Acyclic Stereocontrol in the Claisen Rearrangement

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January 2010

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Imperial College London.
Abstract

This thesis examines the issues of acyclic stereocontrol in the Claisen rearrangement, with particular emphasis on the effects of exopericyclic stereocentres – i.e. those adjacent to the array of atoms directly involved in the sigmatropic process. It is divided into three main parts:

The first section provides a review of the field of acyclic stereocontrol. The models used to explain the development of relationships between stereocenters in systems lacking well-defined conformational constraints are discussed. This is an established field and particular emphasis is given to recent developments in the modelling of such systems.

The second section discusses the results of our studies. Previous examples of exopericyclic stereocontrol in sigmatropic rearrangements are shown. Studies are presented that explore the importance of heteroatom-bearing stereocenters and effects of olefin substitution pattern on the manner and extent of stereoselectivity. Our efforts to exploit these stereochemical effects in the synthesis of small molecules are then presented. A novel reaction sequence is presented in which equilibrating mixtures of allylic azides undergo stereoselective Claisen rearrangements and further chemistry of the products of this transformation is then explored. These studies, and attempts to deploy them in synthesis allow us to draw conclusions on the nature of acyclic stereocontrol in the Claisen rearrangement.

The third section contains experimental procedures and characterisation data for all compounds prepared.
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Declaration

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of this thesis has been submitted previously for a degree at this, or any other university.
Acknowledgements

Firstly, I would like to thank Professor Donald Craig for his guidance, support and sharing of his deep passion for Organic Synthesis.

This work has been partially funded by an industrial CASE award from Pfizer Ltd. I would like to thank my industrial supervisor John Harvey for his continued support of this project, particularly during a placement in his laboratory. Additionally, I would like to thank the chemists of Pfizer Global Research and Development, Sandwich for fruitful discussions.

The DC Group, in all their various forms are thanked for their friendship, for taking my unrelenting abuse of their good nature in their stride and for rapid proofreading of this thesis. I am particularly indebted to both Dr. Jason Camp and Dr. Stephen Johns for sharing with me their considerable experience.

I am grateful to Pete Haycock and Dick Sheppard for their expert NMR analysis, Dr. Andrew White for crystallography studies, John Barton for mass spectrometry and Professor Henry Rzepa for helpful discussions.
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<td>aq</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BBN</td>
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</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
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<tr>
<td>bp</td>
<td>boiling point</td>
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<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>BRSM</td>
<td>based on recovered starting material</td>
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<td>DBU</td>
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<td>DCC</td>
<td>N,N′-dicyclohexylcarbodiimide</td>
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dCr          decarboxylative Claisen rearrangement
Deoxofluor  bis(2-methoxyethyl)aminosulfur trifluoride
DFT         density functional theory
DHP         dihydropyran
DIBAL-H     diisobutylaluminium hydride
DMAP        4-dimethylaminopyridine
DME         dimethoxyethane
DMF         N,N-dimethylformamide
DMS         dimethylsulfide
DMSO        dimethylsulfoxide
dr          diastereomeric ratio
EI          electrical ionisation
equiv       equivalents
E_rel       relative energy
ESI         electrospray ionisation
Et          ethyl
EWG         electron withdrawing group
h           hours
Hex         hexyl
HMBC        heteronuclear multiple bond correlation
HMPA        hexamethylphosphoramide
HOMO        highest occupied molecular orbital
i-          ipso
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<td>isopropanol</td>
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<tr>
<td>$K_a$</td>
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<td>LDA</td>
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<td>LHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
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<tr>
<td>Lig</td>
<td>ligand</td>
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<tr>
<td>LUMO</td>
<td>lowest occupied molecular orbital</td>
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<td>$m$-</td>
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<td>NBSH</td>
<td>$ortho$-nitrobenzenesulfonylhydrazide</td>
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<td>NMO</td>
<td>$N$-methylmorpholine $N$-oxide</td>
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<td>ortho</td>
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<td>para</td>
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<td>PDC</td>
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<td>PNB</td>
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<td>pyridinium para-toluenesulfonate</td>
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<tr>
<td>TBAF</td>
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<td>TBDMS</td>
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<td>TBDPS</td>
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<td>TBME</td>
<td>tert-butylmethyl ether</td>
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<tr>
<td>TEA</td>
<td>triethylamine</td>
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<td>TES</td>
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<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>THP</td>
<td>tetrahydropyran</td>
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<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
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<tr>
<td>Ts</td>
<td>\textit{para}-toluenesulfonyl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
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<tr>
<td>v</td>
<td>volume</td>
</tr>
<tr>
<td>w</td>
<td>weight</td>
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Stereochemical notation

The Maehr convention for indicating relative and absolute stereochemistry has been used throughout this thesis. Solid and broken lines are used to denote racemates, while solid and broken wedges denote absolute configuration. Narrowing of the wedges implies increasing distance from the reader in the latter case.

![Racemate and Single enantiomer](image.png)
Chapter 1

Recent advances in acyclic stereocontrol
1.1 Introduction

1.1.1 Background and scope of the review

The issue of stereochemical control is central to the development of organic synthesis; in particular, the influence of a pre-existing stereocentre upon the new stereocentres established during a reaction is of key importance. Control of the relationship between two or more stereocentres is readily achieved in cyclic systems in which rigorous conformational constraints are imposed; while control of the relationship between stereocentres is more difficult to achieve in acyclic systems that lack such conformational rigidity. Nevertheless, in the 115 years since Fischer’s original report on the stereoselective addition of hydrogen cyanide to aldoses, the patterns governing acyclic stereocontrol have been intensely investigated and modelled. As a consequence of the continuing development of new stereoselective reactions and advances in computational techniques this remains an active area of interest in organic synthesis, with direct relevance to both the synthesis of small molecules and complex biologically active targets.

Although the work presented in this thesis concentrates on particular aspects of acyclic stereocontrol in the Claisen rearrangement, it is appropriate to give a review of the state of the art in this whole field. This review concentrates on the development of models for predicting the sense of acyclic stereocontrol, particularly over the last 10 years. Three major classes of reaction have been reviewed: addition of nucleophiles to carbonyls, addition of both electrophiles and nucleophiles to C=C double bonds, and pericyclic reactions. A brief account of acyclic stereocontrol in reactions of functional groups adjacent to organometallic complexes is given. We concentrate only on the relationships between adjacent stereocentres. Remote acyclic stereocontrol is beyond the scope of this review. Reactions involving chiral auxiliaries, and strategies for establishing absolute asymmetric induction are not covered. Individual examples of acyclic stereocontrol in the Claisen rearrangement are given a more detailed treatment in Chapter 2 of this thesis.
1.1.2 Stereochemical definitions

The term ‘acyclic stereocontrol’ appears to have a somewhat flexible definition in the literature, and below is an attempt to define the term. While a particular reaction may establish a relationship between stereocentres in an acyclic molecule, this can be a result of highly ordered cyclic transition states. As an example, the relationships between pseudoequatorial and pseudoaxial substituents in cyclic Zimmerman–Traxler transition states that determine stereoselectivity in the aldol reaction are an example of cyclic stereocontrol; while the stereoselectivity of nucleophilic addition to a carbonyl adjacent to a stereocentre is an example of acyclic stereocontrol (Scheme 1).

![Scheme 1](image)

A similar dichotomy is shown in the two Claisen rearrangements below (Scheme 2). Although both cases result in acyclic products, in the Ireland–Claisen rearrangement the relative configuration of the two new stereocentres formed during the sigmatropic process is controlled by the relative geometries of the vinylic and allylic portions of the ketene acetal, because the reaction occurs via a cyclic transition state. Conversely, as will be discussed in depth in this thesis, the relationship between a stereocentre outside the pericyclic array and the new C—C bond formed during a Claisen rearrangement $3 \rightarrow 4$ is a function of acyclic stereocontrol.
Therefore, acyclic stereocontrol refers to reactions where the reacting moiety is free to undergo rotation relative to a pre-existing stereocentre but adopts a preferred reactive conformation. Reaction can then occur from either one of two diastereotopic faces as determined by transition state interactions.
1.2 Nucleophilic addition to carbonyls with an adjacent stereocentre

1.2.1 Historical basis of models

Although the historical development of this area has been comprehensively reviewed, a brief overview is given here to aid further discussion, particularly as recent discussions of stereocontrol remain based on these models. In 1952, Cram reported an analysis of 1,2-asymmetric induction in the addition of nucleophiles to carbonyl compounds bearing an adjacent stereocentre. In this case, the largest (L) group adopts a conformation anti to the carbonyl group for steric reasons. The nucleophile then attacks preferentially from the side of the small (S) substituent. The outcome of the reaction is modified if chelation (usually mediated by a metal) between the carbonyl oxygen and one of the substituents on the adjacent stereocentre is possible. The large (L) substituent now eclipses the carbonyl group, yet attack still preferentially occurs from the side of the small (S) substituent (Scheme 3).

The Cram model is generally reliable in its explanation for the diastereoselectivity of carbonyl addition reactions unless polar substituents are present on the adjacent stereocentre. Cornforth, studying the reaction of Grignard reagents and alkyllithiums with α-chloroketones noted that the α-chloro group took the role of the large substituent, even if more sterically demanding substituents were also present. In a Cram-type model, this represents a nearly eclipsing arrangement between the carbonyl dipole and the C—Cl bond. The conformation with antiparallel alignment of the C=O and C—Cl dipoles was suggested. In the same fashion as the Cram model,
attack of the nucleophile then occurs from the side of the smaller substituent (Scheme 4).

![Scheme 4](image)

Karabatsos suggested a transition state model 10 and highlighted the importance of the nucleophile attacking along the less hindered trajectory. An alternative interpretation was given by Felkin, who suggested that if a either Karabatsos or Cram-type transition state was assumed, increasing the size of the large group would lead to a reduction in stereoselectivity due to strain between the L and R substituents. This is not born out experimentally and an investigation into lithium aluminium hydride reduction of ketones adjacent to a stereocentre, in combination with an examination of polar effects suggested the reaction was best described by a staggered transition state 11. In this case, the largest, or most electronegative group lies perpendicular to the plane of the carbonyl, antiparallel to the approach of the nucleophile. Additionally, the staggered Felkin transition state 11 is preferable to the analogous Cram transition state 9 in that it leads directly to the more stable staggered conformation of the product (Scheme 5).

![Scheme 5](image)

Refinements to the model were made by Anh and Eisenstein, who investigated the individual factors involved in attack of the nucleophile antiperiplanar to the largest or most donating group. Arrangement of the C2—L bond perpendicular to the carbonyl group results in overlap of the C2—L σ* and C=O π*orbitals, lowering the energy of
Recent advances in acyclic stereocontrol

the LUMO. Antiperiplanar attack of the nucleophile then gives a more favourable overlap with the combination of orbitals than synperiplanar attack (Scheme 6).

Scheme 6

Computational evidence suggested that the Bürgi–Dunitz angle\(^\text{10}\) should be taken into account (Scheme 7) in agreement with approach of the nucleophile along the least hindered trajectory, reconciling the model with those of Cram and Karabatsos. The combination of the above refinements is now referred to as the polar Felkin–Anh model, and it persists as a widely accepted explanation for acyclic stereocontrol in addition of nucleophiles to carbonyls with adjacent stereocenters.

Scheme 7

1.2.2 Acyclic stereocontrol adjacent to a cyclic transition state

The most important recent developments in attack on carbonyls with an adjacent stereocentre have arisen from investigations into allylboration of aldehydes with an
adjacent stereocentre, and aldol reactions of boron enolates derived from ketones with aldehydes bearing an adjacent stereocentre. Mengel and Reiser have reviewed earlier work in this area.\textsuperscript{4d} In these reactions, stereoselectivity has been rationalised using a combination of the Zimmerman–Traxler and Felkin–Anh models. This is an example of acyclic stereocontrol occurring adjacent to a well-defined, cyclic transition state. Parallels can be drawn with exopericyclic stereocontrol in sigmatropic rearrangements, for which similar transition states are proposed; therefore a discussion of the literature in this area is highly relevant to our studies.

Both Roush\textsuperscript{11} and Gennari\textsuperscript{12} have discussed this area. A transition state analysis is presented in Scheme 8. For each reaction with \(E\)- or \(Z\)-enolates, Zimmerman–Traxler transition states establish the relationship between C2 and C3 in line with the prediction. The relationship between C3 and C4 is determined by acyclic stereocontrol. While reactions of \(E\)-enolates give the product predicted by the Felkin–Anh model, the opposite ‘anti Felkin’ diastereomer is the major product of reaction of \(Z\)-enolates. According to Roush, the dominant stereocontrol element determining aldehyde diastereofacial selectivity is the minimisation of gauche-pentane interactions in the competing transition states. For \(Z\)-enolates the Felkin–Anh transition state 14 contains an unfavourable syn-pentane interaction. A rotation of the aldehyde bond to the adjacent stereocentre of 120° partially relieves this interaction (transition state 15), but this is still destabilised relative to the anti Felkin transition state 16 by a gauche pentane interaction. The case for \(E\)-enolates is somewhat simpler, since the Felkin–Anh transition state 17 contains the fewest gauche pentane interactions and also benefits stereoelectronically from the antiperiplanar alignment of the forming C—C and aldehyde C—R bonds. Hoffmann and Roush have reported similar diastereoselectivity patterns in allylation reactions.\textsuperscript{13}

There have been recent reports of additions of nucleophiles to carbonyls adjacent to a polar stereocentre, where the stereoselectivity is also poorly rationalised by the polar Felkin–Anh model. Indeed, numerous authors have suggested that Cornforth-type transition states, where the polar substituent is orientated antiparallel to the carbonyl group, minimising dipolar interactions might better explain such reactions.\textsuperscript{14}
 Recent advances in acyclic stereocontrol

Transition States for Z(O)-Enolate Aldol Reactions

Transition States for E(O)-Enolate Aldol Reactions

Scheme 8
1.2.3 Recent evidence for the Cornforth model

The dichotomy between Felkin–Anh and Cornforth transition states in the context of allylation reactions was investigated by Gung in 2001 using ab initio computational methods. For the reaction of allylboronic acid 20 with 2-methoxypropanal 19, the relative energies of the Felkin–Anh 22 and Cornforth 21 transition states (which both lead to the same product 23) were calculated, with the former being higher in energy by 1.27 kcal/mol (Scheme 9). The criterion for the Felkin–Anh model, that the nucleophile approaches antiperiplanar to the αC—O bond is poorly satisfied in this case. This deviation is attributed to conformational factors, particularly a syn-pentane interaction between the axial vinyl protons of the allylboron moiety and the α-methyl group of the aldehyde. In light of these results the authors calculated the energies of individual fragments of the transition states with frozen geometry. However, they did not find any evidence of charge separation between the αC—O and carbonyl groups that would be expected for a Cornforth transition state. They concluded that the relative energies of the Felkin–Anh and Cornforth transition states were a function of conformational constraints only.

![Scheme 9](image)

Cornforth transition state models have found continued use in the study of diastereoselective allylation and crotylation reactions. In 2003, Batey reported the diastereoselective allylation and crotylation of α- and β-siloxy substituted aldehydes under phase transfer conditions, which was used in a total synthesis of the anti-obesity drug tetrahydrolipstatin. Both E- and Z- potassium allyl- and crotyltrifluoroborates
25 reacted with α-tert-butyldimethylsiloxy aldehydes 24 to give, in all but one case, the 2,3-anti product 26 in uniformly high yield (Scheme 10, Table 1).

The major product 2,3-anti-26 derived from a Cornforth transition state (TS A) for reactions of Z-crotyl trifluoroborates (entries 3 and 5), while the same product derived from a Felkin–Anh type transition state (TS C) in the reactions of an E-crotyl trifluoroborate (entry 6) in agreement with the predictions of Roush.11,13a The analogous behaviour when R3=Me was unexplained by the authors, but would suggest a greater gauche-pentane interaction between the allyl group and the aldehyde α-methyl than between the allyl group and the α-siloxy substituent. Lower selectivity was observed in allylation reactions (entries 1 and 2), presumably resulting from less significant syn-pentane interactions in the transition state leading to 2,3-syn-26 (TS B) (Scheme 11).
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Detailed studies of Cornforth transition states for the aldol reaction which combine experimental and computational data, have been performed. However, experimental discrimination between Cornforth and polar Felkin–Anh models is difficult, particularly as both often predict the same product. An experiment which would differentiate between the two models was proposed by Evans. As shown in the above examples of allylation and aldol reactions, such discrimination is possible when the nucleophile imposes a conformational constraint on the orientation of the stereocentre adjacent to the electrophilic carbonyl. For reactions of $E$- and $Z$-enolates, both Felkin–Anh and Cornforth transition states were proposed that lead to the 3,4-anti product 27. The 2,3-relationship was set by the choice of $E$- or $Z$-boron enolate, the geometries of which are reliably reflected in the product stereochemistry. Lithium enolates were also included for generality, although they are inherently less diastereoselective (in defining the 2,3-relationship) (Scheme 12).

**Scheme 12**

In the prediction of the polar Felkin–Anh model, the $Z$-enolate substituent causes a destabilising syn-pentane interaction, while the $E$-enolate substituent experiences no such interaction. Therefore, $E$-enolates are predicted to give superior 3,4-anti selectivity relative to $Z$-enolates. Conversely, in the prediction of the Cornforth model, $E$-enolate substituent causes a destabilising syn-pentane interaction, while the $Z$-enolate substituent experiences no such interaction. Therefore, $Z$-enolates are predicted to give superior 3,4-anti selectivity relative to $E$-enolates. Thus, the $E$- and $Z$-boron and lithium enolates of 2-methyl-3-pentanone 28 were combined with a
representative set of $\alpha$-oxy-substituted aldehydes 29 (Scheme 13, Table 2). In general, relative to Z-enolates, the E-isomers showed greatly diminished selectivity for the 3,4-anti diastereomer, in support of the Cornforth model.

**Aldol reactions of Z-enolates**

![Diagram of Aldol reactions of Z-enolates]

**Aldol reactions of E-enolates**

![Diagram of Aldol reactions of E-enolates]

Scheme 13

<table>
<thead>
<tr>
<th>Scheme 13</th>
</tr>
</thead>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Aldol reactions of Z-enolates</th>
<th>Aldol reactions of E-enolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Met</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>9-BBN</td>
<td>Bn</td>
</tr>
<tr>
<td>9-BBN</td>
<td>Bn</td>
</tr>
<tr>
<td>9-BBN</td>
<td>TBS</td>
</tr>
<tr>
<td>9-BBN</td>
<td>TBS</td>
</tr>
<tr>
<td>Li</td>
<td>Bn</td>
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<tr>
<td>Li</td>
<td>Bn</td>
</tr>
<tr>
<td>Li</td>
<td>TBS</td>
</tr>
<tr>
<td>Li</td>
<td>TBS</td>
</tr>
</tbody>
</table>

More recently, Evans has performed a theoretical investigation of boron enolate addition to $\alpha$-heteroatom-substituted aldehydes, comparing polar Felkin–Anh and Cornforth transition state models using DFT methods.18,19 Highly electronegative substituents (F, OMe, Cl) and less electronegative substituents (PMe$_2$, SMe, NMe$_2$) were assessed. For the halopropanals 31 (X=F, Cl) transition states leading to both anti- (TS A and C) and syn-32 (TS B and D) were calculated. For di- and tri-valent heteroatoms, where rotamers of the C—X bond are possible, only the transition states leading to the anti product were calculated (Scheme 14, Table 3). The relative energies of Cornforth and Felkin–Anh transition state structures are highly dependent on the nature of the heteroatom substituent, with chlorine, fluorine and oxygen...
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substituents favouring the Cornforth arrangement and nitrogen, sulfur and phosphorus substituents favouring the polar Felkin–Anh arrangement.

![Scheme 14](image)

**Table 3**

<table>
<thead>
<tr>
<th>X</th>
<th>Cornforth</th>
<th>Polar Felkin–Anh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS A</td>
<td>TS B</td>
</tr>
<tr>
<td>F</td>
<td>166</td>
<td>196</td>
</tr>
<tr>
<td>$\varphi$ (deg)</td>
<td>166</td>
<td>196</td>
</tr>
<tr>
<td>$E_{rel}^a$</td>
<td>0.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Cl</td>
<td>175</td>
<td>186</td>
</tr>
<tr>
<td>$\varphi$ (deg)</td>
<td>175</td>
<td>186</td>
</tr>
<tr>
<td>$E_{rel}^a$</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>OMe</td>
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<tr>
<td>$\varphi$ (deg)</td>
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</tr>
<tr>
<td>$E_{rel}^a$</td>
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</tr>
<tr>
<td>SMe</td>
<td>174</td>
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<tr>
<td>$\varphi$ (deg)</td>
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</tr>
<tr>
<td>$E_{rel}^a$</td>
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<tr>
<td>NMe$_2$</td>
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<td>-</td>
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<tr>
<td>$\varphi$ (deg)</td>
<td>172</td>
<td>-</td>
</tr>
<tr>
<td>$E_{rel}^a$</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>PMe$_2$</td>
<td>175</td>
<td>-</td>
</tr>
<tr>
<td>$\varphi$ (deg)</td>
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<td>-</td>
</tr>
<tr>
<td>$E_{rel}^a$</td>
<td>3.5</td>
<td>-</td>
</tr>
</tbody>
</table>

*Calculated using the B3LYP method with the 6-31G(d) basis set. Energies are given in kcal/mol.

Further analysis suggested that the nucleophile→$\sigma^*_{C-X}$ interaction central to the polar Felkin–Anh model was energetically insignificant in reactions of carbonyls with boron enolate nucleophiles. However, it was shown that when X=SMe and X=PMe$_2$
perpendicular alignment of the C—X bond with the carbonyl group (as in the Felkin–Anh model) was favoured due to $\sigma^*_{C-X} \rightarrow \pi^*_{C=O}$ delocalisation. Transition states were also calculated for the above aldol reactions$^{17}$ in good agreement with experimental data. This work by Evans represents perhaps the most in-depth study in this area to date, and aspects of this methodology have been recently employed in the synthesis of the natural product (+)-peluroside A.$^{20}$

Similar relationships of Cornforth models with heteroatom electronegativity are evident in the investigations of Marco into doubly diastereoselective aldol reactions$^{21}$ of L-erythulose derivatives with aldehydes bearing an adjacent stereocentre.$^{22}$ In the most striking case, aldehydes bearing $\alpha$-fluoro- and $\alpha$-benzyloxy groups reacted via Cornforth transition states, while $\alpha$-amino aldehydes reacted via anti-Felkin–Anh transition states. In these cases, the non-stereogenic ketone 33 was used to form the corresponding Z-boron enolate 34. Additional conformational constraints are placed on the transition states by the dipolar repulsion between the enolate C—O and remaining $\alpha$-C—OTBS bonds resulting in an antiperiplanar alignment (Scheme 15). Aldehydes bearing $\alpha$-methyl groups were also studied, which reacted via Felkin–Anh transition states as predicted, although computational investigations by other groups have recently suggested that Felkin–Anh models might not be as generally applicable for attack on carbonyls adjacent to non-heteroatomic stereocentres.$^{23}$

1.2.4 Conclusions

As the above discussion demonstrates, modelling of nucleophilic addition to carbonyls adjacent to a stereocentre is still a highly active area of development, with numerous studies over the last 10 years that challenge the dominance of the Felkin–Anh model.$^{24}$ Additional factors must be taken into account when the acyclic stereocontrol arises from the presence of stereocentres adjacent to well-defined transition states. In short, the rotational conformation around the $\alpha$-stereocentre is dependent on the nature of the nucleophile. Additionally, although the Felkin–Anh model is still useful, its theoretical basis remains in question.$^{25}$ There is no one model that reliably describes all cases. However, in the case of polar stereocentres, there has been a resurgence in use of the Cornforth model to describe diastereoselectivity.$^{26}$
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Reactions of Z-enolates

\[
\begin{align*}
33 & \xrightarrow{\text{cHex}_2\text{BCl, TEA}} 34 \\
\text{OBn} & \xrightarrow{\text{Et}_2\text{O, 0 °C}} \text{OBcHex}_2
\end{align*}
\]

More electronegative

\[
\begin{align*}
34 & \xrightarrow{X = \text{OBn, F}} \\
35 & \xrightarrow{\text{Cornforth}} 36 \\
\text{OBn} & \xrightarrow{\text{anti-Felkin–Anh}} 36
\end{align*}
\]

Major (\(X = \text{OBn}\)) Only product (\(X = \text{F}\))

Minor (\(X = \text{OBn}\)) Not formed (\(X = \text{F}\))

Less electronegative

\[
\begin{align*}
34 & \xrightarrow{X = \text{NBen}_2} \\
37 & \xrightarrow{\text{Cornforth}} 38 \\
\text{Ph} & \xrightarrow{\text{anti-Felkin–Anh}} 38
\end{align*}
\]

Minor

Major

Scheme 15
1.3 Addition to C=C double bonds with an adjacent stereocentre

The case for addition of both nucleophiles and electrophiles to olefins is somewhat more complicated than for analogous reactions with carbonyls. Felkin–Anh-type models provide a theoretical basis for these reactions where the carbonyl group is replaced by a C=C double bond (Scheme 16).\(^{27}\) However, additional conformational constraints are imposed by the double bond substituents and the level of acyclic stereocontrol is often highly dependent on the double bond substitution pattern. As for the previous section, this area has been reviewed relatively recently by both Reiser\(^{4d}\) and Fleming\(^{36}\) (\textit{vide infra}). A brief historical treatment is given, followed by accounts of recent developments.

![Scheme 16](image)

1.3.1 Electrophilic Addition

Calculations of torsional effects in additions of electrophiles to substituted butenes by Houk suggested that staggered transition states were preferred in additions of electrophiles to C=C double bonds adjacent to a stereocentre.\(^{28}\) Attack of the electrophile in these systems occurs perpendicular to the double bond; deviations from this trajectory suffered large energy penalties. Therefore, the lowest-energy structure is that in which the stereocentre exerts the least hindrance to the incoming electrophile, or in an alternative view, that which interacts least with the forming bond. For hydroboration,\(^{29}\) this corresponds to the staggered transition state 39 with the smaller (S) substituent pointing ‘inside’ the double bond, and attack \textit{anti} to the L group. This conformation has the additional advantage of minimising 1,3-allylic strain. Notably, this corresponds to the \textit{anti}-Felkin product 41, as in the example of Kishi (Scheme 17).\(^ {30}\)
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Kishi reported similar results in the osmylation of protected and unprotected allylic alcohols 42 (Scheme 18, Table 4, showing selected examples). The selectivity is rationalised by invoking the Houk model. The increased selectivity upon switching from $E$- to $Z$-allylic double bond geometry is clear indication of the importance of 1,3-allylic strain in this model. As we will see, 1,3-allylic strain is perhaps the most important control element in additions to C=C double bonds, and is a component of most models. This subject has been reviewed in detail by Hoffmann. 32

| Entry | R          | $E/Z$ | 3,4-anti : 3,4-syn-
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>$E$</td>
<td>$3.3 : 1$</td>
</tr>
<tr>
<td>2</td>
<td>C(O)CMe$_1$</td>
<td>$E$</td>
<td>$4.2 : 1$</td>
</tr>
<tr>
<td>3</td>
<td>TBDPS</td>
<td>$E$</td>
<td>$3.1 : 1$</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>$Z$</td>
<td>$6.1 : 1$</td>
</tr>
<tr>
<td>5</td>
<td>C(O)CMe$_1$</td>
<td>$Z$</td>
<td>$6.3 : 1$</td>
</tr>
<tr>
<td>6</td>
<td>TBDPS</td>
<td>$Z$</td>
<td>$8.0 : 1$</td>
</tr>
</tbody>
</table>

In a more recent example Donohoe has reported that $syn$ selectivity is possible in osmylations of unsaturated alcohols 44 in the presence of TMEDA, which further illustrates the importance of 1,3-allylic strain for acyclic stereocontrol in additions to...
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C=C double bonds.\textsuperscript{33} The OsO$_4$–TMEDA conditions, which exploit OH–O=Os hydrogen-bonding\textsuperscript{34} were compared with the substoichiometric OsO$_4$–NMO ‘Upjohn’ conditions (Scheme 19, Table 5).

\begin{align*}
\text{Scheme 19}
\end{align*}

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
Entry & R & R$_E$ & R$_Z$ & \textbf{Upjohn Conditions} & \textbf{Donohoe Conditions} \\
\hline
1 & nPr & H & H & Ratio & Yield (%) & Ratio & Yield (%) \\
2 & nPr & nPr & H & 25 : 75 & 80 & 60 : 40 & 74 \\
3 & nPr & tBu & H & 25 : 75 & 85 & 75 : 25 & 83 \\
4 & tPr & nPr & H & 17 : 83 & 83 & 80 : 20 & 75 \\
5 & nPr & H & nPr & 20 : 80 & 75 & 75 : 25 & 84 \\
6 & tBu & H & nPr & 20 : 80 & 75 & 75 : 25 & 84 \\
7 & tBu & Me & Me & 66 : 34 & 96 & 96 : 4 & 78 \\
\hline
\end{tabular}
\caption{Table 5}
\end{table}

Transition states were proposed to account for these selectivity patterns (Scheme 20). The increase in magnitude of the observed syn selectivity on switching from E- to Z-isomers under Donohoe conditions is explained by TS A and TS B. In both, the hydrogen-bonding interaction is maintained that leads to attack of the oxidant from the same face as the alcohol. However, although TS B, which leads to the anti product satisfies the conditions for hydrogen-bonding, it is disfavoured by 1,3-allylic strain between the R and R$_Z$ groups. Therefore, when the R$_Z$ substituent is non-hydrogen, reaction via TS A, which leads to the syn product is favoured. Similar transition states TS C/D can be proposed to account for the reversal in selectivity under Upjohn conditions. Although selectivity is comparatively low under these conditions, the preferred anti products from reaction of E-allylic alcohols can be formed via TS C in which the R group eclipses the double bond. Conversely, TS D must be invoked for oxidation of Z-allylic alcohols to minimise 1,3-allylic strain.\textsuperscript{35}
This is defined by in a recent review by Fleming as the ‘inside methyl’ effect,\textsuperscript{36} where, in systems lacking a significant 1,3-allylic strain component, the major product can arise from a transition state in which the smallest group does not eclipse the double bond (cf. \textbf{TS B/D}, Scheme 20). Its occurrence is highly dependent upon both the substrate and reaction in question. The effect is also observed in nucleophilic additions.

### 1.3.2 Nucleophilic additions

The majority of studies in this area have concentrated on the conjugate addition of organocuprate nucleophiles to enoates \textsuperscript{46} bearing a $\gamma$-stereocentre, in particular due to the use of this method in the synthesis of polypropionate building blocks for natural products.\textsuperscript{37} A summary of models for describing this reaction has recently been published by Kornienko.\textsuperscript{38} In the case of $\gamma$-alkoxy and $\gamma$-siloxy stereocentres, the \textit{anti} product \textit{anti-47} generally predominates.\textsuperscript{39} The two most prevalent models for this selectivity are the ‘modified Felkin–Anh’ originally described by Roush,\textsuperscript{40} which parallels that for electrophilic addition to C=C double bonds, and the Yamamoto model,\textsuperscript{41} which has many features in common with the Cieplak\textsuperscript{42} and Houk ‘inside-alkoxy’\textsuperscript{57} models \textit{vide infra} (Scheme 21). Yamamoto argued that the reactive conformation is stabilised by overlap of the electron rich C—R bond with the developing C—Nu $\sigma^*$ orbital. The model correctly predicts a reversal from \textit{anti} to \textit{syn}
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selectivity in reactions of $Z$-enoates, as increased 1,3 allylic strain favours the conformation with the hydrogen roughly eclipsing the double bond.

Kornienko studied the addition of various diarylcuprates to a representative set of $\gamma$-alkoxyenolates, with variations in the alkoxy group, R group and enolate geometry (Scheme 22, Table 6). The high selectivities in addition to $E$-enoates are consistent with the modified Felkin–Anh model, as the selectivity is independent of the size of the R’ group (Entry 1,2) which is orientated antiperiplanar to the incoming nucleophile. The reduction in selectivity with reducing size of the R group is also consistent with this model (Entry 2,3,4). The Yamamoto model leads to the opposite prediction: that selectivity should be highly dependent on the size of the R’ group (OR’ eclipses the enolate in the transition state leading to the $anti$ product); and that selectivity should be largely independent of the R group. The moderate selectivities for addition to $Z$-enoates are poorly explained by both models. The modified Felkin–Anh model suggests $anti$ selectivity should be higher for $Z$-enoates, while the Yamamoto model suggests that $syn$ products should predominate.
A revised model was suggested that takes into account recent mechanistic studies in the conjugate additions of organocuprates, with the assumption that the reductive elimination step of the reaction is both rate- and stereochemistry-determining. This contrasts with the Yamamoto and modified Felkin–Anh models, which assume complexation with the enolate to be the step controlling facial selectivity (Scheme 23).
Mechanism of cuprate addition:

Reductive elimination transition states:

Scheme 23

Both Felkin–Anh and Yamamoto transition states for the reductive elimination step contain eclipsing interactions with the complexed and almost planar organocuprate. The transition states proposed by Kornienko position the R and OR’ groups away from the large cuprate moiety. Also notable are the two roughly antiperiplanar relationships in this transition state: firstly between the Cγ–OR’ and forming Cβ–Ar bonds; and secondly between the Cγ–R and breaking Cβ–Cu bonds. In the former, favourable mixing of the σCβ–Ar and low-lying σ*γ–OR’ orbitals is maintained; while in the latter case overlap of the electron rich σCγ–R and σ*γ–Cβ–Cu orbitals assists the departure of copper. These transition states are consistent with the experimental data.

The sense of selectivity is reversed in the presence of γ-amino stereocentres, and the syn product predominates. This stereochemical divergence was discussed as early as 1991 by Hanessian. Two substrates 50, derived from Garner’s aldehyde and 52 underwent syn-selective addition with dimethylcuprate–TMSCl (Scheme 24).
According to Hanessian, the \textit{syn}-products \textbf{51} and \textbf{53} could derive from either Felkin–Anh or Yamamoto transition states, although neither of these give a convincing explanation of the reversal of selectivity in changing from oxygen to nitrogen.

![Scheme 24]

A more recent treatment of this dichotomy has been given by Kornienko. Substrates similar to those investigated by Hanessian were treated with a variety of diarylcuprates (Scheme 25, Table 7). Although diastereoselectivity was effectively absolute in all cases, much lower yields were observed for the bulkier substrate \textbf{54}.

![Scheme 25]
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<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
<th>Ratio syn- : anti-55</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>58</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>2</td>
<td>4-OMe</td>
<td>50</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>3</td>
<td>4-F</td>
<td>55</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl</td>
<td>58</td>
<td>&gt;20 : 1</td>
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<tr>
<td>5</td>
<td>3,4-OMe</td>
<td>49</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>52</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>7</td>
<td>5-OMe</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

In common with the previous study, considering that the Felkin–Anh model predicts predominance of the anti product, a ‘reductive-elimination’ transition state was proposed to account for the observed syn selectivity (Scheme 26). Although the reduced yields in the case of bulkier R groups (increased 1,3-allylic strain) agree with this model, it is unclear whether this transition state benefits from the favourable orbital interactions of the transition state leading to the anti product.

Scheme 26

In additions of organocuprates to C=C double bonds adjacent to a silicon-containing stereocentre, diastereoselectivity is somewhat lower. Fleming reported the 1,4-addition of silylcuprates to enoates with silicon stereocentres at either the α- or β-position. Attack occurred predominantly syn to the silicon substituent, with the hydrogen eclipsing the double bond. It is difficult to rationalise this result using the above reductive elimination transition states above, although it may be consistent with a Yamamoto-type model in which the anti product is disfavoured by the silicon group roughly eclipsing the double bond (Scheme 27).
Further recent examples of acyclic stereocontrol in organocuprate additions have been reported by Breit, who used phosphine substituents for directed delivery of the cuprate.\(^{50}\) While \(E\)-configured substrates \(E-61\) afforded \(anti\) products, the \(syn\) products were obtained from the isomeric \(Z\)-configured substrates \(Z-61\). The level of selectivity was independent of the size of the nucleophile (Scheme 28).

\(\text{o-DPPB-directed allylic substitution}\)

\[\text{Ph}_2\text{P} \quad \text{Ph}_2\text{P} \quad \text{Ph}_2\text{P} \quad \text{Ph}_2\text{P} \quad \text{Ph}_2\text{P}\]

Stereospecific examples:

\(E-61\)  
\[\text{MeMgBr (2 equiv)} \quad \text{CuBrMe}_2\text{S, Et}_2\text{O, rt} \quad \text{anti-62} \quad \text{dr} = 85:15\]

\(Z-61\)  
\[\text{MeMgBr (2 equiv)} \quad \text{CuBrMe}_2\text{S, Et}_2\text{O, rt} \quad \text{syn-62} \quad \text{dr} = 97:3\]

\(E\)-substrate

Yamamoto  
Felkin–Anh

\(Z\)-substrate

1,3-allylic strain minimising  
\(R' = \text{Boc}\)

Scheme 28
Carbon nucleophiles undergo stereoselective addition to enoates with a γ-stereocentre, and similar models have been used to explain these reactions. The sense of addition of lithium amides varies between syn and anti depending on substrate,\textsuperscript{51,52} while hydroxylamine nucleophiles generally give the syn product.\textsuperscript{53} Alkoxide nucleophiles have also been studied.\textsuperscript{54} The anti sense of rhodium-catalysed conjugate addition of boronic acids to γ,δ-alkoxy enoates has been recently explained using a reductive elimination model.\textsuperscript{55}

\subsection{1.3.3 Conclusions}

Compared to analogous reactions of carbonyls, addition to double bonds adjacent to a stereocentre is less well defined. Although the Houk model correctly predicts the results of electrophilic addition in many cases, there are exceptions in which the major product arises from seemingly hindered transition states (cf. the inside-methyl effect). For nucleophilic additions, in particular 1,4-addition to enoates with γ-stereocentres, the sense of diastereoselectivity follows clear trends. However, neither the modified Felkin–Anh, Yamamoto or reductive elimination models give conclusive explanations for the changing sense of selectivity with changing γ-heteroatom. Above all, 1,3-allylic strain dominates as an essential control element.
1.4 Pericyclic reactions

1.4.1 [3+2] Cycloadditions

Models for [3+2] cycloadditions follow naturally from those for addition to C=C double bonds, although they differ significantly from Felkin–Anh type models. The case for 1,3-dipolar addition to a C=C double bond adjacent to a stereocentre has been extensively investigated, particularly for chiral allyl ethers. This area has been most recently reviewed in 2001, in which the authors highlight the accuracy with which the established theories predict the observed stereoselectivity. The two key factors at work are 1,3-allylic strain and the ‘inside-alkoxy’ effects first postulated by Houk (Scheme 29).

Houk calculated the relative energies of methyl and methoxy substituents at each of the staggered positions in the cycloaddition transition state. The methyl group preferentially adopted the anti configuration, avoiding the inside conformation on steric grounds, and allowing hyperconjugation of the $\sigma_{C-Me}$ and electron-deficient $\pi^*_{C=C}$ bonds. The methoxy group was situated inside in the lowest energy transition state. In the anti OMe position, overlap between the $\pi_{C=C}$ and $\sigma^*_{C-O}$ orbitals removes electron density from the reacting olefin, disfavouring this transition state. Notably, the anti disposition of alkoxy groups relative to reacting olefins is shown to be a
stabilising interaction in other pericyclic reactions, particularly sigmatropic rearrangements, due to a $\pi^*_{C=C}/\sigma^*_{C=O}$ interaction (see Section 2.1). Overall, the most unfavourable orientation is OMe outside, which is electrostatically destabilised by interaction of the partial negative charges of the approaching oxygen atoms.

In the case of Z-configured substrates where 1,3-allylic strain is greater, the alkoxy group adopts the anti position, with the smallest substituent lying inside. An example of this is shown in the intramolecular cycloaddition of Z-allylic ether 65 (Scheme 30). Two possible allylic strain-minimising conformations are possible, yet the outside alkoxy/anti methyl transition state leading to syn-66 is electrostatically disfavoured.

![Scheme 30]

In contrast to the examples shown above of conjugate nucleophilic addition to enoates, alteration of the heteroatom causes little variation in the sense of the selectivity although some exceptions have been reported. Cycloadditions of nitrile oxides with allylic isoxazoles 67 occur in the inside alkoxy sense and the anti product 68 predominates (Scheme 31). Selectivities are slightly lower than those for allylic ethers, which correlates with the lower electronegativity of nitrogen, causing less destabilisation in anti and outside transition states. Selectivities for the anti product are lower still for acyclic allylic amines.

![Scheme 31]
More recently, the preferred conformations of allylic fluorides in transition states for their nitrile oxide cycloadditions have been studied and compared with experimental data.\textsuperscript{61} Allylic fluorides were found to react in the sense predicted by the inside alkoxy model, with fluorine taking the place of the alkoxy substituent.\textsuperscript{62} Three allylic fluorides 69, 71 and 74 were treated with propionitrile oxide to give the corresponding cycloadducts (Scheme 32). 69 reacted in favour of the \textit{anti} adduct. Reaction of 71 and 74 both afforded mixtures of regio- and stereoisomers. For 71 in the series with the stereocentre at the isoxazole 4 position 72, there was a slight preference for the \textit{syn} cycloadduct. For the series with the stereocentre at the isoxazole 5 position 73 (in common with the above examples), a distinct preference for the \textit{anti} cycloadduct was observed. For 74 in the series with the stereocentre at the isoxazole 4 position 75, only the \textit{syn} cycloadduct was observed; while with the stereocentre at the 5 position 76, there was a slight bias for the \textit{anti} product.

\begin{equation*}
\text{Et-}C\equiv N-O^- \\
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{Me} \\
\text{Me} \\
\text{F} \\
\text{Et} \\
\end{array}
\end{equation*}

\begin{equation*}
\text{Et-C\equiv N-O^-} \\
\begin{array}{c}
\text{Et} \\
\text{Me} \\
\text{F} \\
\text{N} \\
\text{O} \\
\text{N} \\
\end{array}
\end{equation*}

\begin{equation*}
\text{Et-C\equiv N-O^-} \\
\begin{array}{c}
\text{Et} \\
\text{Me} \\
\text{F} \\
\text{N} \\
\text{O} \\
\text{N} \\
\end{array}
\end{equation*}

These observations were explained using transition state searches (Scheme 33, calculated at the B3LYP/6-31G* level). For the 5-substituted regioisomer, the lowest
Recent advances in acyclic stereocontrol

Recent progress has also been made in the study of 1,3-dipolar cycloadditions of homoallylic alcohols, a class of substrates for which stereoselectivity is often low. Carreira has recently shown good anti selectivity for cycloaddition of nitrile oxides

Scheme 33

Recent advances in acyclic stereocontrol

energy transition state (A) has fluorine inside, with the methyl group in the anti position. The second lowest transition state (D), which leads to the syn product also has fluorine inside, but in this case, methyl is outside and overlaps poorly with the double bond. However, for transition states leading to the 4-substituted regioisomer, an inside fluorine is destabilising due to electrostatic interactions with the oxygen of the 1,3-dipole (transition states G and J), and the sense of selectivity is reversed. The lowest energy transition state, from which the syn product is formed (K) has fluorine outside, pointing away from the 1,3-dipole and methyl anti in good overlap with the dipolarophile double bond. These transition states are in good agreement with the above data.

Scheme 33

Recent progress has also been made in the study of 1,3-dipolar cycloadditions of homoallylic alcohols, a class of substrates for which stereoselectivity is often low. Carreira has recently shown good anti selectivity for cycloaddition of nitrile oxides
Recent advances in acyclic stereocontrol

derived from oximes 77 with homoallylic alcohol 78 in the presence of a metal
counterion (Scheme 34).\(^6\)

\begin{equation}
\begin{align*}
\text{N} & \text{O} \\
\text{R} & \text{H} \\
\end{align*}
\end{equation}

(i) tBuOCl, -78 °C
(ii) EtMgBr, IPA

\begin{equation}
\begin{align*}
\text{N} & \text{O} \\
\text{R} & \text{H} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{Me} & \text{OH} \\
\text{OH} & \text{Me} \\
\end{align*}
\end{equation}

77

79

78

(66–89%)
dr = 4:1–13:1

Scheme 34

Houk has proposed transition states to account for this selectivity, which are based on
the inside alkoxy model (Scheme 35).\(^6\) Reactions with and without a chelating
magnesium atom between the two oxygens were compared. For both, the lowest
energy transition state had the alcohol in the outside position and the methyl group
anti. This leads to the anti isoxazole product as observed. In the non-chelation case, a
hydrogen-bonding interaction between the 1,3-dipole oxygen and the homoallylic
alcohol was observed. The next lowest transition state, which leads to the syn product
was destabilised by 1 kcal/mol. For the chelated transition state, the lowest syn
transition state was destabilised relative to the lowest energy anti transition state by 3
kcal/mol; consistent with the observed selectivities. Conformations placing the
magnesium ether in an inside arrangement were further destabilised by around 7–8
kcal/mol. For both cases, hydrogen-bonding or chelation withdraw electron density
from the 1,3-dipole, contributing to electron deficiency in the transition state. Thus, it
is important that the methyl group lies in the anti position, in hyperconjugation with
the olefin, which is even more electron deficient in this reaction compared to
cycloadditions of chiral allylic ethers. Similar chelation models have been reported
for allylic alcohol substrates.\(^6\)

\begin{equation}
\begin{align*}
\text{Non-chelation} & \quad \begin{align*}
\text{N} & \text{O} \\
\text{H} & \text{Me} \\
\end{align*} \\
\text{5-membered hydrogen bonding transition state} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{Chelation} & \quad \begin{align*}
\text{N} & \text{O} \\
\text{H} & \text{Me} \\
\end{align*} \\
\text{6-membered transition state} \\
\end{align*}
\end{equation}

Scheme 35
Only a very small section of the literature on [3+2] cycloadditions has been discussed here, and acyclic stereocontrol is certainly not limited to nitrile oxide additions to olefins with adjacent stereocentres. There are many other examples of diastereoselective [3+2] cycloadditions that are beyond the scope of this review. As a representative example, Padwa has reported acyclic stereocontrol in the rhodium-catalysed [3+2] cycloaddition of isomünchone dipoles with a variety of dipolarophiles (Scheme 36). The conformation of the acyclic amide substituent of 81 determined the sense of diastereoselectivity, with the hydrogen eclipsing the oxonium of the 1,3-dipole to minimise 1,3-allylic strain. Attack of the electrophilic dipolarophile occurred on the most electron rich face of the 1,3-dipole. This effect, discussed by Kahn and Hehre, is also observed in [4+2] cycloadditions.

![Scheme 36](image)

1.4.2 [4+2] Cycloadditions

Similarly well investigated and modelled are [4+2] cycloadditions; particularly the Diels–Alder and hetero-Diels–Alder reactions. Electrostatic interactions between the diene and dienophile have been shown to play an important role (cf. Scheme 36 above). Diels–Alder reactions of electron-rich dienes and electron-poor dienophiles should occur preferentially onto the more nucleophilic diene face, and onto the face of the dienophile which exhibits greater electrophilicity (Scheme 37).
Houk has suggested an inside alkoxy-type effect (which has an electrostatic component) to explain the stereoselective reactions of chiral allylic alcohols and ethers \(^{83}\) with highly electron-deficient hexachlorocyclopentadiene \(^{84}\), which is in good agreement with experimental data.\(^{70}\) In the analogous sense to \([3+2]\) cycloadditions of nitrile oxides with chiral allylic ethers, the alkoxy group lies inside, avoiding electrostatic interactions with chlorine, while the alkyl group prefers anti alignment with the olefin (Scheme 38).

Like \([3+2]\) cycloaddition reactions of nitrile oxides with chiral allylic fluorides, Diels–Alder reactions of chiral allylic fluorides can be described by the inside alkoxy model.\(^{71}\) Grée et al. studied the Diels–Alder reactions of allylic fluorides \(^{86}\) with 2,3-dimethyl-1,3-butadiene \(^{87}\) (Scheme 39, Table 8). Where observed (entries 2 and 3), selectivities were in the inside fluorine sense. The reaction was unselective when a nitrile substrate was used (entry 1), although the reason is not clear.
Acyclic stereocontrol in the intramolecular Diels–Alder (IMDA) reaction has also been of recent interest. The reaction can be controlled by stereocentres adjacent to the dienophile moiety. Sherburn studied the IMDA reactions of various ascorbate-derived substrates. The level of selectivity varied greatly with the group P. Based on computational studies, a model was proposed to account for these selectivities, which is in agreement with both the inside alkoxy and Kahn/Hehre models (Scheme 40, Table 9).
Table 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>P</th>
<th>R_E</th>
<th>R_Z</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>Ratio 90 a : b : c : d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>CO₂Me</td>
<td>5</td>
<td>86</td>
<td>56 : 32 : 8 : 4</td>
</tr>
<tr>
<td>2</td>
<td>TMS</td>
<td>H</td>
<td>CO₂Me</td>
<td>12</td>
<td>67</td>
<td>80 : 14 : 4 : 2</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>H</td>
<td>CO₂Me</td>
<td>15</td>
<td>80</td>
<td>86 : 9 : 4 : 1</td>
</tr>
<tr>
<td>4</td>
<td>TIPS</td>
<td>H</td>
<td>CO₂Me</td>
<td>18</td>
<td>68</td>
<td>92 : 7 : 1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>PNB</td>
<td>H</td>
<td>CO₂Me</td>
<td>12</td>
<td>95</td>
<td>49 : 39 : 6 : 6</td>
</tr>
<tr>
<td>6</td>
<td>TBS</td>
<td>CO₂Me</td>
<td>H</td>
<td>53</td>
<td>62</td>
<td>12 : 3 : 82 : 3</td>
</tr>
</tbody>
</table>

1.4.3 [3,3]-Sigmatropic rearrangements

Numerous examples have been reported of acyclic stereocontrol in the Claisen rearrangement. A complete discussion of this area and the models for observed selectivity is given in Section 2.1, as it is directly relevant to our work in this area. However, in addition to the Claisen rearrangement, acyclic stereocontrol has also been reported in the related Overman rearrangement. Chida reports an example of such a reaction during the synthesis of (+)-lactacystin. Trichloracetimidate underwent rearrangement upon heating in toluene to give the product with good diastereoselectivity. The product is derived from a transition state that shares many common features with those of Claisen rearrangement, in particular the antiperiplanar alignment of the incipient C—N and furanose C—O bonds (Scheme 41).

Scheme 41

1.4.4 [2,3]-Sigmatropic rearrangements

Examples of acyclic stereocontrol in [2,3]-sigmatropic rearrangements are comparatively scarce compared to the related [3,3]-sigmatropic case. The seminal contribution to this area was made in 1988 by Brückner, who studied the [2,3]-Wittig rearrangement of allylic dioxolanes and 95. The rearrangement occurred in the syn sense, in the same fashion as analogous Claisen rearrangements of allylic dioxolanes. In the transition state leading to the major syn product, the dioxolane C—O bond lies perpendicular to the allylic C=C bond, maintaining a favourable σ* C—
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\[ \pi^* \text{C} - \text{C} \] overlap, which contributes to overall lowering of the LUMO. As shown by the complete syn selectivity in the rearrangement of Z-allylic substrate 96, 1,3-allylic strain is a component of this model (Scheme 42).

\[ \text{Bu}_3\text{SnO} \] \[ \rightarrow \text{rBuLi} \]

THF, \(-78 \, ^\circ\text{C}\)

1 h, then TMEDA

\[ \text{syn-94} \]

(79%)

\[ \text{anti-94} \]

(6%)

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

(i) \text{rBuLi, THF, \(-78 \, ^\circ\text{C}\)}

30 min, then TMEDA

\[ \text{LiAlH}_4, \text{THF} \]

\[ \text{syn-96} \]

single diastereomer

Scheme 42

Other examples have been reported of acyclic stereocontrol in similar [2,3]-Wittig rearrangements, and the above model explains these well.\(^76\) More recently, Davies has reported stereoselective [2,3]-sigmatropic rearrangements of lithium N-benzyl-O-allylhydroxylamides.\(^77\)

The substrates studied possessed both all-hydrocarbon stereocentres 97 and heteroatom-bearing stereocentres 99/101. In the latter case, both \(E\) - and \(Z\)-configured substrates were compared. All substrates underwent rearrangement to give the syn product. For all-hydrocarbon stereocentres, this can be explained using the same transition state model as Brückner, with attack of the anion antiperiplanar to the phenyl group. For heteroatom-bearing stereocentres, this model predicts the opposite \(anti\) product, and a chelation transition state was proposed to explain formation of the syn product (Scheme 43).
Recent advances in acyclic stereocontrol

All-hydrocarbon stereocentres

\[
\begin{align*}
\text{Scheme 43}
\end{align*}
\]

Heteroatom bearing stereocentres

\[
\begin{align*}
\text{Non-chelation model} & \quad \text{predicts opposite product} \\
\text{Chelation model correctly} & \quad \text{predicts syn product}
\end{align*}
\]

1.4.5 Conclusions

The models presented for describing acyclic stereocontrol in pericyclic reactions have seen less recent development compared to those for acyclic stereocontrol in additions to carbonyls and double bonds. However, for both [3+2] and [4+2] cycloadditions the patterns of stereoselectivity are well defined. The inside alkoxy model developed by Houk is widely applied. The model holds well for other heteroatomic groups, particularly fluorides. Exceptions to the rule occur when chelation or hydrogen-bonding interactions are possible between the heteroatom on the stereocentre and the approaching reactant. Although models have been proposed that explain [3,3]- and [2,3]-sigmatropic rearrangements, there are comparatively few examples in the
literature. In common with reactions of \( \text{C=C} \) double bonds adjacent to a stereocentre, 1,3-allylic strain is an important factor in influencing acyclic stereocontrol.
1.5 Reactions adjacent to a metal stereocentre

In addition to reactions of functional groups adjacent to carbon or sulfur stereocentres, acyclic stereocontrol is also possible for reactions of prochiral organic ligands on organometallic complexes. Widely explored in this sense are tricarbonyliron complexes. The subject has been comprehensively reviewed by Cox and Ley.\(^{78}\) A diene tricarbonyliron complex exhibits planar chirality. If the diene ligand contains an adjacent functional group, for example in 103 a carbonyl group, this may adopt a preferred reactive conformation with its two diastereotopic faces sterically differentiated by the tricarbonyliron moiety.\(^{79}\) S-cis and s-trans conformations of 104 are possible, but the latter is disfavoured by 1,3-allylic strain. Attack of approaching nucleophiles occurs *anti* to the bulky tricarbonyliron moiety. Aldehydes react with lower diastereoselectivity due to the diminished interaction of the diene with the aldehydic hydrogen reducing the level of 1,3-allylic strain in the s-trans conformation (Scheme 44). Similar methodology has recently been used for the synthesis of 2-dienyl piperidines\(^{80}\) and for controlling the sense of intramolecular pinacol couplings.\(^{81}\) Other stereogenic iron complexes have been used to attain acyclic stereocontrol: substituted diphosphaferrocenes have recently been reported to control the sense of addition of phosphorus\(^{82}\) and organometallic\(^{83}\) nucleophiles to an adjacent aldehyde.

\begin{align*}
&\text{Racemic } \eta^4\text{-dien complexes} \\
&\text{103} \quad \text{Fe(CO)}_5 \quad \text{104} \\
&\begin{array}{c}
\text{Fe(CO)}_3 \\
\text{s-cis-104} \\
\text{s-trans-104}
\end{array} \\
&\text{Nu}^- \\
&\text{Nu}^-
\end{align*}

Scheme 44
This chemistry is not limited to iron complexes; tungsten-syn-π-pentadienyl complexes have been used to effect acyclic stereocontrol in the preparation of adjacent 1,3-diols. The Lewis-acid promoted Prins reaction of the tungsten complex 106 with an aldehyde affords a η⁴-trans-diene cationic intermediate 107, which undergoes hydrolysis with water anti to the bulky complex (Scheme 45). This class of reaction is emerging as an interesting new area for investigations into acyclic stereocontrol.

Scheme 45
1.6 Summary

Recent developments in models for acyclic stereocontrol have been discussed in the context of three important classes of organic reaction and some recent organometallic reactions. For additions of nucleophiles to carbonyls with an adjacent stereocentre, both computational and experimental evidence have challenged the predominance of the Felkin–Anh and Cram models for predicting stereoselectivity. Various models for describing electrophilic and nucleophilic addition to double bonds have been proposed that account for variations in selectivity. However, these are often very specific to each particular reaction. In some cases, the major product arises from a seemingly high-energy transition state, for example in examples of the inside-methyl effect. Above all, 1,3-allylic strain appears to be the most important control element in reactions of C=C double bonds adjacent to a stereocentre. Many of the same models have been extended to explain acyclic stereocontrol in pericyclic reactions. In these cases, both stereoelectronic effects, again 1,3-allylic strain in particular, and electrostatic effects must be taken into account. Stereoselective reactions of unsaturated functional groups adjacent to organometallic complexes are also emerging as useful tools for establishing acyclic stereocontrol.

Taking into account the above examples, some general conclusions can be drawn. There is no unified theory that explains all modes of acyclic stereocontrol. Rather, it appears that models are very specific to the individual reaction mechanism and the nature of the incoming electrophile or nucleophile must be considered. Additional complexity is encountered when stereoselectivity is a function of both acyclic and cyclic stereocontrol (double diastereoselection). These cannot be considered in isolation and models must take into account interactions between cyclic and acyclic transition states. Developments in computational methods have contributed to our ability to predict the sense of acyclic stereocontrol, although exceptions to these predictions are often encountered in experiment. Development of models and methods for establishing acyclic stereocontrol remains a highly active area of interest in synthetic chemistry.
Chapter 2

Results and Discussion
2.1 Background

2.1.1 Historical background

The sigmatropic rearrangement of allyl phenyl ether 109 to give ortho-allyl phenol 110 was first reported by Claisen in 1912.\textsuperscript{85} The paper contained an additional report of a rearrangement of O-allylated ethylacetoacetate 111 to 112; a reaction that is now generally referred to as the aliphatic Claisen rearrangement. The reaction, containing two \(\pi^2s\) components and one \(\sigma^2s\) component is thermally allowed under Woodward–Hoffmann rules,\textsuperscript{86} whether it proceeds via a chair or boat transition state (Scheme 46).

Scheme 46

Nearly a century later, the Claisen rearrangement has become a well-established and general method for the synthesis of \(\gamma,\delta\)-unsaturated carbonyl compounds.\textsuperscript{87} When the ketene acetal precursor is disubstituted, diastereomeric products are possible. Nevertheless, the stereochemical patterns governing the rearrangement are similarly well investigated. This statement is more appropriate for cases when substituents are bound directly to the pericyclic array. Explanations of stereoselectivity are generally rationalised by considering well-defined transition state models.\textsuperscript{88}

In addition to the case previously shown, in which the relative geometries of the vinylic and allylic portions of the ketene acetal determine the relationship between the two new stereocentres formed (Chapter 1, Scheme 2), stereochemical information is reliably transferred around the pericyclic array. As an example, Hill and Edwards...
reported 1,3-transfer of the ether stereocentre in the reaction of 113 (Scheme 47). As we have previously defined, this represents cyclic stereocontrol.

![Scheme 47](image)

2.1.2 The effects of exopericyclic stereocentres: acyclic stereocontrol

Less investigated has been the manner and extent to which stereocentres outside of the pericyclic array – which we shall refer to as ‘exopericyclic stereocentres’ – affect the stereochemistry of the new bonds formed during the sigmatropic process. This represents acyclic stereocontrol. In a generic ketene acetal Claisen precursor 115 (Scheme 48), 1,2-induction of the newly formed C1—C6 bond via acyclic stereocontrol is possible when stereocentres are positioned adjacent to the C1 and C5–6 positions. This area has been previously reviewed in the context of the Ireland–Claisen rearrangement, and asymmetric [3,3]-sigmatropic rearrangements and although many of the same examples are cited, it is important that we highlight them here. During the rearrangement C4 becomes, and C5 remains, sp$^2$-hybridised, and although stereocentres adjacent to these positions can affect stereochemistry in a similar sense, it is beyond the scope of this work.

![Scheme 48](image)
2.1.2.1 Effects of stereocentres adjacent to C1

Yamazaki\textsuperscript{92} and Martin\textsuperscript{93} have shown examples of C1 exopericyclic stereocontrol using trifluoromethyl and CO\textsubscript{2}Bn substituents respectively (Scheme 49). In both cases, the observed stereoselectivity is rationalised by invoking the Cieplak model in which attack occurs antiperiplanar to the more electron rich C—C \sigma bond. This allows for hyperconjugation between the C—R (or C—cyclopentyl) groups and the electron-deficient \sigma* orbital of the incipient C1—C6 bond. In the Yamazaki example, isosteric \textit{i}Pr and CF\textsubscript{3} substituents on 117 were used to remove steric bias from the transition state model. Replacement of the CF\textsubscript{3} group by methyl gave significantly reduced selectivity.\textsuperscript{94} Although deriving from different effects, this corresponds to reaction in the same sense as predicted by the Felkin–Anh model.\textsuperscript{95} Similar examples that occur in a Cieplak sense have been reported by Knight.\textsuperscript{96} Other examples have been described of Johnson–Claisen rearrangements with chiral ortholactones, although the selectivity in these processes is controlled by the relative energies of chair and boat transition states.\textsuperscript{97}

\begin{align*}
\text{Yamazaki:} \\
\begin{align*}
\text{117} & \xrightarrow{(i) \text{ LDA, THF, TMSCl}} \text{118} \\
& \xrightarrow{(ii) \text{ PdCl}_2(\text{PhCN})_2 \text{ (2.5 mol\%)} \text{ reflux (78\%)} } \\
\text{Me}_2\text{N} & \xrightarrow{(i) \text{ LDA, THF, TMSCl}} \text{119} \\
& \xrightarrow{(ii) \text{ PdCl}_2(\text{PhCN})_2 \text{ (2.5 mol\%)} \text{ reflux (74\%)} } \\
\end{align*}
\end{align*}

\begin{align*}
\text{Martin:} \\
\begin{align*}
\text{121} & \xrightarrow{\text{LDA, THF, TESCI \text{ -78 °C \to 55 °C}}} \\
& \xrightarrow{\text{‡ \text{ single diastereomer}}} \\
\end{align*}
\end{align*}

\text{Scheme 49}

Attack in the opposite (non-Cieplak, anti-Felkin) sense has been reported by Fujisawa\textsuperscript{98} and Fleming (Scheme 50).\textsuperscript{112} In these examples,\textsuperscript{99} attack occurs preferentially anti to the most electronegative group, with the smallest substituent
eclipsing the vinylic double bond to minimise 1,3-allylic strain: a reactive conformation that is commonplace in examples of C6 exopericyclic stereocontrol *vide infra*.

**Fujisawa:**

\[
\begin{align*}
\text{LDA, THF} & \quad \text{TMSCI} \\
123 \quad \text{reflux} & \quad \text{syn-125} \\
\end{align*}
\]

123

\[
\begin{align*}
\text{R}_2 & \quad \text{R}_2 \\
\text{LDA, THF} & \quad \text{TMSCI} \\
\text{reflux} & \quad \text{syn-125} \\
\end{align*}
\]

125

\[
\text{dr} = 79:21
\]

\[
\begin{align*}
\text{R}_2 & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

**Fleming:**

\[
\begin{align*}
\text{LDA, TMSCI} & \quad \text{THF, } -78^\circ\text{C} \\
126 & \quad \text{127} \\
\end{align*}
\]

126

\[
\begin{align*}
\text{LDA, TMSCI} & \quad \text{THF, } -78^\circ\text{C} \\
\text{HMPA} & \quad \text{127} \\
\end{align*}
\]

127

\[
\begin{align*}
\text{dr} & \quad 98:2 \\
\text{dr} & \quad 97:3 \\
\end{align*}
\]

Scheme 50

In addition to rearrangements with carbon stereocentres, C1-sulfur substituents have been used for exopericyclic stereocontrol. The first reactions of this type were reported by Metzner, in which thiotetene acetals 128 underwent thio-Claisen rearrangement to give thioesters 129 in very high diastereoselectivity (Scheme 51).\textsuperscript{100}

The transition states proposed to account for the sense of the selectivity were derived from the original Felkin model in which the best donor (in this case the sulfur lone pair) is placed antiperiplanar to the incipient bond. The oxygen is the smallest substituent and eclipses the ketene acetal (cf. hydrogen eclipsing in the above examples). Both E- and Z-transition states lead to the same product. Similar examples have been reported from our own laboratories in which C1-sulfoximine stereocentres are used for exopericyclic stereocontrol.\textsuperscript{101} Recently, we have used this methodology
for the stereoselective formation of cyclopropanes via decarboxylative Claisen rearrangement (dCr).\(^{102}\)

\[
\begin{align*}
\text{R}^+&\text{S}\ldots\text{S}\ldots\text{R}^-\text{O}^+ \\
128 &\xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt}} \text{SMe} \\
\text{or} &\text{R}^+\text{S}\ldots\text{S}\ldots\text{R}^-\text{O}^+ \\
129 &\xrightarrow{[3,3]} \text{dr} > 93:7 \\
\text{8 examples (40-60%)} \\
\end{align*}
\]

Scheme 51

2.1.2.1 Effects of stereocentres adjacent to C6

The earliest examples of exopericyclic stereocontrol adjacent to C6 used C6’ dioxolane substituents. *Syn*-selective Ireland–Claisen rearrangements of 130 were reported by Cha,\(^ {103}\) with variations in allylic *E/Z* geometry and C1 substituent (Scheme 52, Table 10). The transition states proposed to account for the selectivity follow a similar pattern to those described for rearrangements with C1 stereocentres.\(^ {104}\) In this case the vinylic portion of the ketene acetal attacks antiperiplanar to the dioxolane C6’—O bond in the conformation where the C6’—H bond eclipses the allylic moiety. Similar, although significantly less selective Johnson–Claisen rearrangements featuring C6’ dioxolane substituents have also been reported by Suzuki\(^ {105}\) and Takano.\(^ {106}\)
Notable in this case is the slight increase in selectivity upon changing the allylic geometry from \( E \) to \( Z \), which is consistent with an allylic strain model; and the significantly reduced selectivity in the absence of a \( \text{C1} \) substituent. Similar rearrangements have been rationalised in terms of Houk’s inside-alkoxy rule although the sense of selectivity is the same\(^{107, 108}\).

Highly diastereoselective rearrangements, in the same sense as those described by Cha and others above have been reported with \( \text{C6’} \) nitrogen substituents. Hauske\(^{109}\) and Mulzer\(^{110}\) studied the Ireland–Claisen rearrangements of the BOC-protected valine- and proline-derived substrates 132 and 134 respectively (Scheme 53).
Two complementary explanations were for the high stereoselectivity were provided by Mulzer. The proposed transition state features, in common with other examples, antiperiplanar alignment of the C6’—N and the incipient C1—C6 bond, with the proline residue positioned in such a way that minimises 1,3-allylic strain. An additional explanation is given according to the model of Kahn and Hehre (modified for the Claisen rearrangement) in which the most electrophilic face of the allylic moiety approaches the most nucleophilic face of the vinylic moiety. The energy of the allylic LUMO is lowered via mixing of $\sigma^{*}_{C6’-N}$ and $\pi^{*}_{C=C}$ orbitals, while the vinylic $\pi$ orbital (HOMO) is raised in energy by the two electron donating OTMS and OBn residues. Overall, this leads to a strong HOMO-LUMO interaction, lowering the activation barrier of the rearrangement.

Fleming, in the same report that presented the effects of C1’ silicon stereocentres, also investigated the effects of C6’ silicon stereocentres (Scheme 54). Attack of the vinylic moiety antiperiplanar to the silicon substituent is maintained in all cases. Evidence for 1,3-allylic strain as a control element was shown by the high selectivity of Z substrates. The isomeric E substrates underwent rearrangement with moderate selectivity for the opposite diastereomer, which arises from a reactive conformation in which the methyl group is ‘inside’. Calculations showed this conformation to be more populated than the alternative in which the hydrogen is ‘inside’. This conformation is accessible in the absence of significant 1,3-allylic strain effects.
Thio-Claisen rearrangements have also been used to study the effects of C6’ stereocentres.\textsuperscript{113} In particular, numerous examples of exopericyclic stereocontrol from C6’ substituents in Belluš–Claisen\textsuperscript{114} (ketene Claisen) rearrangements of allylic sulfides have been reported, which follow the established patterns.\textsuperscript{115} The aza-analogues of these reactions have also been investigated and reduced selectivity was reported for rearrangements lacking a C1 substituent on the pericyclic array (Scheme 55).\textsuperscript{116} During the course of our studies, an additional example of a thio-Claisen rearrangement in the same sense was reported by Porter.\textsuperscript{117}
Recent work in our own laboratories, in the context of the decarboxylative Claisen rearrangement reaction has stimulated our interest in this area. \textsuperscript{118} Esters \textsuperscript{146–148}, when treated with a silylating agent and sub-stoichiometric quantities of acetate underwent Claisen rearrangement followed by concomitant desilylation and decarboxylation to give the homoallylic sulfones \textsuperscript{149–151} in varying diastereoselectivity (Scheme 56). Although the sense of selectivity was not assigned, we were interested in the variable selectivities and particularly in the effect of changing the heteroatom.
2.1.3 Focus of the current work

The work presented herein covers two areas. Firstly, concentrating exclusively on Claisen rearrangements with C6’ stereocentres, we have performed investigations into the importance of the exopericyclic heteroatom in determining selectivity. We have also investigated in depth the relationship between allylic substitution pattern and stereoselectivity.

Secondly, drawing on our own evidence and that already presented in the literature, we have attempted to exploit exopericyclic stereocontrolled Claisen rearrangements for the synthesis of small, stereochemically complex molecules. During investigations into the effects of C6’ azide stereocentres, we have uncovered a novel reaction in which equilibrating mixtures of allylic azides undergo Claisen rearrangements with exopericyclic stereocontrol.
2.2 Effects of hydrocarbon substituents

2.2.1 Background

As an initial investigation, we decided to study the effects of C6’ hydrocarbon exopericyclic substituents on stereoselectivity (Scheme 57). This is relatively poorly explored in the literature, compared to rearrangements where the exopericyclic substituents are heteroatomic.

![Scheme 57](image)

Numerous different variants of the Claisen rearrangement have been used in preceding studies. Most attractive to us was the Johnson orthoester variant. Treatment of an allylic alcohol 152 with an orthoester and sub-stoichiometric acid generates a ketene acetal 153 in situ with loss of ethanol, which can undergo Claisen rearrangement to give either of the esters syn- and/or anti-154. The lack of substitution at C1 removes the complication of setting a third stereocentre. Relative control of the C1 and C6 stereocentres is difficult to attain in the Johnson–Claisen rearrangement when a higher homologue of the orthoester is used, caused by rapid E/Z ketene acetal isomerisation. This should be taken into account if the process is extended to control more than one stereocentre.

Various orthoesters and acid catalysts have been used in the Johnson–Claisen rearrangement. In our case, we chose triethyl orthoacetate as the orthoester, which was used as the solvent, and propionic acid as catalyst. These conditions remained constant throughout our studies.
2.2.2 Synthesis and rearrangement of allylic alcohols

Our strategy for the synthesis of allylic alcohols followed the previous example of Cha,\textsuperscript{103} in which aldehydes bearing an adjacent stereocentre were subjected to Wittig olefination to give the $\alpha,\beta$-unsaturated ester, which in turn was reduced to the corresponding allylic alcohol using DIBAL-H. A variety of alkyl groups of increasing size were chosen as the group $R$. Both aliphatic and branched alkyl groups were studied. Phenyl substituents were also investigated. $\alpha,\beta$-Unsaturated ester intermediates 158a and 158f were prepared by Horner–Wadsworth–Emmons reaction of commercially available aldehydes.\textsuperscript{121} The preparation of non-commercially available aldehydes was attempted using the Levine method,\textsuperscript{122} in which Wittig olefination of a ketone 155 affords a methyl enol ether 156, which is in turn hydrolysed with perchloric acid to give the aldehyde 157. The volatility of enol ether and aldehyde intermediates 156 and 157 was problematic, and therefore we sought a method for the synthesis of $\alpha,\beta$-unsaturated esters in which isolation of the intermediates was not required.

To this end, Wittig reaction\textsuperscript{123} of a representative set of ketones afforded the enol ethers 156b–e and 156g as solutions in diethyl ether. As a heterogeneous alternative to perchloric acid for the hydrolysis, sulfuric acid supported on wet silica gel was used,\textsuperscript{124} affording a dichloromethane solution of the aldehyde 157 after removal of the silica gel by filtration. To this solution was added the phosphorane to afford esters 158b–e and 158f. Reduction of the esters 158a–g with DIBAL-H\textsuperscript{77} afforded the corresponding allylic alcohols 152a–g (Scheme 58, Table 11). The moderate yields of this process are attributed to the high volatility of the products.

![Scheme 58](image-url)
Results and Discussion

Table 11

<table>
<thead>
<tr>
<th>Entry</th>
<th>R⁰</th>
<th>R¹</th>
<th>Yield of 158 (%)</th>
<th>Yield of 152 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>Et</td>
<td>72</td>
<td>30</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>cyclopropyl</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>cHex</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>nC₅H₁₁</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>e</td>
<td>Me</td>
<td>tBu</td>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>Ph</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>g</td>
<td>Et</td>
<td>Ph</td>
<td>24</td>
<td>44</td>
</tr>
</tbody>
</table>

Exclusively E-configured esters were obtained by this method. The isomeric Z-esters and allylic alcohols were not studied. Treatment of allylic alcohols 152a–g under Johnson–Claisen conditions afforded the γ,δ-unsaturated ester products 154a–g in high yield and widely ranging diastereoselectivity (Scheme 59, Table 12).

Scheme 59

Table 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>R⁰</th>
<th>R¹</th>
<th>Yield (%)</th>
<th>Ratio anti- : syn-154⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>Et</td>
<td>98</td>
<td>50 : 50</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>cyclopropyl</td>
<td>89</td>
<td>50 : 50</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>cHex</td>
<td>91</td>
<td>83 : 17</td>
</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>nC₅H₁₁</td>
<td>98</td>
<td>50 : 50</td>
</tr>
<tr>
<td>e</td>
<td>Me</td>
<td>tBu</td>
<td>67</td>
<td>67 : 33</td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>Ph</td>
<td>99</td>
<td>68 : 32</td>
</tr>
<tr>
<td>g</td>
<td>Et</td>
<td>Ph</td>
<td>99</td>
<td>68 : 32</td>
</tr>
</tbody>
</table>

⁰Determined by ¹H-NMR analysis of crude reaction mixtures

The structure of anti-154g was established by preparation of a derivative. Reduction (LiAlH₄–Et₂O) of the 68:32 mixture of diastereomeric products of Johnson–Claisen rearrangement of 152f gave a mixture of isomeric alcohols 159, which were separated and converted into the corresponding 3,5-dinitrobenzoyl esters 160 by treatment with 3,5-dinitrobenzoyl chloride–TEA (Scheme 60).¹²⁵ The anti stereochemistry of the major diastereoisomer anti-160 was assigned by X-ray crystallography (see Appendix).¹²⁶ The same anti stereochemistry was infered for the major products of Johnson–Claisen rearrangement 154c and 154e–f.
As shown previously, the stereoselectivity in the Johnson–Claisen rearrangement of 152c and 152e–g, can be rationalised by invoking a modified Felkin–Anh model in which the C=O group is replaced with the allylic portion of the ketene acetal 153 (Scheme 61). Such a model has been used to describe explain the diastereoselectivity of conjugate organocuprate addition to γ-alkyl-α,β-unsaturated esters. Rearrangement is more likely to occur through the staggered conformation of the C6’ stereocentre in relation to the 6-membered chair transition state and the major product arises from transition state A, in an example of the ‘inside methyl’ effect. Such transition states are easily accessible in E-configured systems. This is also the product that would be predicted by the Felkin–Anh model. However, the generally moderate selectivity points to a low difference in energy between transition states A and B.
2.3 The relationship between the heteroatom and stereoselectivity

2.3.1 Background

In comparison with literature examples of Claisen rearrangements where the C6’ stereocentre bears a heteroatomic substituent, selectivities in the Johnson–Claisen rearrangements of 152a–g are non-existent or low. The next phase of our study concentrated on rearrangement of substrates where the exopericyclic stereocentre bears a heteroatomic substituent. The role of the heteroatom is clearly apparent from studies of Claisen rearrangements of dioxolanes and proline derived systems shown above. The syn product generally predominates, its formation explained in terms of favourable antiperiplanar alignment of the C—X and incipient C—C bond in the reactive conformation, with the allylic exopericyclic C—H bond eclipsing the adjacent C=C bond.

From examination of the literature, exopericyclic oxygen, nitrogen and silicon substituents appear well studied. Relatively unexplored, however are the effects of exopericyclic halogen groups, We decided to investigate the effects of exopericyclic fluorine substituents, inspired both by the analogous Diels–Alder studies of Grée71 and also Evans’ computational studies of aldol reactions of boron enolates18 (see Section 1). Additionally, since Evans showed a change from Cornforth to Felkin–Anh models upon reducing the electronegativity of the heteroatom, we decided to perform a similar study into the comparative effects of exopericyclic (C6’) thiophenyl substituents.

2.3.2 Preparation and rearrangement of γ-fluorinated allylic alcohols

We anticipated that the required fluorinated allylic alcohol 166 could be prepared by reduction of the corresponding γ-fluoro-α,β-unsaturated ester 165. A synthesis of 165 from methyl lactate has been reported by Grée,71 in which fluorine is introduced by dehydroxyfluorination of the γ-hydroxy-α,β-unsaturated ester 164.
In our case, we chose the more acid-stable TBDPS group for protection of (S)-methyl lactate. Treatment of the product 161 with DIBAL-H afforded the O-protected aldehyde 162, which was subjected to Wittig reaction to afford the O-protected α,β-unsaturated ester 163. Deprotection was attempted with both acetic acid and hydrochloric acid, but the reaction was very slow. Instead, TBAF was used to deprotect the alcohol, affording the desired γ-hydroxy-α,β-unsaturated ester 164. Racemisation of 164 occurred under these conditions, though this was inconsequential as the enantiopure compound was not required. Dehydroxyfluorination of 164 mediated by DAST gave 165 in excellent yield, without the need for purification. However, reduction of 165 to the corresponding allylic alcohol 166 could not be achieved using either DIBAL-H or lithium aluminium hydride. Only low yields of unidentifiable decomposition products were observed (Scheme 62).

Considering that 166 was likely to be relatively volatile at atmospheric pressure we prepared the higher homologue, exchanging the terminal methyl group for an n-pentyl chain. From earlier experiments, we predicted that this alteration would have no effect on the stereoselectivity of Johnson–Claisen rearrangement of the target allylic alcohol 179.

The homologous γ-hydroxy-α,β-unsaturated ester intermediate 172 was prepared using an additive Pummerer-type strategy developed in our own laboratory (Scheme 63). Isopropyl benzenesulfinate 168 was prepared from sodium benzenesulfinic acid 167 and subjected to a one-pot Horner–Wadsworth–Emmons procedure to afford the vinyl sulfoxide 169 in good yield. Addition of trifluoroacetic anhydride to 169 effected the Pummerer rearrangement to give 170 in excellent yield, without the need for purification. Base-catalysed methanolysis of 170 gave the lactide 171, which was
shown by mass spectrometry to exist as a mixture of the monomer, dimer and trimer. Finally, Wittig reaction of 171 in refluxing benzene afforded ester 172.

\[
\begin{align*}
\text{PhSO}_2\text{Na} & \quad \text{i)} \text{SOCl}_2 \quad \text{PhSO}_2\text{Pr} \\
167 & \quad \text{ii)} \text{IPA, pyridine} \\
& \quad \text{then C}_2\text{H}_4\text{CHO} \quad \text{PhSO}_2\text{Pr} \\
168 & \quad \text{(87%)} \\
& \quad \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C}, 30 \text{ min} \\
169 & \quad \text{TFAA (2 equiv)} \\
& \quad \text{(98%)}
\end{align*}
\]

Scheme 63

In contrast to 164, dehydroxyfluorination of 172 gave a mixture of products. In addition to the desired $\gamma$-fluoro compound 173, the isomeric product 174 and the eliminated product 175 were observed (Scheme 64).

\[
\begin{align*}
\text{PhS} & \quad \text{OCOCF}_3 \\
\text{C}_2\text{H}_11 & \quad \text{TEA, MeOH} \\
170 & \quad \text{CH}_2\text{C}l_2, 0 ^\circ \text{C} \quad 10 \text{ min} \\
& \quad \text{(90%)} \\
\text{C}_2\text{H}_11 & \quad \text{OH} \\
171 & \quad \text{Ph}_3\text{P} \quad \text{CO}_2\text{Et} \\
\text{PhH, reflux, 4 h} & \quad \text{(63%)} \\
& \quad \text{OH} \\
& \quad \text{C}_9\text{H}_11 \quad \text{CO}_2\text{Et}
\end{align*}
\]

Scheme 64

A mechanism was proposed to explain the formation of the rearranged side product 174 (Scheme 65). It is presumed that the first step of this reaction is in common with the first step of the DAST dehydroxyfluorination mechanism\(^{133}\) involving formation of an O–S bond. 1,4-Attack of the liberated fluoride on the enolate system 176 gives the ester enolate 177 which, through ring closing expulsion of the diethylaminodifluorothiolate group generates the fluorinated cyclopropane 178. Collapse of 178, followed by double bond isomerisation gives the side product 174. The $E$-stereochemistry of the olefin was confirmed by NOESY-NMR.
This mechanism relies on the ability of fluorine to act as a π-donor (even though it is strongly σ-withdrawing); a property exhibited in the ortho/para-directing nature of fluorine in electrophilic aromatic substitution\(^{134}\) and shown by the reported upfield \(^1\)H-NMR shifts of the allylic protons H\(_x\) in fluoroolfins (Scheme 66).\(^{135}\)

\[
\begin{array}{c}
\text{Me} \quad H \quad F \\
\delta H_x (ppm) \quad 1.50 \quad 1.54
\end{array}
\]

The elimination product 175 was inseparable from 173 by both chromatography and distillation; although as it was only produced in small quantities, the mixture was carried through to the next step. We propose that the product forms via an intramolecular elimination of the intermediate 176 (Scheme 67).

Reduction of 173 was attempted using DIBAL-H and lithium aluminium hydride, although, similarly to reactions of 165, only decomposition products were observed. Analysis of the decomposition product showed no signals in the \(^{19}\)F-NMR spectrum. Instead, 179 was prepared by saponification of 173 to give 180, followed by sodium borohydride reduction of the corresponding mixed anhydride 181 (Scheme 68).\(^{136}\) The allylic alcohol 179 was used in the next step directly following purification. Samples of 179 decomposed to an intractable tar overnight, even when refrigerated.
Results and Discussion

Johnson–Claisen rearrangement of 179 afforded a 50:50 mixture of syn- and anti-182 (Scheme 69). This lack of selectivity stands in contrast to that observed in the rearrangements of the proline- and dioxolane-containing substrates reported by Mulzer\textsuperscript{110} and Cha\textsuperscript{103} respectively. The lower yield for this substrate was attributed to its poor stability.

2.3.3 Preparation and rearrangement of γ-thiophenyl allylic alcohols

The Johnson–Claisen rearrangement of the analogous γ-thiophenyl allylic alcohol was then investigated. The previously prepared ester 164 was treated with methanesulfonyl chloride to give methanesulfonate 183, which was treated with sodium thiophenolate to give ester 184a. DIBAL-H reduction of 184a using the procedure of Bach\textsuperscript{147a} afforded 185a (Scheme 70). Other routes towards substrates of this type have been reported, and a full discussion of these is given later. Johnson–Claisen rearrangement of 185a was high-yielding, but like rearrangement of 179, unselective. Rigorously degassed triethyl orthoacetate was required in this reaction to prevent the formation of S-oxidation products.
that the required Johnson
dehydroxylfluorination of terminally protected propargyl d

Although no synth

Scheme 70

Considering the many previous examples in both nucleophilic and electrophilic
addition to C=C double bonds, we predicted that the olefin substitution pattern would
play a role in stereoselectivity. This remains comparatively poorly investigated for
Claisen rearrangements, but we expected a priori that the Z-isomers would show
enhanced selectivity for the syn product via a transition state in which 1,3-allylic
strain was minimised (Scheme 71). Therefore, the behaviour of (E)- and (Z)-allylic
alcohols in the Johnson–Claisen rearrangement were compared using the isomers of
the thiophenyl- and fluoro- compounds 185a and 179 as substrates.

Scheme 71

Although no syntheses of (Z)-γ-fluoroallylic alcohols have been reported, the
dehydroxylfluorination of terminally protected propargyl diols has been
demonstrated. Additionally, fluoroalkynes undergo cis-selective hydrogenation to
the corresponding fluoroolefin in the presence of Lindlar’s catalyst. We predicted
that the required Johnson–Claisen substrate Z-179 could be prepared by such a route
(Scheme 72). The carbanion of THP-protected propargyl alcohol 187 reacted with
hexanal to afford alcohol 188,\textsuperscript{140} which was treated with Deoxofluor [(CH$_2$OCH$_2$CH$_2$)$_2$NSF$_3$] (a more thermally stable alternative to DAST)\textsuperscript{141,131b} to afford propargyl fluoride 189. The yield was moderate for this step, although no side products were identified. Hydrogenation of 189 afforded the protected allylic alcohol 190 in high purity and yield, without the need for further purification. The reaction time was carefully controlled. Longer times resulted in over-reduction to the fully saturated compound, which was inseparable from 190. Deprotection of the alcohol was attempted with CSA and PPTS. In both cases the product decomposed upon isolation. This result, in conjunction with studies on \textit{E}-179 points to the poor stability of these compounds, though analysis by $^1$H-NMR of the decomposed material did not show the formation of a discrete product. We concluded that the fluorinated system above was too unstable for its behaviour in the Johnson–Claisen rearrangement to be studied.

\begin{diagram}
\begin{align*}
\text{Z-179} & \xrightarrow{\text{Pd/CaCO$_3$/Pb(OAc)$_2$}} \text{190} \\
\text{187} & \xrightarrow{n\text{BuLi, THF}} \xrightarrow{-78 \degree C, 30 \text{ min (77\%)}} \text{C}_9\text{H}_{11}\text{OH} \\
\text{THP} & \xrightarrow{\text{Deoxofluor, CH}_2\text{Cl}_2} \xrightarrow{-78 \degree C, 1.5 \text{ h (50\%)}} \text{C}_9\text{H}_{11}\text{F} \xrightarrow{\text{PPTS, EtOH, 55 \degree C or CSA, EtOH,}} \text{C}_9\text{H}_{11}\text{OH} \\
\end{align*}
\end{diagram}

\textit{Scheme 72}

In light of this setback our attention turned towards looking at the behaviour of (Z)-thiophenyl allylic alcohols in the Johnson Claisen rearrangement. We attempted to prepare the Z-configured allylic alcohol 185b \textit{via} a route similar to that above (Scheme 73). Again, the monoprotected diol 191 was prepared from THP-protected propargyl alcohol 187. Ultrasound-assisted Mitsunobu reaction\textsuperscript{142} installed the sulfide 192, which could not be reduced under Lindlar conditions. We attribute this to poisoning of the catalyst by the sulfide.\textsuperscript{143} Instead, diimide,\textsuperscript{144} generated \textit{in situ} from decomposition of NBSH\textsuperscript{145} was used. Tracking of this reaction proved difficult, owing to the very low polarity of 192. Prior deprotection increased the polarity of the system, and the propargyl alcohol 193 was reduced to give 185b. Although yields were generally low and this is clearly an inefficient route, a sufficient quantity of 185b was prepared for further investigation.
In contrast to \(185a\), Johnson–Claisen rearrangement of \(185b\) gave a 91:9 mixture of products \(186a\) in excellent yield. As expected, the reaction time was longer for the \(Z\)-isomer \(^{146}\) (Scheme 74). In the same manner as before, the structure of the major diastereomer was established by the synthesis of a derivative.

The 3,5-dinitrobenzoyl esters of the alcohols derived from Johnson-Claisen products \(186a\) were prepared in the same fashion as \(160\). The corresponding esters were obtained as a viscous liquid, and therefore it was not possible to prepare pure samples suitable for crystallographic analysis. Instead, hydrolysis of the 91:9 mixture of isomers \(186a\) gave a mixture of isomeric acids \(196\), which were converted to the corresponding highly crystalline 2,4-dinitroanilides \(197\) (Scheme 75). Separation of this mixture gave a pure sample of the major isomer \(s\)-\(197\), whose stereochemistry was assigned by X-ray crystallography (see Appendix).
2.4 The effects of olefin substitution pattern on stereoselectivity

2.4.1 Substrate synthesis

Encouraged by the above result, we sought other examples of selectivity in this reaction. We decided to investigate the effects of larger \((nC_5H_{11})\) and branched \((iPr)\) alkyl substituents on the stereoselectivity of the rearrangement. A route was required in which both the alkyl substituent and olefin geometry could be easily varied. The most commonly used route for synthesis of these compounds involves olefination of an \(\alpha\)-sulfenyl aldehyde 200, followed by reduction of the resulting \(\alpha,\beta\)-unsaturated ester 201 (Scheme 76). The \(\alpha\)-sulfenyl aldehyde itself is typically generated either from methyl lactate (Bach/Armstrong)\(^{147}\) or the sulfide 205 (Yadav).\(^{148}\) With the former, variation of the nature of the alkyl chain would be difficult.

More recently, Armstrong has reported a route to both \(E\)- and \(Z\)-\(\gamma\)-sulfenyl-\(\alpha,\beta\)-unsaturated esters 201 by variation of the phosphonate anion.\(^{149}\) The \(\alpha\)-sulfenyl aldehyde 200 was prepared in an organocatalytic, enantioselective fashion using the chemistry of Jørgensen.\(^{150}\) In the same pot (\(\alpha\)-sulfenyl aldehydes racemised during purification over silica gel), use of triethyl phosphonoacetate in a Horner–Wadsworth–Emmons reaction gave the \(E\)-\(\gamma\)-sulfenyl-\(\alpha,\beta\)-unsaturated esters 201, while use of the Ando phosphonate\(^{151}\) gave the \(Z\)-isomers. DIBAL-H reduction of these esters would provide access to the required allylic alcohol substrates 185 and we chose to use a route of this type for our work. Other routes to compounds of this type
via radical isomerisation\textsuperscript{152} and Peterson\textsuperscript{153} olefination have also been reported, although these examples were deemed too specific for our work.

**Armstrong Route**

\[
\begin{align*}
198 & \xrightarrow{\text{PhMe, rt, 5 h}} 199 \text{ (10 mol)} \\
& \quad \text{or} \\
R & \xrightarrow{(\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et}} \quad (\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et} \\
& \quad n\text{BuLi, CH}_2\text{Cl}_2, -78^\circ\text{C}, 1\text{h} \\
& \quad n\text{BuLi, CH}_2\text{Cl}_2, -78^\circ\text{C}, 1\text{h} \\
\end{align*}
\]

199 = \[
\begin{align*}
\text{Ar} &= 3.5-(\text{CF}_3)_2\text{C}_6\text{H}_3
\end{align*}
\]

**Bach Route**

\[
\begin{align*}
\text{Me} & \xrightarrow{\text{PhSH, K}_2\text{CO}_3} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{(\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et}} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{(\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et}} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{(\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et}} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\text{Me} & \xrightarrow{(\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et}} \text{Me} \\
\text{Me} & \xrightarrow{\text{DIBAL-H, CH}_2\text{Cl}_2} \text{Me} \\
\end{align*}
\]

As enantipure substrates were not required we explored other methods of \(\alpha\)-sulfenylation of aldehydes. The reaction was optimised with the substrates 185\textsuperscript{a} and 185\textsuperscript{b}, where \(R=\text{Me}\) was the ultimate targets. We did not attempt to reproduce the chemistry of Yadav\textsuperscript{148} for the synthesis of these intermediates. The preparation of \(\alpha\)-sulfenyl aldehydes by treatment of \(\alpha\)-haloaldehydes with thiolates has been reported,\textsuperscript{154} and our attention turned to this method for the preparation of 204. Treatment of propanal with sulfuryl chloride afforded the \(\alpha\)-chloroaldehyde 207\textsuperscript{a},\textsuperscript{155} which existed in a stable oligomeric form at sub-ambient temperatures.\textsuperscript{156} Gentle
warming of the oligomeric material to room temperature revealed the monomeric aldehyde,\textsuperscript{157} which reacted with sodium thiophenate, generated \textit{in situ} from thiophenol and sodium hydride to afford the \(\alpha\)-sulfenyl aldehyde 204a (Scheme 77).

![Scheme 77](image_url)

However, the isolated material decomposed, to some extent, to thiophenol, which quenched the phosphonate in the subsequent olefination reactions. Pre-washing of the aldehyde with sodium carbonate failed to alleviate this problem. We attempted a one-pot sulfenylation/olefination approach similar to that of Armstrong.

Reasoning that such a strong base as sodium hydride was not required for formation of the thiolate, we found that the \(\alpha\)-chloroaldehyde 207a reacted rapidly at room temperature with triethylammonium thiophenate in THF, generated \textit{in situ} from TEA–thiophenol, to give a solution of 204a. The lower-temperature conditions for use of sodium hydride were not required. The solution of the \(\alpha\)-sulfenyl aldehyde was filtered under nitrogen and added \textit{via} cannula to a solution of the appropriate phosphonate anion. In common with Armstrong, use of triethyl phosphonoacetate in a Horner–Wadsworth–Emmons (HWE) reaction at 0 °C gave the \(E\)-\(\gamma\)-sulfenyl-\(\alpha\),\(\beta\)-unsaturated ester 184a exclusively. Reaction with the anion of the Ando phosphonate\textsuperscript{151} at the lower temperature of –78 °C gave the esters 184b and 184a in a 10:1 ratio respectively (Scheme 78).

![Scheme 78](image_url)

We extended this route to other substrates. The analogous chloroaldehydes were prepared using the organocatalytic method of Jørgensen;\textsuperscript{150b,158} 207b using proline and 207c using prolinamide as the catalyst. Yields for the olefination were moderate,
although the reaction was easily scalable and sufficient material was prepared for further investigation (Scheme 79, Table 13).

![Scheme 79]

**Table 13**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Phosphonate</th>
<th>E/Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>207a</td>
<td>Me</td>
<td>HWE</td>
<td>E</td>
<td>47</td>
</tr>
<tr>
<td>b</td>
<td>207a</td>
<td>Me</td>
<td>Ando</td>
<td>Z</td>
<td>29</td>
</tr>
<tr>
<td>c</td>
<td>207b</td>
<td>nC₅H₁₁</td>
<td>HWE</td>
<td>E</td>
<td>57</td>
</tr>
<tr>
<td>d</td>
<td>207b</td>
<td>nC₅H₁₁</td>
<td>Ando</td>
<td>Z</td>
<td>73</td>
</tr>
<tr>
<td>e</td>
<td>207c</td>
<td>iPr</td>
<td>HWE</td>
<td>E</td>
<td>60</td>
</tr>
<tr>
<td>f</td>
<td>207c</td>
<td>iPr</td>
<td>Ando</td>
<td>Z</td>
<td>27</td>
</tr>
</tbody>
</table>

During the synthesis of these substrates, particularly when the reaction time was extended, formation of the isomeric product 208 was observed as a 30:70 (unassigned) mixture of E and Z stereoisomers, which was inseparable from 184. An NMR experiment suggested a base-catalysed mechanism for the formation of 208 (Scheme 80, Table 14). The ratio of stereoisomers remained constant over time.

![Scheme 80]

<table>
<thead>
<tr>
<th>Table 14</th>
<th>Time (min)</th>
<th>Conversion to 208 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

Reducing the amount of base used for the olefination reaction, reduced the yield. The milder Masamune–Roush (DBU–LiCl) conditions for the synthesis of E-isomers[^121^]
and modified Ando (DBU–NaI) conditions\textsuperscript{15b} for the synthesis of Z-isomers, might be used in future work.

The esters 184a–f were reduced to the corresponding allylic alcohols 185a–f with DIBAL-H (Scheme 81, Table 15). Much lower (ca. 20\%) yields were observed upon switching the chromatography eluent from TBME/heptane to ether/heptane, which may be related to the lower level of ether peroxides present in TBME.

### Scheme 81

![Scheme 81]

#### Table 15

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>E/Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>E</td>
<td>71</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Z</td>
<td>70</td>
</tr>
<tr>
<td>c</td>
<td>nC\textsubscript{5}H\textsubscript{11}</td>
<td>E</td>
<td>83</td>
</tr>
<tr>
<td>d</td>
<td>nC\textsubscript{5}H\textsubscript{11}</td>
<td>Z</td>
<td>60</td>
</tr>
<tr>
<td>e</td>
<td>iPr</td>
<td>E</td>
<td>83</td>
</tr>
<tr>
<td>f</td>
<td>iPr</td>
<td>Z</td>
<td>54</td>
</tr>
</tbody>
</table>

#### 2.4.2 Rearrangements of E- and Z-allylic alcohols

Allylic alcohols 185a–f were subjected to Johnson–Claisen rearrangement conditions (Scheme 82, Table 16) to give 186a–c. The contrasting behaviour observed for 185a,b was also observed with the geometric isomers 185c,d and 185e,f; yields were uniformly excellent. Reaction times followed the expected pattern, with the more hindered substrates undergoing rearrangement more slowly. In light of the results of the X-ray crystallography studies on 186b above, \textit{syn} stereochemistry was inferred also for the major products of the Johnson–Claisen rearrangements of 185d and 185e,f.

![Scheme 82]
We rationalise the marked difference in behaviour of \textit{E}- and \textit{Z}-185 by comparison of the diastereomeric transition states A–D for the rearrangement (Scheme 83). In all cases there is antiperiplanar alignment of the C6’–SPh and incipient C1–C6 bond. For \textit{Z}-185, the major product \textit{syn}-186 arises from an orientation in which the C6’–H bond (transition state A) rather than the C6’–R bond (transition state B) eclipses the allylic C4–C5 double bond. For \textit{E}-185, the corresponding allylic 1,3-interactions are between C5–H and the C6’–H (transition state C leading to \textit{syn}-186) or C6’–R (transition state D leading to \textit{anti}-186) bonds; the lesser steric bulk associated with C5–H compared to C4–C5 leads to lower selectivity for the \textit{E}-substrates. This lack of discrimination is in contrast to that observed in the rearrangement reactions of analogous dioxolane- and proline-containing systems reported by Cha\textsuperscript{103} and Mulzer\textsuperscript{110} respectively, and taking into account the results presented in the next chapter, may be a consequence of the lack of substitution at C1 in our acetate-derived substrates.
Results and Discussion

2.4.3 Preparation and rearrangement of a trisubstituted allylic alcohol

In light of the transition state analysis presented above an additional substrate was prepared and its Johnson–Claisen rearrangement investigated. We reasoned that rearrangement of an *E*-configured substrate possessing a substituent at C5 would be more selective than those of *E*-185, since, upon introducing an unfavourable 1,3-diaxial interaction, there would be a disproportionately greater energy penalty associated with the transition state corresponding to D in Scheme 83, which leads to the *anti* product.

The allylic alcohol 210 bearing an additional olefinic methyl group was prepared in the same manner as 185: addition of the α-sulfonyl aldehyde 204a to the anion of the appropriate phosphonate afforded ester 209, which was subsequently reduced with DIBAL-H to afford 210. Subjection of 210 to the previously established Johnson–Claisen conditions gave in quantitative yield a 71:29 mixture of rearrangement
Results and Discussion

products \( \mathbf{211} \) (Scheme 84). From prior evidence, we tentatively assigned the major product as the \textit{syn} isomer. Additional evidence in support of this assignment is given by the similar rearrangements of azide-bearing systems shown later. This result is in contrast with those of Takano, who observed no selectivity increase in rearrangements of trisubstituted allylic systems. In summary, we have shown that in the case of C6’ thiophenyl substituents, the level of selectivity is highly dependent on the allylic substitution pattern.

![Scheme 84](image-url)
2.5 Synthetic applications of exopericyclic control in Claisen rearrangements

2.5.1 Background

With reliable patterns of stereoselectivity emerging, we wished to exploit these effects in the synthesis of small molecules. We had shown the importance of a heteroatom-bearing stereocentre in attaining stereoselectivity and now wished to explore reactions of the heteroatomic group. This section details our efforts in this area, concentrating on further transformations of rearrangement products. Also described is initial work on elaboration of the new olefin furnished by the Claisen rearrangement.

We envisaged that oxidative cleavage of the olefin of 213 to give the corresponding aldehyde or ketone 214 would provide scope for further transformations of this system (Scheme 85).

\[
\begin{align*}
\ce{[3,3]} & \rightarrow \\
\text{Oxidative cleavage} & \rightarrow \\
\text{Further transformation of functional heteroatoms}
\end{align*}
\]

Scheme 85

In particular, we became interested in Claisen rearrangements of allylic systems bearing nitrogenous \textit{exo}-pericyclic stereocentres, envisaging that the Claisen rearrangement product 216 of a ketene acetal bearing an exopericyclic amine 215 could be converted into the corresponding \(\gamma\)-lactam 217 (Scheme 86).

\[
\begin{align*}
\text{[3,3]} & \rightarrow \\
\text{assuming } & \text{anti-Felkin (syn) stereoselectivity}
\end{align*}
\]

Scheme 86

Free amines are poorly tolerated by the Claisen rearrangement and prior examples of this reaction typically use protecting groups to overcome this problem. In our case, introducing the stereoelectronic complication of a bulky protecting group was
unattractive. Instead, we decided to use the azide group as a surrogate amine, encouraged by its small steric profile and its potential for use in a wide variety of subsequent reactions. We quickly realised that this process would be complicated by a second rearrangement – that of the allylic azide itself; a reaction that has previously been viewed as a synthetic limitation of this functional group.

### 2.5.2 Sigmatropic rearrangements of allylic azides

The rearrangement of allylic azides was discovered in 1960, when Winstein and co-workers found that treatment of \(\gamma,\gamma\)-dimethallyl chloride with sodium azide in acetone gave an equilibrating mixture of \(\alpha,\alpha\)-dimethallyl and \(\gamma,\gamma\)-dimethallyl azides. The rearrangement was rapid at room temperature, although the isomers could be separated by fractional crystallisation at \(-80^\circ\)C. Similar rearrangements of allylic diazides were observed by Heasley, who noted that tertiary and secondary allylic azides rearrange faster than primary allylic azides. A very small solvent effect on the rate of rearrangement was reported by Winstein; which, in addition to NMR studies by Closs indicates charge separation in the transition state. Nevertheless, the stereospecific nature of the rearrangement, as explored by Padwa, suggests a cyclic, concerted transition state and the reaction may be viewed as a \([3,3]\)-sigmatropic rearrangement (Scheme 87).

![Scheme 87](image)

Allylic azides are generally obtained as thermodynamic mixtures. For acyclic allylic azides the rearrangement is rapid at room temperature, while cyclic allylic azides
often rearrange more slowly.\textsuperscript{164} The vast majority of allylic azides described in the literature exist as a single regioisomer in which the olefin is in conjugation with an aryne,\textsuperscript{172,165} carbonyl or nitrile.\textsuperscript{166} Recently, steric factors have been found to influence the equilibrium.

Of key importance for our studies is the small class of reactions in which equilibrating mixtures of allylic azides are transformed into a single product. The earliest report of this reactivity mode is described by Danishefsky in the synthesis of \textit{N}-acetyllactinobolamine.\textsuperscript{167} Osmylation of the mixture 218 and 219 occurred exclusively \textit{via} the more nucleophilic glycal 219 to give 220 exclusively (Scheme 88).

More recently, Sharpless and Fokin studied the behaviour of mixtures of allylic azides in the Cu(I)-catalysed cycloaddition with phenylacetylene and in MCPBA-mediated epoxidation reactions.\textsuperscript{168} The differences between primary, secondary and tertiary allylic azides were explored. Mixtures of primary and tertiary (221,222), and secondary and tertiary azides reacted selectively \textit{via} the most reactive isomer (the less hindered azide, or the more electron-rich olefin), while dramatically reduced selectivity was observed with mixtures of primary and secondary azides 225,226 (Scheme 89). Notably, in all but one example, the most abundant isomer of the mixture was also the most reactive.
2.5.3 Development of a tandem rearrangement process

In light of these examples, we proposed a reaction in which a ketene acetal bearing an allylic azide 231 undergoes a pair of [3,3]-sigmatropic rearrangements via 232 to give the product 233 (Scheme 90). Conceptually related are the isomerisation-Claisen rearrangements most recently explored by Nelson et al.\textsuperscript{169} and other examples in the literature of tandem conjugate addition/enolate Claisen rearrangements.\textsuperscript{170} However, in these prior examples an isomerisation establishes the vinylic portion of the ketene acetal Claisen precursor. To the best of our knowledge, the studies presented herein represent the only example of isomerisation establishing exclusively the allylic portion of a ketene acetal.\textsuperscript{171}
The work presented in this section describes our work into the development, scope and limitations of this reaction. We have continued to explore the stereochemical patterns previously discussed.

2.5.4 Synthesis and initial rearrangements of allylic azidoalcohol substrates

We decided to study this reaction using a Johnson–Claisen rearrangement of the mixture of allylic azidoalcohols 235a and 236a, which would be converted into the required mixture of equilibrating ketene acetals in situ. In particular, for this initial study we chose compounds bearing an n-pentyl chain, in order to reduce volatility and improve thermal stability. A similar compound 235e, reported by Whitesides et al. was prepared by reaction of oxirane 234e with sodium azide. The oxirane was prepared by sulfur-ylide epoxidation of trans-cinnamaldehyde 237 (Scheme 91).

Proposed Reaction:

[Scheme 91: Diagram showing the reaction between oxirane and sodium azide to form ketene acetals and oxiranes]

Our initial attempts to form oxirane 234a from trans-2-octenal 238a under these conditions failed. The oxirane was unstable to chromatography over silica gel and was difficult to separate from the DMSO reaction solvent by distillation. Instead, 234a was prepared via the chlorohydrin 239a (Scheme 92). Addition of
lithiochloromethane to $\text{238a}$ gave the chlorohydrin $\text{239a}$, which was then converted into $\text{234a}$ by treatment with sodium hydride and sub-stoichiometric sodium iodide. When the precursor chlorohydrin was of high purity no purification of the oxirane was required, allowing its use directly in the next step. Reaction of $\text{234a}$ with sodium azide in refluxing acetone/water gave a 73:27 (by $^1$H-NMR) mixture of $\text{235a}$ and $\text{236a}$ respectively in good yield. The regioisomers were partially separable by column chromatography, although they equilibrated prior to analysis to give a mixture having the same ratio as the crude mixture. Assignment of each isomer was performed using COSY and $^{15}$N-HMBC NMR techniques. Notably, the more abundant isomer $\text{235a}$ is that which requires a further isomerisation to participate in the Claisen rearrangement.

To eliminate the possibility that the regioisomeric distribution was controlled by relative rates of 1,2- and 1,4-opening of the oxirane rather than an equilibration process, we studied the ring-opening of $\text{234a}$ with potassium cyanide, which could potentially give a mixture of the non-equilibrating allylic nitriles $\text{240}$ and $\text{241}$ (Scheme 93). Although opening of the oxirane by water competed with opening by cyanide, only the 1,2-opening products $\text{241}$ and $\text{242}$ were observed. This indicated that in the reaction of $\text{234a}$ with sodium azide, the 1,2-product $\text{235a}$ is initially formed, followed by isomerisation via reversible sigmatropic rearrangement to give the observed mixture of regioisomers. The low yield may be attributed to the poor stability of the oxirane at elevated temperature over long periods of time.
The mixture of 235a and 236a was then treated under the Johnson–Claisen conditions used previously (Scheme 94). Complete conversion of the mixture was observed in 6 h and the product was isolated in very high yield. This represents the first example of a reaction that discriminates between two acyclic secondary allylic azides. It is also the first example of any such transformation of allylic azides where the product arises from the significantly less abundant component of the equilibrium mixture.

2.5.5 Attempts to develop a stereoselective rearrangement

In the initial reactions described above, no stereoselectivity was observed, although this was not unexpected considering our previous investigations into the effects of olefin substitution pattern. Although we have shown that Z-allylic alcohols undergo selective Claisen rearrangements, we predicted that Z-allylic azidoalcohols might undergo olefin isomerisation during Winstein rearrangement. Given that the rate of Claisen rearrangement of an E-allylic system is faster than the Z-isomer, we predicted that equilibrating mixtures of Z-allylic azidoalcohols would undergo Claisen rearrangement with significantly reduced stereoselectivity. Thus, in the course of our studies into the scope and limitations of this process, our interest turned to other methods of attaining selectivity in the Claisen rearrangement of E-allylic alcohols.
Specifically, we wished to study trisubstituted allylic systems 244, which we predicted would favour the anti-Felkin product 3,3-syn-245 (Scheme 95).

Scheme 95

The generality of this tandem process was tested using variations of the R and R’ groups. Substrates were prepared by a general route, in the same manner as that reported by Whitesides172 (Scheme 96). Variations of the R group enabled the study of the relative effects of straight chain and branched alkyl groups, and this was examined both for R’=H and R’=Me where possible. In addition, we chose to explore the case where R=aryl, with regard to its effects on product distribution in both the Winstein and Claisen rearrangements.

Scheme 96

As shown above, where R=Ph the allylic azidoalcohol 235e exists as a single isomer which would require isomerisation to participate in the Claisen rearrangement. Aromaticity decreases across the series benzene>pyridine>furan176 so we proposed the series R=Ph, 2-pyridyl and 2-furyl to investigate the effects of lowering aromaticity, and therefore conjugative stabilisation of 235 on the system. In doing so, we predicted that the barrier to isomerisation might be lowered, increasing the rate with which mixtures of these compounds undergo Claisen rearrangement. Conversely, we reasoned that if R’=Ph, then the allylic azidoalcohol would be stabilized as the
Results and Discussion

reactive form 236. Indeed, we were interested to explore whether under appropriate conditions, allylic azidoalcohols that exist exclusively in the unreactive form might still undergo Claisen rearrangement.

Chlorohydrins 239a–f and 239h were prepared using the conditions shown above (Scheme 97, Table 17). In each case, the reaction was complete within 1 h. Where the precursor ketone or aldehyde 238 was not commercially available, it was prepared via Wittig olefination of the corresponding aldehyde. Ketone 238f was prepared by addition of phenylmagnesium chloride to crotonaldehyde and PDC oxidation of the alcohol intermediate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>nC₅H₁₁</td>
<td>H</td>
<td>81</td>
<td>f</td>
<td>Me</td>
<td>Ph</td>
<td>52</td>
</tr>
<tr>
<td>b</td>
<td>nC₅H₁₁</td>
<td>Me</td>
<td>92</td>
<td>g</td>
<td>2-pyridyl</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>Me</td>
<td>35</td>
<td>h</td>
<td>2-pyridyl</td>
<td>Me</td>
<td>88</td>
</tr>
<tr>
<td>d</td>
<td>cHex</td>
<td>Me</td>
<td>84</td>
<td>i</td>
<td>2-furyl</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>H</td>
<td>99</td>
<td>j</td>
<td>2-furyl</td>
<td>Me</td>
<td>0</td>
</tr>
</tbody>
</table>

Yields were generally high, with some exceptions. The low yield of 239c was attributed to its volatility. The furans 239i and 239j decomposed violently upon isolation to give an intractable tar. A similar, albeit slower decomposition of the pyridine 239g was observed. A mechanism is proposed involving formation of the oxirane 234 with loss of HCl. This could be followed by ring-opening of 234 and subsequent acid-assisted decomposition, with the furyl group stabilising the developing partial positive charge on the more substituted oxirane carbon (Scheme 98).
Treatment of the chlorohydrins 239a–f and 239h with sodium hydride and substoichiometric sodium iodide afforded the oxiranes 234a–g (Scheme 99, Table 18). No further purification was required and these compounds were used directly in the next step. 234c (R=Me) was highly volatile, and could only be isolated as a solution in THF. The concentration of the solution was determined by \(^1\)H-NMR analysis.

\[
\begin{align*}
\text{R} & \quad \text{R'} & \text{Yield (%)} & \quad \text{Entry} & \quad \text{R} & \quad \text{R'} & \text{Yield (%)} \\
a & \text{\(n\)C\(_5\)H\(_{11}\)} & \text{H} & 97 & e & \text{Ph} & \text{H} & >99 \\
b & \text{\(n\)C\(_5\)H\(_{11}\)} & \text{Me} & 40 & f & \text{Me} & \text{Ph} & 98 \\
c & \text{Me} & \text{Me} & 46 & g & \text{2-pyridyl} & \text{Me} & 66 \\
d & \text{cHex} & \text{Me} & 98 & \\
\end{align*}
\]

Treatment of the oxiranes 234a–g with sodium azide in acetone/water gave the allylic azidoalcohols 235/236a–f (Scheme 100, Table 19). The reaction was performed under reflux with the exception of 236f, which was isolated in low (<14%) yield under these conditions. Stabilisation of the developing partial positive charge by both phenyl and vinyl groups bound directly to the quaternary carbon enhance the rate of opening of the oxirane 234f. Elevated temperatures are therefore not required and only cause decomposition of the starting material. The reaction was repeated at room temperature, affording the allylic azidoalcohol 236f in good yield.
Mixtures of trisubstituted allylic azidoalcohols 235/236b–d were obtained in similar ratios, favouring the tertiary (vicinal) azidoalcohol. This isomer was less favoured compared to 235a. Azidoalcohols 235e and 235g were obtained as single isomers with the olefin in conjugation with the aryne as predicted. 236f was obtained as an inseparable 3:1 E:Z mixture of isomers (determined by NOESY-NMR), both secondary azides as predicted. A full discussion of the individual factors affecting ratios of allylic azides is given later.

Allylic azidoalcohols 235/236a–g were exposed to Johnson–Claisen conditions. (Scheme 101, Table 20). In addition to the rearrangement product 243a, 243b–d and f were obtained in good yield, although extended reaction times were required for these more sterically demanding substrates.

![Scheme 101](image)

Trisubstituted allylic systems 235/236b–d rearranged with moderate stereoselectivity; of lower magnitude than analogous sulfide systems. 236f was the only example of a
Z-configured allylic system undergoing rearrangement. Interestingly, in contrast to previous examples, no stereoselectivity was observed. **235e** did not rearrange under these conditions. **243g** was obtained as an impure compound in very low yield, thus the magnitude of this selectivity is likely to be invalid. To exclude the effects of neutralisation of the propionic acid catalyst by the 2-pyridyl substituent (examination of pKa values suggests the pyridine would be fully protonated), the reaction was repeated using 1.2 equivalents of propionic acid. The yield was unaffected. Clearly, substrates where R=Ar do not participate in this tandem sigmatropic process.

### 2.5.6 Synthesis of γ-lactams

In the next phase of the work, the conversion of Claisen products into the corresponding lactams was investigated. The intention was both to demonstrate the synthetic utility of the preceding reaction and to impose a conformational constraint, such that the sense of stereoinduction could be assigned by spectroscopic methods. The transformation of azidoesters into lactams via Staudinger reduction\(^ {177}\) of the azide and *in situ* cyclisation of the intermediate aminoester is well preceded.\(^ {178}\) Triphenyl-, tributyl- and trimethylphosphine are commonly used to generate the iminophosphorane intermediate, which is intercepted by water. This technique has been used previously for the cyclisation of Claisen rearrangement products bearing azide groups.\(^ {178c}\) We chose the mixture of stereoisomers **243c** to investigate this process.

Treatment of **243c** with triphenylphosphine in water under microwave irradiation afforded the lactam **244a**, although due to its high polarity it was difficult to separate from the triphenylphosphine oxide by-product. Switching to polystyrene resin-supported diphenylphosphine\(^ {179}\) alleviated this problem as the reagent and by-products could be removed by filtration. Under these conditions the mixture of lactams *syn-* and *anti-*244a was obtained in good yield and with no change in diastereomeric ratio (Scheme 102). The starting material was not consumed when the reaction was performed at room temperature, indicating that heat was required to generate the iminophosphorane intermediate. NOESY-NMR of the product mixtures showed an nOe enhancement between H4-H5 in the major product, confirming its
identity as the predicted syn-diastereomer. Separation of the diastereomers was not attempted.

![Scheme 102](image)

The products of other moderately selective rearrangements 243b and 243d were unreactive under these conditions; neither the lactam product nor the intermediate amine was observed. Reasoning that the lack of reactivity was caused by steric crowding around the internal azide nitrogen, smaller and more nucleophilic trimethylphosphine was used to generate the intermediate iminophosphorane. Neat samples of 243b and 243d were treated with water and a solution of trimethylphosphine in THF at room temperature to give the lactams syn- and anti-244b and 244c respectively (Scheme 103, Table 21). Inspection of 1H-NMR spectra and NOE enhancements showed a change in the product distribution; the anti-diastereomer becoming more abundant. When the reaction of 243c (R=Me) was repeated using trimethylphosphine a similar change in ratio was observed. 243f was also converted into the corresponding lactam 244d.

![Scheme 103](image)

### Table 21

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>Phosphine</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio syn- : anti-244a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>py-PPh2</td>
<td>30 min, 120 °C (m/w)</td>
<td>244a</td>
<td>87</td>
<td>60 : 40</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>PMe3</td>
<td>40 min, rt</td>
<td>244a</td>
<td>59</td>
<td>45 : 55</td>
</tr>
<tr>
<td>nC6H11</td>
<td>Me</td>
<td>PMe3</td>
<td>40 min, rt</td>
<td>244b</td>
<td>75</td>
<td>56 : 44</td>
</tr>
<tr>
<td>cHex</td>
<td>Me</td>
<td>PMe3</td>
<td>18 h, rt</td>
<td>244c</td>
<td>59</td>
<td>33 : 66</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>PMe3</td>
<td>8 h, rt</td>
<td>244d</td>
<td>80</td>
<td>50 : 50</td>
</tr>
</tbody>
</table>

*a*By 1H-NMR analysis
The change in product distribution may be rationalised by considering the relative rates of cyclisation of aminoester intermediates \textit{syn-245} and \textit{anti-245} (Scheme 104). The reactive conformation of \textit{syn-245} exhibits an unfavourable interaction between the R and methallyl groups not present in the reactive conformation of \textit{anti-245}. The yields and product ratios are consistent with this difference in reactivity: in each case, the yields of the \textit{syn} and \textit{anti} products are consistent with the ratio of \textit{syn} and \textit{anti} isomers in the starting material (Table 22). As this model suggests, the \textit{syn} cyclohexyl substrate \textit{243d} appears to be the least reactive, and overall, \textit{syn} azidoesters are significantly less reactive than their \textit{anti} isomers.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{R} & \textbf{Yield} \\
\hline
Me, Yield 59\% & \textbf{60 syn : 40 anti $\rightarrow$ 45 syn : 55 anti} \\
& \text{Yield (syn)} = (45 \times 59\%) = 27\% \quad (27<60) \\
& \text{Yield (anti)} = (55 \times 59\%) = 32\% \quad (33<40) \\
\hline
nC\textsubscript{5}H\textsubscript{11}, Yield 75\% & \textbf{59 syn : 41 anti $\rightarrow$ 56 syn : 44 anti} \\
& \text{Yield (syn)} = (56 \times 75\%) = 42\% \quad (42<59) \\
& \text{Yield (anti)} = (44 \times 75\%) = 33\% \quad (33<41) \\
\hline
cHex, Yield 59\% & \textbf{63 syn : 37 anti $\rightarrow$ 33 syn : 66 anti} \\
& \text{Yield (syn)} = (33 \times 59\%) = 19\% \quad (19<63) \\
& \text{Yield (anti)} = (66 \times 59\%) = 39\% \quad (39<37) \\
\hline
\end{tabular}
\caption{Table 22}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme104}
\caption{Scheme 104}
\end{figure}

\subsection{2.5.7 Decarboxylative Claisen rearrangements of allylic azides}

Our interest returned to the low stereoselectivity of these rearrangements. Considering that further exploration of the effects of olefin substitution pattern would be difficult using this particular system, we decided to investigate the previously unexplored effects of substitution on the vinylic portion (C1) of the ketene acetal.
Examples from our own laboratory and others\textsuperscript{103,110,118} are reported of \textit{trans}-allylic esters bearing substituents adjacent to the carbonyl undergoing stereoselective Ireland–Claisen rearrangements. We proposed that increased steric bulk at C1 would increase the diastereofacial selectivity of attack on the allylic portion of the ketene acetal.

The dCr reaction developed in our own laboratory\textsuperscript{182} appeared particularly attractive for further study of the tandem Winstein–Claisen rearrangement process. \textit{α}-Tosyl esters of the type 246, when treated with a silylating agent (typically BSA, although TBDMSOTf–DBU has been used for tosylmalonate substrates) and substoichiometric KOAc undergo Claisen rearrangement followed by concomitant desilylation and decarboxylation to afford homoallylic sulfones 247. Heating of the ester substrate with BSA in the absence of KOAc affords the non-decarboxylated product, and a catalytic cycle has been proposed which accounts for this (Scheme 105). Reaction of BSA with KOAc gives TMSOAc 249 and the acetamide salt 248, which together effect silylation and enolisation of the substrate, giving 250. Following [3,3]-sigmatropic rearrangement, the nucleophilic acetate anion abstracts the TMS group from the product silyl ester 251 with concomitant loss of carbon dioxide. Abstraction of a proton of the resulting \textit{α}-sulfonyl anion regenerates the active system 248/249 and gives the homoallylic sulfone product 247.

The dCr reaction is a very active area of interest in the Craig group. The reaction has been applied to the synthesis of both small molecules (among which are phenols,\textsuperscript{183} pyridines,\textsuperscript{184} vinylcyclopropanes,\textsuperscript{185,102} dearomatised furans\textsuperscript{125} and other heteroaromatic substrates\textsuperscript{186}) and complex natural products.\textsuperscript{187} We have also performed NMR kinetic studies of the reaction.\textsuperscript{188} We are currently developing total syntheses of several natural products based on this methodology and are developing base-free variants of the reaction.
As with other Claisen rearrangements, the rate of reaction is highly substrate-dependent. Tosylmalonate substrates undergo dCr reaction under mild conditions, while microwave heating has been extensively used to trigger rearrangement of less reactive substrates. Nevertheless, the scope of the transformation is very wide. Indeed, we were very interested to explore the behaviour of equilibrating mixtures of allylic azides in this reaction. The attractiveness of the dCr reaction for this study lies in two factors: the steric bulk of the C1 tosyl group should enhance selectivity; and the subsequent decarboxylation process removes the complication of a third stereocentre. Thus, any observed stereoselectivity in the reaction of the substrates presented herein results exclusively from exopericyclic stereocontrol.

In common with previous studies, the system 235a/236a was used for initial investigation and optimisation of this reaction. Esterification of the mixture of allylic azidoalcohols 235a/236a with DCC and substoichiometric DMAP gave the mixture of esters 252a/253a (Scheme 106). The ratio of allylic azide isomers changed slightly, with the vicinal oxy-azido isomer 252a less abundant than in the corresponding mixture of allylic azidoalcohols.
Results and Discussion

Treatment of the azidoesters 235a/236a with BSA and sub-stoichiometric potassium acetate in toluene under reflux resulted in no reaction taking place. However under microwave conditions, the homoallylic sulfone 254a was obtained in low yield but good diastereoselectivity; particularly when compared to the non-selective rearrangement of the analogous allylic azidoalcohol to give 243a. The diastereomers were separable, and X-ray crystallography (see Appendix) showed the major product to be the predicted syn diastereomer (Scheme 107).

Scheme 106

We performed studies to optimise this reaction and increase its yield. More forcing conditions and removal of the solvent from the reaction mixture gave only a slight increase in yield (Table 23, entry 2). Complete decomposition of the starting material was observed upon increasing the reaction temperature to 200 °C (entry 3). Noting that potassium acetate is required for decarboxylation, the reaction was run in non-decarboxylative mode using TEA as an alternative base (entry 4). Under these conditions complete conversion to the silyl ester was observed, which was hydrolysed to the acid 255 upon workup, confirming that the Claisen rearrangement was occurring under these conditions. In the presence of sub-stoichiometric quantities of TEA, the reaction was sluggish and required high temperatures (only achievable in DMF) to achieve modest conversion.
Results and Discussion

Table 23

<table>
<thead>
<tr>
<th>Entry</th>
<th>BSA (equiv)</th>
<th>Additive</th>
<th>Solvent&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Microwave Heating Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>KOAc (0.1 equiv)</td>
<td>PhMe</td>
<td>1.5 h, 175 °C</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>KOAc (0.1 equiv)</td>
<td>none</td>
<td>2 x 175 °C 5 min</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>KOAc (0.1 equiv)</td>
<td>none</td>
<td>2 x 200 °C, 5 min</td>
<td>0%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>TEA (1.1 equiv)</td>
<td>PhMe</td>
<td>160 °C, 15 min</td>
<td>0%&lt;sup&gt;c&lt;/sup&gt; (100%)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>TEA (0.1 equiv)</td>
<td>DMF</td>
<td>2 x 180 °C, 15 min</td>
<td>0%&lt;sup&gt;c&lt;/sup&gt; (62%)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>TEA (0.1 equiv), KOAc (0.1 equiv)</td>
<td>DMF</td>
<td>180 °C, 15 min</td>
<td>20%</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions, unless solvent-free were performed at 1.0 M. <sup>b</sup>Complete decomposition was observed. <sup>c</sup>Conversion to acid intermediate 255 by <sup>1</sup>H-NMR.

Inspection of the dCr reaction mechanism (Scheme 105) shows the reaction should be catalytic in BSA, so we investigated why such an excess was required in this case. The thermal decomposition of BSA to acetonitrile (and also its stabilisation by 2-mercaptobenzothiazole) has been reported (Scheme 108).<sup>190</sup>

![Scheme 108](image)

Scheme 108

Samples of BSA in <sup>d</sup>8-toluene were heated in a microwave for various periods of time at different temperatures and then analysed by <sup>1</sup>H-NMR. No decomposition was observed, even when heating BSA under solvent-free conditions for extended times. Additionally, no decomposition of BSA was observed in the presence of potassium acetate, indicating that BSA is stable under the dCr reaction conditions (Figure 1).

![Figure 1](image)
Taking into account the above observations, we concluded that the low yield for the dCr reaction was caused by the forcing conditions required for the decarboxylation step. Alternative conditions have been reported for the decarboxylation of α-tosyl acids, and we reasoned that the dCr reaction could be performed over two separate steps (Scheme 109). Treatment of the mixture of esters 252a/253a with BSA and TEA followed by microwave heating afforded the acid 255 upon hydrolytic workup as a mixture of four stereoisomers. The purity of the intermediate acid on isolation and the efficiency of microwave heating were improved by changing the reaction solvent to acetonitrile. Residual BSA and TEA were removed by passing a solution of the crude acid through an SCX ion-exchange column. Decarboxylation with sodium carbonate in DMF gave the dCr products syn- and anti-254a in 86% yield over two steps, with the same diastereoselectivity as was observed previously.

Scheme 109

Having optimised the conditions for rearrangement of 252a/253a, the behaviour of the other previously prepared allylic azides under dCr conditions was investigated. We were particularly interested to explore whether the effects of the olefin substitution pattern would reinforce those of increased steric bulk on the vinylic moiety of the ketene acetal. Treatment of mixtures of allylic azidoalcohols under the same conditions as 235a/236a gave the corresponding allylic azidoesters 252/253b–g (Scheme 110, Table 24). In addition to the change in allylic azide ratio for 252a/253a, an inversion in the position of the equilibrium for substrates 252/253b–d was observed.
Results and Discussion

Scheme 110

![Scheme 110 Diagram](image)

<table>
<thead>
<tr>
<th>Table 24</th>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Ratio of azidoalcohol substrates 235 : 236 (^a)</th>
<th>Yield of 252/253 (%)</th>
<th>Ratio of azidoester products 252 : 253 (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>nC(<em>5)H(</em>{11})</td>
<td>H</td>
<td>73 : 27</td>
<td>99</td>
<td>58 : 42</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>nC(<em>5)H(</em>{11})</td>
<td>Me</td>
<td>61 : 39</td>
<td>69</td>
<td>32 : 68</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>Me</td>
<td>64 : 36</td>
<td>97</td>
<td>30 : 70</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>cHex</td>
<td>Me</td>
<td>63 : 37</td>
<td>92</td>
<td>36 : 65</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>H</td>
<td>100 : 0</td>
<td>97</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>Ph</td>
<td>0 : 100</td>
<td>75</td>
<td>0 : 100</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>2-pyridyl</td>
<td>Me</td>
<td>100 : 0</td>
<td>52</td>
<td>100 : 0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)By 1H-NMR analysis

2.5.8 The equilibrium position of allylic azides

We propose that the equilibrium position for the interconversion of allylic azides via [3,3]-sigmatropic rearrangement depends on the subtle interplay of numerous factors, including olefin substitution pattern, azide–alcohol hydrogen-bonding, conjugation with aromatic groups and to a lesser extent, 1,3-allylic strain. These factors are discussed below:

For equilibrating mixtures of a secondary and tertiary allylic azide the regioisomer containing the more substituted olefin would be expected to predominate. Recent computational studies on the theoretical basis of Saytzeff’s rule show that each additional alkyl substituent contributes 1–2 kcal/mol to the stability of the olefin. However, with the exception of isomers stabilised by conjugation with an aromatic group (vide infra), this is not the case, and the vicinal azidoalcohol 253 (bearing the less substituted olefin) predominates.

Other effects must therefore contribute to the stability of this isomer. Sharpless et al. speculated that an azide–alcohol hydrogen-bonding interaction might exist in
vicinal azidoalcohols. A similar explanation was given by Trost et al. for the position of equilibrium between the cyclic allylic azides 256 and 257 (Scheme 111).\textsuperscript{164a}

![Scheme 111](image)

We decided to investigate this in depth, assuming that the interaction would take the form of a 5-membered ring incorporating a hydrogen bond between the internal nitrogen of the azide and the alcohol hydrogen 260. Hydrogen bonds of this type are reported (supported by extensive spectroscopic evidence) in 2-hydroxyalkylpiperidines 258 and 2-hydroxyalkylpyridines 259 (Scheme 112).\textsuperscript{192}

![Scheme 112](image)

Although the azide ion is reportedly a very strong hydrogen bond acceptor,\textsuperscript{193} studies on the hydrogen-bonding nature of organic azides are scarce. However, a search of the Cambridge X-ray structure database for distances between the internal azide nitrogen and an alcohol hydrogen less than 2.50 Å revealed some examples of hydrogen-bonding interactions 261–264 (Scheme 113).\textsuperscript{194}
Results and Discussion

Enthalpies of hydrogen-bonding are typically within the range 2–10 kcal/mol, and although the reported interactions in 261–264 are relatively long-range and the N–H–O angle deviates from linearity, a hydrogen-bonding interaction could make a significant contribution to the stability of vicinal azidoalcohols 235. An NMR experiment was carried out to explore the effect of hydrogen-bonding on the equilibrium position. We predicted that d4-methanol would compete with the dissolved azidoalcohol for hydrogen-bonding interactions, perturbing the equilibrium away from the vicinal regioisomer 235 (Scheme 114, Table 25). No change in ratio was observed for the mixture of secondary allylic azidoalcohols 235a/236a when spectra were measured on CD3OD rather than CDCl3 solutions. For the mixture of secondary and tertiary allylic azidoalcohols 235c/236c however, a small shift in the equilibrium position towards 236c was observed, suggesting a weak hydrogen-bonding interaction.

Scheme 113

<table>
<thead>
<tr>
<th>Internal N–H–O distance (Å)</th>
<th>2.295</th>
<th>2.383</th>
<th>2.468</th>
<th>2.414</th>
</tr>
</thead>
<tbody>
<tr>
<td>N–H–O angle (deg)</td>
<td>113</td>
<td>110</td>
<td>101</td>
<td>114</td>
</tr>
</tbody>
</table>

Scheme 114

<table>
<thead>
<tr>
<th>Table 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>CDCl3</td>
</tr>
<tr>
<td>CD3OD</td>
</tr>
</tbody>
</table>

*By 1H-NMR analysis

Esterification of azidoalcohols 235/236 removes the possibility of hydrogen-bonding, leaving olefin stability as the dominant effect. Thus, in the absence of hydrogen-
bonding interactions, the isomer containing the more substituted double bond predominates. Furthermore, in the absence of hydrogen-bonding interactions, it appears that 1,3-allylic strain has less effect on the equilibrium position than olefin substitution. A greater, energetically unfavourable 1,3-allylic strain component would be predicted for the more abundant regioisomer in mixtures of allylic azidoesters 252/253b–d and 252/253f–g. These combined effects in total are small compared to those of conjugative stabilisation. Indeed, for both allylic azidoalcohols and their ester equivalents, whenever the olefin can lie in conjugation with an aromatic group, this is the only regioisomer observed.

2.5.9 Further examples of allylic azides in the dCr reaction

Esters 252/253a–g were exposed to the optimised dCr conditions. With the exception of 252g, all underwent Claisen rearrangement (Scheme 115, Table 26). More hindered substrates required increased amounts of BSA and TEA to react efficiently. Aside from conjugatively stabilised substrates there appeared to be no correlation between azide ratios and yields. Syn stereochemistry for the major products 254b–f was inferred from the X-ray crystallography studies carried out previously on syn-254a.

Scheme 115

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>BSA (equiv)</th>
<th>TEA (equiv)</th>
<th>t (min)</th>
<th>Yield (%)</th>
<th>Ratio syn- : anti-254</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>nC5H11</td>
<td>H</td>
<td>3.0</td>
<td>1.2</td>
<td>15</td>
<td>86</td>
<td>84 : 16</td>
</tr>
<tr>
<td>b</td>
<td>nC5H11</td>
<td>Me</td>
<td>5.0</td>
<td>2.0</td>
<td>30</td>
<td>68</td>
<td>68 : 32</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>Me</td>
<td>3.0</td>
<td>1.2</td>
<td>30</td>
<td>82</td>
<td>91 : 9</td>
</tr>
<tr>
<td>d</td>
<td>cHex</td>
<td>Me</td>
<td>5.0</td>
<td>2.0</td>
<td>30</td>
<td>44</td>
<td>82 : 18</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>H</td>
<td>5.0</td>
<td>2.0</td>
<td>90</td>
<td>22</td>
<td>75 : 25</td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>Ph</td>
<td>3.0</td>
<td>1.2</td>
<td>40</td>
<td>32</td>
<td>73 : 27</td>
</tr>
<tr>
<td>g</td>
<td>2-pyridyl</td>
<td>Me</td>
<td>3.0</td>
<td>1.2</td>
<td>30</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*By 1H-NMR analysis; *This substrate partially decarboxylated during first step.
In each case, stereoselectivity was more pronounced than that observed for Johnson–Claisen rearrangement of the corresponding allylic azidoalcohol. We conclude that the effects of C1 substitution and olefin substitution pattern are reinforcing. In contrast to the unreactive phenyl-bearing azidoalcohol 235e, the single-regioisomer azidoester 252e underwent rearrangement and decarboxylation to give 254e in low yield. The pyridyl-bearing substrate 252g decomposed under these conditions, possibly caused by N-silylation of the pyridine moiety with BSA. We therefore conclude that this reaction works generally when R=alkyl. Selectivities are higher, but yields lower (except in the case of 254e) than the related Johnson–Claisen rearrangements of allylic azidoalcohols bearing the same R and R’ groups.

2.5.10 Ireland–Claisen Rearrangements: Control of 3 contiguous stereocentres

Our interest returned to the chelate-controlled Ireland–Claisen rearrangements of Mulzer,\textsuperscript{110} in which three contiguous stereocentres are established. We decided to study the behaviour of allylic azidooesters in this process, allowing us to probe the effects of temperature on both the rate of rearrangement and stereoselectivity. The mixture of esters 265/266 was prepared from 235c/236c by reaction with benzyloxyacetic acid. The ratio of allylic azide isomers was consistent with the analogous α-tosyl ester 252c/253c; and a similar reversal in the position of equilibrium was observed. Ireland–Claisen rearrangement of 265/266 under the reported conditions gave the product 267 as a mixture of 4 diastereomers, accompanied by unreacted starting material (Scheme 116). The structures of the individual diastereomers were not assigned, although the ratio of products shows incomplete stereocontrol at C1. Clearly, further optimisation of this reaction is required.
Nevertheless, although we remain unable to control three contiguous stereocentres using this methodology, our results clearly show that a wide variety of equilibrating allylic azidoesters may be converted to azide-bearing γ,δ-unsaturated esters or homoallylic sulfones via a pair of sigmatropic rearrangements. In the latter case, the reaction occurs with good stereoselectivity in the predicted syn sense.

Scheme 116
2.6 Reactions of β-azidoketones derived from dCr reactions

2.6.1 Background

The work presented in this section demonstrates our investigations into further transformations of dCr products 254. From the outset, we wished to subject these rearranged products to ozonolytic cleavage to form β-azidoketones 268. We envisaged a sequence in which these β-azidoketones are subjected to either Beckmann or Baeyer–Villiger rearrangement. In the former reaction, stereospecific migration of the bulkier moiety would give the 1,2-azidoamide 270, while the same migratory pattern for the latter reaction would give the 1,2-azidoacetate 272. These represent differentially protected 1,2-diamines 271 and 1,2-amino alcohols 273 respectively, which are useful synthetic intermediates (Scheme 117).

![Scheme 117](image)

2.6.2 Ozonolysis of dCr products

We were concerned that commonly used reagents for reductive quench of the intermediate ozonide such as phosphines might also reduce the azide group. However, examples of reductive quench of ozonides in the presence of azides using dimethylsulfide are reported. These reactions are typically performed in a mixture of dichloromethane and methanol. A diastereomerically pure sample of syn-254b was
treated with ozone at –78 °C for 10 min under the reported conditions (Scheme 118) to give not only the ketone syn-274 but also the hemiacetal 275 as the major product, both as single diastereomers.

The hemiacetal 275 was unusually stable and we propose a cyclic, internally hydrogen-bonded structure (Scheme 119) to support this. In addition to the previously discussed examples of N3—H—O hydrogen-bonding, there is strong spectroscopic evidence for this assignment. Firstly the coupling constant \( J_{H3-H4} \) is large (10.0 Hz) compared to ketone syn-274 (\( J_{H3-H4} \), 6.5 Hz). Addition of D2O to the NMR sample caused disappearance of the OH signal and a reduction of \( J_{H3-H4} \) suggesting inhibition of hydrogen-bonding and conversion into an acyclic structure. Additionally, sharp OH signals in both the \(^1\)H-NMR and infrared spectra support this evidence for hydrogen-bonding.

Presuming that 275 could only be formed by addition of methanol to either the intermediate ozonide or the ketone product, the reaction was repeated in its absence, affording solely the diastereomerically pure ketone syn-274 in 88% yield (Scheme 120). We have therefore shown that this methodology may be used for the synthesis of β-azidoketones in good yield and without epimerization of the rearranged product.
2.6.3 Synthesis of a model system

Before studying further chemistry of the ketone syn-274 directly, we chose to study and optimise this work using the model system 276. Although the chemistry described here was not eventually applied to the dCr products, it provides an interesting area for further investigation. We envisaged that 276 could be easily prepared via conjugate addition of hydrazoic acid to the enone 238b (Scheme 121).

Highly toxic and explosive hydrazoic acid is typically generated *in situ* from the disproportionation of an azide source (typically sodium azide or azidotrimethylsilane) and an acid (acetic acid or strong mineral acid).

The reaction may be performed in the presence of a sub-stoichiometric amount of a Lewis-basic amine or phosphine, which accelerates the disproportionation step. Under these conditions, the azide anion does not undergo conjugate addition to the enone and an acid is still required. The transformation can also be carried out in enantioselectively in the presence of a salen/aluminium catalyst. Using the conditions of Miller *et al.*, 238b was converted in very high yield into the β-azidoketone 276 (Scheme 122).
2.6.4 Beckmann rearrangements of β-azioketones

With β-azidoketone 276 in hand, we investigated the Beckmann rearrangement of the corresponding oxime 277. Treatment of 276 with hydroxylamine hydrochloride and sodium acetate afforded the oxime 277 (Scheme 123). Increasing the concentration of the reaction mixture from the reported procedure significantly improved the yield. It should be noted that these conditions may require alteration if used to form the oxime of 274; base-mediated epimerization of the stereocentre adjacent to the ketone is possible.

The product was isolated as a 2:1 mixture of E and Z isomers. This assignment was based on the relative chemical shifts of the methylene group adjacent to the ketoxime, which appeared at lower field for the Z (syn) isomer than the E (anti) isomer. Examination of literature data for analogous ketoximes suggests interconversion of these isomers is likely to be facile at room temperature, favouring the desired migration of the E isomer (Scheme 124, Table 27) in the Beckmann rearrangement. A preference for E-geometry in the oxime of 274 would be strongly expected.

We chose to investigate the Beckmann rearrangement using an intermediate O-tosyloxime, envisaging that E-oxime would be more sterically favoured in this
Formation of the O-tosyloxime 278 under the reported conditions was slow. Addition of sub-stoichiometric DMAP accelerated the reaction. No rearranged product was observed at this stage. Heating of 278 in IPA/water afforded a mixture of both the desired acetamide 279 and the amide 280: the product of methyl migration (Scheme 125).

Scheme 125

The product distribution is related to a subtle combination of effects and it is unclear whether the presence of the methyl migration product 280 is a result of slow E/Z oxime interconversion, or a surprisingly high migratory aptitude of the methyl group in this system. We predict that the branched Claisen products would migrate with higher selectivity under this process. However, the reaction clearly requires further development. This transformation of β-azidoketones could also be carried out under Schmidt rearrangement conditions, although we have not investigated this.

2.6.5 Baeyer–Villiger rearrangements of β-azidoketones

The Baeyer–Villiger rearrangement of the model ketone 276 was also briefly investigated. The ketone was treated with MCPBA in the presence of sodium bicarbonate in chloroform, but no oxidised product was formed and only starting material was recovered (Scheme 126). The reaction may be possible with a more powerful peracid (e.g. trifluoroperacetic acid). It is unlikely that reactions of the ketone 276 will be complicated by acid-mediated intramolecular Schmidt-type processes due to the short distance between the ketone and azide.
Scheme 126

In summary, although the above studies on the model ketone 276 were not applied to a ketone derived from a dCr reaction, we have shown from preliminary results that a Beckmann rearrangement of this substrate will be possible. Further investigation of Beckmann, Baeyer–Villiger and Schmidt processes will allow us to further develop a synthesis of differentially-protected 1,2-aminoalcohols and 1,2-diamines based on a Claisen rearrangement strategy.
2.7 Conclusions

Numerous contributions have been made to the area of acyclic stereocontrol in Claisen rearrangements. Our conclusions are divided into two sections: the former covering contributions to the nature of stereoselectivity in the reaction; and the latter summarising our attempts to exploit these selectivity patterns in synthesis.

2.7.1 Investigations into acyclic stereocontrol

The Johnson–Claisen rearrangements of substrates bearing all-hydrocarbon C6’ stereocentres were investigated. Moderate anti selectivities were observed in the opposite sense to cases where the C6’ stereocentre possessed a heteroatom. The major product arose from a transition state in which the medium-sized group was roughly eclipsing the double allylic double bond of the ketene acetal. Only examples of $E$-configured substrates were investigated; study and comparison of the $Z$-isomers would be recommended for future work.

An investigation was proposed to compare the effects of C6’ fluorine and thiophenyl substituents. No stereoselectivity was observed in either case for $E$-configured substrates, while high syn selectivity, in line with prediction, was observed in the Johnson–Claisen rearrangement of the isomeric $Z$-allylic alcohols in the thiophenyl-substituted series. Work on the fluorine system was hampered by the instability of rearrangement substrates.

Stereoselectivity in rearrangements of $E$-configured allylic systems may be achieved in two ways. Moderate selectivity was observed in the Johnson–Claisen rearrangements of trisubstituted allylic systems and disubstituted allylic systems bearing a C1 substituent on the ketene acetal. Studies in the context of the dCr reaction showed these effects to be reinforcing.

Although attempts were made to combine cyclic and acyclic stereocontrol modes, they form only a small part of this work and were largely unsuccessful. Further work in this area is also recommended.
2.7.2 Synthetic applications of acyclic stereocontrol in Claisen rearrangements

In the course of work to prepare disubstituted γ-lactams *via* a Claisen rearrangement route, we discovered a novel process where equilibrating mixtures of allylic azides can undergo a pair of sigmatropic rearrangements in a tandem process. This was investigated in the context of the Johnson–Claisen and dCr reactions. Our work in this area studied the factors contributing to the equilibrium position of various mixtures of allylic azides. NMR studies, synthetic studies and examination of crystallographic data showed evidence for an intramolecular hydrogen bond between the azide and alcohol functionalities.

Studies were performed to show that the products of allylic azide Claisen rearrangements could be converted into useful compounds. Products of Johnson–Claisen rearrangement of allylic azidoalcohols were converted into γ-lactams *via* Staudinger reduction and cyclisation, although the differing rates of cyclisation of *syn* and *anti* substrates lead to varying product distributions. We have also shown that products of dCr reaction of allylic tosylazidoesters may be converted into β-azidoketones *via* ozonolytic cleavage. Finally, the Baeyer–Villiger and Beckmann chemistry of a model β-azidoketone was investigated in an effort to convert oxidised dCr products into differentially-protected 1,2-aminoalcohol and 1,2-diamine equivalents respectively. This represents an additional interesting area for future studies.
Chapter 3

*Experimental*
3.1 General laboratory procedures

All reactions were performed under nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on Mattson 5000 FT-IR or Perkin-Elmer Spectrum RX FT-IR System spectrometers. Proton nuclear magnetic resonance ($^1$H NMR), carbon nuclear magnetic resonance ($^{13}$C NMR) and fluorine nuclear magnetic resonance ($^{19}$F NMR) spectra were recorded in CDCl$_3$ unless otherwise stated on a Bruker AV-400 or Bruker AV-500 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent ($^1$H NMR: 7.26 ppm for CDCl$_3$; $^{13}$C NMR: 77.0 ppm for CDCl$_3$). Coupling constants are given in Hertz (Hz). Mass spectra (CI, EI and ESI) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Optical rotations were measured on an Optical Activity Ltd. instrument. Analytical thin layer chromatography (TLC) was performed on pre-coated glass-backed Merck Kieselgel 60 F254 plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Flash column chromatography was performed using a Biotage Flash+ reservoir system with Biotage SNAP HP-Sil (30 µm) silica gel cartridges or using a Teledyne Isco Companion system fitted with RediSep (35–70 µm) silica gel cartridges. Kugelrohr distillations were performed using a Büchi D56 Kugelrohr oven and controller system. The quoted boiling point corresponds to the internal oven temperature. Standard solvents were distilled under nitrogen prior to use; ether and THF from sodium-benzophenone ketyl, CH$_2$Cl$_2$ and acetonitrile from CaH$_2$ and toluene from sodium. All other solvents were distilled prior to use. Petrol refers to petroleum ether of the fraction bp 40–60 °C. Ether refers to diethyl ether. All liquid reagents were distilled prior to use with the exception of TMS-azide, DAST and Deoxofluor which are thermally unstable. Potassium acetate was oven-dried at 120 °C for several days prior to use. Microwave reactions were performed in a Biotage Initiator upgraded to version 2.5 and cooled using compressed air (4 bar). Ozone gas was generated from oxygen gas using a Triogen LAB2B ozone generator.
3.2 Safety note

The preparation of numerous potentially explosive low molecular weight organic azides is reported herein. Although we did not experience any explosive behaviour during the course of our studies, all reactions involving azides were carried out behind a blast shield. Particular care was taken during the concentration and purification of organic azides. Sodium azide was handled using non-metallic utensils.

3.3 General synthetic procedures

General procedure A, for the preparation of $\alpha,\beta$-unsaturated esters 158b–e,g

Part 1
To a stirred suspension of (methoxymethylene)triphenylphosphonium chloride (18.8 g, 55.0 mmol 1.12 equiv) in dichloromethane (75 mL) was added potassium tert-butoxide (6.18 g, 55.0 mmol, 1.12 equiv) in three portions at rt. A deep red colour resulted almost immediately upon complete addition. The resulting suspension was stirred at rt for 90 min to complete the formation of the ylide. Ketone 155 (49.0 mmol, 1.0 equiv) was added dropwise at rt over 15 min. The reaction mixture was stirred for 6 h, after which the deep red colour had dissipated and FT-IR showed disappearance of the ketone, and water (60 mL) was added. The phases were separated and the organic layer was washed with water (70 mL) and brine (50 mL). The organic layer was dried (MgSO$_4$), filtered and partially concentrated under reduced pressure (until ca. 10 mL of solvent remained) to afford a solution of the enol ether 156 in dichloromethane.

Part 2
To a suspension of silica gel (18.8 g) in dichloromethane (15 mL) was added water (1.88 mL, 10% by mass of silica gel). After stirring for 5 min, sulfuric acid (98%, 2 mL) was added dropwise. The enol ether 156 solution from Part 1 was added and the resulting suspension was stirred overnight at rt. $^1$H-NMR analysis of a filtered sample
of the reaction mixture showed formation of the aldehyde. Excess solid sodium hydrogencarbonate was added to neutralise the reaction. The resulting suspension was filtered to give a solution of the aldehyde 157 in dichloromethane, to which carbethoxymethylenetriphenylphosphorane (17.07 g, 49.0 mmol, 1.0 equiv) was added in one portion. The resulting suspension was stirred for 48 h and poured onto water (60 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 60 mL). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. The crude product was passed through a silica gel plug (15% EtOAc/petrol) to remove triphenylphosphine oxide. Further purification (if required) over silica gel or by distillation under reduced pressure afforded the ester 158.

**General procedure B, for the preparation of allylic alcohols 152a–g**

To a solution of ester 158 (2.60 mmol, 1.0 equiv) in dichloromethane (15 mL) at −78 °C was added diisobutylaluminium hydride (6.50 mL of a 1.0 M solution in toluene, 6.50 mmol, 2.5 equiv) dropwise via syringe. The resulting mixture was stirred at −78 °C for 1 h, warmed to rt and stirred overnight. MeOH (1.5 mL) was added, followed by sodium sulfate decahydrate (10.0 g). The resulting slurry was stirred for 1 h and filtered over Celite, washing with dichloromethane. The filtrate was washed with aqueous HCl (1 M, 2 x 50 mL) followed by saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give the allylic alcohol 152 as a colourless oil after purification over silica gel or by Kugelrohr distillation as appropriate.

**General procedure C, for the preparation of esters 154a–g, 182 and 243a–g**

To a solution of the allylic alcohol (1.57 mmol, 1.0 equiv) in triethyl orthoacetate (20.4 mmol, 13.0 equiv) was added propionic acid (0.314 mmol, 0.2 equiv) dropwise via syringe. After heating under reflux until the starting material had been consumed, the reaction mixture was cooled to rt and concentrated under reduced pressure to give the ester 154, 182, or 243.
Experimental

General procedure D, for the preparation of \((E)-\gamma\text{-sulfenyl-}\alpha,\beta\text{-unsaturated esters 184a,c,e}\)

To a solution of TEA (3.90 mL, 28.0 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.05 mL, 20.0 mmol, 1.0 equiv) dropwise via syringe. The colourless solution was stirred at rt for 10 min and a solution of chloroaldehyde 207 (20.0 mmol, 1.0 equiv) in THF (20 mL) was added dropwise via syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of triethyl phosphonoacetate (4.80 mL, 24.0 mmol, 1.2 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) in THF (40 mL) at 0 ºC via cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenyl-aldehyde solution was filtered under nitrogen and added via cannula to the phosphonate anion solution at 0 ºC. After stirring for 1 h at 0 ºC saturated aqueous NH\(_4\)Cl (100 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. Purification over silica gel afforded the ester \(E\)-184.

General procedure E, for the preparation of \((Z)-\gamma\text{-sulfenyl-}\alpha,\beta\text{-unsaturated esters 184b,d,f}\)

To a solution of TEA (3.90 mL, 28.0 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.05 mL, 20.0 mmol, 1.0 equiv) dropwise via syringe. The colourless solution was stirred at rt for 10 min and a solution of chloroaldehyde 207 (20.0 mmol, 1.0 equiv) in THF (20 mL) was added dropwise via syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of 2-(diphenylphosphoryl)acetate (6.41 g, 20.0 mmol, 1.0 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) in THF (40 mL) at 0 ºC via cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenyl-aldehyde solution was filtered under nitrogen and added via cannula to the phosphonate anion solution at –78 ºC. After
stirring for 1 h at −78 °C saturated aqueous NH₄Cl (150 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel afforded the ester Z-184.

**General procedure F, for the preparation of allylic alcohols 185a–f**

To a solution of ester 184 (4.91 mmol, 1.0 equiv) in THF (50 mL) at 0 °C was added diisobutylaluminium hydride (14.7 mL of a 1.0 M solution in toluene, 14.7 mmol, 3.0 equiv) dropwise via syringe. The resulting colourless solution was warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with dichloromethane (60 mL) and quenched with MeOH (5 mL). Water (10 mL) was added, followed by saturated aqueous sodium hydrogen carbonate (20 mL) and the mixture was filtered. The filtrate was extracted with dichloromethane (3 x 65 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (5–75 % TBME/heptane) afforded the allylic alcohol 185.

**General procedure G, for the preparation of esters 186a–c**

The general procedure C was followed; with the exception that triethyl orthoacetate was degassed by three freeze-vacuum pump-thaw cycles prior to use.

**General procedure H, for the preparation of α,β-unsaturated ketones 238b,d,h,j**

To a solution of 1-(triphenylphosphanylidene)propan-2-one (22.5 mmol, 1.5 equiv) in dichloromethane (15 mL) was added the aldehyde (15.0 mmol, 1.0 equiv) dropwise via syringe at rt. The resulting mixture was stirred until TLC (20% EtOAc/petrol) confirmed the consumption of starting material. Aqueous HCl (2 M, 15 mL) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was taken up in ether, filtered and purified by Kugelrohr distillation to afford the α,β-unsaturated ketone 238.
**General procedure I, for the preparation of chlorohydrins 239a–g**

To a solution of $\alpha,\beta$-unsaturated carbonyl 238 (10.0 mmol, 1.0 equiv) in THF (20 mL) at −78 ºC was added chloroiodomethane (15.0 mmol, 1.5 equiv), followed by slow addition of $n$-butyllithium (6.0 mL of a 2.50 M solution in hexanes, 15.0 mmol, 1.5 equiv) over 30 min. The resulting yellow solution was stirred at −78 ºC for 1 h and quenched with saturated aqueous NH$_4$Cl (25 mL). The mixture was warmed to rt and ether (50 mL) was added. The phases were separated and the aqueous layer was extracted with ether (2 x 50 mL), dried (MgSO$_4$) and concentrated. Purification over silica gel afforded the chlorohydrin 239.

**General procedure J, for the preparation of oxiranes 234a–g**

To a suspension of pentane-washed sodium hydride (60% w/w in mineral oil, 10.2 mmol, 1.3 equiv) and sodium iodide (0.78 mmol, 0.1 equiv) in THF (11 mL) was added a solution of the chlorohydrin 239 (7.8 mmol, 1.0 equiv) in THF (11 mL) at 0 ºC. The resulting white suspension was stirred at 0 ºC for 1 h and quenched with saturated aqueous NH$_4$Cl (30 mL). The phases were separated and the aqueous layer was extracted with ether (30 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give the oxirane 234, which were used without further purification.

**General procedure K, for the preparation of allylic azidoalcohols 235/236a–g**

To a solution of oxirane 234 (31.5 mmol, 1.0 equiv) in acetone (45 mL) and water (19 mL) was added sodium azide (94.5 mmol, 3.0 equiv) in one portion. After heating the resulting solution under reflux for 8 h, the reaction mixture was cooled to rt and NH$_4$Cl (5.0 g) was added. Water (50 mL) was added and the reaction mixture was concentrated under reduced pressure to remove acetone. The remaining aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (Na$_2$SO$_4$), concentrated under reduced pressure and purified over silica gel to give a mixture of the allylic azidoalcohols 235/236.
Experimental

General procedure L, for the preparation of pyrrolidin-2-ones 244a–d

To a mixture of ester 243 (0.44 mmol, 1.0 equiv) and water (0.66 mmol, 1.5 equiv) was added trimethylphosphine (0.66 mL of a 1 M solution in THF, 0.66 mmol, 1.5 equiv) dropwise via syringe at rt. The resulting solution was stirred until TLC (20% ether/petrol) confirmed consumption of the starting material. Water (5 mL) was added and the mixture was extracted with ether (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford the pyrrolidin-2-one 244 after purification over silica gel.

General procedure M, for the preparation of allylic azidoesters 252/253a–g

To a solution of azidoalcohols 235/236 (5.46 mmol, 1.0 equiv) in dichloromethane (10 mL) was added DMAP (0.546 mmol, 0.1 equiv), followed by a solution of DCC (6.01 mmol, 1.1 equiv) in dichloromethane (10 mL) at rt. The mixture was stirred for 5 min before addition of 2-p-toluenesulfonylacetic acid (1.29 g, 6.01 mmol, 1.1 equiv). After stirring the colourless suspension for 16 h, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. Purification of the residue over silica gel afforded mixtures of the esters 252/253.

General procedure N, for the preparation of homoallylic sulfones 254a,c,f

To a solution of the azidoesters 252/253 (0.132 mmol 1.0 equiv) in acetonitrile (1.0 M) was added N,O-bistrimethylsilylacetamide (0.396 mmol, 3.0 equiv) and TEA (0.158 mmol, 1.2 equiv) in a capped microwave vial. The mixture was heated by microwave at 160 °C until TLC showed consumption of the starting material. The reaction mixture was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were passed through an SCX ion exchange column (conditioned with 10% MeOH/dichloromethane) and concentrated under reduced pressure to afford the acid 255 without further purification. To solution of the crude acid 255 (1.0 equiv) in DMF (1.0 M) was added sodium hydrogencarbonate (1.2 equiv) in a microwave vial. The mixture was heated by microwave at 160 °C for 35 min and cooled to rt. Water (10
mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel afforded sulfone 254.

**General procedure O, for the preparation of homoallylic sulfones 254b,d,e**

To solution of the azidoesters 252/253 (0.132 mmol 1.0 equiv) in acetonitrile (1.0 M) was added N,O-bistrimethylsilylacetamide (0.660 mmol, 5.0 equiv) and TEA (0.264 mmol, 2.0 equiv) in a capped microwave vial. The mixture was heated by microwave at 160 °C until TLC showed consumption of the starting material. The reaction mixture was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were passed though an SCX ion exchange column (conditioned with 10% MeOH/dichloromethane) and concentrated under reduced pressure to afford the acid 255 without further purification. To solution of the crude acid 255 (1.0 equiv) in DMF (1.0 M) was added sodium hydrogen carbonate (1.2 equiv) in a microwave vial. The mixture was heated by microwave at 160 °C for 35 min and cooled to rt. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel afforded sulfone 254.
3.4 Individual procedures

3.4.1 Compounds relevant to section 2.2

(E)-Ethyl 4-methylhex-2,3-enoate (158a)

Lithium chloride (0.509 g, 12.0 mmol, 1.2 equiv) was placed in a 20 mL microwave vial, which was capped and purged with argon. Acetonitrile (10 mL) was added via syringe, followed by DBU (1.79 mL, 12.0 mmol, 1.2 equiv). Triethyl phosphonoacetate (2.38 mL, 12.0 mmol, 1.2 equiv) was added dropwise at rt and the resulting solution was stirred for 5 min. 2-Methylbutyaldehyde (1.05 mL, 10.0 mmol, 1.0 equiv) was added dropwise, resulting in a slightly exothermic reaction, to give a cloudy mixture. After heating by microwave to 100 °C for 5 min, the reaction was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and poured onto ether (20 mL). The phases were separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure. Distillation of the residue under reduced pressure afforded (E)-ethyl 4-methylhex-2,3-enoate 158a (1.18 g, 76%) as a colourless oil: bp$_{30}$ 120–125 °C; ν$_{\text{max}}$ (film) 1720, 1652, 1461, 1269, 1186, 1041, 986 cm$^{-1}$; δ$_{H}$ (400 MHz, CDCl$_3$) 6.88 (1H, dd, $J$ 15.5, 7.0, H-3), 5.80 (1H, d, $J$ 15.5, H-2), 4.21 (2H, q, $J$ 7.0, OCH$_2$), 2.23 (1H, sept, $J$ 7.0, H-4), 1.42 (2H, dq, $J$ 7.5, 7.0, H-5), 1.31 (3H, t, $J$ 7.0, OCH$_2$CH$_3$), 1.06 (3H, d, $J$ 7.0, 4-CH$_3$), 0.90 (3H, t, $J$ 7.5, H-6); δ$_{C}$ (101 MHz, CDCl$_3$) 167.0 (C-1), 154.5 (C-3), 119.7 (C-2), 60.2 (OCH$_2$), 38.1 (C-4), 28.8 (C-5), 18.9 (4-Me), 14.3 (OCH$_2$CH$_3$), 11.6 (C-6); in agreement with published data.$^{212}$
(E)-Ethyl 4-cyclopropylpent-2-enoate (158b)

![Chemical structure](image)

1-Cyclopropylethanone (2.31 g, 23.8 mmol, 1.0 equiv) was reacted according to general procedure A to afford (E)-ethyl 4-cyclopropylpent-2-enoate 158b (0.247 g, 7%) as a colourless oil without further purification: $\nu_{\text{max}}$ (film) 1721, 1652 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 6.54 (1H, dd, $J$ 16.0, 6.5, H-3), 5.86 (1H, d, $J$ 16.0, H-2), 4.22 (2H, q, $J$ 7.0, OCH$_2$), 1.58–1.55 (1H, m, H-4), 1.32 (3H, t, $J$ 7.0, OCH$_2$C), 1.16 (3H, d, $J$ 7.0, H-5), 0.72–0.63 (1H, m, CH(C$_2$H$_2$)$_2$) 0.14–0.18 (2H, m, CH(CHH)$_2$); $\delta_C$ (101 MHz, CDCl$_3$) 167.1 (C-1), 153.6 (C-3), 119.3 (C-2) 60.2 (OCH$_2$), 41.3 (C-4), 18.9 (C-5), 16.4 (CH(CH$_2$)$_2$), 14.3 (OCH$_2$CH$_3$), [4.0 and 3.8 (CH(CH$_2$)$_2$)]; $m/z$ (Cl) 186 [MNH$_4$]$^+$, 169 [MH]$^+$, 100 (Found: [MNH$_4$]$^+$, 186.1494. C$_{10}$H$_{16}$O$_2$ requires [MNH$_4$]$^+$, 186.1494).

(E)-Ethyl 4-cyclohexylpent-2-enoate (158c)

![Chemical structure](image)

1-Cyclohexylethanone (3.00 g, 23.8 mmol, 1.0 equiv) was reacted according to general procedure A to afford (E)-ethyl 4-cyclohexylpent-2-enoate 158c (1.36 g, 37%) as a colourless oil after purification over silica gel (5% EtOAc/petrol): $\nu_{\text{max}}$ (film) 1722, 1650, 1452, 1140, 1086 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 6.91 (1H, dd, $J$ 15.5, 8.5, H-3), 5.77 (1H, d, $J$ 15.5, H-2), 4.21 (2H, q, $J$ 7.0, OCH$_2$), 2.20–2.11 (1H, m, H-4), 1.76–1.62 (6H, m, cyclohexyl), 1.32 (3H, t, $J$ 7.0, OCH$_2$CH$_3$), 1.03 (3H, d, $J$ 7.0, H-5)
1.25–0.89 (5H, m, cyclohexyl); δC (101 MHz, CDCl₃) 166.9 (C-1), 153.9 (C-3), 120.3 (C-2) 60.2 (OCH₂CH₃), 42.6 (C-3), 30.5, 26.5, 16.4, (cyclohexyl), 14.3 (C-5 and OCH₂CH₃); m/z (ESI) 214, 211 [MH]⁺, 165 [M–CO₂Et]⁺ (Found: [MH]⁺, 211.1708. C₁₃H₂₂O₂ requires [MH]⁺, 211.1698).

(E)-Ethyl 4-methylnon-2-enoate (158d)

2-Heptanone (2.72 g, 23.8 mmol 1.0 equiv) was reacted according to general procedure A to afford (E)-ethyl 4-methylnon-2-enoate 158d (1.13 g, 22%) as a colourless oil after purification over silica gel (5% EtOAc/petrol): νmax (film) 1720, 1650 cm⁻¹; δH (400 MHz, CDCl₃) 6.68 (1H, dd, J 15.5, 8.0, H-3), 5.76 (1H, d, J 15.5, H-2), 4.20 (2H, q, J 7.0, OCH₂), 2.31 (1H, m, H-4), 1.37–1.26 (8H, m, H-5,6,7,8), 1.05 (3H, d, J 6.5, 4-Me), 0.90 (3H, t, J 7.0, OCH₂CH₂); δC (101 MHz, CDCl₃) 167.0 (C-1), 154.8 (C-3), 119.5 (C-2), 60.2 (OCH₂), 36.5, 36.0, 31.9, 26.9, 22.6, 19.4, 14.3, 14.1; in agreement with published data.²¹³

(E)-Ethyl 4,5,5-trimethylhex-2-enoate (158e)

3,3-Dimethyl-2-butane (4.91 g, 49.0 mmol, 1.0 equiv) was reacted according to general procedure A to afford (E)-ethyl 4,5,5-trimethylhex-2-enoate 158e (1.35 g, 15%) as a yellow oil after Kugelrohr distillation: bp₀.₅ 100–105 °C; νmax (film) 1722, 1650, 1463, 1367, 1039, 985, 865 cm⁻¹; δH (400 MHz, CDCl₃) 6.95 (1H, dd, J 14.0,
15.5, H-3), 5.80 (1H, d, J 15.5, H-2), 4.15 (2H, q, J 7.0, OCH₂), 2.10 (1H, dq, J 14.0, 7.0, H-4), 1.30 (3H, t, J 7.0, OCH₂CH₃), 1.05 (3H, d, J 7.0, 4-Me), 0.85 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃), 152.7 (C-1), 128.5 (C-3), 120.9 (C-2), 60.1 (OCH₂), 47.0 (C-4) 33.2 (C(CH₃)₃), 27.5 (C(CH₃)₃), 14.6 (OCH₂CH₃), 14.3 (4-CH₃); m/z (CI) 202 [MNH₄]⁺, 185 [MH]⁺ (Found: [MNH₄]⁺, 202.1805. C₁₁H₂₀O₂ requires [MNH₄]⁺, 202.1807).

(E)-Ethyl 4-phenylpent-2,3-enoate (158f)

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \quad \text{CO₂Et}
\end{align*}
\]

To a solution of 2-phenylpropanal (1.49 mL, 11.0 mmol, 1.0 equiv) in dry dimethylsulfoxide (10 mL) in a microwave vial was added carbethoxyphenylenetriphenylphosphorane (3.83 g, 11.0 mmol, 1.0 equiv) and lithium chloride (0.510 g, 12.0 mmol, 1.09 equiv). The reaction mixture was heated by microwave for 30 min at 120 °C to give a colourless solution upon cooling. The reaction mixture was poured onto water (70 mL) and ether (150 mL) was added. The phases were separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford (E)-ethyl 4-phenylpent-2,3-enoate 158f (1.79 g, 80%) as a colourless oil after purification over silica gel (8% EtOAc/petrol): νₘₐₓ (film) 1732, 1651, 1446, 1266, 1177, 1028, 699 cm⁻¹; δH (400 MHz, CDCl₃) 7.40–7.20 (5H, m, Ph), 7.16 (1H, dd, J 15.5, 7.0, H-3), 5.85 (1H, d, J 15.5, H-2), 4.22 (2H, q, J 7.0, OCH₂), 3.65 (1H, dq, J 7.0, 7.0, H-4), 1.47 (3H, d, J 7.0 H-5), 1.21 (3H, t, J 7.0, OCH₂CH₃); δC (101 MHz, CDCl₃) 166.7 (C-1), 152.6 (C-3), 143.4 (i-Ph), 128.7 (m-Ph), 127.3 (o-Ph), 126.7 (p-Ph), 120.2 (C-2), 60.3 (OCH₂), 42.1 (C-4), 20.2 (C-5), 14.3 (OCH₂CH₃); in agreement with published data.⁷⁷
(E)-Ethyl 4-methylhex-2-enolate (158g)

\[
\text{Et} - \text{Ph} \quad \rightarrow \quad \text{Et} - \text{CH} = \text{CH} - \text{CO}_2\text{Et} \quad 158g
\]

1-Phenylpropanone (3.35 g, 25.0 mmol, 1.0 equiv) was reacted according to general procedure A to afford (E)-ethyl 4-methylhex-2-enolate 158g (1.28 g, 24%) as a colourless oil after purification by Kugelrohr distillation: bp\text{5} 170–175 °C; \nu_{\text{max}} (film) 1716, 1650, 1454 cm\text{–1}; \delta_H (400 MHz, CDCl\text{3}) 7.15–7.35 (5H, m, Ph) 7.09 (1H, dd, J 15.5, 8.0, H-3), 5.81 (1H, d, J 15.5, H-2), 4.19 (2H, q, J 7.0, OCH\text{2}), 3.31 (1H, dt, J 8.0, 7.0, H-4), 1.29 (3H, t, J 7.0, OCH\text{2}CH\text{3}), 1.83 (2H, m, H-5), 0.90 (3H, t, J 7.5, H-6); \delta_C (101 MHz, CDCl\text{3}) 166.7 (C-1), 151.7 (C-3), 142.1, 128.6, 127.9, 126.7 (Ph), 120.8 (C-2), 60.2 (OCH\text{2}), 50.2 (C-4), 27.9, 14.2, 12.1; in agreement with published data.\textsuperscript{214}

(E)-4-Methylhex-2-en-1-ol (152a)

\[
\text{Me} - \text{CH} = \text{CH} - \text{CO}_2\text{Et} \quad \rightarrow \quad \text{Me} - \text{CH} = \text{CHOH} \quad 152a
\]

Ester 158a (809 mg, 5.20 mmol, 1.0 equiv) was reacted according to general procedure B to afford (E)-4-methylhex-2-en-1-ol 152a (176 mg, 30%) as a colourless oil after purification over silica gel (20% EtOAc/petrol): \nu_{\text{max}} (film) 3392, 1641, 1461 cm\text{–1}; \delta_H (400 MHz, CDCl\text{3}) 5.66–5.57 (2H, m, H-2,3), 4.91 (2H, d, J 5.0, H-1), 2.11–2.04 (1H, m, H-4), 1.34 (2H, dq, J 7.5, 7.0, H-5), 1.01 (3H, d, J 7.0, 4-Me), 0.87 (3H, t, J 8.0, H-6); \delta_C (101 MHz, CDCl\text{3}) 139.1 (C-3), 127.2 (C-2), 63.9 (C-1), 38.0 (C-4), 29.5 (C-5), 19.9 (4-Me), 11.8 (C-6); \textit{m/z} (CI) 114 [M]\textsuperscript{+}, 103; in agreement with published data.\textsuperscript{215}
(E)-4-Cyclopropylpent-2-en-1-ol (152b)

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Et} \\
\rightarrow & \\
\text{Me} & \quad \text{CH}_2=\text{CHOH} \\
\end{align*}
\]

Ester 158b (224 mg, 1.33 mmol, 1.0 equiv) was reacted according to general procedure B to afford (E)-4-cyclopropylpent-2-en-1-ol 152b (162 mg, 96%) as a colourless oil, which was used without further purification: \(\nu_{\text{max}}\) (film) 3336, 1668 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 5.76 (1H, dd, \(J\ 15.5, 6.0, \text{H-3}\)), 5.67 (1H, dt, \(J\ 15.5, 6.0, \text{H-2}\)), 4.14 (2H, d, \(J\ 6.0, \text{H-1}\)), 1.45–1.43 (2H, m, \text{H-4, OH}), 1.10 (3H, d, \(J\ 6.0, \text{H-5}\)), 0.63–0.61 (1H, m, \(\text{CH(CH}_2)_2\)), 0.46–0.44 (2H, m, \(\text{CH(CHH}_2)_2\)), 0.13–0.12 (2H, m, \(\text{CH(CHH}_2)_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 138.0 (C-3), 126.8 (C-2), 64.0 (C-1) 41.0 (C-5), 19.7, 17.1, [3.7 and 3.6 (cyclopropyl)]; \(m/z\) (CI) 126 [M]\(^+\), 109 (Found: [MNH\(_4\)]\(^+\), 144.1388). \(\text{C}_8\text{H}_{14}\text{O}\) requires [MNH\(_4\)]\(^+\), 144.1387).

(E)-4-Cyclohexylpent-2-en-1-ol (152c)

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Et} \\
\rightarrow & \\
\text{Me} & \quad \text{CH}_2=\text{CHOH} \\
\end{align*}
\]

Ester 158c (1.14 g, 5.41 mmol, 1.0 equiv) was reacted according to general procedure B to afford the (E)-4-cyclohexylpent-2-en-1-ol 152c (0.757 g, 83%) as a colourless oil after purification by Kugelrohr distillation: \(b_p\) \(175\) °C; \(\nu_{\text{max}}\) (film) 3388, 1641 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 5.62–5.51 (2H, m, H-2,3), 4.08 (2H, d, \(J\ 4.5, \text{H-1}\)), 1.99–1.94 (1H, m, H-4), 1.85 (1H, s (br), OH), 1.73–1.61 (6H, m, cyclohexyl), 1.23–1.12 (5H, m, cyclohexyl), 0.96 (3H, d, \(J\ 7.0, \text{H-5}\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 137.8 (C-3), 127.8 (C-2), 63.8 (C-1) 43.0 (C-4), 42.0, 32.0, 30.3, 26.6 (cyclohexyl), 17.3 (C-5); \(m/z\) (CI)
Experimental


(E)-4-Methylnon-2-en-1-ol (152d)

![Chemical structure of (E)-4-Methylnon-2-en-1-ol (152d)]

Ester 158d (1.14 g, 5.73 mmol, 1.0 equiv) was reacted according to general procedure B to afford (E)-4-methylnon-2-en-1-ol 152d (0.313 g, 35%) as a colourless oil after purification by Kugelrohr distillation: bp 95 °C; νmax (film) 3318, 1668, 1457, 1378, 971 cm⁻¹; δH (400 MHz, CDCl₃) 5.61–5.58 (2H, m, H-2,3), 4.10 (2H, d, J 4.5, H-1), 2.14 (1H, m, H-4), 1.40 (1H, s (br), OH), 1.29–1.27 (8H, m, H-5,6,7,8), 0.99 (3H, d, J 7.0, 4-Me), 0.89 (3H, t, J 7.0, H-9); δC (400 MHz, CDCl₃) 139.4 (C-3), 127.0 (C-2), 63.9 (C-1), 36.8, 36.3, 32.0, 26.9, 22.7, 20.4, 14.1; m/z (ESI) 155 [M–H]⁺, 151, 137.

(E)-4,5,5-Trimethylhex-2-en-1-ol (152e)

![Chemical structure of (E)-4,5,5-Trimethylhex-2-en-1-ol (152e)]

Ester 158e (568 mg, 3.10 mmol, 1.0 equiv) was reacted according to general procedure B to afford (E)-4,5,5-trimethylhex-2-en-1-ol 152e (290 mg, 66%) as a colourless oil after purification by Kugelrohr distillation: bp 150 °C; νmax (film) 3450, 1639 cm⁻¹; δH (400 MHz, CDCl₃) 5.70–5.57 (2H, m, H-2,3), 4.12 (2H, d, J 5.0, H-1), 1.95 (1H, dq, J 8.0, 6.5, H-4), 1.42 (1H, s (br), OH), 0.96 (3H, d, J 6.5, 4-Me), 0.87 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 136.6 (C-3), 128.6 (C-2), 64.0 (C-1),
Experimental

46.8 (C-5) 32.8 (C-4), 27.5 (C(CH₃)₃), 15.4 (4-CH₃); m/z (Cl) 142 [M]⁺, 125 [M–OH]⁺ (Found: [M]⁺, 142.1595. C₉H₁₀O requires [M]⁺, 142.1358).

\((E)-4\)-Phenylpent-2-en-1-ol (152f)

\[
\begin{array}{c}
\text{Me} & \text{CO₂Et} \\
\text{Ph} & 158f \\
\end{array} & \xrightarrow{\text{Me} \text{CO₂Et}} & \begin{array}{c}
\text{Me} & \text{OH} \\
\text{Ph} & 152f \\
\end{array}
\]

Ester 158f (527 mg, 2.58 mmol, 1.0 equiv) was reacted according to general procedure B to afford \((E)-4\)-phenylpent-2-en-1-ol 152f (303 mg, 77%) as a colourless oil after purification over silica gel (25% EtOAc/petrol): \(ν_{\text{max}}\) (film) 3420, 1638 cm⁻¹; \(δ_{\text{H}}\) (400 MHz, CDCl₃) 7.35–7.23 (5H, m, Ph), 5.91 (1H, dd, \(J\) 15.5, 7.0, H-3) 5.70 (1H, dt, \(J\) 15.5, 6.0, H-2), 4.15 (2H, d, \(J\) 6.0, H-1), 3.53 (1H, m, H-4), 1.44 (1H, s (br), OH) 1.41 (3H, d, \(J\) 7.0, 4-Me); \(δ_{\text{C}}\) (101 MHz, CDCl₃) 145.5 (i-Ph), 137.5 (C-3), 128.5, 127.7, 127.2 (Ph), 126.3 (C-2), 63.7 (C-1), 42.0 (C-4), 21.1 (C-5); in agreement with published data.⁷⁷

\((E)-4\)-Phenylhex-2-en-1-ol (152g)

\[
\begin{array}{c}
\text{Et} & \text{CO₂Et} \\
\text{Ph} & 158g \\
\end{array} & \xrightarrow{\text{Et} \text{CO₂Et}} & \begin{array}{c}
\text{Et} & \text{OH} \\
\text{Ph} & 152g \\
\end{array}
\]

Ester 158g (1.03 g, 5.04 mmol, 1.0 equiv) was reacted according to general procedure B to afford \((E)-4\)-phenylhex-2-en-1-ol 152g (0.361 g, 45%) as a colourless oil after purification by Kugelrohr distillation: bps 175 °C; \(ν_{\text{max}}\) (film) 3401, 1641, 1492, 1080, 972 cm⁻¹; \(δ_{\text{H}}\) (400 MHz, CDCl₃) 5.85 (1H, dd, \(J\) 15.5, 7.0, H-3), 5.66 (1H, dt, \(J\) 15.5, 6.0, H-2), 4.13 (2H, d, \(J\) 6.0, H-1), 3.18 (1H, dt, \(J\) 7.5, 7.0, H-4), 1.77 (2H, dq, \(J\) 7.5, 7.5, H-5), 0.88 (3H, t, \(J\) 7.5, H-6), 1.44 (1H, s (br), OH); \(δ_{\text{C}}\) (101 MHz, CDCl₃) 144.4
Experimental

(C-3), 136.5 (C-2), 128.5 (i-Ph), 126.0 (p-Ph), 126.2 (m-Ph), 127.6 (o-Ph), 63.7 (C-1), 50.39 (C-4), 12.2 (C-5), 28.6 (C-6); m/z (Cl) 194 [MNH$_4^+$], 176 [M$^+$], 159 [M-OH]$^+$
(Found: [MNH$_4^+$], 194.1539. C$_{12}$H$_{16}$O requires [MNH$_4^+$], 194.1545).

Ethyl 3-ethenyl-4-methylhexanoate (154a)

Allylic alcohol 152a (147 mg, 1.57 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4-methylhexanoate 154a (285 mg, 98%, 50:50 syn:anti mixture of diastereomers) as a colourless oil: $\nu_{\text{max}}$ (film) 1736, 1639, 1463, 1374, 1249, 1035 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 5.73–5.65 (2H, m, syn+anti CHCH$_2$), 5.06–5.00 (4H, m, syn+anti CHCH$_2$), 4.19–4.09 (4H, m, syn+anti OCH$_2$), 2.80–2.04 (4H, m, syn+anti H-3,4), [1.40–1.30 (5H, m) and 0.90–0.80 (6H, m) syn+anti H-5,6,4-Me and OCH$_2$CH$_3$]; $\delta_C$ (101 MHz, CDCl$_3$) 182.3 (C-1), 127.9 (CHCH$_2$), 116.1 (CHCH$_2$), 60.1 (OCH$_2$), 57.4, 26.0, 15.2, 14.3; m/z (Cl) 202 [MNH$_4^+$], 185 [MH$^+$]
(Found: [MH$^+$], 185.1490. C$_{11}$H$_{20}$O$_2$ requires [MH$^+$], 185.1497).

Ethyl 3-ethenyl-4-cyclopropylpentanoate (154b)

Allylic alcohol 152b (156 mg, 1.23 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4-cyclopropylpentanoate 154b (217 mg, 89%, 50:50 syn:anti mixture of diastereomers) as a yellow oil: $\nu_{\text{max}}$ (film) 1737, 1639,
Experimental

1461 cm\(^{-1}\); \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) [5.81 (1H, ddd, \(J\) 17.0, 11.0, 8.5) and 5.73 (1H, ddd, \(J\) 17.0, 10.5, 8.5), \textit{syn}+\textit{anti} CHCH\(_2\)], [5.09–5.07 (2H, m) and 5.05–5.04 (2H, m), \textit{syn}+\textit{anti} CHCH\(_2\)], [4.13 (2H, q, \(J\) 7.0) and 4.12 (2H, q, \(J\) 7.0), \textit{syn}+\textit{anti} OCH\(_2\)], 2.69–2.20 (2H, m, \textit{syn}+\textit{anti} H-3), [2.59–2.45 (2H, m, H-2) and 2.35 (2H, dd, \(J\) 14.0, 7.0), \textit{syn}+\textit{anti} H-2), [1.26 (3H, d, \(J\) 7.0) and 1.25 (3H, d, \(J\) 7.0), \textit{syn}+\textit{anti} OCH\(_2\)CH\(_3\)], 0.96 (6H, d, \(J\) 7.0, \textit{syn}+\textit{anti} H-5), 0.85–0.64 (4H, m, \textit{syn}+\textit{anti} H-4), 0.58–0.40 (10H, m, \textit{syn}+\textit{anti} cyclopropyl); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) [173.1 and 173.0, (C-1)], [139.1 and 139.0, (CHCH\(_2\))], [115.9 and 115.7, (CHCH\(_2\))], 60.1 (OCH\(_2\)), [57.6 and 57.4, (C-4)], 46.3, 42.47, 38.0 (C-2), 20.1, 16.3, 3.5, 3.6; \(m/z\) (Cl) 214 [MNH\(_4\)]\(^+\), 197 [MH]\(^+\) (Found: [MH]\(^+\), 197.1541. C\(_{12}\)H\(_{20}\)O\(_2\) requires [MH]\(^+\), 197.1541).

Ethyl 3-ethenyl-4-cyclohexylpentanoate (154c)

![Diagram of Ethyl 3-ethenyl-4-cyclohexylpentanoate (154c)](image)

Allylic alcohol 152c (300 mg, 1.78 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4-cyclohexylpentanoate 154c (385 mg, 91%, 17:83 \textit{syn}:\textit{anti} mixture of diastereomers) as a colourless oil.

Data for the mixture: \(\nu\)\(_{\text{max}}\) (film) 1738, 1639, 1448, 1368, 1256 cm\(^{-1}\); \(m/z\) (Cl) 239 [MNH\(_4\)]\(^+\), 256 [MH]\(^+\) (Found: [MH]\(^+\), 239.2021. C\(_{15}\)H\(_{26}\)O\(_2\) requires [MH]\(^+\), 239.2011).

NMR data for \textit{syn}-154c: \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 5.71–5.62 (1H, m, CHCH\(_2\)), 5.01–4.99 (2H, m, CHCH\(_2\)), 4.11 (2H, q, \(J\) 7.0, OCH\(_2\)), 2.65–2.58 (1H, m, H-3), 2.48–2.07 (1H, m, H-4), 1.75–1.66 (11H, m, cyclohexyl), 1.28–1.21 (5H, m, H-2, OCH\(_2\)CH\(_3\)), 0.99 (3H, d, \(J\) 7.0, H-5); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 174.3 (C-1), 138.2 (CHCH\(_2\)), 115.1 (CHCH\(_2\)), 60.2 (OCH\(_2\)), 57.4 (C-4); 43.0, 41.4, 36.5, 26.7, 20.0, 17.2, 14.0.
Experimental

NMR data for **anti-154c**: $\delta_H$ (400 MHz, CDCl$_3$) 5.71–5.62 (1H, m, CHCH$_2$), 5.06–5.03 (2H, m, CHCH$_2$), 4.13 (2H, q, $J$ 7.0, OCH$_2$), 2.79–2.72 (1H, m, H-3), 2.48–2.07 (1H, m, H-4), 1.75–1.66 (11H, m, cyclohexyl), 1.28–1.21 (5H, m, H-2, OCH$_2$CH$_3$), 0.97 (3H, d, $J$ 7.0, H-5); $\delta_C$ (101 MHz, CDCl$_3$) 174.6 (C-1), 138.6 (CCH$_2$), 116.0 (CHCH$_2$), 60.2 (OCH$_2$), 57.6 (C-4), 43.2, 41.8, 38.7, 26.9, 19.4, 17.4, 14.5.

**Ethyl 3-ethenyl-4-methylnonate (154d)**

Allylic alcohol **152d** (200 mg, 1.28 mmol, 1.0 equiv) reacted according to general procedure C to afford *ethyl 3-ethenyl-4-methylnonate (154d)* (285 mg, 98%, 50:50 syn:anti mixture of diastereomers) as a yellow oil: $\nu_{\text{max}}$ (film) 1739, 1640, 1463, 1337 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 5.73–5.63 (2H, m, syn+anti CHCH$_2$), 5.07–4.99 (4H, m, syn+anti CHCH$_2$) [4.12 (2H, q, $J$ 7.0) and 4.13 (2H, q, $J$ 7.0), syn+anti OCH$_2$], [2.58 (1H, dt, $J$ 9.0, 5.0) and 2.50 (1H, dt, $J$ 9.0, 4.0), syn+anti H-3], 2.41–2.25 (4H, m, syn+anti H-2), 1.37–1.14 (20H, m, syn+anti H-4,5,6,7,8), 0.92–0.83 (12H, m, syn+anti OCH$_2$CH$_3$ and H-9); $\delta_C$ (101 MHz, CDCl$_3$) 173.1 (syn+anti C-1), [139.6 and 138.2 (CHCH$_2$)], [116.1 and 113.4 (CHCH$_2$)], 60.2 (OCH$_2$), [45.7 and 44.7 (syn+anti C-2)], 37.8, 36.6, 34.6, 33.3, 32.1, 27.0, 22.7, 16.7, 15.5, 14.3, 14.1; $m/z$ (CI) 245 [MH+NH$_4^+$], 187, 169 (Found: [MH+NH$_4^+$], 245.2359. C$_{14}$H$_{26}$O$_2$ requires [MH+NH$_4^+$], 245.2355).
Ethyl 3-ethenyl-4,5,5-trimethyl-hexanoate (154e)

Allylic alcohol 152e (279 mg, 1.96 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4,5,5-trimethyl-hexanoate 154e (280 mg, 67%, 33:67 syn:anti mixture of diastereomers) as a yellow oil.

Data for the mixture: \( \nu_{\text{max}} \) (film) 1738, 1637, 1466, 1366, 1267, 1176 cm\(^{-1}\); \( \delta_c \) (101 MHz, CDCl\(_3\)) 142.8 (anti C-1), 142.7 (syn C-1), 134.0 (syn+anti CHCH\(_2\)), 129.6 (anti CHCH\(_2\)), 129.2 (syn CHCH\(_2\)), 60.2 (OCH\(_2\)), 41.7, 41.6, 21.5, 23.3, 14.4, 12.7; \( m/z \) (CI) 230 [MNH\(^+\)], 213 [MH\(^+\)] (Found: [MH\(^+\)], 213.1859. C\(_{13}\)H\(_{24}\)O\(_2\) requires [MH\(^+\)], 213.1855).

\(^1\)H-NMR data for syn-154e: \( \delta_H \) (400 MHz, CDCl\(_3\)) 5.87–5.77 (1H, m, CHCH\(_2\)) 4.98–4.95 (2H, m, CHCH\(_2\)), 4.12 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.50–2.20 (3H, m, H-2,3), 1.31–1.52 (1H, m, H-4), 1.20 (3H, d, \( J \) 7.0, 4-Me), 0.95 (2H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\)), 0.85 (9H, s, iBu).

\(^1\)H-NMR data for anti-154e: \( \delta_H \) (400 MHz, CDCl\(_3\)) 5.87–5.77 (1H, m, CHCH\(_2\)) 5.07–5.01 (2H, m, CHCH\(_2\)), 4.13 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.50–2.20 (3H, m, H-2,3), 1.31–1.52 (1H, m, H-4), 1.30 (3H, d, \( J \) 7.0, 4-Me), 0.96 (2H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\)), 0.92 (9H, s, iBu).

Ethyl 3-ethenyl-4-phenylpentanoate (154f)
Experimental

Allylic alcohol 152f (200 mg, 1.25 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4-phenylpentanoate 154f (280 mg, 97%, 32:68 syn:anti mixture of diastereomers) as a yellow oil.

Data for the mixture: \( \nu_{\text{max}} \) (film) 1734, 1640, 1494, 1374, 1176, 1032 cm\(^{-1}\); \( m/z \) (CI) 250 [MNH\(_4^+\)], 233 [MH\(^+\)] (Found [MH\(^+\)], 233.1463. C\(_{15}\)H\(_{20}\)O\(_2\) requires [MH\(^+\)], 233.1463).

NMR data for syn-154f: \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.33–7.15 (5H, m, Ph), 5.56 (1H, ddd, \( J \) 17.0, 11.0, 9.0, CHCH\(_2\)), 5.03–4.96 (2H, m, CHCH\(_2\)), 4.11 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.90–2.83 (1H, m, H-4), 2.83–2.77 (1H, m, H-3), [2.42 (1H, dd, \( J \) 15.0, 5.0) and 2.34 (1H, dd, \( J \) 15.0, 7.0), H-2], 1.31 (3H, d, \( J \) 7.0, H-5), 1.21 (1H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\) ); \( \delta_C \) (101 MHz, CDCl\(_3\)) 172.6 (C-1), 138.4 (CHCH\(_2\)), 128.3, 128.1, 126.2, 116.4 (CHCH\(_2\)), 60.1 (OCH\(_2\)), 46.6, 43.1, 37.5, 18.5, 14.3.

NMR data for anti-154f: \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.33–7.15 (5H, m, Ph), 5.68 (1H, ddd, \( J \) 17.5, 10.0, 8.0, CHCH\(_2\)), 5.12–5.08 (2H, m, CHCH\(_2\)), 4.05 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.73–2.68 (1H, m, H-4), 2.67–2.61 (1H, m, H-3), [2.24 (1H, dd, \( J \) 14.5, 9.0) and 2.10 (1H, dd, \( J \) 14.5, 6.0), H-2], 1.25 (3H, d, \( J \) 7.0, H-5), 1.21 (1H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\) ); \( \delta_C \) (101 MHz, CDCl\(_3\)) 172.6 (C-1), 139.4 (CHCH\(_2\)), 128.5, 127.6, 126.3, 116.7 (CHCH\(_2\)), 60.1 (OCH\(_2\)), 47.5, 43.7, 38.6, 19.8, 14.3.

Ethyl 3-ethenyl-4-phenylhexanoate (154g)

Allylic alcohol 152g (307 mg, 1.87 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-ethenyl-4-phenylhexanoate 154g (460 mg, 99%, 32:68 syn:anti mixture of diastereomers) as a yellow oil.
Data for the mixture: \( \nu_{\text{max}} \) (film) 1734, 1640, 1494, 1453 cm\(^{-1}\); \( m/z \) (CI) 264 \([\text{MNH}_4]^+\), 247 \([\text{MH}]^+\) (Found: \([\text{MH}]^+\), 247.1698. \( \text{C}_{16}\text{H}_{22}\text{O}_2 \) requires \([\text{MH}]^+\), 247.1698).

NMR data for \textit{syn-154g}: \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.34–7.16 (5H, m, Ph), 5.56 (1H, ddd, \( J \) 17.0, 9.0, 8.0, CHCH\(_2\)), 5.04–5.01 (2H, m, CHCH\(_2\)), 4.13 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.87 (1H, ddt, \( J \) 8.0, 5.3, H-3), 2.44–2.30 (1H, m, H-4), 2.22–2.13 (2H, m, H-2), .93–1.83 (2H, m, H-5), 1.20 (3H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\)), 0.81 (3H, t, \( J \) 7.5, H-6); \( \delta_C \) (101 MHz, CDCl\(_3\)) 172.7 (C-1), 141.6 (i-Ph), 138.0 (CHCH\(_2\)), 129.1, 127.9, 126.5, 116.4 (CHCH\(_2\)), 60.2 (OCH\(_2\)), 51.1 (C-4), 38.1 (C-2), 25.9 (C-5), 14.9 (OCH\(_2\)CH\(_3\)), 12.3 (C-6).

NMR data for \textit{anti-154g}: \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.34–7.16 (5H, m, Ph), 5.69 (1H, ddd, \( J \) 17.0, 9.0, 8.0, CHCH\(_2\)), 5.16–5.10 (2H, m, CHCH\(_2\)), 4.04 (2H, q, \( J \) 7.0, OCH\(_2\)), 2.75 (1H, ddt, \( J \) 8.0, 4.0, H-3), 2.44–2.30 (1H, m, H-4), 2.08–2.01 (2H, m, H-2), 1.79–1.69 (2H, m, H-5), 1.26 (3H, d, \( J \) 7.0, OCH\(_2\)CH\(_3\)), 0.70 (3H, t, \( J \) 7.5, H-6); \( \delta_C \) (101 MHz, CDCl\(_3\)) 172.6 (C-1), 142.9 (i-Ph), 139.1 (CHCH\(_2\)), 128.5, 126.8, 126.5, 116.6 (CHCH\(_2\)), 60.1 (OCH\(_2\)), 51.7 (C-4), 38.7 (C-2), 26.8 (C-5), 15.2 (OCH\(_2\)CH\(_3\)), 12.1 (C-6).

**4-Phenyl-3-ethenylhexan-1-ol (159)**

To a stirred solution of lithium aluminium hydride (74 mg, 1.95 mmol, 1.2 equiv) in THF (10 mL) was added a solution of ester \textit{154g} (400 mg, 1.62 mmol, 1.0 equiv) in THF (5 mL) at 0 °C. Slight effervescence was observed. The reaction mixture was warmed to rt and stirred for 35 min before quenching with ethanol (1.5 mL), water (3 mL) and aqueous HCl (2 M, 3 mL). The mixture was taken up in EtOAc (25 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were washed with brine (25 mL) before drying.
(MgSO₄) and concentration under reduced pressure. Repeated chromatography over silica gel (50% ether/petrol) afforded analytical samples of the separated diastereoisomers of 4-phenyl-3-ethenylhexan-1-ol 159:

Less polar syn-159 (99 mg, 30%): ν max (film) 3335, 1630 cm⁻¹; δ H (400 MHz CDCl₃) 7.32 (2H, m, m-Ph), 7.22–7.20 (1H, m, p-Ph), 7.15–7.13 (2H, m, o-Ph), 5.63 (1H, ddd, J 17.0, 9.5, 7.5, CHCH₂), 5.13 (2H, m, CHCH₂), [3.59 (1H, ddd, J 11.0, 7.0, 5.0) and 3.50 (1H, ddd, J 11.0, 8.0, 6.5), H-1], 2.40–2.27 (2H, m, H-2), 1.92–1.82 (1H, m, H-4), 1.53–1.41 (2H, m, H-5), 1.34–1.24 (1H, m, H-3), 0.69 (3H, t, J 7.5, H-6); δ C (101 MHz CDCl₃) 143.7, 141.9 (CHCH₂), 128.5, 128.3, 126.1, 116.3, 61.5 (C-1), 52.4, 47.5, 35.6 (C-3), 26.9 (C-4), 12.2 (C-6) m/z (Cl), 222 [MNH₄⁺] (Found: [MNH₄⁺], 222.1856. C₁₄H₂₀O requires [MNH₄⁺], 222.1858).

More polar anti-159 (54 mg, 16%): ν max (film) 3336, 1630 cm⁻¹; δ H (400 MHz CDCl₃) 7.38 (2H, m, m-Ph), 7.22–7.20 (1H, m, p-Ph), 7.12–7.11 (2H, m, o-Ph), 5.49 (1H, ddd, J 17.0, 10.0, 7.0, CHCH₂), 5.06–4.98 (2H, m, CHCH₂), [3.65 (1H, ddd, J 11.0, 7.0, 5.0) and 3.57 (1H, ddd, J 11.0, 7.0 and 5.0), H-1], 2.58–2.43 (2H, m, H-2), 1.82–1.69 (1H, m, H-4), 1.53–1.48 (2H, m, H-5), 1.39–1.32 (1H, m, H-3), 0.81 (3H, t, J 7.5, H-6); δ C (101 MHz CDCl₃) 143.7, 139.8 (CHCH₂), 128.7, 128.4, 126.2, 116.3, 61.4 (C-1), 52.1, 45.9, 35.6 (C-3), 25.9 (C-4), 12.1 (C-6); m/z (Cl), 222 [MNH₄⁺] (Found: [MNH₄⁺], 222.1856. C₁₄H₂₀O requires [MNH₄⁺], 222.1858).

Anti-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate (anti-160)

To a solution of alcohol anti-159 (90 mg, 0.44 mmol, 1.0 equiv) in dichloromethane (1 mL) was added TEA (0.19 mL, 1.32 mmol, 3.0 equiv) followed by a solution of 3,5-dinitrobenzoyl chloride (112 mg, 0.49 mmol, 1.1 equiv) in dichloromethane (1.2
mL) at 0 °C. The resulting orange solution was warmed to rt and stirred for 48 h before quenching with aqueous HCl (2 M, 2 mL). The mixture was partitioned between dichloromethane (7 mL) and water (15 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 7 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (20% ether/petrol) and recrystallisation (EtOAc/60–80 petrol) afforded anti-(±)-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate anti-160 (145 mg, 89%) as yellow crystalline plates: mp 58–60 °C; νₘₐₓ (film) 3085, 3026, 1723, 1629, 1546, 1462, 1344, 1280, 1172, 1078 cm⁻¹; δ H (500 MHz CDCl₃) 9.24 (1H, s, Ar), 9.10 (2H, s, Ar), 7.35 (2H, t, J 7.5, m-Ph), 7.22 (1H, t, J 7.5, p-Ph), 7.17–7.16 (2H, m, o-Ph), 5.62 (1H, ddd, J 17.0, 10.0, 9.0, CHCH₂), 5.20 (1H, d, J 10.0, trans-CHCH₂), 5.12 (1H, d, J 17.0, cis-CHCH₂), 4.31 (1H, dddd, J 6.0, 8.0, 11.0, 15.0, H-1), 2.36 (2H, m, H-2), 1.86 (1H, m, H-4), 1.75 (1H, m, H-3), 1.48 (2H, m, H-5), 0.68 (3H, t, J 7.5, H-6); δ C (126 MHz CDCl₃) 162.3 (C-1), 148.6, 143.3, 140.6, 134.1, 128.4, 126.4, 122.3, 117.1, 65.5, 52.3, 47.6, 31.3 (C-3), 27.1 (C-4), 12.1 (C-6); m/z (ESI) 399 [MH]+, 391, 217 (Found: C, 63.39; H, 5.52; N, 6.95. C₂₁H₂₂N₂O₆ requires C, 63.31; H, 5.57; N, 7.03).

**Syn-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate (syn-160)**

To a solution of alcohol syn-159 (23 mg, 0.11 mmol, 1.0 equiv) in dichloromethane (1 mL) was added TEA (0.046 mL, 0.33 mmol, 3.0 equiv) followed by a solution of 3,5-dinitrobenzoyl chloride (32 mg, 0.14 mmol, 1.1 equiv) in dichloromethane (0.5 mL) at 0 °C. The resulting orange solution was warmed to rt and stirred overnight before quenching with aqueous HCl (2 M, 2 mL). The mixture was partitioned between dichloromethane (7 mL) and water (15 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 7 mL). The combined
organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (20% ether/petrol) afforded syn-(±)-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate syn-160 (24 mg, 53%) as a yellow gum: ν_max (film) 3084, 3026, 2958, 1722, 1546, 1462, 1344, 1280, 1172, 1078 cm⁻¹; δ_H (500 MHz CDCl₃) 9.22 (1H, s, Ar), 9.12 (2H, s, Ar), 7.29 (2H, t, J 7.5, m-Ph), 7.20 (1H, t, J 7.5, p-Ph), 7.14 (2H, m, o-Ph), 5.52 (1H, ddd, J 17.0, 10.0, 7.0, CHCH₂), 5.10 (1H, d, J 10.0, trans-CHCH₂), 5.02 (1H, d, J 17.0, cis-CHCH₂), 4.43–4.34 (1H, m, H-1), 2.48–2.43 (2H, m, H-2), 2.01–2.00 (1H, m, H-4), 1.77 (1H, m, H-3), 1.41 (2H, m, H-5), 0.81 (3H, t, J 7.5, H-6); δ_C (126 MHz CDCl₃) 162.4 (C-1), 148.6 143.3, 140.6, 134.1, 128.4, 126.4, 122.3, 117.1, 65.7 (C-1), 52.0, 45.9, 31.5 (C-3), 25.7 (C-4), 12.2 (C-6); m/z (ESI) 399 [MH]⁺, 391, 217.
3.4.2 Compounds relevant to sections 2.3 and 2.4

Methyl (2S)-2-(tert-butyldiphenylsilyloxy)propanoate (161)

(S)-Methyl lactate (5.67 g, 54.5 mmol, 1.0 equiv) was added dropwise via syringe to a solution of tert-butyldiphenylchlorosilane (16.5 g, 60.0 mmol, 1.1 equiv), TEA (19.0 mL, 136.4 mmol, 2.5 equiv) and DMAP (0.67 g, 5.45 mmol, 0.1 equiv) in THF (50 mL) at 0 °C, to give a white suspension. The reaction mixture was warmed to rt overnight and concentrated under reduced pressure. The remaining white residue was triturated with ether (100 mL) and the solids were removed by filtration. The filtrate was sequentially washed with acetic acid (15% w/w in water, 150 mL), water (150 mL), saturated sodium hydrogen carbonate solution (100 mL) and water (100 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (50% dichloromethane/petrol) afforded methyl (2S)-2-(tert-butyldiphenylsilyloxy)propanoate 161 (12.61 g, 68%) as a colourless oil: [α]D²⁰ –34.1 (c 0.82, CHCl₃), lit –51.8 (c 0.78, EtOH); νmax (film) 1762, 1281, 1137, 1113 cm⁻¹; δH (400 MHz CDCl₃) 7.69–7.68 (4H, m, o-Ph), 7.47–7.38 (6H, m, m,p-Ph), 4.30 (1H, q, J 7.0, H-2), 3.58 (3H, s, OMe), 1.39 (3H, d, J 7.0, H-3), 1.12 (9H, s, C(CH₃)₃); δC (101 MHz CDCl₃) 174.2 (C-1), 135.8, 129.8, 127.6 (Ph), 68.9 (OMe), 51.6 (C-2), 26.8 (C(CH₃)₃), 21.3, 19.3; in agreement with published data.²¹⁶

(2S)-2-(Tert-butyldiphenylsiloxy)propanal (162)
Diisobutylaluminium hydride (15.45 mL of a 1.5 M solution in toluene, 18.54 mmol, 1.0 equiv) was added dropwise via syringe to a solution of ester 161 (6.35 g, 18.54 mmol, 1.0 equiv) in dichloromethane (25 mL) at -78 °C over 15 min. The reaction mixture was stirred for 2 h at -78 °C before the addition of water (16 mL) with vigorous stirring. The reaction mixture was allowed to warm to rt and solid sodium hydrogen carbonate was added to bind the resultant precipitate. The precipitate was filtered and washed with ether (100 mL) before separation of excess water from the filtrate, drying (MgSO₄) and concentration under reduced pressure. Purification over silica gel (40% dichloromethane/petrol) afforded (2S)-2-(tert-butyldiphenylsiloxy)propanal 162 (4.43 g, 77%) as a colourless oil: [α]D²⁰ −15.2 (c 0.56, CHCl₃); νmax (film) 1739, 1445, 1112, 1007, 740 cm⁻¹; δH (400 MHz CDCl₃) 9.68 (1H, s, H-1), 7.67–7.65 (4H, m, o-Ph), 7.43–7.41 (6H, m, m,p-Ph), 4.12 (1H, q, J 7.0, H-2), 1.25 (3H, d, J 7.0, H-3), 1.14 (9H, s, C(CH₃)₃); δC (101 MHz CDCl₃) 203.9 (C-1), 135.9, 130.1, 127.8, 76.7 (C-2), 26.9 (C(CH₃)₃), 19.2, 18.4; m/z (CI) 330 [MNH₄⁺], 312 [M⁺], 235; in agreement with published data.²¹⁶

**Ethyl [4S]-[2E]-4-(tert-butyldiphenylsilyloxy)-2-pentenoate (E-163) and ethyl [4S]-[2Z]-4-(tert-butyldiphenylsilyloxy)-2-pentenoate (Z-163)**

To a solution of aldehyde 162 (4.43 g, 14.16 mmol, 1.0 equiv) in dichloromethane (14 mL) was added carbethoxymethylenetriphenylphosphorane (4.47 g, 14.16 mmol, 1.0 equiv) over 3 min at rt. After stirring for 48 h the reaction mixture was concentrated under reduced pressure. The resultant solid triphenyl phosphine oxide was removed by filtration and the residue was washed extensively with ether. The filtrate was concentrated under reduced pressure and purified over silica gel (5% ether/petrol) to afford the separated esters: desired ethyl [4S]-[2E]-4-(tert-butyldiphenylsilyloxy)-2-pentenoate E-163 (3.81 g, 74%) as a colourless oil: [α]D²⁰ −38.8 (c 0.43, CHCl₃); νmax
Experimental

(film) 1720, 1660, 1590, 1427, 1118 cm⁻¹; δH (400 MHz CDCl₃) 7.71–7.64 (4H, m, o-Ph), 7.46–7.36 (6H, m, m,p-Ph), 6.91 (1H, dd, J 15.5, 4.5, H-3), 6.02 (1H, d, J 15.5, H-2), 4.45–4.47 (1H, m, H-4), 4.21 (2H, q, J 7.0, OCH₂), 1.32 (3H, t, J 7.0, OCH₂CH₃), 1.15 (3H, d, J 6.5, H-5), 1.10 (9H, s, C(CH₃)₃); δC (101 MHz CDCl₃) 190.8 (C-1), 151.5, 135.8, 134.0 129.8, 127.6, 119.13, 68.7, 60.3, 26.9, 23.3, 19.2, 14.3; m/z (CI), 400 [MNH₄⁺]; and undesired ethyl [4S]-2(Z)-4-(tert-butyldiphenylsilyloxy)-2-pentenoate Z-163 (0.347 g, 7% a colourless oil: νmax (film) 1728, 1660, 1591, 1427, 1118 cm⁻¹; δH (400 MHz CDCl₃) 7.68–7.63 (2H, m, o-Ph), 7.40–7.33 (3H, m, m,p-Ph), 6.27 (1H, dd, J 8.0, 11.5, H-3), 5.50 (1H, d, J 11.5, H-2), 5.43–5.41 (1H, m, H-4), 4.00 (2H, q, J 7.0, OCH₂), 1.24 (2H, t, J 7.0, OCH₂CH₃), 1.08 (9H, s, C(CH₃)₃); δC (101 MHz CDCl₃) 190.9, 153.7, 135.8, 134.0 129.8, 127.4, 117.0, 66.8, 60.0, 27.0, 23.3, 19.2, 14.1; m/z (CI), 400 [MNH₄⁺]; as colourless oils, in agreement with literature data.¹²⁹

Ethyl (E)-4-hydroxypent-2-enoate (164)

To a solution of TBAF trihydrate (2.58 g, 8.17 mmol, 3.0 equiv) in THF (15 mL) at 0 °C was added a solution of ester E-163 (1.00 g, 2.61 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was warmed to rt and stirred for 30 min before addition of acetic acid (2.5 mL) and filtration of the mixture over a pad of silica gel (1 cm x 10 cm, 50 % EtOAc/petrol). The filtrate was washed with saturated aqueous sodium hydrogencarbonate (2 x 75 mL) and brine (50 mL) before drying (MgSO₄) and concentration under reduced pressure. Purification over silica gel (25% EtOAc in 40/60 petrol) afforded the ester (±)-164 (264 mg, 70%) as a colourless oil: νmax (film) 3345, 1716, 1653 cm⁻¹; δH (400 MHz CDCl₃) 6.99 (1H, dd, J 15.4, 4.5, H-3), 6.04 (1H, d, J 15.5, H-2), 4.51–4.49 (1H, m, H-4), 4.22 (2H, q, J 7.0, OCH₂), 1.79 (1H, s (br), OH), 1.36 (3H, d, J 6.5, H-5), 1.32 (3H, t, J 7.0, OCH₂CH₃); δC (101 MHz CDCl₃) 166.5 (C-1) 150.9 (C-3), 119.6 (C-2), 67.2 (C-4), 60.5 (OCH₂), 22.8
(OCH₂CH₃), 14.1 (C-5); m/z (CI) 162 [MNH₄]⁺, 145 [MH]⁺, 127 [M-OH]⁺ (Found: [MH]⁺, 145.0873. C₇H₁₃O₃ requires [MH]⁺, 145.0865); in agreement with published data.⁷¹

**Ethyl (E)-4-fluoropent-2-enoate (165)**

To a solution of DAST (1.80 mL, 14.6 mmol, 1.4 equiv) in dichloromethane (10 mL) at rt was added a solution of ester 164 (1.50 g, 10.4 mmol, 1.0 equiv) in dichloromethane (10 mL) via syringe. The resultant solution was stirred at rt for 5 min before sodium carbonate (2.6 g) was carefully added via a wide-bore needle. The mixture was stirred for 25 min and filtered. The filtrate was washed with saturated aqueous sodium carbonate (50 mL), dried (MgSO₄) and concentrated using a rotary evaporator at atmospheric pressure (water bath temperature 40 °C) to give ethyl (E)-4-fluoropent-2-enoate 165 (1.19 g, 98%) as a yellow oil without further purification: ν_max (film) 1722, 1641, 1305 cm⁻¹; δ_H (400 MHz, CDCl₃) 6.94 (1H, ddd, J 20.0, 15.5, 8.0, H-3), 6.07 (1H, dt, J 15.5, 2.0, H-2), 5.26 (1H, ddt, J 48.0, 8.0, 6.5, H-4), 4.24 (2H, q, J 7.0, OCH₂), 1.50 (3H, dd, J 23.5, 6.5, H-5), 1.33 (3H, t, J 7.0, OCH₂CH₃); δ_F (376 MHz, CDCl₃) -176.7 (ddt, J 48.0, 22.0, 20.0); δ_C (101 MHz, CDCl₃) 166.1 (C-1), 146.0, 145.8 (C-3), 120.7 (C-2), 88.7, 87.0 (C-4), 60.7 (OCH₂), 20.8, 20.6 (C-5), 14.2 (OCH₂CH₃); m/z (EI) 124 [M-HF]⁺; in agreement with published data.⁷¹
Isopropyl benzenesulfinate (168)

To a suspension of sodium benzenesulfinate 167 (73.87 g, 450 mmol, 1.0 equiv) in 1,2-dichloroethane (120 mL) was added thionyl chloride (80.31 g, 49.0 mL, 675 mmol, 1.5 equiv) dropwise via syringe at 0 °C. The resulting mixture was warmed to rt and stirred for 2 h before removal of excess thionyl chloride by distillation under reduced pressure. The residue was taken up in ether (200 mL) and added via a syringe fitted with a wide-bore needle to a solution of IPA (42.4 mL, 540 mmol, 1.2 equiv) in pyridine (72.5 mL, 900 mmol, 2.0 equiv) at 0 °C. The solution was warmed to rt, stirred for 2.5 h and water (200 mL) was added. The mixture was poured onto ether (200 mL) and the phases were separated. The organic phase was washed with aqueous HCl (2 M, 4 x 100 mL) followed by brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. Distillation of the residue under reduced pressure afforded isopropyl benzenesulfinate 168 (55.2 g, 67%) as a colourless oil: bp 188–90 °C; ν_max (film) 1444, 1384, 1139, 912, 840, 734 cm⁻¹; δ_H (400 MHz CDCl₃) 7.76–7.73 (2H, m, Ph), 7.57–7.55 (3H, m, Ph), 4.64 (1H, hept, J 6.5, CH(CH₃)₂), [1.42 (3H, d, J 6.5) and 1.28 (3H, d, J 6.5), CH(CH₃)₂]; δ_C (101 MHz CDCl₃) 145.7 (i-Ph), 131.9 (p-Ph), 129.0 (m-Ph), 125.1 (o-Ph), 73.0 (CH(CH₃)₃), 24.0, 23.8 (CH(CH₃)₃); m/z (Cl) 185 [MH]^+, 202 [MNH₄]^+; in agreement with published data.¹³²
**Experimental**

**(E)-(Hept-1-enylsulfinyl)benzene and (Z)-(hept-1-enylsulfinyl)benzene (169)**

![Chemical structures](image)

To a solution of dimethyl methylphosphonate (6.46 mL, 59.5 mmol, 2.2 equiv) in THF (60 mL) at −78 ºC was added n-butyllithium (25.7 mL of a 2.21 M solution in hexanes, 56.8 mmol 2.1 equiv) dropwise via syringe. The resultant colourless anion solution was stirred at −78 ºC for 10 min before dropwise addition of isopropyl benzenesulfinate 168 (5.00 g, 27.0 mmol, 1.0 equiv). The cloudy white reaction mixture was stirred at −78 ºC for 30 min, and hexanal (3.90 mL, 32.4 mmol, 1.2 equiv) was added dropwise via syringe to give a clear, colourless solution. The reaction mixture was warmed immediately to room temperature and quenched with saturated aqueous NH₄Cl (100 mL). The mixture was partitioned between dichloromethane (150 mL) and water (75 mL), and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (20–50% ether/petrol) to afford a mixture of 

**(E)-(hept-1-enylsulfinyl)benzene and (Z)-(hept-1-enylsulfinyl)benzene 169** (3.56 g, 60%, 1:1 E:Z mixture of isomers) as a colourless oil.

Data for the mixture: \( \nu_{\text{max}} \) (film) 1651, 1622, 1583, 1468, 1304, 1050, 922, 775, 701 cm⁻¹; \( m/z \) (EI) 222 [M]+, 205 [M–OH]+ (Found: [M]+, 222.1074. C₁₃H₁₈O₃S requires [M]+, 222.1078).

NMR data for **E-169**: \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.65–7.63 (2H, m, SPh), 7.53–7.51 (3H, m, SPh), 6.65 (1H, dt, \( J \) 15.0, 7.0, H-2), 6.25 (1H, dt, \( J \) 15.0, 1.5, H-1), 2.24 (2H, AB quartet, \( J \) 7.0, 1.5, H-3), 1.55–1.47 (2H, m, H-4), 1.33–1.29 (4H, m, H-5,6), 0.92–0.88 (3H, m, H-7); \( \delta_{\text{C}} \) (101 MHz, CDCl₃) 144.7 142.5, 136.7, 130.8, 128.9, 124.5, 123.7, 31.23, 22.4, 21.6, 13.6, 13.2.
NMR data for Z-169: δH (400 MHz, CDCl3) 7.64 (2H, d, J 6.5, o-SPh), 7.56–7.50 (3H, m, m,p-SPh), 6.26–6.23 (2H, m, H-1,2), 2.72–2.52 (2H, m, H-1,2), 1.57–1.52 (2H, m, H-4), 1.42–1.39 (4H, m, H-5,6), 0.95 (3H, t, J 7.0, H-7); δC (400 MHz, CDCl3) 144.6, 142.5, 136.8, 130.7, 129.3, 124.1, 31.3, 29.4, 28.8, 22.4, 14.0.

1,2-Bis(trifluoroacetoxy)-1-(phenylsulfenyl)heptane (170)

To a solution of vinyl sulfinate 169 (3.58 g, 16.1 mmol, 1.0 equiv, 1:1 E:Z mixture of isomers) in dichloromethane (30 mL) at 0 °C under was added TFAA (2.27 mL, 16.10 mmol, 1.0 equiv) dropwise via syringe. The resulting colourless solution was stirred at 0 °C for 10 min before further addition of TFAA (3.39 g, 2.27 mL, 16.10 mmol, 1.0 equiv) dropwise via syringe. The reaction mixture was stirred for 30 min at 0 °C before quenching with saturated aqueous sodium hydrogencarbonate (75 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were dried (MgSO4) and concentrated under reduced pressure to afford 1,2-bis(trifluoroacetoxy)-1-(phenylsulfenyl)heptane 170 (6.68 g, 96%, 1:1 syn:anti mixture of diastereomers) as a colourless oil without further purification: νmax (film) 1787, 1641, 1226 cm⁻¹; δH (400 MHz, CDCl3) 7.53–7.39 (10H, m, syn+anti SPh), 6.35 (1H, d, J 4.0, anti H-1), 6.19 (1H, d, J 8.5, syn H-1), 5.42 (1H, AB quartet, J 4.0, 2.0, anti H-2), 5.26 (1H, AB quartet, J 8.5, 3.5, syn H-2), 2.01–1.83 (4H, m, syn+anti H-3), 1.45–1.27 (12H, m, syn+anti H-4,5,6), 0.94–0.90 (6H, m, syn+anti H-7); δC (101 MHz, CDCl3) 134.8, 134.3, 130.1, 129.8, 129.7, 129.6, 129.5, 127.8, 86.1, 83.8, 31.1, 30.2, 29.2, 24.5, 23.9, 22.3, 22.2, 13.8; m/z (ESI) 432 [M]+, 276, 203 (Found: [M]+, 432.0885. C17H18F6O4S requires [M]+, 432.0830).
2-Hydroxyheptanal (171)

To a solution of 170 (6.67 g, 15.44 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C were added, consecutively, dropwise via syringe; MeOH (1.56 mL, 38.6 mmol, 2.50 equiv) and TEA (0.22 mL, 1.54 mmol, 0.1 equiv). The resulting solution was stirred at 0 °C for 15 min and concentrated under reduced pressure. The residue was purified over silica gel (40–50% ether/petrol) to afford 2-hydroxyheptanal 171 (1.34 g, 67%) as a white solid: mp 86–88 °C; NMR data were complicated as the aldehyde existed as a mixture of oligomeric forms; m/z (ESI) 413 [M+3Na]+, 283 [M+2Na]+, 131 [M]+ (Found: [M]+, 131.1076. C₇H₁₅O₂ requires [M]+ 131.1027).

Ethyl (E)-4-hydroxynon-2-enoate (172)

To a refluxing solution of aldehyde 171 (1.30 g, 10.0 mmol, 1.0 equiv) in benzene (15 mL) was added a suspension of carbethoxymethylenetriphenylphosphorane (3.83 g, 11.0 mmol, 1.1 equiv) in benzene (20 mL) dropwise via a pressure-equalised dropping funnel. After refluxing for 5.5 h, the reaction mixture was cooled and concentrated under reduced pressure. The residue was purified over silica gel (30% ether/petrol) to afford the ethyl (E)-4-hydroxynon-2-enoate 172 (1.61 g, 81%) as a colourless oil: ν_max (film) 3345, 1717, 1652; δ_H (400 MHz, CDCl₃) 6.97 (1H, dd, J₁₅.₅, 5.0, H-3), 6.07 (1H, d, J₁₅.₅, H-2), 4.35–4.32 (1H, m, H-4), 4.23 (2H, q, J₇.₀, OCH₂), 1.65–1.58 (4H, m, H-5,6), 1.37–1.31 (7H, m, H-7,8,9), 0.92 (3H, t, J 7.₀,
OCH₂CH₃); δC (101 MHz, CDCl₃) 166.5 (C-1), 150.1 (C-3), 120.2 (C-2), 71.2 (C-4), 60.5 (OCH₂), 36.6 (C-5), 31.7 (C-6), 24.9 (C-7), 22.5 (C-8), 14.2, 14.0; m/z (CI) 218 [MNH₄]⁺, 201 [MH]⁺ (Found: [MH]⁺, 201.1485. C₁₁H₂₀O₃ requires [MH]⁺, 201.1491); in agreement with published data.¹²⁹a

Ethyl (E)-4-fluoronon-2-enoate (173) and ethyl (E)-3-(fluoromethyl)oct-2-enoate (174)

To a solution of DAST (367 µL, 3.00 mmol, 1.2 equiv) in dichloromethane (2.5 mL) at –78 °C under a dry nitrogen atmosphere was added ester 172 (500 mg, 2.50 mmol, 1.0 equiv) via syringe. The reaction mixture was allowed to warm to 0 °C over 15 min and was cooled to –78 °C. MeOH (4 mL) was added and the mixture was allowed to warm to rt. Water (6 mL) was poured on and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel (5% EtOAc/20% dichloromethane/petrol) to afford the separated esters: Less polar ethyl (E)-3-(fluoromethyl)oct-2-enoate 174 (25 mg, 5%) as a colourless oil: νmax (film) 1718, 1662, 1462 cm⁻¹; δH (400 MHz, CDCl₃) 5.93 (1H, s, H-2), 4.87 (2H, dd, JHF 47.0, JH₂H₄ 1.5, CH₂F), 4.20 (2H, q, J 7.0, OCH₂), 2.56 (2H, dt, J 8.0, 1.5, H-4), 1.59–1.49 (2H, m, H-5), 1.38–1.32 (7H, m, H-6,7,8), 0.93 (3H, t, J 7.0, OCH₂CH₃); δF (376 MHz, CDCl₃) –219.5 (t, JHF 47.0, CH₂F); δC (101 MHz, CDCl₃) 166.0 (C-1), 156.5 (C-3), 114.6 (C-2), 84.0 (d, JCF 177, CH₂F), 59.9 (OCH₂), 32.0 (C-4), 29.7 (C-5), 28.4 (C-6), 22.4 (C-7), [14.3 and 14.0 (C-8 and OCH₂CH₃)]; m/z (ESI) 203 [MH]⁺, 183 [M-F]⁺ (Found: [MH]⁺, 203.1442. C₁₁H₁₀FO₂ requires [MH]⁺, 203.1447); and more polar ethyl (E)-4-fluoronon-2-enoate 173 (154 mg, 31%) as a colourless oil: νmax (film) 1722, 1647 cm⁻¹; δH (400 MHz, CDCl₃) 6.92 (1H, ddd, JHF 25.0, JHH 16.0, 7.0, H-3), 6.07 (1H, d, J 16.0, H-2), 5.11 (1H, dm, JHF
48.0, H-4), 4.20 (2H, q, J 7.0, OCH₂) 1.78–1.60 (2H, m, H-5), 1.46–1.38 (9H, m, H-6,7,8,9), 0.91 (3H, t, J 7.0 OCH₂CH₃); δF (376 MHz, CDCl₃) –184.1 (ddt, J 48.0, 25.0, 21.0); δC (101 MHz, CDCl₃) 166.1 (C-1), 145.3, 145.1 (C-3), 120.1 (C-2), 91.0 (C-4) 60.6 (OCH₂), 34.8, 31.5, 24.3, 21.7, 14.2; m/z (CI) 220 [MNH₄⁺], 200, 183 [M-F]⁺, (Found: [MNH₄⁺] 220.1719. C₁₁H₁₉F₂O₂ requires [MNH₄⁺] 220.1713); the fraction contained <3% of the elimination product 175 in agreement with published data.²¹⁷

**(E)-4-Fluoronon-2-enoic acid (180)**

![Chemical Structure](image)

To a solution of ester 173 (1.00 g, 4.95 mmol, 1.0 equiv) in THF (8 mL) and water (2 mL) in a microwave vial was added lithium hydroxide monohydrate (0.415 g, 9.90 mmol, 2.0 equiv). After heating by microwave at 110 °C for 45 min, the reaction was cooled to rt and aqueous HCl (2 M, 20 mL) was added. The mixture was poured onto dichloromethane (20 mL) and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL), the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford (E)-4-fluoronon-2-enoic acid 180 (467 mg, 55%) as a white solid which was used without further purification: mp 30–32 °C; δH (400 MHz, CDCl₃) 7.04 (1H, ddd, J₃F₄ 21.0, J 16.0, 9.5, H-3), 6.10 (1H, d, J 16.0, H-2), 5.10 (1H, dm, J₄F₄ 47.0, H-4), 1.81–1.69 (2H, m, H-5), 1.52–1.34 (6H, m, H-6,7,8), 0.93 (3H, t, J 7.0, H-9); δF (376 MHz, CDCl₃) 185.1 (ddt, J₄F₄ 47.0, J₃F₄ 21.0, J₅F₄ 22.5); δC (101 MHz, CDCl₃) 170.9 (C-1), 147.1 (d, J 19.0, C-3), 133.9 (d, J 11.0, C-2), 91.2 (C-4), 34.6 (d, J 21.0, C-5), 31.5 (C-6), 24.2 (C-7), 22.5 (C-8), 14.0 (C-9).
(E)-4-Fluoronon-2-en-1-ol (179)

To a solution of acid 180 (567 mg, 3.26 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C was added TEA (0.489 mL, 3.52 mmol, 1.08 equiv), followed by isobutylchloroformate (0.456 mL, 3.58 mmol, 1.10 equiv). A fine white precipitate of triethylamine hydrochloride developed. The reaction mixture was warmed to rt, stirred for 1.5 h and filtered directly into a suspension of sodium borohydride (492 mg, 13.03 mmol, 4.0 equiv) in dimethoxyethane (10 mL) under nitrogen. The white suspension was stirred for 2.5 h and water (50 mL) was poured on, resulting in vigorous effervescence. The mixture was extracted with dichloromethane (3 x 45 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), concentrated and purified over silica gel (10% EtOAc/petrol) to afford (E)-4-fluoronon-2-en-1-ol 179 (252 mg, 49%) as a colourless oil which decomposed on standing: ν max (film) 3343, 1653, 1379, 1086, 972 cm⁻¹; δ H (400 MHz, CDCl₃) 5.99–5.92 (1H, m, H-3), 5.86–5.77 (1H, m, H-2), 4.93 (1H, ddt, J_H4F4 = 48.0, J_HH = 12.5, 6.0, H-4), 4.24–4.21 (2H, m, H-1), 1.79–1.34 (9H, m, OH, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); δ F (376 MHz, CDCl₃) –174.0 (m); δ C (101 MHz, CDCl₃) 132.1 (d, J 11.0, C-3), 129.6 (d, J 19.5, C-2), 93.1 (d, J 165.5, C-4), 62.7 (C-1), 35.4 (d, J 22.0, C-5), 31.6 (C-6), 24.4 (C-7), 22.6 (C-8), 14.0 (C-9); m/z (Cl) 178 [MNH₄⁺], 158 [M-2H]⁺, 140 [M-HF]⁺, 123.

Ethyl 4-fluoro-3-ethenynonanoate (182)
Allylic alcohol 179 (86 mg, 0.538 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 4-fluoro-3-ethenylmonanoate 182 (82 mg, 66%, 1:1 syn:anti mixture of diastereomers) as a yellow oil: \( \nu_{\text{max}} \) (film) 1726, 1678, 1456, 1355, 1158, 1120, 1026, 903, 871 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl\(_3\)) [5.69 (1H, ddd, J 17.0, 11.0, 9.0) and 5.68 (1H, ddd, J 17.0, 11.0, 9.0), syn+anti CH\(_2\)], 5.17–5.10 (4H, m, syn+anti CHCH\(_2\)), [4.48 (1H, ddt, J\(_{HF}\) 48.5, J\(_{HH}\) 9.0, 6.0) and 4.36 (1H, ddt, J\(_{HF}\) 48.5, J\(_{HH}\) 7.5, 5.0), syn+anti H-4], 3.55 (4H, q, J 7.0, syn+anti OCH\(_2\)), 2.87–2.68 (2H, m, syn+anti H-3), [2.64 (1H, dd, J 15.0, 5.0), 2.57 (1H, dd, J 15.0, 5.5), 2.45 (1H, dd, J 15.0, 8.0) and 2.35 (1H, dd, J 15.0, 9.5), syn+anti H-2], 1.35–1.27 (12H, m, H-6,7,8), 1.22 (4H, ddt, J\(_{HF}\) 22.0, J\(_{HH}\) 7.0, 3.0, syn+anti H-5), [0.89 (6H, t, J 7.0) and 0.88 (6H, t, J 7.0), syn+anti H-9 and OCH\(_2\)CH\(_3\)]; \( \delta_F \) (376 MHz, CDCl\(_3\)) –186.4, –191.4; \( \delta_C \) (126 MHz, CDCl\(_3\)) [172.3 and 172.2 (C-1)], [136.3 and 135.0 (CHCH\(_2\))], [118.3 and 117.8 (CHCH\(_2\))], [96.2 (d, J 24.0) and 94.5 (d, J 24.0), C-4], [60.5 and 60.4 (OCH\(_2\))], [45.4 and 44.7 (C-3)], [36.2 and 35.6 (C-2)], 32.9, 32.5, 24.5, 22.3, 14.8, 14.0; m/z (CI) 248 [MNH\(_4\)]\(^+\), 231 [MHI\(^+\), 211 [M-F]\(^+\) (Found: [MNH\(_4\)]\(^+\), 248.2014. C\(_{13}\)H\(_{23}\)FO\(_2\) requires [MNH\(_4\)]\(^+\), 248.2026).

2-(Prop-2-ynyloxy)tetrahydro-2H-pyran (187)

Propargyl alcohol (5.19 mL, 89.2 mmol, 1.0 equiv) was reacted according to the procedure of Larock et al to afford 2-(prop-2-ynyloxy)tetrahydro-2H-pyran 187 (9.83 g, 79%) as a colourless oil after distillation under reduced pressure (bp 60–61 °C) in agreement with literature data.\(^{139}\)
Experimental

1-(Tetrahydro-2H-pyran-2-yloxy)non-2-yn-4-ol (188)

To a solution of propargyl ether 187 (4.00 g, 28.4 mmol, 1.0 equiv) in THF (50 mL) at −78 °C was added n-butyllithium (11.36 mL of a 2.42 M solution in hexanes, 28.4 mmol, 1.0 equiv) dropwise via syringe. The resulting yellow anion solution was stirred at −78 °C for 30 min before addition of hexanal (3.41 g, 34.08 mmol, 1.2 equiv) dropwise via syringe. The colourless reaction mixture was warmed to 0 °C and saturated aqueous NH₄Cl (100 mL) was added. Dichloromethane (100 mL) and water (20 mL) were added and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 75 mL). The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (25–35% ether/petrol) to afford 1-(tetrahydro-2H-pyran-2-yloxy)non-2-yn-4-ol 188 (5.24 g, 77%) as a colourless oil: ν max (film) 3423, 2360, 2341, 1455, 1388, 1023 cm⁻¹; δH (400 MHz, CDCl₃) 4.83 (1H, t, J 3.5, OCHO), 4.43 (1H, dt, J 6.5, 2.0, H-4), 4.32 (2H, AB quartet, J 15.5, 2.0, H-1), 3.85 (1H, ddd, J 12.0, 9.0, 6.0, OCH axial), 3.58–3.55 (1H, m, OCH equatorial), 1.61 (1H, s (br), OH), 1.83–1.32 (14H, m), 0.91 (3H, t, J 7.0, H-9); δC (101 MHz, CDCl₃) 96.8 (OCHO), 87.1 (C-3), 80.8 (C-2), 62.6 (THP-OCH₂), 62.0 (C-4), 54.3 (C-1), 37.7, 31.5, 30.3, 25.4, 24.8, 22.6, 19.1, 14.0; m/z (Cl) 258 [MNH₄]+, 223, 174, 102; in agreement with published data.²¹⁸

2-(4-Fluoronon-2-ynyloxy)tetrahydro-2H-pyran (189)

To a solution of Deoxofluor (2.12 mL of 50% w/w solution in THF, 4.98 mmol, 1.2 equiv) in dichloromethane (20 mL) at −78 °C was added a solution of propargyl
alcohol 188 (1.00 g, 4.15 mmol, 1.0 equiv). The reaction mixture was stirred at −78 °C for 1.5 h, and quenched at −78 °C with saturated aqueous potassium carbonate (25 mL) before warming to rt. The phases were separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO₄), decolourised with charcoal, concentrated under reduced pressure and purified over silica gel (5% ether/petrol) to afford 2-(4-fluoronon-2-ynyloxy)tetrahydro-2H-pyran 189 (502 mg, 50%) as a colourless oil: ν_max (film) 2359, 2342, 1462, 1379, 1355, 1202, 1121, 1029, 903 cm⁻¹; δ_H (400 MHz, CDCl₃) 5.16 (1H, dt, J₀H₂₅.₅, J_H₄H₅ 6.5, H-4), 4.85–4.83 (1H, m, OCHO), 4.35–4.30 (2H, m, H-1), 3.86 (1H, dt, J₁H₁₁ 11.0, 3.0, OCH_axial), 3.57 (1H, m, OCH_equatorial), 1.84 (4H, m), 1.76 (7H, m), 1.15 (4H, m) 0.92 (3H, t, J 7.0, H-9); δ_F (376 MHz, CDCl₃) –172.9 (m, F-4); δ_C (101 MHz, CDCl₃) 96.9 (OCHO), 84.3 (d, J 10.0), 82.8 (d, J 25.5), 82.7 (d, J 166.5), 62.0 (d, J 5.0, C-4), 54.1 (C-1), 35.9, 35.7, 31.3, 30.2, 25.3, 24.2, 22.5, 19.0, 18.9, 14.0; m/z (Cl) 260 [MNH₄]^⁺, 235, 219, 102, 85 (Found: 260.2030. C₁₄H₂₃FO₂ requires [MNH₄]^⁺, 260.2026) (Found: C, 69.29; H, 9.51. C₁₄H₂₃FO₂ requires C, 69.39; H, 9.57).

(Z)-2-(4-Fluoronon-2-enyloxy)tetrahydro-2H-pyran (190)

![Chemical Structure](image)

A mixture of propargyl fluoride 189 (480 mg, 1.98 mmol, 1.0 equiv) in THF (3 mL) and Lindlar’s catalyst (40 mg) was stirred vigorously under an atmosphere of hydrogen gas for 75 min. The reaction mixture was filtered over a pad of Celite, washing with dichloromethane (20 mL). The filtrate was dried (MgSO₄) and concentrated to afford (Z)-2-(4-fluoronon-2-enyloxy)tetrahydro-2H-pyran 190 (435 mg, 91%) as a colourless oil, without further purification: ν_max (film) 1670, 1461, 1380, 1119, 1032, 904 cm⁻¹; δ_H (400 MHz, CDCl₃) 5.78–5.75 (1H, m, H-3), 5.68–5.65 (1H, m, H-2), 5.25 (1H, ddt, J₀H₂₅.₀, J_H₄H₅ 7.5, 5.5, H-4), 4.66 (1H, t, J 3.5, OCHO), 4.39–4.27 (1H, m, H-1), 4.18–4.08 (1H, m, H-1), 3.88–3.84 (1H, m,
OCH$_{axial}$), 3.55 (1H, m, OCH$_{equatorial}$), 1.80–1.72 (3H, m), 1.63–1.56 (7H, m), 1.39–1.33 (5H, m), 0.92 (3H, t, J 6.5, H-9); δ$_{t}$ (376 MHz, CDCl$_3$) –172.2 (ddt, J 48.0, 27.5, 14.0), δ$_{c}$ (101 MHz, CDCl$_3$) 131.1 (d, J 22.5, C-3), 131.0 (d, J 21.5, C-3), 130.2 (d, J 10.0, C-2); 129.8 (d, J 10.0, C-2), 98.1 (OCHO), 89.2 (d, J 161.5, C-4), 62.9 (d, J 23.0, C-1), 62.2 (d, J 20.0, C-1), 35.6 (d, J 22.5, C-5), 31.6, 30.6, 25.4, 24.4, 22.6, 19.5, 19.3, 14.0; m/z (Cl) 262 [MNH$_4^+$], 225, 102 [THPNH$_4^+$], 85 [THP]$^+$ (Found: [MNH$_4^+$], 262.2178. C$_{14}$H$_{25}$FO$_2$ requires [MNH$_4^+$], 262.2182) (Found: C, 68.76; H, 10.29. C$_{14}$H$_{25}$FO$_2$ requires C, 68.82; H, 10.31).

2-(4-(Hydroxyl)pentynyloxy)tetrahydro-2H-pyran (191)

![Diagram of the reaction](image)

To a solution of propargyl ether 187 (1.00 g, 7.14 mmol, 1.0 equiv) in THF (15 mL) was added n-butyllithium (3.15 mL of a 2.27 M solution in hexanes, 7.14 mmol, 1.0 equiv) dropwise via syringe at –78 °C. The resulting anion solution was stirred at –78 °C for 10 min before addition of acetaldehyde (0.49 mL, 8.57 mmol, 1.2 equiv) dropwise via syringe. The resulting solution was stirred at –78 °C for 30 min and quenched with saturated aqueous NH$_4$Cl (10 mL) followed by water (10 mL). Ether (30 mL) was poured on and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL). The combined organic extracts were dried (MgSO$_4$), concentrated under reduced pressure and purified over silica gel (5–40% EtOAc/petrol) to afford 2-(4-(hydroxyl)pentynyloxy)tetrahydro-2H-pyran 191 (1.12 g, 85%) as a colourless oil $\nu_{max}$ (film) 3391, 1647, 1442, 1202 cm$^{-1}$; δ$_{t}$ (400 MHz, CDCl$_3$) 4.82 (1H, t, J 3.0, OCHO), 4.59–4.56 (1H, m, H-2), [4.25 (1H, dd, J 15.0, 2.0) and 4.35 (1H, dd, J 15.0, 2.0), H-5], 3.86 (1H, ddd, J 12.0, 9.0, 3.0, OCH$_{axial}$), 3.51–3.59 (1H, m, OCH$_{equatorial}$), 1.86 (1H, s, OH), 1.78–1.55 (6H, m, THP), 1.48 (3H, d, J 6.5, H-1); δ$_{c}$ (400 MHz, CDCl$_3$) 96.9 (OCHO), 87.9 (C-3), 80.0 (C-4), 61.9 (THP OCH$_2$), 58.4 (C-2), 54.2, 30.23, 25.3, 24.2, 19.0; m/z (Cl) 202 [MNH$_4^+$], 186 [MH]$^+$.
85 [THP]$^+$ (Found: [MNH$_4$]$^+$, 202.1440. C$_{10}$H$_{16}$O$_3$ requires [MNH$_4$]$^+$, 202.1443); in agreement with literature data.$^{219}$

2-(4-(Thiophenyl)pentnyloxy)tetrahydro-2$H$-pyran (192)

![Structural diagram]

To a solution of propargyl alcohol 191 (500 mg, 2.71 mmol, 1.0 equiv) and diphenyl disulfide (774 mg, 3.55 mmol, 1.3 equiv, recrystallised from ether) in acetonitrile (25 mL) was added tri-$n$-butylphosphine (1.56 mL, 6.24 mmol, 2.3 equiv) dropwise via syringe at rt to give a biphasic mixture. The reaction mixture was immersed in an ultrasound bath at rt for 1.5 h before dilution with dichloromethane (50 mL) and washing with aqueous NaOH (2 M, 2 x 45 mL). The organic phase was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified over silica gel (10 % ether/petrol) to afford 2-(4-(thiophenyl)pentnyloxy)tetrahydro-2$H$-pyran 192 (571 mg, 90%) as a yellow oil: $\nu_{\text{max}}$ (film) 1583, 1480, 1388, 1346 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.54 (2H, $d$, $J$ 6.5, o-SPh), 7.35–7.29 (3H, m, m,p-SPh), 4.73 (1H, $t$, $J$ 3.5, OCHO), [4.28 (1H, $dd$, $J$ 15.5, 5.5) and 4.27 (1H, $dd$, $J$ 15.5, 7.5), H-5], 3.99 (1H, $q$, $J$ 7.0, OCH$_{axial}$), 3.85–3.80 (1H, m OCH$_{equatorial}$), 3.54–3.50 (1H, m, H-2), 1.84–1.63 (2H, m, THP), 1.52 (3H, d, $J$ 7.0, H-1); $\delta_C$ (101 MHz, CDCl$_3$) 133.9 ($i$-SPh), 132.2, 128.8, 127.7 (SPh), 96.5 (OCHO), 86.6 (C-3), 79.3 (C-2), 62.0 (OCH$_2$), 54.3 (C-1), 33.4, 30.2, 25.4, 21.7, 19.1; $m/z$ (Cl) 294 [MNH$_4$]$^+$, 277 [MH]$^+$, 210 [M-THPNH$_4$]$^+$, (Found: [MH]$^+$, 277.1273. C$_{16}$H$_{20}$O$_2$S requires [MH]$^+$, 277.1262).
4-(Phenylthio)pent-2-yn-1-ol (193)

To a solution of propargyl ether 192 (1.76 g, 6.37 mmol, 1.0 equiv), in ethanol (15 mL) was added pyridinium paratoluenesulfonate (160 mg, 0.637 mmol, 0.1 equiv) with stirring. The mixture was heated to 55 °C for 6 h, after which TLC showed some remaining 192. Pyridinium paratoluenesulfonate (160 mg, 0.637 mmol, 0.1 equiv) was added and heating at 55 °C was continued for a further 9 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was purified over silica gel (20% ether/petrol) to afford 4-(phenylthio)pent-2-yn-1-ol 193 (836 mg, 68%) as a yellow oil: \( \nu_{\text{max}} \) (film) 3357, 2351, 1583, 1479, 1483, 1038, 1009, 744, 691 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.54 (2H, dd, \( J \) 8.0, 7.5, m-SPh), 7.38–7.32 (3H, m, o,p-SPh), 4.27 (2H, d, \( J \) 2.5, H-1), 3.97 (1H, ddt, \( J \) 14.0, 7.0, 2.5, H-4), 1.61 (1H, s (br), OH), 1.55 (3H, d, \( J \) 7.0, H-5); \( \delta_C \) (101 MHz, CDCl\(_3\)) 133.8, 133.0, 128.9, 127.9, 86.6 (C-3), 81.7 (C-2), 51.3 (C-1), 33.4 (C-4), 21.7 (C-5); \( m/z \) (Cl) 210 [MNH\(_4\)]\(^+\), 192 [M]\(^+\) (Found: [MNH\(_4\)]\(^+\), 210.0957. C\(_{11}\)H\(_{12}\)OS requires [MNH\(_4\)]\(^+\), 210.0953).

2-Chloropropanal (207a)

To a solution of propanal (54.6 mL, 750 mmol, 1.0 equiv) in dichloromethane (30 mL) at −10 °C was added sulfuryl chloride (60.3 mL, 750 mmol, 1.0 equiv) dropwise via an addition funnel over 30 minutes and the reaction mixture was allowed to warm...
Experimental

to rt overnight. The reaction mixture was heated to reflux for 2 h, cooled and distilled through a 15 cm Vigreux column, collecting the fraction containing 2-chloropropanal **207a** (33.1 g, 66%) as a colourless oil: bp\textsubscript{760} 82–84 °C; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 9.54 (1H, s (br), H-1), 4.30 (1H, dq, J 7.0, 2.0 H-2), 1.63 (3H, d, J 7.0, H-3); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 195.1 (C-1), 58.8 (C-2), 18.3 (C-1), m/z (CI) 388, 294 [(3M)NH\textsubscript{4}]+, 260, 92 [M]+; in agreement with published data.\textsuperscript{155}

**2-Chloroheptanal (207b)**

![Reaction scheme]

To a solution of heptanal (3.94 mL, 26.8 mmol, 1.0 equiv) at 0 °C was added D,L–proline (313 mg, 2.68 mmol, 0.1 equiv), followed by N-chlorosuccinimide (4.85 g, 34.8 mmol, 1.3 equiv). The suspension was warmed to rt, stirred for 16 h and pentane (100 mL) was added. The mixture was filtered and concentrated under reduced pressure. The residue was added to pentane (50 mL), filtered, concentrated under reduced pressure and distilled under reduced pressure to afford 2-chloroheptanal **207b** (3.37 g, 85%) as a colourless oil: bp\textsubscript{90} 80–82 °C; ν\textsubscript{max} (film) 1735, 1466, 1379, 1102 cm\textsuperscript{-1}; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 9.47 (1H, d, J 2.5, H-1), 4.14 (1H, dt, J 5.5, 2.5, H-2), 2.00–1.78 (2H, m, H-3), 1.36–1.29 (6H, m, H-4,5,6), 0.89 (3H, t, J 7.0, H-7); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 185.2 (C-1), 64.1 (C-2), 32.3, 31.1, 25.4, 22.5, 14.1; m/z (CI), 148 [M]+, 166 [MNH\textsubscript{4}]+, 462, 428 [(3M)NH\textsubscript{4}]+; in agreement with published data.\textsuperscript{220}
2-Chloro-3-methylbutanal (207c)

To a solution of 3-methylbutanal (5.36 mL, 50.0 mmol, 1.0 equiv) at 0 ºC was added D,L–prolinamide (571 mg, 5.00 mmol, 0.1 equiv), followed by N-chlorosuccinimide (5.46 g, 65.0 mmol, 1.3 equiv). The reaction mixture was warmed to rt during 16 h and pentane (100 mL) was added. The mixture was filtered and concentrated under reduced pressure. The residue was added to pentane (50 mL), filtered, concentrated under reduced pressure and distilled to afford 2-chloro-3-methylbutanal 207c (3.88 g, 64%) as a colourless oil: bp 760–130–132 ºC; ν max (film) 1737, 1465, 1369, 1058, 830 cm⁻¹; δH (400 MHz, CDCl₃) 9.42 (1H, d, J 3.0, H-1), 3.95 (1H, dd, J 5.5, 3.0, H-2), 2.28 (1H, dsept, J 7.0, 5.5, H-3), [1.00 (3H, d, J 7.0) and 0.98 (3H, d, J 7.0), H-4]; δC (101 MHz, CDCl₃) 196.1 (C-1), 70.6 (C-2), 31.1 (C-3), 17.8 (C-4); m/z (CI) 120 [M]⁺, 138 [MNH₄]⁺, 344, 378 [(3M)NH₄]⁺; in agreement with published data.¹⁵⁸

Ethyl (E)-4-thiophenypent-2-enoate (184a)

From 164:

To a solution of ester 164 (1.00 g, 6.94 mmol, 1.0 equiv) in dichloromethane (15 mL) was added TEA (1.95 mL, 13.9 mmol, 1.0 equiv) followed by methanesulfonyl chloride (0.81 mL, 10.4 mmol, 1.5 equiv) at 0 ºC. After warming to rt and stirring for 8 h, aqueous HCl (2 M, 30 mL) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined...
Experimental

Organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give methanesulfonate 183 (1.49 g, 97%) as a colourless oil. To a solution of sodium hydride (60% w/w on mineral oil, 295 mg, 7.38 mmol, 1.1 equiv) in THF (40 mL) at 0 °C was added thiophenol (813 mg, 0.756 mL, 7.38 mmol, 1.1 equiv) dropwise via syringe. The reaction mixture was allowed to warm to rt for 5 min before cooling to –20 °C and addition of a solution of methanesulfonate 183 (1.49 g, 6.71 mmol) in THF (5 mL) dropwise via syringe. The resulting light orange suspension was stirred at –20 °C for 1 h before warming to 0 °C and quenching with aqueous HCl (2 M, 30 mL). The mixture was partitioned between water (20 mL) and ether (30 mL) and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (35 mL) and brine (35 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel (40% ether in 40/60 petrol) affording ethyl (E)-4-thiophenylpent-2-enoate 184a (1.19 g, 75%) as a colourless oil.

From 207a:

2-Chloropropanal 207a (2.29 mL, 20.0 mmol, 1.0 equiv) was reacted according to general procedure D to afford ethyl (E)-4-thiophenylpent-2-enoate 184a (2.38 g, 47%) as a colourless oil after purification over silica gel (5–20% ether/heptane): ν_max (film) 1716, 1650, 747, 692 cm⁻¹; δ_H (400 MHz, CDCl₃) [7.42–7.40 (2H, m) and 7.34–7.28 (3H, m), SPh], 6.89 (1H, dd, J 15.5, 8.0, H-3), 5.60 (1H, d, J 15.5, H-2), 4.18 (2H, q, J 7.0, OCH₂), 3.81 (1H, dq, J 8.0, 7.0, H-4), 1.45 (3H, d, J 7.0, H-5), 1.28 (3H, t, J 7.0 OCH₂CH₃); δ_C (101 MHz, CDCl₃) 166.3 (C-1), 148.4 (C-3), 133.5 (o-SPh), 133.3, (i-SPh), 128.9 (m-SPh), 127.9 (p-SPh), 120.5 (C-2), 60.4 (OCH₂), 44.9 (C-4), 19.5 (C-5), 14.2 (OCH₂CH₃); m/z (CI) 254 [MNH₄]⁺, 237 [MH]⁺, 146 [M-(SPh)NH₄]⁺ (Found: [MNH₄]⁺, 254.1219. C₁₃H₁₆O₂S requires 254.1215); in agreement with published data.¹⁴⁷ₐ
Ethyl (Z)-4-(phenylthio)pent-2-enoate (184b)

2-Chloropropanal 207a (2.29 mL, 20.0 mmol, 1.0 equiv) was reacted according to general procedure E to afford ethyl (E)-5-methyl-4-thiophenylhex-2-enoate 184b (1.37 g, 29%) as a colourless oil after purification over silica gel (5–20% ether/heptane): \( \nu_{\text{max}} \) (film) 2979, 1715, 1639, 1186, 1029, 744, 692 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) [7.40–7.30 (2H, m) and 7.27–7.21 (3H, m), SPh], 6.02 (1H, dd, J 11.5 10.5, H-3), 5.61 (1H, d, J 11.5, H-2), 5.25 (1H, dq, J 10.5, 7.0, H-4), 4.05 (2H, q, J 7.0, OCH\(_2\)), 1.39 (3H, d, J 7.0, H-5), 1.21 (3H, t, J 7.0, OCH\(_2\)CH\(_3\)); \( \delta_C \) (101 MHz, CDCl\(_3\)) 166.3 (C-1), 150.3 (C-3), 134.1, 133.2, 128.9, 127.5, 118.9 (C-2), 60.2 (OCH\(_2\)), 40.4 (C-4), 32.1, 20.0, 14.4; \( m/z \) (CI) 254 [MNH\(_4^+\)], 237 [MH\(^+\)] (Found: C, 65.84; H, 6.80. \( C_{13}H_{16}O_2S \) requires C, 66.07; H, 6.82).

Ethyl (E)-4-thiophenylnon-2-enoate (184c)

2-Chloroheptanal 207b (743 mg, 5.0 mmol, 1.0 equiv) was reacted according to general procedure D to afford ethyl (E)-4-thiophenylnon-2-enoate 184c (785 mg, 57%) as a colourless oil after purification over silica gel (5–40% ether/heptane): \( \nu_{\text{max}} \) (film) 2931, 1720, 1648, 1438, 1160, 746, 692 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) [7.38–7.35 (2H, m) and 7.31–7.23 (3H, m), SPh], 6.77 (1H, dd, J 15.5, 9.0, H-3), 5.50 (1H, dd, J 15.5, 1.0, H-2), 4.15 (2H, q, J 7.0, OCH\(_2\)), 3.60 (1H, dt, J 9.0, 6.5, H-4), 1.79–
1.61 (2H, m, H-5), 1.47–1.29 (6H, m, H-6,7,8), 1.26 (3H, t, \( J = 7.0 \), OCH\(_2\)CH\(_3\)), 0.89 (3H, t, \( J = 7.0 \), H-9); \( \delta_c \) (101 MHz, CDCl\(_3\)) 166.4 (C-1), 147.9 (C-3), 133.7, 129.1, 128.0, 124.0, 121.3 (C-2), 60.5 (OCH\(_2\)), 51.1 (C-4), 33.8, 31.7, 27.2, 22.7, 14.4, 14.2; \( m/z \) (Cl) 310 [\( \text{MNH}_4^+ \)], 293 [\( \text{MH}^+ \)], 282, 268 (Found: [\( \text{MH}^+ \)], 293.1579. C\(_{17}\)H\(_{24}\)O\(_2\)S requires [\( \text{MH}^+ \)] 293.1575) (Found C, 69.63; H, 8.29. C\(_{17}\)H\(_{24}\)O\(_2\)S requires C, 69.82; H, 8.27).

**Ethyl (Z)-4-(thiophenyl)non-2-enoate (184d)**

![Chemical structure](image)

2-Chloroheptanal **207b** (2.91 ml, 20.0 mmol, 1.0 equiv) was reacted according to general procedure E to afford the ester to afford ethyl (Z)-4-(thiophenyl)non-2-enoate **184d** (4.35 g, 73%) as a colourless oil after purification over silica gel (5–40% ether/heptane): \( \nu_{\text{max}} \) (film) 2931, 2859, 1717, 1640, 1583, 1178, 1026, 744, 692 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) [7.43–7.41 (2H, m) and 7.29–7.45 (3H, m), SPh], 5.99 (1H, dd, \( J = 11.0, 11.5, \) H-3), 5.65 (1H, d, \( J = 11.5, \) H-2), 5.20–5.14 (1H, m, H-4), 4.05 (2H, q, \( J = 7.5, \) OCH\(_2\)), 1.64–1.28 (8H, m, H-5,6,7,8), 1.23 (3H, t, \( J = 7.5, \) OCH\(_2\)CH\(_3\)), 0.93–0.89 (3H, m, H-9); \( \delta_c \) (101 MHz, CDCl\(_3\)) 166.1 (C-1), 149.1 (C-3), 133.9, 133.0, 128.6, 127.2, 119.4 (C-2), 60.0 (OCH\(_2\)), 45.2, 34.0, 31.5, 26.8, 22.5, 14.2, 14.0; \( m/z \) (Cl) 310 [\( \text{MNH}_4^+ \)], 293 [\( \text{MH}^+ \)], 268 (Found: [\( \text{MH}^+ \)], 293.1579. C\(_{17}\)H\(_{24}\)O\(_2\)S requires [\( \text{MH}^+ \)], 293.1575).
Experimental

Ethyl (E)-5-methyl-4-thiophenylhex-2-enoate (184e)

2-Chloro-3-methylbutanal 207c (551 mg, 5.0 mmol, 1.0 equiv) was reacted according to general procedure D to afford ethyl (E)-5-methyl-4-thiophenylhex-2-enoate 184e (795 mg, 60%) as a colourless oil after purification over silica gel (5–40% ether/heptane): $\nu_{\text{max}}$ (film) 1717, 1682, 1583, 1182, 1026, 744, 690 cm⁻¹; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) [7.30–7.27 (2H, m) and 7.22–7.16 (3H, m), SPh], 6.75 (1H, dd, $J$ 15.5, 10.0, H-3), 5.40 (1H, d, $J$ 15.5, H-2), 4.07 (2H, q, $J$ 7.0, OCH$_2$), 3.36 (1H, dd, $J$ 10.0, 6.5, H-5), 1.18 (3H, t, $J$ 7.0, OCH$_2$CH$_3$), [1.03 (3H, d, $J$ 6.5) and 0.98 (3H, d, $J$ 6.5), H-6]; $\delta_{\text{C}}$ (101 MHz, CDCl$_3$) 166.3 (C-1), 146.2 (C-3), 136.5, 133.5, 129.1, 127.8, 121.8 (C-2), 60.5 (OCH$_2$), 59.0 (C-4), 32.4 (C-5), [20.8 and 20.1, (C-6)], 14.4 (OCH$_2$CH$_3$); m/z (CI) 282 [MNH$_4$]$^+$, 265 [MH]$^+$, 233 (Found: [MNH$_4$]$^+$, 282.1357. C$_{15}$H$_{20}$O$_2$S requires [MNH$_4$]$^+$, 282.1528) (Found: C, 67.49; H, 7.68. C$_{15}$H$_{20}$O$_2$S requires C, 68.14; H, 7.62).

Ethyl (Z)-5-methyl-4-(thiophenyl)hex-2-enoate (184f)

2-Chloro-3-methylbutanal 207c (2.41 g, 20.0 mmol, 1.0 equiv) was reacted according to general procedure E to afford ethyl (Z)-5-methyl-4-(thiophenyl)hex-2-enoate 184f (1.41 g, 27%) as a colourless oil after purification over silica gel (5–20% ether/heptane): $\nu_{\text{max}}$ (film) 1716, 1683, 1583, 1182, 1026, 744, 691 cm⁻¹; $\delta_{\text{H}}$ (400
Experimental

MHz, CDCl$_3$) [7.40 (2H, d, J 7.0) and 7.28–7.19 (3H, m, SPh), 6.10 (1H, dd, J 11.5, 11.0, H-3), 5.68 (1H, d, J 11.5, H-2), 5.02 (1H, dd, J 11.0, 7.0, H-4), 4.03 (2H, q, J 7.0, OCH$_2$), 1.96 (1H, sext, J 7.0, H-5), 1.22 (3H, t, J 7.0, OCH$_2$CH$_3$), [1.15 (3H, d, J 7.0) and 1.06 (3H, d, J 7.0), H-6]; $\delta_c$ (101 MHz, CDCl$_3$) 166.2 (C-1), 147.5 (C-3), 134.3 ($i$-SPh) 132.9 ($o$-SPh), 128.6 ($m$-SPh), 127.1 ($p$-SPh), 119.6 (C-2), 59.9 (OCH$_2$), 32.2 (C-5), [20.5 and 19.8, (C-6)], 14.2 (OCH$_2$CH$_3$); m/z (Cl) 282 [MNH$_4^+$], 265 [MH]$^+$ (Found: [MH]$^+$, 265.1265. C$_{15}$H$_{20}$O$_2$S requires [MH]$^+$, 265.1262) (Found: C, 68.19; H, 7.62. C$_{15}$H$_{20}$O$_2$S requires C, 68.14; H, 7.62).

**Ethyl (E)-4-(phenylthio)-pent-3-enoate and ethyl (Z)-4-(phenylthio)-pent-3-enoate (208)**

To a solution of ester 184b (20 mg, 0.09 mmol, 1.0 equiv) in $d_6$-DMSO (0.7 mL) in an NMR tube was added potassium tert-butoxide (5 mg, 0.045 mmol, 0.5 equiv) in one portion. The tube was shaken and a red colour developed. The $^1$H-NMR spectrum of the mixture was measured at intervals of 10 min, 1 h and 16 h showing conversion to a 70:30 mixture of ethyl (E)-4-(phenylthio)-pent-3-enoate E-208 and ethyl (Z)-4-(phenylthio)-pent-3-enoate and Z-208: $\delta_h$ (400 MHz, CDCl$_3$) inter alia 7.35–7.02 (10H, m, E+Z SPh), [6.64 (1H, t, J 7.5) and 6.39 (1H, t, J 7.0) E+Z H-3], 4.07–3.95 (4H, m, E+Z OCH$_2$), 2.50 (4H, m, E+Z H-2).
(E)-4-(Thiophenyl)pent-2-en-1-ol (185a)

Ester 184a (1.16 g, 4.91 mmol, 1.0 equiv) was reacted according to general procedure F to afford (E)-4-(thiophenyl)pent-2-en-1-ol 185a (676 mg, 71%) as a colourless oil after purification over silica gel (5–75 % TBME/heptane): ν<sub>max</sub> (film) 3378, 1639, 1372, 1196, 750, 693 cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) [7.35–7.69 (3H, m,) and 7.43–7.41 (2H, m), SPh], 5.69 (1H, ddt, J<sub>15</sub> 15.5, 9.0, 1.5, H-3), 5.52 (1H, dt, 15.5, 6.0, H-2), 4.05 (2H, m, H-1), 3.80 (1H, dq, J<sub>9</sub> 9.0, 7.5, H-4), 1.42 (3H, d, J 7.5, H-5), 1.15 (1H, s (br), OH); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 134.6 (C-3), 133.7, 133.15, 129.5, 128.7, 127.4 (C-2), 63.1 (C-1), 45.3 (C-4), 20.3 (C-5); m/z (EI) 194 [M]<sup>+</sup>, 163 [M-CH<sub>2</sub>OH]<sup>+</sup>, 110 [SPh]<sup>+</sup>, 84 [M-SPh]<sup>+</sup> (Found: [M]<sup>+</sup>, 194.0765. C<sub>11</sub>H<sub>14</sub>OS requires [M]<sup>+</sup>, 194.0762); in agreement with published data.<sup>147a</sup>

(Z)-4-(Phenylthio)pent-2-en-1-ol (185b)

From 193:

To a solution of propargyl alcohol 193 (377 mg, 1.96 mmol, 1.0 equiv) in dichloromethane (20 mL) was added TEA (1.08 mL, 7.84 mmol, 4.0 equiv) followed by NBSH<sup>221</sup> (1.06 g, 4.91 mmol, 2.5 equiv) in one portion. The suspension was stirred for 12 h to give a dark red solution. Saturated aqueous sodium hydrogen carbonate (50 mL) was poured on and the mixture was stirred for 10 min.
The phases were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (25% TBME/petrol) to afford (Z)-4-(thiophenyl)pent-2-en-1-ol 185b (210 mg, 55%) as a colourless oil.

From 184b:

![Diagram](image)

Ester 184b (1.16 g, 4.91 mmol, 1.0 equiv) was reacted according to general procedure F to afford (Z)-4-(thiophenyl)pent-2-en-1-ol 185b (670 mg, 70%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): ν_max (film) 3366, 1651, 1583, 1474, 1438, 1195, 1041, 1013, 750, 692 cm⁻¹; δ_H (400 MHz, CDCl₃), [7.52–7.50 (2H, m) and 7.36–7.29 (3H, m), SPh], 5.56–5.50 (1H, m, H-2), 5.44 (1H, dd, J 11.0, 10.5, H-3), 4.10 (1H, dq, J 10.5, 7.0, H-4), [3.83 (1H, dd, J 13.0, 6.0) and 3.73 (1H, dd, J 13.0, 7.0), H-1], 1.60 (1H, s, OH), 1.40 (3H, d, J 7.0, H-5); δ_C (101 MHz, CDCl₃) 134.8 (SPh), 134.4 (C-3), 132.1 (i-SPh), 128.9 (SPh), 128.2, 126.8 (C-2), 58.3 (C-1), 42.0 (C-4), 20.7 (C-5); m/z (CI) 212 [MNH₄]⁺, 194, [M]⁺, 177 [M-OH]⁺, 163 (Found: [MNH₄]⁺, 212.1113. C₁₁H₁₃OS requires [MNH₄]⁺, 212.1109).

(E)-4-(Thiophenyl)non-2-en-1-ol (185c)

![Diagram](image)

Ester 184c (746 mg, 2.55 mmol, 1.0 equiv) was reacted according to general procedure F to afford (E)-4-(thiophenyl)non-2-en-1-ol 185c (531 mg, 83%) as a
colourless oil after purification over silica gel (5–60% TBME/heptane): $\nu_{\text{max}}$ (film) 3350, 1663, 1583, 1438, 747, 691 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) [7.38–7.36 (2H, m) and 7.29–7.23 (3H, m), SPh], 5.55 (1H, dd, J 15.5, 9.0, H-3), 5.42 (1H, dt, J 15.5, 5.5, H-2), 3.99 (2H, t, J 6.0, H-1), 3.59 (1H, m, H-4), 1.80–1.20 (8H, m, H-5,6,7,8), 0.85 (3H, t, J, 7.0, H-9); $\delta_C$ (400 MHz, CDCl$_3$) 135.0 (i-SPh), 133.5 (C-3), 133.1 (o-SPh), 130.6 (m-SPh), 128.8 (C-2), 127.4 (p-SPh), 62.3 (C-1), 51.5 (C-4), 34.5 (C-5), 31.8 (C-6), 27.2 (C-7), 22.7 (C-8), 14.2 (C-9); $m/z$ (CI) 268 [MNH$_4$]$^+$, 251 [MH]$^+$, 233 [M-OH]$^+$ (Found: [MNH$_4$]$^+$, 268.1738. C$_{15}$H$_{22}$OS requires [MNH$_4$]$^+$, 268.1735) (Found: C, 71.42; H, 8.81. C$_{15}$H$_{22}$OS requires C, 71.95; H, 8.86).

(Z)-4-(Thiophenyl)non-2-en-1-ol (185d)

![chemical structure](image)

Ester 184d (3.00 g, 10.3 mmol, 1.0 equiv) was reacted according to general procedure F to afford (Z)-4-(thiophenyl)non-2-en-1-ol 185d (1.54 g, 60%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): $\nu_{\text{max}}$ (film) 3388, 1651, 1583, 1467, 1438, 1378, 1176, 1025, 747, 692 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) [7.52–7.50 (2H, m) and 7.36–7.33 (3H, m), SPh], 5.57 (1H, dt, J 11.0, 7.0, H-2), 5.39 (1H, dd, J 11.0, 9.0, H-3), 3.91 (1H, dt, J 9.0, 5.5, H-4), 3.80–3.71 (2H, m, H-1), 1.60 (1H, s (br), OH), 1.44–1.40 (2H, m, H-5), 1.37–1.31 (6H, m, H-6,7,8), 0.91 (3H, t, J 7.0, H-9); $\delta_C$ (101 MHz, CDCl$_3$) 134.9, 134.3, 133.5, 129.4, 128.9, 128.2, 58.4 (C-1), 47.4 (C-4), 34.5, 31.5, 31.3, 27.2, 22.5, 14.0; $m/z$ (CI) 268 [MNH$_4$]$^+$, 251 [MH]$^+$, 233, 158 (Found: C, 72.03; H, 8.72. C$_{15}$H$_{22}$OS requires C, 71.95; H, 8.86).
**Experimental**

(E)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185e)

![Structure of (E)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185e)]

Ester 184e (279 mg, 1.06 mmol) was reacted according to general procedure F to afford (E)-5-methyl-4-(thiophenyl)hex-2-en-1-ol 185e (195 mg, 83%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): $\nu_{\text{max}}$ (film) 3367, 1663, 1583, 1438, 1438, 969, 748, 692 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) [7.38–7.36 (2H, m) and 7.27–7.20 (3H, m), SPh], 5.58 (1H, dd, $J_{15.0, 9.5}$, H-3), 5.38 (1H, dt, $J_{15.0, 6.0}$, H-2), 3.98 (1H, t, $J_{6.0}$, H-1), 3.45 (1H, dd, $J_{9.50, 6.5}$, H-4), 1.96 (1H, sext, $J_{6.5}$, H-5), [1.06 (3H, d, $J_{6.5}$) and 1.03 (3H, d, $J_{6.64}$), H-6], 0.93 (1H, t, $J_{6.0}$, OH); $\delta$C (400 MHz, CDCl$_3$) 135.4, 133.4, 131.3, 131.0, 128.8, 127.3, 63.3 (C-1), 59.3 (C-4), 32.3 (C-5), 20.9, 19.8 (C-6); m/z (CI) 240 [MNH$_4$]$^+$, 223 [MH]$^+$, 205 [M-OH]$^+$ (Found: [MH]$^+$, 223.1166. C$_{13}$H$_{18}$OS requires [MH]$^+$, 223.1157) (Found: C, 70.28; H, 8.13. C$_{13}$H$_{18}$OS requires C, 70.22; H, 8.16).

(Z)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185f)

![Structure of (Z)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185f)]

Ester 184f (81 mg, 0.31 mmol, 1.0 equiv) was reacted according to general procedure F to afford (Z)-5-methyl-4-(thiophenyl)hex-2-en-1-ol 185f (36 mg, 54%) as a colourless oil after purification over silica gel (5–20% TBME/heptane): $\nu_{\text{max}}$ (film) 3350, 1650, 1583, 750, 690 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) [7.51–7.49 (2H, dd, $J_{8.0, 2.0}$) and 7.37–7.29 (3H, m), SPh], 5.62–5.48 (2H, m, H-2,3), 3.77–3.70 (3H, m, H-
1.4), 1.92 (1H, sext, J 6.5, H-5), [1.10 (3H, d, J 6.5) and 1.03 (3H, d, J 6.5), H-6]; δC (101 MHz, CDCl₃) 134.9 (C-3), 134.7, 131.3, 129.5, 128.9, 128.0, 58.2 (C-1), 54.8 (C-4), 32.0 (C-5), 20.8 (C-6), 19.6 (C-6); m/z (CI) 240 [MNH₄]⁺, 223 [MH]⁺ (Found: C, 70.34; H, 8.17. C₁₃H₁₈OS requires C, 70.22; H, 8.16).

**Ethyl 3-ethenyl-4-(phenylthio)-pentanoate (186a)**

From 185a:

![Diagram](image)

Allylic alcohol 185a (100 mg, 0.515 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 3-ethenyl-4-(phenylthio)-pentanoate 186a (133 mg, 98%, 1:1 syn:anti mixture of diastereomers) as a colourless oil.

From 185b:

![Diagram](image)

Allylic alcohol 185b (100 mg, 0.515 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 3-ethenyl-4-(phenylthio)-pentanoate 186a (131 mg, 97%, 91:9 syn:anti mixture of diastereoisomers) as a colourless oil.

Data for the mixture: νₓ max (film) 1734, 1639, 1584, 1479, 1176, 1090 cm⁻¹; m/z (ESI) 454, 391, 265 [MH]⁺, 219, 177 [M-SPhNa]⁺ (Found: [MH]⁺, 265.1269, C₁₅H₂₀O₂S requires [MH]⁺, 265.1262).
Experimental

NMR data for syn-186a: $\delta_H$ (400 MHz, $d_6$-acetone) [7.46 (2H, d, $J$ 7.0), 7.35 (2H, dd, $J$ 7.5, 7.0) and 7.27 (1H, dd, $J$ 7.5, 7.0), SPh], 5.81 (1H, ddd, $J$ 16.5, 11.0, 8.0, CHCH$_2$), 5.11 (1H, d, $J$ 11.0, trans-CHCH$_2$), 5.10 (1H, d, $J$ 16.5, cis-CHCH$_2$), 4.06 (2H, q, $J$ 7.0, OCH$_2$), 3.51 (1H, dq, $J$ 7.0, 3.5, H-4), 2.85–2.80 (1H, m, H-3), [2.75 (1H, dd, $J$ 15.0, 5.5) and 2.43 (1H, dd, $J$ 15.0, 9.0), H-2], 1.27 (3H, d, $J$ 7.0, H-5), 1.18 (3H, t, $J$ 7.0, OCH$_2$CH$_3$); $\delta_C$ (101 MHz, $d_6$-acetone) 172.1 (C-1), 138.3 (CHCH$_2$), 136.1 (i-SPh), 132.2, 129.6, 127.4, 117.1 (CHCH$_2$), 60.3 (OCH$_2$), 47.9 (C-4), 45.3 (C-3), 36.1 (C-2), 18.5 (C-5), 14.2 (OCH$_2$CH$_3$).

NMR data for anti-186a: $\delta_H$ (400 MHz, $d_6$-acetone) [7.46 (2H, d, $J$ 7.0), 7.35 (2H, dd, $J$ 7.5, 7.0) and 7.27 (1H, dd, $J$ 7.5, 7.0), SPh], 5.83 (1H, ddd, $J$ 17.0, 11.0, 8.0, CHCH$_2$), 5.10 (1H, d, $J$ 11.0, trans-CHCH$_2$), 5.07 (1H, d, $J$ 17.0, cis-CHCH$_2$), 4.06 (2H, q, $J$ 7.0, OCH$_2$), 3.41 (1H, dq, $J$ 13.5, 6.5, H-4), 2.82–2.77 (1H, m, H-3), [2.73 (1H, dd, $J$ 15.0, 5.5) and 2.45 (1H, dd, $J$ 15.0, 8.5), H-2], 1.25 (3H, d, $J$ 7.0, H-5), 1.18 (3H, t, $J$ 7.0, OCH$_2$CH$_3$); $\delta_C$ (101 MHz, $d_6$-acetone) 172.8 (C-1), 137.9 (CHCH$_2$), 135.7 (i-SPh), 132.2, 129.5, 127.4, 117.1 (CHCH$_2$), 60.3 (OCH$_2$), 46.6 (C-4), 45.3 (C-3), 37.7 (C-2), 17.8 (C-5), 14.2 (OCH$_2$CH$_3$).

Ethyl 3-ethenyl-4-(phenylthio)-nonate (186b)

From 185c:

![Chemical structure](image)

Allylic alcohol 185c (65 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 3-ethenyl-4-(phenylthio)-nonate 186b (82 mg, 98%, 50:50 syn:anti mixture of diastereomers) as a colourless oil.
From 185d:

\[
\begin{align*}
\text{C}_3\text{H}_1\text{ll} & \quad \text{SPh} \quad \text{185d} \quad \text{OH} \quad \text{CO}_2\text{Et} \\
& \quad \text{SPh} \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

Allylic alcohol 185d (65 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 3-ethenyl-4-(phenylthio)-nonate 186b (78 mg, 94%, 90:10 syn:anti mixture of diastereomers) as a colourless oil.

Data for the mixture: \( \nu_{\text{max}} \) (film) 1733, 1639, 1584, 1479, 1351, 1173, 745, 692 cm\(^{-1}\); \( m/z \) (CI) 328 [MNH\(_4\)]\(^+\), 321 [MH\(^+\)], 264, 233 (Found: [MH\(^+\)], 321.1909. C\(_{19}\)H\(_{28}\)O\(_2\)S requires [MH\(^+\)], 321.1888).

NMR data for syn-186b: \( \delta_H \) (400 MHz, \( d_6 \)-acetone) [7.47 (2H, d, \( J \ 8.0 \)), 7.35 (2H, dd, \( J \ 8.0, 6.5 \)) and 7.26 (1H, dd, \( J \ 8.0, 6.5 \)), SPh], 5.83 (1H, ddd, \( J \ 17.0, 10.0, 8.0 \), \( CHCH_2 \)), 5.13 (1H, d, \( J \ 10.0, \text{trans-CHCH}_2 \)), 5.11 (1H, d, \( J \ 17.0, \text{cis-CHCH}_2 \)), 4.07 (2H, q, \( J \ 7.0, \text{OCH}_2 \)), 3.83–3.33 (1H, m, H-4), 2.92 (1H, m, H-3), [2.79 (1H, dd, \( J \ 15.0, 6.0 \)) and 2.46 (1H, dd, \( J \ 15.0, 8.0 \)), H-2], 1.75–1.27 (8H, m, H-5,6,7,8), 1.18 (3H, t, \( J \ 7.0, \text{OCH}_2\text{CH}_3 \)); \( \delta_C \) (101 MHz, \( d_6 \)-acetone) 171.6 (C-1), 137.6 (CHCH\(_2\)), 131.3 (o-SPh), 136.5, 129.0 (m-SPh), 126.6 (p-SPh), 116.6 (CHCH\(_2\)), 59.8 (OCH\(_2\)), 53.5 (C-4), 43.7 (C-3), 33.0, 31.3, 26.9, 22.3, 13.7, 13.4.

NMR data for anti-186b: \( \delta_H \) (400 MHz, \( d_6 \)-acetone) [7.47 (2H, d, \( J \ 8.0 \)), 7.35 (2H, dd, \( J \ 8.0, 6.5 \)) and 7.26 (1H, dd, \( J \ 8.0, 6.5 \)), SPh], 5.86 (1H, ddd, \( J \ 17.0, 10.0, 8.0 \), \( CHCH_2 \)), 5.13 (1H, d, \( J \ 10.0, \text{trans-CHCH}_2 \)), 5.11 (1H, d, \( J \ 17.0, \text{cis-CHCH}_2 \)), 4.08 (2H, q, \( J \ 7.0, \text{OCH}_2 \)), 3.29–3.24 (1H, m, H-4), 2.90–2.83 (1H, m, H-3), [2.78 (1H, dd, \( J \ 15.0, 5.5 \)) and 2.45 (1H, dd, \( J \ 15.0, 9.0 \)), H-2], 1.75–1.27 (8H, m, H-5,6,7,8), 1.18 (3H, t, \( J \ 7.0, \text{OCH}_2\text{CH}_3 \)); \( \delta_C \) (101 MHz, \( d_6 \)-acetone) 171.4 (C-1), 138.2 (CHCH\(_2\)), 136.5, 131.4 (o-SPh), 128.9 (m-SPh), 127.4 (p-SPh), 116.4 (CHCH\(_2\)), 59.8 (OCH\(_2\)), 52.7 (C-4), 44.5 (C-3), 36.9 (C-2), 36.2 (C-2), 33.0, 31.4, 26.5, 22.3, 13.7, 13.4.
**Experimental**

**Ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate (186c)**

From 185e:

![Diagram](image)

Allylic alcohol 185e (58 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate 186c (71 mg, 93%, 60:40 syn:anti mixture of diastereoisomers) as a colourless oil.

From 185f:

![Diagram](image)

Allylic alcohol 185f (36 mg, 0.16 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate 186c (41 mg, 87%, 90:10 syn:anti mixture of diastereoisomers) as a colourless oil.

Data for the mixture: $\nu$\textsubscript{max} (film) 1734, 1640, 1582, 1351, 745, 692 cm\(^{-1}\); m/z (Cl) 310 [MNH\textsubscript{4}]\(^+\), 293 [MH]\(^+\), 205, 117 (Found: [MH]\(^+\), 293.1587. C\textsubscript{17}H\textsubscript{24}O\textsubscript{2}S requires [MH]\(^+\), 293.1575).

NMR data for syn-186c: $\delta$\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) [7.83–7.80 (2H, m) and 7.67–7.56 (3H, m), SPh], 6.21 (1H, ddd, J 17.0, 10.0, 8.0, CHCH\textsubscript{2}), 5.54 (1H, d, J 17.0, cis-CHCH\textsubscript{2}), 5.48 (1H, d, J 10.0, trans-CHCH\textsubscript{2}), 3.95–3.87 (2H, m, OCH\textsubscript{2}), 3.21–3.13 (1H, m, H-3), [2.74 (1H, dd, J 15.5, 6.0) and 2.51 (1H, dd, J 15.5, 7.0), H-2], 2.00–1.91 (1H, m, H-4), 1.19–1.15 (3H, m, OCH\textsubscript{2}CH\textsubscript{3}), [1.16 (3H, d, J 7.0) and 1.10 (3H, d, J 7.0), H-6], 1.08–1.02 (2H, m, H-5); $\delta$\textsubscript{C} (101 MHz, CDCl\textsubscript{3})
171.9 (C-1), 138.3 (CHCH₂), 134.4, 130.9, 129.5, 126.6, 117.1 (CHCH₂), 60.3 (OCH₂), 43.4 (C-3), 38.7 (C-2), 33.1 (C-4), [21.1 and 21.0 (C-6)], 16.1, 14.7.

NMR data for anti-186c: \( \delta_H \) (400 MHz, CDCl₃) [7.83–7.80 (2H, m) and 7.67–7.56 (3H, m), SPh], 6.36 (1H, ddd, \( J = 16.5, 10.0, 7.0 \), CHCH₂), 5.50 (1H, d, \( J = 16.5 \), cis-CHC₃H₂), 5.42 (1H, d, \( J = 10.0 \), trans-CHC₃H₂), 3.95–3.87 (2H, m, OCH₂), 3.95–3.87 (1H, m, OCH₂), 3.21–3.13 (1H, m, H-3), [2.97 (1H, dd, \( J = 14.5, 4.0 \)) and 2.36 (1H, dd, \( J = 14.5, 9.5 \)), H-2], 2.00–1.91 (1H, m, H-4), 1.19–1.15 (3H, m, OCH₂C₃H₃), 1.08–1.02 (2H, m, H-6); \( \delta_C \) (101 MHz, CDCl₃) 172.0 (C-1), 138.7 (CHCH₂), 133.3, 130.6, 129.4, 126.5, 116.5 (CHCH₂), 60.2 (OCH₂), 43.4 (C-3), 38.6 (C-2), 33.1 (C-4), [22.2 and 21.9 (C-6)], 16.1, 14.2.

4-(Thiophenyl)-3-ethenyl-pentanoic acid (196)

To a solution of ester 186a (1.20 g, 4.24 mmol, 1.0 equiv, 91:9 mixture of diastereomers) in THF (15 mL) and water (15 mL) was added lithium hydroxide (1.01 g, 42.4 mmol, 10.0 equiv) in one portion at rt. The stirred mixture was heated under reflux for 4 h cooled to rt, quenched with aqueous HCl (2 M, 30 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford an inseparable mixture of 4-(thiophenyl)-3-ethenyl-pentanoic acid 196 (0.93 g, 93%, 91:9 mixture of diastereomers) as a colourless oil which was used without further purification.

Data for syn-196: \( \nu_{\max} \) (film) 3075, 1709, 1639, 1584, 1480, 1438, 1284, 923, 741, 692; \( \delta_H \) (400 MHz, CDCl₃) 7.44 (2H, d, \( J = 7.0 \), o-SPh), 7.33–7.24 (3H, m, m,p-SPh), 5.79 (1H, ddd, \( J = 17.0, 10.0, 8.0 \), CHCH₂), 5.18 (1H, d, \( J = 10.0 \), trans-CHCH₂), 5.14 (1H, d, \( J = 17.0 \), cis-CHCH₂), 3.40 (1H, dq, \( J = 7.0, 4.0 \), H-4), 2.91–2.78 (2H, m, H-2'), 2.51 (1H, dd, \( J = 14.0, 8.0 \), H-2'), 1.29 (3H, d, \( J = 7.0 \), H-5); \( \delta_C \) (101 MHz, CDCl₃), 178.0
Experimental

(C-1), 137.0 (CHCH₂), 135.0 (i-SPh), 132.2 (o-SPh), 129.0 (m-SPh), 127.1 (p-SPh), 117.6 (CHCH₂), 47.9 (C-4), 44.3 (C-3), 35.4 (C-2), 18.2 (C-5).

Characteristic NMR signals for anti-196: \( \delta_H \) (400 MHz, CDCl₃) inter alia 4.12–4.04 (1H, m, H-4), 1.39 (3H, d, \( J = 6.5 \), H-5); \( \delta_C \) (101 MHz, CDCl₃) 46.7 (C-4), 44.7 (C-3), 37.2 (C-2), 18.1 (C-5).

N-(2,4-dinitrophenyl)-4-(thiophenyl)-3-ethenyl-pentamide (197)

To a solution of acid 196 (919 mg, 3.89 mmol, 1.0 equiv, 91:9 mixture of diastereoisomers) in dichloromethane (20 mL) was added DCC (803 mg, 3.89 mmol, 1.0 equiv) and DMAP (47.5 mg, 0.389 mmol, 0.1 equiv) at rt. The mixture was stirred for 5 min and a solution of 2,4-dinitroaniline (783 mg, 4.28 mmol, 1.1 equiv) in dichloromethane (20 mL) was added dropwise via syringe. The resulting yellow mixture was stirred overnight at rt and filtered over Celite. The filtrate was washed with sodium hydrogen carbonate (30 mL) and aqueous HCl (2 M, 30 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel (15% ether/hexane) afforded N-(2,4-dinitrophenyl)-4-(thiophenyl)-3-ethenyl-pentamide 197 (967 mg, 62%, 91:9 mixture of diastereoisomers) as a yellow solid. Further purification of the mixture over silica gel (5–15% ether/hexane) and recrystallisation (EtOAc) afforded an analytical sample of syn-197 (435 mg, 28%) as a yellow crystalline solid.
Data for syn-197: mp 82–83 °C; \( \nu_{\text{max}} \) (film) 1712, 1615, 1599, 1499, 1335, 1307, 1141, 748, 696; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 10.54 (1H, s (br), NH), 9.13 (1H, d, J 2.5, 3-Ar), 9.06 (1H, d, J 9.5, 4-Ar), 8.46 (1H, dd, J 9.5, 2.5, 5-Ar), [7.42 (2H, d, J 8.5), 7.28–7.24 (2H, m) and 7.21–7.16 (1H, m), SPh], 5.87 (1H, ddd, J 17.0, 10.0, 8.5, CHCH\(_2\)), 5.22 (1H, d, J 10.0, trans-CHCH\(_2\)), 5.18 (1H, d, J 17.0 cis-CHCH\(_2\)), 3.50 (1H, dq, J 9.5, 7.0, H-4), 3.05–2.96 (2H, m, H-2,3), 2.66 (1H, dd, J 14.0, 7.5, H-2), 1.36 (3H, d, J 7.0, H-5); \( \delta_{\text{C}} \) (101 MHz, CDCl\(_3\)) 171.1 (C-1), 141.7, 139.6, 136.5 (CHCH\(_2\)), 135.1, 134.8, 131.7 (SPh), 130.1 (5-Ar), 129.1 (SPh), 127.0 (SPh), 122.3 (4-Ar), 122.0 (3-Ar), 118.5 (CHCH\(_2\)), 47.7 (C-4), 45.2 (C-3), 40.6 (C-2), 18.8 (C-5); m/z (CI) 419 [MNH\(_4\)]\(^+\), 402 [MH]\(^+\), 369, 326, 201 (Found: [MNH\(_4\)]\(^+\) 419.1388; C\(_{19}\)H\(_{19}\)N\(_3\)O\(_5\)S requires [MNH\(_4\)]\(^+\) 419.1389) (Found: C, 56.88; H, 4.74; N, 10.41. C\(_{19}\)H\(_{19}\)N\(_3\)O\(_5\)S requires C, 56.85; H, 4.77; N, 10.47).

NMR data for anti-197: \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 10.68 (1H, s (br), NH), 9.13 (1H, d, J 2.5, 3-Ar), 9.11 (1H, d, J 9.5, 4-Ar), 8.47 (1H, dd, J 9.5, 2.5, 5-Ar), 7.42–7.19 (5H, m, SPh), 5.80 (1H, ddd, J 17.0, 10.5, 8.5, CHCH\(_2\)), 5.16 (1H, d, J 10.5, trans-CHCH\(_2\)), 5.12 (1H, d, J 17.0, cis-CHCH\(_2\)), 3.49 (1H, dq, J 10.0, 7.0, H-4), 3.01–2.95 (1H, m, H-3), [2.83 (1H, dd, J 15.0, 6.5) and 2.85 (1H, dd, J 15.0, 7.5), H-2], 1.30 (3H, d, J 7.0, H-5); \( \delta_{\text{C}} \) (101 MHz, CDCl\(_3\)) 171.7 (C-1), 153.8, 137.6, 137.2 (CHCH\(_2\)), 135.5, 131.9, 131.1, 129.0, 126.9, 126.7, 122.3, 122.0, 117.6 (CHCH\(_2\)), 47.4 (C-4), 45.4 (C-3), 37.3 (C-2), 18.4 (C-5).

**Ethyl (E)-4-(phenylthio)-2-methylpent-2-enoate (209)**

\[
\begin{align*}
\text{Me} & \quad \text{Cl} & \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{SPh} & \quad \text{EtCO}_2 & \text{H} \\
207a & & 204a & & 209
\end{align*}
\]

To a solution of TEA (3.97 mL, 28.8 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.1 mL, 20.6 mmol, 1.0 equiv) dropwise via syringe. The colourless solution was stirred at rt for 10 min and a solution of 2-chloropropanal 207a (1.89 g,
20.6 mmol, 1.0 equiv) in THF (20 mL) was added dropwise via syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of triethyl 2-phosphonopropionate (6.86 g, 28.8 mmol, 1.0 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.23 g, 30.9 mmol, 1.5 equiv) in THF (40 mL) at 0 ºC via cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenyl-aldehyde solution was filtered under nitrogen and added via cannula to the phosphonate anion solution at –78 ºC. After stirring for 2 h at –78 ºC saturated aqueous NH₄Cl (150 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (10% TBME/petrol) to afford ethyl (E)-4-(phenylthio)-2-methylpent-2-enoate 209 (1.57 g, 31%) as a colourless oil: ν max (film) 1711, 1646, 1439, 1252, 1110, 753, 693 cm⁻¹; δH (400 MHz, CDCl₃) [7.46–7.44 (2H, m) and 7.32–7.29 (3H, m), SPh], 6.62 (1H, dd, J 10.5, 1.5, H-3), 4.20 (2H, q, J 7.0, OCH₂), 4.03 (1H, dq, J 10.5, 6.5, H-4), 1.52 (3H, d, J 1.5, 2-Me), 1.43 (3H, d, J 6.5, H-5), 1.31 (3H, t, J 7.0, OCH₂CH₃); δC (101 MHz, CDCl₃), 167.9 (C-1), 142.3, 134.3, 133.5, 129.2, 128.8, 128.0, 60.7 (OCH₂), 42.4 (C-4), 20.2, 14.2, 12.2; m/z (CI) 268 [MNH₄]⁺, 251 [MH]⁺, 205, 141 (Found: [MNH₄]⁺, 251.1096; C₁₄H₁₈O₂S requires [MNH₄]⁺, 251.1106) (Found: C, 67.19; H, 7.25. C₁₄H₁₈O₂S requires C, 67.16; H, 7.25).

(E)-4-(Thiophenyl)-2-methylpent-2-en-1-ol (210)

Ester 209 (1.18 g, 4.72 mmol, 1.0 equiv) was reacted according to general procedure F to afford (E)-4-(thiophenyl)-2-methylpent-2-en-1-ol 210 (924 mg, 94%) as a colourless oil after purification over silica gel (5–20% TBME/heptane): ν max (film)
Experimental

3349, 1582, 1438, 1024, 752, 692 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) [7.46–7.44 (2H, m) and 7.33 (3H, m), SPh], 5.36 (1H, dd, J 10.0, 1.5, H-3), 4.05 (1H, dq, J 10.0, 7.0, H-4), 3.96 (2H, s, H-1), 1.45 (3H, d, J 1.5, Me), 1.37 (3H, d, J 7.0, H-5); \(\delta_C\) (101 MHz, CDCl\(_3\)) 136.3, 133.8, 129.0, 128.6, 127.9, 127.5, 68.3, 41.7, 21.1, 13.6; \(m/z\) (Cl) 226 [MNH\(_4\)]\(^+\), 209 [MH\(^+\)], 191, 116 (Found: [MH\(^+\)], 209.1008. \(C_{12}H_{16}O_2S\) requires [MH\(^+\)], 209.1000).

**Ethyl 4-(phenylthio)-3-(prop-1-enyl)pentanoate (211)**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{SPh} & \quad \text{OH}  \\
\text{210} & \quad \rightarrow \\
\text{Me} & \quad \text{Me} \\
\text{SPh} & \quad \text{CO}_2\text{Et}  \\
\text{syn-211} & \quad \rightarrow \\
\text{Me} & \quad \text{Me} \\
\text{SPh} & \quad \text{CO}_2\text{Et}  \\
\text{anti-211} & \quad \rightarrow
\end{align*}
\]

Allylic alcohol 210 (150 mg, 0.72 mmol, 1.0 equiv) was reacted according to general procedure G to afford ethyl 4-(phenylthio)-3-(prop-1-enyl)pentanoate 211 (200 mg, >99%, 71:29 syn:anti mixture of diastereoisomers) as a colourless oil.

Data for the mixture: \(\nu_{\text{max}}\) (film) 1738, 1646, 1584, 1439, 1376, 1160, 1051, 749, 693 cm\(^{-1}\); \(m/z\) (Cl), 296 [MNH\(_4\)]\(^+\), 279 [MH\(^+\)], 191, 169, 117 (Found: [MH\(^+\)], 279.1414. \(C_{16}H_{22}O_2S\) requires [MH\(^+\)], 279.1419).

NMR data for syn-211: \(\delta_H\) (400 MHz, CDCl\(_3\)) [7.47–7.43 (2H, m) and 7.34–7.26 (3H, m), SPh], 4.93 (1H, s, trans-CMeCH\(_2\)), 4.82 (1H, s, cis-CMeCH\(_2\)), 4.11 (2H, q, J 7.0, OCH\(_2\)), 3.60–3.52 (1H, m, H-4), 3.43–3.35 (1H, m, H-3), [2.85–2.77 (1H, m) and 2.53–2.44 (1H, m), H-2], 1.76 (3H, s, CMeCH\(_2\)), 1.26–1.22 (6H, m, OCH\(_2\)CH\(_3\), H-5); \(\delta_C\) (101 MHz, CDCl\(_3\)) 171.7 (C-1), 144.8 (CMeCH\(_2\)), 135.2, 132.0, 129.0, 127.2, 112.2 (CMeCH\(_2\)), 60.3 (OCH\(_2\)), 46.6 (syn + anti C-4), 45.0 (C-3), 34.2 (C-2), 21.6, 17.0, 14.2.

NMR data for anti-211: \(\delta_H\) (400 MHz, CDCl\(_3\)) [7.47–7.43 (2H, m) and 7.34–7.26 (3H, m), SPh], 4.87 (1H, s, trans-CMeCH\(_2\)), 4.82 (1H, s, cis-CMeCH\(_2\)), 4.14 (2H, q, J 7.0, OCH\(_2\)), 3.60–3.52 (1H, m, H-4), 3.43–3.35 (1H, m, H-3), [2.85–2.77 (1H, m) and
2.53–2.44 (1H, m, H-2], 1.73 (3H, s, CMeCH₂), 1.26–1.22 (6H, m, OCH₂CH₃, H-5);
δc (101 MHz, CDCl₃) 171.5 (C-1), 144.7 (CMeCH₂), 135.1, 131.0, 128.6, 127.1,
114.3 (CMeCH₂), 60.3 (OCH₂), 46.6 (C-4), 45.0 (C-3), 34.2 (C-2), 21.6, 17.0, 14.2.
3.4.3 Compounds relevant to section 2.5

*(E)-Non-3-en-2-one (238b)*

<image>

Hexanal (1.85 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure H to afford *(E)-non-3-en-2-one 238b* (1.07 g, 51%) as a colourless oil: bp 100–102 °C; ν max (film) 1677, 1628, 1466, 1360, 1253, 1176, 982 cm⁻¹; δ H (400 MHz, CDCl₃) 6.92 (1H, dt, J 16.0, 7.0, H-4), 6.08 (1H, d, J 16.0, H-3), 2.25 (3H, s, H-1), 2.25–2.21 (2H, m, H-5), 1.52–1.44 (2H, m, H-6), 1.36–1.27 (4H, m, H-7,8), 0.90 (3H, t, J 6.5, H-9); δ C (101 MHz, CDCl₃) 198.8 (C-2), 148.7 (C-4), 131.3 (C-3), 32.4, 31.3, 27.8, 26.8, 22.4, 14.0; m/z (Cl) 158 [MNH₄]⁺, 141 [MH]⁺, 125; in agreement with published data.²²²

*(E)-4-(Cyclohexyl)-but-3-en-2-one (238d)*

<image>

Cyclohexanecarboxaldehyde (1.82 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure H to afford *(E)-4-(cyclohexyl)-but-3-en-2-one 238d* (917 mg, 40%) as a colourless oil: bp 95–100 °C, ν max (film) 1698, 1676, 1624, 1449, 1357, 1253, 980 cm⁻¹; δ H (400 MHz, CDCl₃) 6.73 (1H, dd, J 16.0, 7.0, H-4), 6.05 (1H, d, J 16.0, H-3), 2.45 (3H, s, H-1), 2.20–2.12 (1H, m, H-5), 1.78 (4H, d, J 11.0, cyclohexyl), 1.69 (1H, d, J 13.5, cyclohexyl), 1.36–1.15 (5H, m, cyclohexyl); δ C (101 MHz, CDCl₃) 198.8 (C-2), 148.7 (C-4), 131.3 (C-3), 32.4, 31.3, 27.8, 26.8, 22.4, 14.0; m/z (Cl) 158 [MNH₄]⁺, 141 [MH]⁺, 125; in agreement with published data.

²²²
MHz, CDCl3) 199.2 (C-2), 153.4 (C-4), 128.8 (C-3), 40.6 (C-5), 31.8 (cyclohexyl) 26.8 (C-1), 25.9 (cyclohexyl), 25.7 (cyclohexyl); m/z (Cl) 170 [MNH4]+, 153 [MH]+ (Found: [MH]+, 153.1281. C10H16O requires [MH]+, 153.1279).

(E)-1-Phenylbut-2-en-1-one (238f)

A solution of phenylmagnesium chloride (26.3 mL of a 1.90 M solution in THF, 50.0 mmol, 1.0 equiv) was added to a flask containing THF (150 mL) at 0 °C and crotonaldehyde (4.1 mL, 50.0 mmol, 1.0 equiv) was added. After stirring at 0 °C for 30 min, the reaction was quenched with saturated aqueous NH4Cl (25 mL). The reaction mixture was warmed to rt, partially concentrated under reduced pressure to remove THF and extracted with ether (2 x 120 mL). The combined organic extracts were washed with aqueous HCl (2 M, 40 mL), water (2 x 40 mL) and brine (40 mL), dried (MgSO4) and concentrated under reduced pressure. The residue was taken up in DMF (10 mL) and added to a stirred solution of pyridinium dichromate (20.4 g, 1.08 equiv) in DMF (40 mL). After 1 h, the reaction mixture was diluted with ether (100 mL) and poured onto water (100 mL). The phases were separated and the organic layer was washed with water (2 x 100 mL) and brine (40 mL). Concentration under reduced pressure and Kugelrohr distillation afforded (E)-1-phenylbut-2-en-1-one 238f (2.02 g, 28%) as a colourless oil: bp4 120–125 °C; νmax (film) 1668, 1624, 1577, 1449, 1296, 1220, 966 cm⁻¹; δH (400 MHz, CDCl3) 7.58–7.42 (5H, m, Ph), 7.10 (1H, dq, J 15.0, 7.0, H-3), 6.93 (1H, d, J 15.0, H-2), 2.03 (3H, d, J 7.0, H-4); δC (101 MHz, CDCl3) 190.1 (C-1), 145.1, 143.5, 137.9, 132.6, 128.5, 128.2, 18.6 (Me); m/z (Cl) 164 [MNH4]+, 147 [MH]+, 131; in agreement with published data.223
(E)-4-(Pyridin-2-yl)-but-3-en-2-one (238h)

2-Pyridinecarboxaldehyde (1.43 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure H to afford (E)-4-(pyridin-2-yl)-but-3-en-2-one 238h (1.41 g, 64%) as a colourless oil: bp 120–125 °C; ν_max (film) 1667, 1621, 1583, 1469, 1432, 1359, 1312, 1200, 980, 766 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.57 (1H, s (br), 6-pyridyl), 7.75–7.71 (1H, m, pyridyl), 7.52 (1H, d, J 16.5, H-4), 7.50–7.48 (1H, m, pyridyl), 7.30–7.27 (1H, m, pyridyl), 7.14 (1H, d, J 16.5, H-3), 2.41 (3H, s, H-1); δ_C (101 MHz, CDCl₃) 198.6 (C-2), 153.1 (2-pyridyl), 150.1 (6-pyridyl), 141.9 (C-4), 136.9 (pyridyl), 130.2 (C-3), 124.4, 124.3 (pyridyl), 28.1 (C-1); m/z (ESI) 148 [MH]^+, 130, 120 (Found: [MH]^+, 148.0754. C₉H₉NO requires [MH]^+, 148.0762).

(E)-4-(Furan-2-yl)-but-3-en-2-one (238j)

Furfural (1.24 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure H to afford (E)-4-(furan-2-yl)-but-3-en-2-one 238j (1.16 g, 57%) as white crystals: bp 105–110 °C; mp 37–39 °C; ν_max (film) 1657, 1622, 1477, 1272, 1252, 932 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.52 (1H, d, J 2.0, 5-furanyl), 7.29 (1H, d, J 16.5, H-4), 6.69 (1H, d, J 3.0, 3-furanyl), 6.64 (1H, d, J 16.5, H-3), 6.51 (1H, dd, J 3.0, 2.0, 4-furanyl), 2.38 (3H, s, H-1); δ_C (101 MHz, CDCl₃) 197.9 (C-2), 150.9 (C-5), 145.0 (5-furanyl), 129.5 (C-4), 124.3 (C-3), 115.7 (3-furanyl), 112.6 (4-furanyl), 27.9 (C-1); m/z (CI)
Experimental


(E)-1-Chloronon-3-en-2-ol (239a)

Octen-2-al 238a (1.49 mL, 10.0 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloronon-3-en-2-ol 239a (1.42 g, 81%) as a colourless oil after purification over silica gel (20% ether/petrol): νmax (film) 3354, 1671, 972, 760, 730 cm⁻¹; δH (400 MHz, CDCl₃) 5.84 (1H, dt, J 15.5, 7.5, H-4), 5.48 (1H, ddt, J 15.5, 7.5, 1.5, H-3), 4.32 (1H, m, H-2), [3.65 (1H, dd, J 11.0, 3.5) and 3.52 (1H, dd, J 11.0, 7.5), H-1], 2.08 (1H, m, H-5), 1.45–1.29 (6H, m, H-6,7,8), 0.91 (3H, t, J 6.5, H-9); δC (101 MHz, CDCl₃) 135.2 (C-4), 127.9 (C-3), 72.4 (C-2), 50.0 (C-1), 32.2 (C-5), 31.3 (C-6), 28.6 (C-7), 22.5 (C-8), 14.0 (C-9); m/z (CI) 194 [MNH₄]⁺, 176 [M]⁺ (Found: [MNH₄]⁺, 194.1313. C₉H₁₇ClO requires [MNH₄]⁺, 194.1312) (Found: C, 61.08; H, 9.72. C₉H₁₇ClO requires C, 61.18; H, 9.70).

(E)-1-Chloro-2-methylnon-3-en-2-ol (239b)

3-Nonen-2-one 238b (936 mg, 6.68 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloro-2-methylnon-3-en-2-ol 239b (1.17 g, 92%) as a colourless oil after purification over silica gel (20% TBME/petrol): νmax (film)
3411, 1669, 1457, 1376, 973, 745 cm⁻¹; δ_H (400 MHz, CDCl₃) 5.80 (1H, dt, J 15.5, 6.5, H-4), 5.53 (1H, dt, J 15.5, 1.0, H-3), 3.55 (2H, AB quartet, J 10.0, H-1), 2.10 (2H, dt, J 13.0, 6.5, H-5), 1.39 (3H, s, 2-Me), 1.40–1.30 (6H, m, H-6,7,8), 0.92 (3H, t, J 7.0, H-9); δ_C (101 MHz, CDCl₃) 132.8 (C-3), 131.3 (C-4), 72.0 (C-2), 54.7 (C-1), 32.2 (C-5), 31.3 (C-6), 28.8 (C-7), 25.6 (2-Me), 14.1 (C-9); m/z (Cl) 190 [MNH₄–H₂O]⁺, 177, 172 [M–OH]⁺, 137 (Found: [MNH₄–H₂O]⁺, 190.1363. C₁₀H₁₉ClO requires [MNH₄–H₂O]⁺, 190.1357).

(E)-1-Chloro-2-methylpent-3-en-2-ol (239c)

3-Penten-2-one 238c (2.44 mL, 25.0 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloro-2-methylpent-3-en-2-ol 239c (1.18 g, 35%) as a colourless oil after purification over silica gel (20% ether/petrol): ν_max (film) 3419, 1671, 1450, 968, 801, 743 cm⁻¹; δ_H (400 MHz, CDCl₃) 5.82 (1H, dq, J 15.5, 6.5, H-4), 5.55 (1H, d, J 15.5, H-3), 3.53 (2H, AB quartet, J 15.0, H-1), 2.16 (1H, s (br), OH), 1.74 (3H, dd, J 6.5, 1.5, H-5), 1.38 (3H, s, 2-Me); δ_C (101 MHz, CDCl₃) 134.1 (C-3), 125.9 (C-4), 72.0 (C-2), 54.6 (C-1), 25.5 (C-5), 17.8 (2-Me); m/z (Cl) 136 [M–H]⁺, 134 [MNH₄–H₂O]⁺, 100 (Found: [MNH₄–H₂O]⁺, 134.0739. C₆H₁₁ClO requires [MNH₄–H₂O]⁺, 134.0737).
(E)-1-Chloro-4-cyclohexyl-2-methylbut-3-en-2-ol (239d)

(E)-4-(Cyclohexyl)-but-3-en-2-one 239d (508 mg, 3.94 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloro-4-cyclohexyl-2-methylbut-3-en-2-ol 239d (562 mg, 84%) as a colourless oil after purification over silica gel (10% ether/hexane): νmax (film) 3430, 1668, 1449, 1373, 1263, 970, 745 cm⁻¹; δH (400 MHz, CDCl₃) 5.75 (1H, dd, J 15.5, 7.5, H-4), 5.46 (1H, dd, J 15.5, 1.5, H-3), 3.53 (2H, AB quartet, J 11.0, H-1), 2.18 (1H, s (br), OH), 2.04–1.95 (1H, m, H-5), 1.78–1.65 (5H, m, cyclohexyl), 1.39 (3H, s, 2-Me), 1.38–1.05 (5H, m, cyclohexyl); δC (101 MHz, CDCl₃) 136.9 (C-4), 130.3 (C-3), 72.0 (C-2), 54.7 (C-1), 40.3 (C-5), 32.8, 26.1, 26.0 (cyclohexyl), 25.7 (2-Me); m/z (CI) 222, 220 [MNH₄]⁺, 204, 202 [M]⁺, 187, 185 (Found: [MNH₄]⁺, 220.1473. C₁₁H₁₉ClO requires [MNH₄]⁺, 220.1468) (Found: C, 65.13; H, 9.36. C₁₁H₁₉ClO requires C, 65.17; H, 9.45).

(E)-1-Chloro-4-phenylbut-3-en-2-ol (239e)

Cinnamaldehyde 238e (1.50 g, 11.35 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloro-4-phenylbut-3-en-2-ol 239e (2.06 g, 99%) as a colourless oil after purification over silica gel (10% ether/petrol): νmax (film) 3390, 3026, 1659, 1598, 1578, 1494, 1449, 1296, 1071, 967, 754, 693 cm⁻¹; δH (400 MHz, CDCl₃) 7.43 (2H, d, J 7.5, o-Ph), 7.37 (2H, dd, J 13.5, 7.5, m-Ph), 7.31 (1H, dd, J 13.5, 6.5, p-Ph), 6.76 (1H, d, J 15.5, H-4), 6.24 (1H, dd, J 15.5, 6.0, H-3), 4.57 (1H,
Experimental

dt, $J$ 7.0, 6.0, H-2), [3.57 (1H, dd, $J$ 11.0, 3.5) and 3.64 (1H, dd, $J$ 11.0, 6.5), H-1]; $\delta_C$
(101 MHz, CDCl$_3$) 136.1 (i-Ph), 132.8 (C-4), 128.7 (m-Ph), 128.2 (p-Ph), 127.2 (C-3), 126.7 (o-Ph), 72.3 (C-2), 49.7 (C-1); $m/z$ (CI) 200 [MNH$_4^+$], 182 [M$^+$], 165 (Found: [MNH$_4^+$], 200.0842. C$_{10}$H$_{11}$ClO requires [MNH$_4^+$], 200.0842); in agreement
with published data.$^{172}$

(E)-1-Chloro-2-phenyl-pent-3-en-2-ol (239f)

(E)-1-Phenylbut-2-en-1-one 238f (1.89 g, 12.91 mmol, 1.0 equiv) was reacted
according to general procedure I to afford (E)-1-chloro-2-phenyl-pent-3-en-2-ol 239f
(1.31 g, 52%) as a colourless oil after purification over silica gel (10%
ether/hexane): $\nu_{\text{max}}$ (film) 3466, 1667, 1623, 1494, 1448, 1336, 1161, 1050, 967, 724,
699 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.49 (2H, d, $J$ 8.5, o-Ph), 7.40 (2H, dd, $J$ 8.5, 7.0, m-
Ph), 7.32 (1H, dd, $J$ 7.5, 7.0, p-Ph), 5.83–5.80 (2H, m, H-3 and H-4), 3.89 (2H, AB
quartet, $J$ 11.5, H-1), 2.74 (1H, s, OH), 1.78 (3H, dd, $J$ 5.0, 1.5, H-5); $\delta_C$ (101 MHz,
CDCl$_3$) 142.8 (i-Ph), 133.5, 128.5 (m-Ph), 128.4, 127.6, 125.6 (o-Ph), 75.9 (C-2), 54.0
(C-1), 17.8 (C-5); $m/z$ (CI) 216, 214 [MNH$_4^+$], 198, 196 [MH$^+$], 181, 179 (Found:
[MNH$_4^+$], 214.1003. C$_{11}$H$_{13}$ClO requires [MNH$_4^+$], 214.0999) (Found: C, 67.24; H,
6.59. C$_{11}$H$_{13}$ClO requires C, 67.18; H, 6.66).
Experimental

\[(E)-1\text{-Chloro-2-methyl-4-(pyridin-2-yl)but-3-en-2-ol (239h)}\]

\[(E)-4-(Pyridin-2-yl)-but-3-en-2-one 238h (1.00 g, 6.80 mmol, 1.0 equiv) was reacted according to general procedure I to afford (E)-1-chloro-2-methyl-4-(pyridin-2-yl)but-3-en-2-ol 239h (1.18 g, 88\%) as a yellow oil after purification over silica gel (25\% EtOAc, 5\% TEA/hexane): ν\text{max} (film) 3348, 1657, 1589, 1566, 1472, 1432, 1371, 977, 801, 768, 747 cm\(^{-1}\); δ\text{H} (400 MHz, CDCl\(_3\)) 8.58 (1H, d, J 5.5, 6-pyridyl), 7.66 (1H, d, J 8.0, 3-pyridyl), 7.29 (1H, d, J 8.0, 3-pyridyl), 7.16 (1H, ddd, J 7.5, 5.0, 2.0, 5-pyridyl), 6.84 (2H, d, J 17.0, H-3, H-4), 3.67 (2H, AB quartet, J 11.0, H-1), 2.70 (1H, s (br), OH), 1.29 (3H, s, 2-Me); δ\text{C} (101 MHz, CDCl\(_3\)) 154.7 (2-pyridyl), 149.6 (6-pyridyl), 137.0 (C-4), 136.7 (4-pyridyl), 129.4 (C-3), 122.5 (5-pyridyl), 122.4 (3-pyridyl), 72.6 (C-2), 54.2 (C-1), 25.7 (2-Me); m/z (ESI) 201, 200, 198 [MH]\(^+\) (Found: [MH]\(^+\), 198.0680. C\(_{10}\)H\(_{12}\)ClINO requires [MH]\(^+\), 198.0686) (Found: C, 60.69; H, 6.03; N, 6.99. C\(_{10}\)H\(_{12}\)ClINO requires C, 60.76; H, 6.12; N, 7.09).

\[(E)-2-(Hept-1-enyl)oxirane (234a)\]

Chlorohydrin 239a (1.38 g, 7.82 mmol, 1.0 equiv) was reacted according to general procedure J to afford (E)-2-(hept-1-enyl)oxirane 234a (1.06 g, 97\%) as a yellow oil: ν\text{max} (film) 1669, 1466, 1369, 1245, 964, 835, 771, 727 cm\(^{-1}\); δ\text{H} (400 MHz, CDCl\(_3\)) 5.98 (1H, dt, J 15.5, 6.5, H-4), 5.15 (1H, ddt, J 15.5, 8.0, 1.5, H-3), 3.34 (1H, ddd, J 8.0, 4.0, 3.0), [2.95 (1H, dd, J 5.0, 4.0) and 2.67 (1H, dd, J 5.0, 3.0), H-1], 2.09 (2H,
Experimental

dt, J 7.5, 6.5, H-5), 1.46–1.38 (2H, m, H-6), 1.37–1.28 (4H, m H-7,8), 0.91 (3H, t, J 7.0, H-9); δ_c (101 MHz, CDCl_3) 137.4 (C-4), 127.4 (C-3), 52.7 (C-2), 48.8 (C-1), 32.3 (C-5), 31.3 (C-7), 28.6 (C-6), 22.5 (C-8), 14.0 (C-9); m/z (CI) 158 [M NH_4]^+, 141 [MH]^+, 123 [M–OH]^+ (Found: [M NH_4]^+, 158.1545. C_9H_{16}O requires [M NH_4]^+, 158.1545).

(E)-2-Methyl-2-(hept-1-enyl)oxirane (234b)

\[
\text{C}_9\text{H}_{15}\text{Cl} \rightarrow \text{C}_9\text{H}_{13}\text{O}
\]

Chlorohydrin 239b (1.12 g, 5.88 mmol, 1.0 equiv) was reacted according to general procedure J to afford (E)-2-methyl-2-(hept-1-enyl)oxirane 234b (1.06 g, 40%) as a colourless oil: \nu_{\text{max}} (film) 1668, 1585, 1457, 1379, 968, 905 cm\(^{-1}\); \delta_h (400 MHz, CDCl_3) 5.81 (1H, dt, J 16.0, 7.0, H-4), 5.27 (1H, dt, J 16.0, 1.5, H-3), [2.82 (1H, d, J 5.0) and 2.75 (1H, d, J 5.0), H-1], 2.06 (2H, dt, J 8.0, 7.0, H-5), 1.46–1.23 (6H, m, H-6,7,8), 0.90 (3H, t, J 7.5, H-9); δ_c (101 MHz, CDCl_3) 134.0 (C-4), 130.9, (C-3), 55.8 (C-1), 55.6 (C-2), 32.4 (C-5), 31.4 (C-6), 28.8 (C-7), 22.5 (C-8), 19.7 (2-Me), 14.0 (C-9); m/z (CI) 155 [MH]^+ (Found: [MH]^+, 155.1434. C_{10}H_{18}O requires [MH]^+, 155.1436).

(E)-2-Methyl-2-(prop-1-enyl)oxirane (234c)

\[
\text{C}_7\text{H}_{14}\text{Cl} \rightarrow \text{C}_7\text{H}_{12}\text{O}
\]
Chlorohydrin 239c (1.13 g, 8.40 mmol, 1.0 equiv) was reacted according to general procedure J. Incomplete concentration under reduced pressure of the combined organic extracts afforded (E)-2-methyl-2-(prop-1-enyl)oxirane 234c (1.06 g of a colourless solution, 35% w/w in THF by 1H-NMR analysis, 46%): δH (400 MHz, CDCl3) 5.83 (1H, dq, J 15.5, 6.5, H-4), 5.30 (1H, d, J 15.5, H-3), [2.81 (1H, d, J 5.0) and 2.75 (1H, d, J 5.0), H-1], 1.75 (3H, dd, J 6.5, 1.5, H-5), 1.46 (3H, s, 2-Me); δC (101 MHz, CDCl3) 132.2 (C-3), 128.5 (C-4), 60.4 (C-2), 55.7 (C-1), 19.7 (2-Me), 17.8 (C-5).

2-[(E)-2-Cyclohexylethenyl]-2-methyloxirane (234d)

Chlorohydrin 239d (0.533 g, 2.64 mmol, 1.0 equiv) was reacted according to general procedure J to afford 2-[(E)-2-Cyclohexylethenyl]-2-methyloxirane 234d (431 mg, 98%) as a colourless oil: νmax (film) 1677, 1449, 1387, 1064, 968 cm⁻¹; δH (400 MHz, CDCl3) 5.75 (1H, dd, J 16.0, 6.5, H-4), 5.23 (1H, dd, J 16.0, 1.5, H-3), [2.82 (1H, d, J 5.0) and 2.75 (1H, d, J 4.0), H-1], 2.03–1.96 (1H, m, H-5), [1.78–1.61 and 1.35–1.03 (10H, m, cyclohexyl)], 1.46 (3H, s, 2-Me); δC (101 MHz, CDCl3) 139.5 (C-4), 128.5 (C-3), 55.9 (C-1), 55.7 (C-2), 40.5 (C-5), 32.7, 26.1, 26.0, 19.7 (2-Me); m/z (CI) 184 [MNH₄⁺], 165 [M–H]⁺, 149 (Found: [MNH₄⁺], 184.1700. C₁₁H₁₉O requires [MNH₄⁺], 184.1701).
(E)-2-Styryloxirane (234e)

Chlorohydrin 239e (1.20 g, 6.59 mmol, 1.0 equiv) was reacted according to general procedure J to afford (E)-2-styryloxirane 234e (963 mg, >99%) as a yellow oil: $\nu_{\text{max}}$ (film) 3027, 1601, 1578, 1492, 1393, 1244, 1134, 1072, 965 747, 693 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.43–7.27 (5H, m, Ph), 6.85 (1H, d, $J$ 16.5, H-4), 5.91 (1H, dd, $J$ 16.5, 7.5, H-3), 3.56 (1H, ddd, $J$ 7.5, 5.0, 3.0, H-2), [3.10 (1H, dd, $J$ 5.5, 4.0) and 2.81 (1H, dd, $J$ 5.0, 3.0), H-1]; $\delta_{\text{C}}$ (101 MHz, CDCl$_3$) 136.3 (i-Ph), 134.6 (C-4), 128.7, 128.1 (Ph), 127.0 (C-3), 126.5 (Ph), 52.7 (C-2), 49.3 (C-1); $m/z$ (Cl) 164 [MNH$_4^+$], 147 [MH$^+$], 129 [M–H$_2$O$^+$] (Found: [MH$^+$], 147.0812. C$_{10}$H$_{10}$O requires [MH$^+$], 147.0810); in agreement with published data.\(^{172}\)

(E)-2-Methyl-2-styryloxirane (234f)

Chlorohydrin 239f (1.26 g, 6.43 mmol, 1.0 equiv) was reacted according to general procedure J to afford (E)-2-Methyl-2-styryloxirane 234f (1.01 g, 98%): $\nu_{\text{max}}$ (film) 1681, 1598, 1495, 1448, 965, 760, 700 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.44–7.32 (5H, m, Ph), 5.73–5.70 (2H, m, CHCHMe), [3.14 (1H, d, $J$ 5.5) and 3.00 (1H, d, $J$ 5.5), OCH$_2$], 1.77 (3H, dd, $J$ 5.0, 2.0, Me); $\delta_{\text{C}}$ (101 MHz, CDCl$_3$) 153.0 (i-Ph), 131.2, 130.4, 128.2 (o-Ph), 127.7 (p-Ph), 127.0 (m-Ph), 60.1 (C-2), 56.7 (OCH$_2$), 17.8 (Me);
Experimental


2-[(E)-2-(2-Methyloxiran-2-yl)ethenyl]pyridine (234g)

Chlorohydrin 239h (1.16 g, 5.87 mmol, 1.0 equiv) was reacted according to general procedure J to afford 2-[(E)-2-(2-Methyloxiran-2-yl)ethenyl]pyridine 234g (623 mg, 66%) as yellow oil: ν_max (film) 1654, 1555, 1387, 1305, 1150, 1065, 973, 907, 793, 766, 742, 611 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.57 (1H, d, J 5.0, 6-pyridyl), 7.65 (1H, ddd, J 9.5, 8.0, 2.0, 4-pyridyl), 7.29 (1H, d, J 8.0, 3-pyridyl), 7.16 (1H, ddd, J 8.0, 5.0, 2.0, 5-pyridyl), [6.77 (1H, d, J 16.0) and 6.57 (1H, d, J 16.0), H-3,4], [2.94 (1H, d, J 5.0) and 2.89 (1H, d, J 5.0), H-1], 1.61 (3H, s, 2-Me); δ_C (101 MHz, CDCl₃) 154.8 (2-pyridyl), 149.6 (6-pyridyl), 136.6 (4-pyridyl), [135.2 and 131.3 (C-3 and C-4)], 122.4 (5-pyridyl), 121.7 (3-pyridyl), 55.3 (C-1), 55.7 (C-2), 19.7 (2-Me); m/z (ESI) 181, 180, 162 [MH]⁺, 130 (Found: [MH]⁺, 162.0912. C₁₀H₁₁NO requires [MH]⁺, 162.0919).

(E)-2-Azidonon-3-en-1-ol (235a) and (E)-4-azidonon-2-en-1-ol (236a)

Oxirane 234a (4.41 g, 31.5 mmol, 1.0 equiv) was reacted according to general procedure K to afford a 73:27 mixture of (E)-2-azidonon-3-en-1-ol 235a and (E)-4-
azidonon-2-en-1-ol 236a respectively (4.04 g, 70%) as a colourless oil after purification over silica gel (30% TBME/petrol).

Data for the mixture: $\nu_{\text{max}}$ (film) 3352, 2101, 1462, 1240, 1072 cm$^{-1}$; $m/z$ (CI) 201 [MNH$_4^+$], 191, 158, 126 (Found: [MNH$_4^+$], 201.1715. C$_9$H$_{17}$N$_3$O requires [MNH$_4^+$], 201.1715.

NMR data for 235a: $\delta$H (500 MHz, CDCl$_3$) 5.85 (1H, dt, J 15.5, 6.5, H-4), 5.40 (1H, ddt, J 15.5, 8.0, 1.5, H-3), 4.03 (1H, dt, J 11.5, 5.0, H-2), [3.60 (1H, dd, J 11.5, 5.0) and 3.52 (1H, dd, J 11.5, 7.5), H-1], 2.09–2.11 (2H, m, H-5), 1.66 (2H, s (br), OH), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, J 7.0, H-9); $\delta$C (101 MHz, CDCl$_3$) 138.2, 123.4, 66.3, 65.0, 32.3, 31.2, 28.7, 22.4, 14.0.

NMR data for 236a: $\delta$H (500 MHz, CDCl$_3$) 5.88 (1H, dt, J 15.0, 5.5, H-2), 5.66 (1H, ddt, J 15.5, 7.5, 1.5, H-3), 4.21 (2H, dd, J 5.5, 1.5, H-1), 3.85 (1H, dt, J 14.0, 7.5, H-4), 1.66 (2H, s (br), OH), 1.56–1.49 (2H, m, H-5), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, J 7.0, H-9); $\delta$C (101 MHz, CDCl$_3$) 132.9, 128.9, 64.0, 62.6, 34.5, 31.4, 35.5, 22.5, 14.0.

(E)-2-Azido-2-methylnon-3-en-1-ol (235b) and (E)-4-azido-2-methylnon-2-en-1-ol (236b)

Oxirane 234b (497 mg, 3.22 mmol, 1.0 equiv) was reacted according to general procedure K to afford a 61:39 mixture of (E)-2-azido-2-methylnon-3-en-1-ol 235b and (E)-4-azido-2-methylnon-2-en-1-ol 236b respectively (150 mg, 25%) as a colourless oil after purification over silica gel (20% TBME/hexane).
Data for the mixture: $\nu_{\text{max}}$ (film) 3370, 2102, 1666, 1456, 1379, 1247, 1056 cm$^{-1}$; $m/z$ (Cl) 215 [MNH$_4^+$], 172, 155 [M-N$_3^+$], 137 (Found: [MNH$_4^+$], 215.1872. C$_{10}$H$_{19}$N$_3$O requires [MNH$_4^+$], 215.1871).

NMR data for 235b: $\delta$H (400 MHz, CDCl$_3$) 5.82 (1H, dt, J 16.0, 7.0, H-4), 5.50 (1H, dt, J 16.0, 2.0, H-3), 3.46 (2H, AB quartet, J 11.5, H-1), 2.11 (2H, dt, J 9.0, 7.0, H-5), 1.71–1.55 (1H, s (br), OH), 1.40 (3H, s, 2-Me), 1.38–1.27 (6H, m, H-6,7,8), 0.99 (3H, t, J 6.5, H-9); $\delta$C (101 MHz, CDCl$_3$) 134.1 (C-4), 128.5 (C-3), 69.3 (C-1), 66.1 (C-2), 32.5, 31.3, 28.9, 22.4 (2-Me), 20.2, 14.0 (C-9).

NMR data for 236b: $\delta$H (400 MHz, CDCl$_3$) 5.44 (1H, d, J 10.0, H-3), 4.22–4.15 (1H, m, H-4), 4.11 (2H, s, H-1), 1.77 (3H, s, 2-Me), 1.71–1.55 (1H, s (br), OH), 1.38–1.27 (8H, m, H-5,6,7,8), 0.99 (3H, t, J 6.5, H-9); $\delta$C (101 MHz, CDCl$_3$) 140.3 (C-2), 122.7 (C-3), 67.7 (C-1), 59.4 (C-4), 35.0, 31.5, 25.5, 22.5 (2-Me), 14.3, 14.0 (C-9).

(E)-2-Azido-2-methylpent-3-en-1-ol (235c) and (E)-4-azido-2-methylpent-2-en-1-ol (236c)

A solution of oxirane 234c in THF (6.36 mmol, 1.0 equiv) was reacted according to general procedure K to afford a 64:36 mixture of (E)-2-azido-2-methylpent-3-en-1-ol 235c and (E)-4-azido-2-methylpent-2-en-1-ol 236c respectively (634 mg, 71%) as a colourless oil after purification over silica gel (20% ether/petrol).

Data for the mixture: $\nu_{\text{max}}$ (film) 3374, 2105, 1652, 1449, 1379, 1250, 1052, 970 cm$^{-1}$; $m/z$ (Cl) 159 [MNH$_4^+$], 116, 114, 96 (Found: [MNH$_4^+$], 159.1248. C$_6$H$_{11}$N$_3$O requires [MNH$_4^+$], 159.1246).

NMR data for 235c: $\delta$H (400 MHz, CDCl$_3$) 5.85 (1H, dq, J 15.5, 6.5, H-4), 5.53 (1H, dd, J 15.5, 1.5, H-3), 3.47 (2H, AB quartet, J 12.0, H-1), 1.80 (3H, dd, J 6.5, 1.5, H-
5), 1.41 (3H, s, 2-Me); δC (101 MHz, CDCl3) 129.9 (C-3), 128.6 (C-4), 69.2 (C-1), 67.5 (C-2), 20.1 (2-Me), 18.0 (C-5).

NMR data for 236c: δH (400 MHz, CDCl3) 5.46 (1H, dd, J 9.5, 1.5, H-3), 4.37 (1H, dq, J 9.5, 6.5, H-4), 1.77 (3H, s, 2-Me), 1.28 (3H, d, J 6.5, H-5); δC (101 MHz, CDCl3) 139.5 (C-2), 123.7 (C-3), 66.0 (C-1), 54.7 (C-4), 20.8 (C-Me), 14.1 (C-5).

(E)-2-Azido-4-cyclohexyl-2-methylbut-3-en-1-ol (235d) and (E)-4-azido-4-cyclohexyl-2-methylbut-2-en-1-ol (236d)

Oxirane 234d (265 mg, 1.60 mmol, 1.0 equiv) was reacted according to general procedure K to afford a 72:28 mixture of (E)-2-azido-4-cyclohexyl-2-methylbut-3-en-1-ol 235d and (E)-4-azido-4-cyclohexyl-2-methylbut-2-en-1-ol 236d respectively (196 mg, 59%) as a colourless oil after purification over silica gel (15% ether/hexane).

Data for the mixture: νmax (film) 3359, 2103, 1665, 1448, 1250, 1052, 970 cm⁻¹; m/z (CI) 227 [MNH₄⁺], 210 [MH⁺], 184, 149 (Found: [MNH₄⁺], 227.1870. C₁₁H₁₉N₃O requires [MNH₄⁺], 227.1872).

NMR data for 235d: δH (400 MHz, CDCl3) 5.76 (1H, dd, J 15.5, 6.5, H-4), 5.45 (1H, dd, J 15.5, 1.5, H-3), 3.50 (2H, m, H-1), 2.08–0.85 (11H, m, cyclohexyl), 1.40 (3H, s, 2-Me); δC (101 MHz, CDCl3) 139.9 (C-4), 125.9 (C-3), 69.3 (C-1), 42.4 (C-2), 40.7, 33.0, 32.9, 25.9, 20.2.

NMR data for 236d: δH (400 MHz, CDCl3) 5.47 (1H, d, J 10.0, H-3), 4.12 (2H, d, J 4.0, H-1), 3.96 (1H, dd, J 10.0, 7.5, H-4), 2.08–0.85 (11H, m, cyclohexyl), 1.75 (3H, s, 2-Me); δC (101 MHz, CDCl3) 121.2 (C-3), 67.7 (C-1), 65.9 (C-2), 64.6 (C-4), 29.5, 29.3, 26.3, 26.0, 14.3.
(E)-2-Azido-4-phenylbut-3-en-1-ol (235e)

Oxirane 234e (950 mg, 6.50 mmol, 1.0 equiv) was reacted according to general procedure K to afford (E)-2-azido-4-phenylbut-3-en-1-ol 235e (739 mg, 60%) as a yellow oil after purification over silica gel (20% EtOAc/hexane): \( \nu_{\text{max}} \) (film) 2109, 1650, 1449, 1246, 1040, 969, 750, 693 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.45 (1H, d, J 8.0, p-Ph), 7.38 (2H, dd, J 8.0, 7.5, m-Ph), 7.35 (2H, d, J 7.5, o-Ph), 6.76 (1H, d, J 17.0, H-4), 6.18 (1H, dd, J 17.0, 8.0, H-3), 4.28 (1H, dt, J 8.0, 4.5, H-2), [3.76 (1H, dd, J 11.0, 4.5) and 3.67 (1H, dd, J 11.0, 7.0), H-1], 1.99 (1H, s (br), OH); \( \delta_C \) (101 MHz, CDCl\(_3\)) 135.7 (i-Ph), 135.4 (C-4), 128.7 (o-Ph), 128.5 (p-Ph), 126.7 (m-Ph), 122.9 (C-3), 66.3 (C-2), 65.0 (C-1); \( m/z \) (CI) 207 [MNH\(_4^+\)]\(^+\), 189 [M]\(^+\), 164, 147 (Found: [MNH\(_4^+\)]\(^+\), 207.1247. C\(_{10}\)H\(_{11}\)N\(_3\)O requires [MNH\(_4^+\)]\(^+\), 207.1246); in agreement with published data.\(^{172}\)

(E)-4-Azido-2-methyl-4-phenylbut-2-en-1-ol (E-236f) and (Z)-4-azido-2-methyl-4-phenylbut-2-en-1-ol (Z-236f)

To a solution of oxirane 234f (490 mg, 3.06 mmol, 1.0 equiv) in acetone (10 mL) and water (3 mL) was added sodium azide (597 mg, 9.18 mmol, 3.0 equiv) in one portion. The reaction mixture was stirred at rt for 4 h, and ammonium chloride (500 mg) was added. The resulting mixture was stirred at rt for 10 min. Water (10 mL) was added and the mixture was concentrated under reduced pressure to remove acetone. The
aqueous layer was extracted with dichloromethane (3 x 15 mL) and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification of the residue over silica gel (10% EtOAc/petrol) afforded a 75:25 mixture of (E)-4-azido-2-methyl-4-phenylbut-2-en-1-ol \textit{E-236f} and (Z)-4-azido-2-methyl-4-phenylbut-2-en-1-ol \textit{Z-236f} respectively (461 mg, 74%) as a colourless oil.

Data for the mixture: $\nu_{\text{max}}$ (film) 3366, 2101, 1492, 1446, 1238, 1074, 702 cm$^{-1}$; $m/z$ (Cl) 221 [MNH$_4$]$^+$, 210, 178 [MNH$_4$–N$_3$]$^+$, 161 [MH–N$_3$]$^+$ (Found: [MNH$_4$]$^+$, 221.1411. C$_{11}$H$_{13}$N$_3$O requires [MNH$_4$]$^+$, 221.1402).

NMR data for \textit{E-236f}: $\delta$H (500 MHz, CDCl$_3$) [7.47–7.38 (3H, m) and 7.19–7.17 (2H, m), Ph], 5.71 (1H, dt, J 10.0, 1.5, H-3), 4.36 (2H, s (br), H-1), 4.06 (1H, dq, J 10.0, 6.5, H-4), 1.62 (1H, s (br), OH), 1.24 (3H, d, J 6.5, H-5); $\delta$C (126 MHz, CDCl$_3$), 144.5, 136.9, 128.6, 128.5, 126.9, 125.6 (C-3), 66.9 (C-1), 55.4 (C-4), 20.6 (C-5).

NMR data for \textit{Z-236f}: $\delta$H (500 MHz, CDCl$_3$) [7.47–7.38 (3H, m) and 7.19–7.17 (2H, m), Ph], 5.47 (1H, d, J 9.0, H-3), 4.62 (2H, s (br), H-1), 4.59 (1H, dq, J 9.0, 7.0, H-4), 1.57 (1H, s (br), OH), 1.39 (3H, d, J 7.0, H-5); $\delta$C (126 MHz, CDCl$_3$), 142.7, 139.6, 130.0 (C-3), 128.1, 127.9, 126.7, 60.1 (C-1), 54.7 (C-4), 20.8 (C-5).

\textit{(E)-2-Azido-2-methyl-4-(pyridin-2-yl)but-3-en-1-ol (235g)}

Oxirane \textit{234g} (600 mg, 3.73 mmol, 1.0 equiv) was reacted according to general procedure \textit{K} to afford (E)-2-azido-2-methyl-4-(pyridin-2-yl)but-3-en-1-ol \textit{235g} (600 mg, 79%) as a colourless oil after purification over silica gel (20% EtOAc/5% TEA/hexane): $\nu_{\text{max}}$ (film) 3339, 2105, 1656, 1590, 1473, 1260, 1153, 1061, 975, 766 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 8.55 (1H, d, J 5.0, 6-pyridyl), 7.68 (1H, dt, J 7.5, 1.5, 4-pyridyl), 7.32 (1H, d, J 7.5, 3-pyridyl), 7.19 (1H, dd, J 8.0, 7.5, 5-pyridyl), 6.81 (1H,
d, J 16.0, H-4), 6.77 (1H, d, J 16.0, H-3), 3.64 (2H, dd, J 3.0, 2.5, H-1), 1.55 (3H, s, 2-Me); δc (101 MHz, CDCl₃) 154.4 (2-pyridyl), 149.6 (6-pyridyl), 136.8 (4-pyridyl), [133.3 and 131.2, (C-3) and (C-4)], 122.8 (5-pyridyl), 122.5 (3-pyridyl), 69.1 (C-1), 66.0 (C-2), 20.4 (2-Me); m/z (Cl), 205 [MH]+, 164, 145, 102 (Found: [MH]+, 205.1081. C₁₀H₁₂N₄O requires [MH]+, 205.1076) (Found: C, 58.88; H, 5.87; N, 27.59. C₁₀H₁₂N₄O requires C, 58.81; H, 5.92; N, 27.43).

(E)-2-(Hydroxymethyl)non-3-enenitrile (241) and (E)-non-3-ene-1,2-diol (242)

To a solution of oxirane 234a (1.19 g, 8.52 mmol, 1.0 equiv) in acetone (10 mL) and water (5 mL) was added potassium cyanide (0.61 g, 9.37 mmol, 1.1 equiv) in one portion at rt. The resulting solution was stirred at rt for 30 min and heated to reflux for 16 h. The reaction mixture was cooled to rt and NH₄Cl (500 mg) was added. After stirring for 10 min, the reaction mixture was concentrated under reduced pressure to remove acetone and the residue was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel (25% ether/petrol) afforded less polar (E)-2-(hydroxymethyl)non-3-enenitrile 241 (271 mg, 19%) as a colourless oil: υₘₐₓ (film) 3435, 2252, 1671, 1467, 1042, 973 cm⁻¹; δH (400 MHz, CDCl₃) 5.84 (1H, dt, J 15.5, 6.5, H-4), 5.55 (1H, ddt, J 15.5, 6.5, 2.0, H-3), 4.42 (1H, dt, J 6.5, 6.0, H-2), 2.60 (2H, doublet of AB quartets, J 16.5, 6.0, CH₂), 2.33 (1H, s (br), OH), 2.08 (2H, dt, J 7.5, 6.5, H-5), 1.44−1.27 (6H, m, H-6,7,8), 0.91 (3H, t, J 7.0, H-9); δc (101 MHz, CDCl₃) 135.3 (C-4), 129.2 (C-3), 117.4 (CN), 68.7 (C-2), 32.0 (C-5), 31.3 (C-6), 28.5 (C-7), 26.3 (C-1), 22.5 (C-8), 14.0 (C-9); m/z (Cl) 185 [MNH₄]⁺, 52 (Found: [MNH₄]⁺, 185.1660. C₁₀H₁₇NO requires [MNH₄]⁺, 185.1654) (Found: C, 71.89; H, 10.26; N, 8.43. C₁₀H₁₇NO requires C, 71.81; H, 10.25; N, 8.37); and more polar (E)-non-3-ene-1,2-diol 242 (82 mg, 6%) as a colourless oil: υₘₐₓ
(film) 3433, 1671, 1456, 1027, 971 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 5.77 (1H, dt, \(J\) 15.5, 6.5, H-4), 5.44 (1H, dd, \(J\) 15.5, 6.5, H-3), 4.19 (1H, dt, \(J\) 7.0, 3.5, H-2), [3.62 (1H, dd, \(J\) 11.0, 3.5) and 3.47 (1H, dd, \(J\) 11.0, 8.0), H-1], 3.02 (1H, s (br), OH), 2.04 (2H, dt, \(J\) 7.5, 7.0, H-5), 1.42–1.24 (6H, m, H-6,7,8), 0.90 (3H, t, \(J\) 7.0, H-9); \(\delta_C\) (101 MHz, CDCl\(_3\)) 134.2 (C-4), 128.2 (C-3), 73.2 (C-2), 66.6 (C-1), 32.3 (C-5), 31.4 (C-6), 28.7 (C-7), 22.5 (C-8), 14.0 (C-9); \(m/z\) (CI) 176 [MNH\(_4^+\)], 158 [MH\(^+\)], 96 (Found: [MNH\(_4^+\)], 176.1653. C\(_9\)H\(_{18}\)O\(_2\) requires [MNH\(_4^+\)], 176.1651).

**Ethyl 4-azido-3-ethenylnonanoate (243a)**

A 73:27 mixture of allylic azides 235a and 236a respectively (100 mg, 0.546 mmol, 1.0 equiv) was reacted according to general procedure C to afford *ethyl 4-azido-3-ethenylnonanoate* 243a (137 mg, 99%, 50:50 syn:anti mixture of diastereomers) as a colourless oil without further purification: \(\nu_{\text{max}}\) (film) 2102, 1736, 1641, 1465, 1257, 923 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) [5.74 (1H, dddd, \(J\) 17.0, 10.0, 4.0) and 5.65 (1H, dddd, \(J\) 17.0, 10.0, 4.0), syn+anti CHCH\(_2\)], 5.19–5.13 (4H, m, syn+anti CHCH\(_2\)), [4.14 (2H, q, \(J\) 7.5) and 4.15 (2H, q, \(J\) 7.5), syn+anti OCH\(_2\)], [3.84–3.43 (1H, m) and 3.26–3.06 (1H, m), syn+anti H-4], 2.77–2.69 (2H, m, syn+anti H-3), [2.56 (2H, dd, \(J\) 15.0, 5.0) and 2.41 (2H, dd, \(J\) 15.0, 8.0), syn+anti H-2], 1.62–1.32 (16H, m, syn+anti H-5,6,7,8), [1.27 (3H, t, \(J\) 7.5), and 1.26 (3H, t, \(J\) 7.5), syn+anti OCH\(_2\)CH\(_3\)] 0.91 (6H, t, \(J\) 6.0 syn+anti H-9); \(\delta_C\) (101 MHz, CDCl\(_3\)) 172.0 (C-1), [137.2 and 135.6, (CHCH\(_2\))], [118.3 and 117.8, (CHCH\(_2\))], [65.8 and 65.3, (C-4)], 60.5 (OCH\(_2\)), [44.9 and 44.5, (C-3)], [37.0 and 36.3, (C-2)], 32.2, 32.0, 31.5, 26.0, 25.8, 22.5, 14.2, 14.0; \(m/z\) (CI) 271

**Ethyl 4-azido-3-(prop-1-enyl)nonanoate (243b)**

A 61:39 mixture of allylic azides 235b and 236b respectively (88 mg, 0.446 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 4-azido-3-(prop-1-enyl)nonanoate 243b (86 mg, 72%, 59:41 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/hexane).

Data for the mixture: $\nu_{\text{max}}$ (film) 2012, 1733, 1648, 1464, 1379, 1273, 1123, 1073, 899 cm$^{-1}$; $m/z$ (CI) 285 [MNH$_4$]$^+$, 268 [MH]$^+$, 240 (Found: [MH]$^+$, 268.2025 C$_{14}$H$_{25}$N$_3$O$_2$ requires [MH]$^+$, 268.2025).

NMR data for syn-243b: $\delta$$_H$ (400 MHz, CDCl$_3$) 4.94 (1H, t, $J$ 1.5, trans-CMeCH$_2$), 4.86 (1H, s (br), cis-CMeCH$_2$), 4.15 (2H, q, $J$ 7.0, OCH$_2$), 3.44–3.39 (1H, m, H-4), 2.81 (1H, dt, $J$ 8.0, 6.0, H-3), 2.49 (2H, dd, $J$ 15.0, 9.0, H-2), 1.80 (3H, s, Me), 1.60–1.25 (8H, m, H-5,6,7,8), 1.27 (3H, t, $J$ 7.0, OCH$_2$CH$_3$), 0.93 (6H, t, $J$ 6.5, H-9); $\delta$C (101 MHz, CDCl$_3$) 172.1 (C-1), 143.4 (CMeCH$_2$), 114.5 (CMeCH$_2$), 65.1 (C-4), 60.5 (OCH$_2$), 47.0 (C-3), 35.7, 31.7, 31.6, 26.2, 22.5, 21.0, 14.0.  

NMR data for anti-243b: $\delta$$_H$ (400 MHz, CDCl$_3$) 4.93 (1H, t, $J$ 1.5, trans-CMeCH$_2$), 4.86 (1H, s (br), cis-CMeCH$_2$), 4.13 (2H, q, $J$ 7.0, OCH$_2$), 3.24 (1H, dt, $J$ 8.0, 3.0, H-4), 2.67 (1H, dt, $J$ 8.0, 5.0, H-3), 2.57 (2H, dd, $J$ 15.0, 6.0, H-2), 1.74 (3H, s, Me), 1.60–1.25 (8H, m, H-5,6,7,8), 1.26 (3H, t, $J$ 7.0, OCH$_2$CH$_3$), 0.93 (6H, t, $J$ 6.5, H-
Experimental

9); δ_C (101 MHz, CDCl_3) 172.2 (C-1), 143.8 (CMeCH_2), 114.3 (CMeCH_2), 64.6 (C-4), 60.4 (OCH_2), 47.9 (C-3), 36.3, 32.5, 31.5, 25.9, 22.5, 20.1, 14.2.

**Ethyl 4-azido-3-(prop-1-enyl)pentanoate (243c)**

A 64:36 mixture of allylic azides 235c and 236c respectively (88 mg, 0.446 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 4-azido-3-(prop-1-enyl)pentanoate 243c (86 mg, 86%, 60:40 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/hexane).

Data for the mixture: ν_{max} (film) 2101, 1736, 1650, 1446, 1378, 1258, 1034 cm⁻¹; m/z (CI) 229 [MNH₄]^+, 212 [MH]^+, 184, 117 (Found: [MNH₄]^+, 229.1666. C_{10}H_{17}N₃O₂ requires [MNH₄]^+, 229.1665).

NMR data for syn-243c: δ_H (400 MHz, CDCl_3) 4.93 (1H, t, J 1.5, trans-CMeCH₂), 4.83 (1H, s (br), cis-CMeCH₂), 4.13 (2H, q, J 7.0, OCH₂), 3.64 (1H, dq, J 13.0, 6.0, H-4), 2.74–2.69 (1H, m, H-3), 2.56–2.36 (2H, m, H-2), 1.78 (3H, s, CMeCH₂), 1.27 (3H, t, J 7.0, OCH₂CH₃), 1.25 (3H, d, J 6.0, H-5); δ_C (101 MHz, CDCl_3) 176.2 (C-1), 139.3 (CMeCH₂), 116.7 (CMeCH₂), 60.1 (OCH₂), 46.6 (C-4), 43.9 (C-3), 34.8 (C-2), 20.3 (CMeCH₂), 14.3 (C-5), 14.0 (OCH₂CH₃).

NMR data for anti-243c: δ_H (400 MHz, CDCl_3) 4.89 (1H, t, J 1.5, trans-CMeCH₂), 4.83 (1H, s (br), cis-CMeCH₂), 4.12 (2H, q, J 7.0, OCH₂), 3.40 (1H, dq, J 9.0, 6.5, H-4), 2.74–2.69 (1H, m, H-3), 2.56–2.36 (2H, m, H-2), 1.72 (3H, s, CMeCH₂), 1.26 (3H, t, J 7.0, OCH₂CH₃), 1.24 (3H, d, J 6.5, H-5); δ_C (101 MHz, CDCl_3) 176.7 (C-1),
139.9 (CMeCH₂), 116.0 (CMeCH₂), 60.0 (OCH₂), 47.0 (C-4), 44.0 (C-3), 33.4 (C-2), 20.3 (CMeCH₂), 14.3 (C-5), 13.9 (OCH₂CH₃).

Ethyl 4-azido-4-cyclohexyl-3-(prop-1-enyl)pentanoate (243d)

A 63:37 mixture of allylic azides 235d and 236d respectively (50 mg, 0.239 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 4-azido-4-cyclohexyl-3-(prop-1-enyl)pentanoate 243d (86 mg, 94%, 63:37 syn:anti mixture of diastereomers) as a colourless oil without further purification.


NMR data for syn-243d: δH (400 MHz, CDCl₃) [4.92 (1H, s) and 4.88 (1H, s), CMeCH₂], 4.13 (2H, q, J 7.0, OCH₂), 3.17–3.13 (1H, m, H-4), 2.82 (1H, dt, J 10.0, 4.5, H-3), 2.63–2.42 (2H, m, H-2), 1.75 (3H, s, CMeCH₂), 1.70–1.10 (11H, m, cyclohexyl), 1.28–1.23 (3H, m, OCH₂CH₃); δC (101 MHz, CDCl₃) 172.2 (=C-1), 143.7 (CMeCH₂), 114.3 (CMeCH₂), 71.4 (C-4), 60.4 (OCH₂), 45.0 (C-3), 40.6 (C-5), 36.0 (C-2), 31.3, 27.1, 26.0, 20.0, 14.2.

NMR data for anti-243d: δH (400 MHz, CDCl₃) [4.93 (1H, s) and 4.90 (1H, s), CMeCH₂], 4.14 (2H, q, J 7.0, OCH₂), 3.17–3.13 (1H, m, H-4), 2.93 (1H, dt, J 9.0, 6.5, H-3), 2.63–2.42 (2H, m, H-2), 1.79 (3H, s, CMeCH₂), 1.70–1.10 (11H, m, cyclohexyl), 1.28–1.23 (3H, m, OCH₂CH₃); δC (101 MHz, CDCl₃) 171.9 (C-1), 143.6
(CMeCH₅), 115.1 (CMeCH₂), 70.8 (C-4), 60.5 (OCH₂), 44.5 (C-3), 40.3 (C-5), 36.8 (C-2), 31.1, 27.8, 26.3, 26.1, 20.5, 14.2.

**Ethyl 3-(1-azidoethyl)-4-phenylpent-4-enoate (243f)**

A 75:25 mixture of allylic azide *E*-236 and *Z*-236 respectively (100 mg, 0.492 mmol, 1.0 equiv) was reacted according to general procedure C to afford ethyl 3-(1-azidoethyl)-4-phenylpent-4-enoate 243f (100 mg, 75%, 50:50 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (5% ether/hexane):

ν_max (film) 2105, 1734, 1631, 1256, 1176, 1037 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.46–7.33 (10H, m, syn+anti Ph), [5.41 (2H, d, J 3.0) and 5.19 (2H, s (br)), syn+anti CPhCH₂], [4.17 (2H, q, J 7.0) and 4.03 (2H, q, J 7.0), syn+anti OCH₂], [3.65 (1H, dq, J 6.5, 4.5) and 3.54 (1H, dq, J 7.0, 6.5), syn+anti CHN₃], [3.46 (1H, dt, J 6.5, 5.5) and 3.21 (1H, dt, J 6.5, 5.5), syn+anti CHCPhCH₂)], 2.84–2.63 (4H, m, syn+anti CH₂CO₂Et), [1.27 (3H, t, J 7.0) and 1.24 (3H, t, J 7.0), syn+anti OCH₂CH₃)], [1.27 (3H, d, J 6.5) and 1.16 (3H, d, J 6.5), syn+anti Me)]; δ_C (101 MHz, CDCl₃) [172.3 and 172.1 (syn+anti C=O)], [149.2 and 148.1 (syn+anti CPhCH₂)], [142.3 and 142.2 (syn+anti i-Ph)], [128.5, 128.4, 127.8, 127.7, 126.9 and 126.7 (syn+anti Ph)], [115.1 and 114.8 (syn+anti CPhCH₂)], [60.7 and 60.6 (syn+anti OCH₂)], [60.6 and 58.9 (syn+anti CHN₃)], [46.0 and 44.7 (syn+anti CHCPhCH₂)], [36.1 and 34.4 (syn+anti CH₂CO₂Et)], [18.0 and 15.1 (syn+anti Me)], 14.2 (syn+anti OCH₂CH₃); m/z (CI) 291 [MNH₄]^+, 274 [MH]^+, 246, 205 (Found: [MH]^+, 274.1563. C₁₅H₁₉N₃O₂ requires [MH]^+, 274.1556).
Ethyl 4-azido-4-(pyridin-2-yl)-3-(prop-1-enyl)pentanoate (243g)

Allylic azide 235g (80 mg, 0.392 mmol, 1.0 equiv) was reacted according to general procedure C to afford an impure sample of ethyl 4-azido-4-(pyridin-2-yl)-3-(prop-1-enyl)pentanoate 243g (4 mg, <4%, 77:23 syn:anti mixture of diastereomers) as a brown oil after purification over silica gel (10% ether/5% TEA/petrol).

NMR data for syn-243g inter alia: $\delta$H (400 MHz, CDCl$_3$) 8.60 (1H, d, $J$ 5.0, 6-pyridyl), 7.78–7.67 (1H, m, 4-pyridyl), 7.34–7.19 (2H, m, 3,5-pyridyl), 4.80 (1H, s, $trans$-CMeCH$_2$), 4.77 (1H, s, $cis$-CMeCH$_2$), 4.58 (1H, d, $J$ 8.0, H-4), 4.20–4.05 (2H, m, OCH$_2$), 3.26, 1H, dd, $J$ 8.0, 5.0, H-3), [2.73 (1H, dd, $J$ 14.5, 4.0) and 2.59 (1H, dd, $J$ 14.5, 9.5), H-2], 1.69 (3H, s, CMeCH$_2$), 1.31–1.23 (3H, m, OCH$_2$C$_2$H$_5$); $\delta$C (101 MHz, CDCl$_3$) 149.7 (6-pyridyl), 136.8 (4-pyridyl), 114.5 (CMeCH$_2$), 68.9 (C-4), 60.4 (OCH$_2$), 47.4 (C-3), 35.5 (C-2), 20.3 (CMeCH$_2$), 14.0 (OCH$_2$CH$_3$).

NMR data for anti-243g inter alia: $\delta$H (400 MHz, CDCl$_3$) 8.63 (1H, d, $J$ 5.0, 6-pyridyl), 7.78–7.67 (1H, m, 4-pyridyl), 7.34–7.19 (2H, m, 3,5-pyridyl), 5.00 (1H, $trans$-CMeCH$_2$), 4.96 (1H, s, $cis$-CMeCH$_2$), 4.51 (1H, d, $J$ 9.5, H-4), 4.20–4.05 (2H, m, OCH$_2$), 3.35–3.28 (1H, m, H-3), [2.34 (1H, dd, $J$ 15.0, 10.0) and 2.21 (1H, dd, $J$ 15.0, 5.0), H-2], 1.83 (3H, CMeCH$_2$), 1.31–1.23 (3H, m, OCH$_2$CH$_3$); $\delta$C (101 MHz, CDCl$_3$) 149.5 (6-pyridyl), 136.7 (4-pyridyl), 69.1 (C-4), 60.4 (OCH$_2$), 47.4 (C-3), 20.9 (CMeCH$_2$), 14.0 (OCH$_2$CH$_3$).
5-Methyl-4-(prop-1-enyl)pyrrolidin-2-one (244a)

General procedure (using PMe₃):

Ester 243c (85 mg, 0.403 mmol, 1.0 equiv, 60:40 syn:anti mixture of diastereomers) was reacted according to general procedure L to afford 5-methyl-4-(prop-1-enyl)pyrrolidin-2-one 244a (33 mg, 59% 45:55 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (20–30 % EtOAc/dichloromethane).

Alternative procedure (using polystyrene-PPh₂):

To a solution of ester 243c (51 mg, 0.242 mmol, 1.0 equiv) in THF (242 µL) in a 0.2–0.5 mL microwave vial was added polystyrene supported diphenylphosphine (286 mg of a 1.10 mmol/g resin, 0.314 mmol, 1.3 equiv) and water (5.6 µL, 0.314 mmol, 1.3 equiv). The vial was flushed with nitrogen gas and capped. After heating by microwave at 120 °C for 30 min, the mixture was cooled and filtered, washing the resin with dichloromethane (15 mL). The filtrate was concentrated under reduced pressure and the residue purified over silica gel (20–30 % EtOAc/dichloromethane) to afford 5-methyl-4-(prop-1-enyl)pyrrolidin-2-one 244a (33 mg, 87% 60:40 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel.

Data for the mixture: $\nu_{\text{max}}$ (film) 3321, 1693, 1652 cm⁻¹; m/z (CI) 157 [MNH₄]⁺, 140 [MH]⁺ (Found: [MH]⁺, 140.1081. C₇H₁₃NO requires [MH]⁺, 140.1075).

NMR data for syn-244a: $\delta_H$ (500 MHz, CDCl₃) 6.83 (1H, s, NH), 4.81 (1H, s, trans-CMeCH₂) 4.76 (1H, s, cis-CMeCH₂), 3.85 (1H, dq, $J$ 7.0, 6.0, H-5), 3.06 (1H, dt, $J$ 10.0, 7.0, H-4), [2.43 (1H, dd, $J$ 17.0, 4.0) and 2.23 (1H, dd, $J$ 17.0, 8.0), H-3], 1.73
(3H, s, CMeCH₂), 0.97 (3H, d, J 6.0, 5-Me); δc (126 MHz, CDCl₃) 177.5 (C-2), 143.2 (CMeCH₂), 112.5 (CMeCH₂), 51.7 (C-5), 45.6 (C-4), 32.6 (C-3), 21.9 (CMeCH₂), 16.5 (5-Me).

NMR data for anti-244a: δH (500 MHz, CDCl₃) 6.83 (1H, s, NH), 4.93 (1H, s, trans-CMeCH₂), 4.81 (1H, s, cis-CMeCH₂), 3.59 (1H, dq, J 7.0, 6.0, H-5), 2.57 (1H, dt, J 9.5, 7.0, H-4), [2.45 (1H, dd, J 16.5, 4.5) and 2.32 (1H, dd, J 16.5, 10.0), H-3], 1.72 (3H, s, CMeCH₂), 1.21 (3H, d, J 6.0, 5-Me); δc (126 MHz, CDCl₃) 176.9 (C-2), 141.9 (CMeCH₂), 112.4 (CMeCH₂), 53.6 (C-5), 50.7 (C-4), 36.0 (C-3), 20.7 (CMeCH₂), 19.7 (5-Me).

5-Pentyl-4-(prop-1-enyl)pyrrolidin-2-one (244b)

Ester 243b (22 mg, 0.082 mmol, 1.0 equiv, 59:41 syn:anti mixture of diastereomers) was reacted according to general procedure L to afford 5-pentyl-4-(prop-1-enyl)pyrrolidin-2-one 244b (12 mg, 75%, 56:44 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (20% EtOAc/dichloromethane).

Data for the mixture: νmax (film) 3207, 1697, 1450, 1377, 1073, 892, 728 cm⁻¹; m/z (CI) 213 [MNH₄]+, 196 [MH]+ (Found: [MH]+, 196.1694. C₁₂H₂₁NO requires [MH]+, 196.1701).

NMR data for syn-244b: δH (500 MHz, CDCl₃) 6.04 (1H, s (br), NH), 4.97 (1H, s, trans-CMeCH₂), 4.81 (1H, s, cis-CMeCH₂) 3.69–3.65 (1H, m, H-5), 3.14 (1H, dt, J 9.5, 8.0, H-4), 2.44 (1H, dd, J 17.0, 10.5, H₃), 2.28 (1H, dd, J 9.5, 8.0, H₃), 1.76–1.74 (3H, s, CMeCH₂), 1.35–1.21 (8H, m, pentyl), 0.90–0.86 (3H, m, CH₃ of pentyl); δc
(126 MHz, CDCl₃) 177.3 (C-2), 141.9 (CMeCH₂), 112.8 (CMeCH₂), 56.4 (C-5), 45.9 (C-4), 35.5, 31.7, 30.5, 26.2, 22.5, 21.9, 14.0.

NMR data for *anti*-243b: δ_H (500 MHz, CDCl₃) 5.93 (1H, s (br), NH), 4.84 (2H, s (br), CMeCH₂), 3.49 (1H, dt, J 7.0, 6.0, H-5), 2.71 (1H, dt, J 8.0, 7.0, H-4), 2.48 (1H, dd, J 17.0, 9.0 H₃), 2.29 (1H, dd, J 10.0, 8.0, H₅), 1.76–1.74 (3H, s, CMeCH₂), [1.61–1.55 (1H, m) and 1.45–1.39 (1H, m), CH₂ of penty], 1.35–1.21 (6H, m, pentyl) 0.90–0.86 (3H, m, CH₃ of penty); δ_C (126 MHz, CDCl₃) 176.6 (C-2), 144.2 (CMeCH₂), 112.3 (CMeCH₂), 58.0 (C-5), 48.5 (C-4), 35.8, 33.1, 31.7, 25.9, 22.4, 19.6, 14.0.

5-Cyclohexyl-4-(prop-1-enyl)pyrrolidin-2-one (244c)

Ester 243d (122 mg, 0.437 mmol, 1.0 equiv 63:37 syn:anti mixture of diastereomers) was reacted according to general procedure L to afford 5-cyclohexyl-4-(prop-1-enyl)pyrrolidin-2-one 244c (53 mg, 59%, 33:66 syn:anti mixture of diastereomers) as a while solid after purification over silica gel (20–60% EtOAc/dichloromethane).

Data for the mixture: mp 78–82 °C; ν_max (film) 3209, 1690, 1448, 1256, 890, 764 cm⁻¹; m/z (CI) 225 [MNH₄]⁺, 208 [MH]⁺ (Found: [MH]⁺, 208.1704. C₁₃H₂₁NO requires [MH]⁺, 208.1701).

NMR data for *syn*-244c δ_H (500 MHz, CDCl₃) 6.15 (1H, s (br), NH), 4.97 (1H, s, trans-CMeCH₂), 4.81 (1H, s, cis-CMeCH₂), 3.46 (1H, dd, J 7.0, 6.5, H-5), 3.12 (1H, dt, J 7.5, 7.0, H-4), [2.39 (1H, dd, J 16.5, 8.0) and 2.35 (1H, dd, J 16.5, 7.0), H-3], 1.79 (3H, s, CMeCH₂), 1.67–0.84 (11H, m, cyclohexyl); δ_C (126 MHz, CDCl₃) 177.9 (C-2), 142.6 (CMeCH₂), 113.5 (CMeCH₂), 61.8 (C-5), 45.3 (C-4), 38.7 (cyclohexyl CH), 33.9 (C-3), 30.5, 28.8, 25.8, 25.6, 24.9, 21.4 (CMeCH₂).
NMR data for *anti-244c* δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 6.15 (1H, s (br), NH), 4.80 (1H, s, *cis*-CMeCH<sub>2</sub>), 4.77 (1H, s, *trans*-CMeCH<sub>2</sub>), 3.25 (1H, dd, J 5.5, 5.0, H-5), 2.83 (1H, dt, J 9.5, 5.0, H-4), 2.51 (1H, dd, J 17.5, 9.5, H<sup>6</sup>), 2.21 (1H, dd, J 17.5, 5.5, H<sup>5</sup>), 1.74 (3H, s, CMeCH<sub>2</sub>), 1.67–0.84 (11H, m, cyclohexyl); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 177.0 (C-2), 145.9 (CMeCH<sub>2</sub>), 111.5 (CMeCH<sub>2</sub>), 63.2 (C-5), 44.6 (C-4), 42.8 (cyclohexyl CH), 35.6 (C-3), 29.6, 28.3, 26.2, 26.0, 25.9, 19.4 (CMeCH<sub>2</sub>).

5-Methyl-4-(1-phenylethenyl)pyrrolidin-2-one (244d)

Ester 243f (78 mg, 0.286 mmol, 1.0 equiv, 50:50 *syn:anti* mixture of diastereomers) was reacted according to general procedure L to afford 5-methyl-4-(1-phenylethenyl)pyrrolidin-2-one 244d (46 mg, 80%, 50:50 *syn:anti* mixture of diastereomers) as a white solid after purification over silica gel (20% EtOAc/dichloromethane). Data for the mixture: mp 64–68 °C; ν<sub>max</sub> (film) 3202, 1694, 1631, 1262, 905, 764, 697 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.40–7.30 (10H, m, *syn*+*anti* Ph), 6.36 (2H, s (br), *syn*+*anti* NH), 5.47 (1H, d, J 1.0, *syn* trans-CPhCH<sub>2</sub>), 5.32 (1H, s, *anti* trans-CPhCH<sub>2</sub>), 5.19 (1H, s, *anti* cis-CPhCH<sub>2</sub>), 5.13 (1H, d, J 1.0, *syn* cis-CPhCH<sub>2</sub>), 3.85 (1H, dt, J 12.0, 7.5, *syn* H-4), 3.75 (2H, dq, J 12.0, 6.5, *syn*+*anti* H-5), 3.09 (1H, dt, J 8.0, 7.0, *anti* H-4), 2.65 (1H, dd, J 16.0, 11.5, *anti* H<sup>6</sup>), 2.62 (1H, dd, J 17.0, 8.5, *syn* H<sup>6</sup>), 2.41 (1H, dd, J 16.0, 13.5, *anti* H<sup>b</sup>), 2.39 (1H, dd, J 16.0, 14.0, *syn* H<sup>b</sup>), 1.24 (3H, d, J 6.5, *anti* 5-Me), 0.84 (3H, d, J 6.5, *syn* 5-Me); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) [176.7 and 176.3 (*syn*+*anti* C-2)], [148.6 and 145.6 (*syn*+*anti* CPhCH<sub>2</sub>)], [141.3 and 140.7 (*syn*+*anti* i-Ph)], 128.6, 128.4, 127.9, 127.7, 126.7, 126.2, 114.5 (syn CPhCH<sub>2</sub>), 113.2 (*anti* CPhCH<sub>2</sub>), [55.1 and 51.4 (*syn*+*anti* C-5)], 47.5 (anti C-4), 42.8 (*syn* C-4), 37.3 (anti C-3), 32.5 (*syn* C-3), 20.1 (*anti* 5-Me), 16.7 (*syn* 5-Me); m/z (Cl)

(E)-2-Azidonon-3-enyl 2-tosylacetate (252a) and (E)-4-azidonon-2-enyl 2-tosylacetate (253a)

A 73:27 mixture of allylic azides 235a and 236a respectively (1.00 g, 5.46 mmol, 1.0 equiv) was reacted according to general procedure M to afford a 58:42 mixture of the esters (E)-2-azidonon-3-enyl 2-tosylacetate 252a and (E)-4-azidonon-2-enyl 2-tosylacetate 253a (2.05 g, 99%) respectively as a colourless oil after purification over silica gel (25% ether/petrol).

Data for the mixture: νₘₐₓ (film) 2932, 2099, 1747, 1598, 1455, 1330, 1152, 1085, 975, 814, 728, 646, cm⁻¹; δ C (126 MHz, CDCl₃) 162.2, 162.1, 138.7, 133.2, 129.9, 128.5, 125.9, 128.5, 125.9, 122.3, 67.1, 65.5, 63.5, 62.0, 60.8, 34.2, 32.2, 31.4, 31.2, 28.5, 25.4, 22.5, 22.4, 21.7, 14.0; m/z (CI) 397 [MNH₄]+, 352, 243 (Found: [MNH₄]+, 397.1926. C₁₈H₂₅N₃O₄S requires [MNH₄]+, 397.1910).

¹H-NMR data for 252a: δₜ (500 MHz, CDCl₃) 7.85–7.81 (2H, m, o-Ts), 7.39–7.37 (2H, m, m-Ts), 5.82 (1H, dt, J 15.0, 7.0, H-4), 5.31 (1H, ddt, J 15.0, 7.0, 1.5, H-3), 4.62 (2H, d, J 5.0, H-1), 4.13 (2H, d, J 5.0, CH₂Ts), 4.10–3.90 (1H, m, H-2), 2.47 (3H, s, TsMe), 2.10–2.15 (2H, m, H-5), 1.57–1.28 (6H, m, H-6,7,8), 0.89 (3H, t, J 7.5, H-9).

¹H-NMR data for 253b: δₜ (500 MHz, CDCl₃) 7.85–7.81 (2H, m, o-Ts), 7.39–7.37 (2H, m, m-Ts), 5.74–5.65 (2H, m, H-2,3), 4.62 (2H, d, J 5.0, H-1), 4.13 (2H, d, J 5.0,
CH$_2$Ts), 3.82 (1H, dt, $J$ 14.0, 7.0, H-4), 2.47 (3H, s, TsMe), 1.57–1.28 (8H, m, H-5,6,7,8), 0.89 (3H, t, $J$ 7.5, H-9).

(\textit{E})-2-Azido-2-methylnon-3-enyl 2-tosylacetate (252b) and (\textit{E})-4-azido-2-methylnon-2-enyl 2-tosylacetate (253b)

\[
\begin{array}{c}
\text{C}_9\text{H}_{11}\text{N}_3\text{O} \quad \text{C}_9\text{H}_{11}\text{N}_3\text{O} \\
\text{235b} \quad \text{236b}
\end{array}
\]

\[
\text{C}_9\text{H}_{11}\text{N}_3\text{O} \quad \text{C}_9\text{H}_{11}\text{N}_3\text{O} \\
\text{252b} \quad \text{253b}
\]

A 61:39 mixture of allylic azides 235b and 236b respectively (795 mg, 4.03 mmol, 1.0 equiv) was reacted according to general procedure M to afford a 65:35 mixture the esters (\textit{E})-4-azido-2-methylnon-3-enyl 2-tosylacetate 253b and (\textit{E})-2-azido-2-methylnon-2-enyl 2-tosylacetate 252b respectively (1.09 g, 69%) as a colourless oil after purification over silica gel (20% ether/petrol).

Data for the mixture: $\nu_{\text{max}}$ (film) 2099, 1745, 1673, 1597, 1454, 1331, 1157, 1085, 831, 727 cm$^{-1}$; $\delta_C$ (101 MHz, CDCl$_3$) 162.2, 162.1, 145.6, 145.5, 135.8, 134.5, 134.1, 130.2, 129.9, 129.34, 129.1, 128.5, 127.7, 127.3, 70.7, 70.4, 62.9, 61.0, 60.8, 59.1, 34.7, 33.6, 32.4, 31.5, 31.2, 28.8, 27.7, 26.1, 25.4, 22.5, 21.7, 20.9, 14.4; $m/z$ (Cl) 411 [M$\text{NH}_4^+$], 366, 207, 137 (Found: [M$\text{NH}_4^+$], 411.2074. C$_{19}$H$_{27}$N$_3$O$_4$S requires [M$\text{NH}_4^+$], 411.2066).

\textsuperscript{1}H-NMR data for 253b: $\delta_H$ (400 MHz, CDCl$_3$), 7.84 (2H, d, $J$ 7.5, o-Ts), 7.39 (2H, d, $J$ 7.5, m-Ts), 5.42, (1H, d, $J$ 9.5, H-3), 4.16 (2H, s, CH$_2$Ts), 4.02 (2H, AB quartet, $J$ 11.0, H-1), 2.48 (3H, s, TsMe), 1.72 (3H, d, $J$ 1.5, 2-Me), 1.63–1.26 (8H, m, H-5,6,7,8), 0.91 (6H, t, $J$ 7.0, H-9).
1H-NMR data for 252b: \( \delta_H \) (400 MHz, CDCl3), 7.83 (2H, d, J 7.5, o-Ts), 7.40 (2H, d, J 7.5, m-Ts), 5.79 (1H, dt, J 15.5, 7.0, H-4), 4.57 (2H, s, CH2Ts), 4.14–4.11 (2H, m, H-1), 2.48 (3H, s, TsMe), 2.09 (2H, dt, J 7.5, 7.0, H-5), 1.63–1.26 (6H, m, H-6,7,8), 1.35 (3H, s, 2-Me), 0.91 (6H, t, J 7.0, H-9).

\((E)\)-2-Azido-2-methylpent-3-enyl 2-tosylacetate (252c) and \((E)\)-4-azido-2-methylpent-2-enyl 2-tosylacetate (253c)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N}_3 & \quad \text{N}_3 \\
\text{OH} & \quad \text{OH} \\
235c & \quad \downarrow \\
\text{Me} & \quad \text{Me} \\
\text{N}_3 & \quad \text{N}_3 \\
\text{OH} & \quad \text{OH} \\
236c & \quad \downarrow \\
\text{Me} & \quad \text{Me} \\
\text{N}_3 & \quad \text{N}_3 \\
\text{O} & \quad \text{O} \\
\text{Ts} & \quad \text{Ts} \\
252c & \quad \downarrow \\
\text{Me} & \quad \text{Me} \\
\text{N}_3 & \quad \text{N}_3 \\
\text{O} & \quad \text{O} \\
\text{Ts} & \quad \text{Ts} \\
253c & \quad \downarrow \\
\end{align*}
\]

A 64:36 mixture of allylic azides 235c and 236c respectively (300 mg, 2.13 mmol, 1.0 equiv) was reacted according to general procedure M to afford a 70:30 mixture of \((E)\)-4-azido-2-methylpent-3-enyl 2-tosylacetate 253c and \((E)\)-2-azido-2-methylpent-2-enyl 2-tosylacetate 252c respectively (667 mg, 97%) as a colourless oil after purification over silica gel (30% ether/petrol).

Data for the mixture: \( \nu_{\text{max}} \) (film) 2102, 1744, 1664, 1597, 1450, 1328, 1152, 1085, 813, 727 cm\(^{-1}\); \( \delta_C \) (101 MHz, CDCl3) 162.2, 162.1, 145.6, 145.55, 135.9, 133.9, 130.4, 130.0, 129.1, 128.6, 128.3, 70.7, 70.3, 63.0, 61.1, 60.9, 54.5, 32.4, 30.5, 25.9, 24.8, 21.8, 20.8, 20.3, 18.0, 14.3; \( m/z \) (CI) 355 [MNH4]\(^+\), 310, 295, 201 (Found: [MNH4]\(^+\), 355.1446. C\(^{15}\)H\(^{19}\)N\(^3\)O\(^4\)S requires [MNH4]\(^+\), 355.1440).

1H-NMR data for 253c: \( \delta_H \) (400 MHz, CDCl3) 7.85 (2H, d, J 7.5, o-Ts), 7.00 (2H, d, J 7.5 m-Ts), 5.44 (1H, d, J 9.5, H-3), 4.33 (1H, dq, J 9.5, 7.0, H-4), 4.17 (2H, s, CH\(_2\)Ts), 3.98 (2H, s, H-1), 2.46 (3H, s, TsMe), 1.68 (3H, d, J 1.5, 2-Me), 1.24 (3H, d, J 7.0, H-5).
Experimental

$^1$H-NMR data for 252c: $\delta_H$ (400 MHz, CDCl$_3$) 7.85 (2H, d, $J$ 7.5, o-Ts), 7.00 (2H, d, $J$ 7.5 m-Ts), 5.83 (1H, dq, $J$ 15.5, 6.5, H-4), 5.45 (1H, d, $J$ 15.5, H-3), 4.56 (2H, s, CH$_2$Ts), 4.16 (2H, s, H-1), 2.46 (3H, s, TsMe), 1.32 (3H, s, 2-Me), 1.21 (3H, d, $J$ 6.5, H-5).

(E)-2-Azido-4-cyclohexyl-2-methylbut-3-enyl 2-tosylacetate (252d) and (E)-4-azido-4-cyclohexyl-2-methylbut-2-enyl 2-tosylacetate (253d).

A 72:28 mixture of allylic azides 235d and 236d respectively (618 mg, 2.96 mmol, 1.0 equiv) was reacted according to general procedure M to afford a 68:32 mixture of (E)-4-azido-4-cyclohexyl-2-methylbut-3-enyl 2-tosylacetate 253d and (E)-2-azido-4-cyclohexyl-2-methylbut-2-enyl 2-tosylacetate 252d respectively (1.10 g, 92%) as a colourless oil after purification over silica gel (20% ether/petrol).

Data for the mixture: $\nu_{\text{max}}$ (film) 2096, 1742, 1650, 1598, 1450, 1329, 1152, 1085, 813, 727, 697, 603 cm$^{-1}$; $\delta_C$ (101 MHz, CDCl$_3$) 162.2, 145.6, 145.5, 140.1, 135.8, 135.7, 134.6, 129.9, 128.5, 128.4, 128.3, 127.9, 125.9, 125.2, 70.7, 70.5, 64.4, 64.3, 62.9, 61.0, 42.3, 40.6, 32.9, 32.8, 29.5, 26.3, 25.9, 25.8, 21.7, 20.9, 14.5; $m/z$ (ESI) 428 [MNa]$^+$, 378, 309, 149 (Found: [MNa]$^+$, 428.1635. $C_{20}H_{23}N_3O_4S$ requires [MNa]$^+$, 428.1620).

$^1$H-NMR data for 253d: $\delta_H$ (400 MHz, CDCl$_3$) 7.84 (2H, d, $J$ 7.5, o-Ts), 7.39 (2H, d, $J$ 7.5, m-Ts), 5.45 (1H, d, $J$ 9.5, H-3), 4.16 (2H, s, CH$_2$Ts), 4.02 (2H, AB quartet, $J$
11.5, H-1), 3.91 (1H, dd, J 9.5, 8.0, H-4), 4.28 (3H, s, TsMe), [1.77–1.58 and 1.45–0.88 (11H, m, cyclohexyl)], 1.71 (3H, s, 2-Me).

$^1$H-NMR data for 252d: $\delta_H$ (400 MHz, CDCl$_3$) 7.84 (2H, d, J 7.5, o-Ts), 7.39 (2H, d, J 7.5, m-Ts), 5.73 (1H, d, J 16.0, 7.0, H-4), 5.36 (1H, d, J 16.0, H-3), 4.58 (2H, s, CH$_2$Ts), 4.15–4.12 (2H, m, H-1), 4.28 (3H, s, TsMe), 2.05–1.96 (1H, m, A-5), [1.77–1.58 and 1.45–0.88 (10H, m, cyclohexyl)], 1.34 (3H, s, 2-Me).

*(E)-2-Azido-4-phenylbut-3-enyl 2-tosylacetate (252e)*

![Diagram](image)

Allylic azide 235e (500 mg, 2.64 mmol, 1.0 equiv) was reacted according to general procedure M to afford *(E)-2-azido-4-phenylbut-3-enyl 2-tosylacetate* 252e (1.03 g, 97%) as a colourless oil after purification over silica gel (15% EtOAc/hexane): $\nu_{\text{max}}$ (film) 2109, 1747, 1598, 1328, 1151, 1085, 971, 814, 754, 695, 646 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.81 (2H, d, J 8.5, o-Ts), 7.40–7.28 (5H, m, Ph), 7.34 (2H, d, J 8.5, m-Ts), 6.69 (1H, d, J 16.0, H-4), 6.04 (1H, dd, J 16.0, 7.5, H-3), 4.28–4.20 (1H, m, H-2), 4.14 (2H, s, CH$_2$Ts), 4.13–4.07 (2H, m, H-1), 2.42 (3H, s, TsMe); $\delta_C$ (101 MHz, CDCl$_3$) 162.2, 145.6, 135.9 (C-4), 135.7, 135.3, 129.9, 128.9, 128.8, 128.7, 128.6, 126.8 (m-Ts), 121.7 (C-3), 67.0 (C-2), 62.2 (CH$_2$Ts), 60.9 (C-1), 21.7 (TsMe); m/z (Cl) 403 [MNH$_4$]$^+$, 355, 244, 212 (Found: [MNH$_4$]$^+$, 403.1445. C$_{19}$H$_{19}$N$_3$O$_4$S requires [MNH$_4$]$^+$, 403.1440) (Found: C, 59.26; H, 4.16; N, 10.98. C$_{19}$H$_{19}$N$_3$O$_4$S requires C, 59.21; H, 4.97; N, 10.90).
**Experimental**

\((E)-4\text{-Azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (E-236f)} \text{ and (Z)-4-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (Z-236f)}\)

Allylic azide **236f** (212 mg, 1.04 mmol, 1.0 equiv) was reacted according to general procedure M to afford a 75:25 mixture of \((E)-4\text{-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (E-253f)} \text{ and (Z)-4-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (Z-253f)}\) respectively (313 mg, 75%) as a colourless oil after purification over silica gel (25% ether/hexane).

Data for the mixture:

\[\nu_{\text{max}} \text{(film)} \text{ cm}^{-1}; \delta_C \text{ (101 MHz, CDCl}_3) \text{ ppm}\]

\[\text{2101, 1742, 1598, 1329, 1151, 1055, 814; 162.3 (Z C-1), 162.1 (E C-1), 148.5, 138.9, 138.4, 136.4, 136.0, 135.8, 135.7, 133.6, 129.9, 129.6, 128.7, 128.6, 128.5, 128.4, 128.2, 126.4, 69.1 (E C-1), 62.4 (Z C-1), 60.9 (E and Z CH}_2\text{Ts), 55.2 (E C-4), 54.9 (Z C-4), 21.7 (E and Z TsMe), 20.7 (Z C-5), 20.4 (E C-5); m/z (ESI) 423 [MHNa]^+, 422 [MNa]^+, 417, 394, 196, 143 \text{ (Found: [MNa]^+, 422.1153. C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{S requires [MNa]^+, 422.1150).}]]}

\[^1\text{H-NMR data for E-253f: } \delta_{\text{H}} \text{ (400 MHz, CDCl}_3) \text{ ppm}\]

7.80 (2H, d, \text{J} 8.5, \text{m-Ts}), 7.43–7.35 (5H, m, Ph), 7.17 (2H, d, \text{J} 8.5, \text{o-Ts}), 5.72 (1H, dt, \text{J} 9.5, 1.5, \text{H-3}), 4.83 (2H, d, \text{J} 1.5, \text{H-1}), 4.13 (2H, s, \text{CH}_2\text{Ts}), 4.05 (1H, dq, \text{J} 9.5, 6.5, \text{H-4}), 2.48 (3H, s, \text{TsMe}), 1.25 (3H, d, \text{J} 6.5, \text{H-5}).

\[^1\text{H-NMR data for Z-253f: } \delta_{\text{H}} \text{ (400 MHz, CDCl}_3) \text{ ppm}\]

7.77 (2H, d, \text{J} 8.5, \text{m-Ts}), 7.43–7.35 (5H, m, Ph), 7.33 (2H, d, \text{J} 8.5, \text{o-Ts}), 5.93 (1H, d, \text{J} 9.5, \text{H-3}), 5.09 (2H, AB quartet, \text{J} 12.5, \text{H-1}), 4.54 (1H, dq, \text{J} 9.5, 6.5, \text{H-4}), 4.10 (2H, s, \text{CH}_2\text{Ts}), 2.47 (3H, s, \text{Z TsMe}), 1.36 (3H, d, \text{J} 6.5, \text{H-5}).
**(E)-2-Azido-2-methyl-4-(pyridin-2-yl)but-3-enyl 2-tosylacetate (252g)**

Allylic azide **235g** (532 mg, 1.24 mmol, 1.0 equiv) was reacted according to general procedure M to afford (E)-2-azido-2-methyl-4-(pyridin-2-yl)but-3-enyl 2-tosylacetate **252g** (259 mg, 52%) as a yellow oil after purification over silica gel (30% EtOAc/5% TEA/hexane); \( \nu_{\text{max}} \) (film) 2106, 1748, 1586, 1329, 1151, 1085, 970, 768 cm\(^{-1} \); \( \delta_\text{H} \) (400 MHz, CDCl\(_3\)) 8.61 (1H, d, \( J = 5.0 \), 6-pyridyl), 7.85 (2H, d, \( J = 8.0 \), o-Ts), 7.70 (1H, dt, \( J = 7.5, 2.0 \), 4-pyridyl), 7.38 (2H, d, \( J = 8.0 \), m-Ts), 7.35 (1H, d, \( J = 7.5 \), 3-pyridyl), 7.22 (1H, dd, \( J = 7.5, 5.0 \), 5-pyridyl), 6.79 (1H, d, \( J = 16.0 \), H-4), 6.73 (1H, d, \( J = 16.0 \), H-3), 4.19 (2H, s, CH\(_2\)Ts), 4.17 (2H, d, \( J = 2.0 \), H-1), 2.47 (3H, s, TsMe), 1.53 (3H, s, 2-Me); \( \delta_\text{C} \) (101 MHz, CDCl\(_3\)) 162.1 (C=O), 154.0 (2-pyridyl), 149.7 (6-pyridyl), 145.6, 136.8 (4-pyridyl), 135.7, [131.8 and 131.7 (C-3) and [C-4]], 130.0 (m-Ts), 128.5 (o-Ts), 123.0 (5-pyridyl) 122.7 (3-pyridyl), 7.05 (C-1), 63.1 (C-2), 60.9 (CH\(_2\)Ts), 21.7 (TsMe), 21.0 (2-Me); \( m/z \) (CI) 401 [MH\(^+\)], 360, 188 (Found: [MH\(^+\)], 401.1276. C\(_{15}\)H\(_{20}\)N\(_4\)O\(_4\)S requires [MH\(^+\)], 401.1284).

1-[(3-Azido-2-ethyloctane)sulfonyl]-4-methylbenzene (254a)
A 58:42 mixture of allylic azides 252a and 253a respectively (50 mg, 0.132 mmol, 1.0 equiv) was reacted according to general procedure N to afford 1-[(3-azido-2-ethyloctane)sulfonyl]-4-methylbenzene 254a (38 mg, 86%, 84:16 syn:anti mixture of diastereomers) as a white solid after purification over silica gel (2–10% ether/petrol).

An alternative one-step procedure gave 254a in a lower yield:

N,N-bis(trimethylsilyl)acetamide (0.484 mL, 1.98 mmol, 5.0 equiv), a 58:42 mixture of allylic azides 252a and 253a respectively (150 mg, 0.396 mmol, 1.0 equiv) and potassium acetate (4 mg, 0.396 mmol, 0.1 equiv) were combined in a 0.2–0.5 mL microwave vial. The vial was flushed with nitrogen, sealed and heated under microwave irradiation at 170 °C for two cycles of 5 min. The reaction mixture was concentrated under reduced pressure and the residue was purified over silica gel (2–10% ether/petrol) to afford 1-[(3-azido-2-ethyloctane)sulfonyl]-4-methylbenzene 254a (42 mg, 32%, 84:16 syn:anti mixture of diastereomers) as a white solid. Repeated purification over silica gel (2–10% ether/petrol) followed by recrystallisation (EtOAc/petrol) afforded an analytical sample of syn-254a and an analytical sample enriched in anti-254a.

Data for syn-254a: m.p 72–74 °C; ν_max (film) 2902, 2100, 1456, 1142, 880, 771, 706, 670 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.81 (2H, d, J 8.5, o-Ts), 7.39 (2H, d, J 8.5, m-Ts), 5.60 (1H, ddd, J 17.0, 10.0, 8.5, CHCH₂), 5.17 (1H, d, J 10.0, trans-CHCH₂), 5.12 (1H, d, J 17.0, cis-CHCH₂), 3.70 (1H, ddd, J 8.5, 5.5, 3.0, H-3), [3.40 (1H, dd, J 14.0, 7.0) and 3.15 (1H, dd, J 14.0, 6.0), H-1], 2.90 (1H, dddd, J 12.5, 9.5, 6.0, 3.0, H-2), 2.48 (3H, s, TsMe), 1.62–1.31 (8H, m, H-4,5,6,7), 0.92 (3H, t, J 6.0, H-8); δ_C (101 MHz, CDCl₃) 144.9 (Ts), 136.9 (Ts), 133.7 (CHCH₂), 130.0 (m-Ts), 128.0 (o-Ts), 119.5 (CHCH₂), 64.3 (C-3), 58.1 (C-1), 42.5 (C-2), 32.2 (C-4), 31.5 (C-5), 25.8 (C-6), 22.5 (C-7), 21.7 (TsMe), 14.0 (C-8); m/z (Cl) 353 [MH₄]⁺, 310, 226, 174, 152; m/z (Cl) 353 [MH₄]⁺, 310, 226, 152 (Found: [MH₄]⁺, 353.2020. C₁₇H₂₅N₃O₂S requires [MH₄]⁺, 353.2011) (Found: C, 60.95; H, 7.47; N, 12.48. C₁₇H₂₅N₃O₂S requires C, 60.87; H, 7.51; N, 12.53).

NMR data for anti-254a: δ_H (400 MHz, CDCl₃) 7.79 (2H, d, J 8.0, o-Ts), 7.38 (2H, d, J 8.0, m-Ts), 5.68 (1H, ddd, J 17.5, 10.0, 8.5, CHCH₂), 5.17 (1H, d, J 10.0, trans-
CHCH₃), 5.16 (1H, d, J 17.5, cis-CHCH₂), 3.41–3.36 (1H, m, H-3), [3.31 (1H, dd, J 14.5, 3.5) and 3.20 (1H, dd, J 14.5, 9.0), H-1], 2.80–2.74 (1H, m, H-2), 2.48 (3H, s, TsMe), 1.63–1.28 (8H, m, H-4,5,6,7), 0.91 (3H, t, J 7.0, H-8); δc (101 MHz, CDCl₃) 144.4 (Ts), 135.9 (Ts), 135.5 (CHCH₂), 129.9 (m-Ts), 128.1 (o-Ts), 118.9 (CHCH₂), 65.8 (C₃), 56.9 (C₁), 43.0 (C-2), 31.6 (C-4), 31.4 (C-5), 25.3 (C-6), 22.4 (C-7), 21.7 (TsMe), 13.6 (C₈).

1-[(3-Azido-2-(prop-1-en-2-yl)octane)sulfonyl]-4-methylbenzene (254b)

A 68:32 mixture of allylic azides 253b and 252b respectively (161 mg, 0.41 mmol, 1.0 equiv) was reacted according to general procedure O to afford 1-[(3-azido-2-(prop-1-en-2-yl)octane)sulfonyl]-4-methylbenzene 254b (97 mg, 68%, 68:32 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (15% ether/petrol). Further purification over silica gel (10% ether/petrol) afforded an analytical sample of syn-254b and an analytical sample enriched in anti-254b.

Data for syn-254b: νmax (film) 2103, 1647, 1597, 1455, 1303, 1142, 1088, 899, 815 cm⁻¹; δH (400 MHz, CDCl₃) 7.68 (2H, d, J 8.0, o-Ts), 7.34 (2H, d, J 8.0, m-Ts), 4.87 (1H, t, J 1.5, trans-CMeCH₂), 4.78 (1H, s, cis-CMeCH₂), 3.61 (1H, dt, J 7.0, 5.0, H-3), [3.37 (1H, dd, J 14.5, 6.5) and 3.19 (1H, dd, J 14.5, 6.5), H-1], 2.86 (1H, dt, J 6.5, 5.0, H-2), 2.43 (3H, s, TsMe), 1.64 (3H, s, CMeCH₂), 1.49–1.23 (8H, m, H-4,5,6,7), 0.87 (3H, t, J 6.5, H-8); δc (101 MHz, CDCl₃) 144.8, 141.4, 136.9, 129.9 (o-Ts), 128.0 (m-Ts), 116.4 (CMeCH₂), 64.2 (C-3), 57.1 (C-1), 44.7 (C-2), 32.3, 31.5, 26.2,
22.5, 21.0, 14.0 (C-8); m/z (CI) 367 [MNH$_4$]$^+$, 350 [MH]$^+$, 324, 240 (Found: [MNH$_4$]$^+$, 367.2172. C$_{18}$H$_{27}$N$_3$O$_2$S requires [MNH$_4$]$^+$, 367.2168).

NMR data for anti-254b: $\delta$H (400 MHz, CDCl$_3$) 7.74 (2H, d, $J$ 8.0, o-Ts), 7.32 (2H, d, $J$ 8.0, o-Ts), 4.89 (1H, t, $J$ 1.5, trans-CMeCH$_2$), 4.83 (1H, s, cis-CMeCH$_2$), [3.94 (1H, dd, $J$ 14.5, 3.0) and 3.27 (1H, dd, $J$ 14.5, 8.0), H-1], 3.17–3.12 (1H, m, H-3), 2.60 (1H, ddd, $J$ 10.0, 8.0, 3.0, H-2), 2.43 (3H, s, TsMe), 1.63 (3H, s, CMeCH$_2$), 1.49–1.23 (8H, m, H-4,5,6,7), 0.87 (3H, t, $J$ 6.5, H-8); $\delta$C (101 MHz, CDCl$_3$) 144.7, 141.8, 136.8, 129.8 (o-Ts), 128.1 (m-Ts), 116.2 (CMeCH$_2$), 64.7 (C-3), 56.2 (C-1), 45.8 (C-2), 32.1, 31.4, 25.8, 21.6, 19.8, 14.0 (C-8).

1-[2-(1-Azidoethyl)-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene (254c)

A 70:30 mixture of allylic azides 253c and 252c respectively (50 mg, 0.16 mmol, 1.0 equiv) was reacted according to general procedure N to afford 1-[2-(1-azidoethyl)-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene 254c (36 mg, 82%, 91:9 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/petrol). Further purification over silica gel (10% ether/petrol) afforded an analytical sample of syn-254c and an analytical sample enriched in anti-254c.

Data for syn-254c: $\nu_{\text{max}}$ (film) 2110, 1648, 1598, 1452, 1304, 1146, 1087, 871, 693 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 7.81 (2H, d, $J$ 8.0, o-Ts), 7.38 (2H, d, $J$ 8.0, m-Ts), 4.95 (1H, s, trans-CMeCH$_2$), 4.83 (1H, s, cis-CMeCH$_2$), 3.89 (1H, dq, $J$ 6.5, 5.0, H-3), [3.40 (1H, dd, $J$ 14.0, 6.0) and 3.25 (1H, dd, $J$ 14.0, 7.0), H-1], 2.81 (1H, dt, $J$ 6.0,
5.0, H-2), 2.48 (3H, s, TsMe), 1.70 (3H, s, CMeCH2), 1.26 (3H, d, J 6.5, H-4); δC (101 MHz, CDCl3) 144.8, 141.2, 136.8, 129.8 (m-Ts), 128.0 (o-Ts), 116.5 (CMeCH2), 58.7 (C-3), 56.8 (C-1), 45.7 (C-2), 21.7 (TsMe), 21.1 (CMeCH2), 16.9 (C-4); m/z (CI), 311 [MNH4]+, 294 [MH]+, 268 (Found: [MNH4]+, 311.1542. C14H19N3O2S requires [MNH4]+, 311.1542).

NMR data for anti-254c inter alia: δH (400 MHz, CDCl3) 7.79 (2H, d, J 7.5, o-Ts), 7.37 (2H, d, J 7.5, m-Ts), 4.87 (1H, s, trans-CMeCh2), 4.54 (1H, s, cis-CMeCh2), 2.06–1.93 (1H, m, H-3), 1.05 (3H, d, J 7.0, H-4), δC (101 MHz, CDCl3) 129.7 (m-Ts), 128.1 (o-Ts).

1-[2-[Azido(cyclohexyl)methyl]-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene (254d)

A 65:35 mixture of allylic azides 253d and 252d respectively (234 mg, 0.58 mmol, 1.0 equiv) was reacted according to general procedure O to afford 1-[[2-[azido(cyclohexyl)methyl]-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene 254d (92 mg, 44%, 82:18 syn:anti mixture of diastereomers) as a colourless gum after purification over silica gel (15% ether/petrol).

Experimental

NMR data for syn-254d: δH (400 MHz, CDCl3) 7.82 (2H, d, J 8.5, o-Ts), 7.39 (2H, d, J 8.5, m-Ts), 4.90 (1H, t, J 1.5, trans-CMeCH2), 4.85 (1H, s, cis-CMeCH2), 3.85–3.42 (2H, m, H-1 and H-3), 3.21 (1H, dd, J 14.5, 6.0, H-1), 3.08 (1H, dt, J 7.5, 6.0, H-2), 2.49 (3H, s, TsMe), 1.89–1.07 (11H, m, cyclohexyl), 1.67 (3H, s, CMeCH2); δC (101 MHz, CDCl3) 144.8 (i-Ts), 141.9 (p-Ts), 129.9 (m-Ts), 128.1 (o-Ts), 116.6 (CMeCH2), 77.2 (CMeCH2), 70.1 (C-3), 57.7 (C-1), 42.2 (C-2), 40.6, 30.5, 29.1, 26.1, 25.8, 20.8.

NMR data for anti-254d: δH (400 MHz, CDCl3) 7.79 (2H, d, J 8.5, o-Ts), 7.37 (2H, d, J 8.5, m-Ts), 4.95 (1H, t, J 1.5, trans-CMeCH2), 4.91 (1H, s, cis-CMeCH2), 3.43–3.29 (2H, m, H-1), 3.08–3.04 (1H, m, H-3), 2.87 (1H, m, H-2), 2.48 (3H, s, TsMe), 1.89–1.07 (11H, m, cyclohexyl), 1.70 (3H, s, CMeCH2); δC (101 MHz, CDCl3) 144.6 (i-Ts), 136.9 (p-Ts), 129.7 (m-Ts), 128.2 (o-Ts), 115.8 (CMeCH2), 77.2 (CMeCH2), 71.5 (C-3), 56.0 (C-1), 42.6 (C-2), 40.6, 30.8, 27.6, 25.7, 21.7, 20.0.

1-{2-[Azido(phenyl)methyl]but-3-ene-1-sulfonyl}-4-methylbenzene (254e)

Allylic azide 252e (213 mg, 0.55 mmol, 1.0 equiv) was reacted according to general procedure O to afford 1-{2-[azido(phenyl)methyl]but-3-ene-1-sulfonyl}-4-methylbenzene 254e (36 mg, 22%, 75:25 syn:anti mixture of diastereomers) after purification over silica gel (10% ether/petrol).


NMR data for syn-254e: δH (400 MHz, CDCl3) 7.81 (2H, d, J 8.0, o-Ts), 7.38 (2H, d, J 8.0, m-Ts), 7.31–7.17 (5H, m, Ph), 5.68 (1H, ddd, J 17.5, 10.0, 7.5, CHCH₂), 5.38
Experimental

(1H, d, J 17.5, cis-CHCH₂), 5.19 (1H, d, J 10.0, trans-CHCH₂), 4.96 (1H, d, J 8.5, H-3), [3.41 (1H, dd, J 14.5, 9.5) and 3.38 (1H, dd, J 14.5, 5.5), H-1], 3.24–3.18 (1H, m, H-2), 2.48 (3H, s, TsMe); δC (101 MHz, CDCl₃) 144.5, 135.3, 129.9, 129.6, 129.4, 128.0, 127.9, 127.4, 127.3, 117.3, 67.8 (C-3), 56.7 (C-1), 45.7 (C-2), 21.7 (TsMe).

NMR data for anti-254e: δH (400 MHz, CDCl₃) 7.78 (2H, d, J 8.0, o-Ts), 7.37 (2H, d, J 8.0, m-Ts), 7.31–7.17 (5H, m, Ph), 5.57 (1H, ddd, J 17.0, 10.0, 8.5, CHCH₂), 5.10 (1H, d, J 10.0, trans-CHCH₂), 4.91 (1H, d, J 8.5, H-3), 4.85 (1H, d, J 17.0, cis-CHCH₂), [3.26 (1H, dd, J 14.5, 7.0) and 3.10 (1H, dd, J 14.5, 7.0), H-1], 3.03–2.96 (1H, m, H-2), 2.43 (3H, s, TsMe); δC (101 MHz, CDCl₃) interalia 141.1, 133.9, 130.0, 128.5, 119.7, 65.5 (C-3), 57.3 (C-1), 44.7 (C-2), 21.1 (TsMe).

1-[2-(1-Azidoethyl)-3-phenylbut-3-ene-1-sulfonyl]-4-methylbenzene (254f)

A 75:25 mixture of allylic azides E-253f and Z-253f respectively (297 mg, 0.74 mmol, 1.0 equiv) was reacted according to general procedure N to afford 1-[2-(1-azidoethyl)-3-phenylbut-3-ene-1-sulfonyl]-4-methylbenzene 254f (87 mg, 32%, 73:27 syn:anti mixture of diastereomers) as a colourless oil after purification over silica gel (10–40% ether/hexane).

NMR data for syn-254f: $\delta^H$ (400 MHz, CDCl$_3$) 7.82 (2H, d, $J$ 8.0, o-Ts), 7.38–7.32 (7H, m-Ts, CPhCH$_2$), [5.43 (1H, s) and 5.19 (1H, s), CPhCH$_2$], 3.94 (1H, dq, 6.5, 4.0, H-3), 3.63–3.42 (3H, m, H-1,2), 2.48 (3H, s, TsMe), 1.15 (3H, d, $J$ 6.5, H-4); $\delta^C$ (101 MHz, CDCl$_3$) 145.9 (CPhCH$_2$), 144.9, 142.0, 136.9, 129.8, 128.6, 128.1, 128.0, 117.0 (CPhCH$_2$), 58.8 (C-3), 57.1 (C-1), 42.8 (C-2), 21.7 (TsMe), 16.2 (C-4).

NMR data for anti-254f: $\delta^H$ (400 MHz, CDCl$_3$) 7.75 (2H, d, $J$ 8.0, o-Ts), 7.38–7.32 (7H, m-Ts, CPhCH$_2$), [5.12 (1H, s) and 5.39 (1H, s), CPhCH$_2$], 3.63–3.42 (3H, m, H-1,3), 3.20 (1H, ddd, $J$ 9.0, 6.5, 3.0, H-2), 2.46 (3H, s, TsMe), 1.29 (3H, d, $J$ 6.5, H-4); $\delta^C$ (101 MHz, CDCl$_3$) inter alia 147.1 (CPhCH$_2$), 141.1, 128.5, 127.9, 127.0, 126.5, 116.4 (CPhCH$_2$), 60.3 (C-3), 57.0 (C-1), 44.7 (C-2), 21.7 (TsMe), 17.7 (C-4).

(E)-2-Azido-2-methylpent-3-en-1-yl 2-(benzyloxy)acetate (265) and (E)-4-azido-2-methylpent-2-en-1-yl 2-(benzyloxy)acetate (266)

To a solution of a 64:36 mixture of allylic azides 235c and 236c respectively (82 mg, 0.58 mmol, 1.0 equiv) in dichloromethane (2 mL) was added DCC (132 mg, 0.64 mmol, 1.1 equiv) and DMAP (7 mg, 0.06 mmol, 0.1 equiv) at rt and the resulting solution was stirred for 5 min. Benzyloxyacetic acid (91 µL, 0.64 mmol, 1.1 equiv) was added dropwise via syringe to give a white suspension. After stirring for 14 h, the reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure. Purification of the residue over silica gel (10% ether/petrol) afforded a 66:33 mixture of (E)-4-azido-2-methylpent-2-en-1-yl 2-(benzyloxy)acetate
266 and (E)-2-Azido-2-methylpent-3-en-1-yl 2-(benzyloxy)acetate 265 respectively (71 mg, 42%) as a colourless oil.

Data for the mixture: \( \nu_{\text{max}} \) (film) 2104, 1757, 1452, 1243, 1192, 1127 \text{cm}^{-1}; \delta_c \text{ (101 MHz, CDCl}_3) 170.0 (C-1), 132.2, 134.3, 134.2, 130.1, 129.6, 128.9, 128.7, 128.3, 127.8, 73.6 (CH\_2), 69.7 (CH\_2), 69.0 (CH\_2), 67.3 (CH\_2), 67.1 (CH\_2), 63.4, 62.3, 54.7, 21.7, 21.3, 20.9, 20.5, 18.1, 14.6; \text{m/z (Cl)} 307 \text{ [M NH}_4^+], 247 (\text{Found: [M NH}_4^+], 307.1774). \text{C}_{15}H_{19}N_3O_3 \text{requires [M NH}_4^+], 307.1770).

\(^1\text{H}-\text{NMR data for 265:} \delta_H \text{ (400 MHz, CDCl}_3) 7.41–7.36 (5H, m, Ph), 5.85 (1H, dq, } J 15.5, 6.5, \text{ H-4}), 5.50 (1H, d, } J 15.5, \text{ H-3), 4.64 (2H, s), 4.19 (2H, s), 4.10 (2H, s), 1.41 (3H, s, 2-Me), 1.27 (3H, d, } J 6.5, \text{ H-5).}

\(^1\text{H}-\text{NMR data for 266:} \delta_H \text{ (400 MHz, CDCl}_3) 7.41–7.36 (5H, m, Ph), 5.46 (1H, d, } J 9.0, \text{ H-3), 4.68 (2H, s), 4.35 (1H, dq, } J 9.0, 6.5, \text{ H-4), 4.18 (2H, s), 4.07 (2H, s), 1.78 (3H, d, } J 1.5, \text{ 2-Me), 1.28 (3H, d, } J 6.5, \text{ H-5).}

4-Azido-3-(prop-1-enyl)-2-(benzyloxy)-pentanoic acid (267)

To a solution of a 66:33 mixture of allylic azides 266 and 265 respectively (69 mg, 0.24 mmol, 1.0 equiv) in THF (3.4 mL) at –95 °C was added LHMDS (0.72 mL of a 1 M solution in THF, 0.72 mmol, 3.0 equiv) dropwise via syringe. The resulting solution was stirred for 1 h and base-treated chlorotrimethylsilane (0.18 mL, 1.43 mmol, 6.0 equiv) was added at –95 °C. The reaction mixture was stirred at –95 °C for
1 h, warmed to 0 °C over 1 h and warmed to rt during 24 h. Water (10 mL) and aqueous HCl (2 M, 10 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (20% EtOAc/5% formic acid/petrol) to afford recovered starting material 265/266 (20 mg, 29% 66:33 mixture) and 4-azido-3-(prop-1-enyl)-2-(benzyloxy)-pentanoic acid 267 (44 mg, 64%, 90% BRSM, 55:23:17:5 unassigned mixture of 4 diastereomers) as a colourless oil: \( \nu_{\text{max}} \) (film) 3468, 2104, 1747, 1452, 1379, 1240, 1124, 1029, 743, 699 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.43–7.34 (20H, m, Ph), 5.02–4.13 (20H, m, OCH₂, CMeCH₂ and H-2), [4.18 (1H, dq, \( J \approx 7.0, 4.5 \)), 3.93 (1H, dq, \( J \approx 10.0, 6.5 \)), 3.86 (1H, dq, \( J \approx 10.5, 6.5 \)) and 3.78 (1H, dq, \( J \approx 10.0, 6.5 \)), H-4], [2.67 (1H, dd, \( J \approx 10.0, 3.0 \)), 2.59 (1H, dd, \( J \approx 9.5, 4.5 \)), 2.57 (1H, dd, \( J \approx 9.5, 4.0 \)) and (1H, dd, \( J \approx 11.0, 4.0 \)), H-3], [1.89 (3H, s), 1.82 (6H, s), 1.79 (3H, s) and 1.79 (3H, s), CMeCH₂], 1.30–1.22 (12H, m, H-5); \( \delta_{\text{C}} \) (101 MHz, CDCl₃) [177.0, 176.8, 176.7 and 176.4 (C-1)], 166.1, 165.2, 142.8, 142.0, 136.9, 136.8, 136.7, 117.5, 116.7, 115.1, 79.0, 78.9, 78.8, 78.6, 73.6, 73.5, 73.2, 73.1, 56.5, 56.2, 55.9, 55.4, 54.7, 54.6, 54.4, 54.1, 31.9, 29.7, 29.5, 29.4, 29.2, 29.1, [22.7, 22.5, 22.0 and 21.2 (CMeCH₂)], [17.9, 17.7, 17.4 and 17.2 (C-5)]; \( m/z \) (CI), 321, 307 [MNH₄⁺], 288 [M–H⁺], 274, 184 (Found: [MNH₄⁺], 307.1773. C₁₅H₁₉N₃O₃ requires [MNH₄⁺], 307.1770).
3.4.4 Compounds relevant to section 2.6

*Syn*-4-azido-3-[[4-(methylbenzene)sulfonyl|methyl]nonan-2-one (*syn*-274)

[Chemical structure image]

Ozone gas was passed through a stirred solution of sulfone *syn*-254b (24 mg, 0.07 mmol, 1.0 equiv) in dichloromethane (2.5 mL) at −78 °C for 5 min. The solution was purged with nitrogen and dimethylsulfide (0.10 mL) was added at −78 °C. The solution was stirred at −78 °C for 1 h, allowed to warm to rt overnight and concentrated under reduced pressure. Purification of the residue over silica gel (10% EtOAc/petrol) afforded *syn*-4-azido-3-[[4-(methylbenzene)sulfonyl|methyl]nonan-2-one *syn*-274 (21 mg, 88%) as a colourless oil: \( \nu_{\text{max}} \) (film) 2106, 1719, 1598, 1316, 1148, 1087, 816 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.80 (2H, d, \( J = 8.0 \), o-Ts), 7.40 (2H, d, \( J = 8.0 \), m-Ts), [3.73 (1H, dd, \( J = 14.0 \), 9.5) and 3.13 (1H, dd, \( J = 14.0 \), 3.0), CH\(_2\)Ts], 3.59 (1H, dt, \( J = 9.0 \), 6.5, H-4), 3.54 (1H, dt, \( J = 9.5 \), 6.5, H-3), 2.49 (3H, s, TsMe), 2.35 (3H, s, H-1), 1.48–1.27 (8H, m, H-5,6,7,8), 0.91 (3H, t, \( J = 7.0 \), H-9); \( \delta_C \) (101 MHz, CDCl\(_3\)) 206.1 (C-2), 145.3, 136.1, 130.1 (m-Ts), 128.0 (o-Ts), 63.1 (C-4), 54.8 (CH\(_2\)Ts), 49.2 (C-3), 31.5, 31.4, 31.3 (C-1), 25.5, 22.4, 21.7 (TsMe), 13.9 (C-9); \( m/z \) (CI) 369 [MNH\(_4\)]\(^{+}\), 342, 326 (Found: C, 58.00; H, 7.13; N, 11.85. \( \text{C}_{17}\text{H}_{25}\text{N}_{3}\text{O}_{3}\text{S} \) requires C, 58.09; H, 7.17; N, 11.96).
**Experimental**

*Syn*-4-azido-3-{{(4-methylbenzene)sulfonyl}methyl}nonan-2-one (*syn*-274) and *4*-azido-2-methoxy-3-{{(4-methylbenzene)sulfonyl}methyl}nonan-2-ol (275)

When the above reaction was performed with a mixture of dichloromethane and methanol (4:1 v/v) as the solvent, *syn*-274 (17%) and an additional product *4*-azido-2-methoxy-3-{{(4-methylbenzene)sulfonyl}methyl}nonan-2-ol 275 (34%) was isolated as a colourless oil composed of a single diastereomer: $\nu_{\text{max}}$ (film) 3392, 2105, 1598, 1294, 1143, 815 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.86 (2H, d, $J$ 8.0, o-Ts), 7.41 (2H, d, J 8.0, m-Ts), 3.65 (1H, dt, J 10.0, 3.5, H-4), [3.59 (1H, dd, J 14.5, 4.0) and 3.14 (1H, dd, J 14.5, 5.0) CH$_2$Ts], 3.32 (3H, s, OMe), 3.00 (1H, dt, J 10.0, 4.0, H-3), 2.49 (3H, s, TsMe), 1.54 (3H, s, H-1), 1.50–1.25 (8H, m, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); $\delta_{\text{C}}$ (101 MHz, CDCl$_3$) 145.0, 136.5, 130.0 (m-Ts), 128.1 (o-Ts), 106.7 (C-2), 63.3 (C-4), 53.3 (CH$_2$Ts), 49.8 (OMe), 42.8 (C-3), 31.4 (C-5), 31.3 (C-6), 26.7 (C-7,8), 21.7 (TsMe), 18.4 (C-1), 14.0 (C-9).

**4-Azidononan-2-one (276)**

To a solution of azidotrimethylsilane (3.32 mL, 25.0 mmol, 5.0 equiv) in dichloromethane (20 mL) was added acetic acid (1.42 mL, 25.0 mmol, 5.0 equiv) at rt. The solution was stirred for 20 min and 3-nonen-2-one 238b (0.70 g, 5.0 mmol, 1.0 equiv) was added dropwise. TEA (0.14 mL, 1.0 mmol, 0.2 equiv) was then added and
the solution was stirred for 24 h. The reaction mixture was passed through a silica gel plug (10% ether/petrol) and concentrated under reduced pressure to afford 4-azidononan-2-one 276 (863 mg, 94%) as a colourless oil: $\nu_{\text{max}}$ (film) 2102, 1719, 1362, 1260 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 3.90–3.83 (1H, m, H-4), [2.69 (1H, dd, J 17.0, 8.5) and 2.57 (1H, dd, J 17.0, 5.0), H-3], 2.21 (3H, s, H-1), 1.54–1.26 (8H, m, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); $\delta_C$ (101 MHz, CDCl$_3$) 205.9 (C-2), 58.2 (C-4), 48.0 (C-3), 34.4 (C-5), 31.8 (C-6), 30.6 (C-1), 25.6 (C-7), 22.5 (C-8), 14.0 (C-9); $m/z$ (Cl) 201 [MNH$_4]^+$, 184 [MH]$^+$, 156 (Found: [MNH$_4]^+$, 201.1715. C$_{9}$H$_{17}$N$_{3}$O requires [MNH$_4]^+$, 201.1715); in agreement with published data.$^{202e}$

*(E)- and (Z)-4-Azidononan-2-one oxime (277)*

![Chemical Structure](image)

To a solution of azidoketone 276 (2.20 g, 12.0 mmol, 1.0 equiv) in acetonitrile (40 mL) and water (10 mL) was added sodium acetate (1.48 g, 18.0 mmol, 1.50 equiv) at rt. The mixture was stirred for 10 min to give a homogeneous solution and hydroxylamine hydrochloride (0.97 g, 14.0 mmol, 1.17 equiv) was added. The resulting solution was stirred at rt for 2 h and concentrated under reduced pressure to remove acetonitrile. The residue was partitioned between EtOAc (50 mL) and water (50 mL), the phases were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (MgSO$_4$) and concentrated under reduced pressure to afford an inseparable 66:33 mixture of *(E)- and (Z)-4-azidononan-2-one oxime* 277 respectively (2.23 g, 94%) as a colourless oil after purification over silica gel (15% ether/petrol).

Data for the mixture: $\nu_{\text{max}}$ (film) 3234, 2103, 1664, 1468, 1378, 1248, 961, 727; $m/z$ (Cl) 216 [MNH$_4]^+$, 199 [MH]$^+$, 177 (Found: [MH]$^+$, 199.1559. C$_{9}$H$_{17}$N$_{3}$O requires [MH]$^+$, 199.1559).
NMR data for *E*-277: $\delta_H$ (500 MHz, CDCl$_3$) 8.06 (1H, s (br), OH), 3.36 (1H, dt, $J$ 13.0, 6.5, H-4), 2.38 (1H, d, $J$ 6.5, H-3), 1.93 (1H, s, H-1), 1.57–1.25 (8H, m, H-5,6,7,8), 0.89 (3H, t, $J$ 6.5, H-9); $\delta_C$ (101 MHz, CDCl$_3$) 155.5 (C-2), 59.9 (C-4), 40.7 (C-3), 34.5, 31.5, 25.6, 22.5, 14.0 (C-9 and C-1).

NMR data for *Z*-277: $\delta_H$ (500 MHz, CDCl$_3$) 8.06 (1H, s (br), OH), 3.73–3.68 (1H, m, H-4), 2.65 (1H, dd, $J$ 13.0, 5.0) and 2.46 (1H, dd, $J$ 13.0, 9.5), H-3], 1.95 (1H, s, H-1), 1.57–1.25 (8H, m, H-5,6,7,8), 0.90 (3H, t, $J$ 6.5, H-9); $\delta_C$ (101 MHz, CDCl$_3$) 155.8 (C-2), 59.6 (C-4), 34.9, 34.5, 33.9 (C-3), 31.5, 22.5, 21.1 (C-1), 14.0 (C-9).

*N-(2-Azidoheptyl)acetamide (279) and 3-azido-N-methyloctanamide (280)*

![Diagram of N-(2-Azidoheptyl)acetamide (279) and 3-azido-N-methyloctanamide (280)]

To a solution of the oxime 277 (111 mg, 0.56 mmol, 1.0 equiv) in dichloromethane (3.29 mL) was added TEA (0.22 mL, 1.60 mmol, 2.85 equiv), DMAP (14 mg, 0.11 mmol, 0.2 equiv) and p-toluenesulfonyl chloride (305 mg, 1.60 mmol, 2.85 equiv) at rt. The mixture was stirred for 15 min and concentrated under reduced pressure. The residue was purified over silica gel (20% ether/petrol) to remove residual p-toluenesulfonyl chloride. Then, to a solution of the residue in IPA-water (3.29 mL, 4:1 v/v) was added TEA (0.22 mL, 1.60 mmol, 2.85 equiv) and the mixture was heated to reflux at 90 °C for 3 h. The reaction mixture was cooled to rt and water (25 mL) and EtOAc (25 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Purification of the residue over silica gel (50–80% EtOAc/petrol) gave an inseparable 2:1 mixture of N-(2-azidoheptyl)acetamide 279 and 3-azido-N-methyloctanamide 280 respectively (49 mg, 44%) as a yellow oil.
Data for the mixture: $\nu_{\text{max}}$ (film) 3298, 3087, 2107, 1654, 1555, 1462, 1373, 1274 cm$^{-1}$; $m/z$ (CI) 216 [MNHL$_4$]$^+$, 199 [MH]$^+$, 171, 100 (Found: [MH]$^+$, 199.1560. C$_9$H$_{18}$N$_4$O requires [MH]$^+$, 199.1559).

NMR data for 279: $\delta_H$ (400 MHz, CDCl$_3$) 5.83 (1H, s (br), NH), [3.62 (1H, ddd, $J$ 13.5, 7.0, 3.5) and 3.04 (1H, ddd, 13.5, 8.5, 3.5), H-1], 3.56–3.50 (1H, m, H-2), 2.04 (3H, s, Me), 1.59–1.28 (8H, m, H-3,4,5,6), 0.92 (3H, t, $J$ 7.0, H-7); $\delta_C$ (101 MHz, CDCl$_3$) 170.3 (C=O), 62.3 (C-2), 43.0 (C-1), 31.5, 32.2 (C-3), 25.6, 23.2 (Me), 22.5, 14.0 (C-7);

NMR data for 280: $\delta_H$ (400 MHz, CDCl$_3$) 5.72 (1H, s (br), NH), 3.88 (1H, ddt, $J$ 14.0, 6.5, 2.5, H-3), 2.86 (3H, d, $J$ 5.0, NHMe), [2.40 (1H, dd, $J$ 14.0, 4.5) and 2.29 (1H, dd, $J$ 14.0, 8.5), H-2], 1.59–1.28 (8H, m, H-3,4,5,6), 0.92 (3H, t, $J$ 7.0, H-7); $\delta_C$ (101 MHz, CDCl$_3$) 170.4 (C-1), 59.6 (C-3), 41.4 (C-2), 35.5 (C-4), 32.0, 29.9, 26.6 (NHMe), 23.0, 14.1 (C-8).
Chapter 4

Appendix
4.1 Crystallographic data for *anti*-160
Table 1. Crystal data and structure refinement for DC0703.

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Table 2. Bond lengths [Å] and angles [°] for DC0703.

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C(13)–C(14)–C(9)   118.4(2)
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O(17)–N(15)–C(11)  117.93(18)
O(20)–N(18)–O(19)  124.33(19)
O(20)–N(18)–C(13)  117.87(19)
O(19)–N(18)–C(13)  117.8(2)
C(22)–C(21)–C(3)   125.9(3)
C(24)–C(23)–C(28)  117.5(2)
C(24)–C(23)–C(4)   121.4(2)
C(28)–C(23)–C(4)   120.9(2)
C(25)–C(24)–C(23)  121.0(2)
C(24)–C(25)–C(26)  120.4(3)
C(27)–C(26)–C(25)  119.5(2)
C(26)–C(27)–C(28)  119.8(3)
C(27)–C(28)–C(23)  121.7(2)
O(7′)–C(1′)–C(2′)   106.6(2)
C(1′)–C(2′)–C(3′)   114.1(2)
C(21′)–C(3′)–C(2′)  109.4(2)
C(21′)–C(3′)–C(4′)  111.3(2)
C(2′)–C(3′)–C(4′)   110.9(2)
C(23′)–C(4′)–C(3′)  113.4(2)
C(23′)–C(4′)–C(5′)  109.8(2)
C(3′)–C(4′)–C(5′)   110.8(2)
C(6′)–C(5′)–C(4′)   114.9(2)
C(8′)–O(7′)–C(1′)   116.3(2)
O(8′)–C(8′)–O(7′)   125.0(3)
O(8′)–C(8′)–C(9′)   123.2(2)
O(7′)–C(8′)–C(9′)   111.8(2)
C(10′)–C(9′)–C(14′) 120.3(3)
C(10′)–C(9′)–C(8′)  117.8(2)
C(14′)–C(9′)–C(8′)  121.9(3)
C(9′)–C(10′)–C(11′) 119.2(2)
C(10′)–C(11′)–C(12′) 121.8(3)
C(10′)–C(11′)–N(15′) 118.9(2)
C(12′)–C(11′)–N(15′) 119.3(2)
C(13')–C(12')–C(11') 117.5(3)
C(12')–C(13')–C(14') 123.0(2)
C(12')–C(13')–N(18') 118.2(3)
C(14')–C(13')–N(18') 118.8(3)
C(13')–C(14')–C(9') 118.3(3)
O(17')–N(15')–O(16') 123.5(3)
O(17')–N(15')–C(11') 118.5(2)
O(16')–N(15')–C(11') 118.0(2)
O(19')–N(18')–O(20') 125.3(3)
O(19')–N(18')–C(13') 117.3(3)
O(20')–N(18')–C(13') 117.3(3)
C(22')–C(21')–C(3') 125.5(3)
C(24')–C(23')–C(28') 117.5(3)
C(24')–C(23')–C(4') 121.7(3)
C(28')–C(23')–C(4') 120.7(2)
C(25')–C(24')–C(23') 121.2(3)
C(24')–C(25')–C(26') 120.4(3)
C(27')–C(26')–C(25') 119.1(3)
C(26')–C(27')–C(28') 120.2(3)
C(27')–C(28')–C(23') 121.5(3)
4.2 Crystallographic data for syn-197
Table 1. Crystal data and structure refinement for DC0901.

<table>
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<tr>
<th>Property</th>
<th>Value</th>
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<td>Identification code</td>
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<tr>
<td>Empirical formula</td>
<td>C19 H19 N3 O5 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>401.43</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Diffractometer, wavelength</td>
<td>OXcalibur 3, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.0330(2) Å, α = 69.170(3)°</td>
</tr>
<tr>
<td></td>
<td>b = 11.6869(4) Å, β = 78.712(3)°</td>
</tr>
<tr>
<td></td>
<td>c = 12.9973(5) Å, γ = 82.731(3)°</td>
</tr>
<tr>
<td>Volume, Z</td>
<td>977.27(6) Å³, 2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.364 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.201 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>420</td>
</tr>
<tr>
<td>Crystal colour / morphology</td>
<td>Yellow tabular needles</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.45 x 0.24 x 0.10 mm³</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>2.92 to 32.4°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-6&lt;=h&lt;=10, -16&lt;=k&lt;=17, -18&lt;=l&lt;=19</td>
</tr>
<tr>
<td>Reflns collected / unique</td>
<td>12052 / 6353 [R(int) = 0.0204]</td>
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<tr>
<td>Reflns observed [F&gt;4σ(F)]</td>
<td>4267</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Analytical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.980 and 0.938</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>6353 / 21 / 270</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>1.053</td>
</tr>
<tr>
<td>Final R indices [F&gt;4σ(F)]</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0896, wR2 = 0.1467</td>
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<tr>
<td>Largest diff. peak, hole</td>
<td>0.424, -0.637 eÅ⁻³</td>
</tr>
<tr>
<td>Mean and maximum shift/error</td>
<td>0.000 and 0.001</td>
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Table 2. Bond lengths [Å] and angles [°] for DC0901.

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<th>Bond</th>
<th>Length [Å]</th>
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<td>N(1)–C(2)</td>
<td>1.3805(18)</td>
</tr>
<tr>
<td>N(1)–C(7)</td>
<td>1.3878(16)</td>
</tr>
<tr>
<td>C(2)–O(2)</td>
<td>1.2055(18)</td>
</tr>
<tr>
<td>C(2)–C(3)</td>
<td>1.5157(19)</td>
</tr>
<tr>
<td>C(3)–C(4)</td>
<td>1.527(2)</td>
</tr>
<tr>
<td>C(4)–C(19)</td>
<td>1.502(2)</td>
</tr>
<tr>
<td>C(4)–C(5)</td>
<td>1.532(2)</td>
</tr>
<tr>
<td>C(5)–C(6)</td>
<td>1.541(3)</td>
</tr>
<tr>
<td>C(5)–S(21)</td>
<td>1.819(2)</td>
</tr>
<tr>
<td>C(7)–C(12)</td>
<td>1.401(2)</td>
</tr>
<tr>
<td>C(7)–C(8)</td>
<td>1.4095(19)</td>
</tr>
<tr>
<td>C(8)–C(9)</td>
<td>1.3883(19)</td>
</tr>
<tr>
<td>C(8)–N(13)</td>
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</tr>
<tr>
<td>C(8)–N(13′)</td>
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</tr>
<tr>
<td>C(9)–C(10)</td>
<td>1.365(2)</td>
</tr>
<tr>
<td>C(10)–C(11)</td>
<td>1.380(2)</td>
</tr>
<tr>
<td>C(10)–N(16)</td>
<td>1.4636(18)</td>
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<tr>
<td>C(11)–C(12)</td>
<td>1.3754(19)</td>
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<tr>
<td>N(13)–O(15)</td>
<td>1.206(3)</td>
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<tr>
<td>N(13)–O(14)</td>
<td>1.231(3)</td>
</tr>
<tr>
<td>N(13′)–O(15′)</td>
<td>1.218(12)</td>
</tr>
<tr>
<td>N(13′)–O(14′)</td>
<td>1.223(12)</td>
</tr>
<tr>
<td>N(16)–O(17)</td>
<td>1.2162(19)</td>
</tr>
<tr>
<td>N(16)–O(18)</td>
<td>1.2215(19)</td>
</tr>
<tr>
<td>C(19)–C(20)</td>
<td>1.315(2)</td>
</tr>
<tr>
<td>S(21)–C(22)</td>
<td>1.7751(17)</td>
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<tr>
<td>C(22)–C(23)</td>
<td>1.378(3)</td>
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<tr>
<td>C(22)–C(27)</td>
<td>1.390(3)</td>
</tr>
<tr>
<td>C(23)–C(24)</td>
<td>1.383(3)</td>
</tr>
<tr>
<td>C(24)–C(25)</td>
<td>1.383(3)</td>
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<tr>
<td>C(25)–C(26)</td>
<td>1.365(3)</td>
</tr>
<tr>
<td>C(26)–C(27)</td>
<td>1.395(3)</td>
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<table>
<thead>
<tr>
<th>Angle</th>
<th>Angle [°]</th>
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</thead>
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<tr>
<td>C(2)–N(1)–C(7)</td>
<td>127.93(12)</td>
</tr>
<tr>
<td>O(2)–C(2)–N(1)</td>
<td>123.64(13)</td>
</tr>
<tr>
<td>O(2)–C(2)–C(3)</td>
<td>123.04(13)</td>
</tr>
<tr>
<td>N(1)–C(2)–C(3)</td>
<td>113.30(13)</td>
</tr>
<tr>
<td>C(2)–C(3)–C(4)</td>
<td>112.97(12)</td>
</tr>
<tr>
<td>C(19)–C(4)–C(3)</td>
<td>109.77(13)</td>
</tr>
</tbody>
</table>
\[ \begin{align*}
C(19) - C(4) - C(5) & = 112.54(13) \\
C(3) - C(4) - C(5) & = 113.22(12) \\
C(4) - C(5) - C(6) & = 110.63(16) \\
C(4) - C(5) - S(21) & = 114.31(12) \\
C(6) - C(5) - S(21) & = 107.74(18) \\
N(1) - C(7) - C(12) & = 121.63(12) \\
N(1) - C(7) - C(8) & = 121.78(12) \\
C(12) - C(7) - C(8) & = 116.59(12) \\
C(9) - C(8) - C(7) & = 122.07(13) \\
C(9) - C(8) - N(13) & = 114.55(15) \\
C(7) - C(8) - N(13) & = 123.33(15) \\
C(9) - C(8) - N(13') & = 118.0(5) \\
C(7) - C(8) - N(13') & = 119.2(5) \\
C(10) - C(9) - C(8) & = 118.38(13) \\
C(9) - C(10) - C(11) & = 122.03(13) \\
C(9) - C(10) - N(16) & = 119.11(13) \\
C(11) - C(10) - N(16) & = 118.85(14) \\
C(12) - C(11) - C(10) & = 119.16(14) \\
C(11) - C(12) - C(7) & = 121.76(13) \\
O(15) - N(13) - O(14) & = 121.3(2) \\
O(15) - N(13) - C(8) & = 118.6(2) \\
O(14) - N(13) - C(8) & = 120.1(2) \\
O(15') - N(13') - O(14') & = 124.1(13) \\
O(15') - N(13') - C(8) & = 117.4(9) \\
O(14') - N(13') - C(8) & = 117.5(10) \\
O(17) - N(16) - O(18) & = 123.44(14) \\
O(17) - N(16) - C(10) & = 118.27(14) \\
O(18) - N(16) - C(10) & = 118.27(14) \\
C(20) - C(19) - C(4) & = 124.11(17) \\
C(22) - S(21) - C(5) & = 104.50(8) \\
C(23) - C(22) - C(27) & = 119.05(17) \\
C(23) - C(22) - S(21) & = 118.00(13) \\
C(27) - C(22) - S(21) & = 122.86(17) \\
C(22) - C(23) - C(24) & = 120.81(18) \\
C(23) - C(24) - C(25) & = 120.3(2) \\
C(26) - C(25) - C(24) & = 119.12(18) \\
C(25) - C(26) - C(27) & = 121.21(18) \\
C(22) - C(27) - C(26) & = 119.5(2)
\end{align*} \]
4.3 Crystallographic data for syn-254a
Table 1. Crystal data and structure refinement for DC0808.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Identification code</td>
<td>DC0808</td>
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<tr>
<td>Empirical formula</td>
<td>C17 H25 N3 O2 S</td>
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<tr>
<td>Formula weight</td>
<td>335.46</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Diffractometer, wavelength</td>
<td>OD Xcalibur 3, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a = 5.48411(17) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 8.0007(2) Å</td>
<td>β = 90.353(3)°</td>
</tr>
<tr>
<td>c = 41.2338(12) Å</td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Volume, Z</td>
<td>1809.17(9) Å</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.232 Mg/m³</td>
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<tr>
<td>Absorption coefficient</td>
<td>0.192 mm⁻¹</td>
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<tr>
<td>F(000)</td>
<td>720</td>
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<td>Crystal colour / morphology</td>
<td>Colourless platy needles</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.45 x 0.15 x 0.02 mm³</td>
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<td>0 range for data collection</td>
<td>3.91 to 31.68°</td>
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<td>-8&lt;=h&lt;=7, -11&lt;=k&lt;=11, -59&lt;=l&lt;=59</td>
</tr>
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<td>Reflns collected / unique</td>
<td>22930 / 5800 [R(int) = 0.0666]</td>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Max. and min. transmission</td>
<td>1.000000 and 0.88234</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>5800 / 0 / 209</td>
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<td>Goodness-of-fit on F²</td>
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<td>Final R indices [F&gt;4σ(F)]</td>
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<td>R indices (all data)</td>
<td>R1 = 0.1493, wR2 = 0.2018</td>
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<td>Largest diff. peak, hole</td>
<td>0.450, -0.793 eÅ⁻³</td>
</tr>
<tr>
<td>Mean and maximum shift/error</td>
<td>0.000 and 0.000</td>
</tr>
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Table 2. Bond lengths [Å] and angles [°] for DC0808.

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<th>Bond</th>
<th>Length/Angle</th>
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<td>C(1)–C(2)</td>
<td>1.550(4)</td>
</tr>
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<td>C(1)–S(9)</td>
<td>1.772(3)</td>
</tr>
<tr>
<td>C(2)–C(19)</td>
<td>1.502(5)</td>
</tr>
<tr>
<td>C(2)–C(3)</td>
<td>1.531(5)</td>
</tr>
<tr>
<td>C(3)–N(21)</td>
<td>1.498(4)</td>
</tr>
<tr>
<td>C(3)–C(4)</td>
<td>1.524(5)</td>
</tr>
<tr>
<td>C(4)–C(5)</td>
<td>1.513(5)</td>
</tr>
<tr>
<td>C(5)–C(6)</td>
<td>1.539(5)</td>
</tr>
<tr>
<td>C(6)–C(7)</td>
<td>1.498(6)</td>
</tr>
<tr>
<td>C(7)–C(8)</td>
<td>1.515(6)</td>
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<tr>
<td>S(9)–O(11)</td>
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<tr>
<td>S(9)–O(10)</td>
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<tr>
<td>S(9)–C(12)</td>
<td>1.766(3)</td>
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<td>C(12)–C(13)</td>
<td>1.383(5)</td>
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<td>C(12)–C(17)</td>
<td>1.388(5)</td>
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<td>C(13)–C(14)</td>
<td>1.387(5)</td>
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<td>C(14)–C(15)</td>
<td>1.394(5)</td>
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<td>C(15)–C(16)</td>
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<td>C(15)–C(18)</td>
<td>1.518(5)</td>
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<tr>
<td>C(16)–C(17)</td>
<td>1.393(5)</td>
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<tr>
<td>C(19)–C(20)</td>
<td>1.308(6)</td>
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<td>N(21)–N(22)</td>
<td>1.225(5)</td>
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<td>N(22)–N(23)</td>
<td>1.128(5)</td>
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<td>C(2)–C(1)–S(9)</td>
<td>113.1(2)</td>
</tr>
<tr>
<td>C(19)–C(2)–C(3)</td>
<td>112.6(3)</td>
</tr>
<tr>
<td>C(19)–C(2)–C(1)</td>
<td>108.3(3)</td>
</tr>
<tr>
<td>C(3)–C(2)–C(1)</td>
<td>112.5(3)</td>
</tr>
<tr>
<td>N(21)–C(3)–C(4)</td>
<td>109.8(3)</td>
</tr>
<tr>
<td>N(21)–C(3)–C(2)</td>
<td>107.7(3)</td>
</tr>
<tr>
<td>C(4)–C(3)–C(2)</td>
<td>111.9(3)</td>
</tr>
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<td>C(5)–C(4)–C(3)</td>
<td>114.5(3)</td>
</tr>
<tr>
<td>C(4)–C(5)–C(6)</td>
<td>111.9(3)</td>
</tr>
<tr>
<td>C(7)–C(6)–C(5)</td>
<td>114.7(3)</td>
</tr>
<tr>
<td>C(6)–C(7)–C(8)</td>
<td>112.5(4)</td>
</tr>
<tr>
<td>O(11)–S(9)–O(10)</td>
<td>118.62(18)</td>
</tr>
<tr>
<td>O(11)–S(9)–C(12)</td>
<td>107.89(16)</td>
</tr>
<tr>
<td>O(10)–S(9)–C(12)</td>
<td>108.26(15)</td>
</tr>
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<td>O(11)–S(9)–C(1)</td>
<td>109.27(16)</td>
</tr>
</tbody>
</table>
Appendix

O(10)–S(9)–C(1) 107.75(17)
C(12)–S(9)–C(1) 104.11(16)
C(13)–C(12)–C(17) 121.4(3)
C(13)–C(12)–S(9) 119.8(3)
C(17)–C(12)–S(9) 118.8(3)
C(12)–C(13)–C(14) 119.0(3)
C(13)–C(14)–C(15) 121.0(3)
C(16)–C(15)–C(14) 118.6(3)
C(16)–C(15)–C(18) 120.5(3)
C(14)–C(15)–C(18) 120.9(3)
C(15)–C(16)–C(17) 121.6(3)
C(12)–C(17)–C(16) 118.4(3)
C(20)–C(19)–C(2) 124.3(4)
N(22)–N(21)–C(3) 115.1(3)
N(23)–N(22)–N(21) 173.6(4)
Chapter 5

Notes and References
The Cornforth model has also been modified to incorporate the Bürgi–Dunitz trajectory and torsional effects: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. J. Am. Chem. Soc. 1982, 104, 7162–7166.


For a study showing reactant conformation to be more important than hyperconjugative effects in carbene insertion reactions, see: Kaneno, D.; Tomoda, S. Org. Lett. 2003, 5, 2947–2949.

For recent examples see: (a) Jeon, S.-J.; Fisher, E. J.; Carroll, P. J.; Walsh, P. J. J. Am. Chem. Soc. 2006, 128, 9618–9619; (b) Nebot, J.; Figueras, S.; Romea, P.; Urpí, F.; Ji, Y. Tetrahedron 2006, 62, 11090–11099; (c) McNulty, J.; Nair, J. J.; Sliwinski,


34 Treatment of an analogous allylic methyl ether with OsO₄–TMEDA gave a 50:50 mixture of syn and anti diastereomers.

35 For a similar example of aminohydroxylation, see: Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. Org. Lett. 2004, 6, 2583–2585.


37 For a recent review on polypropionate synthesis, see: Jun, L.; Menche, D. Synthesis 2009, 2293–2315.


39 For recent examples, see: (a) Hanessian, S.; Reddy, G. J.; Chahal, N. Org. Lett. 2006, 8, 5477–5840; (b) Hanessian, S.; Chahal, N.; Giroux, S. J. Org. Chem. 2006,


43 For brevity, only the results of diphenylcuprate addition are shown. Addition of other diarylcuprates followed the same pattern.


45 For similar examples, see references 21a–c within reference 38a (this document).


Notes and References


93 (a) Pratt, L. M.; Bowles, S. A.; Courtney, S. F.; Hidden, C.; Lewis, C. N.; Martin, F. M.; Todd, R. S. *Synlett* 1998, 531–533; (b) Pratt, L. M.; Beckett, R. P.; Bellamy, C. L.; Corkill, D. J.; Cossins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.;


104 For a conflicting example in which Cieplak effects are dominant, see: Yadav, V. K.; Jeyaraj, D. A.; Parvez, M.; Yamdagni, R. *J. Org. Chem.* **1999**, *64*, 2928–2932.


We thank Dr. A. J. P. White, Imperial College London for X-ray crystallography.


Notes and References


171. There is a single report of a reaction where a ruthenium catalyst establishes both the vinylic and allylic portions of the ketene acetal _via_ concomitant olefin isomerisation: Schmidt, B. _Synlett_ **2004**, 1541–1544.


181 The value for the *anti* cyclohexyl isomer is still most likely consistent within experimental error and suggests that the *anti* isomer of the substrate reacted completely.


183 Johns, S. *Ph.D Thesis*, Imperial College London, **2009**.


185 Lewis, S. E. *Ph.D Thesis*, University of London, **2006**.


191 Hyperconjugative effects stabilise the olefin by around 6 kcal/mol for each additional alkyl substituent, although this is reduced when taking into account hybridization, π polarization and other effects favouring the anti-Saytseff product: (a) Braida, B.; Prana, V.; Hiberty, P. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5724; (b) Webber, M. J.; Spivey, A. C. *Nature Chemistry*, **2009**, *1*, 435.


