (br s, 1 H, NH), 6.18 (d, \( J \) 11.4 Hz, 1 H, \( \beta\)-H), 5.29 (d, \( J \) 11.4 Hz, 1 H, \( \alpha\)-H), 1.41 (s, 9 H, CMe\(_3\)); \( \delta_C \) 167.5, 164.8, 145.3, 135.1, 131.2, 129.4, 129.3, 124.5, 124.3, 60.7, 52.9, 46.4, 29.1. The structure of this material was confirmed through X-ray crystallographic analysis (Appendix 6). The \(^1\)H and \(^{13}\)C NMR spectra of the mixture of diastereomers showed resonances for the (2RS,3RS)-isomer, \( \delta_H \) 8.26 (d, \( J \) 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, Phth), 7.77 (d, \( J \) 8.9 Hz, 2 H, ArH), 6.27 (br s, 1 H, NH), 6.20 (d, \( J \) 11.7 Hz, 1 H, \( \beta\)-H), 5.09 (d, \( J \) 11.7 Hz, 1 H, \( \alpha\)-H), 1.11 (s, 9 H, CMe\(_3\)); \( \delta_C \) 168.3, 163.9, 148.3, 135.3, 131.6, 130.1, 130.0, 124.6, 124.5, 62.7, 52.4, 49.1, 28.8.

(2S,3S)-3-Bromo-N-tert-butyl-\(N^\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide 72a and (2S,3R)-3-Bromo-N-tert-butyl-\(N^\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide 71b

A 1:1 mixture of these compounds was prepared from (R)-N-tert-butyl-\(N^\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide 78b, as described above for the synthesis of the corresponding racemate, and obtained in 95% yield.
Experimental

(2R,3R)-3-Bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide and

(2R,3S)-3-Bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide

A 1:1 mixture of the title compounds was prepared in quantitative yield from (S)-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate.

Treatment of (R)-3-Bromo-N-phthaloylvaline Methyl Ester 33 with Silver Nitrate in Aqueous Acetone.

To a solution of the bromide 33 (0.66 g, 1.9 mmol) in acetone (10 ml), a solution of silver nitrate (0.49 g, 2.9 mmol) in water (10 ml) was added. The resultant mixture was stirred at room temperature in the dark for 14 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure to afford an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative 98 (40 mg, 8%), m.p. 81-82 °C. δH 8.10-7.40 (m, 4 H, Phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, Me), 1.88 (s, 3 H, Me'); (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for C14H13N04: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the β,γ-dehydrovaline derivative 38 (0.15 g, 34%); νmax/cm⁻¹ 2950, 1780, 1748, 1728, 1700, 1386, 1293, 1245, 1203, 1113, 915, 717; δH 7.92-7.75 (m, 4 H, Phth), 5.38 (br s, 1 H, γ-H), 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe), 1.92 (s, 3 H, β-Me); m/z (%) 259 (M⁺, 8%), 227 (20), 200 (100). Further elution gave the β-hydroxyvaline derivative 34 (0.21 g, 43%), m.p. 86-87 °C; νmax/cm⁻¹ 3544, 1767, 1725, 1275, 717; δH 7.91-7.80 (m, 4 H, Phth), 4.91 (s, 1 H, α-H), 4.41 (br s, 1 H, OH), 3.77 (s, 3 H, OMe), 1.53 (s, 3 H, Me), 1.31 (s, 3 H, Me').
Experimental 179

\[ m/z \text{ (\%)} \ 262 \ (\text{M-CH}_3^+, 10\%), \ 246 \ (5), \ 230 \ (28), \ 219 \ (100), \ 188 \ (74), \ 187 \ (98), \ 160 \ (74); \ (\text{Found: C, 60.6; H, 5.5; N, 5.1}) \. \text{Calc. for C}_{14}\text{H}_{15}\text{NO}_5: C, 60.6; H, 5.5; N, 5.1\%)

Analysis of the crude reaction mixture by \textsuperscript{1}H NMR spectroscopy showed the alcohol 34 and the alkenes 98 and 38 to be present in the ratio ca. 3.5 : 1 : 3.5.

**Treatment of (R)-3-Bromo-\textit{N}-\textit{tert}-butyl-\textit{N}^\alpha-\textit{phthaloylvalinamide} 73 with Silver Nitrate in Aqueous Acetone.**

The reaction of the bromide 73, carried out as described above for the reaction of the ester 33, afforded an oil which was chromatographed. Elution gave the \(\beta,\gamma\)-dehydrovaline derivative 112 as a colourless oil (26%); \(\nu_{\text{max/cm}} \approx 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475, 1385; \delta_\text{H} 7.89-7.73 \text{ (m, 4 H, Phth)}, 6.28 \text{ (br s, 1 H, NH)}, 5.27 \text{ (s, 1 H)}, 5.23 \text{ (s, 1H)}, 5.21 \text{ (s, 1H)}, 1.89 \text{ (s, 3 H, Me)}, 1.43 \text{ (s, 9 H, CMe}_3); \delta_\text{C} 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5, 22.8; \ m/z \text{ (\%)} \ 300 \ (\text{M}^+, 5\%), \ 200 \ (100); \ (\text{Found: C, 68.0; H, 7.0; N, 9.0}) \. \text{Calc. for C}_{17}\text{H}_{20}\text{N}_2\text{O}_3: C, 68.0; H, 6.7; N, 9.3\%). \text{Further elution afforded the alcohol 111, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%)}\text{, m.p. 135-136 °C; } \nu_{\text{max/cm}} \approx 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724, 646; \delta_\text{H} 7.84-7.79 \text{ (m, 2 H, Phth)}, 7.73-7.69 \text{ (m, 2 H, Phth)}, 7.30 \text{ (br s, 1 H, NH)}, 4.61 \text{ (s, 1 H, \(\alpha\)-H)}, 4.25 \text{ (br s, 1 H, OH)}, 1.41 \text{ (s, 3 H, Me)}, 1.30 \text{ (s, 9 H, CMe}_3), 1.22 \text{ (s, 3 H, Me)}; \ m/z \text{ (\%)} \ 318 \ (\text{M}^+, 50), 300 \ (10), 259 \ (50), 201 \ (100), 187 \ (100), 160 \ (95); \ (\text{Found: C, 64.3; H, 7.2; N, 8.7}) \. \text{Calc. for C}_{17}\text{H}_{22}\text{N}_2\text{O}_4: C, 64.1; H, 7.0; N, 8.8\%).

The structure of the alcohol 111 was confirmed through X-ray crystallographic analysis (Appendix 3). Analysis of the crude reaction mixture by \textsuperscript{1}H NMR spectroscopy showed the alcohol 111 and the alkene 112 were present in the ratio ca. 2 : 1.
Treatment of (2S,3S)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester 71a with Silver Nitrate in Aqueous Acetone.

To a solution of the bromide 71a (50 mg, 0.12 mmol) in acetone (3 ml), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 ml) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (Z)-p-nitrophenylalanine derivative 115 as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; νmax/cm⁻¹ 1780, 1720, 1600, 1530, 1345; δH 8.16 (d, J 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, β-H), 7.92-7.83 (m, 4 H, Phth), 7.55 (d, J 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); m/z (%) 352 (M+, 90%), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100), 76 (73); m/z 352.068 (M+) [Calc. for C₁₈H₁₂N₂O₆ (M+) m/z 352.070]. Neither the alcohol 114 nor the alkene 116 were detected in the crude product.

Treatment of (2S,3R)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester 71b with Silver Nitrate in Aqueous Acetone.

The reaction of the bromide 71b, carried out as described above for the reaction of the stereoisomer 71a, afforded an oil which was chromatographed. Elution afforded a 2:3 mixture of the dehydrophenylalanine derivatives 115 and 116 as a viscous oil (25%). The ¹H NMR spectrum of the mixture showed resonances for the (Z)-isomer 115, identical to those described above, and signals for the (E)-isomer 116, δH 8.26 (d, J 8.7 Hz, 2 H, ArH), 7.98-7.80 (m, 4 H, Phth), 7.60 (d, J 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H), 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-p-nitrophenylalanine derivative 114 as colourless needles (63%), after recrystallisation
from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C. \( \nu_{\text{max}}/\text{cm}^{-1} \) 3604, 3421, 1779, 1752, 1714, 1614, 1526, 1392, 1352, 1182; \( \delta_H \) 8.13 (d, J 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, Phth), 7.54 (d, J 8.9 Hz, 2 H, ArH), 5.79 (dd, J 4.4, 10.0 Hz, 1 H, \( \beta \)-H), 5.53 (d, J 4.4 Hz, 1 H, \( \alpha \)-H), 5.34 (d, J 10.0 Hz, 1 H, OH), 3.89 (s, 3 H, OMe); \( m/z \) (FAB) (%) 371 (M+H\(^+\), 9%), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33), 77 (31).

\((2RS,3SR)-3\)-Hydroxy-\(N\)-tert-butyl-\(N\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide

To a solution of a 1:1 mixture of \((2RS,3RS)\) and \((2RS,3SR)\)-3-bromo-\(N\)-tert-butyl-\(N\alpha\)-phthaloyl-\(p\)-nitrophenylalaninamide (265 mg, 0.56 mmol) in acetone (10 ml) and water (10 ml), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with saturated brine, then dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C. \( \nu_{\text{max}}/\text{cm}^{-1} \) 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390, 1110; \( \delta_H \) 8.14 (d, J 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, Phth), 7.54 (d, J 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, J 4.9, 8.3 Hz, 1 H, \( \beta \)-H), 5.17 (d, J 4.9 Hz, 1 H, \( \alpha \)-H), 4.93 (d, J 8.3 Hz, 1 H, OH), 1.37 (s, 9 H, CMe\(_3\)); \( \delta_C \) 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 123.6, 71.7, 59.9, 52.3, 28.6; \( m/z \) (%) 412 (M+H\(^+\), 1%), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100), 204 (30); (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for C\(_{21}\)H\(_{21}\)N\(_3\)O\(_6\): C, 61.3; H, 5.2; N, 10.2%).
(2R,3S)-3-Hydroxy-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide

The title compound 117 was prepared from a 1:1 mixture of the bromides 72a and 72b, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; [α]$_D^{25}$ +84.1° (c, 0.453 in CHCl$_3$). There was no indication of the presence of either of the alkenes 120 or 121 in the $^1$H NMR spectrum of the crude reaction mixture.

(2S,3R)-3-Hydroxy-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide

The title compound 132 was prepared from a 1:1 mixture of (2R,3R)- and (2R,3S)-3-bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; [α]$_D^{20}$ -83.1 (c, 0.083 in CHCl$_3$).

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone.

A 1:1 mixture of (2RS,3RS)- and (2RS,3SR)-3-bromo-N-phthaloyl-p-nitrophenylalanine methyl ester was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides 72a and 72b. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy showed that the racemate of the alcohol 114 and the alkenes 115 and 116 were present in the ratio ca. 1:1:20.
Experimental

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-tert-butyl-N\(\alpha\)-phthaloyl-p-nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone.

The reaction of a 1:1 mixture of (2RS,3RS)- and (2RS,3SR)-3-bromo-N-tert-butyl-N\(\alpha\)-phthaloyl-p-nitrophenylalaninamide, carried out as described above for the reaction of the bromoester 71a, afforded an oil which was chromatographed. Elution afforded the nitrate 118 (19%), m.p. 192 °C (dec.). \(\nu_{\text{max}}/\text{cm}^{-1}\) 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1240, 1200, 1110; \(\delta_H\) 8.30 (d, \(J\) 8.9 Hz, 2 H, ArH), 7.92-7.81 (m, 4 H, Phth), 7.77 (d, \(J\) 8.9 Hz, 2 H, ArH), 7.19 (d, \(J\) 10.7 Hz, 1 H, \(\beta\)-H), 5.89 (br s, 1 H, NH), 4.90 (d, \(J\) 10.7 Hz, 1 H, \(\alpha\)-H), 1.14 (s, 9 H, CMe3); \(\delta_C\) 167.6, 163.1, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2, 28.3; \(m/z\) (%) 457 (M+H+, 30%), 393 (15), 307 (40), 286 (100), 260 (30). Continued elution gave (2RS,3SR)-3-hydroxy-N-tert-butyl-N\(\alpha\)-phthaloyl-p-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes 115 or 116 in the \(^1\)H NMR spectrum of the crude product.

(2RS,3SR)-3-Hydroxy-p-nitrophenylalanine

A suspension of (2RS,3SR)-3-hydroxy-N-tert-butyl-N\(\alpha\)-phthaloyl-p-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 ml) was heated at reflux for 5 h and stirred for 16 h at room temperature, before concentration under reduced pressure. Water (10 ml) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml) and to that solution aniline (0.7 ml) in dichloromethane (10 ml) was added. The mixture was allowed to stand at 4 °C for 24 h.
and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white solid (27 mg, 58%), m.p.
192-193 °C (Lit. \(^{219}\) 187-188 °C (dec.)). \(\nu_{\text{max}}/\text{cm}^{-1}\) 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740, 710; \(\delta_{\text{H}} (\text{CF}_3\text{CO}_2\text{D})\)
8.33 (d, \(J = 8.8\) Hz, 2 H, ArH), 7.74 (d, \(J = 8.8\) Hz, 2 H, ArH), 5.77 (d, \(J = 3.9\) Hz, 1 H, \(\beta\)-H), 4.70 (d, \(J = 3.9\) Hz, 1 H, \(\alpha\)-H); \(\delta_{\text{C}} (\text{D}_2\text{O})\) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7, 62.5; \(m/z\) (FAB) (\%) 227 (M+H\(^+\), 46%). The \(^1\)H NMR spectral data for this compound is consistent with that reported.\(^{189}\)

\[(2R,3S)-3\text{-Hydroxy-}\text{-p-nitrophenylalanine}\]

This compound was prepared from the alcohol \(^{117}\), as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (Lit. \(^{189}\) 174-176 °C); \([\alpha]_D^{25} +35.3^\circ\) (c, 0.102 in 1N HCl) (Lit. \(^{189}\) \([\alpha]_D^{25} +27^\circ\) (c, 0.5 in H\(_2\)O)).

\[(2S,3R)-3\text{-Hydroxy-}\text{-p-nitrophenylalanine}\]

This compound was prepared from the \((2S,3R)-3\text{-hydroxy-}\text{-N-tert-butyl-N}\(\alpha\)-phthaloyl-\text{-p-nitrophenylalaninamide} \(^{132}\), as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; \([\alpha]_D^{20} -36.4^\circ\) (c, 0.176 in 1N HCl) (Lit. \(^{124}\) \([\alpha]_D^{21.5} -33.8^\circ\) (c, 5 in 1N HCl)).

**Competitive Hydrolysis Reactions of the Bromides 18a, 18b, 20a and 20b using Silver Nitrate in Aqueous Acetone.**

The relative rates of reaction of the bromides \(18a, 18b, 20a\) and \(20b\) with silver nitrate were determined by treating 1-3 molar equivalents of the substrates at a concentration of approximately 1.0 mM in aqueous acetone (1:1, v/v) with the silver salt
Experimental

(1.4 equiv.) at room temperature for 16 h, in the presence of N-tert-butylbenzamide (0.1-0.5 equiv.) as an internal standard. The reaction mixtures were worked up as described for the preparative studies, then analysed by $^1$H NMR spectroscopy. Integration of peaks characteristic of the residual bromides 18a, 18b, 20a and 20b and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. The data obtained from these experiments are summarised in Appendix 7.

Competitive Hydrolysis Reactions of the Bromides 33 and 73 using Silver Nitrate in Aqueous Acetone.

The relative rates of reaction of the bromides 33 and 73 with silver nitrate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives 18a, 18b, 20a and 20b. The data obtained from these experiments are summarised in Appendix 8.

Competitive Hydrolysis Reactions of the Bromides 71a, 71b, 72a and 72b using Silver Sulfate in Aqueous Acetone.

The relative rates of reaction of the bromides 71a, 71b, 72a and 72b with silver sulfate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives 18a, 18b, 20a and 20b, except that silver sulfate was used in place of silver nitrate and the mixtures were heated at 65 °C for 48 h. The data obtained from these experiments are summarised in Appendix 9.
Competitive Hydrolysis Reactions of the Bromides 20a and 20b using Silver Nitrate in Deuterium Oxide and Acetone.

The relative rates of reaction of the bromides 20a and 20b with silver nitrate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives 18a, 18b, 20a and 20b, except that deuterium oxide was used in place of water. The data obtained from these experiments are summarised in Appendix 10.

(S)-O-Acetyl-N-tert-butyl-Nα-phthaloyltyrosinamide 79b

The title compound 79b was prepared from (S)-O-acetyl-Nα-phthaloyltyrosine 13659 (537 mg, 1.5 mmol), using the procedure described above for the preparation of the phenylalaninamide 19 (537 mg, 1.5 mmol), by treatment with triethylamine, ethyl chloroformate and then tert-butylamine, and isolated as a white solid (468 mg, 75%). $\delta_H$ 7.81-7.76 (m, 4 H, Phth), 7.20 (d, $J$ 8.4 Hz, 2 H, ArH), 6.93 (d, $J$ 8.4 Hz, 2 H, ArH), 5.81 (br s, 1 H, NH) 4.97 (dd, $J$ 6.9, 10.1 Hz, 1 H, $\alpha$-H), 3.57 (dd, $J$ 6.9, 14.2 Hz, 1 H, $\beta$-H), 3.48 (dd, $J$ 10.1, 14.2 Hz, 1 H, $\beta'$-H), 2.23 (s, 3 H, OAc), 1.31 (s, 9 H, CMe$_3$). The $^1$H NMR spectral data for this material are consistent with reported values.59
Experimental

(2R,3R)-O-Acetyl-3-bromo-N-tert-butyl-Nα-phthaloyltirosinamide 81b and

(2R,3S)-O-Acetyl-3-bromo-N-tert-butyl-Nα-phthaloyltirosinamide 81a

The title compounds 81a and 81b were prepared from (S)-N-tert-butyl-O-acetyl-Nα-phthaloyltirosinamide 79b (205 mg, 0.50 mmol) as described above for the preparation of the bromophenylalanine derivatives 18a and 18b, by treatment with NBS (107 mg, 0.60 mmol) in carbon tetrachloride at reflux whilst irradiating with a 300 W sunlamp (241 mg, 99%). 81b δH 7.96-7.77 (m, 4 H, Phth), 7.63 (d, J 8.6 Hz, 2 H, ArH), 7.15 (d, J 8.6 Hz, 2 H, ArH), 6.20 (d, J 11.8 Hz, 1 H, β-H), 5.78 (br s, 1 H, NH) 5.15 (d, J 11.8 Hz, 1 H, α-H), 2.32 (s, 3 H, OAc) , 1.06 (s, 9 H, CMe3); 81a δH 7.76-7.61 (m, 4 H, Phth), 7.39 (d, J 8.7 Hz, 2 H, ArH), 6.95 (d, J 8.7 Hz, 2 H, ArH), 6.36 (br s, 1 H, NH), 6.08 (d, J 11.5 Hz, 1 H, β-H), 5.29 (d, J 11.5 Hz, 1 H, α-H), 2.21 (s, 3 H, OAc), 1.40 (s, 9 H, CMe3). The 1H NMR spectral data for this material are consistent with literature values.96

(2R,3R)-O-Acetyl-3-bromo-N-phthaloyltirosine Methyl Ester 80b and

(2R,3S)-O-Acetyl-3-bromo-N-phthaloyltirosine Methyl Ester 80a

The title compounds 80a and 80b were prepared from (S)-O-acetyl-Nα-phthaloyltirosine methyl ester 79a (695 mg, 1.97 mmol) by treatment with NBS (420 mg, 2.36 mmol) using the procedure described above for the preparation of the bromophenylalanine derivatives 18a and 18b (799 mg, 94%). 80b δH 7.98-7.91 (m, 2 H, Phth), 7.85-7.77 (m, 2 H, Phth), 7.61 (d, J 8.8 Hz, 2 H, ArH), 7.14 (d, J 8.8 Hz, 2 H, ArH), 6.03 (d, J 11.2 Hz, 1 H, β-H), 5.45 (d, J 11.2 Hz, 1 H, α-H), 3.57 (s, 3 H, OMe), 2.32 (s, 3 H, OAc); 80a δH 7.74-7.61 (m, 4 H, Phth), 7.37 (d, J 8.7 Hz, 2 H, ArH), 6.93 (d, J 8.7 Hz, 2 H, ArH), 5.93 (d, J 10.5 Hz, 1 H, β-H), 5.57
(d, J 10.5 Hz, 1 H, α-H), 3.82 (s, 3 H, OMe), 2.20 (s, 3 H, OAc). The $^1$H NMR spectral data for this material are consistent with literature values.96

**Competitive Reactions of the Phenylalanine, Nitrophenylalanine and Tyrosine Derivatives 17, 19, 78a, 78b, 79a and 79b with NBS**

The relative rates of reaction of the derivatives 17, 19, 78a, 78b, 79a and 79b were determined by treating various mixtures of the substrates in carbon tetrachloride with NBS (ca. 1.0 equiv.) at reflux under nitrogen and in the presence of tert-butylbenzamide (0.1-0.5 equiv.) as an internal standard, whilst being irradiated with a 300 W sunlamp. After being allowed to cool to room temperature, the mixtures were filtered and concentrated under reduced pressure and then analysed using $^1$H NMR spectroscopy. The data obtained from these experiments are summarised in Appendix 1.

**Competitive Reactions of the Bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with Triphenyltin Hydride**

The relative rates of reaction of the bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b were determined by treating various mixtures of the substrates in benzene with triphenyltin hydride (ca. 1.0 equiv.) at reflux under nitrogen and in the presence of tert-butylbenzamide (0.1-0.5 equiv.) as an internal standard, whilst being irradiated with a 300 W sunlamp. After being allowed to cool to room temperature, the mixtures were concentrated under reduced pressure and then analysed using $^1$H NMR spectroscopy. The data obtained from these experiments are summarised in Appendix 12.
Experimental

Treatment of (2S,3R)-3-Deutero-N-phthaloylphenylalanine Methyl Ester 26 with NBS

To a solution of (2S,3R)-3-deutero-N-phthaloylphenylalanine methyl ester $26^{58}$ (5.8 mg, 16 µmol) in carbon tetrachloride (2 ml) was added NBS (3.2 mg, 18 µmol). The resultant mixture was heated at reflux for 2 h whilst being irradiated with a 300 W sunlamp, then was allowed to cool to room temperature and was filtered. Following concentration of the solution under reduced pressure, the crude product was analysed using $^1$H NMR spectroscopy, which showed the diastereomeric bromides 137a and 137b in the ratio ca. 1:1. The percentage deuterium content of the bromides 137a and 137b was determined from the $^1$H NMR spectrum and from the mass spectrum of the crude product as described in Chapter 3 of the Results and Discussion of this thesis, and the results of this experiment are summarised in Table 3.4.

Treatment of (2S,3S)-3-Deutero-N-phthaloylphenylalanine Methyl Ester 29 with NBS

The reaction of (2S,3S)-3-deutero-N-phthaloylphenylalanine methyl ester $29^{58}$ with NBS was carried out in an identical manner to that described above for the reaction of the deuteride 26 with NBS, and the crude product was analysed using $^1$H NMR spectroscopy and mass spectrometry. The bromides 137a and 137b were present in the crude product in the ratio ca. 1:1. The percentage deuterium content of the bromides 137a and 137b determined from the $^1$H NMR and mass spectra of the crude product is given in Chapter 3 of the Results and Discussion of this thesis, and the results obtained from this experiment and those of a duplicate experiment are summarised in Table 3.4.
Treatment of (2S,3R)-3-Deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide 31b with NBS

The reaction of (2S,3R)-3-deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide 31b with NBS was carried out in an identical manner to that described above for the reaction of the deuteride 26 with NBS, and the crude product was analysed using ¹H NMR spectroscopy and mass spectrometry. The bromides 138a and 138b were present in the crude product in the ratio ca. 1:1. The percentage deuterium content of the bromides 138a and 138b, determined from the ¹H NMR and mass spectra of the crude product, is given in Chapter 3 of the Results and Discussion of this thesis and the results of this experiment and those of a duplicate experiment are summarised in Table 3.4.

Treatment of (2S,3S)-3-Deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide 31a with NBS

The reaction of (2S,3S)-3-deutero-N-tert-butyl-Nα-phthaloylphenylalaninamide 31a with NBS was carried out in an identical manner to that described above for the reaction of the deuteride 26 with NBS, and the crude product was analysed using ¹H NMR spectroscopy and mass spectrometry. The bromides 138a and 138b were present in the crude product in the ratio ca. 1:1. The percentage deuterium content of the bromides 138a and 138b was determined from the ¹H NMR and mass spectra of the crude product as described in Chapter 3 of the Results and Discussion of this thesis, and the results of this experiment and those of a duplicate experiment are summarised in Table 3.4.
Treatment of the Phenylalaninamide 19 with Bromine and Aqueous Potassium Hydroxide

\(N\text{-}\text{tert-Butyl}\text{-}N\alpha\text{-phthaloyl} \text{phenylalaninamide}\) 19 (507 mg, 1.5 mmol) was dissolved in bromine (75 µl, 1.5 mmol), then the resultant solution was cooled to 0 °C in an ice bath. Aqueous potassium hydroxide solution (ca. 1 ml, 50%) was added to the solution until the bromine colour was dissipated, then the mixture was stirred for 3 h and sodium chloride (350 mg, 6.0 mmol) was added. The mixture was extracted with chloroform (4 x 3 ml), then the organic extracts were combined and dried, and the solution was concentrated under reduced pressure, affording a crude product (395 mg, 63%). Analysis of the crude product using \(^1\text{H} \text{NMR spectroscopy}\) showed \(p\)-bromo-\(N\text{-}\text{tert-Butyl}\text{-}N\alpha\text{-phthaloyl} \text{phenylalaninamide}\) 139 comprised ca. 80% of that mixture. \(\delta\text{H} 7.82\text{--}7.70 (m, 4 H, Phth), 7.31 (br d, J 8.4 Hz, 2 H, ArH), 7.05 (br d, J 8.4 Hz, 2 H, ArH), 5.87 (br s, 1 H, NH), 4.96 (t, J 8.5 Hz, 1 H, \alpha-H), 3.49 (d, J 8.5 Hz, 2 H, \beta-H), 1.33 (s, 9 H, CMe3); \text{m/z} (\%) 430 (M\text{+}, 58\%), 428 (M\text{+}, 58), 349 (55), 329 (100), 312 (12), 310 (12), 283 (25), 281 (24), 249 (94), 173 (85), 104 (67), 76 (60). Purification of this material using chromatography on silica was unsuccessful due to decomposition. Hence, \(p\)-bromo-\(N\text{-}\text{tert-Butyl}\text{-}N\alpha\text{-phthaloyl} \text{phenylalaninamide}\) 139 was not further purified or characterised.

\(N\text{-Bromo-}N\text{-}\text{tert-Butyl}\text{-}N\alpha\text{-phthaloyl} \text{phenylalaninamide}\) 92

\(\text{tert-Butylhypobromite}\) in carbon tetrachloride (1 ml, 0.4 M)\(^{196}\) was added to the phenylalanine derivative 19 (5 mg, 14 µmol) and the resultant solution was stirred at room temperature for 16 h in the dark. The solution was concentrated under reduced pressure, and the crude product was analysed using \(^1\text{H} \text{NMR spectroscopy}\), which showed that the title compound 92 comprised ca. 90% of that mixture. \(\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}\) 3060, 2970, 2920, 2850, 1775, 1715, 1520, 1470, 1450, 1375, 1220, 1100, 910, 880,
Experimental

740, 720, 700; δH 7.79-7.67 (m, 4 H, ArH), 7.18 (m, 5 H, Ph), 5.69 (dd, J 5.4, 10.5 Hz, 1 H, α-H), 3.59 (dd, J 10.5, 14.4 Hz, 1 H, β-H), 3.52 (dd, J 5.4, 14.4 Hz, 1 H, β-H'), 1.48 (s, 9 H, CMe3). The crude material was not purified and was therefore used in subsequent reactions without further characterisation.

Photolysis of N-Bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 92.

A solution of the N-bromoamide 92 (6 mg, 14 µmol) in carbon tetrachloride (1 ml) at reflux under nitrogen was photolysed for 5 mins with a 300 W sunlamp, then the solution was concentrated under reduced pressure. Analysis of the crude product using 1H NMR spectroscopy showed that a 1:1 mixture of the β-bromides 20a and 20b and the amide 19 were present in the ratio ca. 2:1.

(2S,3S)-3-Deutero-N-bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 140a

The title compound 140a was prepared in approximately 95% yield and with ca. 98% deuterium content from the (2S,3S)-amide 31a as determined by analysis of the crude product using 1H NMR spectroscopy, by treatment with tert-butyl hypobromite, using the procedure described above for the preparation of the N-bromophenylalanine derivative 92. δH 7.78 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.17 (m, 5 H, Ph), 5.66 (d, J 11.4 Hz, 1 H, α-H), 3.56 (br d, J 11.4 Hz, 1 H, β-H), 1.47 (s, 9 H, CMe3). The crude material was not purified and was therefore used in the subsequent reaction without further characterisation. The (2S,3R)-diastereomer 140b was not detected in the crude product.
Experimental

(2S,3R)-3-Deutero-N-bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 140b

The title compound 140b was prepared in approximately 60% yield and with ca. 98% deuterium content from the (2S,3R)-amide 31b\textsuperscript{58,59} as determined using \(^1\)H NMR spectroscopy, by treatment with tert-butyl hypobromite, using the procedure described above for the preparation of the N-bromophenylalanine derivative 92. \(\delta_H\) 7.79 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.19 (m, 5 H, Ph), 5.66 (d, \(J\) 4.5 Hz, 1 H, \(\alpha\)-H), 3.51 (br d, \(J\) 4.5 Hz, 1 H, \(\beta\)-H), 1.47 (s, 9 H, CMe\(_3\)). The crude material was not purified and was therefore used without further characterisation. The (2S,3S)-diastereomer 140a was not detected in the \(^1\)H NMR spectrum of the crude product.

Photolysis of (2S,3S)-3-Deutero-N-bromo-N-tert-butyl-Nα-phthaloylphenylalaninamide 140a

A solution of the crude N-bromoamide 140a at a concentration of approximately 1.5 mM in carbon tetrachloride (1 ml) at reflux under an atmosphere of nitrogen was irradiated for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then the crude product was analysed using \(^1\)H NMR spectroscopy which showed a 1:1 mixture of the \(\beta\)-bromides 138a and 138b and the amide 31a were present in the ratio ca. 2:1. The percentage deuterium content of the bromides 138a and 138b determined from the \(^1\)H NMR and mass spectra as described in Chapter 3 of the Results and Discussion of this thesis for the reactions of the deuterides 26, 29, 31a and 31b with NBS is summarised in Table 4.1.
Photolysis of (2S,3R)-3-Deutero-N-bromo-N-tert-butyl-Nα-phthaloyl-phenylalaninamide 140b

A solution of the crude N-bromoamide 140b at a concentration of approximately 2.3 mM in carbon tetrachloride (1 ml) at reflux under an atmosphere of nitrogen was irradiated for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then the crude product was analysed using $^1$H NMR spectroscopy which showed a 1:1 mixture of the β-bromides 138a and 138b and the amide 31b were present in the ratio ca. 1:1. The percentage deuterium content of each of the bromides 138a and 138b determined from the $^1$H NMR and mass spectra as described in Chapter 3 of the Results and Discussion of this thesis for the reactions of the deuterides 26, 29, 31a and 31b with NBS is summarised in Table 4.1.

Competitive Reaction of the Phenylalaninamide 19 and tert-Butyltoluene with NBS.

The relative rate of reaction of N-phthaloylphenylalaninamide 19 (10.0 mg, 29 µmol) and p-tert-butyltoluene (5.1 µl, 28 µmol) with NBS was determined by treating an approximately equimolar ratio of each substrate in carbon tetrachloride (3 ml) with NBS (3.7 mg, 21 µmol) at reflux under an atmosphere of nitrogen, whilst irradiating the mixture for 30 mins with a 300 W sunlamp. The mixture was allowed to cool to room temperature, then was filtered and the solution was concentrated under reduced pressure. Analysis of the crude product using $^1$H NMR spectroscopy showed a 1:1 mixture of the β-bromides 20a and 20b, the amide 19, p-tert-butyltoluene and p-tert-butylbenzyl bromide were present in the ratio ca. 1:6:2:4. The results of this experiment are summarised in Table 4.2.
Photolysis Reactions of \( N\)-Bromo-\( N\)-tert-butyl-\( N\alpha\)-phthaloylphenylalaninamide 92 and tert-Butyltoluene at a Series of Concentrations.

A sample of the \( N\)-bromoamide 92 was prepared using the procedure described above, which contained approximately 20% of the amide. This material was dissolved in 25 ml of dichloromethane, of which portions (1.0, 2.0 and 4.0 ml) were taken and concentrated under reduced pressure. To each of these samples was added a solution of \( p\)-tert-butyltoluene at concentrations of 0.92, 1.84 or 3.46 mM in carbon tetrachloride (5.0 ml), and the resultant solutions were heated at reflux for 5 mins while being irradiated with a 300 W sunlamp. The concentrations of the \( N\)-bromoamide 92 in these experiments were 0.65, 1.30 and 2.60 mM. Following concentration under reduced pressure, the crude mixtures were analysed using \(^1\)H NMR spectroscopy and the ratio of the bromides 20a and 20b to tert-butylbenzyl bromide was measured from the integrals characteristic of each product. The results of these experiments are given in Table 4.3.

(R)-\( N\)-Bromo-\( N\)-tert-butyl-\( N\alpha\)-phthaloyl-\( p\)-nitrophenylalaninamide 143

The title compound 143 was prepared in ca. 80% yield, as determined using \(^1\)H NMR spectroscopy, using the procedure described above for the preparation of the \( N\)-bromophenylalanine derivative 92, by treatment of the amide 78b (2.0 mg, 5.5 \( \mu \)mol) with a solution of tert-butyl hypobromite in carbon tetrachloride. \( \delta_H \) 8.07 (d, \( J \) 6.6 Hz, 2 H, ArH), 7.82-7.71 (m, 4 H, Phth), 7.40 (d, \( J \) 6.6 Hz, 2 H, ArH), 5.66 (dd, \( J \) 6.6, 9.3 Hz, 1 H, \( \alpha\)-H), 3.64 (d, \( J \) 9.3 Hz, 1 H, \( \beta\)-H), 3.62 (d, \( J \) 6.6 Hz, 1 H, \( \beta\)-H'), 1.47 (s, 9 H, CMe3). The crude material was not purified and was therefore used in the subsequent photolysis reaction without further characterisation.
Photolysis of (R)-N-Bromo-N-tert-butyl-Nα-phthaloyl-p-nitrophenylalaninamide 143 in the Presence of p-tert-Butyltoluene

A solution of the crude N-bromoamide 143 at a concentration of approximately 1.5 mM and p-tert-butyltoluene (1 µl, 5.8 µmol) in carbon tetrachloride (3 ml) at reflux under an atmosphere of nitrogen was photolysed for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then was analysed using $^1$H NMR spectroscopy, which showed the presence of a 1:1 mixture of the β-bromides 72a and 72b, the amide 78b and p-tert-butylbenzyl bromide in the ratio ca. 6.6:3.9:1.

N-Benzoyl-p-methylphenylalanine Methyl Ester 145

N-Benzoyl-α-bromoglycine methyl ester 7b was prepared from N-benzoyl-glycine methyl ester 7a$^{213}$ as described previously,$^{53}$ by treatment with NBS in carbon tetrachloride under photolytic conditions. Using the procedure of Castelhano et al.$^{208}$ 4-methylbenzylmagnesium bromide, prepared from 4-methylbenzyl bromide (4.15 g, 22.4 mmol), magnesium turnings (0.60 g, 24.7 mmol) and a crystal of iodine in ether (50 ml), was added to the bromoglycine derivative 7b (2.77 g, 10.2 mmol) in ether at -78 °C via a cannula. Saturated ammonium chloride solution was added to the mixture, which was then concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with water, then dried and concentrated under reduced pressure. The crude material was chromatographed on silica, affording the title compound 145 as a colourless oil (687 mg, 23%). $\nu_{\text{max}}$(neat)/cm$^{-1}$ 3320, 3060, 3020, 2950, 2925, 2860, 1740, 1650, 1605, 1580, 1525, 1490, 1215, 810, 715, 695. $\delta_H$ 7.75-7.72 (m, 2 H, Bz), 7.51-7.34 (m, 3 H, Bz), 7.10-7.01 (m, 4 H, ArH), 6.76 (br d, $J$ 7.8 Hz, 1 H, NH), 5.06 (m, 1 H, α-H), 3.75 (s, 3 H, OMe), 3.25 (dd, $J$ 5.9, 13.9 Hz, 1 H, β-H), 3.17 (dd, $J$ 5.7, 13.9 Hz, 1 H, β-H$'$), 2.30 (s, 3 H, Me); $\delta_C$ 171.8, 166.6, 136.3, 133.6, 132.5, 131.4, 129.0, 128.8,
Experimental

128.2, 126.7, 53.4, 52.0, 37.0, 20.7; m/z (%) 297 (M**, 5%), 280 (8), 238 (13), 176 (85), 161 (7), 145 (23), 122 (15), 105 (100), 91 (13), 77 (48). m/z 297.1365 (M**) [Calc. for C₁₈H₁₉NO₃ (M**) m/z 297.1364].

p-Methylphenylalanine 146

To N-benzoylphenylalanine methyl ester 145 (697 mg, 2.3 mmol) was added a 2:1 mixture of 6 N hydrochloric acid and acetic acid (15 ml), and the mixture was heated at reflux for 3 h. The resultant solution was cooled to room temperature, then concentrated under reduced pressure and the residue was dissolved in ethanol (20 ml). To this solution was added aniline (2 ml) in dichloromethane (5 ml) and the solution set aside for 16 h at ca. 4 °C. The title compound 146 was isolated by filtration as an off-white powder (211 mg, 51%), m.p. 235-238 °C. νmax/cm⁻¹ 3392, 2920, 2851, 2710, 2542, 1618, 1586, 1502, 1445, 1211, 1346, 1322, 1309, 1290, 856, 805; δH (D₂O) 7.21 (m, 4 H, ArH), 3.94 (dd, J 4.7, 8.0 Hz, 1 H, β-H), 3.23 (dd, J 4.7, 14.6 Hz, 1 H, α-H), 2.31 (s, 3 H, Me); m/z (%) 179 (M, 0.4%), 135 (20), 105 (100), 91 (13), 77 (15), m/z 179.095 (M**) [Calc. for C₁₀H₁₃NO₂ (M**) m/z 179.095]; (Found C, 65.76; H, 7.72; N, 7.23. Calc. for C₁₀H₁₃NO₂: C, 67.02; H, 7.31; N, 7.82%).

N-Phthaloyl-p-methylphenylalanine 147

A mixture of p-methylphenylalanine 146 (100 mg, 0.56 mmol), phthalic anhydride (87 mg, 0.59 mmol) and triethylamine (14 µl) in toluene (7 ml) was heated at reflux for 4 h, in a flask fitted with a Dean-Stark apparatus. The resultant solution was concentrated under reduced pressure, then the residue was partitioned between dichloromethane and 10% hydrochloric acid. The organic solution was washed with
Experimental

water, then dried and concentrated, yielding the title compound 147 as a white crystalline solid (167 mg, 97%); m.p. 194-196°C. \( \nu_{\text{max}}/\text{cm}^{-1} \) 3500, 2920, 2950, 1775, 1715, 1610, 1515, 1470, 1390, 1115, 1100, 1090, 720; \( \delta_H \) 7.80-7.67 (m, 4 H, Phth), 7.05 (d, J 8.2 Hz, 2 H, ArH), 6.99 (d, J 8.2 Hz, 2 H, ArH), 5.20 (t, J 8.3 Hz, 1 H, \( \alpha \)-H), 3.56 (d, J 8.3 Hz, 2 H, \( \beta \)-H), 2.23 (s, 3 H, Me); \( m/z \) (%) 309 (M**, 20%), 264 (7), 246 (9), 162 (100), 130 (19), 105 (55), 91 (13), 77(23); (Found: C, 69.50; H, 4.64; N, 4.09. Calc. for C\(_{18}\)H\(_{15}\)NO\(_4\): C, 69.89; H, 4.89; N, 4.53%).

\textit{N-tert-Butyl-N\( \alpha \)-phthaloyl-\( p \)-methylphenylalaninamide 94}

To a suspension of \( N \)-phthaloyl-\( p \)-methylphenylalanine 147 (100 mg, 0.32 mmol) in carbon tetrachloride (3 ml) was added thionyl chloride (75 \( \mu l \), 1.0 mmol) and pyridine (10 \( \mu l \)), then the mixture was heated at reflux for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then carbon tetrachloride (3 ml) and tert-butylamine (0.1 ml, 1.0 mmol) were added and the mixture was heated at reflux for a further 1 h. The mixture was cooled to room temperature, then washed with 10% hydrochloric acid and water, then dried and concentrated affording the title compound 94 as a white solid (115 mg, 97%), m.p. 210-211°C. \( \nu_{\text{max}}/\text{cm}^{-1} \) 3300, 2920, 2850, 1775, 1715, 1665, 1560, 1460, 1380, 1365, 1300, 1225, 875, 740, 715; \( \delta_H \) 7.81-7.68 (m, 4 H, Phth), 7.04 (m, 4 H, ArH), 5.82 (br s, 1 H, NH), 4.97 (dd, J 6.9, 9.9 Hz, 1 H, \( \alpha \)-H), 3.52 (dd, J 6.9, 14.1 Hz, 1 H, \( \beta \)-H), 3.43 (dd, J 9.9, 14.1 Hz, 1 H, \( \beta \)-H'), 2.23 (s, 3 H, Me), 1.30 (s, 9 H, CMe\(_3\)); \( \delta_C \) 168.0, 167.3, 136.3, 134.0, 133.7, 131.4, 129.2, 128.6, 123.3, 56.6, 51.5, 34.7, 26.5, 20.8; \( m/z \) (%) 364 (M**, 80%), 305 (15), 264 (100), 246 (43), 217 (56), 202 (22), 173 (98), 105 (86); (Found: C, 72.20; H, 6.57; N, 7.55. Calc. for C\(_{22}\)H\(_{24}\)N\(_2\)O\(_3\): C, 72.51; H, 6.64; N, 7.59).
**N-Phthaloyl-p-methylphenylalanine Methyl Ester 93**

To a solution of N-phthaloyl-p-methylphenylalanine 147 (102 mg, 0.33 mmol) in dry methanol (10 ml) was added a catalytic amount of thionyl chloride. The solution was stirred at room temperature for 72 h under anhydrous conditions, then was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with aqueous sodium bicarbonate solution and water, then was dried and concentrated under reduced pressure affording the title compound 93 as a white crystalline solid (94 mg, 88%); m.p. 115-118 °C. v_max/cm⁻¹ 3020, 2950, 2920, 2850, 1775, 1745, 1715, 1615, 1515, 1470, 1425, 1385, 1245, 1200, 1180, 785, 720; δ_H 7.79-7.65 (m, 4 H, Phth), 7.05 (d, J 7.9 Hz, 2 H, ArH), 6.98 (d, J 7.9 Hz, 2 H, ArH), 5.14 (dd, J 5.9, 10.7 Hz, 1 H, α-H), 3.77 (s, 3 H, OMe), 3.56 (dd, J 5.9, 14.1 Hz, 1 H, β-H), 3.50 (dd, J 10.7, 14.1 Hz, 1 H, β-H'), 2.21 (s, 3 H, Me); δ_C 169.2, 167.3, 136.1, 133.9, 133.4, 131.4, 129.0, 128.5, 123.3, 53.2, 52.7, 34.0, 20.8; m/z (%) 323 (M, 9%), 264 (12), 246 (8), 176 (100), 145 (37), 130 (17), 105 (52), 91 (14); m/z 323.116 (M⁺⁺) [Calc. for C₁₉H₁₇NO₄ (M⁺⁺) m/z 323.116].

**Treatment of N-Phthaloyl-p-methylphenylalanine Methyl Ester 93 with NBS.**

N-Phthaloyl-p-methylphenylalanine methyl ester 93 (3.2 mg, 9.9 μmol) was dissolved in carbon tetrachloride (3 ml), then NBS (1.2 mg, 6.7 μmol) was added and the mixture was heated at reflux for 1 h under an atmosphere of nitrogen whilst being irradiated with a 300 W sunlamp. The resultant solution was allowed to cool to room temperature, then was washed with water, then dried and concentrated under reduced pressure. The crude material was analysed using ¹H NMR spectrometry, which showed the p-bromomethyl compound 149, the β-bromides 148a and 148b, and the ester 93 present in the ca. 7.3 : 1 : 9.4 ratio. 149 δ_H 7.82-7.77 (m, 2 H, Phth), 7.73-7.68
Experimental

7.22 (d, J 8.1 Hz, 2 H, ArH), 7.15 (d, J 8.1 Hz, 2 H, ArH), 5.13 (dd, J 5.7, 10.8 Hz, 1 H, α-H), 4.39 (s, 2 H, CH2Br), 3.78 (s, 3 H, OMe), 3.57 (m, 2 H, β-H); 148a δH 7.98-7.92 (m, 2 H, Phth), 7.83-7.74 (m, 2 H Phth), 7.42-7.12 (m, 4 H, ArH), 6.01 (d, J 10.8 Hz, 1 H, β-H), 5.50 (d, J 10.8 Hz, 1 H, α-H), 3.56 (s, 3 H, OMe), 2.31 (s, 3 H, Me); 148b δH 7.74-7.62 (m, 4 H, Phth), 7.42-7.12 (m, 4 H, ArH), 5.93 (d, J 10.5 Hz, 1 H, β-H), 5.59 (d, J 10.5 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 2.18 (s, 3 H, Me). The mixture was chromatographed on silica (CH2Cl2 / hexane, 9:1) affording N-phthaloyl-p-bromomethylphenylalanine methyl ester 149 as a colourless oil (1.2 mg, 30%). v_max(neat)/cm⁻¹ 2950, 2920, 2850, 1775, 1745, 1725, 1470, 1390, 1245, 1110, 1020, 885, 720; m/z (%) 402 (M-H, 17%), 400 (M-H, 17), 322 (38), 299 (38), 277 (32), 262 (32), 256 (34), 254 (34), 249 (45), 218 (40), 175 (100), 130 (34), 104 (76), 76 (52); m/z 400.018 (M-H) [Calc. for C19H15NO479Br (M-H) m/z 400.018]. The β-bromides 148a and 148b were not isolated, and were identified by comparison of their 1H NMR spectra data obtained from the crude reaction mixture with those of the corresponding bromophenylalanine derivatives 18a, 18b, 25 and 28, as described in Chapter 5 of the Results and Discussion of this thesis.

Treatment of N-tert-Butyl-Nα-phthaloyl-p-methylphenylalaninamide 94 with NBS.

N-tert-Butyl-Nα-phthaloyl-p-methylphenylalaninamide 94 (5.9 mg, 16.2 µmol) was dissolved in carbon tetrachloride (3 ml), then NBS (2.1 mg, 11.8 µmol) was added and the mixture was heated at reflux for 30 mins. under a nitrogen atmosphere, whilst irradiating with a 300 W sunlamp. The resultant solution was allowed to cool to room temperature, then was washed with water and dried, then concentrated under reduced pressure. The crude mixture was analysed using 1H NMR spectroscopy, which showed the p-bromomethylphenylalanine derivative 151, a 1:1 mixture of diastereomers of the
Experimental

\[150a\] and \[150b\], and the amide \[94\] in the ratio \(\text{ca. } 1.4 : 1.0 : 4.5\). \(151\)

\[\delta_H 7.81-7.68 \text{ (m, 4 H, Phth), 7.22 \text{ (d, } J 8.1 \text{ Hz, 2 H, ArH), 7.15 \text{ (d, } J 8.1 \text{ Hz, 2 H, ArH), 5.82 \text{ (br s, 1 H, NH), 4.96 \text{ (dd, } J 6.6, 9.9 \text{ Hz, 1 H, } \alpha-\text{H}), 4.38 \text{ (s, 2 H CH}_2\text{Br), 3.57 \text{ (dd, } J 6.6, 14.7 \text{ Hz, 1 H, } \beta-\text{H}), 3.43 \text{ (dd, } J 9.9, 14.7 \text{ Hz, 1 H, } \beta-\text{H}'), 1.31 \text{ (s, 9 H, CMe}_3\}; \]  

\[150a\] \(\delta_H 7.96-7.73 \text{ (m, 4 H, Phth), 7.07-6.98 \text{ (m, 4 H, ArH), 6.17 \text{ (d, } J 11.4 \text{ Hz, 1 H, } \beta-\text{H}), 5.78 \text{ (br s, 1 H, NH), 5.22 \text{ (d, } J 11.4 \text{ Hz, 1 H, } \alpha-\text{H), 2.19 \text{ (s, 3 H, Me), 1.03 \text{ (s, 9 H, CMe}_3\}; \]  

\[150b\] \(\delta_H 7.72-7.62 \text{ (m, 2 H, Phth), 7.24-7.14 \text{ (m, 4 H, ArH), 6.41 \text{ (br s, 1 H, NH), 6.05 \text{ (d, } J 11.4 \text{ Hz, 1 H, } \beta-\text{H), 5.31 \text{ (d, } J 11.4 \text{ Hz, 1 H, } \alpha-\text{H), 2.37 \text{ (s, 3 H, Me), 1.40 \text{ (s, 9 H, CMe}_3\). The bromides \[150a, 150b\] and \[151\] were inseparable using chromatography on silica, and were therefore identified by comparison of the \(^1\text{H NMR spectral data obtained from the mixture of regioisomers with those of the corresponding bromophenylalanine derivatives 20a, 20b, 31a and 31b and the ester 149.}$$

**Competitive Reactions of the Valine Derivatives 95 and 96 with NBS**

The relative rates of reactions of the valine derivatives \[95\] and \[96\] with NBS were carried out as described above for the competitive reactions of the phenylalanine derivatives \[17, 19, 78a, 78b, 79a\] and \[79b\], by treating approximately equimolar amounts of each substrate \[95\] and \[96\] in carbon tetrachloride with NBS (\(ca. 1.0\) equiv.) at reflux in the presence of tert-butylbenzamide (\(ca. 0.1\) equiv.) as an internal standard whilst photolyzing with a 300 W sunlamp. The data obtained from these experiments are summarised in Appendix 13.
Competitive Reactions of the \( p \)-Methylphenylalanine Derivatives 93 and 94 and \textit{tert}-Butyltoluene with NBS

The relative rates of reactions of the methylphenylalanine derivatives 93 and 94, at the \( \beta \)-position and at the \( p \)-methyl substituent, and \textit{tert}-butyltoluene with NBS were determined as described above for the competitive reactions of the phenylalanine derivatives 17, 19, 78a, 78b, 79a and 79b, by treating an approximately equimolar amount of the substrates 93 and 94 and \textit{tert}-butyltoluene in carbon tetrachloride with NBS (\textit{ca.} 1.0 equiv.) in the presence of \textit{tert}-butylbenzamide (\textit{ca.} 0.1 equiv.) as an internal standard, whilst irradiating with a 300 W sunlamp. The data obtained from these experiments are summarised in Appendix 14.

\textit{N}-Bromo-\textit{N-tert}-butyl-\textit{N}\( \alpha \)-phthaloyl-\( p \)-methylphenylalaninamide 144

The title compound 144 was prepared from \textit{N-tert}-butyl-\textit{N}\( \alpha \)-phthaloyl-\( p \)-methylphenylalaninamide 94 (2.5 mg, 6.9 µmol) by treatment with a solution of \textit{tert}-butyl hypobromite (5 ml, 0.4 M), using the procedure described above for the preparation of the \textit{N}-bromophenylalanine derivative 92. \( \delta \text{H} \) 7.80-7.76 (m, 2 H, Phth), 7.71-7.67 (m, 2 H, Phth), 7.10 (br d, \( J \) 8.0 Hz, 2 H, ArH), 6.99 (br d, \( J \) 8.0 Hz, 2 H, ArH), 5.66 (dd, \( J \) 5.0, 10.8 Hz, 1 H, \( \alpha \)-H), 3.57 (dd, \( J \) 10.8, 14.2 Hz, 1 H, \( \beta \)-H), 3.47 (dd, \( J \) 5.0, 14.2 Hz, 1 H, \( \beta \)-H'), 2.23 (s, 3 H, Me), 1.47 (s, 9 H, CMe\(_3\)). The crude material was used without further purification or characterisation.
Photolysis of \(N\)-Bromo-\(N\text{-}\text{tert}\text{-}\text{butyl-}N\alpha\text{-phthaloyl-p-methylphenylalaninamide}\) 144 in the Presence of \(p\text{-}\text{tert\text{-}Butyltoluene}\)

A solution of the crude \(N\)-bromoamide 144 at a concentration of approximately 1.6 mM and \(p\text{-}\text{tert\text{-}Butyltoluene}\) (ca. 1.4 equiv.) in carbon tetrachloride (3 ml) at reflux under an atmosphere of nitrogen was photolysed for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then analysed using \(^1H\) NMR spectroscopy, which showed the presence of a 1:1 mixture of the \(\beta\)-bromides 150a and 150b, the bromide 151 and \(p\text{-}\text{tert\text{-}Butylbenzyl bromide}\) in the ratio ca. 44:1:3.5.
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References


References


References


Introduction

Polyatomic group substitution by chemical and instrumental methods is well known and has numerous and wide-ranging applications at the present time. In the case of polyatomic organic compounds, both theoretical and experimental evidence indicates that the mechanism is connected to the electronic structure of the polyatomic group. For example, in the case of a polyatomic organic compound, the electronic structure of the polyatomic group determines the relative stability of the various possible conformations of the molecule. Consequently, the electronic structure of the polyatomic group plays a significant role in determining the stability of the molecule. In the case of polyatomic organic compounds, the electronic structure of the polyatomic group is often determined by a combination of theoretical and experimental methods.

In this paper, we present a theoretical study of the electronic structure of polyatomic organic compounds. The electronic structure of the polyatomic group is determined by a combination of theoretical and experimental methods. The theoretical methods used in this study include molecular orbital calculations, density functional theory, and ab initio calculations. The experimental methods used in this study include ultraviolet-visible spectroscopy, mass spectrometry, and nuclear magnetic resonance spectroscopy.

In conclusion, the electronic structure of polyatomic organic compounds is determined by a combination of theoretical and experimental methods. The theoretical methods used in this study include molecular orbital calculations, density functional theory, and ab initio calculations. The experimental methods used in this study include ultraviolet-visible spectroscopy, mass spectrometry, and nuclear magnetic resonance spectroscopy.

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Neighbouring Group Effects Promote Substitution Reactions over Elimination and Provide a Stereocontrolled Route to Chloramphenicol

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Abstract: In reactions of β-brominated valine and p-nitrophenylalanine derivatives to give β-hydroxy amino acid derivatives the carboxyl group, when protected as an amide, exerts a neighbouring group effect to facilitate the substitution process, and reduce competing elimination reactions. As a consequence of the effect, the (2R,3R)- and (2R,3S)-stereoisomers of 3-bromo-N-tert-buty1-N2-phthaloyl-p-nitrophenylalaninoamide both react to give (2S,3R)-3-hydroxy-N-tert-buty1-N2-phthaloyl-p-nitrophenylalaninoamide, providing a stereoconvergent route to chloramphenicol.

INTRODUCTION

Neighbouring group participation by amido and aminocarbonyl substituents is well known and the chemical and biochemical implications of this phenomenon in reactions of amino acid derivatives have attracted considerable attention. For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds, while amides derived from either the amino or carboxyl group of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, via 1,5-participation. Recently we reported much greater diastereoselectivity in the synthesis of the hydroxyamides 1d and 2d from the bromoamides 1e and 2c than in the conversion of the corresponding bromoesters 1a and 2a to the hydroxyesters 1b and 2b. The enhanced stereoselectivity was attributed to neighbouring group participation by the aminocarbonyl substituent in the reactions of the bromides 1e and 2c. Consistent with this proposal, the extent of anchimeric assistance displayed by amides is known to be larger than that shown by esters, although 1,4-participation by amides appears to be unusual. We now report reactions of the bromides 3a,c, 4a,c, in which it is apparent that the neighbouring group effect changes the course of reaction, favouring substitution over elimination, as well as controlling the stereochemistry in the conversion of the bromides 3a,c and 4a,c to the alcohols 3b,d and 4b,d.

During the course of the present work a stereospecific route to chloramphenicol was also developed. The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol but a disadvantage of that and other approaches is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide has been reported. Alternatively, (S)-phenylalanine has been used to obtain the chloramphenicol precursor.
in a multi-step synthesis (Scheme 1), in which diastereoccontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide 8.4

(S)-phenylalanine

Scheme 1
RESULTS AND DISCUSSION

The \( p \)-nitrophenylalanine derivatives 10a and 10b were prepared using standard procedures, and treated with \( N \)-bromosuccinimide to give 1:1 mixtures of the diastereomers of the corresponding bromides 3a and 4a, and 3c and 4c. The bromoesters 3a and 4a were separated through fractional crystallisation and their relative stereochemistry was determined through X-ray crystallographic analysis of the (2S,3R)-diastereomer 4a.\(^{11}\) [Note that the Cahn-Ingold-Prelog designation at the \( \alpha \)-carbon of the bromides 3a,c-5a,c is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives 10a,b and 11a,b, due to the change in priority of the substituents.] The stereochemistry of the bromoamides 3c and 4c was assigned by comparison of the spectral properties of the (2S,3R)-diastereomer 4c with those of a racemic sample. That sample was prepared by bromination of the racemic analogue of the nitrophenylalanine derivative 10b, then separated from its diastereomer by fractional crystallisation and its structure was determined through X-ray crystallographic analysis.\(^{11}\) The \(^1\)H NMR spectra of the bromides 3a,c and 4a,c show the same trends as previously observed with the corresponding phenylalanine derivatives 1a,c and 2a,c.\(^{7}\) The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2S,3S)-diastereomers 3a and 3c than for the corresponding (2S,3R)-diastereomers 4a and 4c, while the (2S,3S)-diastereomers 3a and 3c exhibit the \( \beta \)-proton signal at higher chemical shift, the \( \alpha \)-proton at lower chemical shift, and a larger coupling constant between the \( \alpha \)- and \( \beta \)-protons, than for the corresponding (2S,3R)-diastereomers 4a and 4c.

The bromides 5a\(^{12}\) and 5c were prepared by halogenation of the amino acid derivatives 11a and 11b, which had each been prepared from \( (S) \)-valine.

The valine derivative 5a reacted with silver nitrate in aqueous acetone, at room temperature for 24 h, to give a crude product containing the alcohol 5b and the dehydrovaline derivatives 12a and 13a in the ratio ca. 3.5:1:3.5. Chromatography of the mixture afforded the alcohol 5b in 43\% yield, and the alkenes 12a and 13a, in yields of 8 and 34\%, respectively. The corresponding reaction of the valinamide 5c afforded a ca. 2:1 mixture of the alcohol 5d and the alkenes 13b, from which the components were isolated in 63 and 26\% yield, respectively. The \(^1\)H NMR spectrum of the crude product of the reaction of the valinamide 5c showed no indication of formation of the alkenes 12b.

The \( p \)-nitrophenylalanine derivatives 3a,c and 4a,c required more vigorous conditions to react. On one occasion, treatment of the bromoester 4a at 65 °C for 48 h gave the alcohol 3b in 63\% yield, with the dehydrophenylalanine derivatives 14a and 15a also being isolated as a 2:3 mixture in 25\% yield. Repeated experiments afforded the alcohol 3b in only 10-30\% yield, with higher proportions of the alkenes 14a and

\[
\begin{align*}
P &= \text{Ph} \\
\text{PhthN} &\quad \text{COR} \\
\text{Me}_2C &\quad \text{H} \\
\end{align*}
\]

\( 10 \)

\[
\begin{align*}
P &= \text{Ph} \\
\text{PhthN} &\quad \text{COR} \\
\text{Me}_2C &\quad \text{H} \\
\end{align*}
\]

\( 11 \)

a) \( R = \text{OMe} \)
b) \( R = \text{NHCM}_{23} \)
15a. Under similar conditions, the bromide 3a gave only the alkene 15a, in 84% yield, and neither the alcohol 3b nor the alkene 14a were detected in the crude product. The analogous reaction of a 1:1 mixture of the bromides 3a and 4a carried out using silver sulfate, in place of the nitrate salt, gave mainly the alkene 15a and only small quantities of either the (E)-isomer 14a or the alcohol 3b. In contrast, treatment of a 1:1 mixture of the bromoamides 3c and 4c with silver sulfate over 3 days under similar conditions gave only the substitution product 3d in 64% yield. Reaction of the bromoamides 3c and 4c using silver nitrate was complicated by competing formation of a second product, which was tentatively identified as the nitrate 16. There was no indication of the presence of either of the alkenes 14b or 15b in the $^1$H NMR spectra of the crude products obtained from these reactions of the bromoamides 3c and 4c.

The stereochemistry of the dehydrophenylalanine derivatives 14a and 15a was assigned on the basis of their $^1$H NMR spectra, in which the resonance due to the vinylic proton of the (E)-isomer 14a was observed at $\delta$ 7.28, 0.85 ppm upfield from that of the corresponding signal for the (Z)-alkene 15a. This is consistent with the general trend displayed by dehydrophenylalanine derivatives. The stereochemistry of the alcohols 3b and 3d is apparent from their $^1$H NMR spectra, which show a much closer correlation with the spectra of the corresponding hydroxyphenylalanine derivatives 1b and 1d than with those of the respective diastereomers 2b and 2d. The assignment of stereochemistry of the alcohols 3b and 3d is further supported by hydrolysis to the free amino acid 18 and comparison of the physical and spectral properties of that material with literature data.14-16

Elimination reactions of the bromovalinate 5a, to give the alkenes 12a and 13a, compete with the substitution reaction, to give the alcohol 5b. By comparison, the reaction of the bromovalinamide 5c gives a better yield of the substitution product 5d. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination. Under these circumstances, the amide 5c would be expected to react more slowly than the ester 5a, whereas in competitive experiments the opposite was observed, with the amide 5c
reacting ca. six times faster than the ester 5a. Instead, the effect of the aminocarbonyl substituent to promote substitution over elimination, and increase the rate of reaction of the bromide 5c, indicates a neighbouring group effect of the protected carbonyl group to stabilise the carbocation intermediate in the substitution reaction. The neighbouring group effect is also seen in the reactions of the nitrophenylalanine derivatives 3a,c and 4a,c to promote substitution over elimination, and to give the alcohol 3d with a high degree of stereocontrol from the reaction of the bromoamides 3c and 4c. The predominant reaction of the esters 3a and 4a is elimination, whereas the amides 3e and 4e react by substitution. As shown previously, the bromophenylalanine derivatives 1a,c and 2a,c react to give the corresponding alcohols 1b,d and 2b. Presumably, in the absence of an electron withdrawing group on the aromatic ring, the carboxations 17a,b form in the substitution reactions without competing elimination. In that case the only effect of the neighbouring group is to enhance the stereoselectivity in the production of the alcohols 1b,d and 2b. The nitrophenylalanine derivatives 3a and 4a react predominantly by elimination. When the carboxyl group is protected as an amide, however, the destabilising effect of the nitro substituent on the intermediate carbocation is diminished to the extent that substitution now becomes the favoured reaction pathway.

On treatment with hydrochloric acid in aqueous acetic acid, the hydroxynitrophenylalanine derivative 3d hydrolysed to the corresponding free amino acid 18. The synthetic procedure used to prepare the alcohol 18, in 29% yield from (R)-p-nitrophenylalanine, was repeated using racemic p-nitrophenylalanine and the (S)-enantiomer as starting materials, to obtain the corresponding racemate and the (2S,3R)-enantiomer of the alcohol 18. The spectral properties of these compounds were found to be identical to those reported. Previously, the racemate of the alcohol 18 has been converted to the corresponding methyl ester, the enantiomers of that compound have been resolved by complexation with tartaric acid, and the (2S,3R)-stereoisomer has been elaborated to chloramphenicol. Now stereocontrolled access to the (2S,3R)-enantiomer of the alcohol 18, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic 6.

**Experimental**

**General.** M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded as nujol mulls, liquid films or as solutions in chloroform, on a Hitachi 270-30 spectrometer. $^1$H NMR (300 MHz) and $^{13}$C NMR (75.5 MHz) spectra were recorded on a Bruker ACP-300 or a GEMINI 300
spectrometer, in CDCl₃ with Me₄Si as the internal standard, unless otherwise stated. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over MgSO₄.

All solvents were purified and dried using standard methods. (S)-Valine, (RS)-p-nitrophenylalanine, and (S)- and (R)-p-nitrophenylalanine were purchased from Sigma Chemical Co.

(R)-N-Phthaloyl-p-nitrophenylalanine. A mixture of (R)-p-nitrophenylalanine monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 cm³, 7.95 mmol) was heated at reflux in toluene (60 cm³) for 3 h, during which time water was continuously removed using a Dean-Stark condenser. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then it was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; [α]D₂₅ +234.5° (c, 0.31 in MeOH); δH 8.09 (d, J 8.7 Hz, 2 H, ArH), 7.72-7.83 (m, 4 H, phth), 7.36 (d, J 8.7 Hz, 2 H, ArH), 5.26 (dd, J 7.3 and 9.2 Hz, 1 H, a-H) and 3.72 (m, 2 H, ~-H).

(S)-N-Phthaloyl-p-nitrophenylalanine. This compound was prepared from (S)-p-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (R)-isomer, and obtained in 57% yield, m.p. 185-187 °C.

(R)-N-Phthaloyl-p-nitrophenylalanine Methyl Ester 10a. (R)-N-Phthaloyl-p-nitrophenylalanine (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 cm³) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then it was dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound 10a as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; v max/cm⁻¹ 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860 and 720; δH 8.06 (d, J 8.6 Hz, 2 H, ArH), 7.72-7.82 (m, 4 H, phth), 7.45 (d, J 8.6 Hz, 2 H, ArH), 5.31 (dd, J 5.5 and 10.9 Hz, 1 H, a-H), 3.81 (s, 3 H, OMe), 3.77 (dd, J 5.5 and 14.3 Hz, 1 H, β-H) and 3.71 (dd, J 10.9 and 14.3 Hz, 1 H, β'-H); mlz (ei) (%) 354 (M⁺, 12), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17) and 76 (21).

(2S,3S)-3-Bromo-N-Phthaloyl-p-nitrophenylalanine Methyl Ester 3a and (2S,3R)-3-Bromo-N-Phthaloyl-p-nitrophenylalanine Methyl Ester 4a. To a solution of (R)-N-Phthaloyl-p-nitrophenylalanine methyl ester 10a (2.20 g, 6.21 mmol) in carbon tetrachloride (40 cm³), N-bromosuccinimide (1.20 g, 6.74 mmol) was added
and the mixture was heated at reflux for 4 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water and dried, then it was concentrated under reduced pressure, to give a 1:1 mixture of the title compounds 3a and 4a as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2S,3S)-bromide 3a (1.17 g, 43%), m.p. 198-201 °C, $\nu_{\max}^{\text{cm}^{-1}}$ 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820 and 715; $\delta_{\text{H}}$ 8.27 (d, $J = 8.8$ Hz, 2 H, ArH), 7.82-7.99 (m, 4 H, phth), 7.78 (d, $J = 8.8$ Hz, 2 H, ArH), 6.02 (d, $J = 11.2$ Hz, 1 H, $\alpha$-H) and 3.59 (s, 3 H, OMe); $m/z$ (ei) (%) 434/432 (M+, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40) and 76 (37) (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for C_{15}H_{13}BrN_{2}O_{6}: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2S,3R)-bromide 4a (1.07 g, 40%), m.p. 195-197 °C, $\nu_{\max}^{\text{cm}^{-1}}$ 1775, 1755, 1720, 1605, 1525, 1390, 1350, 855 and 720; $\delta_{\text{H}}$ 8.07 (d, $J = 8.7$ Hz, 2 H, ArH), 7.68-7.76 (m, 4 H, phth), 7.56 (d, $J = 8.7$ Hz, 2 H, ArH), 5.97 (d, $J = 8.7$ Hz, 1 H, $\beta$-H), 5.59 (d, $J = 8.7$ Hz, 1 H, $\alpha$-H) and 3.83 (s, 3 H, OMe); $m/z$ (ei) (%) 434/432 (M+, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28) and 76 (26) (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for C_{15}H_{13}BrN_{2}O_{6}: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide 4a was confirmed through X-ray crystallographic analysis. 

(RS)-N-tert-Butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide. To a suspension of (RS)-N-phthaloyl-p-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 cm$^3$), triethylamine (0.81 cm$^3$, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 cm$^3$, 5.86 mmol) was added. That mixture was stirred for 10 min, then tert-butylamine (0.61 cm$^3$, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C, $\nu_{\max}^{\text{cm}^{-1}}$ 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1344, 1220, 1088, 1016, 888, 874, 766 and 726; $\delta_{\text{H}}$ 8.03 (d, $J = 8.6$ Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, phth), 7.56 (d, $J = 8.7$ Hz, 2 H, ArH), 5.97 (d, $J = 10.3$ Hz, 1 H, $\beta$-H), 5.59 (d, $J = 10.3$ Hz, 1 H, $\alpha$-H) and 3.83 (s, 3 H, OMe); $m/z$ (ei) (%) 434/432 (M*, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28) and 76 (26) (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for C_{21}H_{21}N_{3}O_{5}: C, 63.8; H, 5.3; N, 10.6%).

(R)-N-tert-Butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide 10b. This compound was prepared from (R)-N-phthaloyl-p-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); $[\alpha]_{D}^{25} +177.0^{\circ}$ (c, 0.227 in CHCl$_3$).

(S)-N-tert-Butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide. This compound was prepared from (S)-N-phthaloyl-p-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); $[\alpha]_{D}^{21} -120.8^{\circ}$ (c, 0.418 in CHCl$_3$).

(2RS,3RS)-3-Bromo-N-tert-butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide and (2RS,3SR)-3-Bromo-N-tert-butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide. To a solution of (RS)-N-tert-butyl-N\textsuperscript{$\alpha$}-phthaloyl-p-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50
cm$^3$), N-bromosuccinimide (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h. while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3380, 3350, 2950, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720 and 700; m/z (fai) (%) 476/474 (M$^+$/H$^+$, 40%), 420/418 (20), 295 (30), 154 (100) and 136 (90) (Found: C, 53.1; H, 4.2; N, 8.9). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2RS,3SR)-3-bromo-N-tert-butyl-N°-phthaloyl-p-nitrophenylalaninamide. The 1 H and 13C NMR spectra of the mixture of diastereomers showed resonances for the (2RS,3RS)-isomer. $\delta$H 8.26 (d, J 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, phth), 7.55 (d, J 8.9 Hz, 2 H, ArH), 6.21 (br s, 1 H, NH), 6.18 (d, J 11.4 Hz, 1 H, $\beta$-H), 5.29 (d, J 11.4 Hz, 1 H, $\beta$-H) and 1.41 (s, 9 H, CMe3); $\delta$C 28.8, 49.1, 52.4, 62.7, 124.5, 124.6, 130.0, 130.1, 131.6, 148.3, 163.9 and 168.3. (2S,3S)-3-Bromo-N-tert-butyl-N°-phthaloyl-p-nitrophenylalaninamide and (2R,3S)-3-Bromo-N-tert-butyl-N°-phthaloyl-p-nitrophenylalaninamide. A 1:1 mixture of these compounds was prepared in quantitative yield from (S)-N-tert-butyl-N°-phthaloyl-p-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate. Treatment of (2S,3S)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester 3a with Silver Nitrate in Aqueous Acetone. To a solution of the bromide 3a (50 mg, 0.12 mmol) in acetone (3 cm$^3$), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 cm$^3$) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (Z)-p-nitrophenylanline derivative 15a as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 1780, 1720, 1600, 1530 and 1345; $\delta$H 8.16 (d, J 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, $\beta$-H), 7.92-7.83 (m, 4 H, phth), 7.55 (d, J 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); m/z (ei) (%) 352 (M$^+$, 90), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100) and 76 (73); m/z (ei) 352.068 (M$^+$) [Calc. for C$_{18}$H$_{12}$N$_2$O$_6$ (M$^+$) m/z 352.070]. Neither the alcohol 3b nor the alkene 14a were detected in the crude product.
A stereocontrolled route to chloramphenicol showed resonances for the (Z)-isomer 15a, identical to those described above, and signals for the (E)-isomer 14a. δH 8.26 (d, J 8.7 Hz, 2 H, ArH), 7.80-7.98 (m, 4 H, phth), 7.60 (d, J 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H) and 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-p-nitrophenylalanine derivative 3b as colourless needles (63%), after recrystallisation from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C; νmax/cm−1 3604, 3421, 1779, 1752, 1614, 1526, 1352 and 1182; δH 8.13 (d, J 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, phth), 7.54 (d, J 8.9 Hz, 2 H, ArH), 5.79 (dd, J 4.4 and 10.0 Hz, 1 H, β-H), 5.53 (d, J 4.4 Hz, 1 H, α-H), 5.34 (d, J 10.0 Hz, 1 H, OH) and 3.89 (s, 3 H, OMe); m/z (%): 371 (M+H+, 9), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33) and 77 (31).

(2RS,3S)-3-Hydroxy-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide. To a solution of a 1:1 mixture of (2RS,3RS)-3-bromo-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide and the (2RS,3SR)-isomer (265 mg, 0.56 mmol) in acetone (10 cm3) and water (10 cm3), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with saturated brine, then it was dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C; νmax/cm−1 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390 and 1110; δH 8.14 (d, J 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, phth), 7.54 (d, J 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, J 4.9 and 8.3 Hz, 1 H, β-H), 5.17 (d, J 4.9 Hz, 1 H, α-H), 4.93 (d, J 8.3 Hz, 1 H, OH) and 1.37 (s, 9 H, CMe3); δC 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 71.7, 59.9, 52.3 and 28.6; m/z (ei) (%): 412 (M+H+, 1), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100) and 204 (30) (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for C21H21N3O6: C, 61.3; H, 5.2; N, 10.2%).

(2R,3S)-3-Hydroxy-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide 3d. This compound was prepared from a 1:1 mixture of the bromides 3c and 4c, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; [α]D25 +84.1° (c, 0.453 in CHCl3). There was no indication of the presence of either of the alkenes 14b or 15b in the 1H NMR spectrum of the crude reaction mixture.

(2S,3R)-3-Hydroxy-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide. This compound was prepared from a 1:1 mixture of (2R,3R)- and (2R,3S)-3-bromo-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; [α]D20 -83.1° (c, 0.083 in CHCl3).

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone. A 1:1 mixture of the title bromides was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides 3c and 4c. Analysis of the crude reaction mixture by 1H NMR spectroscopy showed that the racemate of the alcohol 3a and the alkenes 14a and 15a were present in the ratio ca. 1:1:10.

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-tert-butylna-phthaloyl-p-nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone. The reaction of a 1:1 mixture of the title bromides, carried out as
described above for the reaction of the bromoester 3a. afforded an oil which was chromatographed. Elution afforded the nitrate 16 (19%), m.p. 192 °C (dec.); $\nu_{\text{max}}$cm$^{-1}$ 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1300, 1240, 1190 and 1110; $\delta_{\text{H}}$ 8.30 (d, 1 H, ArH), 7.77-7.92 (m, 4 H, phth), 7.77 (d, 1 H, ArH), 7.19 (d, 1 H, ArH), 5.89 (br s, 1 H, NH), 4.90 (d, 1 H, ArH), 4.90 (d, 1 H, ArH), 1.14 (s, 9 H, CMe3); $\delta_{\text{C}}$ 167.6, 163.1, 158.6, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2 and 28.3; m/z (ei) (%) 457 (M+H+, 30), 393 (15), 307 (40), 286 (100) and 260 (30). Continued elution gave (2RS,3SR)-3-hydroxy-N-tert-butyI-N-$\alpha$-phthaloyl-p-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes 14b or 15b in the $^1$H NMR spectrum of the crude product.

(2RS,3SR)-3-Hydroxy-p-nitrophenylalanine. A mixture of (2RS,3SR)-3-hydroxy-N-tert-butyI-N-$\alpha$-phthaloyl-p-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 cm$^3$) was heated at reflux for 5 h and stirred overnight at room temperature, before it was concentrated under reduced pressure. Water (10 cm$^3$) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 cm$^3$) and to that solution aniline (0.7 cm$^3$) in dichloromethane (10 cm$^3$) was added. The mixture was let stand at 4 °C for 24 h and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white powder (27 mg, 58%), m.p. 192-193 °C (dec.); $\nu_{\text{max}}$cm$^{-1}$ 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740 and 710; $\delta_{\text{H}}$ (CF$_3$CO$_2$D) 8.33 (d, 2 H, ArH), 7.74 (d, 2 H, ArH), 5.77 (d, 2 H, ArH) and 4.70 (d, 1 H, ArH); $\delta_{\text{C}}$ (D$_2$O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7 and 62.5; m/z (fab) (%) 227 (M+H$^+$). The $^1$H NMR spectral data for this compound is consistent with that reported.$^{14}$

(2R,3S)-3-Hydroxy-p-nitrophenylalanine 18. This compound was prepared from the alcohol 3d, as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (lit.$^{15}$ 174-176 °C); $\nu_{\text{max}}$cm$^{-1}$ 3365, 2920, 2850, 1760, 1710, 1680, 1590, 1530, 1470, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740 and 710; $\delta_{\text{H}}$ (CF$_3$CO$_2$D) 8.33 (d, 2 H, ArH), 7.74 (d, 2 H, ArH), 5.77 (d, 2 H, ArH) and 4.70 (d, 1 H, ArH); $\delta_{\text{C}}$ (D$_2$O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7 and 62.5; m/z (ei) (%) 227 (M+H$^+$). The $^1$H NMR spectral data for this compound is consistent with that reported.$^{14}$

(2S,3R)-3-Hydroxy-p-nitrophenylalanine. This compound was prepared from the (2S,3R)-3-hydroxy-N-tert-butyI-N-$\alpha$-phthaloyl-p-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; $[\alpha]_D$ -36.4° (c, 0.5 in H$_2$O).
A stereocontrolled route to chloramphenicol

(1), 260 (5) and 202 (100) (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for C_{17}H_{22}N_{2}O_{3}: C, 67.5; H, 7.3; N, 9.3%).

(R)-3-Bromo-N-tert-butyl-N-α-phthaloylvalinamide 5e. A mixture of N-bromosuccinimide (1.18 g, 6.6 mmol) and the amide 11b (1.33 g, 4.4 mmol) in carbon tetrachloride (60 cm³) was heated at reflux for 2 h, while it was irradiated with a 250 W mercury lamp. The mixture was then cooled to 0 °C and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound 5e as fine colourless needles. After recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; [α]D^{20} +11.6° (c, 3.03 in CHCl₃); νmax/cm⁻¹ 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080 and 720; δH (m, 4 H, phth), 5.28 (s, 1 H, α-H), 2.07 (s, 3 H, CH₃), 1.86 (s, 3 H, CH₃') and 1.30 (s, 9 H, CMe₃); δC (m, 30.5, 35.0, 35.4, 54.0, 67.7, 68.1, 125.8, 133.3, 136.6, 166.0 and 170.2; m/z (ei) (%) 381/383 (M⁺H⁺, 5), 380/382 (5), 279/381 (5), 365/367 (10), 325/327 (15), 308/310 (15) and 301 (100) (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for C_{17}H_{21}BrN_{2}O_{3}: C, 53.6; H, 5.6; N, 7.3%).

Treatment of (R)-3-Bromo-N-phthaloylvaline Methyl Ester 5a with Silver Nitrate in Aqueous Acetone. The reaction of the bromide 5a,¹² carried out at room temperature for 14 h, but otherwise as described above for the reaction of the nitröphenylalanine derivative 3a, afforded an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative 12a (40 mg, 8%), m.p. 81-82 °C; [α]D^{20} 7.40-8.10 (m, 4 H, phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, CH₃) and 1.88 (s, 3 H, CH₃') (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for C_{14}H_{13}NO_{4}: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the α,γ-dehydrovaline derivative 13a (0.15 g, 34%); νmax/cm⁻¹ 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1293, 1245, 1203, 1113, 915 and 717; δH 7.91-7.92 (m, 4 H, phth), 5.38 (br s, 1 H, γ-H, 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe) and 1.92 (s, 3 H, β-CH₃); m/z (ei) (%) 259 (M⁺, 8), 227 (20) and 200 (100). Further elution gave the α-hydroxyvaline derivative 5b (0.21 g, 43%), m.p. 86-87 °C; νmax/cm⁻¹ 3544, 1767, 1725, 1275 and 717; δH 7.89-7.73 (m, 4 H, phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H, NH), 5.23 (s, 1 H, α-H), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe) and 1.92 (s, 3 H, β-CH₃); δC (m, 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5 and 22.8; m/z (ei) (%) 300 (M⁺, 5) and 200 (100) (Found: C, 69.6; H, 5.5; N, 5.1. Calc. for C_{14}H_{15}NO_{5}: C, 65.6; H, 5.5; N, 5.1%). Analysis of the crude reaction mixture by ¹H NMR spectroscopy showed the alcohol 5b and the alkenes 12a and 13a to be present in the ratio ca. 3.5 : 1 : 3.5.

Treatment of (R)-3-Bromo-N-tert-butyl-N-α-phthaloylvalinamide 5e with Silver Nitrate in Aqueous Acetone. The reaction of the bromide 5e, carried out as described above for the reaction of the ester 5a, afforded an oil which was chromatographed. Elution gave the β,γ-dehydrovaline derivative 13b as a colourless oil (26%); νmax/cm⁻¹ 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475 and 1385; δH 7.89-7.73 (m, 4 H, phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H), 5.23 (s, 1 H), 5.21 (s, 1 H), 1.89 (s, 3 H, CH₃) and 1.43 (s, 9 H, CMe₃); δC (m, 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5 and 22.8; m/z (ei) (%) 300 (M⁺, 5) and 200 (100) (Found: C, 68.0; H, 7.0; N, 9.0. Calc. for C_{17}H_{22}N_{2}O_{3}: C, 68.0; H, 6.7; N, 9.3%). Further elution afforded the alcohol 5d, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%), m.p. 135-136 °C; νmax/cm⁻¹ 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724 and 646; δH 7.84-7.79 (m, 2 H, phth), 7.73-7.69 (m, 2 H, phth), 7.30 (br s, 1 H, NH), 4.61 (s, 1 H, α-H), 4.25 (br s, 1 H, OH),...
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1.41 (s, 3 H, CH₃), 1.30 (s, 9 H, CMe₃) and 1.22 (s, 3 H, CH₃); m/z (ei) (%) 318 (M⁺, 50), 300 (10), 259 (50), 201 (100), 187 (100) and 160 (95) (Found: C, 64.3; H, 7.2; N, 8.7. Calc. for C₁₇H₂₂N₂O₄: C, 64.1; H, 7.0; N, 8.8%). The structure of the alcohol Sd was confirmed through X-ray crystallographic analysis. Analysis of the crude reaction mixture by ¹H NMR spectroscopy showed the alcohol Sd and the alkene 13b were present in the ratio ca. 2 : 1.

Competitive Hydrolysis Reactions of the Bromides 5a and 5c. The relative rates of reaction of the bromides 5a and 5c with silver nitrate were determined by treating an equimolar ratio of the substrates at a concentration of approximately 0.1 mM in aqueous acetone (1:1, v/v) with the silver salt (1.4 equiv.) at room temperature, in the presence of N-tert-butyldimethylamine (0.5 equiv.) as an internal standard. Aliquots of the reaction mixture were sampled at intervals and worked up as described for the preparative studies, then analysed by ¹H NMR spectroscopy. Integration of peaks characteristic of the residual bromides 5a and 5c and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. Relative rates of duplicate experiments varied by less than 10%.

ACKNOWLEDGEMENT. This work was supported by a grant from the Australian Research Council.

REFERENCES

1 B. Capon, Quart. Rev., 1964, 45.

(Received in UK 6 March 1996; accepted 21 March 1996)
Appendix 2


Table 1. Relative Rates of Reaction of the Amino Acid Derivatives 1α-f and 3α-f

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* Relative rates of reaction determined in duplicate experiments varied by less than 20%. 1 Reaction with NBS in CCl4 at reflux under N2, initiated using a 250 W mercury lamp. 2 Data refer to reaction of the three diastereomers in each case. The diastereoselectivity was less than 1:1 in the reactions of 3αa, 3αb, and 3αc and low in the reactions of 3αd, 3αe, and 3αf, but not possible to accurately quantify in the latter cases due to decomposition of the α,β-unsaturated radicals. 3 Reaction with Ph3SnH in benzene at reflux under N2, initiated using either AIBN or a 250 W mercury lamp. 4 Assigned as unry within each column.

The relative activity of 3α-f is similar to that previously reported for radical bromination of series of substituted toluene derivatives, 5 with 1αd and 1αe reacting faster than the corresponding nitro-substituted compounds 1αc and 1αf, respectively. This is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient center at the site of hydrogen abstraction. 6 In the processes involving Ph3SnH, the relative rates of reaction reflect the ease with which 3α-f transfer a bromine atom to the triphenylmethyl radical. In these processes, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds 3αf reacting much faster than 3αd, 3αe, and 3αf, the relative activity of 3α-f is to be expected, however, as the transition state for a reaction of this type involves transfer of the halogen to the nucleophilic stannyl radical with the development of an electron rich center at the site of halogen abstraction. 7

Whether the carboxyl group is protected as an ester or an amide has very little effect on the relative rates of reaction of 3α-f with Ph3SnH, yet in the reactions with NBS, each of the amides 1b. 1d, and 1f reacted approximately 5 times faster than the corresponding ester 1αa. 1αe, and 1αf, respectively. These effects are not consistent with steric constraints resulting from the greater bulk of the amino substituent relative to the ester group, as such factors would be expected to be at least as severe in the reactions of 3α-f, where the large bromine atom is transferred to the bulky triphenylmethyl radical. The most obvious interpretation of the results is that the amido substituent of 1b, 1d, and 1f, being more electron rich than the ester group of 1αa, 1αe, and 1αf, facilitates reaction by interacting directly with the electron deficient center in the bromination transition state (Figure 1). The analogous effect would not be expected in the reactions of 3α-f, where any interaction between the carboxyl group and the electron rich center developing in the transition state would be unfavorable and would therefore be avoided.

Consistent with this interpretation, there was little diastereoselectivity in the reactions of 3α-f with Ph3SnH, indicating that the energetics of these processes are little affected by geometrical constraints on interactions between substrates. To examine the possibility of stereocontrol in the hydrogen transfer

Provided the opportunity to probe for anchimeric assistance in atom transfer reactions.

The relative rates of reaction of 1α-f to give 3α-f were determined in standard competitive experiments, by measuring the relative rates of consumption of the starting materials and of formation of the products, and in a similar manner the relative

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References:


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reactions, the deuterides 4a and 4b were treated with NBS. The (2S,3S)-deuteride 4a gave a 1:1 mixture of the diastereomers of 5, with each diastereomer containing 79% deuterium, whereas the diastereomer 4b gave 5, with 66% deuterium retention.

These results correlate with a deuterium isotope effect of 2.7 for the hydrogen atom transfer and a stereoselectivity of 1.4 for abstraction of the pro-R hydrogen. This selectivity is not simply a result of steric effects. The 1H NMR spectra of 4a and 4b and the respective coupling constants, J_{HH}, of 9.8 and 5.8 Hz indicate that the preferred conformation of the S-enantiomer of 1b is A. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-R-S-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-S hydrogen, as this site is the less hindered to the approach of the bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups. The stereoselectivity is consistent with neighboring group participation by the amido substituent. Considering the conformations B and C of 1b which have the correct orientation to undergo hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient center, the conformer B would be preferred on steric grounds and stereoselective loss of the pro-R hydrogen from this conformer would be expected.

Several alternative explanations for the kinetic effects observed in the reactions of 1a-f and 3a-f were considered, but these are inconsistent with the stereoselectivity observed in the reactions of 4a and 4b. In principal, the phthalimido group of 1a-f could be involved in neighboring group participation, but this would be expected to result in stereoselective loss of the pro-S hydrogen from 1b. This would occur from the conformer A, whereas loss of the pro-R hydrogen would involve the conformer C. Not only is the conformer C of much higher ground-state energy, reaction via that conformer would also involve the development of additional steric interactions between

the phenyl and amido substituents in the reaction transition state. Another possible interpretation of the results is that the amido substituent of 1b, 1d, and 1f coordinates to the bromine atom involved in the hydrogen atom abstraction ([Br::NH(δBu)COR]) thereby facilitating reaction. Similar three-electron-bonded species have been proposed as intermediates, for example, in the reaction of amino acids with hydroxyl radical ([HO::NH-C(H)COR]) and in the radical-induced oxidation of sulfides ([RR'S::OCOR]).

A third alternative is that the reactions of 1b, 1d, and 1f proceed via the corresponding N-bromamides and involve intramolecular 1,4-hydrogen transfer to the amido radical. In these cases, stereoselective loss of the pro-S hydrogen from 1b would be expected, however, as this would involve less steric interactions between the phenyl and phthalimido substituents. To confirm this expectation, the N-bromamides of 4a and 4b were prepared by treatment with tert-butylhypochlorite and photolyzed at reflux in CCl₄. The bromoamide derived from the (2S,3S)-deuteride 4a gave a mixture of the diastereomers of 5, with each diastereomer containing 25% deuterium, whereas the bromoamide of the diastereomer 4b gave 5, with 15% deuterium retention. These results correlate with a deuterium isotope effect of 1.5 for the intramolecular 1,4-hydrogen atom transfer and a stereoselectivity of 3.8 for abstraction of the pro-S hydrogen. Clearly this stereochemical outcome is different to that observed in the reactions of 4a and 4b with NBS and precludes the involvement of amylid radicals as intermediates in the reactions of 1b, 1d, and 1f with NBS.

In conclusion, all of the above evidence indicates that the reactions of 1a-f with NBS involve amionic assistance in hydrogen atom abstraction by the bromine atom, through neighboring group participation by an adjacent protected carboxyl group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously. While 1,3-participation occurs in reactions involving either hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, and is also reflected in the bridging of the product radicals as determined by EPR spectroscopic studies, neighboring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilization of electron deficient reaction transition states.

JA953021F

Appendix 3

Crystal structure of (S)-3-hydroxy-N-tert-butyl-N\(^\alpha\)-phthaloylvalinamide, C\(_{11}\)H\(_{22}\)N\(_2\)O\(_4\)

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C. A. Hutton and E. R. T. Tiekink
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Received July 16, 1995. CSD-No. 402234

Source of material: see ref. 1; m. pt 408 K - 409 K.

The structure features both intra- and inter-molecular H bonding contacts. The N(1)H···O(3) separation is 2.04(1) Å and in the lattice O(3)H···O(1) is 1.88(3) Å such that O(1)···O(3) is 2.739(3) Å.

Table 1. Parameters used for the X-ray data collection

Table 2. Final atomic coordinates and displacement parameters (in Å\(^2\))

Table 3. Final atomic coordinates and displacement parameters (in Å\(^2\))
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Appendix 4

Crystal structure of (2S,3S)-4-hydroxyvaline 3a.
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### Bond Angles (Å) for (2S,3S)-4-hydroxyvaline 3a.

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<td>C(1)</td>
<td>O(2)</td>
<td>126.0(5)</td>
</tr>
<tr>
<td>O(2)</td>
<td>C(1)</td>
<td>C(2)</td>
<td>117.1(5)</td>
</tr>
<tr>
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<td>C(2)</td>
<td>C(3)</td>
<td>114.1(5)</td>
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<tr>
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<td>C(4)</td>
<td>112.8(4)</td>
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<td>C(5)</td>
<td>108.8(5)</td>
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<tr>
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<td>O(3)</td>
<td>H(11)</td>
<td>107(4)*</td>
</tr>
<tr>
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<td>N(1)</td>
<td>H(2)</td>
<td>115(4)*</td>
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<tr>
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<td>N(1)</td>
<td>H(2)</td>
<td>106(5)*</td>
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<td>N(1)</td>
<td>H(3)</td>
<td>107(5)*</td>
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<td>C(2)</td>
<td>H(4)</td>
<td>105(3)*</td>
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<td>C(3)</td>
<td>H(5)</td>
<td>106(3)*</td>
</tr>
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<td>C(4)</td>
<td>H(7)</td>
<td>109(3)*</td>
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<td>H(7)</td>
<td>107(3)*</td>
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<tr>
<td>C(3)</td>
<td>C(4)</td>
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<td>C(5)</td>
<td>H(10)</td>
<td>118(5)*</td>
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</table>

* restrained during refinement
Appendix 5

Crystal structure of (2S,3R)-3-bromo-N-phthaloyl-p-nitrophenylalanine methyl ester 71a.

The structure is shown to be S at both C(2) and C(3). The dihedral angle between the C(41)-C(46) and phthaloyl groups is 11.7° and a small twist about the C(44)-N(44) bond is noted: C(43)/C(44)N(44)/O(44) is 13(1)°.

The final atomic coordinates and displacement parameters are given in Table 1.

---

**Table 1: Final atomic coordinates and displacement parameters (in \(\text{\AA}^2\))**

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<th>z</th>
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<th>U22</th>
<th>U33</th>
<th>U12</th>
<th>U13</th>
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<td>0.4113</td>
<td>0.0965</td>
<td>0.0393</td>
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<td>-0.0003</td>
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<td>0.21577</td>
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<td>0.0404</td>
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</tr>
<tr>
<td>O(2)</td>
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<td>-0.0223</td>
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</table>

**Appendices**

Appendix 5

Crystal structure of (2S,3R)-3-bromo-N-phthaloyl-p-nitrophenylalanine methyl ester 71a.
Appendice s

240

Append ix 6
Crystal structure of (2RS,3SR)-3-bromo-N-tert-butyl-NlCphthaloyl-p-nitropheny lalaninamide
Para.me1en used f()(' the X-ny dara coUection
Crysta!:
Wavelength:
µ:
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Scan mode:

coloriess bioc:k. size 0.07 x 0.16 x 0.36 mm
Mo Ka racfuuion (0.71073 A)
19.J.5 cm- 1
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eu'28
293 K
50°
4058
Fo > 6 CJ(Fo )
271
teXsan

T _ _ ,;
28mu:
N(hkl)..,.,.,_;

Critenon for Fo:
N(param)r,fi,w,f.

Program:

Final atomic coordinateS and displacemem parameters (in
Atom
H(2)
H(3')
H(3)
H(4cl
The dihedral angle between the C(3 l }-C(36) and phthaloyl groups
is 110.6°. Hydrogen bonding the lattice occurs between the N(3}-H
and 0(28) atoms such that H(3)···O(28) is 2.21 A and N(3)···O(28)
is 3.16(1) A.

C21H2oBrN3O5, monocliµic. P121/n I (No. 14), a =10.900(5) A.
b =l l.189(6) A, c =18.285(4) A, ~ =103. 10(2) 0 • V =2172:ifA. 3,
Z=4, R(F) =0.047. Rw(F) =0.037.

Atom
8r(3)

om

Site
~

4e

0(21)
0(28)
0(34)
N(2)

~

N(3)
N(34)
C(l)
C(2)
C(3)
C(4)
C(4a)
C(4b)
C(4c)
C(21)
C(22)
C(23)
C(24)
C(2.5)

~

026)
C(27)
C(28)
C(31)
C(32)
C(33)
C(34)
C(35)
C(36)

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--0.3736(7)
--0.1494<9)
--0.0976(7)
0..226(1-)
--0.1.507(7)
--0.4719(8)
0.177(2)
--0.378(1)
--0.267( I)
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--0.589(1)
--0.563(1)
--0.6575(9)
--0.6695(9)
--0.100( 1)
0.013(1)
0.099(2)
0. 192(2)
0.206(2)
0. 113(1)
0.027(1)
--0.077(1)
--0. 154(1)
--0.093(2)
0.01()(2)
0.0.58(1)
0.002(2)
--0.104{'2)

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--0.2462(8)
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--0.1123(7)
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--0.032(1)
--0.064( 1)
--0.029(1)
--0.100 l(9)
--0.100(1)
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--0.088(2)
0.026(2)
0.081(1)
0.01.5(1)
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--0.049(2)
0.048(1)
0.034(1)
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--0.62516
--0.52359
--0.64110
0.09440
0.2516.5
0.27409
0.13103
--0.12542
0.0.5121
0.03.50.5
--0.14418

~
~

H(4d)

~

4e

H(4f)
H(4g)
H(4h)
H(4i)
H(4a)
H(4b)
HC:?.3)
H(24)
HC25)
H(26)
H(32)
H(33)
H<3.5)
H(36)

.r

~

H(4e)

Final atomic coordinates and displacement parameters (in

Site

~

4e
~

4e
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4e
4e
4e
4e
4e
~
~

4e
~

_v

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--0.18462
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--0.03443
0.08314
0.02175
0.01249
--0.21079
--0.20537
--0.28172
--0. 17.503
--0.09037
--0.24695
--0. l '.!344
0.07115
0.16.55.5
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0.10325
--0.25429
--0.13138

.

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U;YJ

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--0.59803
--0.7 1652
--0.71540
--0.78784
--0.78710
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--0.57853
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0.09406
0.09801
0.1 0167
0. 10167
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0.09288
0.12685
0.09801
0.09801
0.09207
0.09095
0.10727
0 .0784
0.07925
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0.09429

Un

Un

A2)
U11

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0.068(9)

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0.048(7)
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0.06( 1)
0.13(1)
0.10(2)
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0.053(8)
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0.053(7)
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0.016(8)
0.022(7)
0.0.59(8)
0.006(8)
0.022(7)
0.037(8)
0.035{7)
0.07(1)
0.04(1)
0.014(9)
0.033{7)
0.029(7)
0.032(6)
0.02.5(6)
0.020(8)
0.020(8)
0.027(7)
0.05(1)
0.041(9)

~ -004( I)

--0.029(.5)
0.004(6}

0.013(5>
0..03{1)
0.013(7)
--0.012(.5)
0.06(2)
0.011(8)
--0.002(9)
--0.004(9)
--0.006(6)
--0.001(8)
--0.023(8)
--0.016(7)
0.007(9)
0.004<8)
0.02(1)
0.02(2)
--0.05(2)
--0.029<9)
--0.009(7)
0.00(1)
--0.0Hl)
--0.0 HI)
0.00(1)
0.02(1)
0.02(1)
--0.00( I)


Appendix 7

Competitive reactions of the phenylalanine derivatives 18a, 18b, 20a and 20b with silver nitrate in aqueous acetone.

<table>
<thead>
<tr>
<th>Compound</th>
<th>18a</th>
<th>18b</th>
<th>55 + 56</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
<td>α-H</td>
</tr>
<tr>
<td>t0</td>
<td>2.529</td>
<td>0.853</td>
<td>4.147</td>
<td>5.353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1</td>
<td>2.226</td>
<td>0.806</td>
<td>0.387</td>
<td>1.452</td>
<td>2.081</td>
<td>5.952</td>
</tr>
<tr>
<td>log(t0/t1)</td>
<td>0.055</td>
<td>0.025</td>
<td>0.456</td>
<td>0.410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>12</td>
<td>6</td>
<td>65</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>66</td>
<td>24</td>
<td>11</td>
<td>15</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>% accounted for</td>
<td>101</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_rel (Ag+/H2O)</td>
<td>2.2</td>
<td>1.0</td>
<td>18.2</td>
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</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>18a</th>
<th>18b</th>
<th>55 + 56</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
</tr>
</thead>
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<td>1H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
<td>α-H</td>
</tr>
<tr>
<td>t0</td>
<td>1.450</td>
<td>0.500</td>
<td>2.333</td>
<td>3.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1</td>
<td>1.215</td>
<td>0.467</td>
<td>0.359</td>
<td>0.720</td>
<td>0.963</td>
<td>3.785</td>
</tr>
<tr>
<td>log(t0/t1)</td>
<td>0.077</td>
<td>0.030</td>
<td>0.510</td>
<td>0.493</td>
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<td></td>
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<tr>
<td>% Reaction</td>
<td>16</td>
<td>7</td>
<td>69</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>62</td>
<td>24</td>
<td>18</td>
<td>14</td>
<td>18</td>
<td>71</td>
</tr>
<tr>
<td>% accounted for</td>
<td>104</td>
<td></td>
<td>103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_rel (Ag+/H2O)</td>
<td>2.6</td>
<td>1.0</td>
<td>17.0</td>
<td>16.4</td>
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<table>
<thead>
<tr>
<th>Compound</th>
<th>18a</th>
<th>18b</th>
<th>55 + 56</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
<td>α-H</td>
</tr>
<tr>
<td>t0</td>
<td>1.938</td>
<td>0.656</td>
<td>3.219</td>
<td>4.500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1</td>
<td>1.600</td>
<td>0.588</td>
<td>0.495</td>
<td>1.125</td>
<td>1.463</td>
<td>5.625</td>
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<tr>
<td>log(t0/t1)</td>
<td>0.083</td>
<td>0.048</td>
<td>0.457</td>
<td>0.488</td>
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<td></td>
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<tr>
<td>% Reaction</td>
<td>17</td>
<td>10</td>
<td>65</td>
<td>67</td>
<td></td>
<td></td>
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<tr>
<td>% final</td>
<td>62</td>
<td>23</td>
<td>19</td>
<td>15</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>% accounted for</td>
<td>104</td>
<td></td>
<td>107</td>
<td></td>
<td></td>
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</tr>
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Appendix 8

Competitive reactions of the valine derivatives 33 and 73 with silver nitrate in aqueous acetone.

<table>
<thead>
<tr>
<th>Compound</th>
<th>33</th>
<th>34</th>
<th>38 + 98</th>
<th>73</th>
<th>111</th>
<th>112</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1) H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe(_3)</td>
<td>CMe(_3)</td>
<td>CMe(_3)</td>
</tr>
<tr>
<td>(t^0)</td>
<td>2.941</td>
<td>2.486</td>
<td>0.073</td>
<td>0.065</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>(t^1)</td>
<td>9.941</td>
<td>4.000</td>
<td>0.395</td>
<td>0.405</td>
<td>5.4</td>
<td>6.2</td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>14</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>% final</td>
<td>85</td>
<td>1</td>
<td>3</td>
<td>40</td>
<td>34</td>
<td>92</td>
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<tr>
<td>% accounted for</td>
<td>89</td>
<td>2</td>
<td>3</td>
<td>39</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>(k_{rel} (\text{Ag}^+/\text{H}_2\text{O}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Compound</th>
<th>33</th>
<th>34</th>
<th>38 + 98</th>
<th>73</th>
<th>111</th>
<th>112</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1) H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe(_3)</td>
<td>CMe(_3)</td>
<td>CMe(_3)</td>
</tr>
<tr>
<td>(t^0)</td>
<td>2.087</td>
<td>1.796</td>
<td>0.070</td>
<td>2.889</td>
<td>2.556</td>
<td>1.278</td>
</tr>
<tr>
<td>(t^1)</td>
<td>7.348</td>
<td>2.889</td>
<td>0.405</td>
<td>61</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>14</td>
<td>1</td>
<td>3</td>
<td>39</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>% final</td>
<td>86</td>
<td>2</td>
<td>3</td>
<td>39</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>% accounted for</td>
<td>91</td>
<td>2</td>
<td>3</td>
<td>39</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>(k_{rel} (\text{Ag}^+/\text{H}_2\text{O}))</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 9

Competitive reaction of the nitrophenylalanine derivatives 71a, 71b, 72a and 72b with silver sulfate in aqueous acetone.

<table>
<thead>
<tr>
<th>Compound</th>
<th>71b</th>
<th>71a</th>
<th>114</th>
<th>72b</th>
<th>72a</th>
<th>117</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMé$_3$</td>
<td>CMé$_3$</td>
<td>α-H</td>
</tr>
<tr>
<td>$t^0$</td>
<td>0.554</td>
<td>0.649</td>
<td></td>
<td>1.987</td>
<td>2.216</td>
<td></td>
</tr>
<tr>
<td>$t^1$</td>
<td>0.230</td>
<td>0.027</td>
<td>0.014</td>
<td>0.689</td>
<td>0.635</td>
<td>1.635</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.382</td>
<td>1.381</td>
<td></td>
<td>0.460</td>
<td>0.543</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>58</td>
<td>96</td>
<td></td>
<td>65</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>16</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>% accounted for</td>
<td>22</td>
<td></td>
<td></td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (Ag$^+/H_2O$)</td>
<td>1.0</td>
<td>3.6</td>
<td></td>
<td>1.2</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>71b</th>
<th>71a</th>
<th>114</th>
<th>72b</th>
<th>72a</th>
<th>117</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMé$_3$</td>
<td>CMé$_3$</td>
<td>α-H</td>
</tr>
<tr>
<td>$t^0$</td>
<td>0.694</td>
<td>0.861</td>
<td></td>
<td>2.222</td>
<td>2.514</td>
<td></td>
</tr>
<tr>
<td>$t^1$</td>
<td>0.400</td>
<td>0.046</td>
<td>0.015</td>
<td>1.446</td>
<td>1.554</td>
<td>1.138</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.240</td>
<td>1.270</td>
<td></td>
<td>0.187</td>
<td>0.209</td>
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<tr>
<td>% Reaction</td>
<td>42</td>
<td>95</td>
<td></td>
<td>34</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>26</td>
<td>3</td>
<td>1</td>
<td>31</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>% accounted for</td>
<td>30</td>
<td></td>
<td></td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (Ag$^+/H_2O$)</td>
<td>1.3</td>
<td>6.8</td>
<td></td>
<td>1.0</td>
<td>1.1</td>
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Appendix 10

Competitive reactions of the phenylalanine derivatives 20a and 20b with silver nitrate in deuterium oxide and acetone.

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
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</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t⁰</td>
<td>1.588</td>
<td>2.000</td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>0.784</td>
<td>1.081</td>
<td>1.973</td>
</tr>
<tr>
<td>log(t⁰/t¹)</td>
<td>0.307</td>
<td>0.267</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>51</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>22</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>% accounted for</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k₆0 (Ag⁺/H₂O)</td>
<td>1.1</td>
<td>1.0</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t⁰</td>
<td>1.957</td>
<td>2.486</td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>1.313</td>
<td>1.792</td>
<td>1.583</td>
</tr>
<tr>
<td>log(t⁰/t¹)</td>
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<tr>
<td>% Reaction</td>
<td>33</td>
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<td></td>
</tr>
<tr>
<td>% final</td>
<td>30</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>% accounted for</td>
<td>106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k₆0 (Ag⁺/H₂O)</td>
<td>1.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>20a</td>
<td>20b</td>
<td>60</td>
</tr>
<tr>
<td>----------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>$^1$H NMR signal</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
</tr>
<tr>
<td>$t^0$</td>
<td>1.106</td>
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<tr>
<td>$t^1$</td>
<td>0.360</td>
<td>0.500</td>
<td>1.740</td>
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<tr>
<td>log($t^0$/$t^1$)</td>
<td>0.487</td>
<td>0.452</td>
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<tr>
<td>% Reaction</td>
<td>67</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>14</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>% accounted for</td>
<td>103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ ($\text{Ag}^+/\text{H}_2\text{O}$)</td>
<td>1.1</td>
<td>1.0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
</tr>
<tr>
<td>$t^0$</td>
<td>1.106</td>
<td>1.416</td>
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<td>0.597</td>
<td>1.705</td>
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<td>0.430</td>
<td>0.388</td>
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<tr>
<td>% Reaction</td>
<td>63</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>16</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>% accounted for</td>
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<tr>
<td>$k_{rel}$ ($\text{Ag}^+/\text{H}_2\text{O}$)</td>
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Appendix 11

Competitive reactions of the phenylalanine derivatives 17 and 19 with NBS.

<table>
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<th>18a + 18b</th>
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<td>CMe₃</td>
<td>CMe₃</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>t₀</td>
<td>1.694</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>0.381</td>
<td>0.885</td>
<td>0.363</td>
<td>0.071</td>
</tr>
<tr>
<td>log(t⁰/t¹)</td>
<td>0.648</td>
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<td></td>
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</tr>
<tr>
<td>% reaction</td>
<td>78</td>
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<td></td>
</tr>
<tr>
<td>% final</td>
<td>22</td>
<td>52</td>
<td>73</td>
<td>14</td>
</tr>
<tr>
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<td>88</td>
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<tr>
<td>k_{rel} (NBS)</td>
<td>4.8</td>
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<td></td>
<td>1</td>
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<table>
<thead>
<tr>
<th>compound</th>
<th>19</th>
<th>20a + 20b</th>
<th>17</th>
<th>18a + 18b</th>
</tr>
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<tbody>
<tr>
<td>1H NMR signal</td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>t₀</td>
<td>2.657</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>1.360</td>
<td>1.180</td>
<td>0.700</td>
<td>0.160</td>
</tr>
<tr>
<td>log(t⁰/t¹)</td>
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<td></td>
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<tr>
<td>% reaction</td>
<td>49</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>51</td>
<td>44</td>
<td>88</td>
<td>20</td>
</tr>
<tr>
<td>% accounted for</td>
<td>96</td>
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<td></td>
<td>108</td>
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<td>k_{rel} (NBS)</td>
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<table>
<thead>
<tr>
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<th>19</th>
<th>20a + 20b</th>
<th>17</th>
<th>18a + 18b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>t₀</td>
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<tr>
<td>t¹</td>
<td>0.825</td>
<td>0.794</td>
<td>0.421</td>
<td>0.063</td>
</tr>
<tr>
<td>log(t⁰/t¹)</td>
<td>0.339</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>54</td>
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<td>15</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>46</td>
<td>44</td>
<td>85</td>
<td>13</td>
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<td></td>
<td></td>
<td>98</td>
</tr>
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<td>k_{rel} (NBS)</td>
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Competitive reactions of the tyrosine derivatives 79a and 79b with NBS.

<table>
<thead>
<tr>
<th>Compound</th>
<th>79a</th>
<th>80a + 80b</th>
<th>79b</th>
<th>81a + 81b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1H NMR signal</strong></td>
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<td>OMe</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
<td>0.905</td>
<td></td>
<td>2.337</td>
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</tr>
<tr>
<td>t¹</td>
<td>0.600</td>
<td>0.173</td>
<td>0.600</td>
<td>1.433</td>
</tr>
<tr>
<td>log(t₀/t¹)</td>
<td>0.179</td>
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<tr>
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<td>19</td>
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<tr>
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</tr>
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<td>k_rel (NBS)</td>
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Competitive reactions of the nitrophenylalanine derivatives 78a and 78b with NBS.

<table>
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<tr>
<th>compound</th>
<th>78a</th>
<th>71a + 71b</th>
<th>78b</th>
<th>72a + 72b</th>
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</thead>
<tbody>
<tr>
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<td>OMe</td>
<td>OMe</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>τ₀</td>
<td>0.569</td>
<td>1.466</td>
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<tr>
<td>τ₁</td>
<td>0.410</td>
<td>0.128</td>
<td>0.231</td>
<td>0.974</td>
</tr>
<tr>
<td>log(τ₀/τ₁)</td>
<td>0.142</td>
<td>0.803</td>
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<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>28</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>72</td>
<td>22</td>
<td>16</td>
<td>66</td>
</tr>
<tr>
<td>% accounted for</td>
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<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_rel (NBS)</td>
<td>1</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
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<th>compound</th>
<th>78a</th>
<th>71a + 71b</th>
<th>78b</th>
<th>72a + 72b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>τ₀</td>
<td>0.339</td>
<td>0.957</td>
<td></td>
<td></td>
</tr>
<tr>
<td>τ₁</td>
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<td>0.119</td>
<td>0.670</td>
</tr>
<tr>
<td>log(τ₀/τ₁)</td>
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<td>0.905</td>
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<td></td>
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<tr>
<td>% reaction</td>
<td>35</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>65</td>
<td>19</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>% accounted for</td>
<td>85</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_rel (NBS)</td>
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<td>4.9</td>
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Competitive reactions of the phenylalanine derivatives 17 and the nitrophenylalanine derivative 78b with NBS.

<table>
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<th>compound</th>
<th>17</th>
<th>18a + 18b</th>
<th>78b</th>
<th>72a + 72b</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe₃</td>
<td>CMe₃</td>
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<tr>
<td>t₀</td>
<td>0.361</td>
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<td>0.889</td>
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</tr>
<tr>
<td>t¹</td>
<td>0.125</td>
<td>0.229</td>
<td>0.469</td>
<td>0.313</td>
</tr>
<tr>
<td>log(⁰/t¹)</td>
<td>0.461</td>
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<td>0.278</td>
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<tr>
<td>% reaction</td>
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<td></td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>36</td>
<td>63</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>% accounted for</td>
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<td></td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>k_rel (NBS)</td>
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<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>compound</th>
<th>17</th>
<th>18a + 18b</th>
<th>78b</th>
<th>72a + 72b</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
<td>0.393</td>
<td></td>
<td>0.617</td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>0.189</td>
<td>0.171</td>
<td>0.394</td>
<td>0.171</td>
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<tr>
<td>log(⁰/t¹)</td>
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<td>0.195</td>
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</tr>
<tr>
<td>% reaction</td>
<td>52</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>48</td>
<td>44</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>% accounted for</td>
<td>92</td>
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<td>92</td>
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<td>k_rel (NBS)</td>
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Competitive reactions of the tyrosine derivative 79a and the phenylalanine derivative 19 with NBS.

<table>
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<tr>
<th>compound</th>
<th>79a</th>
<th>80a + 80b</th>
<th>19</th>
<th>20a + 20b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>OMe</td>
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<td>CMe3</td>
<td>CMe3</td>
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<td>$t^0$</td>
<td>1.378</td>
<td>1.120</td>
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<td>1.070</td>
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<tr>
<td>$t^1$</td>
<td>0.240</td>
<td>0.425</td>
<td>1.810</td>
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<tr>
<td>log($t^0/t^1$)</td>
<td>0.090</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>19</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>81</td>
<td>17</td>
<td>38</td>
<td>64</td>
</tr>
<tr>
<td>% accounted for</td>
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<td></td>
<td>102</td>
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</tr>
<tr>
<td>$k_{rel}$ (NBS)</td>
<td>1</td>
<td></td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>compound</th>
<th>79a</th>
<th>80a + 80b</th>
<th>19</th>
<th>20a + 20b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
</tr>
<tr>
<td>$t^0$</td>
<td>0.603</td>
<td>0.467</td>
<td>1.863</td>
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</tr>
<tr>
<td>$t^1$</td>
<td>0.121</td>
<td>0.577</td>
<td>1.165</td>
<td></td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.111</td>
<td></td>
<td>0.509</td>
<td></td>
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<tr>
<td>% reaction</td>
<td>23</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>77</td>
<td>20</td>
<td>31</td>
<td>63</td>
</tr>
<tr>
<td>% accounted for</td>
<td>97</td>
<td></td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (NBS)</td>
<td>1</td>
<td></td>
<td>4.6</td>
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### Appendix 12

Competitive reactions of the nitrophenylalanine derivatives $71\text{a}$, $71\text{b}$, $72\text{a}$ and $72\text{b}$ with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$71\text{b}$</th>
<th>$71\text{a}$</th>
<th>$78\text{a}$</th>
<th>$72\text{b}$</th>
<th>$78\text{b}$</th>
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</thead>
<tbody>
<tr>
<td>$^1\text{H NMR signal}$</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
</tr>
<tr>
<td>$t^0$</td>
<td>3.389</td>
<td>2.667</td>
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<tr>
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<td>2.346</td>
<td>1.192</td>
<td>1.795</td>
<td>3.308</td>
<td>1.577</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.160</td>
<td>0.350</td>
<td>0.229</td>
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<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>31</td>
<td>55</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>38</td>
<td>20</td>
<td>30</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>88</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>1.0</td>
<td>2.2</td>
<td>1.1*</td>
<td>1.4</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

---

<table>
<thead>
<tr>
<th>Compound</th>
<th>$71\text{b}$</th>
<th>$71\text{a}$</th>
<th>$78\text{a}$</th>
<th>$72\text{b}$</th>
<th>$72\text{a}$</th>
<th>$78\text{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1\text{H NMR signal}$</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
<td>CMe$_3$</td>
</tr>
<tr>
<td>$t^0$</td>
<td>1.163</td>
<td>0.857</td>
<td>2.061</td>
<td>1.184</td>
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<td></td>
</tr>
<tr>
<td>$t^1$</td>
<td>0.547</td>
<td>0.253</td>
<td>0.886</td>
<td>0.893</td>
<td>0.373</td>
<td>1.360</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.328</td>
<td>0.530</td>
<td>0.363</td>
<td>0.502</td>
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<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>53</td>
<td>70</td>
<td>57</td>
<td>68</td>
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<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>27</td>
<td>13</td>
<td>44</td>
<td>28</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>84</td>
<td>81</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>$k_{rel}$</td>
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<td>1.6</td>
<td>1.0*</td>
<td>1.1</td>
<td>1.5</td>
<td>1.0*</td>
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</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the tyrosine derivatives 81a and 81b and the phenylalanine derivatives 18a and 18b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>81a</th>
<th>81b</th>
<th>79b</th>
<th>18a</th>
<th>18b</th>
<th>17</th>
</tr>
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<tbody>
<tr>
<td>1H NMR signal</td>
<td>β-</td>
<td>β-</td>
<td>α-</td>
<td>β-</td>
<td>α-</td>
<td>α-</td>
</tr>
<tr>
<td>t₀</td>
<td>0.250</td>
<td>0.329</td>
<td>0.250</td>
<td>0.487</td>
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<td></td>
</tr>
<tr>
<td>t₀</td>
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<td>0.166</td>
<td>0.104</td>
<td>0.290</td>
<td>0.321</td>
<td></td>
</tr>
<tr>
<td>log(₀/₁)</td>
<td>0.381</td>
<td>0.297</td>
<td>0.381</td>
<td>0.225</td>
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<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>58</td>
<td>50</td>
<td>58</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>18</td>
<td>29</td>
<td>54</td>
<td>14</td>
<td>39</td>
<td>44</td>
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<tr>
<td>% Accounted for</td>
<td>101</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_rel</td>
<td>1.7</td>
<td>1.3</td>
<td>1.2*</td>
<td>1.7</td>
<td>1.0</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>81a</th>
<th>81b</th>
<th>79b</th>
<th>18a</th>
<th>18b</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR signal</td>
<td>β-</td>
<td>β-</td>
<td>α-</td>
<td>β-</td>
<td>α-</td>
<td>α-</td>
</tr>
<tr>
<td>t₀</td>
<td>0.390</td>
<td>0.520</td>
<td>0.390</td>
<td>0.780</td>
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</tr>
<tr>
<td>t₀</td>
<td>0.144</td>
<td>0.255</td>
<td>0.497</td>
<td>0.183</td>
<td>0.444</td>
<td>0.458</td>
</tr>
<tr>
<td>log(₀/₁)</td>
<td>0.433</td>
<td>0.309</td>
<td>0.329</td>
<td>0.245</td>
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<td></td>
</tr>
<tr>
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<td>51</td>
<td>53</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>16</td>
<td>28</td>
<td>55</td>
<td>16</td>
<td>38</td>
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<tr>
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<td>99</td>
<td>93</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>k_rel</td>
<td>1.8</td>
<td>1.3</td>
<td>1.4*</td>
<td>1.3</td>
<td>1.0</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the tyrosine derivatives 80a and 80b and the nitrophenylalanine derivatives 72a and 72b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>80a</th>
<th>80b</th>
<th>79a</th>
<th>72b</th>
<th>72a</th>
<th>78b</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{1}$H NMR signal</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
</tr>
<tr>
<td>$t^0$</td>
<td>0.335</td>
<td>0.299</td>
<td>0.168</td>
<td>0.323</td>
<td>0.189</td>
<td>0.128</td>
</tr>
<tr>
<td>$t^1$</td>
<td>0.217</td>
<td>0.223</td>
<td>0.072</td>
<td>0.030</td>
<td>0.042</td>
<td>0.163</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.189</td>
<td>0.128</td>
<td>0.746</td>
<td>0.884</td>
<td>0.716</td>
<td>0.875</td>
</tr>
<tr>
<td>% Reaction</td>
<td>35</td>
<td>25</td>
<td>82</td>
<td>87</td>
<td>82</td>
<td>87</td>
</tr>
<tr>
<td>% in final mixture</td>
<td>34</td>
<td>35</td>
<td>11</td>
<td>6</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>80</td>
<td>80</td>
<td>50</td>
<td>48</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>1.5</td>
<td>1.0</td>
<td>1.0*</td>
<td>5.8</td>
<td>6.9</td>
<td>2.9*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>80a</th>
<th>80b</th>
<th>79a</th>
<th>72b</th>
<th>72a</th>
<th>78b</th>
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<tbody>
<tr>
<td>$^{1}$H NMR signal</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
<td>$\alpha$-</td>
</tr>
<tr>
<td>$t^0$</td>
<td>0.596</td>
<td>0.539</td>
<td>0.289</td>
<td>0.577</td>
<td>0.215</td>
<td>0.188</td>
</tr>
<tr>
<td>$t^1$</td>
<td>0.364</td>
<td>0.349</td>
<td>0.126</td>
<td>0.035</td>
<td>0.063</td>
<td>0.294</td>
</tr>
<tr>
<td>log($t^0/t^1$)</td>
<td>0.215</td>
<td>0.188</td>
<td>0.916</td>
<td>0.962</td>
<td>0.962</td>
<td>0.962</td>
</tr>
<tr>
<td>% Reaction</td>
<td>39</td>
<td>35</td>
<td>88</td>
<td>89</td>
<td>88</td>
<td>89</td>
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<tr>
<td>% in final mixture</td>
<td>32</td>
<td>31</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>34</td>
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<tr>
<td>% Accounted for</td>
<td>74</td>
<td>74</td>
<td>50</td>
<td>45</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>1.1</td>
<td>1.0</td>
<td>1.0*</td>
<td>4.9</td>
<td>5.1</td>
<td>3.1*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the tyrosine derivatives 80a, 80b, 81a and 81b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>80b</th>
<th>80a</th>
<th>79a</th>
<th>81b</th>
<th>81a</th>
<th>79b</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>α-</td>
<td>α-</td>
<td>α-</td>
<td>β-</td>
<td>β-</td>
<td>α-</td>
</tr>
<tr>
<td>$t_0$</td>
<td>0.259</td>
<td>0.281</td>
<td>0.273</td>
<td>0.245</td>
<td>0.198</td>
<td>0.469*</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.119</td>
<td>0.076</td>
<td>0.238</td>
<td>0.103</td>
<td>0.086</td>
<td>0.238*</td>
</tr>
<tr>
<td>$log(t_0/t_1)$</td>
<td>0.338</td>
<td>0.568</td>
<td>0.423</td>
<td>0.455</td>
<td>0.364</td>
<td>0.355</td>
</tr>
<tr>
<td>% Reaction</td>
<td>54</td>
<td>73</td>
<td>44</td>
<td>62</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>22</td>
<td>14</td>
<td>44</td>
<td>20</td>
<td>17</td>
<td>46</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>80</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>1.0</td>
<td>1.7</td>
<td>1.0*</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>80a</th>
<th>80b</th>
<th>79a</th>
<th>81b</th>
<th>81a</th>
<th>79b</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>α-</td>
<td>α-</td>
<td>α-</td>
<td>β-</td>
<td>β-</td>
<td>α-</td>
</tr>
<tr>
<td>$t_0$</td>
<td>0.797</td>
<td>0.824</td>
<td>0.703</td>
<td>0.608</td>
<td>0.494*</td>
<td>0.472</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.235</td>
<td>0.364</td>
<td>0.494*</td>
<td>0.272</td>
<td>0.198</td>
<td>0.469*</td>
</tr>
<tr>
<td>$log(t_0/t_1)$</td>
<td>0.530</td>
<td>0.355</td>
<td>0.412</td>
<td>0.487</td>
<td>0.272</td>
<td>0.198</td>
</tr>
<tr>
<td>% Reaction</td>
<td>71</td>
<td>56</td>
<td>41</td>
<td>62</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>14</td>
<td>22</td>
<td>30</td>
<td>21</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>66</td>
<td>72</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>$k_{rel}$</td>
<td>1.5</td>
<td>1.0</td>
<td>1.0*</td>
<td>1.2</td>
<td>1.4</td>
<td>1.2*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the phenylalanine derivatives \textbf{18a}, \textbf{20a} and \textbf{20b} and with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>\textbf{20a}</th>
<th>\textbf{20b}</th>
<th>\textbf{19}</th>
<th>\textbf{18a}</th>
<th>\textbf{17}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{1}H NMR signal</td>
<td>(\alpha)-</td>
<td>(\alpha)-</td>
<td>(\alpha)-</td>
<td>(\beta)-</td>
<td>(\alpha)-</td>
</tr>
<tr>
<td>(t^0)</td>
<td>0.323</td>
<td>0.410</td>
<td></td>
<td>0.268</td>
<td></td>
</tr>
<tr>
<td>(t^1)</td>
<td>0.090</td>
<td>0.138</td>
<td>0.317</td>
<td>0.083</td>
<td>0.110</td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
<td>0.555</td>
<td>0.473</td>
<td>0.509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>72</td>
<td>66</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>12</td>
<td>19</td>
<td>43</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>74</td>
<td></td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(k_{rel})</td>
<td>1.2</td>
<td>1.0</td>
<td>1.1*</td>
<td>1.1</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>\textbf{20a}</th>
<th>\textbf{20b}</th>
<th>\textbf{19}</th>
<th>\textbf{18a}</th>
<th>\textbf{17}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{1}H NMR signal</td>
<td>(\alpha)-</td>
<td>(\alpha)-</td>
<td>(\alpha)-</td>
<td>(\beta)-</td>
<td>(\alpha)-</td>
</tr>
<tr>
<td>(t^0)</td>
<td>0.929</td>
<td>1.295</td>
<td></td>
<td>0.473</td>
<td></td>
</tr>
<tr>
<td>(t^1)</td>
<td>0.629</td>
<td>0.776</td>
<td>0.882</td>
<td>0.310</td>
<td>0.176</td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
<td>0.169</td>
<td>0.222</td>
<td>0.183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>32</td>
<td>40</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>28</td>
<td>35</td>
<td>40</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>103</td>
<td>103</td>
<td>103</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>(k_{rel})</td>
<td>1.0</td>
<td>1.3</td>
<td>1.1*</td>
<td>1.1</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the nitrophenylalanine derivatives \(71a\) and \(71b\) and the phenylalanine derivatives \(20a\) and \(20b\) with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(71b)</th>
<th>(71a)</th>
<th>(78a)</th>
<th>(20a)</th>
<th>(20b)</th>
<th>(19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
<td>CMe3</td>
</tr>
<tr>
<td>(t^0)</td>
<td>1.696</td>
<td>1.674</td>
<td></td>
<td>2.044</td>
<td>2.652</td>
<td></td>
</tr>
<tr>
<td>(t^1)</td>
<td>0.662</td>
<td>0.338</td>
<td>0.506</td>
<td>1.688</td>
<td>2.117</td>
<td>0.519*</td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
<td>0.409</td>
<td>0.695</td>
<td></td>
<td>0.083</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>61</td>
<td>80</td>
<td></td>
<td>17</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>20</td>
<td>10</td>
<td>15</td>
<td>36</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>(k_{rel})</td>
<td>4.9</td>
<td>8.4</td>
<td>1.4*</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(71b)</th>
<th>(71a)</th>
<th>(78a)</th>
<th>(20a)</th>
<th>(20b)</th>
<th>(19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H NMR signal</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>CMe3</td>
<td>CMe3</td>
<td>CMe3</td>
</tr>
<tr>
<td>(t^0)</td>
<td>1.236</td>
<td>1.273</td>
<td></td>
<td>1.709</td>
<td>2.273</td>
<td></td>
</tr>
<tr>
<td>(t^1)</td>
<td>0.449</td>
<td>0.192</td>
<td>0.513</td>
<td>1.487</td>
<td>1.897</td>
<td>0.321*</td>
</tr>
<tr>
<td>(\log(t^0/t^1))</td>
<td>0.440</td>
<td>0.822</td>
<td></td>
<td>0.060</td>
<td>0.079</td>
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<tr>
<td>% Reaction</td>
<td>64</td>
<td>85</td>
<td></td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>18</td>
<td>8</td>
<td>20</td>
<td>37</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>(k_{rel})</td>
<td>7.3</td>
<td>13.7</td>
<td>2.5*</td>
<td>1.0</td>
<td>1.3</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the nitrophenylalanine derivatives 72a and 72b and the phenylalanine derivatives 18a and 18b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>72b</th>
<th>72a</th>
<th>78b</th>
<th>18a</th>
<th>18b</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^1H ) NMR signal</td>
<td>CMe3</td>
<td>CMe3</td>
<td>CMe3</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>( t_0 )</td>
<td>3.111</td>
<td>1.583</td>
<td>1.333</td>
<td>0.472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t^1 )</td>
<td>0.310</td>
<td>0.119</td>
<td>1.071</td>
<td>1.000</td>
<td>0.405</td>
<td>0.095</td>
</tr>
<tr>
<td>( \log(t_0/t^1) )</td>
<td>1.002</td>
<td>1.124</td>
<td>0.125</td>
<td>0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>90</td>
<td>92</td>
<td>25</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>7</td>
<td>3</td>
<td>23</td>
<td>55</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>( k_{rel} )</td>
<td>15.2</td>
<td>17.0</td>
<td>4.3*</td>
<td>1.9</td>
<td>1.0</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>72b</th>
<th>72a</th>
<th>78b</th>
<th>18a</th>
<th>18b</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^1H ) NMR signal</td>
<td>CMe3</td>
<td>CMe3</td>
<td>CMe3</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>( t_0 )</td>
<td>2.600</td>
<td>1.380</td>
<td>1.100</td>
<td>0.420</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t^1 )</td>
<td>0.242</td>
<td>0.091</td>
<td>0.682</td>
<td>0.788</td>
<td>0.349</td>
<td>0.030*</td>
</tr>
<tr>
<td>( \log(t_0/t^1) )</td>
<td>1.030</td>
<td>1.181</td>
<td>0.145</td>
<td>0.081</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>91</td>
<td>93</td>
<td>28</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>6</td>
<td>2</td>
<td>17</td>
<td>52</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>( k_{rel} )</td>
<td>12.7</td>
<td>14.6</td>
<td>8.7*</td>
<td>1.8</td>
<td>1.0</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.
Competitive reactions of the phenylalanine derivatives 20a and 20b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1H NMR signal</strong></td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
<td>0.852</td>
<td>1.120</td>
<td></td>
</tr>
<tr>
<td>t¹</td>
<td>0.496</td>
<td>0.663</td>
<td>0.236</td>
</tr>
<tr>
<td>log(t₀/t¹)</td>
<td>0.235</td>
<td>0.228</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>42</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>58</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_{rel}</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1H NMR signal</strong></td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
<td>1.104</td>
<td>1.420</td>
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</tr>
<tr>
<td>t¹</td>
<td>0.363</td>
<td>0.468</td>
<td>1.105</td>
</tr>
<tr>
<td>log(t₀/t¹)</td>
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<td>0.482</td>
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<tr>
<td>% Reaction</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>33</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_{rel}</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>20a</th>
<th>20b</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1H NMR signal</strong></td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
<td>1.179</td>
<td>1.573</td>
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</tr>
<tr>
<td>t¹</td>
<td>0.668</td>
<td>0.909</td>
<td>0.519</td>
</tr>
<tr>
<td>log(t₀/t¹)</td>
<td>0.247</td>
<td>0.238</td>
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</tr>
<tr>
<td>% Reaction</td>
<td>43</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>57</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_{rel}</td>
<td>1.0</td>
<td>1.0</td>
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Competitive reactions of the phenylalanine derivatives 18a and 18b with triphenyltin hydride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>18a</th>
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<th>17</th>
</tr>
</thead>
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<tr>
<td>1H NMR signal</td>
<td>CMe₃</td>
<td>CMe₃</td>
<td>CMe₃</td>
</tr>
<tr>
<td>t₀</td>
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<td>1.042</td>
<td></td>
</tr>
<tr>
<td>t₁</td>
<td>0.177</td>
<td>0.463</td>
<td>0.415</td>
</tr>
<tr>
<td>log(t₀/t₁)</td>
<td>0.432</td>
<td>0.352</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>63</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>% in final mixture</td>
<td>37</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>% Accounted for</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kₑₗₑ</td>
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<td>1.0</td>
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Appendix 13

Competitive reactions of the valine derivatives 95 and 96 with NBS.

<table>
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<tr>
<th>compound</th>
<th>95</th>
<th>33</th>
<th>96</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
</tr>
<tr>
<td>$t_0$</td>
<td>1.714</td>
<td>1.357</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_1$</td>
<td>1.103</td>
<td>0.414</td>
<td>0.862</td>
<td>0.379</td>
</tr>
<tr>
<td>log($t_0/t_1$)</td>
<td>0.191</td>
<td>0.197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>36</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>64</td>
<td>24</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>% accounted for</td>
<td>88</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (NBS)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>compound</th>
<th>95</th>
<th>33</th>
<th>96</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
</tr>
<tr>
<td>$t_0$</td>
<td>1.172</td>
<td>0.379</td>
<td>0.862</td>
<td>0.379</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.165</td>
<td>0.197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>32</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>68</td>
<td>22</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>% accounted for</td>
<td>90</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (NBS)</td>
<td>1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>compound</th>
<th>95</th>
<th>33</th>
<th>96</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR signal</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
<td>$\alpha$-H</td>
</tr>
<tr>
<td>$t_0$</td>
<td>2.353</td>
<td>2.221</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_1$</td>
<td>1.768</td>
<td>0.337</td>
<td>1.705</td>
<td>0.347</td>
</tr>
<tr>
<td>log($t_0/t_1$)</td>
<td>0.124</td>
<td>0.115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reaction</td>
<td>25</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>75</td>
<td>14</td>
<td>77</td>
<td>16</td>
</tr>
<tr>
<td>% accounted for</td>
<td>89</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{rel}$ (NBS)</td>
<td>1.1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 14

Competitive reactions of the \( p \)-methylphenylalaninamide 94 and tert-butyltoluene (TBT) with NBS.

<table>
<thead>
<tr>
<th>Compound</th>
<th>94</th>
<th>151</th>
<th>150a,b</th>
<th>TBT</th>
<th>( \alpha )-BrTBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^1 )H NMR signal</td>
<td>( p )-Me</td>
<td>( p )-CH(_2)-Br</td>
<td>( p )-Me</td>
<td>( p )-Me</td>
<td>( p )-CH(_2)</td>
</tr>
<tr>
<td>( t_0 )</td>
<td>1.425</td>
<td>(1.041)(^a)</td>
<td>(1.202)(^a)</td>
<td>1.354</td>
<td>(0.660)</td>
</tr>
<tr>
<td>( t_1 )</td>
<td>0.661</td>
<td>0.384</td>
<td>0.223</td>
<td>0.653</td>
<td>0.694</td>
</tr>
<tr>
<td>( \log(\frac{t_0}{t_1}) )</td>
<td>0.334</td>
<td>0.136</td>
<td>0.074</td>
<td>0.317</td>
<td>0.312</td>
</tr>
<tr>
<td>% reaction</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>46</td>
<td>27</td>
<td>16</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>% accounted for</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>( k_{rel} ) (NBS)</td>
<td>2.45</td>
<td>1.0(^b)</td>
<td>0.54(^b)</td>
<td>2.32</td>
<td>2.29(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Rate of product formation.

\(^b\) \( t_1 \) value expressed in terms of the corresponding amount of starting material consumed.

---

<table>
<thead>
<tr>
<th>Compound</th>
<th>94</th>
<th>151</th>
<th>150a,b</th>
<th>TBT</th>
<th>( \alpha )-BrTBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^1 )H NMR signal</td>
<td>( p )-Me</td>
<td>( p )-CH(_2)-Br</td>
<td>( p )-Me</td>
<td>( p )-Me</td>
<td>( p )-CH(_2)</td>
</tr>
<tr>
<td>( t_0 )</td>
<td>1.425</td>
<td>(0.993)(^a)</td>
<td>(1.173)(^a)</td>
<td>1.354</td>
<td>(0.620)</td>
</tr>
<tr>
<td>( t_1 )</td>
<td>0.647</td>
<td>0.432</td>
<td>0.252</td>
<td>0.583</td>
<td>0.734</td>
</tr>
<tr>
<td>( \log(\frac{t_0}{t_1}) )</td>
<td>0.343</td>
<td>0.157</td>
<td>0.085</td>
<td>0.366</td>
<td>0.339</td>
</tr>
<tr>
<td>% reaction</td>
<td>55</td>
<td></td>
<td></td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>45</td>
<td>30</td>
<td>18</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>% accounted for</td>
<td>93</td>
<td></td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( k_{rel} ) (NBS)</td>
<td>2.18</td>
<td>1.0(^b)</td>
<td>0.54(^b)</td>
<td>2.33</td>
<td>2.16(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Rate of product formation.

\(^b\) \( t_1 \) value expressed in terms of the corresponding amount of starting material consumed.
Competitive reactions of the \( p \)-methylphenylalanine derivative \( 93 \) and \( \text{tert-butyltoluene} \) (TBT) with NBS.

<table>
<thead>
<tr>
<th>compound</th>
<th>( 93 )</th>
<th>( 149 )</th>
<th>( 148a,b )</th>
<th>TBT</th>
<th>( \alpha\text{-BrTBT} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^{1}\text{H NMR signal} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-CH}_{2}\text{-Br} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-CH}_{2} )</td>
</tr>
<tr>
<td>( t^{0} )</td>
<td>1.254</td>
<td>(0.828)(^{a})</td>
<td>(1.202)(^{a})</td>
<td>1.197</td>
<td>(0.481)</td>
</tr>
<tr>
<td>( t^{1} )</td>
<td>0.658</td>
<td>0.426</td>
<td>0.052</td>
<td>0.465</td>
<td>0.716</td>
</tr>
<tr>
<td>( \log(t^{0}/t^{1}) )</td>
<td>0.280</td>
<td>0.180</td>
<td>0.018</td>
<td>0.411</td>
<td>0.396</td>
</tr>
<tr>
<td>% reaction</td>
<td>48</td>
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<td></td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>% final</td>
<td>52</td>
<td>34</td>
<td>4</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td>% accounted for</td>
<td>91</td>
<td></td>
<td></td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>( k_{rel} ) (NBS)</td>
<td>1.56</td>
<td>1.0(^{b})</td>
<td>0.10(^{b})</td>
<td>2.28</td>
<td>2.20(^{b})</td>
</tr>
</tbody>
</table>

\(^{a}\) Rate of product formation.

\(^{b}\) \( t^{1} \) value expressed in terms of the corresponding amount of starting material consumed.

<table>
<thead>
<tr>
<th>compound</th>
<th>( 93 )</th>
<th>( 149 )</th>
<th>( 148a,b )</th>
<th>TBT</th>
<th>( \alpha\text{-BrTBT} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^{1}\text{H NMR signal} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-CH}_{2}\text{-Br} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-Me} )</td>
<td>( p\text{-CH}_{2} )</td>
</tr>
<tr>
<td>( t^{0} )</td>
<td>1.254</td>
<td>(0.978)(^{a})</td>
<td>(1.201)(^{a})</td>
<td>1.197</td>
<td>(0.713)</td>
</tr>
<tr>
<td>( t^{1} )</td>
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<td>0.276</td>
<td>0.053</td>
<td>0.651</td>
<td>0.484</td>
</tr>
<tr>
<td>( \log(t^{0}/t^{1}) )</td>
<td>0.176</td>
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<td>0.019</td>
<td>0.265</td>
<td>0.225</td>
</tr>
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<td>46</td>
<td></td>
</tr>
<tr>
<td>% final</td>
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<td>22</td>
<td>2</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>% accounted for</td>
<td>91</td>
<td></td>
<td></td>
<td>94</td>
<td></td>
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<td>( k_{rel} ) (NBS)</td>
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<td>1.0(^{b})</td>
<td>0.18(^{b})</td>
<td>2.45</td>
<td>2.08(^{b})</td>
</tr>
</tbody>
</table>

\(^{a}\) Rate of product formation.

\(^{b}\) \( t^{1} \) value expressed in terms of the corresponding amount of starting material consumed.