A novel hetero Diels - Alder reaction as a route to annelated pyridines and bipyridines

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A novel hetero Diels - Alder reaction as a route to annelated pyridines and bipyridines

by

David A. Riddick

A Doctoral Thesis
submitted in partial fulfilment of the requirements for the award

DOCTOR OF PHILOSOPHY
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1995

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Abstract

A novel hetero Diels - Alder reaction has been developed to facilitate the synthesis of annelated pyridines as models for pyridoacridine alkaloids.

The key reaction is based on an intramolecular Diels - Alder reaction of an aza-1,3-butadiene with an appropriate dienophile, to yield the desired annelated pyridine.

An extension of this methodology is to exploit the Eglinton copper (II) dimerisation of terminal acetylenes. This allows for a unique double intramolecular hetero Diels - Alder reaction, where four new rings are formed in one step. This allows for a facile route to annelated bipyridines.

Ultimately this methodology has led to an approach to the total synthesis of the natural product eilatin, a member of the class of compounds known as pyridoacridines.

Keywords

acetylenes, alkynes, annelated bipyridine, annelated pyridine, aza-1,3-butadiene, chiral bipyridine, cyclisation, Diels - Alder, Eglinton coupling, eilatin, intramolecular Diels - Alder, marine alkaloids, molecular modelling, natural products, pyridoacridine, terminal acetylenes, terminal alkynes.
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The proof-read duties have been excellently performed by Dr. Elizabeth Swann, and Prof. Christopher J. Moody, their patience and precision are amazing!

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A special mention is required for my brother Mark, who has been a good friend and drinking partner though out the years. It is his fault that I studied chemistry in the first place!

I must thank my parents for giving me all the encouragement and help they could during my time at Loughborough.

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## Abbreviations

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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium (IV) ammonium nitrate</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEA</td>
<td>N,N-diethylaniline</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>IC$_{50}$</td>
<td>the dose at which 50% of a cell culture is killed</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMSCl</td>
<td>chlorotrimethylsilane</td>
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Chapter 1

General Introduction
1.1 Introduction

The general introduction has been split into two parts:

1. Pyridoacridine alkaloids
   - isolation
   - biological activity
   - biosynthesis
   - synthetic approaches

2. The Diels - Alder reaction
   - mechanism
   - electronic effects
   - heterodienes
   - intramolecular cyclisations
   - conclusions
1.2 Pyridoacridine alkaloids

Pyridoacridines are an example of a group of compounds known as marine alkaloids,\textsuperscript{1} based on the tetracyclic pyrido[k,l]acridine skeleton (Figure 1).

![Figure 1]

These alkaloids are found in a number of different marine organisms: tunicates and ascidians from Phylum Chordata; sponges from Phylum Porifera; and sea anemones from Phylum Cnidaria.

1.2.1 Isolation

The first fully characterised pyridoacridine was isolated from the sponge *Amphimedon* sp. in 1983 by Schmitz and co-workers,\textsuperscript{2} which they named amphimedine [1].

![Image 1]

\textsuperscript{1} For a comprehensive review of marine alkaloids see *Chem Rev.*, 1993, 93(5), whole edition.
The structure of [1] was unambiguously assigned by the use of INADEQUATE NMR techniques.\(^3\)

Examples of some of the other pyridoacridines that have been isolated and characterised are summarised below.\(^4\),\(^5\),\(^6\)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Source</th>
</tr>
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<tr>
<td><img src="image" alt="Ascididimin" /></td>
<td>Ascididimin [2]</td>
<td>tunicate Didemnum sp.</td>
</tr>
<tr>
<td><img src="image" alt="Cystodytin A" /></td>
<td>Cystodytin A [4]</td>
<td>tunicate Cystodytes dellechiajei</td>
</tr>
</tbody>
</table>

---

Structure determinations were carried out by using a combination of NMR and X-ray crystallographic techniques.

1.2.2 Biological activity

As a group, these alkaloids show a number of general and interesting properties. By far the most common is cytotoxicity. As well as this, many show good anti-leukaemic and anti-tumour activities. Asididemin [2] has an IC$_{50}$ = 0.39 µg/ml against the L1210 leukaemia cell line.

---

It has been suggested\(^9\) that these compounds intercalate with DNA, and in view of their structural similarity to the extensively studied acridines\(^{10}\) this would appear to be a reasonable assumption.

Primarily, intercalation, though inhibiting in vitro DNA polymerases and DNA dependant RNA polymerases,\(^{11}\) does not cause cell death.\(^{12}\) Also, there is only a slight correlation between DNA binding affinities and cytotoxicity.\(^{13}\) From this information it may be deduced that although DNA is involved in the activity of these compounds, there must be another factor.

It has been shown for pyridoacridines and other intercalators that the additional factor involves the enzyme topoisomerase II.\(^{14}\) This enzyme catalyses the passage of a double strand of DNA across another, increasing the linkage number by two. In the case of circular DNA the result is to super-coil the DNA loop. The intercalators appear to stabilise one of two intermediate DNA-topoisomerase complexes leading to hidden single or double DNA strand breaks.


The intercalators so far studied have shown to produce DNA stand breaks at characteristic and specific sites. Furthermore the more selective antineoplastic agents have been shown to produce these breaks within proto-oncogenes, which are known to be linked with tumour proliferation. Since these genes are considerably amplified in tumour cells, it would be reasonable to assume that the selectivity of the drugs is directly related to the activity.

The alkaloids show toxicity to a wide range of organisms, including parasites and microbes. Nordercitin [3] was shown to inhibit viral activity in a number of model systems such as A-59 murine coronavirus. Other less common properties include immunosuppression, reverse transcriptase inactivation, and potent calcium-releasing activity in sarcoplasmic reticulum.

For comprehensive reviews of the biological activity of the pyridoacridine alkaloids see Moody and Thomas 1992, and Molinski 1993.

The obvious importance of the biological activity of these compounds has prompted many synthetic studies into pyridoacridines and their analogues. Some of the more recent syntheses will be discussed later in this chapter (Section 1.2.4).

---

1.2.3 Biosynthesis

It is known that animals, unlike plants, base their quinoline syntheses on kynurenine [7] an oxidation product of tryptophan. It is on this material that the biosynthesis is thought to be based (Scheme 1).^{18}

![Scheme 1](image)

---

1.2.4 Synthetic approaches

Synthetic routes to amphimidine [1], ascididemin [2], and eilatin [5] will be discussed. For comprehensive reviews on the synthesis of pyridoacridines and related compounds see Alvarez and Joule 1993,\(^5\) and Molinski 1993.\(^4\)

1.2.4.1 Amphimidine [1]

The first total synthesis of amphimidine [1] was based on palladium coupling of aryl triflates with organostannanes, followed by a Diels - Alder cyclisation with Ghosez's diene [8] (Scheme 2).\(^19\)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme2.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2} \textit{i)} Pd(PPh\textsubscript{3})\textsubscript{4}, LiCl, 1,4-dioxane, \textit{ii)} a) TFA, b) TFAA, DIPEA, THF \textit{iii)} CAN, MeCN-H\textsubscript{2}O \textit{iv)} THF, pyridinium hydrofluoride, \textit{v)} 1:1 6M HCl-THF, \textit{vi)} Me\textsubscript{2}SO\textsubscript{4}, K\textsubscript{2}SO\textsubscript{4}, DMF

A similar approach was used by Kubo and Nakahara,\textsuperscript{20} in which classical annelation methods were used instead of palladium mediated cross-coupling.

A novel route to [1] was published by Prager and Tsopelas\textsuperscript{21} that used an azide mediated ring expansion (Scheme 3).

Scheme 3: i) TMSCI, Et\textsubscript{3}N; \textit{n}-BuLi, 4-bromopyridine, ii) NaN\textsubscript{3}, PPA, iii) PCl\textsubscript{5}, in POCl\textsubscript{3}, iv) MeOSO\textsubscript{2}F; KOH, K\textsubscript{3}Fe(CN)\textsubscript{6}, v) CuCN, DMSO, vi) PPA

\textsuperscript{21}Prager, R.H. and Tsopelas, C. \textit{Heterocycles}, 1989, 29, 847.
Azido-dehydroxylation of the intermediate [8] was followed by synchronous nitrogen elimination and aryl migration to give [9] in one step. Previous work by Prager had shown that the most electron rich aryl group migrates.\textsuperscript{22}

1.2.4.2 Ascididemin [2]

The first synthesis of ascididemin was based on a regioselective amination of quinoline-5,8-quinone [10] in the presence of cerium (III) (Scheme 4).\textsuperscript{23}

\textbf{Scheme 4}: i) CeCl\textsubscript{3}-7H\textsubscript{2}O, ii) conc. H\textsubscript{2}SO\textsubscript{4}, iii) H\textsubscript{2}(OEt\textsubscript{2})\textsubscript{2}NM\textsubscript{e}\textsubscript{2}, iv) NH\textsubscript{3}Cl, AcOH

\textsuperscript{22} Duong, T., Prager, R.H. and Were, S.T. \textit{Aust. J. Chem.}, 1983, 36, 1431.

\textsuperscript{23} Bracher, F. \textit{Heterocycles}, 1989, 29, 2093.
A shorter but less efficient synthesis appeared in 1990 based on an aza-stilbene cyclisation,\textsuperscript{24} the first of its kind involving a quinoneimine \([11]\) (Scheme 5).

\[
\begin{array}{c}
\text{O} \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{array}
\xrightarrow{i)}
\begin{array}{c}
\text{H} \\
\begin{array}{c}
\text{N} \\
\begin{array}{c}
\text{I} \\
\text{H}
\end{array}
\end{array}
\end{array}
\xrightarrow{ii)}
\begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\xrightarrow{iii)}
\text{ascididemin [2]}
\]

Scheme 5: i) 2-iodoaniline, triethyl aluminium, ii) \(\text{BaMnO}_4\), iii) \(\text{H}_2\text{SO}_4, \text{hv}\)

1.2.4.3 Eilatin [5]

The first total synthesis of eilatin [5] was again based on a regioselective amination of a quinone in the presence of cerium (III) (Scheme 6).²⁵

\[ \text{Scheme 6: } \text{i) CeCl}_3\cdot 7\text{H}_2\text{O, ii) conc. H}_2\text{SO}_4, \text{iii) DMF, iv) H}_2\text{Pd/C} \]

The most elegant synthesis of [5] to date is a two-step biomimetic strategy based on the coupling of o-benzoquinone and kynuramine [12] (Scheme 7).²⁶

Scheme 7: i) NaIO₃, NaOH, ii) NH₃

This route to eilatin lends some credence to the biosynthetic pathway described earlier (Section 1.2.3).

1.3 The Diels - Alder reaction

The Diels - Alder reaction is one of the most useful synthetic reactions in organic chemistry.\textsuperscript{27,28,29} In the reaction a 1,3-diene reacts with a dienophile to form an adduct with a six membered ring (Scheme 8). Two new $\sigma$ bonds and one new $\pi$ bond are formed at the expense of three $\pi$ bonds in the starting materials.\textsuperscript{30,31}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (left) [shape=rectangle,inner sep=1pt] {\includegraphics[width=0.3\textwidth]{diels_alder.png}};
  \node at (0,1.5) {$\text{Scheme 8}$};
\end{tikzpicture}
\end{center}

The usefulness of the Diels - Alder reaction in synthesis arises from its versatility and from its remarkable stereoselectivity. By varying the nature of the diene and dienophile many different types of ring structures can be constructed.

An important criterion for the Diels - Alder reaction is that the diene must be able to adopt the cisoid conformation (Figure 2).

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (left) [shape=rectangle,inner sep=1pt] {\includegraphics[width=0.3\textwidth]{cisoid_transoid.png}};
  \node at (0,1.5) {$\text{cisoid}$ \hspace{1cm} $\text{transoid}$};
\end{tikzpicture}
\end{center}

\textsuperscript{28} Huisgen, R. \textit{J. Org. Chem.}, 1968, 33, 2291.
\textsuperscript{29} Schmidt, R.R. \textit{Angew. Chem., Int. Ed. Engl.}, 1973, 12, 212.
If the diene does not have, or cannot adopt a cisoid conformation no reaction can occur.

The reaction proceeds rigorously, stereospecifically syn with respect to both the diene and the dienophile (Figure 3).\textsuperscript{32}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Figure 3}
\end{figure}

It is also worthy of note that the relative stereochemistry of the starting materials is retained in the product, this is known as the cis principle (Figure 4).\textsuperscript{33}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Figure 4}
\end{figure}

1.3.1 Mechanistic aspects

The precise mechanism of the Diels - Alder reaction has been the subject of much debate.\textsuperscript{34,35,36} There is however general agreement that the rate determining step in adduct formation is bimolecular. The two components approach each other in parallel planes roughly orthogonal to the direction of the new bonds about to be formed. Formation of the two new $\sigma$ bonds takes place by overlap of molecular $\pi$ orbitals in a direction corresponding to endwise overlap of atomic $p$ orbitals. But there has been uncertainty about the nature of the transition state and in particular, about the timing of the changes in covalency that result in the formation of the new bonds.

There are three main views:

- **[A]** the reaction is a concerted; both new bonds are formed at the same time, and to the same extent; \textit{synchronous}\textsuperscript{34}

- **[B]** the reaction is concerted, both new bonds are formed at the same time, but not to the same extent; \textit{asynchronous}\textsuperscript{35}

- **[C]** the reaction is stepwise; first of which is the formation of a single bond which is rate determining, followed by formation of the second bond in a fast reaction\textsuperscript{36}

The transition states for all three mechanisms are shown below (Figure 5).

![Chemical structures](image)

**Figure 5**

The transition state for mechanism [C] may have either diradical or zwitterionic character.

It is now generally believed that most thermal Diels - Alder reactions are concerted. The acceptance of this view has been brought about by the high stereoselectivity observed in such reactions. However, the debate about the synchronicity or asynchronicity of the bond formation still continues.
1.3.2 Electronic effects

In the Diels - Alder cyclisation the feasibility of a particular process is determined by whether overlap can take place between the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other (Figure 6).

In 'normal electron demand' Diels - Alder cycloadditions it is the HOMO of the diene that overlaps with the LUMO of the dienophile. This can be schematically represented on an energy diagram (Figure 7).
Diels - Alder reactions proceed more readily as the energy difference between HOMO and LUMO (ΔE) decreases and the orbital overlap increases.\textsuperscript{37}

Diels - Alder reactions are promoted by electron-donating substituents in the diene and electron withdrawing groups in the dienophile. This is due to the electronic effects such groups have on the reacting molecular orbitals. Increasing the electron density in the diene will \textit{raise} the energy of the diene's HOMO. Conversely a decrease in the electron density in the dienophile will \textit{lower} the energy of the dienophile's LUMO. Therefore there are two ways to increase the reactivity of the system, \textit{i.e.} make ΔE as small as possible;

- introduce electron donating groups in the diene
- introduce electron withdrawing groups in the dienophile

If the substituents in the diene do not change, increasing the conjugation of the dienophile will increase the reactivity of the system, \textit{e.g.} (Scheme 9).

\begin{equation}
\text{Scheme 9}
\end{equation}

Reaction [B] would be expected to proceed more readily than reaction [A].

Lewis acids can be used to catalyse Diels - Alder reactions. For example coordination of a Lewis acid with the non-bonding electrons of a carbonyl or cyano group in the dienophile will lower the dienophile's LUMO, and hence lower the activation energy of the reaction.\(^{38}\)

### 1.3.3 Heterodienes

Of the heterodienes that are available, those that contain nitrogen atoms have received the most interest. It has been found that Diels - Alder reactions of properly chosen derivatives of 1- and 2-aza-butadienes provide a very convenient access to six-membered nitrogen heterocycles.\(^{39,40}\)

In the 2-aza series, substituted 1-dimethylamino-2-azabutadienes react with dienophiles with loss of dimethylamine to give pyridines or dihydropyridines (Scheme 10).\(^{41}\)

![Scheme 10](image)

---


1-Azabutadienes are less reactive than their 2-aza counterpart, however Ghosez and co-workers have found that the \( \alpha,\beta \)-unsaturated hydrazone [13] reacts with a range of electron deficient dienophiles at moderate temperatures (Scheme 11).\(^{42}\)

![Scheme 11](image)

Interestingly the corresponding oxime does not react and the reactivity of [13] is ascribed to the interaction between the lone pair of the dimethylamino group and the \( \pi \) system of the azadiene.\(^{42}\) Such an interaction would increase the energy of the diene's HOMO, and hence increase the reactivity of the system.

---

Incidentally if an $\alpha,\beta$-unsaturated oxime is converted its corresponding $N$-sulfonylimine the Diels - Alder cyclisation proceeds with electron rich dienophiles. This is an example of an 'inverse electron demand' Diels - Alder cyclisation. (Scheme 12).\textsuperscript{43}

\[ \text{Scheme 12: i) triethylamine, benzenesulfinyl chloride, ii) 15 kbar} \]

1.3.4 Intramolecular Diels - Alder reactions

The intramolecular Diels - Alder reaction, in which the diene and dienophile form part of the same molecule, has been widely used in the synthesis of the natural products in the alkaloid, steroid and terpenoid series.\textsuperscript{44,45,46}

A valuable feature of the intramolecular Diels - Alder reaction, is the remarkable stereoselectivity. This is elegantly observed when the triene [14A] forms the indane derivative [15]. In this reaction four new chiral centres are set up selectively in one step, by way of the sterically preferred transition state [14B] (Scheme 13).\textsuperscript{47,48}

![Scheme 13](image)

Scheme 13 : i) 130 °C, toluene

\textsuperscript{44}Oppolzer, W. Pure and Appl. Chem., 1981, 53, 1181.
Intramolecular Diels - Alder reactions with nitrogen containing heterodienes have been used as a route to annelated pyridines.\(^\text{49,50,51}\) The principle method utilises the 'inverse electron demand' cyclisation of suitably substituted \(\alpha,\beta\)-unsaturated \(N\)-sulfonylimines (Scheme 14).\(^\text{51}\)

\[
\text{Scheme 14: } i) \text{ toluene reflux}
\]

The use of \(N\)-acylhydrazones of \(\alpha,\beta\)-unsaturated aldehydes in the intramolecular Diels - Alder reaction has also been reported (Scheme 15).\(^\text{50}\)

\[
\text{Scheme 15: } i) \text{ 1,2-dichlorobenzene, heat}
\]


Gilchrist et al., have reported a very versatile route to annelated pyridines, starting from 2-bromocyclopentene-1-carboxaldehyde. In this procedure the aldehyde was converted to its \(N,N\)-dimethylhydrazone, and the bromine was substituted for a range of dienophiles, via a palladium mediated cross coupling reaction. This system is then ideally set up to undergo an intramolecular Diels-Alder cyclisation (Scheme 16).

![Scheme 16](image)

Scheme 16: i) \(N,N\)-dimethyldrazine, ii) Pd(0), iii) THF reflux

A whole range of annelated pyridines have been synthesised in this manner.

---

1.3.5 Conclusions

- Clearly the Diels - Alder reaction is a very useful synthetic tool for the construction of substituted six membered rings.

- The inclusion of a heteroatom in the diene (or indeed the dienophile) leads to an efficient route to novel heterocyclic compounds.
Chapter 2

Annelated pyridines as models for
pyridoacridines
2.1 Introduction

As described earlier (Section 1.2) pyridoacridine marine alkaloids are based around a common tetracyclic core (Figure 1). This chapter will describe approaches towards a range of simplified analogues based on a tricyclic core shown below (Figure 8).

![Figure 8](image)

Figure 8: X = N, O; R = H, phenyl, pyridyl, etc.

It has been shown in previous studies that three planar fused rings are the minimum requirement for DNA intercalation. It has been shown in previous studies that three planar fused rings are the minimum requirement for DNA intercalation. Studies on models for pyridoacridine alkaloids have previously looked at the ABC ring system, for this study the effects of the ABE are of interest (Figure 9).

![Figure 9](image)

It was envisioned that biological studies would be performed on these simplified systems, in an attempt to compare and contrast biological activity with that of the known natural products.

Since the natural products are known intercalators of DNA a simple experiment to show such activity would be to measure the competitive binding of a test compound versus a standard intercalator such as ethidium bromide. Quantitative results are possible by using fluorescence spectroscopy. A limiting binding assay could then be performed, along the same lines as the LD_{50} pharmaceutical assay. Other physicochemical techniques available to study intercalation include, circular dichroism, optical rotatory dispersion, thermal denaturation, NMR spectroscopy, and X-ray crystallography.

For intercalation to occur, the molecules need to be essentially planar. Metal complexation should force the test molecules into planarity (Scheme 17).

![Scheme 17](image)

Scheme 17: M^{n+} = Cu, Ni, Pd, etc.

Molecular modelling studies to compare and contrast these simple models with the natural product eilatin will be described later (Section 2.4).

---

57 For a review see Thurston, D.E. and Thompson, A.S. *Chemistry in Britain*, 1990, 26, 767.
2.1.1 Retrosynthesis

The key disconnection for the construction of the tricylic systems, is shown below (Figure 10).

![Figure 10](image)

This retrosynthesis would then require an intramolecular hetero Diels - Alder reaction to form the two new rings.

Therefore the key step in the synthesis of the tricyclic adducts would involve the intramolecular Diels - Alder of a 1-aza-1,3-butadiene with a suitable dienophile. If the dienophile is an alkyne, cyclisation would occur with concomitant loss of the dimethylamine moiety to yield the annelated pyridine. However, if the dienophile were an alkene one would expect the reaction to stop at the tetrahydropyridine stage (Scheme 18).
N,N- Dimethylhydrazones of unsaturated aldehydes are capable of acting as 1-azadienes; they were shown to react with electron deficient alkenes and alkynes at moderate temperatures. This reaction has been reported by a number of groups as a route to substituted pyridines. Incidentally oxime ethers of unsaturated aldehydes are much less successful and the success of the dimethylhydrazones has been ascribed to the electron donation from the dimethylamino substituent. One would also expect that the conjugating effect of the substituent R would lower the energy of the dienophile LUMO and hence increase the reactivity of the system.
Further disconnections as detailed below show that the precursor to cyclisation can be synthesised from relatively simple starting materials (Scheme 19).

\[
\text{Scheme 19 : } Y = \text{leaving group}
\]

2.1.2 Structural conventions

For the sake of clarity, the diene and dienophile systems will be drawn so as to make the Diels - Alder reaction appear obvious; as opposed to the more chemically correct conformation (Figure 11).
2.2 Synthesis of benzopyrano[3,4-c]pyridines

This section will be concerned with the syntheses of the following benzopyranopyridines;

\[ 5H-[1]-\text{benzopyrano[3,4-c]pyridine} \quad [16] \]

\[ 4\text{-phenyl-5H-[1]benzopyrano[3,4-c]-pyridine} \quad [17] \]

Also the various approaches to a 2-pyridyl analogue [18] will be discussed.

\[ 4-(2'\text{-pyridyl})-5H-[1]\text{benzopyrano[3,4-c]pyridine} \quad [18] \]
2.2.1 5H-[1]-Benzopyrano[3,4-c]pyridine [16]

Two routes have been developed for the synthesis of [16], both of which rely on an olefination reaction of a substituted benzaldehyde. They differ in that the first route uses Wittig phosphorane chemistry\textsuperscript{58} whilst the second route employs Wadsworth - Emmons phosphonate ester methodology.\textsuperscript{58,59}

2.2.1.1 "Wittig" chemistry

The $\alpha,\beta$-unsaturated aldehyde [19] was formed by the homologation of salicylaldehyde, this was carried out by standard Wittig olefination using formylmethylenetriphenylphosphorane. This was followed by $O$-alkylation with propargyl chloride to give the ether aldehyde [20] (Scheme 20).

\begin{equation}
\begin{align*}
\text{CHO} & \quad \text{i) formylmethylenetriphenylphosphorane, THF, 3 h,} \\
\text{CHO} & \quad \text{ii) propargyl chloride, K_2CO_3, EtOH, reflux, 18 h}
\end{align*}
\end{equation}

Scheme 20: i) formylmethylenetriphenylphosphorane, THF, 3 h, ii) propargyl chloride, K$_2$CO$_3$, EtOH, reflux, 18 h

\textsuperscript{58} For a review see Maryanoff, B.E. and Reitz, A.B. Chem. Rev., 1989, 89, 863.

\textsuperscript{59} Wadsworth, W.S. Org. React., 1977, 25, 73.
The ether aldehyde [20] could then be readily converted in excellent yield to the required hydrazone [21]. This was achieved by stirring a mixture of the aldehyde [20] and N,N- dimethylhydrazine overnight in the presence of anhydrous sodium sulfate.\textsuperscript{49} The ether hydrazone [21] was then heated to reflux in mesitylene for 18 h to afford the desired cycloadduct [16] in an excellent yield (Scheme 21).

The key feature of the proton NMR of the product [16] is the two distinct $\alpha$ protons in the pyridine ring at $\delta$ 8.31 and 8.54 ppm respectively. The doublet at 8.54 ppm acts as an NMR signature for all compounds of this sort (Figure 12).
This procedure however has a major drawback, that being the variable yield for the olefination step. The reaction proceeds to greater than 80% yield when carried out on small scale (≈ 1 mmol). However, upon scale up the procedure leads to the problem of removal of the triphenylphosphine oxide, which co-elutes with the desired product. Trituration of the phosphine oxide with hexane also failed due to the desired product also being insoluble.

2.2.1.2 “Wadsworth - Emmons” chemistry

The solution to the above problem was to utilise Wadsworth - Emmons olefination technology. In this case a phosphonate ester is used and the by-products from the reaction are water soluble.

A suitable phosphonate ester was available that would not only homologate benzaldehyde, but it also contained the N,N- dimethylhydrazone functionality as well, hence cutting out one step.
The phosphonate ester aldehyde [22], was readily obtained by the acid hydrolysis of commercially available diethyl 2,2-diethoxyethylphosphonate.60 This could then be condensed with N,N- dimethylhydrazine to afford the phosphonate ester hydrazone [23] (Scheme 22).

![Scheme 22](image)

Scheme 22: i) 2% aq. hydrochloric acid, reflux 10 min, ii) N,N- dimethylhydrazine, MgSO₄, 0°C, 3 h

The precursor to the cyclisation step [21], can now be synthesised in two steps from salicylaldehyde, starting with O- alkylation with propargyl chloride, followed by Wadsworth - Emmons olefination with the phosphonate ester [23]49 (Scheme 23).

![Scheme 23](image)

Scheme 23: i) propargyl chloride, K₂CO₃, EtOH reflux, 18 h, ii) n-butyllithium, phosphonate ester [23]

---


38
The ether hydrazone [21] undergoes Diels-Alder cyclisation as previously described, affording the cycloadduct [16] in 70% overall yield for 3 steps.

This second approach has three major advantages of the first;

- less expensive and more readily available starting materials
- fewer steps
- ease of work up of olefination step

This procedure is now the preferred method for such olefinations.
2.2.2 4-Phenyl-5\(H\)-[1]-benzopyano[3,4-c]pyridine [17]

Two routes have been developed for the synthesis of [17], though as will become clear only the first route ("desired") should have led to [17]. The second route ("undesired") was designed to afford a tetrahydro variant [26].

2.2.2.1 "Desired" route

The ether aldehyde [24] is formed by O-alkylation of salicylaldehyde with 1-chloro-3-phenylprop-2-yne. Then Wadsworth - Emmons olefination with the phosphonate ester hydrazone [23], leads to the required precursor to cyclisation [25] in excellent yield (Scheme 24).

![Scheme 24](image)

Scheme 24: i) 1-chloro-3-phenylprop-2-yne, K\(_2\)CO\(_3\), EtOH reflux, 18 h,
ii) n-butyllithium, phosphonate ester [23]

1-Chloro-3-phenylprop-2-yne is not commercially available, but it is readily synthesised by the reaction of thionyl chloride with 3-phenylpropargyl alcohol.\(^6\)

---

A solution of the ether hydrazone [25] in xylene was heated to reflux for 18 hours to afford the desired cycloadduct [17] in 60% yield, with an overall yield of 35% from salicylaldehyde (Scheme 25).

\[ \delta_H 8.69 \text{ ppm, doublet } J 5 \text{ Hz} \]

Scheme 25: i) xylene reflux 18 h

Again the characteristic proton NMR signal for the pyridine \( \alpha \) proton at 8.69 ppm allowed the reaction to be followed by NMR.
2.2.2.2 "Undesired" route

The following synthesis is identical to the one previously described, except that cinnamyl bromide was used for the O- alkylation instead of 1-chloro-3-phenylprop-2-yne. The reason for this was that a different product was expected, i.e. the tetrahydropyridine [26] however the fully aromatised pyridine [17] was produced (Figure 13).

![Figure 13](image)

The required precursor to the cyclisation step [27] was prepared analogously to that previously described (Scheme 26).

![Scheme 26](image)

**Scheme 26**: i) trans- cinnamyl bromide, K₂CO₃, EtOH reflux, 18 h,  
ii) n-butyllithium, phosphonate ester [23]
The ether hydrazone [27] was then heated to reflux in xylene for 18 hours, to give the annelated pyridine [17] in 80% yield and not the tetrahydropyridine [26] as the mechanism described earlier (Section 2.1.1) would suggest (Scheme 27).

The aromatisation of the pyridine ring is such a strong driving force that in this case air is sufficient to oxidise the tetrahydropyridine ring to the pyridine. The reaction has also been carried out in lower boiling solvents, benzene and toluene. In the case of benzene no reaction takes place, but with toluene the product [17] is formed but the reaction is a lot slower (≈ 72 hours).

It was unfortunate that this reaction did not proceed as expected since it would have lent credence to the reaction mechanism, and it would have been another pyridoacridine model compound.
2.2.3 Approaches to 4-(2'-pyridyl)-5H-[1]benzopyrano[3,4-c]pyridine [18]

As mentioned at the beginning of this chapter, to mimic the natural products the models should have a heteroatom in the attached ring. The obvious starting point would be the 2-pyridyl moiety [18].

Unfortunately the simple addition of a heteroatom into the model system, was not trivial and indeed has still not yet been successful. The aim was to be able to utilise some sort of coupling procedure of a terminal acetylene (or derivative) with a 2-halopyridine.

There is literature precedent for such coupling of acetylene or phenyl acetylene to 2-halopyridines via a number of methods. These include palladium catalysed couplings, i.e. Stille coupling of alkynyl stannanes, Suzuki coupling of alkynyl boronates, and a organosilane cross coupling reaction. Cross

---

coupling of terminal acetylenes, mediated by copper and palladium has been reported.\textsuperscript{67,68}

The direct method of quenching a lithium acetylide with a 2-halopyridine is also known.\textsuperscript{69}

All these methods have been tried with the range of complex acetylenes used in the previous syntheses and the results are summarised below (Figure 14)

\[ R \equiv \equiv X \xrightarrow{\text{Hal}} R \equiv \equiv \]

\[ R = \]

\[ \text{Figure 14 : NB : In all cases a range of palladium catalysts were used; Pd(OAc)\textsubscript{2}, (Ph\textsubscript{3}P)\textsubscript{4}Pd, (Ph\textsubscript{3}P)\textsubscript{2}Pd(MeCN)\textsubscript{2}, Pd\textsubscript{2}(dba)\textsubscript{3}, [\eta\textsubscript{3} C\textsubscript{3}H\textsubscript{5}]Pd\textsubscript{2}Cl} \]

For all the palladium catalysed cross coupling reactions, apart from the Stille coupling, the parent terminal acetylene was recovered. This suggests that the palladium is inserting into the carbon - halogen bond, and the initial coupled product is being formed. However, the cross coupling reaction in which the new carbon - carbon bond is to be formed is not occurring. Aqueous work-up of the reaction mixture then leads to the dissociation of the coupled product to give the parent acetylene (Figure 15).
In the example of the copper (II) mediated palladium coupling of a terminal acetylene 25% yield of the diyne [28] was noted (Figure 16).

This should not seem too surprising since the copper (II) coupling of terminal acetylenes is a well-known procedures as described by Eglinton and Glazer.\textsuperscript{70}

The application of the Eglinton procedure to these acetylenic - dienes such as

has led to a novel double intramolecular Diels - Alder reaction. This is a facile route to bipyridines and is the topic of Chapter 3.

A successful coupling of 2-bromopyridine and propargyl alcohol was achieved via palladium coupling to give the 3-(2'-pyridyl)-propargyl alcohol [29] (Scheme 28).\(^{71}\)

\[
\text{Scheme 28: } \text{i) (Ph}_3\text{P)}_2\text{PdCl}_2, \text{CuI, Et}_3\text{N, 60}^\circ\text{C, 4 h}
\]

However, all attempts to effect an alkylation with [29] failed, even when derivatised as the triflate.

Probably the best way to proceed, would be the Stille coupling of an alkynyl stannane with the pyridyl triflate (Scheme 29).\(^{72}\)

\[
\text{Scheme 29: } \text{i) (Ph}_3\text{P)}_2\text{PdCl}_2, \text{DMF, 60}^\circ\text{C}
\]

This reaction has been shown to have a wider scope than that for the coupling of halopyridines.\(^{72}\)


2.3 Synthesis of benzo[2,7-c]naphthyridines

This section will be split into two parts; the first part will be concerned with the attempted synthesis of the benzonaphthyridinone [30], and the second part with the successful syntheses of the benzonaphthyridines [31], [32]. These compounds are more closely related to the naturally occurring pyridoacridines, as they have two nitrogen containing rings.

![Diagram of 4-phenylbenzo[2,7-c]naphthyridin-5-(6H)-one [30]](image)

![Diagram of 6-benzoyl-4-phenyl-5,6-dihydrobenzo[2,7-c]naphthyridine [31]](image)

![Diagram of 6-benzoyl-3-dimethylamino-4-phenyl-3,4,4a,5,6,10b-hexahydrobenzo[2,7-c]naphthyridine [32]](image)
2.3.1 4-Phenylbenzo[2,7-c]naphthyridin-5-(6H)-one [30]

The retrosynthesis of the desired product [30] leads to the key intermediate [33] (Scheme 30).

In the next section two routes to the key intermediate will be discussed, along with the attempted Diels - Alder cyclisation to afford the final product.

The initial route was based on simple chemical manipulation of \( \sigma \)-nitrocinnamaldehyde. This was deemed a useful starting material because the \( \alpha,\beta \)-unsaturated moiety was already present, hence removing the need for any "Wittig type" olefination chemistry.
The hydrazone [34] was formed by the condensation of \( N,N \)-dimethylhydrazone with \( \omega \)-nitrocinnamaldehyde, under Dean - Stark conditions.\(^\text{73}\) The subsequent reduction of the nitro group to give the amine [35] was carried out using iron (II) sulfate (Scheme 31).\(^\text{73}\)

\[
\begin{align*}
\text{CHO} & \rightarrow \text{NNMe}_2 \\
\text{NO}_2 & \rightarrow \text{NH}_2 \\
\text{[34]} & \rightarrow \text{[35]}
\end{align*}
\]

**Scheme 31:** i) \( N,N \) dimethylhydrazone, toluene reflux 4 h.  
ii) iron (II) sulfate, ammonium hydroxide, 80°C, 3 h

The reduction of the nitro group to give the amine [35] was an incredibly cumbersome and low yielding procedure. The reaction appeared to go to completion by thin layer chromatography and by IR spectroscopy, but isolation of pure material was very difficult indeed. However, acylation of the amine with 3-phenylpropynoyl chloride, under Schotten - Baumann conditions, gave the required acetylenic hydrazone [36] ready for the Diels - Alder cyclisation albeit in poor overall yield (Scheme 32).

\[
\begin{align*}
\text{[35]} & \rightarrow \text{[36]}
\end{align*}
\]

**Scheme 32:** i) 3-phenylpropynoyl chloride, NaOH aq.

3-Phenylpropynoyl chloride was readily made by the reaction of thionyl chloride with 3-phenylpropynoic acid.\textsuperscript{74}

The reduction of the nitro to an amine was a serious stumbling block, so it was thought that it would be better if the starting material was the amine. Unfortunately \( o \)-aminocinnamaldehyde is unstable and condenses with itself, likewise for \( o \)-aminobenzaldehyde, so the starting material of choice was \( o \)-aminobenzyl alcohol.

In this new synthetic strategy \( o \)-aminobenzyl alcohol was acylated with 3-phenylpropynoyl chloride under Schotten - Baumann conditions to give the amido alcohol \([37]\) in good yield. Subsequent oxidation of the alcohol to the aldehyde \([38]\) was achieved in good yield using Corey's reagent, pyridinium chlorochromate (Scheme 33).\textsuperscript{75}

\[
\begin{align*}
\text{Scheme 33 : i) 3-phenylpropynoyl chloride, NaOH aq., ii) PCC, dichloromethane, RT}
\end{align*}
\]


Conversion of the amido aldehyde [38] to the required amido hydrazone [36] was carried out by treatment of the amido aldehyde [38] with the anion of the phosphonate ester [23] (Scheme 34).

![Scheme 34: i) n- butyllithium, phosphonate ester [23]](image)

This new method gives rise to the key intermediate [36] for the Diels - Alder cyclisation in 37% overall yield (cf. 11% for the previous route).

Despite having an efficient route to the precursor [36] all attempts to effect the Diels - Alder cyclisation have failed (Scheme 35).

![Scheme 35](image)
Methods tried to effect the cyclisation include:

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>toluene reflux for up to 48 h</td>
<td>recovered starting material</td>
</tr>
<tr>
<td>mesitylene reflux for up to 48 h</td>
<td>some starting material, mainly</td>
</tr>
<tr>
<td></td>
<td>decomposition</td>
</tr>
<tr>
<td>toluene at 100°C in a sealed tube for up to 36 h</td>
<td>recovered starting material</td>
</tr>
<tr>
<td>boron trifluoride etherate</td>
<td>decomposition</td>
</tr>
<tr>
<td>titanium tetrachloride</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

None of the thermal methods showed any sign of the desired product, and the Lewis acid catalysed reactions always gave total decomposition of the starting material.

The failure of the cyclisation may be explained by molecular modelling (Section 2.3.1.1).
2.3.1.1 Molecular modelling studies

It is thought that the failure of [36] to cyclise, is because of the conformational constraints about an amide bond. The dienophile and diene may simply not get close enough in space to react with each other, even under high temperature and Lewis acid conditions (Figure 17).

![Figure 17]

It can be clearly seen that the trans- relationship of the amide does not allow the diene and the dienophile to come close enough to react, even at elevated temperatures.
It can be shown by molecular modelling calculations that the preferred conformation of an amide can be switched by $N$- alkylation or $N$- acylation (Figure 18).

Clearly the addition of an $t$-butyl group to the amide has switched the conformation of the amide to the *cis* form. Diels - Alder cyclisation should now be feasible.

The obvious ways to overcome the conformational problem are:

- alkylate or acylate the amide
- remove the amide functionality from the dienophile

The first point was tried and failed due to a lack of starting materials and time.

The second point however will be discussed in the next section.
2.3.2 Synthesis of 6-benzoylbenzo[2-7-c]naphthyridines

[31], [32]

In searching the literature for methods of overcoming the amide conformation problem previously discussed, an interesting paper was found in which Reissert describes an anomalous reaction that occurs between quinoline and benzoyl chloride (Scheme 36).76

\[
\begin{align*}
\text{PhCOCl} & \quad \text{NaOH aq.} \\
\text{only} & \\
\hline
\text{N}^\text{tOPh} & \quad \text{Reissert Compound} \\
\text{[39]} & \\
\text{RCOCI} & \quad \text{NaOH aq.} \\
\text{CN}^- & \\
\text{CHO} & \\
\text{N}^\text{H} & \quad \text{[40]} \\
\text{COPh} & \\
\end{align*}
\]

The classical Reissert reaction involves the treatment of quinoline with an acyl halide in the presence of cyanide ions. This results in what is known as a Reissert compound [39]. However in the absence of cyanide ions, N-benzoylecinnamaldehyde [40] was produced. The isolated product has been

76 Reissert, A. Ber., 1905, 38, 1603, 3415.
shown to be exclusively the trans $\alpha,\beta$-unsaturated aldehyde.\textsuperscript{77} The reaction fails for all other acyl halides, only benzoyl chloride gives the ring opened product.

This $\alpha,\beta$-unsaturated aldehyde is clearly a very synthetically useful starting material in the synthesis of the benzonaphthyridines and related compounds.

2.3.2.1 6-Benzoyl-5,6-dihydrobenzo[2,7-c]naphthyridines

The aldehyde [40] was readily converted to the $\alpha,\beta$-unsaturated hydrazone [41] by condensation with $N,N$-dimethylhydrazine under Dean - Stark conditions. The amide moiety could then be alkylated with a propargyl chloride to give the desired key intermediates [42] for the Diels - Alder cyclisation (Scheme 37).

All attempts to effect the Diels - Alder cyclisation of the propargylic hydrazone [42] have failed. Thermal methods mainly gave back starting material, whilst Lewis acid methods (e.g. boron trifluoride etherate) totally decomposed the material. It is thought that the cyclisation fails because of the preferred conformation of the amide moiety (Section 2.3.2.1.2).
2.3.2.1.1 NMR studies

The propargylic amide [42] exhibits quite an unusual proton NMR spectrum, the key feature being the vastly different shifts of the two methylene protons α to the amide (Figure 19).

![Figure 19: N.B. ppm refer to the shift in $d^6$ - DMSO](image)

It is thought that there must be some sort of hindered rotation about the N - CH$_2$ bond that is causing the two protons to appear non-equivalent.
High temperature NMR studies were undertaken to ascertain whether any such hindered rotation does in fact exist (Figure 20).

It can be seen that at 298 K (25°C) the two protons appear as double-doublets, due to coupling to each other, and long range coupling through the acetylene to the terminal proton. At 348 K (75°C) the long range coupling is no longer observed. The system requires to be heated to 398 K (125°C) for the signals to degenerate to the singlet (the broadness is due to the high temperature). It should be pointed out that the NMR pattern appears the same in CDCl₃, d⁴-methanol and d⁶-acetone. d⁶-DMSO was used because of its high boiling point.
Clearly there is a significant barrier to rotation, so at room temperature the two methylene protons appear non-equivalent. The explanation for this becomes clear when the system is subjected to molecular modelling analysis.

2.3.2.1.2 Molecular modelling studies

The minimum conformation of the amide [42] was calculated using the MM2 package.\textsuperscript{78} The N - CH\textsubscript{2} bond was then rotated through 360°, the energy being calculated every 1°. A graph of energy vs. rotation angle can then be plotted. A schematic representation of the graph is shown below (Figure 21).

![Graph with energy levels](image)

Figure 21

It can be seen that there are three distinct energy minima; A, B and C.

These three minima can be schematically visualised as follows (Figure 22).

![Figure 22](image)

In both conformers A and C there exists some sort of co-ordination between one of the methylene hydrogens and the amide carbonyl oxygen. This conformational lock renders the two methylene protons as non-equivalent, and hence they will have different chemical shifts in the proton NMR spectrum.

It is possible that conformers A and C are the kinetic product of the alkylation step; i.e. the conformation is locked at the time of the N - CH₂, bond formation. As can be seen from the graph (Figure 21) conversion to the thermodynamic product is blocked by a massive energy barrier. X-ray crystallographic analysis has confirmed this theory (Appendix).
The co-ordination of a methylene hydrogen to the amide carbonyl oxygen can be seen more clearly in the following diagram (Figure 23).

![Diagram showing conformers A and C]

Figure 23

Conformer C is the non-superimposable mirror image of conformer A, conversion of A to C is energetically not possible at room temperature.

It should also be noted that in this preferred conformation the acetylene is pointing away from the diene, which helps to explain why this compound failed to undergo the Diels - Alder cyclisation. The geometry of the system simply does not allow the dienophile and the diene to get near enough to each other.
2.3.2.2 6-Benzoyl-4-phenyl-5,6-dihydrobenzo[2,7-c]naphthyridine

[31]

The amide hydrazone [41] was N-alkylated with 3-phenylpropargyl chloride to give the phenylpropargylic hydrazone [43] in excellent yield. In this example the Diels - Alder cyclisation occurs as expected to give the desired cycloadduct [31] in good yield (Scheme 38).

![Scheme 38: i) 3-phenylpropargyl chloride, K₂CO₃, EtOH reflux 18 h, ii) mesitylene reflux 18 h]

Again the proton NMR signal at 8.68 ppm, a doublet J 5 Hz, gave a useful handle for following the course of the reaction. Thin layer chromatography of these systems is not very useful owing to the high polarity of the compounds. It should also be noted in the precursor to cyclisation [43] the two methylene
protons $\alpha$ to the amide appear as two distinct signals at 4.59 and 5.05 ppm (Figure 24).

![Figure 24](image)

The methylene protons in the product [31] appear as the expected singlet; the conformational alignment of one of the protons with the amide oxygen is no longer possible.
2.3.2.2.1 Molecular modelling studies

Molecular modelling studies of the phenylpropargylic hydrazone [43] produced similar results to those discussed earlier. Again there appears to be a preferred solution conformation where one of the methylene protons lies co-planar with the amide carbonyl (Figure 25).

Interestingly, it can be seen that the diene moiety lies directly over the dienophile, thus facilitating the Diels - Alder cyclisation. Also the phenyl substituent on the dienophile extends conjugation and hence increases the reactivity of the system, by virtue of lowering the energy of the dienophile’s LUMO.

In this example there are two factors that govern the conformation of the system.
• co-ordination of a methylene proton with the amide carbonyl

• $\pi - \pi$ orbital interaction between the diene and the conjugated dienophile

Both factors stabilise the reactive conformation which is ideally set-up for the cyclisation step; cf. the earlier example [42].
2.3.2.3 6-Benzoyl-3-dimethylamino-4-phenyl-3,4,4a,5,6,10b-
hexahydrobenzo[2,7-c]naphthyridine [32]

The amido hydrazone [41] can be alkylated with trans cinnamyl bromide to
give the alkenyl hydrazone [44], which can also undergo a Diels - Alder
cyclisation. The reaction proceeds to completion in 18 hours under mesitylene
reflux conditions, to give the desired cycloadduct [32] in reasonable yield
(Scheme 39).

Scheme 39: i) trans cinnamyl bromide, KH, THF, ii) mesitylene reflux, 18 h
In this example the reaction stopped at the tetrahydropyridine stage as predicted by the reaction mechanism, cf. the earlier benzopyrano example [27]. The reasons for why this example stops at this stage, and the previous example does not are not clear. It is interesting to note that upon prolonged standing in air the tetrahydropyridine [32] is indeed oxidised by atmospheric oxygen to the fully aromatic pyridine [31].

The proton NMR spectrum of the cycloadduct [32] is consistent with the stereochemistry as indicated. The existence of the cis ring junction has been shown by nOe studies. The stereochemical assignment is consistent with a concerted pericyclic reaction proceeding through a syn transition state (Figure 26).32

![Figure 26](image)

The transition state follows the 'cis principle' formulated by Alder and Stein.33 This states that the relative stereochemistry of the substituents in both the dienophile and the diene is retained in the adduct.
Also, in this example the precursor to cyclisation [44] exhibited two distinct signals in the proton NMR spectrum for the two methylene protons (Figure 27).

As with the previous examples [42], [43] the NMR spectrum can be explained by the aid of molecular modelling.
2.3.2.3.1 Molecular modelling studies

Molecular mechanics studies of the cinnamyl hydrazone\[44\] gave the same general result as for the previously described systems, \textit{e.g.} three distinct energy minima, two of which are stereoisomers. The graphical representation of the preferred solution conformer is shown below (\textbf{Figure 28}).

It can be clearly seen that one of the methylene protons is co-planar with the amide carbonyl. Also it is apparent that $\pi-\pi$ interactions may exist between the diene and the dienophile, stabilising the structure. Once again the energetically preferred conformer is ideally set up for the Diels - Alder cyclisation.
2.4 Comparative molecular modelling studies

For the model compounds to exhibit biological activity similar to that of the natural products, it is reasonable to assume that they must occupy the same space. Molecular modelling allows molecules to be compared based on the space they occupy, this is achieved by mapping the test molecule against the target molecule (i.e. the natural product).

For the purposes of this study the model compounds have been mapped against the natural product eilatin. This alkaloid has been chosen because of its essentially planar nature, and it contains most of the structural features common to all of the pyridoacridines. The following diagram (Figure 29) is a computer representation of eilatin [5] showing the van der Waals surface (the green dots).

![Diagram of eilatin showing van der Waals surface](image-url)
The model compounds were then subjected to a superimpose routine that is available with the Sybyl suite of programs.\textsuperscript{79} This routine calculates whether any atoms in the model compound can occupy the same space as the atoms in the target molecule. The calculations are based on the linear similarity index $L_{AB}$\textsuperscript{80} which takes into account following molecular properties;

- geometries, refined by MM2\textsuperscript{78}
- charges, defined by Gasteiger methods\textsuperscript{81}
- molecular dynamics\textsuperscript{82}

The results are reported as a colour scheme in the van der Waals surface of the test molecule. Green represents areas of high correlation, whereas magenta represents the poorer areas.

\textsuperscript{79} SYBYL, Tripos Corp., St. Louis, MO 63117, USA.
\textsuperscript{81} Gasteiger, J. and Marsili, M. \textit{Tetrahedron}, 1980, 36, 3219.
2.4.1 Modelling of benzopyrano[3,4-c]pyridines [16],[17]

The following two model compounds were compared with eilatin by the method described above (Figure 30).

![Molecules](image)

**Figure 30**

It can be seen that there is good correlation (green dots) in the A rings and most of the B rings. However, as mentioned earlier (Section 2.1) three planar fused rings are required for DNA intercalation. Unfortunately in the above two cases the ABE rings are out of plane by about 30°.
2.4.2 Modelling of benzo[2,7-c]naphthyridines [31],[32]

The following two model compounds were compared with eilatin by the method described above (Figure 31).

![Figure 31](image)

The molecule on the left-hand side [31] shows good correlation in the A and E rings. Also the ABE rings are almost planar (out of plane by 8°C). Therefore this compound might be expected to show similar properties to eilatin [5]; it
three essentially planar fused rings, and a degree of spatial correlation with the natural product.

The compound on the right-hand side [32] shows very little correlation and would be expected to be a poor model.

2.4.3 The need for planarity

As described earlier (Section 2.2.3) a tricyclic model bearing a 4-(2'-pyridyl) moiety was desired, yet unfortunately unobtainable. However, molecular modelling on such a system shows why the compound was required.

The modelling studies above show that the 4-phenyl substituent is always out of plane with regard to the rest of the molecule. The same would be true of a 4-(2'-pyridyl) system. However, if a metal was allowed to chelate between the D-ring nitrogen and the pyridyl nitrogen, one would expect the system to become planar (Figure 32).

![Figure 32]
This system was also subjected to the superimposition regime described above, an although hypothetical it demonstrates the point well (Figure 33).

![Figure 33](image)

It can be clearly seen that in the compound on the left-hand side [18] only the A and E ring show good correlation with eilatin. However, upon co-ordination with a nickel (II) species the rings AD & E all show good correlation with the ADE rings of eilatin. Also the compound on the right-hand side [18A] is quite planar, the major deviation being the 2'-pyridyl ring which is out a plane by 11°.

Therefore one might expect that the nickel complex [18A] might show similar biological activity to that of eilatin [5].
2.5 Conclusions

- A rapid and efficient route to a range of tricyclic models for pyridoacridine alkaloids has been developed.

- Molecular modelling and NMR studies have been performed on a range of compounds to help explain;
  - NMR spectra.
  - Reactivity of diene - dienophile systems.

- Comparative molecular modelling studies have been performed to compare and contrast the tricyclic core model with the natural product *eilatin*.

- Metal-binding studies have not been performed, as the introduction of a heterocycle to the model system has as yet proved impossible.

- Biological testing has yet to be performed, but upon completion the results will be published at a later date.
Chapter 3

Oxidative dimerisation of terminal acetylenes.

A facile route to annelated bipyridines
3.1 Introduction

In the previous chapter the dimerisation of a terminal acetylene [21] was described. This chapter will consider the wider scope of such dimerisations that have led to the development of a novel double intramolecular Diels - Alder reaction. This methodology has led to a facile route to anelated bipyridines, and a number of syntheses will be discussed.

The synthesis of bipyridines continues to attract attention because of their importance as industrial and medicinal compounds, as analytical reagents, and as ligands for the preparation of metal complexes with catalytic activity.83,84

3.1.1 Copper mediated dimerisation of terminal acetylenes

Terminal acetylenes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This produces symmetrical diynes in high yield, and is known as the Eglinton reaction (Scheme 40).70,85

\[
\text{R} \equiv \text{H} \xrightarrow{\text{CuX}_2, \text{pyridine}} \text{R} \equiv \equiv \equiv \equiv \text{R}
\]

Scheme 40

Large ring annulenes can be prepared via the Eglinton coupling of terminal diynes. The initial product is a cyclic polyyne, that is then hydrogenated to the annulene (Scheme 41).  

![Scheme 41](image)

**Scheme 41**: i) Cu(OAc)$_2$, pyridine, ii) KO-t-Bu, H$_2$, catalyst

Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride. This procedure is known as the Glaser coupling, and requires an external oxidant such as atmospheric oxygen or potassium permanganate.

Unsymmetrical diynes can be prepared by Cadiot-Chodkiewicz coupling (Scheme 42).  

![Scheme 42](image)

**Scheme 42**

The mechanism of the Eglinton and Glazer reactions are thought initially to proceed by base removal of the terminal proton.

---

The last step is the coupling of two carbon centred free radicals (Scheme 43).

\[
\begin{align*}
R & \equiv H \quad \xrightarrow{\text{base}} \quad R \equiv C^- \\
2 \quad R \equiv C^- & \quad \rightarrow \quad R \equiv \equiv \equiv R
\end{align*}
\]

Scheme 43

Just how the carbanion becomes oxidised to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,\(^{88}\) and depend on the oxidising agent.

This chapter will focus on our work towards the synthesis of a range of annelated bipyridines via the intramolecular Diels - Alder reaction of a bi-(aza-1,3-butadiene) with a diyne (Scheme 44).

\[\text{Scheme 44: i) Cu(OAc)}_2, \text{pyridine, ii) heat}\]

It was not in the scope of this project but if the Cadot - Chodkiewicz coupling procedure was employed on a terminal acetylene [45] and a bromo-acetylene [46], unsymmetrical bipyridines would result (Scheme 45).

![Scheme 45](image)

Scheme 45: i) Cu(OAc)_2, pyridine, ii) heat
The following annelated bipyridines have been made and their synthesis will be discussed later in the chapter.

4,4'-bi-\{5H-[1]-benzopyrano[3,4-c]pyridine\} [47]

1,1'-bi-{5,6-dihydro-7H-cyclopenta[c]pyridine} [48]

1,1'-bi-\{(7)R-\text{(+)}-4,7-dimethyl-5,6,7,8-tetrahydroisoquinoline\} [49]

4,4'-bi-\{6-benzoyl-5,6-dihydrobenzo[2,7-c]naphthyridine\} [50]

4,4'-bi-\{5,6-dihydrobenzo[2,7-c]naphthyridine\} [51]

4,4'-bi-{benzo[c]2,7-naphthyridine} [52]
3.1.2 Other routes to bipyridines

The classical synthesis of bipyridines is the coupling of an aryl halide with copper, the Ullmann reaction (Scheme 46).\(^8^9\)

\[
\begin{align*}
2\text{ArI} &\xrightarrow{\text{Cu, heat}} \text{Ar—Ar} \\
\text{Scheme 46}
\end{align*}
\]

The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls and bipyridines.\(^9^0\)

The classical Ullmann reaction requires drastic experimental conditions and in most cases gives low yields of the desired bipyridines.\(^8^9\)

There are a number of modern literature procedures for the synthesis of bipyridines, two of which will be described here. They all share the common feature of being dimerisation reactions of a suitably substituted pyridine (Scheme 47).

\[
\begin{align*}
\text{Scheme 47 : } X &= \text{halogen, or sulfoxide} \\
\end{align*}
\]

The procedures are of wide scope, but are unfortunately limited to the synthesis of C\(_2\) - symmetric bipyridines.

\(^8^9\) For a review see Fanta, P.E. *Synthesis*, 1974, 9.
\(^9^0\) For a review of aryl-aryl coupling see Sainsbury, M. *Tetrahedron*, 1980, 36, 3327.
3.1.2.1 Nickel mediated coupling

By far the most common method for obtaining a bipyridine is the nickel mediated dimerisation of a halopyridine. These methods are usually quite mild and afford the desired bipyridine in reasonable to excellent yields. Nickel (0) complexes are required for the coupling procedure. They are usually prepared in situ by the treatment of a nickel (II) salt with zinc dust and triphenylphosphine (Scheme 48).

![Scheme 48](image)

This methodology has been used to prepare many C₂-symmetric chiral bipyridines which have been used as ligands for asymmetric synthesis (Scheme 49).

![Scheme 49](image)

---

Ligands like \([53]\) have been used in the catalysed enantioselective alkylation of aldehydes, giving enantiomeric excesses greater than 90\% (Scheme 50).\(^9^5\)

\[
\text{R-CHO} + \text{ZnEt}_2 \xrightarrow{i)} \text{R-CH}_2\text{Et}
\]

Scheme 50: i) chiral ligand \([53]\) : ee's > 90\%

### 3.1.2.2 Coupling reactions of alkyl pyridyl sulfoxides

Probably the second most common procedure for the synthesis of bipyridines is the reaction of an alkyl pyridyl sulfoxide with alkyl magnesium bromide (Scheme 51).\(^9^6\)

\[
\begin{array}{c}
\text{S}
\end{array}
\]

Scheme 51

This is a mild procedure which generally leads to high product yields, and can be applied to the synthesis of biquinolines as well.\(^9^6\) The scope of the reaction is wide but is limited to symmetrical products only.

---

An extension of this methodology to allow unsymmetrical products has been reported by Wakabayashi and co-workers.\textsuperscript{97} In this case the reaction proceeds via ipso substitution of a 2-alkylsulfinylpyridine by 2-pyridyl lithium (Scheme 52).

\begin{center}
\textbf{Scheme 52:} i) Et\textsubscript{2}O -78°C
\end{center}

This methodology can also lead to a range of oligopyridines which are useful for host-guest chemistry.

3.2 Synthesis of 4,4'-bi-{5H-[1]-benzopyrano[3,4-c]pyridine} [47]

The synthesis of the bipyridine [47] starts with the monomeric acetylene hydrazone [21], the synthesis of which was described in Chapter 2.

The acetylene hydrazone [21] was oxidatively dimerised under Eglinton conditions to yield the diyne hydrazone [28] in high yield.\textsuperscript{85} Heating of a solution of [28] in xylene at reflux for 3 hours affords the desired annelated pyridine [47] in excellent yield (Scheme 53).

\begin{Scheme}
\centering
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme53.png}};
\end{tikzpicture}
\end{Scheme}

\textbf{Scheme 53} : i) Cu(OAc)$_2$, pyridine, MeOH, Et$_2$O, 70°C 18 h, ii) xylene reflux 3 h
This is the first known example of a symmetrical double intramolecular Diels-Alder reaction. Four new rings are formed in one step in a remarkably good yield.

It is interesting that in the proton NMR spectrum of [47] the shift of the pyridine $\alpha$ proton is slightly downfield to that of the monomeric adduct [16] i.e. 8.63 ppm (cf. 8.54 ppm for the monomer). The extra conjugation in the dimer leads to an increased ring current and hence the signal is shifted further downfield.

A major point to note about the Diels-Alder cyclisation step is that it proceeds at a lower temperature and requires less time than the monomeric equivalent. This is due to the extra conjugating effects of the diyne which lowers the relative energy of the dienophile’s LUMO; hence the energy difference between the diene’s HOMO and the dienophile’s LUMO is lowered.

Also the extended $\pi$ system present in the diyne allows a significant $\pi-\pi$ interaction to occur between the diene and the diyne, creating a conformation that is ideally set-up for the Diels-Alder cyclisation. This can be represented as a molecular model of the minimum energy conformation as calculated by MM2 procedures (Figure 34).
A comparison of the hexacycle [47] and eilatin [5] shows that this methodology could lead to a route to the natural product. All that is required is the changing of the oxygen to a nitrogen and the insertion of a new carbon-carbon bond (Figure 35).

Synthetic approaches to the natural product eilatin [5] will be discussed later in the chapter (Section 3.5).
3.3 Synthesis of a bi-{carbocyclic[c]pyridine}

The synthesis of the cyclopenta[c]pyridine [48] as a model compound to show the generality of the double Diels - Alder reaction will be discussed. Clearly a range of simple carbocyclic[c]pyridines could be constructed analogously (Figure 36).

![Figure 36]

1,1' -bi{5,6-dihydro-7H-cyclopenta[c]pyridine [48]

3.3.1 Retrosynthesis

Retroynthetic analysis of the bipyridine [48A] leads to the starting material being a terminal alkyn-1-ol (Scheme 54).

![Scheme 54]
A range of bi-(carbocyclic[c]pyridines) should be available by suitable chemical manipulation of a range of alkyn-1-ols. As a model to demonstrate this the alkyn-1-ol where \( n = 2 \) was chosen i.e. 5-hexyn-1-ol.

### 3.3.2 Synthesis of 1,1'-bi[5,6-dihydro-7H-cyclopenta[c]pyridine]

The planned starting point was the oxidation of 5-hexyn-1-ol to the corresponding aldehyde [54] (Scheme 55).

```
\[ \text{H} \equiv \text{C} = \text{C} \equiv \text{H} \quad \text{[O]} \quad \text{H} \equiv \text{C} = \text{C} \equiv \text{CHO} \]
```

Scheme 55

Many methods were tried to bring this about;

- pyridinium chlorochromate (Corey's reagent)\(^{75}\)
- pyridinium dichromate\(^{98}\)
- manganese (IV) dioxide\(^{99}\)
- Swern oxidation\(^{100}\)

All of the above methods failed to give any desired product only decomposition of the starting material was observed.

---


Models can be drawn to show a cyclic transition state in which the terminal proton co-ordinates to the oxygen, thus increasing the acidity of the terminal proton and causing the reactions to fail (Figure 37).

![Figure 37](image)

This problem was overcome by altering the sequence of steps initially proposed in the retrosynthesis (Scheme 54).

The synthetic strategy now started with the copper mediated dimerisation of 5-hexyn-1-ol to give the diyne-diol [55]. This was easily oxidised to the corresponding diyne-dial [56] by the standard Corey procedure with PCC (Scheme 56).\(^7^5\)

Scheme 56: i) Cu(OAc)\(_2\), pyridine, 70°C, 18 h, ii) PCC, dichloromethane, 3 h
The diyne-dial [56] was readily converted to the diyne-hydrazone [57] in excellent yield using the Wadsworth - Emmons reaction described earlier.\textsuperscript{49} When a solution of the diyne-hydrazone [57] in xylene was heated at reflux for 3 hours the desired cycloadduct [48] was obtained in excellent overall yield (Scheme 57).

\[\text{[56]} \quad \xrightarrow{i) \text{98\%}} \quad \text{[57]} \quad \xrightarrow{\text{ii) 76\%}} \quad \text{[48]}\]

\textbf{Scheme 57:} i) n-butyllithium, phosphonate ester [23], -78°C, ii) xylene reflux 3 h

The metal binding properties of the compound [48] are discussed later in the chapter (\textbf{Section 3.6.1}).

This methodology is clearly a very quick and efficient route to simple annelated bipyridines. There is also the possibility of introducing functionality into the carbocyclic ring, by using a suitably functionalised alkyn-1-ol.

There is also the opportunity for the rapid construction of a wide range of chiral bipyridines, the use of which in asymmetric synthesis has been described earlier (\textbf{Section 3.1.2.1}). The synthesis of a chiral bipyridine is described in the next section.
3.4 Synthesis of a chiral bipyridine

As mentioned in the preceding section there is great scope for the construction of a range of chiral bipyridines [59] via the intramolecular double Diels - Alder reaction of a chiral diyne (Scheme 58).

\[ \text{Scheme 58: i) } \text{Cu(OAc)}_2, \text{ ii) heat} \]

It can be seen that a chiral acetylenic hydrazone [58] would ultimately lead to a C$_2$-symmetric chiral annelated pyridine [59].
A convenient starting point for the synthesis of a model compound is from the commercially available chiral aldehyde citronellal [60] (Figure 38).

![Image of citronellal structure]

Figure 38

There are many reasons for choosing such a starting material:

- readily available in either enantiomeric form
- conversion of an aldehyde to a terminal acetylene is known\(^\text{101}\)
- allylic oxidation of alkenes is known\(^\text{102}\) and hence conversion to the \(\alpha,\beta\)-unsaturated hydrazone


3.4.1 Synthesis of 1,1'-bi{4,7-dimethyl-5,6,7,8-tetrahydroisoquinoline} [49]

Figure 39

The starting point of this synthesis is the conversion of an aldehyde to a terminal acetylene, achievable using Corey’s methodology.\textsuperscript{101}

(R)-(+)-Citronellal [60] was converted to the terminal acetylene [62] by a reaction sequence that goes via the dibromo-olefin [61].

The dibromo-olefin [61] was prepared by the action of carbon tetrabromide and triphenylphosphine on the starting aldehyde [60], analogously to a Wittig olefination. Treatment of the dibromo-olefin [61] with two equivalents of \textit{n}-butyllithium followed by an aqueous quench afforded the terminal acetylene [62] excellent overall yield (Scheme 59).\textsuperscript{101}
The second step proceeds via a di-lithio species which upon aqueous work up gave the desired acetylene [62] in a very reasonable yield.

Allylic oxidation of the ene-yne [62] using standard selenium dioxide methodology\textsuperscript{102} gave a mixture of the allylic alcohol [63] and the desired (E)-$\alpha,\beta$-unsaturated aldehyde [64]. \textit{In situ} treatment of the crude reaction mixture with manganese (IV) dioxide gave the $\alpha,\beta$-unsaturated aldehyde [64] as the sole product in good overall yield (Scheme 60).
The selenium dioxide allylic oxidation gave exclusively the \((E)\)-aldehyde.

The oxidation is believed to involve an ene reaction between the hydrated form of the selenium dioxide and the alkene. This is followed by a [2,3] sigmatropic rearrangement to give a mixture of the allylic alcohol and the corresponding aldehyde.\(^{103}\) Subsequent oxidation of the alcohol gives exclusively the \((E)\)-\(\alpha,\beta\)-unsaturated aldehyde.

The high selectivity achieved with 1,1-dimethyl alkenes can be rationalised when one considers the favoured transition state of the reaction mechanism (Figure 40).\(^{104}\)

\[\text{[2,3] sigmatropic rearrangement}\]

\[\text{hydrolysis \(\xrightarrow{\text{xs. MnO}}\) [66]}\]

---


The high (E) - selectivity is established by the concerted [2,3] - sigmatropic rearrangement of the allylselenic acid [65] to the selenic ester [66]. Aqueous work-up followed by in situ oxidation with manganese (IV) dioxide yields the desired (E)- α,β- unsaturated aldehyde [64].

Condensation of the acetylenic α,β- unsaturated aldehyde [64] with N,N-dimethylhydrazine gave the required acetylenic hydrazine [67]. Oxidative dimerisation of [67] with copper (II) acetate and pyridine to give the expected dimeric hydrazone [68] in good yield. A solution of the dimeric hydrazone [68] in xylene was heated to reflux for 5 hours to afford the desired C₂-symmetric chiral bipyridine [49] in 37% overall yield (Scheme 61).

Scheme 61 : i) N,N - dimethylhydrazine, ii) Cu(OAc)₂, pyridine 70°C, iii) xylene reflux 5 h
The “fingerprint” proton NMR signal for the pyridine α proton appears at 8.47 ppm in this example.

The final product [49] exhibits an optical rotation; $\alpha_0^{22} + 13^\circ$ (c 2.5 in CHCl₃). It can therefore be deduced that the reaction sequence does not racemise the compounds. However a chiral resolution (e.g. chiral shift NMR, or chiral HPLC) would be needed to prove enantiomeric purity.

It should be noted that full characterisation of the final compound [49] and its precursor [68] has not been achieved due to time constraints.
3.5 Approaches to the total synthesis of eilatin [5]

As described earlier (Section 3.2) the oxidative dimerisation of a suitable terminal acetylene should give a precursor which can be elaborated to give the natural product eilatin [5] (Figure 41).

\[ \text{Figure 41} \]

In Chapter 2 (Section 2.3.2.1) the synthesis of the acetylenic hydrazone [42] was reported, and the attempted Diels - Alder cyclisation was discussed (Scheme 62).

\[ \text{Scheme 62 : i) heat, or Lewis acid catalysis} \]

The explanations for the failure of the reaction are based on the conformation of the precursor [42] and the energy of the dienophile’s LUMO.
The results shown earlier (Section 3.2) suggest that the dimerisation of the terminal acetylene [42] will alter the preferred conformation and lower the energy of the dienophile's LUMO. It should also be clear that this system would lead to the major framework of the eilatin structure (Scheme 63).

Scheme 63

The following section will highlight the approaches to the natural product eilatin, and comment on some of the intermediate bipyridine structures.

The proposed synthesis of eilatin began with the copper mediated oxidative dimerisation of the acetylenic hydrazone [42]. This proceeded in excellent yield to give the diyne hydrazone [69]. Heating of a solution of the diyne [69] in xylene affords the hexacyclic Diels - Alder adduct [50] in good yield (Scheme 64).
It is noteworthy that the cyclisation step only takes 2 hours in refluxing xylene (cf. 18 hours in mesitylene for earlier examples). This is due to two main factors:

- the conjugation effects of the diyne lower the LUMO energy of the dienophile, and hence increase the reactivity of the system [69]
- the conformation of the reacting system [69] is locked in a favourable orientation
The last point can be illustrated in a graphical representation of the minimum energy conformation of [69] as calculated using MM2 methods (Figure 42).

Figure 42

It can be clearly seen that there are two factors locking the conformation of the system

- co-ordination of a methylene hydrogen to an amide carbonyl (cf. the monomer [42])
- $\pi - \pi$ orbital interaction between the dienes and the diyne

The three compounds above [42], [50], [69] all exhibit interesting proton NMR spectra, these will be discussed later in the chapter (Section 3.5.2).
The next stage in the synthesis of eilatin required the de-benzoylation of the cycloadduct [50]. There are a number methods for the removal of a benzoyl group to give the free amine\textsuperscript{105,106} The method of choice however utilised diisobutylaluminium hydride reduction of the amide [50],\textsuperscript{107} the reaction took 3 hours and afforded the required amine [51] in almost quantitative yield (Scheme 65).

![Scheme 65: i) DIBAL, THF, -78°C, 3 h](image)

The amine [51] is quite unstable to air and very unstable to silica gel.

Therefore the amide [50] was reduced as required, and the amine [51] was used immediately without further purification.

\textsuperscript{106} Horner, L. and Neumann, H. \textit{Chem. Ber.}, 1965, 98, 3462.
The amine [51] was converted to the cyclic imine [52] by dehydrogenation with palladium on carbon in excellent yield (Scheme 66).

![Scheme 66: i) Pd/C, 25°C 48 h](image)

The cyclic imine [52] is a very stable entity and is the key precursor for the proposed synthesis of eilatin.
3.5.1 Attempted syntheses of eilatin [5]

The previous section described the synthesis of the key intermediate for the synthesis of eilatin i.e. the cyclic imine [52]. It was thought that it would be a trivial matter to affect the final ring closure to afford eilatin [5] (Scheme 67).

\[ \text{Scheme 67} \]

Alas, trivial matters seldom are in synthetic organic chemistry!

Initial attempts to bring about ring closure were based on oxidative methods; DDQ oxidation,\textsuperscript{108} irradiation with and without the presence of iodine\textsuperscript{109} and treatment with palladium on carbon at elevated temperatures.\textsuperscript{110} All the methods have been used in similar procedures in the literature, however they all failed in this instance.

On close inspection of the precursor [52] it can be seen that an oxidative cyclisation mechanism is impossible. In affect the imine bonds are isolated i.e. not fully conjugated with the rest of the systems. Therefore a reductive approach was needed.

There have been many methods tried to affect the reductive cyclisation of the cyclic imine [52] to afford eilatin [5]:

- McMurry coupling with low valent titanium\textsuperscript{111}
- Heating in the presence of magnesium turnings to affect a pinacol type coupling\textsuperscript{112}
- Samarium iodide as a reductant to promote a pinacol coupling\textsuperscript{113}
- Indium coupling\textsuperscript{114}

Of the above methods only the indium coupling showed any sign of promise.

\textsuperscript{111} McMurry, J.E. \textit{Chem. Rev.}, 1989, 89, 1513.
Indium coupling of aldimines to give vicinal diamines has been reported. The reaction proceeds analogously to that of the pinacol reaction, i.e. addition of an electron to the imine bond to give the radical anion. Reductive dimerisation followed by protonation yields the vicinal diamine (Scheme 68).

\[
2 \text{Ar}^1-\text{CH}=\text{N}^\ominus-\text{Ar}^2 \xrightarrow{\text{i}) \text{e}^-} 2 \text{Ar}^1-\text{CH}^\ominus-\text{N}^\ominus-\text{Ar}^2 \\
\text{H}
\]

> 90%

\[
\text{Ar}^1-\text{CH}=\text{N}^\ominus-\text{Ar}^2 \\
\text{Ar}^1-\text{CH}=\text{N}^\ominus-\text{Ar}^2 \\
\text{H}
\]

Scheme 68 : i) indium wire, H₂O - EtOH, NH₄Cl

Model reactions using indium metal have given access to a new procedure for coupling of cyclic imines (Scheme 69).

\[
\text{[71]} \xrightarrow{\text{i}) 89\%} \text{[70]}
\]

\[
\text{[72]} \xrightarrow{\text{i}) 93\%} 
\]

Scheme 69 : i) indium wire, H₂O - EtOH, NH₄Cl
In the example of the coupling of quinoline the observed product was the over reduced bi-(perhydroquinoline) [70]. Coupling of phenanthridine [71] gave the expected vicinal diamine [72] in excellent yield. In both cases the meso isomer was observed.

However, this methodology failed for the required system (Scheme 67). This is probably due to a number of factors:

- the inherent stability of the precursor [52]

- the fact that the two “halves” of the system are out of plane by 60°

There is no way to overcome the first problem, but complexation of [52] with a metal might solve the second.
Molecular modelling studies have shown that complexation of the upper two nitrogens with a metal such as zinc can reduce the "out of plane angle" from 60° to an almost planar 8° (Figure 43).

The molecule on the left-hand side shows the two "halves" out of plane by 60°. The model on the right is complexed to zinc, and the "out of plane" angle is vastly reduced to 8°. Note also that the two imine carbons have moved from 3.4 Å apart to only 2.5 Å apart. These two factors ought to be enough to allow the final bond to form under favourable conditions.

However, heating a mixture of [52] and a range of zinc salts has failed to produce eilatin [5].
The most likely way to complete the synthesis of eilatin is to affect a McMurry coupling of the lactam [73] to form the carbon-carbon bond. This would then be followed by an oxidation to yield the fully aromatic product, eilatin [5] (Scheme 70).

![Scheme 70: i) "low valent" titanium, ii) DDQ oxidation](image)

The lactam [73] could be made by a ruthenium tetroxide oxidation\textsuperscript{115} of the cyclic amine [51].

Metal binding studies of the cyclic imine [52] have been performed and are reported at the end of this chapter (Section 3.6.2).

3.5.2 NMR studies

The three compounds [42], [50], [69] are shown below with the chemical shift and multiplicity of the methylene protons indicated (Figure 44).

![Figure 44: N.B. ppms refer to CDCl₃ solution]

The key features of the proton NMR spectra are shown below (Figure 45).
These results can be explained by considering the conformations of each molecule. It has been shown by molecular modelling that in both [42], and [69], a methylene hydrogen co-ordinates to the amide carbonyl oxygen (Sections 2.3.2.1.2 and 3.5). Therefore the methylene hydrogens are not chemically equivalent and consequently exhibit different proton NMR signals.

The fine splitting observed in the monomeric acetylene [42] is due to long range coupling to the terminal proton.

The NMR spectrum of the cycloadduct [50] shows the methylene protons as the expected singlet. The geometry of the ring system does not allow any of the methylene protons to co-ordinate to an amide carbonyl oxygen.
3.6 Metal binding studies

Metal binding studies were carried out on the following two bipyridines [48], and [52] (Figure 46).

For comparison purposes 2,2' - bipyridine was also studied.

When a ligand complexes with a metal salt an equilibrium is set up (Figure 47).

\[ M + L \rightleftharpoons ML \]

Figure 47: \( M = \text{metal}, \ L = \text{ligand}, \ ML = \text{complex} \)

The equilibrium constant \( K \) is defined as follows (Equation 1).

\[ K = \frac{[ML]}{[M][L]} \]

Equation 1

Ultra-violet spectroscopy can be used to measure the equilibrium constant of such a reaction. Consider a series of solutions in which increments of ligand \( L \)
are added to a constant amount of metal salt $M$, the UV absorbance being measured with each addition. The change in absorbance is proportional to the concentration of complex formed; this in turn is proportional to the amount of ligand added and the value of the equilibrium constant (Equation 2).

\[
\frac{\Delta A}{[L]} \propto (-K\Delta A)
\]

Equation 2

Therefore a plot of $\Delta A / [L]$ vs. $\Delta A$ should be a straight line with a slope of $-K$.

In this way absorbances measured while $M$ is being titrated with $L$ can be used to find the equilibrium constant for the reaction of $M$ with $L$. This technique is known as the Scatchard Plot, and is a widely used method for determining equilibrium constants.\(^{116}\)

For the purposes of this study complexation reactions were performed using di-
\(\mu\)-chloro(bis([1,2,5,6-\(\eta\)]-1,5-cyclooctadiene) dirhodium) [74]. This dimeric
system has been shown to complex to a wide number of ligands. Upon addition
of a competing ligand the dimer breaks down to the monomeric metal - ligand
complex [75] (Scheme 71).\(^{117}\)

\[ \text{Rh} \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \text{Rh} \]

\[ \text{Rh} \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \text{Rh} \]

\[ + \text{Cl}^- \]

Scheme 71

The typical UV spectra obtained for such a metal-ligand titration are shown below (Figure 48).

\[ \text{Wavelength / nm} \]

\[ 200 \quad \text{Free metal salt 237 nm} \]

\[ 259 \text{nm} \]

\[ 300 \]

**Figure 48**: complexation of rhodium salt [74] with ligand [52] in dichloromethane

As can be seen from the above spectra addition of the ligand to the metal salt causes an absorbance which is due to the $t_{2g} \rightarrow \pi^*$ metal-to-ligand charge transfer transition (Figure 49).\(^{118}\)

\[ \pi^* \text{(Ligand)} \]

\[ \nu_1 \]

\[ e_g \]

\[ t_{2g} \]

**Figure 49**: A simple representation of metal-to-ligand charge-transfer transition

It should also be noted that the absorbance due to the complex increases and the absorbance due to the metal salt decreases, with increasing amounts of added ligand.

3.6.1 Results for 1,1'-bi-[5,6-dihydro-7H-cyclopenta[c]pyridine]

complexation with the rhodium salt [74]

Complexation measured at λ = 245 nm, absorbance due to free metal = 0.100.

Concentration of rhodium salt [74] = 1.2 mmole l⁻¹, ∴ concentration of free rhodium = 2.4 mmole l⁻¹.

<table>
<thead>
<tr>
<th>Concentration of Ligand [L] mmole l⁻¹</th>
<th>Absorbance at 245 nm</th>
<th>Corrected absorbance ΔA</th>
<th>DA /[L] / l.mmole⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.376</td>
<td>0.276</td>
<td>1.106</td>
</tr>
<tr>
<td>0.50</td>
<td>0.432</td>
<td>0.432</td>
<td>0.864</td>
</tr>
<tr>
<td>1.00</td>
<td>0.742</td>
<td>0.642</td>
<td>0.642</td>
</tr>
<tr>
<td>2.00</td>
<td>0.974</td>
<td>0.874</td>
<td>0.437</td>
</tr>
</tbody>
</table>

A Scatchard Plot of ΔA / [L] vs. [L], will have a slope of - K (Figure 50).

![Figure 50](image)

From linear regression analysis of the above data the equilibrium constant can be determined :-

\[ K = 7.32 \times 10^2 \text{ l.mol}^{-1} \]
3.6.2 Results for 4,4'-bi-[benzo[c]-2,7-naphthyridine] [52] complexation with the rhodium salt [74]

Complexation measured at $\lambda = 259$ nm, absorbance due to free metal = 0.220.

Concentration of rhodium salt [74] = 1.2 mmole l$^{-1}$, ∴ concentration of free rhodium = 2.4 mmole l$^{-1}$.

<table>
<thead>
<tr>
<th>Concentration of Ligand [L] mmole l$^{-1}$</th>
<th>Absorbance at 259 nm</th>
<th>Corrected absorbance $\Delta A$</th>
<th>$DA / [L]$ / l.mmole$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.595</td>
<td>0.375</td>
<td>1.23</td>
</tr>
<tr>
<td>0.6</td>
<td>0.785</td>
<td>0.565</td>
<td>0.941</td>
</tr>
<tr>
<td>1.2</td>
<td>0.936</td>
<td>0.716</td>
<td>0.596</td>
</tr>
</tbody>
</table>

A Scatchard Plot of $\Delta A / [L]$ vs. $[L]$, will have a slope of $-K$ (Figure 51).

From linear regression analysis of the above data the equilibrium constant can be determined :-

$$K = 9.08 \times 10^2 \text{ l.mol}^{-1}$$
3.6.3 Results for 2,2′-bipyridine complexation with the rhodium salt

Complexation measured at $\lambda = 282$ nm, absorbance due to free metal = 0.075.

Concentration of rhodium salt [74] = 1.2 mmole l⁻¹, $\therefore$ concentration of free rhodium = 2.4 mmole l⁻¹.

<table>
<thead>
<tr>
<th>Concentration of Ligand [L] mmole l⁻¹</th>
<th>Absorbance at 259 nm</th>
<th>Corrected absorbance $\Delta A$</th>
<th>$DA / [L]$ / l.mmole⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>0.212</td>
<td>0.170</td>
<td>1.363</td>
</tr>
<tr>
<td>0.25</td>
<td>0.272</td>
<td>0.295</td>
<td>1.183</td>
</tr>
<tr>
<td>0.5</td>
<td>0.515</td>
<td>0.496</td>
<td>0.992</td>
</tr>
<tr>
<td>1.0</td>
<td>0.808</td>
<td>0.733</td>
<td>0.733</td>
</tr>
</tbody>
</table>

A Scatchard Plot of $\Delta A / [L]$ vs. [L], will have a slope of $-K$ (Figure 52).

From linear regression analysis of the above data the equilibrium constant can be determined :-

$$K = 1.17 \times 10^3 \text{ l.mol}^{-1}$$
3.6.4 Summary of results

The following table summarises the results for the metal binding studies previously described (Figure 53).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Equilibrium constant $K$ / L.mol$^{-1}$</th>
<th>$K$ relative to 2,2'-bipyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Molecule 1" /></td>
<td>$1.17 \times 10^3$</td>
<td>1.00</td>
</tr>
<tr>
<td><img src="image2.png" alt="Molecule 2" /></td>
<td>$7.32 \times 10^2$</td>
<td>0.62</td>
</tr>
<tr>
<td><img src="image3.png" alt="Molecule 3" /></td>
<td>$9.08 \times 10^2$</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Figure 53

Literature values for the complexation of bipyridine with a variety of transition metals range from $10 \times 10^1$ for cobalt through to $6 \times 10^8$ for mercury.\(^{119}\)

---

3.7 Conclusions

- A fast and efficient route to novel C₂-symmetrical annelated bipyridines has been developed that utilises the Eglinton procedure for coupling of terminal acetylenes.

- It should be noted that if the Cadiot-Chodkiewicz procedure for acetylenic coupling was used unsymmetrical bipyridines would result.

- An approach to the total synthesis of eilatin has been investigated.

- The metal binding properties of two bipyridines [48], [52] have been reported.
Chapter 4

Experimental section
4.1 General experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. "Light petroleum" refers to the fraction boiling between 40 and 60°C, and was distilled through a 36 cm Vigreux column before use. Diethyl ether, xylene, benzene and toluene were dried where necessary by storage over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorus pentoxide. DMF was dried by stirring over calcium hydride for 15 h, decanted and distilled under reduced pressure before storage over 4 Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine, and stored over activated 4 Å molecular sieves.

Analytical thin layer chromatography was carried out using glass-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and / or 360 nm) or by staining with Ehrlich's reagent or phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Pressure
was applied at the column head with hand bellows. Samples were applied pre-
adsorbed on silica or as a saturated solution in an appropriate solvent.

IR spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet FT-205
spectrometer, with internal calibration. Spectra were recorded as follows:
solids as KBr discs; oils as solutions in CCl\(_4\); unless stated otherwise. UV /
visible spectra were obtained using a Shimadzu UV-160 spectrophotometer.
Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental
Analyser. \(^1\)H and \(^13\)C NMR spectra were recorded using Bruker AC-250, DPX-
400 and Bruker WH-400 (EPSRC NMR Spectroscopy Centre, Warwick)
instruments. High- and low-resolution mass spectra were recorded on a Kratos
MS80 instrument or on a VG Analytical ZAB-E instrument (EPSRC mass
spectrometry service, Swansea). Where no fragmentation patterns are shown
this indicates that FAB-MS was used, and no meaningful fragments were
observed. GC-MS analyses were performed on Fisons GC-8000 with MD800
mass detection. M.p.s. were measured on an Electrothermal digital melting
point apparatus and are uncorrected.
4.2 Experimental for Chapter 2

(E)-3-(2-Hydroxyphenyl)propan-1-0 [19]

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

To a stirred suspension of formylmethylene triphenylphosphorane (486 mg, 1.6 mmol) in dry tetrahydrofuran was added a solution of salicylaldehyde (100 mg, 0.8 mmol) in tetrahydrofuran (1 ml). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the crude residue was filtered through a pad of silica gel (light petroleum : ethyl acetate 2:1) to remove base line impurities. Concentration of the filtrate yielded the desired aldehyde as a yellow solid (100 mg, 83%), m.p. 131-132°C; (Found: \(M^+\)
148.0524, C\(_9\)H\(_8\)O\(_2\) requires 148.0524); \(\nu_{\text{max}}\) 3642, 1688, 1375 cm\(^{-1}\); \(\delta_\text{H}\) (250 MHz; CDCl\(_3\)) 6.84 (1H, s, Ar), 6.86-6.93 (3H, m, Ar); 7.57 (1H, td, \(J\) 16, 8 Hz, alkene), 7.91 (1H, d, \(J\) 16 Hz, alkene), 9.60 (1H, d, \(J\) 8 Hz, CHO); \(\delta_\text{C}\) (62.5 MHz; CDCl\(_3\)) 119.6 (CH), 123.3 (CH), 124.9 (C), 131.8 (CH), 133.0 (CH), 136.4 (CH), 154.7(CH), 161.2 (C), 199.5 (CH); \(m/\ell\) 148 (\(M^+\), 68%), 147 (100), 131 (69), 91 (89).
(E)-3-(2-Propargyloxyphenyl)propenal [20]

![Chemical structure]

A mixture of the hydroxyaldehyde [19] (100 mg, 0.6 mmol), propargyl chloride (50 μl, 1.0 mmol) and potassium carbonate (80 mg) in anhydrous ethanol (10 ml) was heated to reflux for 18 h under an inert atmosphere. The mixture was filtered, evaporated *in vacuo* diluted with dichloromethane, washed with sodium hydroxide solution (3 x 50 ml, 10% solution), and washed with water (3 x 50 ml). The organic extracts were dried (MgSO₄) and concentrated *in vacuo* to leave a yellow oil which was chromatographed on silica gel (light petroleum : ethyl acetate 2:1) to give the desired ether as a yellow semi-solid (113 mg, 90%), (Found : \(M^+\) 186.0681, \(C_{12}H_{10}O_2\) requires 186.0680); \(\nu_{\text{max}}\) 3322, 2219, 1703, 976 cm⁻¹; \(\delta_H\) (250 MHz; CDCl₃) 2.58 (1H, s, CCH), 3.62 (2H, s, OCH₃) 6.98-7.38 (4H, m, Ar), 7.51 (1H, d, \(J\) 16 Hz, alkene), 7.83 (1H, d, \(J\) 16 Hz, alkene), 9.65 (1H, d, \(J\) 9 Hz, CHO); \(\delta_C\) (62.5 MHz; CDCl₃) 56.2 (CH₂), 64.0 (C), 70.3 (CH), 112.2 (CH), 121.2 (C), 123.4 (CH), 124.3 (CH), 127.4 (CH), 131.4 (CH), 137.6 (CH), 147.7 (C), 189.3(CH); \(m/z\) 186 (\(M^+\), 78%), 42 (100).
A solution of the ether aldehyde [20] (100 mg, 0.5 mmol) in dichloromethane (10 ml) containing anhydrous magnesium sulfate (200 mg) was cooled to 0°C. \(N,N\)-dimethylhydrazine (0.1 ml, 1.5 mmol) was added dropwise to the reaction vessel. The reaction was allowed to stir at room temperature for 3 h. The mixture was then filtered to remove the magnesium sulfate and concentrated in vacuo to yield the desired hydrazone as yellow solid (120 mg, 98%), m.p. 88-89°C; (Found: \(M^+\) 228.1263, \(C_{14}H_{16}N_2O\) requires 228.1266); \(\nu_{\text{max}}\) \(3309, 1676, 2359\text{ cm}^{-1}\); \(\delta\) \(H\) \((250\text{ MHz}; \text{CDCl}_3)\) 2.54 (1H, s, CCH), 2.87 (6H, s, N(CH\(_3\))\(_2\)), 4.75 (2H, s, OCH\(_2\)), 6.88-7.53 (7H, m, Ar + alkene + hydrazone-H); \(\delta\) \(C\) \((62.5\text{ MHz}; \text{CDCl}_3)\) 43.3 (2xCH\(_3\)), 56.7 (CH\(_2\)), 76.1 (CH), 79.2 (C), 113.2 (CH), 122.3 (CH), 126.7 (C), 126.8 (CH), 127.4 (CH), 128.6 (CH), 128.7 (CH), 136.0 (C), 154.9 (CH); \(m/z\) 228 \((M^+, 32\%), 44\) (100).
The ether-hydrazone [21] (90 mg, 0.3 mmol) was suspended in dry, degassed toluene (5 ml). The suspension was heated at reflux for 18 h. The solvent was removed in vacuo to give the desired product as a pale brown oil (38 mg 92%); (Found: $M^+$ 185.0603, $C_{12}H_9O_2$ requires 185.0602); $\nu_{\text{max}}$. 1483, 756 cm$^{-1}$; $\delta_H$(250 MHz; CDCl$_3$) 5.12 (2H, s, OCH$_2$), 6.98-7.08 (2H, m, Ar), 7.21-7.31 (1H, m, Ar), 7.46 (1H, d, J 5 Hz, Ar), 7.63 (1H, dd, J 5, 1 Hz, Ar), 8.31 (1H, s, Ar), 8.54 (1H, d, J 5 Hz, Ar); $\delta_C$(62.5 MHz; CDCl$_3$) 66.2 (CH$_2$), 116.1 (CH), 118.0 (CH), 120.8 (C), 122.6 (CH), 123.6 (CH), 124.4 (C), 126.1 (C), 146.2 (CH), 147.3 (CH), 150.1 (CH), 155.8 (C); $m/z$ 186 ($M^+$, 77%), 182 (100).

**Diethyl formylmethylphosphonate [22]**

A mixture of diethyl 2,2-diethoxyethylphosphonate (5 g, 19 mmol) and hydrochloric acid (18 ml, 2% aqueous solution) was refluxed for 10 min under a nitrogen atmosphere. The cooled solution was saturated with sodium chloride, and extracted with dichloromethane (3 x 50 ml). The combined organic extracts
were washed with sodium hydrogencarbonate (3 x 75 ml, 5% aqueous solution), water (3 x 75 ml), dried (MgSO$_4$), and evaporated. The residue was fractionally distilled under reduced pressure to yield the desired phosphonate ester as a colourless liquid (2.96 g, 84%), b.p. at 0.8 mmHg 100-103°C (lit., 59 101-103°C at 0.8 mmHg); $\nu_{\text{max}}$ 1729, 1275 cm$^{-1}$; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 1.35 (6H, t, $J$ 7 Hz, CH$_3$CH$_2$), 3.11 (2H, dd, $J$ 22, 3 Hz, PCH$_2$), 4.2 (4H, q, $J$ 7 Hz, CH$_3$CH$_2$), 9.70 (1H, dt, $J$ 3, 1 Hz, CHO); $\delta_{\text{C}}$ (62.5 MHz; CDCl$_3$) 16.2 (CH$_3$), 43.0 (d, $J$ 127 Hz, CH$_2$), 61.3 (CH$_2$), 192.8 (CH).

Diethyl formylmethylphosphonate $N,N$-dimethylhydrazone [23]

![Chemical structure](image)

A solution of diethyl formylmethylphosphonate [22] (800 mg, 4.4 mmol) in dichloromethane (10 ml) containing anhydrous magnesium sulfate (1.7 g) was cooled to 0°C. $N,N$-dimethylhydrazine (1.11 ml 14 mmol) was added dropwise to the reaction vessel over a period of 5 min. The reaction mixture was allowed to stir at room temperature for 3 h. The mixture was then filtered to remove magnesium sulfate and concentrated in vacuo to yield the desired hydrazone as a yellow liquid (927 mg, 94%), b.p. at 10 mmHg 122-124°C (lit., 49 122-124°C at 10 mmHg); $\nu_{\text{max}}$ 3478, 1670, 1621, 1257 cm$^{-1}$; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 1.32 (6H, t, $J$ 7 Hz, CH$_3$CH$_2$), 2.79 (6H, s, N(CH$_3$)$_2$), 2.83 (2H, dd, $J$ 22, 3.5 Hz, PCH$_2$), 4.12 (4H, q, $J$ 7 Hz, CH$_3$CH$_2$), 6.49 (1H, m, NCH).
Salicylaldehyde (5.0 g, 41 mmol) was added to a stirred suspension of anhydrous potassium carbonate (4.0 g) in dry ethanol (40 ml). To this suspension propargyl chloride (3.7 g, 50 mmol) was added dropwise. The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The suspension was then filtered to remove potassium carbonate and concentrated in vacuo. The residue was taken up into dichloromethane (50 ml), washed with sodium hydroxide solution (3 x 50 ml, 10% solution) and water (2 x 50 ml). The organic extract was dried (MgSO₄) and evaporated to yield the crude product which was chromatographed on silica gel (light petroleum : ethyl acetate 2:1), giving the ether as a pale yellow solid (5.7 g, 88%), m.p. 63-64°C; (Found : $M^+$ 160.0524, C₁₀H₆O₂ requires 160.0524); $\nu_{\text{max}}$ 3310, 2218, 1694, 1600 cm⁻¹; $\delta_H$ (250 MHz; CDCl₃) 2.57 (1H, t, 1 Hz, CCH), 4.83 (2H, s, OCH₂), 7.10 (2H, m, Ar), 7.57 (1H, m, Ar), 7.88 (1H, m, Ar), 10.52 (1H, s, CHO); $\delta_C$ (62.5 MHz; CDCl₃) 56.3 (CH₂), 76.4 (C), 77.6 (C), 113.1 (CH), 121.6 (CH), 125.4 (CH), 128.5 (C), 135.6 (CH), 159.6 (C), 188.0 (CH); $m/z$ 160 ($M^+$, 35%), 131 (100), 39 (58).
To a stirred solution of the phosphonate ester [23] (555 mg, 2.5 mmol) in tetrahydrofuran (5 ml) at -78°C was added n-butyllithium (1.88 ml 3.0 mmol). The solution was stirred for 10 min before the dropwise addition of the ether-aldehyde [23A] (300 mg, 1.8 mmol). The reaction mixture was stirred at -78°C for 30 min before being allowed to warm to room temperature for 3 h. The solvent was removed in vacuo and the crude residue was chromatographed on silica gel (diethyl ether) to yield a yellow solid (316 mg, 86 %), m.p. 88-89°C; (Found: $M^+$ 228.1263, C$_{14}$H$_{16}$N$_2$O requires 228.1266); $\nu$ max. 3309, 1676, 2359 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 2.53 (1H, s, CCH), 2.87 (6H, s, N(CH$_3$)$_2$), 4.75 (2H, s, OCH$_2$), 6.88-7.53 (7H, m, Ar + alkene + hydrazone-H); $\delta_C$ (62.5 MHz; CDCl$_3$) 43.3 (2xCH$_3$), 56.7 (CH$_2$), 76.1 (CH), 79.2 (C), 113.2 (CH), 122.3 (CH), 126.7 (C), 126.8 (CH), 127.4 (CH), 128.6 (CH), 128.7 (CH), 136.0 (C), 154.9 (CH); m/z 228 ($M^+$, 32%), 44 (100).

1-Chloro-3-phenylprop-2-yne

Ph=\equiv OH $\rightarrow$ Ph=\equiv Cl
Pyridine (1.4 g, 18 mmol) was added dropwise to a solution of thionyl chloride (2.0 g, 24 mmol) in chloroform (15 ml) at 0°C. This solution in turn was added dropwise to a cold solution of 3-phenylpropargyl alcohol (2.0 g, 15 mmol) in chloroform (15 ml). The mixture was stirred for 10 min followed by heating at reflux for 2 h. The cooled reaction mixture was washed with water (3 x 50 ml), dried (Na₂SO₄), and distilled to yield the product as a straw yellow liquid (1.8 g, 81%), b.p. at 0.1 mmHg 62-65°C (lit., 60 at 7 mmHg 99°C); ν_max. 3417, 3057, 2101, 1634, 1487 cm⁻¹; δ_H (250 MHz; CDCl₃) 4.41 (2H, s, CfuCl); 7.26-7.50 (5H, m, Ar); δ_C (62.5 MHz; CDCl₃) 31.1(CH₂), 83.7 (C), 86.3 (C), 121.9 (C), 128.3 (CH), 128.8 (CH), 131.8 (CH).

2-(3-Phenylpropynyloxy)benzaldehyde [24]

\[
\text{CHO} \quad \begin{array}{c}
\text{OH} \\
\downarrow
\end{array} \quad \text{CHO} \quad \begin{array}{c}
\text{Ph}
\end{array}
\]

Salicylaldehyde (1.0 g, 8.0 mmol) was added to a stirred suspension of anhydrous potassium carbonate (1.0 g) in dry ethanol (10 ml). To this suspension 1-chloro-3-phenylprop-2-yne (1.5 g, 10 mmol) was added dropwise. The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The suspension was then filtered to remove potassium carbonate and concentrated in vacuo. The residue was taken up into dichloromethane (50 ml), washed with sodium hydroxide solution (3 x 50 ml, 10% solution) and water (2
The organic extract was dried (MgSO₄) and evaporated to yield the crude product which was chromatographed on silica gel (light petroleum : ethyl acetate 2:1), giving the desired ether as a yellow solid (1.24 g, 65%), m.p. 82-83°C; (Found : $M^+$ 236.0837, C₁₆H₁₂O₂ requires 236.0837); $\nu_{max}$ 3311, 1695, 1600, 1219 cm⁻¹; $\delta_H$ (250 MHz; CDCl₃) 5.04 (2H, s, OCH₂), 7.00-7.30 (7H, m, Ar), 7.41 (1H, dt, J 10, 2 Hz, Ar), 7.86 (1H, dd, J 10, 2 Hz, Ar), 10.50 (1H, s, CHO); $\delta_C$ (62.5 MHz; CDCl₃) 56.2 (CH₂), 82.8 (C), 88.0 (C), 114.7 (CH), 122.3 (C), 122.4 (C), 126.6 (CH), 128.1 (CH), 128.2 (CH), 131.7 (CH), 132.1 (CH), 135.6 (CH), 160.0 (C), 187.5 (CH); $m/z$ 236 ($M^+$, 10%), 115 (100), 43 (32).

(E)-3-[2-(3-Phenylpropynyloxy)]propenal N,N-dimethylhydrazone

[25]

To a stirred solution of the phosphonate ester [23] (275 mg, 1.2 mmol) in tetrahydrofuran (5 ml) at -78°C was added n-butyllithium (1.0 ml 1.6 mmol). The solution was stirred for 10 min before the dropwise addition of the ether-aldehyde [24] (100 mg, 0.4 mmol). The reaction mixture was stirred at -78°C for 30 min before being allowed to warm to room temperature for 3 h. The solvent was removed in vacuo and the crude residue was chromatographed on
silica gel (diethyl ether) to yield a yellow semi-solid (117 mg, 91%), (Found: 
$M^+$ 304.1577, C$_{20}$H$_{20}$N$_2$O requires 304.1576); $\delta$$_H$ (250 MHz; CDCl$_3$) 2.86 (6H, 
s, N(CH$_3$)$_2$), 4.95 (2H, s, OCH$_2$), 6.97-7.52 (12H, m, Ar + alkene + hydrazone-
H); $\delta$$_C$ (62.5 MHz; CDCl$_3$) 42.7 (2xCH$_3$), 57.2 (CH$_2$), 83.9 (C), 87.3 (C), 112.9 
(CH), 121.6 (C), 122.4 (CH), 126.1 (C), 126.3 (CH), 126.9 (CH), 127.9 (CH), 
128.2 (CH), 128.3 (CH), 128.5 (CH), 131.7 (C), 136.4 (CH), 154.7 (CH); m/z 
304 ($M^+$, 86%), 44 (100).

4-Phenyl-5$H$-[1]-benzopyrano[3,4-c]pyridine [17]

![Chemical structure of 4-Phenyl-5$H$-[1]-benzopyrano[3,4-c]pyridine]

A solution of the ether-hydrazone [25] (20 mg, 0.01 mmol) in xylene (5 ml) 
was heated to reflux for 18 h under an inert atmosphere. The solvent was 
remove in vacuo to yield the crude product (14 mg, 60%). m.p. >300°C; (Found 
: $M^+$ 259.0997, C$_{18}$H$_{13}$NO requires 259.0998); $\nu_{\text{max}}$ 1624, 752 cm$^{-1}$; $\delta$$_H$ (250 
MHz; CDCl$_3$) 5.18 (2H, s, OCH$_2$), 6.99 (1H, d, J 8 Hz, Ar), 7.11 (1H, t, J 8 Hz, 
Ar), 7.32-7.55 (7H, m, Ar), 7.77 (1H, d, J 8 Hz, Ar), 8.69 (1H, d, J 5 Hz, Ar); 
$\delta$$_C$ (62.5 MHz; CDCl$_3$) 65.5 (CH$_2$), 115.1 (CH), 117.5 (CH), 122.4 (CH), 122.9 
(CH), 123.7 (CH), 124.2 (CH), 128.3 (C), 128.4 (CH), 128.5 (C), 128.6 (CH), 
128.7 (C), 128.8 (CH), 130.1 (C), 131.5 (C), 149.0 (CH); m/z 259 ($M^+$, 100%), 
77 (35%).
Salicylaldehyde (5.0 g, 41 mmol) was added to a stirred suspension of anhydrous potassium carbonate (4.0 g) in dry ethanol (40 ml). To this suspension cinnamyl bromide (9.8 g, 50 mmol) was added dropwise. The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The suspension was then filtered to remove potassium carbonate and concentrated in vacuo. The residue was taken up into dichloromethane (50 ml), washed with sodium hydroxide solution (3 x 50 ml, 10% solution) and water (2 x 50 ml). The organic extract was dried (MgSO₄) and evaporated to yield the crude product which was chromatographed on silica gel (light petroleum: ethyl acetate 2:1), giving the desired ether as a pale yellow solid (7.5 g, 78%), m.p. 128-129 °C; (Found : $M^+$ 238.0994, C₁₆H₁₄O₂ requires 238.0993); $v_{\text{max}}$ 1683, 1472 cm⁻¹; δH (250 MHz; CDCl₃) 4.82 (2H, d, $J$ 4 Hz, OCH₂), 6.46 (1H, dd, $J$ 16, 4 Hz, alkene), 6.86 (1H, d, $J$ 16 Hz, alkene), 7.29 (1H, m, Ar), 7.32-7.55 (7H, m, Ar), 7.90 (1H, d, $J$ 4 Hz, Ar), 10.60 (1H, s, CHO); δC (62.5 MHz; CDCl₃) 69.1 (CH₂), 112.9 (CH), 120.8 (CH), 123.4 (CH), 125.1 (CH), 126.5 (CH), 128.1 (CH), 128.4 (CH), 128.6 (C), 129.4 (CH), 133.4 (CH), 135.8 (CH), 136.1 (C), 189.7 (CH); $m/z$ 236 ($M^+$, 56%), 117 (100), 105 (78).
3-[2-(3-Phenyl-(E)-prop-2-enyloxy)]propenyl N,N-dimethylhydrazone [27]

To a stirred solution of the phosphonate ester [23] (555 mg, 2.5 mmol) in tetrahydrofuran (5 ml) at -78°C was added n-butyllithium (1.88 ml 3.0 mmol). The solution was stirred for 10 min before the dropwise addition of the ether-aldehyde [26A] (455 mg, 1.8 mmol). The reaction mixture was stirred at -78°C for 30 min before being allowed to warm to room temperature for 3 h. The solvent was removed in vacuo and the crude residue was chromatographed on silica gel (diethyl ether) to yield a yellow solid (489 mg, 83%), m.p. 149-150°C; (Found: $M^+$ 306.1737, C$_{20}$H$_{22}$N$_2$O requires 306.1738); $\nu$ max. 2386, 1596, 1465 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 2.94 (6H, s, N(C$_6$H$_5$)$_2$), 4.75 (2H, d, $J$ 6 Hz, OCH$_2$), 6.51 (1H, m, alkene), 6.96 (1H, d, $J$ 16 Hz, alkene), 7.08-7.37 (11H, m, Ar + alkene + hydrazone-H), 7.47 (1H, d, $J$ 6 Hz, alkene); $\delta_C$ (62.5 MHz; CDCl$_3$) 42.8 (2xCH$_3$), 69.1 (CH$_2$), 112.5 (CH), 121.1 (CH), 124.6 (CH), 125.4 (CH), 126.5 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 131.1 (C), 132.9 (CH), 136.4 (CH), 138.2 (C), 155.56 (C); $m/z$ 306 ($M^+$, 30%), 133 (80), 44 (100).
4-Phenyl-5H-[1]-benzopyrano[3,4-c]pyridine [17]

A solution of the ether-hydrazone [27] (20 mg, 0.01 mmol) in xylene (5 ml) was heated to reflux for 18 h under an inert atmosphere. The solvent was remove in vacuo to yield the crude product (18 mg, 80%), m.p. >300; (Found: \( M^+ 259.0997 \), \( C_{18}H_{13}NO \) requires 259.0998); \( \nu_{\text{max}} \) 1624, 752 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 5.18 (2H, s, OCH\(_2\)), 6.99 (1H, d, \( J \, 8 \, \text{Hz} \), Ar), 7.11 (1H, t, \( J \, 8 \, \text{Hz} \), Ar), 7.32-7.55 (7H, m, Ar), 7.77 (1H, d, \( J \, 5 \, \text{Hz} \), Ar), 8.69 (1H, d, \( J \, 5 \, \text{Hz} \), Ar); \( \delta_C \) (62.5 MHz; CDCl\(_3\)) 65.5 (CH\(_2\)), 115.1 (CH), 117.5 (CH), 122.4 (CH), 122.9 (CH), 123.7 (CH), 124.2 (CH), 128.3 (C), 128.4 (CH), 128.5 (C), 128.6 (CH), 128.7 (C), 128.8 (CH), 130.1 (C), 131.5 (C), 149.0 (CH); \( m/z \) 259 (\( M^+ \), 100%), 77 (35%).

(E)-3-(2-Nitrophenyl)propenal \( N,N \)-dimethylhydrazone [34]

A solution of 2-nitrocinnamaldehyde (1.21 g, 6.83 mmol) and \( N,N \)-dimethylhydrazine (0.51 ml, 6.62 mmol) in toluene (60 ml) was heated to reflux...
in a Dean-Stark apparatus for 4 h. The solvent was removed \textit{in vacuo} to yield the product as a red solid (0.87 g, 58\%), m.p. 37-38°C (lit., \textit{72} 37-38°C); \(\nu_{\text{max}}\) 1605, 1550, 1520, 1045 cm\(^{-1}\); \(\delta_{\text{H}}\) (250 MHz; CDCl\(_3\)) 2.99 (6H, s, N(CH\(_3\))\(_2\)), 6.98-7.13 (3H, m, alkene + hydrazone-H), 7.31 (1H, dt, \(J\ 8, 2\ \text{Hz}, \text{Ar}\)), 7.52 (1H, dt, \(J\ 8, 2\ \text{Hz}, \text{Ar}\)), 7.69 (1H, dd, \(J\ 8, 2\ \text{Hz}, \text{Ar}\)), 7.88 (1H, dd, \(J\ 8, 2\ \text{Hz}, \text{Ar}\)).

\textbf{(E)-3-(2-Aminophenyl)propenal \textit{N,N}-dimethylhydrazone [35]}

![Chemical Structure](image)

A mixture of the nitro-hydrazone [34] (0.57 g, 2.12 mmol) and FeSO\(_4\).7H\(_2\)O was heated to 80°C in a mixture of methanol (20 ml), ammonium hydroxide (7.5 ml, 25\% solution), and water (5 ml). After 3 h the reaction was cooled to room temperature, diluted with water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with water (2x 50 ml), dried (MgSO\(_4\)), evaporated, and the residue was chromatographed on silica gel (diethyl ether) to afford the desired product as a brown solid (134 mg, 27\%), m.p. 85-86°C (lit., \textit{72} 82-83°C); \(\nu_{\text{max}}\) 2921, 1306, 1266, 1151, 1023 cm\(^{-1}\); \(\delta_{\text{H}}\) (250 MHz; CDCl\(_3\)) 2.93 (6H, s, N(CH\(_3\))\(_2\)), 3.76 (2H, br s, NH\(_2\)), 6.67-6.77
(3H, overlapping m, alkene + hydrazone-H), 6.80 (1H, m, Ar), 7.08 (1H, td, J 8, 2 Hz, Ar), 7.19 (1H, m, Ar), 7.34 (1H, dd, J 8, 2 Hz, Ar).

3-Phenylpropynoyl chloride

\[
\begin{align*}
\text{Ph} & \equiv \text{C} & \text{O} \\
\rightarrow & \text{Ph} & \equiv \text{C} & \text{Cl}
\end{align*}
\]

A mixture of phenylpropynoic acid (472 mg, 3.2 mmol) and thionyl chloride (5 ml, large excess) was heated to 60°C for 3 h. The excess thionyl chloride was evaporated and the residue distilled to yield the acid chloride as a yellow liquid (323 mg, 61%), b.p. at 0.6 mmHg 50°C (lit.,\textsuperscript{73} b.p. at 1 mmHg 56°C), \( \nu_{\text{max}} \) 1779, 742 cm\textsuperscript{-1}.

3-[2-(3-Phenyl-2-propynoylamino)phenyl]propenal \( N,N \)-dimethyl-hydrazone [36]

\[
\begin{align*}
\text{NH}_2 & \rightarrow \text{Ph} \equiv \text{C} & \text{N} & \equiv \text{NMe}_2
\end{align*}
\]

A stirred suspension of the amino-hydrazone [35] (100 mg, 0.5 mmol) in a solution of sodium hydroxide (400 mg in 40 ml), was cooled to 0°C. To this mixture was added 3-phenylpropynoyl chloride (120 mg, 0.7 mmol) portion wise, with vigorous shaking. Upon addition of all the acid chloride the mixture
was stirred for a further 1 h. The mixture was then diluted with water (100 ml) and extracted with dichloromethane (3 x 75 ml). The combined organic extracts were dried (MgSO₄), and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel (light petroleum : ethyl acetate 2:1) to yield the desired product as a yellow solid (127 mg, 76%), m.p. 117-118°C; (Found: M⁺ 317.1528, C₂₀H₁₉N₃O requires 317.1528); νₚₚₑₜmax. 3216, 2213, 1674 cm⁻¹; δH (250 MHz; CDCl₃) 2.95 (6H, s, N(CH₃)₂), 6.66-7.80 (12H multiplet, Ar + alkene + hydrazone-H); δC (62.5 MHz; CDCl₃) 42.6 (2xCH₃), 88.2 (C), 95.8 (C), 118.7 (CH), 120.3 (CH), 124.0 (CH), 126.4 (CH), 126.8 (C), 127.9 (CH), 128.1 (C), 128.2 (CH), 129.7 (CH), 132.1 (CH), 136.5 (C), 136.7 (CH), 154.7 (CH), 180.5 (C); m/z 317 (M⁺, 13%), 273 (96), 120 (100), 44 (42).

**N-(2-Hydroxymethylphenyl)-3-phenylpropynamide [37]**

![Chemical structure](image)

A stirred suspension of the 2-aminobenzy! alcohol (500 mg, 4.0 mmol) in a solution of sodium hydroxide (2.0 g in 125 ml), was cooled to 0°C. To this mixture was added 3-phenylpropynoyl chloride (820 mg, 5.0 mmol) portion wise, with vigorous shaking. Upon addition of all the acid chloride the mixture was stirred for a further 1 h. The mixture was then diluted with water (100 ml)
and extracted with dichloromethane (3 x 75 ml). The combined organic extracts were dried (MgSO₄), and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel (light petroleum : ethyl acetate 2:1) to yield the desired product as a yellow solid (393 mg, 40%), m.p. 101-102°C; (Found : M⁺ 251.0946, C₁₆H₁₃NO₂ requires 251.0946); νmax. 3253, 2260, 1636 cm⁻¹; δH (250 MHz; CDCl₃) 2.59 (1H, br s, OH, exchangeable with D₂O), 4.75 (2H, s, OCH₂), 7.27-7.59 (8H, m, Ar), 8.10 (1H, d, J 8 Hz, Ar), 9.07 (1H, br s, NH, exchangeable with D₂O); δC (62.5 MHz; CDCl₃) 49.7 (CH₂), 72.3 (C), 85.3 (CH), 119.9 (CH), 122.7 (C), 125.0 (CH), 128.7 (CH), 128.8 (CH), 129.9 (C), 130.2(CH), 132.6(CH), 136.5 (C), 157.7 (C); m/z 251 (M⁺, 17%), 129 (100).

N-(2-Formylphenyl)-3-phenylpropynamide [38]

![Chemical structure](image)

A mixture of pyridinium chlorochromate (342 mg, 4.6 mmol) and Celite (342 mg) in dichloromethane (5 ml), was stirred for 30 min to achieve homogeneity. To this stirred mixture was added a solution of the alcohol [37] (200 mg, 0.8 mmol) in dichloromethane (1 ml). The mixture was stirred for a further 2 h at room temperature. Excess pyridinium chlorochromate was precipitated by the
addition of diethyl ether (20 ml). The resulting suspension was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a yellow oil which was then purified by flash chromatography on silica gel (light petroleum : ethyl acetate 2:1), to afford the desired aldehyde as a pale yellow solid (175 mg, 88%), m.p. 94-96°C; (Found: $M^+$ 249.0789 C$_{16}$H$_{11}$N0$_2$ requires 249.0789); $\nu_{\text{max.}}$ 2260, 1674, 1658 cm$^{-1}$; $\delta$$_R$ (250 MHz; CDCl$_3$) 7.26-7.72 (8H, m, Ar), 8.73 (1H, d, $J$ 8 Hz, Ar), 9.95 (1H, s, CHO), 11.49 (1H, br s, NH, exchangeable with D$_2$O); $\delta$$_C$ (62.5 MHz; CDCl$_3$) 84.9 (C), 85.6 (C), 119.7 (CH), 120.4 (CH), 123.6 (C), 125.3 (CH), 128.5 (CH), 130.5 (C), 132.8 (CH), 136.1 (C), 140.0 (CH), 153.2 (CH), 157.9 (C), 195.3 (CH); $m/z$ 249 ($M^+$, 10%), 129 (100).

3-[2-(3-phenyl-2-propynoylamino)phenyl]propenal $N,N$-dimethylhydrazone [36]

The amido-aldehyde and the phosphonate ester were dried prior to use by azeotropic distillation with toluene at room temperature.

A solution of the phosphonate ester [23] (622 mg, 2.8 mmol) in dry tetrahydrofuran (8 ml) was cooled to -78°C under a nitrogen atmosphere. To this cooled solution $n$-butyllithium (2.13 ml, 3.4 mmol) was added dropwise.
The solution was stirred for 10 min, this was followed by dropwise addition of the amido-aldehyde [38] (350 mg, 1.4 mmol). The resulting pale yellow solution was stirred for 30 min at -78°C and then allowed to warm up to room temperature and stirred for a further 3 h. The reaction mixture was quenched with saturated ammonium chloride solution and washed with diethyl ether (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), water (3 x 50 ml), dried (MgSO₄), and concentrated in vacuo. The crude residue was chromatographed on silica gel (diethyl ether : light petroleum 10:1) to yield the desired compound as a yellow solid (240 mg, 52%), m.p. 117-118°C; (Found: $M^+$ 317.1528, C₂₀H₁₉N₃O requires 317.1528); $\nu_{\text{max}}$ 3216, 2213, 1674 cm⁻¹; $\delta_H$ (250 MHz; CDCl₃) 2.95 (6H, s, N(CH₃)₂), 6.66-7.80 (12 H multiplet, Ar); $\delta_C$ (62.5 MHz; CDCl₃) 42.6 (2xCH₃), 88.2 (C), 95.8 (C), 118.7 (CH), 120.3 (CH), 124.0 (CH), 126.4 (CH), 126.8 (C), 127.9 (CH), 128.1 (C), 128.2 (CH), 132.1 (C), 136.5 (C), 136.7 (CH), 154.7 (CH), 180.5 (C); $m/z$ 317 ($M^+$, 13%), 273 (96), 120 (100), 44 (42).

### 4-Phenylbenzo[2,7-c]napththyridin-5-(6H)-one [30]

![Image of chemical structure]
The amido-cinnamaldehyde-hydrazone [36] (75 mg, 2.3 mmol) was suspended in dry mesitylene (5 ml) and heated at reflux under a nitrogen atmosphere for 5 h. The solvent was removed in vacuo and the crude residue was chromatographed on silica gel (diethyl ether : light petroleum 15:1). The main product was isolated (12 mg, 16 %). (At low temperature Found: $M^+$ 317.1528 $C_{20}H_{19}N_3O$ requires 317.1528. At temperature >200°C Found: $M^+$ 272.0949 $C_{18}H_{12}N_2O$ requires 272.0949); $\delta_H$ (250 MHz; CDCl₃) 2.85 (6H, s, N(C₆H₅)_2), 6.98-7.56 (11H, m, Ar); $m/z$ (>200°C) 317 (5), 272 ($M^+$, 62%), 217 (100), 141(55), 77(95).

(E)-3-[(2-benzoylamino)phenyl]propenal [40]

Quinoline (20 g, 155 mmol) was added to aqueous NaOH (40 ml, 10% solution, 140 ml H₂O). To this suspension was added benzoyl chloride (42 g, 300 mmol) portionwise with shaking. Aqueous NaOH (120 ml, 10% solution) was also added portionwise to keep the solution alkaline at all times. Upon standing for 30 min the precipitate was filtered and washed with dilute hydrochloric acid. The resulting white powder was washed with diethyl ether (100 ml) and filtered to yield the desired aldehyde as a white powder (7.0 g, 18%), m.p. 178-179°C
(E)-3-[(2-benzoylamino)phenyl]propenyl N,N-dimethylhydrazone

A mixture of 3-[(2-benzoylamino)phenyl]propenal [40] (8.0 g, 32 mmol) and N,N-dimethylhydrazine (2.2 g, 35 mmol) were heated at reflux in toluene (160 ml) under Dean-Stark conditions for 2 h. Upon cooling the desired product precipitated as a pale yellow powder (7.8 g, 84%), m.p. 185-186°C (lit.,72 184-185°C; \( \nu_{\text{max}} \). 3260, 1671, 1578, 1495 cm\(^{-1}\); \( \delta_{\text{H}} \) (250 MHz; CDCl\(_3\)) 1.61 (1H, s, NH, confirmed by D\(_2\)O exchange), 2.93 (6H, s, N(CH\(_3\))\(_2\)), 6.68 (1H, d, \( J \) 16 Hz, alkene), 6.92 (1H, dd, \( J \) 16, 8, Hz, alkene), 7.06-7.31 (5H, m, Ar), 7.46-7.57 (4H, m, Ar + alkene + hydrazone-H), 7.86 (1H, dd, \( J \) 16, 8 Hz, alkene); \( \delta_{\text{C}} \) (62.5 MHz; CDCl\(_3\)) 122.2 (C), 126.5 (CH), 128.4 (CH), 129.3 (CH), 129.8 (C), 130.7 (CH), 131.9 (C), 132.2 (CH), 133.4 (CH), 135.6 (CH), 138.7 (CH), 148.4 (CH), 150.3 (CH), 167.9 (C), 195.3 (CH).
MHz; CDCl$_3$) 42.3 (2xCH$_3$), 98.2 (C), 122.1 (CH), 123.8 (CH), 125.4 (CH), 126.9 (CH), 128.2 (CH), 129.6 (CH), 130.1 (C), 131.7 (CH), 132.4 (CH), 133.2 (CH), 135.4 (CH), 138.7 (C), 160.7 (C).

(E)-3-(((N-propargyl)-2-benzoylamino)phenyl)propenal N,N-dimethylhydrazone [42]

![](image)

A solution of 3-((2-benzoylamino)phenyl)propenal N,N-dimethylhydrazone [41] (1.0 g, 3.4 mmol) in DMF (5 ml) was added dropwise to a stirred suspension of potassium hydride (0.15 g, 3.8 mmol) in DMF (5 ml) and stirred at 25°C for 1 h. Propargyl chloride (0.25 g, 3.5 mmol) was added and the reaction mixture was heated at 60°C for 18 h. Upon cooling the mixture was diluted with dichloromethane (50 ml) and washed with brine (4 x 50 ml) and water (3 x 50 ml). The organic extracts were pooled, dried (Na$_2$SO$_4$), and concentrated in vacuo. The crude residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale yellow solid (0.94 g, 83%), m.p. 137-138°C; (Found : C, 75.88; H, 6.28; N, 12.44. C$_{21}$H$_{21}$N$_3$O requires C, 76.09; H, 6.39; N, 12.69); (Found : $M^+$ 331.1684, C$_{21}$H$_{21}$N$_3$O requires 331.1684); $v_{max}$. 3442, 3308, 1641, 1618, 1482 cm$^{-1}$; $\delta_H$ (400 MHz; CDCl$_3$) 2.22 (1H, t, $J$ 1 Hz, CCH), 2.90 (6H, s, N(CH$_3$)$_2$), 4.21 (1H, dd, $J$ 17, 2 Hz,
NCHH), 4.91 (1H, dd, J 17, 2 Hz, NCHH), 6.73 (1H, d, J 16 Hz, alkene), 6.86 (1H, d, J 8 Hz, Ar), 6.94-7.20 (8H, m, Ar + hydrazone-H), 7.25 (1H, dd, J 16, 8 Hz, alkene), 7.51 (1H, d, J 8 Hz, alkene); δC (100 MHz; CDCl₃) 39.8 (CH₂), 43.1 (2xCH₃), 72.8 (CH), 78.9 (C), 125.3 (CH), 126.1 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 128.8 (CH), 130.6 (C), 131.0 (C), 134.4 (CH), 135.2 (CH), 135.4 (CH), 140.0 (CH), 171.26 (C); m/z 346 (M⁺, 25%), 134 (80), 44 (100).

(E)-3-[(N-(3-Phenylpropynyl)-2-benzoylamino)phenyl]propenal N,N-dimethylhydrazone [43]

A solution of the benzoylamino hydrazone [41] (1.0 g, 3.4 mmol) in DMF (5 ml) was added dropwise to a stirred suspension of potassium hydride (0.15 g, 3.8 mmol) in DMF (5 ml) and stirred at 25°C for 1 h. 3-Phenylpropargyl chloride (0.57 g, 3.5 mmol) was added and the reaction mixture was heated at 60°C for 18 h. Upon cooling the mixture was diluted with dichloromethane (50 ml) and washed with brine (4 x 50 ml) and water (3 x 50 ml). The organic extracts were pooled, dried (Na₂SO₄), and concentrated in vacuo. The crude residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale orange solid (1.15 g, 83%), m.p. 184-186°C; (Found: M⁺ 407.1997, C₂₇H₂₅N₃O requires 407.1997); νmax 3433, 2197, 973, 762 cm⁻¹; δH
(250 MHz; CDCl₃) 2.93 (6H, s, N(CH₃)₂), 4.59 (1H, d, J 17 Hz, NCHH), 5.05 (1H, d, J 17 Hz, NCHH), 6.86 (1H, t, J 16 Hz, alkene), 7.11-7.68 (15H, m, Ar + alkene + hydrazone-H), 7.90 (1H, d, J 8 Hz, alkene); δC (62.5 MHz; CDCl₃) 37.1 (CH₂), 42.6 (2xCH₃), 81.0 (C), 88.6 (C), 118.7 (CH), 120.3 (CH), 122.3 (C), 124.0 (CH), 126.4 (CH), 126.8 (C), 127.0 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.5 (CH), 132.1 (CH), 134.5 (C), 135.6 (CH), 138.5 (C), 154.7 (CH), 163.4 (C); m/z 407 (M⁺, 25%), 115(55), 105 (80), 44 (100).

**6-benzoyl-4-phenyl-5,6-dihydrobenzo[2,7-c]naphthyridine [31]**

\[
\text{NMe}_2 \quad \text{Ph} \quad \text{COPh}
\]

A solution of the diene hydrazone [43] (50 mg, 0.1 mmol) in mesitylene (5 ml) was heated at reflux for 18 h. Upon cooling the solvent was removed *in vacuo*, the residue was chromatographed on silica gel (diethyl ether) to give the desired product as a pale brown solid (38 mg, 87%); m.p. >300°C; (Found : M⁺ 362.1416, C₂₃H₁₈N₂O requires 362.1419); νmax 3429, 1634 cm⁻¹; δH (250 MHz; CDCl₃) 5.01 (2H, s, NCH₂), 7.16-7.45 (13H, m, Ar), 7.63 (1H, d, J 5 Hz, Ar), 7.80 (1H, d, J 5 Hz, Ar), 8.68 (1H, d, J 5 Hz, Ar); δC (62.5 MHz; CDCl₃) 52.5 (CH₂), 117.6 120.2 (CH), 120.9 (CH), 123.7 (CH), 124.6 (CH), 127.0 (CH), 127.1 (CH), 128.3 (CH), 129.0 (CH), 129.3 (C), 129.5 (CH), 130.3 (CH), 134.5 (C).
(C), 139.2 (C), 139.7 (C), 148.1 (CH), 140.5 (C), 159.1 (C), 163.4 (C); m/z 362
(M⁺, 18%), 105 (100), 77 (40).

(E)-3-[N-(3-Phenyl-(E)-prop-2-enyl)-2-benzoylamino)phenyl]-
propenal N,N-dimethylhydrazone [44]

A solution of 3-((2-benzoylamino)phenyl)propenal N,N-dimethylhydrazone
[41] (1.0 g, 3.4 mmol) in DMF (5 ml) was added dropwise to a stirred
suspension of potassium hydride (0.15 g, 3.8 mmol) in DMF (5 ml) and stirred
at 25°C for 1 h. Cinnamoyl chloride (0.55 g, 3.5 mmol) was added and the
reaction mixture was heated at 60°C for 18 h. Upon cooling the mixture was
diluted with dichloromethane (50 ml) and washed with brine (4 x 50 ml) and
water (3 x 50 ml). The organic extracts were pooled, dried (Na₂SO₄), and
concentrated in vacuo. The crude residue was chromatographed on silica gel
(diethyl ether) to yield the desired product as a pale yellow solid (510 mg,
66%), m.p. 127-129°C; (Found : M⁺ 409.2155, C₂₇H₂₇N₃O requires 409.2154);
ν max. 3418, 1647, 967 cm⁻¹; δ H (250 MHz; CDCl₃) 2.96 (6H, s, N(CH₃)₂), 4.25
(1H, ddd, J 17, 5, 1 Hz, NCHH), 5.09 (1H, ddd, J 17, 5, 1 Hz, NCHH), 6.53
(2H, m, alkene), 6.83-7.40 (16H, m, Ar + alkene + hydrazone-H), 7.68 (1H, d, J
5 Hz, alkene); δ C (62.5 MHz; CDCl₃) 42.3 (2xCH₃), 53.4 (CH₂), 118.7 (CH),
118.8 (CH), 119.3 (CH), 120.3 (CH), 121.8 (CH), 123.4 (CH), 124.0 (CH),
126.2 (CH), 126.4 (CH), 126.8 (C), 127.0 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 129.9 (CH), 134.5 (C), 134.9 (C), 138.8 (C), 154.7 (CH), 163.4 (C); m/z 409 (M⁺, 33%), 105 (56), 44 (100).

6-benzoyl-3-dimethylamino-4-phenyl-3,4,4a,5,6,10b-hexahydrobenzo[2,7-c]naphthyridine [32]

![Chemical Structure]

A solution of the diene [44] (50 mg, 0.1 mmol) in mesitylene (5 ml) was heated at reflux for 18 h. Upon cooling the solvent was removed in vacuo, the residue was chromatographed on silica gel (diethyl ether) to give the desired product as a pale brown oil (27 mg, 54%); (Found: MH⁺ 410.2233, C₂₇H₂₇N₃O + H requires 410.2232); ν₁₆₆₄, 768 cm⁻¹; δₕ (250 MHz; CDCl₃) 2.43 (6H, s, N(C₆H₅)₂), 2.98 (1H, dd, J₄, 2 Hz, CH), 3.55 (1H, d, J 11 Hz), 3.79 (1H, dt, J 11, 2 Hz, CH), 4.11 (1H, d, J 9 Hz, CH), 5.32 (1H, dd, J 9, 2 Hz, CH), 6.46 (1H, d, J 8 Hz, alkene), 6.57 (1H, dd, J 8, 4 Hz, alkene), 7.17–7.55 (14H, multiplet, Ar); δ₁₃C (62.5 MHz; CDCl₃) 35.1 (CH), 46.2 (2×CH₃), 49.7 (CH₂), 65.5 (CH), 98.3 (CH), 122.2 (CH), 122.9 (CH), 123.8 (CH), 125.4 (CH), 126.3 (CH) 126.9 (CH), 127.5 (CH), 128.4 (CH), 129.3 (CH), 129.6 (C), 131.5 (CH), 134.2 (C), 135.4 (CH), 139.5 (C), 148.1 (CH), 159.8 (C), 168.1 (C); m/z 410 (MH⁺, 25%), 105 (100).
4.3 Experimental for Chapter 3

bi-[(E)-3-(2-Propynyloxyphenyl)propenal N,N-dimethylhydrazone] [28]

(E)-3-(2-Propargyloxyphenyl) propenal N,N-dimethylhydrazone [21] (100 mg, 0.4 mmol) and copper (II) acetate monohydrate (200 mg, 1.0 mmol) were heated in a mixture of pyridine (10 ml), methanol (10 ml) and diethyl ether (40 ml) for 18 h. The cooled mixture was filtered and concentrated in vacuo. The residue was washed with dilute hydrochloric acid (50 ml), extracted with dichloromethane (50 ml) and washed with brine (2 x 50 ml) and water (2 x 50 ml). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale brown solid (98 mg, 98%), m.p. 187-188°C; (Found: $M^+$ 455.2367 C₂₈H₃₀N₄O₂+H requires, 455.2367); $\nu_{\max}$. 2268, 1695, 1600, 962 cm⁻¹; $\delta_H$ (250 MHz; CDCl₃) 2.85 (6H, s, N(CH₃)₂), 4.76 (2H, s, OCH₂), 6.89 (1H, m, alkene), 7.18-7.28 (5H, m, Ar + hydrazone-H), 7.55 (1H, m, alkene); $\delta_C$ (62.5 MHz; CDCl₃) 43.2 (2xCH₃), 57.2 (CH₂), 71.3 (C), 74.5 (C), 112.9 (CH), 122.1 (CH), 126.2 (CH), 126.8 (CH), 127.1 (C), 128.0 (CH), 128.6 (CH), 137.3 (CH), 155.4 (C); m/z 455 ($M^+$, 42%), 227 (73), 44 (100).
4,4’-bi-{5H-[1]-benzopyrano[3,4-c]pyridine} [47]

A solution of the dimer [28] (50 mg, 0.1 mmol) in xylene (5 ml) was heated at reflux for 3 h. Upon cooling the solution was removed in vacuo to yield the desired product as a brown solid (35 mg, 87%), m.p. >300°C; ν max. 1644, 738 cm⁻¹; (Found : M⁺ 364.1212, C₂₄H₁₆N₂O₂ requires 364.1211); δH (250 MHz; CDCl₃) 5.33 (2H, s, OCH₃), 7.02 (1H, dd, J 8, 1 Hz, Ar), 7.12 (1H, dd, J 8, 1 Hz, Ar), 7.34 (1H, dt, J 5,1 Hz, Ar), 7.63 (1H, d, J 5 Hz, Ar), 7.80 (1H, dd, J 5, 1 Hz, Ar), 8.63 (1H, d, J 5 Hz, Ar); δC (62.5 MHz; CDCl₃) 75.2 (CH₂), 114.7 (CH), 117.6 (CH), 120.6 (CH), 123.8 (CH), 127.9 (CH), 129.3 (C), 129.8 (CH), 148.1 (CH), 149.5 (C), 157.2 (C), 159.1 (C); m/z 364 (M⁺, 75%).

Dodeca-5,7-diyn-1,12-diol [55]

5-Hexyn-1-ol (100 mg, 1.0 mmol) and copper (II) acetate monohydrate (407 mg, 2.0 mmol) were heated in a mixture of pyridine (10 ml), methanol (10 ml) and diethyl ether (40 ml) for 18 h. The cooled mixture was filtered and concentrated in vacuo. The residue was washed with dilute hydrochloric acid (50 ml), extracted with dichloromethane (50 ml) and washed with brine (2 x 50
ml) and water (2 x 50 ml). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale yellow solid (179 mg, 83%), m.p. 67-69°C, (Found: M⁺ 194.1305, C₁₂H₁₈O₂ requires 194.1306); νmax 3633, 2218, 1372 cm⁻¹, δH (250 MHz; CDCl₃) 1.54-1.73 (4H, m, -CH₂-), 2.29 (2H, t, J 7 Hz, CCCH₂-), 3.67 (2H, t, J 7 Hz, OCH₂); δC (62.5 MHz; CDCl₃) 18.9 (CH₂), 24.5 (CH₂), 31.7 (CH₂), 62.2 (CH₂), 66.1 (C), 74.3 (C); m/z 194 (M⁺, 25%), 111 (100), 45 (65).

**Dodeca-5,7-diyne-1,12-dial [56]**

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A mixture of diol [55] (261 mg, 2.1 mmol) and pyridinium dichromate (2.2 g, 6.4 mmol) and Celite (2.5 g) in dichloromethane (40 ml) were stirred at 25 °C for 3 h. Upon completion of the reaction the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to give a crude residue which was chromatographed on silica gel (diethyl ether). This afforded the desired product as a colourless solid (267 mg, 92%) m.p. 89-91°C, (Found: M⁺ 190.0994, C₁₂H₁₄O₂ requires 190.0994); νmax 2224, 1728 cm⁻¹; δH (250 MHz; CDCl₃) 1.82 (2H, quint, J 7 Hz, -CH₂-), 2.37 (2H, t, J 7 Hz, CCCH₂-), 2.61 (2H, dt, J 7, 1 Hz, CH₂CHO), 9.80 (1H, t, J 1 Hz, CHO); δC (62.5 MHz; CDCl₃)
Dodeca-5,7-diyne-1,12-dial \( N,N \)-dimethylhydrazone [57]

A solution of diethyl formylmethylphosphonate \( N,N \)-dimethylhydrazone [23] (350 mg, 1.6 mmol) in dry tetrahydrofuran (2 ml) was cooled to -78°C under a nitrogen atmosphere. To this cooled solution \( n \)-butyllithium (1.0 ml, 1.6 mmol) was added dropwise. The solution was stirred for 10 min, this was followed by dropwise addition of the di-aldehyde [56] (100 mg, 0.5 mmol). The resulting pale yellow solution was stirred for 30 min at -78°C and then allowed to warm up to room temperature and stir for a further 3 h. The reaction mixture was quenched with saturated ammonium chloride solution and washed with diethyl ether (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), water (3 x 50 ml), dried (MgSO\(_4\)), and concentrated in vacuo. The crude residue was chromatographed on silica gel (diethyl ether : light petroleum 10:1) to yield the desired compound as a pale yellow solid (155 mg, 98%), m.p. 121-124°C, (Found: \( M^+ \) 326.2470, \( C_{20}H_{30}N_4 \) requires 326.2470), \( \nu_{\text{max}} \) 2228, 1648, 962 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 1.64 (2H, t, \( J \) 7 Hz, CH\(_2\)-), 2.19-2.39 (4H, m, -CH\(_2\)-), 2.82 (6H, s, N(CH\(_3\))\(_2\)), 5.75 (1H, dt, \( J \) 16, 8 Hz, alkene), 6.21 (1H, ddt, \( J \) 16, 8, 1 Hz, alkene), 6.99 (1H, d, \( J \) 8 Hz, hydrazone-H); \( \delta_C \) (62.5 MHz;
A solution of the dial hydrazone [57] (74 mg, 0.2 mmol) in xylene (2 ml) was heated at reflux for 3 h. Upon cooling the solvent was removed in vacuo and the crude residue was chromatographed on silica gel (diethyl ether) to give the desired product as a dark yellow solid (36 mg, 76%), m.p. 187-188°C, (Found: $M^+$ 236.1315, $C_{16}H_{16}N_2$ requires 236.1313); $\lambda_{\text{max}}$ (nm) ($\epsilon$) 209 (13900), 279 (2440); $\nu_{\text{max}}$ 1618, 913 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 2.14 (2H, quint, $J_7$ Hz, -CH$_2$CH$_2$CH$_2$-), 2.89 (2H, t, $J_7$ Hz, -CH$_2$CH$_2$CH$_2$-), 3.11 (2H, t, $J_7$ Hz, -CH$_2$CH$_2$CH$_2$-), 7.17 (1H, d, $J_5$ Hz, Ar), 8.41 (1H, d, $J_5$ Hz, Ar); $\delta_C$ (62.5 MHz; CDCl$_3$) 25.5 (CH$_2$), 35.4 (CH$_2$), 38.3 (CH$_2$), 120.6 (CH), 137.1 (C), 148.8 (CH), 149.5 (C), 157.2 (C); $m/z$ 236 ($M^+$, 100%).
Citronellal (100 mg, 0.6 mmol) was added to a stirred mixture of carbon
tetraiodomethane (400 mg, 1.2 mmol) and triphenylphosphine (630 mg, 2.4 mmol)
in dichloromethane (5 ml) at 0 °C for 5 min. The crude mixture was filtered
through a pad of silica gel to yield the desired bromo-olefin as a pale yellow oil
(183 mg, 91%), (Found: $M^+$ 311.9777, C$_{11}$H$_{13}$Br$_2$ requires 311.9775); $\nu_{\text{max}}$
3056, 1640, 983 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 0.94 (3H, d, $J$ 5 Hz, CH$_3$CH),
1.17-1.36 (2H, m, CH$_2$), 1.54 (3H, s, CH$_3$), 1.68 (3H, s, CH$_3$), 1.90-2.16 (4H,
m, CH$_3$CH$_2$), 5.08 (1H, dt, $J$ 8, 5, CH$_3$CH), 6.40 (1H, t, $J$ 8 Hz, alkene), 6.82
(1H, t, $J$ 8 Hz, alkene); $\delta_C$ (62.5 MHz; CDCl$_3$) 19.3 (CH$_3$), 19.4 (CH$_3$), 23.0
(CH$_2$), 23.7 (CH$_2$), 25.3 (CH$_3$), 29.9 (CH), 36.2 (CH$_2$), 104.1 (C), 122.4 (CH),
125.8 (C), 133.2 (C); $m/z$ 310 ($M^+$, 18%), 172 (100), 42 (65).

(4R)-(+-)1,1-Dibromo-4,8-dimethylnona-1,7-diene [61]
(4R)-(+)\text{-}4,8\text{-}\text{Dimethylnon}-7\text{-}ene\text{-}1\text{-}yne [62]

A solution of crude dibromoolefin [61] (174 mg, 0.6 mmol) in THF (2 ml) was treated with n\text{-}butyllithium (731 \mu l, 1.2 mmol) at -78 °C for 2 h. The dilithiated species was then treated with excess water and extracted with diethyl ether. Concentration of the organic extracts in vacuo yielded the desired product as a pale yellow oil (73 mg, 87%), (Found: \(M^+\) 150.1408, \(\text{C}_{11}\text{H}_{18}\) requires 150.1408); \(\nu_{\text{max}}\) 3312, 3063, 2217, 972 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 0.96 (3H, d, \(J 5 \text{ Hz, } \text{CH}_3\text{CH}\)), 1.38 (2H, m, CH\(_2\)), 1.61 (3H, s, CH\(_3\)), 1.65 (1H, s, CH), 1.68 (3H, s, CH\(_3\)), 1.93-2.24 (4H, m, CH\(_2\)CH\(_2\)), 5.09 (1H, dt, \(J 8,5 \text{ Hz, } \text{CH}_3\text{CH}\)), 6.38 (1H, t, \(J 8 \text{ Hz, alkene}\)); \(\delta_C\) (62.5 MHz; CDCl\(_3\)) 19.4 (CH\(_3\)), 19.8 (CH\(_3\)), 23.1 (CH\(_2\)), 25.3 (CH\(_3\)), 27.0 (CH\(_2\)), 30.5 (CH), 36.3 (CH\(_2\)), 66.2 (CH), 83.2 (C), 125.8 (CH), 133.2 (C); \(m/z\) 150 (\(M^+\), 100%), 39 (66).
A solution of selenium dioxide (95 mg, 0.9 mmol) in ethanol (5 ml) was added dropwise to the ene-yne [62] (47 mg, 0.3 mmol) dissolved in methanol (5 ml). Ten minutes was required for the addition which was carried out at 55 °C. The mixture was stirred for 13 h at reflux, cooled, the selenium removed by filtration, and the solvent removed in vacuo. The residue was taken up in diethyl ether (50 ml), washed with sodium bicarbonate (50 ml, 10% solution) and brine (3 x 50 ml), and dried (Na₂SO₄). Evaporation of the organic extract gave a dark orange oil, which, as shown by NMR analysis, consisted of a mixture of the desired product and the allylic alcohol [63]. The total material was dissolved in hexane (5 ml) and added to a stirred suspension of manganese dioxide (450 mg, 5.0 mmol) in hexane (150 ml). After being stirred for 5 h at 25 °C, the mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel (ethyl acetate) to yield the desired product as an orange oil (40 mg, 78%), (Found: $M^+$ 164.1205, C₁₁H₁₆O requires 164.1201); $ν_{max}$ 3308, 2203, 1709, 1695, 1645 cm⁻¹; δH (250 MHz; CDCl₃) 0.92 (2H, m, CH₂), 1.05 (2H, m, CH₂), 1.38 (3H, d, J 5 Hz, CH₃CH), 1.65 (1H, br s, CCH), 1.86 (3H, s, CH₃), 2.29 (2H, m, CH₂), 4.80 (1H,
dt, J 8, 5 Hz, CH₃CH), 6.43 (1H, t, J 8 Hz, alkene), 9.39 (1H, s, CHO); δc (62.5 MHz; CDCl₃) 19.5 (CH₃), 22.9 (CH₂), 27.4 (CH₂), 29.3 (CH₃), 31.2 (CH), 36.0 (CH₂), 68.2 (CH), 83.9 (C), 141.1 (C), 147.7 (CH), 190.2 (CH); m/z 164 (M⁺, 100%), 56 (75).

(6R)-(−)-2,6-Dimethylnon-2-en-8-ynal N,N-dimethylhydrazone [67]

A mixture of the aldehyde [64] (40 mg, 0.3 mmol), N,N-dimethylhydrazine (30 µl, 0.4 mmol) and sodium sulfate (500 mg, excess) in dichloromethane (5 ml) was stirred for 18 h at 25 °C. The mixture was filtered, and the filtrate was concentrated in vacuo to yield the desired product as a pale orange oil (49 mg, 98%), (Found: M⁺ 206.3, C₁₃H₂₂N₂ requires 206.3 (low res. GC-MS)); νmax

2218, 1652, 959 cm⁻¹; δH (250 MHz; CDCl₃) 0.85 (2H, m, CH₃), 1.11 (2H, m, CH₂), 1.33 (3H, d, J 5 Hz, CH₃CH), 1.59 (1H, br s, CCH), 1.82 (3H, s, CH₃), 2.23 (2H, m, CH₂), 2.81 (6H, s, N(CH₃)₂), 4.24 (1H, dt, J 8, 5 Hz, CH₃CH), 6.67 (1H, t, J 8 Hz, alkene), 6.97 (1H, s, hydrazone-H); δC (62.5 MHz; CDCl₃) 19.8 (CH₃), 21.9 (CH₂), 27.0 (CH₂), 30.1 (CH₃), 31.8 (CH), 36.3 (CH₂), 42.8 (2xCH₃), 68.3 (CH), 84.0 (C), 121.3 (CH), 141.1 (C), 147.7 (CH); m/z 206 (M⁺, 65%), 44 (100).
The hydrazone [67] (40 mg, 0.2 mmol) and copper (II) acetate monohydrate (78 mg, 0.4 mmol) were heated in a mixture of pyridine (5 ml), methanol (5 ml) and diethyl ether (20 ml) for 18 h. The cooled mixture was filtered and concentrated in vacuo. The residue was washed with dilute hydrochloric acid (50 ml), extracted with dichloromethane (50 ml) and washed with brine (2 x 50 ml) and water (2 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale yellow oil (38 mg, 98%), $\delta_H$ (250 MHz; CDCl$_3$) 0.84 (2H, m, CH$_3$), 1.14 (2H, m, CH$_2$), 1.31 (3H, d, J 5 Hz, CH$_3$CH), 1.85 (3H, s, CH$_3$), 2.32 (2H, m, CH$_2$), 2.85 (6H, s, N(CH$_3$)$_2$), 4.27 (1H, dt, J 8, 5 Hz, CH$_3$CH), 6.64 (1H, t, J 8 Hz, alkene), 6.99 (1H, s, hydrazone-H); $\delta_C$ (62.5 MHz; CDCl$_3$) 19.7 (CH$_3$), 21.8 (CH$_2$), 27.3 (CH$_2$), 30.3 (CH$_3$), 32.1 (CH), 36.7 (CH$_2$), 42.2 (2xCH$_3$), 76.9 (C), 84.1 (C), 122.6 (CH), 141.8 (C), 149.3 (CH).
A solution of the dimer [68] (38 mg, 0.1 mmol) was heated at reflux in xylene (5 ml) for 5 h. Removal of the solvent in vacuo, and chromatography of the crude residue on silica gel (ethyl acetate) yielded the desired product as a pale brown oil (21 mg, 72%); \[\alpha\]_D^{22} + 13° (c 2.5 in CHCl₃); \(\delta_H\) (250 MHz; CDCl₃) 1.18 (3H, s, CH₃), 1.42 (3H, d, \(J\ 5\ \text{Hz}, \text{CH}_3\text{CH}\)), 2.18 (2H, m, CH₂), 2.76 (2H, m, CH₂), 3.17 (2H, m, CH₂), 4.19 (1H, dt, \(J\ 8, 5\ \text{Hz}, \text{CH}\)), 8.47 (1H, s, Ar)

bi-[(E)-3-(((N-propargyl)-2-benzoylamino)phenyl)propenal \(N,N\)-dimethylhydrazone] [69]

The acetylene [42] (134 mg, 0.4 mmol) and copper (II) acetate monohydrate (200 mg, 1.0 mmol) were heated in a mixture of pyridine (10 ml), methanol (10 ml) and diethyl ether (40 ml) for 18 h. The cooled mixture was filtered and
concentrated in vacuo. The residue was washed with dilute hydrochloric acid (50 ml), extracted with dichloromethane (50 ml) and washed with brine (2 x 50 ml) and water (2 x 50 ml). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed on silica gel (diethyl ether) to yield the desired product as a pale brown solid (110 mg, 83%), m.p. 179-180°C, (Found : MH⁺ 661.3290, C₄₂H₄₀N₆O₂ + H requires 661.3291); v_max. 3430, 2212, 1644, 1619, 1482 cm⁻¹; δ_H (400 MHz; CDCl₃) 2.89 (6H, s, N(CH₃)₂), 4.13 (1H, d, J 17 Hz, NCHH), 4.92 (1H, d, J 17 Hz, NCHH), 6.63 (1H, d, J 16 Hz, alkene), 6.80 (1H, dd, J 16, 8 Hz, alkene), 6.90-7.21 (9H, m, Ar + hydrazone-H), 7.45 (1H, d, J 8 Hz, alkene); δ_C (100 MHz; CDCl₃) 40.8 (CH₂), 43.3 (2xCH₃), 69.6 (C), 74.3 (C), 125.4 (CH), 126.5 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.2 (CH), 130.9 (CH), 131.0 (CH), 131.6 (CH), 131.6 (CH), 134.7 (CH), 135.5 (CH), 135.6 (C), 140.3 (C), 171.51 (C); m/z 661 (MH⁺, 75), 44(100).

4,4'-bi-{benzoyl-5,6-dihydrobenzo[2,7-c]naphthyridine} [50]

A solution of the dimer [69] (100 mg, 0.1 mmol) in xylene (2 ml) was heated at reflux for 2 h. After cooling, the solvent was removed in vacuo and the crude
residue was chromatographed on silica gel (diethyl ether) to yield the desired Diels-Alder adduct as a pale brown solid (58 mg, 68%), m.p. 163-165°C,
(Found: $MH^+$ 571.2133, $C_{39}H_{26}N_4O_2 + H$ requires 571.2134); $\nu_{\text{max}}$ 3432, 1653 cm$^{-1}$; $\delta_H$ (400 MHz; CDCl$_3$) 5.16 (2H, s, NCH$_2$), 6.83 (1H, d, J 5 Hz, Ar), 7.09-7.40 (7H, m, Ar), 7.76 (1H, d, J 5 Hz, Ar), 7.85 (1H, dd J 8, 1 Hz, Ar), 8.66 (1H, d, J 5 Hz, Ar); $\delta_C$ (100 MHz; CDCl$_3$) 44.9 (CH$_2$), 117.6 (CH), 125.3 (C), 125.9 (CH), 126.4 (CH), 126.6 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.5 (CH), 129.8 (CH), 130.3 (CH), 131.0 (CH), 135.3 (CH), 138.2 (C), 139.8 (C), 148.3 (CH), 154.2 (C), 169.8 (C); $m/z$ 571 ($MH^+$, 100).

4,4'-bi-{5,6-dihydrobenzo[2,7-c]naphthyridine} [51]

![Diagram of 4,4'-bi-{5,6-dihydrobenzo[2,7-c]naphthyridine}]

A solution the dimer [50] (44 mg, 0.07 mmol) in toluene (2 ml) at -78°C was treated with DIBAL (0.1 ml, 25% wt solution). The reaction mixture was allowed to warm to room temperature with stirring over 3 h. Upon completion the reaction mixture was diluted with water (5 ml) and aqueous sodium hydroxide (1 ml, 10% solution) and then extracted with toluene (3 x 15 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to yield the desired product as a brown semi-solid (29 mg, 97%), (Found: $MH^+$ 168...
363.1610, C\textsubscript{24}H\textsubscript{18}N\textsubscript{4} + H requires 363.1609); \nu\text{max.} 1640, 1552 cm\textsuperscript{-1}; \delta\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 4.23 (2H, s, CH\textsubscript{2}), 6.56 (1H, d, J 8 Hz, Ar), 6.77 (1H, t, J 8 Hz, Ar), 7.14 (1H, t, J 8 Hz, Ar), 7.43 (1H, d, J 5 Hz, Ar), 7.63 (1H, d, J 8 Hz, Ar), 8.44 (1H, d, J 8 Hz, Ar); \delta\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 42.7 (CH\textsubscript{2}), 115.2 (CH), 116.1 (CH), 119.1 (CH), 119.9 (C), 124.4 (CH), 126.6 (C), 128.1 (C), 129.2 (C), 131.1 (CH), 145.3 (C), 147.5 (CH); m/z 363 (MH\textsuperscript{+}, 100).

4,4'-bi-{benzo[c]-2,7-naphthyridine} [52]

A solution of [51] (29 mg, 0.07 mmol) in ethyl acetate (2 ml) was treated with excess palladium on charcoal, with stirring for 48 h at 25°C. The reaction mixture was filtered through a pad of Celite, and concentrated in vacuo to yield the desired product as a brown semi-solid (27 mg, 97%), (Found: MH, 359.1296 C\textsubscript{24}H\textsubscript{14}N\textsubscript{4}+H requires 359.1298); UV (dichloromethane) \lambda\text{max.} (nm) (ε) 236 (44600), 265 (25800), 316 (3400); \nu\text{max.} 1642, 762 cm\textsuperscript{-1}; \delta\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 7.71-7.87 (2H, m, Ar), 8.16 (1H, dd, J 8, 1 Hz, Ar), 8.54 (1H, dd, J 8, 1 Hz, Ar), 8.64 (1H, dd, J 8, 1 Hz, Ar), 9.26 (1H, d, J 8 Hz, Ar), 9.45 (1H, s, Ar); \delta\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 120.8 (C), 123.5 (CH), 126.3 (CH), 127.8 (CH), 128.0
General procedure for the indium mediated coupling of imines

\[
\begin{align*}
\text{Ar}_1-\text{CH}=\text{N}-\text{Ar}_2 & \rightarrow \text{Ar}_1-\text{CH}-\text{N}-\text{Ar}_2 \\
\text{H} & \text{H}
\end{align*}
\]

The imine (1 eq.) was added in one lot to ethanol (3 ml) - water (3 ml saturated with ammonium chloride) system containing indium pieces (2 g atom eq.). The mixture was stirred under reflux of ethanol until completion of the reaction; approximately 16 h. The reaction mixture was diluted with water, extracted with dichloromethane, dried over magnesium sulfate and concentrated in vacuo. The crude residue was analysed by proton NMR spectroscopy.

e.g. Coupling of quinoline

yield of (meso) [70] = 89%

\[ \delta_H \text{ (250 MHz; CDCl}_3\text{) } 1.92 \text{ (2H, m, CH}_2\text{)}, 2.74 \text{ (2H, m, CH}_2\text{)}, 3.39 \text{ (1H, t, J 3 Hz, CH)}\], 6.47 (1H, d, J 8 Hz, Ar), 6.57 (2H, m, Ar), 6.93 (1H, d, J 8 Hz)

e.g. Coupling of phenanthridine

yield of (meso) [72] = 93%
δ_H (250 MHz; CDCl₃) 3.42 (1H, br s, NH), 4.32 (1H, d, J 2 Hz, NCH), 
6.58 (1H, d, J 8 Hz, Ar), 6.73 (1H, d, J 8 Hz, Ar), 6.84 (1H, d, J 8 Hz, 
Ar), 7.10-7.35 (3H, m, Ar), 7.63-7.77 (2H, m, Ar).

**General procedure for metal binding studies**

A solution of di-μ-chloro{bis([1,2,5,6-η]-1,5-cyclooctadiene) dirhodium} [74] 
(6.1 mg, 0.012 mmol) in dichloromethane (10 ml) (N.B. = 1.2 mmol.l⁻¹) 
*solution* was titrated with the test compounds [48] and [52] through a range of 
concentrations (0.125 - 2.0 mmol.l⁻¹). The UV spectrum was recorded at each 
addition during the titration. A titration against 2,2'-bipyridine was carried out 
for comparison purposes.

The results and data analyses are discussed in Chapter 3 Section 3.6
Chapter 5

References
For convenience references are listed below in numerical order, and they appear in the body text where they are first cited.


57. For a review see Thurston, D.E. and Thompson, A.S. *Chemistry in Britain*, 1990, **26**, 767.


76. Reissert, A. *Ber.*, 1905, 38, 1603, 3415.


79. SYBYL, Tripos Corp., St. Louis, MO 63117, USA.


89. For a review see Fanta, P.E. *Synthesis*, 1974, 9.


Appendix

X-ray structure report
Experimental

Data Collection

A yellow arrowhead crystal of C$_{21}$H$_{21}$N$_3$O having approximate dimensions of 0.28 x 0.18 x 0.32 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-K$_\alpha$ radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range 73.30 < 2\(\theta\) < 74.87$^\circ$ corresponded to a primitive triclinic cell with dimensions:

\[
\begin{align*}
 a &= 8.726(2) \text{ Å} & \alpha &= 95.98(2)^\circ \\
 b &= 15.735(4) \text{ Å} & \beta &= 90.39(2)^\circ \\
 c &= 6.863(2) \text{ Å} & \gamma &= 105.06(2) \\
 V &= 904.5(4) \text{ Å}^3
\end{align*}
\]
For $Z = 2$ and F.W. = 331.42, the calculated density is $1.22 \text{ g/cm}^3$. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P \overline{1}$$

The data were collected at a temperature of $20 \pm 1^\circ \text{C}$ using the $\omega$ scan technique to a maximum $2\theta$ value of $120.2^\circ$. $\omega$ scans of several intense reflections, made prior to data collection, had an average width at half-height of $0.10^\circ$ with a take-off angle of $6.0^\circ$. Scans of $(1.10 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (in $\omega$). The weak reflections ($I < 15.0 \sigma(I)$) were scanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was $1.0 \text{ mm}$ and the crystal to detector distance was $400 \text{ mm}$. The computer-controlled slits were set to $9.0 \text{ mm}$ (horizontal) and $13.0 \text{ mm}$ (vertical).
Data Reduction

Of the 2899 reflections which were collected, 2695 were unique (R_int = 0.085). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.4%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 5.7 cm⁻¹. An empirical absorption correction using the program DIFABS¹ was applied which resulted in transmission factors ranging from 0.76 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods² and expanded using Fourier techniques³. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement⁴ was based on 2139 observed reflections (I > 3.00σ(I)) and 227 variable parameters and converged (largest parameter shift was 3.90 times its esd) with unweighted and weighted agreement factors of:

\[ R = \frac{\sigma |F_{o}| - |F_{c}|}{\sigma |F_{o}|} = 0.059 \]
\[ R_W = \left[ \frac{\sigma w \left( |F_{\text{O}}| - |F_{\text{c}}| \right)^2}{\sigma w F_o^2} \right]^{1/2} = 0.049 \]

The standard deviation of an observation of unit weight was 6.88. The weighting scheme was based on counting statistics and included a factor \( p = 0.002 \) to downweight the intense reflections. Plots of \( \sigma w \left( |F_{\text{O}}| - |F_{\text{c}}| \right)^2 \) versus \( |F_{\text{O}}| \), reflection order in data collection, \( \sin \theta / \lambda \), and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.28 and -0.31 e\(^{-}/\text{Å}^3\), respectively.

Neutral atom scattering factors were taken from Cromer and Waber\(^6\). Anomalous dispersion effects were included in Fcalc\(^7\); the values for \( \Delta f' \) and \( \Delta f'' \) were those of Creagh and McAuley\(^8\). The values for the mass attenuation coefficients are those of Creagh and Hubbel\(^9\). All calculations were performed using the teXsan\(^{10}\) crystallographic software package of Molecular Structure Corporation.
References


(4) Least-Squares:

Function minimised: \( Sw(|F_0| - |F_c|)^2 \)

where \( w = \frac{4F_0^2/s^2(F_0^2)}{[s^2(F_0) + (pF_0/2)^2]^{-1}} \)

\[ F_0^2 = \frac{S(C-RB)}{L_p} \]

and \( s^2(F_0^2) = \frac{[S^2(C+R^2B) + (pF_0^2)^2]}{L_p^2} \)

\( S = \) Scan rate
\( C = \) Total integrated peak count
\( R = \) Ratio of scan time to background counting time
\( B = \) Total background count
\( L_p = \) Lorentz-polarization factor
\( p = p\)-factor
(5) Standard deviation of an observation of unit weight:

\[ \sqrt{\frac{Sw(\|F_0\|-\|F_c\|)^2}{(N_0-N_V)}} \]

where: \( N_0 \) = number of observations

\( N_V \) = number of variables


EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula: \( \text{C}_{21}\text{H}_{21}\text{N}_{3}\text{O} \)

Formula Weight: 331.42

Crystal Colour, Habit: yellow, arrowhead

Crystal Dimensions: 0.28 X 0.18 X 0.32 mm

Crystal System: triclinic

Lattice Type: Primitive

No. of Reflections Used for Unit Cell Determination (2θ range): 25 (73.3 - 74.9°)

ω Scan Peak Width at Half-height: 0.10°

Lattice Parameters:
- \( a = 8.726(2) \text{Å} \)
- \( b = 15.735(4) \text{Å} \)
- \( c = 6.863(2) \text{Å} \)
- \( \alpha = 95.98(2)^\circ \)
- \( \beta = 90.39(2)^\circ \)
- \( \gamma = 105.06(2)^\circ \)
- \( V = 904.5(4) \text{Å}^3 \)

Space Group: \( P \bar{1} \)

Z value: 2

\( D_{\text{calc}} \): 1.217 g/cm³

\( F_{000} \): 352.00

\( \mu (\text{CuK}\alpha) \): 5.69 cm⁻¹
B. Intensity Measurements

Diffractometer          Rigaku AFC7S

Radiation               CuKα (λ = 1.54178 Å)  
graphite monochromated

Attenuator              Ni foil (factor = 9.42)

Take-off Angle          6.0°

Detector Aperture       9.0 mm horizontal  
13.0 mm vertical

Crystal to Detector Distance  400 mm

Temperature             20.0°C

Scan Type               0

Scan Rate               16.0°/min (in 0) (upto 4 scans)

Scan Width              (1.10 + 0.35 tan θ)°

2θmax                   120.2°

No. of Reflections Measured  
Total: 2899  
Unique: 2695  
(Rint = 0.085)

Corrections             Lorentz-polarization  
Absorption  
(trans. factors: 0.7592 - 1.0000)  
Decay (0.38% decline)
C. Structure Solution and Refinement

Structure Solution
Direct Methods (SAPI91)

Refinement
Full-matrix least-squares

Function Minimised
$\sigma w (|F_o| - |F_c|)^2$

Least Squares Weights
$1/2\sigma(F_o) = 4F_o^2/\sigma^2(F_o^2)$

p-factor
0.0020

Anomalous Dispersion
All non-hydrogen atoms

No. Observations ($I>3.00\sigma(I)$)
2139

No. Variables
227

Reflection/Parameter Ratio
9.42

Residuals: $R; Rw$
0.059 ; 0.049

Goodness of Fit Indicator
6.88

Max. Shift/Error in Final Cycle
3.90

Maximum peak in Final Diff. Map
0.28 e^-Å$^3$

Minimum peak in Final Diff. Map
-0.31 e^-Å$^3$
### Atomic coordinates and $B_{iso}/B_{eq}$

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</table>
\begin{align*}
H(2) & \quad 0.4853 & 0.0781 & 0.2714 & 6.5401 \\
H(3) & \quad 0.6242 & 0.2562 & 0.3674 & 6.0217 \\
H(6) & \quad 0.9798 & 0.3232 & -0.1262 & 6.0353 \\
H(7) & \quad 0.9231 & 0.1966 & -0.3534 & 6.5881 \\
H(8) & \quad 0.7248 & 0.0722 & -0.2924 & 6.6097 \\
H(9) & \quad 0.5851 & 0.0742 & -0.0081 & 6.5701 \\
H(10a) & \quad 1.0089 & 0.4176 & 0.4133 & 6.9629 \\
H(10b) & \quad 0.8911 & 0.3338 & 0.4763 & 6.9629 \\
H(12) & \quad 1.2423 & 0.2339 & 0.3086 & 9.3450 \\
H(15) & \quad 0.4992 & 0.3641 & 0.1527 & 6.9890 \\
H(16) & \quad 0.3106 & 0.3574 & -0.0912 & 8.4104 \\
H(17) & \quad 0.3901 & 0.4010 & -0.3940 & 8.6723 \\
H(18) & \quad 0.6558 & 0.4565 & -0.4493 & 8.9065 \\
H(19) & \quad 0.8449 & 0.4679 & -0.2008 & 7.4555 \\
H(20a) & \quad 0.1873 & 0.1220 & 0.9847 & 9.8760 \\
H(20b) & \quad 0.3174 & 0.1856 & 0.8087 & 10.3846 \\
H(20a) & \quad 0.1873 & 0.1220 & 0.9847 & 9.8760 \\
H(21a) & \quad 0.0668 & -0.0186 & 0.8656 & 9.9137 \\
H(21b) & \quad 0.0359 & -0.0164 & 0.6436 & 9.9137 \\
H(21c) & \quad 0.1462 & -0.0714 & 0.7121 & 9.9137 \\
H(22) & \quad 0.2822 & 0.1331 & 0.9898 & 10.3846 \\
H(23) & \quad 0.1432 & 0.1445 & 0.8617 & 10.3846 \\
\end{align*}

\[ \text{Beq} = \frac{8}{3} \pi (U_{11}(aa*)^2 + U_{22}(bb*)^2 + U_{33}(cc*)^2 + 2U_{12}(aa*bb*)\cos \gamma + 2U_{13}(aa*cc*)\cos \beta + 2U_{23}(bb*cc*)\cos \alpha) \]