Reactions of Captodative Radicals

A thesis submitted for the degree of

Doctor of Philosophy

of

The Australian National University

by

Christina Chai Li Lin, B. Sc. (Honours)

The Research School of Chemistry, Canberra, ACT, Australia.

April 1990
DECLARATION

The work described in this thesis is original and has not been submitted for a degree or diploma in any other University or College and to the best of my knowledge, does not contain material previously published or presented by another person, except where due reference is made in the text.

Christina L.L. Chai
ACKNOWLEDGEMENTS

I would like to thank the many individuals who have contributed in one way or another in making my stay at the Research School of Chemistry both rewarding and enjoyable; out of necessity, it is not possible to list everyone here.

A few individuals deserve mention.

First and foremost, I would like to express my profound gratitude to my supervisor and mentor, Professor Athel Beckwith for his support, enthusiasm, guidance and for a gentle and fruitful introduction into radical chemistry.

I am also indebted to Dr. Steven Brumby for running the esr spectra as well as his invaluable help in the interpretation of esr spectra and his extremely helpful discussions in chemistry especially in the field of molecular orbital calculations. My gratitude also goes to my colleagues who have tediously read through my entire thesis: Dr. Ian Davison (for his patience, suggestions and time), Dr. Peter Moeller (for his encouragement and humour) and Dr. Gerry Poulton (for finding time despite his busy schedule). I must also thank others who have read sections of my thesis: Dr. Kevin Raner, Dr. Steven Brumby, Dr. Matt Tozer and Mrs Joanne Jamie. I am also grateful to Dr. Jürg Zimmermann and Dr. Janusz Lusztyk for their helpful suggestions and discussions in chemistry.

I also thank Dr. Anthony Willis for solving the X-ray crystal structures in this thesis, Mr. Alex Wallner (who gave moral support as well as helped in the syntheses of some of the substrates) and to the UNMRC staff at the ANU, who provided lots of advice and time.

I am indebted to my parents, without whom all of this is not possible: their gift of education to me will always be cherished. Finally, I also thank my brother, Andrew and sister, Cecilia for their support and my good friend, Michael Young for his friendship and for keeping me 'sane' through the tough times.
There is no dream that is too great for any human being, no aspiration that is too high, no ideal too wonderful.
What we are capable of conceiving in our souls is also capable of being manifested in the outward world. More than that, what we truly conceive within our souls, and work for, cannot help appearing in our lives.
Derek Neville
To my dad and mum,
with gratitude and love
for their infinite amount of patience and support
through the years.
Contents

Declaration i
Acknowledgements ii
Dedication iv
Abstract viii
Abbreviations x

Chapter 1: Introduction 1

1.1 The Captodative Effect 2
1.1a Methods for the study of the captodative effect 4
1.1b Captodative effect in organic synthesis 12

1.2 Stereoselectivity in radical reactions 15

1.3 Aim of the research 22

References: Chapter 1 23

Chapter 2: A kinetic study of the captodative effect 26

2.1 A study of the effects of different donor and acceptor substituents on the rate constants for reduction by tributyltin hydride 27

2.2 Steric and conformational effects on the relative rate constants for the bromination of captodatively substituted compounds 37

2.3 Alkyl radical addition to captodatively substituted olefins 49

2.4 Conclusion 54

References: Chapter 2 56

Chapter 3: An esr study of the captodative effect 59

3.1 Hydrogen abstraction studies from
substituted 1,3-dioxolan-4-ones by t-butoxy radicals 60

3.1a Considerations of reactivity and selectivity 60

3.1b Analyses of spectra 69

3.1c Linewidth alternation 76

3.1d Reducing properties of radicals derived from 1,3-dioxolanones 81

3.2 Hydrogen abstraction studies from other cyclic acetals 81

3.3 Addition of alkyl radicals to 2-(t-butyl)-5-methylene-1,3-dioxolan-4-one 84

3.4 Conclusion 91

References: Chapter 3 92

Chapter 4: Regio- and diastereo-selective reactions of 1,3-dioxolan-4-ones 95

4.1 N-Bromosuccinimide reactions 97

4.2 Reduction reactions of 1,3-dioxolanones 111

4.3 Carbon-carbon bond forming reactions of 1,3-dioxolanones 119

4.5 Other reactions of 1,3-dioxolan-4-ones 125

4.5 Stereochemical assignments and conformational studies of 1,3-dioxolan-4-ones 133

4.6 Conclusion 138

References: Chapter 4 141

Chapter 5: Regio- and diastereo-selective reactions of 1,3-oxazolidin-5-ones and 1,3-imidazolidin-4-ones 145

5.1 The chemistry of oxazolidinones 147

5.1a The regioselectivity of NBS reactions 147

5.1b The stereoselectivity of NBS reactions 153

5.1c The reactivity of 3-substituted oxazolidinones
5.1d Reduction with tributyltin deuteride
5.1e Carbon-carbon bond forming reactions
5.1f Intramolecular hydrogen abstraction studies
5.1g The synthesis and utility of
2-(t-butyl)-4-methylene-1,3-oxazolidin-5-one

5.2 The chemistry of 1,3-imidazolidin-4-ones
5.2a The regio- and diastereo-selectivity of NBS reactions
5.2b Reduction with tributyltin hydride or deuteride
5.2c Intramolecular hydrogen abstraction studies
5.2d The synthesis and utility of
2-(t-butyl)-5-methylene-1,3-imidazolidin-4-one

5.3 Conclusion

References: Chapter 5

Conclusion

Experimental
Chapter 2
Chapter 4
Chapter 5, section 5.1
Chapter 5, section 5.2
Appendix A
Appendix B
Appendix C
Appendix D
Abstract

Captodative stabilisation of a radical is said to arise from the combined conjugative effects of an electron donating substituent and an electron withdrawing substituent such that the stabilisation of the captodative radical is greater than that expected from the sum of the effects of the individual substituents. In this thesis, the reactivity and selectivity of some radical reactions involving captodatively substituted compounds have been investigated.

As part of the work described in Chapter 2, relative rate constant studies were carried out with captodatively substituted compounds and non-captodatively substituted compounds. The reduction of suitable halides and sulfides with Bu$_3$SnH showed that captodatively substituted compounds display a small captodative kinetic effect. When a study of solvent effects was conducted, no increase in the rates of formation of captodative radicals in polar solvents could be detected. This is contrary to expectation based on the theoretical work by Katritzky who predicted that the captodative effect would be greatly enhanced in solvents of high polarity. The rate constants for addition of alkyl radicals to captodatively substituted olefins were measured relative to the rate constant for addition of alkyl radicals to methyl acrylate but no enhancement attributable to the captodative effect could be found. Other studies on the reactions of N-bromosuccinimide (NBS) with various substituted cyclic and acyclic captodative compounds showed that the relative rates of NBS brominations are dependent to a certain extent on polar effects (evident in the acyclic compounds) as well as sensitive to small conformational changes.

Chapter 3, describes a thorough study of the regioselectivities of hydrogen abstraction of various substituted 1,3-dioxolan-4-ones by t-butoxy radicals. These reactions generally favour attack at the captodative centre over attack at the electron rich acetal centre. The results indicated that abstraction by t-butoxy radicals can be regioselective depending on the substituents present. The relative reactivities per equivalent hydrogen atom (ρ) were also measured. The addition of alkyl radicals to the captodative olefin derived from 1,3-dioxolan-4-one was also studied; the results
show that the reaction is sensitive to some interesting conformational effects.

An investigation of the regioselectivity of NBS reactions with various 1,3-dioxolan-4-ones is described in Chapter 4. It was found that the bromination usually occurs with high regioselectivity at the captodative position. High diastereoselectivities were also observed for NBS brominations, and this prompted an investigation of the diastereoselectivities of other radical reactions involving 1,3-dioxolan-4-ones. Reductions of suitable halides with Bu₃SnH, allylations with tributylallyltin, and radical additions to methyl acrylate gave predominantly the isomer arising from the reaction of the 1,3-dioxolan-4-one-5-yl radical with the reagent (Bu₃SnH or alkene) on the face anti to the substituent at C-2 in the dioxolanone. Alternative syntheses of dehydrolactic derivative of dioxolanones have also been developed and alkyl radical additions to this captodative olefin have been investigated.

The effects of substituents on the diastereoselectivities of reduction reactions with 1,3-oxazolidin-4-ones and 1,3-imidazolidin-5-ones are described in Chapter 5. It was found that diastereoselectivities can be improved by increasing the steric bulk at the acetal position (C-2) as well as the N-acyl substituent. Efforts were also made to elucidate the mechanism of NBS bromination as well as to study the effects of substituents on the relative rates of NBS brominations. Arising from this work new syntheses of the dehydroalanine derivatives of oxazolidinone and imidazolidinone have been developed. The addition of alkyl radicals to these captodatively substituted olefins occurs with high diastereoselectivity and thus provides a potential route to the synthesis of enantiomerically pure amino acids.
Abbreviations used:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>azoisobisbutyronitrile</td>
</tr>
<tr>
<td>Bu₃SnH</td>
<td>tributyltin hydride</td>
</tr>
<tr>
<td>CCl₄</td>
<td>carbon tetrachloride</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulphoxide</td>
</tr>
<tr>
<td>esr</td>
<td>electron spin resonance</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>gc</td>
<td>gas chromatograph</td>
</tr>
<tr>
<td>hv</td>
<td>reaction performed with photolysis</td>
</tr>
<tr>
<td>hplc</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>i-</td>
<td>iso-</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>noesy</td>
<td>two dimensional nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>t-</td>
<td>tert-</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction

The application of free radical reactions in organic synthesis has become increasingly important. Free radical processes have been used successfully in the synthesis of a wide range of compounds. However, for a synthesis to be successful various factors must be considered. There is a question of reactivity (e.g., is the rate of the required reaction fast enough to compete with other possible processes) and selectivity (e.g., does the reaction proceed in the required manner in terms of site of attack and direction of attack). Reactivity is more accurately defined in terms of rate constants and is elegantly determined by Tolbert is dependent on many factors such as the nature of the transition state, steric compensation and polar effects. The regioselectivity depends on the nature and stability of the attacking radical and in some cases, the stability of the product radical. The stereoselectivity of a reaction is less predictable and reflects the propensity which a radical prefers from a preferred conformation in a particular direction.

In this thesis, we are concerned with the study of the reactivity and selectivity of a class of compounds which undergo reactions to give radicals believed to have high stability. This class of compounds is known as captodatively substituted compounds and the radicals are said to be captodatively stabilized.

1.1. The Captodative Effect

The effect of substituents on radical stability has been studied in detail. It is known that electron donors as well as charge acceptors are capable of stabilizing radicals by allowing delocalization of the electrons onto the substituents as shown.
Chapter 1

Introduction

The application of free radical reactions to organic synthesis has become increasingly important.\textsuperscript{1,2} Free radical reactions have been used successfully in the synthesis of a wide range of compounds.\textsuperscript{2,3} However for a synthesis to be successful various factors must be considered. There is a question of reactivity\textsuperscript{4} (e.g. is the rate of the required reaction fast enough to compete with other possible processes) and selectivity (e.g. does the reaction proceed in the required manner in terms of site of attack and direction of attack). Reactivity is most accurately defined in terms of rate constants and as elegantly summarised by Tedder,\textsuperscript{4} is dependent on many factors such as the nature of the transition state, steric compression and polar effects. The regioselectivity of a radical reaction will reflect to some extent on the nature and stability of the attacking radical and in some cases, the stability of the product radical. The stereoselectivity of a reaction is less predictable and reflects the degree to which a radical reacts from a preferred conformation in a particular direction.

In this thesis, we are concerned with the study of the reactivity and selectivity of a class of compounds which undergo reactions to give radicals believed to have high stability. This class of compounds is known as captodatively substituted compounds and the radicals are said to be captodatively stabilised.\textsuperscript{5}

1.1 The Captodative Effect\textsuperscript{5}

The effect of substituents on radical stability has been studied in detail.\textsuperscript{6} It is known that electron donors as well as electron acceptors are capable of stabilising radicals by allowing delocalisation of the electrons onto the substituents as shown.
It has been further postulated that the presence of both an electron withdrawing (captor) substituent and an electron donating (dative) substituent leads to a synergistic stabilisation of the radical, i.e. the total stabilisation is greater than the sum of the individual stabilisation effects of the substituents. This is known as captodative stabilisation or merostabilisation. The basis of this effect is thought to arise from extended conjugation involving both substituents as illustrated in Scheme 1.2.

Scheme 1.2
1.1a Methods for the study of the captodative effect.

Various methods have been used to study this effect. Kinetic and thermodynamic measurements by esr spectroscopy, nmr spectroscopy as well as product analysis are most frequently used. However, the results from the various studies have afforded contradictory conclusions regarding the existence and magnitude of this effect.

Electron spin resonance (esr) spectroscopy is an excellent method for determining the stability of a radical, or radicals formed in a reaction. Sustmann and co-workers measured the spin delocalisation of various substituted benzylic radicals as a function of the $\beta$-hyperfine splitting constant of the freely rotating methyl group in $\alpha, \beta$-disubstituted benzylic radicals 1.4 and the hyperfine splitting constant of the $p$-hydrogen atom in $\alpha, \alpha$-disubstituted benzylic radicals 1.5.

\[
\begin{align*}
\text{(1.4)} & \quad \text{X} & \quad \text{CH}_3 \\
\text{(1.5)} & \quad \text{X} & \quad \text{Y}
\end{align*}
\]

It is believed that spin delocalisation and radical stabilisation are interrelated. Consequently, a parameter known as $S_{\text{exp}}$ (experimental delocalisation parameter) can be defined as

\[
S_{\text{exp}} = 1 - \frac{a_{\text{XY}}}{a_{\text{HH}}} \quad \text{(equation 1)}
\]

where $a = \text{hyperfine splitting constant}$
Furthermore, it is possible to calculate the theoretical delocalisation parameter $S_{\text{calc}}$ and then define $\Delta S$ as a measure of synergism ($\Delta S$ is positive) or antagonism ($\Delta S$ is negative) of radical stabilisation due to its substituents.

\[
S_{XY}^{\text{calc}} = 1 - (1 - S_{XH}^{\text{exp}})(1 - S_{HY}^{\text{exp}}) \quad (\text{equation 2})
\]

\[
\Delta S = \frac{S_{XY}^{\text{exp}} - S_{XY}^{\text{calc}}}{S_{XY}^{\text{calc}}} \quad (\text{equation 3})
\]

It was found that when $X$ and $Y$ are both donor substituents or both captor substituents, $\Delta S$ is negative and the stabilisation of the radical formed is less than additive. However, when $X$ and $Y$ are donor and acceptor substituents respectively, i.e. when the radical formed is captodative, $\Delta S$ is positive and the effects of the two substitutions on radical stabilisation are synergistic. In other words, esr measurements indicate that captodative radicals in benzylic systems like these show enhanced stabilisation.

Esr has also been used to measure the rotational barrier of captodatively substituted radicals. Sustmann and co-workers\(^8\) determined the barrier to internal rotation of 1-cyano-1-methoxyallyl radical (1.6) to (1.7).

\[\text{Scheme 1.3}\]

From studies on 1-cyanoallyl radical and 1-methoxyallyl radical, it was predicted that if the stabilising effects of the substituents are additive, then a rotational barrier for 1.6 to 1.7 of 9 kcal/mol is to be expected. The experimental rotational barrier found was 6 kcal/mol, implying a captodative stabilisation of 3 kcal/mol. Similarly, studies by Walton and co-workers\(^9\) on amino-substituted radicals of type 1.8 indicated captodative stabilisation of up to 7 kcal/mol depending on the nature of the acceptor
group R. This provides evidence for thermodynamic stabilisation of captodative radicals.

Scheme 1.4

However, contrary to the results above, when Rüchardt and co-workers measured the enthalphy for the dissociation of 1.10 to 1.10a, they did not find any captodative stabilisation for radical 1.10a.

Scheme 1.5

Kinetic studies have also been carried out in many systems to see if stabilisation of captodative radicals has a kinetic consequence. Korth and co-workers reported that captodatively stabilised methyl radicals dimerise at rates close to diffusion control and did not appear to possess any extra stability. Louw and Bunk measured the rates of C-C bond homolysis of 1.12 by vapour phase pyrolysis. The bond dissociation energy of the central C-C bond (in the absence of any captodative effect) was calculated to be 63 kcal/mol but the measured value was
found to be 59 kcal/mol. Thus it was inferred that captodative stabilisation of radical 1.12a was ca 4 kcal/mol.

In an esr study by Beckwith and Brumby,\textsuperscript{13} the relative concentrations of radicals formed from the hydrogen abstraction with t-butoxy radicals, of substrates with OH, OR groups as donors and COOR, COR groups as acceptors were measured. Their results qualitatively support the results of Walton\textsuperscript{9} in the suggestion that captodative stabilisation of radicals may be important only when the substituents are strong electron donors or acceptors.

Kinetic measurements by Viehe\textsuperscript{14} on the relative rates of hydrogen abstraction by t-butoxy radicals have been measured for captodative and non-captodative compounds. From the ratio of t-butanol/acetone obtained by $^1$H nmr integration, the relative rates of hydrogen abstraction can be calculated as shown in Scheme 1.6, equation (4).

**Scheme 1.6**

\[
\frac{k_a}{k_d} = \frac{[t\text{-butanol}]}{[acetone]} \cdot \frac{1}{[RH]} \quad (equation \ 4)
\]
As t-butoxy radicals are electrophilic, one expects to see a strong influence of the substituents on the rates of reactions e.g. electron donating substituents should enhance the rate of abstraction. The results show that compounds with captodative substitution display enhanced reactivity, for example, the relative rates of abstraction $k_a/k_{std}$ for some relevant compounds are shown below.

**Table 1.1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$k_a/k_{std}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOCH$_2$OME</td>
<td>1.21</td>
</tr>
<tr>
<td>CH$_2$(COOME)$_2$</td>
<td>0.35</td>
</tr>
<tr>
<td>MeOCH$_2$CO$_2$Me</td>
<td>1.68</td>
</tr>
<tr>
<td>MeSCH$_2$CN</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Where the standard is cyclohexane

These results support the view that captodative stabilisation of product radicals can enhance the rate of formation of radicals. However, we note that the increase in the reactivity of captodatively substituted compounds is not very large.

A further postulated manifestation of the captodative effect is that the $\pi$-bonds in captodatively substituted olefins are weakened and hence activated towards attack by radicals to form the corresponding captodatively stabilised radical.$^5$

**Scheme 1.7**

Measurements on the rate constants of addition to such olefin have been studied. Ito and co-workers,$^{15}$ for example, measured the rate constants of the addition of $p$-substituted phenylthiyl radicals to olefins of type 1.13.
The Y group was varied and the studies revealed that the reactions of olefins with arylthiyl radicals was accelerated in the order of

\[ NR_2 > OR > Cl > OC(O)CH_3 > CH_3 > H \]

These rates show correlation with localisation energies\(^\text{15}\) derived from molecular orbital calculations and indicate that the rate acceleration is due to captodative stabilisation of the product radicals. Further kinetic evidence for the captodative effect in radical addition is provided by Viehe and co-workers\(^\text{16}\) who found that addition of IBN (isobutrylnitrile) radicals to alkenes of type 1.14 showed rate acceleration beyond the expectation of polar effects when X and Y are donor and captor substituents respectively.

In another study, Newcomb\(^\text{17}\) measured the rates of cyclisation of 5-hexenyl radicals with methoxy and/or cyano substituents and compared these rates with that for the unsubstituted 5-hexenyl radical. The difference in the activation energies (\(\Delta E_a\)) for cyclisation for substituted radicals 1.15b-1.15d relative to the unsubstituted radical 1.15a can be calculated. The captodatively substituted radical 1.15d was found to possess a larger \(\Delta E_a\) value compared to the sum of the \(\Delta E_a\)'s for radical 1.15c (methoxy substituent only) and radical 1.15b (cyano substituent only) (see Table 1.2). This extra stabilisation energy of 0.4 kcal/mol is attributed to the captodative effect.
Scheme 1.8

![Scheme 1.8](image)

Table 1.2

<table>
<thead>
<tr>
<th>Radical</th>
<th>$\Delta E_a$(kcal/mol)$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.15b</td>
<td>1.04</td>
</tr>
<tr>
<td>1.15c</td>
<td>0.29</td>
</tr>
<tr>
<td>1.15d</td>
<td>1.73</td>
</tr>
</tbody>
</table>

$^1$ This is the difference in the activation energies of unsubstituted radical 1.15a relative to 1.15c-d.

In another ring closure study by Beckwith and Roberts, similar results were obtained. Ring closure of radical 1.17 can give either the captodatively stabilised radical 1.17a or the acyl stabilised radical 1.17b. The presence of a $\beta$-methoxy substituent only on the alkene was shown in a separate experiment to have a negligible effect on the rate of cyclisation. The kinetic study revealed that the rate of cyclisation to form the captodative radical 1.17a was 40% greater than would be expected on the basis of the sum of its individual substituents.
Both of the studies above show that captodative stabilisation of radicals has
only a small effect on the chemical reactivity of the system. This could be attributed in
part to the early transition state which results from the exothermic addition of radicals
to olefins. Thus the reactant-like transition state does not fully reflect the stabilisation
of the product radical.

Various theoretical calculations have been published on the stabilisation
energies of captodative radicals. Some calculations predict a synergistic effect of
captodative radical stabilisation\textsuperscript{19} whereas others predict no significant
effect\textsuperscript{20} In a
recent paper, Katritzky and co-workers\textsuperscript{21} concluded from their INDO-UHF-SCRF
calculations that one would expect to observe significant captodative stabilisation in
media of high dielectric constants (\(\varepsilon\)). In polar media, charged resonance structures
(see Scheme 1.2) become more important as reflected by the increase in dipole
moment. In captodative radicals, the dipole moment increases 50-60% as \(\varepsilon\) increases
from 1 to 80. This leads to stabilisation of radicals up to 30 kcal/mol. Hence, one
would expect to observe dramatic captodative stabilisation in polar solvents.

This prompted us (see Chapter 2) and Rüchardt and co-workers\textsuperscript{22} to
investigate solvent effects. Rüchardt studied the homolysis of dimer 1.10 (see
Scheme 1.5) in solvents of different polarity, from phenyl ether (\(\varepsilon = 3\)) to succinic
anhydride (\(\varepsilon \text{ at } 60^\circ\text{C} = 50\)). The position of equilibrium, \(\Delta H_{r}\) and \(\Delta S_{r}\) were
measured using techniques such as esr spectroscopy, nmr spectroscopy and
differential scanning calorimetry. It was found that there was no significant difference
in the reaction enthalpy of dissociation of dimer 1.10 to \(\alpha\)-cyano-\(\alpha\)-methoxybenzyl
radical (1.10a) in polar solvents. This study disproves the theoretical predictions by Katritzky\textsuperscript{21} as no significant captodative stabilisation was found in polar solvents. However, it should be noted that this method does not distinguish between steric and electronic effects of the substituents.

1.1b Captodative effect in organic synthesis

The captodative effect may play an important role in synthesis if it is able to affect the regioselectivities of reactions such that captodative radicals are formed preferentially to non-captodative radicals.

Captodatively substituted olefins are radicophiles and it is anticipated that the effect of captodative substitution is to decrease the HOMO-LUMO gap while the coefficients of the HOMO-LUMO orbitals on the β-carbon are increased.\textsuperscript{5} Consequently, reactions resulting in the formation of captodative radicals are facile. Numerous examples of this are found in the literature. For example, captodative olefins are effective in Diels-Alder reactions where the mechanism is proposed to go via a biradical intermediate. The resulting yields with captodative olefins are better than that with a single acceptor substituent (compare 1.18 with 1.19 in Scheme 1.10)\textsuperscript{23} and in most cases, the reaction conditions are milder.

Scheme 1.10
2-Methylthioacrylonitrile (1.23) undergoes spontaneous head to head cyclodimerisation to form 1.24 whereas the corresponding cyclodimerisation of acrylonitrile is very sluggish (see Scheme 1.11).

**Scheme 1.11**

![Scheme 1.11](image)

Competitive experiments involving 1.23 and 1.26 confirm this. Diels-Alder reactions are sensitive to steric and polar effects (i.e. a dienophile is better if it is more electron withdrawing) thus one would expect that the effect of adding a donor substituent to acrylonitrile (1.26) would be to disfavour cycloadditions. However, as can be seen from Scheme 1.12, the reverse is observed. The captodative olefin 1.23 displays the higher reactivity. This is because captodative substitution on the olefin decreases the energy of the LUMO thus leading to more favourable LUMO (dienophile) HOMO (diene) interactions.

**Scheme 1.12**

![Scheme 1.12](image)

\[(1.27a) \rightarrow (1.27b) = 46:54\]

\[(1.28a : 1.28b) = 84:16\]
Captodative olefins are also important in other cycloaddition reactions thought to proceed via a biradical mechanism e.g. 1,3-dipolar cycloadditions and [2+2] cycloadditions as shown below in Schemes 1.13 and 1.14.

**Scheme 1.13**

\[
\begin{align*}
&\text{\textbf{(1.29)}} \\
&\text{\textbf{(1.29a)}}
\end{align*}
\]

**Scheme 1.14**

\[
\begin{align*}
&\text{\textbf{(1.26)}} \\
&\text{\textbf{(1.18)}} \\
&\text{\textbf{(1.31)} 5\%} \\
&\text{\textbf{(1.32)} 83\%}
\end{align*}
\]

Besides these, other syntheses involving captodative olefins include the formation of double adducts or adduct dimers as shown in Scheme 1.15.

**Scheme 1.15**

\[
\begin{align*}
&\text{\textbf{(1.33)}} \\
&\text{\textbf{(1.34)}}
\end{align*}
\]
This has resulted in the synthesis of many bridged compounds including that of macrocyclic polyethers.\textsuperscript{28,29} For example, crown ether radicals can be generated by hydrogen abstraction with t-butoxy radicals. These then add to the captodative olefin \textsuperscript{1.18} which subsequently dimerises to the adduct dimers \textsuperscript{1.36} shown below.

\textbf{Scheme 1.16}

\begin{equation}
\text{(1.35)} \quad \text{DTPO, 60°, 8 hrs} \quad \text{(1.36)}
\end{equation}

\textbf{1.2 Stereoselectivity in radical reactions}

The question of regioselectivity in radical reactions has been addressed in many excellent reviews.\textsuperscript{1-4,30-33} In most radical reactions, the factors influencing the regioselectivity are well understood and it is possible with appropriate choice of substituents and reagents to control the site of attack. For example, the ratio of hydrogen abstraction by bromine radicals from hydrocarbons is in the order of increasing radical stability tertiary > secondary > primary.\textsuperscript{34}

\[
RCH_3 : R_2CH : R_3CH
\]

Ratio of H-abstraction: \[ 1 : 80 : 1700 \]
Another example is in the radical addition of trifluoromethyl radicals (CF$_3$•) to alkenes shown below. The regioselectivity changes with the substituents on the alkene.$^4$

$$\begin{align*}
\alpha & \quad \beta \\
\text{CH}_2 = \text{CH} - \text{CH}_3 & \quad \text{CH}_2 = \text{CH} - \text{CF}_3
\end{align*}$$

Thus, in the former case, the regioselectivity of hydrogen abstraction is governed by polar effects as well as the stability of the product radicals, whereas in the latter case, the regioselectivity of addition is strongly influenced by polar effects alone.

In intramolecular reactions, the regioselectivity of cyclisation is well documented.$^{30,35}$ Due to the molecular geometry of the transition state, the 5-exo mode is preferred to the 6-endo in the radical cyclisation of 5-hexenyl radical (1.37) below.$^{30,35}$

**Scheme 1.17**

The preference for 5-exo cyclisation can be affected by changing the substituents on the unsaturated moiety.$^{36,37}$ In **1.40**, the presence of the amide substituent leads to the exclusive formation of the 6-endo compound **1.41**.$^{37}$ However, on putting a trimethylsilyl substituent on the alkyne **1.42**, the preference is completely reversed.$^{36}$ This is believed to have arisen as a result of steric control.
In a recent review by Giese\textsuperscript{32} on the stereoselectivity of intermolecular free radical reactions, it became apparent that the problem of stereoselectivity is not a trivial one. The review illustrates that stereoselectivity is often unpredictable as it depends on many factors such as the steric influence of substituents on the conformation of the radical, torsional and stereoelectronic effects. In the case of hydrogen abstraction reactions, stereoselectivity may even depend on the nature of the hydrogen donor.\textsuperscript{38} For example, the addition of cyclohexyl radicals to phenylacetylene (1.44) gives radical 1.44a, which can subsequently abstract hydrogen from a hydrogen donor from either the same side as the cyclohexyl group (syn) or the opposite side (anti). It was found that the difference in the activation enthalpies between the anti and the syn approach ($\Delta H(anti)-\Delta H(syn)$) increases with decreasing reactivity of the hydrogen donor (see Table 1.3). This is because slow hydrogen donors have late transition states resulting in a smaller distance between the reacting centres. Since this necessitates a closer approach of the hydrogen donor to the radical centre, the steric interaction between the hydrogen donor and the cyclohexyl group is more severe. Conversely, very reactive hydrogen donors yield products with low selectivity.
Scheme 1.19

Table 1.3

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Rate constant(^\text{1}) (k_H) (L mol(^{-1})s(^{-1}))</th>
<th>(\Delta H\text{(anti)} - \Delta H\text{(syn)}) (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-C(<em>6)H(</em>{11})HgH</td>
<td>10(^7)</td>
<td>2.5</td>
</tr>
<tr>
<td>Bu(_3)SnH</td>
<td>10(^6)</td>
<td>4.6</td>
</tr>
<tr>
<td>c-C(<em>6)H(</em>{12})</td>
<td>1</td>
<td>11.7</td>
</tr>
</tbody>
</table>

\(^1\) The rate constant for hydrogen transfer to alkyl radicals at 20\(^\circ\)C.

In radical additions, it is well established that stereoselectivity is also affected by the substitution on the alkene.\(^32\)

It is therefore difficult to predict and control the stereochemical outcome of radical reactions. Despite this, high diastereoselectivities in radical reactions have been reported. Some examples are illustrated below:

Some reactions are stereospecific. \(S_\text{H2}\) displacement at a sulphoxide centre is similar to \(S_N2\) processes in that it proceeds with concerted bond formation and fragmentation.\(^39\) The net result is inversion of configuration.
The steric course of intramolecular reactions is known to a large extent and the control of stereoselectivity is generally good.\textsuperscript{30,35} For example, the 5-exo cyclisation of 5-hexenyl radical with 2 or 4 substituents occurs with the predominant formation of the \textit{trans}-compound whereas 1 or 3 substituted radicals preferentially form the \textit{cis}-compound (see Scheme 1.21).

Also in radical cyclisation, \textit{cis} fusion of ring systems usually predominates when 5, 5 or 6, 5 rings are constructed.\textsuperscript{18,40}
Other examples of high stereoselectivity in intramolecular cyclisations are shown below.41,42

Cyclisation of the radical derived from 1.55 (Scheme 1.23) gives two products. In the transition states, the overlap between the radical centre and the π-system of the olefin is better when the butenyl substituent is axial. The conformation with the butenyl substituent axial gives rise to 1.56a which was found to be the major product.42
From Scheme 1.24, the exclusive and unexpected 1,5-trans stereochemistry of 1.58 is attributed to steric constraints on the transition state structure caused by the dioxane ring and the bulky substituents, i.e. phenyl and butenyl groups.\(^{41}\)

Intermolecular reactions involving cyclic radicals have been known to give high diastereoselectivities.\(^ {32}\) In the synthesis of 1.60, the intermolecular addition of the sugar radical derived from 1.59 to acrylonitrile occurs stereoselectively to form predominantly the \(\alpha\)-epimer.\(^ {43}\) The high selectivity was attributed to stereoelectronic effects due to the adjacent oxygen.

**Scheme 1.25**

```
\[\text{AcO} \quad \text{AcO} \quad \text{Br} \]
\[\text{AcO} \quad \text{AcO} \quad \text{AcO} \quad \text{Br} \]
\[\text{(1.59)} \]
\[\text{CN} \quad \text{Bu}_2\text{SnH, hv} \]
\[\text{AcO} \quad \text{AcO} \quad \text{AcO} \quad \text{CN} \]
\[\text{(1.60)} \]
\[70\% \text{ yield} \]
```

Another example of high diastereoselectivity is shown below:\(^ {44}\)

**Scheme 1.26**

```
\[(1.61) \]
\[\text{Bu}^1\text{HgCl, NaBH}_4 \]
\[\text{(1.62a)} \quad \text{(1.62b)} \]
\[\text{(1.61a)} \]
\[(1.62a)/(1.62b) = 94:6 \]
```
Here, the bulky t-butyl group controls the direction of attack of the reagent (in this case, alkylmercury hydride) onto the radical 1.61a such that preferential attack occurs opposite to the t-butyl group resulting in the predominant formation of the cis-compound 1.62a.

1.3 Aim of the research

In this study, by measuring the reactivity of captodatively stabilised radicals, we will be able to determine if captodative stabilisation is manifested kinetically. Besides this, we will also attempt to study the regio- and diastereo-selectivity of radical reactions involving these compounds. We will show that with careful choice of the attacking radical, the regioselectivities can be changed. Furthermore, we will also demonstrate that the diastereoselectivities of radical reactions can be profoundly affected by the presence of different substituents in the substrate.
References: Chapter 1


2. For an excellent review on radical reactions in organic synthesis, refer to D.P. Curran, Synthesis, 1988, p 417 (part 1) and 489 (part 2).


Chapter 2: A kinetic study of the Captodative Effect
Chapter 2

Introduction

There is much controversy in the literature regarding the existence of kinetic evidence for captodative stabilisation. In this chapter, attempts will be made to examine some kinetic aspects of this subject by studying the rates of captodatively substituted compounds in three types of reactions - reduction, bromination and addition reactions.

2.1 A study of the effects of different donor and acceptor substituents on the rate constants for reduction by tributyltin hydride

It is well known that radical precursors of the type RX, where X=halogen, SR', SeR', NO₂₁,₂,₃ can be easily reduced by Bu₃SnH via a radical mechanism to the corresponding alkane, RH. The reduction of sulphur and chloro precursors with Bu₃SnH were chosen as the model reactions in our kinetic studies as the rate of the generation of the alkyl radical R•, is known to be relatively slow.⁴ The aim was to study the relative rate constants for reduction of appropriate pairs of compounds R¹X and R²X based on the competition method shown in Scheme 2.1.

Scheme 2.1

\[
\begin{align*}
\text{Bu}_3\text{SnH} & \xrightarrow{AIBN} \text{Bu}_3\text{Sn}^+ \quad (a) \\
\text{Bu}_3\text{Sn}^+ + R^1X & \xrightarrow{k_1} R^1 + \text{Bu}_3\text{SnX} \quad (b) \\
\text{Bu}_3\text{Sn}^+ + R^2X & \xrightarrow{k_2} R^2 + \text{Bu}_3\text{SnX} \quad (c) \\
R^1 + \text{Bu}_3\text{SnH} & \rightarrow R^1\text{H} + \text{Bu}_3\text{Sn}^+ \quad (d) \\
R^2 + \text{Bu}_3\text{SnH} & \rightarrow R^2\text{H} + \text{Bu}_3\text{Sn}^+ \quad (e)
\end{align*}
\]
In this scheme, the rate constants for the generation of the two different types of radicals are not the same, as it is known that the rate constant for the chain propagating step by tributyltin radicals on substrate RX is very dependent on the nature of R.\(^1,4,6\) In our case, the rates of formation of captodative radicals and non-captodative radicals are expected to be different.

The relative rate constants can be calculated from the expression below:\(^5\)

\[
\frac{k_1}{k_2} = \frac{\log[R_1X]_o - \log[R_1X]_t}{\log[R_2X]_o - \log[R_2X]_t},
\]

Two methods for the calculation of relative rate constants \((k_1/k_2)\) can be used. One method involves the measurement of the consumption of starting materials \(R_1X\) and \(R_2X\) and the other, the formation of products \(R_1H\) and \(R_2H\), where

\[
[R_1X]_t = [R_1X]_o - [R_1H]
\]

\[
[R_2X]_t = [R_2X]_o - [R_2H]
\]

\([R_1X]_o\) is the initial concentration of \(R_1X\) and \([R_1X]_t\) is the concentration of \(R_1X\) after time \(t\). These can be determined by gas chromatographic analysis or by \(^2\)H nmr spectroscopy. However, the kinetic equation (1) is based on the assumption that the only significant reactions are those shown in Scheme 2.1, i.e. all the generated alkyl radicals are converted to the alkanes. This is only likely to be true when the rate constants for steps (d) and (e) are large enough so that competing side reactions are not important. The experimentally determined rate constants\(^4\) for the formation of alkyl radicals, steps (b) and (c), where \(X=\text{Cl}\) or sulphides, are in the range of \(10^2-10^4\) M\(^{-1}\)s\(^{-1}\) at \(25^\circ\)C; this can be compared with trapping rate constants for steps (d) and (e) of ca \(10^6\) M\(^{-1}\)s\(^{-1}\).\(^7\) In most cases, trapping rate constants \(k_H\) demonstrate relative insensitivity to the nature of \(R\).\(^7,8\) However, for the highly stabilised captodative radicals, this may no longer be true as the trapping rate constant may be decreased. For instance, the highly stabilised benzyl radical has a value\(^9\) for \(k_H\) at \(25^\circ\)C of \(\sim 10^4\) M\(^{-1}\)s\(^{-1}\) and it seems likely that the trapping rate constant of captodative radicals by Bu\(_3\)SnH will not be smaller than this.
In order to choose an appropriate system for the study of captodative stabilisation, several pairs of compounds were screened. For competition experiments, as analysed by gas chromatography, accurately weighed amounts of the two substrates (~0.1 mmol each), a few crystals of AIBN (ca 2 mg) and an internal standard (t-butylbenzene) in 300 µl of solvent were placed in an ampoule. A known amount of Bu$_3$SnH (0.1 mmol) was introduced and the ampoule was degassed by repeated freeze-thaw cycles, sealed and left overnight in an oil bath at 80°C. The contents were then analysed by gas chromatography (gc) to measure the disappearance of the substrates and to also measure the relative proportions of reaction products. For competition experiments analysed by $^2$H nmr spectroscopy, Bu$_3$SnD replaced Bu$_3$SnH and accurate integration of the deuterated products gave the relative proportions of products A and B formed in the reaction.

From the preliminary studies conducted at 80°C, the following results were obtained.

TABLE 2.1: Relative rates of reduction by tributyltin hydride/deuteride at 80°C.

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>$R^1X$</th>
<th>$R^2X$</th>
<th>$k_1/k_2^a$</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeOCHCICO$_2$Me (2.1)</td>
<td>CH$_3$CH$_2$CHClCICO$_2$Me (2.2)</td>
<td>3.0</td>
<td>gc</td>
</tr>
<tr>
<td>2.</td>
<td>MeOCH(SPh)CO$_2$Me (2.3)</td>
<td>PhSCH$_2$CO$_2$Me (2.4)</td>
<td>12</td>
<td>$^2$H nmr</td>
</tr>
<tr>
<td>3.</td>
<td>MeOCH(SPh)CO$_2$Me (2.3)</td>
<td>CH$_3$CH$_2$CH(SPh)CO$_2$Me (2.5)</td>
<td>2.5</td>
<td>gc</td>
</tr>
<tr>
<td>4.</td>
<td>(PhS)$_2$CHCO$_2$Me (2.6)</td>
<td>CH$_3$CH$_2$CH(SPh)CO$_2$Me (2.5)</td>
<td>9.0</td>
<td>gc</td>
</tr>
<tr>
<td>5.</td>
<td>PhSCHCICO$_2$Me (2.7)</td>
<td>ClCH$_2$CO$_2$CH$_2$CH$_2$Ph (2.8)</td>
<td>1.6</td>
<td>gc</td>
</tr>
<tr>
<td>6.</td>
<td>PhSCHCICO$_2$Me (2.7)</td>
<td>PhSCH$_2$Cl (2.9)</td>
<td>14</td>
<td>gc</td>
</tr>
</tbody>
</table>

$^a$ These values refer to relative rate constants obtained from starting material analysis.
On the basis of the preliminary studies, methyl bis-2-phenylthioacetate (2.6) and methyl 2-phenylthiobutyrate (2.5) (entry 4, Table 2.1) were chosen for further investigation. Gas chromatography was used for the analysis of products and starting materials. It was found that the relative rate constants \(k_1/k_2\) obtained from starting material analysis were inconsistent with those from product analysis. For instance, from starting material analysis, \(k_1/k_2\) was 9 whereas from product analysis, \(k_1/k_2\) was found to be 30. In an attempt to investigate the reason for this large discrepancy, it was revealed that losses of methyl butyrate (product of the reaction of 2.5 with \(\text{Bu}_3\text{SnH}\)) of about 10% were observed. To prove this, an artificial mixture (in proportions approximating a typical reaction mixture) of known amounts of methyl butyrate and an internal standard (t-butylbenzene) was injected into the gc under the conditions used for analysis. From a predetermined plot of response ratios of methyl butyrate versus t-butylbenzene, it was possible to estimate the amount of methyl butyrate present in a reaction mixture. The results indicated that a smaller than expected value for methyl butyrate was obtained, thus indicating that a loss of methyl butyrate had occurred. This loss although small, is magnified through the usage of equation (1) due to the small amounts of methyl butyrate formed in the reaction.* Consequently, the calculation of relative rate constant based on product studies by gc analysis is deemed unreliable especially when the difference in the relative rate constants is large and the products are volatile.

The report\(^{10}\) that large rate enhancements would be predicted for reactions of captodative radicals in polar solvents prompted an investigation of a solvent effect on the relative rates of reaction. In view of the problems encountered with the above analysis, the relative rate constants \(k_1/k_2\) were calculated only on the basis of the

---

* Another potential problem arises from the fact that the product from the reaction of 2.6 with \(\text{Bu}_3\text{SnH}\) was methyl phenylthioacetate (2.4) which can undergo further abstraction to ultimately give methyl acetate. Because of its volatility, this was not detected under our chromatographic conditions. However, if this was a significant problem, then \(k_1/k_2\) determined from product studies would be smaller than that for starting material analysis. In fact, the reverse was observed.
disappearance of starting materials, using both gc and hplc. The results are shown in Table 2.2.

Table 2.2: The relative rate constants for reduction of substrates (2.5) and (2.6) in different solvents at 80°C.

<table>
<thead>
<tr>
<th>entry no.</th>
<th>Solvent</th>
<th>$k_1/k_2$</th>
<th>$\varepsilon_1(25^\circ\text{C})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzene</td>
<td>gc</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>dimethoxyethane</td>
<td>gc</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>ethanol</td>
<td>gc</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>i-propanol</td>
<td>gc</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>t-butanol</td>
<td>gc</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>$N,N$-dimethylformamide</td>
<td>gc</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>acetonitrile</td>
<td>gc</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>dimethylsulphoxide</td>
<td>gc</td>
<td>6</td>
</tr>
</tbody>
</table>

$^1$ Dielectric constants of solvents, taken from reference (11).

From these results, there appears to be some scatter in the relative rate constant data in different solvents. However, there is in fact a slight increase in relative rate constants in alcoholic solvents and a slight decrease in polar solvents. This may not be very significant as due to the nature of the kinetics, the values of the relative rate constants are not very accurate. The large difference in the relative rate constants of these two compounds causes the log term to be very sensitive to small experimental errors. Overall, there appears to be no marked increase in the relative rate constants with changing solvent polarity.

Another system was tested where the relative rate constants ($k_1/k_2$) are closer to each other and hence would not be so sensitive to small experimental errors. Methyl 2-chloro-2-methoxyacetate (2.1) and methyl 2-chlorobutyrate (2.2) were
chosen. A value of $k_1/k_2=3$ was found by both starting material and product analysis using gc analysis (where $R^1X$ is the captodative reactant) (see entry 1, Table 2.1). However, this pair of compounds was not suitable for solvent studies as methyl 2-chloro-2-methoxyacetate (2.1) reacts both with water and alcoholic solvents, and decomposes in polar solvents such as $N,N$-dimethylformamide.

When the sulphur analogs 2.3 and 2.5 (entry 3, Table 2.1) were used, a relative rate constant $(k_1/k_2)$ of 2.5-3.0 was obtained at 80°C. This relative rate constant value was suitable for the competitive studies and the sulphur precursors were stable under a variety of reaction conditions.

Thus with these compounds in hand, attempts were made to measure the relative rate constants of reaction directly by esr spectroscopy. To do this, a weighed mixture of the two substrates, in an appropriate solvent was photolysed in the esr cavity in the presence of either Bu$_6$Sn$_2$/di-t-butylperoxide (to generate tributyltin radicals) or Et$_3$SiH/di-t-butylperoxide (to generate triethylsilyl radicals). A portion of the spectrum was chosen such that there is little or no overlap of the spectrum to be measured. The spectrum is then recorded digitally and the concentrations of the radicals determined by computer simulation.$^{12}$

When the sulphur precursors 2.3 and 2.5 were treated under the above conditions with Bu$_6$Sn$_2$/di-t-butylperoxide or Et$_3$SiH/di-t-butylperoxide, the radicals that resulted from the abstraction of the sulphur group were formed in competition with the abstraction of the $\alpha$-hydrogen in 2.3 by t-butoxy radicals. This is because the rate of generation of radicals from the sulphur precursors is slow.$^4$

To avoid this problem, the chloro compounds 2.1 and 2.2 were used as radical precursors. Photolysis of an accurately determined mixture of substrates with Bu$_6$Sn$_2$/di-t-butylperoxide gave the required radicals 2.1a and 2.2a (see Scheme 2.2).
The ESR spectrum of radical 2.1a was complicated by the formation of two rotamers. This can still be easily analysed and simulated, as the hyperfine splitting constants are already known. The resulting relative rate constants obtained by measurement of the concentration of radicals by computer simulation were found to be $k_1/k_2=20$ at 240 K and $k_1/k_2=17$ at 300 K (where $k_1$ refers to the rate constant of the captodative reactant).

These results show that the relative rate constants can be affected by changes in the temperature, as higher reactivity is now observed for one substrate versus the other. The dependence on temperature implies that the difference in the reactivity must arise from the activation energy term (and not the entropy term) in the Arrhenius expression. No attempts were made to conduct ESR solvent studies on this system as there were problems associated with the solubility of these precursors at low temperatures.

The effect of different solvents on the relative rate constants for reduction of the sulphur precursors 2.3 and 2.5 was examined at 80°C and analysed by GC. The results are summarised below.
Table 2.3: The effect of solvents on the relative rate constants for reduction of (2.3) and (2.5) at 80°C.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$k_1/k_2$ (s. material)</th>
<th>$k_1/k_2$ (product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzene</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>dimethoxyethane</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>t-butanol</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>3.2</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The results clearly indicate that there is no dependence of the relative rate constants ($k_1/k_2$) on the nature of the solvent.

In order to study the individual effect of a donor and acceptor substituent as compared to captodative systems, the relative reactivities of substrates 2.12-2.14 were also studied. The data were combined with that obtained above and a relative reactivity scale was established (see Table 2.4).

Table 2.4: Relative reactivity of substrates in the reduction reactions with tributyltin hydride.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Relative reactivity$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CH$_3$CH(SPh)(CH)$_2$CH$_3$ (2.12)</td>
<td>1.0</td>
</tr>
<tr>
<td>2. BuOCH$_2$SPh (2.13)</td>
<td>1.6</td>
</tr>
<tr>
<td>3. MeOCH(SPh)CH$_3$ (2.14)</td>
<td>2.1</td>
</tr>
<tr>
<td>4. CH$_3$CH$_2$CH(SPh)CO$_2$Me (2.5)</td>
<td>13</td>
</tr>
<tr>
<td>5. MeOCH(SPh)CO$_2$Me (2.3)</td>
<td>38</td>
</tr>
<tr>
<td>6. (PhS)$_2$CHCO$_2$Me (2.6)</td>
<td>117$^b$</td>
</tr>
</tbody>
</table>

$^a$Unless specified otherwise, the data are derived from both starting materials and product analysis.

$^b$From starting material analysis.
From these results (c.f. entry 1 and 4, Table 2.4), we observe that a carbomethoxy substituent greatly enhances the rates of reaction. This is in accordance with results obtained previously by Beckwith and Pigou who found that the order of reactivity of RX with tributyltin radicals is as shown below for any series of compounds where X is a constant.

\[
XCH_2CO_2Et > RCH_2OCH_2X > RCO_2CH_2X > RCH_2X
\]

From entries 2 and 3 in Table 2.4, it is apparent that the presence of a methoxy or butoxy substituent results in small rate increases. The small rate enhancement due to the methoxy group and the large rate enhancement due to the carbomethoxy substituent can be attributed in part to polar effects arising as a result of the nucleophilic nature of the attacking tributyltin radicals. It can also be seen from the results (entry 5, Table 2.4), that the presence of both a methoxy (donor) substituent and a carbomethoxy group (acceptor) causes the relative rate to increase slightly. If the relative rates are additive, then the presence of a methoxy and a carbomethoxy substituent should give rise to a value of 13 (entry 4, Table 2.4) x 2.1 (entry 3, Table 2.4) = 27. However, the experimentally observed value was 38. These results presumably indicate that the expected captodative stabilisation of products is influencing the rate of formation of radicals. It is also interesting to speculate as to the difference in reactivities of compounds 2.3 and 2.6 (entries 5 and 6, Table 2.4). Compound 2.6 is more reactive than compound 2.3. This is attributed to the stabilising effect of a phenylthio group as compared to a methoxy substituent. Previous studies have indicated that sulphur groups are good in electron sharing conjugation, where the sulphur atom accepts the odd electron by expanding its valence shell (see Scheme 2.4). The stabilising effect of a sulphur group was estimated to be as effective as a cyano group.

Scheme 2.4

\[
\begin{align*}
\text{S} & \quad \text{C} \\
\text{S} & \quad \text{C}
\end{align*}
\]
The extent to which the stability of a product is reflected in the transition state energy depends on the shape of the energy diagram.\textsuperscript{16} The results here show that captodative stabilisation of the radicals studied above is manifested kinetically but only to a small extent. A possible reason for this is that in fast reactions like these, the transition state will be reactant-like and the rates of reaction may not or only slightly reflect the stability of the product radical. Also, in a competitive type experiment, if the two reaction curves have similar shapes, then the relative rate constants ($k_1/k_2$) will reflect the relative stability of radicals $R_1^\cdot$ and $R_2^\cdot$. This is not so if the shapes of the two curves are not the same.

From the results obtained in the systems chosen for study, it was found that in polar solvents the relative rate constant did not change. This is in contradiction to the theoretical calculations by Katritzky\textsuperscript{10} who predicted that captodative stabilisation will be greatly enhanced in polar solvents due to the increasing importance of the contributing charged resonance structures. It is inconceivable that a stabilisation with the magnitude predicted by Katritzky\textsuperscript{10} (up to 30 kcal/mol) is not reflected in the reaction rates. Thus one is forced to the conclusion that the magnitude of stabilisation in polar solvents cannot be as large as predicted.

These studies are important in relation to biochemical systems where captodative radicals, e.g. amino acid radicals, may be generated in a polar medium such as water.\textsuperscript{17-19} The stability and reactivity of such captodative radicals could be significant to the study of biological processes.

As an extension to our model experiments, the halogen abstraction of amino acids by tributyltin radicals was studied. The relative rate constant ($k_1/k_2$) was found to be large in a typical competitive experiment involving methyl 2-chloro-hippurate ($R_1^X$, (2.15)) and methyl 2-chlorobutyrate ($R_2^X$, (2.2)) as substrates in dimethoxyethane.

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{CO}_2\text{Me} \\
\text{H} & & \\
(2.15) & & \\
\text{Cl} & & \text{MeOCHClCO}_2\text{Me} \\
(2.2)
\end{align*}
\]
This was rather surprising as earlier studies with model compound, methyl 2-methoxy-2-phenylthioacetate (2.3) did not display a large kinetic effect. However, there were difficulties in the gas chromatographic analysis as methyl 2-chlorohippurate (2.15) could not be detected. There was also the problem of the low volatility of methyl hippurate (2.16, product of reduction of 2.15 with Bu₃SnH) which gave inconsistent ratios from gc analysis. These results were checked by ²H nmr spectroscopy using Bu₃SnD instead of Bu₃SnH and again the amounts of methyl butyrate detected were very small. Due to large differences in the relative rate constants of reaction, quantification using the kinetic equation (1) is inaccurate, and one can only conclude that the relative rate constant (k₁/k₂) is large.

It would seem that there are apparent differences in the substrates 2.3 and 2.15. Large rate enhancement is observed with the amino acid derivative 2.15 which may imply that captodative stabilisation is more significant in that case. However, a definite conclusion cannot be reached as the effect of the amino group (donor substituent only) on the rate constant for reduction has not been studied due to the difficulties in the preparation and handling of the α-chloroamines and α-chloroamides. In the absence of any other additional evidence, one can only speculate that this increase in reactivity may have resulted from polar effects. This will be discussed in Section 2.2. An alternative explanation for the enhanced reactivity of 2.15 compared to 2.3 is that a change of mechanism* may have occurred with the reduction of nitrogen containing substrates; however this has not been proven.

2.2 Steric and conformational effects on the relative rate constants for the bromination of captodatively substituted compounds

Bromination with NBS can occur under free radical conditions although the nature of the chain carrier is still uncertain (this will be discussed in Chapter 4). However, reactions involving the Br• chain transfer (which we believe to be the main chain carrier in the hydrogen abstraction step of these substrates, see Chapter 4) is

* For an alternative mechanism for reduction with Bu₃SnH, refer to reference (21).
believed to have a late transition state and it is partly for this reason that this system was chosen for study.

In these experiments, known quantities of the two substrates (~0.3 mmol each) were weighed and a solution was made up to 5 ml with CD$_2$Cl$_2$ in a volumetric flask. To this was added NBS (0.3 mmol) (the whole procedure was carried out in the dark) and a portion of the reaction mixture was placed in an nmr tube and degassed by either freeze-thaw methods or by bubbling argon through the reaction mixture. The $^1$H nmr spectrum of the reaction mixture at time t=0 was checked. Then the reaction mixture was irradiated with a sunlamp for 30-60 minutes. The reaction was monitored directly in the nmr tube. Integration of absorptions corresponding to the starting materials and products (wherever possible) were obtained and the relative rate constants ($k_1/k_2$) were calculated from equation (1), Section 2.1.

Variations of this method were also used: In some cases, the competitive reactions were conducted by refluxing the two substrates, NBS and AIBN in CC$_4$. After 30 minutes, the reaction mixture was filtered, the filtrate evaporated and its $^1$H nmr spectrum recorded. As before, absorptions corresponding to the starting materials and products were integrated and the relative rate constants were calculated using equation (1). The relative rate constants obtained in this way were the same as those obtained when the reaction was conducted directly in CD$_2$Cl$_2$.

Initial competitive experiments with methyl methoxyacetate (R$_1$H, (2.10)) and methyl hippurate (R$_2$H, (2.16)) with NBS gave a value of $k_1/k_2$=~2.

$$\text{MeOCH}_2\text{CO}_2\text{Me}$$

(2.10)

$$\text{PhN}$$

(2.16)

The observed relative rate constant can be rationalised in terms of polar effects. The chain carrier for the bromination reaction, bromine radical or succinimidyl radical, is electrophilic in nature and therefore the reaction would be faster where there is an electron-rich site. From the $\sigma^+_p$ values of the N-benzoylamino (-0.60) and methoxy...
substituent (-0.78), it is apparent that the N-benzoyleamino substituent is more electron withdrawing than the methoxy substituent; hence the electron density available in the former case is decreased relative to the the reacting centre in compound 2.10. It should be noted that in the previous studies with the Bu3SnH reduction of 2.1 and 2.15 versus methyl chlorobutyrte (2.2, Section 2.1), compound 2.15 displayed higher reactivity compared to compound 2.1. The two studies (NBS bromination and Bu3SnH reduction) do not necessarily contradict each other as, if polar effects are important, then the difference in the two reactions could be attributed to the difference in the nature of the chain carrier, i.e. tributyltin radical is nucleophilic24 whereas the bromine radical is electrophilic.\textsuperscript{22}

There have been suggestions\textsuperscript{13,25} that maximum captodative stabilisation will only occur when the delocalised radical can assume a planar configuration due to the maximum overlap of the orbitals. This was tested by synthesizing the cyclic analogs 2.17 and 2.18.

\[\text{N}\text{pro} (2.17)\]  
\[\text{Ph} (2.18)\]

Though NBS bromination of these compounds will be discussed later (Chapters 4 and 5), it is presently sufficient to note that bromination of 2.17 and 2.18 with NBS occurs with high regioselectivity at the captodative centre. The rate constants for bromination of the cyclic analogs were measured against their acyclic counterparts in the usual manner. These results are shown in Table 2.5.
Table 2.5: Relative reactivities of NBS bromination

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Substrates</th>
<th>Relative reactivities</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td><img src="image1" alt="Image" /></td>
<td>1.0</td>
</tr>
<tr>
<td>(2)</td>
<td><img src="image2" alt="Image" /></td>
<td>2.5</td>
</tr>
<tr>
<td>(3)</td>
<td><img src="image3" alt="Image" /></td>
<td>2.6</td>
</tr>
<tr>
<td>(4)</td>
<td><img src="image4" alt="Image" /></td>
<td>4.4</td>
</tr>
<tr>
<td>(5)</td>
<td><img src="image5" alt="Image" /></td>
<td>6.3</td>
</tr>
<tr>
<td>(6)</td>
<td><img src="image6" alt="Image" /></td>
<td>12.5</td>
</tr>
</tbody>
</table>
In both cases, it was found that contrary to our speculations the cyclic analogs reacted more slowly than their acyclic counterparts (c.f. entry 2 with entry 6, and entry 4 with entry 5 in Table 2.5). A possible rationale for this is that hydrogen abstraction by the bromine radical from the acyclic derivatives can occur from any direction whereas this is not possible in the reactions with the cyclic compounds due to steric constraints imposed by either the t-butyl substituent at C-2 and/or the amide protecting group.

To test this hypothesis, compounds 2.19 and 2.20 were synthesized and the rate constants for bromination relative to the acyclic analogs 2.10 and 2.16 were measured.

Surprisingly, the results show that in the absence of the t-butyl substituent at C-2 the reaction rate was decreased rather than increased (c.f. entries 1, 2, and entries 3, 4 of Table 2.5).

In order to attempt to rationalise these results, AM1-UHF\(^{26a}\) calculations were carried out to probe the conformations of the parent compounds. The resulting parameters were fed into another program (XTAL\(^{26b}\) used in X-ray crystallography) from which it was possible to get additional information, e.g. deviation from planarity and dihedral angles. The data from the calculations are summarised in Table 2.6. It should be noted that although the theoretical calculations are useful in helping in the interpretation of the results, the precision of these calculations is open to question.

The numbering system used in Table 2.6 is as shown below.
Table 2.6: Parameters derived from AMPAC/XTAL calculations.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Charge</th>
<th>Deviation from planes</th>
<th>Dihedral angles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atoms #</td>
<td></td>
<td>defined by</td>
</tr>
<tr>
<td></td>
<td>1 2 3 4 5 6</td>
<td></td>
<td>O(6)-C(4)- C(2)-X(1)-</td>
</tr>
<tr>
<td>2.19</td>
<td>.29 .10 - .27 .28 - .05 - .26</td>
<td>2.23°</td>
<td>C(5)-H(5) C(5)-H(5)</td>
</tr>
<tr>
<td>2.17</td>
<td>-.29 .15 - .27 .28 - .06 - .27</td>
<td>0.95°</td>
<td>63,62 117,122</td>
</tr>
<tr>
<td>2.20</td>
<td>-.33 .07 - .26 .29 - .09 - .26</td>
<td>4.07°</td>
<td>54,66 109,129</td>
</tr>
<tr>
<td>2.18</td>
<td>-.32 .13 - .25 .29 - .09 - .28</td>
<td>2.89°</td>
<td>54,66 110,127</td>
</tr>
</tbody>
</table>

1 The numbering of the atoms is shown above.

2 Deviation of the plane is defined by the difference in the angles of planes defined by atoms 1,5,4 and 5,4,3.

3 The two values given are the absolute magnitude of the dihedral angles of the two hydrogens at C-5.

From the data, the only significant difference found in the parameters for the dioxolanones and oxazolidinones is in the planarity of the ring. This was measured as the deviation between the two planes defined by atoms 1,5,4 and 5,4,3. The planes were chosen so as to include the captodative position. In the dioxolanone series, deviation from planarity for dioxolanone 2.17 is only 0.95° compared to a value of
2.23° in dioxolanone 2.19. Similarly, a deviation of 2.89° was found for oxazolidinone 2.18, compared to a value of 4.07° for oxazolidinone 2.20. The results from the calculations indicate that the greater the deviation from planarity (as with the unsubstituted dioxolanones and oxazolidinones), the slower is the rate of reaction (as demonstrated by the relative reactivities), as the conformation is no longer optimal for hydrogen abstraction. The reaction may be very sensitive to small deviations like these.

One would expect to see decreasing deviation from planarity as the bulkiness of the substituent at the acetal centre increases. Experimentally (see Table 2.7), when the rate constants for the bromination of dioxolanones 2.21 and 2.22 were measured relative to methyl methoxyacetate (2.10) and a relative reactivity scale established, increasing reactivity was observed for increasing size of the substituent at the acetal centre. Thus, the rates were fastest when the substituent at C-2 was an i-propyl or t-butyl and slowest when the substituent at C-2 was a hydrogen. This is consistent with the prediction that decreasing reactivity must arise from increasing deviation from planarity of the ring.

\[
\text{(2.21)} \quad \text{(2.22)}
\]

This brings us back to the original question - why are the acyclic analogs in all these cases much faster than the cyclic analogs? The answer to this, we believe, lies in the torsional angles of the abstracted hydrogen. From Table 2.6, it can be seen that the torsional angles O(6)-C(4)-C(5)-H(5) for all the cyclic compounds are similar and in the region of 54-60°. For the best overlap of orbitals, the optimum torsional angle of 90° is required. This angle is not possible in the cyclic systems where there are
rigid constraints of the ring. However, it is possible with the acyclic compounds. This can account for the difference in the reactivity of cyclic versus acyclic analogs.

Table 2.7: Relative reactivities of bromination for a series of 2-substituted dioxolanones.

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Substrates</th>
<th>Relative reactivities</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td><img src="image1" alt="Image" /> (2.19)</td>
<td>1.0</td>
</tr>
<tr>
<td>(2)</td>
<td><img src="image2" alt="Image" /> (2.21)</td>
<td>1.7</td>
</tr>
<tr>
<td>(3)</td>
<td><img src="image3" alt="Image" /> (2.22)</td>
<td>2.5</td>
</tr>
<tr>
<td>(4)</td>
<td><img src="image4" alt="Image" /> (2.17)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*a*The data were measured from both product and starting materials analysis.
The theoretical calculations also revealed some additional information regarding the heats of formation. The heats of formation of 2.17 and its corresponding captodative radical 2.17a were found to be -140 kcal/mol and -111 kcal/mol respectively. From the literature, the heat of formation of the hydrogen atom (H•) is 52 kcal/mol and hence from the equation below, the theoretical bond dissociation energy of C₅-H₅ at the captodative position was calculated to be 81 kcal/mol.

\[ D (R-H) = \Delta H_f (R^+) + \Delta H_f (H^+) - \Delta H_f (R-H) \]

Scheme 2.5

This is significantly lower than the dissociation energies of the acyclic compounds shown below.

- H-CH₂OCH₃: 93 kcal/mol
- H-CH₂COCH₃: 98 kcal/mol

The weakening of the σ-bond to homolysis could be interpreted as arising as a consequence of the captodative effect or it could simply be the result of steric strain such that relief of strain occurs on formation of the radical. These two possibilities cannot be distinguished on the basis of these calculations alone.

When the rate constants for NBS bromination of 2.17 and 2.18 were measured relative to each other, the results indicated that 2.18 was the more reactive (see Table 2.5).
This was rather surprising as the reverse was observed with the corresponding acyclic derivatives \textit{2.10} versus \textit{2.16}. The reason for this is unclear but upon examination of the charge density (derived from the AM1-UHF calculations\textsuperscript{26a}) at the captodative position of compounds \textit{2.18} and \textit{2.17}, it was found that the charge density at that site was higher in the oxazolidinone than in the dioxolanone (-0.09 compared to -0.06). As before, we can argue that the chain carrier for NBS reaction is electrophilic\textsuperscript{22} and thus one would expect reactions to be faster where there is a higher electron density. This explanation is not entirely satisfactory as the difference in the charge density is small and this also contradicts the known $\sigma^+_{p}$ values\textsuperscript{23} for these substituents.

Easton\textsuperscript{25} reports that the bromination of N-benzoylglycine occurs much faster than N-benzoyl derivatives of alanine and valine despite the fact that with glycine, a secondary radical is formed compared to the more stable tertiary radical from alanine and valine. This is attributed to destabilising non-bonding interactions caused by the presence of the substituent at the captodative centre.

We have reexamined this by making the corresponding derivatives of oxazolidinones. Here, the rate of disappearance of the starting materials relative to methyl hippurate \textit{2.16} was monitored and the results are given in Table 2.8.
Table 2.8: The relative reactivities in the NBS bromination of 4-substituted oxazolidinones.

\[
\text{trans-(2.24)} \quad \text{trans-(2.23)} \quad \text{cis-(2.23)} \quad (2.18)
\]

\[
\begin{array}{cccc}
\text{k/k}_{\text{std}} & 2 & 2 & 0.5 & 0.35
\end{array}
\]

where the standard is methyl hippurate (2.16) and the relative reactivities shown here have been statistically corrected.

As one can see, the reactivities of the two isomers of the alanine derivative 2.23 are very different. The \textit{trans}-isomer is four times faster than the \textit{cis}. This difference in reactivity is presumably due to steric constraints where the hydrogen to be abstracted by the attacking radical is less accessible in the \textit{cis}-isomer. The difference in the reactivities of \textit{cis}- and \textit{trans}-isomers has been observed before in the reactions of 4-t-butyl-substituted cyclohexenes and was attributed to stereoelectronic effects.²⁸

\[
\begin{array}{c}
\text{the trans isomer is 10x faster in the reduction with tributylstannane compared to cis isomer}
\end{array}
\]

In addition, similar NBS bromination studies with the isomers of 2-(t-butyl)-5-methyl-1,3-dioxolan-4-one (2.26) showed that the \textit{cis}-isomer was twelve times faster in the bromination reaction as compared to the \textit{trans}. 
This implies that abstraction of hydrogen from the less hindered face (opposite to the t-butyl substituent) is favoured in 2.26 compared to the situation with the oxazolidinone 2.23 where the hydrogen that was cis to the t-butyl substituent is easier to abstract. This may be an indication that in the oxazolidinones, the effect of the steric interference of the t-butyl group is not as great as the N-benzoyl protecting group and that the latter effect dominates. The relative rates constants ($k/k_{std}$) are in the order of valine-alanine>glycine. This presumably reflects the stability of the intermediate radical; i.e. a tertiary radical is more stable than a secondary one. The non-bonding interactions present in the acyclic system studied by Easton are eliminated due to the ring constraints. An important point to note is that the relative rate constants were measured as the rate of disappearance of starting materials by integration of the absorptions corresponding to the starting materials in the $^1\text{H}$ nmr spectrum. This is because the products of the NBS reaction with oxazolidinones 2.23 and 2.24 (see Table 2.8) were not easily identified by $^1\text{H}$ nmr spectroscopy. For a meaningful comparison of the relative rate data, it must be established that the hydrogen abstraction by bromine radical occurs only at the captodative position. The positions of bromination were determined by treating the crude reaction mixture from the NBS bromination with Bu$_3$SnD in refluxing benzene with catalytic amounts of AIBN and observing the products by $^2\text{H}$ nmr spectroscopy. In the case of the alanine derivative 2.23, the deuterated sites were consistent with products arising from the initial bromination at the captodative position. However, other non-radical processes may also occur (see Chapter 5 for details), but these side reactions do not interfere
with the relative rate constant calculations. The products of the NBS reaction with the valine derivative 2.24 have not been fully characterised. Quenching studies with Bu₃SnD indicate that abstraction may have occurred at the primary position of the i-propyl substituent, suggesting that the relative rate data above for 2.24 may not accurately represent the true value for bromination at the captodative position.

2.3 Alkyl radical addition to captodatively substituted olefins

Attempts were made to measure the rate constant for addition of an alkyl radical to captodative olefins and then compare this to the rate constant for addition to methyl acrylate.

The calibration of bimolecular reactions using radical trapping methods has been developed by Beckwith and Bowry. In a direct competitive method, a radical R• generated in the presence of a nitroxide trap and an alkene can couple with the trap to form R-T or add to the alkene to form S• which can also be trapped by the nitroxide. This is shown in Scheme 2.6 below.

Scheme 2.6

\[
\begin{align*}
\text{Precursor} & \quad \overset{+}{\longrightarrow} \quad \text{R•} \quad \overset{T}{\underset{k_T}{\longrightarrow}} \quad \text{R-T} \\
& \quad \overset{+}{\longrightarrow} \quad \text{S•} \quad \overset{T}{\underset{k_T}{\longrightarrow}} \quad \text{S-T} \\
& \quad \overset{+}{\longrightarrow} \quad \text{S-X} (\text{alkene}) \quad \overset{k_X}{\underset{+}{\longrightarrow}} \quad \text{S•}
\end{align*}
\]

\[S• = \begin{bmatrix} R \end{bmatrix}\]

Under pseudo first order conditions where [T=Trap] >> [precursor], the kinetic equation simplifies to that shown below:

* However, it must be noted that Seebach and Zimmermann (*Helv. Chim. Acta*, 1987, 70, 1104) reported that 30% bromination occurred at the acetal centre of oxazolidinone 2.23. This was not observed in our studies.
\[ \frac{k_s}{k_T} = \frac{[T]}{[S - T]} \times \frac{[S - X]}{[R - T]} \]

where \([S - X] = [alkene]\)  

However, this method would require that the products (R-T and S-T) are stable to analysis and isolation. Apart from that, the rate constants for addition must be sufficiently large to compete with the trapping of \(R^*\). Since these requirements are difficult to meet, we chose to use the radical clock trapping method developed by Beckwith and Bowry to measure the rate constants for addition to alkenes. The reaction scheme (Scheme 2.7) is shown below.

**Scheme 2.7**

From the kinetic equation below (derived from steady state analysis and pseudo first order approximation in trap and alkene), it can be seen that by measuring the amounts
of U-T and C-T formed, and by either keeping the trap or alkene concentration constant while varying the other, the rate constant for addition to alkene can be derived. Products U-T and C-T have been characterised for a variety of radical clocks\textsuperscript{31} and rate constants of radical trapping and radical rearrangement are also known.

\[
\frac{[U-T]}{[C-T]} = \frac{k_T}{k_c} [T] + \frac{k_A}{k_c} [A]
\]

\textit{where} \ A = \text{alkene} \quad \text{equation (3)}

When \([A_i]\) is constant, then

\[
\frac{k_A}{k_c} [A_i]
\]

is constant.

Concentration of trap \([T_i]\) can be varied and a plot of \([U-T]/[C-T]\) vs. \([T_i]\) will give a straight line plot, where

\[
\text{Slope} = \frac{k_T}{k_c}
\]

\[
\text{Intercept} = \frac{k_A}{k_c} [A_i] \quad \text{equation (4)}
\]

The reaction was carried out under conditions where the concentration of the peroxide of the appropriate clock was held at 20% that of the trap. The peroxide was thermolysed at 84\textdegree C in the presence of alkene and trap. The concentration of the alkene was kept constant while the trap concentration was varied. For ease of analysis, the nitrooxide\textsuperscript{32} 2.28, which has a UV chromophore, was used as the trap, instead of the more commonly available TEMPO. The reaction was conducted in cyclohexane and after completion of the reaction, the solvent was evaporated \textit{in vacuo} and the residue dissolved in methanol before analysis by reverse phase hplc. The retention times of R-T and C-T were compared with that of the authentic samples.
Initially, bis-3-(allyloxy)propanoyl peroxide (2.29) was used as the radical precursor but good separation of R-T and C-T from the other products could not be achieved by hplc. Instead, the 5-hexenyl radical, a typical alkyl radical, derived from the corresponding peroxide 2.27 (scheme 2.7) was used. The rate constant for cyclisation of the 5-hexenyl radical is given by the equation below:

\[
\log k_c = 10.37 - \frac{6.85}{\theta} \\
\text{where } \theta = 2.3RT \text{ kcal/mol}
\]

(5)

From the trapping experiments, the rate constant for the addition of alkyl radical to methyl acrylate was found to be \(1.29 \times 10^6 \text{ M}^{-1}\text{s}^{-1}\) at 84°C in cyclohexane. This is in good agreement with literature data, i.e. \(1.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}\) at 20°C in CH₂Cl₂ and \(5.2 \times 10^5 \text{ M}^{-1}\text{s}^{-1}\) at 69°C.* Bowry obtained a value of \(9 \times 10^5 \text{ M}^{-1}\text{s}^{-1}\) at 80°C in neat methyl acrylate using the radical clock/trap method as we have done above; however he used a different clock, bis-(3,3-dimethylpent-4-enyl) (2.30).

**Scheme 2.8**

* This rate constant has not been corrected for the new rate constant for 5-hexenyl cyclisation. The cyclisation rate constant used in the derivation of the Arrhenius parameters for addition to methyl acrylate was \(5.1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}\) at 69°C whereas in actual fact, this value should have been \(9.83 \times 10^5 \text{ M}^{-1}\text{s}^{-1}\) at 69°C using the data from reference (33b).
The experiments were then repeated using 2.31 synthesized according to literature methods from the N-acetylalanine methyl ester.\textsuperscript{35}

\[
\begin{align*}
\text{CH}_3\text{N} & \quad \text{CO}_2\text{Me} \\
\text{CH}_2 & \\
\text{(2.31)}
\end{align*}
\]

The measured rate constant for addition of 5-hexenyl radical to dehydroalanine 2.31 was \(4.02 \times 10^5 \text{M}^{-1}\text{s}^{-1}\) at 84°C. From the literature, it is known that the addition of cyclohexyl radical to a captodatively substituted alkene 2.32\textsuperscript{a} relative to methyl acrylate (2.32\textsuperscript{b}) as shown below gave a ratio of 0.16 at 20°C.\textsuperscript{36,37}

\[\text{Scheme 2.9}\]

\[\text{Scheme 2.10}\]

Another study with cyclohexyl radical and the substituted alkene 2.34 yielded a similar result, i.e. \(k_{\text{relative}} = 0.86\) at 20°C.\textsuperscript{36,37}

\[\text{Scheme 2.10}\]

The ratio of the rate constants for addition of an alkyl radical to the captodative olefin 2.31 versus methyl acrylate obtained in our studies at 84°C was 0.3.
The importance of polar effects in determining the rates of radical addition to olefins is well documented in the literature and is the subject of many important reviews.\textsuperscript{38} The experiments above show that the addition of alkyl radicals to an olefin is not accelerated by captodative substitution on the olefin although addition of this type would yield the highly stabilised captodative radical. Based on our results alone, it is not possible to conclude if captodative stabilisation is manifested kinetically in this system. This is because no attempts were made to study the effect of the second $\beta$-substituent on the rate constant for addition of substituted acrylates. For example, the decrease in the rate constant for alkyl radical addition to olefin 2.31 compared to methyl acrylate may be due to steric effects and not due to the absence of a kinetic captodative effect. Fortunately, a thorough study of this kind had been conducted by Giese.\textsuperscript{37,38b,39} He showed that $\beta$-substitution by radical stabilising groups (e.g. phenyl) and bulky substituents (e.g. t-butyl) have only a small influence on the rate constants for addition of alkyl radicals. Alkyl radicals are nucleophilic in their addition reaction to alkenes, and correlation of rate constants for addition with $\sigma^-$ gives a positive $\rho$ value.

Thus, polar effects are very important in radical addition reactions. In olefin 2.31, the presence of the electron donating amino group is deactivating towards nucleophilic attack and overcomes the expected activating effect determined by the formation of a captodatively stabilised radical. Hence, polar effects dominate and the rate of addition of alkyl radicals to 2.31 is slower compared to the addition to methyl acrylate. We conclude that within the limitations of our experiments, captodative substitution on alkenes does not increase the reactivity of the addition reaction.

2.4 Conclusion

The systems studied (reduction and addition reactions) have shown that captodative stabilisation has little or negligible kinetic consequence.

The relative rate constants for abstraction of halogen and/or sulphur by tributyltin radicals were found to depend strongly on the nature of the substituents. The rates were accelerated by the presence of electron withdrawing substituents
(carbomethoxy) whereas rate acceleration due to electron donating substituents (methoxy or butoxy) was found to be small. These observations indicate that polar effects are important in determining the rates of reaction with Bu₃SnH. The presence of captodative substitution in the substrates leads to small rate enhancements. This small rate enhancement could be attributed in part to the early transition state of reactions with Bu₃SnH where radical stabilising effects are deemed to be not so important. The importance of polar effects in affecting the rates of reaction was also observed in the addition of alkyl radicals to olefins. Here, substitution of the α-hydrogen of methyl acrylate with an electron donating group decreases the rate constant for addition despite the fact that a highly stabilised captodative radical will be formed.

We also failed to find any significant rate acceleration in the reduction of captodatively substituted compounds in polar solvents. The theoretical calculations by Katritzky¹⁰ predicted stabilisation of up to 30 kcal/mol for captodatively stabilised radicals in polar solvents. This amount of stabilisation, if it is truly present, should greatly enhance the rate of formation of captodatively stabilised radicals.

The idea¹³,²⁵ that maximum captodative stabilisation occur with planar delocalised radicals was explored by measuring the relative rate constants for NBS bromination of various cyclic and acyclic captodatively substituted compounds. No definite conclusion regarding this could be reached, although it is obvious from the studies that NBS bromination reactions are subject to polar effects and are also very sensitive to changes in the steric environments as well as changes in the ring conformation.
References: Chapter 2


Chapter 3: An ESR study of the Captodative Effect

Scheme 3.1

\[
\begin{align*}
\text{Mes} & \text{COOC} \text{Mes} \\
\text{Mes} & \text{CO}^+ + \text{AH} \\
\text{Mes} & \text{CO}^+ + \text{H} \\
A^+ & + B^+ \\
B^+ & + B^+ \\
\end{align*}
\]

For equation (1) to be valid, it is necessary to assume that the radical-radical termination has specificities for different radical pairs that are different. This is likely to be studied by Exner and Moust, who showed that inter-nucleophilic attack and interaction of the different...
Introduction

Electron spin resonance (esr) spectroscopy is an excellent method for the direct study of free radicals. In this Chapter, esr investigations of five-membered cyclic radicals, formed by hydrogen abstraction as well as addition reactions, will be reported. One aim of this work is to assess the kinetic importance of the captodative effect in free radical reactions.

3.1 Hydrogen abstraction from substituted 1,3-dioxolan-4-ones by t-butoxy radicals

3.1a Considerations of selectivity and reactivity

In these experiments, t-butoxy radicals were generated by the photolysis of di-t-butyldiperoxide. In the presence of two substrates with abstractable hydrogen atoms, the reaction scheme is as follows.

Scheme 3.1

\[
\begin{align*}
\text{Me}_3\text{COOCMe}_3 & \xrightarrow{\text{hv}} 2\text{Me}_3\text{CO}^* \\
\text{Me}_3\text{CO}^* + \text{AH} & \xrightarrow{k_{\text{AH}}} \text{Me}_3\text{COH} + \text{A}^* \\
\text{Me}_3\text{CO}^* + \text{BH} & \xrightarrow{k_{\text{BH}}} \text{Me}_3\text{COH} + \text{B}^* \\
\text{A}^* + \text{A}^* & \xrightarrow{k_{\text{AA}}} \text{non-radical products} \\
\text{A}^* + \text{B}^* & \xrightarrow{k_{\text{AB}}} \text{non-radical products} \\
\text{B}^* + \text{B}^* & \xrightarrow{k_{\text{BB}}} \text{non-radical products}
\end{align*}
\]

\[
\frac{k_{\text{AH}}}{k_{\text{BH}}} = \frac{[\text{A}^*][\text{BH}]}{[\text{B}^*][\text{AH}]} \quad \text{equation (1)}
\]

For equation (1) to be valid, it is necessary to assume that the radical-radical termination rate coefficients for different radical species are the same (i.e. are diffusion controlled). This is likely, as studies by Korth\(^1\) showed that even captodatively stabilised radicals undergo radical-radical termination at rates close to the diffusion-
controlled limit. In many of the following experiments, hydrogen abstraction occurred from two distinct sites of the same substrate. In this situation, equation (1) is still relevant, but of course the concentrations of AH and BH are necessarily identical.

Ingold and Malatesta\textsuperscript{2} showed that hydrogen abstraction from a variety of cyclic ethers and acetics by t-butoxy radicals is influenced by stereoelectronic factors. Reaction of t-butoxy radicals with THF gave radical 3.1a (Scheme 3.2) exclusively whereas with 1,3-dioxolane (3.2), abstraction at the site between the two oxygens (C-2) was more favourable than abstraction at C-4\textsuperscript{2} (see Scheme 3.3).

\textbf{Scheme 3.2}

\begin{center}
\begin{tikzpicture}
  \node[latent] (A) {\text{O}};
  \node[latent] at (1.5,0) (B) {\text{O}};
  \node[latent] at (3,0) (C) {\text{O}};
  \node[latent] at (1.5,1.5) (D) {\text{O}};
  \node[latent] at (3,1.5) (E) {\text{O}};
  \node[latent] at (4.5,0) (F) {\text{O}};
  \node[latent] at (4.5,1.5) (G) {\text{O}};
  \node[latent] at (6,0) (H) {\text{O}};
  \node[latent] at (6,1.5) (I) {\text{O}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.3}

\begin{center}
\begin{tikzpicture}
  \node[latent] (A) {\text{O}};
  \node[latent] at (1.5,0) (B) {\text{O}};
  \node[latent] at (3,0) (C) {\text{O}};
  \node[latent] at (1.5,1.5) (D) {\text{O}};
  \node[latent] at (3,1.5) (E) {\text{O}};
  \node[latent] at (4.5,0) (F) {\text{O}};
  \node[latent] at (4.5,1.5) (G) {\text{O}};
  \node[latent] at (6,0) (H) {\text{O}};
  \node[latent] at (6,1.5) (I) {\text{O}};
  \node[latent] at (7.5,0) (J) {\text{O}};
  \node[latent] at (7.5,1.5) (K) {\text{O}};
\end{tikzpicture}
\end{center}

\text{Ratio of } 3.2a/3.2b = 29:1

Studies by Brumby\textsuperscript{3} showed that reaction of t-butoxy radicals with \(\gamma\)-butyrolactone (3.3) gave only radical 3.3a, i.e. abstraction occurred at the position \(\alpha\)- to the oxygen (Scheme 3.4). This is presumably due to the electrophilic nature of the t-butoxy radical which favours attack at the site with the higher electron density.

\textbf{Scheme 3.4}

\begin{center}
\begin{tikzpicture}
  \node[latent] (A) {\text{O}};
  \node[latent] at (1.5,0) (B) {\text{O}};
  \node[latent] at (3,0) (C) {\text{O}};
  \node[latent] at (1.5,1.5) (D) {\text{O}};
  \node[latent] at (3,1.5) (E) {\text{O}};
  \node[latent] at (4.5,0) (F) {\text{O}};
  \node[latent] at (4.5,1.5) (G) {\text{O}};
  \node[latent] at (6,0) (H) {\text{O}};
  \node[latent] at (6,1.5) (I) {\text{O}};
\end{tikzpicture}
\end{center}
In our studies, esr spectra were recorded during the photolysis of substrates 3.4-3.10 in the presence of di-t-butylperoxide in an appropriate solvent at -31°C. With all the substrates, abstraction occurred from the captodative position (C-5) to give radicals of type A and from the acetal centre (C-2) to give radicals of type B (see Scheme 3.5). The analyses of spectra will be discussed in the following section: assignments were usually made on the basis of the multiplicities, and in some cases by comparing the g-values and the magnitudes of the splittings.

The ratios of concentrations of radicals of type A to type B, estimated from the esr spectra, are shown in Table 3.1.

**Scheme 3.5**

```
R2
(3.4)-(3.10)  \rightarrow  \frac{O}{O} \frac{O}{O} + \frac{O}{O}
(3.4a)-(3.10a) TYPE A
(3.4b)-(3.10b) TYPE B
```

**Table 3.1: Concentration ratio of type A (captodative) to type B radicals (non-captodative) derived from substrates (3.4)-(3.10).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R²</th>
<th>R¹</th>
<th>[Type A]/[Type B]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3.4</td>
<td>H</td>
<td>H</td>
<td>1.4</td>
</tr>
<tr>
<td>2.</td>
<td>3.5</td>
<td>H</td>
<td>Me</td>
<td>6.9</td>
</tr>
<tr>
<td>3.</td>
<td>3.6</td>
<td>Me</td>
<td>H</td>
<td>1.7</td>
</tr>
<tr>
<td>4.</td>
<td>3.7</td>
<td>t-Bu</td>
<td>H</td>
<td>3.2</td>
</tr>
<tr>
<td>5.</td>
<td>3.8</td>
<td>i-Pr</td>
<td>H</td>
<td>1.3</td>
</tr>
<tr>
<td>6.</td>
<td>3.9</td>
<td>Me</td>
<td>Me</td>
<td>6.6</td>
</tr>
<tr>
<td>7.</td>
<td>3.10</td>
<td>t-Bu</td>
<td>Me</td>
<td>11.3</td>
</tr>
</tbody>
</table>
The ratio of hydrogen abstraction by t-butoxy radicals at C-5 (captodative position) relative to abstraction at C-2 (acetal centre) for 1,3-dioxolan-4-one 3.4 was 1.4 (see entry 1, Table 3.1). This is surprising when one considers the observation that hydrogen abstraction of 1,3-dioxolane (3.2) (Scheme 3.3) occurs mainly at the acetal position whereas hydrogen abstraction of γ-butyrolactone (3.3) (Scheme 3.4) occurs only at the position α- to the oxygen. Both of these results were interpreted in terms of polar effects. Therefore, on the basis of polar effects alone, one would predict that abstraction at the C-5 position of dioxolanone 3.4 should be disfavoured due to the electron withdrawing nature of the ester group. However, the reverse observations suggested either that the formation of the captodatively stabilised radical was important in determining the selectivity or that the rate of hydrogen abstraction at the acetal centre (C-2) was decreased dramatically compared to the abstraction at the captodative position.

The relative rates of formation of captodative radicals can be further enhanced by increasing the acceptor capacity of the captor substituents, i.e. by changing the ester group in 3.4 to a ketone function in 3.11. In this case, only one species of free radical is observed as shown in Scheme 3.6.

Scheme 3.6

The exclusive formation of radical 3.11a again demonstrates that polar effects are no longer the dominant factors in determining the regioselectivities of hydrogen abstraction. Otherwise, the presence of the more electron withdrawing ketone group compared to the ester moiety in dioxolanone 3.4, would be expected to disfavour further abstraction at the captodative position. The results here indicate that the formation of captodatively stabilised radicals can be favoured by the presence of good
donor and acceptor groups. This was also previously observed by Beckwith and Brumby. An example from their work is given below.

Scheme 3.7

\[
\begin{align*}
\text{MeOCH}_2\text{COOMe} &\rightarrow \text{MeOCHCOOMe} + \dot{\text{CH}_2O\text{CH}_2\text{COOMe}} \\
&\text{(3.12)} &\text{(3.12a)} &\text{(3.12b)}
\end{align*}
\]

Concentration ratio of 3.12a/3.12b = 6:1

\[
\begin{align*}
\text{MeOCH}_2\text{COMe} &\rightarrow \text{MeOCHCOMe} \\
&\text{(3.13)} &\text{only}
\end{align*}
\]

When entries 1 and 2 in Table 3.1 were compared, it was found that the effect of a methyl substituent at C-5 was to increase the rate of formation of captodative radicals. Similar observations were made when a substituent was placed at the acetal centre (C-2) although the effect was not as great (c.f. entries 1 and 3, Table 3.1).

As a further aid to interpreting these observations, the relative reactivities per equivalent hydrogen atom \((p)\) as defined by Ingold and Malatesta, were measured against \(t\)-butylmethyl ether \((3.14)\) which was used as a standard.

Scheme 3.8

\[
\begin{align*}
\text{O-Me} &\rightarrow \text{O-CH}_2^* \\
&\text{(3.14)} &\text{(3.14a)}
\end{align*}
\]

In a preliminary experiment, the standard \(3.14\), substrate \(3.1\) and di-\(t\)-butylperoxide in an appropriate solvent was irradiated. A portion of the spectrum was selected such that there was little or no overlap of the signals from the radicals observed. The relative concentrations were then determined and wherever necessary, the ratio of the concentrations of standard to substrate were adjusted so that similarly intense lines
were obtained in the portion of the spectrum studied. Accurately weighed quantities of 3.14 and substrate 3.1 were used and the relative concentrations of the radicals were determined by the simulation method. This was repeated with substrates 3.4 and 3.11. The results are summarised in Table 3.2.

Table 3.2 Relative reactivities per equivalent hydrogen ($\rho$) for the reaction RH + Bu$t^1$O• → R• + Bu$t^1$OH at -31°C.

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>R•</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bu$t^1$OCH$_2$•</td>
<td>1.00</td>
</tr>
<tr>
<td>2.</td>
<td>3.1a</td>
<td>15.67</td>
</tr>
<tr>
<td>3.</td>
<td>3.11a</td>
<td>8.62</td>
</tr>
<tr>
<td>4.</td>
<td>type A, R$^2$=H</td>
<td>0.35</td>
</tr>
<tr>
<td>5.</td>
<td>type B, R$^1$=H</td>
<td>0.29</td>
</tr>
<tr>
<td>6.</td>
<td>type A, R$^2$=Me</td>
<td>4.04</td>
</tr>
<tr>
<td>7.</td>
<td>type B, R$^1$=Me</td>
<td>0.41</td>
</tr>
<tr>
<td>8.</td>
<td>type B, R$^1$=t-Bu</td>
<td>0.32</td>
</tr>
<tr>
<td>9.</td>
<td>type B, R$^1$=i-Pr</td>
<td>0.54</td>
</tr>
</tbody>
</table>

The last four entries were obtained from the data in Table 3.1 by assuming that the hydrogen atom reactivities were unaffected by the substituent R$^1$ or R$^2$, further removed from the hydrogen atom considered. This assumption may not be strictly valid especially when bulky substituents R$^1$ and R$^2$ are involved, as these substituents may impose steric hindrance to abstraction. Despite this potential problem, fairly good agreement between Table 3.1 and 3.2 was obtained. The minor inconsistencies found are probably within the error of the assumption made. Alternatively, these inconsistencies could also be accounted for by the different polarities of the reaction media as no attempt was made to standardize the dielectric constants of the reaction.
media.

The general effect of a substituent at C-2 and C-5 is to activate the hydrogen at that position to abstraction. For example, the relative reactivity per equivalent hydrogen ($p$) in the presence of a methyl substituent at the captodative position (entry 6, Table 3.2) is 4.04, compared with a value of 0.35 in the unsubstituted dioxolanone (entry 4, Table 3.2). Similarly, when entries 5 and 7, Table 3.2 were compared, the relative reactivity $p$ increased in the presence of a substituent at C-2.

![R1 O R2 H6 O H2](image)

Type A:
- $R^2 = H$, $p (H_a) = 0.35$
- $R^2 = Me$, $p (H_a) = 4.04$

Type B:
- $R^1 = H$, $p (H_b) = 0.29$
- $R^1 = Me$, $p (H_b) = 0.41$

This is presumably due to the formation of the more stable tertiary radical compared to the secondary one. However, as noticed previously, the activating effect of a substituent at the captodative centre is greater compared to that at the acetal centre. An attractive explanation for this is in terms of hyperconjugation.\(^5\) Hyperconjugation is favoured when there is maximum overlap between the p-orbital of the unpaired electron and the C\(_\beta\)-H i.e. when $\theta = 0^\circ$ ($\theta$ is the angle between the radical centre and the C\(_\beta\)-H bond). Possibly the more planar captodative radicals (type A) undergo hyperconjugation more effectively than do radicals type B as the latter radicals are bent. Another factor which should be considered is the antagonistic effect,\(^6\) which takes place when donor substituents are placed at the acetal centre (C-2). This effect is also predicted by molecular orbital considerations where putting additional donor substituents (e.g. alkyl groups) to a radical centre does not give rise to additive stabilisation of energies.

From Table 3.2, the relative reactivity per equivalent hydrogen is greatest for THF: these hydrogens are 1.8 x more rapidly abstracted than the captodatively activated hydrogens of 3.11 (see Scheme 3.6). This demonstrates that polar effects are more important than radical stabilising effects, as might be expected for reactions
with t-butoxy radicals which have been shown to possess an early transition state.\textsuperscript{7}

To obtain an idea on the reactivity per equivalent hydrogen ($\rho$) at a position adjacent to two oxygens (acetal centre), a portion of the data from the work of Ingold and Malatesta\textsuperscript{2} is shown below:

\begin{align*}
\text{(3.1)} & & \text{(3.2)} \\
\rho (H_a) &= 1.0 & \rho (H_a) &= 8.8 \\
\rho (H_b) &= 0.32 & \rho (H_b) &= 0.32
\end{align*}

In order to put this data in perspective with the other results in Table 3.2, the $\rho$ value for 1,3-dioxolane (3.2) for abstraction at the acetal centre was estimated to be 8.8 (from the Ingold data) x 15.67 (using data from entry 2, Table 3.2) = 137.9\textsuperscript{*}. This again emphasizes the importance of polar effects in determining the reactivity of the hydrogens involved. At face value, it would seem that the antagonistic effect may not be the dominant factor here. When the reactivity per equivalent hydrogen ($\rho$) at the acetal centre for 1,3-dioxolane (3.2) is compared to that for dioxolanone 3.4, it was found that the reactivity of the latter was very much decreased ($\rho$ value for dioxolane 3.2 is 138 compared to a value of 0.35 for abstraction at the acetal position of 3.4).

The decrease in reactivity can be explained at least in part as due to polar effects: one of the oxygens at the acetal position of dioxolanone 3.4 has a decreased electron donating capacity as it is part of an ester moiety. Similar observations\textsuperscript{4} had also been made in analogous acyclic substrates as shown in Scheme 3.9.

\textsuperscript{*} The data from the work of Ingold and Malatesta\textsuperscript{2} were for spectra recorded at -60°C. Therefore, the relative reactivity ($\rho$) calculated is only an approximation, as the reactivity of 3.2 at the two temperatures may be different.
The replacement of the ketone function in 3.11 with the ester group in 3.4 as the captor substituent, decreases the rate of hydrogen abstraction at the captodative centre dramatically (c.f. entries 3 and 4, Table 3.2).

However, as pointed out previously, these results are inconsistent with predictions of reactivities on the basis of polar effects. Thus the factors that affect the reactivity of hydrogen abstraction from these cyclic compounds are different for the different types of radicals formed. It appears that polar effects are dominant when non-captodative radicals are formed. However, the factors that govern the generation of captodative radicals are not clear cut and the selectivities observed in the dioxolanones could be a consequence of the captodative effect or alternatively due to a large decrease in the reactivity of the hydrogens at C-2. The latter would appear to give rise to an apparent increase in abstraction at the captodative position.

We also studied the effect of light intensities on the concentration ratios of the
radical species observed. The intensity of UV irradiation was decreased by the addition of filters, so as to increase the lifetime of the radicals involved. With radicals 3.4a and 3.4b, the concentration ratio was found to be the same within experimental error for the light intensities used, thus proving that the radicals formed were not interconvertible and that they have very similar bimolecular termination rates.

3.1b Analyses of spectra

The spectral data for the radicals derived from substrates 3.4-3.11 are summarised in Table 3.3 and for comparison, the data for other related radicals known from literature are given in Table 3.4. Radicals 3.17a-3.19a listed in Table 3.4 will be discussed later in the text. Unfortunately, some of the data presented in Table 3.4 were collected at different temperatures and it is well known that the magnitudes of hyperfine splitting constants are, to a certain extent, temperature dependent. However, the variation in the magnitudes of the hyperfine splitting constants over a wide temperature range for the radicals concerned is not large, as illustrated with some of the data in Table 3.4.

The analyses of hyperfine splitting constants can potentially give information on the spin density at the radical centre. However, in reality, the analyses are complicated by considerations of radical geometry. For example, there is good evidence that a radical centre α- to two oxygens in a ring is non-planar12,16 whereas captodative radicals are planar. As a consequence of this, it is difficult to use established methods to obtain information on the spin density at the radical centre. Some of these problems will be illustrated here.
Table 3.3: ESR data from spectra recorded at -31°C.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Radical</th>
<th>α-H</th>
<th>β-H</th>
<th>γ-H</th>
<th>δ/ε-H</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.11</td>
<td>3.11a</td>
<td>14.92(1)</td>
<td>-</td>
<td>3.27(2);5.67(2)</td>
<td>-</td>
<td>2.0052</td>
</tr>
<tr>
<td>3.4</td>
<td>3.4a</td>
<td>17.41(1)</td>
<td>-</td>
<td>9.66(2)</td>
<td>-</td>
<td>2.0043</td>
</tr>
<tr>
<td></td>
<td>3.4b</td>
<td>16.99(1)</td>
<td>-</td>
<td>7.07(2)</td>
<td>-</td>
<td>2.0032</td>
</tr>
<tr>
<td>3.5</td>
<td>3.5a</td>
<td>-</td>
<td>17.32(3)</td>
<td>8.41(2)</td>
<td>-</td>
<td>2.0042</td>
</tr>
<tr>
<td></td>
<td>3.5b</td>
<td>16.19(1)</td>
<td>-</td>
<td>7.23(1)</td>
<td>0.11(3)</td>
<td>2.0032</td>
</tr>
<tr>
<td>3.6</td>
<td>3.6a</td>
<td>17.47(1)</td>
<td>-</td>
<td>9.98(1)</td>
<td>0.30(3)</td>
<td>2.0042</td>
</tr>
<tr>
<td></td>
<td>3.6b</td>
<td>-</td>
<td>14.24(3)</td>
<td>5.94(2)b</td>
<td>-</td>
<td>2.0030</td>
</tr>
<tr>
<td>3.7</td>
<td>3.7a</td>
<td>17.49(1)</td>
<td>-</td>
<td>10.31(1)</td>
<td>0.21(3)</td>
<td>2.0046</td>
</tr>
<tr>
<td></td>
<td>3.7b</td>
<td>-</td>
<td>-</td>
<td>6.71(1);</td>
<td>-</td>
<td>2.0034</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.47(1)b;</td>
<td>c</td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td>3.8a</td>
<td>17.45(1)</td>
<td>-</td>
<td>10.08(1)</td>
<td>0.25(1);</td>
<td>2.0046</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10(6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.8b</td>
<td>-</td>
<td>13.87(1)</td>
<td>0.25(6);6.05(2)b</td>
<td>-</td>
<td>2.0034</td>
</tr>
<tr>
<td>3.9</td>
<td>3.9a</td>
<td>-</td>
<td>17.30(3)</td>
<td>8.82(1)</td>
<td>0.28(3)</td>
<td>2.0043</td>
</tr>
<tr>
<td></td>
<td>3.9b</td>
<td>-</td>
<td>14.22(3)</td>
<td>6.12(1)</td>
<td>.c</td>
<td>2.0031</td>
</tr>
<tr>
<td>3.10</td>
<td>3.10a</td>
<td>-</td>
<td>17.40(3)</td>
<td>9.28(1)</td>
<td>0.20(3)</td>
<td>2.0044</td>
</tr>
<tr>
<td></td>
<td>3.10b</td>
<td>-</td>
<td>-</td>
<td>6.32(1)</td>
<td>.c</td>
<td>2.0033</td>
</tr>
</tbody>
</table>

*Numbers of equivalent nuclei in parentheses.

Lines with Mγ=0 selectively broadened.

Other splittings not resolved.
Table 3.4: ESR data from literature.

<table>
<thead>
<tr>
<th>Radical</th>
<th>T°C</th>
<th>α-H</th>
<th>β-H</th>
<th>γ-H</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1a</td>
<td>80°C</td>
<td>12.29(1)</td>
<td>28.57(2)</td>
<td>0.82(2);1.64(2)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>-90°C</td>
<td>12.83(2)</td>
<td>27.34(2)</td>
<td>0.74(2);1.79(2)</td>
<td>13</td>
</tr>
<tr>
<td>3.2a</td>
<td>20°C</td>
<td>21.50(1)</td>
<td>-</td>
<td>1.40(4)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>-80°C</td>
<td>21.50(1)</td>
<td>-</td>
<td>1.45(4)</td>
<td>14</td>
</tr>
<tr>
<td>3.2b</td>
<td>20°C</td>
<td>10.90(1)</td>
<td>27.00(2)</td>
<td>1.60(2)</td>
<td>12</td>
</tr>
<tr>
<td>3.3a</td>
<td>-31°C</td>
<td>15.81(1)</td>
<td>31.47(2)</td>
<td>0.07(2)</td>
<td>3</td>
</tr>
<tr>
<td>3.17a</td>
<td>-196°C</td>
<td>-</td>
<td>21.00(3)</td>
<td>-</td>
<td>gb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41.00(3)</td>
<td></td>
</tr>
<tr>
<td>3.18a</td>
<td>-31°C</td>
<td>-</td>
<td>37.00(2);21.60(3)</td>
<td>0.62(2)</td>
<td>3</td>
</tr>
<tr>
<td>3.19a</td>
<td>?</td>
<td>-</td>
<td>13.40(3)</td>
<td>1.10(4)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>0°C</td>
<td>-</td>
<td>12.85(3)</td>
<td>1.20(4)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>20°C</td>
<td>-</td>
<td>12.90(3)</td>
<td>1.20(4)</td>
<td>12</td>
</tr>
</tbody>
</table>

*a Number of equivalent nuclei in parentheses.

*b γ-irradiation of solid.
The \( \alpha \)-hyperfine splitting constant \( (a_{\alpha-H}) \) is related to the spin density at the \( \alpha \)-carbon \( (\rho_{\alpha}) \) by the McConnell equation:8

\[
a_{\alpha-H} = Q_{\alpha-H}^C \rho_{\alpha} \quad \text{ equation (2)}
\]

where \( Q_{\alpha-H}^C = -23 \text{G} \)

According to this equation, one should be able to predict the spin density at a radical centre from the \( \alpha \)-hyperfine splitting constants \( (a_{\alpha-H}) \). However, the \( \alpha \)-hyperfine splitting constants are also dependent on the conformation of the radical and are not reliable as indicators of spin density at the \( \alpha \)-carbon: an increase in the degree of s character at a radical centre (e.g. with increasing non-planarity) gives rise to a corresponding increase in the positive contribution to the \( \alpha \)-hyperfine splitting constant.12,16,17 In an ideal situation (where equation (2) holds) then the comparison of the \( \alpha \)-hyperfine splitting constants would have provided an excellent direct method for the measurement of captodative stabilisation in radicals.18

An alternative method frequently used to evaluate the spin density at a delocalised radical centre is to measure the \( \beta \)-proton splittings of freely rotating methyl groups.12,16,17 The \( \beta \)-hyperfine splitting constants are dependent on the dihedral angle \( \theta \) (where \( \theta \) is the angle between the p-orbital and the \( \cdot \text{C-H}_{\beta} \) bond in the projection on a plane perpendicular to the \( \cdot \text{C-C} \) bond).19 In equation (3), \( B_0 \) and \( B \) are constants where \( B_0 \) is small relative to \( B \) (usually < 3 G) and \( B \) is about 50 G.

\[
a_H = B_0 + B\langle \cos^2 \theta \rangle_{av} \quad \text{ equation (3)}
\]

For freely rotating methyl groups, the rotationally averaged value of \( \cos^2 \theta \) is 0.5. Thus \( \beta \)-hyperfine splitting constants can be used to predict the spin density at the \( \alpha \)-carbon according to equation (4) below.

\[
a_{H}^{CH3} = Q_{H}^{CH3} \rho_{\alpha} \quad \text{ equation (4)}
\]

where \( Q_{H}^{CH3} = 29.3 \text{G} \)
A comparison of the β-hyperfine splitting constants of the freely rotating methyl group in radical 3.6b (αβ-CH₃=14.24 G, at -31°C) with that in radical 3.19a (αβ-CH₃=13.40 G) shows that these values are quite similar.

From the literature, the β-hyperfine splitting constant of the methyl group in radical 3.17a is 21.00 G at -196°C and that for radical 3.18a is 21.60 G at -31°C. A combination of these two groups as in radical 3.5a leads to a β-Me hyperfine splitting constant of 17.32 G.

The smaller β-Me hyperfine splitting constant of 3.5a (compared to 3.17a and 3.18a) may imply greater delocalisation at the radical centre. However, this rather simplistic view is probably not accurate as the contribution of other factors (e.g. the extent of hyperconjugation with different substituents and the conformation of the different radicals) to the hyperfine splitting constants cannot be estimated easily. Thus both the α- and β-hyperfine splitting constants are not good indicators of spin density at the radical centre.

The γ-hyperfine splittings observed for radicals derived from our substrates were unusually large compared to the analogous splitting in radicals 3.2a and 3.2b (see Scheme 3.3 for the structures). Abnormally large values of γ-hyperfine splitting constants have been observed before and explained as a manifestation of the captodative effect. However, this reasoning is not valid here as both the captodative
and non-captodative radicals (type A and B radicals) display large $\gamma$-hyperfine splitting constants. The $\gamma$-hyperfine splitting constants for radical $3.4a$ and $3.4b$ are $9.66$ G, and $7.07$ G respectively compared to values for radicals $3.2a$ and $3.2b$ of $1.4$ G and $1.6$ G respectively (see Tables 3.3 and 3.4). It is possible that a special type of hyperconjugation involving groups attached to the unconjugated $\gamma$-carbon atom occurs. This could account for the enhanced $\gamma$-hyperfine splitting constants observed.

**Scheme 3.10**

![Scheme 3.10](image)

However, semiempirical molecular orbital calculations (AM1-UHF$^{20}$/INDO$^{21}$) carried out in our laboratories$^3$ for radicals $3.4a$ and $3.4b$ predicted values for the $\gamma$-hyperfine splitting constants which were considerably smaller than the observed values. The reason for this discrepancy is not clear.

Another interesting observation that arose from the study of radicals $3.7a$ and $3.10a$ was that for both of these radicals, splitting by only three of the protons of the $\text{t}$-butyl group was observed.

![3.7a](image)

![3.10a](image)

A small region of the observed spectra for substrate $3.10$ is shown in Figure 3.1. The signal on the right hand side of the spectra is attributed to radical $3.10b$ whereas the left hand side of the spectra shows a multiplet due to radical $3.10a$ and showing splitting by the three protons of the $\text{t}$-butyl group. The smooth line indicates the
Figure 3.1
A selected portion of the esr spectrum of radicals 3.10a and 3.10b at 240 K.
spectra obtained by computer simulation. For radicals 3.7a and 3.10a respectively, this long range splitting was found to be 0.21 and 0.20 G. The fact that only three of the t-butyl protons show splitting is probably a consequence of restricted rotation of the t-butyl group, such that only the methyl group above the ring gives resolvable splittings. Calculations of spin densities with the AM1-UHF and INDO methods support the view that the protons of the other two methyl groups, directed away from the ring give rise to unresolvably small splittings.

This hypothesis was tested with dioxolanone 3.8 where radical 3.8a showed splitting at -31°C due to six equivalent ε hydrogens and one δ hydrogen of the i-propyl group.

Upon lowering the temperature, an increase in the linewidths was observed such that at the lowest temperature available, no resolvable splittings were observed. This could be the result of increasingly restricted rotation at lower temperatures.

Studies by Norman and Pritchett have shown that g-values are useful aids to identifying free radicals. We found that the g-values for the two types of radicals (type A and type B) formed were distinctly different. The non-captodative radicals (type B) had g-values of ca. 2.0032 ± 0.002 (c.f. to the literature value for radical 3.2a of 2.0032) whereas the captodative radicals (type A) had g-values of ca. 2.0044 ± 0.002 (c.f. to g= 2.0041 for radical 3.12a in Scheme 3.7)

3.1c Linewidth alternation

We observed that the esr spectra of 3.6b and 3.7b displayed linewidth alternation, probably arising from interconversion of the type shown below.
The rate of inversion depended strongly on the nature of R': when R' was small (e.g. hydrogen), the rate of inversion was rapid and no linewidth alternation was observed even at the lowest temperature used. At -31°C, a fast regime spectra was observed with R'=Me, and a slow regime (rate of inversion slow), with R'=t-butyl. The temperature dependence of the spectra of radical 3.7b, R'=t-butyl, was studied in detail and the spectra were recorded digitally so that the exchange rates could be determined as accurately as possible and fitted to the Arrhenius equation.

Portions of the spectra of radical 3.7b are shown in Figure 3.2. At 240 K, radical 3.7b showed evidence of inequivalent γ-protons due to the relatively slow exchange, whereas at 280 K, the γ-protons appeared equivalent due to rapid inversion of the radical centre.

The exchange rates were obtained from the analysis of the spectra at different temperatures. Spectra were simulated by means of a computer program and requires as input, the limiting low temperature hyperfine splitting of the exchanging protons and the rate for the exchange. The rate was varied until a satisfactory fit between the experimental spectrum and the simulated spectrum was obtained. The data used for the Arrhenius plot are shown in Table 3.5 (see Figure 3.3 for plot).
Figure 3.2
Esr spectra for radical 3.7b showing linewidth alternation effects at 240 K (top diagram) and 280 K (bottom diagram).
Table 3.5: Rate of inversion of the radical centre (3.7b) at different temperatures

<table>
<thead>
<tr>
<th>Rate (x10^4 kHz)</th>
<th>Temp (Kelvin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28610</td>
<td>240</td>
</tr>
<tr>
<td>0.76590</td>
<td>250</td>
</tr>
<tr>
<td>1.62940</td>
<td>260</td>
</tr>
<tr>
<td>3.16960</td>
<td>270</td>
</tr>
<tr>
<td>5.97460</td>
<td>280</td>
</tr>
</tbody>
</table>

An activation energy of 39.87 ± 0.49 kJ/mol was obtained along with a pre-exponential factor of (1.64 ± 0.35) 10^{12} s^{-1}. The rate of inversion of radical 3.19a has been studied by other workers and an activation energy of 23.9 ± 2 kJ/mol found.\textsuperscript{15}

\[
\text{O} \quad \text{O} \\
(3.19a)
\]

With the inversion of substituted cyclopentyl radicals, activation energies were found to increase with the size of the substituent.\textsuperscript{24} Thus, our larger value for the activation energy for the inversion of radical 3.7b (R'=t-butyl) does not necessarily conflict with the literature data for radical 3.19a.
Figure 3.3
Arrhenius plot on the rate of inversion of the radical 3.7b at different temperatures (T).

\[ \log(\text{rate}) = -k \cdot \frac{1}{T} + c \]

Where:
- \( k \) is the frequency factor,
- \( c \) is the activation energy,
- \( T \) is the temperature in Kelvin.

The Arrhenius plot shows a linear relationship between the logarithm of the rate and the inverse of temperature, indicating a first-order reaction with respect to the radical concentration.
3.1d Reducing properties of radicals derived from 1,3-dioxolanones

It has been shown that α-oxygenated radicals of type 3.20a are capable of behaving as reducing agents\textsuperscript{11,25} such that \( \cdot \text{CH}_2\text{COOMe} \) radicals (3.21a) can be generated from methyl bromoacetate and detected by esr spectroscopy.

**Scheme 3.12**

\[
\begin{array}{c}
\cdot C-OR + \text{BrCH}_2\text{COOMe} \\
\rightarrow \cdot C-OR + \text{Br}^- + \cdot \text{CH}_2\text{COOMe}
\end{array}
\]

This was tested qualitatively by irradiating a mixture of t-butylmethylether (3.14), substrate 3.4 and di-t-butylperoxide. In the presence of chloromethylacetate (CICH\( _2\)COOMe), the concentrations of the radicals 3.14a, 3.4b and 3.4a remained unchanged. However on addition of bromomethylacetate (BrCH\( _2\)COOMe), the concentrations of radicals 3.14a and 3.4b decreased and a new radical species 3.21a appeared but the concentration of the captodative radical 3.4a remained unaffected. Thus, both radicals 3.14a and 3.4b were capable of acting as reducing agents. The reducing power of a radical depends on whether the reduction process will cause an increase or decrease in ring strain.\textsuperscript{11} We do not believe that this is the reason for the reluctance of the captodative radical 3.4a to act as a reducing agent, as to go from a nearly planar radical centre to a planar carbonium ion would not affect the ring strain tremendously. Instead, it is possible that captodative radicals cannot be easily oxidised due to the loss of radical stabilisation on formation of the carbonium ion. Alternatively, the electron donating group in radicals 3.14a and 3.4b stabilises the incipient carbonium ion whereas in the captodative radical 3.4a, the effect of the donating group is cancelled (partly) due to the captor group.

3.2 Hydrogen abstraction studies of other cyclic acetals

Attempts were also made to study the hydrogen abstraction from various substituted 1,3-oxazolidin-5-ones by esr spectroscopy. However, difficulties were
encountered due to the low solubility of these compounds in typical esr solvents e.g. ethylene oxide. We attempted to improve the low solubility of 3.22 by changing the N-protecting group. However, compound 3.23 gave broad lines in the esr spectra which could be attributed to slow tumbling rates due to the long alkyl chain. Eventually, a suitable compound 3.24 (with reasonable solubility) was found and hydrogen abstraction from this, as described for the 1,3-dioxolan-4-ones, gave the complex spectrum shown in Figure 3.4.

![Scheme 3.13](image)

The computer simulated spectra\textsuperscript{22} is shown on the bottom half of Figure 3.4. The radical was identified as 3.24a, arising from hydrogen abstraction at the captodative centre. The \(\alpha\)-proton hyperfine splitting constant was 15.60 G whereas the hyperfine splitting constant due to the nitrogen was 2.85 G. Other long range splittings observed were due to the two methylene protons of the N-protecting group (0.65 G) and the nine protons of the t-butyl group (0.22 G). The latter observation was surprising in view of the fact that radicals 3.7a and 3.10a derived from the
Figure 3.4
Esr spectrum of the radical derived from oxazolidinone 3.24.
corresponding 1,3-dioxolanones (p. 74 for the structures) showed splittings due to only three of the nine protons of the t-butyl group. This probably results from the different conformation of the rings.

Although the major species contributing to the esr spectra was the captodative radical 3.24a, the complexity of the spectra made it difficult to rule out the possibility that small amounts of radical 3.24b might also have been present.

3.3 Addition of radicals to 2-(t-butyl)-5-methylene-1,3-dioxolan-4-one (3.25)

The addition of alkyl radicals to olefins has been studied by esr spectroscopy. In this work, the method was used to generate captodatively stabilised radicals for study by esr spectroscopy. A suitable olefin for this purpose, is the dioxolanone 3.25 which can be synthesized using procedures developed by us (see Chapter 4) and Seebach. In principle, alkyl radicals could either add to the double bond to give the captodatively stabilised radical (3.26) or to the carbonyl group to give rise to an allylic radical 3.27 as shown in Scheme 3.14.

Scheme 3.14

In our radical addition studies, two sources of alkyl radicals were used. Methyl radicals may be conveniently generated by the photolysis of diacetylperoxide. The reaction scheme as usually written, is shown below.
However, it has been observed previously\textsuperscript{30} that when diacetyl peroxide decomposes in the presence of furan, at low temperatures, radicals resulting from the addition of acetyl (not methyl) radicals are generated. It is not certain whether acetyl radicals formed in the primary photolytic process are sufficiently long lived to react with furan, or whether the excited peroxide molecule undergoes a charge transfer reaction with the olefin.

Nucleophilic t-butyl radicals can be generated by photolysis of di-t-butylperoxide.\textsuperscript{31} The scheme is shown below.

\begin{scheme}
\begin{align}
\text{CH}_3\text{C}==\!\text{O} \quad (3.28) \\
\text{hv} \quad \rightarrow \quad 2\text{CH}_3^* + 2\text{CO}_2
\end{align}
\end{scheme}

Photolysis of di-t-butylketone produces t-butyl radicals and pivaloyl radicals (3.28) by a Type 1 cleavage.\textsuperscript{31,32} Radical 3.28 can decarboxylate to produce more t-butyl radicals as well as carbon monoxide.\textsuperscript{32} However, the rate of decarboxylation at low temperatures is sufficiently slow that addition of 3.28 to olefins may be significant.\textsuperscript{31,32} From the literature,\textsuperscript{31} radicals that result from the addition of t-butyl and pivaloyl radical to acrylonitrile have similar hyperfine splitting constants. Thus it seems unlikely that the two possible radicals formed by addition to 3.25 could be
distinguished on the basis of their esr spectra.

To distinguish between the two possible sites of addition (Scheme 3.14), the hyperfine splitting constants for $\alpha, \alpha$-dimethoxyallyl radical (3.29) were compared with the values obtained from the recorded esr spectra. The hyperfine splitting constants did not seem to provide a good basis for distinguishing between the two types of addition. However, the g-value for the allyl radical 3.29 was 2.0028 whereas the observed g-values were 2.0041 (consistent with the g-values observed for captodative radicals, type A in section 3.1 above). Thus, we conclude that radical addition occurred preferentially to form the captodative (type 3.26) radicals.

Hyperfine splitting constants (G) at 205 K

Data from the esr spectra recorded during the photolysis with diacetylperoxide or di-tert-butylketone in the presence of 3.25 in cyclopropane/ethylene oxide as solvent, are summarised in Table 3.6. We tentatively assume that alkyl radicals were the reacting species although the other possibilities (acetyl or pivaloyl radical) cannot be ruled out.

Table 3.6 Esr data from the addition of radicals to dioxolanone (3.25) at -31°C.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$\beta$-H$^a$</th>
<th>$\gamma$-H</th>
<th>$\delta/e$-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.26a</td>
<td>12.45, 13.52</td>
<td>9.25</td>
<td>0.20$^b$</td>
</tr>
<tr>
<td>3.26b</td>
<td>11.23, 9.02</td>
<td>9.40</td>
<td>c</td>
</tr>
</tbody>
</table>

$^a$ Averaged splittings, see text. $^b$ Quartet splitting. $^c$ Not resolved.
As shown in Table 3.6, the β-protons appeared non-equivalent for both radicals 3.26a and 3.26b. This could be taken to indicate restricted rotation about the Cα-Cβ bond. However, this conclusion does not seem reasonable, as the barrier to rotation of the Cα-Cβ bond would be expected to be small. An alternative explanation for the observation follows:

The radicals 3.26a and 3.26b are examples of the general type I. It is tempting to compare these radicals with molecules of the type II, for which the methylene protons are diastereotopic, and as a result, generally appear inequivalent in nmr spectra.34

However, the same argument does not apply to type I radicals, because the trigonal carbon atom is not a chiral centre: this conclusion follows from the fact that geometry at the trigonal carbon atom is either planar, or, if it is not planar, the inversion rate is fast on the esr time scale. In spite of this, the methylene protons of type I radicals may appear inequivalent in the esr spectra, as the following argument shows. Two conformations (III and IV) of a type I radical can be envisaged.35

Because the substituents a and b are different, θ₁ ≠ θ₂, and each of the conformations should give rise to different β-hyperfine splitting constants as shown in (a) and (b) in Figure 3.5. Actually, the populations of the two conformations are not necessarily the
same, a fact not evident in Figure 3.5. In the limit of slow exchange, eight lines would be expected (as shown in (c)- Figure 3.5), whereas when a fast exchange limit is reached, these eight lines coalesce to become four (see (d) Figure 3.5). Thus, in the event of fast exchange, the methylene protons of a type I radical appear equivalent.

The analysis in Table 3.6 is based on the fast exchange limit where the $\beta$-hyperfine splitting constants listed are the averaged values (see (d) Figure 3.5). Both the fast and the slow exchange limits are observed in the photolysis of 3.25 with di-t-butylketone at different temperatures (see Figure 3.6). Complete analysis of the line width effects to support this hypothesis is in progress and at present, only limited success has been achieved.

For radical (3.26a, R=Me), only the fast exchange limit was observed in the temperature range studied (see Figure 3.7). This is because the methyl group is not as bulky as the t-butyl substituent and the difference between the energies of the two conformations is small.

Figure 3.5

(a)  

(b)  

(c)  

(d)
Figure 3.6
Esr spectra of radical 3.26b at different temperatures. The temperatures at which the spectra were recorded (from top to bottom) are 160, 180, 200, 220, 240, 250 K.
Figure 3.7
Esr spectrum derived from the addition of radical generated from diacetyl peroxide to the captodative olefin 3.25 at 200 K.
3.4 Conclusion

Substituted 1,3-dioxolan-4-one-5-yl and 1,3-dioxolan-4-one-2-yl radicals have been generated by hydrogen abstraction and radical addition reactions, and studied by esr spectroscopy. The results show that the regioselectivities of hydrogen abstraction can be affected by changing the substituents at the captodative and non-captodative positions as well as by changing the nature of the donor and acceptor groups. Relative reactivities per equivalent hydrogen atom (p) have also been measured and these give valuable information regarding the kinetic effect of captodative stabilisation.
References: Chapter 3.

3. S. Brumby, unpublished observations.
35. This argument also applies to radicals of general type CYZCH$_2$NO$_2$ due to the chirality of the neighbouring carbon atom, see B.C. Gilbert, J.P. Larkin and R.O.C. Norman, J. Chem. Soc., Perkin Trans. 2, 1972, 1272.
Chapter 4: Regio- and Diastereo-selective Reactions of 1,3-dioxolan-4-ones
Chapter 4

Introduction

α-Hydroxy carboxylic acids are an important class of compounds frequently used as building blocks in organic synthesis. The carboxylic acid and hydroxy functional groups can be readily protected by conversion of the acid to the corresponding dioxolanone. Further transformation and extension of the carbon framework can be conducted and then finally the protecting group can be easily removed by hydrolysis to give the corresponding carboxylic acid.

Carbon-carbon bond forming reactions of dioxolanones by non-radical methods are known. However, by and large, radical reactions of 1,3-dioxolanones have not been fully explored. The only reported study is that of Seebach and Zimmermann who found that the reaction of dioxolanone 4.9 with N-bromosuccinimide (NBS) occurs with significant regio- and diastereo-selectivity.

Scheme 4.1

As a result of this interesting observation, we embarked on a detailed study of the regio- and diastereo-selectivity of radical reactions of 1,3-dioxolanones. Furthermore, some of the radicals formed in these reactions are captodatively stabilised and our study should provide further insight into the chemical consequences, if any, of the captodative effect. It should be noted that unless stated otherwise, all reactions were conducted with racemic materials.

* The diagrams in this chapter only show relative stereochemistry, unless specified otherwise.
4.1 N-Bromosuccinimide (NBS) reactions

4.1a The regioselectivity of NBS reactions.

Early studies on the reaction of NBS with 1,3-dioxolane (4.1) showed that bromination occurred at both the 2- and 4-positions. We reexamined this by refluxing the 1,3-dioxolane (4.1) with 1.1 equivalents of NBS in the presence of catalytic amounts of AIBN in CC\textsubscript{4}: the $^1$H nmr spectrum of the crude reaction mixture after 45 minutes showed that the reaction had proceeded cleanly\textsuperscript{6b,6c} to give 4.2 as a single product. The yield was determined to be 92\% from $^1$H nmr spectroscopy.

Scheme 4.2

Product 4.2 can be envisaged as arising from two possible reaction pathways. The first involves the initial bromination at the acetal centre, followed by the formation of the stabilised oxonium ion\textsuperscript{7} 4.1c which is then attacked by bromide ion at C-4 (see Scheme 4.3a) to give product 4.2. The other pathway (Scheme 4.3b), involves a $\beta$-scission of the radical 4.1a which leads to the open chain alkyl radical 4.1d which then subsequently abstracts a bromine atom from NBS. From the results of our experiments, it is not possible to distinguish between these two mechanisms. However, one conclusion is clear - hydrogen abstraction occurs only at the position with the highest electron density, i.e. at the acetal centre. This is consistent with the electrophilic nature\textsuperscript{8} of either of the possible chain carriers, bromine atom or succinimidyld radical.
By contrast, Seebach and Zimmermann\textsuperscript{4} reported that bromination of the 1,3-dioxanone 4.3 with NBS gave products arising from attack at C-6.

The discrepancy in the regioselectivity observed in these two systems (dioxolane versus dioxanone) can be attributed to the differences in the electron density at the acetal centre. In the dioxanones, one of the acetal oxygens has a decreased electron donating capacity due to the presence of a carbonyl group. This may be the reason for the lack of reactivity at C-2 although this argument is not completely convincing and the results are still surprising.
The reaction of dioxolanones 4.4-4.11 with NBS in refluxing CCl₄ was investigated. The products of these reactions are shown in Table 4.1. The yields were obtained by ¹H nmr spectroscopy relative to an internal standard. In a typical experiment to determine the reaction yields, a solution of equimolar amounts of the dioxolanone and NBS in CD₂Cl₂ was made up in an nmr tube and degassed. The ¹H nmr spectrum of the solution was recorded and accurate integration of starting material relative to NBS (long delay times were required) was obtained. The solution was then irradiated with a sunlamp for 15 minutes, following which another nmr spectrum was recorded. The spectrum showed the conversion of NBS to succinimide (i.e. δ 2.68 to δ 2.50 ppm). Portions of the spectrum corresponding to the product were integrated relative to the succinimide absorptions and comparison of this ratio with the initial ratio of starting material to NBS (at time t=0 minutes) gave a measure of reaction yields. The method is relatively accurate as long as the conversion of NBS to succinimide is quantitative. This is true for substrates displaying high reactivity in NBS reactions. The regioselectivity of the NBS reaction was determined by examining the crude reaction mixture by ¹H nmr spectroscopy and, in some cases, also by ¹³C nmr spectroscopy. The diastereoselectivity of these reactions will be discussed later. From the ¹H nmr spectrum of the parent dioxolanone, the proton at C-5 has a chemical shift in the region of 4.2-4.4 ppm. However, examination of the ¹H nmr spectrum of the crude reaction mixture from the NBS bromination showed the disappearance of this peak. The chemical shifts of the acetal proton and the substituent at C-2 (e.g. t-butyl) do not change very much but the chemical shift corresponding to the group at C-5 (e.g. H, CH₂ and CH₃) is shifted downfield. For example, dioxolanone 4.7 has two protons at C-5 with different chemical shifts (4.24 and 4.34 ppm). Upon bromination, these peaks disappear and are replaced by a one proton absorption at ~6.48 ppm corresponding to the proton at C-5 α- to the bromine. In all these cases, it was observed that bromination was highly regioselective with the reaction occurring exclusively at the captodative position.
Table 4.1: NBS bromination of 1,3-dioxolan-4-ones.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yields¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diagram 4.4" /></td>
<td><img src="image2" alt="Diagram 4.4a" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="image3" alt="Diagram 4.5" /></td>
<td><img src="image4" alt="Diagram 4.5a" /></td>
<td>91%</td>
</tr>
<tr>
<td><img src="image5" alt="Diagram 4.6" /></td>
<td><img src="image6" alt="Diagram 4.6a" /></td>
<td>94%</td>
</tr>
<tr>
<td><img src="image7" alt="Diagram 4.7" /></td>
<td><img src="image8" alt="Diagram 4.7a" /></td>
<td>96%</td>
</tr>
<tr>
<td><img src="image9" alt="Diagram 4.8" /></td>
<td><img src="image10" alt="Diagram 4.8a" /></td>
<td>95%</td>
</tr>
<tr>
<td><img src="image11" alt="Diagram 4.9" /></td>
<td><img src="image12" alt="Diagram 4.9a" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="image13" alt="Diagram 4.10" /></td>
<td><img src="image14" alt="Diagram 4.10a" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="image15" alt="Diagram 4.11" /></td>
<td><img src="image16" alt="Diagram 4.11a" /></td>
<td>92%</td>
</tr>
</tbody>
</table>

¹ Nmr yields. ² Literature reference (4).
The high regioselectivity observed was rather surprising in view of the results reported for dioxolanes and dioxanones. Furthermore, esr studies (refer to Chapter 3) on hydrogen abstraction from 1,3-dioxolanones by the electrophilic t-butoxy radical showed that in most cases, attack occurred at both the captodative as well as the acetal centre. For example, hydrogen abstraction from dioxolanone 4.4 by t-butoxy radicals gave a ratio of products 1.4:1.0 favouring attack at the captodative position. As the chain carrier for the bromination with NBS is also electrophilic, similar regioselectivities are expected for these two reactions. However, only one regioisomer was observed in the bromination of dioxolanones. The difference in the regioselectivities of the two hydrogen abstraction reactions can be attributed to the difference in the nature of the transition states. Reactions with t-butoxy radicals have an early transition state whereas reactions with bromine radicals have a late transition state. Thus in the latter case, the transition state is more product-like and is sensitive to radical stabilising effects so that abstraction at the captodative position to form the highly stabilised captodative radical is favoured. However, there is a certain amount of ambiguity regarding the nature of the chain carrier in NBS reactions as succinimidyl radicals may also be involved. The situation for reactions involving succinimidyl radicals as intermediates is less clear cut and will be discussed below. The two postulated mechanisms, the Bloomfield mechanism (involving succinimidyl radicals as the chain carrier) and the Goldfinger mechanism (where bromine radicals are the chain carrier) are shown below.

Scheme 4.4a (Bloomfield mechanism)

\[
\begin{align*}
\text{NBS} & \quad \rightarrow \quad \text{NS}^\bullet \quad + \quad \text{Br}^\bullet \\
\text{NS}^\bullet \ + \ \text{RH} & \quad \rightarrow \quad \text{NSH} \quad + \quad \text{R}^\bullet \\
\text{R}^\bullet \ + \ \text{NBS} & \quad \rightarrow \quad \text{RBr} \quad + \quad \text{NS}^\bullet 
\end{align*}
\]
There have been various reports indicating that the two different chain carriers can be distinguished by changing the reaction conditions. In general, it is believed that reactions conducted in solvents such as CH₂Cl₂ (solubility of NBS is 0.25 M) or in the presence of olefins (Br₂/Br• traps) favour succinimidyl radicals whereas reactions in CCl₄ (where the solubility of NBS is 0.006 M) favour bromine radicals. However, when the NBS reactions were conducted under various brominating conditions, essentially the same products were obtained as those in Table 4.1. For example, when the NBS reactions were conducted in solvents such as CH₂Cl₂ (succinimidyl radical conditions), CCl₄ (bromine radical conditions) and CH₃CN (succinimidyl radical conditions), there was no change in the regioselectivity. Similar results were also obtained when dioxolanones 4.4 and 4.9 were treated with NBS in the presence of 5-10 equivalents of 1,2-dichloroethylene which acts as a bromine radical trap. Furthermore, bromination of dioxolanone 4.4 with 1.1 mole equivalent of bromine in CCl₄ in the presence of light under slow addition conditions gave similar results to the reaction with NBS carried out in the same solvent.

From these results, one is unable to reach a definite conclusion regarding the identity of the chain carrier. The experiments above, with different chain carrying conditions, gave similar results. We are forced to the conclusion that the experimental procedures used for distinguishing different chain carriers cannot completely eliminate the participation of the other chain. In NBS reactions, bromine is inevitably released and although the concentration of bromine may be low, this can produce bromine radicals in the manner shown.
The equilibrium between the succinimidyl radical and bromine lies mainly to the right even at low concentrations of \( \text{Br}_2 \).\(^{17}\) Furthermore, reactions carried out in the presence of 1,2-dichloroethylene do not completely eliminate the bromine radical chain as the trapping of bromine radicals and bromine is not very efficient due to the low reactivity of the olefin.

The other interesting aspect is that the properties of the succinimidyl radical and the bromine radical may not be distinguishable in terms of the regioselectivities displayed. This was initially proposed by Skell\(^{18,19}\) and he also suggested that two types of succinimidyl radicals (\( S_{\sigma^*} \) and \( S_{\pi^*} \)) exist and that they display significantly different selectivities.\(^{20}\) However, the existence of these two succinimidyl radicals has not been proven and current opinions strongly disfavour the hypothesis of the \( S_{\sigma^*} \) and \( S_{\pi^*} \) radicals.\(^{21-24}\)

Although we have not been successful in identifying the actual chain carrier in the NBS reaction, it is probably a valid assumption that under the standard brominating conditions used (NBS, \( \text{CCl}_4 \), initiated with AIBN or light), the predominant chain carrier is the bromine radical. The high regioselectivities observed with NBS could be explained in terms of the reactivity-selectivity principle as discussed before. Radical stabilising effects are therefore important in determining the regioselectivities observed. This becomes more apparent in the bromination of 4.12 with NBS under standard conditions. Product 4.13 was observed in the crude reaction mixture and this could have arisen from hydrogen abstraction at the acetal centre, followed by ring opening (\( \beta \)-scission) and abstraction of bromine from NBS. Abstraction at the acetal centre is now preferred because the resulting radical is now a benzylic radical which possibly has greater stabilisation compared to captodatively stabilised radicals.

\[
\text{NS}^* + \text{Br}_2 \rightleftharpoons \text{NBS} + \text{Br}^*
\]
It is interesting however to speculate on an alternative explanation for the high regioselectivities observed. If a complex between a bromine atom and the carbonyl group of 1,3-dioxolanone was formed, then the likely site of attack by this complex might be at the captodative centre, as it is within "reach" of the complex. Walling had earlier observed that addition of carbonyl containing compounds caused the regioselectivities in the system studied to change. The idea of a bromine atom-substrate complex can also be extended to explain the change in the regioselectivities observed in dioxolanone. Complexes between chlorine atoms and aromatic groups are known to exist and these give rise to high regioselectivities in chlorination reactions. We propose that where there is a choice, the bromine atom preferentially forms a complex with the aromatic group as this interaction will be stronger compared to that with the carbonyl group. If this proposal is true, then abstraction at the acetal centre is favoured (as observed with dioxolanone) due to the close vicinity of the bromine atom-aromatic complex. As part of the present study, the feasibility of these ideas was tested by carrying out molecular orbital calculations.

The structure of 4.4 below was first optimised using the MNDO method. Then a bromine atom was positioned 4Å out of the plane of the ring, directly above (or below) C-2, and the heat of formation of this supermolecule was computed without
allowing the geometry to vary. This was repeated for other positions of the bromine atom and the results are summarised in Table 4.2.

The calculations were repeated for the AM1 methods. Here, positions were optimised when bromine was placed at position 2 and consequently chlorine atoms were used instead. The results are shown in Table 4.3 and the resulting optimised geometry is shown in Figure 4.2. The optimized geometry of the supermolecule was found to correspond to the interaction energy +0.58 kcal/mol.

![Diagram](4.4)

**TABLE 4.2: Energies of interaction between Br• and 1,3-dioxolanone, as calculated by the MNDO method.**

<table>
<thead>
<tr>
<th>Nearest atom to bromine</th>
<th>Energies of interaction(^1) in kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-2</td>
<td>+0.58</td>
</tr>
<tr>
<td>C-4</td>
<td>+0.24</td>
</tr>
<tr>
<td>C-5</td>
<td>+0.58</td>
</tr>
<tr>
<td>O-6</td>
<td>-0.06</td>
</tr>
<tr>
<td>O-1</td>
<td>+0.42</td>
</tr>
<tr>
<td>O-3</td>
<td>+0.23</td>
</tr>
</tbody>
</table>

\(^1\) This corresponds to the difference in the heats of formation of the supermolecule and the sum of the heats of formation for the isolated species i.e. dioxolanone 4.4 and bromine atom.
These preliminary results indicate that the most favourable position of the bromine atom is near O-6. This geometry was therefore used as the "starting" geometry in an MNDO calculation in which the atomic coordinates were allowed to vary freely - the resulting optimised geometry is shown in Figure 4.1. The interaction energy of the supermolecule after optimisation was found to be -0.19 kcal/mol.

The calculations were repeated using the AM1 methods. Here, problems were encountered when bromine was used: consequently chlorine atoms were used instead. The results are shown in Table 4.3 and the resulting optimised geometry is shown in Figure 4.2. The optimised geometry of the supermolecule was found to possess an interaction energy of -3.94 kcal/mol.

**TABLE 4.3: Energies of interaction between Cl• and 1,3-dioxolanone, as calculated by the AM1 calculations**

<table>
<thead>
<tr>
<th>Nearest atom to chlorine</th>
<th>Energy of interaction in kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-2</td>
<td>-0.84</td>
</tr>
<tr>
<td>C-4</td>
<td>+0.88</td>
</tr>
<tr>
<td>C-5</td>
<td>-0.22</td>
</tr>
<tr>
<td>O-6</td>
<td>+0.35</td>
</tr>
<tr>
<td>O-1</td>
<td>+0.63</td>
</tr>
<tr>
<td>O-3</td>
<td>+1.53</td>
</tr>
</tbody>
</table>

* The positive values for the interaction energies show destabilisation of the supermolecule compared to the isolated species, whereas the negative values indicate stabilisation.
Figure 4.1
Interaction of Br with dioxolanone 4.4 as optimised by MNDO calculations.
Figure 4.2

Several views of the interaction of Cl• with dioxolanone 4.4 as optimised by AM1 calculations.
The preliminary calculations summarised in Tables 4.2 and 4.3 lead to different conclusions regarding the most favourable position for interaction. MNDO calculations suggest that the most favourable interaction of the halogen atom is that with O-6 whereas AM1 calculations predict best interaction with C-2. These discrepancies may be attributable to the tendency of MNDO calculations to overestimate steric repulsions.\textsuperscript{27} Thus, we believe, of the two types of calculations, the AM1 method is probably the more reliable.

In this study, only a few of the conceivable positions of the halogen atom were tested. Of these positions, the AM1 calculations do not predict a favourable halogen atom-carbonyl complex but instead favourable interaction energies are observed at both C-2 (acetal position) and C-5 (captodative position). The best interaction is where the halogen atom is near C-2 and this corresponds to a stabilisation energy of 3.94 kcal/mol. If one assumes that the chlorine atom is an adequate model for the bromine atom, then the results indicate that the experimentally observed regioselectivities for the NBS bromination reactions are not mirrored in the theoretical calculations.

In order to assess the importance of aromatic groups versus carbonyl groups in the complex formation, the interaction between chlorine atom and benzaldehyde was investigated using AM1 calculations.\textsuperscript{27}

![The optimised geometry is shown in Figure 4.3. From Figure 4.3, it is observed that the most favourable interaction of the halogen atom is that near the aromatic carbon atom, C-1. This qualitatively supports the view of a better interaction with aromatic groups compared to carbonyl functional groups.](image-url)

Due to the lack of time available, it was not possible to explore every facet of the calculations. For example, it would be desirable to be able to compute and plot the
Figure 4.3
Interaction of Cl\* with benzaldehyde as optimised by AM1 calculations.

4.1b The stereochemistry of NBS reactions

The bromination of 4.6-4.11 gave high diastereoselectivities so only the trans-isomer was detected. In some cases, mixtures of diastereomers of the 1,2-dichloro derivative were formed with only one diastereomer of the bromo compound was detected by 1H and/or 13C nmr spectroscopy. It is interesting that even with a smaller substituent at C-2 (i.e. a methyl group instead of a benzyl group), the 1H diastereoselectivity of the bromo-chlorobenzene was found to be significantly enhanced (98-99%). The stereochemistry of the benzocarbazolium methylates 4.9a (Scheme 4.1) was determined previously by Sackl and Zimmerman\(^4\) by difference saturation nuclear Overhauser enhancement (nOe) methods. In addition, we have also checked the stereochemistry of the bromo compound 4.7a (see entry 4, Table 4.1) by difference saturation nOe where estimation of the 1-benzyl substitution showed a 19% enhancement to H-5 which implies that the stereochemistry of the other benzyl compound was assumed to be the same by analogy. The stereo-isomer resulting from the intermediate transfer to the radical derived from the benzyl group from the reagent (NBS or bromine) at the opposite side to the substituted at the C-2 position.

From the ground state AM1-UHF calculations of the disubstituted radical of 4,7, the bulky substituent seems to be directed away from the methyl group (see Figure 4.4). However, if one accepts the argument that the transition state for the bromine transfer in this case, then it is apparent from Figure 4.4 that approach from the same side of the substituent at C-2 is subject to steric effects.

4.2 Reduction reactions of 1,3-disubstituteds

The diastereoselectivity of reduction by Bu\(2\)SnH of the bromo derivative 4.6a-4.11a is shown in Table 4.4.
energies of interaction of the halogen atom with the substrate at varying distances and orientations from different atoms. It is apparent from the preliminary studies that more work is required to obtain a complete picture of the behaviour of halogen atom with substrates.

4.1b The stereoselectivity of NBS reactions

The bromination of 4.6-4.11 gave high diastereoselectivities as only the trans-isomer was detected. In some cases, mixtures of diastereomers of the 1,3-dioxolanones were employed and even in these cases, only one diastereomer of the bromo compound was detected by $^1$H and/or $^{13}$C nmr spectroscopy. It is surprising that even with a smaller substituent at C-2 (i.e. a methyl group instead of a t-butyl group), the other diastereomer of the bromo dioxolanone was not formed in significant amounts (ds >85%). The stereochemistry of the bromo dioxolanone 4.9a (Scheme 4.1) was determined previously by Seebach and Zimmermann 4 by difference saturation nuclear Overhauser enhancements (nOe) methods. In addition, we have also checked the stereochemistry of the bromo compound 4.7a (see entry 4, Table 4.1) by difference saturation nOe where irradiation of the t-butyl substituent showed a 15% enhancement to H-5 which implies trans stereochemistry. The stereochemistry of the other bromo compounds was assumed to be trans by analogy. The trans-isomer resulted from the bromine transfer to the radical derived from the substrate, from the reagent (NBS or bromine) at the opposite side to the substituent at the C-2 position. From the ground state AM1-UHF calculations of the dioxolanone radical of 4.7, the bulky substituent seems to be directed away from the radical centre (see Figure 4.4). However, if one accepts the argument that the transition state for the bromine transfer is colinear, then it is apparent from Figure 4.4 that approach from the same side of the substituent at C-2 is subject to steric effects.

4.2 Reduction reactions of 1,3-dioxolanones

The diastereoselectivity of reduction by Bu$_3$SnH/D of the bromo derivatives 4.6a-4.11a is shown in Table 4.4.
Figure 4.4

The structure of the captodative radical derived from dioxolanone 4.7 as optimised by AM1 calculations.
Table 4.4: Reduction of bromo dioxolanones with Bu₃SnH/D

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>Ratio of isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6a</td>
<td><img src="4.6a" alt="Diagram" /></td>
<td>1.3:1 (80°C) 2:1 (10°C)</td>
</tr>
<tr>
<td>4.7a</td>
<td><img src="4.7a" alt="Diagram" /></td>
<td>3:1 (80°C) 6:1 (10°C)</td>
</tr>
<tr>
<td>4.8a</td>
<td><img src="4.8a" alt="Diagram" /></td>
<td>3:1 (80°C) 3.7:1 (10°C)</td>
</tr>
<tr>
<td>4.9a</td>
<td><img src="4.9a" alt="Diagram" /></td>
<td>7:1 (80°C) 11:1 (10°C)</td>
</tr>
<tr>
<td>4.11a</td>
<td><img src="4.11a" alt="Diagram" /></td>
<td>8:1 (80°C)</td>
</tr>
</tbody>
</table>

The bromo dioxolanones were treated with 1.1 equivalents of Bu₃SnH/D in the presence of catalytic amounts of AIBN in refluxing benzene at 80°C or with UV irradiation at 10°C. The diastereoselectivities were determined by integration of the
appropriate peaks in $^1$H nmr spectrum. The chemical shifts of the diastereomers are quite different and the assignments of the cis/trans diastereomers will be discussed briefly here and elaborated on later. For example, the two protons at C-5 of dioxolanone 4.7 have different chemical shifts (4.24 and 4.34 ppm). The chemical shift which is further downfield (4.34 ppm) is assigned to the proton cis to the substituent at C-2 (H-5a) on the basis of 1-D nOe experiments as well as 2-D noesy experiments. Thus, from the integration of the absorptions at 4.2 and 4.3 ppm in the $^1$H and/or $^2$H nmr spectrum of the crude reaction mixture after reduction, it is possible to determine the diastereoselectivity of the reaction.

From Table 4.4, it is observed that the favoured isomer in all cases is the one resulting from the attack of Bu$_3$SnH/D on the opposite face to the substituent at C-2. Replacing the methyl substituent with a t-butyl substituent at C-2 increases the selectivity from 1.3:1.0 to 3:1 at 80°C for compounds 4.6a and 4.7a. The improvement in the diastereoselectivity can be explained in terms of the size of the substituent where the t-butyl substituent is bulkier than the methyl substituent and hence is better in shielding one face of the molecule from attack. Furthermore, the presence of substituents at the radical centre (C-5) enhances the diastereoselectivity even more (4.8a, 4.9a and 4.11a). This can be rationalised in terms of radical stability where a tertiary radical is more stable than a secondary one, hence resulting in a less reactive and more selective radical as reflected by the improvement in the diastereoselectivity. The low reactivity, high selectivity principle is generally true although exceptions have been recorded in literature.$^{28}$ As expected, the reduction of bromo compound 4.11a gave similar diastereoselectivity as the reduction of compound 4.9a at the same temperature. This is because the intermediate radical is

![Diagram](image_url)
similar to the radical derived from dioxolanone 4.9a, i.e. a tertiary radical with a bulky substituent at C-2 (see Scheme 4.6).

Scheme 4.6

There is also an expected increase in the diastereoselectivity of reduction reactions when the temperature of the reaction is lowered. This can be attributed to the temperature dependent term in the Arrhenius expressions of these reactions. Attempts were also made to improve the diastereoselectivity by using triphenyltin hydride (a bulkier reagent) instead of Bu3SnH. Reduction of 4.9a at 100°C with triphenyltin hydride gave the same selectivity as that when Bu3SnH was used.

A surprising result was obtained when the bromo dioxolanone 4.10a (see entry 7, Table 4.1 for structure) was reduced with Bu3SnH. In this study, the optically active dioxolanone 4.10 derived from S(+) mandelic acid was used. Reduction of the bromo dioxolanone 4.10a only gave a small amount of reduced product. The major product from the reaction was found to be the dimer 4.14 which must have resulted from the coupling of the very stable intermediate radical which is both benzylic and captodative (see Scheme 4.7). The rate constant for hydrogen abstraction of benzylic radicals from Bu3SnH is \(-4 \times 10^4\) at 25°C\(^{29d}\) compared to a rate constant of \(1.8 \times 10^6\) M\(^{-1}\)s\(^{-1}\) at 27°C for a tertiary radical.\(^{29b,c}\) This difference in the trapping rate constants of the radicals is due to the increased stability of benzylic radicals. To best of our knowledge, the data for the hydrogen abstraction of
captodatively stabilised radicals from Bu$_3$SnH are not available. However, it is apparent that the formation of a radical which is both benzylic and captodative will decrease the rate constant of trapping even further. Radicals **4.14a** combine to form **4.14** (Scheme 4.7). The rate constants for radical-radical termination of benzylic radicals are not significantly decreased compared to t-butyl radicals (2 - 7 x 10$^9$ M$^{-1}$s$^{-1}$ compared to a value for the latter of 2.1 x 10$^9$ M$^{-1}$s$^{-1}$).$^{29a}$

**Scheme 4.7**

There is precedence in the literature for the dimerisation of captodatively stabilised radicals.$^{30,31}$

The identity of the dimer was supported by $^1$H nmr data from which it was evident that two out of the three possible diastereomers were formed. The $^1$H nmr spectrum of the crude reaction mixture showed signals at 0.80 ppm and 0.85 ppm corresponding to the t-butyl groups and 5.18 ppm and 5.30 ppm corresponding to the acetal protons (H-2) as well as absorptions corresponding to the aromatic protons. Upon recrystallisation, one isomer precipitates out: the $^1$H nmr spectrum of which showed (apart from the aromatic protons) only one acetal proton (5.18 ppm) and one t-butyl group (0.80 ppm). From the data at hand, it is not possible to assign the actual stereochemistry of the isomers formed although the $^1$H nmr data rule out routes 1 and 2, as two sets of signals should be observed for the dimer with this stereochemistry (see Scheme 4.8). Elemental analysis supported the assignment of the structure. As an additional proof, the dimer was heated in an esr cavity to 400 K and the resulting radical **4.14a** was detected. An authentic esr spectrum of radical **4.14a** was
observed when compound 4.10 was treated with t-butoxy radicals. Hence, the structural identity of the dimer is unambiguous, but not its stereochemistry.

Scheme 4.8
Possible routes for the dimerisation of radical (4.14a).

(1) no symmetry- 2 signals for acetal H
  cis syn trans

(2) no symmetry- 2 signals

(3) C2 symmetry- 1 signal
  trans anti trans

(4) C2 symmetry- 1 signal
  cis anti cis
We also attempted some other reduction procedures and found that catalytic hydrogenation with 10% Pd on charcoal (in ethyl acetate) of the bromo dioxolanone 4.9a gave only the cis-isomer along with the hydroxy compound 4.15 (Scheme 4.9).

Scheme 4.9

Earlier reports on the catalytic hydrogenation of dioxolanone 4.16 (derived from the elimination of the corresponding bromo compound) gave exclusively the cis-isomer with a diastereoselectivity of greater than 95%. It was suggested that the t-butyl substituent on the dioxolanone ring 4.16 directs hydrogenation to the opposite face of the ring.

Our attempts to synthesize the trans-compound 4.17 (Scheme 4.10) by reducing the bromo derivative 4.9a with superhydride, zinc borohydride and sodium borohydride under different conditions did not succeed as reduction with these metal hydrides was too harsh and ring opened products were detected.

Scheme 4.10
4.3 Carbon-carbon bond forming reactions of 1,3-dioxolanones

Bromo dioxolanones 4.4a, 4.7a and 4.9a were treated with tributylallyltin in an attempt to form new carbon-carbon bonds. A degassed solution of the bromo dioxolanone (3-7 M), AIBN and 1.1 equivalents of tributylallyltin in benzene was irradiated at room temperature until all the starting materials were consumed. The diastereoselectivity was checked by examining the crude reaction mixture by $^1$H nmr or $^{13}$C nmr spectroscopy. The results are shown in Table 4.5.

The yields were determined by $^1$H nmr spectroscopy relative to an internal standard and were found to be 60-70%. However, upon separation by repeated flash chromatography (to remove completely the tin byproducts), the yields were decreased significantly. The major diastereomer 4.7c from the reaction with 4.7a was assigned to be trans by 1-D nOe as well as 2-D noesy experiments whereas the physical data for 4.9c agreed with the literature data for the trans-isomer 4.9c. As in the reaction with Bu$_3$SnH, the diastereoselectivity of the allylation reaction is better in the presence of a substituent at C-5. In the presence of the substituent at C-5, the reaction becomes less exothermic due to the formation of a tertiary radical, and hence more selective. However, the diastereoselectivity observed is not as good as in the reduction studies with Bu$_3$SnH. This result is surprising as reduction reactions with Bu$_3$SnH/D are fast compared to reactions with tributylallyltin. Thus, in the transition state of the former, the distance between the reacting centres is longer (the transition state is reactant-like) and the steric interference between the reacting centres is smaller (as the hydride/deuteride transferred is small). This should lead to poorer diastereoselectivity compared to that observed in the allylation reactions. Instead, the reverse was observed. Seebach and co-workers used enolate chemistry to allylate dioxolanone 4.9 and obtained diastereoselectivity of >95% in favour of compound 4.9c. They suggested that the approach of the electrophiles on the enolate occurs with ul-1,3 topicity and comes from the opposite face to the t-butyl substituent. Attempts were also made to form new carbon-carbon bonds by intermolecular addition to alkenes. The results are shown in Table 4.5.
Table 4.5: Diastereoselectivities of carbon-carbon bond forming reactions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Products</th>
<th>Yields</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4a</td>
<td>tributylallyltin</td>
<td><img src="image" alt="4.4c" /></td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>4.7a</td>
<td>tributylallyltin</td>
<td><img src="image" alt="4.7c" /></td>
<td>68%</td>
<td>2:1 (nmr) 1.9:1 (gc)</td>
</tr>
<tr>
<td>4.9a</td>
<td>tributylallyltin</td>
<td><img src="image" alt="4.9c" /></td>
<td>72%</td>
<td>7:1 (gc)</td>
</tr>
</tbody>
</table>

1 Determined by $^1$H nmr spectroscopy relative to an internal standard (benzene).
Table 4.5 (cont): Diastereoselectivities of carbon-carbon bond forming reactions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Products</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7a</td>
<td>Bu$_3$SnH, methyl acrylate</td>
<td><img src="image1" alt="4.7" /></td>
<td>mixture of isomers $^3$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>directly reduced: trans:cis $^5$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>addition products $^2$ isolated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1 is 4:1</td>
</tr>
<tr>
<td>4.9a</td>
<td>Bu$_3$SnH, methyl acrylate</td>
<td><img src="image2" alt="4.9" /></td>
<td>only one $^4$ isomer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>directly reduced: addition products</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5:1 isolated</td>
</tr>
</tbody>
</table>

$^2$ Ratio determined by gc.

$^3$ Only 1 peak corresponding to the mixture of isomers could be detected on capillary gc.

$^4$ Both isomers may have been formed but only 1 isomer was isolated.

$^5$ This ratio may not be accurate as flash chromatography may have selectively removed one isomer.
In a typical procedure, a degassed solution of 10 equivalents of methyl acrylate and 1 equivalent of the bromo compound in benzene was irradiated with a UV lamp and a solution of Bu$_3$SnH/ AIBN in benzene was added dropwise. Upon completion of the addition of Bu$_3$SnH, the reaction was irradiated for a further 3-4 hours and the reaction mixture was evaporated. In all these cases, the reduction products were also obtained such that the ratio of directly reduced products to addition products was 2.5-3.0:1. In both cases 4.7a and 4.9a, the major isomer isolated from the addition reactions was that where the resulting radical adds to the alkene, opposite to the substituent at C-2. The stereochemistry of the isomer 4.7e and 4.9e was determined by nOe experiments. Only the trans-isomer 4.9e was isolated in the reaction of 4.9a with Bu$_3$SnH and methyl acrylate. As the total isolated yields for the addition products are low (approximately 20-25%), the cis-isomer may have been lost in the isolation procedure. The yields of these intermolecular addition reactions had not been optimised as reaction mixtures were complex and difficult to workup and separate.

A similar approach to forming carbon-carbon bonds by intermolecular addition of radicals to alkenes was to utilise the dehydro compound 4.16 which was readily synthesized from the bromo compound in a literature procedure using DBU as base.

Scheme 4.11

We were encouraged by reports that captodative olefins react readily with radicals, as captodative radicals are formed upon addition of alkyl radicals to these olefins. Our experiments were conducted by generating alkyl radicals from alkyl iodides in the presence of 4.16 under low concentrations of Bu$_3$SnH. However, as the dehydro compound 4.16 was prone to dimerisation (in presence of traces of acid) and therefore inconvenient to make and store, the iodo compound was used in excess.
Typically, the ratio of RI/olefin/Bu$_3$SnH used is 1.5:1.0:1.5. As before, Bu$_3$SnH was added dropwise while the reaction mixture was irradiated with a UV lamp for 6-12 hours. The $^1$H nmr spectrum of the crude reaction mixture was usually too complex to be of use in determining products and diastereoselectivities. It was necessary to chromatograph the reaction mixture and determine the diastereoselectivity of the products isolated by $^1$H and $^{13}$C nmr spectroscopy.

Scheme 4.12

$$\text{RI/ Bu}_3\text{SnH or C}_6\text{H}_{11}\text{HgCl and NaBH}_4$$

$$^{\text{captodatively stabilised radical}}$$

$$\text{(4.16)}$$

$$\text{(4.28)}$$

$$\text{(4.29)}$$

Table 4.6 The diastereoselectivities of radical addition to (4.16).

<table>
<thead>
<tr>
<th>R</th>
<th>Diastereoselectivity (cis/trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) PhCH$_2$</td>
<td>6:1$^a$</td>
</tr>
<tr>
<td>(b) PhCH$_2$CH$_2$</td>
<td>7:1$^a$</td>
</tr>
<tr>
<td>(c) C$<em>6$H$</em>{11}$</td>
<td>$&gt;$5:1$^b$, $&gt;$7:1$^c$</td>
</tr>
</tbody>
</table>

$^a$ Tin method: diastereoselectivity determined after chromatography.

$^b$ Tin method: diastereoselectivity of crude reaction mixture, determined by $^{13}$C nmr spectroscopy.

$^c$ Mercury method: diastereoselectivity of crude reaction mixture determined by $^{13}$C nmr spectroscopy.
When benzyl iodide was used to generate the alkyl radical, two diastereomers were isolated by flash chromatography and the ratio was found to be 6:1 by $^1$H and $^{13}$C nmr spectroscopy. The stereochemistry of the major isomer was determined to be cis by nOe methods. Using (2-iodoethyl)benzene yielded similar results, i.e. a diastereomeric ratio of 7:1 was observed. An attempt was also made to improve the reaction yield by conducting the reaction with 0.05 M concentration of Bu$_3$SnH. However, in this case no addition products were detected.

As in the case of the intermolecular addition to methyl acrylate (Table 4.5), the reaction yields were extremely poor (<10% isolated yields relative to the alkene). This can be attributed to problems associated with the purification of compound on the column (it is usually necessary to run 2-3 successive columns to remove all tin byproducts as the polarity of the dioxolanones was similar to the tin byproducts). In addition, the low yields could have resulted from other competing reactions for example, the direct reduction of the iodo compound which is very likely as the iodo compound is in excess. Alkyl iodides were used because the rate constant for abstraction of iodine by tributyltin radicals is in the order of $10^9$ M$^{-1}$s$^{-1}$ (at 25°C).$^{29a}$ The trapping rate constant of alkyl radicals by Bu$_3$SnH is in the order of $10^6$ M$^{-1}$s$^{-1}$ which is an order of magnitude faster than the rate constant for addition to olefins ($\sim 10^5$ M$^{-1}$s$^{-1}$ at 25°C).$^{29b, 36}$ This suggests that a large excess of olefin should be used and thus, the reaction was repeated with 3 equivalents of alkene and 1 equivalent of cyclohexyl iodide. The reaction mixture was irradiated at room temperature while a solution of 1 equivalent of Bu$_3$SnH and AIBN (0.09 M solution) was added dropwise under infinite dilution methods. The diastereoselectivity as determined from $^{13}$C nmr spectroscopy of the crude reaction mixture was found to be >5:1. The isolated yields of the corresponding addition products were only marginally better (26%). A recent paper indicates that captodatively stabilised radicals do not propagate radical chains well due to their extreme stability.$^{37}$ The paper$^{37}$ reports that methods involving alkylmercury halides and NaBH$_4$ results in a marked improvement of yields. Attempts were then made to add cyclohexyl radical generated from cyclohexylmercury chloride and NaBH$_4$ to the dehydro compound 4.16. The unoptimised isolated yield
of the addition product was found to be 33%. The diastereoselectivity observed by $^1$H nmr spectroscopy was >7:1. The low yields probably resulted from hydrolysis and ring opening of the dioxolanone. However, the method using alkylmercury hydrides has the virtue that separation of products is much easier as there are no tin byproducts.

4.4 Other reactions of 1,3-dioxolanones

4.4a The fragmentation method

Barton$^{38}$ reported that tartaric acid can be protected as the dioxolane 4.18a and this can be converted to the corresponding N-hydroxy-2-thiopyridone ester 4.18b. Reaction of the ester in the presence of activated olefins such as methyl acrylate gave addition products 4.18c as that shown below.

Scheme 4.13

\begin{align*}
(a) R &= \text{COOH} \\
(b) R &= \text{COO-N} \\
(c) R &= \text{CH}_2\text{CHCOOCH}_3
\end{align*}

The stereochemistry of the product was controlled by the bulk of the methyl ester of the dioxolane which shields one face of the ring from attack. We have attempted to conduct similar kinds of experiments using 4.19 which was derived from tartronic acid.
The N-hydroxy-2-thiopyridone ester was made and treatment of this ester with Bu$_3$SnD gave a complex reaction mixture. Upon purification, only 20% of the reduced product (deuterated 4.7) was obtained. To determine the diastereoselectivity of the reduction, the chemical shifts of dioxolanone 4.7 were compared with the chemical shifts of the isolated product by $^2$H nmr spectroscopy. The deuterium in the reduced product was shown to be trans to the t-butyl group. It should be noted that reduction experiments starting from the bromo dioxolanone 4.7a gave a ratio of trans-D: cis-D of 3:1 at 80°C. The different diastereoselectivity may be because of the low yields of isolated product (hence loss of the other isomer) and/or exchange occurring as a result of chromatography. The higher homologue of 4.19 is 4.11 which was synthesized from the condensation of malic acid with pivaldehyde under conditions reported in the literature$^3$ to afford a mixture of the cis/trans diastereomers in the ratio of 6:1. In our initial experiments, no attempts were made to recrystallise the unwanted isomer, and the conversion to the thiopyridone ester was made using DCC, N-hydroxypyridin-2-thione and catalytic amounts of dimethylaminopyridine (DMAP). The crude reaction mixture was then filtered on a short column of silica in the dark and evaporated. No attempts were made to purify this further although $^1$H nmr spectroscopy showed that the reaction had proceeded cleanly to yield the ester 4.20 (see Scheme 4.14). The ester was dissolved in benzene and refluxed in the presence of an equivalent of Bu$_3$SnH and catalytic amounts of AIBN until the yellow colour of the Barton ester disappears. The product identified by $^1$H nmr spectroscopy was found to be the corresponding dioxolanone 4.9 - the protected form of lactic acid. The stereochemistry of dioxolanone 4.9 depended on the initial stereochemistry of the ester 4.20 which in turn reflects the stereochemistry of the starting dioxolanone 4.11. Hence, in the reaction, the ratio of the starting dioxolanone 4.11 was 6:1 (cis:trans) and the ratio of the dioxolanone 4.9 observed was also 6:1 (cis:trans) by $^1$H nmr spectroscopy. Correspondingly, when the pure trans-isomer of dioxolanone 4.11 was used, only the trans-dioxolanone 4.9 was detected upon similar treatment. The reaction was repeated with optically active cis-(2S, 5S)-dioxolanone 4.11 and following the sequence described above, cis-(2S, 5S)-dioxolanone 4.9 was obtained
in high optical purity $[\alpha]_D^{23} = +44.6^\circ$ in CHCl$_3$ compared to a literature value$^3$
$[\alpha]_D^{20} = +44.8^\circ$ in CHCl$_3$.

Scheme 4.14

The N-hydroxy-2-thiopyridone ester 4.20 can undergo a variety of reactions (see Scheme 4.14). When the solution of the ester is irradiated using a sunlamp, the sulphurpyridyl 4.21 was formed. When one isomer of the ester 4.20 was used, then only one isomer of 4.21 was formed. The stereochemistry is presumed to be the same as the stereochemistry of the ester by analogy with the reaction with Bu$_3$SnH.
above. It is also possible to conduct an alternative to the Hunsdiecker reaction\textsuperscript{39} by refluxing 4.20 in BrCCl\textsubscript{3}. From the \textsuperscript{1}H nmr spectrum of the crude reaction mixture, the reaction had proceeded cleanly to form the corresponding bromo derivative 4.22, again with retention of configuration. This product was debrominated using DBU to form 4.16. This provides a different route to the synthesis of 4.16. When optically active cis-(2\textit{S}, 5\textit{S})-dioxolanone 4.11 was used, the dehydro derivative (2\textit{S})-dioxolanone 4.16 was obtained ([\textgreek{a}]\textsubscript{D}\textsuperscript{23} = -14.8° in CHCl\textsubscript{3}\textsuperscript{40}, see Scheme 4.15).

\textbf{Scheme 4.15}

Potentially, the methods discussed above for the malic acid derivative provide easy routes to the synthesis of optically active compounds (i.e. in the synthesis of 4.9 and enantiomerically pure 4.16). The literature procedures for both of these compounds involve the initial conversion of lactic acid to the diastereomers of 1,3-dioxolanones followed by the often difficult recrystallisation of the required low melting point diastereomer at -70°C.\textsuperscript{3,4,40} This method avoids that problem as the diastereomers of dioxolanone 4.11 can be easily recrystallised and handled as they are solids at room temperature. On the whole, we have shown that the pyridinethione method above is very useful as a variety of products can be obtained with different trapping reagents. Furthermore, the diastereoselectivity of these reactions can be controlled when starting from derivatives of malic acid, as reaction will always occur with retention of configuration at C-5.
4.4b Chlorination of 1,3-dioxolanones

Attempts to synthesize the chloro derivatives of dioxolanones using chlorine/pyridine,⁴¹ t-butyl hypochlorite⁴² and sulphuryl chloride⁴³ were not successful, as complicated mixtures were obtained. In most of these cases, an early transition state is involved implying that the chain carrier is reactive and hence less selective in these chlorination reactions than it is in NBS brominations.

4.4c Nucleophilic attack on bromo dioxolanones

Attempts to convert the bromo derivative 4.7a to the cyano derivative by SN₂ displacements failed to give any desired products as the cyanide ion was not sufficiently nucleophilic to displace the bromide.

The possibility of making sulphur and selenium precursors from the bromo compounds by SN₂ displacement of the corresponding nucleophile was also investigated. The results are summarised in Table 4.7. The cis stereochemistry of 4.24 was determined by 1-D nOe experiments and confirmed by X-ray crystallography. Thus, by analogy, the dioxolanones 4.23a, 4.25 and 4.26 were assigned to be cis. In all the reactions, only the cis-isomer was detected with the exception of the reaction 4.7a with p-chlorothiophenol and DBU, where some trans-isomer 4.23b was formed from the epimerisation at C-5 in the presence of base.*

The availability of these different precursors is important as the rate constants for the generation of radicals vary⁴⁴ for different precursors in the order

\[ \text{Br} > \text{Se-C}_6\text{H}_5 > \text{S-C}_6\text{H}_5 \].

* Dioxolanone 4.7a was also treated with thiophenol (1 equivalent), silver carbonate (1.1 equivalent) in benzene (SN1 conditions) and the ratio of the products 4.23a and 4.23b, where Ar=phenyl, was found to be 2.2:1 in favour of the cis-dioxolanone.
Table 4.7: Nucleophilic displacement of bromo dioxolanones.

<table>
<thead>
<tr>
<th>Substrate Reagent</th>
<th>Product</th>
<th>Yields</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7a p-chlorothiophenol, DBU</td>
<td><img src="4.23a" alt="Image" /></td>
<td>81%</td>
<td>7:1</td>
</tr>
<tr>
<td>4.9a p-chlorothiophenol, DBU</td>
<td><img src="4.23b" alt="Image" /></td>
<td>88%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4.9a sodium phenylselenate</td>
<td><img src="4.24" alt="Image" /></td>
<td>80%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4.10a p-chlorothiophenol, DBU</td>
<td><img src="4.25" alt="Image" /></td>
<td>91%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

1 Ar is p-chlorophenylthio.
2 Isolated yields.
3 Diastereoselectivity determined by $^1$H nmr spectroscopy.
4.4d Dehydrobromination reactions of bromo dioxolanones

The dehydro compound 4.16 has great potential for future synthetic work. In a recent paper, Mattay and co-workers\textsuperscript{40} utilised 4.16 in Diels -Alder reactions and obtained products in excellent yields and high diastereoselectivities. The two literature procedures\textsuperscript{4,40} for the synthesis of 4.16 both start from the dioxolanone 4.9. We have already shown that 4.16 can be made \textit{via} an alternate route (Scheme 4.14 and 4.15) starting from 4.11.

Attempts were made to synthesize the corresponding dehydro compound 4.27 in the usual manner by treating the bromo dioxolanone 4.11a with 1.1 mol equivalent of DBU.

\textbf{Scheme 4.16}

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {4.11a};
\node[above] at (2,0) {4.27};
\draw[->] (0,0) -- (2,0);
\end{tikzpicture}
\end{center}

Surprisingly, upon examination of the \textsuperscript{1}H nmr spectrum, the required compound 4.27 was found to be present in only 10\% yield. The major product was subsequently identified as the dehydro compound 4.16. Further experiments revealed that by using slightly less than an equivalent of DBU, the formation of compound 4.27 can be completely eliminated. An alternate method is to use potassium carbonate in the presence of catalytic amounts of 18-crown-6 and this also gives the exclusive formation of 4.16.

The formation of 4.16 arises as the result of decarboxylative-debromination shown below.
This provides yet another route to the synthesis of 4.16. Starting from optically active cis-(2S, 5S)-dioxolanone 4.11, the (2S)-dehydro compound 4.16 can be obtained in 60% yield ([α]D^22 = -15.1° in CHCl3 compared to the literature value^40 of [α]D^20 = -14.8° in CHCl3). Correspondingly, the other enantiomer of (2R)-dioxolanone (4.16) can be obtained from trans-(2R, 5S)-dioxolanone 4.11 and has an optical rotation of [α]D^22 = +15.3° in CHCl3. This proves that the method is applicable to the synthesis of optically active 4.16.

4.4e Hydrolysis of 1,3-dioxolanones

In all these experiments with 1,3-dioxolanones, no attempt was made to hydrolyse the dioxolanone back to the α-hydroxy acids. We have, however, briefly investigated the conditions for the hydrolysis. For this purpose, the hydrolysis of dioxolanone 4.10 to the corresponding methyl ester, methyl mandelate was chosen since monitoring the hydrolysis was easy (using either nmr spectroscopy or gc). An authentic sample of methyl mandelate could be made easily by stirring methyl mandelic acid in MeOH in the presence of Amberlyst-15 (A-15)^45 Some readily available acid catalysts^46 were tested and the results are shown below.
Table 4.8 Hydrolysis of dioxolanone (4.10) under different conditions.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Reaction¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH/A-15, stir, rt, 2 days</td>
<td></td>
</tr>
<tr>
<td>MeOH/ BF₃·MeOH, r.t. overnight</td>
<td>+</td>
</tr>
<tr>
<td>MeOH/ BF₃·Et₂O (3 equivalents), r.t. overnight</td>
<td>+</td>
</tr>
<tr>
<td>DOWEX-50/MeOH/ 3 days</td>
<td>+</td>
</tr>
<tr>
<td>silica/ MeOH, r.t. overnight</td>
<td>+</td>
</tr>
</tbody>
</table>

¹ + indicates conversion to the methyl ester, - indicates no conversion.

It is surprising to note that the hydrolysis of 4.10 in the presence of A-15 did not proceed though the esterification of mandelic acid to the ester was successful. The reason for this is unclear and may be because the A-15 used at the time of hydrolysis was not sufficiently active. Generally, the other methods worked well and it seems that the hydrolysis is simple to carry out.

4.5 Stereochemical assignments and conformational studies of 1,3-dioxolanones

The assignment of stereochemistry to 1,3-dioxolan-4-one systems is not trivial. Earlier reports² suggest that long range coupling is only present in the cis-dioxolanone where the two hydrogens on the same side of the ring have long range coupling. This has later been found to be incorrect, as long range coupling has been found in both the cis and trans forms.⁴⁷-⁵⁰ For example, 2,5-dimethyl-1,3-dioxolan-4-one (4.8) have J₂,₅ coupling of 1.0 Hz and 0.9 Hz respectively.
Also, the form having the greater value of \( J_{2,5} \) coupling does not always correspond to the \textit{trans} arrangement of substituents at C-2 and C-5. This is because the electronegativity of substituents also influences the magnitude of \( J_{2,5} \) couplings.\(^\text{48}\)

There has also been a discrepancy in the reported literature regarding the observed trend in the chemical shifts of the \textit{cis} and \textit{trans} compounds. The assignments made by Polonski\(^\text{51}\) were based on the argument that H-2 and H-5 for \textit{trans} compounds are shielded by the substituents and should show signals at higher field compared with those for the \textit{cis} compounds. However, other workers\(^\text{47-50}\) have used the reverse argument. Hence, there is an uncertainty in the literature regarding the relationship between stereochemistry and nmr data in this type of compound.

Consequently, we have relied on chemical data which have been verified by nuclear Overhauser enhancements (nOe) nmr experiments, chemical correlations and/or X-ray methods, and have made inferences based on similar chemical reactions. Wherever possible, in this work, the stereochemistry of new compounds was checked using one dimensional (1-D) or two dimensional (2-D) nuclear Overhauser (nOe) experiments as described below.

The stereochemistry of the parent dioxolanones has been documented in the literature where the assignments of stereochemistry were based on 1-D difference saturation nOe spectroscopy.\(^\text{3}\) Furthermore, under the reaction conditions used for acetalisation, the major isomer in every case was the \textit{cis} compound.\(^\text{2,3}\) For the C-5 unsubstituted 1,3-dioxolanones it was necessary to assign the chemical shifts of the two protons at C-5. As discussed previously, the assignment was made by 1-D nOe and 2-D noesy experiments. It was observed that the hydrogen at C-5 (H-5) \textit{cis} to the \text{t-butyl} group at C-2 was downfield compared to the H-5 \textit{trans}, due to deshielding
effects. This agrees with the general trend observed in the "parent" dioxolanones, i.e. the H-5 (proton at C-5) cis to a substituent at C-2 is shifted further downfield compared with the corresponding trans compound. Hence in cases where both isomers are formed, the stereochemistry of the isomers can be assigned. In this work, nmr studies were usually carried out for the major isomer in each reaction. As it is not possible to identify the stereochemistry of all new compounds by nmr methods, we have inferred that the same stereochemical route is taken for the same reaction. In addition, where both cis- and trans-isomers are formed, the chemical shift "trend" can be used as an additional check.

However, a severe problem arises with the bromo dioxolanones as only one diastereomer is formed in the bromination reactions. Fortunately, the stereochemistry of 5-bromo-2-(t-butyl)-5-methyl-1,3-dioxolan-4-one (4.9a) has been previously established.4 As mentioned before, we redetermined the stereochemistry of the bromo dioxolanone 4.9a by effecting an SN2 displacement of the bromide (a reaction that should occur with inversion) and checking the stereochemistry of the resulting compound by nOe. Our results were confirmed by a single crystal X-ray analysis of the resulting compound. The stereochemistry was found to be cis, thus reconfirming the stereochemistry of the parent bromide as trans.

We also determined the stereochemistry of the bromo dioxolanone 4.7a and found using 1-D nOe methods that irradiation of the t-butyl group at C-2 gave a 15% enhancement at H-5. This implies that the bromo compound is trans which agrees with the stereochemistry shown for 4.9a. By analogy, the stereochemistry of the bromides 4.6a-4.11a is assigned as trans.

The percentage enhancements observed for different compounds had values of up to 15% in a 1-D experiment. We were aware of problems associated with the misinterpretation of saturation nOe difference spectroscopy. Transfer of magnetisation when the system is being saturated may occur and this has been shown to be the case when a multi spin system is present. The assumption of an isolated two spin system does not hold in most cases. More problems also arise as a result of oversaturating or
undersaturating a multiplet as in the latter case, selective population transfer can occur.52,53

Consequently, we have been very cautious in interpreting the results of our saturation nOe difference experiments. Wherever possible, we have tried to confirm the stereochemistry by the use of another method of measuring nOes. This was done using transient nOes which were obtained by inverting the population of spins and observing the build up of nOe. The 2-D equivalent of this experiment is the noesy experiment. Noesy experiments have not been used much for small molecules due to the inherent nature of small molecules having small nOes. This is due to long correlation times which in turn means long relaxation times and corresponding fast relaxation rates.

In a saturation nOe experiment, the maximum first order nOe observable is 50% for a 2-spin system. However, the maximum nOe observable in a transient nOe experiment is only 19%. This reduction in nOe observable in these two experiments as well as further reduction in the sensitivity of 2-D experiments is one of the main reasons why the latter method is generally deemed unsuitable for small molecules.

The stereochemistry of compounds 4.7c, 4.7e, 4.9e, 4.24 and 4.28a-d were assigned using a combination of 1-D and 2-D methods wherever possible.

The conformation of the dioxolanones has been discussed and predicted from optical activity studies.51 The closely related γ-lactones are known to be in an envelope form where the α- and γ-carbons along the O=C-O group all lie in one plane and the β-atom lies above or below the plane. Three possible conformations that have been suggested for 1,3-dioxolanones are:

(a) a structure analogous to the γ-lactones with the ether oxygen out of the plane. This is preferred when the 2,5 substituents are bulky and where substituents are cis to each other.
(b) a nearly planar conformation. This is the conformation preferred for mono substituted compounds and disubstituted compounds provided that the substituents are small as this arrangement is susceptible to bulky substituents.

\[
\text{conformation B}
\]

(3) conformation where C-2 is out of plane. This conformation is probably not favoured due to distortion of the ester group from planarity.

\[
\text{conformation C}
\]

X-ray crystallographic data for 2-(t-butyl)-5-(p-chlorophenylthio)-5-methyl-1,3-dioxolan-4-one (4.24) demonstrated cis stereochemistry and provided interesting detail regarding the conformation of the 5-membered ring (see Appendix A). This compound has an envelope conformation consistent with the conformation predicted by CNDO/2 calculations and similar to the conformation of \( \gamma \)-lactones. The ether oxygen is out of the plane by 32.5°. The preference for this conformation over conformation B is presumably due to interactions present in the latter conformation as a result of the bulkiness of the substituents, both of which occupy pseudoequatorial positions. The data also reveal that the two ring oxygens (O1 and O2) have very similar bonding parameters. O1 and O2 form a COC bond angle of 106° and 109° (sp\(^3\)) respectively, whereas from the literature,\(^{54}\) the two ring oxygens of dioxanone
4.3 are different such that O1 forms an angle of 110° (sp\(^3\)) and O2 an angle of 120° (sp\(^2\)). This difference is probably due to the rigid ring constraints imposed by the 5-membered ring compared to the 6-membered one.

![Diagram](image)

For dioxolanone 4.24, the C-O bond distances at the acetal centres were found to be different; C2-O2 (1.46Å) is longer compared to C2-O1 (1.42Å) suggesting that the former bond is weaker and easier to break. A similar observation was made in the dioxanone (4.3) where O1-C2 is 1.38Å and O2-C2 is 1.47Å.\(^{54}\) The difference in the bond lengths at the acetal centre is thought to arise from stereoelectronic effects.\(^{55}\)

The AM1/UHF\(^{27}\) calculations on 2-(t-butyl)-1,3-dioxolan-4-one (4.7) showed that the ring structure is more or less planar. This agrees with the prediction that conformation B would be preferred when there is only one bulky substituent (Figure 4.5).

**Conclusion**

Radical reactions of dioxolanones exhibit interesting regio- and diastereoselectivity. Bromination of dioxolanones with NBS proceeds with high regioselectivity at the captodative centre. This reaction is believed to involve a late transition state thus allowing captodative stabilisation of the intermediate radical to affect the outcome of the reaction. Esr studies indicate that more exothermic reactions of dioxolanones are much less regioselective. Bromination of dioxolanones is also highly diastereoselective, but other radical reactions of these compounds are generally less diastereoselective than their ionic counterparts. In general, the diastereoselectivity of radical reactions at C-5 is greater for 5-substituted systems than it is for the
Figure 4.5
The structure of dioxolanone 4.7 as optimised by AM1 calculations.
unsubstituted systems: the diastereoselectivity also increases with increasing size of the substituent at C-2.

Other radical precursors, e.g. thioethers, can be formed by SN2 reactions of bromo dioxolanones. Since these reactions proceed with inversion, the products have the stereochemistry at C-2 opposite to that for radical reaction products.

Further investigation is required to define more precisely the factors which control the regio- and stereo-selectivity. However, the work described in this chapter clearly indicates that radical reactions of dioxolanones, especially those derived from readily available optically active hydroxy acids, could provide useful tools for the enantioselective synthesis of a wide variety of natural products and related compounds.
References: Chapter 4


6. (a) L.A. Cort and R.G. Pearson, J. Chem. Soc., 1960, Part 2, 1682. (b) It is not clear if the authors had isolated the 4-bromodioxolanes or if they inferred it from the formation of polymeric material. (c) Under our reaction conditions, no polymeric material was produced.


36. For rates of addition to captodative olefins, refer to Chapter 2, section 2.3 and references quoted therein.


Chapter 5: Regio- and Diastereo-selective Reactions of 1,3-oxazolidin-5-ones and 1,3-imidazolidin-4-ones
Chapter 5

Introduction

The importance of amino acids in biological studies has been reflected by the amount of work surrounding the enantioselective synthesis of amino acids, both proteinogenic and non-proteinogenic. Many approaches have been taken and these include the use of temporary metal centres or use of chiral auxiliaries and reagents. An important method developed successfully by Seebach involves the conversion of amino acids to diastereomeric cyclic oxazolidinones and imidazolidinones by condensation with pivaldehyde. Thus a temporary auxiliary is created at the acetal centre. The diastereomers can be separated and subsequent alkylation can be achieved with very high diastereoselectivity, controlled by the bulky t-butyl group. Hydrolysis of the alkylated diastereomer will then give the corresponding amino acid in high optical purity. This method is known as "self-reproduction of centre of chirality" as the net reaction is the replacement of hydrogen at the α-position of the amino acid with a carbon-carbon bond with either retention or inversion of configuration depending on which diastereomer was used in the alkylation. The strategy of converting amino acids to an appropriate cyclic form which can control the diastereoselectivity of reactions was also exploited by Williams. Here, 1,4-oxazin-2-ones were used as electrophilic glycine templates for the asymmetric synthesis of amino acids.

The concept of using protected amino acids in the form of oxazolidinones and imidazolidinones in amino acid synthesis was appealing. Since there are only very few literature reports of radical reactions of these compounds, our aim was to examine the properties of these compounds in radical reactions as well as to study factors that could affect the diastereoselectivities of radical reactions. For this purpose, racemic materials have been used unless otherwise specified.

* In the context of this chapter, the diagrams shown only illustrate the relative stereochemistry of the compounds and do not imply absolute stereochemistry unless otherwise specified.
5.1 The chemistry of oxazolidinones

The first synthesis of oxazolidinones was reported in 1957 by Ben Ishai. Since then, methods have been developed by Jung and Seebach to synthesize 2-substituted 1,3-oxazolidin-5-ones by first synthesizing the Schiff base of the amino acid followed by cyclisation of the Schiff base with the appropriate acid chloride.

**Scheme 5.1**

The Schiff base is not stable to prolonged storage as upon exposure to air and moisture, the aldehyde is evolved. Thus, for the synthesis of the oxazolidinones, freshly prepared Schiff base is used wherever possible, otherwise the reaction yields are poor.

5.1a The regioselectivity of NBS reactions

Seebach and Zimmermann reported that bromination of oxazolidinone occurred mainly at the captodative centre, with 30% bromination observed at C-2. Moreover, they report that the reaction occurred diastereoselectively but the stereochemistry of the product was not discussed.

**Scheme 5.2**

In our studies, the brominated oxazolidinone 5.1 was reacted with equivalents of NBS in the presence of a catalyst. The reaction proceeded smoothly to give the desired product in high yields.
In another study by Williams, 4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (5.2) was treated with NBS and t-butylhypochlorite. In both cases, free radical bromination and chlorination occurred regio- and diastereo-selectively.

Scheme 5.3

The high regioselectivity displayed by the oxazinone 5.2 in this reaction is surprising as the alternative radicals formed at C-5 and C-6 are highly stabilised benzylic radicals. In addition, the formation of radical at C-6 is favoured further by polar effects as the electron density at C-6 is high due to the electron donating capacity of the oxygen (as bromine and t-butoxy radicals are electrophilic). The high regioselectivity observed at C-3 may be a consequence of the captodative effect (as the highly stabilised captodative radical is formed). However, this explanation is not completely satisfactory since one does not expect captodative stabilisation to be important in reactions with early transition states (such as free radical chlorination reactions with t-butylhypochlorite).

In our studies, the unsubstituted oxazolidinone 5.3 was treated with 1.1 equivalents of NBS in refluxing CCl4 under standard conditions. The crude reaction mixture was then examined by ¹H nmr spectroscopy where it was found that bromination occurred mainly at the captodative centre (>90%) with only one diastereomer formed in the reaction.
As with the dioxolanones, attempts were made to study the regioselectivities of NBS brominations under various chain carrying conditions (see Chapter 4). The results are summarised in Table 5.1.

**TABLE 5.1 The effect of reaction conditions on NBS reactions on oxazolidinone (5.3).**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Observations&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NBS</td>
<td>CCl₄</td>
<td>reflux, t=50'</td>
<td>5.3a (90%)</td>
</tr>
<tr>
<td>2. NBS</td>
<td>CH₂Cl₂</td>
<td>hv, t=30', 60'</td>
<td>5.3a (80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.3 (20%)</td>
</tr>
<tr>
<td>3. NBS</td>
<td>C₆H₆</td>
<td>hv, t=45'</td>
<td>5.3a (90%)</td>
</tr>
<tr>
<td>4. NBS</td>
<td>CH₃CN</td>
<td>reflux, t=50', 24h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5. NBS</td>
<td>CCl₄</td>
<td>reflux, 1eq. K₂CO₃ t=50'</td>
<td>5.3a (90%)</td>
</tr>
<tr>
<td>6. NBS</td>
<td>CCl₄</td>
<td>reflux, 10 eq dichloroethylene, t=50'</td>
<td>5.3a (70-80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.3 (20-30%)</td>
</tr>
<tr>
<td>7. Br₂</td>
<td>CCl₄</td>
<td>hv, t=60'</td>
<td>5.3a (50-90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y (10-50%)</td>
</tr>
<tr>
<td>8. Br₂</td>
<td>CCl₄</td>
<td>hv, 1 eq. K₂CO₃, t=60'</td>
<td>5.3a (70-80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.3 (20-30%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>% of products/starting materials quoted were estimated from ¹H nmr spectroscopy.

Abbreviations used:

- hv for irradiation with a sunlamp.
- t for time in ' (minutes) or h (hours).
Entries (1) and (5) show that the reaction products are the same in the absence or presence of potassium carbonate implying that HBr is not important in the NBS bromination reaction. Bromination with bromine radical as the chain carrier generated from the photolysis of bromine (entry 7) gave the required bromo compound (reaction at the captodative centre) together with Y (sometimes in substantial amounts). The amounts of Y formed in the reaction varied in the different experiments from 10-50%. The $^1$H nmr spectrum of Y was simple, i.e. it showed chemical shifts corresponding to the t-butyl group ($\delta$ 1.07, 9H), the acetal proton ($\delta$ 6.31, 1H) and the aromatic region. The IR showed the presence of 3 carbonyl peaks (at 1710, 1770 and 1820 cm$^{-1}$) and the structure of Y was tentatively assigned as the following.

\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{Ph}
\end{align*}

(5.4) Compound Y

A possible route for the formation of Y can be envisaged. The iminium ion 5.4a can be formed by the elimination of HBr from the bromo compound formed initially. This highly reactive intermediate$^{12-15}$ could then react rapidly with adventitious water in an acid catalysed reaction (HBr) to lead to Y. Bromination with bromine produces one equivalent of HBr for every hydrogen abstracted. This rationale is consistent with the observation that in the presence of potassium carbonate, the formation of Y can be reduced or eliminated.

\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{Ph}
\end{align*}

(5.4a)
Further examination of Table 5.1 revealed that under the so-called "succinimidyl" conditions (refer to Chapter 4, Section 4.1a) (entries 2 and 6, Table 5.1), the reaction does not go to completion. This could be interpreted as lending support to the postulate that bromine radicals are the main chain carrying species in NBS bromination reactions.

An attempt was also made to convert oxazolidinone 5.5 (used as a 1:1 mixture of isomers) to the bromo compound 5.5a in the manner described by Seebach and Zimmermann.\(^\text{10}\)

**Scheme 5.5**

\[
\begin{align*}
\text{NBS} & \quad \text{Ph} \quad \text{O} \\
\text{(5.5)} & \quad \text{Ph} \quad \text{O} \\
\end{align*}
\]

NBS was refluxed with an equivalent of oxazolidinone 5.5 in CCl\(_4\) and the disappearance of NBS and the starting material 5.5 was monitored by \(^1\)H nmr spectroscopy. It was observed that only half an equivalent of the oxazolidinone 5.5 was consumed for every equivalent of NBS used and that two equivalents of NBS were required to fully consume the starting material. Even then, nmr examination of the crude reaction mixture showed no trace of oxazolidinone 5.5a. Similar behaviour was also observed for the oxazolidinone 5.6 derived from valine.

\[
\begin{align*}
\text{O} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{(5.6)} & \\
\end{align*}
\]
It was not possible to characterise the products formed from these bromination reactions as attempted purification by flash chromatography gave decomposition products. However, there is precedent in the literature for the formation of the dibromides 5.8 and 5.10 in the NBS bromination reactions of N-benzoylated valine$^{12}$ 5.7 and alanine derivative$^{16,17}$ 5.9 respectively.

Scheme 5.6

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
\text{O} & \quad \text{OCH}_3 \\
\text{O} & \\
\text{Br} & \\
\text{NBS} & \\
\text{O} & \quad \text{OCH}_3 \\
\text{Br} & \\
\text{Br} & \\
\end{align*}
\]

Scheme 5.7

By analogy, the absorptions observed in the $^1$H nmr spectrum of the reaction of oxazolidinone 5.5 with 2 equivalents of NBS were assigned as those arising from the dibromide 5.11 and its diastereomers (see Scheme 5.8). The bromo compound 5.5a must have been formed initially but undergoes rapid HBr elimination assisted by the participation of the nitrogen lone pair. This results in the formation of a very reactive alkene which then traps bromine rapidly.$^{16,17}$ The HBr formed from the elimination of 5.5a will generate more bromine in a fast reaction as shown below.

\[
\text{NBS} + \text{HBr} \quad \rightarrow \quad \text{NSH} + \text{Br}_2.
\]
Attempts were made to prevent the formation of the dibromide by addition of solid potassium carbonate as well as the addition of a bromine trap (10 equivalents of dichloroethylene). Both methods failed to prevent the dibromide formation presumably because these traps were not sufficiently effective as scavengers for HBr and bromine compared to the reactivity of the intermediate alkene.

In another attempt to synthesize the α-bromo compound, the nucleophilicity of the nitrogen was decreased by changing the N-protecting group from a benzoyl to a benzoyloxycarbonyl group. However, the reaction of oxazolidinone 5.12 with one equivalent of NBS under standard conditions did not give the required bromo compound but appeared to also give rise to the corresponding dibromide.

5.1b The stereoselectivity of NBS reactions

The stereochemistry of 4-bromo oxazolidinones was not checked directly as these compounds are unstable, and were usually synthesized immediately prior to use. The experiments in Chapter 2, section 2.2 indicated that for oxazolidinone 5.5, the
hydrogen cis to the t-butyl substituent was abstracted four times faster than the hydrogen trans to the t-butyl group.

\[
\text{H} \\
\text{Ph} \\
\text{cis-(5.5)} \\
\text{O} \\
\text{N} \\
\text{H} \\
\text{Ph} \\
\text{trans-(5.5)} \\
\text{O} \\
\text{N} \\
\text{H}
\]

Relative rate of bromination \text{trans/cis}=4

If the same argument is extended to the 4-unsubstituted oxazolidinones e.g. oxazolidinone 5.3 and it is assumed that in NBS brominations, the bromine is likely to approach from the same side as that from which the hydrogen is abstracted, it may be implied that the brominated product 5.3a should have cis stereochemistry (see Scheme 5.4). The bromo oxazolidinones can also be converted to thioether derivatives by treating the freshly synthesized bromo derivatives with thiolate ions.* In most cases, the displacement of bromine with the thiolate ion proceeded to give a predominance of one diastereomer. If one assumes that the thioethers were formed by \text{SN2} displacement of the bromine, then the stereochemistry of the sulphur compounds could in turn give information on the stereochemistry of the bromo compounds.

When oxazolidinone 5.13 (Scheme 5.9) was treated with NBS followed by the reaction with the thiolate ion, the thioether 5.13b was found by X-ray crystallography to have cis stereochemistry. This implies that the bromo derivative was trans (refer to Appendix B for the crystal structure).

* The other 4-unsubstituted oxazolidinones studied were oxazolidinones 5.13-5.18 (see Table 5.2 for the structures). The corresponding 4-bromo derivatives are 5.13a-5.18a and were characterised, wherever possible, as the 4-thio derivatives, 5.13b-5.17b. As the bromination of oxazolidinone 5.18 was extremely slow, good yields of the bromo compound 5.18a could not be obtained and hence, the thio derivative 5.18b was not synthesized.
This is in contradiction to the previous deductions. A likely explanation for the apparent anomalies is that in the oxazolidinones the displacement of bromine does not occur via an SN2 mechanism. Indirect evidence for this was observed when oxazolidinone 5.3a was treated with the thiolate ion in the manner as that for oxazolidinone 5.13a but failed to give any substituted sulfur compounds. Instead, the debrominated product was observed. This must have arisen from the attack of the thiolate ion on the bromide. It is not clear as to why this was not observed in the reaction of the thiolate ion with bromo oxazolidinones with alkylcarbonyl amino protecting groups.

Scheme 5.9

\[
\text{Scheme 5.10}
\]

where \( \text{Ar is } p\text{-chlorophenylthio} \)
5.1c The reactivity of 3-substituted oxazolidinones in NBS bromination reactions

During the study of the reactions of oxazolidinones with NBS with different N-protecting groups, it was observed that there seemed to be differences in the rates of bromination. It was decided therefore to investigate the reactivity of various N-protected 2-(t-butyl)-1,3-oxazolidin-5-ones in the reaction with NBS. The method used for the measurement of relative rate constants was that described in Chapter 2, section 2.2. This method had been previously used by workers attempting to quantify the relative rate constants of NBS reactions in aromatic systems. In brief, a deficiency (a known amount) of NBS was added to a solution of standard and substrate in CD₂Cl₂, in an nmr tube. The solution was degassed and the ratio of the two starting materials was determined by accurate integration of the ¹H nmr spectrum. The reaction mixture was then irradiated with a sunlamp for 15 minutes, after which, the nmr spectrum was recorded. Accurate integration of the absorptions corresponding to starting materials and products enabled relative rate calculations using equation (1) in Chapter 2. Alternatively, CCl₄ was used as the solvent and the reaction mixture was refluxed and subsequently, the ratios of starting materials and products determined by ¹H nmr spectroscopy. The standard chosen for this work was methyl hippurate as the chemical shifts of methyl hippurate and bromo methyl hippurate did not overlap with those of the tested compounds in most cases. The results are summarised in Table 5.2.

It must be appreciated that large experimental error is involved when the difference in the relative rate constants (k₁/k₂) is large. Therefore, as an additional check, competitions between two cyclic pairs were carried out and the expected calculated value was checked with the values observed. These demonstrated reasonable agreement in most cases. In fact, the relative rate constant (k₁/k₂) value for oxazolidinone 5.18 was obtained in this way.

1 The µ value listed here refers to the primary of the compound protecting group.
2 The value of µ listed here refers to the protact of the compound protecting group.
TABLE 5.2: Rates of NBS bromination relative to methyl hippurate.

<table>
<thead>
<tr>
<th>Code no.</th>
<th>Substrates</th>
<th>Relative Rate</th>
<th>$pK_a$ (^{1(°C)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.19</td>
<td>methyl hippurate</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>5.14</td>
<td>R=t-butyl</td>
<td>1.2</td>
<td>5.03 (18)</td>
</tr>
<tr>
<td>5.15</td>
<td>R=CH(_2)CH(_3)</td>
<td>1.3</td>
<td>4.87 (25)</td>
</tr>
<tr>
<td>5.16</td>
<td>R=(CH(_2))(_6)CH(_3)</td>
<td>1.1</td>
<td>4.89 (25)</td>
</tr>
<tr>
<td>5.13</td>
<td>R=CH(_2)Ph</td>
<td>1.0</td>
<td>4.28 (18)</td>
</tr>
<tr>
<td>5.3</td>
<td>R=Ph</td>
<td>0.7</td>
<td>4.19 (25)</td>
</tr>
<tr>
<td>5.17</td>
<td>R=OPh</td>
<td>0.2</td>
<td>2.93 (25)(^2)</td>
</tr>
<tr>
<td>5.18</td>
<td>R=CCl(_3)</td>
<td>0.03</td>
<td>0.70 (25)</td>
</tr>
</tbody>
</table>

1 The $pK_a$ values listed here refer to the acidity of the acids of the protecting groups.

2 The value of $pK_a$ used here is that for phenoxyacetic acid (R=CH\(_2\)OPh).
A correlation was found between log(relative rate) versus the pK_a for the acids of the protecting groups. A plot of the correlation is shown below.

\[ y = -4.1145 + 0.88764x \quad R^2 = 0.986 \]

It appears that the relative reactivities of 3-substituted oxazolidinones in the NBS reactions are governed predominantly by the electron donating ability of the N-acyl protecting groups. The hydrogen abstraction by the bromine (or succinimidyl) radical is subject to rate enhancements as the substituent at the nitrogen becomes more electron releasing. This implies that polar effects are important in determining the rates of NBS reactions. This has been previously observed in the NBS bromination of \( \alpha \)-substituted toluenes where a correlation of relative rate with \( \sigma^+ \) values was found.\(^{19}\)

The spread of reactivity observed in the system studied here was much smaller compared to that for the \( \alpha \)-substituted toluenes.\(^{19b}\) This may be because the extent of polarisation at the transition state is not as great in the former case as the substituents in question are not directly attached to the radical centre.
5.1d Reduction with tributyltin deuteride

To study the diastereoselectivity of radical reactions, the bromo and sulphur derivatives of oxazolidinones were treated with Bu₃SnD in the presence of catalytic amounts of AIBN in refluxing benzene (80°C), or irradiated for 2 days with UV light at 10°C.

Scheme 5.11

![Scheme 5.11](image)

**Substrates**

| 5.16a  | R= (CH₂)₆CH₃, X=Br |
| 5.15b  | R= CH₂CH₃, X=SAr  |
| 5.3a   | R=Ph, X=Br        |

**Ratio of cis-D/ trans-D (temperature)**

<table>
<thead>
<tr>
<th></th>
<th>1:1 (80°C)</th>
<th>1.3:1.0 (10°C)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.16a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.15b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Tentative assignment.

The reduction of the corresponding bromo and sulphur derivatives under radical conditions occurred with no selectivity. In view of these poor selectivities, the assignment of the stereochemistry is only tentative and has not been proven by any nmr methods. The poor selectivities were rather surprising and were a little disappointing in view of the high diastereoselectivities observed with the NBS brominations.

5.1e Carbon-carbon bond forming reactions

Bromo oxazolidinone 5.3a was refluxed with tributylallyltin²² in benzene for several days in the presence of AIBN. It was not possible to determine the diastereoselectivity by ¹H or ¹³C nmr spectroscopy as the reaction mixture was too
complex. Compound 5.20 was isolated but the yield was extremely poor (<10%). The stereochemistry of 5.20 was determined to be trans by 1-D difference saturation nOe as well as 2-D noesy experiments. The cis-isomer was not isolated. This may not be a reflection of the diastereoselectivity of the reaction as the other isomer may have been lost in the isolation procedure. An alternative explanation is that the allylation reaction occurs with high diastereoselectivity (albeit with low yields) due to the coordination of tributylallyltin to the amide carbonyl. Thus assuming a trans relationship between the t-butyl and the N-protecting group, the reaction preferentially occurs at the same side as the N-protecting group, resulting in the trans-isomer. Similar unpublished observations in our laboratories20 have also led to the conclusion that the coordination of tributylallyltin to carbonyl groups may be a real phenomenon in determining the diastereoselectivities of radical allylation reactions.

Scheme 5.12

![Scheme 5.12](image)

It should be noted that similar reactions with the acyclic amino acids 5.21 with tributylallyltin give product 5.22 in good yields (see Scheme 5.13).21 The reason for the discrepancy in the efficiencies of this reaction with oxazolidinone 5.3a and amino acid 5.21 is not clear although it is possible that the cyclic amino acid is more stable due to the planarity of the resulting radical and does not propagate the chain efficiently as the acyclic form. An alternative reason is that the radical addition of the cyclic radical to tributylallyltin is strongly disfavoured due to steric reasons. The results from Chapter 2 have indicated that acyclic compounds undergo NBS reactions much faster than do the cyclic derivatives. The rate determining step for NBS reactions is hydrogen abstraction, whereas in allylation reactions the slow step is the addition to
tributylallyltin. However, the same factors (e.g. steric) may control the rates of reactions such that radical addition of cyclic radicals to tributylallyltin is slower than in the acyclic derivatives. This may account for the difference in the efficiencies of the two allylation reactions.

Scheme 5.13

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \quad \text{CO} \quad \text{OCH}_3 \\
\text{Br} & \quad \overset{\text{Bu}_3\text{Sn}}{\text{-}} \\
(5.21) & \quad \rightarrow \\
\text{Ph} & \quad \text{NH} \quad \text{CO} \quad \text{OCH}_3 \\
(5.22)
\end{align*}
\]

5.1f Intramolecular hydrogen abstraction studies

In view of the difficulties encountered in generating captodative radicals efficiently, it was desirable to develop an alternative method for the generation of the captodative radical from 1,3-oxazolidin-5-ones. This is especially important in systems like 4-substituted oxazolidinones where the captodative radical cannot be generated from the 4-halo compounds, as these compounds are unstable and cannot be isolated.

One possible method of generating such a radical indirectly would be to use a system where the initial radical centre is formed at one position but undergoes a rapid intramolecular hydrogen abstraction to form the required radical. An example of this is shown in the compound 5.23, which can be synthesized from the Schiff base of glycine and o-bromobenzoyl chloride.

\[
\begin{align*}
\text{O} & \quad \text{N} \quad \text{C} = \text{O} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \quad \text{C} \\
\text{N} & \quad \text{Br} \\
(5.23)
\end{align*}
\]
Treatment of this compound with tributyltin radicals initially generates the phenyl radical by abstraction of the bromine. This radical can then potentially undergo trapping with the reagent or may undergo hydrogen abstraction at both C-2 and C-4 to form the acetal radical or the captodative radical respectively. This can then be trapped by the reagent and the ratio of the trapped products will give a good indication of the relative amounts of abstraction at each position.

When oxazolidinone 5.23 was treated with Bu₃SnD (and catalytic amounts of AIBN) under infinite dilution conditions in refluxing benzene, the products shown in Scheme 5.14 (as determined by ²H nmr spectroscopy) were obtained. The ratios were obtained from the integration of the required peaks.

From the results shown in Scheme 5.14, it is immediately obvious that very little product arises from the direct trapping of the initially formed phenyl radical. Intramolecular hydrogen abstraction occurs rapidly and the abstraction at the captodative position is favoured compared to the abstraction at the acetal centre (the observed concentration ratio was 9:1). Thus this method seems viable for the generation of captodative radicals. Furthermore, the ratio of cis-D/trans-D (compounds 5.24a and 5.24b) was found to be ~1.1:1.0 which agrees with the value obtained by the direct generation of captodative radicals starting from compound 5.3a where the diastereoselectivity was 1:1 (see Scheme 5.11).

The oxazolidinone 5.27, derived from alanine, was treated with Bu₃SnD in a similar manner to that above (see Scheme 5.15). As before, the amount of direct deuteration of the aromatic ring is very small. The ratio of abstraction at C-4: C-2 was found to be 7:1 whereas the ratio of cis-D/trans-D (at C-4) was found to be 1:1. The latter value reflects the diastereoselectivity in the reaction of compound 5.5a (refer to Scheme 5.5 for the structure) with Bu₃SnD and had not been obtained previously due to the difficulties in synthesizing the bromo compound. These results indicate that the selectivity was not improved by the presence of a methyl substituent at C-4.
Scheme 5.14

Ratio of 5.24a:5.24b is ~1:1.1 (tentative assignment)
Ratio of 5.24a/b:5.25 is 9:1 (not statistically corrected for the number of hydrogens)
Ratio of 5.24a/b:5.26 is 6:1
Attempts were made to utilise the results of these experiments in the synthesis of new carbon-carbon bonds. For this purpose, the iodo compound 5.31 was synthesized, treated with tributylallyltin and irradiated with UV light in an nmr tube. The reaction was monitored by $^1$H nmr spectroscopy and after irradiation for 2 days, the absorptions corresponding to that of tributylallyltin had disappeared. It was observed that among the identifiable products formed, the trans-allylated product 5.20 as well as the directly reduced compound 5.3 were formed. The latter observation was rather surprising and suggested that oxazolidinone 5.3 must have arisen from the abstraction of hydrogen from tributylallyltin to generate the stabilised allyl radical.

Scheme 5.16
The preference to abstract hydrogen rather than add to tributylallyltin has been reported in the case when methylallyltributyltin\textsuperscript{22} was used but to our knowledge, this has not been observed before in reactions with tributylallyltin.\textsuperscript{*} Abstraction of this kind was not observed in the \textsuperscript{1}H nmr spectrum of the crude reaction mixture of bromo oxazolidinone \textbf{5.3a} with tributylallyltin (see Scheme 5.12). This suggests that abstraction of hydrogen from tributylallyltin occurred via the phenyl radical in competition with intramolecular hydrogen abstraction at positions 2 and 4.

These experiments show that it is possible to conduct intramolecular reactions of this type. We are currently examining the scope of these reactions in the intramolecular cyclisation of oxazolidinones.

\textbf{5.1g The synthesis and utility of the dehydro compound (5.33)}

2-Acylaminoacrylic acid derivatives \textbf{5.32} are important in organic synthesis as precursors for the synthesis of other amino acids as well as peptides\textsuperscript{23}

\begin{center}
\begin{tikzpicture}
\node [draw, rectangle] (a) at (0,0) {COOR};
\node [draw, rectangle] (b) at (1,0) {NHR'};
\node [align=center] (c) at (0.5,0) {{\textbf{(5.32)}}};
\end{tikzpicture}
\end{center}

However, difficulties are encountered in the stereoselective synthesis involving the aminoacrylic derivatives \textbf{5.32} as high diastereoselectivities are often very difficult to achieve even in the presence of chiral protecting groups\textsuperscript{29} From our experiments with the dehydro compound of 1,3-dioxolan-4-one \textbf{4.16} (Chapter 4), it became apparent that the diastereoselectivity of reactions could be controlled much better if the cyclic form of the aminoacrylic ester was used. To date, only one synthesis of the dehydro compound of oxazolidinone \textbf{5.33} had been reported and this was done by Seebach via the bromide \textbf{5.5a}.\textsuperscript{10} However as discussed before, in our hands, the synthesis of the bromide \textbf{5.5a} could not be reproduced.

\textsuperscript{*} With methylallyltributyltin, the hydrogen abstracted was from the methyl group and not the allylic positions adjacent to Sn.
The dibromide 5.11 (see Scheme 5.8) was always formed in the reaction and attempts to prevent this (by changing the reaction conditions) failed. Fortunately, it was discovered that the dibromide 5.11 formed from the reaction of oxazolidinone 5.5 with two equivalents of NBS could be converted into the dehydro compound 5.33 by refluxing the dibromide with an excess of NaI in acetone. The isolated yield of the dehydro compound was 50-60% (from 2 steps). This method had been tested on the cis-(2S, 4S)-oxazolidinone 5.5 \( \alpha = -210 \) (CHCl₃, 23°C) and using the sequence described above, (2S)-oxazolidinone 5.33 \( \alpha = -186.3° \) (CHCl₃, 23°C) was synthesized with no loss of optical purity at the 2S-centre.

With this compound in hand, we endeavoured to proceed with some radical addition studies in the same manner as that with 1,3-dioxolanones.

A solution of the dehydro compound 5.33 and cyclohexylmercury chloride was stirred at room temperature in CH₂Cl₂ and to this was added slowly a solution of NaBH₄ in water. The reaction mixture was stirred for a further 1.5 hours after the addition was complete. Upon workup and chromatography, the addition product 5.34 was obtained in 33% yield. The poor recovery of the product was attributed to ring opening reactions by NaBH₄, but the reaction yields can be improved further to 68% by increasing the amounts of CH₂Cl₂ used in the reaction. The diastereoselectivity was determined to be 4:1 by ¹H nmr spectroscopy. When the reaction was carried out under conditions of infinite dilution where a solution of Bu₃SnH and AIBN was added slowly to a solution of two equivalents of alkene and one equivalent of cyclohexyl iodide (0.09M) while irradiating at room temperature, only one diastereomer could be observed from the ¹H nmr spectrum of the crude
reaction mixture. The compound, which corresponded to the major isomer isolated in the mercury reaction was isolated in 60-70\% yield. The synthesis was also repeated with the (2S)-dehydro compound 5.33 \([\alpha]_D = -186.3^\circ\) (CHCl\(_3\), 23\(^\circ\)C). When the mercury method was used, the optical rotation of the major diastereomer (2S, 4R) oxazolidinone 5.34 was found to be \([\alpha]_D = -94.9^\circ\) (CHCl\(_3\), 23\(^\circ\)C). When the reaction was repeated with the tin method, the value obtained was \([\alpha]_D = -94.5^\circ\) (CHCl\(_3\), 23\(^\circ\)C), both values agreeing within experimental error.

Various other alkyl iodides were treated under similar conditions; the results are summarised in Table 5.3. Wherever possible, the diastereoselectivity was determined by \(^1\)H nmr spectroscopy. Otherwise, the diastereoselectivity was estimated using \(^{13}\)C nmr spectroscopy.

**Scheme 5.17**

\[
\begin{align*}
\text{RI, Bu}_3\text{SnH} & \quad \text{RI, Bu}_3\text{SnH} \\
\text{(5.33)} & \quad \text{(5.34)-(5.37)}
\end{align*}
\]

**TABLE 5.3:** Diastereoselectivities of radical addition to oxazolidinone (5.33).

<table>
<thead>
<tr>
<th>RI</th>
<th>Products</th>
<th>ds</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)I</td>
<td>5.37</td>
<td>2.5:1(^2)</td>
<td>60%</td>
</tr>
<tr>
<td>PhCH(_2)I</td>
<td>5.35</td>
<td>2.7:1(^1)</td>
<td>71%</td>
</tr>
<tr>
<td>C(<em>6)H(</em>{11})I</td>
<td>5.34</td>
<td>7:1(^1)</td>
<td>70-85%</td>
</tr>
<tr>
<td>C(_4)H(_9)I</td>
<td>5.36</td>
<td>&gt;7:1(^2)</td>
<td>70%</td>
</tr>
</tbody>
</table>

\(^1\) Diastereoselectivity determined by \(^1\)H nmr spectroscopy.
\(^2\) Diastereoselectivity determined by \(^{13}\)C nmr spectroscopy.
The stereochemistry of the products 5.35 and 5.36 was checked by 2-D noesy experiments and was found to be trans. The result was surprising in two ways. First, this implies that the major product arose from the trapping of the radical by Bu3SnH from the same face as the bulky t-butyl group (contrary to the results observed in 1,3-dioxolanones). Secondly, our direct (see Scheme 5.11) and indirect reduction studies (see Section 5.1f) with the bromo- and sulphur-oxazolidinones suggested that no selectivity was observed with the oxazolidinones derived from glycine or alanine, whereas the results in Table 5.3 suggest that the diastereoselectivity improves with an increase in the bulk of the group at C-4.

The results can be best accounted for by assuming that the radical centre is planar and that the nitrogen is pyramidalised.25 The evidence from X-ray crystallography of oxazolidinone 5.13b showed that pyramidalisation of the nitrogen is observed (see Appendix B). The sum of the angles at the nitrogen was found to be 353.4° compared to an expected value for an sp² nitrogen of 360° and sp³ nitrogen of 327°.

\[ \text{(5.13b)} \]

Similar pyramidalisation for the nitrogen in oxazolidinone 5.38 has been observed previously.25a

\[ \text{(5.38)} \]
The oxazolidinone 5.13b also shows that the ring is in an envelope conformation,\textsuperscript{26} with the nitrogen out of plane by 10.9°. This envelope conformation may or may not be important in the radical. However the three substituents on the oxazolidinone ring will attempt to adopt a conformation where the three groups are as far away as possible from each other. Also, pyramidalisation of the nitrogen implies that the influence of the substituent on the nitrogen is greater. Our observations suggest that the direction of attack is controlled by the substituents on the nitrogen, leading to products resulting from the attack from the side \textit{cis} to the substituent at C-2. The results are also consistent with the observation that diastereoselectivities are increased when the size of the substituent on C-4 increases. As the bulk increases on C-4, then one would expect pyramidalisation to also increase, leading to greater steric interference at the side of the nitrogen protecting group.

A problem frequently encountered when Bu\textsubscript{3}SnH is used as the reducing agent is the difficulty in removing traces of tin compounds from the reaction mixture. Attempts were made to avoid this by irradiation of a solution of 2.5 equivalents of alkene, 1 equivalent of the N-hydroxypyridine-2-thione ester of cyclohexane carboxylic acid (5.39) in benzene with a sunlamp while a 0.09 M solution of t-butylthiol was added dropwise.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {O
\node at (0,0) {C-O-N};}
\node at (1.5,0) {S};
\end{tikzpicture}
\end{center}

(5.39)

An aliquot of the reaction mixture was removed, evaporated \textit{in vacuo} and checked by \textsuperscript{1}H nmr spectroscopy after 3 and 24 hours. No products resulting from the addition of cyclohexyl radicals to the pyridinethione 5.39 or the alkene 5.33 were observed by \textsuperscript{1}H nmr spectroscopy although tlc showed consumption of the Barton ester after 3 hours. The reason for the discrepancy between the two reducing agents (Bu\textsubscript{3}SnH and t-butylthiol) is presumably because the latter is a better hydrogen donor and reduces the Barton ester 5.39 to cyclohexane before addition to alkene or pyridinethione can
occur. The rate constants for the reduction of primary alkyl radicals using these two reagents support the reasoning above (with t-butylthiol, $k_H (50^\circ C, \text{THF}) = 1 \times 10^7 \text{M}^{-1} \text{s}^{-1}$, compared to $\text{Bu}_3\text{SnH} (50^\circ C, \text{THF}) = 4.9 \times 10^6 \text{M}^{-1} \text{s}^{-1}$) although this argument is not completely satisfactory as there is only a two-fold difference in the rate constants for reduction. No further attempts were made to improve this reaction.

It is worth noting at this stage that radical addition studies by Crich\textsuperscript{28} in the open chain dehydroalanine series \textbf{5.40} encountered difficulties in sustaining the radical chain (using the O-acyl thiohydroxamate method) as well as problems in hydrostannylation (when $\text{Bu}_3\text{SnH}$ method was used). With the successful application of alkyl mercury halides,\textsuperscript{29} di- and tri-peptides were synthesized but the diastereoselectivities reported were poor.

\[
\text{ZNH} \quad \text{NH} \quad \text{COOMe} \\
(5.40)
\]

\textbf{5.2 The chemistry of 1,3-imidazolidin-4-ones}

The imidazolidinones were synthesized according to the procedures developed by Seebach.\textsuperscript{3} This involved the cyclisation of the Schiff base to form the aminal \textbf{(5.41)}, which was then acylated to form the N-protected imidazolidinones.

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{CONHCH}_3 \\
\text{R} & \quad \text{N} \\
\text{R'} & \quad \text{R'} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]
5.2a The regio- and diastereo-selectivity of NBS reactions

Seebach and Zimmermann\textsuperscript{10} reported that the NBS bromination of 1-(benzoyl)-2-(t-butyl)-3-methyl-1,3-imidazolidin-4-one (5.43) occurred predominantly at the captodative position. However, the amount of bromination observed at the acetal centre was substantially increased by comparison with the bromination of 1,3-dioxolanones and 1,3-oxazolidinones. The stereochemistry of the 5-bromo imidazolidinone 5.43a was deduced indirectly by the authors\textsuperscript{10} by converting the bromo imidazolidinone to the more stable methoxy derivative 5.43c. The stereochemistry of the methoxy derivative 5.43c was found to be cis by difference saturation nOe method. If it is assumed that an $S_N2$ displacement of the bromo derivative occurs then it follows that the stereochemistry of the bromo derivative must be trans.

Scheme 5.19

For ease of handling and storage, we converted the bromo derivatives of the imidazolidinones to the sulphur derivatives (which in turn can be used as radical precursors) by displacement of the bromine with the thiolate ion generated from $p$-chlorothiophenol and DBU in a general procedure as that shown in Scheme 5.20.
When the reaction was worked up after 45 minutes, one isomer predominated in the reaction mixture (for example, the ratio of isomers of imidazolidinone 5.43b was 4:1). However, with prolonged reaction time, both isomers were formed in approximately equal amounts. This is presumably due to the initial formation of the kinetic product which then equilibrates (in the presence of base, either DBU or ArS⁻) to give a 1:1 mixture of isomers. This sort of equilibration was also observed in the absence of base (but presumably in the presence of traces of acid) for the methoxy derivative 5.43c. Thus in most cases, the reaction was worked up as soon as possible to ensure that the kinetic product predominated. The stereochemistry of the major diastereomer of the sulphur derivatives 5.43b and 5.44b was determined by 1-D difference saturation nOe and 2-D noesy experiments, and surprisingly it was found to be trans.* If one assumes that an SN₂ displacement of the thiolate ion had occurred, then this would imply that the stereochemistry of the bromo derivative was cis. This

* It should be noted that small long range couplings between H-2 and H-5 were observable only for the major diastereomer of imidazolidinones 5.43b and 5.44b, consistent with the literature observation that only a trans arrangement of H-2 and H-5 gives long range couplings.³⁰
is in conflict with the stereochemistry deduced by the previous authors. Both methods assume an $S_N2$ displacement of bromine but both lead to a different conclusion regarding the stereochemistry of the bromo imidazolidinones. Attempts to observe nOes for the bromo compounds were not successful. Small positive nOes ($< 2\%$ enhancements) were recorded for 5.43a and 5.44a but the percentage enhancement was too small to make any definite conclusions. No nOes were observed in the 2-D experiment.

All the evidence so far is indirect. However, we prefer to believe that the NBS bromination occurred to give the cis-bromo imidazolidinones based in part on the observation that radical reductions of these bromo- and sulphur-imidazolidinones (see later, Section 5.2b) occur such that the hydride or deuteride approaches preferentially from the same side as the substituent at C-2. Assuming that the same reaction course is taken for all radical reactions leads to the conclusion that the bromine from NBS bromination reactions must come from the same side as the deuteride, i.e. giving rise to the cis-bromo compound. To validify this assumption, then one must establish the radical nature of NBS reactions. To do this, the imidazolidinone 5.43 was treated with NBS under different conditions. The results are summarised in Scheme 5.21.

All the reactions shown in Scheme 5.21 were conducted in CD$_2$Cl$_2$ and monitored directly by $^1$H nmr spectroscopy. From the experiments, it was clear that NBS bromination of imidazolidinones occurs via a radical mechanism. In the absence of initiator (light and/or t-butylhyponitrite (TBHN)), the bromination did not occur. On addition of TBHN, the reaction went to completion in 10 minutes. The NBS reaction can also be initiated by a sunlamp. However, when the reaction was irradiated in the presence of a radical inhibitor (nitrosobenzene), the bromination did not proceed. It was also interesting to note that a sample which had not been degassed prior to initiation reacted after a short induction period.

* It is of course possible that the displacement of bromine by thiolate ions does not occur via an $S_N2$ mechanism (see Section 5.1b, for the argument with the oxazolidinones). However, we did not find any evidence for this in the syntheses of the sulphur imidazolidinones.
Attempts to brominate imidazolidinone 5.48 (used as a mixture of isomers) with 1.1 equivalents of NBS failed to give the desired bromo compound 5.48a and as in the case with 4-substituted oxazolidinones, the reaction only went to half completion. We suspect that a similar problem is encountered as in the case with
oxazolidinones, i.e. the dibromide is formed as a consequence of the participation of the lone pair on the nitrogen.

Scheme 5.22

\[ \begin{align*}
\text{N} & \quad \text{N} \\
\text{C} = & \quad \text{O} \\
\text{Ph} & \quad \text{Ph}
\end{align*} \]

\( \text{(5.48)} \)

\[ \begin{align*}
\text{N} & \quad \text{O} \\
\text{Br} & \quad \text{C} = \quad \text{O} \\
\text{Ph} & \quad \text{Ph}
\end{align*} \]

\( \text{(5.48a)} \)

5.2b Reduction with tributyltin hydride or deuteride

To study the reduction of the corresponding bromo or sulphur derivative with Bu\(_3\)SnD, the positions of H-\( \text{cis} \) and H-\( \text{trans} \) at C-5 in the reduced compound were checked by 1-D difference saturation nOe as well as 2-D noesy experiments. It was found that one could no longer generalise regarding a "trend" for the relation of chemical shifts to stereochemistry with different substituents at the nitrogen. In the previous cases with dioxolanones and oxazolidinones, it was found that when the hydrogen at C-5 is \( \text{cis} \) to the substituent at C-2, then the chemical shift is further downfield due to deshielding effects. However, when the correlation of chemical shifts with stereochemistry was determined for compounds 5.43, 5.44 and 5.45, the following results as shown in Table 5.4 were found (refer to Appendix C and D for the 2-D noesy spectra of imidazolidinones 5.43 and 5.45).

From Table 5.4, it can be seen that for the imidazolidinones, the chemical shift of the hydrogen at C-5 \( \text{cis} \) to the t-butyl substituent at C-2 is further downfield compared to the \( \text{trans} \) hydrogen only when \( R=\text{aromatic} \). Attempts were made to check this for the case when \( R=1\)-naphthyl and 2-naphthyl but no enhancement was observed in the 1-D or the 2-D nOe experiments. This could be due to the increase in the molecular weight of imidazolidinones bringing it within the regime where no nOe can be observed.\(^{32}\)
TABLE 5.4: Chemical shifts of some substituted imidazolidinones

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Chemical Shifts (δ ppm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H-5a</td>
<td>H-5b</td>
</tr>
<tr>
<td>5.43</td>
<td>Ph</td>
<td>4.15</td>
<td>3.85</td>
</tr>
<tr>
<td>5.44</td>
<td>t-butyl</td>
<td>4.08</td>
<td>4.25</td>
</tr>
<tr>
<td>5.45</td>
<td>CH₂Ph</td>
<td>3.85</td>
<td>4.10</td>
</tr>
</tbody>
</table>

The results of the reduction study with Bu₃SnD are shown in Table 5.5. The experiments were conducted under standard conditions (at 80°C in refluxing benzene or at 10°C by UV irradiation). The two hydrogens at C-5 have different chemical shifts as shown in Table 5.4. Thus, it is possible to determine the ratio of cis and trans deuteration by the integration of the absorptions attributed to H-5a and H-5b from the ¹H and/or ²H nmr spectroscopy.

From Table 5.5, it is clear that the stereochemistry of reduction depended on the bulk of the substituent at the nitrogen. Changing a benzoyl to the bulkier 1-naphthoyl changed the diastereoselectivity from 2.5:1.0 to 3.0:1.0 at 80°C. With the 2-naphthoyl substituent, the diastereoselectivity dropped to 1.7:1.0 at 80°C and on this basis alone, it appears that the 2-naphthoyl substituent is less bulky compared to the benzoyl. The reason for this is unclear.
Scheme 5.23

![Scheme 5.23](image)

### TABLE 5.5: Reduction of bromo- and sulphur-imidazolidinones with tributyltin deuteride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>X&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ratio of cis-D/trans-D&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.43a</td>
<td>Ph</td>
<td>Br</td>
<td>2.7:1.0</td>
</tr>
<tr>
<td>5.43b</td>
<td>Ph</td>
<td>SAr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.5:1.0 3.4:1.0</td>
</tr>
<tr>
<td>5.46b</td>
<td>1-naphthyl</td>
<td>SAr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.0:1.0 3.7:1.0</td>
</tr>
<tr>
<td>5.47b</td>
<td>2-naphthyl</td>
<td>SAr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.7:1.0 2.2:1.0</td>
</tr>
<tr>
<td>5.44a</td>
<td>t-butyl</td>
<td>Br</td>
<td>a</td>
</tr>
<tr>
<td>5.44b</td>
<td>t-butyl</td>
<td>SAr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.0:1.0 14.0:1.0</td>
</tr>
<tr>
<td>5.45b</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>SAr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4:1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Some reduction takes place at room temperature during the freeze-thaw cycle.

<sup>b</sup> The reduction of the sulphur compounds was clean whereas the reduction of the unpurified bromo compounds was not due to the presence of side products from the bromination reactions.

<sup>c</sup> Where Ar is p-chlorophenylthio.
With a phenylacetyl substituent, the diastereoselectivity is lowered further still (1.4:1.0) on account of the phenyl group being further away, and not able to exert much influence on the diastereoselectivity of radical reactions. Conversely, when a bulkier substituent like a pivaloyl group is used, then the diastereoselectivity increases to 7:1 at 80°C. An interesting point is that the favoured diastereomer is the one where the deuteride comes from the same side (cis) as the t-butyl substituent at C-2. This is in contrast to the reduction experiments of bromo dioxolanones where the favoured diastereomer is that where the deuteride comes from the opposite side (trans) to the substituent at C-2. These results support our stereochemical assignment of the bromo imidazolidinone 5.43a as cis (that is, if one assumes that the same stereochemical route is taken by radical reactions).

We also investigated the effect of changing the substituent at C-2 from t-butyl to i-propyl. The sulphur derivatives were used as radical precursors and were either synthesized indirectly from the bromo derivative by the reaction with thiolate ion (e.g. 5.49b), or directly using LDA and diphenyldisulfide as the electrophile (e.g. 5.50b). For 5-unsubstituted imidazolidinones, alkylation with LDA/diphenyldisulfide, gave a 1:1 mixture of diastereomers (this mixture was used for the reduction studies) whereas analogous alkylation with 5-substituted imidazolidinones gave only one diastereomer, presumably trans by analogy with alkylation studies by Seebach.3a,33

Although the chemical shifts of the H-cis and H-trans were not determined for the reduced compounds 5.49 and 5.50, it was assumed that the same relationship would hold for the same N-protecting group as that in imidazolidinones 5.43, 5.44 and 5.45 (e.g. the chemical shift of H-5 cis to a substituent at C-2 is further downfield compared to H-5 trans when R=aromatic). Reduction of 5.49b with Bu3SnD at 80°C gave a ratio of 1.7:1.0 in favour of the cis compound. When the N-protecting group was changed from a benzoyl to a pivaloyl as in the phenylthio imidazolidinone 5.50b, the ratio improved to 2.5:1.0. As before, the ratio of diastereomers was determined by either 1H or 2H nmr spectroscopy.
The phenylthio imidazolidinone 5.48b was synthesized by treatment of imidazolinone 5.48 with LDA followed by diphenyldisulphide (see Scheme 5.26). The diastereoselectivity observed by the reaction of imidazolidinone 5.48b with Bu₃SnH at 80°C gave a ratio of 2.5:1.0 in favour of the trans-compound. The chemical shifts of cis- and trans-compounds of 5.48 are reported in the literature.³ This ratio is similar to that obtained in the reduction of 5.43a. This is surprising, as in the 1,3-dioxolanones series, the selectivity improves with the presence of a substituent at C-5 due to the reactivity-selectivity principle. This is not observed here as it seems that the selectivity is dependent only on the N-protecting group as long as the substituent at C-2 remains the same. However, substituents at C-5 larger than a methyl group have not been tested.
The diastereoselectivities exhibited by reactions of the imidazolidinones can be rationalised on the same grounds as those for the oxazolidinones. The difference between the imidazolidinone series compared to the oxazolidinones is the diastereoselectivities are good even when the substituent at the radical centre (C-5) is not bulky (R=H, CH₃). This requires that the attack from the same side as the t-butyl group is favoured. This implies that the steric bulk at the N-acyl side is substantially greater compared to that for the oxazolidinones. We do not know the exact reason for this although one can speculate that this could be due to changes in the conformation which could have arisen from the C-N bond lengths, or the N-Me substituent at the 3-position. Our observations that diastereoselectivities can be lowered by increasing the bulk of the N-acyl substituent or be decreased by decreasing the bulk at the aminal centre (e.g. changing from a t-butyl group to an i-propyl group) are consistent with the above postulate.

A possible problem is that the diastereoselectivity observed is not a reflection of the kinetic ratio but results from the thermodynamic equilibration of products. Attempts to study this were carried out by monitoring the reduction of imidazolidinone **5.48b** which was irradiated with UV light in an nmr tube. It was observed that the

---

**Scheme 5.26**

[Scheme image]

---

The conformations of imidazolidinones have been determined by circular dichroism studies in which it is believed to have an envelope shape with the amide nitrogen out of the plane.³⁴
ratio of cis/trans diastereomers of the reduced product (5.48) remained constant throughout the experiment regardless of the extent of the reaction.

5.2c Intramolecular hydrogen abstraction studies

In our attempts to generate radicals from the imidazolidinones by intramolecular reactions, compound 5.51 (0.1 M) was treated with Bu$_3$SnD under infinite dilution conditions in refluxing benzene. The reaction mixture was analysed by $^2$H nmr spectroscopy and the following products were observed (Scheme 5.27).

Scheme 5.27

![Scheme 5.27](image)

Hydrogen abstraction occurred mainly at C-5 (the captodative centre) with the ratio of deuteration at C-5:C-2 of 14:1 (not statistically corrected). There was only a small amount of reduction on the aromatic ring. The ratio of cis-D/trans-D from these experiments was found to be 2.5:1, consistent with results obtained from the direct
reduction of the bromo- and sulphur-imidazolidinones 5.43a and 5.43b with Bu₃SnH at 80°C (see Table 5.5). When compound 5.55 was treated with Bu₃SnD under the same conditions, the following results were obtained (see Scheme 5.28).

Scheme 5.28

![Diagram showing the reaction of compound 5.55 with Bu₃SnD](image)

As before, deuteration occurred predominantly at C-5 (ratio C-5:C-2 = 12:1).

The amount of deuteration at the aromatic ring is increased slightly relative to the imidazolidinone 5.51. The ratio of isomers formed from the deuteration at C-5 was found to be 2.6:1.0 which was again consistent with the direct reduction studies of the sulphur imidazolidinone 5.48b (refer to Scheme 5.26).

In the same manner as the oxazolidinones, the corresponding iodo imidazolidinone 5.59 was treated with tributylallyltin in an nmr tube in d₆-benzene and irradiated. The reaction gave a complex reaction mixture which consisted of
possible addition products (not characterised) and some directly reduced compound, 5.43 as previously observed with the oxazolidinones.

5.43

The synthesis and utility of dehydro compound (5.60)

As in the case of the oxazolidinones, attempts were also made to make the dehydro compound 5.60. The method used for the synthesis of the dehydro compound oxazolidinone 5.33 was applicable to the synthesis of 5.60. The isolated yield (starting from a mixture of diastereomers of 5.48), after treatment with NBS and NaI in the usual manner, was 49%.

The possibility of synthesizing imidazolidinone 5.60 using other methods was also explored. The parent imidazolidinone 5.48 was treated with 1 equivalent of LDA followed by 1.5 equivalents of N-iodosuccinimide in a one pot procedure. It was hoped that in the absence of any halogen, the iodo compound formed would eliminate to the dehydro compound in situ and subsequently isolated. However, the $^1$H nmr
spectrum showed that after 24 hours at -20°C, there was still starting material present as well as some of the required dehydro compound in the ratio of 1:2.

The other alternative explored briefly was to convert the sulphur imidazolidinone 5.48b (formed from LDA reaction on 5.48) to the dehydro compound by oxidation of the sulphide to a sulphoxide, followed by elimination. Oxidation of the sulphide using sodium m-periodate in methanol did not go to completion. A better oxidising agent was m-chloroperbenzoic acid (MCPBA) which gave a mixture of the sulphoxide, the dehydro compound and some unreacted starting material. When the reaction mixture was then refluxed in toluene in the presence of some CaCO₃, the elimination occurred cleanly to give the dehydro compound. This method is viable for the synthesis of the dehydro compound 5.60 but is rather lengthy and involves several chromatographic separations. It would seem that the best (and easiest) method for the synthesis of 5.60 is still the NBS/NaI method.

Compound 5.60 was treated with cyclohexylmercury chloride in the presence of NaBH₄ in the manner described before. The ¹H nmr analysis of the mixture after 2 hours indicated that the reaction had not gone to completion (ratio of product to starting alkene 5.60 was 1:1), although all the cyclohexylmercury chloride had been consumed. The diastereoselectivity was 4:5:1 as determined from both ¹H and ¹³C nmr spectroscopy and the isolated yield for the addition product was only 25%. The analogous reaction with Bu₃SnH was carried out in the usual manner and this time, only 1 diastereomer could be observed from both the ¹H and ¹³C nmr spectra. The addition product 5.61 was isolated in a better yield (44% relative to the alkyl halide). Attempts were made to determine the stereochemistry of the major compound but severe overlap of signals in the ¹H nmr spectrum make the assignment ambiguous. This has been tentatively assigned as trans through comparison of the chemical shifts of the two diastereomers formed, and from the 2-D noesy experiment.
5.3 Conclusion

The experiments with oxazolidinones and imidazolidinones demonstrate the viability of using radical reactions in these systems. The NBS brominations of oxazolidinones and imidazolidinones occur with high diastereoselectivities, though the stereochemistry of the bromo derivatives has not yet been proven unambiguously. These bromo-oxazolidinones and imidazolidinones are good radical precursors but they cannot be handled or stored easily. Consequently, they are routinely converted to the thioethers (which are also radical precursors) by displacement with thiolate ions. Alternatively, the sulphur imidazolidinones can also be synthesized directly by alkylation of the parent imidazolidinone with LDA/diphenyldisulphide.

The effect of substituents on the diastereoselectivities of radical reactions of bromo- and sulphur-oxazolidinones as well as imidazolidinones has not been thoroughly explored. However, our preliminary study indicates that the diastereoselectivities of radical reactions can be affected by changing the steric bulk at the acetal centre and the nitrogen protecting group. This is especially true with the imidazolidinones. With the oxazolidinones, the diastereoselectivities improve with increasing steric bulk at C-4 when the substituents at positions 2 and 3 are constant. These results are encouraging as these imply that the diastereoselectivities of radical reactions of oxazolidinones and imidazolidinones can be controlled by appropriate choice of substituents. More work is required to understand fully the interplay of steric and conformational effects on the diastereoselectivities of these reactions.

The addition of radicals to the dehydro derivatives of oxazolidinone and imidazolidinone occurs with high diastereoselectivities. This is potentially useful as a...
method to synthesize new carbon-carbon bonds and thus various amino acids, as these oxazolidinones and imidazolidinones can be subsequently hydrolysed to the corresponding amino acids. It is clear that radical reactions of these kind provide an attractive alternative for the synthesis of enantiomerically pure amino acids.
References: Chapter 5


20. P.J. Duggan, unpublished observations.


CONCLUSION

These studies began with the question of whether capto-substrate stabilization affects the hydride of radical reactions, i.e. is capto-substrate stabilization manifested kinetically. To answer this, a variety of reactions involving capto-substituted substrates were studied. They included reduction reactions with Bu$_3$SnH, additions to capto-substituted olefins, NBS bromination reactions as well as hydrogen abstraction reactions with allyl radicals.

Studies of reaction rates, both relative and absolute, and regioselectivity led to the conclusion that the kinetic consequence of the capto-substitution effect are rather small (in the case of reduction with Bu$_3$SnH) or negligible (as in addition to olefins) for reactions with early transition states. This is probably because such reactions have transition structures which, although they possess some stability, do not significantly affect the stability of the product radical to only a small extent. On the other hand, polar effects were found to be important in many of these reactions (reductive addition and, to a certain extent, hydrogen abstraction by allyl radicals). Thus, addition of alkyl radicals to alkenes bearing both a donor substituent and a capto-substituent (capto- and steric) occurs more slowly than the analogous reaction with alkenes bearing the donor group only i.e. there appears to be an anti-capto-stabilizing kinetic effect. This is probably a result of the polar effect of the donor substituent on attack by alkyl radicals which are known to be nucleophilic.

Product analysis and sm studies showed that 1,3-dihalo-1-butenes undergo hydrogen atom abstraction by allyl radicals more readily at the capto-substituted centre than at the normal centre. However, the measurement of kinetic isotope effects for equivalent hydrogen atoms (D) showed that the preference for reaction at the capto-substituted centre may not reflect radical stability. Indeed, it appears that the formation of the capto-substituted radical probably arises from the decrease in the reactivity of the hydrogen atom (D) by the capto-substituent (capto-stabilizing and steric), with the decrease at the normal centre being greater.

The importance of capto-substrate stabilization in reactions with late transition
Conclusion

These studies began with the question of whether captodative stabilisation affects the outcome of radical reactions, i.e. is captodative stabilisation manifested kinetically. To answer this, a variety of reactions involving captodatively substituted compounds were studied. They included reduction reactions with Bu₃SnH, additions to captodative olefins, NBS bromination reactions as well as hydrogen abstraction reactions with t-butoxy radicals.

Studies of reaction rates, both relative and absolute, and regioselectivities led to the conclusion that the kinetic consequence of the captodative effect are either small (in the case of reduction with Bu₃SnH) or negligible (as in addition to olefins) for reactions with early transition states. This is probably because such reactions have transition structures which are reactant-like and thus reflect the stability of the product radical to only a small extent. On the other hand, polar effects were found to be important in many of these reactions (reduction, addition and, to a certain extent, hydrogen abstraction by t-butoxy radicals). Thus, addition of alkyl radicals to alkenes bearing both a donor substituent and carbomethoxy substituent, (captodative olefins) occurs more slowly than the analogous reaction with olefins lacking the donor group; i.e. there appears to be an anti-captodative kinetic effect. This is probably a manifestation of the polar effect of the donor substituent on attack by alkyl radicals which are known to be nucleophilic.

Product analysis and esr studies showed that 1,3-dioxolan-4-ones undergo hydrogen atom abstraction by t-butoxy radicals more rapidly at the captodative centre than at the acetal centre. However, the measurement of relative reactivity per equivalent hydrogen atom (ρ) revealed that the preference for reaction at the captodative centre may not reflect radical stability. Indeed, it appears that the formation of the captodative radical probably arises from the decrease in the reactivity of the hydrogens at both positions (captodative and acetal), with the decrease at the acetal centre being greater.

The importance of captodative stabilisation in reactions with late transition
states is less clear cut. It is generally true that NBS brominations of 1,3-dioxolanones, oxazolidinones and imidazolidinones occur regioselectively at the captodative position. However, it is not clear at present if this is a genuine reflection of the captodative effect or, alternatively, a result of some other effect e.g. complex formation of bromine atoms with certain functional groups.

The work described in Chapters 4 and 5, showed that slow reactions (e.g. reactions of captodative radicals with tributylallyltin) involving captodatively stabilised radicals are inefficient due to the reluctance of captodative radicals to propagate chain reactions. However, it also revealed that good to high diastereoselectivities can be achieved with radical reactions of dioxolanones, oxazolidinones and imidazolidinones, depending on the type of reaction (e.g. reduction or addition reactions) and on the steric bulk of the substituents. All the results suggest that such reactions are of considerable potential utility for the syntheses of enantiomerically pure α-hydroxy acids and α-amino acids.
EXPERIMENTAL
General notes:

1. Melting points were determined on a Reichert hot-stage microscope and were uncorrected. Distillations were carried out with a Kugelrohr apparatus and the boiling points were uncorrected.

2. Elemental analyses were carried out by the ANU Analytical Service Unit.

3. Electron Impact (EI) Mass Spectra were measured on a VG Micromass 7070 F Mass Spectrometer operating at 70 eV. The molecular ion (M⁺) (where appropriate) and selected fragment ions are reported as their mass/charge ratios (m/z) followed by their relative intensities as compared with the base (100%) fragment. All Mass spectra recorded are EI unless otherwise stated. High resolution Mass spectra (Exact Mass) were determined on an AEI MS 902 High Resolution Mass Spectrometer.

4. Infrared spectra were measured on a Perkin and Elmer 683 Infrared Spectrophotometer. Samples were run as liquid films (neat) or as a solution in CCl₄ or CHCl₃ in 0.5 mm NaCl cells. Significant peaks were reported (cm⁻¹).

5. Ultraviolet spectra were measured on a Varian DBS-90 UV-Visible spectrophotometer.

6. Optical rotations were recorded on a Perkin and Elmer 241 polarimeter (Na lamp at 589 nm) in CHCl₃ at 23°C. The c value refers to concentration of sample in g/100 ml.

7. Gas liquid chromatography (gc) was carried out with the following columns with helium as the carrier gas:
   a. 2m x 1.5mm, 2% OV-17 on Gaschrom Q (60-80 mesh).
   b. 25m x 0.2mm, Vitreous Silica Capillary Column (SGE25QC2/BP1-1.0).
   c. 25m x 0.2mm, Vitreous Silica Capillary Column (SGE25QC2/BP5-1.0).

   GC analyses were performed on a Varian 3400 and 6000 gas chromatograph equipped with a Flame Ionisation Detector.

9. Thin layer chromatography was conducted on Whatman silica precoated microscopic slides (75 x 25mm). Preparative Thin Layer Chromatography was performed on Merck precoated glass plates. Chromatograms were visualised under UV light, or upon exposure to iodine vapour, or by spraying with a colour reagent
(5% vanillin in sulphuric acid) followed by heating at 200°C.

10. Column chromatography was carried out by one of the following:
   (a) flash chromatography on silica (Merck mesh 0.004-0.063 mm) as described by Still et al.\textsuperscript{1}
   (b) Chromatotron (model 7924T) with 1 and 2 mm rotors coated with Merck silica gel 60PF\textsubscript{254}.
   (c) Normal phase high pressure liquid chromatography with Waters 510 High Pressure Liquid Chromatography. Compounds were detected with Waters differential refractometer R401. A Waters Radial-PAK cartridge 5\mu column was used.
   (d) Reversed-phased high pressure liquid chromatography was performed with a Spectra Physics SP-8000B ternary proportionating pump, digital integrator and UV-VIS (analytical cell). The column used was Alltech ODS (5\mu) 4.6 x 250 mm.

11. Routine \textsuperscript{1}H and \textsuperscript{13}C nmr spectra were recorded on the following instruments: Jeol FX-200 (\textsuperscript{13}Cnmr at 50.1MHz), Varian XL-200 (\textsuperscript{13}Cnmr at 50.3MHz), Gemini-300 (\textsuperscript{13}Cnmr at 75MHz), Varian VXR-300 (\textsuperscript{13}C nmr at 75MHz).
   Spectra were usually recorded in deuterochloroform (CDCl\textsubscript{3}, 99.8\% deuterium incorporation) unless otherwise stated. For \textsuperscript{1}Hnmr spectra, chemical shifts (\delta) are reported in parts per million (ppm) downfield from the internal standard tetramethylsilane (TMS, \delta 0.00 ppm), followed by their intensities (number of protons) and coupling constants. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), etc. For \textsuperscript{13}Cnmr spectra recorded in CDCl\textsubscript{3}, the centre line of the triplet due to CDCl\textsubscript{3} was referenced to 77.0 ppm.

12. Deuterium nmr spectra were recorded on a Varian VXR-300 spectrometer (\textsuperscript{2}Hnmr at 42.4MHz). Spectra were recorded in benzene or CHCl\textsubscript{3} and were referenced with a trace of deuterated solvent.

13. Nuclear Overhauser enhancement (nOe) experiments (1D and 2D) were conducted on a Varian VXR-500. One dimensional nOe data were obtained in the interleave mode by taking difference spectra with data sets using an on resonance and an off resonance selective pre-irradiation pulse. Two dimensional noesy spectra were
acquired in the pure absorption mode with 2048 data points in the $t_2$ dimension stored in alternate blocks and 128 FID's in the $t_1$ dimension. FID's were apodized by either a 45° sine bell or a 45° squared sine bell in the first dimension and by gaussian multiplication in the second dimension. Samples were made up in CDCl$_3$ (99.6% deuterium incorporation) in special Wilmad Taperlok Nmr tubes and were degassed by freeze-thaw methods.

14. Electron spin resonance spectra were recorded on a Bruker 200D-SRC EPR spectrometer with a Bruker ER 4111 variable temperature unit and an irradiation unit which used a Hanovia L5173 Hg(Xe) lamp. The method used for numerical analyses in the determination of the relative concentrations of the radicals had been previously described by Beckwith and Brumby.  

15. The crystallographic data were collected with a Phillips PW-1100/20 diffractometer equipped with MoKα radiation.

16. Solvents and reagents were purified according to published procedures and solvents were dried over sodium wire or molecular sieves 3Å or 4Å. Organic extracts were dried using anhydrous sodium sulphate or magnesium sulphate and the bulk of the solvent removed under reduced pressure using a Büchi Rotavapor.

17. All reactions were conducted under a positive pressure of nitrogen. All radical reactions were degassed (by either freeze-thaw methods or by bubbling Ar into the solution).

References:


Experimental: Chapter 2

Compounds 2.9, 2.10 and 2.16 are commercially available from Aldrich. Compounds 2.1, 2.13, 2.15, 2.28, 4, 2.29, 2.27, and 2.31 were synthesized according to literature procedures. Chlorobutyric acid was purchased from Fluka Chemie and converted to the methyl ester (2.2) by standard procedures.

Methyl 2-bromo-2-methoxyacetate

The title compound was synthesized by adding methyl methoxyacetate (2g, 19 mmol) and dibenzoyl peroxide (50mg) to a suspension of N-bromosuccinimide (NBS) (3.7g, 21 mmol) in 100 ml of dry carbon tetrachloride. The reaction mixture was refluxed under nitrogen for 1 hour, cooled and the succinimide formed filtered. The filtrate was evaporated under reduced pressure to give a yellowish liquid which was distilled at 40 mm Hg/90-100°C. The resulting liquid was clear and was stored under nitrogen in reactivi-vials (yield was ca 80-85%). 

\[ \text{Hnmr (CDCl}_3, 200MHz) \delta 3.60 (s, 3H), 3.89 (s, 3H), 6.05 (s, 1H); \text{Cnmr (CDCl}_3, 200MHz) \delta 53.17, 58.57, 83.07, 165.70; \text{v}_{\text{max}} (\text{neat}) 2958, 1750, 1440, 1212, 1111 \text{ cm}^{-1}; \text{Anal. Calculated for C}_4\text{H}_7\text{BrO}_3: C 26.25, H 3.86. Found C 26.0, H 3.71. \]

Methyl 2-phenylthio-2-methoxyacetate (2.3)

This was prepared in two ways:

1. To a solution of thiophenol in dry benzene, under nitrogen, was added 1 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The solution became warm and after 10 minutes, a solution of methyl 2-bromo-2-methoxyacetate (1 equivalent, as prepared above) in benzene was added. A precipitate was formed immediately and the reaction mixture stirred for an additional hour. The reaction mixture was then filtered, the filtrate washed with dilute HCl, dried and evaporated to give a yellow oil which was purified by Chromatotron in 75% yield.

2. Addition of silver perchlorate (0.11g, 0.49 mmol) to a solution of methyl 2-chloro-2-phenylthioacetate (2.7) (0.106g, 0.49 mmol) in 11 ml of dry methanol
resulted in the formation of a precipitate. Stirring was continued until no starting material could be detected by tlc. The precipitate was filtered and the filtrate was extracted with ether, dried and evaporated to give the crude product (in 70-80% yield) which was purified by Chromatotron. \(^{1}H\)nmr (CDCl\(_3\), 200MHz) \(\delta\) 3.55 (s, 3H), 3.65 (s, 3H), 5.10 (s, 1H), 7.47-7.30 (m, 5H); \(^{13}C\)nmr (CDCl\(_3\), 200MHz) \(\delta\) 52.43, 56.01, 86.53, 128.79, 128.99, 130.92, 134.29, 167.77; \(\nu_{\text{max}}\) (neat) 2950, 1750, 1440, 1195, 1100, 750, 690 cm\(^{-1}\); Anal. Calculated for C\(_{10}\)H\(_{12}\)O\(_3\)S: C 56.58, H 5.70, S 15.10. Found C 56.88, H 5.82, S 14.85.

**Methyl 2-phenylthioacetate (2.4)**

To a stirred solution of DBU (1.52g, 10 mmol) and thiophenol (1.10g, 10 mmol) in 30 ml of dry benzene was added methyl 2-chloroacetate (1.09g, 10 mmol). On addition, the reaction mixture became warm and a precipitate was formed. After stirring for 2 hours, the precipitate (DBU.HCl salt) was filtered and the filtrate washed with dilute HCl, water and dried over magnesium sulphate and evaporated to give methyl 2-phenylthioacetate (2.4) which was purified by Chromatotron (1.68g, 90%). This is a commercially available product. \(^{1}H\)nmr (CDCl\(_3\), 200MHz) \(\delta\) 3.64 (s, 2H), 3.69 (s, 3H), 7.2-7.4 (m, 5H).

**Methyl 2-phenylthiobutyrate (2.5)**

To a stirred solution of DBU (1.72g, 11 mmol) and thiophenol (1.24g, 11 mmol) in 50 ml benzene was added methyl 2-bromobutyrate (2.05g, 11 mmol). The solution became warm and a precipitate was formed. After stirring for 4 hours at room temperature, the precipitate was filtered, the filtrate washed with water, dried and evaporated to give methyl 2-phenylthiobutyrate (2.5) (2.17g, 94%) which was purified by flash chromatography (ether/hexane=1:9) in 85-90% isolated yield. \(^{1}H\)nmr (CDCl\(_3\), 200MHz) \(\delta\) 1.00 (t, 3H, J=8 Hz), 1.80 (m, 2H), 3.60 (t, 1H, J=8 Hz), 3.65 (s, 3H), 7.29-7.45 (m, 5H); \(^{13}C\)nmr (CDCl\(_3\), 200MHz) \(\delta\) 11.77, 25.11, 52.01, 52.44, 127.78, 128.86, 132.71, 133.53, 172.57; \(\nu_{\text{max}}\) (neat) 2970, 1740,

**Methyl bis-phenylthioacetate (2.6)\(^9,10\)**

To a stirred solution of DBU (1.52 g, 10 mmol) and thiophenol (1.10 g, 10 mmol) in 30 ml of dry benzene under nitrogen was added methyl dichloroacetate (1.43 g, 10 mmol). The reaction mixture was stirred for 16 hours following which the reaction was isolated in the usual manner i.e. filtration of the precipitate, followed by washing of the organic layer with dilute HCl, water, drying and evaporation. From the \(^1\)H nmr spectrum of the crude reaction mixture, it was ascertained that the reaction gave a 1:1 mixture of the required compound and unchanged starting material, methyl dichloroacetate. The required compound 2.6 was separated by Chromatotron.

\(^1\)Hnmr \((CDCl_3, 200MHz) \delta 3.71 \text{ (s, 3H)}, 4.86 \text{ (s, 1H)}, 7.47-7.35 \text{ (m, 5H)}; \ ^{13}\text{Cnmr (CDCl}_3, 200MHz) \delta 52.99, 58.33, 128.77, 129.13, 132.60, 133.45; \nu_{\text{max}} \text{ (neat) 2950, 1640, 1440, 1285, 1145, 740, 690 cm}^{-1}; \text{Anal. Calculated for C}_{15}\text{H}_{14}\text{O}_2\text{S}_2: C 62.04, H 4.86, S 22.08. Found C 62.15, H 5.14, S 21.77.

**Methyl 2-chloro-2-phenylthioacetate (2.7)\(^11\)**

The title compound was synthesized by adding dry grounded \(N\)-chlorosuccinimide (2.27 g, 17 mmol) to a solution of methyl 2-phenylthioacetate (2.4) (1.55 g, 8.5 mmol) in 70 ml of dry carbon tetrachloride. The reaction mixture was stirred at room temperature under nitrogen and on completion of the reaction (as monitored by tlc), the succinimide was filtered and the filtrate evaporated to give methyl 2-chloro-2-phenylthioacetate (2.7) (1.5 g, 81%) which was purified by Chromatotron in good yields. \(^1\)Hnmr \((CDCl_3, 200MHz) \delta 3.75 \text{ (s, 3H)}, 5.56 \text{ (s, 1H)}, 7.3-7.6 \text{ (m, 5H)}; \ ^{13}\text{Cnmr (CDCl}_3, 200MHz) \delta 53.23, 64.47, 129.06, 129.41, 130.11, 133.85, 166.02; \nu_{\text{max}} \text{ (neat) 2960, 1750, 1440, 1270, 1155, 1000, 740, 690 cm}^{-1}; \text{Anal. Calculated for C}_{9}\text{H}_{9}\text{ClO}_2\text{S: C} 49.89, \text{H} 4.19, \text{Cl} 16.36. \text{Found C} 50.02, \text{H} 4.10, \text{Cl} 16.23.
Phenylethyl 2-chloroacetate (2.8)

A solution of 2-phenylethanol (2.44g, 20 mmol) in 40 ml dry ether was cooled to 0°C and chloroacetyl chloride (2.26g, 20 mmol) was added. The reaction mixture was stirred until no starting material could be detected on tlc. The reaction mixture was then neutralised by the slow addition of saturated sodium bicarbonate solution. This was extracted with ether and the ethereal solution washed with sodium bicarbonate solution, dried and evaporated to give phenylethyl 2-chloroacetate (2.8) (2.54g, 63%), which was purified by Chromatotron. 

\[
\text{\textsuperscript{1}Hnmr (CDCl}_{3}, 200MHz) \delta 2.98 (t, 2H, J=8 Hz), 4.06 (s, 2H), 4.41 (t, 2H, J=8 Hz), 7.25-7.29 (m, 5H);
\]

\[
\text{\textsuperscript{13}Cnmr (CDCl}_{3}, 200MHz) \delta 34.86, 40.83, 66.54, 126.73, 128.56, 128.87, 137.13, 167.00; v_{\text{max}} \text{ (neat) 3105, 2920, 1750, 1500, 1455, 1315, 1290, 1175, 1000, 750, 700 cm}^{-1} ;
\]

Anal. Calculated for C\textsubscript{10}H\textsubscript{11}ClO\textsubscript{2}: C 60.46, H 5.58, Cl 17.85. Found C 60.74, H 5.50, Cl 17.70.

Octan-2-mesylate \textsuperscript{12}

A stirred solution of octan-2-ol (2.60g, 17.7 mmol) in 50 ml of dry pyridine was cooled to 0°C and to this was added methanesulphonyl chloride (2.75g, 24 mmol). A colour change was observed and the reaction was stirred for 16 hours at 0°C, following which the solution was poured into ice-cold water and extracted with ether. The ethereal layer was then washed with cold HCl, cold water, dried and evaporated to give the corresponding mesylate (3.3g, 89%) which was used without further purification in the synthesis of 2.12. 

\[
\text{\textsuperscript{1}Hnmr (CDCl}_{3}, 200MHz) \delta 0.80-1.80 (m, 16H), 3.00 (s, 3H), 4.80 (m, 1H);
\]

\[
\text{\textsuperscript{13}Cnmr (CDCl}_{3}, 200MHz) \delta 13.96, 21.11, 22.46, 25.05, 28.85, 31.57, 36.62, 38.76, 80.39.
\]

Potassium thiophenate

To a stirred solution of potassium hydroxide (2.8g, 50 mmol) in 40 ml of absolute ethanol was added thiophenol (5.51g, 50 mmol). The solution immediately became warm and after stirring for 16 hours, the solution was evaporated and a yellowish solid (7g, 94%) was obtained.
2-Phenylthiooctane (2.12)

The title compound was prepared by adding octan-2-mesylate (0.5g, 2.4 mmol) to a solution of potassium thiophenate (0.5g, 3.4 mmol) in 10 ml of dimethylformamide (DMF). The reaction mixture was stirred for 2 hours after which dichloromethane was added and the reaction mixture was washed several times with water. The separated organic layer was then dried and evaporated to give 60-70% of 2-phenylthiooctane which was then purified by flash chromatography (ethyl acetate/hexane=1:9). \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.8-1.7 (m, 16H), 3.18 (m, 1H), 7.1-7.45 (m, 5H); \(^{13}\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 14.05, 21.14, 22.60, 27.00, 28.65, 29.11, 31.74, 36.78, 126.52, 128.71, 131.89, 134.47; \(\nu_{\text{max}}\) (neat) 2960, 2930, 2860, 690 cm\(^{-1}\); Anal. Calculated for C\(_{14}\)H\(_{22}\)S: C 75.61, H 9.97. Found C 75.35, H 9.80.

1-Phenylthio-1-methoxyethane (2.14)

To a mixture of acetaldehyde dimethal acetal (16.4g, 182 mmol) and thiophenol (2g, 18 mmol) was added Amberlyst-15 (1.5g). This was stirred for 16 hours at room temperature, after which the Amberlyst-15 was filtered and the filtrate stirred over 2 pellets of potassium hydroxide for 10 minutes. This was decanted to remove the pellets of potassium hydroxide and the solution was evaporated to yield 3g of 1-phenylthio-1-methoxyethane (2.14) (85% pure by gc) which was distilled by Kugelrohr at 0.2 mm Hg/30°C. \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 1.49 (d, 3H, J=6 Hz)), 3.45 (s, 3H), 4.85 (q, 1H), 7.2-7.6 (m, 5H); \(^{13}\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 22.25, 55.22, 86.17, 127.51, 128.68, 130.03, 133.70; \(\nu_{\text{max}}\) (neat) 2930, 1440, 1200, 1082, 855, 745, 691 cm\(^{-1}\); M.S. (%) 168.0 (3.4), 137.0 (2.3), 110.0 (7.0), 91.0 (0.9), 59.2 (100.0); Exact mass calculated for C\(_9\)H\(_{12}\)OS (M\(^+\)) is 168.0609. Found 168.0609.
Typical competitive experiments: reduction with tributyltin hydride/deuteride

For competition experiments analysed by gas chromatography, a pyrex ampoule was charged with approximately equimolar amounts of the two substrates (0.1 mmol each), a few crystals of AIBN (ca 2mg) and an internal standard (t-butyl benzene) in 300 µl of solvent. Tributyltin hydride (0.1 mmol) was introduced and the ampoule was then degassed by repeated freeze-thaw cycles, sealed and left overnight in an oil bath at 80°C. The contents were analysed by gc to measure the amounts of products and starting materials present.

For competition experiments analysed by $^2$H nmr spectroscopy, tributyltin deuteride replaced tributylstannane. The purity of tributyltin deuteride was checked by IR [Sn-D 1305 cm$^{-1}$, Sn-H 1810 cm$^{-1}$]. Accurate integration of the two deuterated products was obtained and this enabled relative rate constant calculations.

The synthesis of substrates (2.17)-(2.19) and (2.21) used in the competitive bromination reactions are described in the experimental for Chapters 4 and 5.

2-(t-Propyl)-1,3-dioxolan-4-one (2.22)

This was synthesized from glycollic acid and isobutyaldehyde and distilled at 100°C/100 mm Hg. $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.95 (d, 6H, J=15 Hz), 1.95 (m, 1H), 4.15 (d, 1H, J=16 Hz), 4.30 (d, 1H, J=16 Hz), 5.32 (d, 1H, J=16 Hz); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 15.54, 32.21, 64.04, 109.89, 171.46; $\nu_{\text{max}}$ (neat) 2970, 1810, 1220, 1090, 950 cm$^{-1}$; Anal. Calculated for C$_6$H$_{10}$O$_3$: C 55.37, H 7.74. Found C 55.68, H 8.01.

3-Benzoyl-1,3-oxazolidin-5-one (2.20)$^{13}$

Hippuric acid (4.48g, 25 mmol) was refluxed with paraformaldehyde (1.72g) and p-toluenesulphonic acid (0.25g) in benzene with azeotropic distillation of water. After 16 hours, the reaction mixture was cooled and the solution washed with 5% sodium bicarbonate, dried and evaporated. The required compound was recrystallised from chloroform/ether to give colourless needles. (mp=150-151°C); $^1$Hnmr (CDCl$_3$,
Typical competitive experiments: NBS bromination

In these experiments, quantities of the 2 substrates (~ 0.3 mmol each) were accurately weighed and a solution was made up to 5 ml with CD$_2$Cl$_2$ in a volumetric flask. To this was added NBS (0.3 mmol) (the whole procedure was carried out in the dark) and a portion of the reaction mixture placed in an nmr tube and degassed by either freeze-thaw methods or by bubbling argon through the reaction mixture. The $^1$H nmr spectrum of the reaction mixture at time $t=0$ was recorded. Then the reaction mixture was irradiated with a sunlamp for 10-30 minutes. The reaction can be monitored directly in the nmr tube and it was found that the reaction was usually completed within 10 minutes. Integration of peaks corresponding to the starting materials and products (wherever possible) were obtained and the relative rate constants were calculated.

Variation of this method has also been used: In some cases, the competitive reactions had been conducted by refluxing the 2 substrates, NBS and AIBN in carbon tetrachloride. After 30 minutes, the reaction mixture was filtered and the filtrate evaporated and the $^1$H nmr spectrum recorded. The relative rate constants obtained in this way were the same as that obtained when the reaction was conducted and monitored directly in CD$_2$Cl$_2$.

Radical Trapping experiments

Bis(3-(allyloxy)propanoyl) peroxide$^5$ (2.29) and bis(6-heptenoyl) peroxide$^6$ (2.27) were prepared by literature methods.

Stock solutions of nitroxide (1,1,3,3-tetramethylisoindoline-2-oxyl)$^4$ (2.28) at different concentrations were made in cyclohexane (concentrations were 1.055,
1.516, 2.111, 2.638 and 3.165 mM). A solution of diacyl peroxide (0.0610 M) in cyclohexane was also made up. In a typical experiment, a 5 fold excess of the nitroxide relative to the diacyl peroxide was present. The alkene concentration was kept constant at 0.288 M for methyl acrylate and 0.301 M for the dehydro compound 2.31.

Accurately determined mixtures of the nitroxide, the radical precursor and alkene in cyclohexane were degassed by 4 freeze-thaw cycles and sealed in vacuo. These were immersed in a constant temperature bath at 84°C and left for 18 hours. Then the reaction mixture was evaporated and diluted with methanol. The product mixture was analysed by reversed-phase high performance liquid chromatography with isocratic elution (methanol/water). The retention times of R-T and C-T were checked with that of authentic samples. As the trap contained an aromatic chromophore isolated from the coupling site, UV detection at 270 nm was uniformly sensitive to the trap and R-T and C-T.

References:


Experimental: Chapter 4

The 1,3-dioxolan-4-ones were synthesized in the manner described by Seebach et al. Dioxolanones 4.4, 4.5, 4.8, 4.9, 4.10, 4.11, 4.9a, 4.12, 4.16, 4.19 and 4.9c are literature compounds.

2-Methyl-1,3-dioxolan-4-one (4.6)

This was synthesized from glycollic acid and acetaldehyde and was distilled at 60°C/200 mm Hg (Kugelrohr) in 50-60% yield. 

\[ \text{IHNmr (CDCl}_3, 200MHz) \delta 1.57 (d, 3H, J=5 Hz), 4.22 (d, 1H, J=15 Hz), 4.36 (d, 1H, J=15 Hz), 5.73 (q, 1H); \]

\[ \text{ICNmr (CDCl}_3, 200MHz) \delta 20.29, 69.14, 104.08, 171.47; \]

\[ \text{Vmax (neat) 1800, 1410, 1225, 1200, 1115, 1080, 920, 820 cm}^{-1}; \]

\[ \text{Anal. Calculated for C}_4\text{H}_6\text{O}_3: C 47.06, H 5.92. \text{Found C 49.96, H 5.85.} \]

2-(t-Butyl)-1,3-dioxolan-4-one (4.7)

This was synthesized from glycollic acid and trimethylacetaldehyde and was distilled at 50-60°C/200 mm Hg in good yields (80-85%).

\[ \text{IHNmr (CDCl}_3, 200MHz) \delta 0.96 (s, 9H), 4.24 (d, 1H, J=15 Hz), 4.34 (d, 1H, J=15 Hz), 5.26 (s, 1H); \]

\[ \text{ICNmr (CDCl}_3, 200MHz) \delta 23.26, 35.01, 64.44, 111.82, 171.62; \]

\[ \text{Vmax (neat) 2980, 1810, 1488, 1409, 1215, 1100, 960 cm}^{-1}; \]

\[ \text{Anal. Calculated for C}_7\text{H}_{12}\text{O}_3: C 58.32, H 8.39. \text{Found C 58.25, H 8.27.} \]

2-(t-Butyl)-5-carboxy-1,3-dioxolan-4-one (4.19)

This was synthesized from tartronic acid and trimethylacetaldehyde with dichloromethane as solvent in poor yields (10-20%). When the reaction was conducted in benzene and refluxed for several days, the reaction yields were slightly higher. The poor yield is probably due to the low solubility of tartronic acid in benzene and dichloromethane. The product can be recrystallised from dichloromethane/hexane. The data given below are for the mixture of diastereomers and assignments have not been made for each diastereomer.

\[ \text{IHNmr (CDCl}_3, \]
200MHz) δ 1.01 (s, 9H), 1.04 (s, 9H), 4.96 (s, 2H), 5.34 (s, 1H), 5.56 (s, 1H); 
$^{13}$Cnmr (CDCl$_3$, 200MHz) δ 23.09, 23.17, 34.81, 35.82, 73.57, 73.75, 111.03, 112.39, 166.37, 166.47, 168.66, 169.58; $v_{\text{max}}$ (CHCl$_3$) 2970, 1810, 1725, 1480, 1370, 1190 cm$^{-1}$; M.S. (%) 189.1 (0.1), 144.0 (0.3), 131.0 (9.1), 57.1 (100.0); 
Exact mass calculated for C$_8$H$_{12}$O$_5$ (M$^+$) is 188.0685. Found 188.0684.

**General procedure for bromination of 1,3-dioxolan-4-ones**

A mixture of the corresponding dioxolanone (1 equivalent), NBS (1.1 mol equivalent) and AIBN in dry carbon tetrachloride was refluxed under nitrogen for 1-4 hours. This was then cooled to 0°C, the succinimide formed was filtered and the solvent removed under reduced pressure. The crude product was purified by Kugelrohr distillation and the boiling points quoted below have not been corrected. The distillation yields were good (>85%) but the bromo compounds were not stable to prolonged storage (HBr is released upon prolonged storage and the clear liquid or solid becomes yellow). The stereochemistry of the bromo compounds has been assigned as *trans* by analogy to bromo dioxolanones 4.7a and 4.9a which had been assigned on the basis of nmr methods.

**5-Bromo-1,3-dioxolan-4-one (4.4a)**

From dioxolanone 4.4 (1g, 11.4 mmol) and NBS (2.2g, 12.5 mmol) was obtained the bromo dioxolanone 4.4a (1.51g, 79% crude yield) which was distilled by Kugelrohr at 60°C/100 mm Hg to give an unstable colourless liquid. $^1$Hnmr (CDCl$_3$, 200MHz) δ 5.58 (m, 2H), 6.43 (s, 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 71.83, 93.76, 165.71; $v_{\text{max}}$ (CCl$_4$) 2920, 1835, 1400, 1290, 1200, 1160, 1082, 1025, 955, 890 cm$^{-1}$; Anal. Calculated for C$_3$H$_3$BrO$_3$: C 21.58, H 1.81. Found C 21.78, H 1.82.

**5-Bromo-5-methyl-1,3-dioxolan-4-one (4.5a)**

From dioxolanone 4.5 (1.52g, 14.9 mmol) and NBS (2.94g, 16.5 mmol) was obtained dioxolanone 4.5a (2.45g, 91%) which was purified by Kugelrohr
distillation at 75°C/10 mm Hg. \( ^1H \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 2.23 (s, 3\text{H}), 5.43 (d, 1\text{H}, J=1.8 \text{ Hz}), 5.48 (d, 1\text{H}, J=1.8 \text{ Hz}); ^{13}C \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 26.78, 87.71, 91.98, 166.64; \nu_{\text{max}} \text{ (neat) } 2920, 1815, 1270, 1215, 1110, 1070, 1050, 970, 915, 785 \text{ cm}^{-1}; \) Anal. Calculated for C_4H_5BrO_3: C 26.55, H 2.78, Br 44.15. Found C 26.95, H 2.80, Br 44.03.

5-Bromo-2-methyl-1,3-dioxolan-4-one (4.6a)

From dioxolanone 4.6 (1.27 g, 12.5 mmol) and NBS (2.46 g, 13.8 mmol) was obtained the bromo derivative 4.6a (2.07 g, 91%) which was distilled by Kugelrohr at 80°C/50 mm Hg to give a colourless liquid which rapidly hydrolyses upon standing. \( ^1H \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 1.68 (d, 3\text{H}, J=5 \text{ Hz}), 5.87 (q, 1\text{H}, J=5 \text{ Hz}), 6.47 (s, 1\text{H}); ^{13}C \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 18.66, 73.67, 102.46, 165.91; \nu_{\text{max}} \text{ (CCl}_4) 1830, 1405, 1340, 1285, 1210, 1175, 1110, 1080, 1055, 930, 890 \text{ cm}^{-1}; \) Anal. Calculated for C_4H_5BrO_3: C 26.55, H 2.78, Br 44.15. Found C 26.23, H 2.78, Br 43.97.

5-Bromo-2-(t-butyl)-1,3-dioxolan-4-one (4.7a)

From dioxolanone 4.7 (3 g, 20.8 mmol) and NBS (4.1 g, 23.0 mmol) was obtained the bromo derivative 4.7a (4.4 g, 95% yield), which was distilled by Kugelrohr at 90°C/80 mm Hg to give a white solid. (mp=47-49°C); \( ^1H \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 1.00 (s, 9\text{H}), 5.38 (s, 1\text{H}), 6.48 (s, 1\text{H}); ^{13}C \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 23.25, 33.81, 73.86, 109.76, 165.94; \nu_{\text{max}} \text{ (CCl}_4) 2980, 1830, 1300, 1220, 1205, 1170, 1090, 960, 890 \text{ cm}^{-1}; \) M.S. (%) 166.8 (4.3), 164.8 (4.3), 142.9 (12.9), 87.1 (100.0); Exact mass calculated for C_7H_{11}O_3 (M^+-Br) is 143.0708. Found 143.0708.

5-Bromo-2,5-dimethyl-1,3-dioxolan-4-one (4.8a)

From dioxolanone 4.8 (1.8 g, 15.5 mmol) and NBS (2.97 g, 16.7 mmol) was obtained the bromo derivative 4.8a (2.86 g, 95% yield). This was distilled at 60°C/10 mm Hg by Kugelrohr to give a colourless liquid. \( ^1H \text{nmr} (\text{CDCl}_3, 200\text{MHz}) \delta 1.66 \)
(d, 3H, J=5 Hz), 2.22 (s, 3H), 5.71 (q, 1H, J=5 Hz); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 18.34, 27.01, 89.06, 100.56, 166.86; $\nu_{\text{max}}$ (CCl$_4$) 3000, 2940, 1820, 1450, 1405, 1380, 1348, 1260, 1210, 1155, 1100, 1070, 940, 920, 880 cm$^{-1}$; Anal. Calculated for C$_5$H$_7$BrO$_3$: C 30.79, H 3.62, Br 40.97. Found C 31.05, H 3.72, Br 40.73.

5-Bromo-2-(t-buty1)-5-phenyl-1,3-dioxolan-4-one (4.10a)

From dioxolanone 4.10 (2g, 9.1 mmol) and NBS (1.79g, 10 mmol) was obtained the bromo derivative 4.10a in essentially quantitative yield, which was purified by Kugelrohr distillation at 110°C/1 mm Hg to give a white solid. $^1$Hnmr (CDCl$_3$, 200MHz) δ 1.06 (s, 9H), 5.40 (s, 1H), 7.41 (m, 3H), 7.88 (m, 2H); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 23.4, 33.7, 89.5, 107.8, 126.6, 128.6, 130.3, 135.1, 166.1; $\nu_{\text{max}}$ (CCl$_4$) 2980, 1815, 1455, 1416, 1370, 1275, 1205, 1100, 1080, 1005 cm$^{-1}$; Anal. Calculated for C$_{13}$H$_{15}$BrO$_3$: C 52.19, H 5.05, Br 26.71. Found C 51.65, H 5.10, Br 27.27.

5-Bromo-2-(t-buty1)-5-carboxymethyl-1,3-dioxolan-4-one (4.11a)

From dioxolanone 4.11 (0.99g, 4.90 mmol) and NBS (0.97g, 5.45 mmol), the bromo derivative 4.11a was obtained in essentially quantitative yield as a white solid. $^1$Hnmr (CDCl$_3$, 300MHz) δ 1.01 (s, 9H), 3.67 (d, 2H, J=2 Hz), 5.23 (s, 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 23.60, 33.64, 43.35, 87.08, 108.57, 166.27, 172.07; $\nu_{\text{max}}$ (CHCl$_3$) 2980, 1815, 1725, 1480, 1410, 1298, 1170, 1055 cm$^{-1}$; M.S. (%) 156.1 (2.7), 99.0 (7.5), 86.1 (7.8), 71.1 (7.8), 57.1 (100.0); Exact mass calculated for C$_8$H$_{12}$O$_3$ (M$^+$-Br-COOH) is 156.0786. Found 156.0785.

Benzyloxyacetic acid (4.13a)

The bromination of dioxolanone 4.12 was conducted in the usual manner. From the $^1$H nmr spectrum, it was found that 4.13a (product of hydrolysis of 4.13) was formed. $^1$Hnmr (CDCl$_3$, 200MHz) δ 4.8 (s, 2H), 7.4-7.7 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) The multiplicities given in parentheses were obtained by
DEPT/APT methods. δ 60.56 (t), 128.45 (d), 128.86 (d), 129.86 (d), 133.53 (s), 165.91 (s), 173.74 (s); ν\textsubscript{max} (CHCl\textsubscript{3}) 2970, 1810, 1725, 1480, 1370, 1190 cm\textsuperscript{-1};
M.S. (%) 180.0 (6.2), 136.0 (5.0), 105.0 (100.0), 77.1 (61.5); Exact mass calculated for C\textsubscript{9}H\textsubscript{8}O\textsubscript{4} (M\textsuperscript{+}) is 180.0423. Found 180.0422.

**General procedure for reduction of bromo dioxolanones with tributyltin hydride/deuteride**

The corresponding bromo dioxolanone, tributyltin hydride or deuteride (1 mol equivalent) and catalytic amounts of AIBN in dry benzene were mixed in an ampoule. The reaction mixture was degassed 3x using freeze-thaw methods and the ampoule was sealed. For reactions at 80°C, the ampoule was placed in a constant temperature bath (80°C) for 12-16 hours, whereas reactions at 10°C was conducted in a constant cooling bath and the reaction mixture was irradiated with UV light for 16-24 hours. On completion, the reaction mixture was immediately analysed by \textsuperscript{1}H nmr spectroscopy. The ratio of the isomers was determined by the integration of \textsuperscript{1}H nmr and/or \textsuperscript{2}H nmr spectrum.

5-bis-\{2-(t-ButyD-5-phenyl-1,3-dioxolan-4-one)\} (4.14)

The reduction of the bromo dioxolanone 4.10a with Bu\textsubscript{3}SnH under the conditions described above gave two diastereomers. Upon recrystallisation from ether/hexane, one diastereomer precipitated out. The data below are for that diastereomer, the stereochemistry of which has not been determined. \textsuperscript{1}H nmr (CDCl\textsubscript{3}, 200MHz) δ 0.80 (s, 9H), 5.18 (s, 1H), 7.2-7.6 (m, 5H); \textsuperscript{13}C nmr (CDCl\textsubscript{3}, 200MHz) δ 23.24, 35.25, 84.50, 110.73, 127.22, 127.39, 128.89, 132.77, 169.18; \textsuperscript{ν}\textsubscript{max} (CHCl\textsubscript{3}) 2400, 1790, 1470, 1098, 920 cm\textsuperscript{-1}; Anal. Calculated for C\textsubscript{26}H\textsubscript{30}O\textsubscript{6}: C 71.21, H 6.89. Found C 71.16, H 7.20.

**Catalytic hydrogenation of bromo dioxolanone 4.9a**

A solution of the bromo dioxolanone 4.9a (0.386g, 1.63 mmol), triethylamine (0.3 ml) and 10% Pd/C (38.6 mg) in 25 ml ethyl acetate was stirred
vigorously for 16 hours under hydrogen. The reaction mixture was then filtered through celite, washed with ethyl acetate (3 x 10 ml), followed by washing with ice-cold dilute HCl and ice-cold water, dried over sodium sulphate and evaporated. The crude reaction mixture was then checked by \(^1\)H nmr spectroscopy.

**General procedure for allylation**

A solution of the bromo derivative of 1,3-dioxolan-4-one (3-6 M), tributylallyltin (1 mol equivalent) and AIBN (catalytic amounts) in dry benzene was degassed by bubbling argon in the solution for 10 minutes. The reaction mixture was irradiated with UV light at room temperature until all the starting materials were consumed. The reaction mixture was then evaporated and subjected to flash chromatography.

**5- Allyl-1,3-dioxolan-4-one (4.4c)**

\(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 2.5-2.7 (m, 2H), 4.33 (t, 1H), 5.13-5.28 (m, 2H), 5.45 (s, 1H), 5.53 (s, br., 1H), 5.83 (m, 1H); \(^13\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 34.63, 72.59, 94.34, 119.37, 131.34, 172.22; \(v_{\text{max}}\) (neat) 3080, 2905, 1805, 1200, 1030, 985 cm\(^{-1}\); Anal. Calculated for C\(_{6}\)H\(_8\)O\(_3\): C 56.25, H 6.29. Found C 56.12, H 5.97.

**5-Allyl-2-(t-butyl)-1,3-dioxolan-4-one (4.7c,d)**

From bromo dioxolanone 4.7a (0.94g, 4.2 mmol) and tributylallyltin (1.3 ml, 4.21 mmol) was obtained the allylated product as a mixture of isomers 4.7c,d. The yield as shown by \(^1\)H nmr spectroscopy (relative to an internal standard, C\(_6\)H\(_6\)) was found to be 61%. The products can be isolated by flash chromatography (ether/hexane=1:9) in only 33% yield. The ratio of isomers (trans:cis=2:1) were determined by \(^1\)H and \(^13\)C nmr spectroscopy as well as gas chromatographic analysis.

**trans-isomer (4.7c)**

\(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.93 (s, 9H), 2.53 (m, 2H), 4.45 (t, 1H, J=5 Hz), 5.28 (s, 1H), 5.15-5.28 (m, 2H), 5.83 (m, 1H); \(^13\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 23.24, 35.57, 35.77, 74.58, 110.75, 119.57, 131.51, 172.86; \(v_{\text{max}}\) (CCl\(_4\)) 3080,
2960, 2905, 1800, 1485, 1402, 1320, 1200, 1100, 1035, 985 cm\(^{-1}\); Anal. Calculated for C\(_{10}\)H\(_{16}\)O\(_3\): C 65.19, H 8.75. Found C 65.08, H 8.89.

cis-isomer (4.7d)

\(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.95 (s, 9H), 2.49 (m, 1H), 2.65 (m, 1H), 4.31 (t, 1H), 5.11 (s, 1H), 5.15-5.23 (m, 2H), 5.80 (m, 1H); \(^{13}\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 23.51, 34.34, 34.87, 74.60, 109.47, 118.87, 131.86, 172.51; \(\nu_{\text{max}}\) (CC\(_4\)) 3080, 2980, 2905, 2880, 1800, 1485, 1410, 1365, 1315, 1198, 1105, 990 cm\(^{-1}\).

5-Allyl-2-(t-butyl)-5-methyl-1,3-dioxolan-4-one (4.9c,d)

This was synthesized from the reaction of the bromo derivative 4.9a (1g, 4.22 mmol) with tributylallyltin (1.35 ml) in 72% yield as determined from \(^1\)H nmr spectroscopy. The ratio of isomers (trans:cis=7:1) was determined from gas chromatographic analysis. The physical data from the trans-isomer agreed with the literature data.\(^1\)

General procedure for intermolecular addition of bromo dioxolanones to acrylates

To a solution of the bromo dioxolanone (1 equivalent, 0.4 M) in dry benzene, 10 equivalents of distilled methyl acrylate was added and the solution degassed. The reaction mixture was irradiated with UV light at room temperature while a solution of Bu\(_3\)SnH (1.5 equivalent, 0.1-0.3 M) and AIBN in benzene was added by infinite dilution method with a syringe pump at the rate of 0.15 ml/min. The ratio of the reduced and addition products was determined by gas chromatography. However, in both cases tried (with dioxolanone 4.7a and 4.9a), it was not possible to determine the ratio of the diastereomers obtained from the addition reaction by gas chromatography or \(^1\)H nmr spectroscopy.

2-(t-Butyl)-5-(2-methoxycarbonylethyl)-1,3-dioxolan-4-one (4.7e,f)

From the reaction of the bromo compound 4.7a (1g, 4.48 mmol) and methyl acrylate (3.86g, 45 mmol), the title dioxolanones 4.7e,f were isolated by flash chromatography (ethyl acetate/hexane=1:9) as a mixture of isomers (ratio of isomers
is 4:1) in only 10% yield. The data below are for the major isomer. The stereochemistry was determined by 1-D nOe experiments and was found to be trans. 

1Hnmr (CDCl3, 200MHz) δ 0.95 (s, 9H), 2.13 (m, 2H), 2.50 (m, 2H), 3.70 (s, 3H), 4.44 (t, 1H, J=6 Hz), 5.29 (d, 1H, J=1.3 Hz); 13Cnmr (CDCl3, 200MHz) δ 23.08, 25.99, 29.26, 35.50, 51.69, 73.58, 110.25, 172.63, 172.78; \( \nu_{\text{max}} \) (neat) 2960, 1805, 1745, 1490, 1470, 1440, 1200, 1125, 1115, 1105, 1035, 982 cm\(^{-1}\);

Anal. Calculated for C\(_{11}\)H\(_{19}\)O\(_{5}\): C 57.38, H 7.88. Found C 57.15, H 7.91

2-(t-Butyl)-5-methyl-5-(2-methoxycarbonyl)ethyl)-1,3-dioxolan-4-one (4.9e)

From the bromo derivative 4.9a (1.83g, 7.72 mmol) and methyl acrylate (6.6g, 76.7 mmol), the corresponding addition product 4.9e was isolated by flash chromatography (ethyl acetate/hexane=5:95) in only 8% yield. The stereochemistry of the product was determined to be trans by nOe techniques. The cis-isomer was not isolated. 

1Hnmr (CDCl3, 200MHz) δ 0.90 (s, 9H), 1.43 (s, 3H), 2.00 (m, 1H), 2.17 (m, 1H), 2.45 (m, 2H), 3.68 (s, 3H), 5.19 (s, 1H); 13Cnmr (CDCl3, 200MHz) δ 21.82, 23.09, 28.17, 30.14, 34.29, 51.70, 78.66, 108.07, 172.89, 175.04; \( \nu_{\text{max}} \) (neat) 2960, 2880, 1800, 1740, 1485, 1440, 1380, 1250, 1220, 1180, 1140, 1080, 980, 915 cm\(^{-1}\); Anal. Calculated for C\(_{12}\)H\(_{20}\)O\(_{5}\): C 59.00, H 8.25. Found C 59.25, H 8.47.

General procedure for the addition of alkyl radicals to 2-(t-butyl)-5-methylene-1,3-dioxolan-4-one (4.16)

Method 1:

The dehydro compound 4.16 (1 equivalent, 0.2 M) and 1.5 mol equivalent of alkyl iodide (RI) were dissolved in dry benzene and the solution degassed. The reaction mixture was irradiated with UV light at room temperature while a solution of Bu3SnH (1.5 equivalent)/AIBN (0.2-0.4 M) in benzene was added slowly by infinite dilution method with a syringe pump at the rate of 0.15 ml/min. After 8-12 hours, the reaction mixture was evaporated and the diastereoselectivity checked by 1H nmr.
spectroscopy (wherever possible). Then the reaction mixture was chromatographed on silica.

Method 2

The procedure above was used except 3 equivalents of the dehydro compound 4.16 and 1 equivalent of alkyl iodide (0.09 M) was used. A solution of 1 mol equivalent Bu3SnH (0.09 M) was added as done previously.

Method 3

To a solution of dioxolanone 4.16 (186mg, 1.19 mmol) in 10 ml of dichloromethane was added cyclohexylmercury chloride (900mg, 2.82 mmol). This was stirred vigorously at room temperature while a solution of sodium borohydride (0.4 g in 7 ml of water) was added dropwise over 45 minutes. This was stirred for another 2 hours after which the reaction mixture was filtered through celite and the aqueous layer of the filtrate separated. The organic layer was dried and then evaporated. The diastereoselectivity was checked by \(^1\text{H}/\text{\(^{13}\text{C}\)}\) nmr spectroscopy. The crude reaction mixture was then chromatographed (ether/hexane=1:9) to give 33% of the required addition product 4.28c, 4.29c (see below for data).

2-(t-Butyl)-5-(2-phenylethyl)-1,3-dioxolan-4-one (4.28a, 4.29a)

This was synthesized by method 1 and isolated in only 15% yield from flash chromatography (elution with ether/hexane=1:9). \(^1\text{H}nmr\) (CDCl3, 300 MHz) \(\delta\): 1.02 (s, 9H), 2.1-2.3 (m, 2H), 2.83 (t, 2H, J=5 Hz), 4.25 (dd, 1H, J=1, 4 Hz), 5.17 (d, 1H, J=1 Hz), 7.3-7.4 (m, 5H); \(^{13}\text{C}nmr\) (CDCl3, 200 MHz) \(\delta\): 23.51, 31.84, 32.44, 34.34, 74.11, 109.47, 126.26, 128.51, 140.45, 173.30, quartenary carbon of the aromatic group was not detected; \(v_{\max}\) (neat) 2960, 2920, 2870, 1800, 1195, 1115, 1072, 970 cm\(^{-1}\); M.S. (%): 191.2 (3.6), 157.1 (3.2), 117.1 (29.9), 91.1 (56.3), 77.1 (3.7), 57.2 (100.0); Exact mass calculated for C\(_{11}\)H\(_{11}\)O\(_3\) (M\(^+\)-57) is 191.0708. Found 191.0708.
2-(t-Butyl)-5-(3-phenylpropyl)-1,3-dioxolan-4-one (4.28b, 4.29b)

This was isolated in 34% yield (flash chromatography, ether/hexane=1:9) when method 1 was used. $^1$Hnmr (CDCl$_3$, 200MHz) δ 0.97 (s, 9H), 1.2-1.9 (m, 4H), 2.15 (m, 2H), 4.25 (m, 1H), 5.12 (s, 1H), 7.1-7.4 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 23.41, 29.08, 30.06, 34.18, 35.29, 74.91, 109.23, 125.86, 128.30, 141.47, 173.38, quartenary carbon of the aromatic ring was not detected; $\nu_{\text{max}}$ (neat) 2970, 2920, 2880, 1800, 1482, 1460, 1410, 1365, 1195, 1115, 1075, 972, 698 cm$^{-1}$; M.S. (%) 262.2 (1.0), 205.2 (7.7), 157.2 (1.5), 117.1 (8.1), 77.1 (4.7), 57.2 (100.0); Exact mass calculated for C$_{12}$H$_{13}$O$_3$ (M$^+$-57) is 205.0865. Found 205.0863.

2-(t-Butyl)-5-cyclohexylmethyl-1,3-dioxolan-4-one (4.28c, 4.29c)

This was synthesized by 2 methods. When method 2 was used, starting from dehydro compound 4.16 (0.209g, 1.34 mmol) and cyclohexyl iodide (0.45 mmol), the dioxolanones 4.28c, 4.29d were isolated in 26% yield (elution with ether/hexane=1:9). The yield was calculated relative to the iodide. The other method used was method 3 and dioxolanones 4.28c, 4.29c were isolated in 33% yield. Only the data for the major (cis) isomer are listed below. $^1$Hnmr (CDCl$_3$, 200MHz) δ 0.97 (s, 9H), 1.2-1.8 (m, 13H), 4.31 (ddd, 1H, J=1, 4, 9 Hz), 5.13 (d, 1H, J=1 Hz); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 23.39, 25.98, 26.05, 26.28, 32.52, 33.46, 34.19, 34.27, 38.29, 73.35, 109.33, 174.22; $\nu_{\text{max}}$ (neat) 2910, 1800, 1485, 1450, 1410, 1300, 1215, 1190, 1110, 1040, 970 cm$^{-1}$; Anal. Calculated for C$_{14}$H$_{24}$O$_3$: C 69.96, H 10.06. Found C 70.09, H 10.00.

General procedure for the synthesis of sulphur dioxolanones

DBU (1 equivalent) was added to a solution of p-chlorothiophenol (1 equivalent) in dry benzene and stirred for 10 minutes. The corresponding bromo dioxolanone (1 equivalent) was then added. Upon addition, the reaction mixture became warm and a white precipitate formed. This was stirred for a further 2-4 hours. The reaction mixture was then filtered to remove the DBU.HBr salt, washed
with ice-cold water, dried over sodium sulphate and evaporated to give good yields of product. The sulphur dioxolanones can be recrystallised from ether and/or hexane or can be purified by column chromatography. The stereochemistry of these sulphur dioxolanones were assigned to be cis by analogy to the stereochemistry of the sulphur dioxolanone 4.24 which was determined by X-ray crystallography (see Appendix A).

2-(t-Butyl)-5(p-chlorophenylthio)-1,3-dioxolan-4-one (4.23a/b)

From the bromo dioxolanone 4.7a (1.17g, 5.24 mmol), p-chlorothiophenol (0.76g, 5.25 mmol) and DBU (0.79g, 5.25 mmol), the corresponding sulphur compounds 4.23a/b (1.22g, 81% yield) were obtained. The ratio of diastereomers was 7:1 and the major isomer (cis by analogy to dioxolanone 4.24) was obtained by recrystallisation from hexane. (mp= 56-57°C); \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.83 (s, 9H), 5.10 (s, 1H), 5.50 (s, 1H), 7.23-7.50 (m, 4H); \(^1\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 23.24, 34.49, 81.47, 109.82, 128.51, 129.29, 135.72, 135.80, 168.57; \(\nu_{\text{max}}\) (CCl\(_4\) 2990, 2970, 1810, 1480, 1410, 1340, 1225, 1175, 1098, 1080, 1017, 980 cm\(^{-1}\); Anal. Calculated for C\(_{13}\)H\(_{15}\)ClO\(_3\)S: C 54.45, H 5.27, S 11.18, Cl 12.36. Found C 54.59, H 5.62, S 10.81, Cl 12.00.

2-(t-Butyl)-5(p-chlorophenylthio)-5-methyl-1,3-dioxolan-4-one (4.24)

The compound 4.24 (1.48g, 88% yield) was obtained from the bromo dioxolanone 4.9a (1.33g, 5.6 mmol), p-chlorothiophenol (0.81g, 5.60 mmol) and DBU (0.85g, 5.58 mmol). From \(^1\)H nmr spectrum of the crude reaction mixture, only one isomer was obtained (diastereoselectivity of the reaction was > 95%). This sole product was recrystallised from ether and hexane to give a crystalline white solid. (mp=114-115°C). X-ray crystallography of a single crystal of 4.24 established that the stereochemistry of the sulphur dioxolanone 4.24 was cis (Appendix A). \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.76 (s, 9H), 1.70 (s, 3H), 5.08 (s, 1H), 7.3-7.63 (m, 4H); \(^1\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 21.79, 23.24, 34.17, 87.98, 107.45, 127.07, 129.18, 136.62, 138.32, 171.66; \(\nu_{\text{max}}\) (CCl\(_4\) 2980, 2960, 1800, 1480, 1225,
2-(t-Butyl)-5-(p-chlorophenylthio)-5-phenyl-1,3-dioxolan-4-one (4.26)

The sulphur dioxolanone 4.26 (0.91g, 91% yield) was obtained from bromo dioxolanone 4.10a (0.79g, 2.62 mmol), p-chlorothiophenol (0.38g, 2.62 mmol) and DBU (0.39g, 2.62 mmol). The crude product was recrystallised from ether and hexane to give a white solid which was assumed to have cis stereochemistry by analogy to 4.24. (mp= 78-80°C); ¹Hnmr (CDCl₃, 200MHz) δ 0.80 (s, 9H), 4.95 (s, 1H), 7.2-7.7 (m, 9H); ¹³Cnmr (CDCl₃, 200MHz) δ 23.24, 34.05, 91.10, 107.19, 125.94, 126.27, 128.74, 129.00, 129.53, 133.56, 136.65, 138.44, 169.47; Vmax (CCl₄) 2970, 1800, 1480, 1450, 1410, 1340, 1185, 1170, 1100, 1080, 1020 cm⁻¹; Anal. Calculated for C₁₉H₁₉ClO₃S: C 62.92, H 5.28, S 8.84, Cl 9.77. Found C 62.89, H 5.57, S 9.04, Cl 9.58.

2-(t-Butyl)-5-methyl-5-(phenylselenyl)-1,3-dioxolan-4-one (4.25)

A solution of diphenyldiselenide (0.208g, 0.67 mmol) in 5 ml ethanol was stirred at room temperature while sodium borohydride (55mg, 1.46 mmol) was added in small portions. The yellow colour dissipated when the formation of sodium phenylselenide was completed. This was then added to a solution of the bromo dioxolanone 4.9a (315mg, 1.33 mmol) in 10 ml benzene at room temperature and stirred for 4 hours. Subsequent workup and evaporation of the solvent gave dioxolanone 4.25 in 80% yield (only one product was detected by ¹H nmr spectroscopy). The product was then recrystallised from ether/hexane. The stereochemistry was assumed to be cis by analogy to compound 4.24. ¹Hnmr (CDCl₃, 200MHz) δ 0.78 (s, 9H), 1.68 (s, 3H), 5.15 (s, 1H), 7.3-7.7 (m, 5H); ¹³Cnmr (CDCl₃, 200MHz) δ 23.28, 23.63, 34.31, 81.41, 108.88, 126.10, 129.10, 129.64, 137.74, 173.35; Anal. Calculated for C₁₄H₁₈O₃Se: C 53.68, H 5.79, Se 25.21. Found C 54.09, H 5.74, Se 25.21.
Alternative synthesis of 2-(t-butyl)-5-methylene-1,3-dioxolan-4-one (4.16) and synthesis of (2S)- and (2R)-dioxolanone 4.16

Dioxolanone 4.11 (0.56g, 2.78 mmol) was converted in the usual manner to the bromo compound 4.11a. The bromo compound was then dissolved in 20 ml benzene and less than an equivalent of DBU (~0.98 mol equivalent) was added and stirred for 45 minutes. This was filtered through a short column of silica and evaporated to give the dehydro compound 4.16 (0.240g, 55% yield). Further purification was not necessary as starting from optically active compound (2S, 5S)-dioxolanone 4.11 \([\alpha]_D^{23} = -2.1^\circ\), it was found that (2S)-dioxolanone 4.16 was formed in high optical purity \([\alpha]_D^{23} = -15.1^\circ\) (CHCl₃, c=1.3); lit. value⁵ \([\alpha]_D^{24} = -14.9^\circ\) (CHCl₃, c=1.6). The synthesis of the other enantiomer of (2R)-dioxolanone 4.16 was also conducted starting from (2R, 5S)-dioxolanone 4.11 (optical rotation \([\alpha]_D^{23} = +24.8^\circ\)) to give (2R)-dioxolanone 4.16 with an optical rotation of \([\alpha]_D^{23} = +15.3^\circ\) (CHCl₃, c=1.5).

2-(t-butyl)-5(\(N\)-(2-thionopyridyl)-oxycarbonylmethyl)-1,3-dioxolan-4-one (4.20)

To dioxolanone 4.11 (0.406g, 2 mmol) was added of N-hydroxypyridine-2-thione (0.306g, 1.2 mol equivalent), 4-dimethylanilinopyridine (DMAP) (25mg, 0.1 mol equivalent) in 20 ml of dichloromethane at room temperature. The flask was wrapped with aluminium foil and the reaction was conducted in the absence of light. A solution of 1,3-dicyclohexylcarbodiimide (DCC) (0.622g, 1.5 mol equivalent) in 10 ml of dichloromethane was added slowly to the reaction mixture and stirred overnight. The reaction mixture was then filtered through a short column of silica to remove the polar byproducts. This was washed with several mls of ethyl acetate and the filtrate (which is yellow in colour) was then evaporated under reduced pressure. The light sensitive ester was found to have >90% purity by \(^1\)H nmr spectroscopy and was used in subsequent reactions without further purification.

When cis-dioxolanone 4.11 was used, cis-dioxolanone 4.20 was obtained. \(^1\)Hnmr (CDCl₃, 200MHz) \(\delta\) 0.95 (s, 9H), 3.52 (dd, 1H, J=6.7, 14.5 Hz), 3.95 (dd,
1H, J=6.7, 14.5 Hz), 4.62 (ddd, 1H, J=1.4, 4.6, 5.4 Hz), 5.16 (d, 1H), 7.0-8.5 (m, 4H).

2-(t-Butyl)-5-(2-pyridylthiomethyl)-1,3-dioxolan-4-one (4.21)

A solution of the ester 4.20 (1 mmol, cis/trans mixture of 6:1) in benzene was irradiated with a sunlamp until the yellow colour of the Barton ester disappeared. The crude reaction mixture was then evaporated and purified by preparative tlc (ether/hexane= 4:1) to give 107 mg (40% yield from dioxolanone 4.11) of the corresponding cis/trans (ratio 6:1) thio derivative. The data below are for the cis-compound: 1Hnmr (CDCl₃, 200MHz) δ 0.92 (s, 9H), 3.50 (dd, 1H, J=6.6, 14.5 Hz), 3.90 (dd, 1H, J=6.6, 14.5 Hz), 4.65 (ddd, 1H, J=1.2, 4, 6.7 Hz), 5.14 (d, 1H, J=1.2 Hz), 7.0-8.5 (m, 4H); 13Cnmr (CDCl₃, 200MHz) δ 23.33, 29.85, 34.10, 74.43, 109.38, 119.72, 122.25, 135.92, 149.18, 157.06, 171.66; vmax (CCl₄) 2966, 1795, 1580, 1450, 1300, 1215, 1190, 1120, 1045, 960, 760 cm⁻¹; Anal. Calculated for C₁₃H₁₇NO₃S: H 6.41, N 5.24, S 11.99. Found H 6.76, N 5.26, S 11.98; M.S. (%) 266.9 (0.6), 209.9 (5.9), 181.9 (3.1), 165.9 (2.11), 153.9 (8.0), 135.9 (21.4), 124.0 (34.8), 110.9 (100.0); Exact mass calculated for C₁₃H₁₇NO₃S (M⁺) is 267.0929. Found 267.0928.

2-(t-Butyl)-5-methyl-1,3-dioxolan-4-one (4.9)

The trans-dioxolanone 4.11 (2 mmol) was converted to the Barton ester 4.20 and after the usual workup procedure, the ester was dissolved in 10 ml of benzene. Then 1.1 mol equivalent of Bu₃SnH and catalytic amounts of AIBN were added. This was refluxed overnight and from the 1H nmr spectrum of the crude reaction mixture, only the trans-dioxolanone 4.9 was detected. This was chromatographed (ethyl acetate/hexane=1:9) to give the required compound (0.19g, 60% from two steps).

The physical data of the trans-dioxolanone 4.9 agreed with the literature data.¹
Synthesis of (2S,5S)-2-((t-butyl)-5-methyl-1,3-dioxolan-4-one (4.9)

This was synthesized as above starting from cis-(2S, 5S) dioxolanone 4.11. The cis-(2S, 5S)-dioxolanone 4.9 was obtained in high optical purity $[\alpha]_D^{23} = 44.6^\circ$ (CHCl$_3$, c=0.6); literature value$^1$ $[\alpha]_D^{23} = 44.8^\circ$ (CHCl$_3$, c=1.8).

Synthesis of 2-(t-butyl)-5-methylene-1,3-dioxolan-4-one via 2-(t-butyl)-5-(bromomethyl)-1,3-dioxolan-4-one (4.22)

The trans-dioxolanone 4.11 (2.01 mmol) was converted to the Barton ester in the usual manner. The ester was dissolved in 25 ml of bromotrichloromethane (BrCCl$_3$) and AIBN was added in catalytic amounts. The reaction mixture was refluxed for 3 hours after which an aliquot was removed and evaporated. The $^1$H nmr spectrum of the crude reaction mixture showed that the reaction had proceeded cleanly (>85% purity) to give the corresponding trans-bromo compound 4.22. $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.99 (s, 9H), 3.69 (d, 2H, $J$=3 Hz), 4.78 (dt, 1H), 5.51 (d, 1H, $J$=1.7 Hz).

No attempts were made to purify this but to further prove the identity of this compound, 1 equivalent of DBU was added to the reaction mixture at room temperature. Upon addition of the base, the solution warmed up slightly and a precipitate was formed. This was stirred for an additional hour following which, the reaction mixture was filtered through a short plug of silica and the filtrate concentrated under reduced pressure. The $^1$H nmr spectrum of the crude reaction mixture showed that the reaction had proceeded cleanly. The reaction mixture was then chromatographed (ether/hexane=1:4) and the dehydro compound 4.16 was obtained (170mg, 54% isolated yield from dioxolanone 4.11).

Synthesis of (2S)-2-(t-butyl)-5-methylene-1,3-dioxolan-4-one via dioxolanone (4.22)

Starting from cis-(2S, 5S)-dioxolanone 4.11, the bromo dioxolanone 4.22 was synthesized in the manner described above.
The $^1$H nmr data for the cis-dioxolanone 4.22 are listed below; $^1$H nmr (CDCl$_3$, 200MHz) $\delta$ 1.04 (s, 9H), 3.66 (dd, 1H, J=5, 12 Hz), 3.74 (dd, 1H, J=5, 12 Hz), 4.60 (dt, 1H, J=1, 4 Hz), 5.22 (d, 1H, small J). The dehydro compound (2S)-dioxolanone 4.16 was obtained using the same procedure above $[\alpha]_D^{23} = -14.8^\circ$ (CHCl$_3$, c=1.3).

References:

Experimental: Chapter 5, Section 5.1

General procedure for the synthesis of various substituted 1,3-oxazolidin-5-ones

The 1,3-oxazolidin-5-ones were synthesized according to literature procedures and the procedures are summarised here. Oxazolidinones 5.3, 5.5, 5.6, and 5.33 have been described before in the literature. Compound 5.19 is commercially available from Aldrich.

The synthesis of the Schiff base of amino acids

The amino acid (0.1 mol) was dissolved in 100 ml of 1N NaOH solution (0.1 mol). The solution was then evaporated under reduced pressure on the rotary evaporator until a precipitate was formed. The solid was suspended in dichloromethane or pentane (200 ml) and 1.5 equivalent of pivaldehyde was added and the suspension refluxed overnight under azeotropic removal of water. The solvent was then removed and the resulting Schiff base was dried under high vacuum overnight. The Schiff base was not stable to prolonged storage due to decomposition, so whenever possible it was prepared fresh. The Schiff base could be stored for short periods under argon at 0°C.

General procedure for the synthesis of 1,3-oxazolidin-5-ones

The corresponding acid chloride (0.1 mol) in 50 ml of dichloromethane was added in one portion to a suspension of the Schiff base (0.1 mol) in 400 ml of dichloromethane at 0°C. This was stirred at the same temperature for 4 hours and then refluxed overnight. The cloudy solution was washed with water, followed by 5% sodium bicarbonate, 5% sodium sulphite and water. This was dried over sodium sulphate and the 1H nmr spectrum was recorded. In most cases, the reaction occurred to give good to moderate yields and the product was purified by either recrystallisation or flash chromatography. The yields were not optimised and some of the poor yields could be attributed to the partial decomposition of the Schiff base as it was not always practical to synthesize the Schiff base immediately prior to use.
2-(t-Butyl)-3-phenylacetyl-1,3-oxazolidin-5-one (5.13)

From the Schiff base of glycine (6.6g, 40 mmol) and phenylacetyl chloride (6.78g, 44 mmol), oxazolidinone 5.13 was isolated by flash chromatography (6.9g, 66% yield) as a white solid (ethyl acetate/hexane=2:5). (m.p.=126-129°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.93 (s, 9H), 3.65 (d, 1H, J=15 Hz), 3.75 (d, 1H, J=15 Hz), 3.85 (d, 1H, J=16 Hz), 4.20 (d, 1H, J=16 Hz), 5.95 (s, 1H), 7.2-7.5 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.49, 38.97, 42.91, 46.89, 95.61, 127.51, 128.82, 129.07, 133.05, 169.78, 170.70; $\nu_{\text{max}}$ (CCl$_4$) 2980, 1810, 1680, 1385, 1240, 1020 cm$^{-1}$; Anal. Calculated for C$_{15}$H$_{19}$N$_2$O$_3$: C 68.94, H 7.33, N 5.36. Found C 68.89, H 7.65, N 5.45.

2-(t-Butyl)-3-trimethylacetyl-1,3-oxazolidin-5-one (5.14)

Trimethylacetyl chloride was synthesized from trimethylacetic acid and oxalyl chloride in dichloromethane in the presence of catalytic amounts of DMF. The Schiff base of glycine (5.81g, 35 mmol) was reacted with the acid chloride to give oxazolidinone 5.14, which was purified by flash chromatography (ethyl acetate/hexane=1:9) in only 10% yield. (mp=200-202°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.95 (s, 9H), 1.26 (s, 9H), 4.10 (d, 1H, J=16 Hz), 4.58 (d, 1H, J=16 Hz), 6.13 (s, 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.49, 27.42, 38.73, 39.52, 47.63, 96.19, 170.84, 178.18; $\nu_{\text{max}}$ (CHCl$_3$) 2970, 1790, 1655, 1470, 1400, 1355, 1044, 1015, 1000 cm$^{-1}$; Anal. Calculated for C$_{12}$H$_{21}$N$_2$O$_3$: C 63.41, H 9.31, N 6.16. Found C 63.06, H 9.40, N 6.04.

2-(t-Butyl)-3-propionyl-1,3-oxazolidin-5-one (5.15)

The title oxazolidinone 5.15 was synthesized from the Schiff base derived from glycine (3.64g, 22 mmol) and propionyl chloride (2.47g, 26.7 mmol) as a white solid (2.23g, 51% yield). This was recrystallised from ether/hexane (30-40% yield). (mp=177-178°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.00 (s, 9H), 1.19 (t, 3H, J=8 Hz), 2.32 (m, 2H), 4.03 (d, 1H, J=16 Hz), 4.16 (d, 1H, J=16 Hz), 5.92 (s, 1H); $^{13}$Cnmr
(CDCl$_3$, 200MHz) $\delta$ 8.80, 24.51, 28.36, 38.69, 46.64, 95.65, 170.01, 173.29; $\nu_{\text{max}}$ (CCL$_4$) 1810, 1680, 1550, 1265, 1220, 1005, 980 cm$^{-1}$; M.S. (%) 199.1 (0.7), 142.1 (1.6), 114.1 (100.0), 86.1 (48.0), 57.1 (49.2); Exact mass calculated for C$_{10}$H$_{17}$N$_{03}$ (M$^+$) is 199.1208. Found 199.1208.

2-(t-Butyl)-3-octanoyl-1,3-oxazolidin-5-one (5.16)

The Schiff base from glycine (7g, 42 mmol) was cyclised using octanoyl chloride (6.88g, 42 mmol) to afford oxazolidinone 5.16 which was purified by flash chromatography. $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 0.87-0.89 (m, 3H), 0.98 (s, 9H), 1.3 (m, 8H), 1.68 (m, 2H), 2.32 (m, 2H), 4.06 (d, 1H, J=17 Hz), 4.22 (d, 1H, J=17 Hz), 5.96 (br., 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 13.75, 22.31, 24.25, 24.40, 28.75, 28.89, 31.38, 34.90, 38.56, 46.61, 95.57, 170.37, 173.13; $\nu_{\text{max}}$ (CCL$_4$) 2960, 2930, 1815, 1685, 1390, 1230, 1165, 1010, 830 cm$^{-1}$; Anal. Calculated for C$_{15}$H$_{27}$N$_{03}$: C 66.88, H 10.10, N 5.20. Found C 67.27, H 10.35, N 5.12.

2-(t-Butyl)-3-phenoxycarbonyl-1,3-oxazolidin-5-one (5.17)

Oxazolidinone 5.17 was synthesized from the Schiff base derived from glycine (12.1g, 73 mmol) and phenylchloroformate (8.1g, 52 mmol) in a modified procedure where phenylchloroformate was added to the suspension of the Schiff base in dichloromethane at -15°C. This was stirred at -15°C for 30 minutes and then at room temperature for 2 days. After the usual workup procedure, oxazolidinone 5.17 was obtained and purified by flash chromatography (ethyl acetate/hexane=1:5) in 48% yield. (mp=120-122°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.05 (s, 9H), 4.06 (br., 1H), 4.50 (d, 1H, J=18 Hz), 5.79 (br., 1H), 7.1-7.5 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.27, 38.52, 46.62, 96.78, 121.29, 126.14, 129.55, 150.33, 153.07, 170.05; $\nu_{\text{max}}$ (CCL$_4$) 1815, 1750, 1550, 1380, 1265, 1210, 1008, 980 cm$^{-1}$; Anal. Calculated for C$_{14}$H$_{17}$NO$_{4}$: C 63.87, H 6.51, N 5.32. Found C 64.04, H 6.74, N 5.38.
2-(t-Butyl)-3-trichloroacetyl-1,3-oxazolidin-5-one (5.18)

This was synthesized in the usual manner from the Schiff base derived from glycine (6g, 36 mmol) and trichloroacetyl chloride (6.7g, 36 mmol). The oxazolidinone 5.18 was isolated as a white solid and purified by either recrystallisation from chloroform/ether or by flash chromatography (ethyl acetate/hexane=1:5) in low yields. (mp=110-111°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.05 (s, 9H), 4.30 (d, 1H, J=20 Hz), 4.85 (d, 1H, J=20 Hz), 6.00 (s, 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.59, 39.34, 48.18, 92.18, 96.94, 159.75, 168.42; V$_{max}$ (CCl$_4$) 1820, 1710, 1382, 1225, 1190, 1120, 1052, 890, 845, 715, 670 cm$^{-1}$; Anal. Calculated for C$_9$H$_{12}$Cl$_3$N$_2$O$_3$: C 37.46, H 4.19, N 4.85, Cl 36.86. Found C 37.58, H 4.40, N 4.80, Cl 37.14.

3-(o-Bromobenzoyl)-2-(t-butyl)-1,3-oxazolidin-5-one (5.23)

This was synthesized as above starting from the Schiff base of glycine and o-bromobenzoyl chloride in 41% isolated yield (ethyl acetate/hexane=2:5). $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.09 (s, 9H), 3.74 (d, 1H, J=17 Hz), 4.09 (d, 1H, J=17 Hz), 6.09 (s, 1H), 7.3-7.7 (m, 4H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.54, 39.03, 47.48, 95.63, 118.88, 128.18, 128.69, 131.77, 133.34, 136.68, 168.69, 169.49; V$_{max}$ (CCl$_4$) 2960, 1810, 1672, 1380, 1238, 1148, 1018 cm$^{-1}$; M.S. (%) 327.0 (0.1), 325.0 (0.1), 312.0 (0.2), 310.0 (0.2), 270.0 (12.8), 268.0 (13.2), 185.0 (96.3), 183.0 (100.0), 157.0 (11.9), 155 (11.7), 105.1 (12.7); Exact mass calculated for C$_{14}$H$_{16}$BrNO$_3$ (M$^+$) is 325.0314. Found 325.0313.

3-(o-Bromobenzoyl)-2-(t-butyl)-4-methyl-1,3-oxazolidin-5-one (5.27)

The oxazolidinone 5.27 was synthesized as above starting from the Schiff base derived from alanine and o-bromobenzoyl chloride. This was obtained as a mixture of isomers (ca 1:1) and was purified by flash chromatography (ethyl acetate/hexane=2:5) in low yields (20-30%). Only the chemical shift of one isomer is given. The stereochemistry of this isomer was not determined. $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.11 (s, 9H), 1.33 (d, 3H, J=6 Hz), 4.15 (m, 1H), 6.07 (s, 1H), 7.25-
7.7 (m, 4H); $^{13}$Cnmr (CDCl$_3$, 300MHz) δ 17.26, 25.10, 37.38, 53.06 (br.), 95.53, 118.59 (br.), 127.65, 131.96, 132.96, 137.06, 169.76, 172.32; $\nu_{\text{max}}$ (CHCl$_3$) 2980, 1790, 1675, 1370, 1240, 1155, 1010 cm$^{-1}$; M.S. (%) 326.0 (0.2), 324.0 (0.2), 284.0 (11.4), 282.0 (11.4), 184.9 (99.8), 182.9 (100.0), 157.0 (11.4), 155.0 (11.4), 105.0 (8.5); Exact mass calculated for C$_{15}$H$_{18}$BrNO$_3$ (M$^+$) is 324.0235. Found 324.0233.

2-(t-Butyl)-3-(o-iodobenzoyl)-1,3-oxazolidin-5-one (5.31)

From the Schiff base of glycine (2.5g, 15 mmol) and 1 equivalent of o-iodobenzoyl chloride, oxazolidinone 5.31 (4.2g, 75%) was synthesized and purified by flash chromatography (ethyl acetate:hexane=2:5). $^1$Hnmr (CDCl$_3$, 300MHz) δ 1.13 (s, 9H), 3.75 (d, 1H, J=17 Hz), 4.02 (d, 1H, J=17 Hz), 6.09 (s, 1H), 7.2-7.9 (m, 4H); $^{13}$Cnmr (CDCl$_3$, 300MHz) δ 24.34, 38.84, 47.62, 95.76, 128.27, 128.54, 128.97, 131.78, 139.98, 140.96, 169.79, 170.61; $\nu_{\text{max}}$ (CHCl$_3$) 2970, 1810, 1675, 1575, 1380, 1245, 1015 cm$^{-1}$; M.S. (%) 373.0 (1.0), 358.0 (0.2), 316.0 (15.7), 230.9 (100.0), 203.0 (0.6), 105.1 (13.4), 76.1, 57.2; Exact mass calculated for C$_{14}$H$_{16}$INO$_3$ (M$^+$) is 373.0175. Found 373.0178.

Synthesis of bromo oxazolidinones from 1,3-oxazolidin-5-ones

The corresponding oxazolidinone was treated with NBS (1.1 mol equivalent) in carbon tetrachloride in the presence of catalytic amounts of AIBN. This was heated under reflux conditions for 30-40 minutes and was then cooled, filtered and evaporated. From $^1$H nmr spectroscopy, the purity of the bromo oxazolidinone was found to be > 90%.

3-Benzoyl-4-bromo-2-(t-butyl)-1,3-oxazolidin-5-one (5.3a)

$^1$Hnmr (CDCl$_3$, 200MHz) δ 1.18 (s, 9H), 6.08 (s, 1H), 6.24 (s, 1H), 7.1-7.8 (m, 5H).
4-Bromo-2-(t-butyl)-3-phenylacetyl-1,3-oxazolidin-5-one (5.13a)

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.08 (s, 9H), 3.85 (d, 1H, J=16 Hz), 4.00 (d, 1H, J=16 Hz), 5.92 (s, 1H), 6.32 (s, 1H), 7.2-7.5 (m, 5H).

4-Bromo-2-(t-butyl)-3-trimethylacetyl-1,3-oxazolidin-5-one (5.14a)

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.08 (s, 9H), 1.46 (s, 9H), 6.16 (s, 1H), 6.73 (s, 1H).

4-Bromo-2-(t-butyl)-3-propionyl-1,3-oxazolidin-5-one (5.15a)

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.05 (s, 9H), 1.21 (t, 3H, J=8 Hz), 2.5-2.7 (m, 2H), 5.92 (s, 1H), 6.47 (s, 1H).

4-Bromo-2-(t-butyl)-3-octanoyl-1,3-oxazolidin-5-one (5.16a)

$^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.08 (s, 9H), 0.89-1.72 (m, 13H), 2.33-2.61 (m, 2H), 5.93 (s, 1H), 6.36 (s, 1H).

4-Bromo-2-(t-butyl)-3-phenoxy carbonyl-1,3-oxazolidin-5-one (5.17a)

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.16 (s, 9H), 5.77 (s, 1H), 6.62 (s, 1H), 7.15-7.50 (m, 5H).

4-Bromo-2-(t-butyl)-3-trichloroacetyl-1,3-oxazolidin-5-one (5.18a)

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.16 (s, 9H), 6.08 (s, 1H), 6.92 (s, 1H).

Competitive bromination studies

The oxazolidinone (0.3 mmol) and a reference compound, usually methyl hippurate (0.3 mmol) were dissolved in carbon tetrachloride along with catalytic amounts of AIBN. A weighed amount of NBS (0.3 mmol) was then added, the solution refluxed for 45 minutes and then allowed to cool. The succinimide was filtered, the reaction mixture evaporated and $^1$H nmr spectrum of the crude reaction mixture immediately recorded, which gave the ratios of the starting materials and products. When the solubility of the oxazolidinone was a problem, the two reactants
were refluxed in carbon tetrachloride before a weighed amount of NBS was added. An alternative procedure used was to conduct and monitor the reaction directly by nmr in CD$_2$Cl$_2$. In these cases, the reaction mixture was irradiated with a sunlamp for 15 minutes and the nmr spectrum was recorded after irradiation.

**Synthesis of the sulphur derivatives from the bromo 1,3-oxazolidin-5-ones**

To a solution of p-chlorothiophenol (1 mol equivalent) in benzene was added DBU (0.98 mol equivalent). Then the corresponding bromo compound (1 equivalent) in benzene was added and a precipitate was formed almost immediately. This was left to stir for another hour, following which the reaction mixture was filtered, washed with cold dilute HCl, dried and evaporated to give the corresponding sulphur compound. In most cases, the bromo oxazolidinones were synthesized just prior to reaction with the thiolate and the yields quoted (unless specified otherwise) refer to yields based on the parent 1,3-oxazolidin-5-ones. The $^1$H nmr spectra of the crude reaction mixtures show that in most cases, one diastereomer was formed preferentially.

**2-(t-Butyl)-4-(p-chlorophenylthio)-3-phenylacetyl-1,3-oxazolidin-5-one (5.13b)**

This was synthesized from oxazolidinone 5.13 (0.41g, 1.56 mmol) using the procedures outlined above. The product was purified by flash chromatography (ethyl acetate/hexane=1:5) to give 38% of compound 5.13b. The data below are for the major diastereomer which was identified by X-ray crystallography to have cis stereochemistry. (mp=149-151°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.03 (s, 9H), 3.68 (d, 1H, J=15 Hz), 3.89 (d, 1H, J=15 Hz), 5.17 (s, 1H), 5.86 (s, 1H), 6.96-7.7 (m, 9H); $^{13}$Cnmr (CDCl$_3$, 300MHz) $\delta$ 24.86, 37.18, 41.31, 63.77, 95.76, 127.63, 128.87, 129.03, 129.91, 131.33, 132.44, 134.66, 135.70, 170.68, 171.29; $\nu_{max}$ (CHCl$_3$) 2980, 1792, 1685, 1478, 1368, 1095, 1015 cm$^{-1}$; Anal. Calculated for C$_{21}$H$_{22}$CINO$_3$S: C 62.44, H 5.49, N 3.47, S 7.94, Cl 8.78. Found C 62.29, H 5.79, N 3.60, S 7.84, Cl 8.79.
2-(t-Butyl)-4-(p-chlorophenylthio)-3-trimethylacetyl-1,3-oxazolidin-5-one (5.14b)

The sulphur compound 5.14b was synthesized from the corresponding oxazolidinone 5.14 (0.44g, 1.92 mmol) using the procedures outlined above. This was purified by flash chromatography (ethyl acetate/hexane=1:5) in only 28% yield. The data below are for the major diastereomer. (mp=190-192°C); $^{1}$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.83 (s, 9H), 1.48 (s, 9H), 5.58 (s, 1H), 5.65 (d, 1H, J=1 Hz), 7.3-7.5 (m, 4H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.58, 29.01, 38.83, 43.22, 64.04, 95.63, 125.78, 129.87, 137.35, 137.75, 168.51, 184.40; $\nu$$_{max}$ (CHCl$_3$) 2970, 1790, 1660, 1478, 1012 cm$^{-1}$; Anal. Calculated for C$_{15}$H$_{24}$ClN$_{2}$O$_3$S: C 58.45, H 6.54, N 3.79, S 8.67, Cl 9.58. Found C 58.30, H 6.65, N 3.63, S 8.39, Cl 9.47.

From the corresponding bromo compound 5.15a (0.75g, 2.69 mmol) and p-chlorothiophenol (0.39g, 2.69 mmol), oxazolidinone 5.15b was obtained in 76% yield and was recrystallised from chloroform/ether. The data below are for the major diastereomer. (mp=102-103°C); $^{1}$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.03 (s, 9H), 1.16 (t, 3H, J=7 Hz), 2.25 (m, 1H), 2.60 (m, 1H), 5.13 (br., 1H), 5.85 (br., 1H), 7.3-7.7 (m, 4H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 8.66, 25.14, 27.90, 37.40, 64.39, 95.70, 129.7, 131.09, 134.92, 135.71, 170.56, 174.02; $\nu$$_{max}$ (CCl$_4$) 1800, 1700, 1480, 1292, 1200, 1190, 1100, 1018 cm$^{-1}$; Anal. Calculated for C$_{16}$H$_{20}$ClN$_{2}$O$_3$S: C 56.22, H 5.90, N 4.10, S 9.38. Found C 55.98, H 6.00, N 4.07, S 9.68.

2-(t-Butyl)-4-(p-chlorophenylthio)-3-octanoyl-1,3-oxazolidin-5-one (5.16b)

From oxazolidinone 5.16 (0.32g, 1.19 mmol) and following the procedures outlined above, oxazolidinone 5.16b was isolated in 55% yield by flash chromatography (ethyl acetate/hexane=1:5). The data below are for the major diastereomer. (mp=66-67°C); $^{1}$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.88 (m, 3H), 1.03 (s, 9H), 1.26-1.75 (m, 12H), 2.1-2.3 (m, 1H), 2.4-2.6 (m, 1H), 5.13 (br., 1H), 5.87 (br., 1H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 14.07, 22.59, 24.46, 25.13, 28.90, 29.08, 31.63, 34.64, 37.37, 64.69, 95.59, 129.78, 131.19, 134.94, 135.76,
2-((t-Butyl)-4-(p-chlorophenylthio)-3-phenoxycarbonyl-1,3-oxazolidin-5-one (5.17b)

This was synthesized from oxazolidinone 5.17 (0.22g, 0.83 mmol) using the procedures outlined above. The sulphur compound 5.17b was obtained in 51% isolated yield (flash chromatography, ethyl acetate/hexane=1:5). The data below are for the major diastereomer. $^1$Hnmr (CDCl$_3$, 200MHz) δ 1.11 (s, 9H), 5.50 (s, 1H), 5.71 (s, 1H), 7.0-7.7 (m, 9H); $^{13}$Cnmr (CDCl$_3$, 200MHz) δ 24.72, 37.06, 65.56, 96.63, 121.23, 126.57, 129.27, 129.76, 131.46, 135.95, 136.02, 150.37, 152.83, 170.07; $v_{\text{max}}$ (CHCl$_3$) 2980, 1790, 1740, 1475, 1350, 1330, 1300, 1165 cm$^{-1}$; Anal. Calculated for C$_{20}$H$_{20}$ClN$_2$O$_4$S: C 59.18, H 4.97, N 3.45, S 7.90, Cl 8.73. Found C 59.05, H 4.95, N 3.44, S 7.98, Cl 8.76.

General procedures for the reduction with tributyltin hydride or deuteride

The bromo- or sulphur- derivatives of 1,3-oxazolidin-5-ones were treated with tributyltin hydride or deuteride as described before for the 1,3-dioxolan-4-ones. The ratio of the isomers were determined from the integration of $^1$H nmr and/or $^2$H nmr spectra.

For the intramolecular reactions of 3-o-iodo or bromo-benzoyl 1,3-oxazolidin-5-ones 5.23 and 5.27, a 0.09 M solution of the oxazolidinone was refluxed in benzene while a solution of tributyltin deuteride was added dropwise with a syringe pump. The reaction mixture was evaporated after 4 hours and the product distribution determined by $^2$H nmr spectroscopy.
Reactions with tributylallyltin

4-Allyl-3-benzoyl-2-(t-butyl)-1,3-oxazolidin-5-one (5.20)

A solution of the bromo oxazolidinone 5.3a, tributylallyltin (1 equivalent) and AIBN in dry benzene was degassed. The reaction mixture was refluxed for several days and the reaction was monitored by $^1$H nmr spectroscopy. Then the reaction mixture was evaporated and subjected to chromatography to give a very poor yield of the product 5.20 (yield was <10%). The stereochemistry of the product isolated was determined by 2-D noesy experiments and was found to be trans. (mp=156-157°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.06 (s, 9H), 2.03 (br., 1H), 2.50 (d, 1H), 4.53 (d, 1H), 5.00 (d, 1H, J=14 Hz), 5.20 (d, 1H, J=9 Hz), 5.50 (m, 1H), 6.20 (br., 1H), 7.5-7.8 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 24.66, 34.98, 39.76, 58.49, 95.00, 121.65, 127.65, 128.97, 129.12, 132.06, 135.84, 170.76, 172.53; $\nu_{\max}$ (CCl$_4$) 2965, 1800, 1665, 1370, 1360, 1241, 1195, 1010 cm$^{-1}$; Anal. Calculated for C$_{17}$H$_{21}$N$_2$O$_3$: C 71.06, H 7.37, N 4.87. Found C 70.77, H 7.71, N 4.73.

3-Benzoyl-2-(t-butyl)-4-methylene-1,3-oxazolidin-5-one (5.33)

A solution of oxazolidinone 5.5 (1.53g, 5.86 mmol), NBS (2.09g, 11.7 mmol) and catalytic amounts of AIBN in dry carbon tetrachloride (55 ml) was refluxed under nitrogen. On completion of the reaction (~2 hours), the reaction mixture was cooled and the succinimide was filtered. The filtrate was evaporated under reduced pressure. The resulting residue was then taken up in acetone (130 ml) and to this was added sodium iodide (3.5g, 23.4 mmol). This was refluxed for 4 hours after which the reaction mixture was cooled, the excess sodium iodide filtered and the solution evaporated. The residue was dissolved in chloroform and washed once with sodium thiosulphate solution. The organic layer was then dried over magnesium sulphate and evaporated. The required dehydro compound 5.33 was isolated by flash chromatography with ether/hexane=1:5 (0.81g, 53%). The physical data agreed with the data reported in literature.²
The synthesis of (2S)-3-benzoyl-2-(t-butyl)-4-methylene-1,3-oxazolidin-5-one (5.33)

This was synthesized from cis-(2S, 4S)-3-benzoyl-2-(t-butyl)-4-methyl-1,3-oxazolidin-5-one (5.5) in the usual manner as that described above, to give (2S)-oxazolidinone 5.33 \([\alpha]_D^{23} = -186.4^\circ\) (CHCl\(_3\), c=0.8); literature value\(^2\) \([\alpha]_D^{20} = -148.6^\circ\) (CHCl\(_3\), c=0.68).

General procedure for the addition of alkyl radical to 5.33.

**Method 1: The mercury method**

To a solution of oxazolidinone 5.33 (0.23g, 0.89 mmol) was added cyclohexylmercury chloride (0.72g, 2.3 mmol) in 8 ml of dichloromethane. This was stirred vigorously at room temperature. A solution of sodium borohydride (0.34g in 7 ml of water) was added dropwise over 45 minutes and the reaction mixture was stirred for an additional 1.5 hours. Then the reaction mixture was filtered through celite and the organic layer was dried and evaporated to give the crude product. This was purified by flash chromatography (ether/hexane=1:5) to give the required product 5.34 (0.21g, 68% yield).

**Method 2: The tin method**

The dehydro compound 5.33 (0.23g, 0.89 mmol) and alkyl iodide (0.45 mmol) in dry benzene (5 ml) were degassed. The reaction mixture was then irradiated with UV light at room temperature while a solution of Bu\(_3\)SnH (0.447 mmol in 5 ml benzene) and AIBN was added slowly with a syringe pump at the rate of 0.15 ml/min. After 8-12 hours, the reaction mixture was evaporated and the diastereoselectivity of the reaction was determined by \(^1\)H and \(^13\)C nmr spectroscopy. Then the reaction mixture was chromatographed (ether/hexane=1:5). The reaction yields were determined relative to the alkyl halide.

3-Benzoyl-2-(t-butyl)-4-cyclohexylmethyl-1,3-oxazolidin-5-one (5.34)

When method 1 was used, oxazolidinone 5.34 was isolated in 68% yield (210mg) (yield based on alkene) when the above scale was used. With method 2, the
isolated yield (based on alkyl iodide) was 72%. The data below are for the major diastereomer (trans by analogy to oxazolidinone 5.35 and 5.36) isolated in the reaction. (mp=180-182°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.06 (s, 9H), 0.5-1.6 (m, 13H), 4.40 (dd, 1H, J=1.6, 7 Hz), 6.22 (s, 1H), 7.4-7.7 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 300MHz) $\delta$ 24.69, 25.65, 25.88, 25.96, 31.64, 32.66, 33.51, 38.60, 39.96, 59.79, 94.67, 127.51, 128.97, 131.96, 135.99, 170.96, 173.51; $\nu_{\text{max}}$ (CCl$_4$) 2930, 1798, 1660, 1448, 1380, 1358, 1248, 1195, 1150, 1050, 1010 cm$^{-1}$; M.S. (%) 286.1 (2.9), 105.0 (100.0), 77.1 (21.0); Exact mass calculated for C$_{17}$H$_{20}$N$_{0}$O$_{3}$ (M$^+$.57) is 286.1443. Found 286.1441.

3-Benzoyl-2-(t-butyl)-4-(2-phenylethyl)-1,3-oxazolidin-5-one (5.35)

This was synthesized by method 2 and oxazolidinone 5.35 was isolated in 69% yield (0.11g, ethyl acetate/hexane=1:5). The stereochemistry of the major isomer was determined by 1-D nOe and 2-D noesy experiments and was found to be trans. (mp=149-151°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.06 (s, 9H), 1.5-2.5 (m, 4H), 4.50 (dd, 1H, J=2, 6 Hz), 6.27 (s, 1H), 6.9-7.7 (m, 10H); $^{13}$Cnmr (CDCl$_3$, 300MHz) $\delta$ 24.74, 29.32, 33.19, 39.89, 58.41, 94.91, 126.30, 127.49, 128.21, 128.43, 129.14, 132.25, 135.69, 139.43, 170.86, 172.83; $\nu_{\text{max}}$ (CCl$_4$) 2970, 1798, 1700, 1660, 1378, 1365, 1355, 1245, 1200, 1150, 1045, 1010 cm$^{-1}$; Anal. Calculated for C$_{22}$H$_{25}$N$_{0}$O$_{3}$: C 75.19, H 7.17, N 3.99. Found C 75.26, H 7.20, N 3.84.

3-Benzyol-2-(t-butyl)-4-(2,2-dimethylpropyl)-1,3-oxazolidin-5-one (5.36)

This was isolated in 70% yield (0.10g, ethyl acetate/hexane=1:5) when method 2 was used. The stereochemistry of the major diastereomer (the data listed below) was found to be trans by 2-D noesy studies. (mp=162-163°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 0.74 (s, 9H), 1.01 (s, 9H), 1.60 (m, 2H), 4.43 (dd, 1H, J=2, 8 Hz), 6.13 (s, 1H), 7.5-7.7 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 300MHz) $\delta$ 24.69, 29.48, 30.23, 40.08, 45.45, 55.97, 94.75, 128.19, 129.24, 132.19, 136.46, 171.49, 173.64; $\nu_{\text{max}}$ (CCl$_4$) 2960, 1800, 1660, 1370, 1330, 1230, 1190, 1140, 1055, 1015 cm$^{-1}$; M.S.
(%) 260.1 (2.7), 188.1 (0.3), 105.0 (100.0), 77.1 (46.1), 57.1 (16.9); Exact mass calculated for C\textsubscript{15}H\textsubscript{18}N\textsubscript{O}\textsubscript{3} (M\textsuperscript{+}-57) is 260.1287. Found 260.1287.

3-Benzoyl-2-(t-butyl)-4-ethyl-1,3-oxazolidin-5-one (5.37)

This was synthesized by method 2 and was obtained in 60% isolated yield. The data below are for the major diastereomer (trans, by analogy to oxazolidinone 5.35 and 5.36) isolated from the reaction. 1Hnmr (CDCl\textsubscript{3}, 300MHz) δ 0.68 (t, 3H, J=7 Hz), 1.05 (s, 9H), 1.2-1.8 (m, 2H), 4.6 (dd, 1H, J=2, 5 Hz), 6.23 (s, 1H), 7.3-7.7 (m, 5H); 13Cnmr (CDCl\textsubscript{3}, 300MHz) δ 6.77, 24.53, 39.70, 47.35, 59.54, 94.97, 127.53, 129.27, 132.23, 136.15, 173.44, 180.38; \textit{v}_{\text{max}} (CHCl\textsubscript{3}) 2970, 1790, 1655, 1370, 1345, 1180, 1150, 1040, 1015 cm\textsuperscript{-1}; M.S. (%) 260.0 (0.1), 218.0 (4.2), 105.0 (100.0); Exact mass calculated for C\textsubscript{12}H\textsubscript{12}N\textsubscript{O}\textsubscript{3} (M\textsuperscript{+}-57) is 218.0817. Found 218.0819.

(2S,4R)-3-Benzoyl-2-(t-butyl)-4-cyclohexylmethyl-1,3-oxazolidin-5-one (5.34)

This was synthesized from the (2S)-dehydro compound 5.33 by both the tin method as well as the mercury method. The observed rotations were [\(\alpha\)]\textsubscript{D}\textsuperscript{23} = -94.5º (CHCl\textsubscript{3}, c=0.9) by the tin method and [\(\alpha\)]\textsubscript{D}\textsuperscript{23} = -94.9º (CHCl\textsubscript{3}, c=0.87) by the mercury method. (mp=202-204ºC).

References:

Experimental: Chapter 5, Section 5.2

Synthesis of 2-(t-butyl)-3-methyl-imidazolidin-4-ones

Imidazolidinones 5.43 and 5.48 have been described in the literature.\textsuperscript{1,2} The two methods described in the literature\textsuperscript{1,2} for the syntheses of imidazolidinones will be summarised here as some modifications have been used. Both methods have been tested and generally yields of the aminal were much better when method 1 was used.

Method 1\textsuperscript{1}

The required amino acid ester hydrochloride (50 mmol) was dissolved in 100 ml of ethanol which was added dropwise to a solution of 8 M methylamine in ethanol at 0°C over a period of one hour. The reaction mixture was warmed up to room temperature within 4 hours and was stirred for another 30 hours, after which 300 ml of ether was added and the reaction mixture cooled to -20°C to precipitate the amine salt that had been formed. The precipitate was filtered, washed and the filtrate was evaporated. The residue was dissolved in 40 ml of dichloromethane and was left standing at -20°C. This procedure was repeated twice.

The total filtrate was evaporated and to this, 100 ml of dichloromethane and 1.5 mol equivalent of pivaldehyde (or the corresponding aldehyde) was added and this was refluxed overnight with azeotropic distillation of water. The Schiff base obtained after evaporation of the solvent was identified by \textsuperscript{1}H nmr spectroscopy.

The crude compound was dissolved in 15 ml of methanol, cooled to 0°C, while a solution of 30 ml of methanol saturated with HCl was added via a double ended needle. This was stirred at 0°C for 30 minutes followed by 2 hours at room temperature. Upon evaporation, the crude cyclised aminal compound 5.41 was obtained. In some cases, the product was redissolved in dichloromethane and washed with aq. sodium hydroxide and then evaporated.
Method 2

The amino acid ester hydrochloride (0.2 mol) was added to 75 ml of 8 M ethanolic methylamine at 0°C and stirred for 16 hours at room temperature. Then the reaction mixture was concentrated and the resulting residue taken up in 40 ml of dichloromethane and concentrated. This was repeated 3 times. The residue after evaporation was redissolved in 50 ml of dichloromethane and 0.3 mol of pivaldehyde (or the corresponding aldehyde) and 0.3 mol of triethylamine was added and refluxed overnight under azeotropic distillation of water. After cooling, the mixture was filtered and the filter cake was washed with 100 ml of ether. The filtrate was concentrated, then redissolved in 60 ml of methanol and cooled to 0°C. To this, 120 ml of methanol that had been saturated with HCl was added slowly and stirred at 0°C for 30 minutes. After another two hours at room temperature, the mixture was concentrated, dissolved in 150 ml of dichloromethane and washed with 3 M sodium hydroxide and evaporated to give the crude aminal.

The reaction yields for these 2-(t-butyl)-3-methyl-imidazolin-4-ones 5.41 varied between 40-80%. The reason for this is unclear.

N-acylation of 2-(t-butyl)-3-methyl-imidazolidin-4-one

2 procedures have been used. Unless specified otherwise, method 2 was used.

Method 1:

To a vigorously stirred solution of the aminal 5.41 in dichloromethane at 0°C was added 1 equivalent of benzoyl chloride and 1 equivalent of 1 N sodium hydroxide. After 2 hours, the aqueous layer was separated and the organic phase was dried and evaporated.

Method 2:

The aminal 5.41 was dissolved in dichloromethane and cooled to 0°C. Triethylamine (2-4 equivalents) was added followed by 1 equivalent of the
corresponding acid chloride. This was stirred at room temperature for 16 hours after which the reaction mixture was filtered and the filtrate washed with cold dilute HCl, water, dried and evaporated.

2-(t-Butyl)-3-methyl-1-trimethylacetyl-imidazolidin-4-one (5.44)

From aminal 5.41 (R'=t-butyl, R=H) (1.56g, 10 mmol) and trimethylacetyl chloride (1 equivalent), imidazolidinone 5.44 was obtained (1.2g, 50% yield). This was purified by flash chromatography (ethyl acetate/hexane=3:5). (mp=169-170°C); 
$^{1}$Hnmr (CDCl₃, 500MHz) δ 1.00 (s, 9H), 1.20 (s, 9H), 3.06 (s, 3H), 4.10 (d, 1H, J=20 Hz), 4.25 (d, 1H, J=20 Hz), 5.54 (s, 1H); $^{13}$Cnmr (CDCl₃, 200MHz) δ 26.12, 27.87, 31.69, 39.51, 39.77, 51.13, 81.37, 169.69, 177.88; $\nu_{max}$ (CCl₄) 2970, 1728, 1658, 1480, 1398, 1370, 1355, 1300, 1260, 1225, 1210, 1175, 1120, 1005 cm⁻¹; Anal. Calculated for C₁₃H₂₄N₂O₂: C 64.97, H 10.06, N 11.66. Found C 64.96, H 10.42, N 11.59.

2-(t-Butyl)-3-methyl-1-phenylacetyl-imidazolidin-4-one (5.45)

From aminal 5.41 (R'=t-butyl, R=H) (1.56g, 10 mmol) and phenylacetyl chloride (1.54g, 9.98 mmol), the required imidazolidinone 5.45 was obtained and purified by flash chromatography (ethyl acetate/hexane=3:5) in 23% yield (0.63g). (mp=139-140°C); $^{1}$Hnmr (CDCl₃, 300MHz) δ 0.88 (s, 9H), 3.02 (s, 3H), 3.67 (d, 1H, J=15 Hz), 3.72 (d, 1H, J=15 Hz), 3.85 (d, 1H, J=15 Hz), 4.07 (d, 1H, J=15 Hz), 5.35 (s, 1H), 7.25-7.40 (m, 5H); $^{13}$Cnmr (CDCl₃, 300MHz) δ 26.04, 31.62, 39.95, 42.29, 50.20, 80.97, 127.23, 128.86, 128.95, 133.71, 169.25, 170.77; $\nu_{max}$ (CCl₄) 2970, 1720, 1670, 1482, 1410, 1388, 1370, 1300, 1255, 1120, 712 cm⁻¹; Anal. Calculated for C₁₆H₂₂N₂O₂: C 70.04, H 8.08, N 10.21. Found C 69.99, H 8.19, N 9.95.

2-(t-Butyl)-3-methyl-1-(1-naphthoyl)-imidazolidin-4-one (5.46)

The acid chloride was synthesized from 1-naphthoic acid (1.72g, 10 mmol) and oxalyl chloride (1.45g, 11.5 mmol) in the presence of catalytic amount of DMF.
The acid was not very soluble in dichloromethane but as the reaction proceeded, the reaction mixture became clear, indicating the formation of the acid chloride. From the aminal **5.41** (R'=t-butyl, R=H) (1.56g, 10 mmol), imidazolidinone **5.46** was obtained and purified by flash chromatography (ethyl acetate/hexane=2:5) in 60% yield. (mp=116-118°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.18 (s, 9H), 3.08 (s, 3H), 3.56 (d, 1H, J=16 Hz), 3.88 (d, 1H, J=16 Hz), 5.68 (s, 1H), 7.4-8.1 (m, 7H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 26.71, 31.66, 39.97, 51.98, 81.04, 124.52, 124.88, 125.84, 126.53, 127.47, 128.69, 129.41, 130.84, 132.70, 133.58, 169.23, 171.01; $\nu_{\text{max}}$ (CCL$_4$) 2970, 1720, 1665, 1510, 1480, 1408, 1365, 1300, 1253, 1150 cm$^{-1}$; Anal. Calculated for C$_{19}$H$_{22}$N$_2$O$_2$: C 73.52, H 7.14, N 9.03. Found C 73.21, H 7.22, N 8.75.

2-(t-Butyl)-3-methyl-1-(2-naphthoyl)-imidazolidin-4-one (**5.47**)  
This was synthesized from the crude aminal derived from glycine (**5.41**, R'=t-butyl, R=H) (1.56g, 10 mmol) and 2-naphthoyl chloride (1.91g, 10 mmol). Compound **5.47** was then purified by flash chromatography (ethyl acetate/hexane=2:5) in 32% (1g) yield. (mp=149-152°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.14 (s, 9H), 3.07 (s, 3H), 3.91 (d, 1H, J=16 Hz), 4.24 (d, 1H, J=16 Hz), 5.67 (s, 1H), 7.50-8.10 (m, 7H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 26.09, 31.64, 39.81, 53.10, 80.94, 124.43, 126.99, 127.85, 127.89, 128.57, 128.62, 128.71, 131.48, 132.41, 134.59, 169.26, 171.69; $\nu_{\text{max}}$ (CCL$_4$) 2970, 1720, 1665, 1510, 1480, 1408, 1365, 1300, 1253, 1150 cm$^{-1}$; M.S. (%) 253.1 (13.6), 155.0 (100.0), 127.0 (43.7), 77.1 (5.7), 57.1 (3.7); Exact mass calculated for C$_{15}$H$_{13}$N$_2$O$_2$ (M$^+$-57) is 253.0977. Found 253.0977.

1-Benzoyl-3-methyl-2-(i-propyl)-imidazolidin-4-one (**5.49**)  
The aminal **5.41** (R'=i-propyl, R=H) used was synthesized by method 2 from glycine methyl ester hydrochloride and isobutyraldehyde. The aminal (4.18g, 29 mmol) and benzoxy chloride (1 equivalent) (method 1 for N-acylation was used) afforded imidazolidinone **5.49** which was purified by flash chromatography (ethyl
acetate/hexane=4:5) (3.06g, 43% yield). (mp= 98-100°C); ¹Hnmr (CDCl₃, 200MHz) δ 0.99 (d, 3H, J=7 Hz), 1.08 (d, 3H, J=7 Hz), 2.32 (m, 1H), 2.94 (s, 3H), 3.87 (d, 1H, J=15 Hz), 4.09 (d, 1H, J=15 Hz), 5.72 (s, 1H), 7.30-7.7 (m, 5H); ¹³Cnmr (CDCl₃, 200MHz) δ 15.83, 17.39, 27.79, 32.21, 52.47, 77.61, 127.57, 128.42, 131.08, 134.76, 167.49, 170.85; vₙₐₓ (CCl₄) 2970, 1720, 1665, 1550, 1375, 1330, 1260, 1220, 1005, 980 cm⁻¹; Anal. Calculated for C₁₄H₁₈N₂O₂: C 68.27, H 7.37, N 11.37. Found C 68.10, H 7.62, N 11.16.

3-Methyl-2-(i-propyl)-1-trimethylacetyl-imidazolidin-4-one (5.50)

From the corresponding aminal 5.41 (R'=i-propyl, R=H) (4.26 g, 30 mmol) and trimethylacetyl chloride (30 mmol), imidazolidinone 5.50 (2.7g, 40% yield) was obtained. This was purified by either flash chromatography (ethyl acetate/hexane=7:10) or by recrystallisation to give colourless needles. (mp=129-130°C); ¹Hnmr (CDCl₃, 500MHz) δ 0.89 (d, 3H, J=7 Hz), 0.97 (d, 3H, J=7 Hz), 1.28 (s, 9H), 2.30 (m, 1H), 2.95 (s, 3H), 4.10 (d, 1H, J=15 Hz), 4.30 (d, 1H, J=15 Hz), 5.48 (t, 1H, J=2 Hz); ¹³Cnmr (CDCl₃, 200MHz) δ 16.56, 17.18, 27.43, 28.73, 32.10, 39.38, 50.86, 79.36, 168.24, 176.71; vₙₐₓ (CCl₄) 2970, 1720, 1648, 1480, 1410, 1400, 1365, 1261, 1220 cm⁻¹; Anal. Calculated for C₁₂H₂₂N₂O₂: C 63.69, H 9.80, N 12.38. Found C 63.83, H 10.22, N 12.44.

1-(α-Bromobenzoyl)-2-(t-butyl)-3-methyl-imidazolidin-4-one (5.51)

This was synthesized from aminal 5.41 (R'=t-butyl, R=H) (2.34g, 15 mmol) and 1 equivalent of α-bromobenzoyl chloride (synthesized immediately prior to use from α-bromobenzoic acid and oxalyl chloride). Compound 5.51 was purified by recrystallisation from ether to give 3.05g (60%) of a white solid. (mp=122-123°C); ¹Hnmr (CDCl₃, 300MHz) δ 1.13 (s, 9H), 3.07 (s, 3H), 3.61 (d, 1H, J=16 Hz), 4.01 (d, 1H, J=16 Hz), 5.49 (s, 1H), 7.3-7.7 (m, 4H); ¹³Cnmr (CDCl₃, 200MHz) δ 26.19, 31.71, 40.15, 50.80, 81.43, 118.99, 127.97, 128.86, 131.40, 133.25, 136.99, 168.91, 169.19; vₙₐₓ (CHCl₃) 2970, 1700, 1665, 1390, 1305, 1258, 1040,
908 cm\(^{-1}\); Anal. Calculated for C\(_{15}\)H\(_{19}\)BrN\(_2\)O\(_2\): C 53.11, H 5.65, N 8.26. Found C 53.05, H 5.72, N 8.20.

1-(o-Bromobenzoyl)-2-(t-butyl)-3,5-dimethyl-imidazolidin-4-one (5.55)

This was synthesized as above but starting from the aminal derived from alanine 5.41 (R'=t-butyl, R=CH\(_3\)) to afford imidazolidinone 5.55 which was separated by flash chromatography (ethyl acetate/hexane=2:5) in only 20% yield. This was obtained as a 1:1 mixture of isomers. The chemical shifts of the two isomers have not been differentiated and will be given here. \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 0.85 (d, 3H, J=6 Hz) and 1.03 (d, 3H, J=2 Hz), 1.14 (s, 9H) and 1.09 (s, 9H), 3.10 (s, 3H) and 3.10 (s, 3H), 4.40 (q, 1H) and 4.10 (q, 1H), 5.64 (s, 1H) and 5.67 (s, 1H), 7.3-7.8 (m, 8H); \(^{13}\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 18.15, 18.97, 26.26, 26.43, 32.03, 32.15, 40.73, 56.04, 56.76, 79.55, 80.92, 118.61, 121.46, 127.76, 127.99, 131.71, 133.07, 134.64, 138.41, 138.97, 168.21, 168.76, 172.19, 172.53; \(\nu\)\(^{\text{max}}\) (CHCl\(_3\)) 3300, 1700, 1640, 1515, 1480, 1388, 1255, 1170, 1030 cm\(^{-1}\); M.S. (%) 339.1 (0.2), 337.1 (0.2), 297.1 (31.1), 295.1 (32.8), 184.97 (96.8), 182.98 (100.0), 156.98 (12.5), 155.0 (12.7), 105.1 (27.5), 77.1 (23.4), 57.15 (14.7); Exact mass calculated for C\(_{12}\)H\(_{12}\)BrN\(_2\)O\(_2\) (M\(^+\)-57) is 295.0082. Found 295.0082.

2-(t-Butyl)-1-(o-iodobenzoyl)-3-methyl-imidazolidin-4-one (5.59)

From aminal derived from glycine 5.41 (R'=t-butyl, R=H) (2.34g, 15 mmol) and o-iodobenzoyl chloride (1 equivalent) was obtained imidazolidinone 5.59 which was recrystallised from dichloromethane/hexane (2.07g, 36% yield). (mp=157-159\(^0\)C); \(^1\)Hnmr (CDCl\(_3\), 200MHz) \(\delta\) 1.14 (s, 9H), 3.07 (s, 3H), 3.59 (d, 1H, J=16 Hz), 3.98 (d, 1H, J=16 Hz), 5.48 (s, 1H), 7.0-8.0 (m, 4H); \(^{13}\)Cnmr (CDCl\(_3\), 200MHz) \(\delta\) 26.14, 31.59, 40.06, 51.01, 81.35, 91.66, 128.13, 128.48, 131.11, 139.63, 141.06, 168.98, 170.23; \(\nu\)\(^{\text{max}}\) (CCl\(_4\)) 1720, 1665, 1550, 1380, 1255, 1220, 1005, 980 cm\(^{-1}\); Anal. Calculated for C\(_{15}\)H\(_{19}\)IN\(_2\)O\(_2\): C 46.65, H 4.96, N 7.25. Found C 46.73, H 5.26, N 7.16.
Synthesis of bromo imidazolidinones

The corresponding imidazolidin-4-one was treated with NBS (1 mol equivalent) in carbon tetrachloride in the presence of a catalytic amount of AIBN under reflux conditions for 30-45 minutes. The reaction mixture was then cooled, filtered and evaporated to give the crude bromo imidazolidin-4-one for which the 5-unsubstituted imidazolidinones were > 80% pure by $^1$H nmr spectroscopy. The bromo imidazolidin-4-ones were not stable to storage and were used immediately.

1-Benzoyl-5-bromo-2-(t-butyl)-3-methyl-imidazolidin-4-one (5.43a)

$^1$Hnmr (CDCl$_3$, 200MHz) δ 1.21 (s, 9H), 3.09 (s, 3H), 5.66 (s, 1H), 5.95 (s, 1H), 7.4-7.9 (m, 5H).

5-Bromo-2-(t-butyl)-3-methyl-1-trimethylacetyl-imidazolidin-4-one (5.44a)

$^1$Hnmr (CDCl$_3$, 200MHz) δ 1.14 (s, 9H), 1.43 (s, 9H), 3.07 (s, 3H), 5.60 (s, 1H), 6.54 (s, 1H).

5-Bromo-2-(t-butyl)-3-methyl-1-phenylacetyl-imidazolidin-4-one (5.45a)

$^1$Hnmr (CDCl$_3$, 200MHz) δ 1.12 (s, 9H), 3.05 (s, 3H), 3.90 (d, 1H, J=15 Hz), 4.05 (d, 1H, J=15 Hz), 5.41 (s, 1H), 6.46 (s, 1H), 7.25-7.45 (m, 5H).

5-Bromo-2-(t-butyl)-3-methyl-1-(1-naphthoyl)-imidazolidin-4-one (5.46a)

$^1$Hnmr (CDCl$_3$, 300MHz) δ 1.28 (s, 9H), 3.11 (s, 3H), 5.78 (s, 1H), 5.83 (s, 1H), 7.4-8.0 (m, 7H).

5-Bromo-2-(t-butyl)-3-methyl-1-(2-naphthoyl)-imidazolidin-4-one (5.47a)

$^1$Hnmr (CDCl$_3$, 200MHz) δ 1.26 (s, 9H), 3.10 (s, 3H), 5.74 (s, 1H), 6.03 (s, 1H), 7.5-8.5 (m, 7H).
Synthesis of sulphur imidazolidin-4-ones

This was prepared in two different ways: method 2 gives high yields but both methods were used depending on the availability of starting materials at the time of synthesis. The yields of the reactions below have not been optimised.

Method 1:

To a solution of p-chlorothiophenol (1 equivalent) in dry benzene was added DBU (0.98 mol equivalent). A freshly prepared solution of the corresponding bromo imidazolidin-4-one in benzene was then added and immediately, a precipitate was formed. This was stirred for a further 30 minutes, filtered and washed with dilute HCl, water, dried and evaporated. The yields of the sulphur imidazolidin-4-ones synthesized by this method were poor (varying from 20-50% isolated yields). The products from the reaction also depended on the reaction time. When stirring was continued for longer periods, 2 diastereomers were detected in a ratio of ca. 1:1. Thus, in most cases, the reactions were worked up as soon as possible. For most of the cases below, only the chemical shift of one diastereomer (the major) is given. The stereochemistry of the major isomer for derivatives 5.43b and 5.44b was determined to be trans by nOe methods.

Method 2:

This was the method predominantly used for the synthesis of sulphur imidazolidinones where the bromo imidazolidinones were difficult to synthesize or handle. This can be used for the synthesis of all the sulphur imidazolidinones as high yields were usually obtained (>70% yields in most cases). A 1:1 mixture of diastereomers were obtained by this method when 5-unsubstituted imidazolidinones were used.

A 0.17 M solution of imidazolidinone 5.42 in THF was cooled to -70°C and to this a solution of 1.2 equivalents of 1 M LDA added dropwise. In most but not all cases, a colour change was observed. After stirring for 30 minutes at -70°C, diphenyldisulfide (1.5 equivalent, 0.5 M solution) was added slowly and the reaction
was warmed up to 0°C within 2.5 hours and stirred overnight at that temperature. The reaction mixture was then poured into a cold half-saturated solution of ammonium chloride, extracted with ether (2 x 100 ml), washed with water, dried and evaporated.

**1-Benzoyl-2-(t-butyl)-5-((p-chlorophenylthio)-3-methyl-imidazolidin-4-one (5.43b)**

This was synthesized from the corresponding bromo imidazolidinone by method 1 in 48% isolated yield. The ratio of the diastereomers after stirring for 1 hour was 4:1 whereas after stirring for 16 hours, the ratio of diastereomers was ca 1:1. The data below are for the major diastereomer (assigned as *trans* by 2-D noesy experiments) isolated from the reaction after an hour. (mp=199-202°C); ¹Hnmr (CDCl₃, 200MHz) δ 1.97 (s, 9H), 2.63 (s, 3H), 5.26 (s, 1H), 5.37 (s, 1H), 7.4-7.7 (m, 9H); ¹³Cnmr (CDCl₃, 200MHz) δ 26.21, 31.71, 40.56, 68.77, 80.20, 127.62, 127.90, 128.96, 131.87, 136.14, 136.99, 137.19, the other aromatic carbon was not detected, 166.86, 172.77; νₘₐₓ (CCl₄) 2970, 1720, 1670, 1480, 1350, 1345, 1140, 1098 cm⁻¹; Anal. Calculated for C₂₁H₂₃C₁N₂O₂S: C 62.60, H 5.75, N 6.95, Cl 8.80. Found C 62.37, H 5.95, N 6.88, Cl 9.06.

**1-Benzoyl-2-(t-butyl)-3-methyl-5-phenylthio-imidazolidin-4-one**

To compare the 2 methods for the synthesis of the sulphur imidazolidinones, the phenylthio-imidazolidinone was synthesized starting from imidazolidinone 5.43 and diphenyldisulphide (method 2 was used) in 80% isolated yield. The data given below are for the 2 diastereomers obtained from the reaction and the stereochemistry of one isomer (*trans*) was determined by 2-D noesy; ¹Hnmr (CDCl₃, 200MHz) cis-isomer δ 1.19 (s, 9H), 3.09 (s, 3H), 4.83 (s, 1H), 5.62 (s, 1H), 7.15-7.8 (m, 10H) and *trans*-isomer δ 0.97 (s, 9H), 2.55 (s, 3H), 5.25 (d, 1H, J=1.5 Hz), 5.42 (d, 1H, J=1.5 Hz), 7.25-7.73 (m, 10H). For each isomer, exact mass calculated for C₁₇H₁₅N₂O₂S (M⁺-57) is 311.0854. Found 311.0852.
2-(t-Butyl)-5-(p-chlorophenylthio)-3-methyl-1-trimethylacetyl-imidazolidin-4-one

(5.44b)

The ratio of the two diastereomers formed after an hour was 2.2:1. The sulphur imidazolidinone 5.44b was isolated in only 10% yield. Only the data for the major diastereomer (assigned as trans by 2-D noesy studies) are given below. (mp= 197-202°C); \(^1\text{Hnmr} (\text{CDCl}_3, 200\text{MHz}) \delta 0.84 (s, 9\text{H}), 1.48 (s, 9\text{H}), 2.40 (s, 3\text{H}), 5.16 (d, 1\text{H}, J=2 \text{ Hz}), 5.55 (d, 1\text{H}, J=2 \text{ Hz}); \(^{13}\text{Cnmr} (\text{CDCl}_3, 200\text{MHz}) \delta 26.15, 29.39, 31.59, 39.88, 43.35, 67.56, 80.70, 126.97, 129.03, 136.52, 137.99, 166.52, 184.52; \nu_{\text{max}} (\text{CCl}_4) 2960, 1720, 1655, 1475, 1170, 1092, 1015 \text{ cm}^{-1}; \text{Anal. Calculated for} \text{C}_{19}\text{H}_{27}\text{ClN}_{2}\text{O}_{2}\text{S:} \text{C} 59.59, \text{H} 7.11, \text{S} 8.37. \text{Found} \text{C} 59.40, \text{H} 7.26, \text{S} 8.41.

2-(t-Butyl)-5-(p-chlorophenylthio)-3-methyl-1-phenylacetyl-imidazolidin-4-one

(5.45b)

This was synthesized by method 1 from the bromo imidazolidinone 5.45a in 38% isolated yield. As before, only the data for the major diastereomer are given (the stereochemistry was not established but was assumed to be trans by analogy to the stereochemistry of other sulphur imidazolidinones synthesized by method 1). (mp=211-214°C); \(^1\text{Hnmr} (\text{CDCl}_3, 200\text{MHz}) \delta 0.75 (s, 9\text{H}), 2.44 (s, 3\text{H}), 4.15 (d, 1\text{H}, J=15 \text{ Hz}), 4.33 (d, 1\text{H}, J=15 \text{ Hz}), 4.95 (d, 1\text{H}, J=1.7 \text{ Hz}), 5.11 (d, 1\text{H}, J=1.7 \text{ Hz}), 7.25-7.5 (m, 9\text{H}); \(^{13}\text{Cnmr} (\text{CDCl}_3, 200\text{MHz}) \delta 26.26, 31.85, 41.06, 45.71, 66.75, 80.36, 126.60, 127.43, 128.82, 129.17, 129.67, 134.17, 136.73, 137.79, 166.49, 173.48; \nu_{\text{max}} (\text{CCl}_4) 2970, 2930, 1725, 1680, 1480, 1400, 1370, 1355, 1138, 1098 \text{ cm}^{-1}; \text{Anal. Calculated for} \text{C}_{22}\text{H}_{25}\text{ClN}_{2}\text{O}_{2}\text{S:} \text{C} 63.37, \text{H} 6.04, \text{N} 6.72, \text{Cl} 8.50. \text{Found} \text{C} 63.38, \text{H} 6.09, \text{N} 6.42, \text{S} 7.92, \text{Cl} 8.81.

2-(t-Butyl)-5-(p-chlorophenylthio)-3-methyl-1-(1-naphthoyl)-imidazolidin-4-one

(5.46b)

This was synthesized by method 1 and was isolated in only 20% yield. The assignment of stereochemistry is tentative and was made by analogy to the chemical
shifts of the *cis*- and *trans*-isomers of imidazolidinone **5.43b**. The ratio of diastereomers (*trans*: *cis*) after an hour was 2.6:1. *cis*-isomer (mp=176-178°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.25 (s, 9H), 3.14 (s, 3H), 4.86 (br., 1H), 5.68 (s, 1H), 6.67-7.78 (m, 11H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 27.06, 31.84, 37.63, 68.89, 80.94, 124.62, 126.66, 127.39, 128.52, 128.66, 129.19, 130.00, 131.46, 132.09, 133.43, 168.91, 172.07; $\nu_{\text{max}}$ (CCl$_4$) 2970, 1718, 1675, 1475, 1400, 1345, 1205, 1092, 1015 cm$^{-1}$; Anal. Calculated for C$_{25}$H$_{25}$ClN$_2$O$_2$S: C 66.29, H 5.56, N 6.18, S 7.08, Cl 7.83. Found C 66.28, H 5.90, N 6.02, S 6.80, Cl 7.73. The chemical shifts ($^1$H nmr) of the *trans*-isomer is as follows: $\delta$ 1.09 (s, 9H), 2.73 (s, 3H), 5.43 (s, 1H), 5.52 (s, 1H), 7.0-8.5 (m, 11H).

2-(t-Butyl)-5-(p-chlorophenylthio)-3-methyl-1-(2-naphthoyl)-imidazolidin-4-one (**5.47b**)  

This was synthesized by method 1 and was isolated in 44% yield. The assignment of stereochemistry is tentative and was made by analogy to the chemical shifts of the *cis*- and *trans*-isomers of imidazolidinone **5.43b**. *cis*-isomer $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.21 (s, 9H), 3.12 (s, 3H), 4.87 (s, 1H), 5.66 (s, 1H), 6.8-8.3 (m, 11H). The physical data for the *trans*-isomer are shown below: (mp=221-224°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 1.05 (s, 9H), 2.73 (s, 3H), 5.40 (s, 1H), 5.50 (s, 1H), 7.1-8.1 (m, 11H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 26.29, 31.82, 40.62, 69.23, 80.31, 124.57, 127.01, 127.90, 128.05, 128.11, 128.85, 129.06, 132.65, 134.12, 134.85, 135.94, 136.70, 167.02, 172.90; $\nu_{\text{max}}$ (CCl$_4$) 2930, 1720, 1672, 1550, 1255, 1220, 1008, 980 cm$^{-1}$; Anal. Calculated for C$_{25}$H$_{25}$ClN$_2$O$_2$S: C 66.29, H 5.56, N 6.18, S 7.08, Cl 7.83. Found C 66.34, H 5.85, N 6.16, S 7.11, Cl 7.72.

1-Benzoyl-2-(t-butyl)-3,5-dimethyl-5-phenylthio-imidazolidin-4-one (**5.48b**)  

Only one diastereomer (79% isolated yield) was obtained from the reaction starting from the imidazolidinone **5.48** by method 2. The stereochemistry of this compound is assumed to be *trans* by analogy to the alkylation studies by Seebach.  

$^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.94 (s, 9H), 1.74 (s, 3H), 2.36
(s, 3H), 5.20 (s, 1H), 7.2-7.7 (m, 10H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 26.43, 27.11, 31.55, 39.23, 75.61, 79.65, 127.73, 128.75, 129.19, 129.93, 130.31, 131.07, 136.89, 138.29, 168.54, 176.13; $\nu_{\text{max}}$ (CCl$_4$) 2980, 1720, 1665, 1480, 1400, 1325, 1310, 1265, 1152, 1125, 700 cm$^{-1}$; Anal. Calculated for C$_{22}$H$_{26}$N$_2$O$_2$S: C 69.08, H 6.85, N 7.32, S 8.38. Found C 69.04, H 6.88, N 7.43, S 8.66.

1-Benzoyl-5-(p-chlorophenylthio)-3-methyl-2-(i-propyl)-imidazolidin-4-one (5.49b)

This was synthesized by method 1. $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.89 (d, 3H, J=7 Hz), 1.01 (d, 3H, J=7 Hz), 2.42 (m, 1H), 2.63 (s, 3H), 4.92 (m, 1H), 5.40 (d, 1H, J= 1.5 Hz), 7.3-7.8 (m, 9H); $\nu_{\text{max}}$ (CHCl$_3$) 1710, 1665, 1480, 1380, 1370, 1340, 1098, 1018 cm$^{-1}$; Anal. Calculated for C$_{20}$H$_{21}$ClN$_2$O$_2$S: C 61.77, H 5.44, N 7.20, S 8.24, Cl 9.12. Found C 61.52, H 5.31, N 7.12, S 8.16, Cl 9.09.

3-Methyl-5-phenylthio-2-(i-propyl)-1-trimethylacetyl-imidazolidin-4-one (5.50b)

This was synthesized by method 2 in 35% isolated yield and was obtained as a 1:1 mixture of isomers. The data below are for the isomer which recrystallised out preferentially (ether/chloroform). The stereochemistry has not been established. (mp= 148-150°C); $^1$Hnmr (CDCl$_3$, 200MHz) $\delta$ 0.69 (d, 3H, J=7 Hz), 0.87 (d, 3H, J=7 Hz), 1.46 (s, 9H), 2.38 (s, 3H), 2.1 (m, 1H), 4.65 (s, 1H), 5.65 (s, 1H), 7.3-7.6 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 200MHz) $\delta$ 15.03, 18.04, 28.18, 29.02, 30.81, 42.60, 66.93, 79.24, 128.18, 128.91, 130.10, 136.86, 166.06, 181.63; $\nu_{\text{max}}$ (CCl$_4$) 2870, 1725, 1650, 1550, 1490, 1440, 1408, 1395, 1360, 1310, 1255, 1180, 1005, 980, 910 cm$^{-1}$; Anal. Calculated for C$_{18}$H$_{26}$N$_2$O$_2$S: C 64.64, H 7.83, N 8.38. Found C 64.65, H 8.13, N 8.43, S 9.28. The $^1$H nmr chemical shifts for the other isomer is $\delta$ 1.04 (d, 3H, J=2Hz), 1.08 (d, 3H, J=2 Hz), 1.29 (s, 9H), 2.1 (m, 1H), 3.02 (s, 3H), 5.36 (d, 1H, J=4 Hz), 5.45 (s, 1H), 7.3-7.6 (m, 5H).
Reduction of sulphur- or bromo-imidazolidinones with tributyltin hydride or deuteride.

This was done in the manner described before for the derivatives of oxazolidinones.

**Synthesis of 1-Benzoyl-2-(t-butyl)-3-methyl-5-methylene-imidazolidin-4-one (5.60)**

1-Benzoyl-2-(t-butyl)-3,5-dimethyl-imidazolidin-4-one (5.48) (0.35 g, 1.28 mmol) (a mixture of isomers was used) was treated with 2 equivalents of NBS in 15 ml carbon tetrachloride for 1-2 hours. The succinimide formed in the reaction was filtered and the reaction mixture was evaporated. This was redissolved in 30 ml acetone, sodium iodide (0.77 g, 5.1 mmol) was added and the reaction mixture refluxed for 4 hours. Then the reaction mixture was filtered and evaporated. The resulting residue was taken up in chloroform, washed with sodium thiosulphate, dried and evaporated to give imidazolidinone 5.60 which was subsequently purified by flash chromatography (ethyl acetate/hexane=2:5) in 49% yield (0.170 g). 

\[ \text{Hnmr (CDCl3, 200MHz)} \delta 1.06 (s, 9H), 3.17 (s, 3H), 4.16 (br., 1H), 5.25 (d, 1H, J=1.6 Hz), 5.63 (s, 1H), 7.50 (s, 5H); \text{Cnmr (CDCl3, 200MHz)} \delta 25.91, 31.92, 39.87, 79.06, 98.75, 127.53, 128.60, 131.12, 135.36, 136.52, 163.86, 170.56; \nu_{max} (CCL4) 2960, 1715, 1672, 1345, 1295, 1270, 1145, 885 \text{ cm}^{-1}; \text{M.S. (%) 272.2 (0.2), 215.1 (8.3), 105.0 (100.0), 77.1 (32.5); Exact mass calculated for C12H11N2O2 (M+-57) is 215.0821. Found 215.0821.} \]

Addition of alkyl radicals to dehydro compound 5.60

The two methods used have been described earlier in similar addition reactions with oxazolidinones.

**Method: The Mercury method.**

The reaction of the dehydro imidazolidinone 5.60 (0.12 g, 0.45 mmol) and cyclohexylmercury chloride (0.35 g, 1.09 mmol) gave the addition product 5.61 in only 25% isolated yield (purified by flash chromatography, ethyl acetate/hexane=2:5).
From, the $^1$H nmr spectrum of the crude reaction mixture, it was apparent that only half of the alkene was consumed.

**Method: The Tin method.**

The reaction of alkene **5.60** (0.10g, 0.38 mmol) and cyclohexyl iodide (40.6 mg, 25 µl, 0.19 mmol) afforded imidazolidinone **5.61** which was purified by flash chromatography in 44% yield (ethyl acetate/hexane=2:5).

**1-Benzoyl-2-(t-buty)-5-cyclohexylmethyl-3-methyl-imidazolidin-4-one (5.61)**

(mp= 172-173°C); $^1$Hnmr (CDCl$_3$, 300MHz) $\delta$ 1.07 (s, 9H), 0.5-1.60 (m, 13H), 3.08 (s, 3H), 4.32 (d, 1H, J=6 Hz), 5.66 (s, 1H), 7.4-7.7 (m, 5H); $^{13}$Cnmr (CDCl$_3$, 300 MHz) $\delta$ 25.74, 25.83, 25.99, 26.20, 31.64, 31.95, 32.68, 33.50, 38.16, 41.07, 59.67, 80.08, 127.89, 128.96, 131.73, 136.96, 171.64, 172.58; $\nu_{max}$ (CHCl$_3$) 2930, 1700, 1640, 1450, 1410, 1380, 1365 cm$^{-1}$; Anal. Calculated for C$_{22}$H$_{32}$N$_2$O$_2$: C 74.12, H 9.05, N 7.86. Found C 73.75, H 9.37, N 7.87.

**References:**

APPENDICES
Appendix A: X-ray crystal structure of 2-(t-butyl)-5-(p-chlorophenylthio)-5-methyl-1,3-dioxolan-4-one
Supplementary data to Appendix A:

X-ray data for 2-(t-butyl)-5-(p-chlorophenylthio)-5-(methyl)-1,3-dioxolan-4-one.

Selected Interatomic Distances (Å) and Angles (°) for dioxolanone 4.24.

<table>
<thead>
<tr>
<th>Bond/Distance</th>
<th>Value</th>
<th>Bond/Distance</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-C(8)</td>
<td>1.734</td>
<td>S-C(1)</td>
<td>1.809</td>
</tr>
<tr>
<td>S-C(5)</td>
<td>1.775</td>
<td>O(1)-C(1)</td>
<td>1.434</td>
</tr>
<tr>
<td>O(1)-C(2)</td>
<td>1.415</td>
<td>O(2)-C(2)</td>
<td>1.457</td>
</tr>
<tr>
<td>O(2)-C(3)</td>
<td>1.340</td>
<td>O(3)-C(3)</td>
<td>1.191</td>
</tr>
<tr>
<td>C(1)-C(3)</td>
<td>1.526</td>
<td>C(1)-C(4)</td>
<td>1.521</td>
</tr>
<tr>
<td>C(2)-C(11)</td>
<td>1.513</td>
<td>C(5)-C(6)</td>
<td>1.388</td>
</tr>
<tr>
<td>C(5)-C(10)</td>
<td>1.384</td>
<td>C(6)-C(7)</td>
<td>1.374</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.370</td>
<td>C(8)-C(9)</td>
<td>1.377</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.374</td>
<td>C(11)-C(12)</td>
<td>1.517</td>
</tr>
<tr>
<td>C(11)-C(13)</td>
<td>1.528</td>
<td>C(11)-C(14)</td>
<td>1.520</td>
</tr>
<tr>
<td>C(1)-S-C(5)</td>
<td>102.76</td>
<td>C(1)-O(1)-C(2)</td>
<td>106.42</td>
</tr>
<tr>
<td>C(2)-O(2)-C(3)</td>
<td>108.8</td>
<td>S-C(1)-O(1)</td>
<td>110.59</td>
</tr>
<tr>
<td>S-C(1)-C(3)</td>
<td>113.7</td>
<td>S-C(1)-C(4)</td>
<td>107.7</td>
</tr>
<tr>
<td>O(1)-C(1)-C(3)</td>
<td>102.1</td>
<td>O(1)-C(1)-C(4)</td>
<td>111.8</td>
</tr>
<tr>
<td>C(3)-C(1)-C(4)</td>
<td>110.9</td>
<td>O(1)-C(2)-O(2)</td>
<td>104.2</td>
</tr>
<tr>
<td>O(1)-C(2)-C(11)</td>
<td>112.9</td>
<td>O(2)-C(2)-C(11)</td>
<td>111.8</td>
</tr>
<tr>
<td>O(2)-C(3)-O(3)</td>
<td>123.3</td>
<td>O(2)-C(3)-C(1)</td>
<td>107.8</td>
</tr>
<tr>
<td>O(3)-C(3)-C(1)</td>
<td>128.8</td>
<td>S-C(5)-C(6)</td>
<td>120.6</td>
</tr>
<tr>
<td>S-C(5)-C(10)</td>
<td>120.2</td>
<td>C(6)-C(5)-C(10)</td>
<td>119.1</td>
</tr>
<tr>
<td>C(5)-C(6)-C(7)</td>
<td>120.5</td>
<td>C(6)-C(7)-C(8)</td>
<td>119.7</td>
</tr>
<tr>
<td>Cl-C(8)-C(7)</td>
<td>119.7</td>
<td>Cl-C(8)-C(9)</td>
<td>119.7</td>
</tr>
<tr>
<td>C(7)-C(8)-C(9)</td>
<td>120.6</td>
<td>C(8)-C(9)-C(10)</td>
<td>119.8</td>
</tr>
<tr>
<td>C(5)-C(10)-C(9)</td>
<td>120.3</td>
<td>C(2)-C(11)-C(12)</td>
<td>111.6</td>
</tr>
<tr>
<td>C(2)-C(11)-C(13)</td>
<td>107.5</td>
<td>C(2)-C(11)-C(14)</td>
<td>107.2</td>
</tr>
<tr>
<td>C(12)-C(11)-C(13)</td>
<td>110.4</td>
<td>C(12)-C(11)-C(14)</td>
<td>110.7</td>
</tr>
<tr>
<td>C(13)-C(11)-C(14)</td>
<td>109.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix B: X-ray crystal structure of 2-(t-butyl)-4-(p-chlorophenylthio)-3-(phenylacetyl)-1,3-oxazolidin-5-one.
Supplementary data to Appendix B:
X-ray data for 2-((t-butyl)-4-(p-chlorophenylthio)-3-(phenylacetyl)-1,3-oxazolidin-5-one (5.13b).

Selected Interatomic Distances (Å) and Angles (°) for oxazolidinone 5.13b.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
<th>Bond</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-C(14)</td>
<td>1.738</td>
<td>S-C(1)</td>
<td>1.849</td>
</tr>
<tr>
<td>S-C(11)</td>
<td>1.781</td>
<td>C(1)-C(2)</td>
<td>1.487</td>
</tr>
<tr>
<td>C(1)-N(5)</td>
<td>1.455</td>
<td>C(11)-C(12)</td>
<td>1.372</td>
</tr>
<tr>
<td>C(11)-C(16)</td>
<td>1.37</td>
<td>C(12)-C(13)</td>
<td>1.38</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.36</td>
<td>C(14)-C(15)</td>
<td>1.36</td>
</tr>
<tr>
<td>C(15)-C(16)</td>
<td>1.39</td>
<td>C(2)-O(2)</td>
<td>1.200</td>
</tr>
<tr>
<td>C(2)-O(3)</td>
<td>1.347</td>
<td>O(3)-C(4)</td>
<td>1.440</td>
</tr>
<tr>
<td>C(4)-C(41)</td>
<td>1.536</td>
<td>C(4)-N(5)</td>
<td>1.471</td>
</tr>
<tr>
<td>C(41)-C(42)</td>
<td>1.52</td>
<td>C(41)-C(43)</td>
<td>1.521</td>
</tr>
<tr>
<td>C(41)-C(44)</td>
<td>1.52</td>
<td>N(5)-C(51)</td>
<td>1.372</td>
</tr>
<tr>
<td>C(51)-O(51)</td>
<td>1.227</td>
<td>C(51)-C(52)</td>
<td>1.51</td>
</tr>
<tr>
<td>C(52)-C(53)</td>
<td>1.488</td>
<td>C(53)-C(54)</td>
<td>1.36</td>
</tr>
<tr>
<td>C(53)-C(58)</td>
<td>1.35</td>
<td>C(54)-C(55)</td>
<td>1.38</td>
</tr>
<tr>
<td>C(55)-C(56)</td>
<td>1.31</td>
<td>C(56)-C(57)</td>
<td>1.30</td>
</tr>
<tr>
<td>C(57)-C(58)</td>
<td>1.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(1)-S-C(11)</td>
<td>102.1</td>
<td>S-C(1)-C(2)</td>
<td>111.9</td>
</tr>
<tr>
<td>S-C(1)-N(5)</td>
<td>111.5</td>
<td>C(2)-C(1)-N(5)</td>
<td>103.8</td>
</tr>
<tr>
<td>S-C(11)-C(12)</td>
<td>118.2</td>
<td>S-C(11)-C(16)</td>
<td>121.4</td>
</tr>
<tr>
<td>C(12)-C(11)-C(16)</td>
<td>120.0</td>
<td>C(11)-C(12)-C(13)</td>
<td>119.9</td>
</tr>
<tr>
<td>C(12)-C(13)-C(14)</td>
<td>119.6</td>
<td>Cl-C(14)-C(15)</td>
<td>119.7</td>
</tr>
<tr>
<td>Cl-C(14)-C(15)</td>
<td>119.1</td>
<td>C(13)-C(14)-C(15)</td>
<td>121.2</td>
</tr>
<tr>
<td>C(14)-C(15)-C(16)</td>
<td>119.5</td>
<td>C(11)-C(16)-C(15)</td>
<td>119.7</td>
</tr>
<tr>
<td>C(1)-C(2)-O(2)</td>
<td>127.4</td>
<td>C(1)-C(2)-O(3)</td>
<td>109.8</td>
</tr>
<tr>
<td>O(2)-C(2)-O(3)</td>
<td>122.8</td>
<td>C(2)-O(3)-C(4)</td>
<td>111.7</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle</td>
<td>Bond</td>
<td>Angle</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td>----------------------</td>
<td>--------</td>
</tr>
<tr>
<td>O(3)-C(4)-C(41)</td>
<td>109.9</td>
<td>O(3)-C(4)-N(5)</td>
<td>104.5</td>
</tr>
<tr>
<td>C(41)-C(4)-N(5)</td>
<td>117.0</td>
<td>C(4)-C(41)-C(42)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(41)-C(43)</td>
<td>111.5</td>
<td>C(4)-C(41)-C(44)</td>
<td>107.7</td>
</tr>
<tr>
<td>C(42)-C(41)-C(43)</td>
<td>109.5</td>
<td>C(42)-C(41)-C(44)</td>
<td>109.2</td>
</tr>
<tr>
<td>C(43)-C(41)-C(44)</td>
<td>109.4</td>
<td>C(1)-N(5)-C(4)</td>
<td>109.0</td>
</tr>
<tr>
<td>C(1)-N(5)-C(51)</td>
<td>124.9</td>
<td>C(4)-N(5)-C(51)</td>
<td>119.5</td>
</tr>
<tr>
<td>N(5)-C(51)-O(51)</td>
<td>120.2</td>
<td>N(5)-C(51)-C(52)</td>
<td>117.0</td>
</tr>
<tr>
<td>O(51)-C(51)-C(52)</td>
<td>122.8</td>
<td>C(51)-C(52)-C(53)</td>
<td>111.5</td>
</tr>
<tr>
<td>C(52)-C(53)-C(54)</td>
<td>120.0</td>
<td>C(52)-C(53)-C(58)</td>
<td>122.4</td>
</tr>
<tr>
<td>C(54)-C(53)-C(58)</td>
<td>117.6</td>
<td>C(53)-C(54)-C(55)</td>
<td>122</td>
</tr>
<tr>
<td>C(54)-C(55)-C(56)</td>
<td>114</td>
<td>C(55)-C(56)-C(57)</td>
<td>132</td>
</tr>
<tr>
<td>C(56)-C(57)-C(58)</td>
<td>111</td>
<td>C(53)-C(58)-C(57)</td>
<td>123</td>
</tr>
</tbody>
</table>
Appendix C: 2-D Noesy spectrum of 1-benzoyl-2-(t-butyl)-3-methyl-1,3-imidazolidin-4-one (5.43).
Appendix D: 2-D Noesy spectrum of 2-(t-butyl)-1-phenylacetyl-3-methyl-1,3-imidazolidin-4-one (5.45).
Addendum

p. 5, Figures in Scheme 1.3 should be as follows:

\[
\begin{align*}
\text{CN} & \quad \text{OCH}_3 \\
\iff \\
\text{CN} & \quad \text{OCH}_3
\end{align*}
\]

(1.6)

(1.7)

p. 12, Figures in Scheme 1.10 should be as follows:

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{SBut} & \quad \text{CN}
\end{align*}
\]

(1.21)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{SBut}^t
\end{align*}
\]

(1.22)

p. 12, line 16 should read ‘...than that with a single donor substituent’

p. 67, line 13 should read ‘... 3.2 is 138 compared to a value of 0.29 for abstraction at the acetal position of 3.4).’

p. 74, line 18 should read ‘...splitting by only three protons of the t-butyl group.’

p. 81, line 5 ‘t-butylmethylether’ should read ‘t-butyl methyl ether’

p.81, line 6 ‘di-t-butylperoxide’ should read ‘di-t-butyl peroxide’

p.81, line 6 ‘chloromethylacetate’ should read ‘methyl chloroacetate’

p. 81, line 8 ‘bromomethylacetate’ should read ‘methyl bromoacetate’

p. 85, lines 7 and 8 ‘di-t-butylperoxide’ should read ‘di-t-butyl ketone’

pg. 132, section 4.4e ‘hydrolysis’ should read ‘methanolysis’

p. 132, line 14 should read ‘...authentic sample of methyl mandelate could be made easily by stirring mandelic acid in MeOH ...’

p. 153, line 8 ‘benzyloxycarbonyl’ should read ‘benzyloxy carbonyl’

pg. 160, line 16 should read ‘....it is possible that the radical derived from the cyclic amino acid is more stable...’

p. 183, line 13 should read ‘....to the dehydro compound in situ which could be subsequently isolated.’