A Cycloaddition Route to

Pyrrolidines

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by

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Declaration

I declare that the work presented in this thesis is the result of my own investigations, and where the work of others is cited, it is fully acknowledged. The material embodied in the thesis has not been submitted, nor is currently being submitted for any other degree.

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Xiaohui Zhang

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Prof. R. C. F. Jones and Dr. Jim Iley
Supervisor
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Abstract

The work presented in this thesis focuses on the development of base-free 1,3-dipolar cycloaddition reactions of azomethine ylides to produce homochiral pyrrolidines. Previous work within our group has shown the suitability of using 1-benzyl-4,5-dihydroimidazole as the starting point for the generation of an azomethine ylide that undergoes 1,3-dipolar cycloadditions with a range of dipolarophiles in a highly regio- and stereoselective fashion.

1-Benzyl-2-imidazoline reacts with ethyl diazoacetate in the presence of Cu(acac)$_2$ to form an azomethine ylide that reacts with dimethyl fumarate to yield a hexahydropyrrolo[1,2-a] imidazole. Similarly, the 2-imidazoline reacts with diazoacetate and fumaronitrile in the presence of copper(II) triflate to form analogous bicyclic systems. Other Cu(II) salts were found to be less effective catalysts, as was the Rh(II) acetate dimer.

In the course of the above reactions, we isolated two diastereomeric products that proved to be 1:2 adducts between the dihydroimidazole and the electron deficient alkene. These compounds also contained the hexahydropyrrolo[1,2-a] imidazole core and their formation can be rationalised by (i) a Michael-type addition of the dihydroimidazole onto one molecule of the electron-deficient alkene to form a 1,3-zwitterion, (ii) a 1,2-proton shift within the zwitterion to form an azomethine ylide, and (iii) 1,3-dipolar cycloaddition of the ylide onto a second alkene molecule acting as a dipolarophile. Other electron-deficient alkenes, e.g. maleate, maleimides and fumaronitrile also undergo this reaction but ethyl cinnamate and p-nitrostyrene do not.

The reaction with a mixture of two alkenes allows 1:1:1 products to be isolated. In these situations maleimides act as the Michael acceptor and the second alkene as the
dipolarophile. In this way we found the order of reactivity to be maleimide > fumarate/maleate ester > fumaronitrile. The stereochemistry of the four new chiral centres was elucidated by X-ray crystallography and n.O.e. difference spectroscopy. The formation of the major diastereoisomer can be rationalised by a transition-state model in which (i) the α-carbonyl of the ylide is syn to the 2-H of the dihydroimidazole, (ii) the dipolarophile approaches in an endo fashion. Formation of the minor diastereomer may involve a subsequent epimerisation at the C7a position of the fused system or endo mode of attack on the alternative ylide rotamer. Incorporation of a chiral centre into the imidazoline through the use of a phenyl substituent affords complete facial selectivity for the 1,3-dipolar cycloaddition reaction.

Some electron-deficient systems that are unable to participate in the 1,2-proton shift (e.g. DMAD, β-nitrostyrene) form 1:2 adducts in which the product contains a 5,6-fused system. These products can be understood as arising from two sequential Michael additions to form a 1,5-zwitterion that is able to ring close onto the imidazoline iminium ion.
**Abbreviations used in the thesis**

The following symbols and abbreviations are used in this text:

<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu&lt;sup&gt;l&lt;/sup&gt;</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>Cl MS</td>
<td>chemical ionisation mass spectrometry</td>
</tr>
<tr>
<td>COSY</td>
<td>two-dimensional correlated spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>days</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>1,3-DC</td>
<td>1,3-dipolar cycloaddition</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI MS</td>
<td>electron impact mass spectrometry</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>Equiv.</td>
<td>molar equivalents</td>
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<tr>
<td>FMO</td>
<td>frontier molecular orbital</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
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<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MH⁺</td>
<td>protonated molecular ion</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
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<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>n.O.e.</td>
<td>nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Pr'</td>
<td>isopropyl</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>4-toluenesulfonic acid</td>
</tr>
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Chapter 1

Introduction
Introduction

1.1 General introduction

Heterocyclic compounds are of particular interest in medicinal chemistry, and this has catalysed the discovery and development of much new heterocyclic chemistry. Molecules that are based on rings containing nitrogen atoms, whether occurring naturally or made synthetically, are widely known for their biological activity. For example, derivatives of the purines 1.1 together with pyrimidines 1.2 are constituents bases of DNA and RNA and consequently of fundamental importance in life processes. Moreover, there is a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin G 1.3, but the large majority are synthetic heterocycles which have found widespread use, for example as anticancer agents (Levamisole 1.4) and analgesics (Figure 1.1).

![Chemical structures](image)
The occurrence of heterocyclic compounds in Nature is widespread, and the use of natural and synthetic heterocyclic compounds in many commercially important spheres is enormous. For example, pyrrolidines are important structural units that are found in many naturally occurring alkaloids, such as hygrine 1.5, nicotine 1.6, tropine 1.7 and cocaine 1.8, which show strong biological activity \[2-4\]. Other compounds shown in Figure 1.2 having this moiety belong to the amino acid kingdom, such as proline 1.9 or kainic acid 1.10. In addition, prolinol derivatives, such as SAMP 1.11 and its enantiomer RAMP, have found important applications as chiral auxiliaries, mainly in stereoselective deprotonation of hydrazones \[5\]. Application of heterocyclic compounds in these, and many other, ways and their appeal as materials in applied chemistry and in more fundamental theoretical studies, proceeds from their potential complexity which ensures a virtually limitless series of structurally novel compounds \[6\].

![Figure 1.2](image-url)
Hence, the efficient assembly of heterocyclic rings constitutes a chief objective for heterocyclic chemists. An important sub-goal of this task is the construction of heterocycles as single enantiomers (in other words, these should be "homochiral") through asymmetric synthesis.

The enantioselective generation of the bonds of nitrogen heterocyclic rings in as few steps or operations as possible is an ongoing challenge for the fine chemicals industry. The best way to achieve this goal is by bringing the components together in a highly organised way. Cycloaddition reactions minimise the number of separate bond-forming steps by generating more than one bond simultaneously, and 1,3-dipolar cycloadditions are an obvious way to apply this strategy to heterocycles.

1.2 The 1,3-dipolar cycloaddition reaction

The addition of a 1,3-dipole to an alkene for the construction of a five-membered ring in a convergent and stereocontrolled manner is a classic reaction in organic chemistry. 1,3-Dipolar cycloaddition reactions are becoming increasingly important and popular in academia and industry.

1.2.1 The history of 1,3-dipolar cycloaddition

The history of 1,3-dipoles goes back to 1883 when, at the age 25, Theodor Curtius in Munich discovered diazoacetic ester, the first aliphatic diazo compound. In 1888, his younger colleague, Eduard Buchner on Curtius’ suggestion studied the reaction of ethyl diazoacetate with unsaturated carboxylic esters. This was the first report of 1,3-dipolar cycloaddition. Five years later, Beckmann, Werner and Buss discovered nitrones and
nitrile oxides respectively \cite{9,10}. The synthetic value of cycloadditions had not been
c recognised until the Diels-Alder reaction was discovered in 1928 \cite{11}. The general
application of 1,3-dipoles in organic chemistry was first established by systematic studies
by Huisgen in the 1960s \cite{12}. Since Huisgen's definition of the general concept of both 1,3-
dipoles and 1,3-dipolar cycloaddition reactions \cite{13,14}, this class of reaction has undergone
impressive development \cite{12}. Significantly, 1,3-dipolar cycloadditions have exceeded the
traditional role of entry into 5-membered heterocycles and thus have acquired a prominent
place in the synthetic strategy towards a variety of targets, including natural products such
as sugars and alkaloids \cite{15,16}.

In recent years, the studies of 1,3-dipolar cycloaddition have developed a new aspect,
namely the control of the stereochemistry. Dipolar cycloaddition has proved to be amongst
the most important and versatile methods for the construction of five-membered
heterocyclic rings with a high degree of regio- and stereochemical control. The reaction
requires two components: a three-atom fragment, the 1,3-dipole a-b-c; and a multiply
bonded two-atom fragment, the dipolarophile d-e (Scheme 1.1) \cite{13,14}.

![Scheme 1.1](image-url)
1.2.2 The 1,3-dipole

The 1,3-dipole is a three-atom \( a-b-c \) structure that has zwitterionic resonance forms. One of these has the formal charges at the termini \(^{12, 17, 18}\). In general, 1,3-dipoles can be divided into two types. One of these contains a single bond between atoms \( a \) and \( b \) in the sextet resonance form (and thus a double bond in the octet form); and another contains a double bond between atoms \( a \) and \( b \) in the sextet form (and thus a triple bond in the octet form), shown in Figure 1.3.

Firstly, the allyl anion type, has an arrangement of three atoms with an allyl anion-like \( \pi \) system, characterized by four electrons in three parallel atomic \( p_z \) orbitals-perpendicular to the plane of the dipole and the 1,3-dipole is bent. The 1,3-dipole can be drawn in one of two canonical forms, the sextet and the octet, with these names arising from the number of electrons in the outer shell of atom \( a \) in each form. It should be noted that it is only in the sextet form that the 1,3-nature of the dipole is revealed, however, it is normally the octet form that is used to represent the dipole in reaction schemes and mechanisms.

![Type 1 and Type 2](image)

**Figure 1.3**

Secondly, the propargyl/allenyl anion type, has an additional \( \pi \) orbital system located in a plane orthogonal to the allenyl anion-type molecular orbital (MO); the former orbital is therefore not directly involved in the resonance structures and reactions of the dipole. The
extra double bond means that octet form contains a triple bond and inevitably results in a linear structure for the dipole compared with the bent allyl anion type. The central atom b is limited to an atom having a lone pair, and an extra allenyl resonance form is possible, as shown in Figure 1.4.

![Figure 1.4](image_url)

The elements a, b, c of the 1,3-dipoles mainly come from main groups IV, V and VI, and are largely restricted to the permutations of nitrogen, carbon and oxygen. Sulfur and phosphorus also are found in 1,3-dipoles, but only a few asymmetric reactions involving these 1,3-dipoles have been reported.

The choice of atoms, within the first period, for a, b and c is as follows:

Atom a: **type 1**- carbon or nitrogen or oxygen

**type 2**- carbon or nitrogen

Atom b: **type 1**- nitrogen or oxygen

**type 2**- nitrogen only

Atom c: **types 1 and 2**- carbon, nitrogen or oxygen

Within these constraints, 12 dipoles of the allyl anion type and 6 dipoles of the propargy/allenyl anion type were proposed by Huisgen, although not all are accessible in practice. The classification of 1,3-dipoles is shown Figure 1.5 and Figure 1.6.
Allyl-type 1,3-dipoles (type 1)

Azomethine ylides

Azomethine imines

Azimines

Azoxy compounds

Nitro compounds

Carbonyl ylides

Carbonyl imines

Carbonyl oxides

Nitrosimines

Nitrosoxides

Nitrones

Ozone

Figure 1.5
1.2.3 The dipolarophile

As outlined in Section 1.2.1, the dipolarophile is the two-atom multiply bonded component of the cycloaddition reaction, and there is a large degree of flexibility in the choice of such a component. Perhaps the most obvious choice for a dipolarophile is an alkene or an alkyne, though there is no reason why either atom has to be carbon. This, then, allows for the possible use of carbonyls, thiocarbonyls, imines, nitriles, nitroso compounds, diazo compounds and sulfinyl compounds amongst others [6].

Given the variety of 1,3-dipoles mentioned in Section 1.2.2, together with the numerous possible dipolarophiles outlined above, it is easy to imagine the huge scope of this reaction,
although this is not to suggest that every possible dipolarophile will react with every possible 1,3-dipole.

1.2.4 Proposed mechanism

For the 1,3-dipolar cycloaddition reaction, it is very important to suggest a possible mechanism in order to understand its regio- and stereo-chemistry. However, in the 1960s, Huisgen and Firestone separately proposed two different mechanisms. Huisgen and co-workers, after studies on kinetic measurements, stereochemical results, and the effects of solvent and substituents, developed a detailed rationale for a concerted mechanism\cite{14,19,20}. They thought that the 4-electron system of the 1,3-dipole interacts with the π-bond of the dipolarophile in a concerted fashion with the proposed model for the transition state shown in Figure 1.7. The nature of the orbitals depicted will be explained in the next section.

![Figure 1.7](image)

Firestone, however, considered the 1,3-dipolar cycloaddition reaction to proceed via a singlet diradical intermediate\cite{21-24}, as shown in Figure 1.8.
Their arguments were both based on a series of experimental results. Although their mechanisms were subject to a great deal of debate, the stereospecificity of 1,3-dipolar cycloaddition reactions agreed with the concerted mechanism: exclusively trans isoxazoline 1.14 was formed in 98% yield by the 1,3-dipolar cycloaddition reaction of benzonitrile oxide 1.12 with trans-dideuterated ethylene 1.13\textsuperscript{[25]}, as shown in Scheme 1.2. A diradical intermediate would allow for a 180° rotation of the terminal bond and would thus be expected to yield a mixture of the cis and trans isomers.

Later, Huisgen \textit{et al.} showed that the 1,3-dipolar cycloaddition reaction can in some cases proceed by a stepwise sequence involving an intermediate, and in these cases the stereospecificity of the reaction may be destroyed. Taken together with the work of Houk, who showed that analysis of the concerted mechanism in terms of frontier molecular orbital theory could rationalise the regioselectivity of the reaction, this ultimately settled the dispute in favour of the concerted mechanism\textsuperscript{[26]}. 

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1.2.5 Frontier molecular orbital theory (FMO)

In the 1960s, Woodward and Hoffman established the famous frontier molecular orbital theory (FMO) \cite{27, 28}, which proposed *a majority of chemical reactions should take place at the position of, and in the direction of, maximum overlap of the HOMO (highest occupied molecular orbital) and the LUMO (lowest unoccupied molecular orbital) of the reactant species* \cite{29}. Later, Fukui suggested that maximum orbital overlap takes place in orbitals which are separated by the narrowest energy gap; the narrower the gap the faster the reaction \cite{29}. The mechanistic scheme of a concerted 1,3-dipolar cycloaddition involving the allyl anion system as described in 1963 fits precisely the selection rules for concerted cycloadditions according to Woodward and Hoffman. 1,3-Dipolar cycloaddition reactions involve 4 electrons from the dipole and 2 electrons from the alkene. If they take place by a concerted mechanism it is thermally allowed with the description [4+2] according to the Woodward-Hoffman rules. This means that the three \( p_z \) orbitals of 1,3-dipole and the two \( p_z \) orbitals of the alkene combine suprafacially.

The transition state (TS) of the concerted 1,3-dipolar cycloaddition reaction is thus controlled by the FMO of the substrates. The LUMO_dipole can interact with the HOMO_alkene or HOMO_dipole with LUMO_alkene. Three types of 1,3-dipolar cycloaddition reactions were proposed by Sustman according to the relative FMO energies between the dipole and the alkene as follows: (Figure 1.9) \cite{30-33}.

**Type I**, controlled by a HOMO_dipole-LUMO_alkene interaction

including azomethine ylide, azomethine imines

**Type II**, interaction of both HOMO_dipole-LUMO_alkene and LUMO_dipole-HOMO_alkene

including nitrones, nitrile oxides

**Type III**, controlled by a LUMO_dipole-HOMO_alkene interaction

Including ozone, nitrile oxides
Although Sustmann classified 1,3-dipolar cycloaddition reactions into three types, there is some confusion about different 1,3-dipoles, especially since the introduction of electron-donating or electron-withdrawing substituents on the dipole or the alkene can alter the relative FMO energies and the effect on the 1,3-dipolar cycloaddition reaction type can be dramatic. For example, the 1,3-dipolar cycloaddition reaction of A-methyl-C-phenylnitrone with methyl acrylate is controlled by the HOMO\textsubscript{dipole}-LUMO\textsubscript{alkene} interaction, whereas the 1,3-dipolar cycloaddition reaction of the same nitrone with methyl vinyl ether is controlled by LUMO\textsubscript{dipole}-HOMO\textsubscript{alkene} interaction.

1.2.6 The stereochemistry of 1,3-dipolar cycloaddition reactions

In the course of 1,3-dipolar cycloaddition reactions, the p-orbitals at the end of a 1,3-dipole form σ-bonds to the p-orbitals at the ends of the dipolarophile. The p-orbitals must therefore approach each other head on, leading to cycloaddition with the new σ-bonds
forming between C-1 and C-1’ and between C-3 and C-2’. The high regio- and stereoselectivity are tightly controlled by the highly ordered transition state (TS), shown in Figure 1.10[34].

![Figure 1.10](image)

Reactions where the two new bonds are formed on the same face of one reactant are called suprafacial on that particular reactant, (Figure 1.10a). In contrast, the opposite of suprafacial is called antarafacial, where attack takes place with one bond forming to one face but the other bond forming to the other face of a reactant, (Figure 1.10b). Such reactions are rare. Theoretical and experimental results suggested that the formation of major products occurs by the suprafacial approach[34], and antarafacial transition states are difficult to achieve geometrically. Thus, suprafacial transition states are more favourable for 1,3-dipolar cycloaddition reactions since orbital overlap is maximised.

For a suprafacial transition state, we must consider two models of approach for a dipolarophile carrying a substituent. First, an endo transition state is formed when the dipolarophile approaches the 1,3-dipole with its substituent directly under the plane of the dipole (Figure 1.11). This transition state may lie on the most energetically favourable pathway if it involves a secondary non-covalent orbital interaction between the 1,3-dipole
and the substituent $Z$ that provides extra stabilisation in the transition state. Second, when $Z$ is bulky, steric hindrance constitutes an obstacle to bond formation, and the dipolarophile may prefer to approach the 1,3-dipole with its substituent pointing away from the TS; this is called the *exo* transition state. *Exo* and *endo* transition states lead to products that are diastereomeric, but for steric reasons the *exo* approach can be expected to lead to the major isomer, and in many cases it does.

![Figure 1.11](image)

Figure 1.11

In addition to *endo/exo* selectivity, it is possible to control the face of attack on the dipole, by introducing a substituent $R$ onto the 1,3-dipole to block the approach of the dipolarophile from one face, only allowing approach from the non-hindered face. Figure 1.12 illustrates the *endo* upper face approach (a) to such a dipole, in preference to the hindered approach (b) of the dipolarophile to the lower face of the dipole. We will return to this point when discussing some of the results later in this thesis.
However, the stereochemistry of 1,3-dipolar cycloaddition is not so clear. Often the selectivity is low. The *endo* model is sometimes favoured, and sometimes it is the *exo*, depending on the dipole, the dipolarophile and their substituents. For example, 1,3-dipolar cycloaddition of an azomethine ylide with dimethyl maleate gives largely (3:1) the *endo* adduct 1.16, whereas 1,3-dipolar cycloaddition of a nitrone with a cyclic vinyl ether gives largely (92:3) the *exo* adduct 1.19, shown in Scheme 1.3. It is also not clear in every case what is the geometry of the dipole, or whether the results are kinetically or thermodynamically controlled \[^{[35]}\].
1.1.5

Scheme 1.3

1.2.7 The regiochemistry of 1,3-dipolar cycloaddition reactions

FMO theory has successfully explained the regiochemistry of 1,3-dipolar cycloaddition (1,3-DC) reactions according to the suggestions of Sustmann, Houk and Bastide. Sustmann classified 1,3-DC reactions into three types, introduced previously in Figure 1.10. The key to the explanation of regioselectivity in 1,3-DC reactions is the unequal magnitudes of the terminal coefficients in the HO and LU $\pi$ orbitals of the dipoles. The reactions take place in the direction that allows maximal FO overlapping between orbitals, hence the significance of the FO coefficients and their closeness in energy.
Regioisomeric transition state A (Figure 1.13) is more stable than B because of its more efficient overlap. The favoured regioisomer will be the one formed through the transition state in which atoms bond where orbitals with large coefficients overlap.

The ratio of regioisomers mirrors the ratio of the respective rate constants for the two orientations of cycloaddition, so the regioselectivity is associated with this relative reactivity. To explain the regioselectivity in 1,3-DC reaction, the overlapping of HOMO(dipole) and LUMO(dipolarophile), or LUMO(dipole) and HOMO(dipolarophile), must be assessed to determine which type of orbital interaction is dominant.

Having determined which interaction is of primary importance, focus shifts to the coefficients of the relevant orbital. Consider a reaction that is dipole-HOMO controlled, i.e. type I. The relevant orbital coefficients are then those of the dipole-HOMO and dipolarophile-LUMO (Figure 1.13). The regioselectivity of the reaction is then expected to be that which maximises the size of the wave functions of the overlapping orbitals during bond formation. Maximum overlap of the relevant molecular orbitals and matching of the magnitude of the orbital coefficients, i.e. large (dipole) with large (dipoarophile) and small (dipole) with small (dipolarophile), is achieved in example A (Figure 1.13) giving rise to 4-substituted adduct (Figure 1.14). In the alternative case B, however, despite the fact that the molecular orbitals are appropriately phased for overlap, the magnitudes of the orbital
coefficients involved do not match and this represents the formation of less favourable 5-substituted regioisomer (Figure 1.14), which would constitute a minor product.

![Diagram of 4-substituted and 5-substituted adducts]

Figure 1.14

1.3 Azomethine Ylides

According to his definition in the framework of 1,3-dipoles \(^{12}\), Huisgen assigned azomethine ylides to the class of azomethinium betaines without a double bond in the sextet structure but with internal octet stabilization. This class has been referred to as the allyl type (see earlier) to distinguish members of the class from those with a double bond in the sextet structure and with internal octet stabilization, which are now described as the
propargyl-allenyl type. There are acyclic and cyclic examples of azomethine ylides, e.g. 

Figure 1.15.

1.3.1 The Generation of Azomethine Ylides

It has been mentioned that the 1,3-dipolar cycloaddition reaction is of great synthetic use for five-membered ring heterocycles, such as pyrrolidines. Pyrrolidines are an important heterocyclic unit and have been assembled in the preparation of a variety of alkaloids. If one wishes to prepare pyrrolidines, one of the important methods available is 1,3-dipolar cycloaddition of azomethine ylides with alkenes (Scheme 1.4). Azomethine ylides are unstable species which have to be prepared in situ in low concentration and trapped directly by added dipolarophiles\(^{[12]}\).
Although 1,3-dipolar cycloadditions of azomethine ylides represent one of the most powerful methods for pyrrolidine synthesis, no general methodology for generation of differently substituted dipoles exists; development of new methods is therefore attractive. Several standard methods for generating azomethine ylides involve thermolysis or photolysis of readily prepared aziridines \cite{36-38}, the proton abstraction from imine derivatives of \( \alpha \)-amino acids \cite{39,40}, and the desilylation \cite{41} or the dehydrohalogenation \cite{13,42} of iminium salts, and so on. Furthermore, non-stabilized non-substituted azomethine ylides may be obtained, whereas stable azomethine ylides have also been obtained. Some of these methods will be discussed in the following section according to the precursor functional group.

\subsection*{1.3.1.1 The thermal or photolytic ring opening of aziridines}

In 1967, Huisgen and co-workers reported the electrocyclic ring-opening by thermolysis and photolysis of the stereoisomeric aziridines, \textit{cis-1.21} and \textit{trans-1.21}, generating stereochemically distinct azomethine ylides, \textit{trans-1.22} and \textit{cis-1.22}, which were then trapped \textit{in situ} by dimethyl acetylenedicarboxylate (DMAD) as dipolarophile. Both \textit{trans-1.21} and \textit{cis-1.21} gave the same pyrrole after chloranil dehydrogenation in 84% and 81% yield, respectively \cite{43}.
Thermal conrotatory ring-opening of *cis*-1.21 afforded *trans*-1.22 whereas thermal conrotatory ring-opening of *trans*-1.21 affords *cis*-1.22 (Scheme 1.5). Disrotatory photolytic ring opening of *cis*-1.21 generated *cis*-1.22 whereas disrotatory photolytic ring-opening of *trans*-1.21 generated *trans*-1.22. Although the yields of the direct disrotatory photolysis were not as high as those obtained from thermolysis, a very reasonable yield (69%) of these adducts was obtained by this protocol. A limitation of this methodology is that ring-opening of aziridines only works well when the substituent groups are capable of stabilising the dipole centres, failing completely when simple alkyl substituents are used.

![Scheme 1.5](image-url)
1.3.1.2 Imine Route

a) Desilylation of iminum salts

Vedejs and co-worker reported a method for the generation of unstabilised azomethine ylides by fluoride-induced desilylation of $N$-(trimethylsilylmethyl)iminium salts $^{[44, 45]}$. Alkylation of an imine with trimethylsilylmethyl triflate afforded the required salts, or alkylation of imines already containing an $\alpha$-silyl group with simple alkyl triflates could also be used, as shown in Scheme 1.6.

\[ \text{Scheme 1.6} \]

\[ \text{1.23} \]

\[ \text{1.24} \]

b) Decarboxylation from imine derivatives of $\alpha$-amino acids

In a series of papers Grigg et al. $^{[46-48]}$ have reported that all classes of $\alpha$-amino acid (except tertiary $\alpha$-amino acids) react with a wide range of carbonyl compounds (aliphatic and aromatic aldehydes and ketones) to result in imines (Schiff bases). For example, treatment of the 2,2'-bipyridyl ketone 1.27 with $\alpha$-amino acids 1.28 give imines 1.29, which generate azomethine ylides 1.30 by decarboxylation, as shown in Scheme 1.7.
Tsuge and co-workers extended this approach to N-substituted acyclic and cyclic amino acids, 1.31 and 1.34 respectively, which afford the acyclic 1.33 and cyclic 1.36 azomethine ylides \cite{49, 50}, shown in Scheme 1.8.
c) 1,2-Prototropy

Grigg et al. reported a method involving isomerisation of an imine derivative of an \( \alpha \)-amino ester containing an enolisable hydrogen, to generate an azomethine ylide (Scheme 1.9) which then underwent 1,3-dipolar cycloaddition with the appropriate dipolarophile\(^{[51]}\).

\[ \text{Scheme 1.9} \]

This approach has also been extended to the formation of azomethine ylides catalysed by both Brønsted acids and Lewis acids\(^{[52]}\), and metal salts in combination with a tertiary amine base, allowing the reaction to occur at room temperature\(^{[53, 54]}\) (Scheme 1.10).
The metallo-azomethine ylides have been found to be substantially more reactive than the corresponding NH-azomethine ylides, although the use of titanium salts as Lewis acids leads to reversal of regiochemistry in the cycloaddition reaction \([54]\).

d) Deprotonation of Iminium ion salts

Huisgen reported this method involving the deprotonation of \(N\)-alkyl salts of aromatic six-membered nitrogen heterocyclic compounds, to yield the azomethine ylides which retain the ability to undergo addition even though the \(C=N\) bond is an integral part of the heteroaromatic ring \([42]\), as shown in Scheme 1.11.

Other methods, such as reduction of oxazolium salts \([55]\), deprotonation-deoxygenation of amine \(N\)-oxides \([56]\) and dehydrogenation \([57]\), will not be discussed here. However, the generation of azomethine ylides by decomposition of diazo compounds in the presence of imines with a transition metal catalyst will be discussed in a later section.
1.4 Asymmetric 1,3-dipolar cycloaddition

1.4.1 Chiral Azomethine Ylides

The first diastereofacially selective 1,3-dipolar cycloaddition reaction of chiral azomethine ylides with alkenes leading to optically active products was reported by Padwa in 1985 [58]. The 1,3-dipolar cycloaddition reaction of the azomethine ylide 1.48 with 1-nitro-2-[3,4-(methylenedioxy)phenyl]ethane led to the formation of the product 1.49a, having 20% de, while 1.49b was obtained with a de of 60% [58] (Scheme 1.12).

![Scheme 1.12](image)

In explanation of these results, Padwa and co-workers suggested two different conformations of the azomethine ylide, 1.50A and 1.50B, each of which has one or other of the 'large' group perpendicular to the plane of dipole. They argued that approach of the alkene toward 1.50A is to the face of the azomethine ylide anti to the phenyl group, while anti attack in 1.50B results in an approach of the alkene to the opposite face of dipole [58], as shown in Figure 1.16, and production of the alternative diastereoisomer. It was assumed that the large group occupies the perpendicular position, but that in these cases the relatively small difference in size between the groups resulted in small d.e.s. It should be
noted that this argument assumes approach of the alkene such that the NO$_2$ group is *exo*, and the aryl group is *endo* to the dipole.

![Diagram](image)

**Figure 1.16**

Houk and co-workers$^{[59-61]}$ and Anh and Eisenstein$^{[62]}$ have reached the same conclusion where there was only a small difference in either the size or the electronic make-up of the groups attached to the chiral centre substituted on the nitrogen atom of the ylide, and the diastereomeric excess was small$^{[58]}$.

Husson and co-worker have published a series of papers and reported a new methodology for the facile formation of a chiral azomethine ylide 1.53 from $N$-cyanomethyl-4-phenyloxazolidine 1.51a and $N$-methoxycarbonylmethyl-4-phenyloxazolidine 1.51b$^{[63-65]}$ on O-silylation (Scheme 1.13).
In reactions with N-phenylmaleimide as dipolarophile, 1.51a gave four cycloadducts 1.54 (ratio~44:32:16:8), in 41% yield, while 1.51b formed two isomers (ratio~1:1) in 85% yield. It is very interesting that when the phenyl group was moved from C-4 to C-5, a significant improvement in diastereoselectivity in the 1,3-dipolar cycloaddition reaction was observed, as both the exo and endo products 1.54 are formed with excellent de’s > 95% [63].

This low diastereofacial selectivity for the dipolarophile was not improved by modification of the C-4 or C-5 substituent on the oxazolidine. Later Husson proposed the introduction of a chiral group in the ester moiety, and then only the exo product was obtained with a de > 95% [64].

Recently, Harwood and co-workers developed a new method to form a chiral azomethine ylide from an α-amino acid precursor by the use of a chiral template, shown in principle in Scheme 1.14 [66-75].
In the Harwood study, the chiral azomethine ylide precursor was constructed by reaction of (R)- or (S)-phenylglycinol with phenyl bromoacetate using the method of Dellaria (Scheme 1.15) \(^{[73]}\). Upon reaction with an appropriate aldehyde such as methanal followed by loss of water, a chiral azomethine ylide was formed, which then reacted with an alkene having electron-withdrawing substituents to give the 1,3-dipolar cycloaddition reaction product. Subsequent removal of the chiral template permits the generation of proline derivatives with high enantiometric purity.
This principle had been developed previously by Williams \cite{76,77} who reported that 5(R),6(S)-diphenylmorpholinone can act as an azomethine ylide precursor which undergoes stereocontrolled cycloaddition, and by Caplar \cite{78} who demonstrated that hydrogenation of the cyclic condensation products derived from α-bromoacetophenone (1.63) and α-amino acids (1.64) occurs stereospecifically, forming homochiral 3-substituted-5-phenylmorpholinones (1.66) with total 1,3-transfer of chirality from the α-amino centre to the newly formed benzylic centre (Scheme 1.16).

In the Harwood model study, the desired chiral azomethine ylide was trapped \textit{in situ} with a variety of dipolarophiles. For example, the \textit{endo} products 1.70 and \textit{exo} products 1.71 were formed by trapping of the chiral azomethine ylide 1.69 with maleimides, with the former product in excess (Scheme 1.17) \cite{74}. When maleic anhydride was used as the alkene, the \textit{endo} cycloadduct was generated as sole product.
Thermolysis or photolysis of aziridines is also a means of generating chiral azomethine ylides \[79-84\]. Garner and co-workers have published a series of papers showing that thermolysis of aziridines 1.72 produced the corresponding \(N\)-substituted azomethine ylides 1.73 which underwent 1,3-dipolar cycloadditions to electron-deficient alkenes (Scheme 1.18).
Garner also reported that photolysis of aziridine 1.76 produced the azomethine ylide 1.77, which underwent clean 1,3-dipolar cycloaddition with dipolarophiles carrying electron-withdrawing groups. (Scheme 1.19) \[^{[80,82-84]}\]

Grisoni and co-workers developed other chiral azomethine ylides, derived from 2-(tert-butyl)-3-imidazolidin-4-one 1.79 with paraformaldehyde in refluxing toluene. The azomethine ylides 1.80 were trapped with a series of dipolarophiles leading to various cycloadducts, with moderate diastereoselectivity, up to 60% (Scheme 1.20) \[^{[85]}\].
Azomethine ylides 1.85 also can be generated from tertiary amine N-oxides 1.83 by reaction with LDA (Scheme 1.21). Several different azomethine ylides 1.85 substituted with chiral (R*) groups at nitrogen, were prepared in this manner and used in 1,3-dipolar cycloaddition reactions with various alkenes, but the de’s obtained in the products 1.86 were low\(^{[86]}\).

A recent method for the synthesis of homochiral heterocycles has been developed by our group which employs both enantiomers of a chiral imidazoline 1.87 for the assembly of pyrrolidines 1.90 by azomethine ylide cycloaddition (Scheme 1.22)\(^{[87,88]}\).
Scheme 1.22

The imidazoline 1.87 (one enantiomer shown; both readily available) is treated first with an alkylating agent then with a dipolarophile, followed by addition of a base. The ‘one-pot’ reaction cascade involves quaternisation of the heterocycle, deprotonation \textit{in situ} of the so-formed salt to give an ylide 1.88, and cycloaddition to the dipolarophile. Three of the five bonds of the new five-membered ring are formed in the cascade. Excellent stereochemical control derives from the restricted conformational mobility of the chiral template relative to the dipole. Removal of the templating atoms from the cycloadducts 1.89 by successive reductions (without isolation of intermediates) reveals new optically active pyrrolidines 1.90.
1.4.2 Chiral dipolarophiles

1.4.2.1 Reactions with Metallo-azomethine Ylides

Grigg and co-workers have published a series of papers to report the 1,3-dipolar cycloaddition reactions of various azomethine ylides with chiral dipolarophiles \(^{[90-98]}\). These cycloadditions are catalysed by a wide range of metal ions, such as Ag(I), Li(I), Zn(I), Mg(I), Co(I), Mn(I), and Ti(I) and in some cases proceed by the metallo-dipole (metalloazomethine ylide) \(^{1.92}\). This can react with an electron-deficient dipolarophile, for example menthyl acrylate \(^{1.93}\), to give a good yields with high \textit{endo} and diastereofacial selectivity and de's up to 95\% \(^{[94]}\) (Scheme 1.23).

![Scheme 1.23](image)

Replacing methyl acrylate by menthyl acrylate as dipolarophile led to noticeably slower reactions with azomethine ylides, and the slower reactions were associated with significantly reduced yields (33-35\% with menthyl acrylate) due to a slow metal ion-induced hydrolysis of imine by traces of water \(^{[92]}\). To overcome this, a base such as DBU or Et\(_3\)N, was added to increase the rate of cycloaddition, the stronger the base the faster the reactions \(^{[91, 92]}\). X-Ray results confirmed the stereochemistry of the 1,3-dipolar
cycloadducts of these metalloazomethine ylides which are generated from an imine with 
LiBr or AgOAc. It has been found by X-ray analysis of a series of representative 
cycloadducts that the established absolute configuration of pyrrolidine stereocentres is 
independent of the metal salt and the size of the pyrrolidine C-2 substituent for a series of 
aromatic and aliphatic imines.

A transition state model was suggested by Grigg et al. (Scheme 1.24) after studying the 
observed regioselectivities, the endo and diasterofacial selectivities of 1,3-dipolar 
cycloaddition reactions together with the established absolute configuration of the 
cycloadducts and the facial shielding effect of the menthyl isopropyl substituent [90, 92].

This involved addition of the 1-si, 3-re face of the dipole to the re-face of the s-cis 
acrylate. The menthyl isopropyl group effectively shielded the si-face in the s-cis acrylate. 
In this transition state the C(6) equatorial hydrogen atom of the menthyl moiety infringes 
slightly on the π-bond of any C(3)-aryl substituent on the dipole.

The 1,3-dipolar cycloaddition reaction of metalloazomethine ylides with chiral cyclic 
dipolarophiles in the presence of silver acetate and various bases [90, 91, 99] has been
implemented in excellent yield and the absolute stereochemistry of cycloadducts confirmed by X-ray crystallography (Scheme 1.25).

Grigg has also published an intriguing and synthetically useful reversal of regiochemistry for the cycloaddition of the metalloazomethine ylide, formed from both aryl and aliphatic aldimines and Ti(OPr')₃Cl, with acrylate esters, shown in Scheme 1.26.

Kanemasa and co-workers have studied 1,3-dipolar cycloaddition reactions mediated by lithium bromide and base (e.g. DBU or triethylamine) of N-alkylidene-2-amino esters and amides with chiral electron-deficient alkenes (Scheme 1.27). These reactions proceed with high regio- and stereoselectivities and the first example of efficient
asymmetric 1,3-dipolar cycloaddition of the reactive azomethine ylides 1.102 with $\alpha,\beta$-unsaturated ester 1.103 (having a chiral perhydropyrrolo[1,2-c]imidazol-3-yl moiety at the $\beta$-position) was reported. In this reaction, complete regioselectivity, endo selectivity, and diastereofacial selectivity were achieved by the attack of syn-azomethine ylide to the $\alpha$-si face of the alkene. Changing of metal from lithium to magnesium slowed reaction with the chiral alkene $^{[103]}$.

![Scheme 1.27](image)

Waldmann et al. reported a related approach using $N$-acryloyl-(S)-proline ester 1.105 as the chiral alkene $^{[105, 106]}$ (Scheme 1.28). The desired cycloadducts 1.108 and 1.109 were formed with almost complete endo/exo selectivity (>99:1) in favour of 1.108.
To explain the almost total endo selectivity and the very high facial selectivity for this 1,3-dipolar cycloaddition reaction, a transition state model was proposed by Waldmann (Figure 1.17), in which the lithium cation is coordinated to the azomethine ylide and to the dipolarophile, in such a way that a compact and efficient ordering of the reaction partners results. If the dipole took an exo approach, such double coordination would not be possible. To allow the lithium cation to coordinate through the amide and ester carbonyl groups of the dipolarophile, the acrylamide must assume the proposed cis-anti conformation. 

Figure 1.17
1.4.2.2 Reactions with other azomethine ylides

The 1,3-dipolar cycloaddition of the azomethine ylide 1.113 with homochiral cyclic dipolarophiles proceeds with high facial selectivity\(^{[100]}\), whereas for a homochiral acyclic dipolarophile, the \(\pi\)-facial selectivity and mode of cycloaddition is dependent on the structure of the dipolarophile (Scheme 1.29).

\[
\text{Scheme 1.29}
\]

In a series of papers, Meyers and co-workers have applied chiral unsaturated bicyclic lactams 1.119 to the 1,3-dipolar cycloaddition with azomethine ylides 1.118\(^{[107-110]}\) (Scheme 1.30).
In this reaction, a catalytic amount of trifluoroacetic acid was used with 1.117 to generate the azomethine ylides which reacted with the unsaturated lactams to afford diastereomeric mixtures of pyrrolidine-fused tricyclic lactams 1.120, 1.121 in excellent yields (82-100%) [107, 108]. The diastereoselectivities are dependent on the various substituents R¹-R⁴. When R¹= Me, Ph, the major stereoisomer is 1.121 from α-approach 1.123. When R¹=H, the other diastereomer 1.120 from β-approach 1.122 is obtained [107]. Furthermore, if R³=H, the π-facial selectivity is insensitive to the R⁴ substituents of the dipolarophile, whereas when R²=CO₂Me or CO₂Bu, the products showed lower selectivities. Accordingly, a transition state was suggested to account for the results as shown in Figure 1.18: for reaction of angular methyl bicyclic lactams (R¹=Me) with (R)-dipole (G₅≠H, G₆=H), high selectivity is observed; with achiral (G₅=G₆=H) or (S)-dipole (G₅≠H, G₆=H), decreased selectivity is found [107].
The 1,3-dipolar cycloaddition with chiral unsaturated bicyclic lactams was used for the synthesis of the (+)-conessine precursor (+)-benzohydrindan 1.124 \[109\] (Figure 1.19).

Grée and co-worker reported that that cross-conjugated polyenones 1.125 having planar chirality introduced by an organometallic moiety reacted with an azomethine ylide to afford a mixture of two diastereoisomers 1.127 and 1.128, with lower diastereoselectivity for 1.127a and 1.128a as a 70/30 mixture; diastereomers 1.127b and 1.128b were easily separated by chromatography\[111\] (Scheme 1.31).
1.4.3 Intramolecular Cycloadditions

There are many carbon-carbon forming reactions in synthetic organic chemistry, and amongst the most efficient are intramolecular cycloaddition reactions. This method commonly sets up two new sigma bonds and two new rings in one step, often with a high degree of stereoselectivity. Intramolecular cycloaddition reactions are used to construct rapidly many different and complex bicyclic and polycyclic systems from relatively simple precursors. To date, intramolecular cycloaddition has proved to be one of the less investigated aspects of azomethine ylide chemistry. Recently, the intramolecular version of this reaction has been finding increasing use for the synthesis of substituted pyrrolidines, dihydropyrroles and pyrroles, and will become more and more important in the future.
1.4.3.1 Aziridine Precursors

DeShong Philip et al. reported the thermolytic generation of azomethine ylides from aziridines and their intermolecular reactions. The protocol has been further extended to intramolecular cycloaddition \[^{[112a]}\]. Treatment of 1.129 under standard conditions led to the formation of 1.130 in 80% yield as a single cis isomer; similarly, the cis precursor 1.131 also gave cycloadducts in 52% yield as a 1:1 diastereomeric mixture of 1.132 and 1.133 (Scheme 1.32).

\[
\begin{align*}
1.129 & \quad \rightarrow \quad 1.130 \\
1.131 & \quad \rightarrow \quad 1.132 \quad + \quad 1.133
\end{align*}
\]

Scheme 1.32

Takano et al. also reported aziridines as the precursors for azomethine ylides that were applied to intramolecular 1,3-dipolar cycloaddition reactions. This approach was applied to natural products such as acromelic acid \[^{[112]}\], (-)-kainic acid \[^{[113]}\] and (-)-mesembrine \[^{[114]}\]. For example, acromelic acid A 1.137 was synthesised from aziridine 1.134 in very high
diastereofacial selectivity, the product 1.136 being produced via transition state 1.135 (Scheme 1.33)\textsuperscript{[112]}.

For synthesis of the complex marine alkaloid sarain\textsubscript{A}, 1.141, Heathcock et al. set up an approach using intramolecular azomethine ylide cycloaddition as one of the key stages in the construction of the tricyclic central core \textsuperscript{[115]}. Weinreb and co-workers reported a very similar protocol in the total synthesis of sarain\textsubscript{A} \textsuperscript{[116]}. The five-membered ring of the tricyclic central array was constructed via thermolysis of aziridine 1.138 to furnish the intramolecular [3+2]-cycloaddition product 1.140 in 73% yield as a single regio- and stereoisomer (Scheme 1.34).
Garner and co-workers described a novel approach to controlling the diastereofacial selectivity of intramolecular dipolar cycloadditions of azomethine ylides by varying the structure of a silicon-based tether. An example is shown in Scheme 1.35.\textsuperscript{[117]} Reactions with products having a ring size greater than nine atoms showed a preference for products such as 1.143 arising from a si-face attack, whereas reactions with products with a ring size equal to nine atoms led to the opposite facial selectivity. Both methyl and phenyl substituents in the tether gave results.\textsuperscript{[117]}
1.4.3.2 Amino Ester Condensation

Harwood and co-workers developed a method to generate azomethine ylides shown in Scheme 1.36, which has been extended to include intramolecular cycloaddition\cite{70, 71}. Condensation of 5-hexenal with chiral template 1.144 under standard conditions led to *in situ* generation of azomethine ylide 1.146 which undergoes an intramolecular 1,3-dipolar cycloaddition to furnish 1.147 as a single enantiomer in 95% yield after purification (Scheme 1.36). Removal of the template using H$_2$/Pd-C gave the bicyclic amino acid 1.148 in 75% yield.
The construction of numerous, complex polycyclic systems by an intramolecular approach was reported by Grigg and co-workers \[^{[118]}\]. Thiazolidine-4-carboxylic acid 1.149 was shown to react with 1.150 in refluxing toluene to furnish a 2:1 mixture of 1.152 and 1.153 in 63% yield (Scheme 1.37). The azomethine ylide was generated by condensation of aldehyde 1.150 and amino acid 1.149 to afford the iminium salt. Subsequent thermal decarboxylation generates either a syn dipole leading to 1.152 from an exo transition state, or an anti dipole and endo transition state generating cycloadduct 1.153.
Confalone and co-workers \[119\] reported that the cycloadducts \(1.157\) were formed as the major product on refluxing \(N\)-methylglycine ethyl ester and the aldehydes \(1.154\) in xylene with camphorsulfonic acid (CSA) as essentially single steroisomers after \textit{in situ} cycloaddition (Scheme 1.38).

\textbf{Scheme 1.38}
1.4.4 Asymmetric Cycloaddition induced by Chiral Catalysis

An important advance in azomethine ylide 1,3-dipolar cycloadditions is the use of metal-mediated catalysis, some examples of which have been discussed in the previous section. Of greater synthetic interest is asymmetric induction by the use of chiral catalysis, but this is a little explored area as yet. Grigg and co-workers were the first to report that anhydrous MnBr$_2$ and CoCl$_2$ in conjunction with a chiral ephedrine ligand effect substantial asymmetric induction in cycloadducts derived from methyl acrylate and imines of glycine ester $^{[120]}$. A typical example is shown in Scheme 1.39. Cycloaddition of the azomethine ylide derived from 1.158 with methyl acrylate 1.159 in the presence of a stoichiometric amount of Co(II) or Mn(II) and the chiral ephedrine ligand 1.161 afforded 45-84% yields of cycloadducts 1.160 with 84-96% ee. Replacing acetonitrile with methyl acrylate as solvent resulted in a better yield of 84% with an excellent ee of 96%.

![Scheme 1.39](image)

Changing the metal salt to MnBr$_2$, CoBr$_2$ and CoF$_2$, in the presence of ephedrine, camphor and other ligands led to a very slow 1,3-dipolar cycloaddition reaction with low chiral induction compared with CoCl$_2$ $^{[120]}$. The asymmetric induction is rationalized by the transition state 1.162. The cis arrangement of the methyl and phenyl group of the ligand

51
results in a pseudo-equatorial conformation of the phenyl group, effectively blocking one face of the imine that forms the dipole (Figure 1.20) \[^{120}\].

![Image](image)

**Figure 1.20**

Grigg et al. also developed an Ag(I) salt catalyst system with a range of chiral ligands \[^{90}\]. The reaction occurred in good chemical yield of 64-83% and reasonable ee of 70% (Scheme 1.40).

![Scheme 1.40](image)

**Scheme 1.40**
1.5 Formation of Nitrogen Ylides by Transition-metal Catalysed Decomposition of Diazo Compounds

The interaction of a carbene or carbenoid with an imine nitrogen atom to give a transient azomethine ylide has attracted some attention over the past decade. In this section, we introduce the formation of nitrogen ylides by transition-metal catalysed decomposition of diazo compounds.

1.5.1 Azomethine Ylides by Decomposition of Diazo Compounds

Transition metal derivatives are versatile reagents for bond forming reactions that would be much more difficult with conventional organic reagents alone. Aziridines 1.168 have been synthesized, albeit in low yield, by copper-catalyzed decomposition of ethyl diazoacetate 1.167 in the presence of an imine 1.166 (Scheme 1.41)\[^{[121]}\].

\[
\text{PhHC≡NPh} + \text{N}_2\text{CHCO}_2\text{Et} \xrightarrow{\text{Cu}, 80^\circ\text{C}, 24\text{h}} \begin{cases} \text{PhH} \quad \text{EtO}_2\text{C} \\ \text{Ph} \quad \text{PhHNN} \quad \text{CO}_2\text{Et} \end{cases}
\]

1.166 1.169 1.168 15% 1.169 40%

Scheme 1.41

It seems that such a carbenoid aziridination pathway may not occur with other diazo compounds. The reported preparation of 1,2,3-trisubstituted aziridines 1.172 by reaction of phenyldiazomethane with N-alkyl aldimines or ketimines 1.170 in the presence of zinc iodide \[^{[122]}\] most certainly does not proceed through carbenoid intermediates; rather, the
metal salt serves to activate the imine to nucleophilic attack from the diazo carbon (Scheme 1.42).

\[
\begin{align*}
\text{Ar.} & \quad \text{ZnI}_2 \\
\text{C} = \text{N} - \text{R}^2 & \xrightarrow{2^-} \text{Ar.} \quad \text{ZnI}_2 \\
\text{Ph-CH=NCH}_3 & \quad \text{Ph-Ch=N}_2 \\
\end{align*}
\]

Scheme 1.42

Replacement of ZnI\(_2\) by one of the traditional copper catalysts resulted in formation of pyrrolidine derivatives via an intermediate azomethine ylide 1.175 (Scheme 1.43) \(^{123}\).

\[
\begin{align*}
\text{PhCH:} & + \text{PhCH}=\text{NCH}_3 \\
\text{CuBr} & \quad \text{PhCH}_2=\text{CH}_2 \\
\end{align*}
\]

Scheme 1.43
Baret and co-workers first reported the formation of azomethine ylides by decomposition of diazo compounds under the catalysis of Cu(I) salts. The ylides then undergo 1,3-dipolar cycloadditions with a series of dipolarophiles\textsuperscript{[124]}. The decomposition of ethyl diazoacetate 1.179 with copper bronze in the presence of excess benzalimine 1.180 gave imidazolidine 1.182. The formation of this product is presumed to involve generation of azomethine ylide 1.181 from carbenoid addition onto the imine nitrogen followed by a 1,3-dipolar cycloaddition reaction with another molecule of imine to produce the cycloadducts (Scheme 1.44).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 1.44}};
\end{tikzpicture}
\end{center}

Subsequently, Bartnik and co-worker also used this approach for furnishing pyrrolidines and oxazolidines by using other dipolarophiles \textsuperscript{[125]} (Scheme 1.45). Treatment of aryl diazoethane 1.183 and N-benzylidenemethylamine 1.180 with copper bronze in the presence of dimethyl maleate or benzaldehyde afforded the desired product, and it is interesting that no cycloadducts resulted from trapping of the azomethine ylide with an imine molecule. So far, the reactivity of double bonds with azomethine ylides thus was found to decrease in the order C=C > C=O > C=N\textsuperscript{[125]}.
The reaction of the imine moiety of 1.186 with excess ethyl diazoacetate in the presence of Cu(acac)$_2$ led to the cyclopentane-annulated product 1.187$^{[126]}$. It is assumed that 1.187 results from reaction between a carbene dimer (diethyl fumarate) as dipolarophile and an intermediate $N$-ylide or the isomeric aziridine. Indeed, a three-component reaction between ethyl diazoacetate, 1.186 and dimethyl fumarate produced the tricyclic system 1.188, as shown in Scheme 1.46.
Padwa and co-workers reported that the rhodium(II)-catalysed reaction of \( \alpha \)-diazo ketones with a neighboring oxime ether generates cyclic azomethine ylides which undergo ready 1,3-dipolar cycloaddition \[^{127}\]. This was the first example of the formation and intramolecular dipolar cycloaddition to a C-N double bond of an azomethine ylide formed by carbenoid addition. Treatment of diazo ketone 1.189 using rhodium(II) octanoate as catalyst with dimethyl acetylenedicarboxylate (DMAD) afforded cycloadduct 1.191 via azomethine ylide 1.190, as a 4:1 mixture of diasteromers in 65% yield (Scheme 1.47).

![Scheme 1.47](image)

The facility of the tandem cyclization-cycloaddition process with this oxazolidine derivative suggested that acyclic oxime ethers would also function as suitable azomethine ylide precursors \[^{127,128}\]. Treatment of 2-(diazoacetyl)benzaldehyde O-methyl oxime 1.192 with rhodium(II) octanoate in the presence of dimethyl acetylenedicarboxylate (DMAD) or \( N \)-phenylmaleimide afforded the cycloadducts 1.196 (80%) and 1.197 (64%), respectively, derived from the azomethine ylide 1.193. For cycloadduct 1.197, a 1:1 mixture of \textit{exo:endo} diasteromers was obtained (Scheme 1.48).
The cycloaddition was also carried out with p-quinone as the dipolarophile. The major product isolated corresponded to cycloadduct 1.194 in high yield. Treatment of this material with excess acetic anhydride in pyridine afforded diacetate 1.195 in 67% overall yield from 1.192.

A new method for azomethine ylide formation by use of a Rh-catalyzed system was also reported by Padwa [129-131]. It involved a rhodium(II) acetate-induced diazoketone cyclization onto a neighbouring carbonyl group to generate a carbonyl ylide, which then formed an azomethine ylide via a hydrogen shift (Scheme 1.49) followed by 1,3-dipolar cycloaddition [129].

Scheme 1.48
Jacobsen and Hansen have reported asymmetric induction up to 67% ee in the formation of aziridine 1.203 from benzylidene imines 1.202 and ethyl diazoacetate 1.201 catalyzed by a chiral copper(I) bis(oxazoline) complex (Scheme 1.50)\textsuperscript{[132]}.

Enantiomerically enriched aziridine 1.203 was formed as mixture of two diastereomers, along with racemic pyrrolidine 1.204. The pyrrolidine by-products obtained in these reactions, were probably formed by cycloaddition of an azomethine ylide intermediate with diethyl fumarate (generated from ethyl diazoacetate by carbene dimerisation). Various transition metals, such as Cu, Rh, Ru, were employed for catalyzing transfer of diazocarbonyl-derived carbenes to imines, and it was found that copper(I) salts, in association with bis(oxazoline) ligands, were most effective in catalyzing aziridination reactions.
1.5.2 Other Nitrogen Ylides by Decomposition of Diazo Compounds

Surpateanu prepared an isoquinoline-carboethoxymethylide 1.206 by the thermal decomposition of ethyl diazoacetate in the presence of isoquinoline. The same ylide could also be obtained from N-carboethoxyxymethylene isoquinolinium bromide by the elimination of hydrogen bromide. Ylide 1.206 is a red crystalline solid which is stable in the absence of moisture. The dipolar character of 1.206 was established by its reaction with dimethyl acetylenedicarboxylate which led to the formation of cycloadduct 1.207 \[^{133}\], as shown in Scheme 1.51.

![Scheme 1.51](image)

Kostik and co-workers reported the synthesis of a series of stable tetrahydroquinolizinium ylides 1.209 by the Cu(II)-catalyzed cyclization of 2-(4-diazo-3-oxoalkyl)pyridines, which undergo 1,3-dipolar cycloaddition with dipolarophiles to afford cycloadducts 1.211. (Scheme 1.52) \[^{134}\].
1.6 Our aim and strategy

The initial aim of the project described in this thesis was to develop a concise, clean and efficient route for the synthesis of homochiral pyrrolidine derivatives using 1,3-dipolar cycloaddition of imidazolinium ylides. The focus of this work was to discover new cleaner catalytic ways to generate these ylides via carbenoid insertion, avoiding a deprotonation step and removing one reagent (the base) from the reaction arena.

This stems from the limitation of the assembly of heterocycles by 1,3-dipolar cycloaddition that stoichiometric base is needed to generate ylides by quaternary iminium salt deprotonation. We proposed a base-free formation of azomethine ylides by carben(oid) insertion reactions of diazocarbonyl compounds (replacing the alkylating agent of Scheme 1.22) onto the ‘imine’ nitrogen lone pair of the homochiral heterocycles 1.212 (Scheme 1.53). Such insertions could be metal-mediated (e.g. by Cu(II) or Rh(II)), photolytic or...
thermal\textsuperscript{[14]} and the heterocycle could be an oxazoline or thiazoline as well as an imidazoline. The cycloadducts would be elaborated as before.

Scheme 1.53

In addition, a catalytic cycle can be envisaged for metal-mediated ylide generation; a requirement for stoichiometric metal would thus be avoided, rendering the process even cleaner, with gaseous dinitrogen as by-product, and minimal transition metal residues for recovery (Scheme 1.54). We planned to investigate this system to elucidate the optimum protocol before applying it to further examples.
Investigations in this area uncovered a novel and unexpected azomethine ylide generation (by conjugate addition and proton transfer) and cycloaddition sequence that diverted our efforts, as will be described.
Chapter 2

Results and Discussion
Results and Discussion

2.1 Base-promoted dipolar cycloaddition reactions of azomethine ylides

2.1.1 Cycloaddition using an achiral azomethine ylide

Previous work\textsuperscript{[147, 148]} has shown the suitability of using a 4,5-dihydroimidazole (2-imidazoline) \textbf{2.1} as the starting point for the generation of the azomethine ylide \textbf{2.3} via the iminium species \textbf{2.2} (Scheme 2.1). The azomethine ylide \textbf{2.3} is formed by deprotonation of \textbf{2.2} using a base, and the ylide can be trapped by a suitable dipolarophile, such as methyl methacrylate, to produce the tetrahydropyrrolo[1,2-\textit{a}]imidazole \textbf{2.4}. The use of azomethine ylides such as \textbf{2.3} as the 1,3-dipole in a cycloaddition reaction to form five-membered nitrogen-containing rings is one of the most powerful methods for the synthesis of the pyrrolidine skeleton\textsuperscript{[147]}.

\begin{center}
\textbf{Scheme 2.1}
\end{center}

In these reactions, the ylide \textbf{2.3} affords two cycloadducts, the predominant one arising from endo approach, with only traces of the diastereomer from exo approach being found\textsuperscript{[135]}. The stereochemical preference of adduct formation has been accounted for by the dipole adopting an anti orientation, and the dipolarophile approaching in a regioselective,
pseudo-Michael, manner with the electron-withdrawing group on the dipolarophile endo to the imidazoline ring. The proposed transition state for the 1,3-dipolar cycloaddition (1,3-DC) reaction involving azomethine ylides is summarised in Figure 2.1.

\[ X = \text{CO}_2\text{Me}, \text{CO}_2\text{Et}, \text{CO}_2\text{Bu} \]
\[ Y = \text{CO}_2\text{Me} \]

**Figure 2.1** Proposed transition state for the 1,3-dipolar cycloaddition reaction between an azomethine ylide and a dipolarophile

The relative stereochemistry of the alkoxy carbonyl groups of the pyrroloimidazole 2.4 was determined to be trans by n.O.e. difference spectroscopy; a trans-relationship between the C-7 alkoxy carbonyl group and the C-7a proton was also found \cite{135}. Thus irradiation of the C-7 methyl group protons causes enhancement of the signal for the C-7a bridgehead proton, confirming that these are on same face of the molecule.

The hydrogen bonded interaction that is believed to favour the anti-dipole in ester-stabilised ylides is illustrated in Figure 2.2.
The observed regiochemistry of cycloaddition is as expected for the stabilised azomethine ylide with an electron-deficient dipolarophile, with HOMO-dipole/LUMO-dipolarophile orbital control [30, 31, 32, 33].

2.1.2 Cycloaddition using a chiral azomethine ylide

Previous researchers in the Jones group have developed an asymmetric cycloaddition reaction using optically active azomethine ylides [135, 136, 147, 148]. This was achieved by incorporating a chiral centre into the imidazoline ring of the ylide; the appropriate homochiral dihydroimidazoles, (R)-2.9 and (S)-2.10, were synthesised in four steps from the corresponding enantiomer of phenylglycine 2.5 (Scheme 2.2) [147, 148].
Scheme 2.2 The synthesis of a chiral imidazoline: (i) PhCH₂OCl/NaOH; N-methylmorpholine/EtOCOCl/BnNH₂ (ii) H₂/Pd/C (iii) BH₃, THF (iv) HC(OEt)₃/p-TsOH

The chiral azomethine ylides formed from both imidazoline enantiomers (R)-2.9 and (S)-2.10 resulted in complete facial discrimination in their 1,3-DC reactions, as shown in Scheme 2.3 for (S)-2.10.

Scheme 2.3

As before, the relative stereochemistry of the cycloadduct at C-5 reflects the dipole configuration (anti), C-6 and C-7 reflect the double bond geometry (E/Z), though in the
example shown this is not apparent, whilst the relationship between C-7 and C-7a reflects
the dipolarophile approach (*endo*), and the relationship between the C-7a proton and the C-
3 phenyl group reflects the facial selectivity of the reaction.

In summary, the aim of this project was to study the 1,3-DC reactions of azomethine ylides
generated in the absence of base. Work towards this goal is described in the following
sections. Generally, 1,3-dipolar cycloadduct formation from imidazoline-derived ylides
needs stoichiometric amounts of base to generate the ylides by deprotonation of quaternary
salts. Our interest is to find a novel “base-free” method of ylide formation, such as
carben(oid) insertion reactions of diazocarbonyl compounds to replace the alkylating
agent. In the course of these investigations, we observed an alternative “base-free” method,
and the major part of this Chapter relates to our investigation of this latter reaction.

2.2 Carbene insertion for base-free ylide generation

2.2.1 Copper(II) acetylacetonate, Cu(acac)₂, catalysed reactions

The cycloaddition reaction of thiazolines using ethyl diazoacetate and dimethyl fumarate
catalysed by Cu(acac)₂ has already been noted [123]. Therefore, the first cycloaddition
carried out in this project was the reaction between 1-benzylimidazoline 2.1, ethyl
diazoacetate and dimethyl fumarate in the presence of Cu(acac)₂. The required 2-
imidazoline for this reaction, 2.1, was obtained in two steps from 1,2-diaminoethane
(Scheme 2.4).
The benzylation of 1,2-diaminoethane was achieved, in good yield, with benzyl chloride. By using the diamine (five equivalents) as both reagent and solvent formation of monobenzylated product 2.14 was favoured. Ring closure to the 2-imidazoline 2.1 was achieved by heating with triethyl orthoformate in the presence of catalytic amounts of 4-toluenesulfonic acid.

The cycloaddition reaction (Scheme 2.5) was initially carried out in “one-pot”. Treatment of 2-imidazoline 2.1 with ethyl diazoacetate and an excess of the dimethyl fumarate dipolarophile 2.15 in the presence of Cu(acac)$_2$ in dry dichloromethane (DCM) at reflux for 20 h led to promising results. Work-up and careful purification by column chromatography yielded three products. The desired compound 2.16 was isolated as the major product in 33% yield, while the other two products, isolated in low yields, were found to be two pyrroloimidazole diastereoisomers 2.17 and 2.18.
Using $^1$H and $^{13}$C NMR spectroscopy, as well as mass spectrometry, confirmation of the molecular structure of compound 2.16 was straightforward. Firstly, the HRMS showed $\text{MH}^+ 391.1864$, (calculated $\text{MH}^+ 391.1869$). Secondly, the $^1$H NMR spectrum revealed two doublets, integrating to one proton each, at $\delta 3.35$ and $\delta 4.08$ that correspond to the benzylic methylene protons. Thirdly, the presence of a doublet integrating to one proton at $\delta 4.55$ in the $^1$H NMR spectrum is consistent with the C-7a proton. Finally, DEPT $^{13}$C NMR shows four CH signals at $\delta 68.44$, $\delta 47.57$, $\delta 51.92$, and $\delta 86.13$ p.p.m., corresponding to the C-5, C-6, C-7 and C-7a carbon atoms.

The formation of 2.16 can be rationalised as outlined in Scheme 2.6. Reaction of diazoacetate with Cu$^{2+}$ forms the ethoxycarbonyl carbene (or its metallocarbene equivalent) which can attack the C=N system to give either the aziridine 2.19 or the ylide 2.20, either of which, via 1,3-DC reaction with dimethyl fumarate, can account for the product.
Unfortunately, compound 2.16 is an oil, precluding X-ray crystallographic analysis. Therefore, its stereochemistry was determined by n.O.e. difference spectroscopy (Figure 2.3). For example, irradiation of the C-7 hydrogen produces a 9.1% enhancement of the C-7a proton, but no enhancement of the C-5 or C-6 protons. Irradiation of the C-6 hydrogen produces an 8.9% enhancement of C-5 proton, but no enhancement of the C-7 proton, implying a cis-relationship between the C-5 and C-6 protons and confirming the trans-relationship between the C-6 and C-7 protons. Irradiation of the C-5 hydrogen produces a 15.6% enhancement of one of the NCH$_2$CH$_2$N protons and an 8.9% enhancement of the C-6 proton thereby confirming the cis-relationship between these two protons.

The formation of compounds 2.17 and 2.18 (Scheme 2.5) is particularly interesting; these appear not to involve ethyl diazoacetate at all but can be rationalised by reaction of the imidazoline with two molecules of dimethyl fumarate. This reaction will form the basis of the discussion later in this Chapter.
For now, it only needs to be noted that when the two pyrroloimidazoles, 2.17 and 2.18, were analysed by $^1$H NMR spectroscopy immediately after chromatographic separation (silica gel, ethyl acetate-hexane eluent) both were found separately to consist of a single diastereoisomer. The stereochemistry of the two hexahydropyrroloimidazoles 2.17 and 2.18 was studied by $^1$H NMR spectroscopy (Table 2.1).

<table>
<thead>
<tr>
<th></th>
<th>2.17</th>
<th>2.18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>δ/p.p.m.</td>
<td>J/Hz</td>
</tr>
<tr>
<td>C-6H</td>
<td>4.45</td>
<td>11.8</td>
</tr>
<tr>
<td>C-7H</td>
<td>3.66</td>
<td>4.6, 11.8</td>
</tr>
<tr>
<td>C-7aH</td>
<td>3.85</td>
<td>4.6</td>
</tr>
</tbody>
</table>

From the sizes of the coupling constants, we were led to the conclusion that for compound 2.17 the C-7a and C-7 protons are *anti*, and the C-7 and C-6 protons are also *anti*. In compound 2.18 the C-7a proton appears downfield from that in 2.17, probably because of the two facing esters at the C-5 and C-6; further, the coupling constant between the C-7 and C-7a protons implies a *cis* relationship, while that for the C-7 and C-6 protons implies an *anti* relationship. Our deductions were confirmed in the course of an X-ray
Having employed dimethyl fumarate, a non-cyclic dipolarophile, in the carbenoid 1,3-DC reaction, we next investigated N-methylmaleimide 2.21. Treatment of 2-imidazoline 2.1 with ethyl diazoacetate in the presence of copper(II) acetylacetonate at reflux under nitrogen for 1 h, followed by addition of N-methylmaleimide, afforded after 23 h reaction and purification by column chromatography, the cycloadducts 2.22 in 36% yield and 2.23 in 3.4% yield (Scheme 2.7).

Scheme 2.7

It is self-evident that neither of these products involve reaction between the imidazoline and ethyl diazoacetate. We shall return to the structure of compound 2.22, which was supported by standard spectral data as well as an X-ray crystal structure determination in a later section, but before describing our efforts to obtain products from desired reaction, we
shall discuss compound 2.23. New compound 2.23 was confirmed by $^1$H NMR and $^{13}$C NMR and by mass spectrometry. Indeed, $^1$H and $^{13}$C NMR spectral analysis of compound 2.23 revealed the usual features characteristic of an eight-membered ring cycloadduct: the characteristic C-1H proton was clearly present at $\delta$ 7.91, as was the corresponding C-1 carbon at $\delta$ 146.6. In addition, the singlet one proton signal at $\delta$ 3.90 corresponded to C-6aH, while the carbon atom corresponding to C-6a is present at $\delta$ 51.13. The methylene protons in the spiro-fused ring appear as doublets of 2.85 and 3.17 p.p.m., indicating diastereotopicity. HRMS also found a measured mass $\text{MH}^+$ 383.1718 in agreement with the calculated mass, $\text{MH}^+$ 383.1719. IR absorptions at $\nu_{\text{max}}$ 1674 cm$^{-1}$ (conjugated imide C=O) and 1607 cm$^{-1}$ (C=C) supported the ring-opened structure.

The X-ray crystal structure of compound 2.23 (Figure 2.4) confirmed the relative stereochemistry of the chiral centres. It is interesting to note that whereas 1,3-DC via an endo transition state produces 2.22, compound 2.23 has the opposite stereochemistry at C-6a. This would appear to imply that 2.23 arises from an eliminative ring opening of the precursor 2.24 (Scheme 2.8), which would be the product of an exo transition state.

Figure 2.4 X-Ray crystal structure of product 2.23
The structure of 2.24 reveals that the C-H bond involving the C-7 has an anti relationship with the C7a-N bond; this potentially makes eliminative ring-opening to form 2.23 a facile process (Scheme 2.8).

Since imidazoline 2.1 reacts with the maleimide in preference to the diazoacetate, we therefore adopted a syringe-pump method of addition for both the diazo compound and the dipolarophile. Cycloaddition of 2-imidazoline 2.1 with ethyl diazoacetate was attempted, separately, in the presence of methyl methacrylate, N-methylmaleimide, diethyl fumarate and dimethyl acetylenedicarboxylate (DMAD) as dipolarophiles.

Thus, using the syringe pump method of addition, attempted reaction of 2-imidazoline 2.1 and N-methylmaleimide 2.21 with ethyl diazoacetate in the presence of copper(II) acetylacetonate gave the cycloadducts 2.22 and 2.25 (Scheme 2.9), neither of which involve a fragment originating from the diazo compound.
Thus, it would appear that reaction between the maleimide and imidazoline is faster than either formation of the metallocarbene or the reaction of the latter with the imidazoline. This limits the scope of the reaction. Over time compound \textbf{2.22} converts into compound \textbf{2.25}. In compound \textbf{2.25} the alkene proton appears at \( \delta \) 7.89, while the \text{CHCONCH}_3 proton appears at \( \delta \) 4.49 with a coupling constant \( J = 0.93 \) Hz. A further feature of the \(^1\text{H} \) NMR spectrum is that both the \text{CCH}_2\text{CONCH}_3 protons (two doublets at \( \delta \) 2.11 and \( \delta \) 2.31) and also the benzylic methylene protons (two doublets at \( \delta \) 4.41 and \( \delta \) 4.48) exhibit diastereotopicity. However, the most characteristic aspects of the \(^1\text{H} \) NMR spectrum are the \text{NH} resonance at \( \delta \) 1.53, which is typical of an amine (an amide would resonate about \( \delta \) 6-7 p.p.m.) and \text{N}-methyl singlets of both imide groups (an \text{N}-methyl secondary amide, which might be formed by imide ring opening, would be a doublet). In the \(^{13}\text{C} \) NMR spectrum, resonate observed at \( \delta \) 147.30 and \( \delta \) 90.03 correspond to the \text{NCH=CCO} carbon atoms. These correspond nicely to the alkene resonances of vinylogous carbamates at \( \delta \) ca. 85 and \( \delta \) ca. 150 p.p.m. \textsuperscript{157}. Furthermore, according to DEPT \(^{13}\text{C} \) NMR studies, only two signals, at \( \delta \) 48.42 and \( \delta \) 147.30, correspond to two \text{CH} carbon atoms. The infrared spectrum for \textbf{2.25} shows \( \nu_{\text{max/cm}^{-1}} \) at 3336 (NH), 1779 (imide \text{C}=\text{O}), 1702 (imide \text{C}=\text{O}), 1681 and 1615 (C=C). Finally, the HRMS showed \text{MH}^+ 383.1717 in agreement with the
expected MH$^+$ 383.1719. On the basis of these spectroscopic data we assign the structure of this product as 2.25.

The formation of compound 2.25 can be rationalised as shown in Scheme 2.10. We propose initial formation of compound 2.22 in a 1,3-dipolar cycloaddition. Eliminative ring-opening of compound 2.22, perhaps because of the presence of trace amounts of acid, leads to the formation of compound 2.25.

![Scheme 2.10](image)

Treatment of a DCM solution of 2-imidazoline 2.1 and copper(II) acetylacetonate, at room temperature and under nitrogen, with ethyl diazoacetate, followed by syringe-pump addition DMAD over 18 h afforded in a disappointingly low yield of 12% a single cycloadduct 2.27 which we formulate as having the stereochemistry in 2.27 based on the TS model that has been proposed elsewhere $^{[34]}$ (Scheme 2.11).
For compound 2.27, the two doublet signals each one proton, at δ 3.63 and δ 3.92, correspond to the benzylic methylene protons. The singlets at δ 4.97 and at δ 4.73, each one proton, are those of the C-5 proton and C-7a proton, suggesting the presence of the double bond between the C-6 and C-7. Indeed, the chemical shift of the C-7aH in compound 2.27 is ca. 0.2 p.p.m. downfield of the corresponding proton in 2.16, presumably due to the deshielding effect of the adjacent double bond. The $^{13}$C NMR spectrum contains one signal at δ 149.52; we assign this to accidental equivalence of the alkene carbon atoms C-6 and C-7. Low-resolution mass spectrometric analysis showed the molecular ion $m/z$ 388, as expected for 2.27. IR absorption analysis revealed $\nu_{\text{max}}$ at 1736 cm$^{-1}$ (C=O), 1666 cm$^{-1}$ (C=C-C=O) and 1613 cm$^{-1}$ (C=C) are consistent with the proposed structure.
Reaction with diethyl fumarate using the syringe-pump method afforded the desired cycloadduct 2.28 in reasonable yields (Scheme 2.12). Similar reaction of dimethyl maleate produced an identical sample of compound 2.16 as was formed from dimethyl fumarate. We assume that under the experimental conditions dimethyl maleate isomerises to dimethyl fumarate prior to the cycloaddition reaction. \(^{150}\)

The stereochemistry of the 2.28 was determined by n.O.e difference spectroscopy (Figure 2.5). Irradiation of the bridgehead proton at C-7a (δ 4.54) effects an 11.97% enhancement of the signal for the C-7 proton, whilst irradiation of C-6H (δ 3.84) effects a 7.94% enhancement of the signal for C-5H. These show the cis-relationship of the protons at C-7 and C-7a, and of the protons at C-6 and C-5. This is consistent with an endo approach of dipolarophile to the azomethine ylide dipole. The trans-relationship between C-6H and C-7H is strongly supported by the low enhancement (0.18%) of C-7H when C-6H is irradiated, or for C-6H when C-7H is irradiated.
2.2.2 Rhodium(II) acetate dimer, Rh₂(OAc)₄-catalysed reactions

We anticipated that a change of catalyst might allow better access to the 1,3-DC reaction; thus, in this section our efforts focused on the rhodium(II) acetate dimer, Rh₂(OAc)₄, as this has been previously reported to effect carbene formation from diazo compounds [127, 159, 160].

Accordingly, 2-imidazoline 2.1 was treated with methyl methacrylate in anhydrous DCM and Rh₂(OAc)₄ followed by the dropwise addition of ethyl diazoacetate over 16 h. The expected 1,3-DC reaction cycloadduct was not isolated; instead, the product of this reaction is adduct 2.29 on the basis of its ¹H NMR and ¹³C NMR (Scheme 2.13).
This adduct, 2.29, is formed by direct 1,3-DC of ethyl diazoacetate (as the 1,3-dipole) with methyl methacrylate (as dipolarophile) (Scheme 2.14).

The $^1$H NMR spectrum contained two three-proton singlets at $\delta$ 1.56 and $\delta$ 3.77, corresponding to the C-Me and CO$_2$Me protons. The presence of two doublets, each of integrating to one proton, at $\delta$ 2.83 and $\delta$ 3.31, and with a coupling constant 17.7 Hz, is consistent with the diastereotopicity of the ring methylene group. Further, the broad singlet integrating to one proton at $\delta$ 6.69 is typical of an NH proton. IR absorptions at $\nu_{max}$ 1734 cm$^{-1}$ (ester C=O), 1446 cm$^{-1}$ (C=N), and 3800-2500 cm$^{-1}$ (NH) are consistent with this
structure. The HRMS provided a measured mass of MH\(^+\) 214.1243, in agreement with that calculated for compound 2.29 of mass MH\(^+\) 214.1237.

Since the reaction of 2-imidazoline 2.1 with ethyl diazoacetate/ethyl methacrylate/Rh\(_2\)(OAc)_4 failed to produce the desired imidazopyrrole we decided to adopt dimethyl maleate and dimethyl fumarate as the dipolarophiles. In the event, these reactions afforded cycloadduct 2.18 (Scheme 2.15), which does not contain any fragment from the diazo compound.

![Scheme 2.15](image)

Thus, in order to determine if the imidazoline reacts with a diazo compound under the conditions of the attempted 1,3-DC reactions, and also to ascertain

![Scheme 2.16](image)
Whether or not the aziridine 2.19 (Scheme 2.6, Page 72) is involved in these reactions, we investigated the reaction of 2-imidazoline 2.1 with ethyl diazoacetate in the presence of Rh$_2$(OAc)$_4$ but in the absence of a dipolarophile. This reaction afforded the product 2.30 in 32% yield (Scheme 2.16). For compound 2.30, the benzylic methylene two-proton signal appears as a singlet at $\delta$ 3.85, while the N=CHN proton was found as a singlet at $\delta$ 8.23. In the $^{13}$C NMR spectrum, a signal at $\delta$ 128.9 is observed, which, according to DEPT-90 NMR studies, corresponds to a CH carbon atom (N=CHN). Furthermore, the signal at $\delta$ 140.1 corresponds, according to DEPT-45 NMR studies, to a quaternary carbon, which we assign to the EtO$_2$CC=N carbon atom. IR absorptions at $\nu_{\text{max/cm}^{-1}}$ 1728 (ester C=O), 1673, 1534 (C=N), and 3320 (NH) are consistent with this structure. Finally, the HRMS showed MH$^+$ 275.1503, in agreement with the expected MH$^+$ 275.1501.

These results probably imply that the formation of the aziridine does not occur in this system.

2.2.3 Copper(II) trifluoroacetylacetonate, Cu(Tfacac)$_2$, catalysed reactions

Since Cu(acac)$_2$ was more effective than the rhodium catalyst, we decided to examine a Cu(II) salt with a different ligand, namely, copper(II) trifluoroacetylacetonate. Thus, treatment of a solution of 2-imidazoline 2.1 and copper(II) trifluoroacetylacetonate in anhydrous DCM, by the slow, dropwise addition of ethyl diazoacetate over 12-14 h, followed by addition of diethyl fumarate afforded, after 48 h, the cycloadducts 2.16 in 7.8% and 2.31 in 8.9% yield, respectively (Scheme 2.17). The former is the desired cycloadduct, while the latter arises from 1,3-DC of ethyl diazoacetate with diethyl fumarate.
Unfortunately, the yield of the desired compound 2.16 is low. Increasing the temperature to reflux improved its yield to 20%, while the minor product 2.31 was only observed in trace amounts, presumably due to more efficient conversion of the diazo compound.

For compound 2.31, the $^1$H NMR spectrum displayed two doublet signals at δ 4.35 and δ 4.69, both integrating to one proton and with $^3J = 5.49$ Hz, confirming the anti-relationship of the two H atoms at C3/C4 $^{[158]}$. IR absorptions at $\nu_{\text{max}}/\text{cm}^{-1}$ 1717 (C=O), 1579 (C=N) and, especially 3346 (NH), support this structure. The X-ray structure confirmed its structure (Figure 2.6).
Similar reaction of 2-imidazoline 2.1 at room temperature with the slow, dropwise addition of ethyl diazoacetate in the presence of copper(II) trifluoroacetylacetonate followed by the slow addition of $N$-methylmaleimide by syringe pump afforded the cycloadduct 2.22 as the major product (40% yield) and the cycloadduct 2.32 as the minor product (5% yield) (Scheme 2.18). The former is the previously described 2:1 adduct of 2.1 with $N$-methylmaleimide, while the latter is the adduct of a 1,3-DC reaction between ethyl diazoacetate and $N$-methylmaleimide. Thus, once again, $N$-methylmaleimide failed to give the desired cycloadduct. From these results, we infer that $N$-methylmaleimide is a more reactive dipolarophile than diethyl fumarate.
For compound 2.32, the $^1$H NMR spectrum shows no evidence for the presence of either the benzylic methylene or aromatic protons that would correspond to the N-benzyl group from the parent imidazoline. Moreover, the two doublet signals observed at $\delta$ 4.51 and $\delta$ 4.87, each integrating to one proton with $J=10.8$ Hz, can be assigned to a cis relationship of the two protons at the ring fusion. Further, HRMS gave a measured MH$^+$ of 226.0828, calculated 226.0828. IR absorptions at $v_{\text{max}}$/cm$^{-1}$ 1709 (C=O), 1552 (C=N) and 3338 (NH) also support this structure.

![Figure 2.7 X-ray crystal structure of compound 2.32](image)

The stereochemistry of 2.32 was confirmed by an X-ray crystal structure (Figure 2.7), which shows the crystal to contain enantiomeric pairs.

### 2.2.4 Copper(II) trifluoromethanesulfonate, Cu(OTf)$_2$ catalysed reactions

An alternative copper(II) catalyst is copper(II) trifluoromethanesulfonate (copper triflate). Treatment of 2.1 and ethyl diazoacetate in anhydrous DCM under nitrogen at ice-bath temperature with copper(II) trifluoromethanesulfonate results in a blue solution, but by TLC no reaction took place after 2 d. Even at room temperature no reaction occurred after 2 d. Upon heating, the colour of the solution changed to brown over 2 d. Work-up of the
reaction at this point afforded a mixture of diethyl maleate, a trace of dimethyl fumarate, and the compound 2.33 in 17.2% yield (Scheme 2.19).

![Scheme 2.19](image)

The formation of diethyl maleate and diethyl fumarate from ethyl diazoacetate is well known, and presumably arises in this case through the eliminative coupling of two molecules of ethyl diazoacetate, probably involving a transient copper-carbene complex. The $^1$H NMR of 2.33 showed the presence of the benzylic methylene and NCH$_2$CO$_2$C$_2$H$_5$ protons as singlets at $\delta$ 4.01 and $\delta$ 4.40, respectively, each integrating to two protons. The $^{13}$C NMR spectrum of the product shows the presence of two carbonyl carbon atoms at $\delta$ 160.76 and $\delta$ 169.65, as expected for compound 2.33, while DEPT NMR revealed five CH$_2$ carbon atoms, and two quaternary carbon atoms (the C=O atoms). HRMS showed the correct MH$^+$ ions m/z 263.1393 and infrared absorptions at $\nu_{\text{max/cm}^{-1}}$ 1745 (ester C=O), 1700 (cyclic urea C=O) are also consistent with the structure. Formation of compound 2.33 is likely to occur via reaction of ylide with adventitious water (Scheme 2.20). The final step requires an oxidation; this may involve Cu$^{2+}$ but similar oxidation products have been obtained by other workers in our group in reactions where no metal ion oxidant was present.
Despite this lack of success, we also attempted the copper(II) triflate-catalysed 1,3- dipolar cycloaddition of 2-imidazoline 2.1, ethyl diazoacetate and other dipolarophiles. Thus, treatment of the 2-imidazoline 2.1 and copper(II) triflate by slow, dropwise addition of ethyl diazoacetate and dimethyl acetylenedicarboxylate (DMAD) followed by reflux for 12 h afforded the cycloadduct 2.27 in 14% yield as the major product and compound 2.34 in 9.5% yield. (Scheme 2.21)
Compound 2.27 has been described earlier (Page 79). The minor product 2.34 could not be adequately characterised, but its $^1$H NMR spectrum exhibited the following features: three singlets at $\delta$ 8.33, $\delta$ 5.52 and $\delta$ 4.85 each integrating to one proton which we assign to the formyl proton, the vinyl proton of the enamide and the vinyl proton of the enamine. A singlet, integrating to two protons, at $\delta$ 4.50 is assigned to the benzylic methylene protons. The $^{13}$C NMR spectrum reveals CH carbon signals at $\delta$ 160.48 H-C(=O)N, $\delta$ 103.42 enamide and $\delta$ 86.65 enamine$^{[161,162]}$. Quaternary C resonances at $\delta$ 145.28 and $\delta$ 153.78 belong to the two NCCO$_2$CH$_3$ carbon atoms. DEPT $^{13}$C NMR studies established three CH$_2$ carbon atoms, three CH carbon atoms, four CH$_3$ carbon atoms and four quaternary C=O carbon atoms, and a formamide HC(=O)N at $\delta$ 160.48. In addition, low-resolution MS showed $M^+$ at $m/z$ 462, while IR absorptions at $\nu_{\text{max}}/\text{cm}^{-1}$ 1743 (ester C=O), 1697 (H-C=O), and 1614 (C=C) were also obtained.
Assuming structure of 2.34 is correct, we rationalize its formation through initial addition of DMAD, incorporation of a molecule of water and the reaction with a further molecule of DMAD (Scheme 2.22).

Having successfully obtained the 1,3-dipolar cycloadduct 2.27, we adopted a similar approach involving fumaronitrile. Thus, treatment of 2-imidazoline 2.1 and copper(II) triflate, with ethyl diazoacetate followed by fumaronitrile gave the cycloadducts 2.35 and 2.36 in 23% yield as a mixture of diastereomers (Scheme 2.23).
The $^1$H NMR spectra of compounds 2.35 and 2.36 exhibit evidence of a chiral centre due to the diasterotopicity of benzylic methylene protons; in 2.35 there are two doublet signals at $\delta$ 3.65 and $\delta$ 3.84 and in 2.36 a similar pair at $\delta$ 3.47 and $\delta$ 4.15. DEPT NMR studies reveal four CH signals for compound 2.35 at $\delta$ 69.73, $\delta$ 36.32, $\delta$ 38.65 and $\delta$ 88.56 and four such signals for compound 2.36 at $\delta$ 68.07, $\delta$ 34.75, $\delta$ 39.13 and $\delta$ 84.25; these correspond to the C-5, C-6, C-7 and C-7a carbon atoms. The high-resolution EIMS give a molecular ion at 325.1662 for compound 2.35 and 325.1656 for compound 2.36, both of which are in agreement with the calculated mass for MH$^+$ of 325.1664.

The stereochemistry of the major isomer 2.35 was established by X-ray crystallographic analysis (Figure 2.8). This X-ray crystal structure shows that the substituents at C6/C7 have trans-stereochemistry and that the orientation of substituents at C5/C6 is cis. The stereochemical outcome is consistent with the transition state that we depicted earlier.
As compound 2.36 is an oil, we were unable to determine its stereochemistry by crystallography. However, selected $^1$H NMR and $^{13}$C NMR data for compounds 2.35 and 2.36 are collected in Table 2.2.

### Table 2.2 Comparison of selected NMR data for compounds 2.35 and 2.36

<table>
<thead>
<tr>
<th></th>
<th>2.35</th>
<th></th>
<th></th>
<th>2.36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>δ (p.p.m.)</td>
<td>J/Hz</td>
<td>δ (p.p.m.)</td>
<td>J/Hz</td>
</tr>
<tr>
<td>C-7a-H</td>
<td>4.19</td>
<td>4.38</td>
<td>4.40</td>
<td>4.92</td>
</tr>
<tr>
<td>C-7-H</td>
<td>3.12</td>
<td>9.15, 4.56</td>
<td>3.58</td>
<td>3.66, 4.59</td>
</tr>
<tr>
<td>C-6-H</td>
<td>3.73</td>
<td>8.61, 8.97</td>
<td>3.58</td>
<td>6.03, 3.66</td>
</tr>
<tr>
<td>C-5-H</td>
<td>3.83</td>
<td>8.61</td>
<td>3.96</td>
<td>5.85</td>
</tr>
<tr>
<td>Cyano group CN</td>
<td>116.38, 116.47</td>
<td></td>
<td>115.37, 116.09</td>
<td></td>
</tr>
<tr>
<td>C-7a</td>
<td>88.56</td>
<td></td>
<td>84.25</td>
<td></td>
</tr>
<tr>
<td>C-7</td>
<td>38.65</td>
<td></td>
<td>39.13</td>
<td></td>
</tr>
<tr>
<td>C-6</td>
<td>36.32</td>
<td></td>
<td>34.75</td>
<td></td>
</tr>
<tr>
<td>C-5</td>
<td>69.73</td>
<td></td>
<td>68.07</td>
<td></td>
</tr>
</tbody>
</table>

Possibly the most significant observation is the difference in the $^3J$ coupling between the C-6H and C-7H, which is much smaller in 2.36. This may imply a change in relative stereochemistry between these two centres. This could occur in one of two ways. First,
fumaronitrile might isomerise under the reaction conditions to form maleonitrile \cite{155, 156}, which then adds in the usual *endo-* and *exo-*model way to form structures A and B (Figure 2.9). Second, 2.35 undergoes eliminative ring opening followed by ring closure *via* readdition to form structure C. Given that the $^3J$ value for the coupling between the C-7 and C-7a protons remains similar and that coupling between the C-5 and C-6 protons, as well as between the C-6 and C-7 protons, changes, it would seem that structure A is the more likely for 2.36.

![Figure 2.9 Possible structures of 2.36](image)

Given the success of the above protocol, we anticipated that 2.37 would be accessible from reaction of 2-imidazoline, ethyl diazoacetate and E-1-phenyl-2-nitroethene (Scheme 2.24). In the event, we obtained only the adducts 2.38 (7.2%) and 2.39 (2.8%). Obviously, neither involves ethyl diazoacetate, and their formation will be discussed later (Section 2.3.4). We did not obtain any evidence for desired compound 2.37.
Using methyl \( E \)-cinnamate as the dipolarophile proved unsuccessful, with only starting material being recovered from the crude residue.

Since we decided to examine the formation of compounds such as 2.17 and related structures in more depth, we have not had the opportunity to subject \((S)\)- or \((R)\)-4-phenylimidazoline to this 1,3-DC-reaction and the preliminary studies described above remain to be exploited.

### 2.2.5 Brief summary

Our brief survey of the reaction conditions of the transition metal-catalysed decomposition of ethyl diazoacetate should that copper(II) salts were found to be superior to rhodium(II) acetate \([137, 139, 159, 160]\). The only successful approach for the formation of cyclic adducts,
(see Scheme 2.25), has been the catalytic activation using various copper salts, namely, copper(II) acetylacetonate, copper(II) trifluoroacetylacetonate and copper(II) trifluoromethanesulfonate as the catalysts \[139\].

Table 2.3 summarises the results obtained, and though the reactions were carried out under a standard set of conditions no attempt was made to optimise the yield. From Table 2.3 copper(II) acetylacetonate was found to be the best catalyst.

![Scheme 2.25](image-url)
Table 2.3 Summary of metal salts as catalysts for the formation of 2.40

<table>
<thead>
<tr>
<th>Catalyst (MLn)</th>
<th>Dipolarophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(acac)$_2$</td>
<td>(E)-MeO$_2$CCH=CHCO$_2$Me</td>
<td>√</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>(Z)-MeO$_2$CCH=CHCO$_2$Me</td>
<td>√</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>N-methylmaleimide</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMAD</td>
<td>√</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>(E)-EtO$_2$CCH=CHCO$_2$Et</td>
<td>√</td>
<td>25%</td>
</tr>
<tr>
<td>Cu(Tfacac)$_2$</td>
<td>(E)-EtO$_2$CCH=CHCO$_2$Et</td>
<td>√</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>N-methylmaleimide</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Cu(OTf)$_2$</td>
<td>DMAD</td>
<td>√</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>(E)-EtO$_2$CCH=CHCO$_2$Et</td>
<td>√</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>(E)-NCCH=CHCN</td>
<td>√</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>(E)-PhCH=CHNO$_2$</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(E)-PhCH=CHCO$_2$CH$_3$</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>H$_2$C=C(Me)CO$_2$Me</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Z)-MeO$_2$CCH=CHCO$_2$Me</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

2.2.6 Catalytic mechanism of the 1,3-DC-reaction

Metal catalysis in the decomposition of diazo compounds has been known for more than 80 years [149]. To our knowledge, their use in the formation of ylides from imidazolines for further elaboration has not been reported. Nevertheless, our results show that although yields are low, these reactions do occur and allow us to suggest a likely mechanism [149]. The formation of ylide intermediates by carbenoid insertion using a transition metal catalyst is known [124, 127, 137, 159, 160]. The reaction results in the loss of dinitrogen and formation of the metal-stabilized carbene; in our reactions, the latter reacts with an imidazoline to form an ylide and regenerate the metal ion (Scheme 2.26). This accounts for the metal ion acting as a catalyst in these carbenoid transformations.
Metal-carbene complexes of transition-metals have not been isolated or identified in the decomposition of organic diazo compounds. Instead, indirect evidence for their involvement comes from the products observed. As well as the products of 1,3-DC, formation of an ethene from carbene dimerisation is indicative of, but not conclusive evidence for, metal carbene intermediates (Scheme 2.27)\(^{[141]}\).

\[
2 \text{R}_2\text{C}=\text{N}_2 \xrightarrow{\text{MLn}} \text{R}_2\text{C}==\text{CR}_2 + 2\text{N}_2 \uparrow
\]

Scheme 2.27

2.3 Cycloaddition reactions of imidazolines with electron-deficient alkenes

In the course of studying a catalytic method to generate azomethine ylides \textit{via} carbenoid insertion, we observed a novel dipolar cycloaddition involving an imidazoline and two molecules of “dipolarophile”. Given the rather poor yields of the metal ion catalysed
reactions, we decided to concentrate our efforts on these reactions. The results of this investigation follow.

2.3.1 Fumarate and maleate esters as dipolarophiles

Since we obtained compounds \(2.17\) and \(2.18\) as by-products from the metal-ion catalysed reaction of diazoacetate with an imidazoline and dimethyl fumarate, we decided to explore their formation in the absence of ethyl diazoacetate and the metal ion. Thus, reaction of \(2.1\) with an excess of dimethyl fumarate (two equiv.) at reflux in \(\text{CHCl}_3\) for 20 h gave \(2.17\) in 9.5% and \(2.18\) in 4% yields, respectively. The yield of \(2.17\) was improved to 45% upon reflux in DCM for 48 h, and the yield of \(2.18\) increased to 10% (Scheme 2.28). Dimethyl maleate gave the same major product in 38% yield and the same minor product in 2% yield. These results suggest that fumarate reacts easily with 2-imidazoline \(2.1\) to afford to the cycloadducts \(2.17\) and \(2.18\), and that maleate isomerises to fumarate upon heating \[150\].

\[
\begin{align*}
\text{DCM, Reflux 48h} & \quad \\
\text{Fumarate} & \quad 45\% \ 2.17 \\
\text{Maleate} & \quad 38\% \ 2.17 \\
\end{align*}
\]

\(\text{Scheme 2.28}\)

The structures of the cycloadducts \(2.17\) and \(2.18\) follow from their NMR and mass spectra as well as X-ray crystallography. Thus, the mass spectra, which show molecular ions at \(M=449\), are consistent with the compounds being formulated as 1:2 adducts between the imidazoline and the fumarate/maleate esters. HRMS showed the measured mass of
compound 2.17 to be MH⁺ 449.1924 and of compound 2.18 to be 449.1925 in agreement with required mass for MH⁺ of 449.1922. The 13C NMR spectra (Table 2.4, p109) contain signals for 4 x CH₂, 3 x CH and 1 x C, alongside the signals for the 4 x C=O carbon atoms, the aromatic carbon atoms and the methyl groups. ¹H NMR spectroscopic data for 2.17 and 2.18 are also tabulated in Table 2.4 (Page 109). The salient features are: (i) each benzylic methylene group appears as two doublets, each doublet integrating to one proton; (ii) the signals corresponding to the CH₂CO₂CH₃ protons also both appear as two doublets, implying that the methylene CH₂ protons are diastereotopic, and point to the presence of at least one chiral centre in the molecule; the doublet, double doublet, and doublet resonances, which we assign to the C-6, C-7 and C-7a protons, are indicative of three contiguous CH groups. The C-7a proton resonance of 2.18 appears downfield from that in 2.17, possibly because of the facing ester at C-5 (See later). Furthermore, the coupling constant between the C-7 and C-7a protons is consistent with the trans relationship in compound 2.18.

On the basis of these data, we can discount the alternative structure 2.41 (Figure 2.10), which requires three CH₂ groups and five contiguous CH groups.

![Figure 2.10](image-url)
The observed cycloadducts can be conceived as arising from a Michael-type addition of
the imidazoline to the unsaturated esters, followed by proton shift to generate the ylide
2.42 and a subsequent 1,3-DC reaction between the so-formed ylide and a second molecule
of the unsaturated ester (Scheme 2.29).

Scheme 2.29 A mechanism for the 1,3-DC reaction of an imidazoline with an unsaturated
ester

Based on the transition state model for similar reactions developed by Jones and co­
workers\cite{135}, compound 2.18 is expected to be the first-formed cycloadduct. That both 2.17
and 2.18 are the products we obtained probably arises from an epimerisation of 2.18 under
the conditions of the experiment \textit{via} a sequence such as that shown in Scheme 2.30.
Scheme 2.30 The epimerisation of 2.18 and 2.17

Figure 2.11 X-Ray crystal structure of minor product 2.18

It proved possible to obtain an X-ray crystal structure of the minor product 2.18 and this is shown in Figure 2.11. The relative stereochemistry of the four new chiral centres is apparent, the two CO₂Me groups at C-6 and C-7 being trans, and the C-7 and C-7a protons being cis. The downfield shift of the C7a-H ¹H NMR signal in the minor product 2.18, as compared with that in 2.17, is probably the result of the deshielding effect of the CO₂Me group at C-5, rather than the corresponding cis C-6 group. Indeed, as will be seen later, when the reaction is carried out with maleimides (next section) the product has inverted C-
6 stereochemistry yet the chemical shift of the C7a-H remains in a similar position (δ 4.8 p.p.m.).

For compound 2.17 an X-ray crystal structure was not forthcoming, the compound being an oil. We therefore studied this compound using n.O.e. effects in the ¹H NMR spectrum. These indicate that the C-7a proton is cis to both the C-6 proton and the C-5 methylene group and trans to the C-7 proton (Figure 2.12).

![Figure 2.12 n.O.e. effects seen in the ¹H spectrum of 2.17](image)

Interestingly, the epimerisation was observed to occur in an NMR tube (solvent CDCl₃) when, after approximately one day, the single compound 2.18 had become a mixture of the two compounds 2.17 and 2.18. This would seem to imply that 2.18 is the kinetic product, formed via a transition state discussed previously and in which the ylide adopts a conformation shown in Figure 2.13, and that 2.17 is the thermodynamic product. The loss of stereochemical integrity at C-7a, due to epimerisation may be because it is catalysed by small quantities of acid present in the CDCl₃ solvent (Scheme 2.30).
Having demonstrated the cycloaddition reaction between 2-imidazoline \textbf{2.1} and fumarate or maleate methyl esters, we decided to examine the reaction with diethyl fumarate. In this case, after heating for 10 d, we obtained a mixture of three isomers \textbf{2.43}, \textbf{2.44} and \textbf{2.45} (Scheme 2.31) in a combined yield of 36%.
Interestingly, in this case where heating was carried out over an extended period, the product corresponding to the ethyl ester analogue of the primary cycloadduct 2.18 was not observed. Repeated column chromatography enabled compounds separation, although with some loss of material, affording a 20% yield of compound 2.43, 3% yield of compound 2.44 and 6.3% yield of compound 2.45.

For 2.43, the ethyl analogue of 2.17, HRMS showed a measured mass for MH\(^+\) of 505.2551, in agreement with the required mass for MH\(^+\) of 505.2550. Moreover, comparison of the \(^1\)H and \(^{13}\)C NMR data in Table 2.4 (p109) reveals that the resonances of 2.43 closely match those of 2.17, both in terms of chemical shift and coupling constants. For this reason, we propose 2.43 to have the same structure and stereochemistry as compound 2.17. Additionally, the stereochemical assignment of adduct 2.43 was based on n.O.e. experiments (Figure 2.14) and coupling constants. Thus, the \(J_{7,7\text{a}}\)-value of 11 Hz supports a \textit{trans}-relationship; at the same time we observed a 0.9% n.O.e. from H-7a to H-7.

![Figure 2.14 n.O.e. spectrum of 2.43](image)
Interestingly, the solution of compound 2.43 used for $^1$H NMR showed, after some 6 h, the presence of a new compound. The spectrum showed no further changes after this time and we infer an equilibrium had been set up. Careful inspection of the $^1$H and $^{13}$C spectra allowed us to deduce the resonances for this new structure, and these are contained in Table 2.4. The correspondence of these with those of 2.18 leads us to suggest this new compound is the ethyl analogue, 2.46.

The ratio of compounds 2.43 and 2.46 in solution was approximately 2:1, from which we infer 2.43 is the thermodynamically more stable isomer.

Of particular interest was the formation of the ring-opened product 2.44 and the lactam 2.45. Compound 2.44 has the structure of an intermediate that may also be involved in the epimerisation at C-7α that interconverts the kinetic and thermodynamic products. Evidence for its structure comes from the NMR and mass spectra. The HRMS showed an MH$^+$ of 505.2550 in agreement with the expected MH$^+$ of 505.2550. The $^1$H NMR spectrum contained a one-proton singlet at δ 7.28, reminiscent of an H$_2$C=CCO$_2$CH$_2$CH$_3$ proton, and another singlet at δ 4.30 corresponding to the CHCO$_2$CH$_2$CH$_3$ proton. The two doublets at δ 3.05 and δ 3.13, both with $J$=17.2Hz, each integrating to one proton, belong to the
CH$_2$CO$_2$CH$_2$CH$_3$ system. Most significantly, we can observe a broad singlet at $\delta$ 1.62 that corresponds to the NH proton. The $^{13}$C spectrum reveals two CH carbon resonances at $\delta$ 54.15 and $\delta$ 150.84 for the CHCO$_2$CH$_2$CH$_3$ and HC=CCO$_2$CH$_2$CH$_3$ carbon atoms. Absorptions observed at $\delta$ 73.09 and $\delta$ 100.23 correspond to the quaternary carbon atoms at C-5 and HC=CCO$_2$CH$_2$CH$_3$. The infrared absorptions at $\nu_{\text{max}}$/cm$^{-1}$ 3332 (NH), 1736 (unconjugated ester C=O), 1683 (conjugated enaminoo ester C=O), and 1607 (C=C), and especially at 3340 (NH) are also consistent with the proposed structure.

Evidence for the structure of 2.45, postulated to be formed as shown in Scheme 2.32 via collapse of 2.44, came from its $^1$H NMR and $^{13}$C NMR spectra and its mass spectrum. In particular, the signals at $\delta_H$ 7.02 p.p.m. and $\delta_C$ 151.24 p.p.m. (methine) are characteristic of the H-C=C fragment, while the mass spectrum reveals a molecular ion at $m/z$ 458 that is consistent with the loss of EtOH from 2.43/2.44. HRMS showed an MH$^+$ of 459.2125, in agreement with the expected MH$^+$ of 459.2131. In the $^1$H NMR we can observe two singlets at $\delta$ 7.02 and at $\delta$ 3.88, each integrating to one proton, that are characteristic of NCH=CCO$_2$CH$_2$CH$_3$ and CHCO$_2$CH$_2$CH$_3$ protons. Also, the presence of proton resonances at $\delta$ 3.05 and $\delta$ 3.37, integrating to one proton each, both of which are doublets, is consistent with the CH$_2$CO$_2$CH$_2$CH$_3$ protons. Further evidence of a chiral centre comes from the diastereotopicity of the benzylic methylene (NCH$_2$Ph) protons, which were found as two doublets at $\delta$ 4.53 and $\delta$ 4.63, $J$=14.6 Hz. The $^{13}$C NMR shows the presence of two alkene carbon atoms at $\delta$ 98.98 and $\delta$ 151.24. The infrared absorptions at $\nu_{\text{max}}$/cm$^{-1}$ 1744 (C=O), 1681 (conjugated C=O), 1654 (six-membered ring lactam C=O) and 1604 (C=C) are consistent with formation of a lactam (Scheme 2.32).
Scheme 2.32
<table>
<thead>
<tr>
<th></th>
<th>2.17</th>
<th>2.18</th>
<th>2.43</th>
<th>2.46</th>
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<tbody>
<tr>
<td>C-2 H</td>
<td>2.28 and 3.14/Hz</td>
<td>2.56/Hz</td>
<td>2.30/Hz</td>
<td>2.51/Hz</td>
</tr>
<tr>
<td>C-3 H</td>
<td>2.95/m</td>
<td>2.88/m</td>
<td>3.00/m</td>
<td>2.87/m</td>
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<tr>
<td>C-5 CH2</td>
<td>3.08, 3.13/J = 14.6</td>
<td>2.91, 3.64/J = 17.2</td>
<td>2.92, 3.08/J = 14.6</td>
<td>2.88, 3.64/J = 17.2</td>
</tr>
<tr>
<td>C-6 H</td>
<td>4.45/J = 10.8</td>
<td>3.55/J = 11.3</td>
<td>4.50/J = 11</td>
<td>3.52/J = 11.4</td>
</tr>
<tr>
<td>C-7 H</td>
<td>3.66/J = 4.6, 10.8</td>
<td>3.61/J = 7, 11.3</td>
<td>3.68/J = 5.3, 11</td>
<td>3.60/J = 7.3, 11.5</td>
</tr>
<tr>
<td>C-7a H</td>
<td>3.85/J = 4.6</td>
<td>4.90/J = 6.96</td>
<td>3.86/J = 5.3</td>
<td>4.90/J = 7.32</td>
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<tr>
<td>CH2Ph</td>
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<td>3.43, 4.21/J = 13.6</td>
<td>3.04, 4.21/J = 13.5</td>
<td>3.44, 4.23/J = 13.4</td>
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<tr>
<td>Me</td>
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<td>3.62, 3.70, 3.73, 3.74</td>
<td>3.68, 3.70, 3.73, 3.74</td>
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<tr>
<td>Ph</td>
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<tr>
<td>C-2</td>
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<td>47.92</td>
<td>45.02</td>
<td>47.95</td>
</tr>
<tr>
<td>C-3</td>
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<td>51.93</td>
<td>53.05</td>
<td>52.02</td>
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<td>50.53</td>
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<tr>
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<tr>
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<td>56.37</td>
<td>59.36</td>
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<tr>
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<td>40.15</td>
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<td>53.12</td>
<td>52.81</td>
<td>14.30</td>
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<tr>
<td>C=O</td>
<td>170.70</td>
<td>170.22</td>
<td>170.42</td>
<td>169.79</td>
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<tr>
<td></td>
<td>170.94</td>
<td>170.29</td>
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<td></td>
<td>171.39</td>
<td>171.32</td>
<td>170.86</td>
<td>170.91</td>
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<tr>
<td></td>
<td>172.81</td>
<td>171.46</td>
<td>172.55</td>
<td>170.95</td>
</tr>
<tr>
<td>Ph carbon</td>
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<td>126.96</td>
<td>126.95</td>
<td>126.87</td>
</tr>
<tr>
<td></td>
<td>128.32</td>
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<td></td>
<td>128.53</td>
<td>128.34</td>
<td>128.57</td>
<td>128.37</td>
</tr>
<tr>
<td></td>
<td>138.35</td>
<td>138.80</td>
<td>138.92</td>
<td>138.88</td>
</tr>
</tbody>
</table>
2.3.2 Maleimides as dipolarophiles

Following the observation of cycloadducts from the reaction of imidazoline 2.1 and fumarate/maleate esters, we extended our investigations to other dipolarophiles. Cyclic dipolarophiles, in particular, such as \( N \)-methyl- and \( N \)-phenylmaleimides should lead to cycloadducts with relative stereochemistry at the C-5 and C-6 fixed in a \( cis \) configuration, in contrast to the \( trans \) configuration observed with fumarates and maleates.

Thus, addition of \( N \)-methylmaleimide to 2-imidazoline 2.1 in dry DCM at reflux for 24 h led to endo-cycloadduct 2.22 as the major product, isolated as a light yellow solid in 30% yield, together with a trace amount of the exo-adduct 2.24 (Scheme 2.33).

![Scheme 2.33](image)

The structure of the compound 2.22 was solved by X-ray crystallography (Figure 2.15), which established the stereochemistry of the new chiral centres. The NMR data for compounds 2.22 and 2.24 will be discussed shortly, together with those from similar reaction of \( N \)-phenylmaleimide.
The above procedure was repeated using $N$-phenylmaleimide. Separation of the diastereoisomers by column chromatography enabled the major product 2.47 to be isolated in 36% yield as a white solid, whilst the minor product 2.48 was isolated in 8% yield (Scheme 2.34). The stereochemistry of the two products was studied by X-ray crystallography or NMR spectroscopy. The stereogenic centres at C-5 and C-7a were created selectively since examination of the product mixture by $^1$H and $^{13}$C NMR spectroscopy revealed the presence of only two diastereoisomers.
The structure of major cycloadduct 2.47 was determined by a crystal structure analysis (Figure 2.16). The $^1$H NMR spectrum contains resonances for the aromatic protons at $\delta$ 7.28. The anticipated doublet resonances, each integrating to one proton at $\delta$ 3.44 and $\delta$ 4.79, correspond to the C-6 and C-7a proton, and the signal at $\delta$ 4.00 integrating to one proton had the expected doublet of doublets corresponding to the C-7 proton. The benzylic methylene protons, being diasterotopic, appeared as two separate doublets at $\delta$ 3.29 and 4.31 with $J$=11.7 Hz. The CH$_2$ protons of NPhCOCH$_2$CO, which are also diasterotopic, resonated at $\delta$ 3.05 and $\delta$ 4.19 with a $J$ value of 19.05 Hz. According to DEPT $^{13}$C NMR studies, three CH carbon atoms at $\delta$ 49.82, $\delta$ 51.33 and $\delta$ 86.48 were observed, with the resonance at $\delta$ 70.16 corresponding to the quaternary C-5 carbon atom.

The n.O.e. difference spectrum, summarised in Figure 2.17, reveals enhancements of ca. 10% between C6-H and C7-H and between C7-H and C7a-H, consistent with an all cis arrangement of the three protons.

Figure 2.16 X-Ray crystal structure of major product 2.47
For the minor product 2.48, the n.O.e. difference experiment is summarised in Figure 2.18. We observed a small enhancement (2%) at the C-7a for the bridgehead proton on irradiation of the C-7 signal provides tentative evidence that they are on the opposite faces of the molecule and therefore to have the relative stereochemistry expected from exo approach of the dipolarophile. Irradiation of the C-6 proton led to an enhancement of the C-7 proton; thus, these two protons are on the same face of the molecule. Observation of an enhancement of the proton at C-6 on irradiation of the protons of the methylene group attached at C-5 confirms that they are on the same face of the molecule.
Relevant \( ^1H \) NMR data for the two \( N \)-methylmaleimide adducts and the two \( N \)-phenylmaleimide adducts are summarised in Table 2.5. The crucial observation is the size of the \( ^3J \) coupling between the C-7 and C-7a protons. Molecular models show that for compounds 2.22 and 2.47, the major product of these reactions, the dihedral angle between these protons is close to 0°, and as expected from the Karplus relationship the coupling constant is relatively large \(^{154}\). For 2.24 and 2.48, however, the corresponding dihedral angle is close to 90° which is consistent with a much smaller coupling constant of ca. 2 Hz.

**Table 2.5** Comparison of selected NMR, data for the major and minor cycloadducts of 2.1 with maleimides

<table>
<thead>
<tr>
<th></th>
<th>Major product</th>
<th>Minor product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \delta ) (p.p.m.)</td>
<td>( J/\text{Hz} )</td>
</tr>
<tr>
<td>R=Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.70</td>
<td>7.6</td>
</tr>
<tr>
<td>C7-H</td>
<td>3.93</td>
<td>7.9, 7.6</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.22</td>
<td>7.9</td>
</tr>
<tr>
<td>R=Ph</td>
<td>4.79</td>
<td>7.6</td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.00</td>
<td>7.8, 7.6</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.44</td>
<td>7.8</td>
</tr>
</tbody>
</table>

From the relative yields of the cycloadducts, 2.22/2.24 and 2.47/2.48, it can be seen that the favoured cycloaddition pathway occurs *via* the ylide possessing the *anti*- conformation (Figure 2.19). Thus, the stereochemical outcome can be rationalised by envisaging *exo-* or *endo-* attack of the dipolarophile on the ylide, the major cycloadducts 2.22 and 2.47 resulting from *endo* addition (Figure 2.20).
Following successful cycloaddition involving unsaturated esters and imides, we studied the analogous unsaturated nitrile system, namely fumaronitrile. Thus, treatment of a DCM solution of 2-imidazoline \(2.1\) with fumaronitrile as dipolarophile at room temperature for 48 h afforded, after column chromatography, the bicyclic adducts \(2.49\) and \(2.50\), but in 5% very low yield (Scheme 2.35).
HRMS showed these compounds to have the same molecular composition, and one that is consistent with their formulation as shown; for compound 2.50, MH⁺ was determined as 317.1511, in agreement with the calculated MH⁺ of 317.1514, and for compound 2.49, MH⁺ was 317.1512. However, these compounds are clearly different by \(^1\)H NMR (Table 2.6 and Figure 2.21) and \(^13\)C NMR spectroscopy,

**Table 2.6 Comparison of selected \(^1\)H NMR data for compounds 2.49 and 2.50**

<table>
<thead>
<tr>
<th></th>
<th>2.49</th>
<th>2.50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>δ (p.p.m.)</td>
<td>(J/\text{Hz})</td>
</tr>
<tr>
<td>C-7a H</td>
<td>4.26</td>
<td>5.49</td>
</tr>
<tr>
<td>C-7 H</td>
<td>3.32</td>
<td>6.96, 5.49</td>
</tr>
<tr>
<td>C-6 H</td>
<td>4.01</td>
<td>6.96</td>
</tr>
<tr>
<td>CCH₂CN</td>
<td>2.99 apparent singlet</td>
<td>2.92, 2.99</td>
</tr>
</tbody>
</table>

As with the previous compounds of this general structure, the \(^{13}\)C NMR for compound 2.50 contained three CH carbon atoms corresponding to C-6, C-7 and C-7a at \(δ\) 43.24, \(δ\) 36.95 and \(δ\) 86.98; and at \(δ\) 44.43, \(δ\) 36.49 and \(δ\) 87.23 for compound 2.49. The 2-dimensional \(^1\)H-\(^{13}\)C cosy allowed the corresponding protons to be identified (as given in Table 2.6), and the proton-proton couplings showed the three CH systems to be contiguous. In both compounds, the benzylic methylene peak comprises two doublets, each doublet integrating to one proton; these doublets resonate at \(δ\) 3.64 and \(δ\) 3.75 p.p.m. for compound 2.49 and at
δ 3.61 and δ 3.76 p.p.m. for compound 2.50. Interestingly, the signal corresponding to the CCH-CN protons is an apparent singlet at δ 2.99 for compound 2.49, but a doublet of doublets (J=17.2 Hz) for compound 2.50.

Figure 2.21 $^1$H NMR spectra for (a) 2.49 and (b) 2.50

n.O.e. studies were used to assign the stereochemistry of the two compounds 2.49 and 2.50 (Figure 2.22).
In compound **2.49**, irradiation of the C-7 proton produces a 6.6% enhancement of the C-6 proton; for **2.50**, similar irradiation of the C-7 proton produces a smaller enhancement (1.5%). We interpret this to means that the C-7 and C-6 protons are in a *cis*-relationship for compound **2.49**, but *anti*-relationship in **2.50**. In compound **2.49**, irradiation of the C-7a proton displays an enhancement of 1.9% of the C-7 proton, while for compound **2.50**, similar irradiation of the C-7 proton enhances the C-7a proton by 0.6%, confirming an *anti*-relationship between the C-7a and C-7 protons in both compounds.

Irradiation of the CH$_2$CN resonance for compound **2.50** leads to an enhancement of the C-6 proton of 8.7%, consistent with a *cis*-relationship between these hydrogen atoms, while similar irradiation for compound **2.49** reveals an enhancement of the C-6 proton of only 0.24%, consistent with the proposed *trans*-relationship.

When the reaction was carried out in DCM at reflux (rather than room temperature) for 48 h, the isolated compound as was **2.51** in 10% yield (Scheme 2.36).
Fortunately, the stereochemistry of this third adduct could be studied by an X-ray crystallographic analysis; together with n.O.e. difference spectroscopy, this was able to confirm the structural assignment made on the basis of the NMR data (Figure 2.23).

This structure reveals compound 2.51 to be the endo adduct. Given the stereochemistry of the adducts isolated from other dipolarophile systems, the structure of these nitrile adducts reveals that the stereochemistry at C5 is inverted compared to the corresponding carbonyl systems. This could well be because the linear nitrile group is unable to stabilise the conformation of the ylide in the anti rotamer.
Clearly, like fumarate/maleate esters and maleimides, fumaronitrile reacts with the imidazoline to form an azomethine ylide that reacts with a second molecule fumaronitrile to trap the dipole. We rationalize the formation of compounds 2.49, 2.50 and 2.51 through formation of a dipole that has the conformation 2.52 shown in Scheme 2.37. This is an syn conformer, whereas for the esters the favoured conformer is anti. We attribute this change to an inability of the nitrile system to stabilise the anti conformer, as it is unable to adopt a suitable conformation that involves H-bonding to the C-2 H atom in the imidazolinium ring.

Products 2.49, 2.50 and 2.51 can then be accounted for as follows: for 2.49, either fumaronitrile isomerises to maleonitrile \(^{155, 156}\) and the latter adds in the exo mode, or fumaronitrile adds as shown in Scheme 2.37, followed by ring-opening and re-closure; for 2.50, fumaronitrile adds as shown in Scheme 2.37; for 2.51, either maleonitrile adds in an endo-fashion, or it is formed by ring-opening and re-closure of 2.50.
Interestingly, the “kinetic” product, 2.53 was not found in these reactions. We have no explanation as to why this would be so.
2.3.4 \( \beta \)-Nitrostyrene and DMAD as dipolarophiles

Given the success of the 1,3-DC reaction between an imidazoline and symmetrically substituted electron-deficient alkenes, we decided to investigate the reaction between an imidazoline and other electron-deficient C-C multiple bonds. This section describes the results obtained from the reaction of 2-imidazoline 2.1 with, separately, \( \beta \)-nitrostyrene and dimethyl acetylenedicarboxylate.

In the 1,3-DC reaction discussed in previous sections, the 2-imidazoline reacts first with a molecule of the electron-deficient multiple bond of the ‘dipolarophile’ in a Michael sense. Subsequent cycloaddition requires a crucial proton shift to generate an ylide. This proton shift is facilitated by a carbonyl or nitrile on the incipient ylide carbon atom. To examine how facile this proton shift is, we next studied the reaction of \( \beta \)-nitrostyrene (Scheme 2.38). Here, the group on the incipient ylide carbon atom is a phenyl group. Cycloaddition, if it were to occur, would afford the heterocyclic adduct 2.54.

![Scheme 2.38](image)

In the event, reaction of 2-imidazoline 2.1 in anhydrous DCM under nitrogen at reflux for 28 h with \( \beta \)-nitrostyrene as dipolarophile gave products 2.38 (in 3.1% yield) and 2.39 (in 36% yield), which were separable by silica gel column chromatography (Scheme 2.39).
Significantly, in this case six-membered ring adducts were formed, and no evidence of a bicyclic 1,3-dipolar cycloadduct was obtained. A rationalization for the cyclization is that the phenyl group provides insufficient carbanion stabilisation to allow proton transfer prior to reaction with a second molecule of electron-deficient alkene.

The structure of both adducts 2.38 (Figure 2.24) and 2.39 (Figure 2.25) were supported by standard spectral data as well as X-ray crystal structure determinations.

The X-ray technique in particular enabled us to determine the relative stereochemistry for the five new chiral centres in adduct 2.38 and the three chiral centres in 2.39.
The NMR spectra of these compounds are consistent with these structures. Firstly, for compound 2.38 DEPT $^{13}$C NMR analysis showed the presence of five $CH$ carbon atoms at $\delta$ 50.32, $\delta$ 68.74, $\delta$ 84.39, $\delta$ 91.15 and $\delta$ 93.76, in contrast to the expected three $CH$ for the usual cycloadduct 2.54. Secondly, the anticipated $^{13}$C NMR resonance for the quaternary PhCH$_2$NO$_2$ carbon atom (at about $\delta$ 65-75 p.p.m.) of the cycloadduct 2.54 was absent. Thirdly, for 2.38, the $^1$H NMR spectrum contained one-proton doublets at $\delta$ 3.93 and $\delta$ 4.14 for the C-8a and C-5 protons, and double doublets at $\delta$ 4.16, $\delta$ 4.93 and $\delta$ 5.02 for the C-7, C-6 and C-8 protons, respectively.

For compound 2.39 the $^1$H NMR spectrum contained a one-proton singlet at $\delta$ 8.21 ppm, corresponding to the C=CH proton. Further, the $^{13}$C DEPT NMR contained four signals at $\delta$ 42.72, $\delta$ 57.02, $\delta$ 88.63 and $\delta$ 146.88, corresponding to four $CH$ carbon atoms. Additionally, while the IR spectrum of 2.38 contained absorptions at $\nu_{\text{max}}$/cm$^{-1}$ 1557 (C-NO$_2$ symm) and 1368 (C-NO$_2$ anti-symm), the IR absorption of 2.39 additionally contained on absorption at $\nu_{\text{max}}$/cm$^{-1}$ 3338 (NH) and 1618 (C=C).
Thus, it is possible to conclude that the phenyl group is not sufficiently electron withdrawing to allow the proton transfer that forms the ylide, and formation of the six-membered ring products arises by a Michael addition of a second molecule of alkene to the initially formed NO\textsubscript{2}-stabilised carbanion followed by ring-closure (Scheme 2.40). It is obvious that 2.39 is formed by an eliminative ring opening of a bicyclic product.

One explanation for the stereochemistry of these products is as follows. Attack of the imidazoline on the first \( \beta \)-nitrostyrene molecule produces the zwitterion 2.56 (Scheme 2.41) and introduces the first chiral centre at the carbon atom that will become C5 of the bicyclic ring system. This chiral centre can have either \( R \)- or \( S \)-chirality since there will be no selectivity in this initial reaction, and the zwitterion can have one of two conformations, 2.56 and 2.57, that are interconvertible by rotation.
Reaction of the either zwitterion with a second $\beta$-nitrostyrene molecule can potentially occur in one of four orientations. Consider zwitterion 2.56 first; $\beta$-nitrostyrene can approach the imidazoline ring with the NO$_2$ group either $\text{endo}$ or $\text{exo}$ to the ring and either from above or below the imidazoline ring (Scheme 2.42). Similar considerations can be made for zwitterion 2.57 (Scheme 2.43).
Scheme 2.42
Inspection of the stereochemical outcomes of these processes reveals that the stereochemistry of the three chiral centres in the major isolated product 2.39 can be accommodated either by reaction of 2.56 via an endo/above mode or from 2.57 via an exo/below mode. Either of these processes forms 2.58, in which the C-8 proton and the piperidine C-N bond to C-8a are in a trans relationship. Thus, the formation of compound 128.
2.39 must result from a facile a $\beta$-elimination. In an analogous fashion the minor product 2.38 can arise from 2.56 via an *exo*/above mode or from 2.57 via an *endo*/below. Product 2.38 has an unfavourable disposition of the C-8 proton and the C-N bonds such that eliminative ring-opening is disfavoured. The most likely pathway to both 2.38 and 2.39 is that in which the alkene approaches from the opposite side to the phenyl group at the initially-formed chiral centre; for both isolated products this would imply reaction via zwitterion 2.57.

A number of fruitless attempts was made to extend the scope of these cycloaddition reactions to similar less electron-poor alkenes. For example, when methyl $E$-cinnamate or cinnamonitrile were employed as dipolarophiles, the reaction met with no success, only the starting materials being recovered.

However, under the usual reactions conditions, treatment of 2-imidazoline 2.1 with DMAD for 10 d afforded a product to which we assign the six-membered ring structure 2.59, rather than the alternative 2.60; the yield, though, was only 5.3% after silica gel column chromatography (Scheme 2.44).

\[
\begin{array}{c}
\text{CH}_3\text{Ph} \quad \text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{CH}_3 \\
\text{2.1}
\end{array}
\rightarrow
\begin{array}{c}
\text{CH}_3\text{Ph} \\
\text{H} \\
\text{N} \\
\text{2.59} \quad 5.3\%
\end{array}
\]
The colourless, oily product had an HRMS that gave MH\(^+\) at 455.1609, in agreement with the expected MH\(^+\) of 445.1661 for a 1:2 imidazoline: DMAD adduct. The \(^1\)H NMR spectrum exhibits: (i) a group of signals at \(\delta\) 3.62, \(\delta\) 3.64, \(\delta\) 3.67 for three of the CO\(_2\)CH\(_3\) group, and a further CO\(_2\)CH\(_3\) singlet at \(\delta\) 3.83 for implying that one of the methyl ester groups differs from the rest, (ii) two doublets at \(\delta\) 3.67 and \(\delta\) 3.78 \((J=13.38)\) for diasterotopic methylene benzylic protons, (iii) multiplets at \(\delta\) 2.89 and \(\delta\) 3.10, each corresponding to one proton, and a multiplet at \(\delta\) 3.59-3.75 corresponding to two protons, assigned to the NCH\(_2\)CH\(_2\)N protons, and (iv) a one proton singlet \((1H)\) at \(\delta\) 7.77. The low-field position of this latter singlet requires the proton to be vinylic, consistent with the C-5 proton in 2.59 rather than the C-8a proton in 2.60. The \(^{13}\)C NMR spectrum reveals a CH carbon signal at \(\delta\) 146.67 and a quaternary C at \(\delta\) 84.44, which correspond to C-5 and C-8a in 2.59 rather than the equivalent positions in the alternative formulation 2.60. The remainder of the resonances in the \(^{13}\)C NMR account for the presence of the benzylic CH\(_2\) carbon atom at \(\delta\) 55.99, as well as the CH\(_2\) carbon atoms belonging to the dihydroimidazole at \(\delta\) 47.79 and \(\delta\) 48.60, while those observed at \(\delta\) 98.27, \(\delta\) 109.34 and \(\delta\) 146.67 correspond to the carbon atoms C-8, C-7 and C-5. DEPT NMR studies also established one CH carbon atom, three CH\(_2\) carbon atoms and four C carbon atoms.

These data, and their interpretation, are consistent with those obtained for products of similar reactions between DMAD and quinazoline\(^{[152]}\) and thiazoles\(^{[152,153]}\). For example, the adduct 2.61\(^{[153]}\) affords NMR data (Table 2.7) that are similar to those for 2.59, the differences relating to replacement of N-1 by S-1.
Table 2.7 comparison of selected NMR data for 2.59 and 2.61

<table>
<thead>
<tr>
<th></th>
<th>2.61*</th>
<th>2.59</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ/ppm</td>
<td>δ/ppm</td>
<td></td>
</tr>
<tr>
<td>C-5 H</td>
<td>8.01</td>
<td>7.77</td>
</tr>
<tr>
<td>C-5</td>
<td>144.3</td>
<td>146.67</td>
</tr>
<tr>
<td>C-6</td>
<td>139.1</td>
<td>141.1</td>
</tr>
<tr>
<td>C-7</td>
<td>104.6</td>
<td>109.34</td>
</tr>
<tr>
<td>C-8</td>
<td>100.6</td>
<td>98.27</td>
</tr>
<tr>
<td>C-8a</td>
<td>74.9</td>
<td>84.44</td>
</tr>
</tbody>
</table>

* Data taken from ref. 153.

A possible mechanism for the formation of compound 2.59 involves the successive addition of two molecules of DMAD to 2-imidazoline 2.1 leading to 2.60. Ring opening, probably catalysed by traces of acid in the DCM solvent, would afford an intermediate that can re-cyclise via attack at the alternative position adjacent to the pyridinium nitrogen atom to afford the isomeric, and presumably thermodynamically more stable, compound 2.59 as shown in Scheme 2.45.
2.3.5 A mixed fumarate-maleimide dipolarophile system

In the proceeding two sections, we investigated the generation of an azomethine ylide from a 2-imidazoline and a conjugated double bond in which the subsequent cycloaddition reaction involved the same conjugated system as the dipolarophile. Here we describe the results obtained from an investigation involving the reaction of the 2-imidazoline 2.1 with mixed conjugated systems.
Since reaction times were observed to be significantly shorter for the maleimides than for the fumarate/maleate esters, we chose to set up the mixed imide/ester reactions by slowly adding (syringe pump, 3 d) the maleimide to a mixture of imidazoline and fumarate ester. Thus, imidazoline 2.1, dimethyl fumarate and N-phenylmaleimide afforded a mixture of three products: the two stereoisomeric cycloadducts derived from N-phenylmaleimide described previously, and adduct 2.62, formed from reaction of the imidazoline with one molecule of fumarate and one of maleimide. The latter was isolated in 37% yield as the major product (Scheme 2.46).

The structure of 2.62 was confirmed by X-ray crystallography (Figure 2.26) but follows from the mass spectrum and NMR spectral data. First, HRMS give a measured mass of $\text{MH}^+$ 478.1974 in agreement with the required mass $\text{MH}^+$ of 478.1978. Second, in the $^1\text{H}$
NMR spectrum there are three one-proton signals at $\delta$ 3.99, $\delta$ 4.00 and $\delta$ 4.9, corresponding to the C-6, C-7 and C-7a protons. The benzylic methylene resonances at $\delta$ 3.51 and $\delta$ 4.22, each integrating to one proton, are doublets, as are the resonances corresponding to the CCH$_2$CO$_2$CH$_3$ protons. The latter appear as two doublets at $\delta$ 3.21 and $\delta$ 3.32 ($J$=17.9 Hz), each integrating to one proton. DEPT $^{13}$C NMR analysis demonstrated the presence of three CH carbon atoms at $\delta$ 50.25, $\delta$ 52.10 and $\delta$ 85.35, corresponding to C-6, C-7 and C-7a. The quaternary carbon atom at C-5 is observed at $\delta$ 69.78.

![Figure 2.26 X-Ray crystal structure of major product 2.62](image)

The structure reveals that the C-7/C-7a protons have syn-stereochemistry and the orientation of substituents at C-6/C-7 is anti. The X-ray structure also allows us to establish the relative stereochemistry of the C-5 chiral centre (Figure 2.26).

The structure of 2.62 (indeed, all of three products) implies that N-phenylmaleimide reacts with the imidazoline preferentially to form the 1,3-dipole. This observation is consistent with the reaction times involved in the independent reactions of the two alkenes. The dipole is then trapped by the fumarate, which is always present in excess over the imide.
The stereochemistry of the mixed adducts is consistent with the transition state model previously described for the reaction of the individual alkenes \(^{144}\), that is, \textit{endo} approach of the dipolarophile to the \textit{anti}-configured dipole (Figure 2.27).

![Figure 2.27](image)

An analogous reaction was observed between the 2-imidazoline 2.1 and dimethyl fumarate and \(N\)-methylmaleimide. The two main products obtained were 2.63 (24% yield) yield and 2.64 (6.7% yield), together with compounds 2.22 and 2.24 in trace amounts (Scheme 2.47).
The stereochemical assignment of compound 2.63 is based on its X-ray crystal structure (Figure 2.28). NMR data (Table 2.8) are consistent with this stereochemistry. Thus, $J_{7,7a}$ values for compound 2.63 ($J=7.44$ Hz) supports a syn orientation of the two protons (dihedral angle close to 0°), while the $J_{6,7}$ value ($J=10.44$ Hz) supports the anti-relationship between these two hydrogen atoms (dihedral angle close to 180°). The $^{13}$C the chemical shift data for carbon atoms C-6, C-7 and C-7a in 2.63, are similar to those previously reported for the structurally related compound 2.18.

The data in Table 2.8 for the minor product 2.64 are remarkably similar to those for 2.17 and 2.43 (Table 2.4, page 109). We therefore assign the analogous stereochemistry to compound 2.64, as that shown in Scheme 2.47.
Figure 2.28 X-Ray crystal structure of major product 2.63

Table 2.8 shows that in compound 2.63 the C-7a proton resonance appears to higher frequency of the corresponding signal for 2.64. The coupling between the C-7a and C-7 protons in this minor product is notably smaller, consistent with a dihedral angle close to 120°.

Table 2.8 Comparison of selected NMR data for compounds 2.63 and 2.64

<table>
<thead>
<tr>
<th></th>
<th>2.63</th>
<th>2.64</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ /p.p.m.</td>
<td>J/Hz</td>
<td>δ /p.p.m.</td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.83</td>
<td>7.44</td>
</tr>
<tr>
<td>C7-H</td>
<td>3.99</td>
<td>10.44, 7.44</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.92</td>
<td>10.44</td>
</tr>
<tr>
<td>C-7a</td>
<td>85.2</td>
<td>86.95</td>
</tr>
<tr>
<td>C-7</td>
<td>52.09</td>
<td>52.76</td>
</tr>
<tr>
<td>C-6</td>
<td>52.26</td>
<td>49.03</td>
</tr>
</tbody>
</table>
2.3.6 Mixed fumarate-fumaronitrile and maleimide-fumaronitrile systems

Given the successful isolation of the mixed maleimide/fumarate cycloadducts, we wished to examine further mixed dipolarophile systems.

Fumarate-fumaronitrile systems

Treatment of a solution of 2-imidazoline 2.1 and dimethyl fumarate in DCM at room temperature with a solution of fumaronitrile (using a syringe pump) allowed compound 2.66, the product of reaction with both alkenes, to be isolated along with compounds 2.17 and 2.18, the products of reaction with fumarate alone (Scheme 2.48).

![Scheme 2.48](image)

Compound 2.66 is an oil, precluding a crystal structure. However, we are confident that the two alkenes have added in the order (i) dimethyl fumarate, (ii) fumaronitrile. Evidence for this comes from comparison of the $^{13}$C NMR resonances for the C6 and C7 carbon atoms in 2.66 with those of other bicyclic cycloadducts that bear ester and nitrile groups on these atoms (Table 2.9).
Table 2.9 $^{13}$C NMR resonances for the C6 and C7 atoms of various bicyclic cycloadducts

<table>
<thead>
<tr>
<th></th>
<th>Ester (δ/p.p.m.)</th>
<th></th>
<th>Nitrile (δ/p.p.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.17 2.18 2.43 2.46</td>
<td></td>
<td>2.49 2.50 2.51</td>
</tr>
<tr>
<td>C-6</td>
<td>37.99 53.79 51.74 54.14 51.88</td>
<td></td>
<td>44.44 43.24 43.14</td>
</tr>
<tr>
<td>C-7</td>
<td>39.77 49.90 51.09 50.23 50.96</td>
<td></td>
<td>36.49 36.95 37.98</td>
</tr>
</tbody>
</table>

Compounds 2.17/2.18/2.43/2.46 carry an ester group on the C6 and C7 atoms, for which the chemical shifts are around 50 p.p.m.; compounds 2.49/2.50/2.51, which carry nitrile group on the C6 and C7 atoms, have δ values around 40 p.p.m. The C6/C7 resonances for 2.66 are near to 40 p.p.m., from which we conclude the C6/C7 atoms bear nitrile groups.

![Figure 2.29 n.O.e. found for compound 2.66](image)

A comparison (Table 2.10) of the $^1$H NMR and $^{13}$C NMR chemical shifts for the C-6, C-7 and C-7a protons and carbon atoms with those of the corresponding products from reaction of 2.1 with fumaronitrile and N-substituted maleimides (2.70 and 2.72, see p 146), for which we have crystal structures, leads us to propose the stereochemistry of the major product as that shown in Scheme 2.48. However, one problem with such an interpretation is the observed n.O.e. between the C-6 and C-7 protons as revealed by the n.O.e. difference spectrum, the results of which summarised in Figure 2.29. There is a significant reciprocal enhancement between the protons at C-7 and C-7a, and also an interaction between the
proton at C-6 and the exocyclic methylene protons. These are both consistent with the structure shown, but the C6-C7 interaction seems too large.

**Table 2.10** Comparison of selected \(^1\)H NMR data for compound 2.66 and analogous compounds 2.70/2.72

<table>
<thead>
<tr>
<th></th>
<th>2.66</th>
<th>2.70</th>
<th>2.72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>δ/p.p.m.</td>
<td>J/Hz</td>
<td>δ/p.p.m.</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.15</td>
<td>11.34</td>
<td>3.27</td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.52</td>
<td>6.42</td>
<td>4.54</td>
</tr>
<tr>
<td>(\text{C}-5)</td>
<td>71.79</td>
<td></td>
<td>71.33</td>
</tr>
<tr>
<td>(\text{C}-6)</td>
<td>37.99</td>
<td></td>
<td>37.06</td>
</tr>
<tr>
<td>(\text{C}-7)</td>
<td>39.77</td>
<td></td>
<td>39.23</td>
</tr>
<tr>
<td>(\text{C}-7a)</td>
<td>83.38</td>
<td></td>
<td>83.75</td>
</tr>
</tbody>
</table>

Repeating the reaction using diethyl fumarate in place of dimethyl fumarate furnished a mixture, the major product being 2.67 (31% yield) and the minor product 2.68 (trace). As before, the products of reaction between the imidazoline and diethyl fumarate alone were also isolated (Scheme 2.49).
The stereochemistry of the cycloadduct 2.67 was assigned as follows. First, the $J_{6,7}$ coupling of 8.97 Hz (Table 2.11) is smaller than the equivalent coupling in 2.68 ($J_{6,7} = 11.16$ Hz) but is similar to the 7.35 Hz observed for compound 2.51, for which we have an X-ray structure. Second, for compound 2.67 n.O.e. difference spectra revealed enhancements between the C-7a/C-7 proton resonances (12%) and C-7/C-6 proton resonances (11.2%), respectively, supporting an all-cis relationship of these protons. Moreover, an n.O.e. between one of the CH$_3$CO$_2$Et methylene protons and the C-6 proton (21%) also placed these on the same face of the ring (Figure 2.30).
The NMR data for compound 2.68 are very similar to those for compound 2.66 (Table 2.11). Thus, we infer that the stereochemistry for 2.68 is identical to that in compound 2.66.

A possible mechanism that accounts for the formation of both products is shown in Scheme 2.50. Compound 2.68 is the product of endo-attack; initial formation of this followed by ring opening produces an intermediate in which the stereochemical integrity of C7/C7a is lost. However, such a species would be capable of ring closing from two
directions (above and below the ring plane), from above to form 2.67 and from below to reform 2.68.

\[ \text{Scheme 2.50} \]

**Maleimide-fumaronitrile systems**

To further widen the scope of the mixed cycloaddition reaction, we examined the use of fumaronitrile together with \( N \)-methylmaleimide or \( N \)-phenylmaleimide as dipolarophiles. Thus, reaction of 2-imidazoline 2.1 and fumaronitrile with \( N \)-methylmaleimide (added by syringe pump) afforded compound 2.70 (22% yield) as the major product and 2.69 (3.8% yield) as the minor product, while compounds 2.22 and 2.23 were present in trace amounts (Scheme 2.51).
The structures of compounds 2.69 and 2.70 were determined by X-ray crystallography (Figures 2.31 and 2.32).

Figure 2.31 X-ray crystal structure of compound 2.69
In compound 2.69, the protons at C-7/C-7\textsubscript{a} are \textit{cis} to one another and the protons at C-6/C-7 are \textit{trans}. Compound 2.70 has the same relative relationships for the protons at C-7\textsubscript{a}/C-7, and C-6/C-7.

Similar reaction fumaronitrile and N-phenylmaleimide gave the products 2.71 and 2.72, together with 2.47/2.48. The major product is 2.72 (21\% yield) with 2.71 the minor product (trace amounts).

\textbf{Table 2.12} tabulates selected \textsuperscript{1}H NMR data for the mixed cycloadducts for both N-phenylmaleimide and N-methylmaleimide. Compound 2.71 has chemical shifts and coupling constants very similar to those for compound 2.69; thus, we infer that 2.71 has a structure analogous to 2.69, which has been determined by X-ray crystallography. Likewise, 2.72 has \textsuperscript{1}H NMR data analogous to those for 2.70. Interestingly, the proton at C-7 in the major products, 2.70 and 2.72, resonates to higher frequency compared to the corresponding proton in the minor products, 2.69 and 2.71. This is presumably because the carbonyl group at C-5 deshields the C-7 proton when it resides on the same face.
Table 2.12 Selected NMR data for compound 2.69/2.70 and 2.71/2.72

<table>
<thead>
<tr>
<th></th>
<th>Major product</th>
<th></th>
<th>Minor product</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$ /ppm</td>
<td>$J$/Hz</td>
<td>$\delta$ /ppm</td>
<td>$J$/Hz</td>
</tr>
<tr>
<td>R=Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.54</td>
<td>6.42</td>
<td>4.27</td>
<td>6.42</td>
</tr>
<tr>
<td>C7-H</td>
<td>4.13</td>
<td>11.37, 6.42</td>
<td>3.23</td>
<td>11.34, 6.42</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.27</td>
<td>11.37</td>
<td>3.83</td>
<td>11.34</td>
</tr>
<tr>
<td>R=Ph</td>
<td>2.72</td>
<td></td>
<td>2.71</td>
<td></td>
</tr>
<tr>
<td>C7a-H</td>
<td>4.58</td>
<td>6.39</td>
<td>4.33</td>
<td>6.42</td>
</tr>
<tr>
<td>C7-H</td>
<td>4.10</td>
<td>11.34, 6.39</td>
<td>3.30</td>
<td>11.34, 6.42</td>
</tr>
<tr>
<td>C6-H</td>
<td>3.34</td>
<td>11.34</td>
<td>3.87</td>
<td>11.34</td>
</tr>
</tbody>
</table>

Compound 2.72 was further investigated by n.O.e. difference spectroscopy. The results, shown in Figure 2.33, are consistent with the structure inferred by comparison of $^1$H NMR data of 2.70 and 2.72. For example, irradiation of the C-7a proton produces a 12.7% enhancement of the C-7 proton, signifying these two protons have a cis-relationship. Irradiation of the C-7 proton produced a negligible enhancement of the C-6 proton (0.03%) confirming their anti-disposition. Finally, irradiation of one of the CH$_2$CONPh protons led to an enhancement of the C-6 proton implying a cis-relationship between the two.

![n.O.e. spectrum of compound 2.72](image)

Figure 2.33 n.O.e. spectrum of compound 2.72

146
The major products of these reactions, 2.70 and 2.72, are those expected from the transition state model involving an *endo* mode of approach by the dipolarophile (Scheme 2.52).

![Scheme 2.52](image)

The minor cycloadduct can be accounted for by an *exo* mode of approach of the dipolarophile, followed by epimerisation of the C-7a proton (Scheme 2.53).

![Scheme 2.53](image)

It is unclear why the relative stereochemistry of the fumaronitrile system in these mixed adducts (i.e. a *trans* arrangement of the CN groups) differs from that in the product obtained using fumaronitrile on its own (*cis* arrangement).
Having successfully observed ‘mixed’ dipolarophile products, we decided to re-examine those systems that did not react on their own. Thus, we anticipated the use of alkenes that were capable of forming an ylide together with less electron-poor alkenes as dipolarophiles. In the event, attempted reaction of 2-imidazole 2.1 with dimethyl fumarate/methyl cinnamate, dimethyl fumarate/methyl acrylate, dimethyl fumarate/β-nitrostyrene, N-phenylmaleimide/β-nitrostyrene and N-phenylmaleimide/methyl acrylate all proved unsuccessful.

### 2.3.7 Further mixed dipolarophile systems

We previously found that certain electron-deficient alkenes, e.g. fumarate esters and the like, were able to react with 2-imidazoline 2.1, whereas others, e.g. β-nitrostyrene, were not. We were interested to find out if, by combining one molecule of each type, we were able to effect mixed cycloadducts in a manner similar to those observed in previous section.

*Dimethyl fumarate/DMAD*

Treatment of a DCM solution of 2-imidazoline 2.1 at room temperature with dimethyl fumarate and DMAD for 3 d afforded the cycloadducts 2.73 (7.5%) and 2.59 (1.5%), respectively (Scheme 2.54). The latter compound is, of course, the product of reaction between 2.1 and DMAD described previously in Section 2.3.4. We saw no evidence for the formation of 2.18, the product of reaction of 2.1 with dimethyl fumarate itself.
Low-resolution EIMS analysis of compound 2.73 indicated a molecular ion at 446 and Cl (NH$_3$) MH$^+$ at m/z 447. It is obvious from this that a cycloaddition of 2-imidazoline 2.1 with DMAD and dimethyl fumarate has occurred. The $^1$H NMR spectrum of compound 2.73 exhibits resonances at $\delta$ 3.64, $\delta$ 3.67, $\delta$ 3.68 and $\delta$ 3.88 for the four CO$_2$CH$_3$ groups, two doublets at $\delta$ 3.86 and $\delta$ 3.91 ($J$=4.23 and 1.29 Hz) for the C-8a and C-7 protons, and one doublet of doublets at $\delta$ 3.39 ($J$=4.23 and 1.29 Hz) for the C-8 proton. These data suggest that the three CH groups are contiguous. In contrast, in the alternative structure 2.74, such a pattern would be absent and the C-7a proton would be singlet. $^{13}$C NMR DEPT analysis also showed the presence of three CH carbon atoms at $\delta$ 38.99, $\delta$ 40.45 and $\delta$ 74.06, consistent with 2.73 but not 2.74. Moreover, the quaternary carbon signal anticipated for 2.74, generally seen at 80 p.p.m. in such structures, is absent. The stereochemistry of compound 2.73 was assigned by NMR; the coupling between the C-7 H and the C-8 H for 2.73 is notably small ($J$=1.29 Hz); the coupling between the C-8 and C-8a protons is also small ($J$=4.23 Hz); these are consistent with anti rather than syn arrangements. Compound of 2.73 was also supported by IR absorptions at $\nu_{\text{max}}$/cm$^{-1}$ 1742 (unconjugated ester C=O) and 1693 (vinylogous carbamate C=O) and 1595 (C=C).
DMAD/N-Phenylmaleimide

2-Imidazoline 2.1 was treated in refluxing DCM by dropwise, slow addition of a mixture of N-phenylmaleimide and DMAD over 44 h. However, the only products isolated were those shown in Scheme 2.55; these are clearly those from reaction with the maleimide system alone.

Significantly, $^1$H NMR analysis of 2.75 shows the presence of a one-proton resonance at $\delta$ 8.03 p.p.m. and the absence of the signals normally seen for the C-7 and C-7a protons of the fused imidazopyrrolo systems such as cycloadducts 2.47 and 2.48.
The structure of 2.75, and its stereochemistry, was confirmed by a single crystal X-ray determination (Figure 2.34). The chiralities of the C-6 and C-6a centres (numbering as in Scheme 2.55) are identical to those of the minor cycloadduct 2.48 formed by exo approach of the second maleimide molecule.

Figure 2.34 X-Ray crystal structure of major product 2.75
We therefore suspect that \textbf{2.75} arises from the cycloadduct \textbf{2.48}, since the C-7a and N4 bond in the latter is \textit{anti}-periplanar to the C-7 hydrogen atom making it susceptible to \(\beta\)-elimination (\textbf{Scheme 2.56}).

![Scheme 2.56](image)

In the \(^{13}\text{C}\) NMR spectrum of compound \textbf{2.75}, the two signals at \(\delta\) 51.70 and \(\delta\) 147.56 correspond, according to DEPT \(^{13}\text{C}\) NMR, to CH carbon atoms. The former is the C-6a signal while the latter is due to the CH of the double bond at C-1.

\textit{Dimethyl fumarate/cinnamoniitrile}

Treatment of 2-imidazoline \textbf{2.1} and excess cinnamoniitrile in refluxing DCM with dimethyl fumarate (added slowly by syringe pump), afforded a range of cycloadducts. After chromatography, a mixture of \textbf{2.76} and \textbf{2.77} was isolated in 10\% yield, alongside the usual dimethyl fumarate 1:2 cycloadducts, namely, \textbf{2.17} (trace) and \textbf{2.18} (12\% yield) (\textbf{Scheme 2.57}).
The evidence for 2.76/2.77 is as follows. First, the mass spectrum showed a molecular ion at \( m/z \) 416, rather than the \( m/z \) 448 for the usual 1:2 fumarate product 2.17/2.18, or the \( m/z \) 433 expected for a 1:1:1 cycloadduct formed from 2.1, dimethyl fumarate and cinnamonicnitrile. The observed mass is consistent with a 1:2 fumarate product having lost a molecule of methanol.

The \(^1\)H NMR reveals evidence for an alkene proton at \( \delta \) 6.97 for compound 2.76 and \( \delta \) 7.00 for compound 2.77, and the \(^{13}\)C NMR spectra contain resonances for two alkene carbon atoms: at \( \delta \) 104.46 (C) and \( \delta \) 150.52 (CH) for 2.76 and \( \delta \) 103.15 (C) and \( \delta \) 150.03 (CH) for 2.77. Both compounds contain three methyl group resonances, so we conclude that ring opening of the primary cycloadducts followed by ring closure of the secondary amino group onto one of the ester groups, to form a six-membered lactam, has taken place. The infrared absorptions at \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1739 (C=O), 1692 (conjugated C=O), 1651 (six-membered ring lactam C=O) and 1604 (C=C) are supportive of such a structure. Moreover, no absorptions for any C≡N groups could be discerned. Clearly, these data tell us that \( E \)-cinnamonicnitrile plays no part in the formation of these products.
Given the general inability to observe mixed cycloadducts involving less electron-deficient multiple bonded systems, we decided at this point to conclude our studies of the 1,3-DC reaction of 2.1 with the mixed dipolarophile systems, and to direct our efforts toward the corresponding 1,3-DC reaction of involving a chiral imidazoline. The results and discussion of this follow.

2.3.8 Reaction of a chiral imidazoline with unsaturated substrates

Previous researchers in our group have successfully developed a concise synthesis of (R) and (S)-1-benzyl-4-phenyl-4,5-dihydroimidazole 2.9 \(^{147,148}\). We therefore chose to utilise the (R)-stereoisomer of this chiral imidazoline in 1,3-DC reactions described above for the achiral imidazoline 2.1.

*Fumarate ester adducts*

Reaction of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole 2.9 with dimethyl fumarate afforded 2.78 in 33% yield (Scheme 2.58).

![Scheme 2.58](image-url)
The structure of compound 2.78 was elucidated by X-ray crystallography and by analysis of the $^1$H and $^{13}$C NMR spectra, and also its mass spectrum. First, the mass spectrum had the expected molecular ion at $m/z$ 525 for a 2:1 adduct and the correct HRMS (found 525.2237, calculated 525.2237). Second, the $^{13}$C spectrum contains resonances at $\delta$ 51.18, $\delta$ 51.32, $\delta$ 71.87 and $\delta$ 85.60 p.p.m. as expected for the C-6, C-7, C-5 and C-7a carbon atoms. Further, DEPT $^{13}$C NMR analysis showed the presence of four CH carbon atoms, including the CH carbon atom of the NCH$_2$CHPhN system, in contrast to the three CH carbon atoms for the corresponding achiral compound, 2.17 or 2.18.

The X-ray crystallographic analysis of (Figure 2.35) established the stereochemistry compound 2.78 demonstrating that the hydrogen atoms at C7/C7a have syn-stereochemistry, and that the orientation of the substituents at C6/C7 is anti.

![Figure 2.35 X-ray crystal structure of the compound 2.78](image)

This stereochemical outcome can be nicely explained by proposing the formation of the anti ylide from (R)-2.9 followed by endo attack of the dipolarophile from the (upper) face opposite the 4-phenyl group of the imidazoline (Scheme 2.59).
Scheme 2.59 Rationalisation of the product stereochemistry observed in the reaction between a chiral imidazoline and dimethyl fumarate.
Similar reaction between (R)-2.9 and diethyl fumarate gave the analogous cycloadduct 2.79 in 48% yield, as well as two further cycloadducts, 2.80, 2.81 in trace amounts (Scheme 2.60).

The low resolution mass spectrometric analysis showed a molecular ion at m/z 580 in all three compounds; however, the $^1$H and $^{13}$C NMR of the three compounds are different. Thus, these compounds are isomeric.

Cycloadduct 2.79 gives rise to $^1$H chemical shifts and $J$-coupling for the C-6, C-7 and C-7a protons, together with $^{13}$C NMR chemical shifts, that are very similar to those for 2.78. Consequently, we assign to 2.79 the same stereochemistry as 2.78, and this is confirmed by the X-ray crystal structure determination shown in Figure 2.36. The assignment of stereochemistry by n.O.e. for 2.79 is consistent with the X-ray data.

![Figure 2.36 X-ray crystal structure and n.O.e.of the compound 2.79](image)

The chemical shifts and coupling constants of the C-5, C-6, C-7 and C-7a hydrogen and carbon atoms for compounds 2.78-2.81 are collected in Table 2.13.
Table 2.13 Chemical shifts and coupling constants of selected $^1$H and $^{13}$C resonance of the cycloadducts 2.78-2.81

<table>
<thead>
<tr>
<th></th>
<th>2.78</th>
<th></th>
<th>2.79</th>
<th></th>
<th>2.80</th>
<th></th>
<th>2.81</th>
</tr>
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<tr>
<td>$\delta$ p.p.m.</td>
<td>$J$/Hz</td>
<td>$\delta$ p.p.m.</td>
<td>$J$/Hz</td>
<td>$\delta$ p.p.m.</td>
<td>$J$/Hz</td>
<td>$\delta$ p.p.m.</td>
<td>$J$/Hz</td>
</tr>
<tr>
<td>C-7a H</td>
<td>3.67</td>
<td>4.59</td>
<td>3.57</td>
<td>4.59</td>
<td>4.25</td>
<td>4.95</td>
<td>4.56</td>
</tr>
<tr>
<td>C-7 H</td>
<td>5.08</td>
<td>2.91, 4.41</td>
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<td>2.04, 4.59</td>
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<td>10.62, 4.92</td>
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</tr>
<tr>
<td>C-6 H</td>
<td>3.71</td>
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<td>3.57</td>
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<td>4.27</td>
<td>10.44</td>
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</tr>
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<td>C-7a</td>
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<td>85.32</td>
<td>87.13</td>
<td>86.20</td>
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<td></td>
</tr>
<tr>
<td>C-7</td>
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<td>51.71</td>
<td>50.00</td>
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<td>53.58</td>
<td>55.43</td>
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<tr>
<td>C-5</td>
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<td>71.46</td>
<td>69.60</td>
<td>70.59</td>
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<td></td>
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<tr>
<td>PhCH$_2$</td>
<td>59.55</td>
<td>59.46</td>
<td>56.72</td>
<td>55.83</td>
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</tr>
</tbody>
</table>

The salient features of the n.O.e. difference spectra obtained for compounds 2.80 and 2.81 are summarised in Figures 2.37 and 2.38.

For 2.80 the enhancements observed between C-2Ha and C-3H, C-3H and the C5-methylene, the C5-methylene and both C7-H and C7a-H, and between C7-H and C7a-H place all these protons on the same face of the bicyclic ring system, as shown.

Figure 2.37 n.O.e. difference spectral data for compound 2.80
In contrast, the C5 methylene protons in 2.81 show no interaction with the protons at C6, C7 or C7a, but do enhance the C3 proton. Thus, we infer the latter proton and the C5 methylene group lie on the same face, while the protons at C6, C7 and C7a lie on the opposite face. Certainly, the large interaction between the protons at C6 and C7 put these on the same face as each other. We therefore assign 2.80 the stereochemistry shown.

![Figure 2.38 n.O.e. difference spectral data for the compound 2.81](image)

As mentioned earlier, the stereochemistry of adduct 2.79 is consistent with a transition state model involving *endo* approach of the dipolarophile to the *anti*-configured dipole, with facial selectivity controlled by the 4-phenyl substituent (Scheme 2.61).

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Scheme 2.61 TS model for the formation of adduct 2.78/2.79

Compound 2.80 can arise by exo addition from the face opposite to the phenyl group followed by epimerisation of the C7a proton.

Compound 2.81 can be rationalised either by the conversion of diethyl fumarate to diethyl maleate \(^{150}\) followed by endo cycloaddition of the latter from opposite face to the phenyl group in the imidazoline, or by the interconversion of 2.80 and 2.81 as shown in Scheme 2.62.

Scheme 2.62
Maleimide adducts

Reaction of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole with N-methylmaleimide afforded the expected product 2.82, in 52% yield, as the only identifiable product (Scheme 2.63).

Scheme 2.63

The low-resolution Cl(NH₃) mass spectrum contained an MH⁺ at m/z 459, in agreement with the product as formulated (M=458). The structure of 2.82 was supported by the ¹H and ¹³C NMR spectra, which revealed some of the usual features of the fused five membered ring systems. In the ¹H NMR spectrum, these are: (i) the diastereotopicity of the benzylic methylene peaks at δ 3.13 and δ 4.33, suggesting the presence of at least one chiral centre; (ii) the doublet signal, integrating to one proton at δ 4.88, corresponding to the C-7α proton; (iii) the resonance at δ 3.97, integrating to one proton and corresponding to C-7 H, is an apparent triplet due to identically sized coupling to both the C-7α H and C-6 protons; (iv) the two doublets integrating one proton each at δ 2.71 and δ 3.69, that have a coupling constant of J=18.8 Hz, which can be assigned to the two CCH₂CONCH₃ protons.

In the ¹³C NMR spectrum, a resonance for a quaternary carbon atom, corresponding to C-5, is present at δ 69.87. Moreover, DEPT ¹³C NMR analysis also shows the presence of the
three aliphatic CH carbon atoms at $\delta$ 50.11, $\delta$ 51.03 and $\delta$ 87.10, corresponding to C-6, C-7 and C-7a.

The stereochemistry of compound 2.82 was studied by X-ray crystallography and n.O.e. difference spectroscopy. The X-ray structure is illustrated in Figure 2.39. This shows that the 3-phenyl substituent and the bridgehead proton at C-7a are located on the same face of the molecule. Also, the substituents at C-6 and C-7, not surprisingly, have syn-stereochemistry, and the two hydrogen atoms at C-7 and C-7a have a syn-relationship. The X-ray analysis also allows us to establish the stereochemistry at C-5: the CH$_2$ of the spiro ring is on the same face as the C-3 hydrogen, and the C-5 C=O group is on the same face as the C-3 phenyl ring. The C-5 centre therefore has an R-configuration. The results of n.O.e. difference spectroscopy are given in Figure 2.40. The large interactions between the C6 and C7 protons, the C7 and C7a protons, and between the C7a and C6 protons, are entirely consistent with the X-ray structure.

Figure 2.39 X-ray crystal structure of the compound 2.82 (N.B. the crystal structure has been solved as the enantiomer)
Having obtained compound 2.82 by 1,3-DC of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole with N-methylmaleimide, it is obvious that the 4-phenyl ring of the imidazoline controls the approach of the maleimide system. By way of confirmation, we performed the corresponding reaction using N-phenylmaleimide (Scheme 2.64). This afforded 2.83 as white solid in 72% yield and a trace of a compound to which we assign the structure 2.84. Analysis of the spectral data for 2.83 (Table 2.14) suggests an analogous structure to that of compound 2.82.
Table 2.14 Chemical shifts and coupling constants for 2.82, 2.83 and 2.84

<table>
<thead>
<tr>
<th></th>
<th>2.82</th>
<th></th>
<th>2.83</th>
<th></th>
<th>2.84</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>δ/ p.p.m.</td>
<td>J/Hz</td>
<td>δ/ p.p.m.</td>
<td>J/Hz</td>
<td>δ/ p.p.m.</td>
<td>J/Hz</td>
</tr>
<tr>
<td>C-7aH</td>
<td>4.88</td>
<td>7.68</td>
<td>5.01</td>
<td>7.5</td>
<td>4.62</td>
<td>7.14</td>
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<td>C-7 H</td>
<td>3.97</td>
<td>7.89, 7.68</td>
<td>4.13</td>
<td>7.86, 7.68</td>
<td>3.83</td>
<td>9.33, 7.14</td>
</tr>
<tr>
<td>C-6 H</td>
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<td>3.76</td>
<td>9.33</td>
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</tr>
<tr>
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</tr>
<tr>
<td>PhCH₂</td>
<td>58.71</td>
<td></td>
<td>58.81</td>
<td></td>
<td>58.65</td>
<td></td>
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</tbody>
</table>

The El mass spectrum of 2.83 displays a molecular ion at m/z 582, consistent with the proposed structure of the cycloadduct. The $^1$H NMR spectrum contained the anticipated doublet signals each integrating to one proton, at δ 3.50 and δ 5.01 that can be assigned to the C-6 and C-7a protons, and an apparent triplet signal at δ 4.13 integrating to one proton corresponding to the C-7 H proton. Another feature that stands out in the $^1$H NMR spectrum is that both the benzylic and spiro ring methylene protons are diastereotopic, the benzylic pair appearing as doublets at δ 3.20 and δ 4.36 and the ‘spiro’ pair similarly at δ 2.91 and δ 3.80, the coupling constant of the latter being $J$=19.05 Hz. The $^{13}$C NMR spectrum contains the expected four carbonyl group signals at δ 172.41, δ 174.69, δ 175.27 and δ 176.20, and the DEPT $^{13}$C NMR spectra display three CH aliphatic carbon atom resonances at δ 49.98, δ 50.88 and δ 87.35, the latter consistent with the C-7a atom. The resonance at δ 70.18 corresponds to the C-5 carbon atom.

The stereochemical assignment for compound 2.83 is based on n.O.e. difference spectroscopy. Irradiation of the C-7a H proton produces a 10.2% enhancement of C-7 H proton, and irradiation of C-7 H proton causes a 11.1% enhancement of C-6 H proton. These imply an all cis-relationship between these three protons. Irradiation of the C-6
proton yields no enhancement of either diastereotopic methylene proton at C-5, consistent with a *trans*-relationship between the C-6 proton and the C-5 methylene group. However, one of the C-5 methylene protons is enhanced by irradiation of the C-3 proton confirming the *syn* relationship of these two groups. These data are summarised in Figure 2.41.

![Figure 2.41 n.O.e. difference spectroscopy of compound 2.83](image)

The stereochemistry obtained in the maleimide cycloadducts 2.82 and 2.83 can be rationalised as shown in Scheme 2.65.

![Scheme 2.65](image)
The ylide adopts a conformation in which the C=O is syn to the C-2 hydrogen atom together with an endo approach of the dipolarophile. The steric bulk of the 4-phenyl group forces the dipolarophile to approach the dipole from the opposite face of the imidazoline ring system. The high reactivity of the maleimide dipolarophile has been noted earlier, and it has been shown to trap the dipoles formed under endo control and not to permit dipole equilibration[146].

For compound 2.84, the $^1$H NMR spectrum revealed doublets at $\delta$ 2.99 and $\delta$ 3.09 corresponding to the CH$_2$CONPh protons. In addition, the resonances at $\delta$ 3.14 and 4.56 are doublets, integrating to one proton each, which correspond to the benzylic methylene protons. Doublet signals, each integrating to one proton, at $\delta$ 3.76 and $\delta$ 4.62 can be assigned to the C-6H and C-7aH protons, while the signal at $\delta$ 3.83, integrating to one proton is the expected double doublet corresponding to the C-7 proton.

We assign the stereochemistry of compound 2.84, on the basis of a comparison of its $^1$H NMR with that of compound 2.83 together with that of 2.82 (Table 2.14). The $^3$J coupling constants of 2.83 (and, for that matter, the analogue 2.82) are both close to 8 Hz, an observation previously noted for the product 2.24 and 2.48 formed from the achiral imidazoline 2.1. The C-6, C-7 and C-7a protons are therefore all on the same face of the bicyclic ring system. For 2.84, the corresponding $^3$J values are also similar magnitude, ca. 7-9 Hz. This contrasts with compounds 2.24 and 2.48 formed from the achiral imidazoline, for which of the $^3$J$_{7,7a}$ proton coupling is ca. 2 Hz. Thus, we infer that for 2.84 all three protons are also on the same face of the bicyclic ring system. Formation of 2.84 can occur by exo-mode cycloaddition of the maleimide from the face opposite to the 4-phenyl group of the imidazolinium ring, followed by epimerisation at C-7a (Scheme 2.66).
Reaction of the \((R)\)-imidazoline 2.9 with \(\beta\)-nitrostyrene afforded four products: an inseparable mixture of the compounds 2.85 and 2.86 in 6\% yield, and the compounds 2.87 (2\% yield) and 2.88 (trace quantities) (Scheme 2.67).

Scheme 2.66

Scheme 2.67
Table 2.15 comparison of selected NMR data for 2.39, 2.85 and 2.86

<table>
<thead>
<tr>
<th></th>
<th>2.39</th>
<th></th>
<th>2.85</th>
<th></th>
<th>2.86</th>
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<tbody>
<tr>
<td></td>
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<td>Hz</td>
<td>p.p.m.</td>
<td>Hz</td>
<td>p.p.m.</td>
</tr>
<tr>
<td>C-6 H</td>
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<td>5.7</td>
<td>4.87</td>
<td>6.42</td>
<td>5.51</td>
</tr>
<tr>
<td>C-5 H</td>
<td>5.20</td>
<td>10.6, 5.7</td>
<td>5.19</td>
<td>10.62, 5.67</td>
<td>2.73</td>
</tr>
<tr>
<td>C-4 H</td>
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<td>4.38</td>
<td>10.8</td>
<td>3.86</td>
</tr>
<tr>
<td>C-2 H</td>
<td>8.21</td>
<td>s</td>
<td>8.45</td>
<td>s</td>
<td>8.96</td>
</tr>
<tr>
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<td>s</td>
<td>3.59</td>
<td>s</td>
<td>3.69</td>
</tr>
</tbody>
</table>

(a) General conformation of 2.86

(b) Newman projection along the C5-C4 bond

(c) Newman projection along the C6-C5 bond

Compounds 2.85/2.86 are analogous to 2.39. The resonances assigned to 2.85 are similar to those of 2.39, particularly as far as the $J$ values are concerned (Table 2.15), and so we assign the same stereochemistry. Compound 2.86, meanwhile, has a small coupling constant between the C-5 and C-6 protons ($J=2.01$ Hz) and a large coupling between the C-5 and C-4 protons ($J=13.74$ Hz). This can be accommodated by the stereochemistry shown for 2.86 if the ring adopts the conformation shown in Figure 2.42. Newman projections along the C5-C4 and C6-C5 bonds reveal an antiperiplanar orientation of the C5/C4 protons (large $J$) and a gauche orientation of the C6/C5 protons (small $J$).
Compounds 2.87 and 2.88 are clearly cyclic trimers of β-nitrostyrene. Compound 2.87 was identified by X-ray crystallography (Figure 2.43) and its HRMS of MH$^+$ 447.1436 was in agreement with the calculated MH$^+$ 447.1430. The stereochemistry of 2.88 was assigned by $^1$H NMR on account of its symmetry.

![Figure 2.43 X-Ray crystal structure of major product 2.87](image)

2.3.9 Further elaboration of a cycloadduct via reduction

Previous results have shown that the N-1 bond and C-7a bond in these cycloadducts can be reductively cleaved using acidic sodium cyanoborohydride $^{[135, 147]}$, this, together with a phenyl substituent at the chiral centre in the imidazoline should allow cleavage of the C3-C4 bond by hydrogenolysis, thus revealing the optically active pyrrolidine (Scheme 2.68).
Furthermore, the reduction of cycloadduct 2.89 has been reported previously \cite{147,148}.

For this reason, we decided to conduct, as a preliminary investigation, reduction of cycloadduct 2.17 by LiAlH₄, but we were surprised to find that similar treatment of compound 2.17 with a solution of lithium aluminium hydride in anhydrous THF at ice-water bath temperature failed to yield anything other than the starting material (Scheme 2.70).
However, reaction of the adduct 2.18 under the same conditions afforded a compound, which we assign 2.90 in 2% yield (Scheme 2.71). For example, DEPT $^{13}$C NMR analysis of the product revealed the presence of three CH carbon atoms at $\delta$ 46.68, $\delta$ 50.75 and $\delta$ 88.69, and only one CH$_3$ carbon at $\delta$ 52.06 was observed. For compound 2.90, the $^1$H NMR spectrum contained a one-proton broad singlet at $\delta$ 0.83, corresponding to a CH$_2$OH proton; two doublets at $\delta$ 2.77 ($J=16.83$) and 2.81 ($J=16.68$) in total integrating to two protons can be assigned to the C-5 methylene group; and the benzylic methylene signal was diasterotopic, appearing as two doublets integrating to one proton each at $\delta$ 3.34 and $\delta$ 3.89. This was also supported by an IR absorption at $\nu_{max}/\text{cm}^{-1}$ 1734 (C=O), 1654, and especially 3368 (CH$_2$OH).
On the basis of spectral analysis, we formulated the product as 2.90. Clearly, two ester groups at C6 and C7 have been reduced and the lactone results from intramolecular ester exchange. While there was insufficient time to investigate this in more detail, this is an obvious area for further investigation. This reaction demonstrates that there is some differentiation of the four ester functionalities. As expected, the two secondary ester groups are more reactive than the tertiary one, but surprisingly they also appear to react more readily than the primary ester. (Had the primary ester reacted then the product would contain a –CH₂-CH₂- unit, which the product isolated clearly does not).

2.3.10 Summary

We have demonstrated that a concise cycloaddition route to (homo)chiral pyrrolidines from imidazolines is possible, either from diazoesters using a metal ion catalyst or from electron-deficient alkenes. Thus, isolation of compounds 2.16, 2.17 and 2.18 shows that 1,3-dipolar cycloaddition reactions of imidazolines involving a metal-catalysed reaction with diazo compounds is feasible.

Further, we have discovered a novel 1,3-dipolar cycloaddition reaction between imidazolines and electron-deficient alkenes that involves conjugate addition-proton transfer. The method utilises an achiral or homochiral imidazoline to form an azomethine ylide by conjugated addition to an alkene bearing an electron-withdrawing groups at either end of the C=C bond. One of these groups promotes the conjugate addition, the second enhances a 1,2-proton transfer. Where proton transfer is facilitated, subsequent 1,3-DC is observed; when proton transfer is not facilitated, the zwitterion 2.91 has been found to undergo 6-membered ring formation with a further electron-deficient system. (Scheme 2.72)
Clearly, the proton transfer will be promoted by a suitable electron-withdrawing group on the carbon atom adjacent to the iminium N-atom in the ylide. We have found that ester and amide carbonyl groups, and the nitrile functionality, are sufficient to sustain such a proton transfer, but a phenyl group is not.

**Reactivity**

From the reaction of the separate dipolarophiles, it is clear from reaction times that the order of reactivity is maleimide > fumarate > fumaronitrile. This order was reinforced by the reactions involving mixed dipolarophiles; it was invariably found that the maleimides reacted preferentially to form the azomethine ylide, thereby positioning this group at C5 in the bicyclic cycloadduct. Subsequent addition of the fumarate ester/fumaronitrile generated the ring C6 and C7 positions. Likewise, fumarate esters reacted faster than fumaronitrile to
position the ester groups at C5, and the nitrile groups at C6 and C7. This differential reactivity can be utilised to generate cycloadducts derived from mixed alkene units.

1,3-Cycloaddition transition state

The stereochemistry of the major initially-formed cycloadduct can be predicted by assuming the dipolarophile approaches the azomethine ylide, which adopts an anti conformation, from below in such a way as to form the endo product (Scheme 2.73).

Ring opening of the imidazolidine ring in the bicyclic adduct, either via pyrrolidinium ion formation and dihydropyrrole formation, allows for epimerisation of the C7a and C7 positions (Scheme 2.74). Epimerisation of the C7a centre is commonly observed when the R groups are ester or nitrile, but not for the cyclic imides. Epimerisation of C7 has also been observed when R=CN.
Scheme 2.74 Epimerisation of C7 and C7a centres

The presence of a chiral centre in the imidazoline involving a relatively bulky group forces the dipolarophile to approach the ylide from the opposite face of the ring system. In this way, homochiral products are formed.

2.3.11 Future work

The work described in this thesis consists of our efforts to increase the scope of the 1,3-dipolar cycloaddition of imidazolinium ylides, in particular the asymmetric cycloaddition. We have discovered two new reactions. First, a base-free, copper(II) and rhodium(II)-mediated generation of a 1,3-dipole by carbenoid insertion onto the imine nitrogen of an imidazoline. There is plenty of scope to optimise this protocol (e.g. metal, ligands, reaction conditions). During our study of this process we uncovered a base-free/metal-free approach
to the generation of an azomethine ylide. This is a novel cycloaddition reaction for imidazolines wherein the dipolarophile also functions in ylide generation, as a Michael acceptor. The possibility of different acceptors and dipolarophiles has been established. Thus, future objectives are:

- the optimisation of the metal-mediated cycloaddition reactions using different solvents, reaction times, metals and ligands;
- to explore the range of dipolarophiles and acceptors that will react with imidazolines under the metal-free conditions discovered;
- to explore chiral imidazoline as templates to examine the possibility of chiral induction in both processes;
- to explore chemistry of the 2:1 cycloadducts for generation of novel $\alpha$-substituted proline derivatives; and
- to examine other heterocycles as precursors to the 1,3-dipole, including oxazolines, thiazolines and tetrahydropyrimidines.
Chapter 3

Experimental
Experimental

General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. $^1$H Nuclear magnetic resonance (NMR) spectra and $^{13}$C NMR spectra were recorded using a JEOL LA300 spectrometer at 300 and 75MHz, respectively. $^1$H NMR and $^{13}$C NMR spectra were determined in CDCl$_3$ solution (except where indicated) and chemical shifts are quoted in parts per million (p.p.m.) from tetramethylsilane as internal standard. Coupling constants ($J$), where appropriate, are quoted in Hz with multiplicities; d-doublet, t-triplet, q-quartet and m-multiplet. The prefix br-broad is used where applicable. Optical rotations were measured on POL AA R 2001 digital polarimeter.

Infra-red spectra were recorded using a Perkin-Elmer 1710 spectrophotometer using either KBr discs or thin films.

Low resolution mass spectra were record using a VG20-250 mass spectrometer by electron impact (EI) or chemical ionisation (CI) modes; accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (University of Swansea). X-ray crystallography was performed by the EPSRC X-Ray Crystallographic Service (University of Southampton).

Column chromatography was carried out at medium pressure using Merck Kiesegel 60 (Art. 9385). Thin layer chromatography was carried out on silica plates (Kiesegel 60,
F 254, Merck Art. 554) on a plastic backing and visualised by ultraviolet light or aqueous potassium permanganate spray (KMnO₄:K₂CO₃:water, 6:1:100, w/w/v).

All chemicals were purified by distillation or recrystallisation where appropriate. Solvents were removed on a Buchi rotary evaporator. Solvent extracts were dried over anhydrous magnesium sulfate or sodium sulfate for at least 30 min. All dry solvents were prepared as described in Perrin et al. Anhydrous reactions were carried out using flame-dried glassware with all transfers performed using oven-dried syringes and needles.
**N-Benzyl-1,2-diaminoethane, 2.14**

Benzyl chloride (22.89 g; 0.179 mol) was added dropwise to cooled (0-5 °C), stirred 1,2-diaminoethane (53.94 g; 0.879 mol) and the resulting solution was heated at reflux for 8 h. After cooling to ambient temperature, the solution was extracted with diethyl ether (2 x 10 cm³). The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was fractionally distilled under vacuum to afford the desired compound as a colourless oil 2.14 (26.85 g; 62%).

B.p. 84-86 °C at 0.12mmHg (lit.¹⁴⁷ 68-75 °C/0.07mmHg).

δH 1.38 (3H, br, NH₂ and NH), 2.68 (4H, m, NHCH₂CH₂N), 3.37 (2H, s, CH₂Ph), 7.20 (5H, m, Ar-H);

δC 41.70, 51.89, 53.82 (3 x CH₂), 128.06, 128.35, 128.87 (3 x Ar-CH), 140.40 (Ar-C).

**1-Benzyl-4,5-dihydroimidazole 2.1**

N-Benzyl-1,2-diaminoethane (8.00 g; 0.053 mol), triethyl orthoformate (31.60 g; 0.21 mol) and 4-toluenesulfonic acid (0.18 g; 0.001 mol) were heated together at reflux for 23
h. After cooling the mixture to ambient temperature, aqueous sodium hydroxide (5% w/v; 50 cm³) was added and the mixture extracted with chloroform (2 x 100 cm³). The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was fractionally distilled under vacuum to afford the desired compound as a colourless oil 2.1 (8.48 g; 51%).

B.p. 112-116 °C / 0.15mmHg (lit.[148] 120 °C/2.0mmHg, m.p. 39-42 °C).

δH 3.15 (2H, t, J=9.9 NCH₂CH₂N), 3.83 (2H, t, J=9.9 NCH₂CH₂N), 4.29 (2H, s, CH₂Ph), 7.04 (1H, s, NCH/N) and 7.34 (5H, m, Ar-H);

δC 48.14, 51.74, 54.70 (3 x CH₂), 127.69, 127.76, 128.71 (3 x Ar-CH), 136.76 (Ar-C), 157.48 (N=CH-N).

(R)-N-Benzyloxycarbonylphenylglycine

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{Ph} & \quad \text{NH₂}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{Ph} & \quad \text{NZ}
\end{align*}
\]

Benzyl chloroformate (17.05 g, 0.10 mol) and aqueous sodium hydroxide (1M, 100 cm³) were simultaneously added dropwise, over 1h, to stirred cooled (R)-(−)-phenylglycine (15.10 g, 0.10 mol) in aqueous sodium hydroxide (1M, 100 cm³). The resulting mixture was stirred at 0°C for 0.5h and at room temperature for 2 h. The solution was washed with ether (2 x 50 cm³), cooled to 0°C and acidified to pH 1 with hydrochloric acid (5M, 20 cm³). The solid was collected by filtration, washed with water and dried in vacuo over P₂O₅ to yield the title compound as colourless solid (25.71g, 90%).

M.p. 131-132 °C (lit. [147,148] 136-138 °C); νmax (KBr)/cm⁻¹ 3401, 3037, 2958, 1744, 1734, 1669, 1533, 1247, 1173, 1054, 719, 696.

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\( \delta_H \) 4.99 and 5.07 (2H, 2 x s PhCH\(_2\)), 5.26 and 5.35 (1H, 2 x d \( J=7.3 \) and 5.6, NHCH\( \text{PhCO} \)), 5.87 and 6.93 (1H, 2 x d, \( J=6.9 \) and 5.6, NH), 7.32 (10H, m, ArH), 8.07 and 8.09 (1H, 2 x s, CO\(_2\)H).

\textbf{\( (R)\)-2-(Benzyloxy carbonylamino)-2-phenyl-\( N \)-benzyacetamide, 2.6}

\begin{center}
\begin{tikzpicture}
\draw[->] (0,0) -- (2,0);
\draw (0,0) node[anchor=east] {O};
\draw (0,0) node[anchor=north] {\text{OH}};
\draw (1,0) node[anchor=north] {\text{NH}_{\text{H}}Z};
\draw (2,0) node[anchor=north] {\text{Ph}};
\draw (1,0) -- (2,0);
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\draw[->] (0,0) -- (2,0);
\draw (0,0) node[anchor=east] {O};
\draw (0,0) node[anchor=north] {\text{NH}_{\text{H}}Z};
\draw (1,0) node[anchor=north] {\text{Ph}};
\draw (1,0) -- (2,0);
\end{tikzpicture}
\end{center}

\( N \)-Methylmorpholine (8.51 g, 0.004 mol) in DCM (30 cm\(^3\)) was added dropwise with stirring to \( (R)\)-\( N \)-benzyloxy carbonyl phenylglycine (24.00 g, 0.0084 mol) in DCM (600 cm\(^3\)) at 0 °C, under nitrogen. Ethyl chloroformate (9.13 g, 0.0084 mol) in DCM (30 cm\(^3\)) was then added to the resulting mixture, followed by benzylamine (9.01 g, 0.0084 mol) in DCM (40 cm\(^3\)). The solution was stirred at 0 °C for 2h and at room temperature for 16h. The mixture was washed successively with water (100 cm\(^3\)), aqueous sodium hydrogen carbonate (8% w/v; 100 cm\(^3\)), water (100 cm\(^3\)), hydrochloric acid (2M, 100 cm\(^3\)) and saturated brine (100 cm\(^3\)). The organic phase was dried (MgSO\(_4\)) and the solvent was evaporated under reduced pressure. The residue was recrystallised from DCM:hexane to yield the title compound as colourless solid 2.6 (26.25 g, 83%).

M.p. 189-191 °C (lit.\(^{[147,148]}\) 196-197 °C); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 3312, 1688, 1651, 1527, 1247, 699.

\( \delta_H \) 4.35 (2H, m PhCH\(_2\)NH), 5.00 (2H, m, PhCH\(_2\)O), 5.26 (1H, d, \( J=6.7 \), PhCH(NH)CO), 6.20 (2H, br s, 2 x NH) and 7.36 (15H, m, ArH).
(R)-2-Amino-2-phenyl-N-benzylacetamide, 2.7

A suspension of (R)-2-(benzyloxy carbonylamino)-2-phenyl-N-benzylacetamide (18.30 g, 0.049 mol) and 10% palladium-charcoal catalyst (0.5 g) in methanol (800 cm³) was stirred under an atmosphere of hydrogen at room temperature for 19.5 h. After this time only the catalyst remained undissolved. The mixture was filtered through a pad of kieselguhr and the filtrate was evaporated under reduced pressure to yield the title compound as a pale yellow solid (11.72 g, 100%).

M.p. 78-80 °C (lit.[147,148] 77-78 °C); νmax (KBR)/cm⁻¹ 3337, 3297, 3085, 3030, 2925, 2892, 1649, 1521, 1475, 1453, 1429, 938, 751, 699.

δH 1.81 (2H, br s, CHN₂), 4.39 (2H, d, J=5.9, PhCH₂N), 4.51 (1H, s, PhCH₂O), 7.29 (10H, m, Ar-H) and 7.53 (1H, br s, CONH).

(R)-1-Phenyl-2-2-(benzylamino)ethylamine, 2.8

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Borane-tetrahydrofuran complex (1M in THF, 400 cm³, 0.40 mol) was added dropwise to a stirred solution of (R)-2-amino-2-phenyl-N-benzylacetamide (24.0 g, 0.10 mol) in dry THF (400 cm³) at room temperature under nitrogen. The resulting mixture was heated at reflux for 19h. After cooling to room temperature, hydrochloric acid (2M, 200 cm³) was added dropwise and stirring was continued for 3 h. The organic solvent was evaporated under reduced pressure and the suspension filtered. The filtrate was cooled to 0 °C, basified to pH 12 by the portionwise addition of solid sodium hydroxide and the resulting mixture was extracted with ethyl acetate (2 x 200 cm³). The organic phase was dried (Na₂SO₄), evaporated under reduced pressure and the residue purified by vacuum distillation to provide the title compound as a pale yellow oil (15.82 g, 70%).

B.p. 121-122 °C at 0.05mmHg (lit.¹⁻¹⁸⁸, 140-145 °C at 0.25mmHg); νmax (film)/cm⁻¹, 3361, 3298, 3060, 3026, 2922, 2830, 1493, 1452, 735, 699.

δH 1.89 (3H, br s NH and NH₂), 2.80 (2H, m, CH₂NH), 3.78 (2H, s, PhCH₂), 4.02 (1H, m, PhCH₂NH₂) and 7.30 (10H, m, Ar-H).

(R)-1-Benzyl-4-phenyl-4,5-dihydroimidazole, 2.9

(R)-1-Phenyl-2-(benzylamino)ethylamine (6 g, 26.5 mmol) and 4-toluenesulfonic acid (0.04 g, 0.22 mmol) in triethyl orthoformate (15.72 g, 0.106 mol) were heated at reflux for 20h. After cooling to room temperature, aqueous sodium hydroxide (5%, 5 cm³) was added and the mixture extracted with chloroform (3 x 25 cm³). The organic phase was
dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate: triethylamine (99:1 v/v) and fractionally distilled under vacuum to yield the title compound as a colourless oil 2.9 (5.40 g, 86%), b.p. 146-148 °C/0.08 mmHg lit.[147]; [α]D²³ 168.9 (c 1.01 in EtOH).

δH 2.96 (1H, t, J=9.4, PhCHCHH) 3.58 (1H, dd, J=9.1 and 10.7, PhCHCHH), 4.20 (1H, d, J=14.9, PhCHH), 4.36 (1H, d, J=14.9, PhCHH), 5.14 (1H, m, PhCHCH₂), 7.10 (1H, s, NCHN) and 7.28 (10H, m Ar-H);

δC 51.34 (PhCH₂), 55.55 (PhCHCH₂), 69.69 (PhCHCH₂), 128.43, 128.18, 127.46, 127.40, 126.72, and 126.31 (6 x ArCH), 136.41 and 143.54 (2 x ArC), 156.69 (NCHN).

Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and dimethyl fumarate

Ethyl diazoacetate (0.285 g, 2.5 mmol) was added dropwise to a solution 1-benzyl-4,5-dihydroimidazole (0.4 g, 5 mmol), dimethyl fumarate (0.72 g, 5 mmol) and Cu(acac)₂
(0.065 g, 2.5 mmol) in dried DCM under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and then stirred at reflux for 24 h. The reaction mixture was cooled, diluted with DCM, washed with water, dried (MgSO₄) and concentrated under reduced pressure to give an oil (1.31 g) which was chromatographed repeatedly on silica (eluting with ethyl acetate and hexane, 2:8 containing 5% NEt₃) to give 0.63 g of the compound 2.16 as colourless oil (yield 33%):

\[ v_{\text{max}}(\text{film})/\text{cm}^{-1} \]
\[ 3009, 2953, 1733(\text{C}=\text{O}), 1604, 1436, 1352, 1211, 1094, 1030, 753, 703. \]

\[ \delta_H \]
\[ 1.27 (3H, t, J=7.1, \text{CH}_2\text{CH}_3), 2.50 (1H, m, \text{NCH}_2\text{CH}HN), 2.82 (1H, m, \text{NCH}_2\text{CH}HN), 2.88 (1H, m, \text{NCH}HN), 3.27 (1H, m, \text{NCH}HN), 3.35 (1H, d, J=13.6, \text{PhCH}HN), 3.67 (6H, 2 x s, 2 x \text{OCH}_3), 3.75 (1H, dd, J=6.8, 8.9, \text{C-7H}), 3.87 (1H, dd, J=7.7, 8.9, \text{C-6H}), 4.03 (1H, d, J=7.7, \text{C-5H}), 4.08 (1H, d, J=13.6, \text{PhCH}HN), 4.17 (2H, q, J=7.1, \text{OCH}_2\text{CH}_3), 4.55 (1H, d, J=6.8, \text{C-7aH}), 7.25 (5H, m, Ar-H); \]

\[ \delta_C \]
\[ 14.08 (\text{CH}_2\text{CH}_3), 47.57 (\text{C}-6), 51.92 (\text{C}-7), 50.92 and 51.26 (2 x \text{OCH}_3), 53.13 and 53.36 (\text{NCH}_2\text{CH}_3), 58.93 (\text{PhCH}_2) 61.19 (\text{OCH}_2\text{CH}_3), 68.44 (\text{C}-5), 86.13 (\text{C}-7a), 126.94, 128.19 and 128.26 (3 x \text{Ar-CH}), 138.74 (\text{Ar-C}), 171.10, 171.17 and 171.30 (3 x \text{C}=\text{O}). \]

\[ m/z (M^+) \]
\[ 390, 20\%. \] Found: MH⁺ 391.1864; C₂₀H₂₆N₂O₆ requires MH⁺ 391.1869.

and diastereomer 2.17 as a colourless oil (0.19 g, 5.7%):

\[ v_{\text{max}}(\text{film})/\text{cm}^{-1} \]
\[ 3027 (\text{Aryl C-H}), 2953, 1733 (\text{C}=\text{O}), 1437, 1353, 1207, 754, 702. \]

\[ \delta_H \]
\[ 2.28 (1H, m, \text{NCH}_2\text{CH}HN), 2.95 (2H, m, \text{NCH}HN), 3.08 (1H, d, J=14.64 \text{CH}H\text{CO}_2\text{CH}_3), 3.09 (1H, d, J=13.17, \text{PhCH}HN), 3.12 (1H, m, \text{NCH}_2\text{CH}HN), 3.13 (1H, d, J=14.64, \text{CH}H\text{CO}_2\text{CH}_3), 3.66 (1H, dd, J=10.8, 4.6, \text{C-7H}), 3.68, 3.69, 3.71, 3.14 (12H, 4 x s, 4 x \text{CH}_3), 3.85 (1H, d, J=4.6, \text{C-7aH}), 4.12 (1H, d, J=13.02, \text{PhCH}HN), 4.45 (1H, d, J=10.8, \text{C-6H}), 7.28 (5H, m, 5 x \text{Ar-H}); \]

\[ \delta_C \]
\[ 39.78 (\text{CH}_2\text{CO}_2\text{CH}_3), 47.90 and 53.79 (\text{NCH}_2\text{CH}_3), 49.90 (\text{C}-7), 52.14, 52.20, 52.37 and 53.12 (4 x \text{OCH}_3), 53.79 (\text{C}-6), 56.18 (\text{PhCH}_2), 71.06 (\text{C}-5), 86.94 (\text{C}-7a), 126.99, \]
128.32 and 128.53 (3 \times \text{Ar-CH}), 138.85 (\text{Ar-C}), 170.70, 170.94, 171.39 and 172.81 (4 \times C=O);

\textit{m/z} (\text{Cl}) (\text{MH}^+ 449.4, 100\%); \text{Found: } \text{MH}^+ 449.1924. \text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_8 \text{requires } \text{MH}^+ 449.1922

and diastereomer 2.18 as a white solid (0.07 g, 2.1\%):

\text{M.p.105.7-106.9 °C; } v_{\text{max}}(\text{film})/\text{cm}^{-1} 3028 (\text{Aryl C-H}), 2952, 1736 (\text{C=O}), 1437, 1352, 1205, 741, 698.

$\delta_H$ 2.56 (1H, m, NCH$_2$CHHN), 2.88 (3H, m, NCH$_2$CHHN), 2.91 (1H, d, \textit{J}=17.01, CH$_2$CO$_2$CH$_3$), 3.43 (1H, d, \textit{J}=13.6, PhCHH), 3.55 (1H, d, \textit{J}=11.3, C-6H), 3.61 (1H, dd, \textit{J}=11.3, 7, C-7H), 3.62 (3H, s, OCH$_3$), 3.64 (1H, d, \textit{J}=17.22 CH$_2$CO$_2$CH$_3$), 3.70 (3H, s, OCH$_3$), 3.73, 3.74 (6H, 2 x s, 2 x OCH$_3$), 4.21 (1H, d, \textit{J}=13.6, PhCHH), 4.90 (1H, d, \textit{J}=6.96, C-7aH), 7.28 (5H, m, Ar-H);

$\delta_C$ 38.30 (CH$_2$CO$_2$CH$_3$), 47.92 and 51.93 (NCH$_2$CH$_2$N), 51.09 (C-7), 51.74 (C-6), 52.063, 52.24, 52.45 and 52.81 (4 x OCH$_3$), 59.40 (PhCH$_2$), 71.95 (C-5), 84.55(C-7a), 126.96, 128.05 and 128.34 (3 \times \text{Ar-CH}), 138.80 (\text{Ar-C}), 170.22, 170.29, 171.32 and 171.46 (4 \times C=O).

\textit{m/z} (\text{Cl}) (\text{MH}^+ 449.2 100\%); \text{Found: } \text{MH}^+ 449.1925. \text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_8 \text{requires } \text{MH}^+ 449.1922.
Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and dimethyl maleate

Ethyl diazoacetate (0.285 g, 2.5 mmol) was added dropwise to a solution 1-benzyl-4,5-dihydroimidazole (0.4 g, 5 mmol), dimethyl maleate (0.72 g, 5 mmol) and Cu(acac)$_2$ (0.065 g, 2.5 mmol) in dried DCM under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 24 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO$_4$) and concentrated under reduced pressure to give an oil 1.31 g which was chromatographed repeatedly on silica (eluted with ethyl acetate and hexane, 2:8 in 5% NEt$_3$) to give 0.33 g of the title compound 2.16 as colourless oil (yield 17.4%), and diastereomer 2.17 as a colourless oil (trace amount). and diastereomer 2.18 as a white solid (trace amount).
Reaction of 1-benzyl-4,5-dihydroimidazole with N-methylmaleimide in the presence of Cu(acac)$_2$

A solution of ethyl diazoacetate (0.285 g, 2.5 mmol), 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and Cu(acac)$_2$ (0.065 g, 0.25 mmol) was stirred at reflux for 1 h in dried DCM (4 ml) under nitrogen, then N-methyl maleimide (0.55 g, 5 mmol) was added dropwise to the solution. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 24 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO$_4$) and concentrated under reduced pressure to give an oil mixture which was chromatographed repeatedly on silica (eluted with ethyl acetate and hexane, 3:7) to give compound 2.22 as the major product (0.34 g, yield 36%):

M.p. 160.6-163.4 °C; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3027 (Aryl C-H), 2930, 2835, 2811, 1772 (five membered ring imide antisymm C=O), 1714 (five membered ring imide symm C=O), 1692, 1436, 1378, 1282, 1129, 964, 742, 698.

$\delta_H$ 2.42 (1H, m, NCH$_2$CH/HN), 2.60 (1H, m, NCH/HCCH$_2$N), 2.79 (1H, m, NCH/HCCH$_2$N), 2.93 (1H, d, $J=18.8$, CCH/HC-O), 3.00 and 3.01 (6H, 2 x s, 2 x NCH$_3$ ), 3.03 (1H, m, NCH$_2$CH/HN), 3.22 (1H, d, $J=7.9$, C-6H), 3.30 (1H, d, $J=12.1$, Ph/CHH), 3.93 (1H, dd, $J=7.9$, 7.6, C-7H), 4.10 (1H, d, $J=18.8$, CCH/HC-O), 4.35 (1H, d, $J=12.1$, Ph/CHH), 4.70 (1H, d, $J=7.6$, C-7aH), 7.28 (5H, m, Ar-H);
δC 24.91, 25.02 (2 x NCH3), 32.68 (CH2CONCH3), 49.51, 51.92 (NCH2CH2N), 49.55 (C-6), 51.23 (C-7), 58.46 (PhCH2), 69.43 (C-5), 85.77 (C-7a), 127.25, 128.34, 129.07 (3 x Ar-CH), 137.91 (Ar-C), 174.38, 175.40, 176.32, 177.69 (4 x C=O);

m/z (Cl) (MH⁺ 383.3, 100%); Found: MH⁺ 383.1761. C20H22N4O4 MH⁺ requires 383.1719;

and 0.13 mg of the title compound 2.23 as a white solid (yield 3.4%).

M.p. 168.6-171.5 °C; νmax(film)/cm⁻¹ 3311 (NH), 3027, 2958, 2947, 1780 (five membered ring antisymm C=O), 1703 (five membered ring symm C=O), 1677 (C=C-C=O), 1616 (C=C), 1495, 1436, 1385, 1288, 1123, 1075, 1001, 750, 701.

δH 2.27 (1H, t, J=11.16, NH), 2.76-3.02 (3H, m, NCHHCHHN), 2.85 (1H, d, J=17.4, CCHHCONCH3), 2.90 and 2.93 (6H, s, 2 x NCH3), 3.17 (1H, d, J=17.22, CCH/HCONCH3), 3.58 (1H, m, NCH2CHHN), 3.90 (1H, d, J=1.11, C-6a H), 4.46 (2H, s, PhCH2), 7.35 (5H, Ar-H), 7.91 (1H, s, C-1H);

δC 24.5 and 24.8 (2 x CH3), 41.19 (CCH2CONCH3), 45.46 (NCH2NCH2), 48.58 (NCH2NCH2), 51.13 (C-6a), 61.23 (PhCH2N), 64.79 (CCH2CONCH3), 91.71 (CH=CCONCH3), 127.72, 128.72 and 129.26 (3 x Ar-CH), 136.04 (1 x Ar-C), 146. 60 (C-1), 171.64, 174.51, 175.46 and 176.96 (4 x C=O).

m/z (Cl) (MH⁺ 383.3, 100%); Found: MH⁺ 383.1716. C20H22N4O4 MH⁺ requires 383.1719.
Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and N-methylmaleimide using Cu(acac)$_2$

Ethyl diazoacetate (0.28 g, 2.5 mmol) in DCM (3 cm$^3$) was added dropwise slowly by syringe pump to a solution 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol), and Cu(acac)$_2$ (0.065 g, 0.25 mmol) in dried DCM (4 cm$^3$) under nitrogen, followed by addition of N-methylmaleimide (0.55 g, 5 mmol) by syringe pump. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 18 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO$_4$) and concentrated under reduced pressure to give an oily mixture which was chromatographed repeatedly on silica (eluted with ethyl acetate and hexane, 3:7) to give compound 2.22 and compound 2.25 as a light pink solid (0.055 g, 6%).

Compound 2.25 had: m.p. 155.4-156.8 °C; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3336 (NH), 3027, 2928, 1779 (five membered ring imide antisym C=O), 1735 (C=O), 1702 (five membered ring imide symm C=O), 1681, 1615 (C=C), 1496, 1432, 1382, 1287, 1270, , 1199, 1098, 1012, 998, 967, 753, 700.

$\delta_{\text{H}}$ 1.53 (1H, br, NH), 2.11 (1H, d, $J$=17.94, CCHHCONHCH$_3$), 2.31 (1H, d, $J$=17.94, CCHHCONHCH$_3$), 2.56 (1H, m, NCHHCH$_2$N), 2.98 (3H, s, NCH$_3$), 3.03 (1H, m, NCH$_2$CHHN), 3.03 (3H, s, NCH$_3$), 3.47 (1H, m, NCH$_2$CHHN), 3.90 (1H, m,
NCH(\text{HCH}_2\text{N})_2, 4.40, 4.48 (2H, 2 × d, J=14.82, \text{PhCH}_2\text{H}), 4.49 (1H, d, J=0.93, \text{CHCONCH}_3\text{CO}), 7.25-7.42 (5H, m, \text{Ar-H}), 7.89 (1H, s, NCH=\text{CCO});

δ_c 24.40 and 25.07 (2 × NCH), 41.02 (CCH\text{2CONCH}_3), 43.78 (NCH\text{2CH}_2\text{N}), 48.42 (CH\text{CONCH}_3), 48.94 (NCH\text{2CH}_2\text{N}), 61.59 (\text{PhCH}_2), 64.58 (CCH\text{2CONCH}_3), 90.3 (NCH=\text{CCO}), 127.72, 128.81 and 129.30 (3 × \text{Ar-CH}), 135.98 (\text{Ar-C}), 147.30 (NCH=\text{CCO}), 171.70, 174.04, 174.87 and 177.07 (4 × C=O).

m/z (Cl) (MH+ 383, 30%); Found: MH+383.1717. \text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4, \text{MH}^+ \text{requires 383.1719.}

**Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and dimethyl acetylenedicarboxylate (DMAD) using Cu(acac)\text{2}**

![Reaction Scheme](image)

Ethyl diazoacetate (0.29 g, 2.5 mmol) in DCM (4 cm³) was added dropwise slowly by syringe pump to a solution 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol), dimethyl acetylenedicarboxylate (DMAD) (0.71 g, 5 mmol) and Cu(acac)\text{2} (0.65 g, 0.25 mmol) in DCM (4 cm³) under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 48 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO₄) and concentrated under reduced pressure to give an oil which was chromatographed repeatedly on silica (ethyl acetate and hexane, 3:7) to give 0.11 g of compound 2.27 (yield 12%).
$\nu_{\text{max}}$(film)/cm$^{-1}$ 2956, 2928, 2872, 1736 (C=O), 1666 (C=C-C=O), 1613 (C=C), 1438, 1257, 1220, 1073, 1018, 677.

$\delta_h$ 1.28 (3H, t, $J=7.14$, CO$_2$CH$_2$CH$_3$), 2.67 (1H, m, NCHHCH$_2$N), 3.07 (1H, m, NCHHCH$_2$N), 3.41 (2H, m, NCH$_2$CH$_2$N), 3.61 (1H, d, $J=13.2$, PhCHH), 3.63 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.93 (1H, d, $J=13.2$, PhCHH), 4.23 (2H, q, $J=7.14$, CO$_2$CH$_2$CH$_3$), 4.73 (1H, s, C-7aH), 4.97 (1H, s, C-5H), 7.28 (5H, m, Ar-CH);

$\delta_c$ 14.42 (CO$_2$CH$_2$CH$_3$), 46.90 and 49.24 (NCH$_2$CH$_2$N), 50.95 and 53.08 (2 x CO$_2$CH$_3$), 55.62 (PhCH$_2$), 61.09 (CO$_2$CH$_2$CH$_3$), 75.78 (C-5), 88.26 (C-7a), 127.60, 128.49 and 128.60 (3 x Ar-CH), 136.96 (Ar-C), 149.52 (C-7 and C-6), 164.97, 165.24 (2 x conjugated C=O), 167.66 (C=O).

Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and diethyl fumarate using Cu(acac)$_2$

1-Benzyl-5,6,7-tris(ethoxycarbonyl)hexahydro-1H-pyrrolo[1,2a]imidazole, 2.28

This compound was prepared from 1-benzyl-4,5-dihydroimidazole (1.2 g, 7.5 mmol) using the method described above but using ethyl diazoacetate (1.14 g, 10 mmol), diethyl fumarate (2.58 g, 15 mmol) and Cu(acac)$_2$ (0.196 g, 10 mmol). Purification by column
chromatography on silica, eluting with hexane and ethyl acetate (9:1 containing 5% NEt₃) yielded the title compound as a colourless oil (0.79 g, 25%);

ν_max(film)/cm⁻¹ 3030 (Aryl C-H), 2961, 2932, 2873, 1747 (C=O), 1455, 1372, 1260, 1203, 1029, 745, 702.

δ_H 1.17 (3H, t, J=7.14, CO₂CH₂CH₃), 1.24 (3H, t, J=7.14, CO₂CH₂CH₃), 1.29 (3H, t, J=7.14, CO₂CH₂CH₃), 2.48 (1H, m, NCH/HCH₂N), 2.81 (1H, m, NCH₂CHHN), 2.97 (1H, m, NCH/HCH₂N), 3.27 (1H, m, NCH₂CHHN), 3.34 (1H, d, J=13.56, PhCH₃), 3.73 (1H, dd, J=6.6, 9.15, C-7H), 3.84 (1H, dd, J=7.68, 9.15, C-6H), 4.02 (1H, d, J=7.68, C-5H), 4.07 (1H, d, J=13.6, PhCH₃), 4.14 (2H, q, J=7.14, CO₂CH₂CH₃), 4.16 (2H, q, J=7.14, CO₂CH₂CH₃), 4.25 (2H, q, J=7.14, CO₂CH₂CH₃), 4.54 (1H, d, J=6.6, C-7aH), 7.25 (5H, m, 5 x Ar-H);

δ_C 14.02 (CO₂CH₂CH₃), 14.08 (CO₂CH₂CH₃), 14.12 (CO₂CH₂CH₃), 47.74 (C-6), 51.11 (C-7), 53.16 and 53.50 (NCH₂CH₂N), 58.92 (PhCH₂), 60.98, 61.11 and 61.19 (3 x CO₂CH₂CH₃), 68.55 (C-5), 86.08 (C-7a), 126.96, 128.22 and 128.28 (3 x Ar-CH), 138.82 (Ar-C), 170.74, 170.94 and 171.30 (3 x C=O);

m/z (CI) (MH⁺ 419.2, 100%); Found: MH⁺ 418.2315. C₂₂H₃₀N₂O₆ requires MH⁺ 418.2322

Reaction of 1-benzyl-4,5-dihydroimidazole with methyl methacrylate and ethyl diazoacetate in the presence of Rh(II)acetate

Ethyl 4,5-dihydro-4-methoxycarbonyl-4-methyl-1H-pyrazole-3-carboxylate, 2.29
Ethyl diazoacetate (0.57 g, 5 mmol) in dried DCM (2 cm³) was added dropwise slowly by syringe pump to a solution of 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol), methyl methacrylate (0.75 g, 7.5 mmol) and rhodium(II) acetate (0.046 g, 0.125 mmol) in DCM (10 cm³) for 1 h. The reaction was allowed to reflux for 20 h. The reaction mixture was then diluted with DCM and concentrated under reduced pressure to give an oil that was chromatographed repeatedly on silica (ethyl acetate and hexane 5:5) to give the title compound as an oil (trace amount).

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3800-2500 (NH), 2985, 1734 (C=O), 1718 (C=O), 1446 (C=N), 1374, 1219, 1121, 1021, 931, 860, 758

$\delta_H$ 1.26 (3H, t, $J$=7.14, $CH_2CH_2C\equiv$), 1.55 (3H, s, CCH$_3$), 2.82 (1H, d, $J$=17.60, $H_a$), 3.31 (1H, d, $J$=17.60, $H_b$), 3.77 (3H, s, CO$_2CH_3$), 4.30 (2H, q, $J$=7.14, CO$_2CH_2CH_3$), 6.69 (1H, br, NH$_2$);

$\delta_C$ 14.25 (CO$_2CH_2CH_3$), 24.11 (CCH$_3$), 41.31 (CH$_3$H$_b$), 52.97(CO$_2CH_3$), 61.21 (C=CO$_2CH_2CH_3$), 69.77 (CH$_3$CCO$_2CH_3$), 142.27 (N=CCO$_2CH_2CH_3$), 162.17 (conjugated CO$_2CH_2CH_3$), 174.27 (CH$_3$CCO$_2CH_3$);

$\text{m/z}$ (Cl) (MH$^+$ 214.1, 10%); Found: MH$^+$ 214.1243. C$_9$H$_{14}$N$_2$O$_4$ MH$^+$ requires 214.1237.

**Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate in the presence of Rh$_2$(OAc)$_4$**

![Reaction scheme](https://example.com/chemistry.png)
Ethyl diazoacetate (0.28 g, 2.5 mmol) was added dropwise to a solution 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol), and rhodium(II) acetate (0.046 g, 0.125 mmol) in dried DCM (3 cm³) under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 2 d. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO₄) and concentrated under reduced pressure to give an oil which was chromatographed repeatedly on silica (ethyl acetate and hexane, 4:6) to give compound 2.30 (0.21g, 32%).

\( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3320 (NH), 3063, 2983, 2844, 2247, 1728, 1673 (ester C=O), 1648, 1605 (N=C), 1543, 1378, 1349, 1205, 1114, 1042, 740, 700

\( \delta_H \) 1.41 (3H, t, \( J=7.14 \), CH₃CH₂O), 1.62 (1H, br, NH), 2.95 (2H, t, \( J=6.39 \), NCH₂CH₂N),
3.80 (2H, s, PhCH₂), 4.43 (2H, d, \( J=7.14 \), CH₃CH₂CO₂CH), 4.50 (2H, t, \( J=6.39 \), NCH₂CH₂N), 7.23-7.35 (5H, m, Ar-H), 8.20 (1H, s, N=CHN)

\( \delta_C \) 14.34 (CH₃CH₂O), 48.10 and 50.73 (NCH₂CH₂N), 53.40 (PhCH₂), 61.19 (CH₃CH₂O),
127.28, 128.07, 128.55 (3 x Ar-CH), 128.9 (N=CHN), 139.53 (1 x Ar-C), 140.10 (CH₃CH₂O₂CC=N), 160.83 (conjugated C=O)

\( m/z \) (CI) (MH⁺ 275.2, 100%); Found: MH⁺ 275.1503. C₁₄H₁₈N₄O₂, MH⁺ requires 275.1501.

Reaction of 1-benzyl-4,5-dihydroimidazole with diethyl fumarate and ethyl diazoacetate in the presence of Cu(trifluoracac)₂

4,5-Dihydro-1H-pyrazole-3,4,5-tricarboxylic acid triethyl ester, 2.31
Ethyl diazoacetate (0.143 g, 1.25 mmol) in DCM (3 cm$^3$) was added dropwise slowly by syringe pump to a solution of 1-benzyl-4, 5-dihydroimidazole (0.2 g, 1.25 mmol) and copper(II) trifluoroacetylacetonate (0.046 g, 0.125 mmol) for 13 h in dried DCM (4 cm$^3$) under nitrogen, then diethyl fumarate (0.43 g, 2.5 mmol) was added over 2 d. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO$_4$) and concentrated under reduced pressure to give an oil that was chromatographed repeatedly on silica (ethyl acetate and hexane 2:8) to give 0.065 g of the title compound as a white solid (yield 9%).

M.p. 96.5-98.3 °C; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3346 (NH), 2961, 2874, 1717 (C=O), 1579 (C=N), 1465, 1377, 1281, 1029, 860, 745, 705.

$\delta$H 1.22 (3H, t, $J=7.14$, CO$_2$CH$_2$CH$_3$), 1.24 (3H, $J=7.14$, CO$_2$CH$_2$CH$_3$), 1.28 (3H, t, $J=7.14$, CO$_2$CH$_2$CH$_3$), 4.17 (2H, q, $J=7.14$, CO$_2$CH$_2$CH$_3$), 4.19 (2H, q, $J=7.14$, CO$_2$CH$_2$CH$_3$), 4.25 (2H, q, $J=7.14$, CO$_2$CH$_2$CH$_3$), 4.35 (1H, d, $J=5.49$, Ha), 4.69 (1H, d, $J=5.49$, Hb), 6.74 (1H, br, NH);

$\delta$C 13.96, 14.01 and 14.14 (3 x CO$_2$CH$_2$CH$_3$), 52.39 (N=CCHCO$_2$CH$_2$CH$_3$), 61.48, 62.15 and 62.52 (3 x CO$_2$CH$_2$CH$_3$), 66.15 (HNCHCO$_2$CH$_2$CH$_3$), 140.08 (N=CCO$_2$CH$_2$CH$_3$), 161.18 (conjugated CO$_2$CH$_2$CH$_3$), 168.98 and 169.76 (2 x CHCO$_2$CH$_2$CH$_3$);

m/z (Cl) (MH$^+$ 287.1, 70%); Found: MH$^+$ 287.1243. C$_{12}$H$_{18}$N$_2$O$_6$ MH$^+$ requires 287.1237.

**Reaction of 1-benzyl-4,5-dihydroimidazole with N-methylmaleimide and ethyl diazoacetate in the presence of Cu(trifluoroacac)$_2$**
Ethyl diazoacetate (0.143 g, 1.25 mmol) in DCM (3 cm³) was added dropwise slowly by syringe pump to a solution of 1-benzyl-4, 5-dihydroimidazole (0.2 g, 1.25 mmol) and copper(II) trifluoroacetylacetonate (0.046 g, 0.125 mmol) for 13 h in dried DCM (4 ml) under nitrogen, then N-methylmaleimide (0.27 g, 2.5 mmol) was added by syringe pump over 4 d. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO₄) and concentrated under reduced pressure to give an oil which was chromatographed repeatedly on silica (eluted with ethyl acetate and hexane 2:8) to give 0.028 g of compound 2.32 as a light yellow solid (yield 5%).

M.p. 150.7-152.7 °C; νmax (film)/cm⁻¹ 3338 (NH), 2983, 1788 (five membered ring antisymm C=O), 1709 (five membered ring symm C=O), 1552 (C=N), 1436, 1381, 1285, 1217, 1135, 1015, 862, 760.

δH 1.30 (3H, t, J=7.14, CO₂CH₂CH₃), 2.95 (3H, s, NCH₃), 4.28 (2H, q, J=7.14, CO₂CH₂CH₃), 4.51 (1H, d, J=10.8, Ha), 4.87 (1H, d, J=10.8, Hb), 7.03 (1H, br, NH);

δC 14.16 (CO₂CH₂CH₃), 25.48 (NCH₃), 51.62 (C-a), 61.81 (CO₂CH₂CH₃), 63.59 (C-b), 136.64 (C=CCO₂CH₂CH₃), 160.70 (conjugated CO₂CH₂CH₃), 171.55 (CH₃NC=O), 174.10 (CH₃NC=O).

m/z (CI) (MH⁺ 226.0, 15%); Found: MH⁺ 226.0828. C₉H₁₁N₃O₄, MH⁺ requires 226.0828.
Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate in the presence of Cu(OTf)₂

Ethyl diazoacetate (0.14 g, 1.25 mmol) was added dropwise to a solution 1-benzyl-4,5-dihydroimidazole (0.22 g, 1.25 mmol) and copper(II) trifluoromethanesulfonate Cu(OTf)₂ (0.046 g, 0.125 mmol) in dried DCM (4 cm³) under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 48 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO₄) and concentrated under reduced pressure to give an oily mixture that was chromatographed repeatedly on silica (ethyl acetate and hexane, 4:6) to give 0.058 g (17.1%) of compound 2.33.

ν_max(film)/cm⁻¹: 3030 (Aryl C-H), 2982, 2934, 1745 (ester C=O), 1700 (cyclic urea C=O), 1496, 1449, 1263, 1187, 935, 758, 700.

δ_H 1.29 (3H, J=7.14, CO₂CH₂CH₃), 3.21 (2H, m, NCH₂CH₂), 3.44 (2H, m, NCH₂CH₂N), 4.01 (2H, s, PhCH₂), 4.21 (2H, q, J=7.14, CO₂CH₂CH₃), 4.40 (2H, s, NCH₂CO₂CH₂CH₃), 7.34 (5H, m, Ar-H);

δ_C 14.21 (CH₃CH₂O), 42.05 (NCH₂CH₂N), 43.02 (NCH₂CH₂N), 45.77 (PhCH₂), 48.26 (NCH₂CO₂CH₂CH₃), 61.11 (NCH₂CO₂CH₂CH₃), 127.44, 128.09 and 128.60 (3 x Ar-CH), 137.05 (Ar-C), 160.76 (cyclic urea C=O) and 169.65 (ester C=O);

m/z (CI) (MH⁺ 263.1, 100%); Found: MH⁺ 263.1393. C₁₄H₁₈N₂O₃, MH⁺ requires 263.1395.
Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and DMAD in the presence of Cu(OTf)$_2$

Ethyl diazoacetate (0.14 g, 1.25 mmol) in DCM (3 cm$^3$) was added dropwise slowly by syringe pump to a solution 1-benzyl-4,5-dihydroimidazole (0.2 g, 1.25 mmol), and Cu(OTf)$_2$ (0.46 g, 0.125 mmol) in dried DCM (4 cm$^3$) under nitrogen, then DMAD (0.425 g, 2.5 mmol) was added by syringe pump over 20 h. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 24 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO$_4$) and concentrated under reduced pressure to give an oil which was chromatographed repeatedly on silica (ethyl acetate and hexane, 3:7) to give 0.07 g (yield 14%) of the title compound 2.27 and 2.34 as a colourless oil (0.055 g, 9.5% yield).

Compound 2.34 had: $\nu_{max}(\text{film}/\text{cm}^{-1})$ 3006, 2954, 1743 (C=O), 1697 (C=O), 1674, 1614 (C=C), 1438, 1263, 1203, 1166, 1045, 755, 703;

$\delta_H$ 3.44 (2H, m, NCH$_2$CH$_2$N), 3.63 (3H, s, CO$_2$CH$_3$), 3.72 (2H, m, NCH$_2$CH$_2$N), 3.75 (3H, s, CO$_2$CH$_3$), 3.93 (3H, s, CO$_2$CH$_3$), 3.97 (3H, s, CO$_2$CH$_3$), 4.5 (2H, s, PhCH$_2$N), 4.85 (1H, s, CH$_3$CO$_2$CH=CNCH$_2$PhCO$_2$CH$_3$), 5.52 (1H, s, CH$_3$CO$_2$CH=CNCHOCO$_2$CH$_3$), 7.32 (5H, m, Ar-H), 8.33 (1H, s, $HC=O$)

200
δc 40.00 (NCH<sub>2</sub>CH<sub>2</sub>N), 47.00 (NCH<sub>2</sub>CH<sub>2</sub>N), 50.98, 52.10, 53.32 and 53.68 (4 x CO<sub>2</sub>CH<sub>3</sub>), 54.13 (PhCH<sub>2</sub>N), 86.65 (CH<sub>3</sub>CO<sub>2</sub>CH=CNCH<sub>3</sub>Ph), 103.42 (CH<sub>3</sub>CO<sub>2</sub>CH=CNCHO<sub>2</sub>CH<sub>3</sub>), 127.29, 128.12 and 129.05 (3 x Ar-CH), 134.94 (Ar-C), 145.28 (CH<sub>3</sub>CO<sub>2</sub>CH=CNCH<sub>2</sub>Ph), 153.78 (CH<sub>3</sub>CO<sub>2</sub>CH=CNCHO<sub>2</sub>CH<sub>3</sub>), 160.48 (1 x HC=O), 163.73, 165.21, 166.04 and 167.93 (4 x CO<sub>2</sub>CH<sub>3</sub>)

Reaction of 1-benzyl-4,5-dihydroimidazole with ethyl diazoacetate and fumaronitrile
1-Benzyl-5-ethoxycarbonyl-6,7-bis(cyano)hexahydro-1H-pyrrolo[1,2-a]imidazole, stereoisomers 2.35 and 2.36

![Chemical Structure](image)

Ethyl diazoacetate (0.14 g, 1.25 mmol) in DCM (3 cm<sup>3</sup>) was added dropwise slowly by syringe pump to a solution 1-benzyl-4, 5-dihydroimidazole (0.2 g, 2.5 mmol), fumaronitrile (0.20 g, 2.5 mmol) and Cu(OTf)<sub>2</sub> (0.46 g, 0.125 mmol) in dried DCM (4 cm<sup>3</sup>) under nitrogen. The solution was warmed gently (30-40 °C) until effervescence subsided, and was stirred at reflux for 48 h. The reaction mixture was then diluted with DCM, washed with water, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give an oily product which was chromatographed repeatedly on silica (ethyl acetate and hexane, 2:8) to give 0.19 g of stereoisomer 2.35 as a white solid (yield 23%) and stereoisomer 2.36 as an oil (trace amount).
Compound 2.35 had: m.p. 109.3-110.1°C; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3030 (Aryl C-H), 2980, 2926, 2851, 2823, 2246, 2200 (C=\( \equiv \)N), 1737, 1657 (C=O), 1603, 1454,1098, 1027, 835, 755, 701.

\( \delta_H \) 1.33 (3H, t, \( J=7.14 \), CO\(_2\)CH\(_2\)CH\(_3\)), 2.67 (1H, m, NCH\( \equiv \)HCH\(_2\)N), 2.98 (1H, m, NCH\(_2\)CH\( \equiv \)HN), 3.12 (1H, dd, \( J=9.15 \), 4.56, C-7\( \equiv \)H), 3.23 (1H, m, NCH\( \equiv \)HCH\(_2\)N), 3.23(1H, m, NCH\(_2\)CH\( \equiv \)HN), 3.65 (1H, d, \( J=13.02 \), PhCH\( \equiv \)H), 3.73 (1H, dd, \( J=8.61 \), 8.97, C-6\( \equiv \)H), 3.83 (1H, d, \( J=8.61 \), C-5\( \equiv \)H), 3.84 (1H, d, \( J=14.28 \), PCH\( \equiv \)H), 4.19 (1H, d, \( J=4.38 \), C-7\( \equiv \)a\( \equiv \)H), 4.28 (2H, q, \( J=7.14 \), CO\(_2\)CH\(_2\)CH\(_3\)), 7.34 (5H, m, Ar-\( \equiv \)H);

\( \delta_C \) 14.07 (CO\(_2\)CH\(_2\)CH\(_3\)), 36.32 (C-6), 38.65 (C-7), 52.68 and 53.54 (NCH\(_2\)CH\(_2\)N), 57.25 (PhCH\(_2\)), 62.54 (CO\(_2\)CH\(_2\)CH\(_3\)), 69.73 (C-5), 88.56 (C-7a), 116.38 and 116.47 (2 x CN), 127.91, 128.74 and 128.78 (3 x Ar-CH), 136.86 (Ar-C), 168.60 (C=O).

m/z (Cl) (MH\(^+\) 325.0, 100%); Found: MH\(^+\) 325.1662. C\(_{18}\)H\(_{20}\)N\(_4\)O\(_2\) requires MH\(^+\) 325.1664.

Compound 2.36 had: \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3069, 2958, 2234, 2202 (C\( \equiv \)N), 1737 (C=O), 1671, 1644, 1378, 1215, 910, 889, 761, 703.

\( \delta_H \) 1.34 (3H, t, \( J=7.14 \), CO\(_2\)CH\(_2\)CH\(_3\)), 2.65 (1H, m, NCH\( \equiv \)HCH\(_2\)N), 2.79 (1H, m, NCH\(_2\)CH\( \equiv \)HN), 3.12 (1H, m, NCH\( \equiv \)HCH\(_2\)N), 3.36 (1H, m, NCH\(_2\)CH\( \equiv \)HN), 3.47 (1H, d, \( J=12.45 \), PhCH\( \equiv \)H), 3.57 (1H, dd, \( J=3.66 \), 6.03, C-6\( \equiv \)H); 3.58 (1H, dd, \( J=3.66 \), 4.56, C-7\( \equiv \)H), 3.96 (1H, d, \( J=5.85 \) C-5\( \equiv \)H), 4.15 (1H, d, \( J=12.45 \), PhCH\( \equiv \)H), 4.29 (2H, q, \( J=7.14 \), CO\(_2\)CH\(_2\)CH\(_3\)), 4.40 (1H, d, \( J=4.92 \), C-7\( \equiv \)a\( \equiv \)H), 7.25-7.44 (5H, m, Ar-\( \equiv \)H);

\( \delta_C \) 14.06 (CO\(_2\)CH\(_2\)CH\(_3\)), 34.75 (C-6), 39.13 (C-7), 53.41 and 53.48 (NCH\(_2\)CH\(_2\)N), 58.32 (PhCH\(_2\)), 62.34 (CO\(_2\)CH\(_2\)CH\(_3\)), 68.07 (C-5), 84.25 (C-7a), 115.37 and 116.09 (2 x CN), 127.69, 128.50 and 129.19 (3 x Ar-CH), 137.16 (Ar-C), 168.85 (C=O).

m/z (Cl) (MH\(^+\) 325.1, 45%); Found: MH\(^+\) 325.1656. C\(_{18}\)H\(_{20}\)N\(_4\)O\(_2\) requires MH\(^+\) 325.1664.
Reaction of 1-benzyl-4,5-dihydroimidazole with trans-β-nitrostyrene

trans-β-Nitrostyrene (1.12 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was left at room temperature for 3 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (8:2) containing triethylamine (1%) on silica to afford compound 2.38 as a white solid (35.4 mg, 3.1%).

M.p. 137.5-140.1 °C; νmax (film)/cm⁻¹ 3032 (Aryl C-H), 2927, 1664, 1558 (C-NO₂ anti-symm), 1496, 1455, 1368 (C-NO₂ symm), 1078, 755, 700.

δH 2.41 (1H, m, NCH₂CH₂N), 2.55 (1H, m, NCH₂HNCH₂), 2.75 (1H, m, NCH₂NCH₂H), 3.09 (1H, m, NCH₂NCH₂H), 3.45 (1H, d, J=13.2, PhCH₂H), 3.72 (1H, d, J=13.2, PhCHH), 3.93 (1H, d, J=7.9, C-5H), 4.15 (1H, d, J=9.5, C-8aH), 4.18 (1H, t, J= 11.7, C-7H), 4.93 (1H, dd, J=9.5, 11.5, C-8H), 5.02 (1H, dd, J=7.9, 11.7, C-6H), 7.29 (15H, m, 3 x Ar-H);

δC 47.87 and 51.28 (NCH₂CH₂N), 50.32 (C-7), 59.11 (PhCH₂), 68.74 (C-5), 84.39 (C-8a), 91.15 (C-8), 93.76 (C-6), 127.35, 127.86, 127.88, 128.41, 128.66, 129.21, 129.38, 129.47 and 129.57 (9 x Ar-CH), 132.22, 135.13 and 138.04 (3 x Ar-C);

m/z (Cl) (459.2 100%); Found: MH⁺ 459.2031; C₂₆H₂₆N₄O₄ requires MH⁺ 459.2031.

and compound 2.39 as solid (0.396 g, 36%).
M.p. 151.9-154.2 °C; $\nu_{\text{max}}($film)/cm$^{-1}$ 3338 (NH), 3030 (Aryl C-H), 2926, 1618 (C=C), 1557 (C-NO$_2$ anti-symm), 1495, 1456, 1368 (C-NO$_2$ symm), 1316, 1265, 1114, 1084, 1030, 754, 702;

$\delta^H$ 1.45 (1H, br, NH), 2.75 (2H, m, NCHHCH$_2$N), 3.10 (1H, m, NCH$_2$CHHN), 3.20 (1H, m, NCH$_2$CHHN), 3.85 (2H, s, PhCH$_2$), 4.87 (1H, d, $J=10.6$, CHPhNO$_2$C=C), 5.04 (1H, d, $J=5.7$, NCHPhCHNO$_2$), 5.20 (1H, d, $J=10.6$, 5.7, CHNO$_2$), 7.28 (15H, m, 3 x Ar-H), 8.21 (1H, s, C=CH$_2$).

$\delta^C$ 42.72 (CHCPhCN0$_2$), 46.51 and 53.29 (HNCH$_2$CH$_2$N), 53.87 (PhCH$_2$), 57.02 (NCHPhCN0$_2$), 88.63 (HCPhCHNO$_2$CHPh), 120.45 (HC=CNO$_2$), 127.40, 127.66, 128.07, 128.62, 128.69, 128.78, 128.92, 129.44, and 129.79 (9 x Ar-CH), 133.50, 135.77 and 139.42 (3 x Ar-C), 146.88 (HC=CNO$_2$);

$m/z$ (Cl) (MH$^+$ 459.2 20%); Found: MH$^+$ 459.2037; C$_{26}$H$_{26}$N$_4$O$_4$ MH$^+$ requires 459.2032.

**Reaction of 1-benzyl-4,5-dihydroimidazole with dimethyl fumarate**

**1-Benzyl-5,6,7-tris(methoxycarbonyl)-5-methoxycarbonylmethylhexahydro-1H-pyrrolo[1,2-a]imidazole stereoisomers, 2.17 and 2.18**

Dimethyl fumarate (1.11 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm$^3$) under an atmosphere of nitrogen.
The mixture was refluxed for 48 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (2:8) containing triethylamine (3%) on silica to afford diastereomer 2.17 as a colourless oil (0.49 g, 45%) and diastereomer 2.18 as a white solid (0.11 g, 9.4%).

**Reaction of 1-benzyl-4,5-dihydroimidazole with dimethyl maleate**

1-Benzyl-5,6,7-tris(methoxycarbonyl)-5-methoxycarbonylmethylhexahydro 1H-pyrrolo[1,2-a]imidazole stereoisomers, 2.17 and 2.18

![Chemical structures](image)

These compounds were prepared from 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol) using the method described above but using dimethyl maleate (1.11 g, 7.5 mmol) and reflux for 48 h. The crude product was purified as before to afford diastereomer 2.17 as a colourless oil (0.43 g, 38%) and diastereomer 2.18 as a white solid (23 mg, 2.1%).
Reaction of 1-benzyl-4,5-dihydroimidazole with diethyl fumarate

1-Benzyl-5,6,7-tris(ethoxycarbonyl)-5-ethoxycarbonylmethylhexahydro-1-H-pyrrolo[1,2-a]imidazole stereoisomer, 2.43, triethyl 1-(2-benzylaminoethyl)-2,3-dihydro-2-ethoxycarbonylmethylpyrrole-2,3,4-tricarboxyate, 2.44, and 2-benzyl-7,8-(ethoxycarboxyl)-9-ethylhexahydro-octahydropyrrolo[1,2-a]pyrazin-1-one, 2.45

This reaction was carried out using 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and employing the method described above but using diethyl fumarate (1.29 g, 7.5 mmol) and reflux for 10 d. The crude product was purified by column chromatography eluting with ethyl acetate and hexane (2:8) on silica to afford compound 2.43 as an colourless oil (0.24 g, 20%):

$\nu_{\text{max}}$(film)/$\text{cm}^{-1}$ 3029 (Aryl C-H ), 2982, 2811, 1734 (C=O), 1455, 1370, 1206, 1031, 732, 702.
δ_H 1.29 (12H, m, 4 x OCH_2CH_3), 2.30 (1H, m, NCHHCH_2N), 2.92 (1H, d, J=14.60, CHPCH_2CH_3), 3.00 (3H, m, NCHHCH_2N), 3.04 (1H, d, J=13.5, PhCHH), 3.08 (1H, d, J=14.64, CHPCH_2CH_3), 3.68 (1H, dd, J=11, J=5.3, C-7H), 3.86 (1H, d, J=5.3, C-6H), 4.17 (8H, m, 4 x OCH_2CH_3), 4.21 (1H, d, J=13.5, PhCHH), 4.50 (1H, d, J=11, C-7aH), 7.28 (5H, m, Ar-H);

δ_C 14.02, 14.24, 14.24, 14.30 (4 x CH_3), 40.15 (CH_2CO_2C_2H_5), 45.02, 53.50 (NCH_2CH_2N), 50.23 (C-7), 54.14 (C-6), 56.37 (PhCH_2), 60.37, 60.91, 61.05, 61.32 (4 x OCH_2CH_3), 70.87 (C-5), 87.33 (C-7a), 126.95, 128.19, 128.57 (3 x Ar-CH), 138.92 (Ar-C), 170.42, 170.55, 170.86, and 172.55 (4 x C=O);

m/z (Cl) (MH^+ 505, 100%); Found: MH^+ 505.2551; C_{26}H_{36}N_{2}O_{8} requires MH^+ 505.2550.

and compound 2.44 as a colourless oil (34 mg, 2.7%);

ν_{max}(film)/cm^{-1} 3332 (NH), 3064, 2982, 2938, 2906, 1736 (C=O), 1683 (C=C=C=O), 1607 (C=C), 1496, 1446, 1372, 1196, 1096, 1029, 754, 702.

δ_H 1.25 (12H, m, 4 x CO_2CH_2CH_3), 1.62 (1H, br, NH), 2.72 (2H, m, NCH_2CH_2N), 3.05 (1H, d, J=17.2, CHHCO_2CH_2CH_3), 3.13 (1H, d, J=17.2, CHHCO_2CH_2CH_3), 3.31 (2H, m, NCH_2CH_2N), 3.79 (2H, s, PhCH_2), 4.17 (8H, m, 4 x CO_2CH_2CH_3), 4.30 (1H, s, CHHCO_2CH_2CH_3), 7.02 (1H, s, HC=CCO_2CH_2CH_3), 7.28 (5H, m, Ar-H);

δ_C 14.07, 14.07, 14.14 and 14.50 (4 x CH_3), 36.98 (CH_2CO_2CH_2CH_3), 46.05 and 48.34 (NCH_2CH_2N), 53.69 (PhCH_2), 54.15 (CHCO_2CH_2CH_3), 59.23, 61.11, 61.15 and 62.21 (4 x CO_2CH_2CH_3), 73.09 (quaternary C), 100.23 (HC=CCO_2CH_2CH_3), 127.06, 128.05 and 128.45 (3 x Ar-CH), 139.97 (Ar-C), 150.84 (HC=CCO_2CH_2CH_3), 164.96, 169.80, 170.26 and 171.10 (4 x C=O);

m/z (Cl) (MH^+ 505, 100%); Found: MH^+ 505.2550; C_{26}H_{36}N_{2}O_{8} requires MH^+ 505.2550.

and compound 2.45 as a colourless oil (72.1 mg, 6.3%).
$v_{\text{max}}$ (film) $/ \text{cm}^{-1}$: 3064, 3027 (Aryl C-H), 2983, 2937, 1744 (C=O), 1681 (enamino C=O), 1654 (lactam C=O), 1604 (C-C), 1475, 1392, 1370, 1337, 1198, 1161, 1099, 1026, 736, 701

$\delta_H$: 1.25 (9H, m, 3 x CO$_2$CH$_2$CH$_3$) 3.05 (1H, d, $J=14.1$, CHHCO$_2$CH$_2$CH$_3$), 3.25 (1H, m, NCHHCH$_2$N), 3.27 (1H, d, $J=14.1$, CHHCO$_2$CH$_2$CH$_3$), 3.52 (1H, m, NCHHCH$_2$N), 3.73 (1H, m, NCH$_2$CHHN), 3.88 (1H, s, CHHCO$_2$CH$_2$CH$_3$), 4.22 (6H, m, 3 x CO$_2$CH$_2$CH$_3$), 4.29 (1H, m, NCH$_2$CHHN), 4.53 (1H, d, $J=14.6$, PhCHH), 4.63 (1H, d, $J=14.6$, PhCHH), 7.02 (1H, m, $H$-C=C), 7.29 (5H, m, Ar-H).

$\delta_C$: 13.66, 14.08 and 14.46 (3 x CH$_3$), 47.22 (CH$_2$CO$_2$C$_2$H$_3$), 48.07 and 48.73 (NCH$_2$CH$_2$N), 51.36 (PhCH$_2$), 58.40 (CHCO$_2$C$_2$H$_5$), 59.41, 61.26 and 62.12 (3 x CH$_2$CH$_3$), 72.63 (C-8a), 98.98 (HC=CCO$_2$C$_2$H$_5$), 128.33, 128.37 and 128.76 (3 x Ar-CH), 136.61 (Ar-C), 151.24 (HC=C), 164.59, 168.52, 169.26 and 170.95 (4 x C=O);

$m/z$ (M+ 458, 100%); Found: MH$^+$ 459.2125. C$_{24}$H$_{30}$N$_2$O$_7$ requires MH$^+$ 459.2131.

and compound 2.46 (not isolated)

$\delta_H$: 1.08 (3H. t, $J=7.14$, CO$_2$CH$_2$CH$_3$), 1.21-1.32 (9H, m, 3 x CO$_2$CH$_2$CH$_3$), 2.51 (1H, m, NCH$_2$CHHN), 2.87 (3H, m, NCH$_2$CHHN), 2.88 (1H, d, $J=17.2$, CH$_2$CO$_2$CH$_3$), 3.44 (1H, d, $J=13.4$, PhCHH), 3.52 (1H, d, $J=11.4$, C-6H), 3.60 (1H, dd, $J=11.4$, 7.3 C-7H), 3.64 (1H, d, $J=17.22$ CH$_2$CO$_2$CH$_3$), 4.11-4.21 (8H, m, 4 x OCH$_2$CH$_3$), 4.23 (1H, d, $J=13.4$, PhCHH), 4.90 (1H, d, $J=7.32$, C-7aH), 7.28 (5H, m, Ar-H);

$\delta_C$: 38.43 (CH$_2$CO$_2$CH$_3$), 47.95 and 52.02 (NCH$_2$CH$_2$N), 50.96 (C-7), 51.88 (C-6), (4 x OCH$_3$), 59.36 (PhCH$_2$), 71.66 (C-5), 84.32 (C-7a), 126.87, 128.24 and 128.37 (3 x Ar-CH), 138.88 (Ar-C), 169.79, 169.82, 170.91 and 170.95 (4 x C=O);
Reaction of 1-benzyl-4,5-dihydroimidazole with N-methylmaleimide

\[ \text{CH}_2\text{Ph} \quad \xrightarrow{\text{N}} \quad \begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{N-CH}_3
\end{array} \]

\[ \begin{array}{c}
\text{H}_3\text{C-N} \\
\text{O} \\
\text{N-CH}_3
\end{array} \quad + \quad \begin{array}{c}
\text{H}_3\text{C-N} \\
\text{O} \\
\text{N-CH}_3
\end{array} \]

\[ \text{2.1} \quad \xrightarrow{2.22} \quad \text{2.24} \]

\( N\) -Methylmaleimide (0.83 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm\(^3\)) under an atmosphere of nitrogen. The mixture was refluxed for 24 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (5: 5) on silica to afford diastereomer 2.22 as a white solid (0.29 g, 30%) and stereoisomer 2.24 as a white solid (trace amount).

Compound 2.24 had: m.p. 171.2-173.8 °C; \( v_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3027 (Aryl C-H), 2958, 2931, 2874, 2858, 1778 (five membered ring imide antisym C=O), 1712 (five membered ring imide symm C=O) 1673, 1435, 1383,1287, 1128, 979, 749, 699.

\( \delta_H \) 2.51 (1H, m, NCH\text{HCH}_2\text{N}), 2.77 (1H, m, NCH\text{HCH}_2\text{N}), 2.86 (1H, m, NCH\text{HCH}_2\text{N}), 2.94 (3H, s, NCH\text{H}_3), 2.96 (2H, s CH\text{CONCH}_3), 2.99 (3H, s, NCH\text{H}_3), 3.10 (1H, m, NCH\text{HCH}_2\text{HNN}), 3.39 (1H, dd, \( J=1.83, 9.33 \), C-7\text{H}), 3.48 (1H, d, \( J=9.33, \) C-6\text{H}), 3.60 (1H, d, \( J=13.17, \) PhCH\text{H}), 4.11 (1H, d, \( J=13.35, \) PhCH\text{H}), 4.42 (1H, d, \( J=1.83, \) C-7\text{aH}), 7.28 (5H, m, Ar-H);

\( \delta_C \) 25.12, 25.27 (2 x NCH\text{H}), 39.22 (CH\text{CHONCH}_3), 46.86 and 51.92 (NCH\text{HCH}_2\text{N}), 52.02 (C-7), 53.55 (C-6), 57.11 (PhCH\text{H}), 71.85 (C-5), 87.51 (C-7\text{a}), 127.37, 128.49 and 128.56 (3 x Ar-CH), 137.86 (Ar-C), 173.46, 175.07, 175.91 and 176.31 (4 x C=O).
m/z (MH⁺ 383.2, 100%); Found: MH⁺ 383.1723, C_{20}H_{22}N_{4}O_{4} MH⁺ requires 383.1719.

**Reaction of 1-benzyl-4,5-dihydroimidazole with N-phenylmaleimide, stereoisomers 2.47 and 2.48**

N-Phenylmaleimide (1.30 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4, 5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was carried out at room temperature for 6 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (5: 5) on silica to afford diastereomer 2.47 as a light yellow solid (0.43 g, 36%).

M.p. 176.3-178.1 °C; ν_{max}(film)/cm⁻¹ 3064, 3027 (Aryl C-H), 2933, 2853, 1783 (antisym in five membered ring imide C=O), 1712 (symm in five membered ring imide C=O), 1598, 1498, 1383, 1189, 754, 694.

δH 2.52 (1H, m, NCH₂CHHN), 2.74 (1H, m, NCHHCH₂N), 2.83 (1H, m, NCHHCH₂N), 3.04 (1H, d, J=19.05, CHCONPh), 3.04 (1H, m, NCH₂CHHN), 3.29 (1H, d, J=11.7, PhCHH₂), 3.44 (1H, d, J=7.8, C-6H), 4.00 (1H, dd, J=7.8, 7.6, C-7H), 4.19 (1H, d, J=19.05, CCHCONPh), 4.31 (1H, d, J=11.7, PhCHH), 4.79 (1H, d, J=7.6, C-7aH), 7.28 (15H, m, Ar-H);
δc 33.15 (CH₂CONPh), 49.74 and 52.09 (NCH₂CH₂N), 49.82 (C-6), 51.33 (C-7), 58.82 (PhCH₂), 70.16 (C-5), 86.48 (C-7a), 126.29, 126.76, 127.48, 128.27, 128.93, 129.06, 129.29, 129.36, and 129.74 (9 x Ar-CH), 131.31, 131.96 and 137.64 (3 x Ar-C), 173.28, 174.79, 175.40 and 176.31 (4 x C=O);

m/z (Cl) (MH⁺ 507.3, 67%); Found: MH⁺ 507.2037. C₃₀H₂₆N₄O₄ MH⁺ requires 507.2032; and stereoisomer 2.48 as a light yellow solid (0.1 g, 8.3%):

M.p. 171.3-173.8 °C; vₓ (film)/cm⁻¹ 3027 (Aryl C-H), 2927, 2854, 1779 (antisymm in five membered ring imide C=O), 1708 (symm in five membered ring imide C=O), 1616, 1493, 1390, 1198, 750.

δh 2.50 (1H, m, NCHHCH₂N), 2.75 (1H, m, NCH₂CHHN), 2.89 (1H,m, NCH₂CHHNPh), 3.05 (1H, m, NCHHCH₂N), 3.10 (2H, s, CH₂CONPh), 3.47 (1H, d, J=9.69, C-6H), 3.54 (1H, dd, J=9.69, 2.19, C-7H), 3.54 (1H, d, J=13.4, PhCHH), 4.01 (1H, d, J=13.20, PhCHH), 4.54 (1H, d, J=2.19, C-7aH), 7.28 (15H, m, Ar-H);

δc 39.27 (CH₂CONCH₃), 47.69 and 51.88 (NCH₂CH₂N), 53.34 (C-7), 53.49 (C-6), 57.43 (PhCH₂), 72.16 (C-5), 86.11 (C-7a), 126.72, 126.82, 127.51, 128.62, 128.82 and 128.97, 129.09, 129.29 and 129.34 (9 x Ar-CH), 131.38, 131.72 and 137.97 (3 x Ar-C), 172.53, 174.55, 175.12 and 175.7 (4 x C=O).

m/z (MH⁺ 507.3, 75%); Found: MH⁺ 507.2035, C₃₀H₂₆N₄O₄ MH⁺ requires 507.2032.

**Reaction of 1-benzyl-4,5-dihydroimidazole with fumaronitrile (1)**

![Chemical structure](image)
Fumaronitrile (0.58 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4,5-
dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was reacted at room temperature for 48 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford compound 2.49 as an oil (0.04 g, 5%).

v<sub>max</sub>(film)/cm⁻¹ 3024 (Aryl C-H), 2927, 2853, 2233 (CH-C≡N), 2202(CH₂-C≡N), 1652, 1599, 1538, 1455, 1384, 1175, 1103, 1029, 803, 752, 702

δ<sub>H</sub> 2.69 (2H, m, NCH/HCH/NN), 2.99 (2H, s, CCH₂CN), 3.21 (1H, m, NCH/HCH₂N), 3.32 (1H, dd, J=6.96, 5.49, C-7H), 3.39 (1H, m, NCH₂CHHN), 3.64 (1H, d, J=13.35, PhCHH), 3.75 (1H, d, J=13.35, PhCHH), 4.01 (1H, d, J=6.96, C-6H), 4.26 (1H, d, J=5.49, C-7aH), 7.26 (5H, m, Ar-H);

δ<sub>C</sub> 27.45 (CCH₂CN), 36.49 (C-7), 44.43 (C-6), 47.38 (NCH₂CH₂N), 54.09 (NCH₂CH₂N), 55.98 (PhCH₂), 64.01 (C-5), 87.23 (C-7a), 111.18, 1123.74, 113.95 and 114.03 (4 x CN), 128.09, 128.23 and 128.50 (3 x ArCH), 135.78 (Ar-C);

m/z (Cl) (MH<sup>+</sup> 317.2, 30%); Found: MH<sup>+</sup> 317.1512. C<sub>18</sub>H<sub>16</sub>N<sub>6</sub>MH<sup>+</sup> requires 317.1514.

and compound 2.50 as an oil (trace yield)

v<sub>max</sub>(film)/cm⁻¹ 3030 (Aryl C-H), 2923, 2852, 2232 (CH-C≡N), 2202(CH₂-C≡N), 1658, 1599, 1537, 1454, 1380, 1177, 1097, 1028, 801, 746, 701

δ<sub>H</sub> 2.62 (1H, m, NCH/HCH₂N), 2.92 (1H, d, J=17.22, CCH/HCN), 2.99 (1H, d, J=17.22, CCH/HCN), 3.17 (2H, m, NCH/HCH/HN), 3.32 (1H, dd, J=11.73, 5.31, C-7H), 3.39 (1H, m, NCH₂CH/HN), 3.61 (1H, d, J=13.35, PhCH/H), 3.67 (1H, d, J=11.73, C-6H), 3.76 (1H, d, J=13.35, PhCH/H), 4.13 (1H, d, J=5.49, C-7aH), 7.27 (5H, m, Ar-H);

δ<sub>C</sub> 26.78 (CCH₂CN), 36.95 (C-7), 43.24 (C-6), 47.16 (NCH₂CH₂N), 54.14 (NCH₂CH₂N), 56.04 (PhCH₂), 65.40 (C-5), 86.98 (C-7a), 112.08, 112.38, 113.40 and 114.64 (4 x CN), 128.20, 128.57 and 128.92 (3 x Ar-CH), 135.84 (Ar-C);

m/z (Cl) (MH<sup>+</sup> 317.2, 50%); Found: MH<sup>+</sup> 317.1515, C<sub>18</sub>H<sub>16</sub>N<sub>6</sub> MH<sup>+</sup> requires 317.1514.
Reaction of 1-benzyl-4,5-dihydroimidazole with fumaronitrile (2)

1-Benzyl-5,6,7-tris(cyano)-5-cyanomethylhexahydro-1H-pyrrolo[1,2-a]imidazole, 2.51

Fumaronitrile (0.58 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was reacted at reflux for 48 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford the title compound 2.51 as a light pink solid (0.08 g, 10%).

M.p. 158.1-159.7 °C; νmax (film)/cm⁻¹ 3063, 3026 (Aryl C-H), 2951, 2937, 2829, 2253 (CH-CN), 2209 (CH₂-C=N), 1659, 1604, 1494, 1453, 1387, 1170, 753, 692.

δH (d₆-acetone), 2.75 (2H, m, NCH₂CH₂N), 3.34 (1H, m, NCH₂CH₂N), 3.39 (1H, d, J=17.01, CCH/HCN), 3.44 (1H, d, J=12.81, PhCH₂H), 3.51 (1H, d, J=17.01, CCH/HCN), 4.12 (1H, d, J=13.02, PhCH₂H), 4.32 (1H, dd, J=7.35, 5.67, C-7H), 4.37 (1H, d, J=5.67, C-7aH), 4.44 (1H, d, J=7.35, C-6H), 7.32 (3H, m, Ar-H), 7.49 (2H, m, Ar-H);

δC 28.92 (CCH₂CN), 37.98 (C-7), 43.14 (C-6), 48.93 and 54.98 (NCH₂CH₂N), 57.44 (PhCH₂), 65.62 (C-5), 84.87 (C-7a), 114.46, 114.96, 115.32 and 115.43 (4 x CN), 128.21, 129.16 and 129.78 (3 x Ar-CH), 138.59 (Ar-C);

m/z (CI) (MH⁺ 317.2, 100%); Found: MH⁺ 317.1511. C₁₈H₁₆N₆MH⁺ requires 317.1514.
Reaction of 1-benzyl-4,5-dihydroimidazole with DMAD

Tetranethyl 4aH-pyrido[2,1-b]-N-benzyl-6,7,8,8a-tetracarboxylate, 2.59

DMAD (1.07 g, 7.5 mmol) was added to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The reaction was carried in room temperature for 10 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford the title compound as a colourless oil 2.59 (0.06 g, 5.3%).

νmax (film)/cm⁻¹ 3026 (Aryl C-H), 2953, 1741 (unconjugated C=O), 1701 (conjugated C=O), 1536 (C=C-O-C), 1437, 1261, 1211, 751, 705.

δH 2.89 (1H, m, NCH2CH2N), 3.10 (1H, m, NCH2CHHN), 3.56-3.75 (2H, m, NCHHCHHN), 3.62 (3H, s, CO2CH3), 3.64 (3H, s, CO2CH3), 3.67 (1H, d, J=13.38, PhCH), 3.71 (3H, s, CO2CH3), 3.78 (1H, d, J=12.66, PhCHH), 3.83 (3H, s, CO2CH3), 7.23 (5H, Ar-H), 7.77 (1H, s, C-1H);

δC 47.79 and 48.60 (NCH2CH2N), 51.68, 52.38, 52.84 and 53.34 (4 x CO2CH3), 55.99 (PhCH3), 84.44 (C-8a), 98.27 (C-8), 109.34 (C-7), 127.53, 128.66 and 128.71 (3 x Ar-CH), 138.53 (Ar-C), 141.1 (C-6), 146.67 (C-5), 164.47, 164.64, 168.07 and 169.24 (4 x C=O);

m/z (Cl) (MH⁺ 445.2, 100%); Found: MH⁺ 445.1609, C22H24N2O8 MH⁺ requires 445.1611.
Reaction of 1-benzyl-4,5-dihydroimidazole with N-phenylmaleimide and dimethyl fumarate

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule.png}
\end{center}

N-Phenylmaleimide (0.43 g, 2.5 mmol) in dry DCM (5 cm³) was added slowly by syringe pump to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and dimethyl fumarate (0.37 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. After 3 d, the mixture was concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (2:8) on silica to afford compound 2.62 as a colourless solid (0.44 g, 37%).

M.p. 114.7-117.1 °C; \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3063, 3026 (Aryl C-H), 2953, 2846, 1786 (antisymm in five membered ring imide C=O), 1718 (symm in five membered ring imide C=O), 1599, 1499, 1438, 1387,1206, 1027, 966, 749, 699;

\( \delta_{\text{H}} \) 2.47 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}HN), 2.87 (1H, m, NCHH\textsubscript{2}CH\textsubscript{2}N), 2.01 (1H, m, NCHHCH\textsubscript{2}N), 3.12 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}HHN), 3.21 (1H, d, \( J=17.94 \), CCHHCONPH), 3.32 (1H, d, \( J=17.97 \), CCHHCONPh), 3.51 (1H, d, \( J=13.56 \) PhCH\textsubscript{2}H), 3.69 (3H, s, CO\textsubscript{2}CH\textsubscript{3}), 3.72 (3H, s, CO\textsubscript{2}CH\textsubscript{3}), 3.97 (1H, d, \( J=10.26 \), C-6H), 4.00 (1H, dd, \( J=10.26, 7.68 \), C-7H), 4.22 (1H, d, \( J=13.38 \), PhCH\textsubscript{2}H), 4.88 (1H, d, \( J=7.68 \), C-7aH), 7.25 and 7.41 (10H, m, 2 x Ar-H).

\( \delta_{\text{C}} \) 37.38 (CCH\textsubscript{2}CO\textsubscript{2}NPh), 49.24 (NCH\textsubscript{2}CH\textsubscript{2}N), 50.25 (C-7), 51.97 (NCH\textsubscript{2}CH\textsubscript{2}N), 52.25 (C-6), 52.37 (CO\textsubscript{2}CH\textsubscript{3}), 52.66 (CO\textsubscript{2}CH\textsubscript{3}), 59.76 (PhCH\textsubscript{2}), 69.78 (C-5), 85.35 (C-7a),
Reaction of 1-benzyl-4,5-dihydroimidazole with N-methylmaleimide and dimethyl fumarate

N-Methylmaleimide (0.28 g, 2.5 mmol) in dry DCM (5 cm³) was added slowly by syringe pump to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and dimethyl fumarate (0.37 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. After 3 d, the solution was concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford diastereomer 2.63 as a colourless solid (0.24 g, 24%): M.p. 113-115 °C; ν_{max}(film)/cm⁻¹ 3028 (Aryl C-H), 2952, 2846, 1784 (five membered ring imide antisym C=O), 1735 (C=O), 1707 (five membered ring imide symm C=O), 1438, 1386, 1349, 1288, 1166, 1030, 968, 739, 700;

δ_H 2.42 (1H, m, NCHHCH₂N), 2.81 (1H, m, NCH₂CH=HN), 2.95 (1H, m, NCHHCH₂N), 2.99 (3H, s, NCH₃), 3.03 (1H, d, J=17.76, CCH/HCONCH₃), 3.05 (1H, m, NCH₂CH=HN), 3.17 (1H, d, J=17.76, CCH/HCONCH₃), 3.35 (1H, d, J=13.38, PhCH/II), 3.65 (1H, s, CO₂CH₃). 3.72 (3H, s, CO₂CH₃), 3.92 (1H, d, J= 10.44, C-6H), 3.99 (1H, dd, J=10.44,
7.44, C-7H), 4.13 (1H, d, J=13.35, PhCHH), 4.83 (1H, d, J=7.44, C-7aH), 7.28 (5H, m, Ar-H);

δc 24.83 (NCH₃), 37.11 (CH₂CONCH₃), 49.18 (NCH₂CH₂N), 49.67 (C-7), 52.09 (NCH₂CH₂N), 52.26 (C-6), 52.38 (CO₂CH₃), 52.58 (CO₂CH₃), 59.79 (PhCH₂), 69.83 (C-5), 85.2 (C-7a), 127.08, 128.28, 128.33 (3 x Ar-CH), 138.43 (Ar-C), 171.39, 172.14, 174.37 and 177.53 (4 x C=O).


and diastereomer 2.64 as a white light yellow solid (0.072 g, 6.7%):

M.p. 127.5-129.4 °C; νₘₐₓ(film)/cm⁻¹ 3030 (Aryl C-H), 2954, 2927, 2855, 2361, 1784 (five membered ring imide antisymm C=O), 1733 (C=O), 1708 (five membered ring imide symm C=O), 1610, 1437, 1384, 1262, 1138, 1018, 805, 752, 698.

δh 2.29 (1H, m, NCH₂CHHN), 2.55 (1H, d, J=19.05, CCHHCONCH₃), 2.58 (1H, m, NCHHCH₂N), 2.93 (1H, d, J=19.05, CCHHCONPh), 2.98 (1H, d, J= 13.35, PhCHH), 3.06 (1H, m, NCHHCH₂N), 3.07 (3H, s, NCH₃), 3.14 (1H, m, NCH₂CHHN), 3.35 (1H, dd, J=10.8, 3.48, C-7H), 3.67 (3H, s, CO₂CH₃), 3.76 (3H, s, CO₂CH₃), 4.00 (2H, d, J=3.48, C-7aH), 4.23 (1H, d, J=13.38, PhCHH), 4.25 (1H, d, J=10.8, C-6H), 7.26 (5H, m, Ar-H).

m/z (Cl) (MH⁺ 416.2, 100%); Found: MH⁺ 416.1824. C₂₁H₂₅N₃O₆ MH⁺ requires 416.1821.
Fumaronitrile (0.20 g, 2.5 mmol) in dry DCM (5 cm³) was added slowly by syringe pump to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and dimethyl fumarate (0.37 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was reacted at room temperature for 48 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford compound \textbf{2.66} as a light yellow solid (0.25 g, 27%).

M.p. 81-83 °C; \( v_{\text{max}} \) (film)/cm\(^{-1} \) 3026 (Aryl C-H), 2954, 2850, 2247, 2198 (C≡N), 1740 (C=O), 1666, 1439, 1366, 1209, 1142, 1020, 756, 703.

\( \delta_H \) 2.51 (1H, m, NCH\(_2\)CH(N)), 2.70 (1H, m, NCH\(_{2}\)CH\(_2\)N), 2.91 (1H, d, \( J=16.86 \), CCH\(_{2}\)CO\(_2\)CH\(_3\)), 2.91 (2H, m, NCH\(_{2}\)CH\(_{2}\)N), 3.15 (1H, d, \( J=11.16 \), C-6H), 3.20 (1H, d, \( J=16.83 \), CCH\(_{2}\)CO\(_2\)CH\(_3\)), 3.45 (1H, d, \( J=12.27 \) PhCH\(_{2}\)H), 3.49 (1H, dd, \( J=11.16 \), 6.42, C-7H), 4.17 (1H, d, \( J=12.27 \) PhCH\(_{2}\)H), 4.52 (1H, d, \( J=6.42 \), C-7aH), 7.30 (5H, m, Ar-H).

\( \delta_C \) 36.84 (CCH\(_2\)CO\(_2\)CH\(_3\)), 37.99 (C-6), 39.77 (C-7), 47.46 (NCH\(_2\)CH\(_2\)N), 51.35 (NCH\(_2\)CH\(_2\)N), 52.52 and 53.35 (2 x CH\(_3\)), 58.24 (PhCH\(_2\)), 71.79 (C-5), 83.38 (C-7a), 115.14 and 116.36 (2 x CN), 127.60, 128.43 and 129.25 (3 x Ar-C), 137.03 (Ar-C), 168.68 and 169.38 (2 x C=O);
Reaction of 1-benzyl-4,5-dihydroimidazole with diethyl fumarate and fumaronitrile
1-Benzyl-5-ethoxycarbonyl-5-ethoxycarbonylmethyl-6,7-bis(cyano)hexahydro-1H-
pyrrolo[1,2-a]imidazole, stereoisomers 2.67 and 2.68

The reaction was carried out as above using diethyl fumarate in place of dimethyl
fumarate. Purification by column chromatography eluting with ethyl acetate and hexane
(2:8) on silica afforded 2.67 as a light brown solid (0.31g, 31% yield):
M.p. 145.6-147.6 °C; v_{max} (film)/cm\(^{-1}\) 3027 (Aryl C-H), 2982, 2245, 2200 (C\equiv N), 1733
(C=O), 1662, 1203, 1026, 701.
\(\delta_H\) 1.19 (3H, t, \(J=7.14, \text{CO}_2\text{CH}_2\text{CH}_3\)), 1.21 (3H, t, \(J=7.14, \text{CO}_2\text{CH}_2\text{CH}_3\)), 2.52 (1H, m,
NCH\(_2\)CHHN), 2.98 (1H, m, NCH\(_2\)HCH\(_2\)N), 3.05 (1H, m, NCH\(_2\)HCH\(_2\)N), 3.20 (1H, d,
\(J=17.22, \text{CCH} / \text{CO}_2\text{CH}_2\text{CH}_3\)), 3.22 (1H, m, NCH\(_2\)CHHN), 3.38 (1H, d, \(J=17.22,
\text{CCH} / \text{CO}_2\text{CH}_2\text{CH}_3\)), 3.41 (1H, d, \(J=12.45 \text{PhCH} / \text{H}\)), 3.81 (1H, dd, \(J=8.97, 6.42, C-7H\),
4.10 (1H, dd, \(J=8.97, C-6H\)), 4.12 (2H, q, \(J=7.14, \text{CO}_2\text{CH}_2\text{CH}_3\)), 4.15 (2H, q, \(J=7.14,
\text{CO}_2\text{CH}_2\text{CH}_3\)), 4.15 (1H, d, \(J=12.45, \text{PhCH} / \text{H}\)), 4.18 (1H, d, \(J=6.42, C-7aH\)), 7.31 (5H, m,
Ar-\(H\)).
\(\delta_C\) 13.83 and 14.03 (\text{CO}_2\text{CH}_2\text{CH}_3), 37.09 (CCH\(_2\)CO\(_2\text{NCH}\(_2\)), 39.09 (C-6), 39.63 (C-7),
47.64 (NCH\(_2\)CH\(_2\)N), 52.56 (NCH\(_2\)CH\(_2\)N), 58.45 (PhCH\(_2\)), 61.62 and 62.61 (2 x 219
$\text{CO}_2\text{CH}_2\text{CH}_3$, 70.33 (C-5), 83.94 (C-7a), 116.37 and 116.58 (2 x CN), 127.50, 128.44, and 129.07 (3 x Ar-C), 137.40 (Ar-C), 169.42 and 169.83 (2 x C=O).

$m/z$ (Cl) (MH$^+$ 411.3, 40%); Found: MH$^+$ 411.2032. C$_{22}$H$_{28}$N$_4$O$_4$MH$^+$ requires 411.2032; and stereoisomer 2.68 as light brown solid (trace).

M.p. 134.8-136.5 °C; $\nu_{\text{max (film)}}$ cm$^{-1}$ 3064, 3027 (Aryl C-H), 2983, 2939, 2246, 2199 (C≡N), 1735 (C=O), 1666, 1203, 1027, 751, 703.

$\delta_H$ 1.24 (3H, t, $J$=7.14, CO$_2$CH$_2$CH$_3$), 1.32 (3H, t, $J$=7.14, CO$_2$CH$_2$CH$_3$), 2.58 (1H, m, NCH$_2$HCH$_2$N), 2.75 (1H, m, NCH$_2$CHHN), 2.91 (1H, d, $J$=16.83, CCHHCO$_2$CH$_2$CH$_3$), 2.98 (1H, m, NCHHCH$_2$N), 3.18 (1H, d, $J$=11.16, C-6H), 3.25 (1H, d, $J$=16.83, CCHHCO$_2$CH$_2$CH$_3$), 3.40 (1H, d, $J$=12.27, PhCH$_2$H), 3.44 (1H, m, NCH$_2$CH/N), 3.52 (1H, dd, $J$=11.16, 6.42, C-7H), 4.17 (2H, q, $J$=7.14, CO$_2$CH$_2$CH$_3$), 4.19 (1H, d, $J$=12.66, PhCH$_2$H), 4.29 (1H, q, $J$=7.14, CO$_2$CH$_2$CH$_3$), 4.60 (1H, d, $J$=6.42, C-7aH), 7.28 (5H, m, Ar-H);

$\delta_C$ 13.95 and 14.03 (2 x CO$_2$CH$_2$CH$_3$), 38.01 (CCH$_2$CO$_2$CH$_2$CH$_3$), 39.11 (C-6), 39.82 (C-7), 47.55 and 51.36 (NCH$_2$CH$_2$N), 58.30 (PhCH$_2$), 61.63 and 62.85 (2 x CO$_2$CH$_2$CH$_3$), 71.69 (C-5), 83.50 (C-7a), 115.18 and 116.46 (2 x CN), 128.46, 129.08, 129.30 (3 x Ar-CH), 137.07 (Ar-C), 168.25 and 168.40 (2 x C=O).

$m/z$ (Cl) (MH$^+$ 411.3, 100%); Found: MH$^+$ 411.2031. C$_{22}$H$_{28}$N$_4$O$_4$MH$^+$ requires 411.2032.
Reaction of 1-benzyl-4,5-dihydroimidazole with \(N\)-methylmaleimide and fumaronitrile

Fumaronitrile (0.20 g, 2.5 mmol) and \(N\)-methylmaleimide (0.27 g, 2.5 mmol) in dry DCM (4 cm\(^3\)) were added slowly by syringe pump to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm\(^3\)) under an atmosphere of nitrogen. The mixture was reacted at room temperature for 48 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford diastereomer 2.69 as a light yellow solid (0.031 g, 3.8%):

M.p. 140-141 °C; \(v_{\text{max}}\) (film)/cm\(^{-1}\) 3028 (Aryl C-H), 2939, 2851, 2248 (C=N), 1789 (five membered ring imide antisym C=O), 1712 (five membered ring imide symm C=O), 1440, 1387, 1289, 1142, 1103, 1029, 758, 702.

\(\delta_h\) 2.43 (1H, m, NCH\(_2\)CHHN), 2.60 (1H, d, \(J=17.01\), CCH\(/\text{CONCH}_3\)), 2.72 (1H, m, NCH\(/\text{HCH}_2\)N), 2.91 (1H, d, \(J=17.01\), CCH\(/\text{CONCH}_3\)), 3.00 (1H, m, NCH\(/\text{HCH}_2\)N), 3.04 (3H, s, NCH\(_3\)), 3.12 (1H, m, NCH\(_2\)CHHN), 3.23 (1H, dd, \(J=11.34, 6.42\), C-7\(H\)), 3.42 (1H, d, \(J=12.45\), PhCH\(_H\)), 3.83 (1H, d, \(J=11.34\), C-6\(H\)), 3.85 (1H, d, \(J=12.63\), PhCH\(_H\)), 4.27 (1H, d, \(J=6.42\), C-7\(aH\)), 7.28 (5H, m, Ar-\(H\)).
\( \delta_c \) 25.98 (NCH\(_3\)), 35.57 (CCH\(_2\)CONCH\(_3\)), 40.14 (C-6), 40.87 (C-7), 48.41 (NCH\(_2\)CH\(_2\)N), 52.39 (NCH\(_2\)CH\(_2\)N), 58.72 (PhCH\(_2\)), 69.37 (C-5), 83.39 (C-7a), 115.59 and 115.72 (2 x CN), 128.01, 128.80, and 129.37 (3 x Ar-CH), 137.10 (Ar-C), 172.32 and 172.41 (2 x C=O);

\( m/z \) (Cl) (MH\(^+\) 350.3, 100%); Found: MH\(^+\) 350.1616. C\(_{19}\)H\(_{19}\)N\(_5\)O\(_2\) MH\(^+\) requires 350.1617.

and stereoisomer 2.70 as a white solid (0.19 g, 22%).

M.p. 112-114 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3028 (Aryl C-H), 2942, 2246 (C\(=\)N), 1788 (five membered ring imide antisymm C=O), 1713 (five membered ring imide symm C=O), 1665, 1439, 1385, 1288, 1140, 1021, 756, 701.

\( \delta_H \) 2.45 (1H, m, NCH/CH\(_2\)N), 2.60 (1H, m, NCH\(_2\)CH/N), 2.87 (1H, d, \( J=18.51 \), CCHHCONCH\(_3\)), 2.93 (1H, m, NCH/HCH\(_2\)N), 2.99 (3H, s, NCH\(_3\)), 3.00 (1H, m, NCH\(_2\)CHHN), 3.03 (1H, d, \( J=18.51 \), CCHHCONCH\(_3\)), 3.27 (1H, d, \( J=11.37 \), C-6H), 3.34 (1H, d, \( J=12.45 \), PhCHH), 4.13 (1H, dd, \( J=11.37, 6.42 \), C-7H), 4.23 (1H, d, \( J=12.45 \), PhCH/H), 4.54 (1H, d, \( J=6.42 \), C-7aH), 7.28 (5H, m, Ar-H);

\( \delta_c \) 25.32 (NCH\(_3\)), 35.02 (CCH\(_2\)CONCH\(_3\)), 37.06 (C-6), 39.23 (C-7), 49.45 and 51.20 (NCH\(_2\)CH\(_2\)N), 58.48 (PhCH\(_2\)), 71.33 (C-5), 83.75 (C-7a), 115.01 and 116.48 (2 x CN), 128.66, 128.84, 129.40 (3 x Ar-CH), 136.98 (Ar-C), 171.95 and 175.13 (2 x C=O).

\( m/z \) (Cl) (MH\(^+\) 350.2, 70%); Found: MH\(^+\) 350.1619. C\(_{19}\)H\(_{19}\)N\(_5\)O\(_2\) MH\(^+\) requires 350.1617.
Reaction of 1-benzyl-4,5-dihydroimidazole with N-phenylmaleimide and fumaronitrile

The above reaction was repeated using N-phenylmaleimide in place of N-methylmaleimide. Purification by column chromatography eluting with ethyl acetate and hexane (3:7) on silica afforded diastereomer 2.71 as a yellow solid (trace).

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3028 (Aryl C-H), 2935, 2854, 2246, 2199 (C≡N), 1791 (antisymm in five membered ring imide C=O), 1718 (symm in five membered ring imide C=O), 1664, 1599, 1499, 1444, 1392, 1207, 1126, 981, 853, 756, 698.

$\delta_{\text{H}}$ 2.50 (1H, m, NCH$_2$CH$_2$N), 2.75 (1H, d, $J=17.22$, CCHHCONPh), 2.83 (1H, m, NCHHCH$_2$N), 3.02 (1H, m, NCHHCH$_2$N), 3.10 (1H, d, $J=17.22$, CCHHCONPh), 3.21 (1H, m, NCH$_2$CH$_2$N), 3.30 (1H, dd, $J=11.34$, 6.42, C-7H), 3.44 (1H, d, $J=12.45$, PhCHH), 3.87 (1H, d, $J=11.34$, C-6H), 4.17 (1H, d, $J=12.45$, PhCHH), 4.33 (1H, d, $J=6.42$, C-7aH), 7.25 and 7.41 (10H, m, 2 x Ar-H).

$\delta_{\text{C}}$ 36.34 (CH$_2$CONPh), 39.88 (C-6), 40.72 (C-7), 48.27 and 52.17 (NCH$_2$CH$_2$N), 58.48 (PhCH$_2$), 69.40 (C-5), 83.16 (C-7a), 114.28 and 114.28 (2 x CN), 126.22, 127.79, 128.58, 129.15, 129.43 and 129.60 (6 x Ar-CH), 130.61 and 136.63 (2 x Ar-C), 170.77 and 174.24 (2 x C=O)

$m/z$ (Cl) (MH$^+$ 412.2, 100%); Found: MH$^+$ 412.1821. $C_{24}H_{21}N_3O_2$ MH$^+$ requires 412.1773.
and stereoisomer 2.72 as a light yellow solid (0.18g, 21%)
M.p. 161.9-163.6 °C; v_{max} (film)/cm^{-1} 3028 (Aryl C-H), 2920, 2246, 2197 (C≡N), 1780 (antisymmetric in five-membered ring imide C=O), 1716 (symmetric in five-membered ring imide C=O), 1662, 1599, 1498, 1444, 1390, 1204, 754, 704.

δ_H 2.49 (1H, m, NCH/HCH_2N), 2.65 (1H, m, NCH_2CH/HN), 2.97 (1H, m, NCH/HCH_2N),
3.04 (1H, d, J=18.3, CCH/HCONPh), 3.13 (1H, m, NCH_2CH/HN), 3.23 (1H, d, J=18.3, CCH/HCONPh), 3.34 (1H, d, J=11.34, C-6H), 3.35 (1H, d, J=12.27, Ph/CHH), 4.10 (1H, dd, J=11.34, 6.34, C-7H), 4.24 (1H, d, J=12.27, Ph/CHH), 4.58 (1H, d, J=6.39, C-7aH),
7.23 (5H, m, Ar-H), 7.41 (5H, m, Ar-H);

δ_C 35.22 (CH_2CONPh), 37.43 (C-6), 39.10 (C-7), 49.36 and 51.08 (NCH_2CH_2N), 58.33 (Ph/CH_2), 71.14 (C-5), 83.79 (C-7a), 114.95 and 116.28 (2 x CN), 126.51, 127.75, 128.52, 129.27, 129.43 and 129.60 (6 x Ar-CH), 130.61 and 136.82 (2 x Ar-C), 170.77 and 174.24 (2 x C=O).

m/z (Cl) (MH^+ 412.2, 100%); Found: MH^+ 412.1768. C_{24}H_{21}N_{5}O_{2} MH^+ requires 412.1773

**Reaction of 1-benzyl-4,5-dihydroimidazole with DMAD and dimethyl fumarate**

![](https://example.com/diagram.png)

Dimethyl fumarate (0.37 g, 2.5 mmol) and DMAD (0.36 g, 2.5 mmol) together were added to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5
cm$^3$) under an atmosphere of nitrogen. After 3 d at room temperature the mixture was concentrated under reduced pressure. The crude oil was purified by column chromatography, eluting with ethyl acetate and hexane (3:7) on silica to afford compound 2.73 as a colourless oil (0.09 g, 8%).

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3023 (Aryl C-H), 2882, 2844, 2952, 1742 (unconjugated C=O), 1693 (vinylogous amide C=O), 1595 (C=C), 1436, 1235, 1122, 753, 702.

$\delta_H$ 2.50 (1H, m, NCH/NHN), 3.01 (1H, m, NCH/NHN), 3.38 (2H, m, NCH/NHN), 3.38 (1H, d, $J=12.09$, PhCHH), 3.39 (1H, dd, $J=1.29$, 4.2, C-8H), 3.64 (3H, s, CO$_2$CH$_3$), 3.67 (3H, s, CO$_2$CH$_3$), 3.68 (3H, s, CO$_2$CH$_3$), 3.88 (1H, d, $J=4.23$, C-8aH), 3.88 (3H, s, CO$_2$CH$_3$), 3.91 (1H, d, $J=1.29$, C-7H), 4.09 (1H, d, $J=12.63$, PhCHH), 7.23 (5H, m, Ar-H); $\delta_C$ 38.99 (C-8), 40.45 (C-7), 46.20 and 50.44 (NCH$_2$CH$_2$N), 51.44, 51.87, 52.79 and 53.04 (4 x CO$_2$CH$_3$), 56.71 (PhCH$_2$), 74.06 (C-8a), 92.28 (C-6), 127.67, 128.53 and 128.83 (3 x Ar-CH), 137.12 (Ar-C), 146.64 (C-5), 165.34, 166.96, 169.79 and 173.08 (4 x CO$_2$CH$_3$); $m/z$ (Cl) (MH$^+$ 447.2, 100%); Found: MH$^+$ 447.1766. C$_{22}$H$_{26}$N$_2$O$_8$ MH$^+$ requires 447.1767.

**Reaction of 1-benzyl-4,5-dihydroimidazole with N-phenylmaleimide and DMAD**

![](image)

$N$-Phenylmaleimide (0.43 g, 2.5 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.36 g, 2.5 mmol) in dry DCM (5 cm$^3$) were added slowly by syringe pump to a stirred
solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was reacted at room temperature for 2 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (3:7) on silica to afford 0.19 g (yield 17%) of compound 2.47 and compound 2.75 as a white solid (0.076 g, 6%).

M.p. 116.1-118.3 °C; v_{max}(film)/cm^{-1} 3308 (NH), 3029 (Aryl C-H), 2921, 2852, 2361, 1782 (five membered ring imide antisymm C=O), 1714 (five membered ring imide symm C=O), 1685 (C=C-C=O), 1615 (C=C), 1500, 1386, 1195, 1129, 749, 693.

δ_H 2.49 (1H, dd, J=10.98 NH), 2.90 (1H, m, NCHHCH₂N), 3.08 (2H, m, NCHHCHHN), 3.06 (1H, d, J=17.19, CCHHCONPh), 3.38 (1H, d, J=17.37, CCHHCONPh), 3.67 (1H, m, NCH₂CH₂N), 4.15 (1H, d, J=1.11, C-6aH), 4.49 (2H, dd, J=15.57, 15.54, PhCH₂), 7.12-7.52 (15H, 3 x Ar-H), 8.03 (1H, s, C-1H);

δ_C 41.50 (CCH₂CONPh), 45.65 (NCH₂NCH₂), 48.59 (NCH₂NCH₂), 51.70 (C-6a), 61.41 (PhCH₂N), 65.00 (CCH₂CONPh), 91.14 (CH=CCONPh), 126.65, 126.88, 127.76, 128.18, 128.79, 128.92, 129.08, 129.31 and 131.42 (9 x Ar-CH), 132.33, 135.89 and 137.95 (3 x Ar-C), 147.56 (C-1), 173.41, 174.61, 175.92 and 177.16 (4 x C=O).
Reaction of 1-benzyl-4,5-dihydroimidazole with cinnaminitrile and dimethyl fumarate

2-Benzyl-7,8-dis(methoxycarboxyl)-9-methoxycarbonylmethylhexahydrooctahydropyrrolo[1,2-a]pyrazin-1-one, 2.76 and 2.77

Dimethyl fumarate (0.37 g, 2.5 mmol) in dry DCM (3 cm³) was added slowly by syringe pump to a stirred solution of 1-benzyl-4,5-dihydroimidazole (0.4 g, 2.5 mmol) and cinnaminitrile (0.64 g, 2.5 mmol) in dry DCM (3 cm³) under an atmosphere of nitrogen. The mixture was reacted at reflux for 2 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (2:8) on silica to afford diastereomer 2.76 as a colourless solid (0.11 g, 10%).

M.p. 94.4-97.1 °C; νmax (film)/cm⁻¹ 3009, 2953, 1739 (C=O), 1692 (enamino C=O), 1651 (lactam C=O), 1615 (C=C), 1486, 1438, 1353, 1206, 1179, 1094, 1018, 929, 754, 702.

δH 2.84 (1H, d, J=15.72, CCHHCO2CH3), 3.09 (2H, m, NCHHCH2N), 3.23 (1H, d, J=15.72, CCHHCO2CH3), 3.50 (2H, m, NCH2CHHN), 3.60 (3H, s, CO2CH3), 3.61 (3H, s, CO2CH3), 3.72 (3H, s, CO2CH3), 4.17 (1H, d, J=14.49, PhNCHH), 4.35 (1H, d, J=0.9, CHCO2CH3), 4.90 (1H, t, J=14.49, PhCHHN), 7.00 (1H, d, J=1.1, NCH=CO2CH3), 7.20-7.30 (5H, m, Ar-H);

δC 42.76 (CCH2CO2CH3), 44.29 (NCH2CH2N), 46.15 (NCH2CH2N), 50.93 (PhCH2N), 50.95, 51.87 and 52.38 (3 x CO2CH3), 57.97 (CHCO2CH3), 70.71 (CCH2CO2CH3), 106.46
(NCH=CCO₂CH₃), 127.73, 128.25 and 128.73 (3 x Ar-CH), 136.03 (Ar-C), 150.52
(NCH=CCO₂CH₃), 164.58, 168.47, 170.35 and 172.42 (4 x C=O).

m/z (Cl) (MH⁺ 417.2, 100%); Found: MH⁺ 417.1656  C₂₁H₂₄N₂O₇, MH⁺ requires
417.1656.

and diastereomer 2.77 as a colourless solid (trace).

νmax (film)/cm⁻¹: 3009, 2953, 1739 (C=O), 1692 (enamin C=O), 1651 (lactam C=O), 1615
(C=C), 1486, 1438, 1353, 1206, 1179, 1094, 1018, 929, 754, 702.

δH 2.81 (1H, d, J=15.75, CCHHCO₂CH₃), 3.09 (2H, m, NCHHCH₂N), 3.16 (1H, d,
J=15.54, CCHHCO₂CH₃), 3.50 (2H, m, NCH₂CHHN), 3.60 (3H, s, CO₂CH₃), 3.58 (3H, s,
CO₂CH₃), 3.56 (3H, s, CO₂CH₃), 3.86 (1H, s, CHCO₂CH₃), 4.27 (1H, d, J=14.67,
NCHHPh), 4.85 (1H, d, J=14.28, NCHHPh), 6.97 (1H, d, J=0.54, NCH=CCO₂CH₃), 7.20-
7.30 (5H, m, Ar-H);

δC 39.33 (CCH₂CO₂CH₃), 44.00 (NCH₂CH₂N), 45.95 (NCH₂CH₂N), 50.56 (PhCH₂N),
50.58, 51.09 and 51.91 (3 x CO₂CH₃), 56.85 (CHCO₂CH₃), 70.59 (CCH₂CO₂CH₃), 103.15
(NCH=CCO₂CH₃), 127.59, 128.20 and 128.64 (3 x Ar-CH), 135.98 (Ar-C), 150.03
(NCH=CCO₂CH₃), 164.30, 167.59, 170.24 and 171.25 (4 x C=O).

m/z (Cl) (MH⁺ 417.2, 100%); Found: MH⁺ 417.1656  C₂₁H₂₄N₂O₇, MH⁺ requires 417.1656.
Reaction of (R)-4-phenyl-1-benzyl-4,5-dihydroimidazole with dimethyl fumarate

1-Benzyl-3-phenyl-5,6,7-tris(methoxycarbonyl)-5-methoxycarbonylmethylhexahydro-1H-pyrrolo[1,2-α]imidazole, 2.78

Dimethyl fumarate (0.66 g, 4.5 mmol) was added to a stirred solution of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole (0.36 g, 1.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was refluxed for 17 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (2:8) on silica to afford compound 2.78 as colorless solid (0.26 g, 33%).

M.p. 140-141 °C; [α]D 23 60.07 (c 0.61 in DCM), νmax(film)/cm⁻¹ 3028 (Aryl C-H), 2952, 2815, 1737 (C=O), 1494, 1436, 1359, 1297, 1206, 1172, 1064, 753, 702.

δH 2.27 (1H, dd, J=9.72, 9.15, NCHPhCH2N), 2.80 (1H, d, J=18.12, CCHHCO2CH3), 3.03 (3H, s, CO2CH3), 3.10 (1H, dd, J=8.97, 5.31, NCHPhCH2N), 3.37 (1H, d, J=13.17, PhCHH), 3.43 (1H, d, J=18.12, CCHHCO2CH3), 3.67 (3H, s, CO2CH3), 3.67 (1H, d, J=4.59, C-6H), 3.68 (3H, s, CO2CH3), 3.71 (1H, d, J=2.91, C-7aH), 3.71 (3H, s, CO2CH3), 4.21 (1H, d, J=12.81, PhCHH), 4.22 (1H, dd, J=9.72, 5.49, NCHPhCH2), 5.08 (1H, dd, J=4.41, 2.91, C-7H), 7.27 (10H, m, 2 x Ar-H);

δC 37.47 (CCHHCO2CH3), 51.18 (C-7), 51.32 (C-6), 52.06 (CO2CH3), 52.32 (CO2CH3), 52.38 (CO2CH3), 59.55 (PhCH2), 63.36 (NCHPhCH2N), 64.06 (NCHPhCH2N), 71.87 (C-
Reaction of (R)-4-phenyl-1-benzyl-4,5-dihydroimidazole with diethyl fumarate

1-Benzyl-3-phenyl-5,6,7-tris(ethoxycarbonyl)-5-ethoxycarbonylmethylhexahydro-1H-pyrrolo[1,2-a]imidazole stereoisomers, 2.79, 2.80 and 2.81

The above reaction was repeated using diethyl fumarate in place of dimethyl fumarate. Purification by column chromatography eluting with ethyl acetate and hexane (2:8) on silica afforded diastereomer 2.79 as a colourless solid (0.41 g, 48%): M.p. 88.1-89.7 °C. [α]D 23 41.52 (c 0.49 in DCM), νmax(film)/cm⁻¹ 3064, 3024 (Aryl C-H), 2983, 2931, 2800, 1735 (C=O), 1602, 1450, 1372, 1179, 1109, 1094, 849, 1030, 754, 698. δH 0.84 (3H, t, J=7.14, CO₂CH₂CH₃), 1.08 (3H, t, J=7.14, CO₂CH₂CH₃), 1.15 (3H, t, J=7.14, CO₂CH₂CH₃), 1.21 (3H, t, J=7.14, CO₂CH₂CH₃), 2.18 (1H, dd, J=9.36, 9.33
NCHPhCH2HN), 2.72 (1H, d, J=18.12, CCHHCO2CH2CH3), 3.02 (1H, dd, J=8.97, 5.49, NCHPhCH2HN), 3.28 (1H, d, J=13.17, PhCHH), 3.38 (1H, d, J=18.33, CCHHCO2CH2CH3), 3.56 (1H, d, J=4.59, C-6H), 3.57 (1H, d, J=2.22, C-7aH), 3.85-4.18 (8H, m, 4 x CO2CH2CH3), 4.16 (1H, d, J=12.99, PhCHH), 4.17 (1H, dd, J=9.36, 5.67, NCHPhCH2HN), 4.98 (1H, dd, J=2.04, 4.59 C-7H), 7.20 (10H, m, 2 x Ar-H);

δc 13.56, 13.93, 13.96 and 14.12 (4 x CO2CH2CH3), 37.56 (CCHHCO2CH2CH3), 51.05 (C-7), 51.39 (C-6), 59.46 (PhCH2), 60.35, 60.97, 61.14, and 61.27 (4 x CO2CH2CH3), 63.32 (NCHPhHCH2N), 63.96 (NCHPhCH2N), 71.46 (C-5), 85.32 (C-7a), 126.93, 127.69, 127.99, 128.16, 128.24, and 128.70 (6 x Ar-CH), 138.53 and 140.52 (2 x Ar-C), 169.09, 169.75, 170.95 and 171.03 (4 x C=O).

m/z (Cl) (MH+ 581.4, 100%); Found: MH+ 581.2870. C32H40N2O8 MH+ requires 581.2863.

and stereoisomer 2.80 as colourless oil (18 mg, 1.5%): [α]D 23° -82.09 (c 0.54 in DCM),

νmax(film)/cm⁻¹ 2979, 2937, 2802, 1747 (C=O), 1610, 1454, 1244, 1038, 763, 702.

δH 0.80 (3H, t, J=7.14, CO2CH2CH3), 1.14 (3H, t, J=7.14, CO2CH2CH3), 1.19 (3H, t, J=7.14, CO2CH2CH3), 1.292 (3H, t, J=7.14, CO2CH2CH3), 2.12 (1H, dd, J=9.15, 8.97 NCHPhCH2HN), 2.96 (1H, d, J=17.22, CCHHCO2CH2CH3), 3.10 (1H, d, J=12.99, PhCHH), 3.16 (1H, d, J=17.22, CCHHCO2CH2CH3), 3.36 (1H, dd, J=9.33, 7.14, NCH/H/CHPhN), 3.45 (1H, dd, J=5.10, 4.92, C-7H), 3.96-4.11 (8H, m, 4 x CO2CH2CH3), 4.12 (1H, d, J=12.99, PhCHH), 4.25 (1H, d, J=4.95, C-7aH), 4.27 (1H, d, J=10.44, C-6H), 4.50 (1H, dd, J=8.43, 7.14, NCHPhCH2N), 7.20 (10H, m, 2 x Ar-H);

δc 13.64, 14.20, 14.23 and 14.30 (4 x CO2CH2CH3), 34.24 (CCHHCO2CH2CH3), 51.71 (C-7), 53.58 (C-6), 56.72 (PhCH2), 59.53 (NCHPhCH2N), 60.78, 61.34, 61.34 and 61.43 (4 x CO2CH2CH3), 64.31 (NCHPhHCH2N), 69.60 (C-5), 87.13 (C-7a), 126.27, 127.00, 127.25, 128.30, 128.46, and 128.92 (6 x Ar-CH), 138.62 and 143.50 (2 x Ar-C), 170.40, 170.95, 171.83 and 171.01 (4 x C=O).

m/z (Cl) (MH+ 581.4, 40%); Found: MH+ 581.2869. C32H40N2O8 MH+ requires 581.2863;
and stereoisomer 2.81 as a colourless oil (36 mg. 3%): [α]D23 18.75 (c 0.32 in DCM), νmax(film)/cm⁻¹ 2980, 2931, 2800, 1735 (C=O), 1597, 1447, 1371, 1340, 1293, 1210, 1094, 1026, 750, 700.

δH 1.12 (3H, t, J=7.14, CO₂CH₂CH₃), 1.16 (3H, t, J=7.14, CO₂CH₂CH₃), 1.20 (3H, t, J=7.14, CO₂CH₂CH₃), 1.29, (3H, t, J=7.14, CO₂CH₂CH₃), 2.09 (1H, dd, J=8.79, 8.58, NCHPhCH₂HN), 2.10 (1H, d, J=18.12, CCHHCO₂CH₂CH₃), 2.87 (1H, d, J=17.94, CCHHCO₂CH₂CH₃), 3.10 (1H, d, J=13.38, PhCHH), 3.33 (1H, dd, J=8.79, 7.86, NCHPhCH₂HN), 3.78 (1H, dd, J=7.14, 5.31, C-7H), 3.94-4.19 (8H, m, 4 x CO₂CH₂CH₃), 4.09 (1H, d, J=13.74, PhCHH), 4.22 (1H, d, J=7.14, C-6H), 4.49 (1H, dd, J=7.86, 7.84, NCPPh/CH₂N), 4.56 (1H, d, J=5.13, C-7aH), 7.15-7.24 (10H, m, 2 x Ar-H);

δC 13.97, 13.98, 14.03 and 14.12 (4 x CO₂CH₂CH₃), 40.85 (CCH₂CO₂CH₂CH₃), 50.0 (C-7), 55.43 (C-6), 55.83 (PhCH₂), 58.68 (NCHPhCH₂N), 60.47, 60.79, 60.99 and 61.41 (4 x CO₂CH₂CH₃), 64.86 (NCPPhHCH₂N), 70.59 (C-5), 86.20 (C-7a), 126.20, 126.78, 127.30, 128.23, 128.35, and 128.38 (6 x Ar-CH), 139.14 and 144.00 (2 x Ar-C), 170.30, 170.64, 171.37 and 171.41 (4 x C=O).

m/z (Cl) (MH⁺ 581.4, 10%); Found: MH⁺ 581.2867. C₃₂H₄₀N₂O₈ MH⁺ requires 581.2863.

Reaction of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole with N-methylmaleimide
N-Methylmaleimide (0.50 g, 4.5 mmol) was added to a stirred solution of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole (0.354 g, 1.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was refluxed for 3 d, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (1:1) on silica to afford compound 2.82 as a light pink solid (0.36 g, 52%).

M.p. 142.7-143.7 °C; [α]D23 35.29 (c 0.44 in DCM), νmax(film)/cm⁻¹ 3022 (Aryl C-H), 2942, 2823, 1777 (five membered ring imide antisymm C=O), 1678 (five membered ring imide symm C=O), 1605, 1497, 1437, 1380, 1290, 1133, 1074, 965, 877, 757.

δH 2.15 (1H, t, J=9.51, NCHPhCH₂N), 2.71 (1H, d, J=18.8, CCHHCONCH₃), 2.89 (3H, s, NCH₃), 2.93 (1H, dd, J=9.15, 5.13, NCPHCH²HN), 3.03 (3H, s, NCH₃), 3.13 (1H, d, J=12.09, PhCH₂H), 3.15 (1H, d, J=7.89, C-6H), 3.69 (1H, d, J=18.8, CCHHCONCH₃), 3.97 (1H, dd, J=7.89, 7.68, C-7H), 4.02 (1H, dd, J=9.89, 5.13, NCPHCH²HN), 4.33 (1H, d, J=12.0, PhCH₂H), 4.88 (1H, d, J=7.68, C-7aH), 7.28 (10H, m, 2 x Ar-H);

δC 24.98 and 25.37 (2 x NCH₃), 32.13 (CH₂CONPh), 50.11 (C-6), 51.03 (C-7), 58.71 (PhCH₂), 63.05 (NCPHCH₂N), 64.94 (NCPHCH₂N), 69.87 (C-5), 87.10 (C-7a), 126.06, 127.52, 128.35, 128.47, 129.80 and 129.35, (6 x Ar-CH), 137.98 and 140.70 (2 x Ar-C), 174.05, 175.61, 176.41 and 178.15 (4 x C=O).

Reaction of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole with N-phenylmaleimide

The above reaction was repeated using N-phenylmaleimide in place of N-methylmaleimide. Purification by column chromatography eluting with ethyl acetate and hexane (2:8) on silica afforded 2.83 as a light pink solid (0.63 g, 73%):

M.p. 147-148 °C; [α]D23 101.32 (c 0.60 in DCM), νmax (film)/cm⁻¹ 3064, 3028 (Aryl C-H), 2958, 2843, 1784 (five membered ring imide antisymmetric C=O), 1714 (five membered ring imide symmetric C=O), 1590, 1496, 1384, 1199, 750.

δH 2.33 (1H, dd, J=9.69, 9.51, NCHPhCH₂N), 2.91 (1H, d, J=19.02, CCHHCONPh), 3.08 (1H, dd, J=9.18, 5.13, NCPPhHCH₂N), 3.20 (1H, d, J=11.52, PhCH₇H), 3.50 (1H, d, J=8.04, C-6H), 3.80 (1H, d, J=19.05, CCHHCONCH₃), 4.13 (1H, dd, J=7.86, 7.68, C-7H), 4.20 (1H, dd, J=9.91, 5.13, NCPHCH⁻H₂N), 4.36 (1H, d, J=11.52, PhCICH), 5.01 (1H, d, J=7.5, C-7aH), 7.23 (10H, m, 2 x Ar-H), 7.41 (10H, m, 2 x Ar-H);

δC 32.60 (CH₂CONPh), 49.98 (C-6), 50.88 (C-7), 58.81 (PhCH₂), 63.04 (NCPHCH₃N), 64.85 (NCPHCH₂N), 70.18 (C-5), 87.35 (C-7a), 125.95, 126.07, 126.88, 127.46, 128.19, 128.38, 128.67, 128.78, 129.11, 129.24, 129.35, and 129.72, (12 x Ar-CH), 131.39, 131.94, 137.31, and 140.27 (4 x Ar-C), 172.41, 174.69, 175.27 and 176.20 (4 x C=O).

m/z (Cl) (MH⁺ 583.4, 100%); Found: MH⁺ 583.2355. C₃₆H₃₀N₄O₄ MH⁺ requires 583.2345; and trace amount of stereoisomer 2.84: [α]D²³ 18.52 (c 0.22 in DCM),
$\nu_{\text{max}}$(film)/cm$^{-1}$ 2963, 2925 (Aryl C-H), 2853, 1788 (five membered ring imide antisymm C=O), 1714 (five membered ring imide symm C=O), 1498, 1444, 1384, 1262, 1220, 773, 696.

$\delta_H$ 2.32 (1H, dd, $J$=9.15, 9.5 NCHPhCH$_2$N), 2.99, 3.09 (2H, dd, $J$=18.33, 18.12, CH$_2$CONPh), 3.14 (1H, d, $J$=11.91, PhCHH), 3.34 (1H, dd, $J$=9.54, 6.24, NCHHCHNPh), 3.76 (1H, d, $J$=9.33, C-6H), 3.83 (1H, dd, $J$=9.33, 7.14, C-7H), 4.48 (1H, dd, $J$=8.97, 6.21, NCHHCHNPh), 4.56 (1H, d, $J$=12.09, PhCHH), 4.62 (1H, d, $J$=7.14, C-7aH), 6.83-7.70 (20H, m, 4 x Ar-H);

$\delta_C$ 46.89 (CH$_2$CONPh), 49.36 (C-6), 51.02 (C-7), 58.65 (PhCH$_2$), 62.83 (NCHHCHNPh), 64.96 (NCHHCHNPh), 70.43 (C-5), 87.86 (C-7a), 124.75, 126.62, 126.90, 127.31, 127.83, 128.18, 128.34, 128.56, 128.78, 129.03, 129.06 and 129.25 (12 x Ar-CH), 131.38, 131.88, 137.98 and 141.45 (4 x Ar-C), 172.40, 173.61, 174.37 and 176.20 (4 x C=O).

$m/z$ (Cl) (MH$^+$ 583.4, 100%); Found: MH$^+$ 583.2355. C$_{36}$H$_{30}$N$_4$O$_4$ MH$^+$ requires 583.2345.

Reaction of (R)-1-benzyl-4-phenyl-4,5-dihydroimidazole with trans-β-nitrostyrene

\[ \text{(R)-2.9} \xrightarrow{\text{DCM, Heating}} \]

\[ \text{2.85} + \text{2.86} \]

\[ \text{2.87} + \text{2.88} \]
Trans-β-nitrostyrene (0.67 g, 4.5 mmol) was added to a stirred solution of (R)-4-phenyl-1-benzyl-4,5-dihydroimidazole (0.354 g, 1.5 mmol) in dry DCM (5 cm³) under an atmosphere of nitrogen. The mixture was refluxed for 24 h, then concentrated under reduced pressure. The crude oil was purified by column chromatography eluting with ethyl acetate and hexane (1.5:8.5) on silica to afford the compound 2.85 as an oil (0.047 g, 6%): νmax(film)/cm⁻¹ 3330 (NH), 3063, 3031 (Aryl C-H), 1667, 1616 (C=C), 1553 (C-NO₂ anti-symm), 1495, 1455, 1355 (C-NO₂ symm), 1318, 1248, 1073, 755, 700.

δH 1.41 (1H, br, NH), 3.11 (2H, m, NCHPhCH₂N), 3.25 (1H, m, NCHPhCHHN), 3.59 (2H, s, PhCH₂), 4.38 (1H, d, J=10.8, CHPhCHNO₂=C), 4.87 (1H, d, J=6.42, CHNO₂CHPh), 5.19 (1H, dd, J=10.62, 5.67, CHPhCHNO₂CHPh), 6.74-7.38 (20H, m, 4 x Ar-H), 8.45 (1H, s, H=CH=CNO₂)

and stereoisomer 2.86 as a light yellow oil:

νmax(film)/cm⁻¹ 3330 (NH), 3063, 3031 (Aryl C-H), 1667, 1616 (C=C), 1553 (C-NO₂ symm), 1495, 1455, 1355 (C-NO₂ anti-symm), 1318, 1248, 1073, 755, 700.

δC 1.41 (1H, b, NH), 3.63 (1H, d, J=13.56, PhCHH), 3.70 (1H, d, J=13.38, PhCHH), 3.73 (1H, dd, J=2.19, 13.74 NCHPhCHNO₂CHPh), 3.86 (1H, d, J=13.74, CHPhCHNO₂=C), 4.08 (1H, m, NCHPhCHHN), 4.43 (1H, m, NCHPhCHHN), 5.51 (1H, d, J=2.01, CHNO₂CHPh), 6.74-7.38 (20H, m, 4 x Ar-H), 8.96 (1H, s, H=CH=CNO₂)

m/z (Cl) (MH⁺ 535.5, 100%); Found: MH⁺ 535.2333 C₃₂H₃₀N₄O₄ MH⁺ requires 535.2340.

and stereoisomer 2.87 as a light yellow solid (0.038 g, 2%):

M.p. 88.7-91.3 °C; νmax(film)/cm⁻¹ 3034 (Aryl C-H), 2924, 1561 (C-NO₂ symm), 1496, 1456, 1367 (C-NO₂ anti-symm), 755, 698 (C-H of Ph).

δH 4.57 (dd, 3H, J=12.45, 12.09 and 6.03, -HCNO₂CHPh-), 4.88 (t, 1H, J=11.73, -HCNO₂CHPh-), 5.45 (dd, 2H, J=12.63, 6.03, -HCNO₂CHPh-), 7.18-7.40 (15H, m, 3 x Ar-H).
δC 45.19 and 48.94 (-HCNO₂CHPh-), 86.56 and 93.74 (-HCNO₂CHPh-), 129.43, 129.63, 129.85 (3 x Ar-CH), 133.11 (3 x Ar-C);


and compound 2.88 as a colourless oil (trace):

νmax(film)/cm⁻¹ 3034 (Aryl C-H), 2924, 1561 (C-NO₂ anti-symm), 1496, 1456, 1367 (C-NO₂ symm), 755, 698.

δH 4.15 (t, 3H, J=11.73, -HCNO₂CHPh-), 5.12 (t, 3H, J=11.73, -HCNO₂CHPh-), 7.18-7.40 (15H, m, 3 x Ar-H).

δC 51.69 (3 x CHPh), 90.70 (3 x CHNO₂), 127.53, 129.56 and 130.14 (3 x Ar-CH), 130.09 (3 x Ar-C)


Reduction of 1-benzyl-5,6,7-tris(methoxycarbonyl)-5-methoxycarbonylmethyl hexahydro-1H-pyrrolo[1,2-a]imidazole by LiAlH₄

A suspension of 1-benzyl-5,6,7-tris(methoxycarbonyl)-5-methoxycarbonylmethylhexahydro-1H-pyrrolo[1,2-a]imidazole (2.18) (0.112 g, 0.25 mmol and LiAlH₄ (21.1 mg, 0.56 mmol) in THF (6 cm³) was stirred under an atmosphere of nitrogen at ice-water temperature for 2 h. The reaction was quenched by the addition of
ethyl acetate. The residue was washed with water (20 cm$^3$), neutralized using dilute H$_2$SO$_4$, then extracted with DCM (3 x 20 cm$^3$). The organic phase was dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate: methanol (8:2) in 5% isopropylamine, to yield compound 2.90 as a yellow oil (in 0.067 g, 2% yield).

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3368 (O-H), 2927, 2855, 1734 (C=O), 1654, 1455, 1360, 1216, 1072, 755, 702.

$\delta_H$ 0.83 (1H, br, OH), 2.02 (1H, m, NCHHCH$_2$N), 2.17 (1H, dd, $J=8.61$, 4.74, CHCHHOOCOCH$_2$ at C-8), 2.77 (1H, d, $J=16.83$, C-5H), 2.84 (1H, d, $J=16.68$, C-5H), 2.92-3.07 (4H, m, C-9H and NCHHCH$_2$N), 3.33 (1H, d, $J=13.71$, PhCHH), 3.47 (1H, d, $J=8.4$ C-9aH), 3.61 (1H, m, CHCHHOOCOCH$_2$ at C-6), 3.63 (3H, s, CO$_2$CH$_3$), 3.83 (1H, m, C-8aH), 3.89 (1H, d, $J=13.56$, PhCHH), 4.06 (1H, dt, $J=8.97$, 8.79 and 2.2, CHHOH at C-9), 4.53 (1H, dd $J=8.79$, 8.61, CHHOH at C-9), 7.14-7.27 (5 x Ar-H);

$\delta_C$ 40.90 (C-5), 43.74 (NCH$_2$CH$_2$N), 46.68 (C-9), 50.75 (C-8a), 51.89 (NCH$_2$CH$_2$N), 52.06 (CO$_2$CH$_3$), 56.10 (PhCH$_2$), 65.17 (C-8), 69.15 (C-4a), 72.40 (CH$_2$OH at C-7), 88.69 (C-9a), 127.22, 128.02 and 128.67 (Ar-CH), 137.03 (Ar-C), 171.30 and 178.29 (2 x C=O).
References
References:


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156. Young, Jr.; Harold, W., *United States Patent 4814481*


159. Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph., *Tetrahedron*
