AN INVESTIGATION INTO A SERIES OF ASYMMETRIC INTRAMOLECULAR NICHOLAS CYCLISATION REACTIONS

THESIS

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Declaration

This thesis entitled "*An investigation into a series of asymmetric intramolecular Nicholas cyclisation reaction*" is based upon the work conducted by the author in the School of Pharmacy and Chemistry, Faculty of Science, Engineering and Computing at Kingston University London between June 2009 and June 2013. All of the work described herein is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other universities.

Khatebeh Mazloumi

Dedicated to

My husband Ali reza haddadi Ci Sakht

&

All my family

&

My nephews

Amir Hossein, Ahoora and Amir Reza

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Abstract

The Nicholas reaction is the reaction of a cobalt-stabilised propargyl cation with a nucleophile and the aim of this project was to attempt this reaction with a chiral substrate in an effort to effect an asymmetric Nicholas reaction. A range of contemporary techniques were applied to reach this goal.

Initially an attempt was made to reproduce an earlier successful racemic synthesis of a fused carbocyclic compound using a chiral precursor. It was envisaged that this would be approached using a 1,4-conjugate addition to an enone using a chiral ligand to install the C-3 alkenyl group selectively. Although the conjugate addition reactions were successful, using well tried and tested ligands, the enantiomeric excesses were very low and unfortunately a suitable chelating catalyst that prevent fulfil the requirements was not identified at this stage of the investigation.

The next approach made use of an asymmetric alkynylation reaction to an aldehyde. This was successfully carried out using a Carreira asymmetric alkynylation reaction to afford optically active propargyl alcohols with good to excellent enantiomeric excess (50%-82% ees). The desired optical active propargyl alcohols were then complexed, with dicobalt octacarbonyl, to afford the corresponding dicobalt hexacarbonyl complexes. These then successfully underwent the corresponding Nicholas cyclisation reaction to afford, after oxidative decomplexation of the cobalt species, a range of optically active chromane and isochromanes with ees of (45%-81%). In a second study a series of optically active benzopyran derivatives were also successfully synthesised, using the same methodology, again with high levels of enantiomeric excess (87% - 94%)

In the final phase of this investigations it was explored the use of chiral derivatives of the chiral pool molecule citronellal as well as an achiral analogue in an effort to afford novel chiral aldehydes for propargylation and cyclisation. The new chiral centres were successfully installed using chiral auxiliary technology however unexpectedly difficulties were encountered in the removal of the chiral auxiliary. A lack of time, in order to further explore the removal step, unfortunately meant that this was put on hold for further studies.

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Abbreviations

[α]	specific rotation
δ_H	proton chemical shift
δ_C	carbon chemical shift
μM	micromolar
^{13}C NMR	^{13}carbon nuclear magnetic resonance
^{1}H NMR	^{1}proton nuclear magnetic resonance
BINOL	2,2'- dihydroxy-1,1'-dinaphthyl (binaphthol)
Bn	benzyl
n-Bu	n-butyl group
n-BuLi	butyllithium
t-Bu	*tertiary*-butyl
CAN	cerium ammonium nitrate
cm^3	cubic centimetre
COSY	correlation spectroscopy
DCM	dichloromethane
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact
eq	equivalent
Et	ethyl group
FDA	food and drug administration
g	gram
GC-MS	gas chromatography coupled with mass spectrometry
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
K_{ATP}	ATP- controlled potassium channels
LDA	Lithium diisopropylamide
LRMS	low resolution mass spectrometry
M^+	molecular ion
m-CPBA	*Meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
mL	mililitre
mp	melting point

MS	mass spectrometry
NMR	nuclear magnetic resonance
OTMS	trimethylsiloxy
OTf	Trifluoromethanesulfonate
PCC	Pyridinium chlorochromate
p-TSA	*para*-toluenesulfonic acid
p-TsCl	*para*-toluenesulfonyl chloride
PCOs	potassium channel openers
r.t.	room temperature
R_f	retention factor
THF	tetrahydrofuran
tlc	thin layer chromatography
TMSCl	Trimethylsilyl chloride
t_R	retention time
TS	transition state

1 Introduction

1.1 Aims of the Project

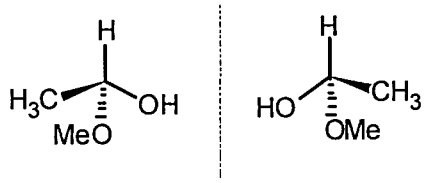
The main aim of this study has been an investigation into an asymmetric Nicholas reaction. During the course of this study it was explored a number of different strategies in order to achieve this aim. These include:

- the use of a chiral catalyst (discussed in sections 2.4.1)
- the use of a chiral pool (section 2.7)
- the use of a chiral auxiliary (section 2.8).
- The final and most successful approach involved the participation of a chiral propargyl alcohol in a series of asymmetric Nicholas cyclisation reactions (sections 2.5, 2.6).

This chapter has been organised such that each of the key methodologies that were investigated in this project such as methods for asymmetric synthesis, conjugate addition strategies and the key Nicholas reaction itself are presented. Further detailed descriptions will then be forthcoming, where appropriate, in the results and discussion section.

1.2 Stereochemistry and Chirality

Stereochemistry attempts to define the three dimensional configuration of a molecule. [1,2] The arrangement of the groups around an sp^3 hybridised carbon atom that is bonded to four different groups may result in one of two arrangements (Figure 1.1).[3] Although the four groups around 1 and 2 are the same, the two compounds are not identical. Compounds 1 and 2 are non-superimposable mirror images of each other and they are termed enantiomers (Figure 1.1). Molecules that demonstrate this property are called chiral molecules and the atom that the groups are bonded to is called the chiral centre. For compounds 1 and 2 the chiral centre is a carbon atom however, this is not a prerequisite for chirality.[2b]



1 **2**

Figure 1.1: *Non-superimposable mirror image compound* **1** *and* **2**

Enantiomers are an example of stereoisomerism and for a chiral compound with an n chiral centre; the maximum number of possible stereoisomers are 2^n. If n =1. In the case of compounds **3-6**, the number of stereoisomers is 2 (hence 2 enantiomers).[2a] When n = 2 four stereoisomers such as compounds 3-6 are possible (Figure 1.2).

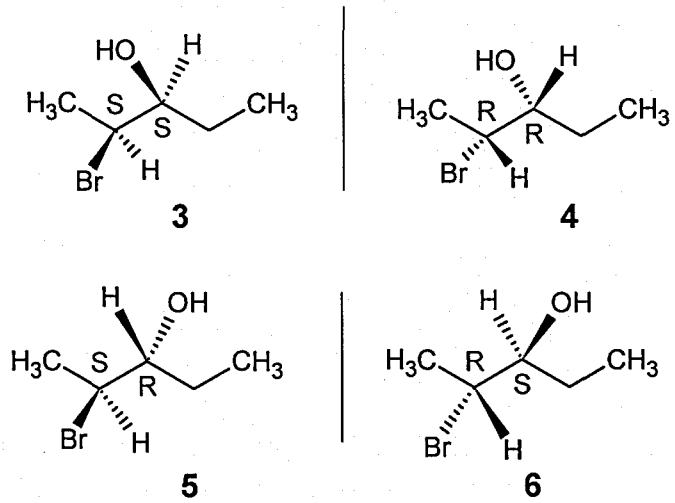


Figure 1.2: *Four stereoisomers for a compound with 2 chiral centres*

Compounds 3 and 4 are non-superimposable mirror-images of each other and as such they are enantiomers (as are compounds 5 and 6). Compounds 3 and 6 or 5 and 4 are not mirror-images and are referred to as diastereoisomers.[2b] By convention, chiral centres are identified with either *R* (for *rectus*) or as *S* (for *sinister*). The *R*- or *S*-chiral centres are designated according to the Cahn–Ingold–Prelog (CIP) priority rules.[4] The substituents, about the chiral centre, are each assigned a priority based upon the corresponding atomic number. Consider compound 7 (Figure 1.3) in which the four functional groups have been prioritised according to the CIP rules thus Br > Et > Me > H. Viewing the groups in descending priority Br, Et, Me occurs in an anti-clockwise direction hence the absolute configuration is designated as (*S*). The enantiomer to 7 will therefore be assigned an (*S*)-configuration.[4]

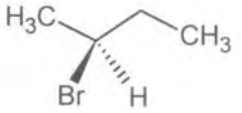


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Figure 1.3: *A compound with (S)-Configuration*

Enantiomers have the same physicochemical properties. An important feature of enantiomers is their interaction with the plane of plane polarised light. This is measured using an instrument called a polarimeter (Figure 1.4).[5]

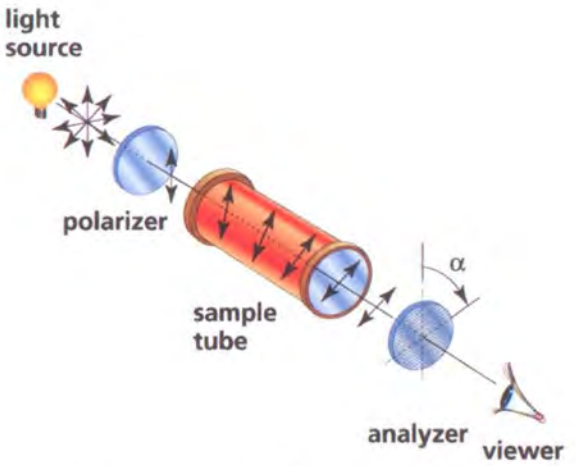

Figure 1.4: *The principles of a polarimeter*[6]

The polarizer filter provides light which oscillates in one plane and as this plane polarised light interacts with the optically pure compound in the sample tube the plane of the plane polarised light is rotated. The degree of rotation is called the angle of rotation (α), and can be rotated either clockwise or anticlockwise depending on the enantiomer. This is converted to a positive or negative integer on a digital screen. In the diagram above, the angle of rotation (α), as observed by the viewer has been rotated clockwise by about 80°. If an equimolar mixture of (*R*) and (*S*)-enantiomers (a racemic mixture) are placed in a polarimeter tube the angle of rotation measured will be zero as each enantiomer will interact with the plane of plane polarised light in an equal amount and will rotate it in opposite directions.

The optical activity of chiral molecules are usually designated as either (+) or (-) depending upon whether the plane polarised light is rotated clockwise, (+), or anticlockwise (-). Optically pure (*S*)-(-)-2-methyl-1-butanol 8 has a specific rotation $[\alpha]_D$ = -5.8°. The prefix (*S*)-describes the absolute configuration about the chiral centre, the (-) indicates that this compound rotates the plane of plane

polarised light in an anticlockwise direction. Compound 8 (Figure 1.5) has a specific rotation of [α] = -5.8 °.[5] The specific rotation of a chiral compound is the observed angle of optical rotation (α) divided by the length of the cell (l) and the concentration of the solution (c) [7] and is characteristic of a compound ($[\alpha] = \frac{\alpha}{l.c}$).

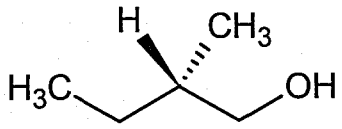

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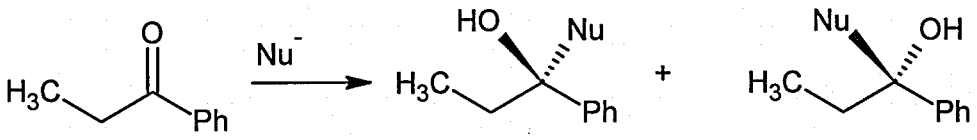
Figure 1.5: *(S)-(-)-2-Methyl-1-butanol*

A synthetic procedure that results in the formation of a single enantiomer is called an asymmetric synthesis.[8] In the field of chemistry forming one stereoisomer is an important challenge because in an achiral environment, i.e. experimental reaction conditions that are devoid of any chiral control, equimolar quantities of enantiomers, (ie a racemic mixture) will result when a chiral centre is formed. Consider the nucleophilic addition to ketone 9 (Scheme 1.1).[8]



9 **10** **11**

Scheme 1.1: *Formation of racemic alcohols*

In the absence of an asymmetric environment there is an equal probability that the incoming nucleophile (Nu^-) may add from either side of the planar carbonyl in 9 resulting in an equimolar mixture of both enantiomers **10** and **11**.[9] Such a 50:50 mixture of enantiomers is called a racemic mixture and results from the fact that the transition state to either **10** or **11** are enantiomeric and hence identical in energy (Figure 1.6).

According to the IUPAC defenistion enantiomeric excess is the absolute difference between the mole fractions of each enantiomer which expressed as a percent enantiomer excess. To determine enantiomeric excess percentage, if the amount of each enantiomer is available, enantiomer excess can be determined by: $\frac{major\ enantiomer - minor\ enantiomer}{major\ enantiomer + minor\ enantioer}$ x 100, if specific rotation and observed rotations are available can be determined by: $\frac{observed\ rotation\ (\alpha)}{specific\ rotation\ [\alpha]}$ x 100.

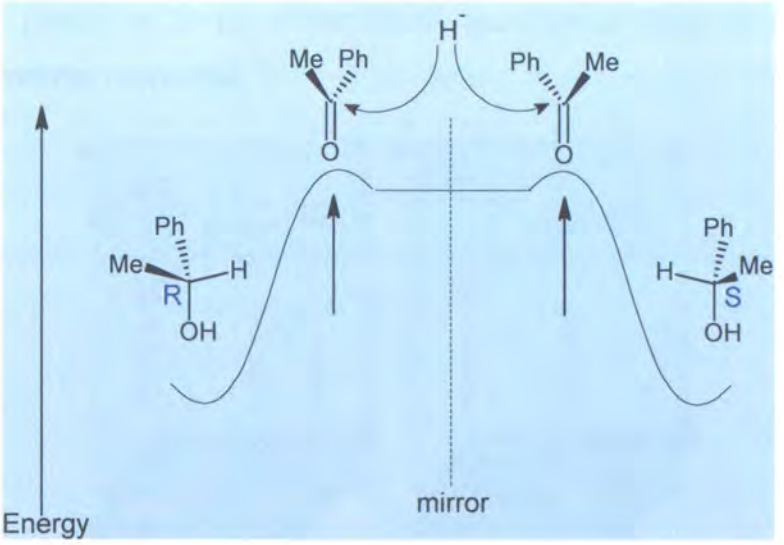
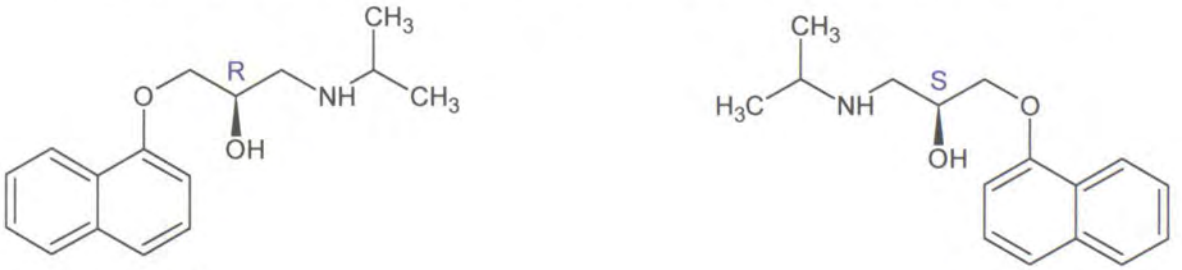


Figure 1.6: *Enantiomeric transition state*

1.2.1 The Importance of Stereochemistry

To an organic chemist asymmetric synthesis is a process that selectively produces one or more new elements of chirality [1,10] This is important in the field of pharmaceuticals and natural products as the physiological effects of enantiomers are often different (Figure 1.7).[11] For example, (*R*)-(-)-propranolol **12** was introduced in the 1960s for use as a β-blocker for the treatment of heart disease. The (*S*)-(+) enantiomer **13**, in contrast, is used as a contraceptive.[12]



12 **13**

Figure 1.7: *Enantiomers of propranolol*

A possible explanation for this phenomenon is shown below in (Figure 1.8). It attempts to portray how an optically active compound might interact with a binding site. The active enantiomer (Figure 1.8**A**) has the correct 3-point interaction with the drug binding site in order to elicit the correct physiological response such as dilate the pupil, contract a muscle or release a hormone. In contrast, the enantiomer (Figure 1.8**B**) is only able to make a two-point interaction as there is a mismatch between the "blue ligand" and the corresponding "green binding site" on the receptor. As a result of this the

enantiomer is predicted to be either totally inactive or elicit an alternative and possibly detrimental response.[11]

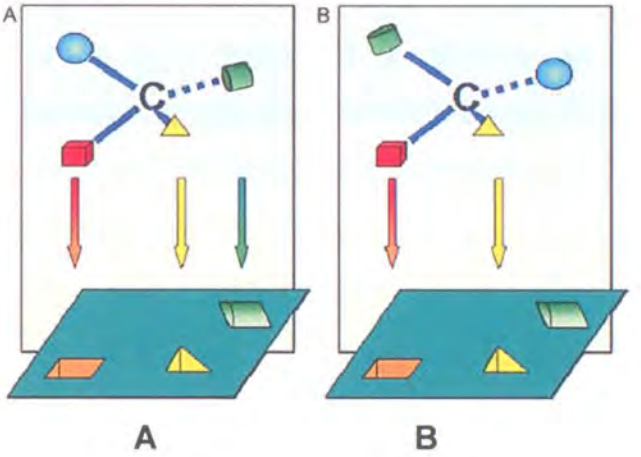


Figure 1.8: *Interaction of receptors and drugs*[11]

Chiral drug molecules, therefore, interact with receptors and enzymes and elicit a response because they are chiral and possess the correct shape and size to interact with the binding/active site.[12] These effects are also evident in senses such as the sense of smell for instance. The two enantiomers of carvone which are (R)-(-)-carvone **14**, the principal component of spearmint oil and (S)-(+)-carvone **15**, the principal component of caraway seed oil (Figure 1.9). The two enantiomers do not smell the same with each enantiomer having its own characteristic odour.[13] The effect is subjective as the spearmint smell of **14** is not always detected by all. However most people do detect a difference in their smells. Again this difference is explained in terms of their different behaviour towards receptor sites in the nose. These volatile molecules occupy only those odour receptors that have the complimentary shape to accommodate them. Because the receptor binding sites are themselves chiral, one enantiomer fits one kind of receptor while the other enantiomer fits a different kind.[14]

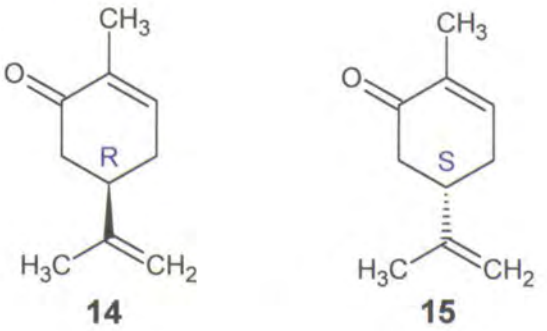
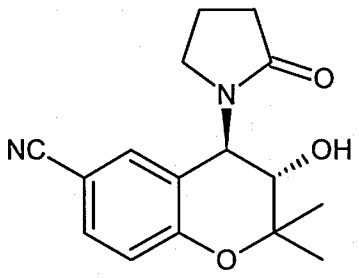


Figure 1.9: *Enantiomers of Carvone*

Over 80 % of small drugs approved by food and drug administration (FDA) are small chiral molecules for clinical applications of which 75 % exist as single enantiomers.[15] Considering the different effects that optical isomers can have on biological systems, it is very important to ensure an efficient asymmetric synthesis in order to prepare single enantiomeric drugs. A single optical isomeric compound that is of relevance to this project is cromakalim **16** a K_{ATP} - dependant potassium channel activator (Figure 1.10).



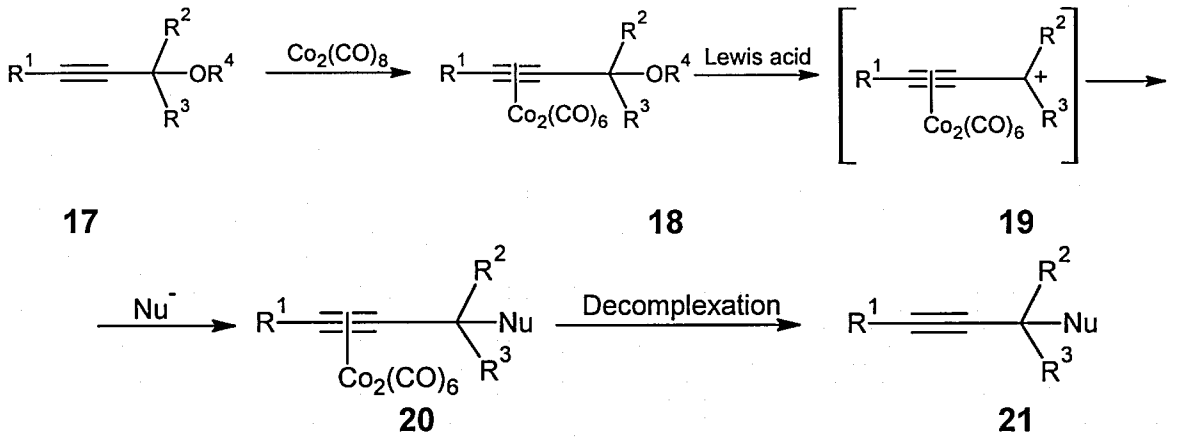
16

Figure 1.10: *Structure of cromakalim* **16**

Potassium channels are membrane proteins that selectively conduct potassium ions across the cell membrane. Among the various types of potassium channels are the adenosine triphosphate (ATP) sensitive potassium channel (K_{ATP} channels) which are regulated by changes in the intracellular [ATP]/[ADP] ratio.[16] Compounds, such as cromakalim **16**, open K_{ATP} - channels and have thus been named "potassium channel openers" (PCOs).[17,18] The net effect of their action is the reduction of high blood pressure.[19] However, cromakalim **16**, lacks specificity resulting in undesirable side effects.[20] New vasorelaxant analogues of this benchmark drug that retain the potency of cromakalim **16** but lack the toxicity, have been explored in recent years.[21] Tyrrell et al [22a, 22i] have reported novel benzopyran derivatives that were obtained *via* an intramolecular Nicholas reaction, with antihypertensive activity. The Nicholas reaction will be discussed below.

1.3 The Nicholas reaction

The Nicholas reaction is the reaction of a propargyl cation stabilized as the corresponding dicobalt hexacarbonyl complex, with a nucleophile [23] (Scheme 1.2).

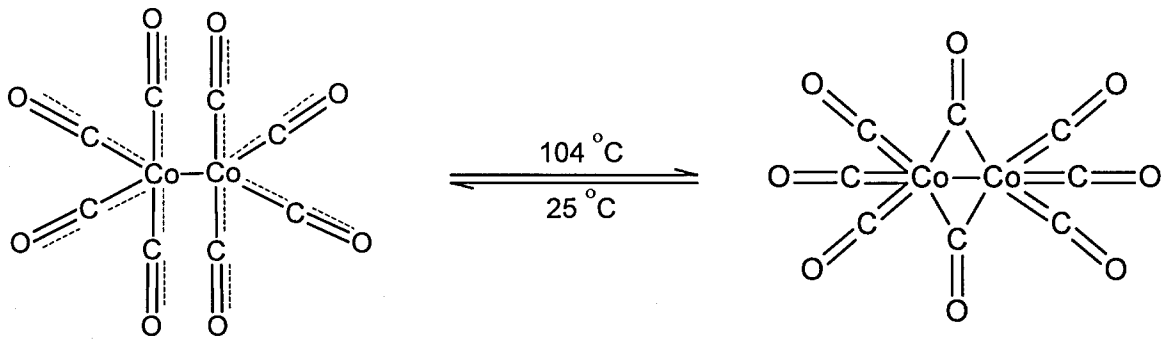


Scheme 1.2: *The Nicholas reaction*

Initially the propargyl alcohol/ether **17** is protected, by reaction with dicobalt octacarbonyl, to afford the corresponding hexacarbonyl complex **18**. Upon exposure to a protic /Lewis acid, a dicobalt hexacarbonyl stabilised propargylic cation **19** is formed. Subsequent reaction of the cation **19** with a nucleophile affords the complexed product **20** in which the –OR moiety has been substituted by a nucleophile (Nu). Oxidative decomplexation of complex **20** affords the Nicholas adduct **21**. The Nicholas reaction thus enables the efficient substitution reaction of propargyl alcohols/ethers. [24]

1.3.1 Role of the complex

Clearly the role of cobalt is essential to the reliability of the Nicholas reaction. Cobalt is a transition metal element with electron configuration [Ar] $4s^2$ $3d^7$. In its pure form, it is a steel-grey to black shiny hard metal. It also exists as cobalt (II) and cobalt (III), which can form a number of organic and inorganic salts.[25] Two structures, **22a** and **22b** are thought to exist in solution the dicobalt octacarbonyl complex and to be rapidly interconverted (Figure 1.11) In each structure dicobalt octacarbonyl complex is a stable complex as each cobalt atom has eighteen electrons in the outer shell and therefore follows the 18-valence electron rule (Table 1.1).[26,27]



22a **22b**

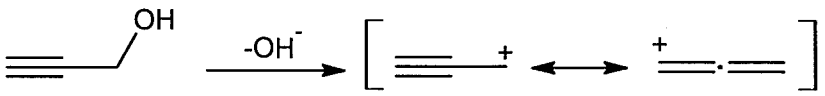
Figure 1.11: *The structures for dicobalt octacarbonyl*

Table 1.1: *The Eighteen Electron Rule of the Dicobaltoctacarbonyl*

isomers	**22a**	**22a**
Cobalt	9 valence electrons	9 valence electrons
CO groups	2 X 4 terminal CO = 8 electrons	(2 Bridged CO + 2 x3 terminal CO) = 2+6 = 8 electrons
Co-Co bond	1 electron	1 electron
Total	18 electrons	18 electrons

Evidence for these structural types have been obtained from various spectroscopic analyses. The bridging carbonyl **22b** has a ν(CO) stretch in the infra-red (IR) spectrum at about 1800 cm^{-1} this is much lower than that of terminal carbonyls and more analogous to an organic ketone $R_2C{=}O$ which has a ν(CO) stretch at 1750 cm^{-1}. In solution $Co_2(CO)_8$ has a structure with only terminal carbonyl moieties, i.e. four carbonyl groups per cobalt atom as suggested by structure **22a**. The terminal ν(CO) stretch occurs at about 1950-2000 cm^{-1}.[28,29]

By complexing the alkyne functional group in compound **17** with dicobalt hexacarbonyl, there is both an increased stability and ease of formation of the propargylic cation **19**. The principal role of the cobalt complex, however, is one of protecting the alkyne by avoiding the formation of a competing allene such as **23**. Indeed allene formation is frequently an unwanted side reaction that occurs in the absence of dicobalt hexacarbonyl complexation however this is completely prevented by co-ordination with dicobalt hexacarbonyl (Scheme 1.3).



Scheme 1.3: *Allene formation*

The stabilisation by the complex may be rationalised when one considers the accepted structure of complexes such as **19**. The use of the arrow, or the vertical line, that projects from the triple bond to the cobalt complex is the accepted "shorthand" depiction of the cobalt complex however in reality the structure of the complex is more like that shown in structure **24** (Figure 1.12).

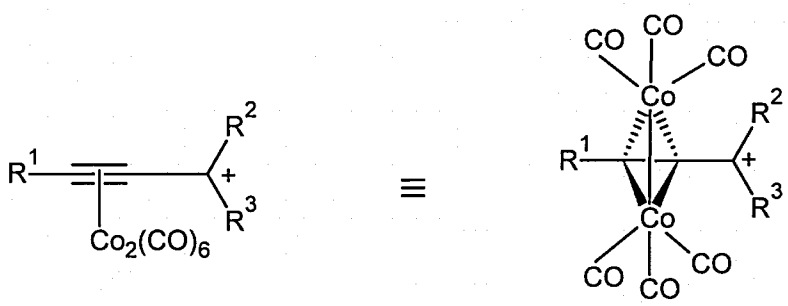


Figure 1.12: *Structure of cobalt complexed cation* **24**

The role of the cobalt atom, in the dicobalt hexacarbonyl complex, was initially elucidated by Seyferth [30] in 1970 who suggested that the additional stabilisation of the cation resulted from the delocalisation of the positive charge from the propargylic position in **25** onto the two corresponding cobalt moieties as shown in structures **26** and **27** (Figure 1.3).[30a]

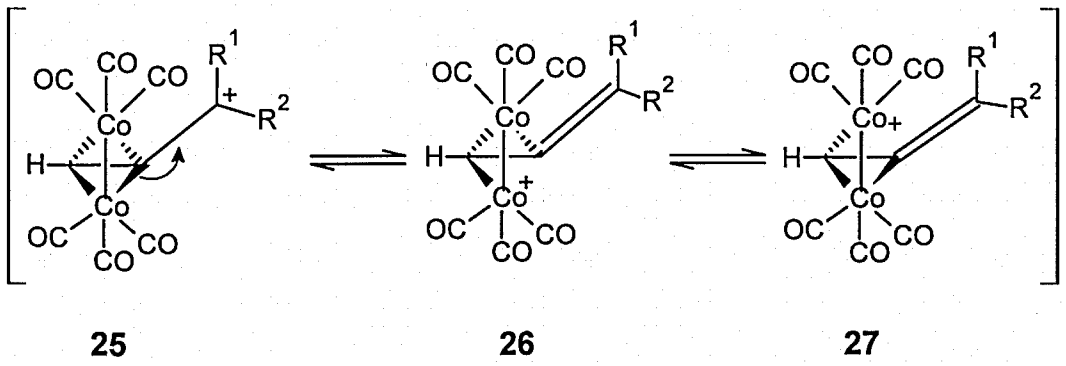


Figure 1.13: *Stability of dicobalt hexacarbonyl cation* **25** using the Seyferth model

There is spectroscopic evidence [31] in support of this suggestion. It has been observed that, upon complexation with dicobalt octacarbonyl, the sp-hybridised

C≡C alkyne bond assumes more sp^2 bond characteristics and this may be readily observed by both IR and NMR spectroscopy. In the IR spectrum of a propargyl alcohol, the C≡C bond is readily observed at 2975 cm^{-1} however this absorbance is significantly reduced or absent in the corresponding dicobalt hexacarbonyl complex. In the ^1H NMR of a terminal uncomplexed alkyne the C≡C<u>H</u> proton resonates at about δ 3.00 ppm however in the corresponding complex this resonance is shifted downfield to about δ 6.00 ppm. Schreiber has also offered an analogous model for the stability of the cobalt complexed cation.[32,33]

1.3.2 Dynamic behaviour of hexacarbonyl dicobalt

Dicobalt hexacarbonyl complexed propargylic cations are stabilised by the presence of the metal species. Hoffman[34] suggested that additional stabilisation of the dicobalt hexacarbonyl cation is experienced when the cationic carbon atom is bent toward one of the cobalt atoms, shown in structure **28b** and **28c**, compared to the perpendicular structure **28a**. The calculated energy for the perpendicular structure **28a** is about 17.5 kcal/mol higher than **28b** and **28c** and is attributed to hyperconjugation (Figure 1.14).[31b]

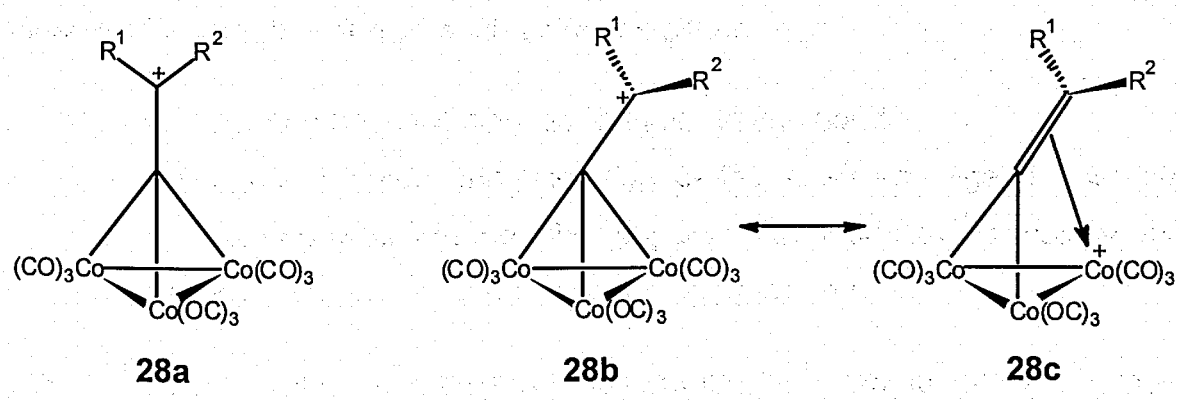


Figure 1.14: *Hoffman's additional stability of tricobalt nonacarbonyl cation*

Mislow and Norton[27a,35] provided further experimental evidence for the bent structure of dicobalt hexacarbonyl stabilised cations *via* the use of ^{13}C NMR experiments (Figure 1.15). Low temperature (-52 °C) NMR studies showed that for the proposed complexes **29a** and **29b,** two distinct doublets were observed for the isopropyl (CH_3) substituents. The bent structures for **29a** and **29b** are suggested by the evidence of the two methyl groups being seen, on the NMR timescale as diastereotopic.

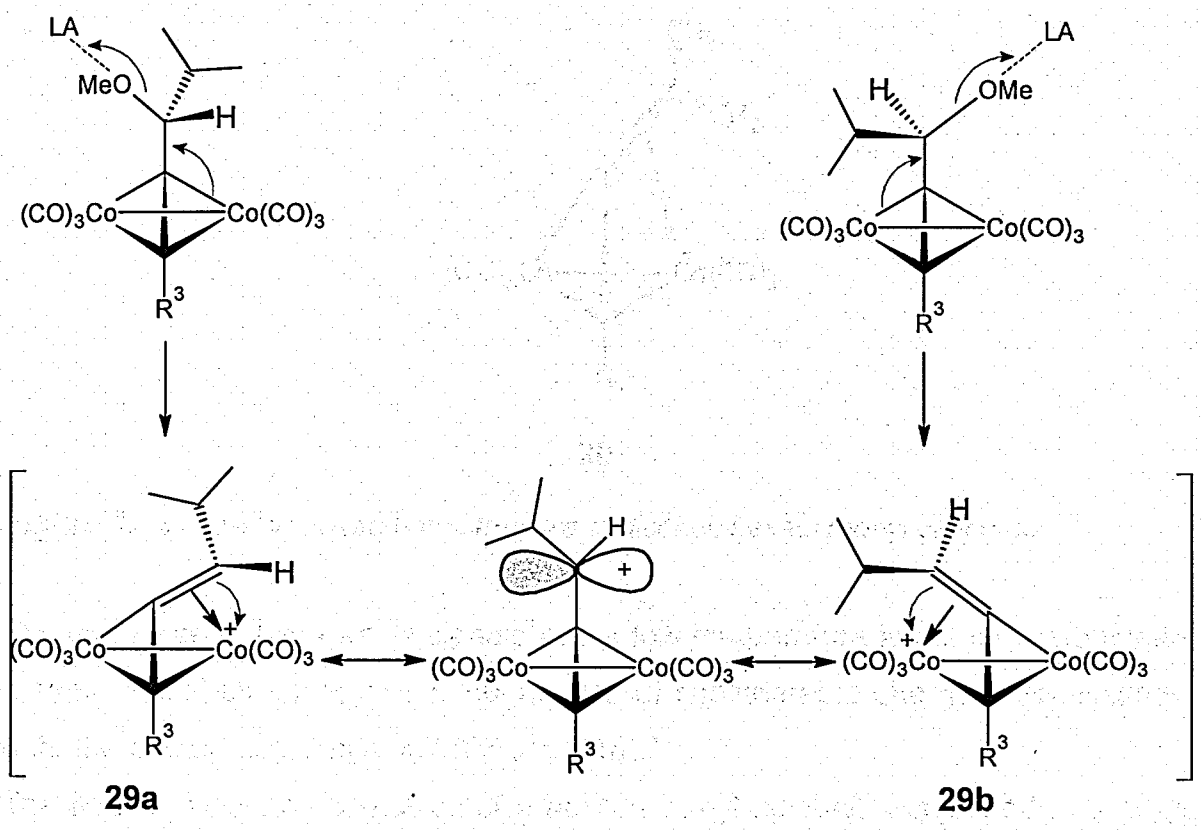


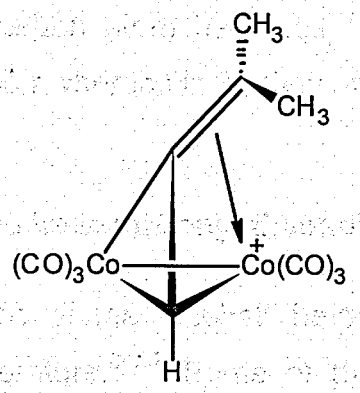
Figure 1.15: *Evidence of the proposed bent structure of dicobalt hexacarbonyl cation*

Schreiber [25] proposed two mechanisms for the apparent interconversion of the diastereotopic methyl groups such as these, either:

1. carbon-carbon bond rotation around the double bond
2. simultaneous rotation and migration of the alkylidene ligand from one cobalt tricarbonyl unit to the other (Figure 1.15). Hoffman[34] calculated that this process should involve a lower energy pathway.

The second process led to the use of the term the "fluxional nature" of the cobalt cation to describe the additional stabilisation obtained. Schreiber went on to provide an explanation for this phenomenon using transition state and orbital symmetry models.[23]

Nicholas also used NMR studies to show the temperature dependant behaviour of cobalts complexes such as **30**. Whereas ^{13}C NMR spectroscopy at 0 °C showed one methyl signal for the 2 vinyl methyl groups, the corresponding lower temperature study, at -40 °C, clearly showed two signals for cation **30**.[31b] An energy barrier of 11.5 kcal/mol was calculated on the basis of these observations.[36]

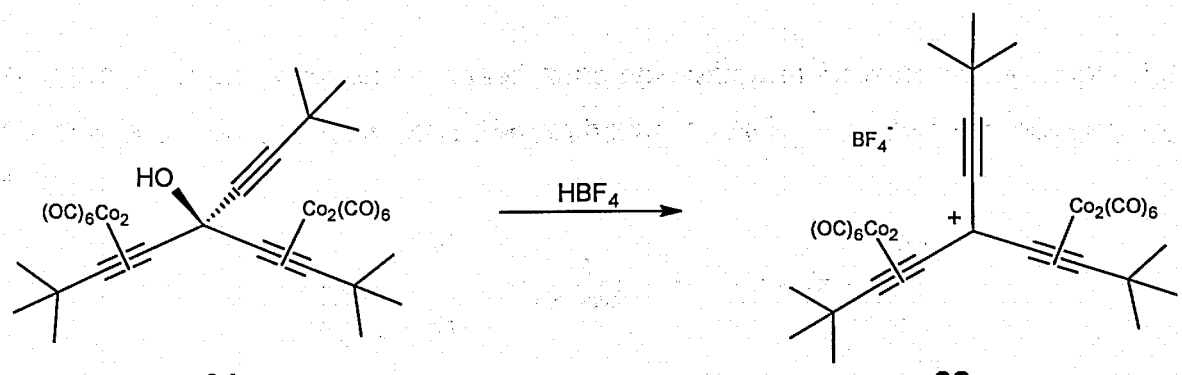


30

Figure 1.16: The *proposed bent structure of dicobalt hexacarbonyl cation* ***30***

The existence of two methyl signals at the low temperature is not consistent with a symmetrical structure and is suggestive of considerable charge delocalization onto the cobalt tricarbonyl unit (Figure 1.16).[36]

The first X-ray crystal structure of a hexacarbonyl dicobalt complexed propargyl cation was published by Melikyan[27a] in 1998. This was obtained from the stabilised cation **32** and helped to confirm the role played by the two $Co_2(CO)_6$ groups in providing enhanced stability as well as greater crystallinity of the cation (Scheme 1.4).



31 **32**

Scheme 1.4: *Melikyan's cation* **32**

The crystal structure of **31** was compared to the structure of the corresponding sp^2 hybridised cation **32.** In general, the orbitals of the covalent bonds around the central carbon atom in **32** are shorter than normal. The dicobalt hexacarbonyl complexes in **31** are essentially equal with the C≡C and Co-Co bonds lying perpendicular to each other with angles very close to 90°. However in **32** the metal complexes are non-equivalent with one adopting a twist of 7.7° away from

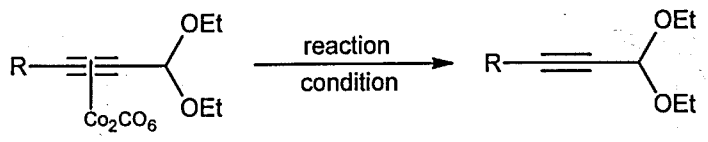
perpendicular. The central carbon atom becomes shifted towards one of the cobalt atoms in each Co-Co pair whereas in **31** they are equidistant.

1.3.3 Decomplexation of the hexacarbonyl dicobalt complex

The oxidative decomplexation of the dicobalt hexacarbonyl complex is now widely established in the literature.[24,37] Some of the oxidative and reductant methods include:

1. Ferric nitrate[38]
2. Ceric ammonium nitrate (CAN) $[(NH_4)_2Ce(NO_3)_6]$[39]
3. Trimethylamine *N*-oxide[22d,40] or *N*-morpholine *N*-oxide, often in conjuction with 1,4-cyclohexandiene[41]
4. Tetrabutylammonium fluoride[40]
5. Sodium methanethiolate[24]
6. Pyridine[24]
7. Dimethylsulfoxide/water[24]

A comparison of methods for cobalt decomplexation of **33** is shown in Table 1.2. From this study it is clear that *N*-morpholine *N*-oxide provided the better yield.[24,40,42]



33

Scheme 1.5: *Decomplexation reaction*

Table 1.2: *Oxidative Decomplexation Reaction Conditions*

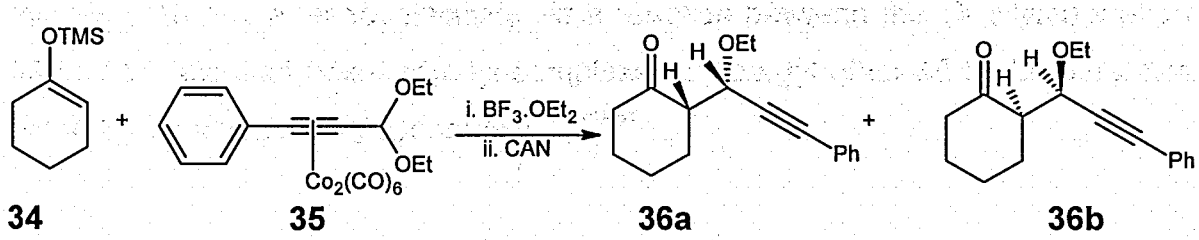
R	Conditions	Yield
Me	CAN, NEt_3 THF/acetone 0 °C	72
Me	$NMO.H_2O$ CH_2Cl_2, r.t	80
Me	$(CH_3)_3NO.H_2O$ CH_2Cl_2, -78 °C	0

1.3.4 Stereoselective Nicholas reactions

Several general reviews on the Nicholas reaction have been disseminated in the past decade [24] however in this section the focus will be on stereoselectivity in the Nicholas reaction.

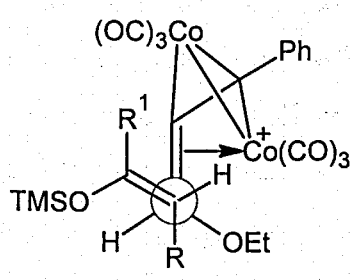
1.3.4.1 Stereoselective intermolecular Nicholas reactions

The *syn* diastereoselective aldol products **36a-b** were generated by treating the complexed alkynyl acetal **35** with prochiral enolsilane **34** at -78 °C. Standard cobalt decomplexation conditions with CAN were used.[37]

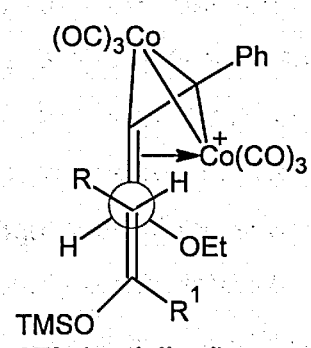


Scheme 1.6: *Stereoselective intermolecular Nicholas reaction*

It has been suggested by the author that both **36a** and **36b** are derived from a less crowded anticlinal transition state **37b**. They differ only in the degree of crowding between the complex and the ring in **38a** and the complex and the OTMS group in **38b**. It is clear from the distribution of diastereoisomers, that favour **38a**, that the repulsion is minimal in this transition state (Figure 1.17).[37]



37a (synclinal)



37b (anticlinal)

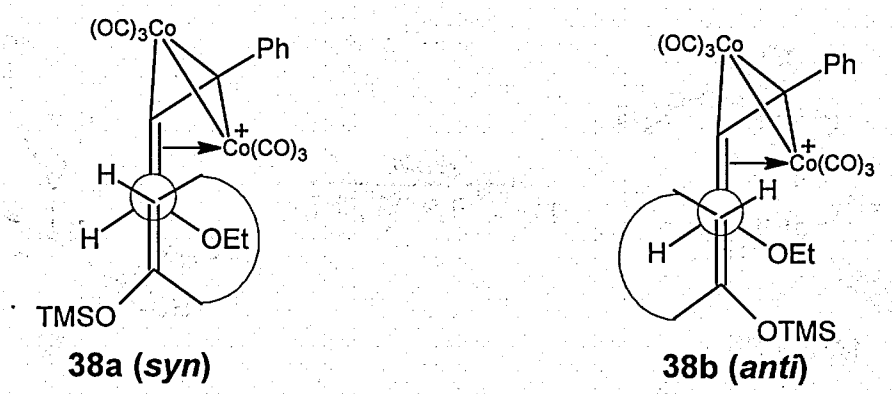
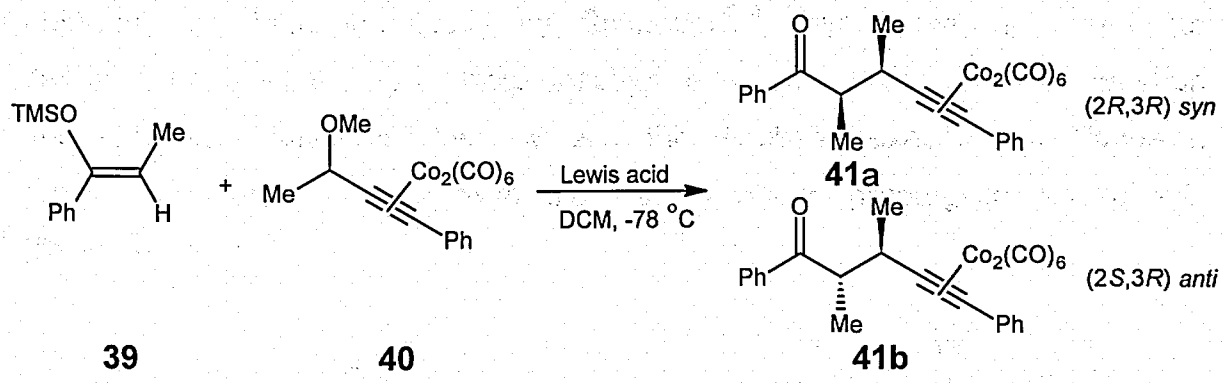


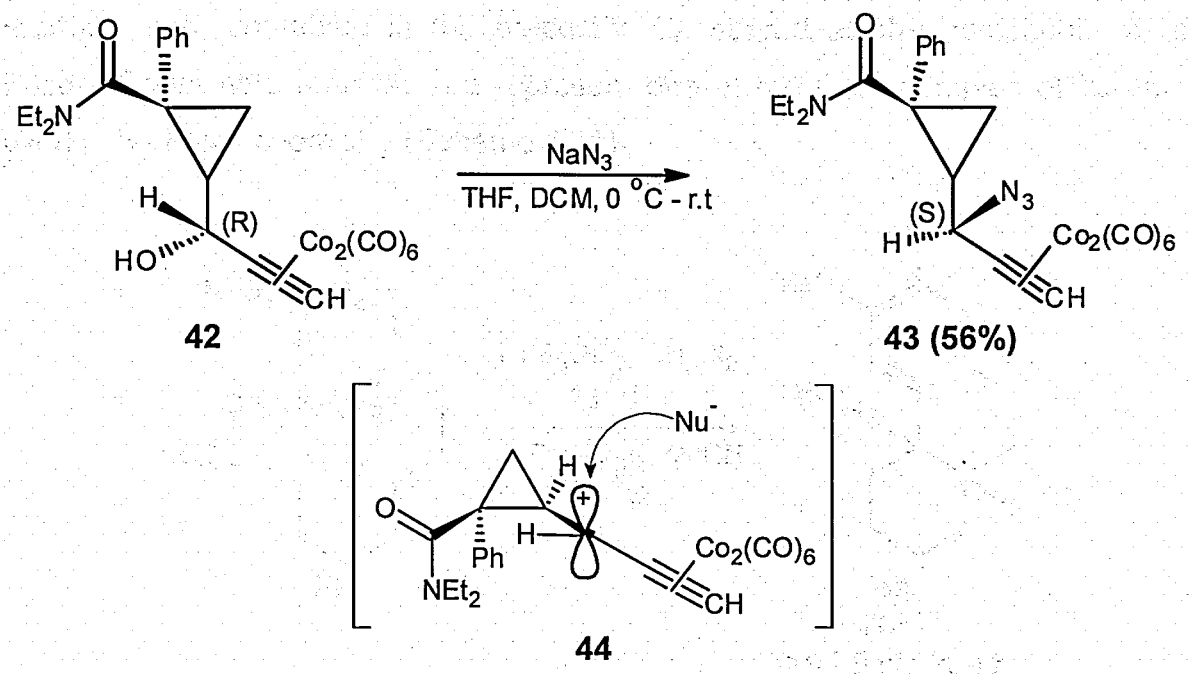
Figure 1.17: *Syn and anti-diastereomeric transition states*

The Schreiber group synthesised the ketones **41a** and **41b** with high levels of (syn:anti, 18:1) diastereoselectivity *via* a reaction between the *O*- silylenol ether **39** and the dicobalt hexacarbonyl complexed propargyl ether **40** in the presence of the Lewis acid $EtAlCl_2$ (Scheme 1.7).[40-41]



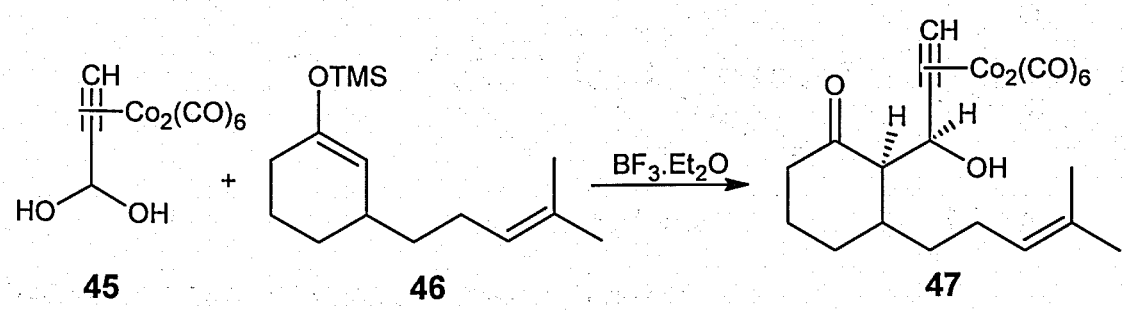
Scheme 1.7: *Synthesis of the diastereoselective ketone*

Shuto[43] and co-workers reported a diastereoselective Nicholas reaction by using an azide, as a nucleophile, with the amide **42**. The propargylic chiral centre which is -(R) in the substrate **42** was converted to an -(S) in the product **43** *via* the proposed transition state **44** (Scheme 1.8). This outcome serves to confirm that despite the stabilised cation **44** being planar the configuration of the substrate **42** is "remembered" and the nucleophile attacks *anti* to the leaving group to provide product **43** in a consistently diastereoselective way consistent with Schreiber's hypothesis.



Scheme 1.8: *A diastereoselective Nicholas reaction of the amide* **42**

Following on from the study by Schreiber[40-41] Tyrrell was also able to demonstrate a similar *syn* diastereoselective intermolecular Nicholas reaction between the O-silylenol ether **46** and the dicobalt hexacarbonyl stabilised propargylic cation, derived from diol **45**, to obtain propargylic alcohol **47**. (Scheme 1.9)[44]



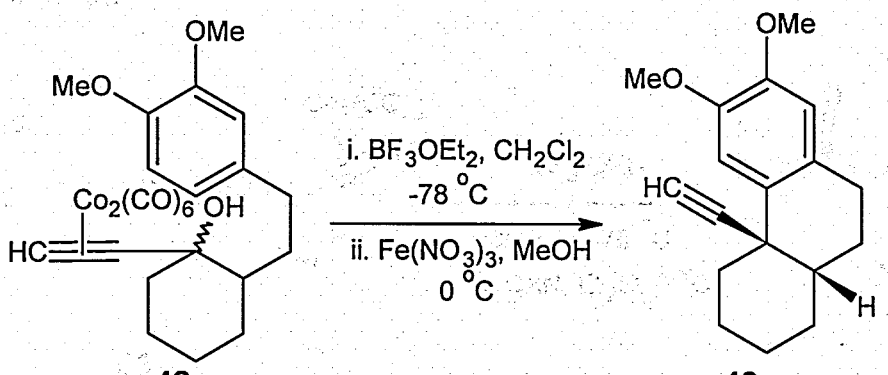
Scheme 1.9: *A syn diastereoselective intermolecular Nicholas reaction*

1.3.4.2 Stereoselective intramolecular Nicholas reactions

An intramolecular reaction involves only one molecule that contains both the nucleophile and the electrophile. The reaction is faster because the nucleophile and electrophile are held close together and results in the formation of a ring.[45]

Grove[46] reported the generation of a *cis*-tricycle **49**, using an intramolecular ring closure in their intramolecular Nicholas reaction. In this particular example the

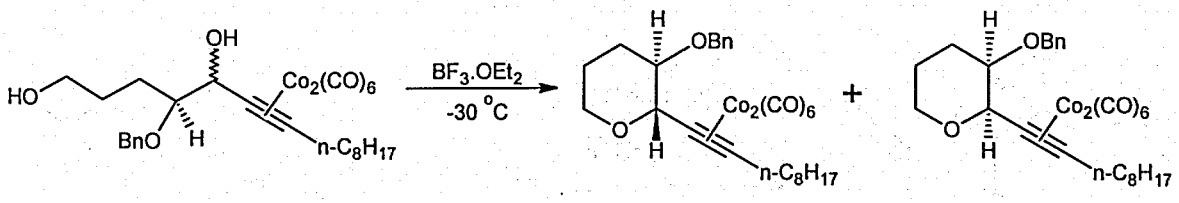
aromatic ring, contained in the precursor **48**, served as the nucleophile in a Friedel Crafts type reaction and represent one of the first examples of its type used in Nicholas chemistry (Scheme 1.10).



48 **49**
78%
>95:5 *cis.trans*

Scheme 1.10: *An intramolecular Nicholas reaction*

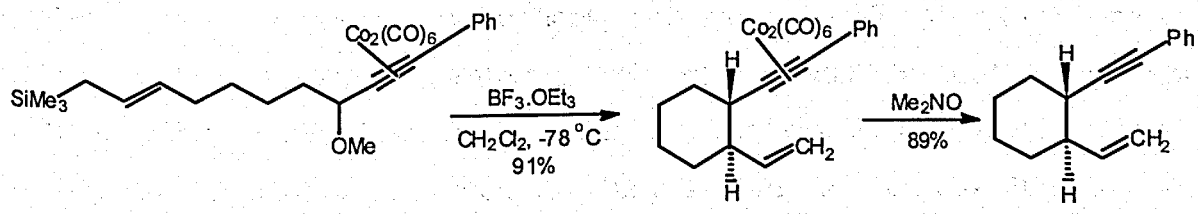
Martin and Palazón[47] reported an intramolecular Nicholas reaction of the linear diol **50**. Treatment of the complex with boron trifluoride dietherate at -30 °C gave the corresponding monocyclic ethers **51** *trans* and **52** *cis* in good yield with a 3:1 *trans*:*cis* diastereoselectivity (Scheme 1.11).



50 **51 *trans*** **52 *cis***

Scheme 1.11: *An intramolecular Nicholas reaction*

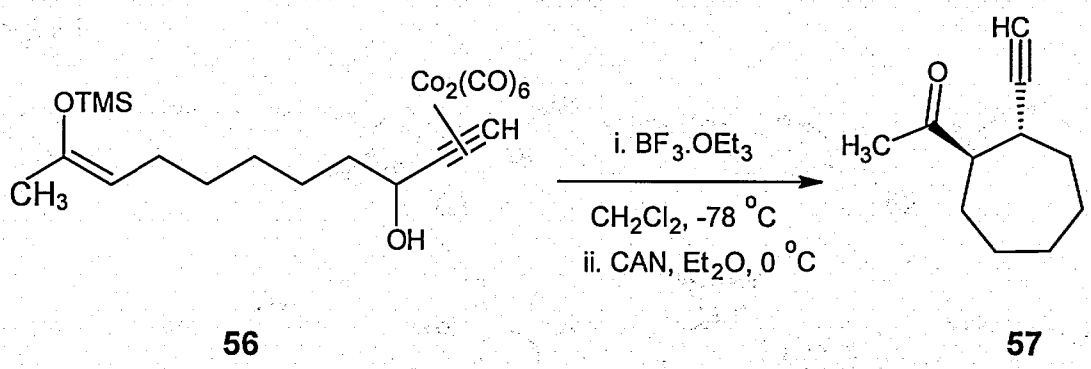
Schreiber[40] reported the synthesis of the exocyclic enyne **55** from the allylic silane **53**. This underwent an intramolecular Nicholas reaction with complete *trans* stereo control to afford, after decomplexation, the alkyne **55** in 89 % yield (Scheme 1.12).[40]



53 **54** **55**

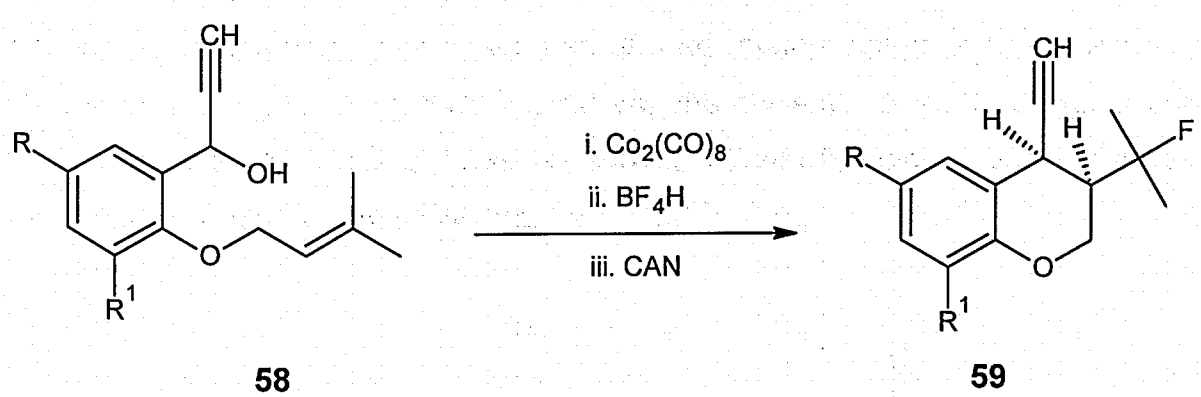
Scheme 1.12: *Synthesis of the exocyclic enyne*

Tyrrell reported [48] a similar *trans* selectivity in the synthesis of the carbocycle **57** *via* an intramolecular Nicholas reaction of **56**, this resulted in the *exo*-cyclic keto compound **57** with *trans* stereoselectivity from hexacarbonyl O-silylether dicobalt **56** (Scheme 1.13).



Scheme 1.13: *Synthesis of exocyclic enyne*

In 1997, Tyrrell [22a] used an intramolecular Nicholas Reaction in the cyclisation reaction to synthesise derivatives of the benzopyran **59** from propargyl alcohol **58**. The various precursors analogous to **58** were synthesised from salicylaldehyde derivatives. NMR studies of **59** were used to elucidate the *cis*-configuration of the key cyclisation reaction (Scheme 1.14).

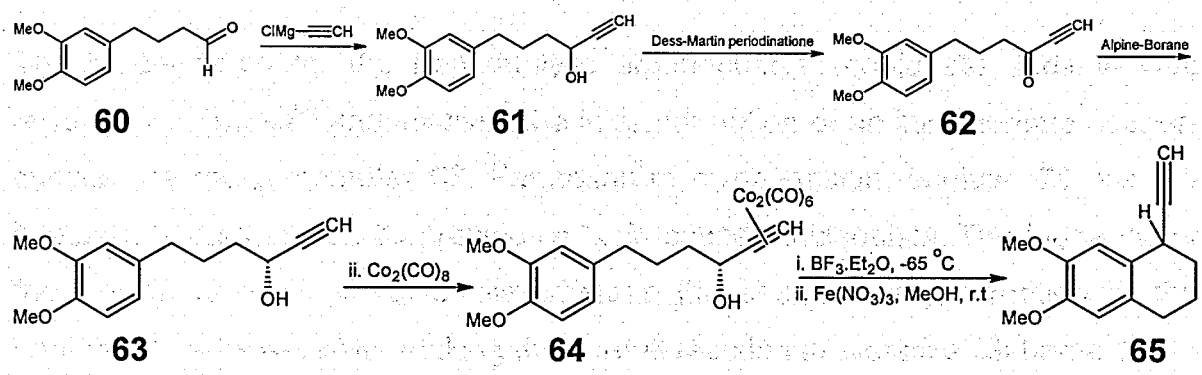


Scheme 1.14: *Synthesis of benzopyrans*

1.3.4.3 The Nicholas reaction of optically active substrates

A stereospecific Nicholas Reaction was reported by Muehldorf in 1994.[49] (Scheme 1.15) and showed that optically active product **65**, formed with limited racemisation. This could result from a Nicholas cyclisation reaction using chiral substrate **63** in an enantiospecific manner. The optically active propargyl alcohol **63** was used to control the selectivity. The author established that three criteria were important in controlling the levels of enantioselectivity, namely the size of the ring being formed, the substitution pattern of the aromatic ring and the type of

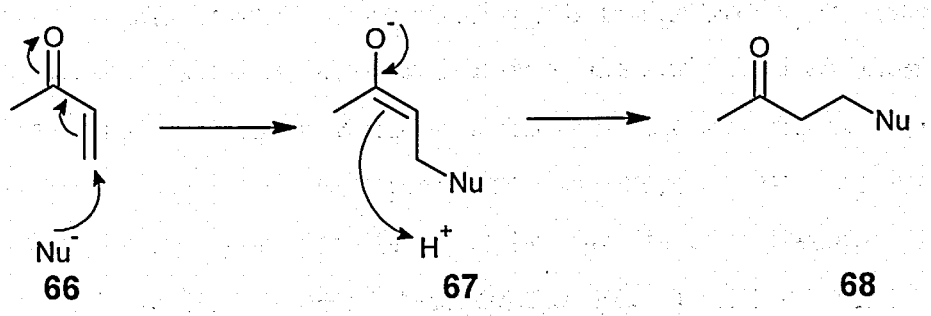
Lewis acid used. The chiral propargyl alcohol in **63** was formed using a three step procedure. This consisted of propargylation of the corresponding aldehyde **60**, oxidation of the propargyl hydroxyl group **61** a ketone **62**, using a Dess-Martin reaction,[50] and then an asymmetric hydroboration using Alpine-Borane[51] to afford **63**.



Scheme 1.15: *A stereospecific Nicholas reaction*

1.4 Conjugate Addition Reaction

The conjugate addition reaction[52] of organometallic reagents to α,β-unsaturated compounds is one of the fundamental methodologies for the construction of C-C bonds.[53] It occurs with enones such as **66** and related compounds i.e. when a C=C bond is conjugated to a C=O bond and the nucleophile (Nu^-) attacks at the C=C instead of the C=O to form the enolate **67** which then adds a proton to afford the extended carbonyl **68** (Scheme 1.16).[54]



Scheme 1.16: *A conjugate addition reaction*

Addition reactions such as this have been used as key steps in the synthesis of numerous biologically active compounds[55,56] and show wide applications because of the use of enone acceptors and the various donors types such as diorganozinc ($ZnEt_2$)[57], triorganoaluminum[58] and Grignard reagents.[59]

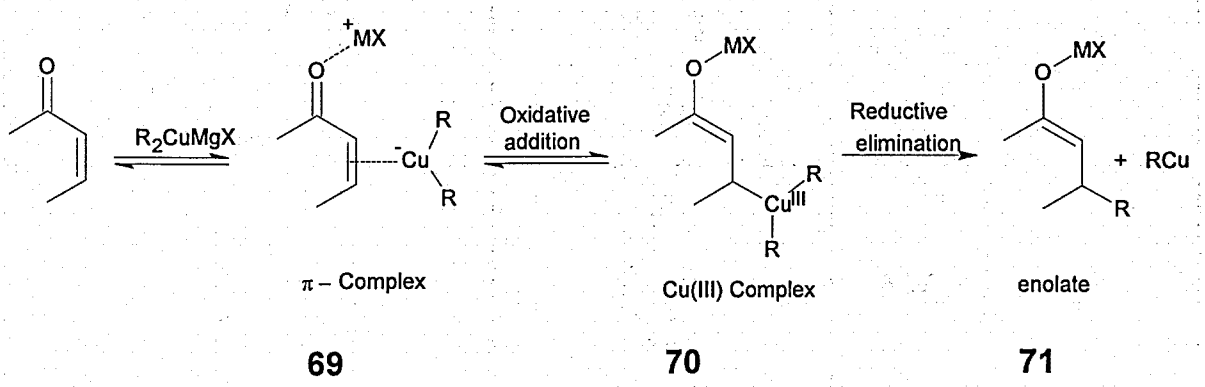
1.4.1 The mechanism of the conjugate addition reaction

The mechanism follows two steps:

(i) addition of the nucleophile to an enone

(ii) protonation of the enolate anion

The mechanisms for the non-catalytic organocuprate conjugate addition was reported by Krauss[60] and involves the initial formation of an intermediate copper-species *via* the π–complex **69**. Formation of a magnesium enolate, **71**, via the copper (III) intermediate **70** provides a "soft" copper nucleophile. The formation of the Cu(III) complex, is reversible whereas the second step, formation of the enolate **71**, is irreversible, making the overall reaction irreversible (Scheme 1.17).[61]



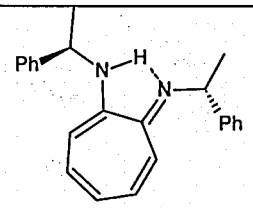
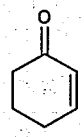
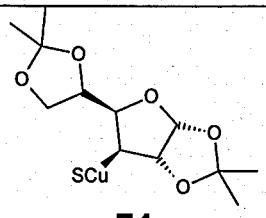
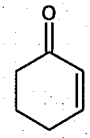
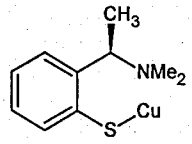
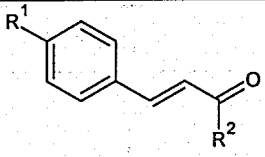
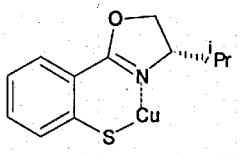
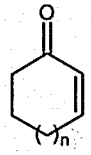
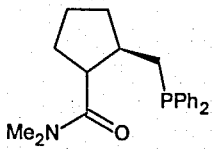
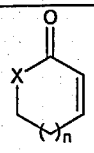
Scheme 1.17: *The pathway of the conjugate addition reaction with organocuprates*

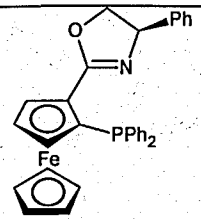
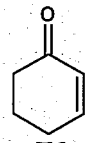
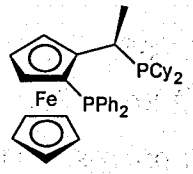
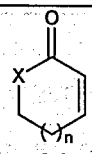
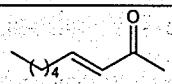
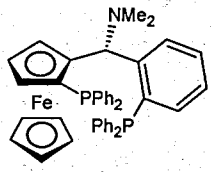
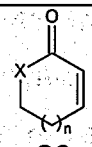
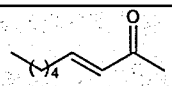
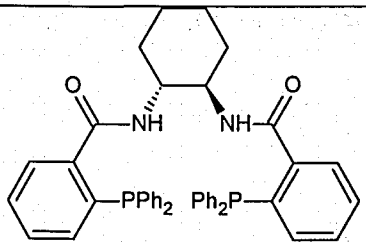
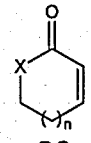
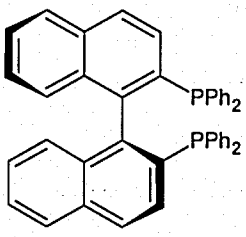
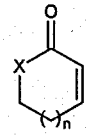
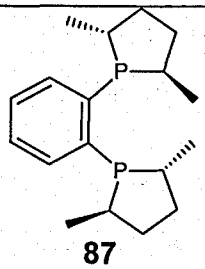
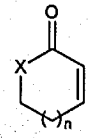
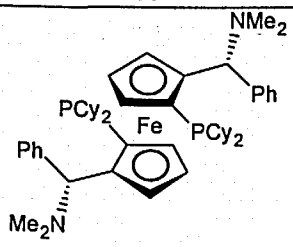
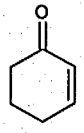
The principle of hard and soft Acid or Base (HSAB)[62] suggests that hard acids favour binding to hard bases whereas soft acids prefer binding to soft bases. A Grignard reagent is identified as a hard nucleophile and therefore usually reacts with the carbonyl carbon atom, which is considered to be a hard electrophile in a 1,2-addition reaction. In the presence of copper (I), however, the Grignard/Copper reagent is considered to be "softer" and therefore undergoes 1,4-addition instead. During the process copper undergoes transmetallation with the Grignard reagent to give an organocopper species which provides a softer centre, compared to the Grignard reagent, which thus favours attack at the corresponding softer C=C bond. Conjugate addition reactions nevertheless tend to compete with 1,2–carbonyl addition reaction in α,β-unsaturated carbonyl compounds.[63] As a general rule in enones, the keto form is more stable than the enol form, however, from a synthesis point of view the enol form is more useful hence the interest in this chemistry.[64]

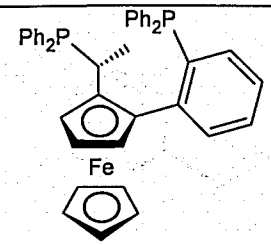
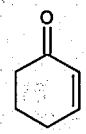
1.4.2 Asymmetric conjugate addition reaction

The first asymmetric conjugate addition to an α,β-unsaturated compound via the use of chiral auxiliary technique [65] a Grignard reagent as a nucleophile was reported in 1988. Other strategies made use of organocopper compounds containing chiral non-transferable groups such as chiral alkoxycuprates and amidocuprates.[55,66] Corey reported[67] enantioselectivities of over 90 % by using a chiral ephedrine-derived lithium alkoxycuprate ($(RO)_2CuLi$).[43,53,68] A representative selection of catalysts are shown in Table 1.3.

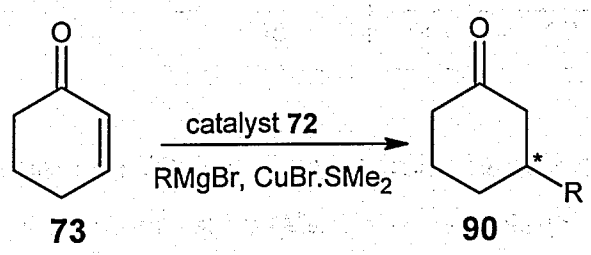
Table 1.3: *Chiral Catalyst for Conjugate Addition Reaction*

Catalyst type	substrate	ee%	references
 **72**	 **73**	4-14%	65
 **74**	 **73**	60%	69
 **75**	 **76**	0-76%	70,71
 **77**	 **78**	16-87%	69
 **79**	 **80**	4-92%	72

 **81**	 **73**	83%	73
 **82**	 **80**	94	59g,74
	 **83**	86	
 **84**	 **80**	96	59g,74
	 **83**	48	
 **85**	 **80**	4	75
 **86**	 **80**	18	76
 **87**	 **80**	25	77
 **88**	 **73**	45	78

 **89**	 **73**	70	79

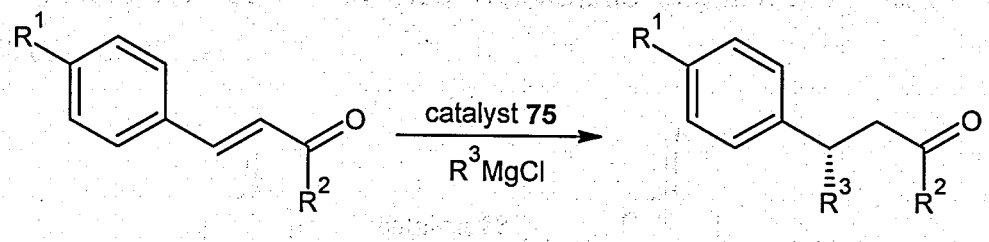
The first truly catalytic reagent **72** was developed by Lippard in 1988 for the conjugate addition of Grignard reagents to enones.[65] This prototype catalyst was successful in carrying out an enantioselective 1,4-conjugate addition to cyclohex-2-en-1-one **73**. Although the yield of the corresponding adduct **90** was acceptable (28-94%) the enantiomeric excess were variable for instance when the R-group of the Grignard reagent was Ph the ee = 4% this rose to 14% when the R-group was changed to *n*-butyl. These values, while low, were comparable to earlier results in this area of catalysis and were nevertheless significant because they were achieved in a system where the chiral ligand-to-substrate ratio was only 0.04, about 200 times less than in recently published work where values of 88% enantiomeric excess were observed [74] (Scheme 1.18).



Scheme 1.18: *Asymmetric conjugate addition reaction*

The chiral catalyst **74** was prepared *in situ* in the presence of the cuprate $CuI.SBu_2$ and *n*-BuLi and then examined for asymmetric conjugate addition to the enone **73**.[69] The highest enantioselectivity was reported with *n*-BuMgBr (ee%: 60 %) using 4 mol % catalyst at -78 °C.

The thiolate **75** was also reported as an active catalyst for asymmetric conjugate addition reactions with Grignard reagents and the enone **76** (Scheme 1.19).[70] Data for the addition reaction with catalyst **75** are summarised in Table 1.4.



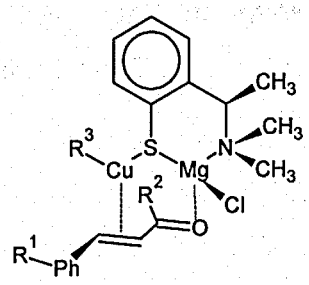
76 **91**

Scheme 1.19: *Asymmetric conjugate addition in presence of catalyst* ***75***

Table 1.4: *Effect of Catalyst* ***75*** *on the Enantiomeric Excess*

R^1	R^2	R^3	ee%
H	Me	Me	76
H	i-Pr	Me	72
Cl	Me	Me	69
CN	Me	Me	13
OMe	Me	Me	56
H	t-Bu	Me	45
H	Ph	Me	0
H	Me	n-Bu	45
H	Me	i-Pr	10

The suggested intermediate **92** was formed from interaction of the catalyst **75** and Grignard reagent with the substrate **76**. The catalyst **75** first reacts with R^3MgBr and the enone bonded with both the copper and magnesium. The double bond is coordinated to copper and the oxygen atom binds to magnesium (Figure 1.18).[71]

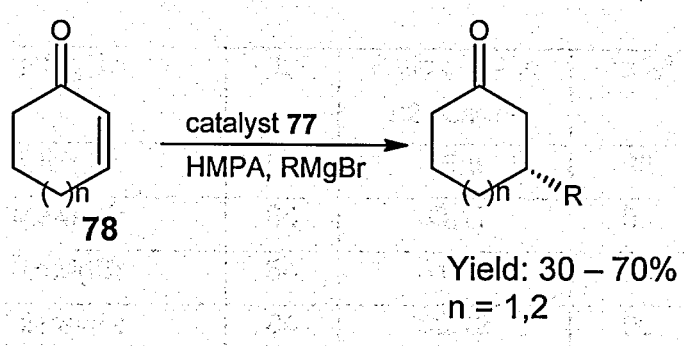


92

Figure 1.18: *The proposed intermediate between catalyst* **75**, *Grignard reagent and substrate* **76**

Zhou and Pfaltz[69] modified the structure of catalyst **75** to the oxazoline **77**. This catalyst showed the highest levels of enantiomeric excess in an asymmetric conjugate addition reaction. This catalyst was evaluated against

several enones such as **78** and also with various Grignard reagents in yields of 30-70% (Scheme 1.20).



Scheme 1.20: *Asymmetric conjugate addition in presence of the catalyst* ***77***

Sammakia[73] reported high enantioselectivities in the conjugate addition to the enone **72** using 12 mol % of the chiral catalyst **81** in conjunction with 10 mol% of CuI in Et_2O. The highest enantiomeric excess (83%) was reported for the addition of the *n*-BuMgCl to **72** in the presence of additive such as HMPA, TMSCl or MeI.

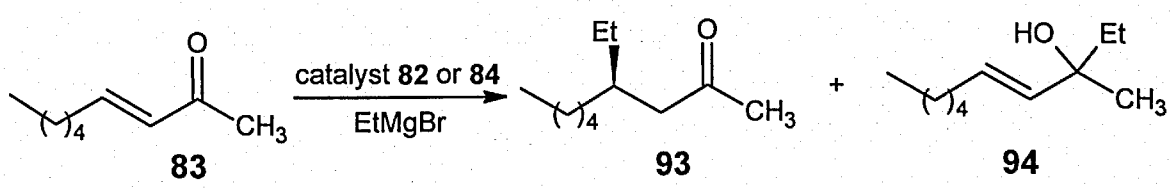
A breakthrough in this area of catalysis came in 2004 when Feringa[52,74,80] synthesised the novel ligands Josiphos **82** and Taniaphos **84** as chiral diphosphines suitable for the 1,4-addition reaction to enone. These catalysts were then used by several groups in 1,4-asymmetric conjugate reactions. [69,81] These ferrocene-based ligands provided high enantioselectivities in conjunction with the cyclic enone **73** with enantiomeric excess up to 96 %[52] (Scheme 1.20). Their results indicated that these ligands in combination with P, S, Se, N or O donor atoms extend the use of copper and magnesium organometallic species in the highly active and selective 1,4-conjugate addition of a wide range of substrates.[72a,b,73,82] The data derived from an investigation into the use of various Grignard reagents are shown in Table 1.5

Table 1.5: *Enantioselective Conjugate Addition to **73** with Catalysts **82** and **84***

RMgBr	L	Ratio of 1:4 to 1:2 addition	ee%[a]
EtMgBr	84	95:5	96
MeMgBr	84	83:17	90
^{n}PrMgBr	84	81:19	94
^{n}BuMgBr	84	88:12	96
^{i}PrMgBr	84	78:22	1
^{i}BuMgBr	84	62:38	33
(2-methyl)BuMgBr	84	76:24	95
4-Cl-BuMgBr	84	79:21	85
^{i}PrMgBr[b]	82	99:1	54
^{i}BuMgBr[b]	82	99:1	92
EtMgBr[b]	82	99:1	56

[a] 98% Conversion after 15 min at 0 °C using CuCl. [b] 98% conversion after 2 h at -60 °C using $CuBr.SMe_2$

Analysis of the data in Table 1.5 reveals that Josiphos **82** controlled the enantioselectivity in the conjugate addition reaction to 2-cyclohexen-2-one **73** with good to excellent enantiomeric excess (54-92%) and very high levels of 1,4-regioselectivity. Taniaphos **84**, on the other hand provided higher levels of enantiomeric excess (90-96% apart from one example) but lower levels of 1,4-regioselectivity.[74] Acyclic enones, such as **83** were also examined in an enantioselective conjugate addition reaction with **82** and **84** (Scheme 1.21). This resulted in the synthesis of β-substituted linear ketones, **93**, and the corresponding 1,2-adduct **94**. The best ratio (**93:94**) was 99:1 and also the best enantiomeric excess was 90 % with EtMgBr in the presence of $CuBr.SMe_2$ at -78 °C.



Scheme 1.21: *Asymmetric conjugate addition to acyclic enones in presence of chiral catalyst **82** or **84***

A tentative model for the stereocontrol was suggested by Feringa[52] who suggested that chelation occurs through the magnesium atom with the carbonyl moiety of the enone as well as between the enone double bond and the copper centre shown in **95**. Formation of a σ-bond between the Cu (III) species and the β-carbon as well as between magnesium and the oxygen generates the enolate **96** *in situ*, via a seven-membered chair-like ring transition state. This sets up the absolute configuration that facilitates attack of the methyl nucleophile from the copper (III) species to the β-carbon of the enone. The transfer of the methyl group is the rate-determining step and is the step where the enantioselective product **97** is formed (Figure 1.19).[52]

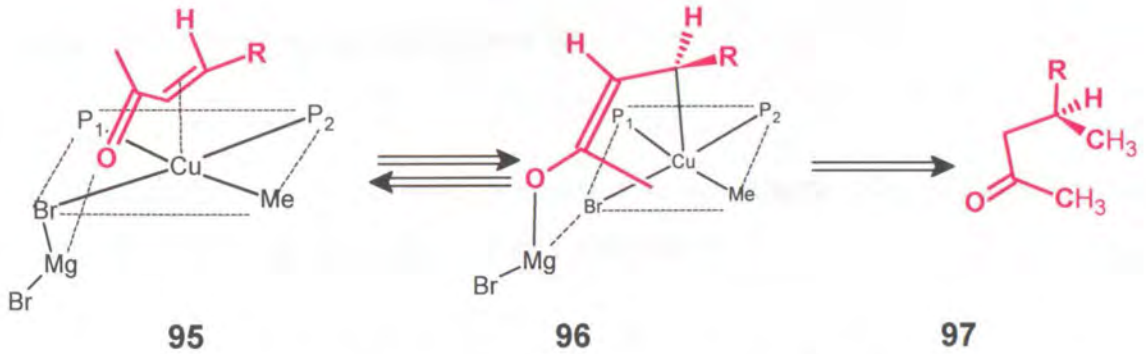
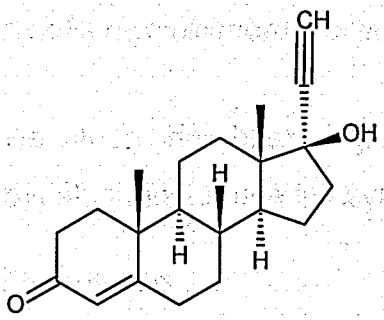


Figure 1.19: *Feringa's model for the enantioselective CA of Grignard reagents*[52]

Monodentate and bidentate chiral diphosphine ligands such as Trost ligand **85**[75], BINAP **86**[76], DuPhos **87**[77] have been employed in a variety of asymmetric conjugate addition reactions. In general the reported enantiomeric exces are quite low (5-28%) which Feringa[74] suggests might be attributed to a mismatch between for instance the diphosphine ligands of the catalysts with the metal atom (Cu, Mg,...) therefore efficiency would be very low. The chiral catalyst containing ferrocenyl-based diphosphine ligands such as MandyPhos **88**[78] and WalPhos **89**[79] have been shown to produce high levels of enantioselectivity (45-70%), (Table 1.3).

1.5 Alkynylation of an aldehyde

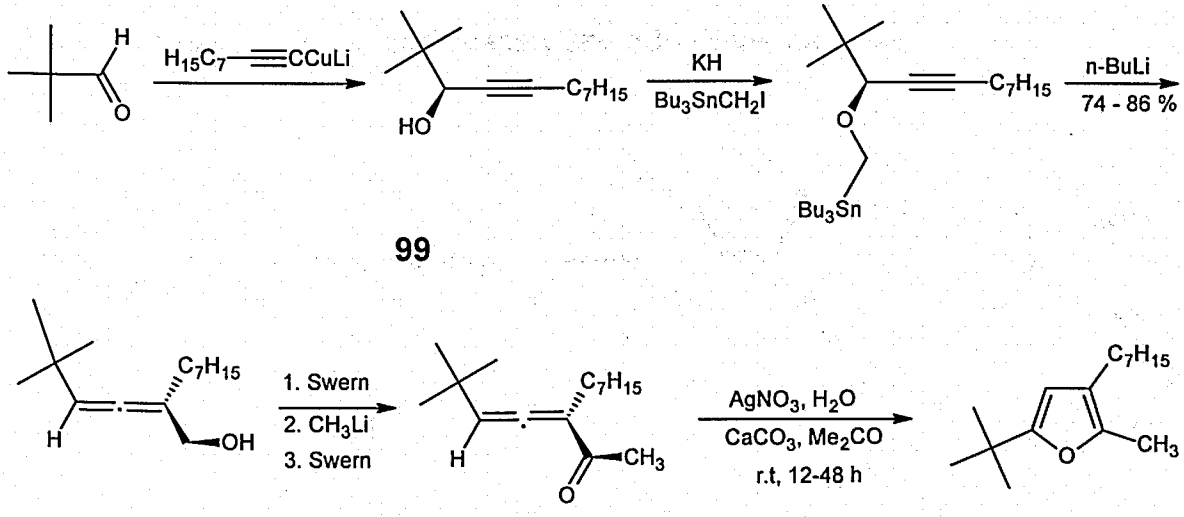
Optically active propargyl alcohols can be found in many natural products and bioactive compounds such as ethisterone **98** (Figure 1.20) and are also widely used as precursors in organic synthesis.



98

Figure 1.20: *Bioactive propargyl alcohol* ***98***

The propargyl alcohol **99** was converted to an allene **100** which was then converted to the furan derivatives with a yield (99%).[83]

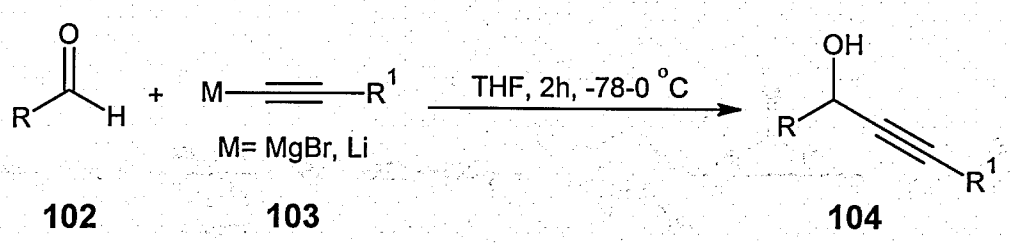


99

100 **101**

Scheme 1.22: *Furan synthesis*

The 1,2-addition of an alkyne to an aldehyde is another variation of an organometallic reaction.[84] The synthesis of a tertiary alcohol from the reaction of an alkynyl Grignard reagent with a ketone is a standard method which has been applied in a variety of applications.[85] A typical example is the addition of a alkyne such as **103** to aldehyde **102** to afford the propargyl alcohol **104** (Scheme 1.23).[86]



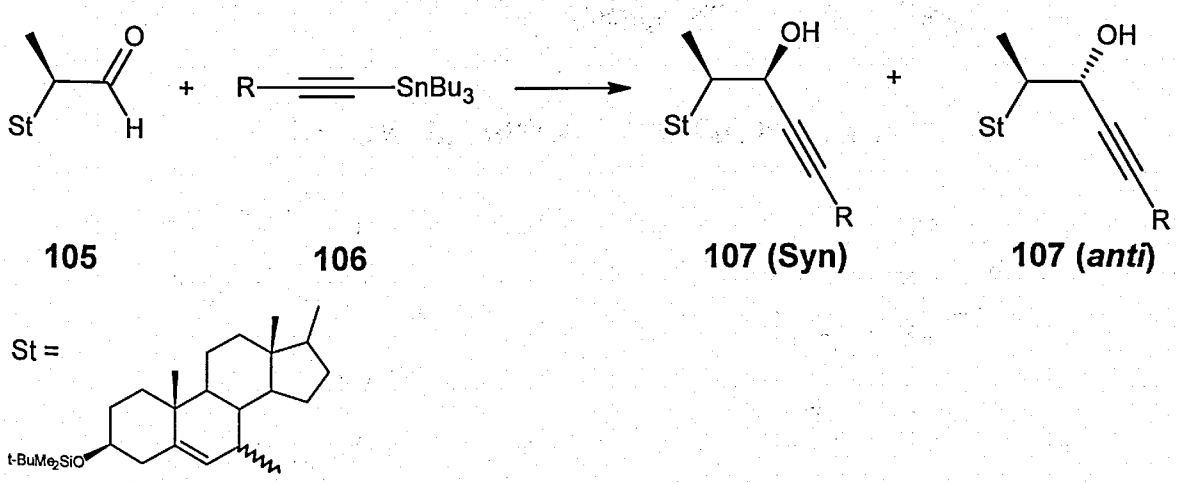
Scheme 1.23: *Synthesis of a racemic mixture of the propargyl alcohol **104***

In recent years, however, there has been a growing interest in the synthesis of optically active propargyl alcohols for use in asymmetric synthesis.

1.5.1 Asymmetric alkynylation

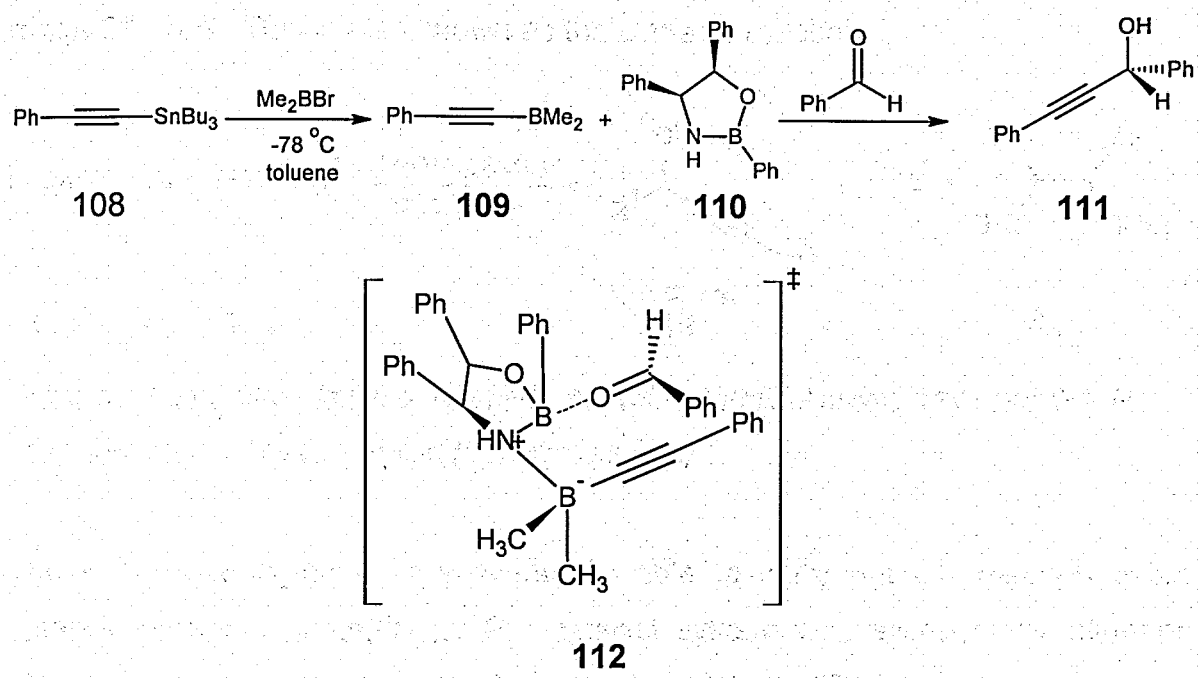
Asymmetric alkynylation reactions are such important transformations in contemporary organic synthesis that several reviews have been published over the past few years.[87] The enantioselective alkynylation of aldehydes has been reported extensively in the literature using a variety of a chiral catalysts, chiral pool molecules and chiral auxiliaries. [87a,b]

Yamamoto[88] reported a highly *syn* diastereoselective (85:15, syn:anti) synthesis of steroidal propargyl alcohol **107** by treating of the steroidal aldehyde **105**, a chiral substrate, with the stannylacetylene **106** (Scheme 1.24).



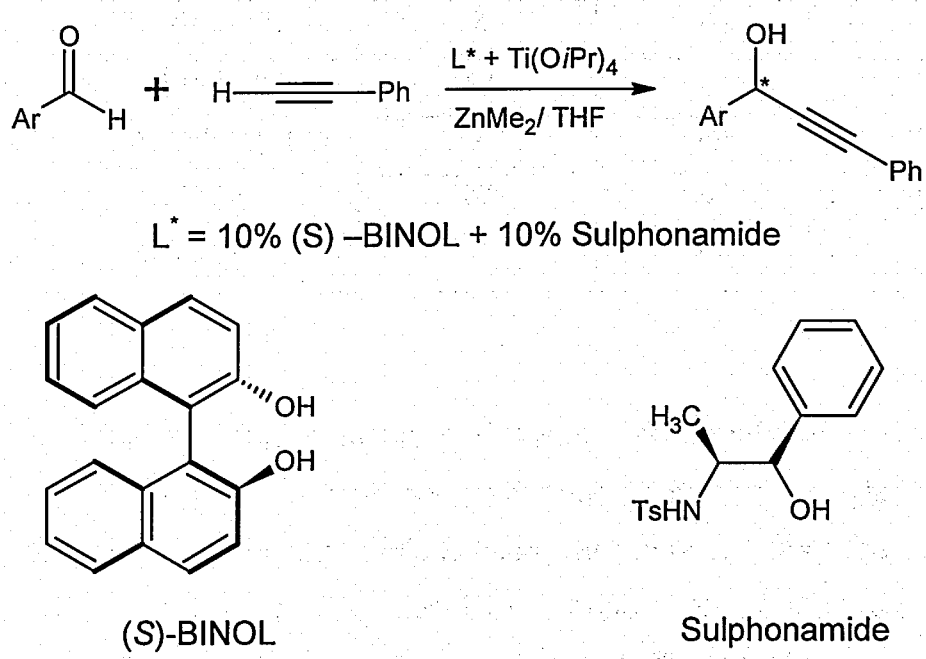
Scheme 1.24: *The syn-diastereoselective synthesis of steroidal propargyl alcohol **107***

A highly enantioselective, (ee = 97 %), alkynylation of benzaldehyde was reported with the use of the chiral oxazaborolidine **110** in the presence of the phenylacetylene dimethylborane **109** formed *in situ* from bromodimethylborane and the corresponding alkynylstannane **108** *via* the transition state **112** (Scheme 1.25) [89]



Scheme 1.25: *The enantioselective alkynylation of benzaldehyde using* oxazaborolidine **110**

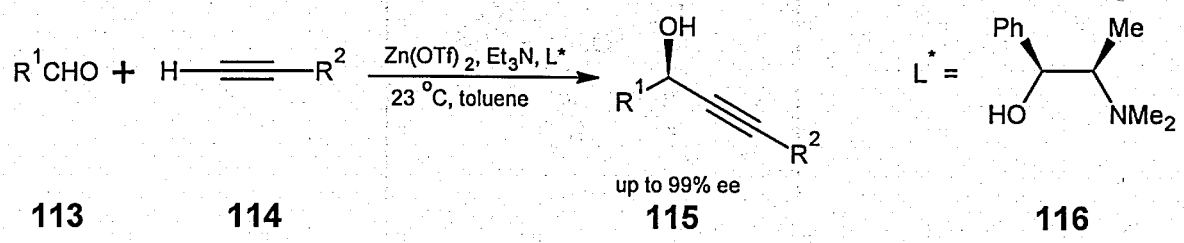
BINOL ligands have been shown to give high enantioselectivities (up to 96 % ee) and yields of 85 % in asymmetric alkynylation reactions (Scheme 1.26).[23d,90]



Scheme 1.26: *Asymmetric alkynylation using (S)-BINOL and sulphonamide*

An efficient system for the enantioselective alkynylation of aromatic and aliphatic aldehydes **113** with terminal alkynes **114** using stoichiometric amounts of (+)-*N*-methylephedrine **116** and $Zn(OTf)_2$ have been reported (Scheme 1.27).[91-92]

Propargyl alcohols, **115** have been obtained with enantiomeric excess in the range 92-99 %. This is also known as the Carreira reaction.



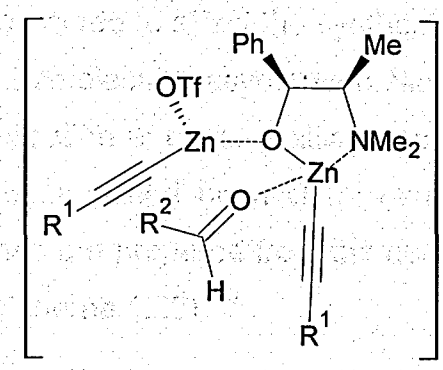
Scheme 1.27: *Alkynylation of aldehyde **113** with a terminal alkyne **114** using (+)- N-methylephedrine **116*** as a ligand *(Carreira reaction)*

The same investigators were eventually able to carry out the reaction using catalytic amounts of $Zn(OTf)_2$. The catalyst system was excellent for aliphatic aldehydes but was less effective for aromatic aldehyde (Table 1.6).

Table 1.6: *Enantioselective Additions of Terminal Alkyne to Aldehyde*[91a,b]

Aldehyde(113)	Alkyne(114)	Time (h)	Yield%	ee %
113a *c*-C_6H_{11}	**114a** Ph	1	99	96 (R)
113b *iso*-Pr	**114b** $Ph(CH_2)_2$	2	90	99(R)
113c PhCH=CH	**114c** $Ph(CH_2)_2$	20	39	80(R)
113d tert-Bu	**114d** $Ph(CH_2)_2$	2	84	99(R)
113e Ph	**114e** Ph	20	53	94(R)
113f Me_3CCH_2	**114f** Ph	2	90	97(R)

The data in Table 1.6 show that the best yields and enantiomeric exces were obtained from the reaction of *iso*-propionaldehyde **113b** and benzylalkyne **114b** and the lowest yield and enantiomeric excess were obtained from the reaction of the **113c** and alkyne **114c**. The absolute configuration of the products was established by correlation with known compounds or by analogy. Thus when (-)-*N*-methylephedrine was used as the ligand, the opposite enantiomer was obtained in comparable yields and enantiomeric excess. The transition state for this reaction, **117**, was proposed by Carreira (Figure 1.21).

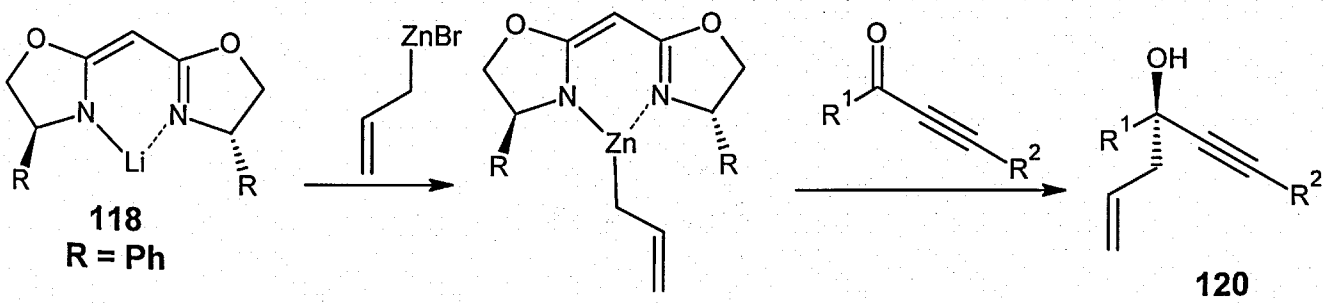


117

Figure 1.21: *The transition state, **117** proposed by Carreira*[91a,91c]

The selectivity is then proposed to arise by chelating the zinc with two alkynes with the nitrogen and oxygen atoms of *N*-methylephedrine therefore the aldehyde is held between two alkynes and shielded by the chiral ligand as showed in **117**.

The asymmetric addition of allylzinc reagents to alkynyl ketones in the presence of a bisoxazoline catalyst, **118** was recently reported.[93] The corresponding propargyl alcohol **120** were obtained in 54-93 % yield and moderate to high enantiomeric excess 25 – 99 % (Scheme 1.28).



118
R = Ph

119

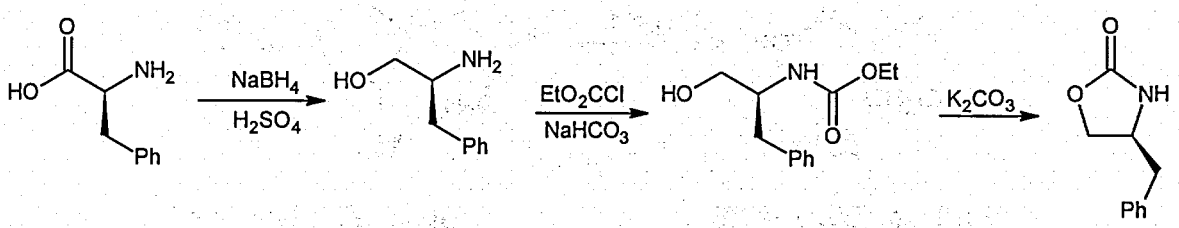
120

Scheme 1.28: *Asymmetric addition of allylzinc reagents to alkynyl ketones*

1.6 Chiral auxiliary

Chiral auxiliary technology has become one of the most powerful strategies for controlling stereoselectivity in an organic synthesis.[94] A chiral auxiliary is a molecule that when added to an achiral compound facilitates an asymmetric reaction to occur by directing the reaction and controlling the 3-D structure of the intermediate which results in the formation of the new chiral center. As part of

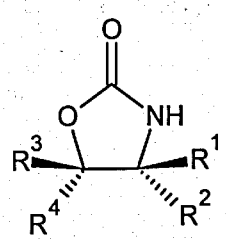
this study an attempt was made to affect the synthesis of a novel chiral aldehyde as a precursor to an intramolecular asymmetric Nicholas reaction. Therefore it was considered the application of chiral auxiliary technology. The most effective chiral auxiliaries have been based upon chiral oxazolidinones such as **122**.[95] Most chiral oxazolidinones are prepared from the corresponding amino acid **121**, a chiral pool molecule (Scheme 1.29).[96]



121 **122**

Scheme 1.29: *Synthesis of chiral auxiliary from amino acid*

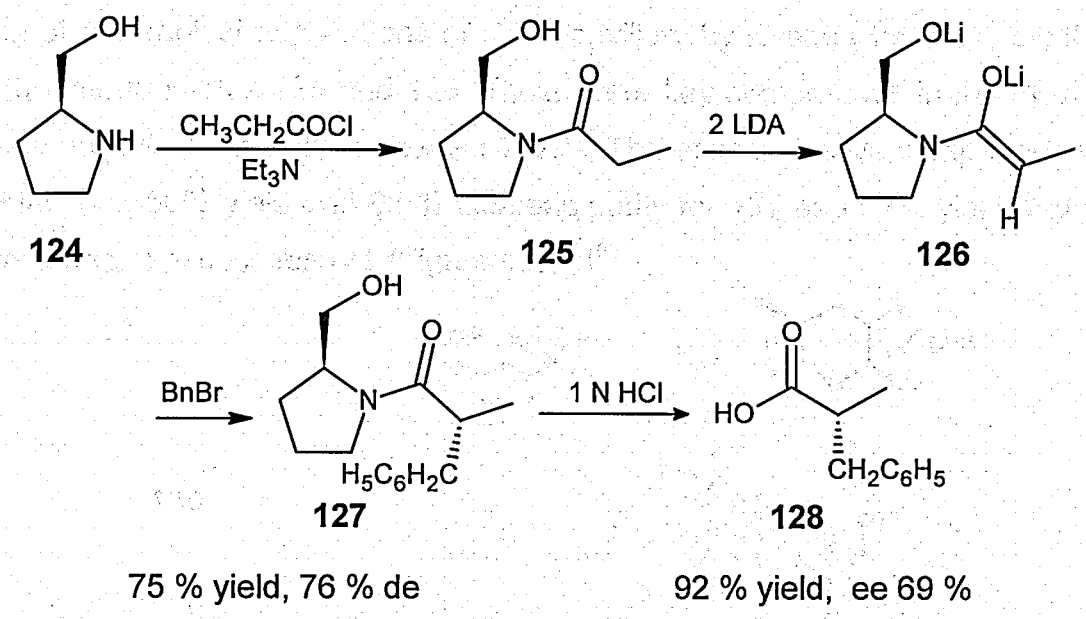
There are three fundamental features of a good chiral auxiliary. First, it must be readily attached under mild experimental conditions, secondly it should be robust and mediate a highly stereoselective transformation and thirdly it must be easily removed without racemization of the newly-created stereogenic center(s), and be separable from the cleaved product.[94a] The class of chiral oxazolidinone, such as **122** and **123** (Figure 1.22) were first introduced by Evans in 1981[94b] and have been used extensively since they readily comply with these three points above.[94a,97]



123

Figure 1.22: *Evan chiral oxazolidinone*

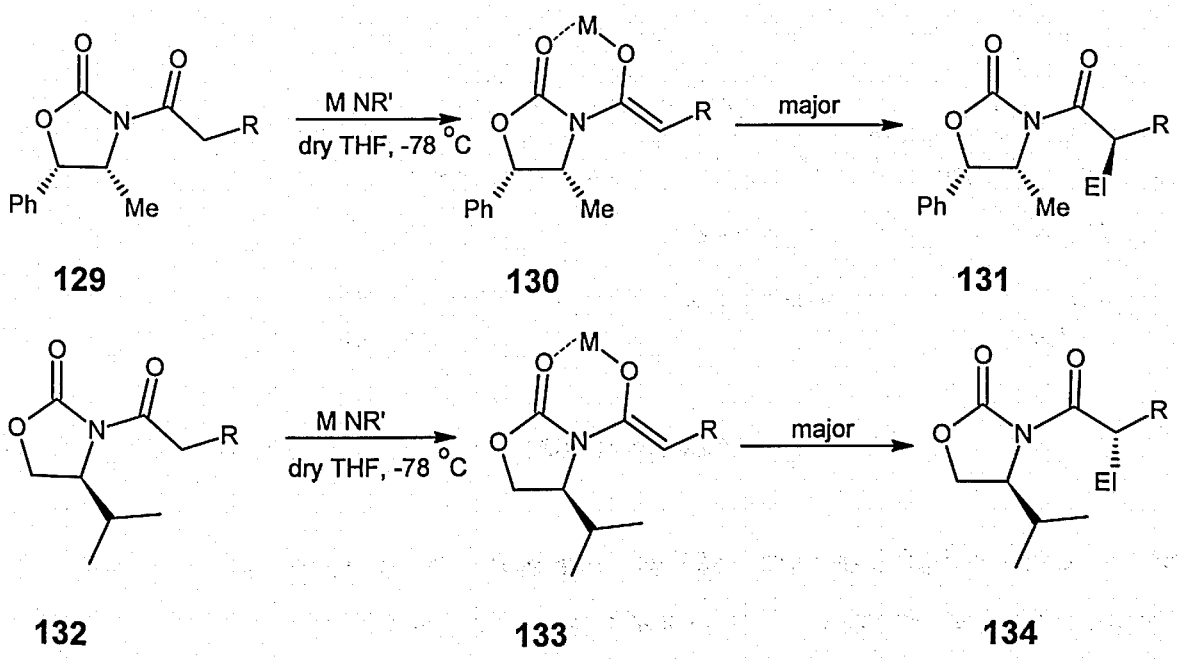
The use of a prolinol amine **124** (chiral amino-alcohol) was one of the first examples of Evan's use of an azolidinone in asymmetric synthesis. The acylation reaction occurred to afford **125** which upon exposure to lithium diisopropylamide (LDA) provided the prolinol amide enolate **126** (Scheme 1.30).[98] Benzylation of the lithium enolate followed by cleavage of the chiral auxiliary provided the chiral acid **128** in 92% yield and an enantiomeric excess of 69 %.[98]



75 % yield, 76 % de 92 % yield, ee 69 %

Scheme 1.30: *Synthesis of an Evan's azolidinone using prolinol amide **124***

Evans also developed the asymmetric alkylation reaction of chiral oxazolidinones using sodium as well as lithium bases [LDA or $NaN(TMS)_2$] which cleanly converted the imides **129** and **132** into the respective (Z)-metal enolates **130** and **133** in quantitative yields around 94 – 99%. The final products optically active carboxylic acids were obtained from the cleavage of the chiral auxiliaries **131** and **134** (Scheme 1.31).[99]



MNR' = $LiN(i\text{-}C_3H_7)_2$ or $NaN(SiMe_3)_2$
El = Electrophile

Scheme 1.31: *Asymmetric alkylation of chiral oxazolidinones via (Z)-metal enolates*

One of the earliest applications of chiral auxiliary by Evans was in his synthesis of the intermediates **135** and **136**. These were key components in the synthesis of the polyether antibiotic monensin **137**.[100] The optically active compounds were achieved in 60% yield and 98 % isomeric purity for **136** and 52% yield and 90% enantiomeric excess for **135** (Figure 1.23).[100]

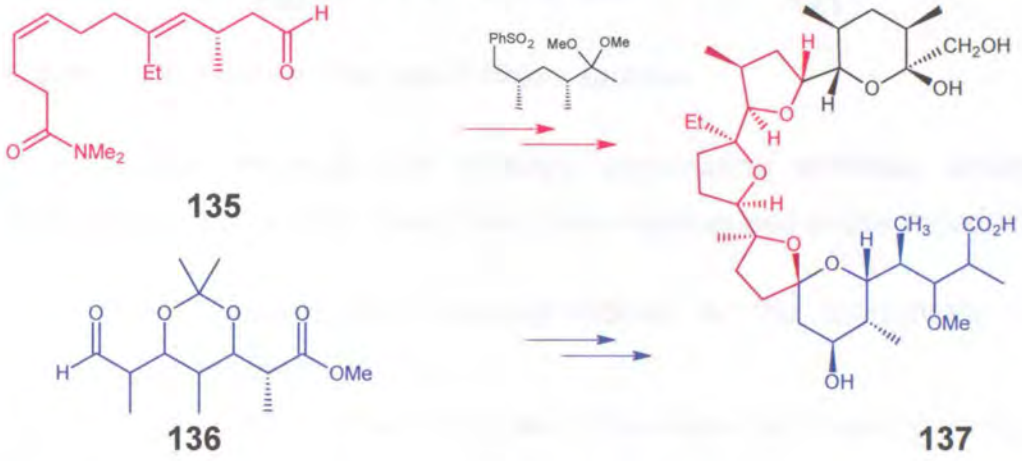
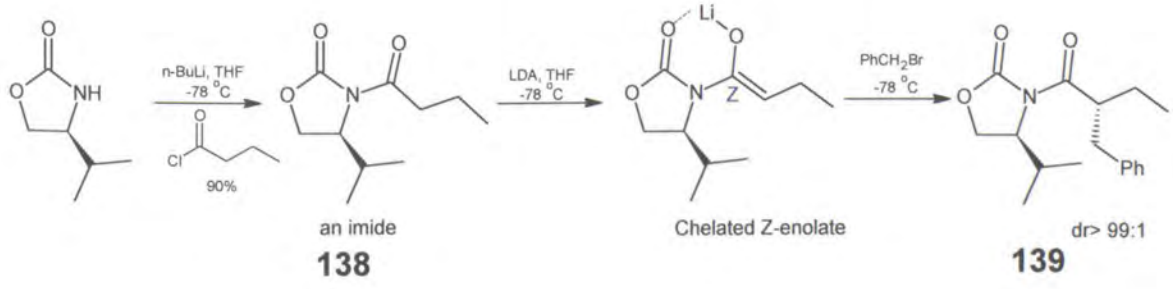


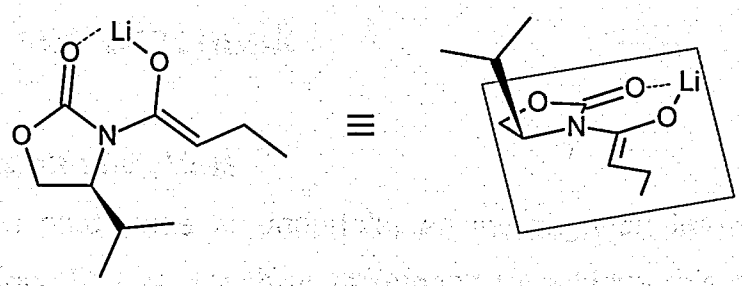
Figure 1.23: *Structure of monensin **137** and two precursors*

In general chiral oxazolidinone auxiliaries control the alkylation reaction to produce the inverse configuration to the auxiliary itself. For example the alkyl oxazolidine **139** has an (*R*)-configuration in the newly formed chiral center due to the chelated Z-form lithium enolate in the precursor (Scheme 1.32)[95,100]



Scheme 1.32: *Alkylation of the oxazolidinone auxiliary*

Generally, *N*-butanoyloxazolidinones such as **138** form the *Z*-lithium enolate **140** selectively rather than E-form and this chelate then controls the subsequent alkylation reaction as preferential attack occurs from the face of the enolate **141** that is opposite the bulky isopropyl group (minimization of steric interactions) (Figure 1.24)



140 **141**

Figure 1.24: *Evans imides form Z-lithium enolates*

In conclusion because four different asymmetric synthetic strategies were attempted in this project, these have been summerised in this Introduction:

(i) Chiral catalyst (+)-N-methylephedrine for the asymmetric alkynylation reaction

(ii) Josiphos **82** and Taniaphos **84** for the asymmetric conjugate additions.

(iii) Chiral pool synthesis for the formation of novel chiral propargylic alcohols

(iv) Chiral auxiliary technology

2 Results and Discussion

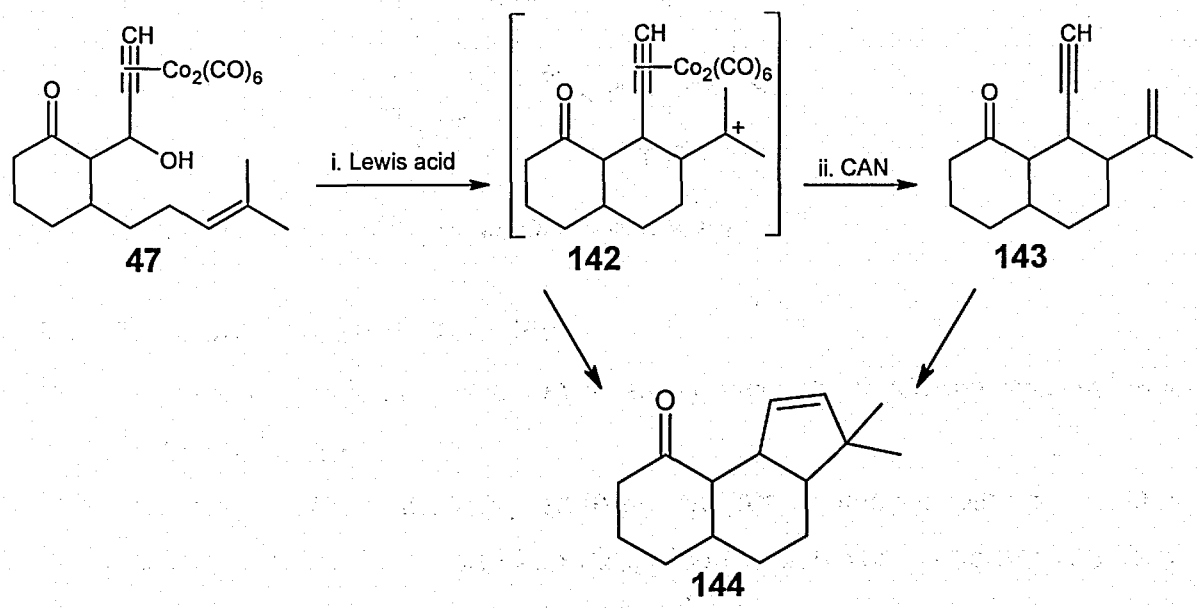
2.1 Introduction and Aims

The aim of this study was to undertake an investigation into an asymmetric Nicholas reaction. The approach in attempting to achieve this goal involved a number of different methodologies that are available to synthetic organic chemists:

(i) The use of a chiral catalyst (section 2.3.1)
(ii) The use of chiral substrate (chiral pool) (section 2.6)
(iii) The use of chiral auxiliary technology (section 2.7)

At the commencement of this study however it was decided to explore an interesting tandem reaction that had previously been investigated in the Kingston University laboratories, but not optimised. A tandem reaction is one in which several bonds are formed in sequence without changing the reaction conditions.[101]

The reaction sequence is shown in Scheme 2.1.



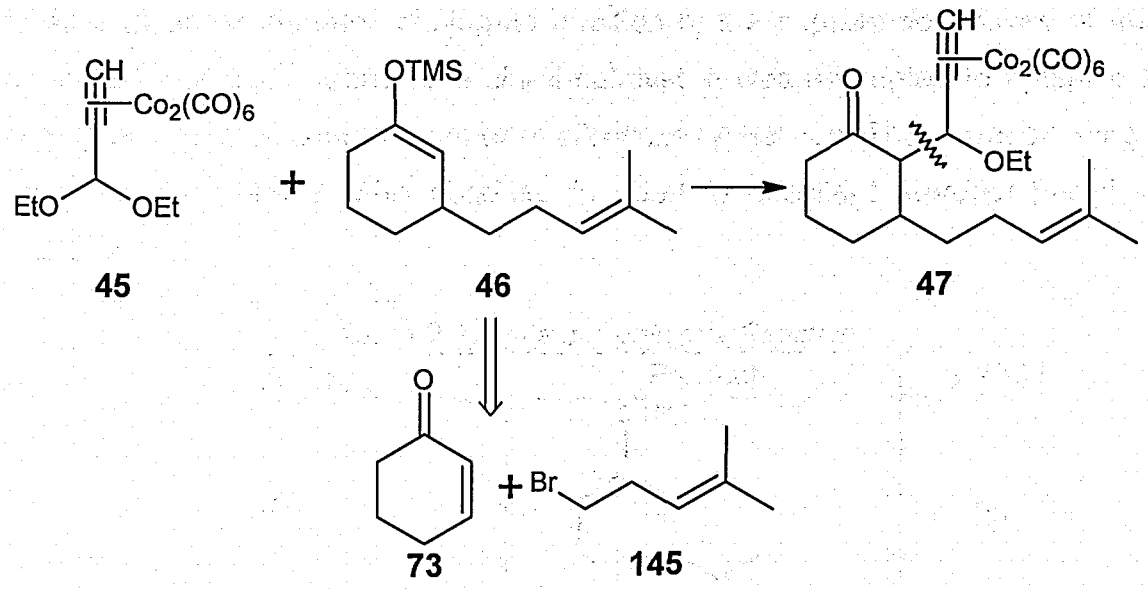
Scheme 2.1: *Tandem cyclisation reaction*

The expected decalone **143**, resulting from a Nicholas cyclisation reaction, was not isolated however the tricyclic compound **144** was obtained instead. It was deduced that during the decomplexation reaction an additional tandem cyclisation occurred to afford the tricyclic compound **144**. This was an unprecedented sequence of reactions.[44] Optimising this chemistry would provide

a sound introduction to the later more challenging techniques that would be required. The initial investigation focussed upon the non-asymmetric tandem reaction sequence and once this was optimised the asymmetric synthesis would be undertaken.

2.2 The tandem cyclisation reaction

The cobalt complex **47** was synthesised by an intermolecular Nicholas reaction between the O-silylenol ether **46** and the complexed propargylic diacetal **45** shown in the Scheme 2.2. The O-silylenol ether **46** was formed by the conjugate addition reaction of cyclohexen-1-one **73** with the cuprate-derivative of 5-bromo-2-methylpent-2-ene **145**.

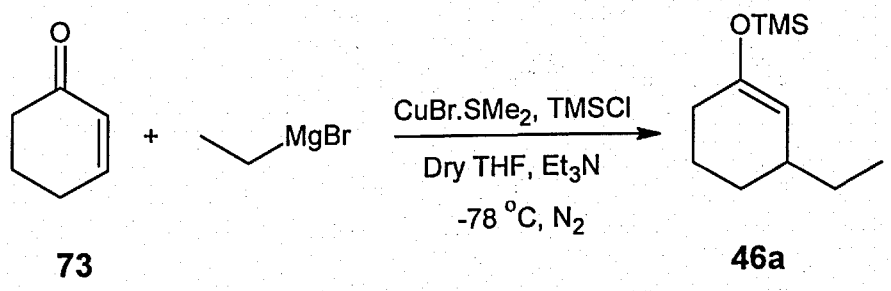


Scheme 2.2: *Synthesis of the cyclisation precursor 47*

2.2.1 Conjugate Addition Reaction

The 1,4–conjugate addition reaction in the presence of copper catalyst was described in section 1.4.

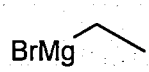
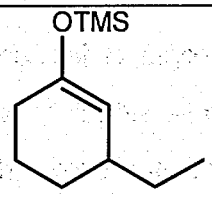
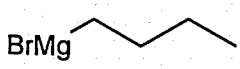
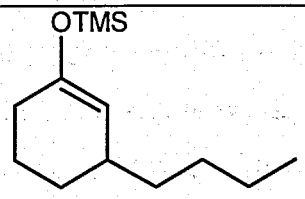
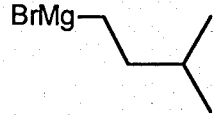
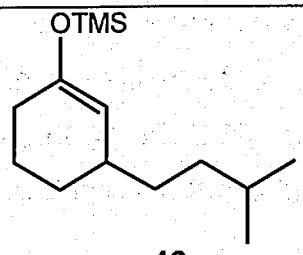
In a model study it was first attempted the conjugate addition of ethylmagnesium bromide with 2–cyclohexen-1-one **73** entrapping the corresponding enolate as an O-silylenol ether derivative **46a** (Scheme 2.3). [102]

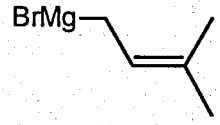
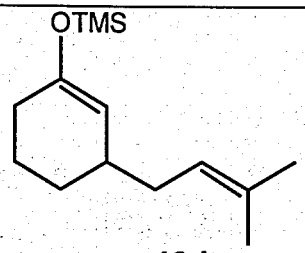
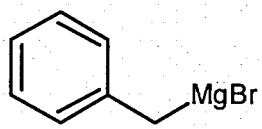
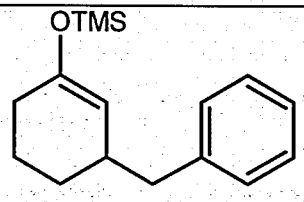
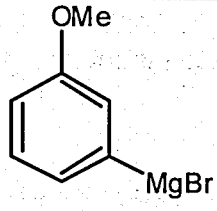
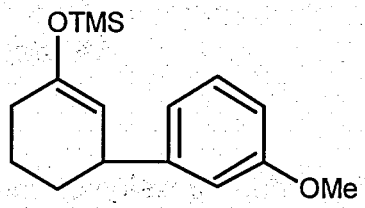


Scheme 2.3: *1,4-conjugate addition of Grignard reagent with 2-cyclohexen -1- one*

This involved the addition of TMSCl and the enone **73** to a solution of ethylmagnesium bromide and $CuBr.Me_2S$ maintained at a temperature of -78 °C under an atmosphere of nitrogen. The reaction mixture was quenched when the solution acquired a dark blue coloration. Analysis by tlc showed a fast moving compound with an R_f = 0.81 (petroleum spirit: ether 80: 20). Purification by flash chromatography on silica gave the desired enone **46a** in a yield of 90 % as a colourless oil. IR analysis revealed the loss of the carbonyl peak (C=O, stretch) of enone **73**, at 1720 cm^{-1}, and the presence of peaks at 1095.1, 1186.1, 1251.6 cm^{-1} attributed to O-Si and $Si(CH_3)_3$ bonds. The ^1H NMR spectrum showed relevant resonance at δ 0.00 ppm, attributed to $Si(CH_3)_3$ and a doublet at δ 4.9 ppm attributed to the =C<u>H</u> proton. As the eventual aim in this present study was to attempt an asymmetric conjugate addition of the cuprate derivatives of **46** to enone **73**, using an appropriate chiral catalyst, it was attempted to optimise the conjugate addition using a number of alkyl/alkenyl halides. The corresponding O-silylenol ethers **46a-f** were obtained in good to excellent reproducible yields. (Table 2.1)

Table 2.1: *Data of Conjugate Reaction*

R–Mg	Product	% Yield
	 **46a**	90
	 **46b**	99
	 **46c**	97

	 **46d**	90
	 **46e**	80
	 **46f**	82

2.3 Nicholas Reactions

2.3.1 Intermolecular Nicholas reaction

Having successfully synthesised a range of O-silylenol ethers **46a-f** the project focussed on the intermolecular Nicholas reaction between the O-silylether **46** and the cobalt cluster **45** (Scheme 2.2). This was carried out by stirring a equimolar mixture of the cobalt cluster **45** and O-silylenol ether **46** in a flame-dried two-neck flask containing dry DCM maintained at a temperature of -78 °C. Boron trifluoride diethyletherate ($BF_3.OEt_2$) was added and the solution was left to stir for 3 hours at -78 °C before allowing it to reach room temperature. TLC analysis of the reaction mixture confirmed the presence of a new compound with R_f = 0.6 (Petroleum ether (60 °C – 80 °C): diethyl ether 70:30). After purification the desired complex **47** was obtained in a yield of 85 %. IR analysis (Figure 2.1) disclosed the ketone carbonyl peak of at 1712.13 cm^{-1} as well as peaks at 2025.76, 2054.07 and 2094.31 cm^{-1} attributed to the cobalt carbonyl moieties.

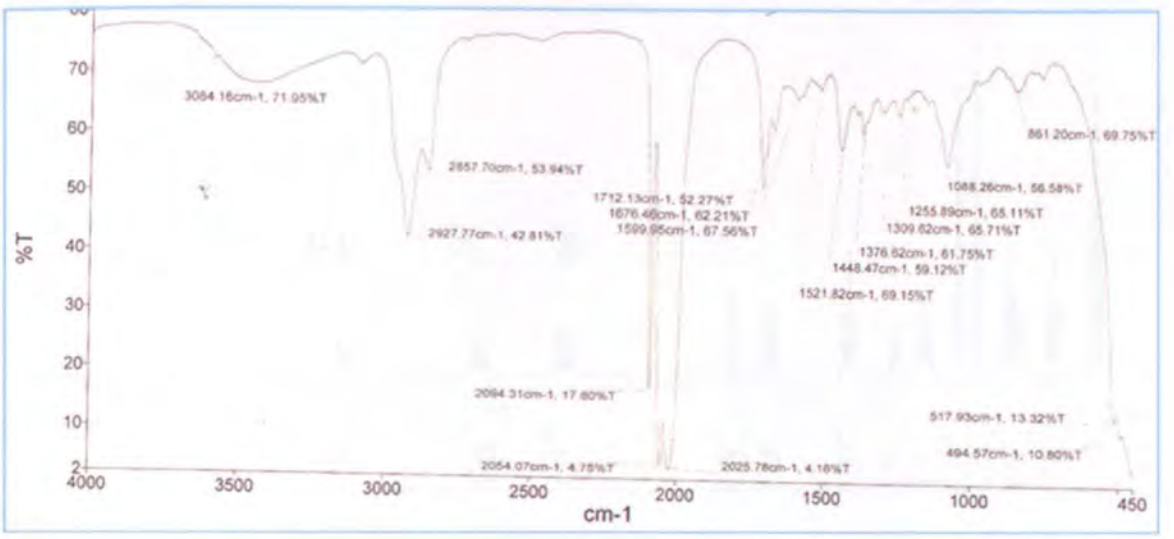
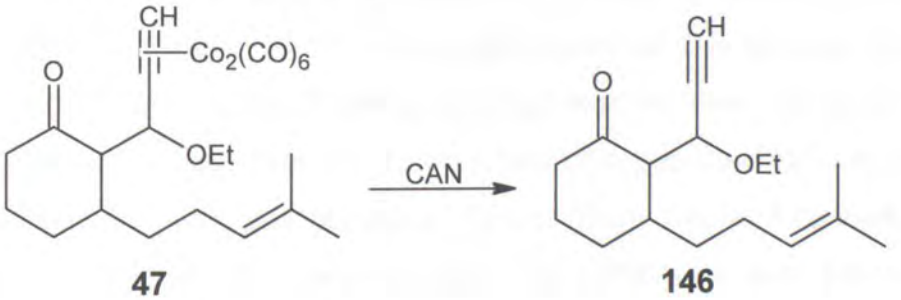


Figure 2.1: *IR spectrum of cobalt complex* ***47***

As spectral characterisation of cobalt complexes such as **47** can sometimes be thwarted by the presence of paramagnetic cobalt species, that lead to signal broadening and loss of acuity in the NMR spectra, a sample of the complex **47** was decomplexed to afford **146**.



Scheme 2.4: Decomplexation of **47**

The ^{1}H NMR spectrum for **146** confirmed the structure of the product (Figure 2.2). ^{1}H NMR showed a multiplet at δ 5.15-5.10 ppm (1H) attributed to H̲C=C, a doublet of doublets at δ 4.10 ppm (1H, J = 8.0, 1.9 Hz) attributed to CH̲OEt, a multiplet at δ 3.6-3.5 ppm (1H) and a multiplet at δ 3.25 – 3.18 ppm (1H) attributed to CH_2̲CH_3. The terminal alkyne proton showed a broad singlet at δ 2.55 ppm. A multiplet at δ 2.38-2.45 ppm (2H) attributed to CH_2̲C=O, 10 proton showed multiplets at different resonaces, at δ 2.13-1.33 ppm attributed to four CH_2̲ and two CH̲); 2 singlets at δ 1.65 ppm and 1.69 ppm are attributed to (6H, 2 x =$C(CH_3)_2$); a triplet at δ1.15 ppm (3H, J = 7.2 Hz) attributed to CH_2̲CH_3.

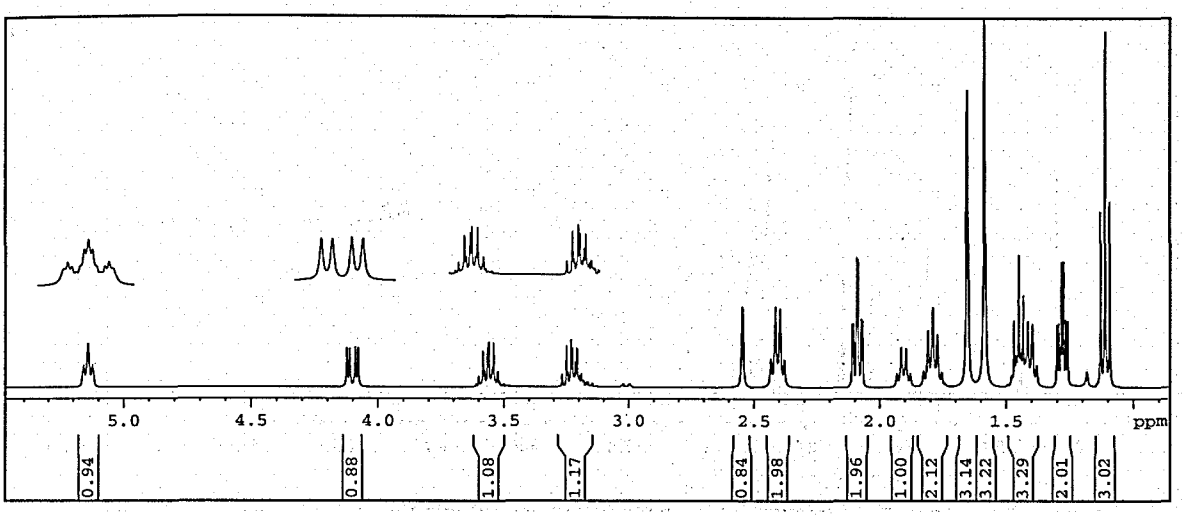


Figure 2.2: *^{1}H NMR spectrum of **146***

2.3.2 Intramolecular Nicholas Reaction

The corresponding intramolecular Nicholas reaction was achieved by adding Lewis acid $BF_3.Et_2O$ to a solution of **47** dissolved in DCM at -78 °C. Tlc analysis after 3h showed the presence of a new compound with an Rf 0.5 (petroleum ether: ether 70:30). Decomplexation, of the dicobalt hexacarbonyl cluster, was achieved by an oxidative addition reaction using CAN at 0 °C.
GC–MS analysis of the product showed only one peak with a mass of m/z 218 and extensive NMR studies confirmed the structure was **144** obtained in a yield of 35 % from **47**. The spectra were in agreement with those previously published.[44] Thus from the ^{1}H NMR spectrum (Figure 2.3) resonances at δ 0.65 and 0.85 ppm showed the existence of the dimethyl group and two olefinic resonances were seen at δ 5.42 ppm (1H, dd, J = 5.8, 4.2 Hz) and δ 5.72 ppm (1H, d, J = 5.8 Hz). Of significance was a complete absence of a resonance for the terminal alkynyl-H hydrogen at approximately δ 2.5 ppm. The ^{13}C DEPT revealed the presence of two sp^2 hybridised carbon atoms (=CH) at δ 130.86 and δ 142.35 ppm and four methine (C-H) carbon atoms between δ 46.65 ppm and 60.50 ppm.[44]

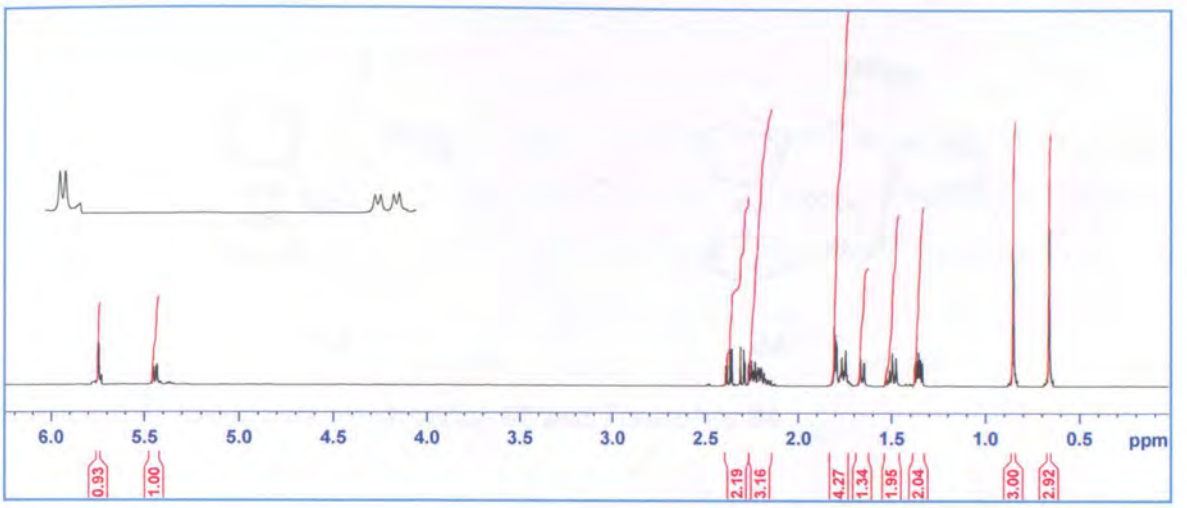
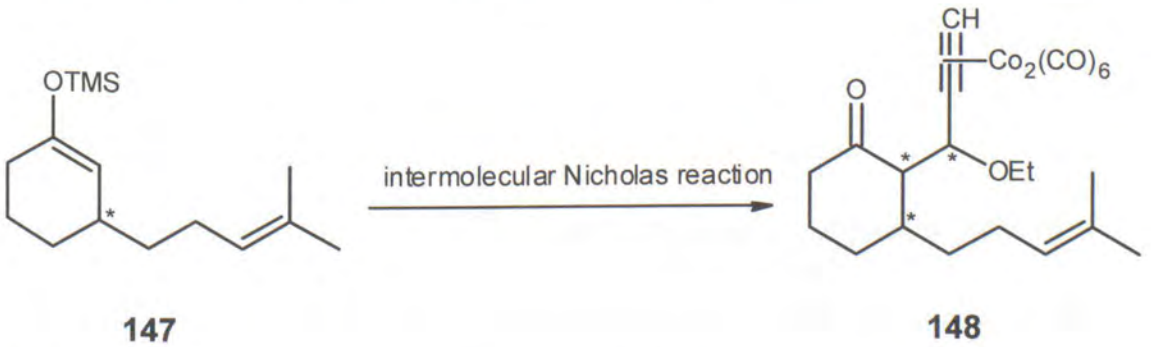


Figure 2.3: *^{1}H NMR spectrum of tricycle **144***

2.4 Asymmetric Tandem Reaction

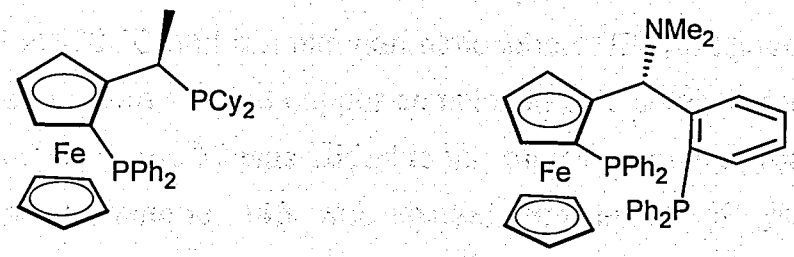
The reactions exposed in the previous sections were repeated asymmetrically. This envisaged that the reaction sequence began with the use of a chiral catalyst to control the stereochemistry of the initial conjugate addition step. This would provide enantio enriched O-silylenol ether **147**. With the C-3 chiral centre in **147** controlled this envisaged that it would then influence the stereochemical outcome of the corresponding intermolecular Nicholas reaction to provide **148** (Scheme 2.5)



Scheme 2.5: *Asymmetric intermolecular Nicholas reaction*

2.4.1 Chiral catalyst

A survey of the literature highlighted two potential catalyst candidates for the asymmetric conjugate addition reactions [59g,74] these are Josiphos **82** and Taniaphos **84** (Figure 2.4).



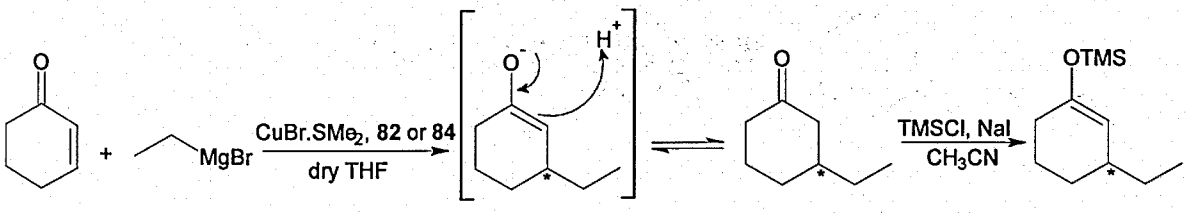
82 **84**

Figure 2.4: *Chiral catalyst Josiphos* **82** *and Taniaphos* **84**

According to the literature these have been used to good effect and produced enantiomeric excess of 80 – 96 %[59g,74] in conjugate addition reactions to substrates such as enone **73**. The enantioselectivity observed has been rationalised upon the basis that the ligands cover one face of the substrate allowing attack of the cuprate from the other face.[52]

2.4.2 Asymmetric 1, 4 – conjugate addition

A model asymmetric conjugate addition reaction was carried out between enone **73** and the organometallic species in the presence of either catalyst **82** or catalyst **84** (Scheme 2.6).



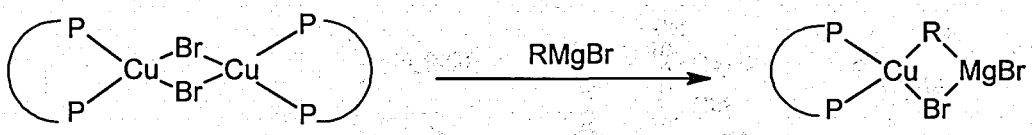
73 **149** **150**

Scheme 2.6: *Asymmtric 1,4-conjugate addition in presence of catalyst* ***82*** *or* ***84***

In the literature procedure the compound isolated from the initial asymmetric conjugate addition was the ketone, equivalent of **149** rather than the corresponding O-silylenol ether derivative **150** and so there was no assurance that these catalysts would perform in the desired way.

In the initial attempt at the synthesis of **150** the literature procedure was followed, however, TMSCl was added in order to quench the enol form. The isolated yield for this was low and purification very challenging. It was then decided to initially isolate the chiral ketone **149** and then generate the enolate derivative **150** in a second step. To prepare the copper complex (Scheme 2.7) copper bromide

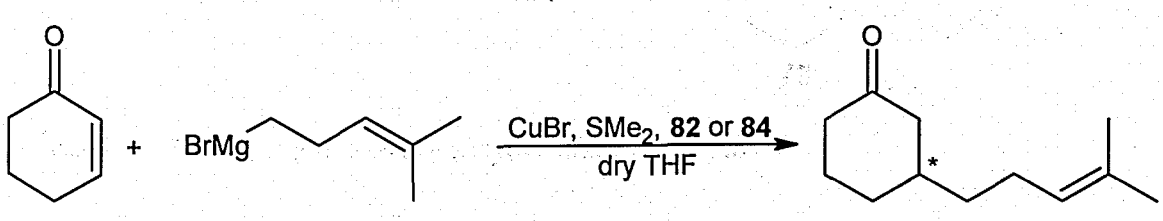
dimethyl sulfoxide (5 mol %) was mixed with Josiphos **82** or Taniaphos **84** (6 mol %) in dry THF at -78 °C under a nitrogen atmosphere. Ethylmagnesium bromide was then added to form a chiral copper complex in 5 % catalytic amount, where upon cyclohex-2-en-1-one **73** was added to this mixture and the product isolated. The optical active ketone **149** was synthesised in 98 % yield, with an enantiomeric excess of 70 % which was determined by divided observed rotation by maximum rotation. The specific rotation $[\alpha]_D^{21}$ = +11° (c = 2.5% in chloroform) compared favourably with the literature value for the enantiomer of **150** is -10.3° (c = 2.9% $CHCl_3$)[59g,103]



Complex A

Scheme 2.7: *Copper complex from mixture of chiral catalyst **82** or **84** with copper catalyst and Grignard reagent*

The same reaction conditions were used with the alkenyl Grignard derivative of **145** to afford the desired ketone **151** (Scheme 2.8)



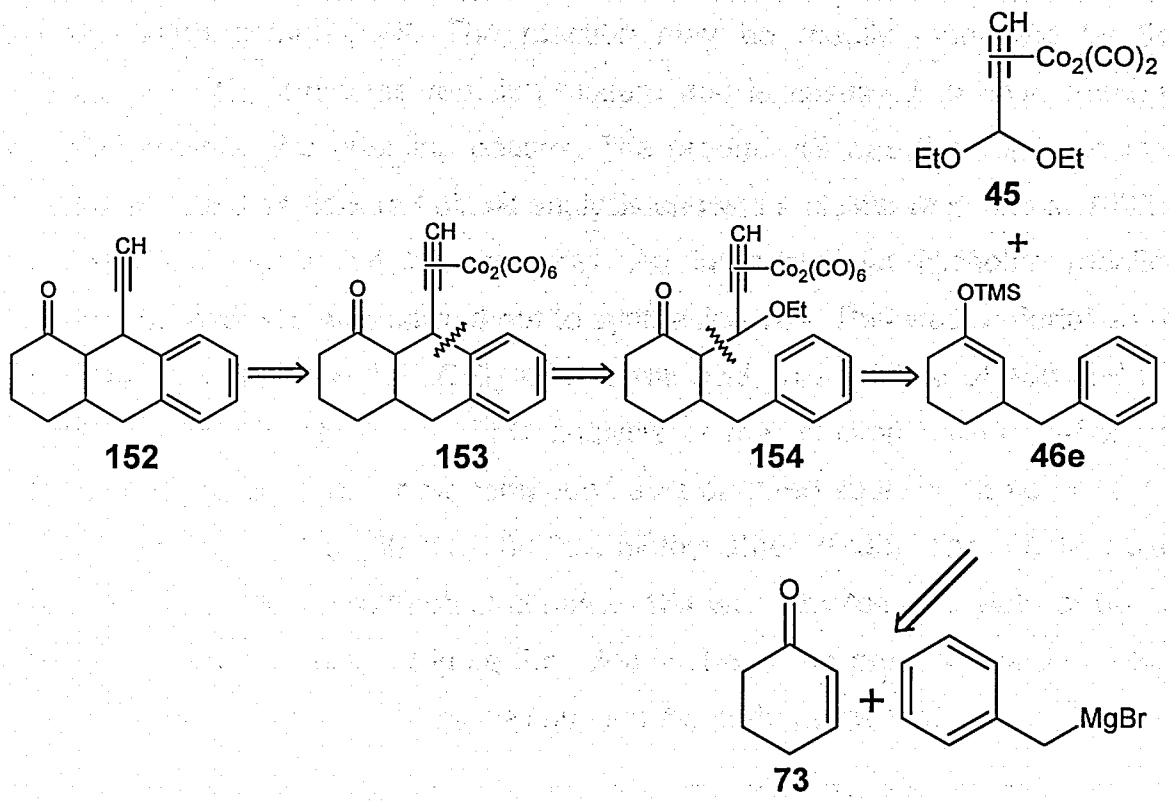
73 **151**

Scheme 2.8: *Asymmetric 1,4-conjugate addition*

This was obtained in an excellent yield of (92 %) however unlike ketone **149** it was devoid of any optical activity. This is despite the fact that both Josiphos **82** and Taniaphos **84** are reported to be potent chiral catalysts for asymmetric conjugate addition reactions of aromatic, alkyl and alkenyl Grignard reagents with cyclohexenones.[59g,74] It would appear however that for longer chain substrates these were not effective catalysts. Having been thwarted by the poor performance of these catalysts an alternative strategy involving the conjugate addition of a benzyl derivative was adopted.

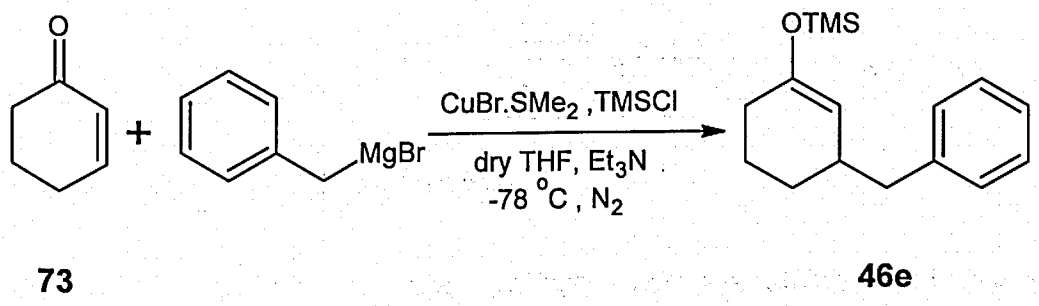
2.4.3 Retrosynthetic analysis

An alternative strategy to achieve the goal was in the synthesis of the tricyclic compound **152** formed in an analogous sequence of reactions that begins with the conjugate addition of benzylmagnesium bromide to the enone **73** (Scheme 2.9).



Scheme 2.9: *Retrosynthesis of tricyclic compound **152***

The first step was to achieve the synthesis of the O-silylenol ether **46e** which was synthesised using standard reaction conditions (Scheme 2.10).



Scheme 2.10: *1,4-conjugate addition of Grignard reagent with 2-cyclohexen-1-one **73***

Analysis of the reaction mixture by tlc showed the presence of a new compound (R_f = 0.3 hexane: diethyl ether 70:30) and a complete absence of the starting

material. The new compound was isolated (96 %), purified and spectroscopically analysed. GC-MS showed one peak with m/z 260 and the ^{1}H NMR spectrum revealed a multiplet at δ 7.34–7.26 ppm (5H) and a doublet of triplets at δ 4.87 ppm (1H) J = 7.0, 2.3 Hz consistent with the vinyl proton. A single sharp resonance at δ 0 ppm (9H) confirmed the presence of the TMS group. Reaction of diethoxypropyne, dissolved in DCM, with dicobalt octacarbonyl gave the corresponding complex **45**. The reaction may be readily monitored by the evolution of $CO_{(g)}$ from the reaction mixture and is assumed to have reached completion when the bubbling ceases. The product **45** was then isolated in a quantitative yield as dark red oil. IR analysis showed a cluster of peaks at 2023.8 cm^{-1} attributed to cobalt hexacarbonyl. An intermolecular Nicholas reaction between **45** and **46e** was carried out to synthesise **154**. This was undertaken by the dropwise addition of $BF_3.OEt_2$, as a Lewis acid, to a mixture of **46e** and the cobalt complex **45** at -78 °C. TLC analysis of the reaction mixture, after 3h, showed the presence of a new compound as a dark red spot on the tlc plate (R_f = 0.51 petroleum ether (60 °C – 80 °C): diethyl ether 70:30). The reaction was quenched and the desired cobalt complex **154** was isolated in a yield of 65 %. The IR spectrum of **154** in Figure 2.5, clearly shows the presence of the cobalt carbonyl cluster at 2000 cm^{-1} as well as the keto-carbonyl at 1712 cm^{-1}.

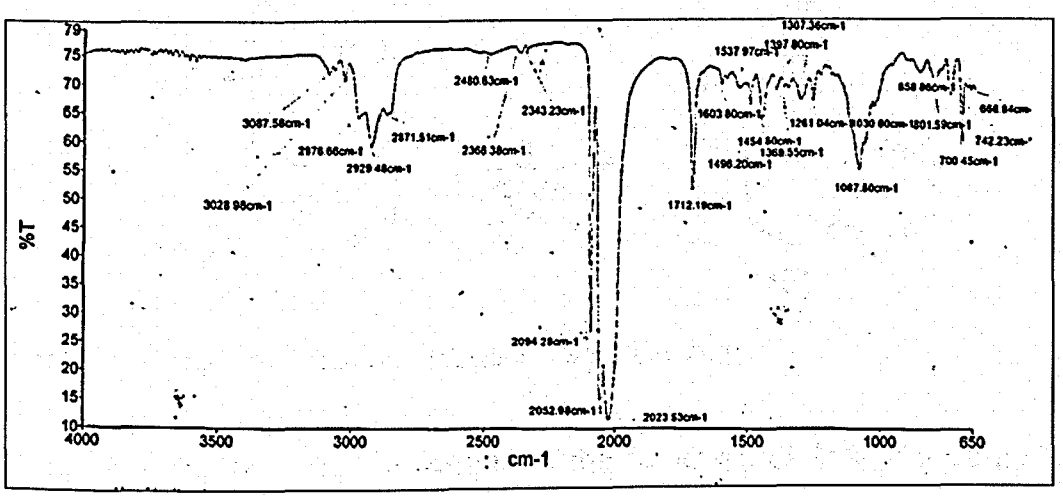
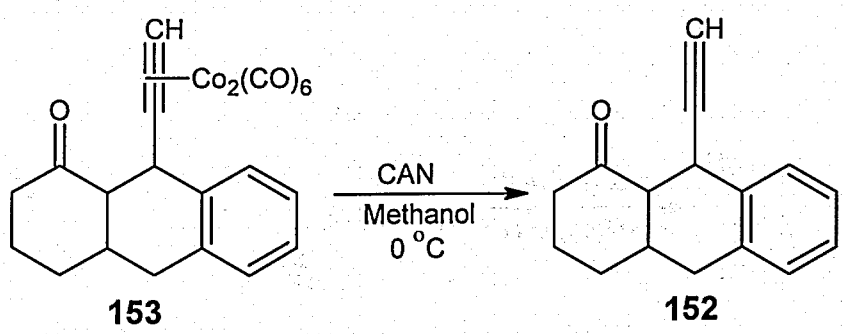


Figure 2.5: *IR spectrum of complex* **154**

The corresponding ^{1}H NMR spectrum confirmed the structure of **154** with a multiplet at δ 7.39- 7.09 ppm (5 H) attributed to the aromatic protons and a doublet at δ 4.92 ppm (J = 9.0 Hz) attributed to the CHC<u>H</u>OEt. The two methylene protons OC<u>H</u>$_2$CH$_3$ resonate at δ 4.04-3.87 and 3.59-3.34 ppm (1H) and a multiplet at δ 3.60-3.55 ppm (1H). From δ 2.55–1.30 ppm there is a

complex multiplet intergrating for 11 protons and a triplet peak at δ 1.30 ppm attributed to CH_3. Decomplexation **154** was accomplished using CAN to afford the decomplexed derivative **154a** for detailed analysis.

The intramolecular Nicholas reaction was obtained by slow dropwise addition of a stoichiometric amount of Lewis acid at 0°C to the complex **154**. The reaction was very rapid and tlc analysis after 5 minutes showed the presence of a new compound R_f = 0.7 (petroleum ether (60 °C – 80 °C): diethyl ether 70:30). The desired tricyclic compound **153** was obtained as a red oil in a yield of 40 %. ^{1}H-NMR of cobalt complexes may sometimes be obtained, but they often require careful serial dilutions of the sample in order to obtain a spectrum with well defined resonances. The presence of paramagnetic impurities tend to lead to signal broadening and poor definition nevertheless the NMR of complex **153** showed the correct number of protons at the appropriate chemical shifts but the peaks were too broad to analyse the multiplicities. The oxidative decomplexation of **153** was achieved by cooling a methanolic solution to 0 °C before the addition of a solution of CAN dissolved in methanol. Tlc analysis revealed a colourless compound **152** with an R_f = 0.6 (hexane: ethyl acetate 85:15), in a yield of 38 % (Scheme 2.11)



Scheme 2.11: *Decomplexation of tricyclic compound **153***

^{1}H NMR analyse was used to confirmed the structure of **152** (Figure 2.6). The benzylic methine proton resonated at δ 4.0 ppm, the α-methine proton at 2.9 ppm and the terminal alkynyl proton at δ 2.04 ppm.

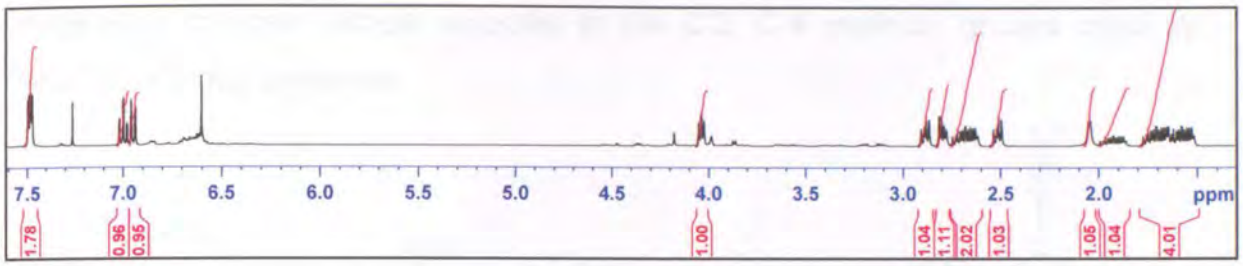
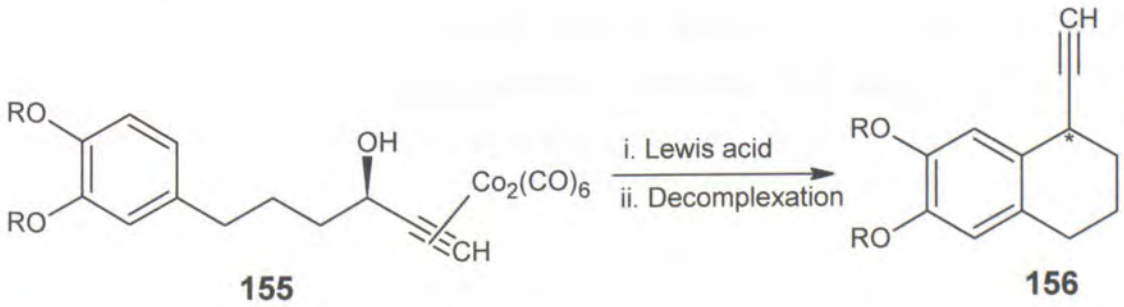


Figure 2.6: *^{1}H NMR spectrum of* ***152***

In contrast to the cyclisation of **47** shown (Scheme 2.1) the cyclisation of **154** was actually a variant of a Friedel-Craft alkylation using the Nicholas cation. With this in mind it was decided to focus upon this reaction in more detail in a simpler model system. In this approach the asymmetry is not derived from an asymmetric conjugate addition, as described above, but more directly from the synthesis of an optically active propargyl alcohol.

2.5 Asymmetric Nicholas reaction from an optically active propargyl alcohol

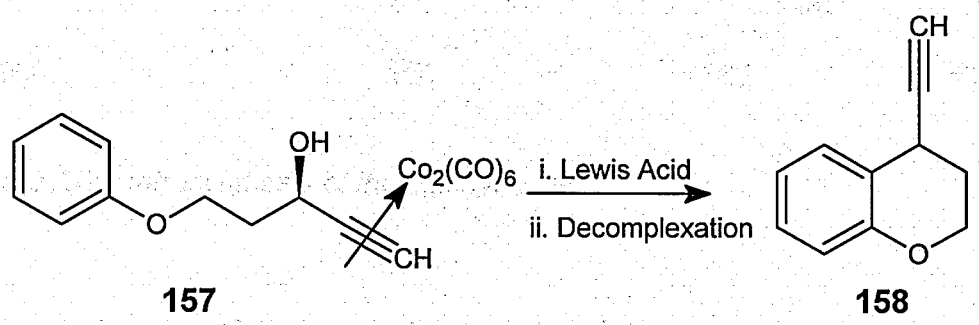
Muehldorf [49] had showed that the use of a Friedel–Craft variation of a Nicholas reaction could be put to good use in the enantiospecific synthesis of **156** (Scheme 2.12).



Scheme 2.12: *Enantioselective Nicholas cyclisation*

In his approach the optically active propargyl alcohol was formed in two steps from the racemate *via* oxidation to the ketone followed by a Midland[104] asymmetric reduction using Alpine-Borane. It was envisaged that this methodology could be applied to the asymmetric synthesis of benzopyrans such as **158** (Scheme 2.13). The interest in this class of molecule lay in their antihypertensive activity.[16-18] In addition it was envisaged that the optically active propargyl alcohol **157** could be accessed directly by a Carreira asymmetric alkynylation[9a,91a,92b] of an aldehyde. Furthermore it was reasoned that the phenolic oxygen, present in **157**, would activate the aromatic ring for the

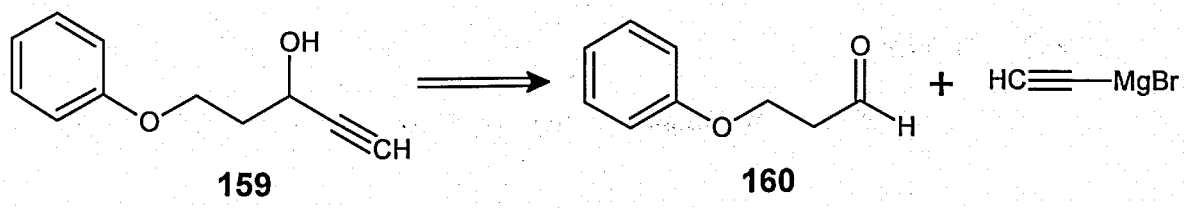
cyclisation to occur without recourse to the C-3, C-4 methoxy groups used by Muehldorf in his synthesis.



Scheme 2.13: *Asymmetric cyclisation of optically active propargyl alcohol **157***

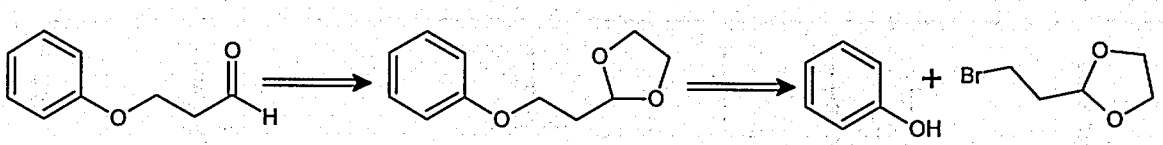
The most common approach to the synthesis of propargyl alcohols is the direct reduction of alkynyl ketones [87b-d] or the alkynylation of an aldehyde by organometallic reagents.[87,105] This last approach has a strategic advantage because it forms a new C-C bond with related creation of a stereogenic center in a single transformation, while in the approach used by Muehldorf the C-C bond and the new chiral centre are formed separately.

For the initial synthesis of a racemic propargylic alcohol **159**, the alkynylation of aldehyde **160** using a stochiometric amount of a Grignard reagent such as ethynyl magnesium bromide in an anhydrous organic solvent may be employed (Scheme 2.14).[87a-d] For optically active propargyl alcohols the Carreira reaction[91a,92b] may be applied between aldehyde **160** and an alkyne in the presence of N-methylephedrine as a chiral catalyst.



Scheme 2.14: *Retrosynthesis of propargyl alcohol **159***

Aldehyde **160** can be obtained from the deprotection of the corresponding dioxolane **161**, which itself is obtained from the Williamson ether synthesis of phenol **162** and the dioxolane **163**.

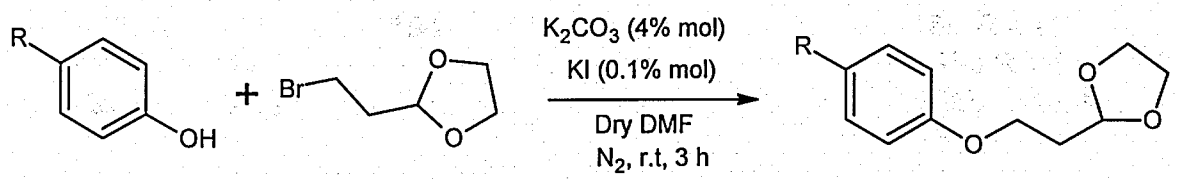


160 **161** **162** **163**

Scheme 2.15: *Retrosynthesis of the aldehyde **160***

2.5.1 O-Alkylation (Williamson ether synthesis)

A Williamson reaction [106] was carried out between phenol **162** and 2-(2-bromoethyl)-1,3-dioxolane **163**. Potassium carbonate, in the presence of potassium iodide, was stirred for 10 minutes at an ambient temperature before phenol **162** was added. Tlc analysis of the reaction mixture revealed the presence of a new compound with R_f = 0.45 (hexane: diethyl ether 70:30) and the desired compound **161** was isolated in quantitative yield as a colourless oil (Scheme 2.16).



162 R = H
162a R = Me
162b R = OMe
162c R = CN
162d R = Br

163

161 R = H
161a R = Me
161b R = OMe
161c R = CN
161d R = Br

Yield 97 – 100%

Scheme 2.16: *O-alkylation reaction of phenol **162** and dioxolane **163***

^{1}H NMR analysis of dioxolane **161** showed a multiplet at δ 7.37-7.25 ppm that integrated for two protons and at δ 7.03-6.94 ppm for three protons attributed to the five aromatic protons. A triplet at δ 5.15 ppm (J = 4.8 Hz) which integrated for 1H and attributed to the methine proton and a second triplet peak at δ 4.17 ppm (J = 6.5 Hz) and integrating for 2 protons attributed to the $OC\underline{H_2}CH_2$ moiety. The use of COSY confirmed the resonance for the following methylene groups δ 2.25 – 2.17 ppm attributed to $OCH_2C\underline{H_2}CH$, and a multiplet at δ 4.08–4.00 and 3.94-3.88 ppm attributed to $OC\underline{H_2}C\underline{H_2}O$ respectively (Figure 2.7).

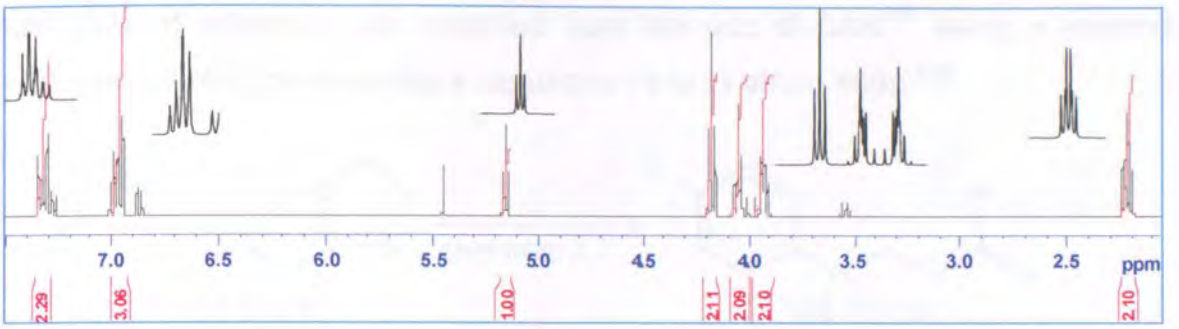
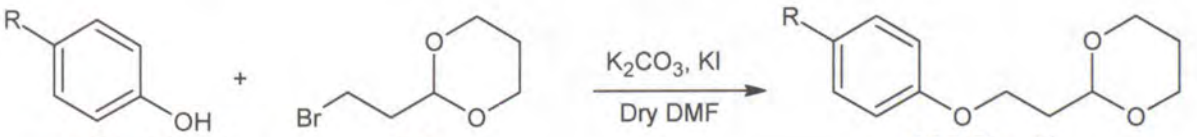


Figure 2.7: *^{1}H NMR spectrum of **161***

The rationale for the synthesis of dioxane **165**, **165a-c** as well as the corresponding dioxolanes **161** and **161a-d** was based upon the ease and mildness of the corresponding deprotection step. Also, as aldehydes are reactive species, both protected forms were used to avoid possible side reactions (Scheme 2.17).



162 R = H
162a R = Me
162b R = OMe
162c R = Br

164

165 R = H
165a R = Me
165b R = OMe
165c R = Br

Scheme 2.17: *O-alkylation reaction of phenol **162** and dioxane **164***

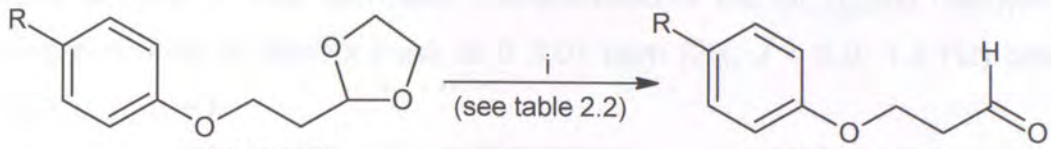
2.5.2 The Deprotection step-synthesis of aldehydes as prochiral precursors

The next part of the synthesis required the deprotection of the dioxolane **161** to reveal the desired aldehyde **160**. This was obtained upon a simple acid hydrolysis of the dioxolane.

2.5.2.1 Acid hydrolysis of a dioxolane

Deprotection of the dioxolane[107] **161** and its derivatives were examined using a range of weak, mild and strong acids and oxidants in different solvent systems and at different temperatures and for a range of reaction times (Table 2.2). It was clear that the deprotection step was not as straight forward as forecast and the

best yield of aldehyde was obtained from the use of CAN[108] using a method published by Maulide involving a dioxolane **161c** to afford **160c**.[109]



161 R = H
161a R = Me
161b R = OMe
161c R = CN
161d R = Br

160 R = H
160a R = Me
160b R = OMe
160c R = CN
160d R = Br

Scheme 2.18: *Deprotection of dioxolanes to achieve the desired aldehydes*

Table 2.2: i. *Conditions of the Deprotection Reaction*

i	Temp °C	Time	% YIELD				
			R = H	Me	OMe	CN	Br
pTSA THF/H_2O	r.t	7-10 d	10	0	0	10	10
pTSA THF/H_2O	20-70	30 d	10	0	0	10	0
pTSA Acetone/H_2O	r.t	7-8 d	65	0	0	50	0
pTSA MeCN/H_2O	r.t	20 d	0	0	0	0	0
HCl Acetone/H_2O	r.t	7 d	>10	0	0	0	0
HCl Acetone/H_2O	20-70	7 d	>10	0	0	>10	0
Acetic acid Acetone/H_2O	r.t	7 d	>10	0	0	>10	0
CAN MeCN/H_2O	r.t	20 d	0	0	0	0	0
CAN MeCN/H_2O	70	5 min	70-80	0	0	67	-
CAN MeCN/H_2O	70	<5min	cyclised 100%	cyclised 100%	cyclised 100%	0	0

The deprotection reaction was carried out by dissolving **161c** for instance, in a 1:3 solvent mixture of acetonitrile and water followed by the addition of a stoichiometric amount CAN. The reaction mixture was heated to 70 °C for 5–10 minutes during which the dark red colour changed to a yellowish solution. Tlc showed the presence of a new compound with an R_f = 0.55 (hexane: ether 70:30). The aldehyde **160c** was isolated in a yield of 67 % as a colourless oil. The corresponding ^{1}H NMR spectrum (Figure 2.8) showed a triplet at δ 9.9 ppm

(J = 1.2 Hz) attributed to the aldehyde proton, a doublet at δ 7.66 ppm (J = 8.5 Hz) and 7.03 ppm (J = 8.5 Hz) representing the 4 aromatic protons. A triplet resonating at δ 4.38 ppm was characteristic of the $OC\underline{H_2}CH_2$ methylene group and a doublet of triplets peak at δ 3.01 ppm (2H, J = 6.0, 1.2 Hz) belonged to $OCH_2C\underline{H_2}CHO$.

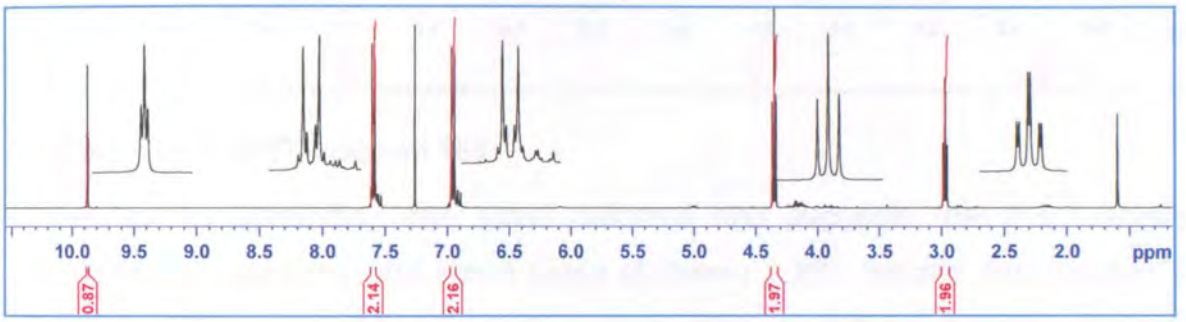
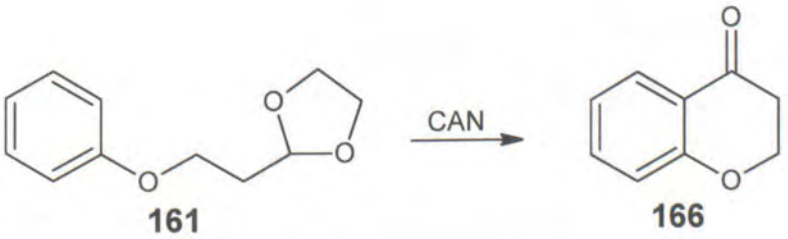


Figure 2.8: *^{1}H NMR spectrum of aldehyde **160c***

The synthesis of aldehyde **160**, using CAN, was anticipated to be as straightforward as that for **160c**. The ^{1}H NMR spectrum seemed largely to be consistent with the desired aldehyde however the characteristic triplet at δ 9.9 ppm, consistent with the aldehyde proton coupling to an adjacent methylene group, was absent. Detailed analysis of the NMR spectrum revealed only 4 aromatic protons suggesting that a cyclisation reaction had taken place to afford the corresponding chromanone **166** (Scheme 2.19). This was later confirmed by high resolution mass spectroscopy.



Scheme 2.19: *Unexpected cyclisation of dioxolane to chromenone*

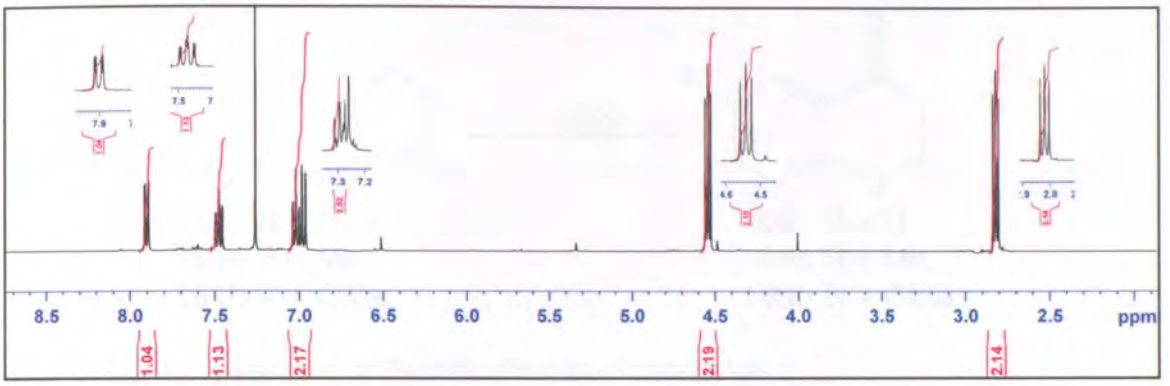
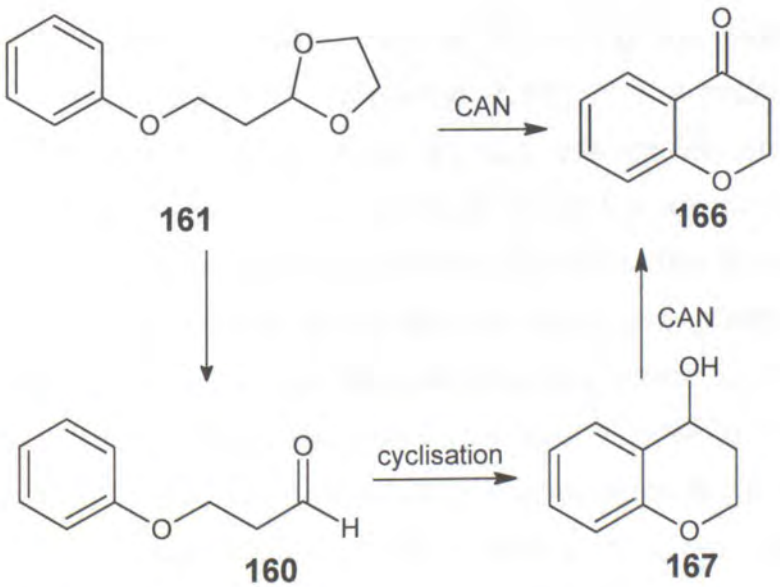


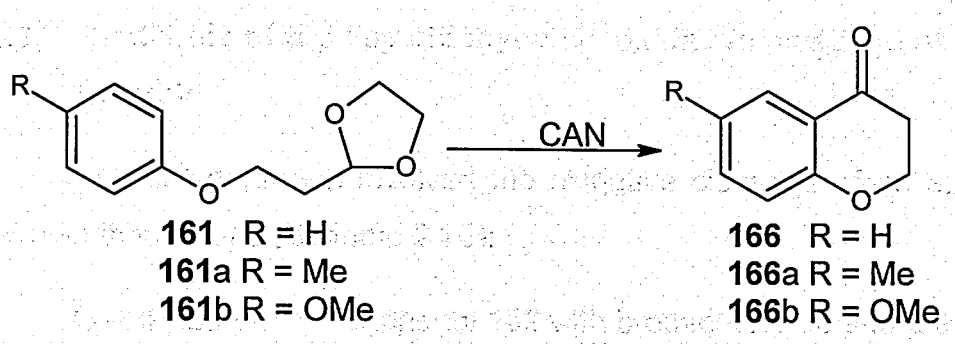
Figure 2.9: *^{1}H NMR spectrum* ***166***

This was an interesting and novel outcome and suggests that the following sequence of reactions had taken place (Scheme 2.20). Initially deprotection of dioxolane **161** occurred to afford the desired aldehyde **160** however the aromatic ring was sufficiently electron rich (nucleophilic), unlike aldehyde **160c**, to cyclise to afford chromanol **167**. In the presence of CAN this was then oxidised further to afford **166**.



Scheme 2.20: *Proposed route to chromenone* ***166***

If this was a general outcome then other electron-rich dioxolanes such as **161a**, **161b** should also undergo the same series of oxidations to afford the corresponding chromanones.[110] Inspection of the data in Table 2.2 confirms this to be the case thus exposure to dioxolanes **161**, **161a-b** to CAN for 5 minutes gave the corresponding aldehyde, in variable yields, however longer exposure times provided the chromanones **166**, **166a**, **166b** in yields of **70-80 %** (Scheme 2.21).

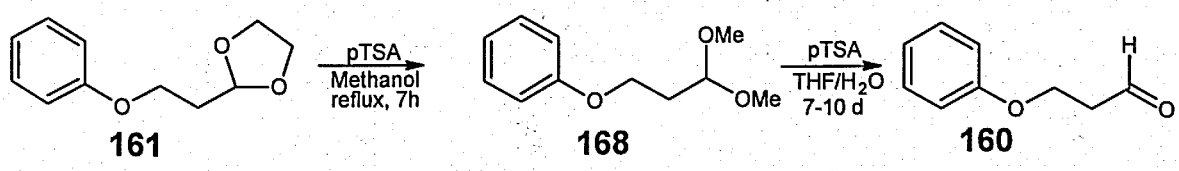


Scheme 2.21: *Cyclisation of the dioxolane to chromenone*

Despite these interesting results it was still necessary to establish a reliable methodology for the synthesis and isolation of the key aldehydes. For the synthesis of the key aldehyde other methods were investigated.

2.5.2.2 Synthesis of aldehydes via deprotection of dioxolane as the corresponding dimethoxy-derivative

An alternative strategy involved accessing the aldehyde **160** *via* the dimethoxy ether **168** [107b,111] (Scheme 2.22) thus avoiding exposure of the sensitive aldehyde to CAN. This reaction was carried out by dissolving the dioxolane **161** in methanol and adding pTSA to the reaction mixture which was then heated to a reflux temperature for 7–8 hours. The desired compound **168** was analysed by tlc analysis R_f = 0.46 (petroleum ether: diethyl ether 70:30), with a very low yield (8 %) and purification was very messy. In the second step the dimethoxy ether derivative **168** was added to a mixture of THF/H_2O (1:1) in the presence of pTSA and stirred at room temperature for about 7 days. Tlc analysis of the reaction mixture showed the presence of a new compound R_f = 0.2 (hexane: diethyl ether 70:30). The desired aldehyde **160** was then isolated with a yield of 12 % partly attributed to its instability to purification by chromatography on silica gel. Given the low yield obtained, this methodology offered no advantage over the reaction with CAN.



Scheme 2.22: *An alternative approach to the synthesis of aldehyde **160***

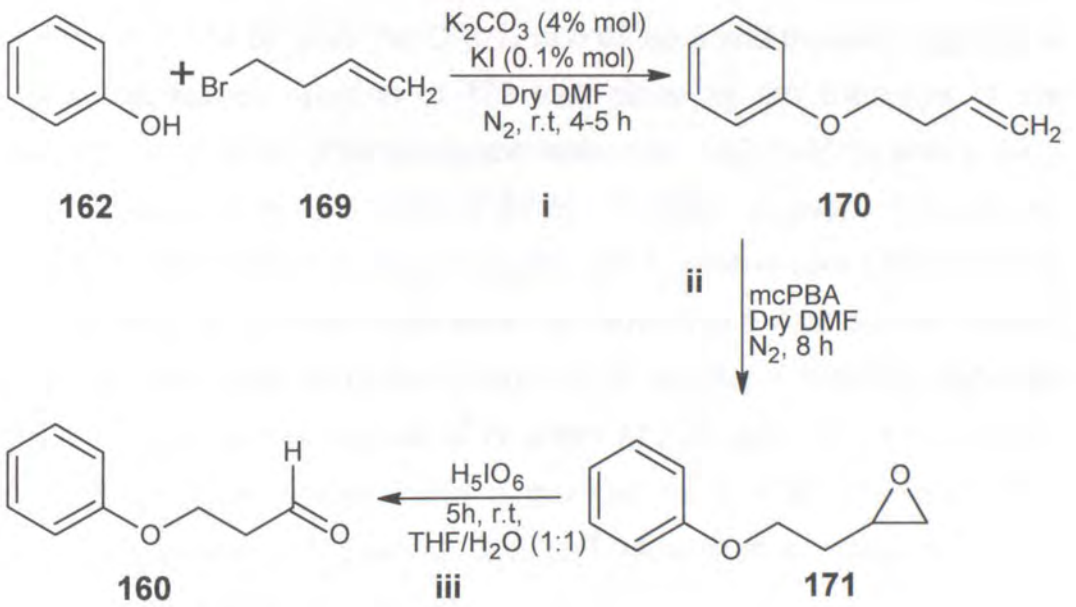
2.5.2.3 Synthesis of the key aldehyde via oxidative cleavage of an epoxide

The third approach involved the oxidative cleavage of an epoxide which occurs in three steps (Scheme 2.23):

i) O–Alkylation [106b-e] of phenol **162** with bromide **169** to afford ether **170**

ii) Epoxidation of **170** to afford epoxide **171**

iii) Oxidative cleavage of **171** to aldehyde **160**



Scheme 2.23: *The synthesis of aldehyde **160** via an oxidative cleavage of an epoxide*

The O–alkylation of phenol **162** was carried out to afford **170** as a colourless oil in 97% yield. The ^{1}H NMR spectrum (Figure 2.10) showed the presence of the =CH as a multiplet at δ 6.0-5.95 ppm and the =CH_2 as a multiplet at δ 5.22-5.14 ppm.

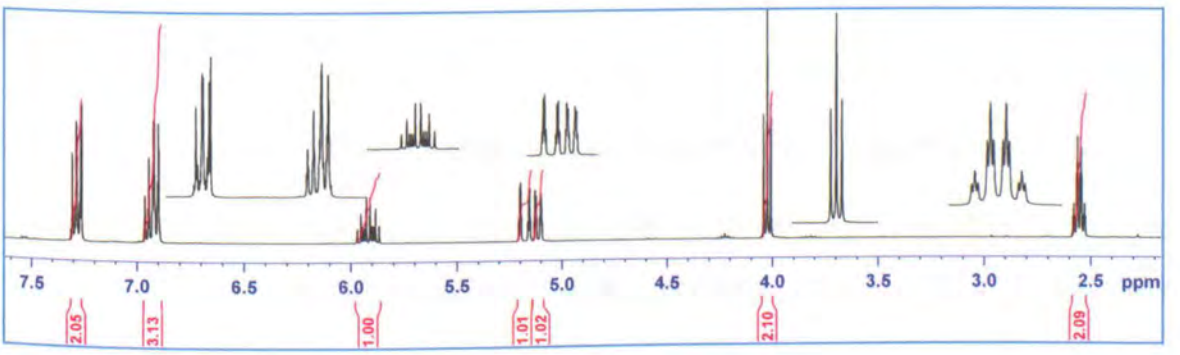


Figure 2.10: *^{1}H NMR spectrum of alkene **170***

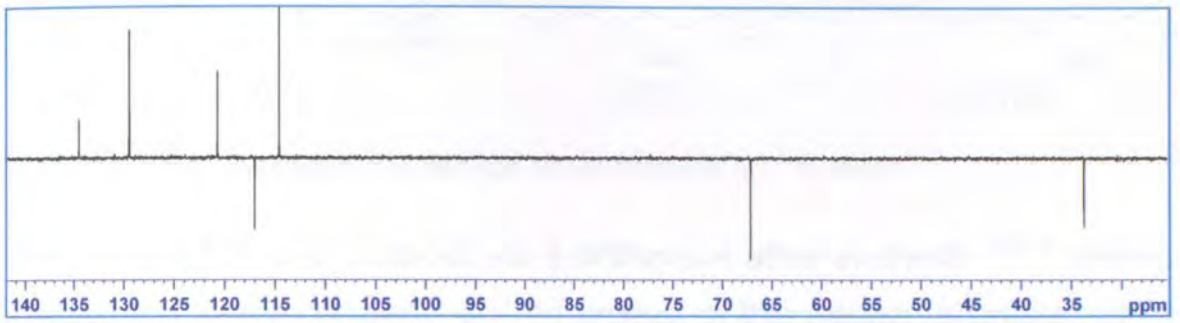


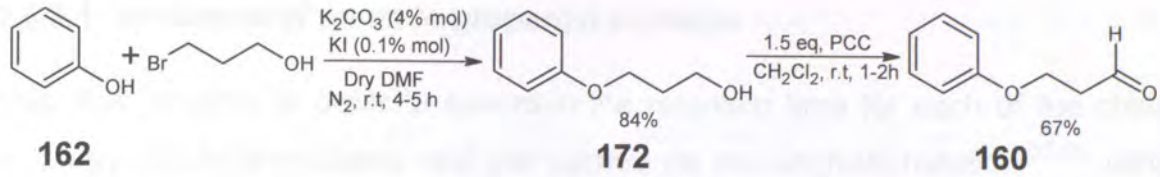
Figure 2.11: *^{13}C DEPT spectrum of alkene **170***

The corresponding ^{13}C DEPT NMR spectrum (Figure 2.11) showed the alkenyl CH_2 resonating at δ 114.59 ppm the O-$\underline{C}H_2$ at δ 67 ppm and the O-$CH_2\underline{C}H_2$ at δ 34 ppm. The epoxidation reaction of **170** took place by the exposure of the alkene **165** R = H to *meta*-chloroperoxybenzoic acid (mCPBA) to afford 2-(2-phenoxyethyl) oxirane **171** in a yield of 87 %. ^1H NMR analysis showed two multiplets at δ 7.3 and 6.9 ppm that integrated for 5 protons and attributable to the aromatic protons. In addition there were resonances at δ 4.08 ppm of a triplet (2H, t, J = 5.8 Hz) that were attributed to $ArOCH_2$, a doublet of doublets at δ 3.20 ppm (J = 8.8, 6.0 Hz) and a doublet of doublets at 2.89 ppm (J = 8.8, 6.0 Hz) attributed to CH_2 of the epoxide and a multiplet at δ 2.80-2.76 ppm (1H) attributed to C$\underline{H}$, a multiplet peak at δ 2.02-1.98 ppm that integrated for 2 protons, attributed to C$\underline{H_2}$CH group.

The conversion of the epoxide to the aldehyde **160** using periodic acid in a mixture of THF: H_2O (1:1) was achieved in a good yield (66 %). Aldehyde **160** was clean enough to use directly without further purification. In comparison to the use of CAN however this procedure was time consuming, more expensive and for reasons of atomic economy, the use of mCPBA was to be avoided. Furthermore there was still 20-30% of the corresponding cyclised compound **166** formed as side product.

2.5.2.4 Synthesis of the aldehyde via oxidation of a 1° alcohol

A fourth approach in the quest to obtain aldehyde **160** was from the Corey and Suggs oxidation of the corresponding primary alcohol **172**[112] (Scheme 2.24).[112b,113]



Scheme 2.24: *Synthesis of aldehyde via oxidation of a 1° alcohol*

The alcohol **172** was produced *via* a Williamson ether synthesis [106b-e] between phenol and 3-bromopropan-1-ol. The product of this reaction phenoxypropanol **172** was obtained with a yield of 84 %. GC-MS analysis gave a single peak with a molecular weight of 152. ^{1}H NMR analysis revealed the following characteristics of **172**. A multiplet at δ 7.67-7.60 ppm integrating for two protons and a multiplet at δ 7.32-7.28 ppm attributed to 3 aromatic protons. At δ 4.46 ppm there was a triplet (J = 6.5 Hz) representing OC$\underline{H}_2$, a multiplet at δ 3.40– 3.36 ppm attributed to CH_2OH and a broad singlet at δ 2.42 ppm for the O$\underline{H}$ (Figure 2.12)

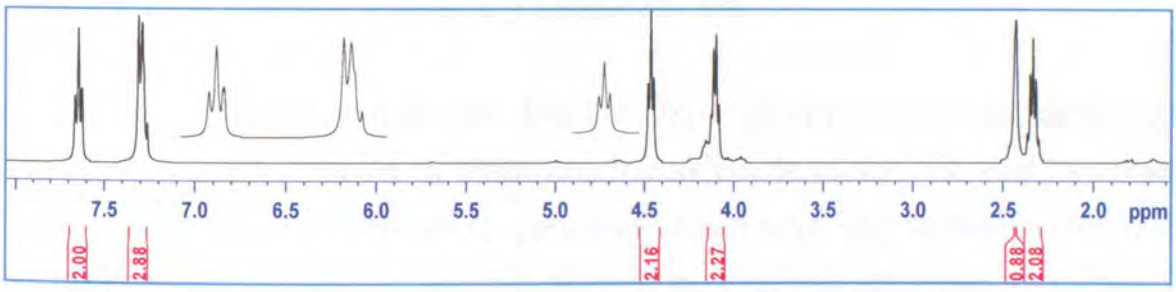


Figure 2.12: *^{1}H NMR spectrum of alcohol **172***

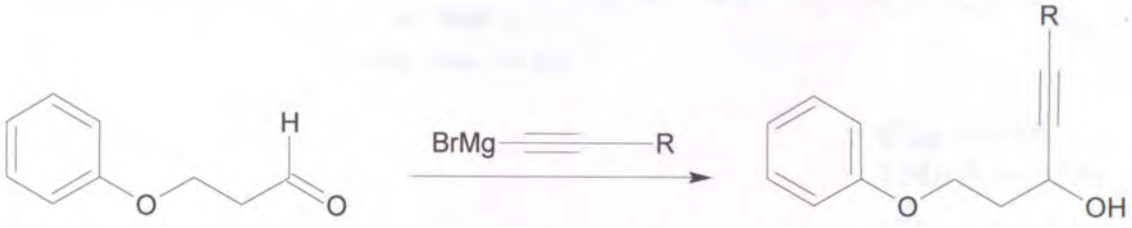
In the second step the alcohol **172** was dissolved in dry dichloromethane and a stoichiometric amount of pyridinium chlorochromate (PCC) was added to the solution as an oxidising agent. The colour of the solution changed to a red hue and it was left to stir for 5 hours and monitored by tlc. This showed a new spot consistent with the R_f = 0.55 for the aldehyde **160**. The reaction was quenched and the product isolated with a yield of 67 %. Although the overall yield for this sequence was good it was concluded that the method that used CAN to cleave the dioxolane directly to afford aldehyde **160** was the best way forward in the synthesis of the aldehyde.

2.5.3 The alkynylation reaction

An alkynylation reaction was carried out to synthesise the propargyl alcohol **159** on derivatives **159a** - **159c**.

2.5.3.1 Synthesis of racemic propargyl alcohols

This was required in order to ascertain the retention time for each of the chiral propargyl alcohols produced and was carried *via* the Grignard reaction [52,54] using commercially available organometallic-alkynyl reagents (Scheme 2.25).



160

159 R = H
159a R = Me
159b R = Ph
159c R = PhMe

Scheme 2.25: *Synthesis of racemic propargyl alcohols*

Due to the instability of aldehyde **160** the alkynylation reaction was carried out immediately upon isolation by dissolving the aldehyde in dry THF that had been cooled to -78 °C. The Grignard reagent was added drop-wise to the solution over a period of 15 - 20 minutes and the reaction mixture was left to stir for at least 1 hour. Tlc monitoring showed a new spot with an R_f = 0.14 (hexane: diethyl ether 80:20). The product was then isolated and purified, by chromatography on silica, to afford (+/-) propargyl alcohol **159** as a colourless oil in 85 % yield.

The corresponding ^{1}H NMR spectrum (Figure 2.13) showed the presence of peaks attributed to the aromatic ring at δ 7.32 - 7.26 ppm which integrated for two protons and also at δ 6.96-6.89 ppm integrating for a further 3 protons. Another multiplet at δ 4.74-4.69 attributed to the methine proton C<u>H</u>-OH. At δ 2.50 ppm a doublet (*J* = 2.0 Hz) represented the C≡C<u>H</u> and another doublet slightly upfield at δ 2.42 (*J* = 5.8 Hz) attributed to the O<u>H</u> moiety.

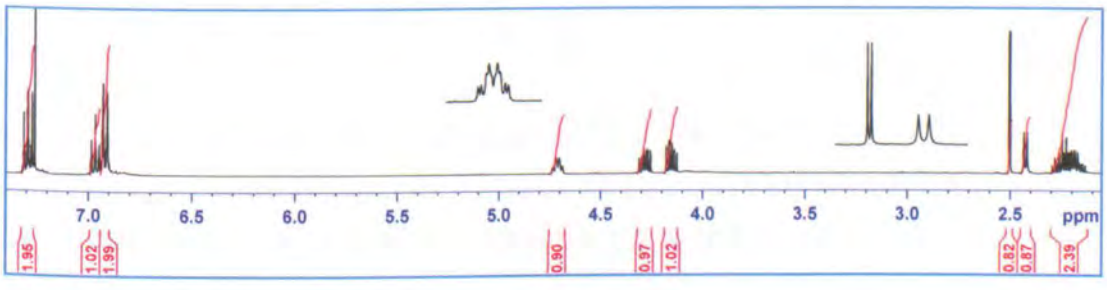
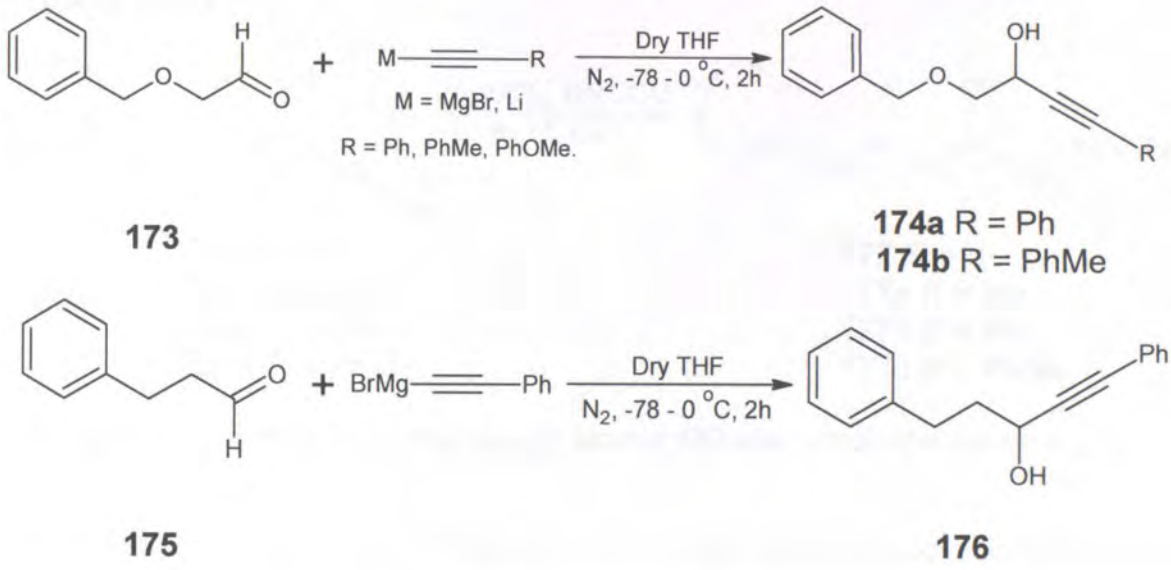


Figure 2.13: *^{1}H NMR spectrum of propargyl alcohol **159***

To complement this study it was decided to include the following library of propargyl alcohols to include **159**, **159a-c** as well as **174a** and **174b** derived from the propargylation of the readily available aldehyde **173** and propargyl alcohol **176** from the propargylation of aldehyde **175** (Scheme 2.26).



Scheme 2.26: *Synthesis of racemic propargyl alcohols*

Interestingly the ^{1}H NMR spectrum for **176** (Figure 2.14) showed a multiplet at δ 7.46-7.29 ppm integrating for 10 aromatic protons. A multiplet centred at δ 4.64 attributed to C<u>H</u>OH and a triplet at δ 2.87 ppm (J = 7.8 Hz) attributed to the benzylic protons PhC<u>H</u>$_2$. This assignment was confirmed from the corresponding COSY analysis which showed an interaction with an adjacent methylene group but not with the -C<u>H</u> or -O<u>H</u> peaks.

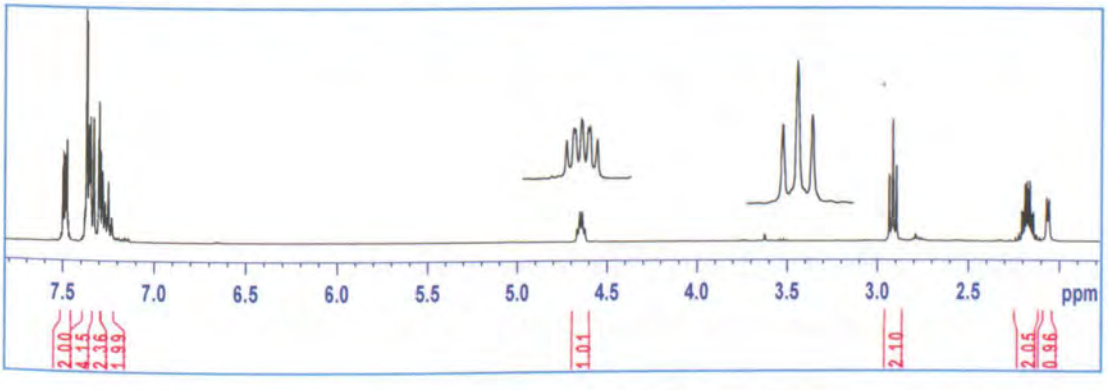
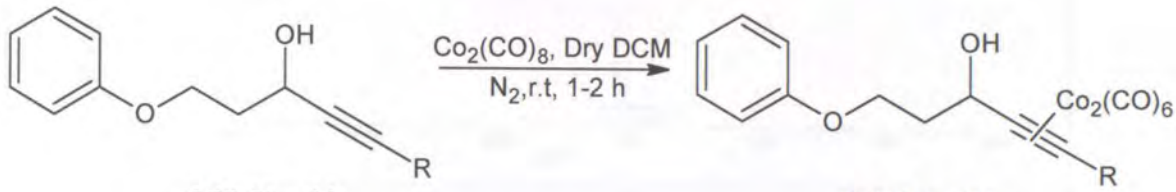


Figure 2.14: *^{1}H NMR spectrum of propargyl alcohol* ***176***

2.5.4 Complexation reaction of the propargyl alcohol

Complexation of the propargyl alcohols **159**, **159a-c**, **174a/b** and **176** with dicobalt octacarbonyl is the first step in the Nicholas reaction. This was

undertaken by dissolving the propargyl alcohol in dry DCM at ambient temperature followed by the addition of a stoichiometric amount of dicobalt octacarbonyl. As a representative example the dicobalt hexacarbonyl complex of propargyl alcohol **177** was obtained as a dark red oil in a quantitative yield (Scheme 2.27).



159 R = H
159a R = Me
159b R = Ph
159c R = PhMe

177 R = H
177a R = Me
177b R = Ph
177c R = PhMe

Scheme 2.27: *Complexation of propargyl alcohol **159** using dicobalt octacarbonyl*

The ^{1}H NMR spectrum of **177** (Figure 2.15) showed the characteristic features of these cobalt clusters i.e. broadened resonances that are devoid of any fine structure. An important feature of the alkyne clusters however is the downfield resonance attributed to C≡C<u>H</u> proton. In **159** this is at δ 2.5 ppm however in the complex **177** this was resonant at δ 6.0 ppm consistent with the sp^2 character of the carbon atoms associated with the complex.

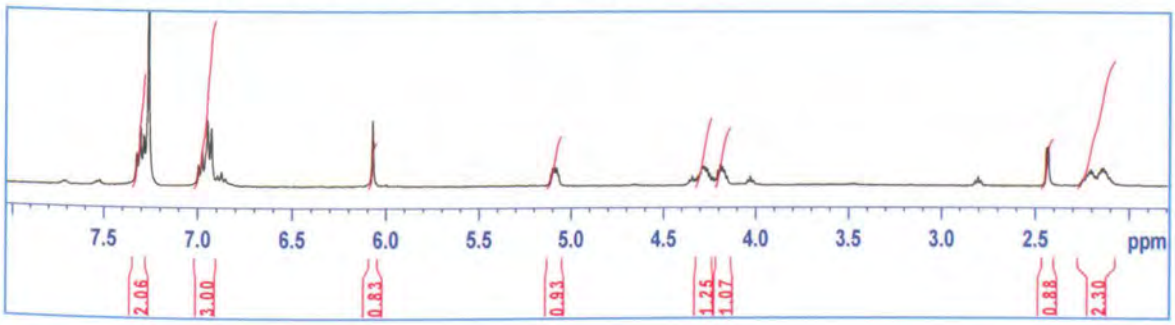


Figure 2.15: *^{1}H NMR spectrum of complex **177***

A ready way to ascertain that the complexation step has been successful, apart from the red colour of the complex, is from the corresponding infrared spectrum. Here the carbonyl signals indicative of this metal carbonyl are clearly visible at 2012 cm^{-1} along with the disappearance of the alkyne signal another sign of this insertion (Figure 2.16).

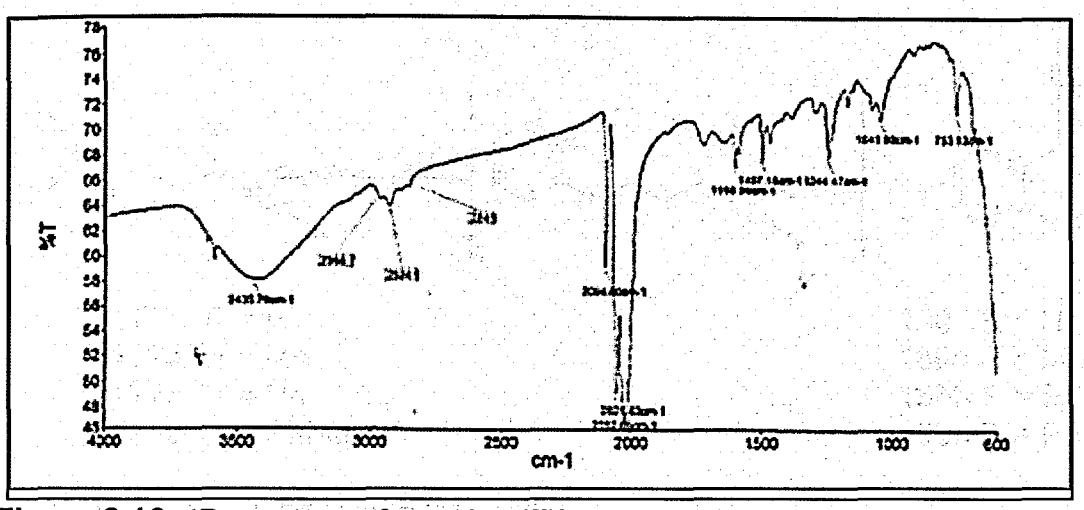
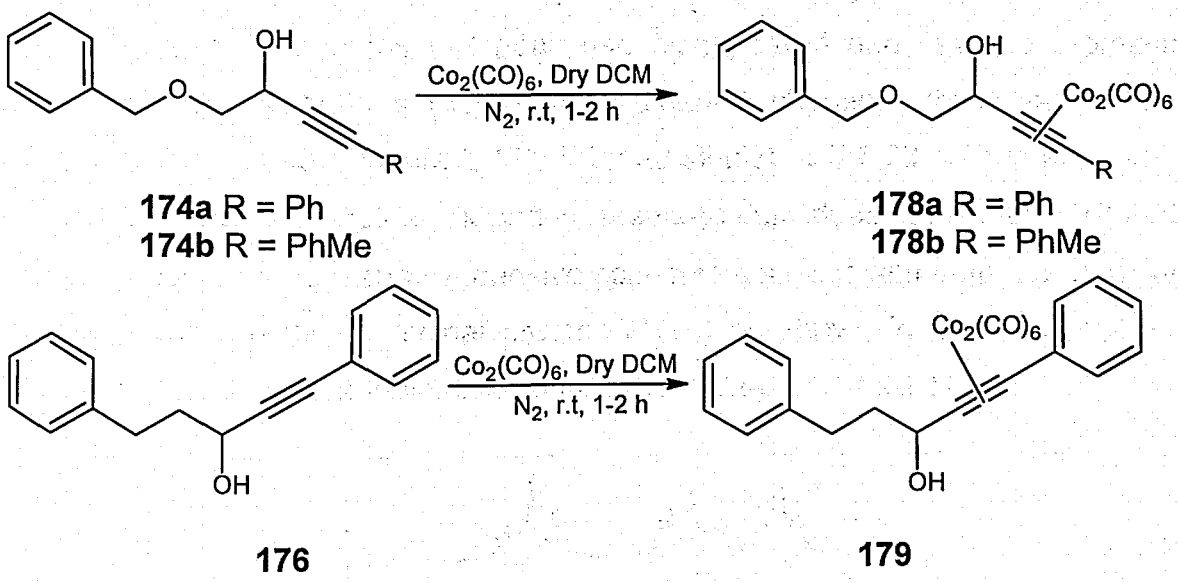


Figure 2.16: *IR spectrum of complex **177***

The complexation of **159a-c** was accomplished in quantitative yield to afford the coresponding complexes **177a-c**.

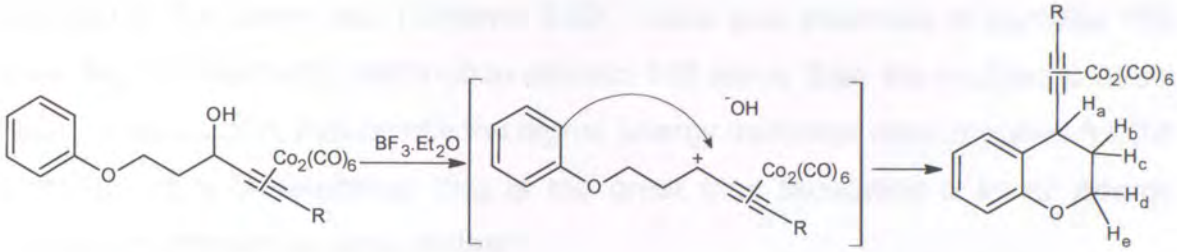
Complexation of **174a/b** and **176** was also successfully accomplished using the same complexation procedure to afford the corresponding complexes **178a/b** and **179** in quantitative yields (Scheme 2.28).



Scheme 2.28: *Complexation of propargyl alcohol **174a/b** and **176***

2.5.5 The Nicholas reaction–cyclisation

With the range of complexes in hand the key intramolecular Nicholas cyclisation reaction in the presence of a Lewis acid at 0°C could now be attempted (Scheme 2.29).



177 R = H
177a R = Me
177b R = Ph
177c R = PhMe

180 R = H
180a R = Me
180b R = Ph
180c R = PhMe

Scheme 2.29: *The Nicholas–cyclisation*

Addition of the Lewis acid to **177** led to a very rapid cyclisation reaction as determined by a tlc taken within 5 minutes of the addition. This confirmed the presence of a new compound R_f = 0.86 (hexane: diethyl ether 70:30) which was isolated and purified by removing most of the solvent and passing the crude product down a short silica column eluting with DCM. This gave the corresponding product **180** in 67 % yield. ^{1}H NMR analysis revealed that the resonance attributed to the OH peak had disappeared and that the aromatic protons showed 4 protons (not 5) in 4 different chemical shifts each peak integrating for 1 proton (Figure 2.17). A broad singlet at δ 6.28 ppm is attributed to C≡C<u>H</u>. The O-CH_2 protons H_d and H_e resonate individually at δ 4.44-4.40 and 4.30-4.24 ppm and both show extensive spin-spin coupling with both the geminal proton ($^2J_{H-H}$) and the 2 viscinal protons ($^3J_{H-H}$) as shown in the NMR below. Proton H_a is an apparent triplet is resonant at δ 4.2 ppm (J = 6.2 Hz).

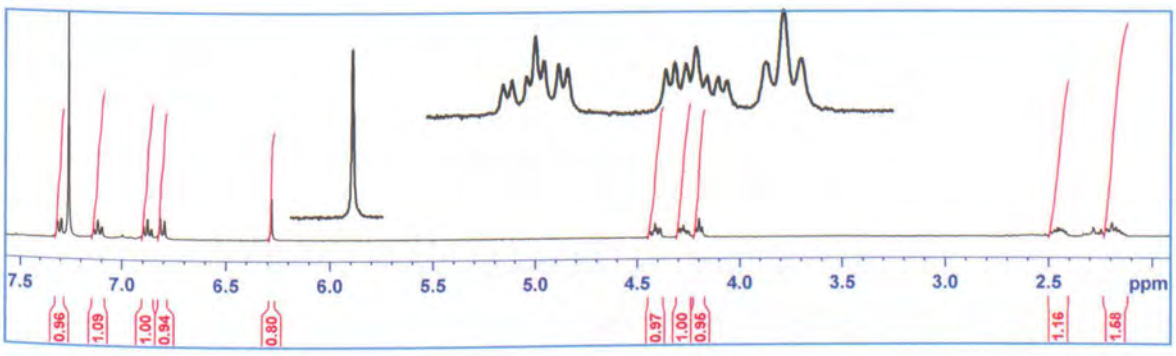
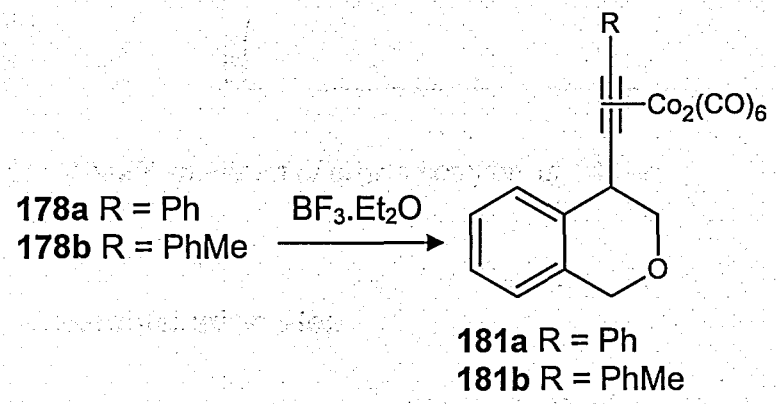


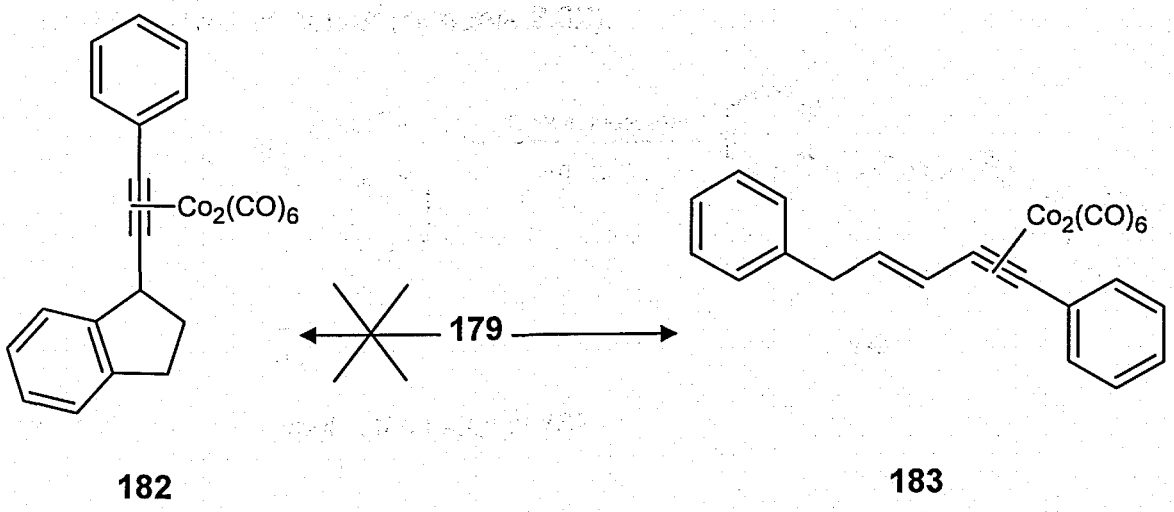
Figure 2.17: *^{1}H NMR spectrum of complex **180***

The same cyclisation conditions were applied to propargyl alcohols **178a** and **178b**. These underwent successful Nicholas cyclisation reaction to afford the corresponding cyclic complexes **181**a / **181b** in yields of 77.6 and 71.2% when

exposed to the Lewis acid (Scheme 2.30). Lewis acid treatment of complex **179** gave the corresponding elimination product **183** rather than the cyclised product **182** (Scheme 2.31). Apparently the higher energy transition state required for the formation of a 5-membered ring is too great thus facilitating a lower energy elimination reaction to occur instead.



Scheme 2.30: *Nicholas cyclisation of **178a, 178b***



Scheme 2.31: *Elimination of propargyl alcohol*

The corresponding ^{1}H NMR spectrum for the complex **183** (Figure 2.18) confirmed that an elimination reaction had taken place by showing 10 aromatic protons at δ 7.56 – 7.20 ppm and resonances for the olefinic protons at δ 6.8 ppm (1H adjacent) to the complex motif) and a second at δ 6.4 ppm (1H adjacent to a methylene group).

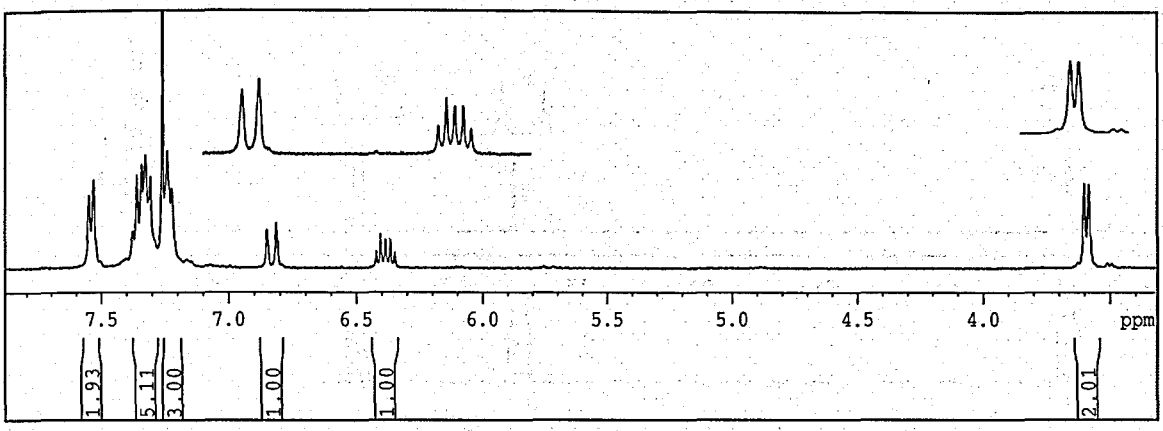
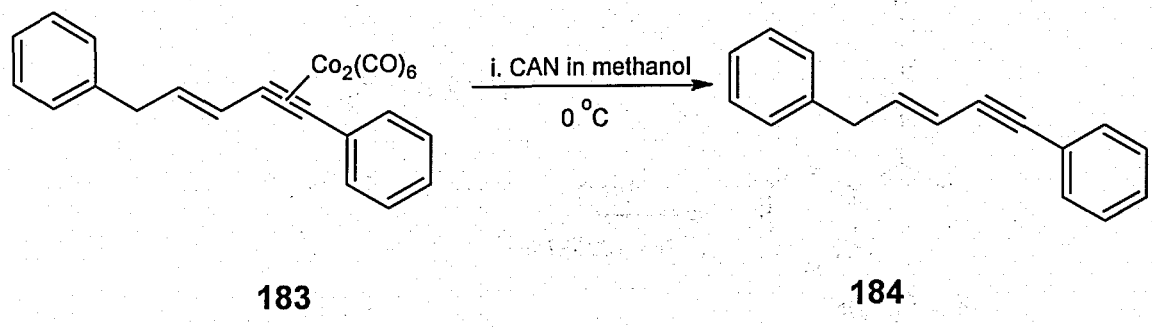


Figure 2.18: *^{1}H NMR spectrum of enyne complex of **183***

2.5.6 The decomplexation step

The decomplexation step, to remove the dicobalt hexacarbonyl cluster, was carried out by addition of a methanolic solution of CAN to **183** at 0 °C. The complex was dissolved in methanol, cooled down to 0 °C and a solution of CAN in methanol was added dropwise, with stirring, until the dark red solution changed to an orange/yellow colour (Scheme 2.32).



Scheme 2.32: *Decomplexation step of **183***

The yield of enyne **184** was 78 % and the ^{1}H NMR spectrum for **184** showed resonances of 10 H at δ 7.2 – 7.5 ppm characteristic of aromatic protons, a doublet of triplets at δ 6.4 ppm (J = 15.8, 7.0 Hz) for $CH_2C\underline{H}$=CH and an upfield doublet of triplets at δ 5.7 ppm (J = 15.8, 1.5 Hz) for the second vinyl proton. The two methylene protons were resonant at δ 3.5 ppm as a doublet of doublets (J = 7.0, 1.5 Hz) (Figure 2.19).

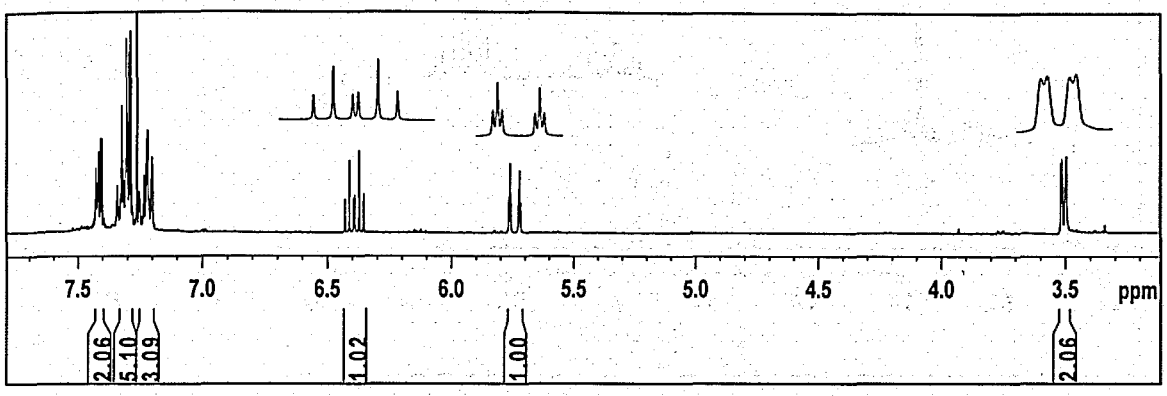
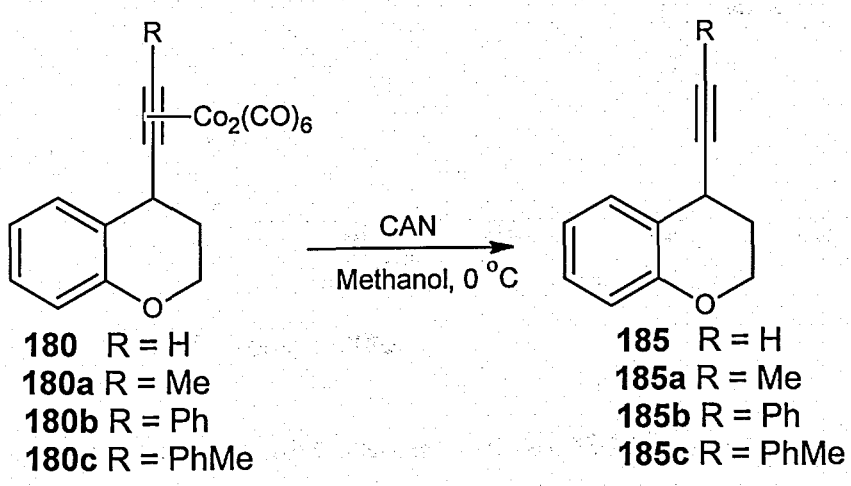


Figure 2.19: *^{1}H NMR spectrum of enyne **184***

The decomplexation procedure was carried out upon the remaining cyclised complexes **180**, **180a-c**, **181a/b** to afford the corresponding cyclised products **185**, **185a-c**, **186a/b**. Tlc analyses of the reaction mixture confirmed the presence of a new compound R_f = 0.6 (hexane: EtOAc 90:10). The new compound was isolated and purified by chromatography on silica gel to afford the desired chromane **185** in a yield of 97% (Scheme 2.33).



Scheme 2.33: *Decomplexation reaction*

The ^{1}H NMR spectrum for **185** (Figure 2.20) showed the alkyne proton resonated as a doublet (J = 2.5 Hz) at δ 2.22 ppm. The CH_2 protons α– to the ring oxygen resonated at δ 4.3 ppm (1H) and 4.2 ppm (1H). The benzylic proton resonated slightly upfield at δ 3.85 ppm as a triplet of doublets (J = 6.0, 2.5 Hz) coupling to the adjacent methylene group as well as to the alkynyl proton.

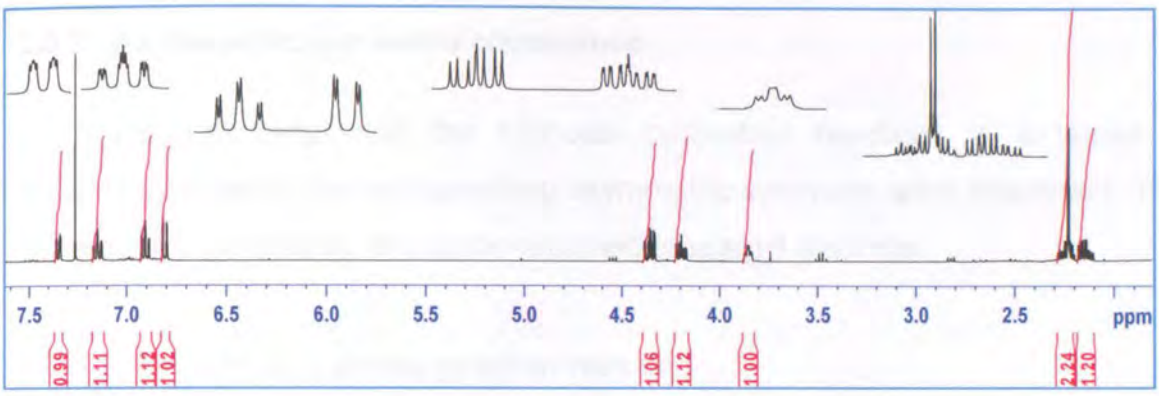


Figure 2.20: *^{1}H NMR spectrum of chromene **185***

The corresponding IR spectrum for **185** (Figure 2.21) clearly showed that the cobalt carbonyl peaks had disappeared at 2092.9, 2053.4 and 2022.1 cm^{-1} and showed the peak attributed to the alkyne moiety at 2054/2025 cm^{-1}.

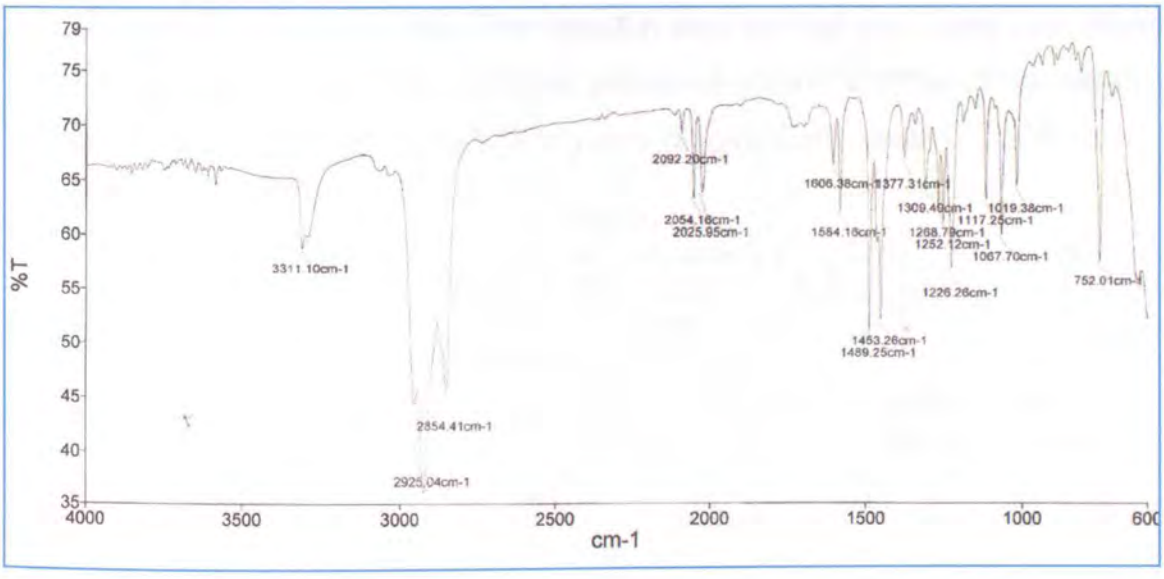
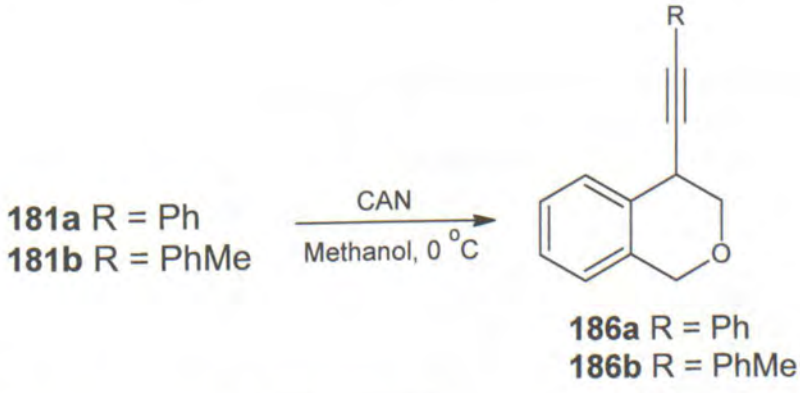


Figure 2.21: *IR spectrum of chromene **185***

The decomplexation step was also carried out on **181a/b** to provide the novel isochromane derivatives **186a** and **186b** in yields of 89 and 86 % respectively (Scheme 2.34).



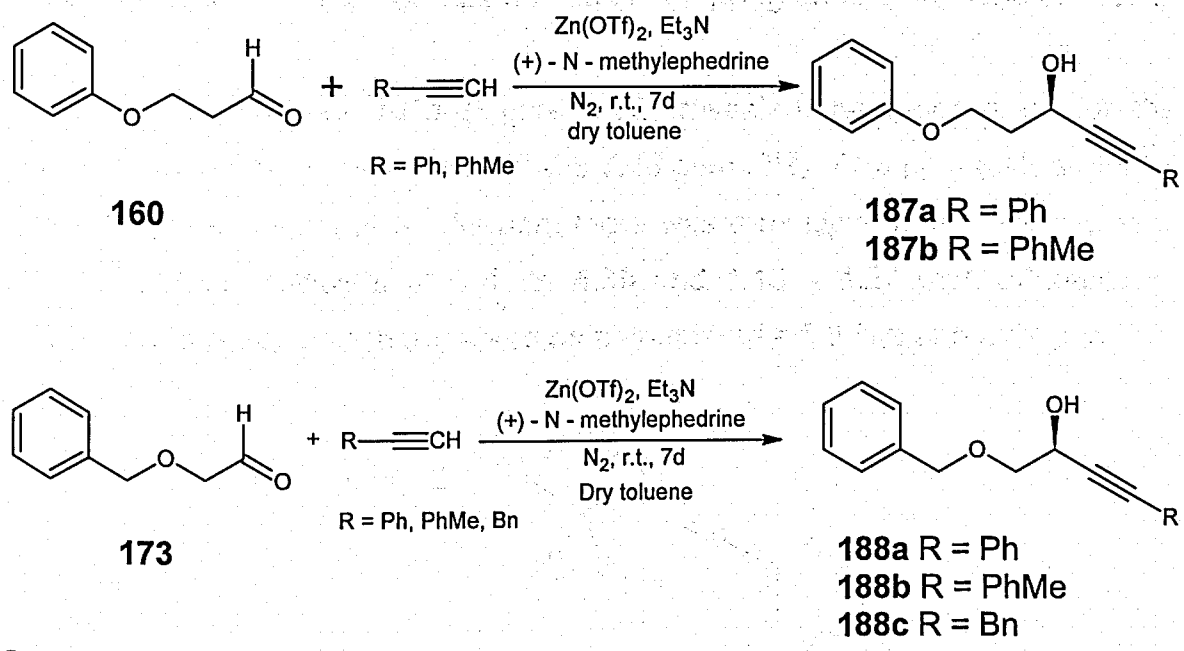
Scheme 2.34: *Decomplexation of isochromene*

2.5.7 Asymmetric synthesis chromenes

Having accomplished the Nicholas cyclisation reactions in a series of racemic syntheses the corresponding asymmetric synthesis were attempted. This required the synthesise of enantio-enriched propargyl alcohols.

2.5.7.1 Asymmetric propargylation reaction

The desired aldehyde **160** was obtained as previously described however the isomeric aldehyde **173** was commercially available. The method for effecting the asymmetric alkynylation reaction was the method described by Carreira[9a] and requires the use of (+)-N-methylephedrine which acts as a chiral catalyst and serves as a template during the reaction between the organometallic species and the aldehyde. (Scheme 2.35). The reaction was carried out using two different alkynes to afford the enantio-enriched propargyl alcohols **187a/b** from aldehyde **160** and **188a-c** from aldehyde **173** in yields ranging from 75-98% (Table 2.3)



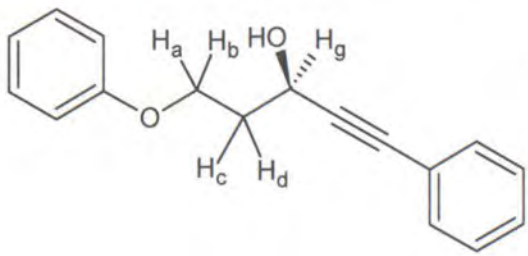
Scheme 2.35: *Asymmetric alkynylation of **160** and **173***

Table 2.3: *Data for the Synthesis of Optically Active Propargyl Alcohols*

Propargyl alcohol	$[\alpha]_D$	Yield %	ee%
187a	+17	76.2	50
187b	+12	63.0	74
188a	+15	98.1	80.6
188b	-8	87.3	82.22
188c	+10	81.5	77.12

The Carreira reaction was carried out on aldehydes, **160** and **173**, by mixing (+)-*N*-methylephedrine and zinc triflate, under a nitrogen atmosphere, with toluene and Et_3N. The resulting mixture was left to stir for 2 hours whereupon the alkyne was added. After stirring for a further 15 minutes the aldehyde was added and the reaction mixture was left to stir for about 7 days to effect the alkynylation reaction. Tlc analysis for the synthesis of **187a**, as an example, showed the presence of a new compound with an R_f value of 0.4 (hexane: diethyl ether, 70:30). Isolation and purification of the product gave **187a** in a yield of 76% as a colourless oil. Chiral hplc was used in order to determine the enantiomeric excess for each asymmetric alkynylation reaction. For **187a** the major enantiomer had a retention time t_{maj} = 7.49 min (74.61%) and the t_{min} was 14.38 minutes (25.38%) giving an enantiomeric excess of 50%. The enantiomeric excess of this asymmetric alkynylation reaction was modest. As all of the later asymmetric alkynylation reactions significantly improved enantiomeric excess it must be assumed that this initial data may be optimised. For example for **187b** t_{maj} = 19.65 minute (87 %) and t_{min} = 24 min (13.1 %) giving an enantiomeric excess of 74%.

The ^{1}H NMR of **187a** (Figure 2.22) revealed the resonances for the aromatic protons as three multiplets at δ 7.46 ppm (2H), 7.33 ppm (6H) and 6.87 ppm (2H) ppm. Upfield at δ 4.99 ppm there was a multiplet attributed to C<u>H</u>OH and two further multiplets at δ 4.29- 4.39 and 4.15 – 4.27 ppm attributed to OC<u>H</u>$_2$. The hydroxyl proton appeared as a doublet (*J* = 5.8 Hz) at δ 2.47 ppm.



187a

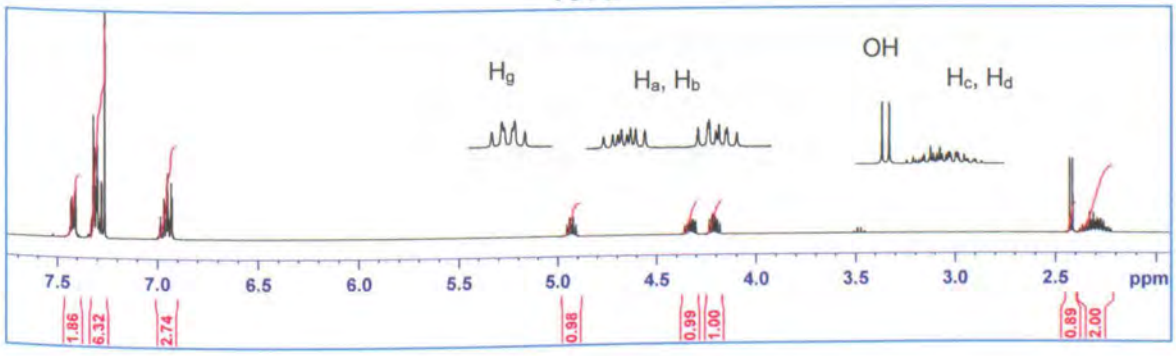
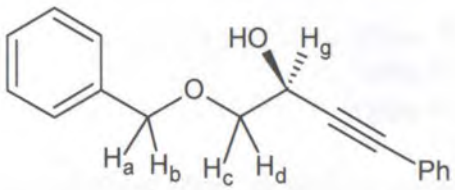


Figure 2.22: *^{1}H NMR spectrum of **187a***

Chiral hplc also was also used to determine enantiomeric excess for the isomeric propargyl alcohols **188a-c**. For **188a** major enantiomer had a retention time t_{maj} = 28.99 min (90.3%) and the t_{min} was 23.97min (9.7%) providing an ee% = 80.6%.

The ^{1}H NMR for **188a** (Figure 2.23) revealed the resonance for C<u>H</u>OH at δ 4.80 ppm as a doublet of doublets of doublets (*J* = 7.49, 5.04, 3.58 Hz), a doublet at δ 4.60 (1H) (*J* = 12.0 Hz) attributed to PhC<u>H</u>$_2$O and a second doublet at δ 4.59 ppm (1H) (*J* = 12.0 Hz) attributed to the second benzylic proton. At δ 3.7-3.8 ppm there is a multiplet attributed to OC<u>H</u>$_2$CH and a doublet at δ 2.60 ppm (1H) (*J* = 5.0 Hz) attributed to O<u>H</u>.



188a

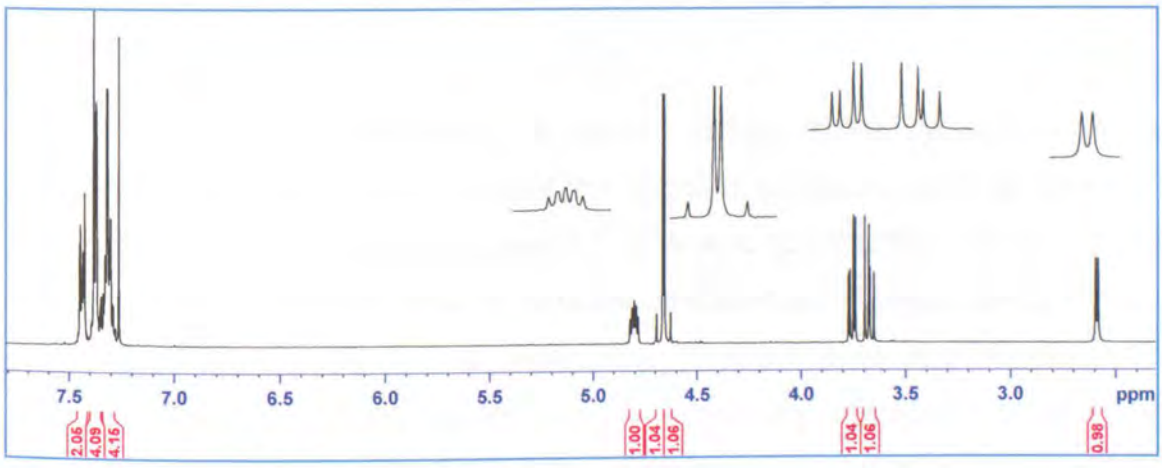
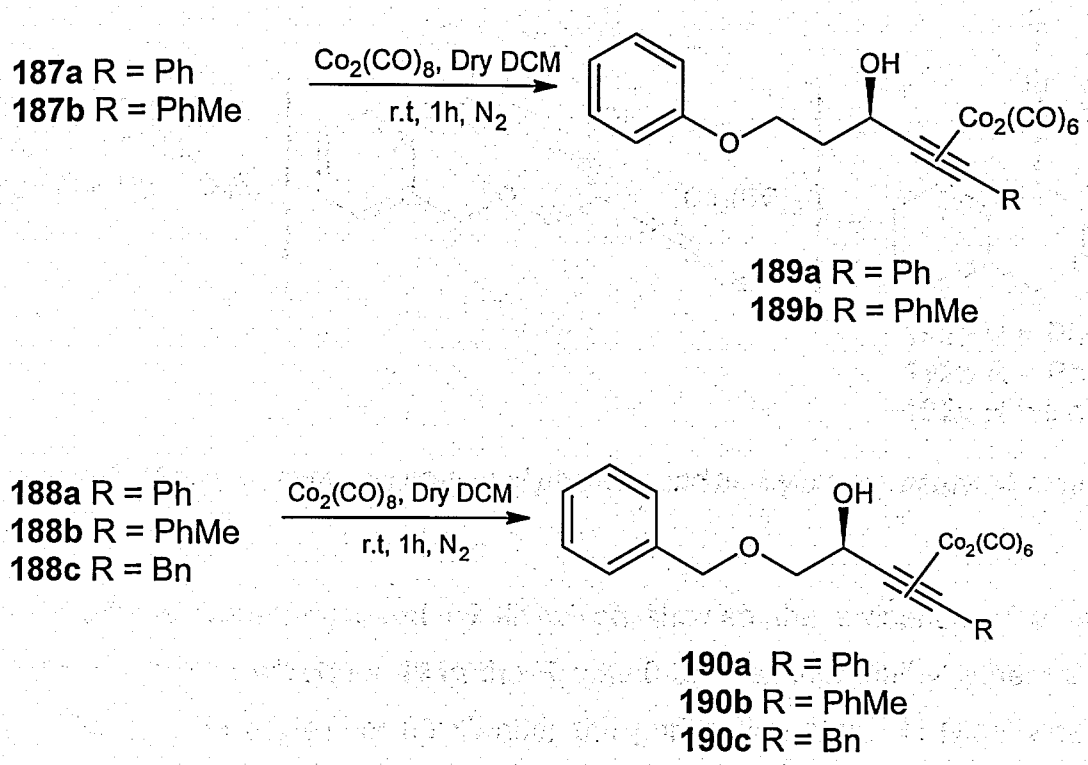


Figure 2.23: *^{1}H NMR spectrum of **188a***

2.5.8 The complexation reaction

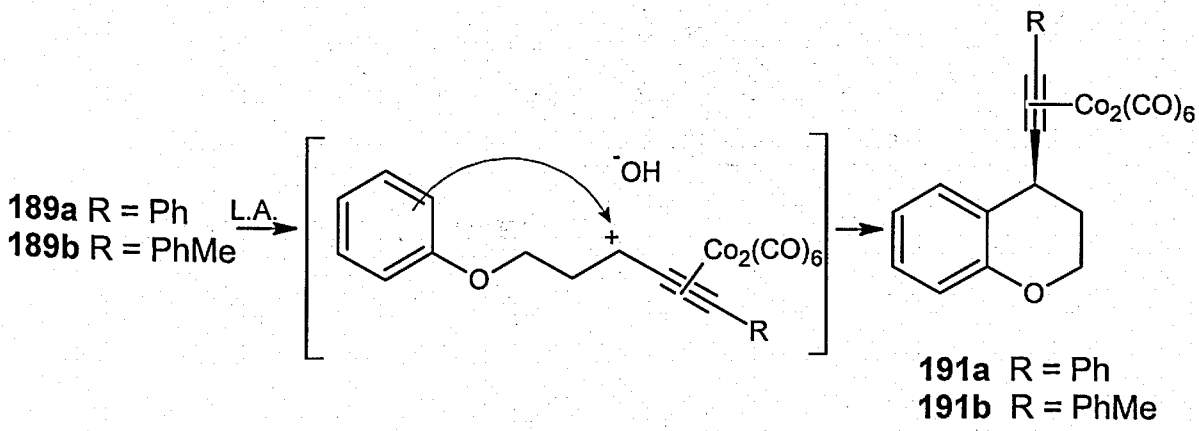
This step was carried out using the same procedure as that for the racemic propargyl alcohols to afford the enantio enriched dicobalt hexacarbonyl complexes **189a/b** and also for the **190a-c** (Scheme 2.36).

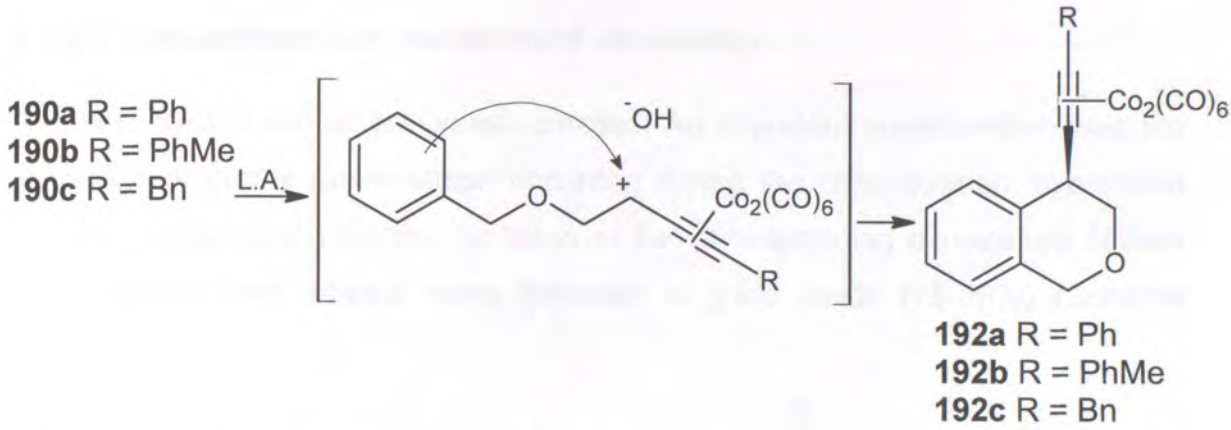


Scheme 2.36: *Complexation of chiral phenoxy and benzyloxy propargyl alcohol*

2.5.8.1 The Nicholas (cyclisation) reaction with an optically active substrate

The key factor in controlling the stereochemistry of the cyclisation reaction was temperature. As the two faces of the Nicholas cation are equally exposed to the nucleophile at temperatures above 0 °C low temperatures (-78 °C) must be maintained.[25,40] Then the rate of fluxional stabilisation is significantly reduced providing an opportunity for the nucleophile to attack onto one face only. The cyclisation reactions were carried out as previously described to afford the complexed chromanes **191a/b** and the corresponding isochromane complexes **192a-c** (Scheme 2.37)





Scheme 2.37: *Asymmetric cyclisation of phenoxy and benzyloxy propargyl alcohol complexes*

The reactions were monitored by tlc which showed the presence of a faster moving compound which for **191a** the R_f was 0.66 (hexane: diethyl ether 90:10). It was isolated in a yield of 63 % after the purification step. ^{1}H NMR analysis showed the presence of 9 aromatic protons (R = Ph) at δ 7.35-7.22 ppm (5H), 7.1-7.00 ppm (2H), 6.84 ppm (1H) and 6.73 ppm (1H). The presence of only 9 aromatic protons confirmed that cyclisation had taken place. The benzyl proton (C<u>H</u>C≡CPh) appeared as a doublet of doublets at δ 4.51(1H) (*J* = 6.0, 6.0 Hz, C<u>H</u>), and there were multiplets at δ 4.3-4.2 (1H) and 4.2-4.1 ppm (1H) attributed to (OC<u>H</u>$_2$CH$_2$). The adjacent protons to the benzyl proton (CH$_2$C<u>H</u>$_2$CH) showed two multiplets at 2.50 – 2.32 and 2.2-2.1 ppm as they are diastereotopic protons and the OH peak was not apparent (Figure 2.24). The same procedure was repeated for compound **191b** and **192b-c**.

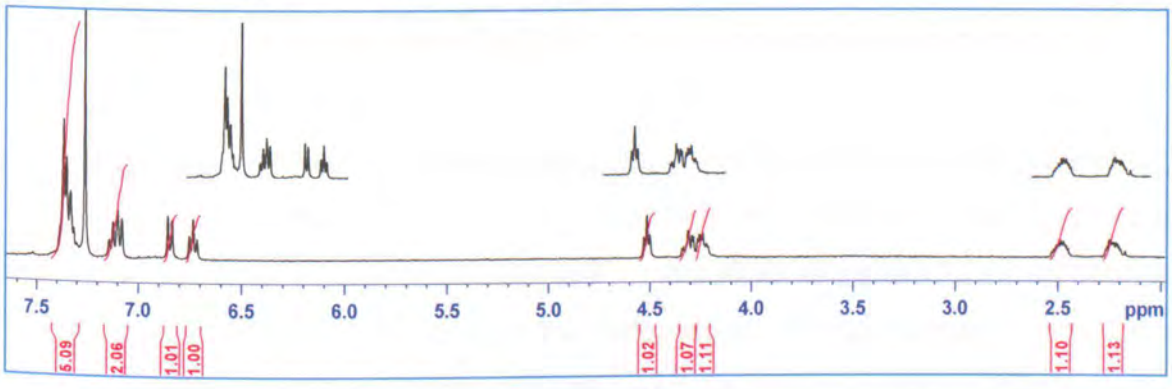
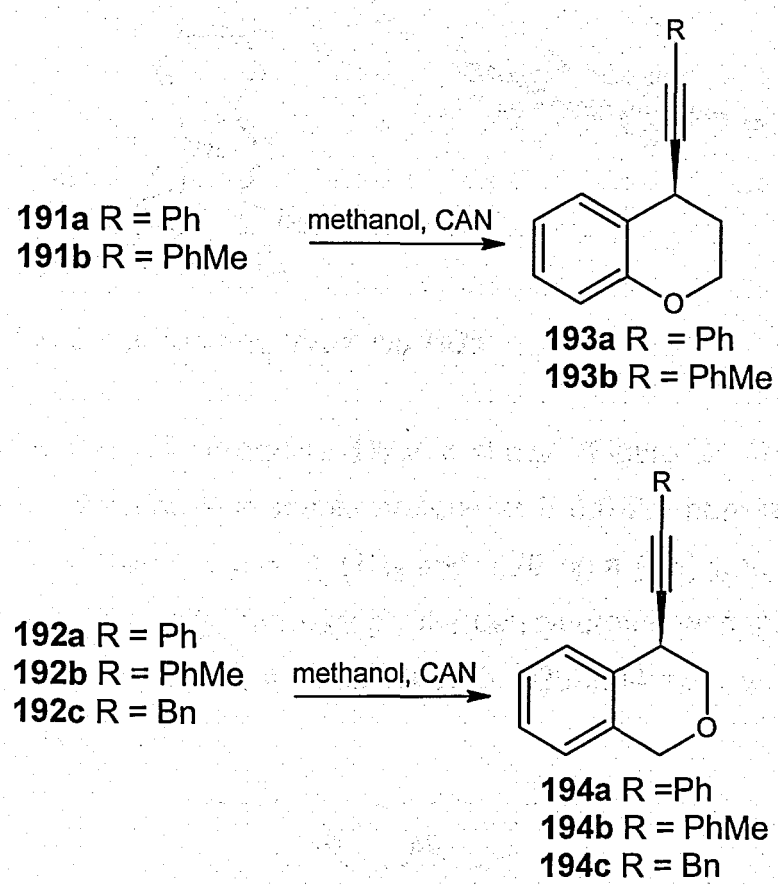


Figure 2.24: *^{1}H NMR spectrum of **191a***

2.5.8.2 Decomplexation reaction and discussion

This was carried out as previously detailed. An important consideration was the possibility of partial racemisation occurring during the complexation, cyclisation and decomplexation reaction. Isolation of the corresponding chromanes **193a/b** and isochromanes **194a-c** were achieved in good yields (76-89%) (Scheme 2.38).



Scheme 2.38: *Decomplexation of optically active chromenes and iso-chromenes*

Hplc analysis of chromane **193a** showed t_{major} = 8.58 minutes (72.61%) and t_{minor} = 16.73 min (27.39%) for **193b** t_{major} = 13.60 min (85.26%) and t_{minor} 16.96 minutes (14.74%). From these data the corrected enantiomeric excess[49] for the syntheses of **193a** and **193b** may be determined. The corrected enantiomeric excess is determined as the enantiomeric excess of the products **193a/b** divided by the enantiomeric excess of the cyclisation precursors **187a/b** expressed as a percentage. For the syntheses of chromane **193a** the corrected enantiomeric excess was 45/50 x 100 = 90% and for the synthesis of **193b** the corrected enantiomeric excess was 71/74 x 100 = 96%.

Consideration of the Nicholas cyclisation of propargyl alcohol **187a**, from molecular mechanical modelling experiments, suggests that the pyran ring may

be formed as a twisted chair in which the alkynyl functional group is appropriately orientated so as to minimise the non-aromatic ring energy.[114] This is achieved by the alkyne group adopting a pseudo-equatorial position. This tends to reduce steric interactions such as 1,3-diaxial interactions between the alkyne and protons $H_{3a\ \&3e}$ as well as ensuring that the the cobalt-stabilised cation is aligned in close proximity to the adjacent nucleophilic aromatic ring (Figure 2.25).

Figure 2.25: *3D structure of chromene* ***193a***

^{1}H NMR analysis of chromane **193a** is shown (Figure 2.26) and confirmed the structure by showing 9 aromatic protons at δ 6.6-7.5 ppm and two doublet od doubltes of doubltes at δ 4.44 (1H) and 4.26 ppm (1H) with (J = 11.0, 7.5, 3.0 Hz), attributed to $OC\underline{H}_2$. Interestingly the benzyl proton was shifted to δ 4.10 ppm as a triplet (J = 6.2 Hz), a multiplet at δ 2.26-2.04 ppm was attributed to the $OCH_2C\underline{H}_2CH$ protons.

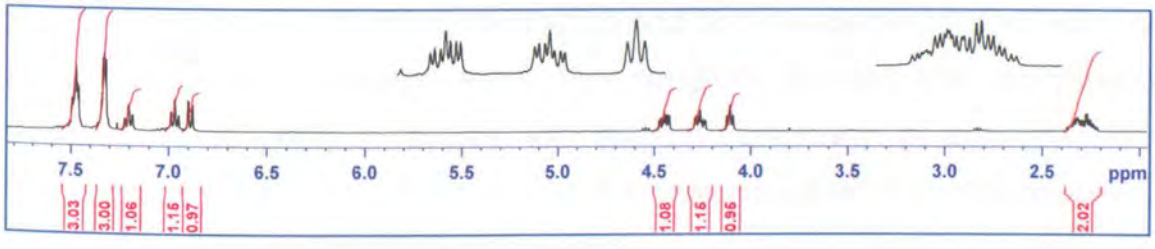


Figure 2.26: *^{1}H NMR spectrum of chromene* ***193a***

The corresponding ^{13}C NMR spectrum (Figure 2.27) showed resonances for the aromatic carbon atoms attached to oxygen at δ 153.93 ppm and the remaining 9 aromatic carbons at δ 131.74, 129.86, 128.45, 128.31, 128.04, 123.43, 121.88, 120.64, 117.07 ppm. Peaks at δ 91.31 and 82.21 ppm may be attributed to (C≡C) and at δ 64.44 ppm attributed to ($PHO\underline{C}H_2CH_2CH$). Further peaks at δ 29.16 and 28.13 ppm may be attributed ($OCH_2\underline{C}H_2\underline{C}H$).

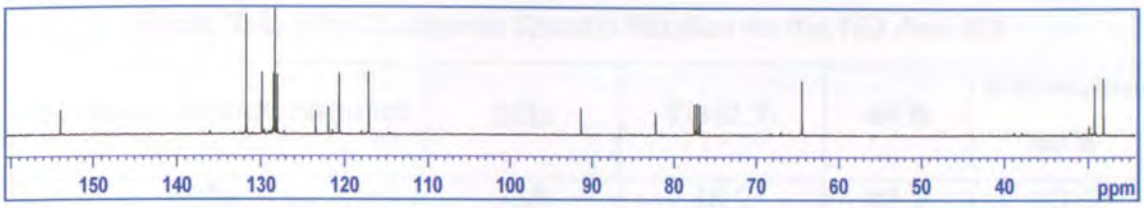


Figure 2.27: *^{13}C NMR spectrum of chromene **193a***

An associated ^{13}C DEPT experiment of **193a** (Figure 2.28) showed two CH_2 carbons at δ 64.44 and 29.16 ppm and one CH carbon at δ 28.13 ppm. The resonances attributed to the alkynyl carbon atoms between δ 80-92 ppm have disappeared.

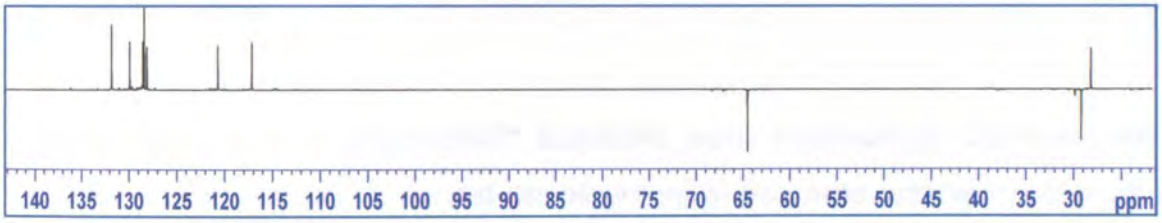


Figure 2.28: *^{13}C DEPT of the chromene **193a***

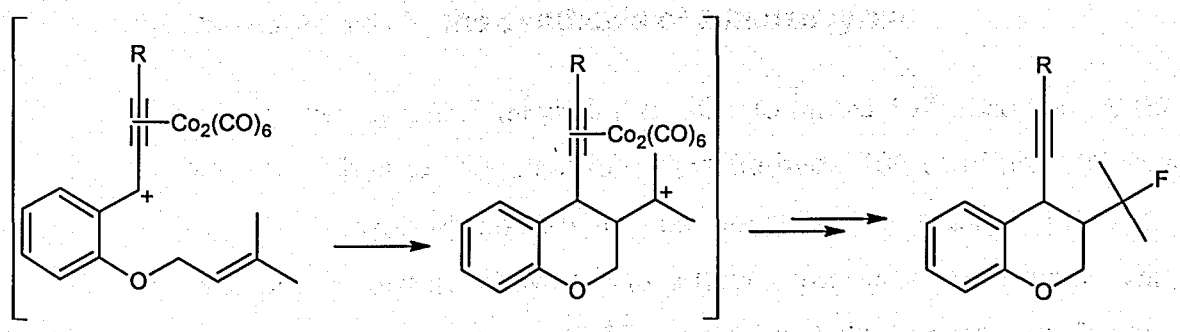
The data associated with chromanes **193a, b** and for isochromanes **194a-c** are included in (Table 2.4). Analyses of these data reveal that the Nicholas cyclisation reactions took place with high levels of enantioselectivity. It confirms that having secured the propargyl alcohol enantioselectively the subsequent cycle of complexation, Nicholas cyclisation and decomplexation occurs with very low to zero levels of racemisation. This suggests that the low experimental temperatures required to secure this level of selectivity is attributed to a combination of slow rates of diffusion of the "leaving group" from the complex in combination with minimal fluxional rotation of the cobalt stabilised cation that allows the nucleophile to attack one face only.

Table 2.4: *HPLC Data and Specific Rotation for the **193** And **194***

Chromenea/isochromenes	$[\alpha]_D$	Yield %	ee%	Corrected ee%
193a	-38	76.2	45.2	90.5
193b	-10	79.0	70.5	95.3
194a	+13	79.0	77.3	95.9
194b	-21	89.3	81.6	99.2
194c	-9	88.6	76.1	98.6
194d[1]	-13	85.0	77.3	90.5

[1]*For comparison purposes e.g hplc retention times etc it was also carried out the reaction using (-)-N-methylephedrine*

In conclution these enantiospecific reactions were successfully achieved with high enantioselectivities. The next development in this area was to consider the Nicholas cyclisation in which the stabilised cation **195** is quenched not by an aromatic ring but by the comparatively electron rich double bond. Note that the initial stereogenic centre, formed from the Nicholas cyclisation, then results in the formation of an adjacent second stereocenter in the second cation **196** (Scheme 2.39).



195 **196**

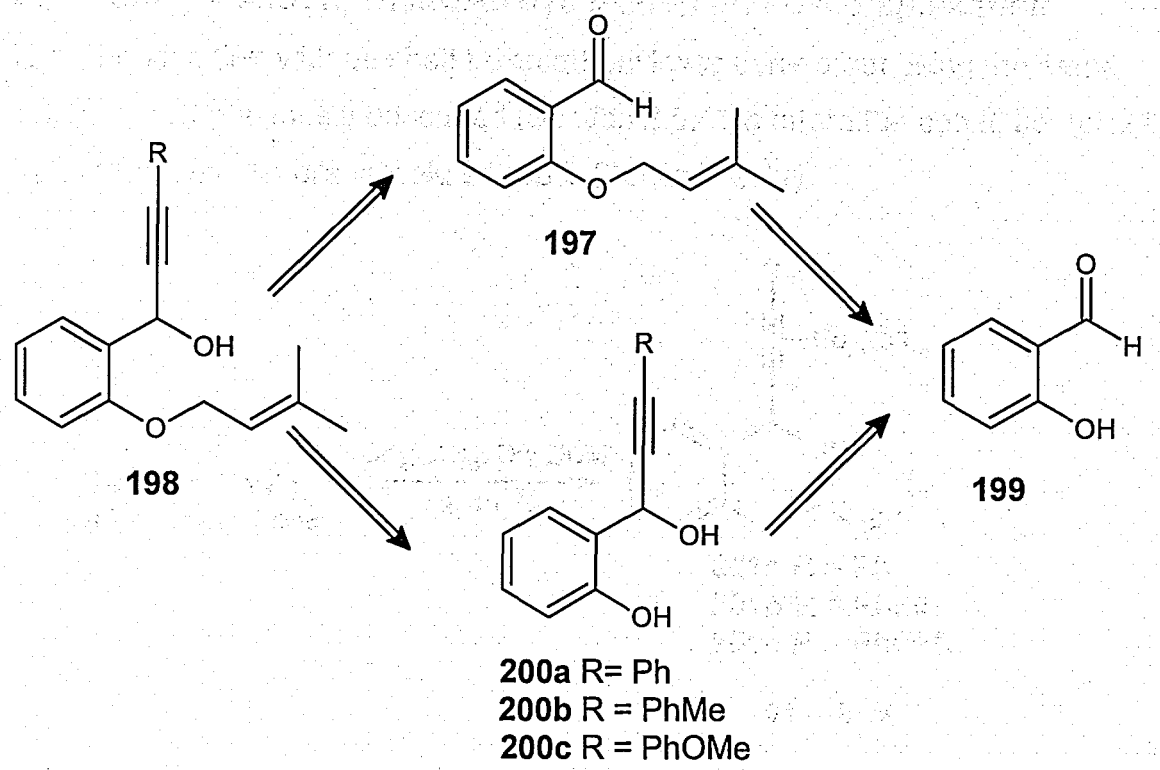
Scheme 2.39: *Nicholas cyclisation via cation **195***

2.6 The synthesis of a benzopyran

2.6.1 Retrosynthesis

Different approaches for accessing the Nicholas cyclisation precursor **198** are shown in the following retrosynthesis (Scheme 2.40). It is based upon a strategy that was used to synthesise benzopyrans for biological screening as

hypertensive reagents.[115] The two approaches shown, either via the aldehyde **197** or the propargyl alcohol **200**, both begin with salicylaldehyde **199** which is commercially available.



Scheme 2.40: *Two routes to propargyl alcohol **198***

2.6.2 Racemic approach to the synthesis of a benzopyran

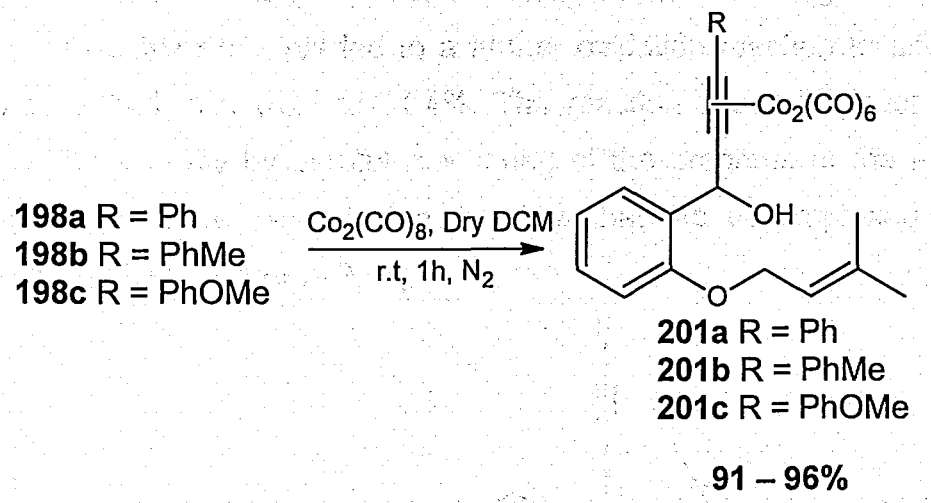
Initially **198** was formed by the O-alkylation of **199**, to afford **197**, followed by the alkynylation reaction. Thus O-alkylation of salicylaldehyde **199** to afford **197** was carried out using a similar procedure to that described in section 2.5.1. Tlc analysis of the reaction mixture showed that a new compound was present with an R_f value of 0.5 (petroleum ether (60 °C – 80 °C): diethyl ether, 80:20). The desired compound **197** was isolated in a quantitative yield 99 – 100%. ^{1}H NMR spectroscopy confirmed the structure of **197** by showing the aldehyde resonance (1H) at δ 10.39 ppm as a singlet. A doublet of doublets at δ 5.46 ppm (J = 6.71, 1.09 Hz) attributed to C<u>H</u>=C, and two singlets at δ 1.79 ppm and 1.71 ppm attributed to the two vinyl methyl groups.

The alkynylation reaction of **197** was carried out using the analogous procedure to that described (Section 2.5.3) using three different Grignard reagents to afford desired propargyl alcohols **198a-c** in excellent yield of 81- 93 %. The ^{1}H NMR

spectrum for **198a** showed that the resonance attributed to the aldehyde C<u>H</u>O group had disappeared and a new doublet at δ 3.30 ppm (J = 6.2 Hz) was seen attributed to O<u>H</u>.

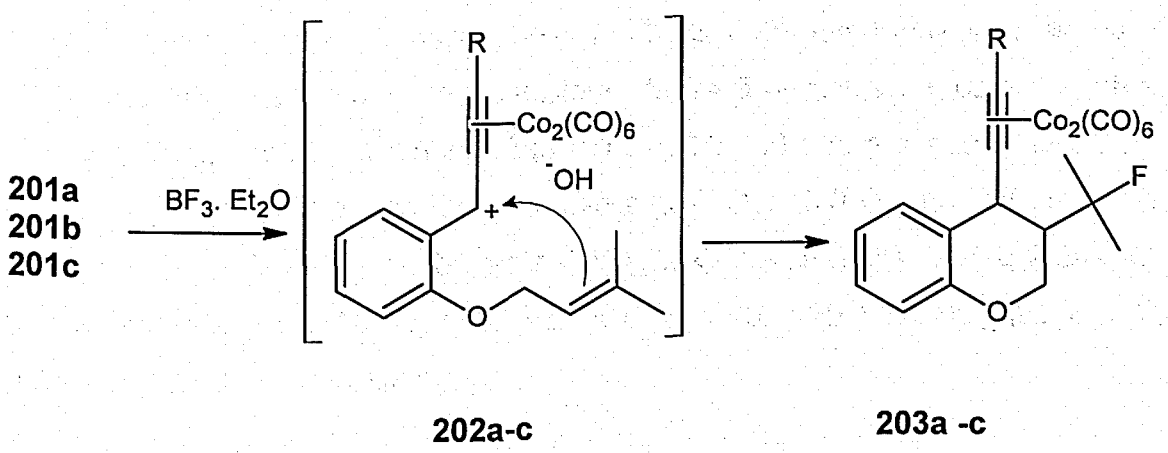
2.6.3 Complexation, Nicholas cyclisation and decomplexation

The complexation with dicobalt hexacarbonyl was carried out using the same procedure as previously described (Section 2.5.4) to afford the cobalt complexes **201a-c** as dark red oils in yield 91- 96% (Scheme 2.41)



Scheme 2.41: *Complexation of **198a-c** using dicobaltoctacarbonyl*

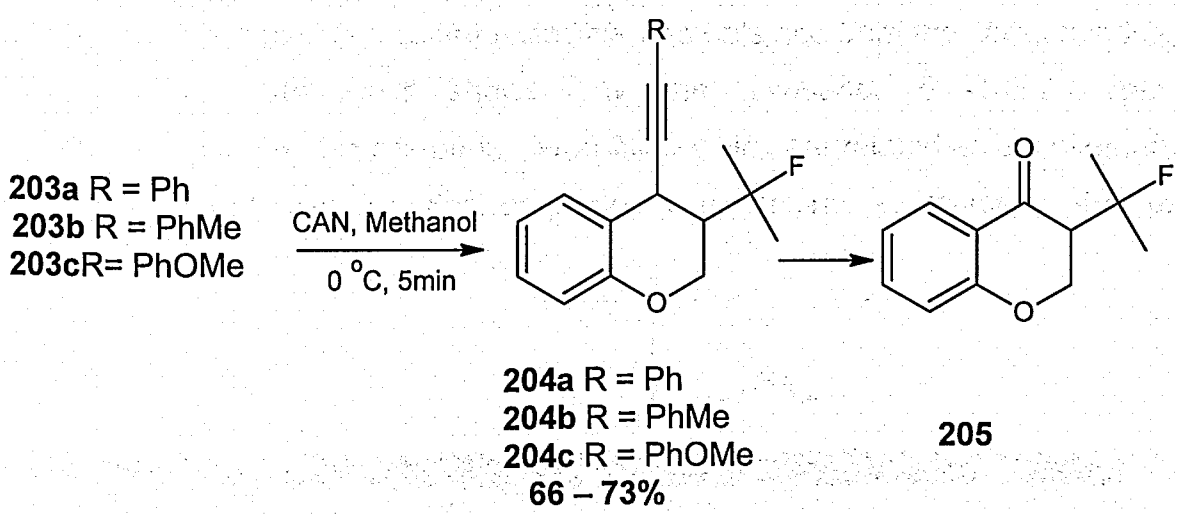
The Nicholas cyclisation was carried out by exposing each of the complexes **201a-c**, maintained at a temperature of 0 °C, to the Lewis acid BF_3OEt_2. From the previous investigations[22a] it was noted that the probable outcome of the cyclisation reaction would be the formation of the fluorinated complex **203a-c** (Scheme 2.42).



Scheme 2.42: *Cyclisation of propargyl alcohol **201a-c***

This arises as a result of the halogenation of the incipient second cation, such as **196**, that is formed as a result of the cyclisation of **202a-c**. It is probable that the fluorine atom is derived from the dissociation of the Lewis acid during the cyclisation sequence. This was a very useful outcome and enabled the use of ^{19}F NMR spectroscopy to be used in the analyses of the products.

The decomplexation step was carried out using CAN as described earlier (Section 2.5.6) to afford the fluorinated benzopyrans **204a-c** in yields of 66.4%, 70% and 73%. It was noted, for the first time, that prolonged exposure of the benzopyran **204a** to CAN led to a further oxidation reaction to afford the novel chromene **205** in a yield of 71.4%. The reaction could, however, be tuned to favour **204a-c** only by careful monitoring of the progress of the reaction by tlc analysis and therefore reducing the time that the decomplexed product was exposed to CAN (Scheme 2.43).



Scheme 2.43: *Decomplexation of flouro-benzopyran derivatives*

Spectroscopic analyses of the benzopyrans **204a-c** were undertaken and the ^{1}H NMR of **204a** is shown (Figure 2.29). At δ 7.52- 6.85 ppm there are a series of resonances attributed to 9 aromatic protons. At δ 4.5 ppm is an apparent doublet of triplets intergrating for 1H ($OC\underline{H}_2$) (J = 11.7, 3.3 Hz) and a second resonance at δ 4.18 ppm (1H) as a doublet of doublets (J = 11.7, 6.0 Hz) for $OC\underline{H}_2$, 4.12 ppm (1H, d (J = 5.6 Hz), attributed to $PhC\underline{H}C{\equiv}C$) and a multiplet at δ 2.58-2.63 (1H) attributed to $CH_2C\underline{H}CF$), δ 1.55 ppm (3H, d, (J = 20.1 Hz,$CC\underline{H}_3F$), δ 1.48 ppm (3H, d (J = 20.1 Hz), $CC\underline{H}_3F$).

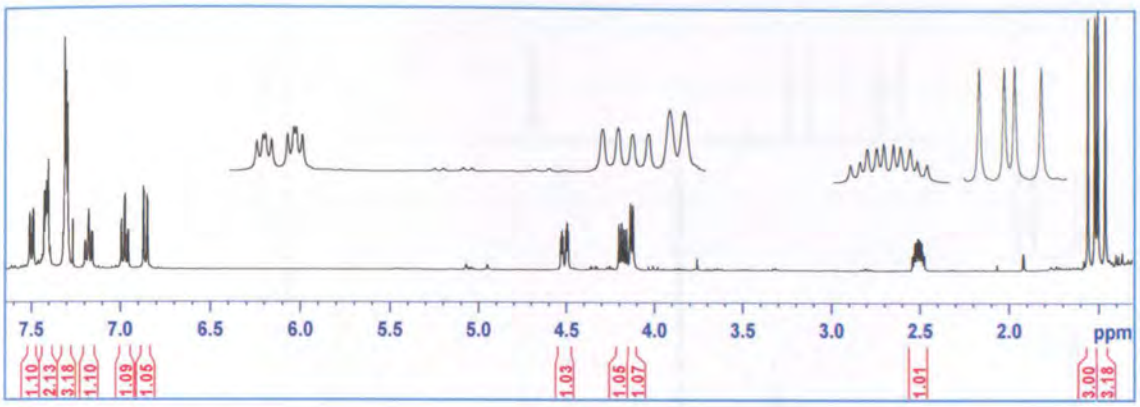


Figure 2.29: *^{1}H NMR spectrum of flouro-benzopyran* ***204a***

It was previously demonstrated that the Nicholas cyclisation reactions are completely diastereoselective and in keeping with the previous investigations the coupling constant *J* for the benzylic proton at δ 4.12 ppm of 4.2 Hz is suggestive of a *cis*-relative stereochemistry. Further evidence to confirm that the cyclisation reactions are completely diastereoselective was obtained from the corresponding ^{19}F NMR spectrum which shows only one resonance δ -135.25 ppm, corresponding to the two cis- benzopyran **204a** which are related as enantiomers and thus have identical physical properties in an achiral environment (Figure 2.30).

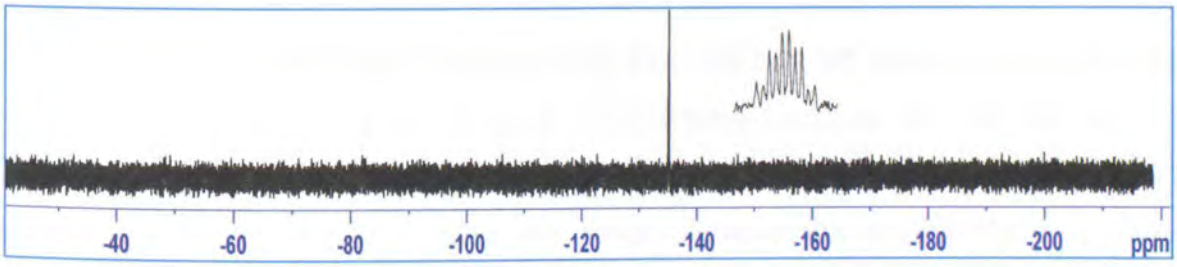


Figure 2.30: *^{19}F NMR spectrum of flouro-benzopyran* ***204a***

The corresponding ^{13}C spectrum showed resonances for 10 aromatic carbons at δ 153.97, 131.59, 130.18, 128.28, 128.26, 128.08, 123.27, 121.89, 121.27, 116.94 ppm consistent with the structure **204a**. In addition there were further resonances at δ 96.64 ppm (CF, d, J_F = 168.5 Hz) and δ 91.92, 82.58 ppm attributed to (C≡C), peaks at δ 64.53 (d, $^{4}J_{C\text{-}F}$ = 9.9 Hz), 47.57 (d, $^{3}J_{C\text{-}F}$ = 22.5 Hz), 28.96 (d, $^{4}J_{C\text{-}F}$ = 5.6 Hz), 26.16 (d, $^{3}J_{C\text{-}F}$ = 24.5 Hz), 25.19 (d, $^{3}J_{C\text{-}F}$ = 24.5) (Figure 2.31).

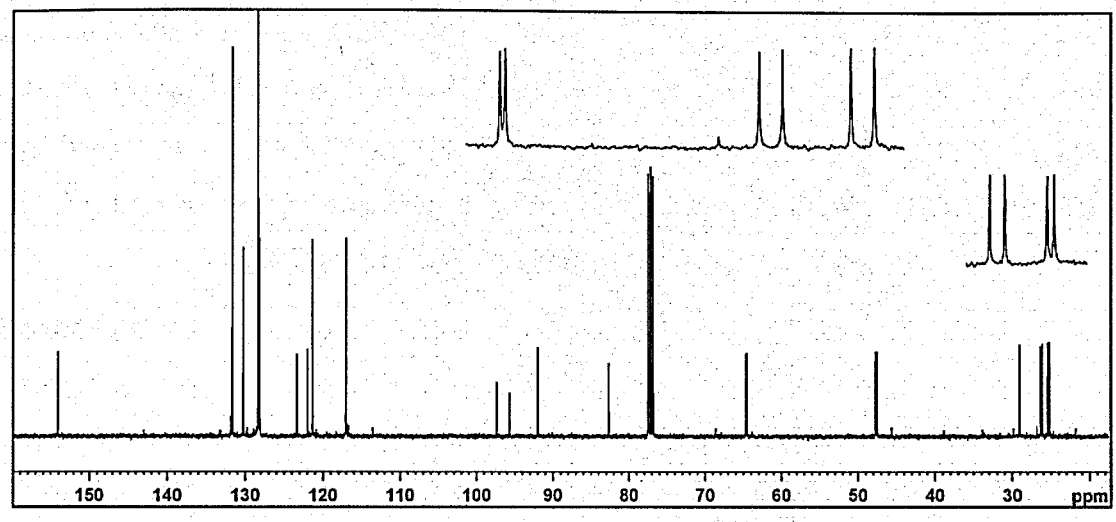
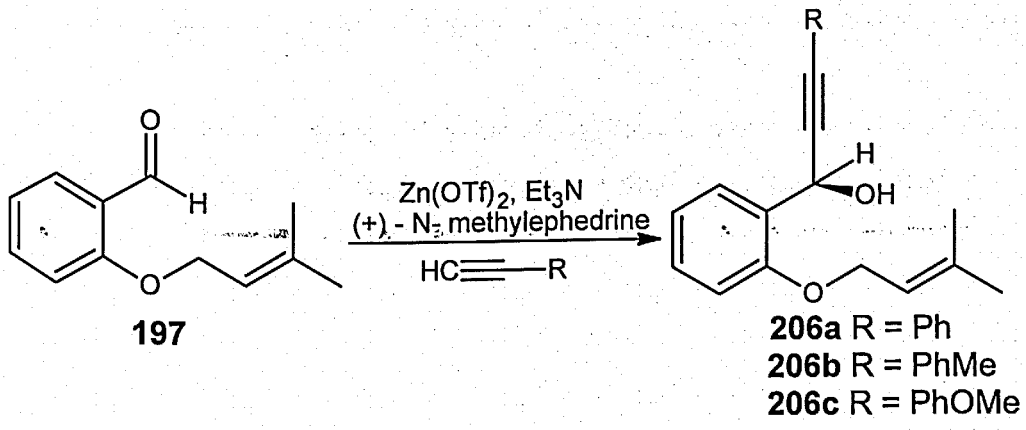


Figure 2.31: *^{13}C NMR spectrum of flouro-benzopyran **204a***

From this study it was concluded that the synthesis of the (+/-) - benzopyrans **204a-c** was successfully accomplished and that the key cyclisation reaction took place with complete control over the diastereoselectivity of the contiguous chiral centres. The next phase of this study was an attempt at the corresponding asymmetric variant.

2.6.4 Asymmetric synthesis of benzopyrans

The asymmetric alkynylation of aldehyde **197** was carried out with three different Grignard reagents using the Carreira methodology to afford the desired optically active propargyl alcohols **206a-c** in yield of 72.7%, 83.8%, and 92.5% respectively. The spectral data for these compounds was similar to those synthesised under racemic conditions however they were analysed by polarimetry and chiral HPLC (Scheme 2.44).



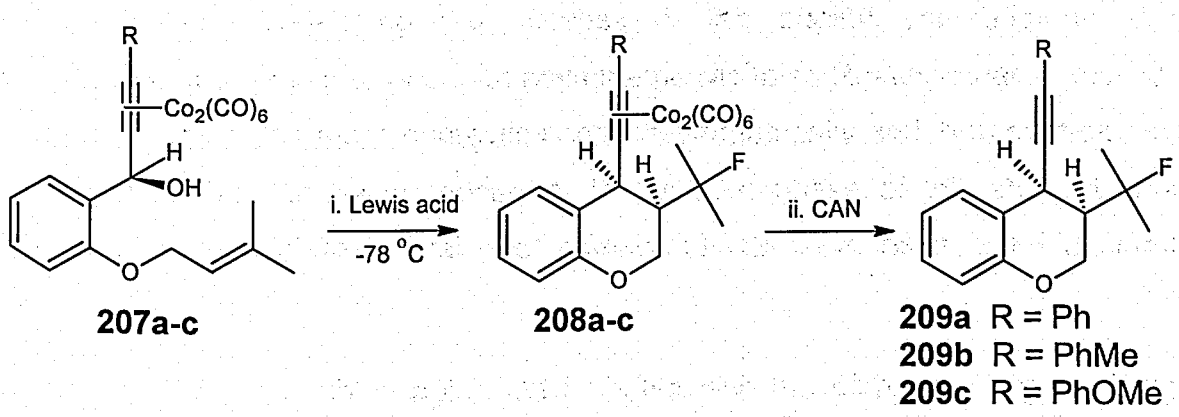
Scheme 2.44: *Asymmetric synthesis of propargyl alcohols **206a-c***

The specific rotation for **206a** was measured as $[a]_D^{23}$ = +10 ° (c = 1% ethanol) and the melting point was 52 °C. Chiral hplc analysis for **206a** gave t_{minor} = 16.6 min (2.5%) and t_{major} = 12 min (97.5%) which provides an enantiomeric excess of 95 %. Data for the same analyses for **206b** and **206c** are provided in Table 2.5.

Table 2.5: *Data for Chiral Propargyl Alcohols* ***206a-c***

Propargyl alcohol	$[a]_D^{23}$	t_{minor}	t_{major}	ee%
206a	+10	2.5	97.5	95
206b	-13	2	98.0	96
206c	+11	1.5	98.5	97

Having secured the syntheses of the important cyclisation precursors the next step involved the key Nicholas cyclisation of the corresponding dicobalt hexacarbonyl complexes **207a-c** (formed in yields of 97.5%,97.8%, 95.4% respectively) (Scheme 2.45). The reactions were performed as previously described, although the cyclisation was conducted at -78°C as these were chiral substrates, to afford the corresponding benzopyrans **209a-c**.



Scheme 2.45: *Asymmetric synthesis of flouro-benzopyran derivatives* ***209a-c***

The spectroscopic data for these benzopyrans was similar to those previously described however polarimetry and chiral hplc data was collected and shown in (Table 2.6).

Table 2.6: *Data for Optically Active Benzopyrans* ***209a-c***

Benzopyran	$[a]_D^{23}$	t_{minor}	t_{major}	ee%	corrected ee
209a	-9	3	97	94	**98**
209b	-11	5.7	94.3	88.6	**92**
209c	+15	6.5	93.5	87	**90**

At the present time the absolute configuration of the stereocentres in **209a-c** was not confirmed, the future aims however include the synthesis of a solid crystalline derivative in order to obtain an X-Ray structure. The Nicholas reaction occurs by attack of the nucleophile from the rear side of the leaving group i.e. the other face away from the leaving group. At -78 °C this leads to a stereospecific cyclisation, as the synthesis chromanes such as **193a-b** and **195a-c**. In these examples, however, the stereospecific nature of the cyclisation step also ensures that no scrambling can occur as the contiguous chiral centre is sequentially generated and therefore affording (*cis*-diastereoselectivity the J = 4.0 Hz value of the benzylic proton (C<u>H</u>C≡C) confirmed the *cis* configuration. The corrected enantiomeric excess of the three benzopyrans **209a-c** of 98 %, 92 % and 90 % were excellent, confirming the success of the original methodology and suggesting that the aim to effect an asymmetric Nicholas Reaction was achieved. This initially provides the propargylic centre asymmetrically and then controls the formation of the second stereocentre. In the next phase of this study it was explored the use of the chiral pool compound citronellal as a suitable chiral precursor.

A comparison of the chiral hplc data for **209a** with the corresponding products from the racemic reaction are shown in Figure 2.33. These data showed that the major diastereoisomer has a retention time t_R at 13.35 minutes and the minor at 9.83 minutes. The corresponding ^{19}F NMR spectrum (Figure 2.32) reveals the presence of one resonance only for the enantiomeric mixture that resonates at δ-135 ppm.

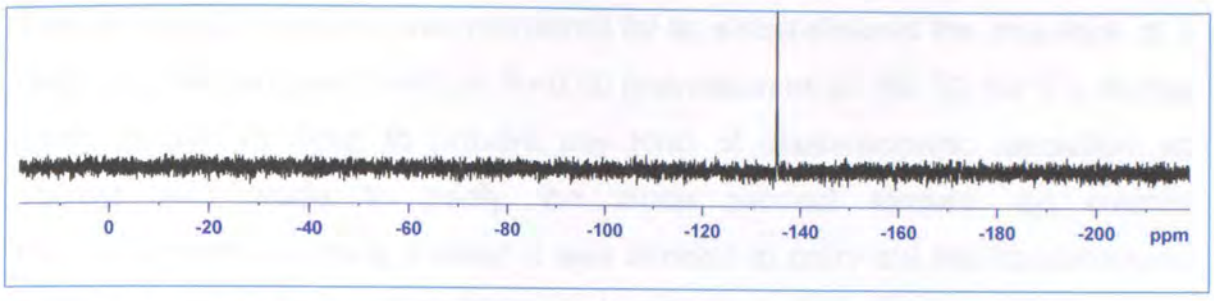
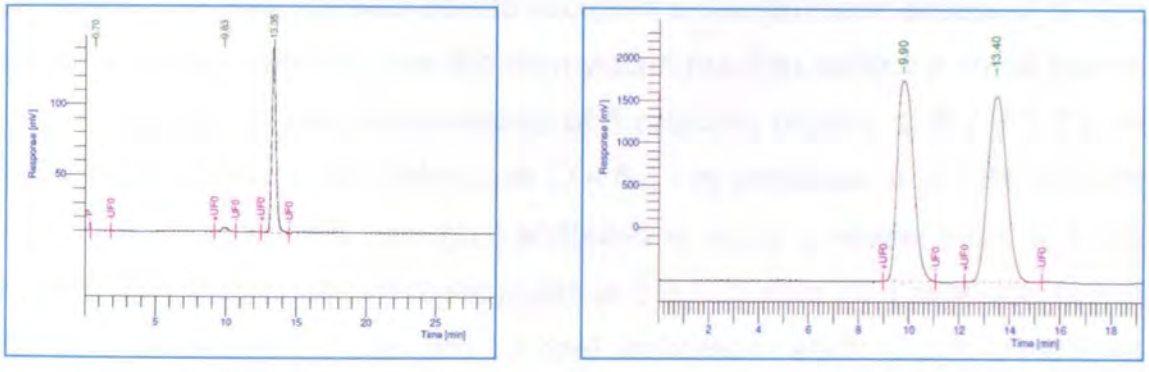


Figure 2.32: *^{19}F NMR spectrum of chiral flouro-benzopyran* **209a**

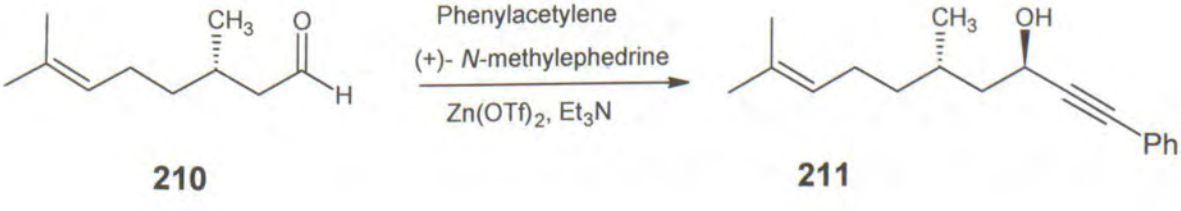


opticaly acitve **209a** racemic mixture **204a**

Figure 2.33: *hplc of the* ***209a*** *and* ***204a***

2.7 Chiral pool

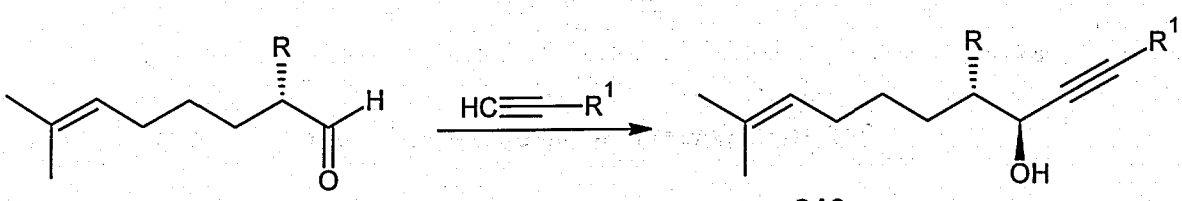
An asymmetric alkynylation was one of the key reactions to achieve the corresponding propargyl alcohol from aldehyde as a precursor in the Nicholas reactions. (*S*)-Citronellal **210** is a chiral aldehyde which it has previously demonstrated undergoes alkynylation with minimal stereocontrol from the β-asymmetric centre. The corresponding propargyl alcohols are formed as a 48:52 mixture of diastereoisomers. To improve upon this diastereoselectivity, a Carreira asymmetric alkynylation on **210** was performed to afford the diastereo enriched propargyl alcohol **211** (Scheme 2.46).



Scheme 2.46: *Asymmetric alkynylation of the citronellal* ***210***

The alkynylation reaction was monitored by tlc which showed the presence of a faster moving compound with an R_f=0.90 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). In order to prevent any form of diastereomeric resolution no attempt was made to purify the crude product mixture, by column chromatography on silica, instead it was decided to carry out the spectroscopic analysis on the crude product. This was isolated in a yield of 88%, and the optical rotation for **211** was measured as $[a]_D^{23}$ = +11 °(c = 1% ethanol). From the ^{1}H NMR spectrum it was possible able to ascertain a diasteromeric excess of 57% a considerable improvement upon the alkynylation reaction without a chiral ligand. ^{1}H NMR analysis showed the presence of 5 aromatic protons at δ 7.5-7.2 ppm (5H), at δ 5.0 ppm a broad triplet peak (*J* = 6.3 Hz) attributed to C<u>H</u>OH, a triplet peak (*J* = 5.5 Hz) at 4.55 ppm (1H) attributed to =C<u>H</u>), a singlet peak at δ 2.3 ppm (1H) attributed to O<u>H</u>, multiplet peaks at 2.0-1.25 ppm (4H) attributed to two C<u>H</u>$_2$, two singlets at δ 1.6 ppm and 1.5 ppm attributed to each =CC<u>H</u>$_3$, a multiplet at δ 1.45-1.08 ppm (4H) attributed to C<u>H</u>CH$_3$ and C<u>H</u>$_2$); a doublet at 0.92 and 0.76 ppm (3H) (*J* = 6.5 Hz) attributed to C<u>H</u>$_3$, major = 78%, minor = 21%.

In order to improve upon the diastereoselectivity of the propargylation reaction it was considered the synthesis of a derivative of citronellal **210** based upon **212** in which the chiral centres are contiguous (Scheme 2.47).

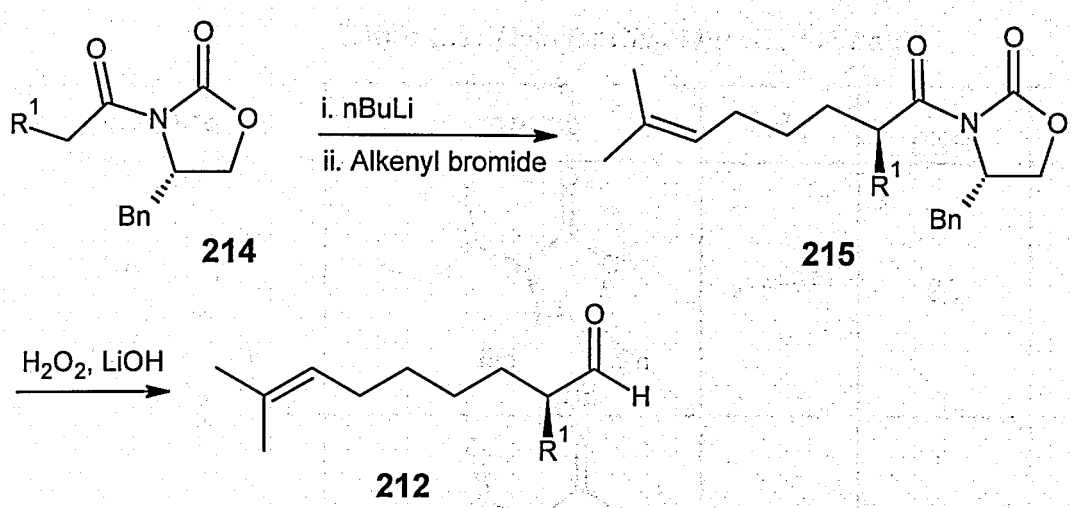


212 **213**

Scheme 2.47: *Synthesis of novel diastereoselective propargyl alcohol **213***

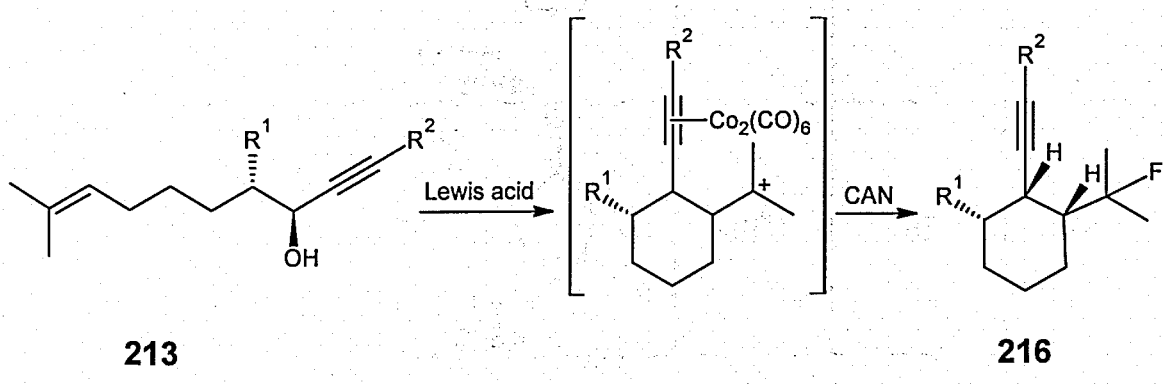
In this example chiral auxiliary technology could be employed to stereoselectively install the R group α- to the carbonyl where it may be able to control the subsequent alkynylation reaction (Scheme 2.48).

The preparation of aldehyde **212** is shown in Scheme 2.48 which involves alkylation of the acylated chiral auxiliary **214** to achieve **215.** The synthesis of aldehyde **212** is then obtained from the hydrolysis of the auxiliary from **215.**



Scheme 2.48: *Synthesis of novel chiral aldehyde* **212**

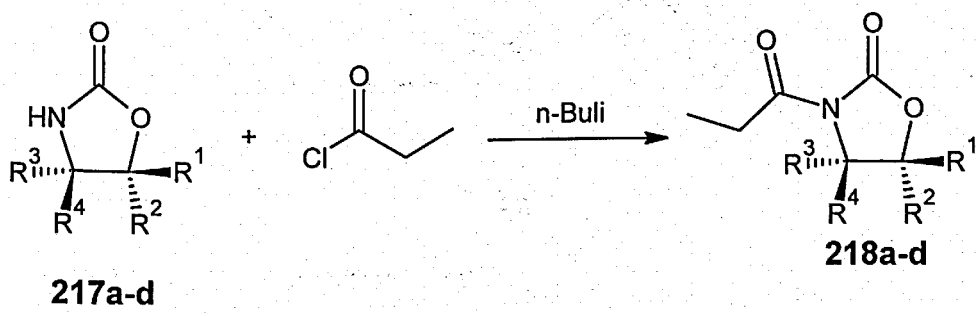
It was envisaged that complexation of the propargyl alcohol **213** and Nicholas cyclisation would afford the corresponding trisubstituted cyclohexane **216** with possible stereocontrol over the three contiguous chiral centres (Scheme 2.49)



Scheme 2.49: *Synthesis of novel trisubstituted cyclohexane* **216**

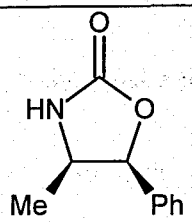
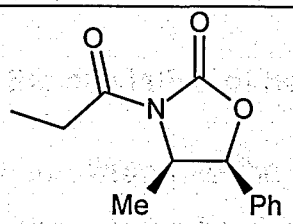
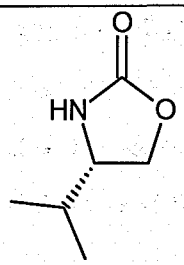
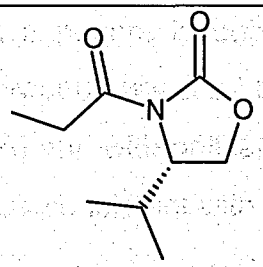
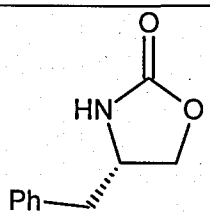
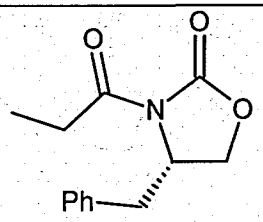
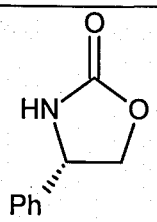
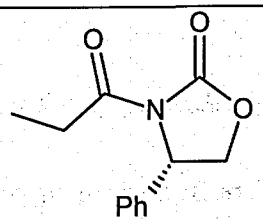
2.8 Chiral Auxiliary

As a preparation it was investigated the chemistry of a small range of Evans chiral auxiliaries **217a-d** in an acylation reaction with an acid chloride to afford **218a-d** (Scheme 2.50)

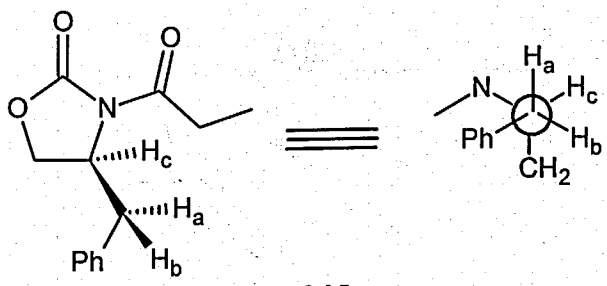


Scheme 2.50: *Acylation of Evans chiral auxiliary*

Table 2.7: *Data for Chiral Auxiliary* ***218a-d***

Oxazolidine	product	$[\alpha]_D$	ee or de%	Yield%
 **217a**	 **218a**	$+75^{98-99}$	98	99
 **217b**	 **218b**	$+73^{116}$	78.5	98
 **217c**	 **218c**	$+47^{117}$	97.6	99
 **217d**	 **218d**	-40^{94c}	95	98.5

Analysis of **218c** revealed that as H_a, H_b (see below) are diastereotopic the ^1H NMR showed that they resonate at different chemical shifts. The Newman projection shows H_a is close with H_c and interacts with both H_b and H_c likewise H_b is interaction with H_a and H_c. (Figure 2.34)



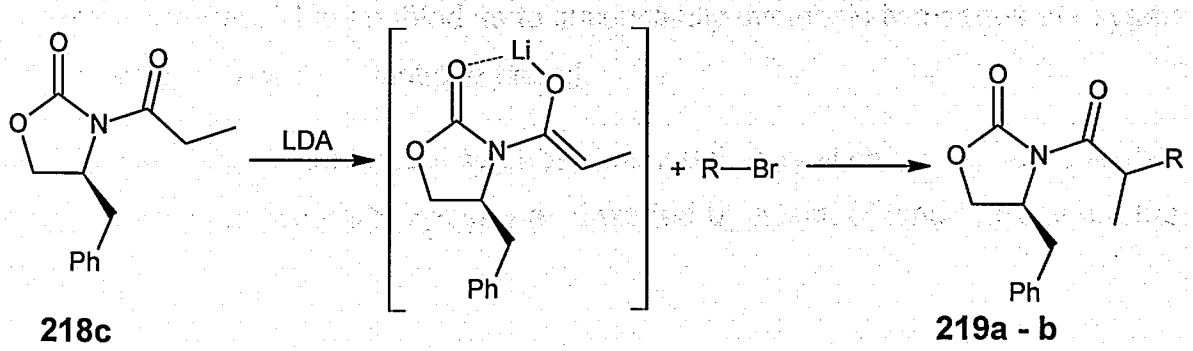
218c

Figure 2.34: Newman projection of ***218c***

The ^{1}H NMR spectrum showed H_a as a dd δ 3.25 – 3.21 ppm (1H, dd, J = 13.4, 3.2 Hz) and H_b at δ 2.79 – 2.67 ppm (1H, dd, J = 13.4, 9.6 Hz). In addition H_c was noted δ 4.6 ppm (1H, m).

2.8.1 Model study of the alkylation of benzyl oxazolidinone

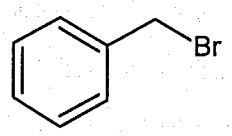
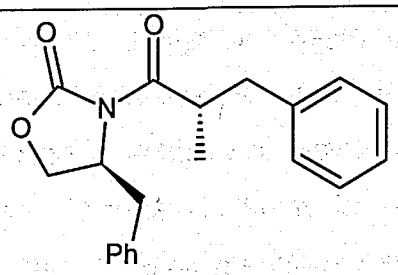
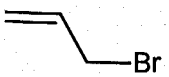
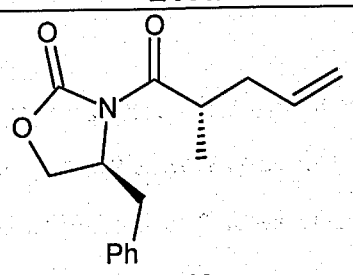
As the benzyloxazolidinone **218c** had the highest enantiomeric excess this was selected to carry out the next step the alkenylation reaction. Thus lithium chelation of **218c**, from exposure to butyllithium, and alkylation with (i) benzyl bromide or (ii) 3-bromopropene provided the corresponding derivatives **219a/b** in excellent yields (78, 87%) and with optical data ($[\alpha]_D^{23}$ = +123° for **219a** and $[\alpha]_D^{23}$ = + 75° for **219b**) that was consistent with literature values (Scheme 2.51).



Scheme 2.51: *Evans alkylation to oxazolidinone* **218c**

Data for the derivatives is summarised in Table 2.8

Table 2.8: *Data for Chiral Auxiliary Derivatives* ***218***

R-Br	product	$[\alpha]_D$	de %	Yield %
	 **219a**	+123[94c,98]	82	86
	 **219b**	+75[118]	78	84

The next phase involved the cleavage of the chiral auxiliary, however unfortunately due to limitations in time this stage of the project was not completed.

2.9 Achievements and Conclusions

This project involved a number of approaches to an asymmetric Nicholas reaction. The most successful approach involved the use of a chiral propargyl alcohol which acts to control the subsequent bond forming reaction/s during the key Nicholas reaction. Despite the, known, fluxional behaviour of the stabilised cation the chiral "memory" of the optically pure propargyl alcohol is retained at low temperatures. This enabled us to successfully synthesis two series of oxygen heterocycles that were enantio enriched.

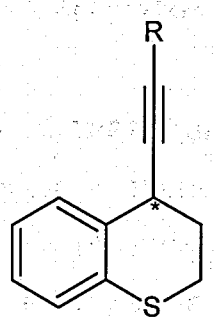
This study involved chiral pool synthesis, although very likely to provide a further set of optically active carbocycles was thwarted by a lack of time to carry out the study.

2.10 Future Direction

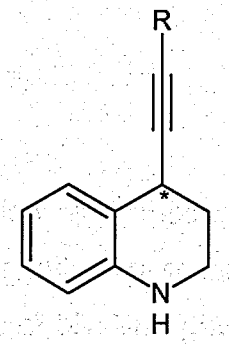
A number of further investigates are suggested by the results of this work. Therefore it would be interesting to investigate the following aspects in more detail:

1- Find an appropriate chiral catalyst for asymmetric 1,4-conjugate addition of cyclohexane with desired haloalkane. As it was described in section 2.4.2, chiral catalyst system was applied to achieve an asymmetric 1,4-conjugate addition by using Josiphos **82** and Taniaphos **84** which was abortive (Scheme 2.8). Therefore using other chiral catalyst mentioned in Table 1.3 would be valuable work to do in future.

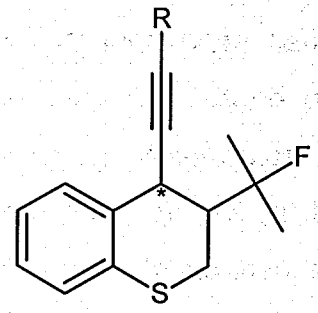
2 – As the asymmetric synthesis of the chromene and isochromene and also benzopyran was succeed. It would be favourable to carry out the same method to synthesis optically pure thiochromene and also quinolone derivatives.



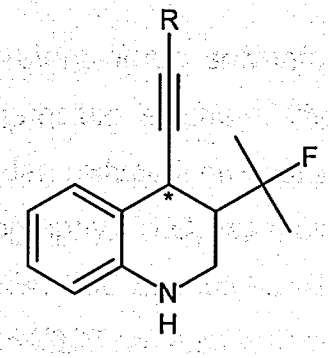
2*H*-thiochromene



Tetrahydroquinoline

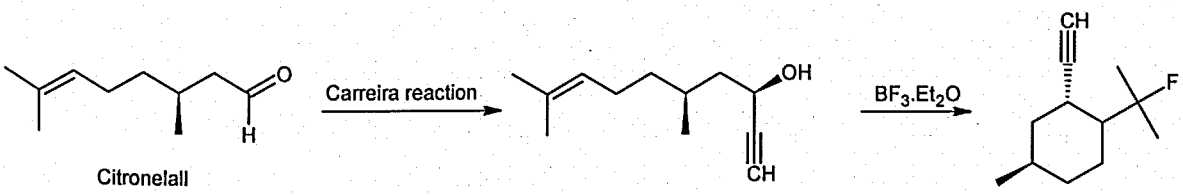


Fluoro-2*H*-thiochromene



Fluoro-tetrahydroquinoline

3- Asymmetric alkynylation of the Citronelall to accomplish a stereospecific Nicholas reaction by using chiral auxiliary. As the Citronelall is a chiral aldehyde an asymmetric alkynylation to provide corresponding optically active alcohol would be applied. An asymmetric inramoecular Nicholas reaction could accomplish the cyclisation reaction.



3 Experimental

3.1 General procedures

Starting materials were provided from Sigma-Aldrich and Fischer Scientific unless otherwise stated. Except for the decomplexation reaction all other reactions were carried out under an inert atmosphere of N_2. The glassware was oven dried at 150 °C overnight prior to use. Dry solvents such as toluene, THF, diethyl ether, DCM and DMF were purchased from Sigma-Aldrich.

Organic extractions were carried out using laboratory grade solvents and the organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated by evaporation of the solvents under reduced pressure using a rotary evaporator. Analytical thin layer chromatography, TLC, was carried out using silica gel with fluorescent indicator (60 F254, 200 μm thick). They were visualised using either UVGL-58 multiband UV – 254/365 nm mineralight lamp or/ and by heating after immersion in aqueous potassium permanganate. Reactions were monitored by TLC using a solvent system with various ratios of hexane, diethyl ether, light petroleum spirit (bp 60 °C- 80 °C), chloroform and DCM. Column chromatography was carried out using silica gel 60 (particle size 35-70 μm) purchased from Fischer Scientific. The mobile phase systems were mixtures of laboratory grade solvents mentioned above for the TLC monitoring.

3.2 Instrumentation

NMR data were acquired using a Bruker 400 MHz (^{1}H) spectrometer using Topspin version 2.1 control and processing software. Chemical shifts are reported using the chemical shift of the solvent residual proton(s) as internal standard. The operating frequencies are 400 MHz and 100 MHz for proton and carbon and fluorine nuclei respectively. Infra Red (IR) spectrophotometer using was a Perkin-Elmer Paragon 100 series FT-IR spectrophotometer using spectumversion 5.3.1 control and processing software. The spectra were obtained after placing a drop of the sample on a NaCl plate and allowing the solvent to evaporate. Low resolution mass spectra were recorded on an Agilent Technologies Quadrupole Mass Spectrometer under Electron Impact (EI) conditions at an ionising potential of 70 eV. Also in a Hewlett Packard GC-MS instrument, HP 5890 II (GC) with capillary column and BP X5 (MS), using a direct insertion probe with a probe temperature controller from Scientific instrument. Services, Inc, Ringose, NJ, USA on a version 1200L Quadrupole MS controlled using Varian Saturn GC/MS system controle version 6.41. Accurate mass analyses were performed and reported on a MAT95 or MAT900 instrument under various conditions (EI, CI, FAB, and ES) by the EPSRC National Mass Spectrometry Service Centre (Swansea). Enantiomeric excesses were measured by HPLC (Perkin Elmer Series 225), (Chiralcel OD-H column). Detector of HPLC was Waters 996 photodiode array diode detector. UV spectra were extracted and obtained directly from HPLC analysis via diode array detector. $[\alpha]_D^T$ Values were recorded using "Optically Activity LTD, AA-10 Automatic polarimeter" where T was the temperature at the time of measuring.

3.3 Conventions

The following conventions have been adopted for quoting physical data.

R_f data (Solvent system)

ee (given in percentage)

de (given in percentage)

t_R data (major), data (minor). The retation time (T_R) is coated in minutes.

$[\alpha]_D^T$ data ° (c = data, solvent)

mp data °C

ν_{max} (NaCl)/cm^{-1} are data refers to major bands in wavenumbers.

δ_H (MHz; solvent) ^{1}H NMR data where s = singlet, br s = broad singlet, d, = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet and the coupling constant *J* are given in Hertz (Hz). H-Ar represents aromatic proton.

δc (MHz; solvent) ^{13}C NMR data where C = quaternary carbon, CH = methine, CH_2 = methylene, CH_3 = methyl and the coupling constant with fluorine atom $J_{C\text{-}F}$ are given in Hz. In all cases, Ar represents aromatic carbon.

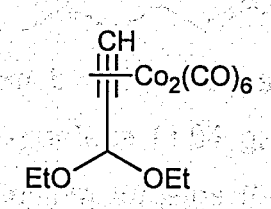
LRMS (condition) (m/z) M^+ data (where M^+ refers to the parent ion and EI could be different condition).

HRMS (condition) $[M]^+$ observed data for (molecular formula) theoretical data

3.4 Experimental procedures

3.4.1 Model study

The synthesis of hexacarbonyl [propioaldehyde diethyl acetal] dicobalt (45)



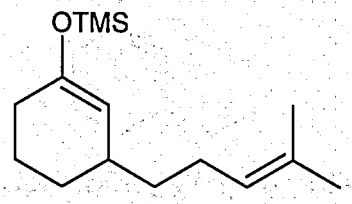
Dicobalt octacarbonyl (1.71 g, 5 mmol) was transferred, under a nitrogen atmosphere, to a dry pre-weighed 100 mL round bottom flask. Anhydrous dichloromethane (50 mL) was introduced *via* a syringe, followed by 3,3-diethoxy-1-propyne (0.64 g, 5 mmol). The solution was stirred for an hour until CO evolution was no longer visible, tlc analysis after 1 hour showed the loss of the starting material and the presence of a new compound with an R_f = 0.4 (hexane: diethyl ether 80:20) whereupon the solvent was removed *in vacuo*. The compound was purified by chromatography on silica gel[119] (75:25 petroleum ether (60 °C- 80 °C): diethyl ether) to afford the desired product as a dark red oil (2.0 g, 99 %).

IR ν_{max} (neat)/cm^{-1}: 2980.2 (w); 2872.1 (w); 2090.0 (s); 2023.8(s); 1655.1, 953.3, 841.5, 730.0

^{1}H NMR (400MHz, $CDCl_3$) δppm: 6.00 (1H, s, OC<u>H</u>); 5.5 (1H, s, C≡C<u>H</u>); 3.5 (4H, m, 2 x C<u>H</u>$_2$); 1.3 (6H, m, 2 x C<u>H</u>$_3$).

^{13}C NMR (100MHz) ($CDCl_3$) δppm: 187.50 (<u>C</u>≡CH); 102.56 (C≡<u>C</u>H); 91.20 (<u>C</u>H(OEt)$_2$); 70.91 (<u>C</u>H$_2$); 63.04 (<u>C</u>H$_2$); 15.00 (2x<u>C</u>H$_3$).

The synthesis of trimethylsily 3- (4-methylpent-3-en-1-yl) cyclohex-1-en-1-olate (46)



3-Methylpentyl-3-enylmagnesium bromide was synthesisd *in situ* by dropwise addition of 2-bromo-2-methyl-2-pentene (3.04 g, 18.64 mmol) to a flame dried 250 mL flask containing magnesium turnings (0.48 g, 20 mmol) in anhydrous THF (10 mL) and a crystal of iodine and heated to a reflux temperature. The dropwise addition was done at such as to maintain a vigorous reaction. Upon completion the reaction was heated to a reflux temperature for half an hour whereby the solution was colourless with small amounts of residual solid material.

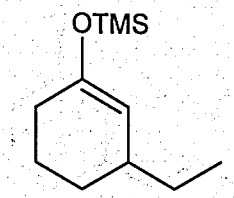
The reaction mixture was cooled to an ambient temperature whereupon THF (10 mL) was added. The mixture was then cooled to -78 °C, and CuBr.Me_2S (0.14 g, 0.67 mmol) was added and stirred for 10-15 minutes after this time trimethylsilyl chloride (4 g, 37.4 mmol) and 2-cyclohexen-1-one **73** (1.28 g, 13.35 mmol) were added and left to stir. Tlc analysis after 1 hour showed the loss of the starting material and the presence of a new compound with an R_f = 0.88 (80:20, hexane: ethyl acetate). Triethylamine (2.75 g, 27.18 mmol) was added, the solution was filtered through a plug of ceilite. The solvent was removed in *vacuo*. The aqueous phase was extracted with hexane (3 x 20 mL) and the organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was isolated and purified by chromatography on silica (80:20 hexane: ethyl acetate) to afford the title product **46** as a colourless oil (3.0 g, 89 %). **IR ν_{max} (neat)/cm^{-1}:**1365.6 (s); 1255.1 (m); 1175.0(s); 1190.5 (s); 850.3 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 5.00 (1H, t, *J* = 6.1 Hz, C<u>H</u>=); 4.8 (1H, d, *J* = 2.0 Hz, C<u>H</u>=COSI$(CH_3)_3$); 2.0-1.95 (3H, m, CH_2C<u>H</u>CH_2C<u>H_2</u> chain); 1.64-1.60 (4H, m, 2xCH_2); 1.55-1.50 (4H, m, 2 x C<u>H_2</u>); 1.2 (6H, s, 2xC<u>H_3</u>); 0.01 (9H, s, Si$(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.0 (<u>C</u>OSi$(CH_3)_3$); 153.2 (=<u>C</u>); 150.2 (=<u>C</u>HCO); 142.8 (=<u>C</u>HC); 55.6 (<u>C</u>H); 36.6 (<u>C</u>H_2); 36.4 (<u>C</u>H_2); 28.7 (<u>C</u>H_2); 25.8 (<u>C</u>H_2); 25.5 (<u>C</u>H_3); 23.4 (<u>C</u>H_2); 17.7 (<u>C</u>H_3); 0.4 (Si(<u>C</u>$H_3)_3$).

HRMS (EI): [M^+] observed 252.4680 for $C_{15}H_{28}SiO$ theoretical 252.4677

The synthesis of 1-trimethylsilyl-3-ethylcyclohex-1-en-1-olate (46a)



To a stirred suspension of $CuBr.SMe_2$ (2.14 g, 10.4 mmol, 1 eq) in anhydrous THF (10 mL) maintained under an atmosphere of nitrogen at -78 °C, was added a solution of cyclohex-2-en-1-one (1.0 g, 10.4 mmol, 1 eq) in THF (5 mL) and left to stir for 10 minutes. To the stirred solution was added, dropwise, ethylmagnesium bromide dissolved in THF (7 mL of a 3 M solution in diethyl ether, 20.8 mmol, 2 eq). After stirring for a further 15 minutes trimethylsilyl chloride (2.3 g, 21 mmol, 2 eq) was added to the solution and the mixture was left to stir for a further 1 hour at -78 °C. After this time the acetone ice bath was removed and the solution was allowed to warm to an ambient termperature, with stirring, for about 3 hours. During this time the solution darkened. After 1 hour Tlc analysis (petroleum ether (60 °C- 80 °C): diethyl ether, 8:2) showed the loss of the starting material and the presence of a new compound (R_f = 0.81). Triethylamine (2.12 g, 21 mmol, 2 eq) was added to the mixture followed by water (20 mL). The solution was filtered through a plug of celite and the solvent, THF, was removed in *vacuo*. The aqueous phase was extracted with hexane (3 x 20 mL) and the organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the title compound **46a** as yellow oil (1.8 g, 90%). This was considered sufficiently pure to use in the next step without further purification.

IR ν_{max} (neat)/cm^{-1}: 1095.1(s); 1186.1(m); 1251.6(s); 846.3 (m).

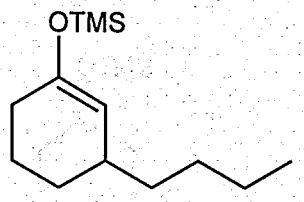
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 4.9 (1H, d (bd); =C<u>H</u>); 2.3-2.2 (1H, m, C<u>H</u>CH_2); 2.01-1.96 (2H, m, C<u>H</u>$_2$); 1.71-1.64 (2H, m, C<u>H</u>$_2$); 1.60-1.50 (2H, m, C<u>H</u>$_2$); 1.38-1.34 (2H, m, C<u>H</u>$_2$); 0.96 (3H, t, J = 6.0 Hz, C<u>H</u>$_3$); 0.03 (9H, s, Si(C<u>H</u>$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.23 (<u>C</u>OSi(CH_3)$_3$); 150.09 (=<u>C</u>H); 50.76 (<u>C</u>H); 36.5 (<u>C</u>H_2); 34.9 (<u>C</u>H_2); 33.20 (<u>C</u>H_2); 25.03 (<u>C</u>H_2); 23.99 (<u>C</u>H_3); 0.35 (Si(CH_3)$_3$).

LRMS (m/z): (M^+198), 126, 110, 97, 83, 70, 55

HRMS (EI): [M^+] observed 198.3774 for $C_{11}H_{22}SiO$ theoretical 198.3772

The synthesis of trimethylsily 3-butylcyclohex-1-en-1-olate (46b)



The same method was employed as described for the synthesis of compound **46** using the following quantities: 1-butylmagnesium bromide was synthesised in *situ* by dropwise addition of 1-bromobutane (2.55 g, 18.64 mmol) to a flask containing magnesium turnings (0.48 g, 20 mmol) in THF (10 mL) and a crystal of iodine. $CuBr.Me_2S$ (0.14 g, 0.67 mmol) was added and stirred for 10-15 minutes after this time trimethylsilyl chloride (4.08 g, 37.6 mmol) and 2-cyclohexen-1-one (1.28 g, 13.35 mmol) were added and left to stir. Tlc analysis with an R_f = 0.95 (8:2, hexane: ethyl acetate), after 1 hour showed the loss of the starting material and the presence of a new compound. Triethylamine (2.75 g, 27.18 mmol) was added. The organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the title compound **46b** as colourless oil (2.34 g, 77.9 %). This was considered sufficiently pure to use in the next step without further purification.

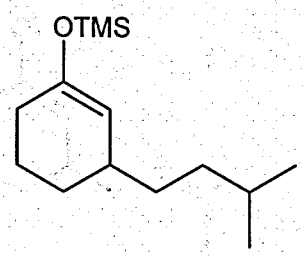
IR ν_{max} (neat)/cm^{-1}: 1310.5 (s); 1250.4 (w), 1110.1(st); 870.8 (m); 712.2 (w);

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.7 (1H,s, C<u>H</u>=); 2.15 -2.11 (1H, m, $CH_2C\underline{H}$); 1.96-1.90 (2H, m, $C\underline{H_2}$); 1.85-1.78 (2H, m, $C\underline{H_2}$); 1.67-1.60 (2H, m, $C\underline{H_2}$); 1.25 – 1.19 (6H, m , 3 x $C\underline{H_2}$); 0.81 (3H, t, J = 6.1 Hz, $C\underline{H_3}$); 0.081 (9H, s, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 205.1 ($\underline{C}OSi(CH_3)_3$); 150.5 (=$\underline{C}$H); 45.17 ($\underline{C}$H); 36.5 ($\underline{C}H_2$); 34.7 ($\underline{C}H_2$); 33.2 ($\underline{C}H_2$); 26.0 ($\underline{C}H_2$); 25.0 ($\underline{C}H_2$); 23.3 ($\underline{C}H_2$); 22.24 ($\underline{C}H_3$); 0.35 ($Si(C\underline{H_3})_3$).

LRMS (m/z): (M^+ 226), 211, 169, 153, 73.
HRMS (EI): [M^+] observed 226.4320 for $C_{13}H_{26}SiO$ theoretical 226.4304

The synthesis of trimethylsilyl 3- (3-methylbutyl) cyclohex-1-en-1-olate (46c)



The same method was employed as described for the synthesis of compound **46**, using the following quantities: Magnesium turning (0.51 g, 20 mmol); 4-bromo-3-methylbutane (3.02 g, 20 mmol). In next step $CuBr.NMe_2$ (0.13 g, 0.6 mmol) and trimethylsilyl chloride (8.52 g, 7.82 mmol) and 2-cyclohexen -1-one (1.14 g, 11.89 mmol) in THF (7 mL) were added. Tlc analysis with an R_f = 0.92 (8:2, hexane: ethylacetate), after 1 hour showed the loss of the starting material and the presence of a new compound Purification by column chromatography (9:1 hexane: ethylacetate) gave the title product **46c** as a colourless oil (2.56 g, 90.2 %).

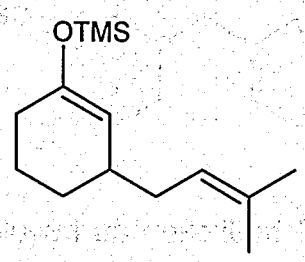
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 4.8 (1H,d, *J* = 6.0 Hz, C<u>H</u>=COSI(CH3)3);1.97-1.90 (2H, m, C<u>H</u>$_2$); 1.90-1.87 (1H, m, C<u>H</u>); 1.65-1.61 (2H, m, C<u>H</u>$_2$); 1.45-1.41 (2H, m , C<u>H</u>$_2$); 1.12 (6H, m, 3 x C<u>H</u>$_2$); 0.82-0.85 (1H, m, C<u>H</u> $(CH_3)_2$); 0.80 (6H, bd s, 2x C<u>H</u>$_3$); 0.08 (9H, s, $Si(C\underline{H}_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.2 (<u>C</u>$OSi(CH_3)_3$); 150.4 (<u>C</u>H); 51.2 (<u>C</u>H); 47.3 (<u>C</u>H) 36.7 (<u>C</u>H_2); 35.0 (<u>C</u>H_2); 33.3 (<u>C</u>H); 33.2 (<u>C</u>H_2); 25.0 (<u>C</u>H_2); 23.3 (<u>C</u>H_3); 23.2 (<u>C</u>H_3); 20.5 (<u>C</u>H_2); 0.3 ($Si(CH_3)_3$).

LRMS (m/z): (M^+ 240), 225, 176,169, 153, 114, 73.

HRMS (EI): [M+H] observed 240.9880 for $C_{14}H_{29}SiO$ theoretical 241.9877

The synthesis of trimethylsilyl 3- (3-methylbut-2-en-1-yl) cyclohex-1-en-1-olate (46d)



The same method was employed as described for the synthesis of compound **46**, however 3-methylbutyl-2-enylmagnesium bromide was synthesised *in situ* using the following quantities: Magnesium turnings (0.243 g, 10.0 mmol) and 2 crystals of iodine and dry THF (10 mL) followed by 4-bromo-2-methyl-2-butane (1.0 g, 6.65 mmol). In the next phase $CuBr.Me_2S$ (0.05 g, 0.26 mmol); trimethylsilyl chloride (1.6 g, 14.7 mmol) and 2-cyclohexen-1-one (0.5 g, 5.23 mmol) in THF (7 mL). Tlc analysis with an R_f = 0.95 (hexane: ethylacetate, 8:2), after 1 hour showed the loss of the starting material and the presence of a new compound with an R_f = 0.95 (hexane: ethylacetate, 8:2).The crude product was isolated, as described above, and purified by flash chromatography on silica gel (9:1 hexane: ethylacetate) to afford the title product **46d** as a colourless oil (0.78 g, 62.9 %).

IR ν_{max} (neat)/cm^{-1}:1371.5 (s); 1263.0(m); 1101.3(s); 848.6 (m).

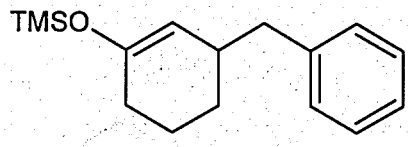
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 4.7 (1H, t, *J* = 6.1 Hz, C<u>H</u>=C $(CH_3)_2$); 4.6 (1H, d, *J* = 2.1, Hz, C<u>H</u>=COSi$(CH_3)_3$); 2.7 (1H,m, C<u>H</u>CH_2); 1.95-1.90 (2H, m, CH_2); 1.7-1.8 (4H, m, C<u>H</u>$_3$,C<u>H</u>$_2$); 1.24-1.20 (4H, m, C<u>H</u>$_3$,C<u>H</u>$_2$); 0.80-0.84 (2H, d, *J* = 6.5 Hz C<u>H</u>$_2$); 0.1 – 0.08 (2H, m, C<u>H</u>$_2$); 0.00 (9H, s, Si(C<u>H</u>$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.0 (<u>C</u>OSi$(CH_3)_3$); 151.3 (<u>C</u>H); 149.1 (<u>C</u>); 128.7 (<u>C</u>H); 50.5 (<u>C</u>H); 40.0 (<u>C</u>H_2); 39.0 (<u>C</u>H_2); 38.7 (<u>C</u>H_2); 27.8 (2 x <u>C</u>H_3); 18.6 (<u>C</u>H_2); 1.7 (Si(<u>C</u>H_3)$_3$).

LRMS (m/z): (M^+ 238), 233, 208,169, 73.

HRMS (EI): [M+H] observed 239.1835 for $C_{14}H_{26}SiO$ theoretical 239.1831

The synthesis of trimethylsilyl 3-benzylcyclohex-1-en-1-olate (46e)



The same method was employed as described for the synthesis of compound **46a,** using benzylmagnesium chloride (12.3 mL of a 2 M solution in THF, 24.6 mmol, 2 eq); 2-cyclohexen-1one (1.2 g, 12.30 mmol) and CuBr.Me_2S (0.126 g, 0.615 mmol) in THF and trimethylsilyl chloride (3.34 g, 30.75 mmol). Tlc analysis with an R_f = 0.3 (7:3, hexane: diethyl ether), after 1 hour showed the loss of the starting material and the presence of a new compound. Isolation and purification by chromatography on silica gel (9:1 hexane: ethylacetate) gave the title product **46e** as a colourless oil (3.10 g, 95.4 %).

IR ν_{max} (neat)/cm^{-1}: 2903.9 (m); 2634.0 (m); 1325.7 (s); 1218.0 (s); 850.4 (m).

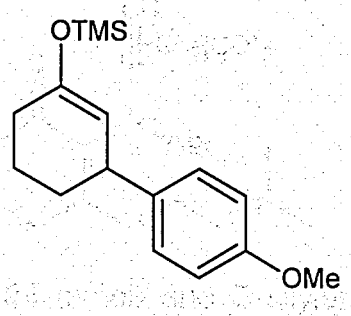
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.34-7.26 (2H, m, Ar); 7.24-7.16 (3H, m, Ar); 4.87 (1H, d (brd); *J* = 3.4 Hz, C<u>H</u>=CO); 2.62 (2H, d, *J* = 7.0 Hz, C<u>H</u>$_2$Ar); 2.15-1.90 (4H, m, 2 x C<u>H</u>$_2$); 1.87-1.73 (1H, m, C<u>H</u>C=); 1.74-1.63 (1H, m, C<u>H</u>$_2$); 1.25-1.12 (1H, m, C<u>H</u>$_2$); 0.0 (9H, m, Si(CH_3)$_3$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 153.22 (C, Ar); 149.30 (<u>C</u>O); 128.73 (<u>C</u>H, Ar); 127.82 (<u>C</u>H, Ar); 125.40 (<u>C</u>H, Ar); 108.35 (<u>C</u>H); 45.81 (<u>C</u>H); 42.34 (<u>C</u>H$_2$); 36.03 (CH_2); 27.81 (<u>C</u>H$_2$); 22.90 (<u>C</u>H$_2$); 2.25 (Si (CH_3)$_3$).

LRMS (m/z): (M^+ 260), 259, 245, 183, 169, 91, 73.

HRMS (EI): [M+H] observed 261.1671 for $C_{16}H_{25}OSi$ theoretical 261.1669

The synthesis of trimethylsilyl 3- (4-methoxyphenyl) cyclohex-1-en-1-olate (46f)



The same method was employed as described for the synthesis of compound **46a,** using cyclohexan-1-one (1.5 g, 15.6 mmol) and 4-methoxyphenylmagnesium bromide in THF (34.32 mL of a 0.5 M solution, 17.16 mmol). Subsequently trimethylsilyl chloride (4.24 g, 39 mmol) was added. $CuBr.SMe_2$ (0.78 g, 0.16 mmol) was added then triethyl amine (1.85 g, 31.2 mmol). Tlc analysis with an R_f = 0.93 (hexane: ethylacetate, 8:2), after 1 hour showed the loss of the starting material and the presence of a new compound. Isolation and purification by chromatography on silica (hexane: ethylacetate, 9:1) gave the title product **46f** as a colourless oil (3.53 g, 82 %).

IR v_{max} (neat)/cm^{-1}: 2879.0 (m); 1387.7 (s); 1201.0 (s); 851.5 (m).

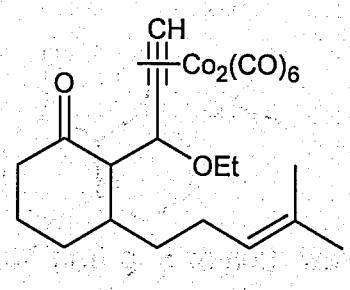
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (2H, dt, *J* = 7.6, 1.0 Hz, C<u>H</u>CO, Ar); 6.82 (2H, dt, *J* = 7.6, 1.0 Hz, C<u>H</u>C, Ar); 4.92 (1H, dt, *J* = 2.9,1.4 Hz, C<u>H</u>=CO); 3.8 (1H, s, OCH_3); 3.47-3.48 (1H, m, C<u>H</u>Ar); 2.12-2.05 (2H, m, C<u>H</u>$_2$CO); 1.76-1.60 (1H, m, CH_2); 1.55-1.60 (1H, m, C<u>H</u>$_2$); 1.41 (1H, m, C<u>H</u>$_2$); 0.00 (9H, s, 3 x $SiCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.18 (<u>C</u>O, Ar); 151.44 (<u>C</u>O); 148.64 (<u>C</u>, Ar); 128.73 (C<u>H</u>, Ar); 119.70 (C<u>H</u>, Ar); 110.96 (<u>C</u>H); 54.72 (<u>C</u>H$_3$); 45.3 (<u>C</u>H); 32.15 (<u>C</u>H$_2$); 31.16 (<u>C</u>H$_2$); 17.56 (<u>C</u>H$_2$); 0.40 (Si(C<u>H</u>$_3$)$_3$).

LRMS (m/z): (M^+ 276), 261, 245, 233, 217,169, 141,115, 91, 73, 59.

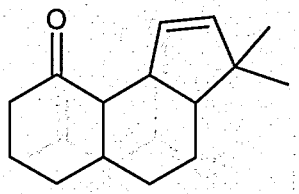
HRMS (EI): [M^+] observed: 276.1538 for $C_{16}H_{24}O_2Si$, theoretical: 276.1540

The synthesis of hexacarbonyl [1-ethoxy-2-propynal)-3- (4-methylpent-3-enyl) cyclohexan-1-one] dicobalt (47)



Cobalt cluster **45** (2.80 g, 7.84 mmol) and O-silylenol ether **46** (2.00 g, 7.84 mmol) were mixed in a 3-necked round bottomed flask containing dry DCM (20 mL). The resulting solution was cooled to -78 °C, with continuous stirring, whereupon boron trifluoride diethyl etherate (11.18 g, 70.8 mmol) was added. The reaction was stirred for 3 hours at -78 °C, before allowing it to reach an ambient temperature. Tlc analysis with an (R_f = 0.6) (petroleum ether (60 °C- 80 °C): diethyl ether, 3:1), after 1 hour showed the loss of the starting material and the presence of a new compound in relation to the cobalt cluster. The reaction mixture was quenched, by the addition of a saturated sodium bicarbonate solution (20 mL) and the aqueous layer was partitioned, washed with DCM (3 X 20 mL) and the combined organic layers were dried over anhydrous magnesium sulphate, fitered and the solvent removed *in vacuo* to give the desired product as a dark red oil, (3.36 g, 85%). This was decomplexed. Please see page 108 for data.

The synthesis of 3,3-dimethyl-3,3a,4,5,5a,6,7,8,9a,9b-decahydro-9*H*-cyclopenta[*a*]naphthalen-9-one (144)



The cobalt complex cluster **47** (1.6 g, 3 mmol); was dissolved in DCM (20 mL); and the reaction was cooled to -78 °C whereupon tetrafluoroboric acid (1.04 g, 6.50 mmol) was added *via* a syringe. The reaction mixture was left to stir for 3 hours. Tlc analysis with an (R_f = 0.6) (8:2 hexane: ethyl acetate), after 3 hours showed the loss of the starting material and the presence of a new faster moving compound. The solvent, DCM, was removed *in vacuo* and dicobalt hexacarbonyl complex (1 g, 1.9 mmol) was dissolved in methanol (30 mL) and the reaction was cooled to 0 °C. Ceric ammonium nitrate (4.7 g, 8.5 mmol); dissolved in methanol (20 mL); was added portiowise, with continuous stirring, until the evolution of CO ceased and the orange colour of CAN persisted. Tlc analysis after 15 minutes showed the loss of the starting material and the presence of a new compound with an R_f = 0.7, (hexane: diethyl ether 70:30) The reaction mixture was then poured into a separating funnel containing diethyl ether (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with sodium hydrogen carbonate (3 x 30 mL) and brine (3 x 30 mL) solutions and dried over anhydrous $MgSO_4$. The reaction mixture was filtered and the solvent removed *in vacuo*, to yield a yellow oil. Purification on silica gel eluted with (80:20 petroleum ether (60 °C- 80 °C): diethyl ether) was carried out to yield the title product **144** as a yellow oil (0.15 g, 35 %);

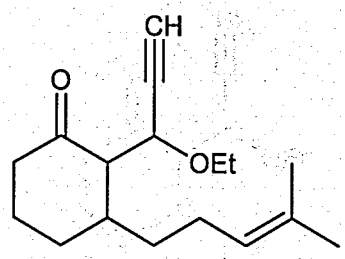
IR ν_{max} (neat)/cm^{-1}: 3070.3 (w); 1715.0 (s); 1649.2 (s); 1485.0 (m).

^{1}H NMR (400 MHz, CDCl3) δppm 5.72 (1H, d, *J* = 5.8 Hz, =C<u>H</u>); 5.42 (1H, dd, *J* = 5.8, 4.2 Hz, =C<u>H</u>); 2.23-2.19 (3H, m, C<u>H</u>, C<u>H</u>$_2$); 1.8-1.75 (3H, m, C<u>H</u>, C<u>H</u>$_2$); 1.65-1.63 (1H, m, C<u>H</u>); 1.50-1.44 (3H, m, C<u>H</u>, C<u>H</u>$_2$); 1.30-1.27 (2H, m, C<u>H</u>$_2$); 1.05-1.00 (2H, m, C<u>H</u>$_2$); 0.85 (3H, s, C<u>H</u>$_3$); 0.65 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 210.00 (<u>C</u>=O); 142.35 (=<u>C</u>HC(CH$_3$)$_2$); 130.89 (=<u>C</u>H); 60.50 (<u>C</u>H); 57.80 (<u>C</u>H); 48.04 (<u>C</u>H); 46.65 (<u>C</u>H); 44.02 (<u>C</u>); 41.98 (<u>C</u>H$_2$); 35.03 (<u>C</u>H$_2$); 32.89 (<u>C</u>H$_2$); 26.99 (<u>C</u>H$_2$); 26.01 (<u>C</u>H$_3$); 24.00 (<u>C</u>H$_2$); 19.50 (<u>C</u>H$_3$).

HRMS (EI): [M$^+$] observed 218.1665 for $C_{15}H_{22}O$ theoretical 218.1671

The synthesis of 2- (1-ethoxy-2-propynal)-3- (4-methylpent-3-nyl) cyclohexan- 1-one (146)



The dicobalt hexacarbonyl complex **47** (2.0 g, 3.65 mmol) was dissolved in methanol (20 mL) and the reaction was cooled to 0 °C in an ice bath. Ceric ammonium nitrate (8.5 g, 15 mmol) dissolved in methanol (15 mL), was added portionwise with stirring, until the evalution of CO finished and the orange colour of CAN persisted. Tlc analysis with an R_f = 0.89 (hexane: ethyl acetate, 8:2), after 1 hour showed the loss of the starting material and the presence of a new compound. After removing the solvent the reaction mixture was poured into a separating funnel containing diethyl ether (50 mL) and water (50 mL). The layers were separated and the aqueous layer was washed with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and solvent was removed *in vacuo,* to yield a yellow oil. Purification by chromatography on silica (hexane: ethyl acetate, 85:15) gave the title product as a colourless oil (0.55 g, 58%).

IR vmax (neat/cm^{-1}): 3040.2 (m); 2114.0 (m); 1715.0 (s); 1640.5(m); 1095.8(m).

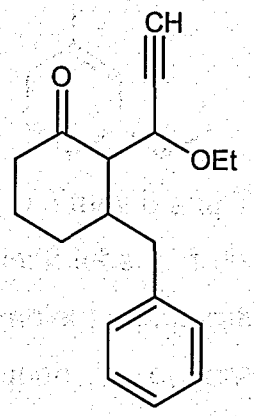
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 5.15-5.10 (1H, m, H̲C=C); 4.10 (1H, dd, *J* = 8.0, 1.9 Hz, CH̲OEt); 3.60-3.50 (1H, m, CH_2̲CH_3); 3.25 – 3.18(1H, m, CH_2̲CH_3); 2.55 (1H, s, CH̲≡C); 2.38-2.45 (1H, m, CH̲C=O); 2.13-1.13 (11H, m, 5 x CH_2̲, CH̲); 1.69 and1.65 (6H, s, 2 x =$C(CH_3)_2$; 1.15 (3H, t, *J* = 7.2 Hz, CH_2̲CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 210.50 (C̲=O); 153.45 (C̲); 138.25 (C̲H); 80.16 (C̲); 75.30 (C̲H); 68.07 (C̲H); 64.55 (C̲H_2); 60.01 (C̲H); 48.26 (C̲H_2); 41.65 (C̲H_2); 40.02 (C̲H); 38.55 (C̲H_3); 36.77 (C̲H_2); 31.35 (C̲H_2); 22.75 (C̲H_3) 22.35 (CH_2); 17.70 (C̲H_3).

LRMS (m/z): (M^+ 262), 232, 220, 207, 173, 145, 97, 83, 69, 55, 41.

HRMS (EI): [M^+] observed 262.1926 for $C_{17}H_{26}O_2$ theoretical 262.1933

The synthesis of the 3-benzyl-2- (1-hydroxyprop-2-yn-1-yl) cyclohexanone (146a)



The cobalt complex **154** (0.2 g, 0.37 mmol) was dissolved in methanol (10 mL) and cooled to 0 °C in an ice bath. A saturated solution of CAN in methanol (15 mL) was added dropwise over a 10 minute period until the dark red colour of the mixture diminished. A saturated solution of sodium hydrogen carbonate (50 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (3 x 30 mL). The combined organic phases were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo*. Tlc analysis with an R_f = 0.42 (70:30, hexane: diethyl ether), after 10 minuts showed the loss of the starting material and the presence of a new compound. Purification by chromatography on silica gel (70:30, hexane: diethyl ether) provided the title compound as a colourless oil title product (75 mg, 83 %).

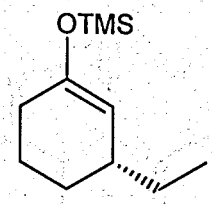
IR ν_{max} (neat)/cm^{-1}: 2977.0 (s); 2930.0(m); 2872.5 (s); 1710.9 (s); 1498.5 (m); 1089.2 (w); 712.1(w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.31-7.26 (2H, m, Ar); 7.20 (1H, dd, J = 7.4, 1.2 Hz, Ar); 7.15-7.11 (2H, m, Ar); 4.55 (1H, dd, J = 7.0, 2.0 Hz, C$\underline{H}$OEt); 3.79-3.65 (1H, m, OC$\underline{H}_2$CH$_3$); 3.42-3.37 (1H, m, OC$\underline{H}_2$CH$_3$); 2.73-2.65 (1H, m, C$\underline{H}$CO); 2.67-2.57 (2H, m, C$\underline{H}_2$CO); 2.49 (1H, s (brd); C$\underline{H}$≡C); 2.47-2.39 (1H, m, C$\underline{H}$CH$_2$Ar); 2.27-2.19 (2H,m, C$\underline{H}_2$Ar); 2.09-2.02 (2H, m, C$\underline{H}_2$); 1.87-1.77 (1H, m, C$\underline{H}_2$); 1.72-1.65 (1H, m, C$\underline{H}_2$); 1.19 (3H, t, J = 7.0 Hz, C$\underline{H}_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 211.40 ($\underline{C}$O); 139.82 (C, Ar); 128.60 (CH, Ar); 128.37 (CH, Ar); 126.00 (CH, Ar); 82.67 ($\underline{C}$≡); 70.45 ($\underline{C}$H); 64.70 ($\underline{C}$H); 54.34 ($\underline{C}$H); 45.00 ($\underline{C}$H$_2$CO); 40.26 ($\underline{C}$H$_2$); 30.84 ($\underline{C}$H$_2$); 27.54 ($\underline{C}$H); 25.20 ($\underline{C}$H$_2$); 22.54 ($\underline{C}$H$_2$); 19.90 (CH$_3$).

HRMS (EI): [M+H] observed 271.1697 for $C_{18}H_{23}O_2$ theoretical 271.1693.

The synthesis of (3R) - (+) - 3-ethyl-1-[(trimethylsilyl) oxy]-1-cyclohexene (150)

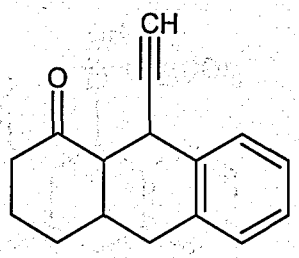


A mixture of $CuBr.SMe_2$ (0.06 g, 0.3 mmol) and Taniaphos[74] (23 mg, 0.36 mmol) was added to a flame dried schlenk tube and dissolved in diethyl ether (3 mL). This was left to stir at an ambient temperature for 30 minutes under an atmosphere of nitrogen, whereupon the cyclohex-2-en-1-one (0.57g, 6 mmol) was added. Temperature reduced to -78 °C, stirring continued for a further 10 minutes followed by the dropwise addition of ethylmagnesium bromide (4 mL of the 3 M solution in diethyl ether, 12 mmol). After about 15 minutes $Si(CH_3)_3Cl$ (1.3 g, 12 mmol, 2 eq) was added to the solution and the mixture was left to stir for a further 1 hour at -78 °C. After this time the acetone ice bath was removed and the solution was allowed to warm to an ambient temperature, with stirring, for about 3 hours. During this time the solution darkened. After 3 hours tlc analysis with an (R_f = 0.80) (hexane: diethyl ether, 8:2) showed the loss of the starting material and the presence of a new compound. Triethylamine (1.2 g, 12 mmol) was added to the mixture followed by water (20 mL). The solution was filtered through a plug of ceilite and the solvent, THF, was removed in *vacuo*. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the title compound **150** as yellow oil (0.73 g, 98 %).

The ^1H, ^{13}C, IR and LRMS spectra were identical with the data obtained for compound **46a**. The following additional data was obtained. $[\alpha]_D$ = +11° (c = 2.5%, chloroform); (ee% = 70%) (enantiomeric exces in lit. is for enantiomer of the **150** -10.3, c = 2.9%, $CHCl_3$)[103]

HRMS (EI): [M+H] observed 199.1520 for $C_{11}H_{23}SiO$ theoretical 199.1518

The synthesis of the 9-ethynyl-3, 4, 4a, 9, 9a, 10-hexahydro anthracen-1 (2*H*)-one (152)



The same method was employed as described for the synthesis of the **146** with the following quantities; cobalt complex cluster **153** (0.2 g, 0.415 mmol) was dissolved in methanol (10 mL) and cooled down to 0 °C in ice bath. The saturated solution of the CAN in methanol (20 mL) was added drop wise to give the desired compound **152** as a yellow oil, tlc analysis with an R_f = 0.6 (85:15, hexane: ethyl acetate), after 15 minutes showed the loss of the starting material and the presence of a new compound. Purification by chromatography on silica gave the title product as a colourless oil (35 mg, 38 %)

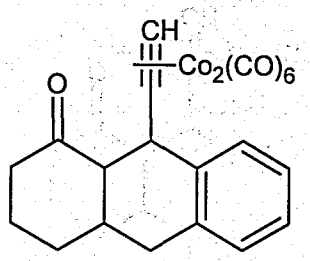
IR ν_{max} (neat)/cm^{-1}: 3298.0 (s); 2110 (w); 1720.7 (s); 1653.0 (s); 760.0 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.51-7.44 (2H, m, Ar); 6.99-6.86 (1H, m, Ar); 6.94 (1H, dd, *J* = 8.3, 0.9 Hz, Ar); 4.03 (1H, dd, *J* = 6.5, 2.3 Hz, C<u>H</u>C≡CH); 2.88 (1H, dd, *J* = 7.0, 6.2 Hz, C<u>H</u>$_2$Ar); 2.79 (1H, dd, *J* = 7.0, 6.2 Hz, C<u>H</u>$_2$Ar); 2.71 (1H, ddd, *J* = 7.7, 6.0, 3.5 Hz, C<u>H</u>$_2$CO); 2.64 (1H, ddd, *J* = 7.7, 6.0, 3.5 Hz, CH$_2$CO); 2.51 (1H, dd, *J* = 6.5, 4.7 Hz, COC<u>H</u>CH); 2.04 (1H, d, *J* = 2.3 Hz, C<u>H</u>≡C); 1.98-1.83 (1H, m, CH$_2$C<u>H</u>CH$_2$); 1.79-1.47 (4H, m ,C<u>H</u>$_2$C<u>H</u>$_2$CHAr).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 210.00 (<u>C</u>O); 138.20 (<u>C</u>, Ar); 136.01 (<u>C</u>, Ar); 133.83 (<u>C</u>H, Ar); 129.20 (<u>C</u>H, Ar); 128.5 (<u>C</u>H, Ar); 126.32 (CH, Ar); 57.20 (<u>C</u>); 46.30 (<u>C</u>H); 40.53 (<u>C</u>H); 36.75 (<u>C</u>H$_2$); 35.50 (<u>C</u>H); 31.01 (<u>C</u>H); 30.00 (<u>C</u>H$_2$); 28.08 (<u>C</u>H$_2$); 26.68 (<u>C</u>H$_2$).

HRMS (EI): [M-H] observed 223.0760 for $C_{16}H_{15}O$ theoretical. 223.0765

The synthesis of hexacarbonyl [9-ethynyl-3, 4, 4a, 9, 9a, 10- hexahydro anthracen-1 (2H)-one] dicobalt (153)



The cobalt complex **154** (0.6 g, 1.13 mmol); was dissolved in DCM (20 mL) and the reaction was cooled to -78 °C whereupon tetrafluoroboric acid (0.36 g, 3 mmol) was added *via* a syringe. The reaction mixture was left to stir for 40 minutes and a Tlc analysis with an (R_f = 0.7) (7:3 petroleum ether (60 °C- 80 °C): diethyl ether), after 40 minutes showed the loss of the starting material and the presence of a new compound. The reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate (30 mL). The organic layer was separated, using a separating funnel, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over anhydrous $MgSO_4$. The solid was then filtered and the solvent removed in *vacuo* and purified on silica gel eluted with (80:20, hexane: diethyl ether) to gave title compound as a dark red/brown oil (0.22 g, 40%).

IR ν_{max} (neat)/cm^{-1}: 2925.4 (s), 2899.8 (m), 2094.6 (m), 1678.08 (s), 1580.4 (s), 1454.7 (w), 739.9 (s).

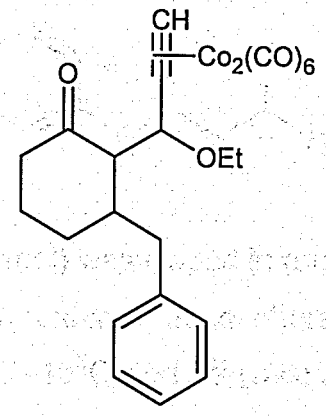
^{1}H NMR (400 MHz, $CDCl_3$) δppm: All peaks are broad: 7.30-7.26 (2H, m, Ar); 7.17-7.11 (2H, m, Ar); 2.85 (1H, dd, *J* = 7.2, 3.6 Hz, C<u>H</u>C≡CH); 2.66-2.58 (3H, m, C<u>H</u>$_2$CO & COC<u>H</u>); 2.35-2.22 (1H, m, CH$_2$C<u>H</u>CH$_2$); 2.20 (1H, s (brd); C≡C<u>H</u>); 2.03-1.87 (2H, m, C<u>H</u>$_2$Ar); 1.50-1.33 (3H, m, C<u>H</u>$_2$C<u>H</u>$_2$); 1.23-1.22 (1H, m, C<u>H</u>$_2$).

^{13}C NMR (100 MHz) (CDCl3) δppm: 211.01 (<u>C</u>O); 199.59 (<u>C</u>O); 139.31 (<u>C</u>, Ar); 135.96 (<u>C</u>, Ar); 131.82 (<u>C</u>H, Ar); 129.11 (<u>C</u>H, Ar); 128.30 (<u>C</u>H, Ar); 127.25 (<u>C</u>H, Ar); 68.52 (<u>C</u>H); 46.27 (<u>C</u>H$_2$); 36.73 (<u>C</u>H$_2$); 35.47 (<u>C</u>H); 31.51 (<u>C</u>); 33.01 (<u>C</u>H); 30.97 (<u>C</u>H$_2$); 29.72 (<u>C</u>H$_2$); 27.78 (<u>C</u>H).

LRMS (m/z):(M^+482), 454, 426.

HRMS (EI): [M-CO] observed 482.3582 for $C_{21}H_{16}O_6Co_2$ theoretical 482.3582

The synthesis of hexacarbonyl [3-benzyl-2- (1-hydroxyprop-2-yn-1-yl) cyclohexanone] dicobalt (154)



The cobalt cluster **45** (2.0 g, 5.9 mmol) and the O-silylenol ether **46e** (0.6 g, 2 mmol) were mixed in a 3-necked round bottomed flask containing dry DCM (20 mL). The resulting solution was then cooled to -78 °C with continuous stirring whereupon boron trifluoride diethyl etherate ($BF_3.OEt_2$) (0.2 g, 1 mmol) was added. The reaction was stirred for 3 hours at -78 °C, before allowing it to reach an ambient temperature. Tlc analysis with an (R_f = 0.51) (light petroleum (60 °C-80 °C): diethyl ether, 7:3), after 1 hour showed the loss of the starting material and the presence of a slower moving new compound.The reaction mixture was quenched by the addition of a saturated sodium bicarbonate solution (20 mL) and the aqueous layer was partitioned and washed with DCM (3 X 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound **154** as a dark red oil, (0.8 g, 65 %).

IR ν_{max} (neat)/cm^{-1}: 2976.7 (m); 2929.5 (m); 2871.5 (m); 2094.3 (s); 2053.0(s); 2000.5(s); 1712.2(s); 1496.2(w); 1454.8(m); 700.5 (w).

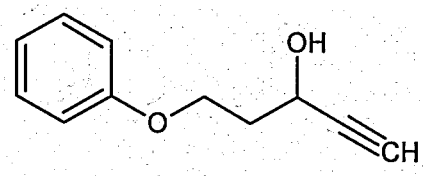
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.39-7.09 (5H, m, Ar); 4.92 (1H, d, J = 9.0 Hz, C<u>H</u>OCH$_2$); 4.04-3.87 (1H, m, OC<u>H$_2$</u>CH$_3$); 3.59-3.43 (1H, m, OC<u>H$_2$</u>); 3.60-3.55 (1H, m, COC<u>H</u>); 2.80-2.75 (2H, m, C<u>H$_2$</u>Ar); 2.55-2.50 (1H, m, C≡C<u>H</u>); 2.4-2.3 (1H, m, COC<u>H</u>); 2.31-2.20 (2H, m, C<u>H$_2$</u>); 2.10-1.85 (2H, m, C<u>H$_2$</u>); 1.75-1.70 (2H, m, C<u>H$_2$</u>); 1.3 (3H, t, J = 7.0 Hz, C<u>H$_3$</u>)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: Due to the presence of paramagnetic impurities complete NMR data was not obtained.

LRMS (m/z): (M^+528), 500, 472, 444, 416, 388, 342, 249, 203, 143, 101

HRMS (EI): [M-CO] observed. 528.0024 for $C_{23}H_{22}O_7Co_2$ theoretical. 528.0024

The synthesis of 5-phenoxypent-1-yn-3-ol (159)



Aldehyde **160** (0.48 g, 3.2 mmol) was placed in round-bottom flask containing dry THF (10 mL) and maintained under an atmosphere of nitrogen gas. The reaction temperature was reduced to -10°C and ethynylmagnesium bromide (7.0 mL of the 0.5 M solution in THF, 3.52 mmol,) was added drop wise over a period of 20 minutes. Stirring at -10 °C was continued for about 1 hour and then allowed to reach an ambient temperature. After 1 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.14 (80:20, hexane: diethyl ether). The reaction mixture was quenched by the addition of HCl (10 mL of a 2M solution) and the mixture extracted with diethyl ether (3 x 20 mL). The combined organic solvent was dried over magnesium sulphate, filtered and the solvent removed *in vacuo*. Purification on silica gel eluted with hexane/diethyl ether (80:20) was carried out to afford title compound as a colourless oil (0.5 g, 85%).

IR ν_{max} (neat)/cm^{-1}: 3290.5 (brd, s); 2922.8 (s); 1598.8 (m); 1496.8 (m); 1244.0 (s); 1045.7 (s); 753.9 (s).

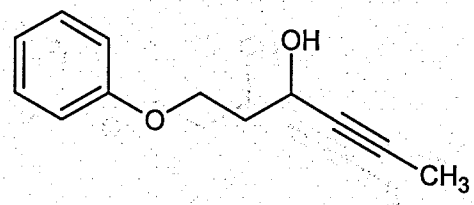
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.32-7.26 (2H, m, Ar); 6.96-6.90 (1H, m, Ar); 6.94-6.89 (2H, m, Ar); 4.74-4.69 (1H, m, C<u>H</u>OH); 4.30-4.27 (1H,m, OC<u>H$_2$</u>); 4.25-4.20 (1H, m, OC<u>H$_2$</u>); 2.50 (1H, d, *J* = 2.0 Hz, C≡C<u>H</u>); 2.42 (1H, d, *J* = 5.8 Hz, O<u>H</u>); 2.22-2.12 (1H, m, C<u>H$_2$</u>CH); 2.12-2.07 (1H, m, C<u>H$_2$</u>CH)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.5 (<u>C</u>, Ar); 129.5 (<u>C</u>H, Ar); 121.1 (<u>C</u>H, Ar); 114.5 (<u>C</u>H, Ar); 84.10 (<u>C</u>); 73.5 (<u>C</u>H); 64.5 (<u>C</u>H); 60.2 (<u>C</u>H$_2$); 39.2 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 176), 148, 120, 94, 77, 65, 55.

HRMS (EI): [M+H] observed 177.0905 for $C_{11}H_{12}O_2$ theoretical: 177.0910

The Synthesis of 1-phenoxyhex-4-yn-3-ol (159a)



The same method was employed as described for the synthesis of the **159** with the following quantities; aldehyde **160** (0.8 g, 5.34 mmol) and 1-propynylmagnesium bromide solution (12 mL of the 0.5 M solution in hexane, 6 mmol) mixed in anhydrous THF (10 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.26, (petroleum ether (60 °C- 80 °C): diethyl ether 80:20); Purification on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford title compound as a colourless oil (1 g, 99%).

IR ν_{max} (neat)/cm^{-1}: 3020.5 (brd, s); 3009.1 (s); 2957.0 (m); 1534.3 (w); 1151.2 (m); 912.5 (s); 889.5 (s); 700.1 (s).

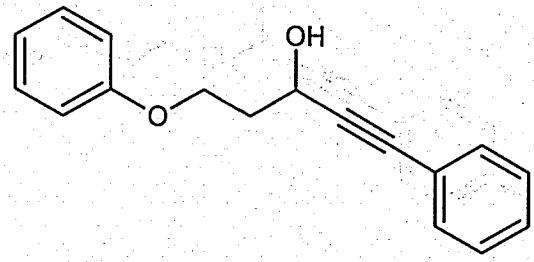
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.25-7.10 (2H, m, Ar); 7.01-6.73 (3H, m, Ar); 4.72-5.53 (1H, m, C<u>H</u>OH); 4.32-4.09 (2H, m, OC<u>H</u>$_2$); 2.30 (1H, d, J = 5.5 Hz, O<u>H</u>); 2.33-2.07 (2H, m, C<u>H</u>$_2$CH); 1.84 (3H, d, J = 2.1 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.64 (<u>C</u>, Ar); 129.51 (<u>C</u>H, Ar); 120.95 (<u>C</u>H, Ar); 114.55 (<u>C</u>H, Ar); 91.71 (<u>C</u>); 79.61 (<u>C</u>); 60.6 (<u>C</u>H); 60.0 (<u>C</u>H$_2$); 37.24 (<u>C</u>H$_2$); 3.60 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 190), 175, 145, 117, 94, 77, 69, 51.

HRMS (EI): [M^+] observed 190.0989 for $C_{12}H_{14}O_2$ theoretical: 190.0988

The synthesis of 5-phenoxy-1-phenylpent-1-yn-3-ol (159b)



The same method was employed as described for the synthesis of the **159** with the following quantities; aldehyde **160** (1.2 g, 8.0 mmol) and phenylethynylmagnesium bromide solution (9 mL of the 1M solution in hexane, 8.8 mmol). After 1 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.4 (hexane: diethyl ether 70:30); Purification on silica gel eluted with (85:15, petroleum ether (60 °C- 80 °C): diethyl ether) was carried out to afford title compound as a colourless oil (1.87 g, 93%).

IR ν_{max} (neat)/cm^{-1}: 3023.1 (brd, s); 3012.1 (s); 2945.0 (m); 1525.6 (w); 1110.2 (m); 905.5 (s); 814.5 (s); 717.1 (s).

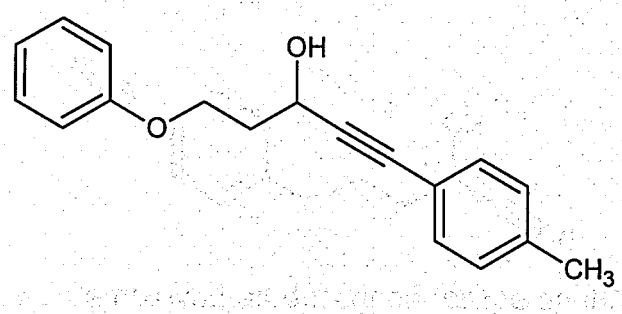
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.46-7.37 (2H, m, Ar); 7.33-7.26 (5H, m, Ar); 7.07-6.87 (3H, m, Ar); 5.30-5.25 (1H, m, C<u>H</u>OH); 4.37-4.13 (2H, m, OC<u>H$_2$</u>); 2.40 (1H, d, J = 5.5 Hz, O<u>H</u>); 2.35-2.22 (2H, m, C<u>H$_2$</u>CH).

^{13}CNMR (100 MHz) ($CDCl_3$) δppm: 157.50 (<u>C</u>, Ar); 132.32 (<u>C</u>, Ar); 129.43 (<u>C</u>H, Ar); 128.72 (<u>C</u>H, Ar); 128.55 (<u>C</u>H, Ar); 122, 90 (<u>C</u>H, Ar); 120.73 (<u>C</u>H, Ar); 117.6 (<u>C</u>H, Ar); 88.62 (<u>C</u>); 81.00 (<u>C</u>); 60.56 (<u>C</u>H); 59.90 (<u>C</u>H$_2$); 39, 32 (<u>C</u>H$_2$)

LRMS (m/z): (M^+252), 235, 207, 144, 131, 93.

HRMS (EI): [M+H] observed 253.1230 for $C_{17}H_{16}O_2$ theoretical 253.1228

The synthesis of 1- (4-methylphenyl)-5-phenoxypent-1-yn-3-ol (159c)



The same method was employed as described for the synthesis of the **159** with the following quantities; however 4–methylphenylethynyl lithuim solution was synthesised *in situ* by adding 1-ethynyl-4-methylbenzene (0.40 g, 3.5 mmol) in a pre dried round-bottom flask and anhydrous THF (5 mL) under nitrogen atmospher. The flask was then cooled down to -78 °C whereupon *n*-BuLi (2.2 mL of the 2.5 M solution in hexane, 5.5 mmol) was added drop-wise to the mixture. The solution left to stir for 45 minutes and then the aldehyde **160** (0.5 g, 3.34 mmol) was added in one portion and solution warmed up to ambient temperature for 1 hour more. After 1 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.2, (70:30, hexane: diethyl ether). Purification on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford title compound as a colourless oil (0.652 g, 73.6%).

IR ν_{max} (neat)/cm^{-1}: 3100.1 (s); 2900.5 (m); 1554.3 (w); 1100.2 (m); 975.5 (s); 888.5 (s); 774.1(s).

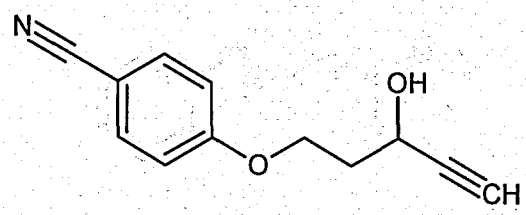
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.30-7.25 (4H, m, Ar); 7.15-7.10 (2H, m, Ar); 7.01-6.90 (3H, m, Ar); 4.90-4.86 (1H, m, C<u>H</u>OH); 4.30-4.25 (1H, m, OC<u>H</u>$_2$); 4.25-5.20 (1H, m, OC<u>H</u>$_2$); 2.35 (1H, d, *J*= 5.5 Hz, O<u>H</u>); 2.35 (3H, s, C<u>H</u>$_3$); 2.35-2.30 (1H, m, C<u>H</u>$_2$CH); 2.30-2.25 (1H, m, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 160.30 (<u>C</u>, Ar); 139.75 (<u>C</u>, Ar); 131.52 (<u>C</u>, Ar); 129.15 (<u>C</u>H, Ar); 129.41 (<u>C</u>H, Ar); 126.45 (<u>C</u>H, Ar); 119.45 (<u>C</u>H, Ar); 116.50 (<u>C</u>H, Ar); 90.51 (<u>C</u>); 87.50 (<u>C</u>); 64.70 (<u>C</u>H); 62.67 (<u>C</u>H$_2$); 37.50 (<u>C</u>H$_2$); 21.55 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 266), 251, 235, 131, 93.

HRMS (EI): $[M]^+$ Observed 266.1300 for $C_{18}H_{18}O_2$ theoretical 266.1301

The synthesis of 4-[(3-hydroxypent-4-yn-1-yl) oxy] benzonitrile (159d)



The same method was employed as described for the synthesis of the **159** with the following quantities; aldehyde **160c** (4- (3-oxopropoxy) benzonitrile) (1.75 g, 10 mmol) and ethynylmagnesium bromide (22 mL of the 0.5 M solution in hexane, 11 mmol). After 1 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.5, (hexane: diethyl ether 80:20) Purification on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford title compound as a colourless oil (2.16 g, 98%).

IR ν_{max} (neat)/cm^{-1}: 3429.4 (s); 2928.7 (m); 2556.9 (m); 1605.8 (m); 1508.5 (w); 1259.4 (m); 1172.6 (m); 1040.2 (s); 835.6 (s).

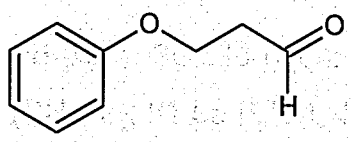
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.60 (2H, d, *J* = 8.0 Hz, Ar); 6.98 (2H, d, *J* = 8.0 Hz, Ar); 4.70-4.65 (1H, m, C<u>H</u>OH); 4.30-4.22 (1H, m, ArOC<u>H</u>$_2$); 4.20-4.10 (1H, m, ArOC<u>H</u>$_2$); 2.50 (1H, d, *J* = 2.0 Hz, ≡C<u>H</u>); 2.20-2.24 (3H, m, C<u>H</u>$_2$CH &O<u>H</u>)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 161.45 (<u>C</u>, Ar); 133.56 (<u>C</u>, Ar); 118.67 (CN); 114.73 (<u>C</u>H, Ar); 103.70 (<u>C</u>H, Ar); 83.32 (<u>C</u>); 73.29 (<u>C</u>H); 64.05 (<u>C</u>H); 62.85 (<u>C</u>H$_2$); 36.07 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 201), 172, 156, 145, 128, 119, 102, 90, 82, 65, 55.

HRMS (EI): [M+H] observed 202.0861for $C_{12}H_{12}O_2N$ theoretical 202.0863

The synthesis of 3-phenoxypropanal (160)



Method 1: The 2-(2-phenoxyethyl)-1, 3-dioxolane **161** (1.0 g, 5.15 mmol, 1 eq) was placed in round bottom flask and ceric ammonium nitrate (CAN) (1.76 g, 5.15 mmol, 1 eq) was added. The solvent mixture of water and acetonitrile (30 mL) in 1:2 ratios was added and the mixture was warmed to 70°C and stirred for 5 minutes. After 5 minutes tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.5 (hexane: diethyl ether, 70:30). The reaction mixture was quenched by the addition of water (30 mL) and extracted with DCM (3 x 30 mL). The organic phase was then washed with saturated solution of $NaHCO_3$ (3 x 30 mL) and brine (5 x 30 mL). The organic phase was dried over anhydrous magnesium sulphate, filtered and solvent was removed under vacuum. Light yellow oil was extracted from organic layer and was purified by column chromatography on silica gel using a mixture of hexane and diethyl ether in ratio of 60:40 as a mobile phase. Aldehyde **160** was not stable therefore it was synthesised *in situ* for each propargyl alcohol derivatives. The best yield for the title compound was (0.2 - 0.5 g, 60-70%)

Method 2: The epoxide **171** (1.26 g, 7.7 mmol) was placed in a 250 mL round bottom flask and a solvent system consisting of THF:H_2O (1:1) (15 mL) was added followed by periodic acid (H_5IO_6) (1.75 g, 7.7 mmol). The solution was stirred for 5 h and tlc monitoring showed a new compound with an R_f = 0.5 (hexane: diethyl ether, 70:30), as aldehyde **160** was not stable on silica gel purification, it was used as crude (0.76 g, 66%).

Method 3: The alcohol **172** (2 g, 13.15 mmol) was placed in a dry 250 mL round bottom flask, under nitrogen, at an ambient temperature. Pyridinium chlorochromate (PCC) (2.84 g, 13.15 mmol) in anhydrous DCM (15 mL) was added. The mixture was stirred for 6-8 hours. Tlc analysis showed a new spot with an R_f = 0.5 (hexane: diethyl ether, 70:30), (1 g, 50 %).

IR ν_{max} (neat)/cm^{-1}: 2990.7 (s); 2930.5 (m); 2600.9 (m); 1724.1 (s); 1650.1 (s); 1497.3 (m); 1244.2 (m); 1082.8 (m); 755.7 (s); 692.5 (s).

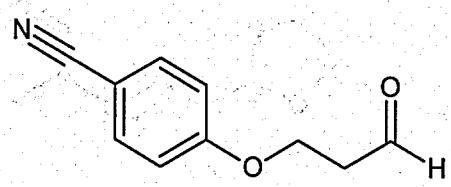
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.90 (1H, t, *J* = 1.60 Hz, C<u>H</u>O); 7.25-7.20 (2H, m, Ar); 6.90 (3H, d, *J* = 9.0 Hz, Ar); 4.30 (2H, t, *J* = 6.1 Hz, C<u>H</u>$_2$O); 2.90 (2H, td, *J* = 6.1, 1.60 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δ ppm: 200.30 (<u>C</u>O); 158.00 (<u>C</u>, Ar); 129.50 (<u>C</u>H, Ar); 121.29 (<u>C</u>H, Ar); 116.51 (<u>C</u>H, Ar); 61.55 (<u>C</u>H$_2$); 43.29 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 150), 122, 94, 77, 66, 51.

HRMS (EI): [M^+] observed150.0672 for $C_9H_{10}O_2$ theoretical150.0675

The synthesis of 4- (3-oxopropoxy) benzonitrile (160c)



The same method was employed as described for the synthesis of the **160** with the following quantities; 4-[2- (1, 3-dioxolan-2-yl) ethoxy] benzonitrile **161c** (1 g, 5.71 mmol) and CAN (1.76 g, 5.15 mmol) mixed in the same solvent mixture. After 30 minutes tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.55 (hexan: diethyl ether, 70:30). Purification on silica gel eluted (hexane: diethyl ether, 70:30) was carried out to afford title compound as a colourless oil (0.71 g, 88%)

Method 2: The same method was employed as described in method 2 for the synthesis of the **160a** with the following quantities; epoxide **171b** (1.95 g, 10.6 mmol) followed with the mixture of solvent THF and water in the ratio of 1:1 (20 mL) was added subsequently periodic acid (H_5IO_6) (2.41 g, 10.6 mmol) was poured in the solution mixture and stirred for 5 hours. After 5 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.55 (hexane: diethyl ether, 70:30) compound sufficiently was pure (1.2 g, 66.7%).

IR ν_{max} (neat)/cm^{-1}: 3434.3 (s); 2930.5 (m); 2849.0 (m); 2248.5 (m); 1723.9 (s); 1656.0 (s); 1508.8 (m); 1258.8 (m); 1173.1 (s); 835.5 (s).

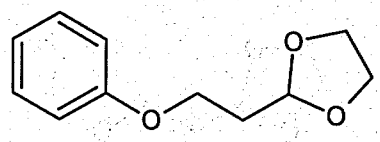
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.90 (1H, t, J = 1.2 Hz, C<u>H</u>O); 7.66 (2H, d, J = 8.5 Hz, Ar); 7.03 (2H, d, J = 8.5 Hz, Ar); 4.38 (2H, t, J = 6.0 Hz, OC<u>H$_2$</u>); 3.01 (2H, td, J = 6.0, 1.2 Hz, C<u>H$_2$</u>CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 198.90 (<u>C</u>O); 162.15 (<u>C</u>N); 133.55 (<u>C</u>H, Ar); 120.20 (<u>C</u>, Ar); 115.09 (<u>C</u>H, Ar); 105.40 (<u>C</u>, Ar); 61.15 (<u>C</u>H$_2$); 43.00 (<u>C</u>H$_2$).

LRMS (m/z): (M$^+$175), 119, 91, 64, 57.

HRMS (EI): [M$^+$] observed 175.0633 for $C_{10}H_9O_2N$ theoretical 175.0633

The synthesis of 2- (2-phenoxyethyl)-1, 3-dioxolane (161)



To a mixture of phenol (2.5 g, 26.6 mmol, 1 eq); potassium carbonate (14.70g, 106.4 mmol, 4 eq) and potassium iodide (0.44 g, 2.66 mmol). To this mixture was added DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxolane (4.8 g, 26.6 mmol) under nitrogen atmosphere. The mixture was stirred at an ambient temperature for 3 hours. After 3 hours tlc analysis with an (R_f = 0.45) (hexane: diethyl ether, 70:30) showed the loss of the starting material and the presence of a new compound. The reaction was quenched by the addition of water (30 mL) and placed in a separating funnel. The mixture was then extracted with diethyl ether (3 x 25 mL). The organic layers were combined and washed successively with a saturated solution of lithium chloride (4 x 25 mL) to remove any residual DMF. The combined organic layers were then dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford the title compound (5.1 g, 98 %) as colourless oil. This was sufficiently pure to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2923.4(s); 2854.7(s); 2728.5(s); 1599.2(m); 1498.0(m); 1053.3(s); 976.3(m); 753.5(s).

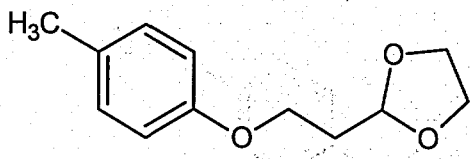
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.37-7.25 (2H, m, Ar); 7.03-6.94 (3H, m, Ar); 5.15 (1H, t, C<u>H</u>, *J* = 4.8 Hz); 4.17 (2H, t, ArOC<u>H</u>$_2$, *J* = 6.5 Hz); 4.08-4.00 (2H, m, OC<u>H</u>$_2$CH$_2$); 3.98-3.87 (2H , m, OC<u>H</u>$_2$CH$_2$); 2.25-2.17 (2H, m, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.8 (<u>C</u>, Ar); 129.5 (<u>C</u>H, Ar); 120.8 (<u>C</u>H, Ar); 115.3 (<u>C</u>H, Ar); 111.1 (<u>C</u>H); 65.0 (<u>C</u>H$_2$); 63.5 (<u>C</u>H$_2$); 33.9 (<u>C</u>H$_2$).

LRMS (m/z): (M$^+$ 194), 177, 145, 133,121,107, 99, 86, 73, 57.

HRMS (EI): [M$^+$] observed 194.0943 for $C_{11}H_{14}O_3$ theoretical, 194.0943

The synthesis of 2-[2- (4-methylphenoxy) ethyl]-1, 3-dioxolane (161a)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-methylphenol (3.5 g, 32.40 mmol); potassium carbonate (17.88 g, 129.6 mmol) potassium iodide (0.53 g, 3.24 mmol,), dry DMF (30 mL) and 2- (2-bromoethyl)-1,3-dioxolane (5.86 g, 32.40 mmol). After 3 hours tlc analysis with an R_f = 0.66 (70:30, hexane: diethyl ether), showed the loss of the starting material and the presence of a new compound. The title compound was obtained as a colourless oil (6.5 g, 96.44 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2883.4 (s); 1613.3 (s); 1512.5(m); 1243.4(w); 1141.0(m); 817.2(s).

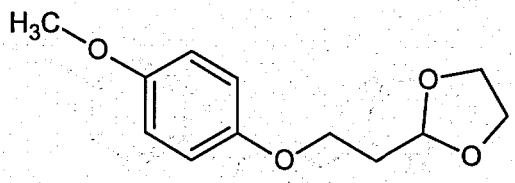
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.10 (2H, d, J = 7.9 Hz, Ar); 6.78- 6.82 (2H, m, Ar); 5.15 (1H ,t, J = 5.0 Hz, C$\underline{H}$); 4.10 (2H, t, J = 6.5 Hz, ArOC$\underline{H}_2$); 4.08-4.00 (2H, m, $OCH_2C\underline{H}_2O$); 3.98-3.87 (2H , m, $OC\underline{H}_2CH_2O$); 2.25 - 2.17 (2H, td, J = 6.5, 5.0 Hz, $C\underline{H}_2CH$); 2.30 (3H, s, $C\underline{H}_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 159.00 ($\underline{C}$, Ar); 129.70 ($\underline{C}$H, Ar); 129.48 ($\underline{C}$H, Ar); 128.65 ($\underline{C}$H, Ar); 110.40 ($\underline{C}$H); 75.00 ($\underline{C}H_2$); 67.02 ($\underline{C}H_2$); 25.3 ($\underline{C}H_2$); 22.90 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 208), 177, 145, 133,121,107, 99, 86, 73, 57

HRMS (EI): [M+ Na]: observed 231.0990, for $C_{12}H_{16}O_3Na$ **theoretical:** 231.0992

The synthesis of 2-[2- (4-methoxyphenoxy) ethyl]-1, 3-dioxolane (161b)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-methoxyphenol (1.00g, 8.00 mmol); potassium carbonate (4.42 g, 32 mmol); potassium iodide (0.13 g, 0.8 mmol) dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxolane (1.45 g, 8 mmol). After 3 hours tlc analysis with an (R_f = 0.36, hexane: diethyl ether, 70:30), showed the loss of the starting material and the presence of a new compound. The title compound was obtained as colourless oil (1.74 g, 98 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2957.0 (s); 2884.7(m); 2834.5(s); 1508.7(m); 1471.8(w); 1232.4(s); 1141.3(m); 837.9(s); 741.4(m).

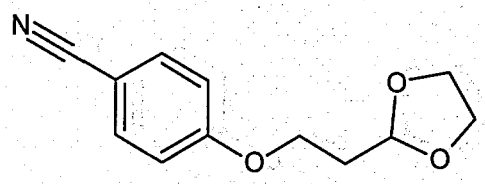
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 6.86 (2H, d, *J* = 7.0 Hz, Ar); 6.80 (2H, d, *J* = 7.0, Ar); 5.08 (1H, t, *J* = 4.6 Hz, C<u>H</u>); 4.07 (2H, t, *J* = 6.5 Hz, ArOC<u>H</u>$_2$); 4.02-3.96 (2H, m, OC<u>H</u>$_2$CH$_2$O); 3.92-3.89 (2H, m, OCH$_2$C<u>H</u>$_2$O); 3.76 (3H, s, C<u>H</u>$_3$); 2.13 (2H, td, *J* = 6.5, 4.6 Hz, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 152.20 (<u>C</u>, Ar); 149.70 (<u>C</u>, Ar); 115.41 (<u>C</u>H, Ar); 114.9 (<u>C</u>H, Ar); 107.30 (<u>C</u>H); 86.12 (<u>C</u>H$_2$); 68.76 (<u>C</u>H$_2$); 63.20 (<u>C</u>H$_2$); 55.8 (<u>C</u>H$_3$).

LRMS (m/z): (M$^+$224), 124, 109, 86, 73, 57

HRMS (EI): [M+H] observed 225.1130 for $C_{12}H_{17}O_4$ theoretical 225.1126

The synthesis of 4-[2- (1, 3-dioxolan-2-yl) ethoxy] benzonitrile (161c)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-hydroxybenzonitrile (1.7 g, 14.5 mmol); potassium carbonate (8 g, 58 mmol); potassium iodide (0.24 g, 1.45 mmol) dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxolane (2.6 g, 14.5 mmol). After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.23, hexane: diethyl ether, 50:50). The title compound was obtained as colourless oil (3.12 g, 98 or 99 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 3434.3(s); 2930.5(s); 2224.8(m); 1723.9(m); 1606.0(m); 1508.8(s); 1258.8(m); 1173.1(w); 835.5(s).

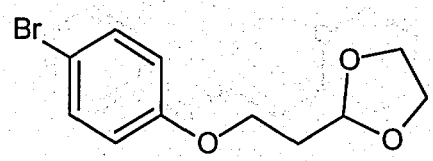
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.62 (2H, d, *J* = 7.3 Hz, Ar); 7.03 (2H, d, *J* = 7.3 Hz, Ar); 5.08 (1H, t, *J* = 4.7 Hz, C<u>H</u>); 4.16 (2H, t, *J* = 6.5 Hz, ArOC<u>H</u>$_2$); 4.03-3.95 (2H, m, OC<u>H</u>$_2$CH$_2$O); 3.94-3.86 (2H, m, OCH$_2$C<u>H</u>$_2$O); 2.18 (2H, td, *J* = 6.5, 4.7 Hz, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 162.10 (<u>C</u>, Ar); 133.50 (<u>C</u>, Ar); 115.18 (<u>C</u>H, Ar); 104.00 (<u>C</u>H, Ar); 115.55 (<u>C</u>N); 110.4 (<u>C</u>H); 81.13 (<u>C</u>H$_2$); 62.60 (<u>C</u>H$_2$); 59.2 (<u>C</u>H$_2$).

LRMS (m/z): (M$^+$ 219), 207, 189, 132, 119, 102, 86, 73, 57

HRMS (EI): [M$^+$] observed 219.0900 for $C_{12}H_{13}O_3N$ theoretical 219.0895

The synthesis of 2-[2- (4-bromophenoxy) ethyl]-1, 3-dioxolane (161d)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-bromophenol (2.9 g, 16.5 mmol); potassium carbonate (9 g, 66 mmol); potassium iodide (0.27 g, 1.65 mmol) dissolved in dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxolane (2.98 g, 16.5 mmol) was added. After 3 hours tlc analysis showed the presence of a new slower moving compound (R_f = 0.38, hexane: diethyl ether, 70:30). The title compound was obtained as colourless oil (4.49 g, 99 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2974.0 (s); 2898.8 (m); 1591.6 (s); 1286.9 (m); 1180.0 (w); 822.9 (s); 642.0 (m).

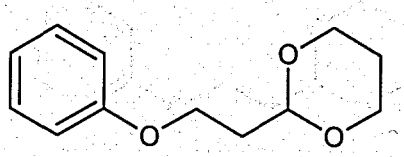
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.35 (2H, d, *J* = 7.0 Hz, Ar); 6.80 (2H, d, *J* = 7.0 Hz, Ar); 5.07 (1H, t, *J* = 4.8 Hz, C<u>H</u>); 4.08 (2H, t, *J* = 6.5 Hz, ArOC<u>H</u>$_2$); 4.01-3.94 (2H, m, OC<u>H</u>$_2$CH$_2$O); 3.92-3.83 (2H,m, OCH$_2$C<u>H</u>$_2$O); 2.14 (2H, td, *J* = 6.5, 4.8 Hz, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 159.8 (<u>C</u>, Ar); 132.00 (<u>C</u>, Ar); 117.2 (<u>C</u>H, Ar); 113.5 (<u>C</u>H, Ar); 109.2 (<u>C</u>H); 83.4 (<u>C</u>H$_2$); 63.6 (<u>C</u>H$_2$); 59.7 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 272), 244, 229, 211, 172, 116, 100, 86, 73, 57

HRMS (EI): $[M-H]^+$; observed. 270.9958 for $C_{11}H_{12}O_3Br$, theoretical 270.9964

The synthesis of 2- (2-phenoxyethyl)-1, 3-dioxane (165)



The same method was used as described for the synthesis of **161**. The following quantities were employed: phenol (1.9 g, 20 mmol); potassium carbonate (10.9 g, 80 mmol) potassium iodide (0.32 g, 2 mmol) mixed in dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxane (3.9g, 20 mmol) was added. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.4, hexane: diethyl ether, 70:30). The title compound was obtained as colourless oil (4.0 g, 97 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2953.4 (m), 1586.8 (w), 1599.1 (s), 1245.5 (s), 753.5 (s).

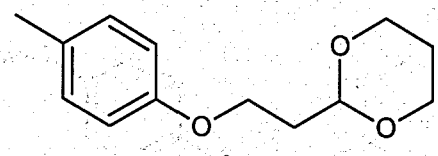
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.37-7.28 (2H, m, Ar); 7.02-6.92 (3H, m, Ar); 4.83 (1H, t, J = 5.2 Hz, C<u>H</u>); 4.18-4.10 (2H, m, CHOC<u>H</u>$_2$); 4.11 (2H, t, J = 6.3 Hz, ArOC<u>H</u>$_2$); 3.88-3.80 (2H, m, CHOC<u>H</u>$_2$); 2.15-2.10 (2H, m, C<u>H</u>$_2$CH); 1.38-1.34 (1H, m, CH_2C<u>H</u>$_2$$CH_2$); 1.34-1.30 (1H, m, CH_2C<u>H</u>$_2$$CH_2$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.92 (<u>C</u>, Ar); 129.66 (<u>C</u>H, Ar); 120.66 (<u>C</u>H, Ar); 114.56 (<u>C</u>H, Ar); 99.60 (<u>C</u>H); 66.95 (<u>C</u>H_2); 63.16 (<u>C</u>H_2); 35.17 (CH_2); 25.85 (<u>C</u>H_2);

LRMS (m/z): (M^+208), 166, 149, 131, 114, 107, 100, 94, 87, 77, 65, 59, 51

HRMS (EI): [M + Na] observed. 231.0994 for $C_{12}H_{16}O_3$ theoretical: 231.0992

The synthesis of 2-[2- (4-methylphenoxy) ethyl]-1, 3-dioxane (165a)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-methylphenol (2.16 g, 20 mmol); potassium carbonate (10.9 g, 80 mmol); potassium iodide (0.32 g, 2 mmol) dissolved in dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxane (3.9 g, 20 mmol) was added. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.39, hexane: diethyl ether, 70:30). The title compound was obtained as a colourless oil (4.4 g, 99 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2966.5 (s); 2855.5 (s); 1612.9 (m); 1584.7 (s); 1289.7 (m); 1141.7 (w); 816.5 (s); 735.7 (s).

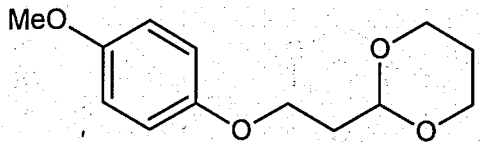
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.07 (2H, dt (brd); J = 8.7, 0.6 Hz, Ar); 6.80 (2H, d, J = 8.7 Hz, Ar); 4.78 (1H, t, J = 5.2 Hz, C<u>H</u>); 4.18-4.10 (2H, m,CHOC<u>H</u>$_2$); 4.04 (2H, t, J = 6.3 Hz, ArOC<u>H</u>$_2$); 3.82-3.74 (2H, m, CHOC<u>H</u>$_2$); 2.28 (3H, s, CH_3); 2.08-2.03 (2H, m, C<u>H</u>$_2$CH); 1.40-1.35 (1H, m, CH_2C<u>H</u>$_2$$CH_2$); 1.35-1.30 (1H, m, CH_2C<u>H</u>$_2$$CH_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.12 (<u>C</u>, Ar); 130.60 (<u>C</u>, Ar); 129.85 (<u>C</u>H, Ar); 114.65 (<u>C</u>H, Ar); 100.00 (<u>C</u>H); 67.07 (<u>C</u>H_2); 64.26 (<u>C</u>H_2); 35.20 (CH_2); 26.77 (<u>C</u>H_2); 24.20 (<u>C</u>H_3);

LRMS (m/z): (M^+221), 163, 121, 107, 100, 87, 77, 57

HRMS (EI): [M+H] observed 222.1256 for $C_{13}H_{18}O_3$ theoretical 222.1255

The synthesis of 2-[2- (4-methoxyphenoxy) ethyl]-1, 3-dioxane (165b)



The same method was used as described for the synthesis of **161**. The following quantities were employed: 4-methoxyphenol (1.24 g, 10 mmol); potassium carbonate (5.45 g, 40 mmol) potassium iodide (0.16 g, 1mmol)dissolved in dry DMF (30 mL) and 2- (2-bromoethyl)-1,3-dioxane (1.95 g, 10 mmol) was added. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.6, hexane: diethyl ether, 70:30). The title compound was obtained as a colourless oil (2.34 g, 98 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2963.4 (s); 2854.8 (s); 1508.8 (s); 1469.6 (m); 1232.9 (m); 1141.5 (w); 826.7 (s); 734.0 (s).

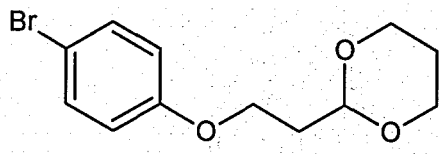
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.23 (2H, d, *J* = 8.0 Hz, Ar); 7.09 (2H, d, *J* = 8.0 Hz, Ar); 4.77 (1H, t, *J* = 5.25 Hz, C<u>H</u>); 4.14-4.08 (2H, m, CHOC<u>H</u>$_2$); 4.01 (2H, t, *J* = 6.3 Hz, ArOC<u>H</u>$_2$); 3.83–3.77 (2H, m, CHOC<u>H</u>$_2$); 3.76 (3H, s, C<u>H</u>$_3$); 2.05 (2H, td, *J* = 6.3, 5.4 Hz, CH$_2$C<u>H</u>$_2$CH); 1.40-1.35 (1H, m, CH$_2$C<u>H</u>$_2$CH$_2$); 1.35-1.30 (1H, m, CH$_2$C<u>H</u>$_2$CH$_2$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 159.80 (<u>C</u>, Ar); 150.01 (<u>C</u>, Ar); 119.91 (<u>C</u>H, Ar); 118.85 (<u>C</u>H, Ar); 100.70 (<u>C</u>H); 70.24 (<u>C</u>H$_2$); 67.43 (<u>C</u>H$_2$); 57.12 (<u>C</u>H$_3$); 35.95 (<u>C</u>H$_2$); 27.09 (<u>C</u>H$_2$).

LRMS (m/z): (M$^+$ 238), 136, 124, 109, 87, 73, 59, 57.

HRMS (EI): [M$^+$] observed 238.1210 for $C_{13}H_{18}O_4$ theoretical 238.1205

The synthesis of 2-[2- (4-bromophenoxy) ethyl]-1, 3-dioxane (165c)



The same method was used as described for the synthesis of **161**. The following quantities were employed: bromophenol (0.86 g, 5 mmol); potassium carbonate (2.72 g, 20 mmol) potassium iodide (0.08 g, 0.5 mmol) dissolved in dry DMF (30 mL) and 2- (2-bromoethyl)-1, 3-dioxane (0.97 g, 5 mmol) was added. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.4, hexane: diethyl ether, 70:30). The title compound was obtained as a colourless oil (1.4 g, 98 %) of sufficient purity to use in the next stage without further purification.

IR ν_{max} (neat)/cm^{-1}: 2949.2 (s); 2853.4 (s); 1590.8 (s); 1285.5 (m); 1092.6 (w); 913.8 (s); 802.9 (s).

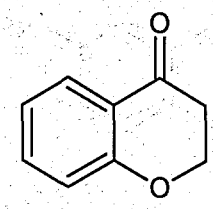
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 6.70 (2H, d, *J* = 7.5 Hz, Ar); 6.80 (2H, d, *J* = 7.5 Hz, Ar); 4.80 (1H, t, *J* = 5.3 Hz, C<u>H</u>); 4.14-4.10 (2H, m, CHOC<u>H</u>$_2$); 4.00 (2H, t, *J* = 6.3 Hz, ArOC<u>H</u>$_2$); 3.80-3.78 (2H, m, CHOC<u>H</u>$_2$); 2.05-1.96 (2H, m, C<u>H</u>$_2$CH); 1.43-1.35 (1H, m, CH$_2$C<u>H</u>$_2$CH$_2$); 1.35-1.30 (1H, m, CH$_2$C<u>H</u>$_2$CH$_2$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.50 (<u>C</u>, Ar); 132.4 (<u>C</u>, Ar); 119.60 (<u>C</u>H, Ar); 115.27 (<u>C</u>H, Ar); 100.76 (<u>C</u>H); 70.58 (<u>C</u>H$_2$); 64.00 (<u>C</u>H$_2$); 36.15 (<u>C</u>H$_2$); 24.50 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 286), 229, 185, 171, 156, 142, 114, 100, 87, 59, 57.

HRMS (EI): [M^+] observed 286.0206 for $C_{12}H_{15}O_3Br$ theoretical 286.0204

The Synthesis of 2,3-dihydro-4*H*-chromen-4-one (166)



To a mixture of dioxolane **161** (1.20 g, 6.18 mmol, 1eq) in solvent system of CH_3CN and water (10 mL) (1:2) was added CAN (5.0 g, 9.27 mmol, 1.5 eq). The reaction mixture was heated, with stirring, at 70 °C for 30 minutes. After 30 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an $R_f = 0.6$ (hexane: diethyl ether 70:30). The solution was allowed to cool slowly to an ambient temperature and distilled water (20 mL) was added. The dark red mixture poured into a separating funnel and extracted with diethyl ether (3 x 25 mL). The combined organic layer was washed with a saturated solution of sodium bicarbonate (5 x 25 mL) to remove any residue of CAN. The diethyl ether layer was then dried over anhydrous magnesium sulphate and filtered and the solvent removed *in vacuo* to give a yellow waxy solid as the product (0.64 g, 70%). This was sufficiently pure.

IR ν_{max} (neat)/cm^{-1}: 2923.3 (m); 1688.0 (s); 1255.1 (m); 1038.3 (m); 764.7 (m).

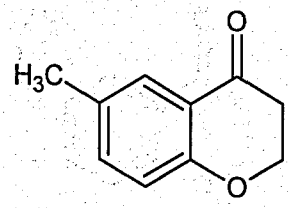
^{1}H NMR (400 MHz, CDCl3) δppm: 7.90 (1H, dd, *J* =7.8, 1.6 Hz, Ph); 7.47 (1H, ddd, *J* = 8.5, 7.0, 1.6 Hz, Ph); 7.01 (1H, ddd, *J* = 7.8, 7.0, 0.8 Hz, Ph); 6.97 (1H, dd, *J* = 8.5, 0.8 Hz, Ph); 4.54 (2H, t, *J* = 6.5 Hz, $OC\underline{H}_2$); 2.81 (2H, t, *J* = 6.5 Hz, $C\underline{H}_2CO$).

^{13}C NMR (100 MHz) (CDCl3) δppm: 191.86 (<u>C</u>O); 161.88 (<u>C</u>, Ar); 136.02 (<u>C</u>, Ar); 127.18 (<u>C</u>H, Ar); 121.41 (<u>C</u>H, Ar); 121.38 (<u>C</u>H, Ar); 117.91 (<u>C</u>H, Ar); 67.04 ($O\underline{C}H_2$); 37.82 ($\underline{C}H_2CO$).

LRMS (m/z): (M^+ 148), 120, 92, 74, 65, 63, 51.

HRMS (EI): [M^+] observed. 148.0520 for $C_9H_8O_2$ theoretical. 148.0519.

The synthesis of 6-methyl-2, 3-dihydro-4*H*-chromen-4-one (166a)



The same method was employed as described for the synthesis of the **166** with the following quantities, dioxolane **161a** (1.5 g, 7.2 mmol); CAN (5.93 g, 10.81 mmol) in solvent mixture (15 mL) of the acetonitrile and water (2:1). After 30 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.63 (hexane: diethyl ether, 7:30). Compound was sufficiently pure (0.90 g, 77%).

IR ν_{max} (neat)/cm^{-1}: 2931.3 (w); 1651.5 (s); 1255.1 (m); 765.0 (m).

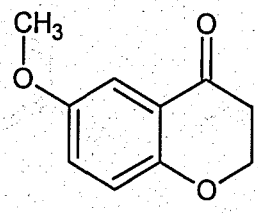
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.70-7.68 (1H, m, Ph); 6.88 (1H, d, *J* = 8.4 Hz, Ph); 6.75 (1H, d, *J* = 8.3 Hz, Ph); 4.51 (2H, t, *J* = 6.5 Hz, OC$\underline{H}_2$); 2.79 (2H, t, *J* = 6.5 C$\underline{H}_2$CO); 1.54 (3H, s, $\underline{C}H_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 190.50 ($\underline{C}$O); 160.05 ($\underline{C}$, Ar); 136.00 ($\underline{C}$, Ar); 130.20 ($\underline{C}$, Ar); 121.50 ($\underline{C}$H, Ar); 121.40 ($\underline{C}$H, Ar); 120.00 ($\underline{C}$H, Ar); 67.00 ($\underline{C}H_2$); 38.00 ($\underline{C}H_2$); 30.10 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 163), 149, 145, 135, 121, 107, 91, 77, 65, 51

HRMS (EI): [M-H] observed. 162.0676 for $C_{10}H_{10}O_2$ theoretical. 162.0675

The synthesis of 6-methoxy-2, 3-dihydro-4*H*-chromen-4-one (166b)



The same method was employed as described for the synthesis of the **166** with the following quantities, dioxolane **161b** (1.5 g, 6.7 mmol); CAN (5.5 g, 10.13 mmol) in solvent mixture (15 mL) of the acetonitrile and water (2:1). After 30 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.63 (hexane: diethyl ether, 70:30). Title compound was sufficiently pure as a yellow oil (0.95 g, 79.2%).

IR v_{max} (neat)/cm^{-1}: 2933.3 (w); 1598.1 (s); 1209.9 (m); 1153.4 (m); 747.80 (m).

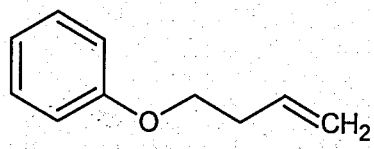
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.30-7.28 (1H, m, Ph); 7.24-7.21 (2H, m, Ph); 4.67-4.62 (2H, m, OC$\underline{H}_2$); 4.20 (3H, s, C$\underline{H}_3$); 2.62-2.48 (1H, m, C$\underline{H}_2$C); 2.48-2.38 (1H, m, C$\underline{H}_2$C);

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 195.50 ($\underline{C}$O); 165.90 ($\underline{C}$O, Ar); 138.00 ($\underline{C}$, Ar); 129.20 ($\underline{C}$, Ar); 121.83 ($\underline{C}$H, Ar); 120.50 ($\underline{C}$H, Ar); 119.91 ($\underline{C}$H, Ar); 65.46 ($\underline{C}H_2$); 56.30 ($\underline{C}H_3$) 37.09 ($\underline{C}H_2$).

LRMS (m/z): (M^+ 180), 165, 152, 137, 119, 109, 91, 65, 53.

HRMS (EI): [M-H] observed 179.0710 for $C_{10}H_{11}O$ theoretical 179.0708

The synthesis of but-3-en-1-yloxy) benzene (170)



The same method was employed as described for the formation of the **161** with the following quantities; phenol (0.95 g, 10 mmol); potassium carbonate (5.45 g, 40 mmol) and potassium iodide (0.16g, 1mmol) was mixed, 30 mL dry DMF was added and then 4-bromobut-1-ene (1.35 g, 10 mmol) was added to the solution. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.5, hexane: diethyl ether, 70:30). Title compound as a colourless oil resulted (1.45 g - 97%).

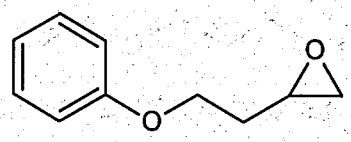
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.31-7.26 (2H, m ,Ar); 6.97-6.88 (3H, m, Ar); 6.0-5.95 (1H, m, C<u>H</u>=CH_2); 5.22-5.14 (1H, m, =C<u>H_2</u>); 5.14-5.08 (1H, m, =C<u>H_2</u>); 4.02 (2H,t, *J* = 6.7 Hz, OC<u>H_2</u>); 2.55 (2H,ddd, *J* = 13.4, 6.7, 1.4 Hz, C<u>H_2</u>CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 158.91 (<u>C</u>, Ar); 133.52 (=<u>C</u>H); 129.45 (<u>C</u>H, Ar); 120.70 (<u>C</u>H, Ar); 117.00 (<u>C</u>H, Ar); 114.59 (=<u>C</u>H_2); 67.12 (<u>C</u>H_2); 33.69 (<u>C</u>H_2).

LRMS (m/z): (M^+148), 120, 107, 94, 77, 55

HRMS (EI): [M^+] observed.148.0881 for $C_{10}H_{12}O$ theoretical.148.0883

The synthesis of 2- (2-phenoxyethyl) oxirane (171)



To a dried 250 ml round bottom flask charged with a magnetic stirrer, under an atmosphere of nitrogen, (but-3-en-1-yloxy)benzene **170** (1.55 g, 10.53 mmol, 1 eq) and anhydrous DCM (10 mL) were added then 3 - chloroperoxybenzoic acid, (mCPBA) (2 g, 12 mmol, 1.1 eq) was added to the solution. The mixture was stirred at an ambient temperature for 3 hours. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.21) (hexane: diethyl ether 60:40). The reaction was quenched by the addition of sodium hydrogen carbonate (30 mL) and placed in a separating funnel. The mixture was then extracted with DCM (3 x 25 mL). The organic layer was then dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo*. Compound was purified by chromatography on silica gel to afford the title compound (1.50 g, 87%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.31-7.24 (2H, m, Ar); 6.97-6.88 (3H, m, Ar); 4.08 (2H, t, *J* = 5.8 Hz, ArOC$\underline{H}_2$); 3.20 (1H, dd, *J* = 8.8, 6.0 Hz, CHC$\underline{H}_2$O); 2.89 (1H, dd, *J* = 8.8, 6.0 Hz, CHC$\underline{H}_2$O); 2.80-2.76 (1H, m,C$\underline{H}$); 2.02-1.98 (2H, m, $CH_2C\underline{H}_2CH$).

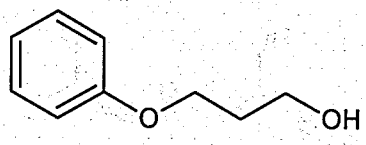
^{13}C NMR (100 MHz) ($CDCl_3$) δppm; 158.91 ($\underline{C}$, Ar); 129.45 ($\underline{C}$H, Ar); 120.70 ($\underline{C}$H, Ar); 114.59 ($\underline{C}$H, Ar); 67.12 ($\underline{C}H_2$); 52.00 ($\underline{C}$H); 50.10 ($\underline{C}H_2$); 33.69 ($\underline{C}H_2$)

LRMS (m/z): (M^+ **164**), 133, 119, 107, 94, 77, 71, 65, 51

HRMS (EI): [M^+] observed 164.0840 for $C_{10}H_{12}O_2$ theoretical 164.0837

Please see page 116 for the details of the periodate cleavage reaction.

The synthesis of 3-phenoxypropan-1-ol (172)



The same method was employed as described for synthesis of the **161a** using the following quantities; phenol (1.0 g, 10.63 mmol); potassium carbonate (5.8 g, 42.55 mmol) and potassium iodide (0.17 g, 1.06 mmol) was mixed, 30 mL dry DMF was added and then 3-bromopropan-1-ol (1.48 g, 10.63 mmol) was added to the solution. After 3 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.5, (hexane: diethyl ether, 70:30). Product was sufficiently pure, colourless oil resulted as a title compound (1.35 g, 84%).

^{1}H NMR (400 MHz, Acetone D_6) δppm: 7.67-7.60 (2H, m, Ar); 7.32-7.28 (3H, m, Ar); 4.46 (2H, t, *J* = 6.5 Hz, ArOC$\underline{H}_2$); 3.40-3.36 (2H, m, C$\underline{H}_2$OH); 2.42 (1H, s (brd); O$\underline{H}$); 2.35-2.30 (2H, m, $CH_2C\underline{H}_2CH_2$).

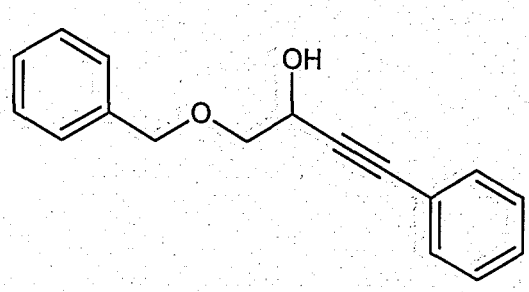
^{13}C NMR (100 MHz) (Acetone D_6) δppm: 160.15 ($\underline{C}$, Ar); 130.20 ($\underline{C}$H, Ar); 120.76 ($\underline{C}$H, Ar); 115.57 ($\underline{C}$H, Ar); 65.00 ($\underline{C}H_2$); 60.61 ($\underline{C}H_2$); 32.13 ($\underline{C}H_2$)

LRMS (m/z): (M^+ 152), 121, 107, 94, 77, 66, 51

HRMS (EI): [M^+] observed 152.1904 for $C_9H_{12}O_2$ theoretical 152.1904

Please see page 116 for the details of PCC oxidation reaction.

The synthesis of 1- (benzyloxy)-4-phenylbut-3-yn-2-ol (174a)



The same method was employed as described for the synthesis of the **159** with the following quantities; aldehyde ((benzyloxy) acetaldehyde) was commercially available **173** (0.7 g, 4.67 mmol) and phenylethynylmagnesium bromide (5.14 mL of the solution 1 M in hexane, 5.14 mmol) in anhydrouse THF (15 mL). After 2 hours tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.26, pethrpleum ether (60 °C- 80 °C): diethyl ether 70:30) Purification by chromatography on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford title compound as a colourless oil (1.15 g, 97.8%).

IR v_{max} (neat)/cm^{-1}: 3045.5 (s); 2821.0 (m); 1500.3 (w); 1109.2 (s); 901.5 (s); 855.5 (s).

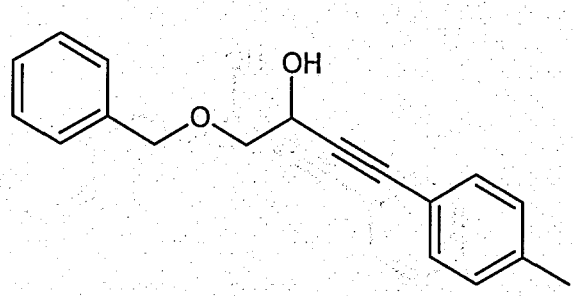
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.55-7.47 (2H, m, Ar); 7.40-7.35 (4H, m, Ar); 7.35-7.30 (4H, m, Ar); 4.82-4.79 (1H, m, C<u>H</u>); 4.60 (1H, d, *J* = 12.0 Hz, ArC<u>H</u>$_2$); 4.59 (1H, d, *J* = 12.0 Hz, ArC<u>H</u>$_2$); 3.75 (1H, dd, *J* = 9.7, 3.6 Hz, C<u>H</u>$_2$CH); 3.67 (1H, dd, *J* = 9.7, 7.5 Hz, C<u>H</u>$_2$CH); 2.60 (1H, d, *J* = 5.0 Hz, O<u>H</u>).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 137.72 (<u>C</u>, Ar); 131.86 (<u>C</u>, Ar); 128.69 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 128.35 (<u>C</u>H, Ar); 127.90 (<u>C</u>H, Ar); 127.84 (<u>C</u>H, Ar); 122.43 (<u>C</u>H, Ar); 90.56 (<u>C</u>); 85.66 (<u>C</u>); 73.64 (<u>C</u>H$_2$); 73.51 (<u>C</u>H$_2$); 62.32 (<u>C</u>H).

LRMS (m/z): (M$^+$252), 236, 131, 108, 91, 73.

HRMS (EI): [M+H] observed 253.11228 for $C_{17}H_{17}O_2$, theoretical 253.1228

The synthesis of 1- (benzyloxy)-4- (4-methylphenyl) but-3-yn-2-ol (174b)



The same method was employed as described for the synthesis of the **159** with the following quantities; however 4-methyl phenyl ethynyllithium solution synthesised *in situ* by addition of 4-ethynyltoluene (0.85 g, 7.4 mmol) and n-BuLi (4.5 mL of the 2.5 M in hexane, 11.1 mmol) in ahydrous THF (10 mL) under nitrogen atmosphere and -78 °C, after 1 houre aldehyde ((benzyloxy) acetaldehyde) **173** (0.94 g, 6.7 mmol) was added in one portion to the solution and left to stir for 2 more hour. After 2 hour tlc analysis showed the loss of the starting material and the presence of a new compound with an (R_f = 0.13, hexane: diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford the title compound as a colourless oil (1.5 g, 84.74%).

IR v_{max} (neat)/cm^{-1}: 3065.0 (s); 2941.0 (m); 1523.3 (w); 1100.2 (s); 876.5 (s); 798.1 (s).

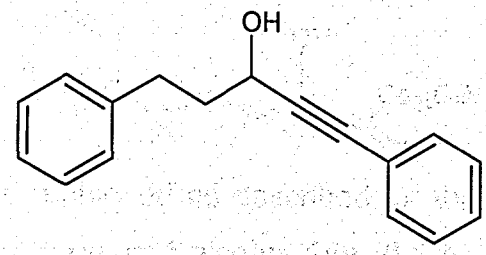
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.43-7.38 (4H, m, Ar); 7.37-7.33 (3H, m, Ar); 7.13 (2H, ddd, *J* = 7.8, 4.0, 0.6 Hz, Ar); 4.85-4.81 (1H, m, C<u>H</u>); 4.67 (1H, d, *J* = 12.0 Hz, ArC<u>H</u>$_2$O); 4.63 (1H, d, *J* = 12.0 Hz, ArC<u>H</u>$_2$O); 3.77 (1H, dd, *J* = 9.8, 3.5 Hz, C<u>H</u>$_2$CH); 3.69 (1H, dd, *J* = 9.8, 7.5 Hz, C<u>H</u>$_2$CH); 2.59 (1H, d, *J* = 5.0 Hz, O<u>H</u>); 2.37 (3H, s, CH_3)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 138.74 (<u>C</u>, Ar); 137.71 (<u>C</u>, Ar); 131.70 (<u>C</u>, Ar); 129.05 (<u>C</u>H, Ar); 128.55 (<u>C</u>H, Ar); 127.95 (<u>C</u>H, Ar); 127.85 (<u>C</u>H, Ar); 119.24 (<u>C</u>H, Ar); 85.92 (<u>C</u>); 85.82 (<u>C</u>); 73.73 (<u>C</u>H$_2$); 73.50 (<u>C</u>H$_2$); 62.30 (<u>C</u>H); 21.53 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 266), 248, 233, 221, 205, 189, 173, 165, 155, 145, 129, 115, 105, 91, 77, 65, 51

HRMS (EI): [M^+] observed. 266.1301 for $C_{18}H_{18}O_2$ theoretical. 266. 1301

The synthesis of 1, 5-diphenylpent-1-yn-3-ol (176)



The same method was employed as described for the synthesis of the **159** with the following quantities; aldehyde (3-phenylpropanal) was commercially available (1.02 g, 7.60 mmol) and phenylethynylmagnesium bromide (8.4 mL of the 1 M solution in hexane, 8.36 mmol) in anhydrous THF (15 mL) under nitrogen atmospher and -10 °C. The solution left to stir for 2 hours then tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.4, (hexane: diethyl ether 90:10) Purification on silica gel eluted with (9:1, hexane: diethyl ether) was carried out to afford title compound as a colourless oil (1.71 g, 97%).

IR ν_{max} (neat)/cm^{-1}: 3096.4 (s); 2931.0 (s); 1520.3 (w); 765.1 (m).

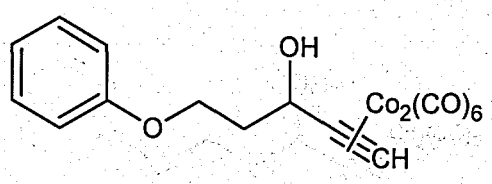
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.46-7.42 (2H, m, Ar); 7.39-7.33 (4H, m, Ar); 7.33-7.29 (4H, m, Ar); 4.64-6.60 (1H, m, C<u>H</u>OH); 2.87 (2H, t, *J* = 7.8, Hz, ArC<u>H</u>$_2$); 2.20-2.15 (2H, m, C<u>H</u>$_2$CH); 1.89 (1H, d, *J* = 5.5 Hz, O<u>H</u>).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 139.23 (<u>C</u>, Ar); 131.75 (<u>C</u>, Ar); 129.0 (<u>C</u>H, Ar); 128.9 (<u>C</u>H, Ar); 128.51 (<u>C</u>H, Ar); 128.36 (<u>C</u>H, Ar); 126.06 (<u>C</u>H, Ar); 122.58 (<u>C</u>H, Ar); 89.84 (<u>C</u>); 85.34 (<u>C</u>); 62.30 (<u>C</u>H); 39.30 (<u>C</u>H$_2$); 31.53 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 236), 219, 116, 91

HRMS (EI): [M^+] observed 236.1201 for $C_{17}H_{16}O$ theoretical 236.1201

The synthesis of hexacarbonyl 5-phenoxypent-1-yn-3-ol dicobalt (177)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **159** (0.4 g, 2.27 mmol) and dicobalt octahexacarbonyl (0.85 g, 2.5 mmol) in dry DCM (15 mL). The mixture was maintained under a nitrogen atmospher in ambient temperature for 1 hours. After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an R_f = 0.56 (hexane: ethyl acetate, 7:3). Purification on silica gel eluted with (9:1, petroleum ether (60 °C- 80 °C): diethyl ether) to afford title compound as a dark red oil (1.0 g, 96%).

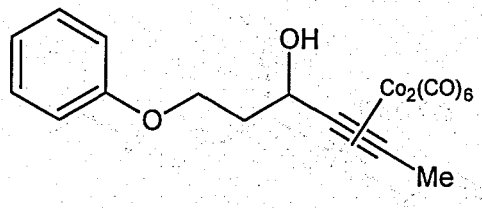
IR v_{max} (neat)/cm^{-1}: 3435.76 (s); 2924.5 (s); 2094.6 (m); 2012.7 (m); 1600.0 (s); 1497.2 (s); 1244.5 (w); 1046.0 (s); 753.5 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.34-7.27 (2H, m, Ar); 7.01-6.90 (3H, m, Ar); 6.06 (1H, s (bd); C≡C<u>H</u>); 5.08 (1H, dt, *J* = 7.8, 4.0 Hz, C<u>H</u>OH); 4.32-4.23 (1H, m, C<u>H</u>$_2$O); 4.23-4.12 (1H, m , C<u>H</u>$_2$O); 2.43 (1H, d, *J* = 4.0, O<u>H</u>); 2.26-2.15 (1H, m, C<u>H</u>$_2$CH); 2.15-2.10 (1H, m, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 129.7 (C, Ar); 129.6 (<u>C</u>H, Ar); 129.55 (<u>C</u>H, Ar); 129.48 (<u>C</u>H, Ar); 104.52 (<u>C</u>).

LRMS (m/z): (M^+ 462), 433, 405, 385, 377, 350, 322, 294, 249, And 227.
HRMS (EI): [M-H] observed 460.9123 for $C_{17}H_{11}O_8Co_2$ theoretical 460.9123

The synthesis of hexacarbonyl 1-phenoxyhex-4-yn-3-ol dicobalt (177a)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **159a** (0.22 g, 1.15 mmol) and dicobalt octahexacarbonyl (0.47 g, 1.22 mmol) in dry DCM (10 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an R_f = 0.36 (8:2) (petroleum ether (60 °C- 80 °C): diethyl ether). Dark red oil crude product was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ether (9:1) to afford a dark red oil title product (0.55 g, 100%).

IR ν_{max} (neat)/cm^{-1}: 3467.9 (s); 2931.2 (s); 2090.6 (m); 1600.5 (s); 1497.5 (s); 1244.5 (w); 1050.7 (s); 753.9 (s).

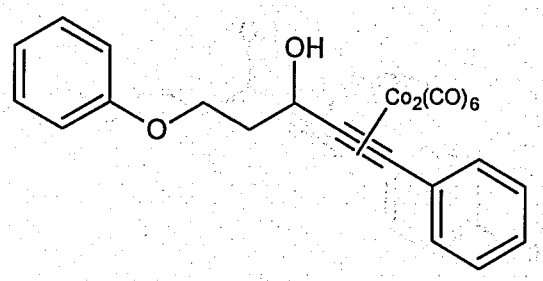
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.30-7.25 (2H, m, Ar); 7.10-6.90 (3H, m, Ar); 5.20-5.12 (1H, m, C<u>H</u>); 4.38-4.29 (1H, m, ArOC<u>H</u>$_2$); 4.27-4.18 (1H, m, ArOC<u>H</u>$_2$); 2.71 (3H, s, C<u>H</u>$_3$); 2.4 (1H, d, *J* = 4.3 Hz, O<u>H</u>); 2.32-2.22 (1H, m, CH_2CH); 2.21-2.09 (1H, m, CH_2CH)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 160.48 (<u>C</u>, Ar); 130.50 (<u>C</u>H, Ar); 122.52 (<u>C</u>H, Ar); 116.00 (<u>C</u>H, Ar); 62.16 (<u>C</u>H$_2$); 61.07 (<u>C</u>H); 40.10 (<u>C</u>H$_2$); 4.95 (<u>C</u>H$_3$)

LRMS (m/z): (M^+ 475), 449, 419, 391.

HRMS (EI): [M-CO] observed 447.9410 for $C_{17}H_{14}O_7Co_2$ theoretical 447.9403

The synthesis of hexacarbonyl 5-phenoxy-1-phenylpent-1-yn-3-ol dicobalt (177b)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **159b** (0.22 g, 0.87 mmol) and dicobalt octahexacarbonyl (0.34 g, 0.92 mmol) in dry DCM (15 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an R_f = 0.38 (petroleum ether (60 °C- 80 °C): diethyl ether, 8:2). Dark red oil crude product was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ether (9:1) to afford a dark red oil title product (4.7 g, 100%).

IR v_{max} (neat)/cm^{-1}: 3401.0 (s); 2926.9 (s); 2025.5 (m); 1725.0 (s); 1600.1 (s); 1497.0 (m); 1244.3 (w); 1044.0 (s); 753.0 (s).

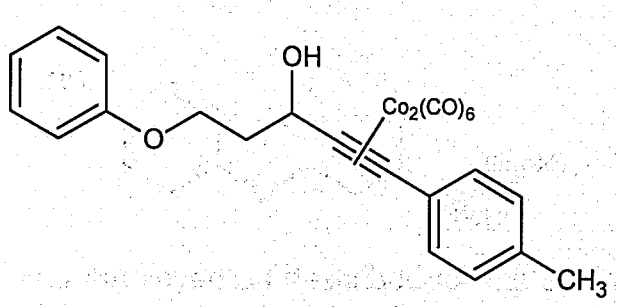
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.60-7.55 (2H, m, Ar); 7.40-7.12 (5H, m, Ar); 7.05-6.95 (3H, m, Ar); 5.40-5.35 (1H, m, C<u>H</u>); 4.41-4.31 (1H,m, OC<u>H</u>$_2$); 4.31-4.20 (1H, m, OC<u>H</u>$_2$); 2.70 (1H, d, *J* = 4.0 Hz, O<u>H</u>); 2.44-2.32 (1H, m, C<u>H</u>$_2$CH); 2.32-2.36 (1H, m, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 161.02 (<u>C</u>, Ar); 132.30 (<u>C</u>, Ar); 130.52 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 128.01 (<u>C</u>H, Ar); 123.21 (<u>C</u>H, Ar); 121.17 (<u>C</u>H, Ar); 119.10 (<u>C</u>H, Ar); 61.15 (<u>C</u>H$_2$); 61.05 (<u>C</u>H); 40.50 (<u>C</u>H$_2$).

LRMS (m/z): (M^+ 537), 481,453, 359,331, 303.

HRMS (EI): [M+NH_4] observed. 555.9843 for $C_{23}H_{16}O_8Co_2NH_4$ theoretical. 555.9847

The synthesis of hexacarbonyl 1- (4-methylphenyl)-5-phenoxypent-1-yn-3-ol dicobalt (177c)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **159c** (0.23 g, 0.94 mmol) and dicobalt octahexacarbonyl (0.35 g, 1.03 mmol) was mixed in dry DCM (10 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an R_f = 0.32 (9:1) (hexane: diethyl ether). The mixture was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ether (9:1) to afford the title product as a dark red oil (0.5 g, 98.6 %).

IR ν_{max} (neat)/cm^{-1}: 3450.3 (s); 3010.1 (s); 2101.0 (m); 2025.4 (w); 1700.6 (s); 1612.1 (s); 1267.3 (m); 1051.0 (s); 760.4 (s).

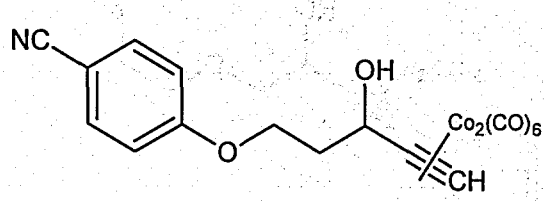
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.45-7.55 (2H, m, Ar); 7.30-7.25 (3H, m, Ar); 6.98 (2H, d, *J* = 7.5 Hz, Ar); 6.93 (2H, d, *J* = 7.5 Hz, Ar); 5.39 (1H, dt, *J* = 9.1, 3.5 Hz, C<u>H</u>OH); 4.36-4.28 (1H, m, ArOC<u>H</u>$_2$); 4.25-4.17 (1H m, ArOC<u>H</u>$_2$); 2.65 (1H, d, *J* = 3.5 Hz, O<u>H</u>); 2.39-2.35 (1H, m, C<u>H</u>$_2$CH); 2.33 (3H, s, CH_3); 2.23-2.14 (1H, m C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 138.21 (<u>C</u>, Ar); 134.23 (<u>C</u>, Ar); 132.17 (<u>C</u>, Ar); 129.72 (<u>C</u>H, Ar); 129.56 (<u>C</u>H, Ar); 129.53 (<u>C</u>H, Ar); 122.00 (<u>C</u>H, Ar); 121.15 (<u>C</u>H, Ar); 65.30 (<u>C</u>H$_2$); 60.1 (<u>C</u>H); 38.75 (<u>C</u>H$_2$); 21.40 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 570), 534, 450, 422, 387, 249.

HRMS (EI): [M+NH_4] observed 570.0001 for $C_{24}H_{18}O_8Co_2NH_4$ theoretical. 570.004

The synthesis of hexacarbonyl 4-[(3-hydroxypent-4-yn-1-yl) oxy] benzonitrile dicobalt (177d)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **159d** (0.43 g, 2.5 mmol) and dicobalt octacarbonyl (0.9 g, 2.7 mmol) dissolved in dry DCM (15 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an (R_f = 0.21, Hexane: EtOAC, 80:20). Purification *via* a column filled with the silica gel and mobile phase (8:2, hexane: diethyl ether) to afford title compound as dark red oil (0.98 g, 94%).

IR v_{max} (neat)/cm^{-1}: 3468.8 (s); 2966.7 (s); 2250.9 (m, CN); 2093.8 (m); 1605.6 (s); 1261.1 (m); 1172.0 (s).

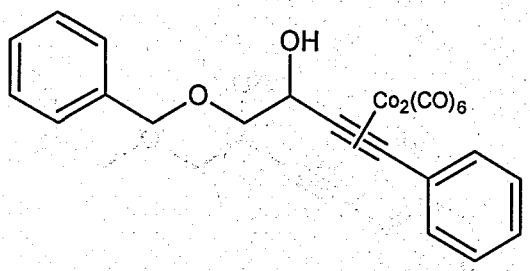
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.65 (2H, d, *J* = 8.0 Hz, Ar); 7.00-6.95 (2H, d, *J* = 8.0 Hz, Ar); 6.15-6.07 (1H, m, C<u>H</u>); 5.05 (1H, s (bd); OC<u>H</u>$_2$); 4.70 (1H, s (bd); C<u>H</u>$_2$); 4.43-4.02 (2H, m, O<u>H</u> & C≡C<u>H</u>); 2.38-1.90 (2H, m, C<u>H</u>$_2$CH)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 184.75 (<u>C</u>O); 140.90 (<u>C</u>, Ar); 138.57 (<u>C</u>, Ar); 133.61 (<u>C</u>H, Ar); 129.22 (<u>C</u>H, Ar); 115.75 (<u>C</u>N); 64.90 (<u>C</u>H$_2$); 64.68 (<u>C</u>H$_2$); 39.92 (<u>C</u>H); 38.49 (<u>C</u>H)

LRMS (m/z): (M$^+$486), 458, 430, 402, 311, 283, 255, 227, 171.

HRMS (EI): [M+H] observed 487.9230 for $C_{18}H_{12}O_8NCo_2$ theoretical 487.9226

The synthesis of hexacarbonyl 1- (benzyloxy)-4-phenylbut-3-yn-2-ol dicobalt (178a)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **174a** (0.75 g, 3 mmol) and dicobalt octa carbonyl (1.13 g, 3.3 mmol) dissoveld in dry DCM (20 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an $R_f = 0.3$, (pethrpleum ether (60 °C- 80 °C): diethyl ether 70:30) purified *via* a column filled with the silica gel and mobile phase petroleum (60 °C- 80 °C) and diethyl ether (9:1) to afford title product as a dark red oil (1.59 g, 99 - 100%).

IR ν_{max} (neat)/cm^{-1}: 3444.0 (s); 2924.0 (s); 2053.3 (m); 1755.1 (s); 1599.4 (s); 1496.2 (w); 1205.7 (m); 1114.4 (s); 737.4 (s).

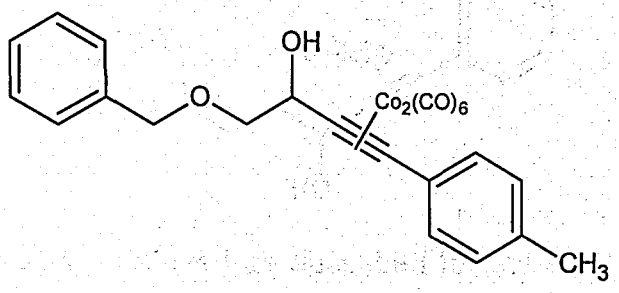
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.5-7.58 (2H, m, Ar); 7.42-7.31 (8H, m, Ar); 5.26 (1H, dt, J = 7.2, 4.0 Hz, C<u>H</u>); 3.52 (1H, d, J = 10.0 Hz, ArC<u>H$_2$</u>); 3.49 (1H, d, J = 10.0 Hz, ArCH$_2$); 3.90-3.80 (1H, m, C<u>H$_2$</u>CH); 3.80-3.75 (1H, m, C<u>H$_2$</u>CH); 2.95 (1H, d, J = 4.0 Hz, O<u>H</u>)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 200.01 (<u>C</u>O); 137.36 (<u>C</u>, Ar); 137.14 (<u>C</u>, Ar); 129.58 (<u>C</u>H, Ar); 128.85 (<u>C</u>H, Ar); 128.55 (<u>C</u>H, Ar); 128.00 (<u>C</u>H, Ar); 127.90 (<u>C</u>H, Ar); 124.13 (<u>C</u>H, Ar); 95.20 (<u>C</u>); 91.45 (<u>C</u>); 74.85 (<u>C</u>H$_2$); 73.55 (<u>C</u>H$_2$); 71.10 (<u>C</u>H)

LRMS (m/z): (M^+ 509.9), 482, 453.9, 425.9, 398.0, 369.9, 241.9, 211.9, 107.0, 91.0, 76.9.

HRMS (EI): [M-CO] observed 510.0000 for $C_{22}H_{16}O_7Co_2$ theoretical.509.9560

The synthesis of hexacarbonyl 1- (benzyloxy)-4- (4-methylphenyl) but-3-yn-2-ol dicobalt (178b)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **174b** (1.3 g, 4.9 mmol) and dicobalt octacarbonyl (1.8 g, 5.4 mmol) dissolved in dry DCM (20 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an $R_f = 0.4$, (pethroleum ether (60 °C- 80 °C): diethyl ether 70:30) purified *via* a column filled with the silica gel and mobile phase (9:1, hexane: diethyl ether) to afford title product as a dark red oil to afford title compound (2.66 g, 99%).

IR ν_{max} (neat)/cm^{-1}: 3402.0 (s); 2925.1 (s); 2055.4 (m); 1610.5 (s); 1253.3 (w); 1054.4 (s); 753.7 (s).

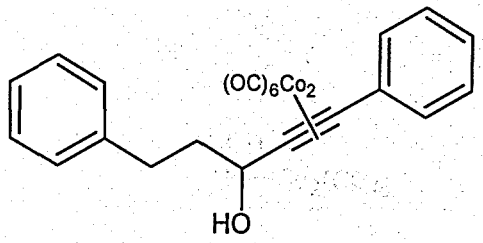
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.50 (2H, d (brd); J = 8.0 Hz, Ar); 7.45-7.35 (5H, m, Ar); 7.2 (2H, d (brd); J = 8.0 Hz, Ar); 5.35-5.30 (1H, m, C<u>H</u>); 4.62 (1H, d, J = 11.7 Hz, Ar$C\underline{H_2}$); 4.60 (1H, d, J = 11.7 Hz, Ar$C\underline{H_2}$); 3.89-3.81 (1H, m, $C\underline{H_2}CH$); 3.75-3.70 (1H, m, $C\underline{H_2}CH$); 2.80 (1H, d, J = 3.6 Hz, O<u>H</u>); 2.40 (3H, s, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.98 (<u>C</u>O); 138.11 (<u>C</u>, Ar); 137.40 (<u>C</u>, Ar); 134.39 (<u>C</u>, Ar); 132.21 (<u>C</u>H, Ar); 129.72 (<u>C</u>H, Ar); 129.59 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 127.95 (<u>C</u>H, Ar); 74.86 ($\underline{C}H_2$); 73.54 ($\underline{C}H_2$); 71.01 (<u>C</u>H); 21.43 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 551), 467, 391, 295.

HRMS (EI): [M-3CO-H] observed 466.9722 for $C_{21}H_{17}O_5Co_2$ theoretical. 466.9726

The synthesis of hexacarbonyl 1, 5-diphenylpent-1-yn-3-ol dicobalt (179)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **176** (0.79 g, 3.4 mmol) and dicobalt octacarbonyl (1.28 g, 3.74 mmol) dissolved in dry DCM (15 mL). After 1 hour tlc analysis showed the loss of the starting material and the presence of a dark red new compound with an (R_f = 0.29, hexane: diethyl ether, 80:20) purified *via* a column filled with the silica gel and mobile phase (hexane: diethyl ether, 9:1) to afford title compound (1.35 g, 77.27%).

IR v_{max} (neat)/cm^{-1}: 3471.9 (s); 2955.7 (m); 2060.2 (m); 1655.4 (s); 1500.8 (w); 1260.0 (s); 1172.0 (s).

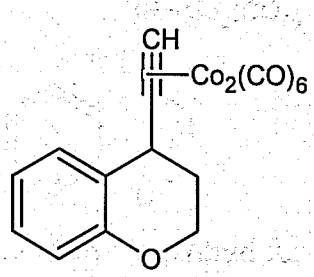
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.47-7.27 (7H, m, Ar); 7.25-7.19 (3H, m, Ar); 5.00-4.93 (1H, m, C<u>H</u>); 3.07-2.94 (1H, m, ArC<u>H</u>$_2$); 2.94-2.80 (1H, m, ArC<u>H</u>$_2$); 2.22-2.10 (1H, m, C<u>H</u>$_2$CH); 2.10-1.99 (1H, m, C<u>H</u>$_2$CH); 1.96 (1H, d, *J* = 4.5 Hz, O<u>H</u>)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 141.10 (<u>C</u>, Ar); 137.40 (<u>C</u>, Ar); 129.47 (<u>C</u>H, Ar); 128.97 (<u>C</u>H, Ar); 128.58 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 127.99 (<u>C</u>H, Ar); 126.20 (<u>C</u>H, Ar); 89.54 (<u>C</u>); 84.90 (<u>C</u>) 70.63 (<u>C</u>H); 40.88 (<u>C</u>H$_2$); 32.54 (<u>C</u>H$_2$).

HRMS (EI): [M-CO] observed 493.9611 for $C_{22}H_{16}O_6Co_2$ theoretical 493.9610

3.4.2 Novel racemic Nicholas cyclisations

The synthesis of hexacarbonyl 4-ethynyl-3, 4-dihydro-2*H*-chromene dicobalt (180)



Hexacarbonyl propargyl alcohol dicobalt **177** (0.155 g, 0.335 mmol, 1 eq) was placed in a dry round bottom flask (100 mL) in dry DCM (10 mL) under N_2. The solution then cooled in ice to 0°C whereupon $BF_3.Et_2O$ (0.1 g, 0.67 mmol, 2 eq) was added drop-wise over 5 minutes. After 5 minutes tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with an R_f = 0.86 (hexane: diethyl ether, 70:30). The reaction was quenched by the adition of distilled water (20 mL) and extract with DCM (3 x 20 mL). The organic layer was separated from the aqueous layer by a separating funnel and dried over anhydrous magnesium sulphate. The magnesium sulphate was filtered and the DCM was removed *in vacuo*. The dark red compound was purified by chromatography using the solvent system petroleum ether (60°C -80°C) and ether (90:10) and the title compound was isolated as a dark red oil (0.1 g, 67%).

IR ν_{max} (neat)/cm^{-1}: 2925.28 (w); 2854.64 (m); 2092.89 (m); 2053.40 (s); 2022.14 (s); 1487.68 (m); 1452.46 (s); 1223.52 (s); 1071.16 (s); 752.62 (s).

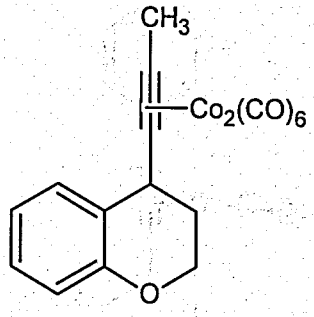
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.30 (1H, d, *J* = 7.5, Hz, Ar); 7.11 (1H, td, *J* = 8.0, 0.5 Hz, Ar); 6.87 (1H, td, *J* = 7.5, 0.5 Hz, Ar); 6.80 (1H, d, *J* = 8.0 Hz, Ar); 6.28 (1H, s (brd), C≡C<u>H</u>); 4.44-4.40 (1H, m, OC<u>H</u>$_2$); 4.30-4.24 (1H, m, OC<u>H</u>$_2$); 4.20 (1H, t, *J* = 6.2 Hz, C<u>H</u>CH$_2$); 2.50-2.38 (1H, m, CHC<u>H</u>$_2$); 2.23-2.10 (1H, m, CHC<u>H</u>$_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 130.35 (<u>C</u>, Ar); 129.75 (<u>C</u>, Ar); 128.47 (<u>C</u>H, Ar); 122.30 (<u>C</u>H, Ar); 120.61 (<u>C</u>H, Ar); 117.12 (<u>C</u>H, Ar); 63.83 (<u>C</u>H$_2$); 37.38 (<u>C</u>H$_2$); 31.91 (<u>C</u>H).

LRMS (m/z): (M^+ 444), 399, 352, 305, 261, 217.

HRMS (EI): [M-CO] observed 415.9136 $C_{16}H_{10}O_6Co_2$ theoretical 415.9136.

The synthesis of hexacarbonyl 4- (prop-1-yn-1-yl)-3, 4-dihydro-2*H*-chromene dicobalt (180a)



The same method was employed as described for the synthesis of the **180** with the following quantities obalt complex propargyl alcohol **177a** (0.5 g, 1 mmol); $BF_3.Et_2O$ (0.3 g, 2 mmol) mixed in dry DCM (10 mL) after 5 minutes tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with aR_f = 0.9 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). The dark red oil was purified by chromatography on silica using the solvent system petroleum ether (60°C -80°C) and ether (90:10); dark red oil was isolated (0.45 g, 93.5 %).

IR ν_{max} (neat)/cm^{-1}: 2927.9 (m); 2088.0 (s); 2046.3 (s); 2015.0 (s); 1604.9 (s); 1582.8 (s); 1488.3 (s); 1267.0 (m); 1011.6 (s); 753.5 (s).

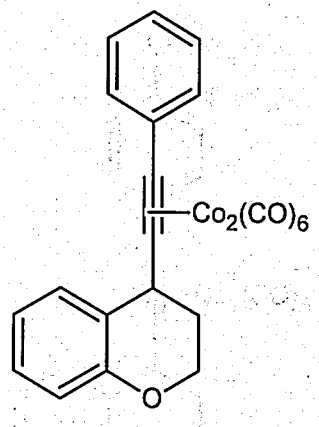
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.25-7.20 (1H, m, Ar); 7.16-7.10 (1H, m, Ar); 6.90-6.85 (1H, m, Ar); 6.85-6.78 (1H, m, Ar); 4.42-4.34 (1H, m, C<u>H</u>); 4.30-4.25 (1H, m, OC<u>H</u>$_2$); 4.23 (1H, m, OC<u>H</u>$_2$); 2.77 (3H, d (br); *J* = 0.5 Hz, Me); 2.50-2.40 (1H, m, C<u>H</u>$_2$CH); 2.25-2.17 (1H, m, C<u>H</u>$_2$CH)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 130.17 (<u>C</u>, Ar); 128.52 (<u>C</u>, Ar); 120.38 (<u>C</u>H, Ar); 117.24 (<u>C</u>H, Ar); 80.45 (<u>C</u>); 77.23 (<u>C</u>); 63.45 (<u>C</u>H$_2$); 37.32 (<u>C</u>H); 30.67 (<u>C</u>H$_2$); 20.30 (<u>C</u>H$_3$).

LRMS (m/z): (M$^+$454), 427, 405, 387, 305, 261, 217, 173

HRMS (EI): [M-CO] observed 429.9295 for $C_{17}H_{12}O_6Co_2$ theoretical 429.9297

The synthesis of hexacarbonyl 4- (phenylethynyl)-3, 4-dihydro-2*H*-chromene dicobalt (180b)



The same method was employed as described for the synthesis of the **180** with the following quantities hexa carbonyl propargyl alcohol dicobalt **177b** (0.46 g, 0.85 mmol); $BF_3.Et_2O$ (0.25g, 1.71mmol) mixed in dry DCM (10 mL) after 5 minutes tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with aR_f = 0.81 (Petroleum ether (60 °C- 80 °C): diethyl ether, 90:20). The dark red oil was purified by chromatography on silica using the solvent system petroleum ether (60°C -80°C) and ether (90:10); dark red oil compound was isolated (0.397 g, 89.21 %).

IR ν_{max} (neat)/cm^{-1}: 2934.5 (m); 2100.8 (w); 2057.9 (s); 2028.0 (s); 1589.0 (s); 1490.5 (s); 1225.5 (m); 1075.6 (s); 761.5 (s).

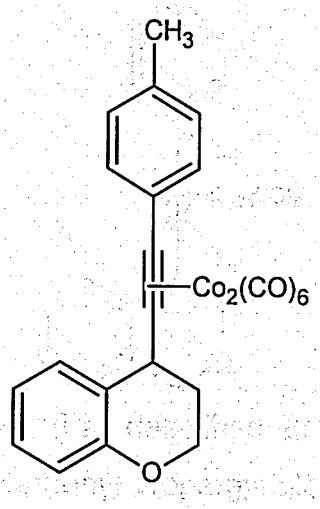
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.40-7.30 (5H, m, Ar); 7.10-7.00 (2H, m, Ar); 6.80- 6.75 (1H, m, Ar); 6.75-6.65 (1H, m, Ar); 4.4 (1H, t, *J* = 6.0 Hz, C<u>H</u>); 4.30-4.10 (2H, m, OC<u>H</u>$_2$); 2.50-2.42 (1H, m, C<u>H</u>$_2$CH); 2.20- 2.10 (1H, m, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 211.00 (<u>C</u>O); 155.60 (<u>C</u>, Ar); 131.50 (<u>C</u>, Ar); 130.35 (<u>C</u>, Ar); 129.00 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 127.90 (<u>C</u>H, Ar); 125.55 (<u>C</u>H, Ar); 122.32 (<u>C</u>H, Ar); 121.30 (<u>C</u>H, Ar); 118.35 (<u>C</u>H, Ar); 63.10 (<u>C</u>H$_2$); 32.50 (<u>C</u>H$_2$); 38.70 (<u>C</u>H).

LRMS (m/z): (M^+492), 463, 408, 380, 368, 233, 180

HRMS (EI): [M-CO] observed 491.9001 for $C_{22}H_{14}O6Co_2$ theoretical 491.002

The synthesis of hexacarbonyl 4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene dicobalt (180c)



The same method was employed as described for the synthesis of the **180** with the following quantities hexacarbonyl propargyl alcohol dicobalt **177c** (0.7 g, 1.27 mmol); $BF_3.Et_2O$ (0.36 g, 2.54 mmol) mixed in dry DCM (10 mL) after 5 minutes tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with a R_f = 0.86 (Petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). A dark red oil was isolated by chromatography on silica using a solvent system petroleum ether (60°C-80°C) and ether (90:10) (0.5 g, 75%).

IR ν_{max} (neat)/cm^{-1}: 2100.8 (s); 1952.1 (s); 1723.2 (m); 1560.0 (m); 765.0 (w).

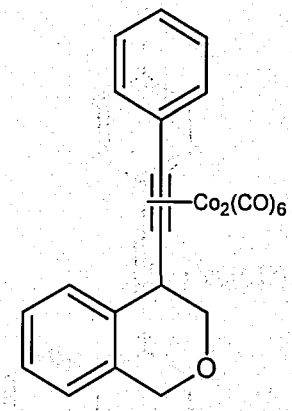
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.70 (1H, dd, *J* = 5.6, 3.4 Hz, Ar); 7.53 (1H, dd, *J* = 5.6, 3.4 Hz, Ar); 7.34 (1H, d, *J* = 8.0 Hz, Ar); 7.20-7.05 (3H, m, Ar); 7.00-6.89 (1H, m, Ar); 6.83 (1H, d, *J* = 8.0 Hz, Ar); 4.45-4.30 (1H, m, OC$\underline{H}_2$); 4.32-4.10 (1H, m, OC$\underline{H}_2$); 4.21 (1H, t, *J* = 5.7 Hz, C$\underline{H}$); 1.40-1.32 (1H, m, C$\underline{H}_2$CH); 1.21-1.09 (1H, m, C$\underline{H}_2$CH); 0.95 (3H, s, C$\underline{H}_3$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 200.00 ($\underline{C}$O); 134.08 ($\underline{C}$, Ar); 132.40 ($\underline{C}$, Ar); 131.59 ($\underline{C}$, Ar); 130.67 ($\underline{C}$, Ar); 130.55 ($\underline{C}$H, Ar); 129.36 ($\underline{C}$H,Ar); 128.50 ($\underline{C}$H,Ar); 128.31 ($\underline{C}$H, Ar); 128.0 ($\underline{C}$H, Ar); 127.50 ($\underline{C}$H, Ar); 68.25 ($\underline{C}H_2$); 38.85 ($\underline{C}H_2$); 30.45 ($\underline{C}$H); 29.55 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 534), 450, 422, 387, 249

HRMS (EI): [M^+] observed 534.9630 for $C_{24}H_{16}O_7Co_2$ theoretical 534.9628

The synthesis of hexacarbonyl 4- (phenylethynyl)-3, 4-dihydro-1*H*-isochromene dicobalt (181a)



The same method was employed as described for the synthesis of the **180** with the following quantities hexacarbonyl propargyl alcohol dicobalt **178a** (1 g, 1.86 mmol); $BF_3.Et_2O$ (0.5 g, 3.71 mmol) mixed in dry DCM (15 mL) after 10 mintues tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with an $R_f = 0.83$ (Petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). The crude red oil was purified by chromatography on silica using a solvent system petroleum ether (60 °C- 80 °C) and diethyl ether (90:10); (0.75 g, 77.6 %).

IR ν_{max} (neat)/cm^{-1}: 2260.9 (s); 2112.5 (s); 1665.0 (m); 1251.7 (w); 705.1 (w).

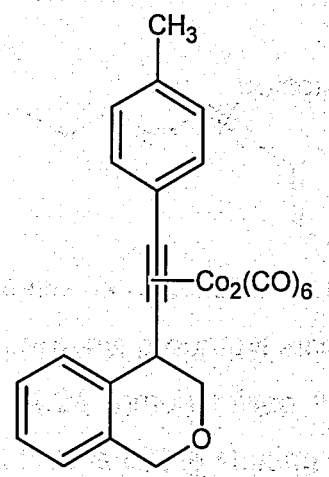
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.53-7.51 (3H, m, Ar); 7.45-7.44 (2H, m, Ar); 7.38-7.31 (2H, m, Ar); 7.21-7.00 (2H, m, Ar); 5.03 (1H, dd, *J* = 6.2, 4.7 Hz, C<u>H</u>); 4.57 (1H, d, *J* = 11.6 Hz, ArC<u>H</u>$_2$O); 4.53 (1H, d, *J* = 11.6 Hz, ArC<u>H</u>$_2$O); 3.87 (1H, dd, *J* = 9.8, 6.2 Hz, C<u>H</u>$_2$CH); 3.80 (1H, dd, *J* = 9.8, 4.7 Hz, C<u>H</u>$_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.40 (<u>C</u>O); 139.51 (<u>C</u>, Ar); 137.55 (<u>C</u>, Ar); 130.80 (<u>C</u>, Ar); 128.85 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 127.88 (<u>C</u>H, Ar); 127.49 (<u>C</u>H, Ar); 95.48 (<u>C</u>); 91.60 (<u>C</u>); 75.58 (<u>C</u>H$_2$); 73.72 (<u>C</u>H$_2$); 72.00 (<u>C</u>H).

LRMS (m/z): (M^+409), 385, 368, 353, 323, 301, 246, 217, 202, 181, 165.

HRMS (EI): [M-CO] Observed 491.9460 for $C_{22}H_{14}O_6Co_2$ theoretical 491.9454

The synthesis of hexacarbonyl 4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-1*H*-isochromene dicobalt (181b)



The same method was employed as described for the synthesis of the **180** with the following quantities hexacarbonyl propargyl alcohol dicobalt **178b** (1.97 g, 3.6 mmol); $BF_3.Et_2O$ (1.2 g, 7.2 mmol) mixed in dry DCM (20 mL) after 10 mintues tlc analysis showed the loss of the starting material and the presence of a faster moving new compound with an $R_f = 0.7$ (hexane: diethyl ether, 80:20). Reaction was quenched with distil water and extract with DCM (3 x 20 mL). Organic layer was separated from aqueous by a separating funnel and dried over magnesium sulphate, filtered, and DCM was removed *via vacuum*. Dark red oil compound was purified by by chromatography on silica using a solvent system petroleum ether (60 °C- 80 °C) and ether (90:10); dark red oil compound was isolated (1.36 g, 71.2%).

IR ν_{max} (neat)/cm^{-1}: 2821.5 (m); 2290.8 (m); 2030.2 (s); 1951.5 (s); 1722.2 (s); 1665.1 (m); 1006.5 (s); 895.0 (s).

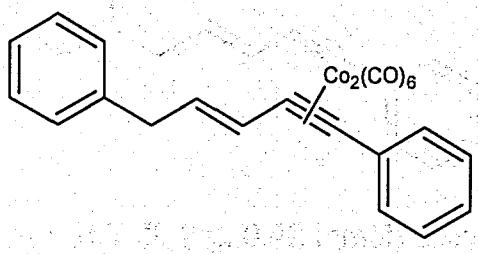
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.45-7.21 (6H, m, Ar); 7.12-6.97 (2H, m, Ar); 4.90 (1H, s (brd); C<u>H</u>); 4.77-4.62 (2H, m (brd); ArC<u>H</u>$_2$O); 3.98-3.68 (2H, m (brd); C<u>H</u>$_2$CH); 2.36 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 152.90 (<u>C</u>, Ar); 138.10 (<u>C</u>, Ar); 134.12 (<u>C</u>, Ar); 130.80 (<u>C</u>, Ar); 129.59 (<u>C</u>H, Ar); 129.42 (<u>C</u>H, Ar); 128.50 (<u>C</u>H Ar); 128.31 (<u>C</u>H Ar); 127.95 (<u>C</u>H Ar); 127.70 (<u>C</u>H Ar); 90.00 (<u>C</u>); 89.63 (<u>C</u>); 77.23 (<u>C</u>H$_2$); 74.98 (<u>C</u>H$_2$); 73.52 (<u>C</u>H); 21.42 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 534), 506, 450, 422, 360, 295, 249, 181.

HRMS (EI): [M+H] Observed 534.9621 for $C_{24}H_{17}O_7Co_2$ theoretical 534.9633

The synthesis of hexacarbonyl 1, 1'- (3*E*)-pent-3-en-1-yne-1, 5-diyldibenzene dicobalt (183)



The same method was employed as described for the synthesis of the **180** with the following quantities, hexacarbonyl propargyl alcohol dicobalt **179** (0.5 g, 2.12 mmol) and $BF_3.Et_2O$ (0.6 g, 4.24 mmol) mixed in dry DCM (15 mL) after 5 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.4 (hexane: diethyl ether, 70:30). Purification *via* column chromatography on silica gel with mobile phase hexane: diethyl ether 80:20 affords dark red oil as a product (0.3 g, 62.5%).

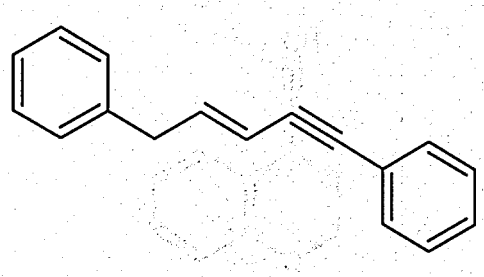
IR v_{max} (neat)/cm^{-1}: 2300.1 (s); 2050.0 (s); 1954.5 (s); 1662.1 (m); 1001.5 (m); 891.0 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.56-7.50 (2H, m, Ar); 7.40-7.27 (5H, m, Ar); 7.3-7.2 (3H, m, Ar); 6.83 (1H, d, *J* = 14.8 Hz, =C<u>H</u>C≡C); 6.38 (1H, dt, *J* = 14.8, 7.0 Hz, =C<u>H</u>); 3.59 (2H, d, *J* = 7.0 Hz, CH_2)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.35 (<u>C</u>O); 139.40 (<u>C</u>, Ar); 138.38 (<u>C</u>, Ar); 136.65 (<u>C</u>H, Ar); 129.22 (<u>C</u>H, Ar); 128.92 (<u>C</u>H, Ar); 128.50 (<u>C</u>H, Ar); 127.88 (<u>C</u>H, Ar); 126.39 (<u>C</u>H, Ar); 92.78 (<u>C</u>); 90.14 (<u>C</u>); 39.22 (<u>C</u>H); 29.75 (<u>C</u>H); 14.17 (<u>C</u>H_2).

HRMS (EI): [M-CO] observed 475.9507 for $C_{22}H_{14}O_5Co_2$ theoretical 475.9505

The synthesis of 1, 1'- (3*E*)-pent-3-en-1-yne-1, 5-diyldibenzene (184)



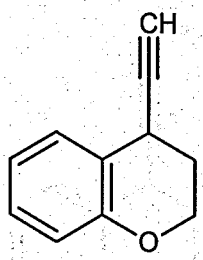
The cobalt complex cluster **183** (0.2 g, 0.42 mmol) dissolved in methnol (10 mL) cool down to 0 °C while solution was stirred, saturated solution of the CAN in methanol (20 mL) was added drop wise untill dark red colour vanished. After 10 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.55 (Hexane. EtOAC, 80:20). Saturated solution of $NaHCO_3$ (30 mL) was added to the solution directly and extract with diethyl ether (3 x 20 mL). The organics were isolated and dried using anhydrous magnesium sulphate. Filtration and solvent removal *in vacuo* provided a crude product. Purification was carried out *via* flash chromatography using silica gel (hexane: diethyl ether, 80:20) to afford the title compound as a colourless oil (72 mg, 78%)

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.43 – 7.39 (2H, m, Ph), 7.34 – 7.27 (5H, m, Ph), 7.25 – 7.18 (3H, m, Ph), 6.40 (1H, dt, J= 15.8, 7.0 Hz, $CH_2C\underline{H}$=CH), 5.7 (1H, ddd (dt), J = 15.8, 1.5 Hz, CH_2CH=$C\underline{H}$), 3.50 (2H, dd, J = 7.0, 1.5 Hz, CH_2)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 142.95 ($\underline{C}$=C); 138.89 ($\underline{C}$, Ar); 131.46 ($\underline{C}$, Ar); 128.74 ($\underline{C}$H, Ar); 128.60 ($\underline{C}$H, Ar); 128.29 ($\underline{C}$H, Ar); 128.02 ($\underline{C}$H, Ar); 126.45 ($\underline{C}$H, Ar); 123.45 ($\underline{C}$H, Ar); 110.92 (C=$\underline{C}$); 88.73 ($\underline{C}$≡C); 87.96 (C≡$\underline{C}$); 39.44 ($\underline{C}H_2$).

HRMS (EI): [M^+] observed 219.1023 for $C_{17}H_{15}$ theoretical 219.1020

The synthesis of 4-ethynyl-3, 4-dihydro-2*H*-chromene (185)



The cobalt complex cluster **180** (0.1 g, 0.23 mmol) dissolved in methnol (10 mL) cool down to 0 °C while solution was stirred, saturated solution of the CAN in methanol (20 mL) was added drop wise untill dark red colour vanished. After 10 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.6 (Hexane. EtOAC, 90:10). Saturated solution of $NaHCO_3$ (30 mL) was added to the solution directly and extract with diethyl ether (3 x 20 mL). The organics were isolated and dried using anhydrous magnesium sulphate. Filtration and solvent removal *in vacuo* provided a crude product. Purification was carried out *via* flash chromatography using silica gel (hexane: diethyl ether, 90:10) to afford the title compound as a colourless oil (87 mg, 97%)

IR v_{max} (neat)/cm^{-1}: 3311.10 (w); 2925.0 (s); 2054.1 (w); 2025.9 (w); 1606.3 (w); 1268.7 (m); 1019.3 (m); 752.0 (m).

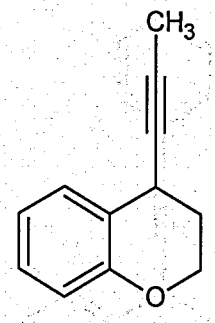
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.36-7.30 (1H, m, Ar); 7.17-7.07 (1H, m, Ar); 6.90-6.80 (2H, m, Ar); 4.39-4.30 (1H, m, OC$\underline{H}_2$); 4.22-4.15 (1H, m, OC$\underline{H}_2$); 3.85 (1H, td, *J* = 6.0, 2.5, C$\underline{H}$); 2.27-2.20 (1H, m, CHC$\underline{H}_2$); 2.22 (1H, d, *J* = 2.5 Hz, C≡C$\underline{H}$); 2.14 (1H, m, CHC$\underline{H}_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 153.79 ($\underline{C}$, Ar); 129.58 ($\underline{C}$, Ar); 128.53 ($\underline{C}$H, Ar); 121.17 ($\underline{C}$H, Ar); 120.61 ($\underline{C}$H, Ar); 117.07 ($\underline{C}$H, Ar); 85.85 ($\underline{C}$); 70.04 ($\underline{C}$H); 64.11 ($\underline{C}H_2$); 29.75 ($\underline{C}H_2$); 28.80 ($\underline{C}$H).

LRMS (m/z): (M^+ 157), 139, 128, 115, 102, 89, 77, 63, 51.

HRMS (EI): [M^+] observed 158.0722 for $C_{11}H_{10}O$ theoretical 158.0726.

The synthesis of 4- (prop-1-yn-1-yl)-3, 4-dihydro-2*H*-chromene (185a)



The same method was employed as described for the synthesis of the **185** with the following quantities, Cobalt complex cluster **180a** (0.4g, 0.87mmol); saturated solution of the CAN (35 mL). After 10 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.4 (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20). Purification have carried out *via* flash chromatography (hexan: diethyl ether, 90:10) to afford the title compound as a colourless oil (137 mg, 91.3 %).

IR v_{max} (neat)/cm^{-1}: 2925.04(w); 2054.16(w); 1584.16(s); 1226.26(s); 752.01(m).

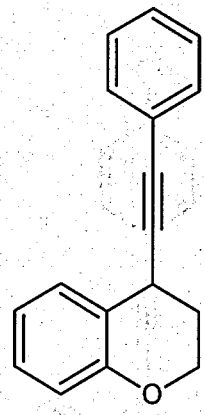
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.36-7.33 (1H, m, Ar); 7.15-7.08 (1H, m, Ar); 6.89 (1H, dd, *J* = 7.5, 1.3 Hz, Ar); 6.79 (1H, dd, *J* = 7.5, 1.3 Hz, Ar); 4.38-4.30 (1H, m, OC$\underline{H}_2$); 4.20-4.10 (1H, m, OC$\underline{H}_2$); 3.82-3.75 (1H, m, C$\underline{H}$); 2.23-2.14 (1H, m, C$\underline{H}_2$CH); 2.13-2.03 (1H, m, C$\underline{H}_2$CH); 1.83 (3H, d, *J*= 2.5 Hz, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 153.75 ($\underline{C}$, Ar); 129.70 ($\underline{C}$, Ar); 128.27 ($\underline{C}$H, Ar); 120.43 ($\underline{C}$H, Ar); 116.92 ($\underline{C}$H, Ar); 80.91 ($\underline{C}$); 78.05 ($\underline{C}$); 64.34 ($\underline{C}H_2$); 39.30 ($\underline{C}H_2$); 29.45 ($\underline{C}$H); 3.64 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 172), 157,144, 128, 115, 89, 77, 63, 51

HRMS (EI): [M^+] observed 172.0885 for $C_{12}H_{12}O$ theoretical 172.0883

The synthesis of 4- (phenylethynyl)-3, 4-dihydro-2*H*-chromene (185b)



The same method was employed as described for the synthesis of the **185** with the following quantities, Cobalt complex cluster **180b** (0.3g, 0.58mmol); saturated solution of the CAN (35 mL). After 10 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.67 (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20). Purification have carried out *via* flash chromatography (hexane: diethyl ether, 80:20) to afford colourless oil (101 mg, 74.81%).

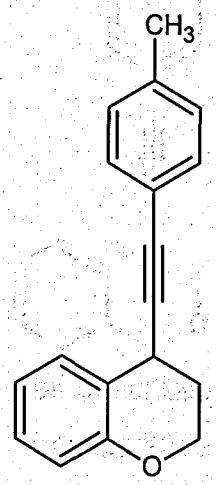
IR ν_{max} (neat)/cm^{-1}: 2976.43 (w); 2060.16(m); 1600.20(s); 1230.29 (s); 1120.32 (s); 765.31(m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.52-7.44 (3H, m, Ar); 7.32 (2H, t, *J* = 3.2 Hz, Ar); 7.25-7.15 (1H, m, Ar); 6.90-6.85 (1H, m, Ar); 6.70-6.60 (2H, m, Ar); 4.44 (1H, ddd, *J* = 11.0, 7.5, 3.0 Hz, OC$\underline{H}_2$); 4.26 (1H, ddd, *J* = 11.0, 7.5, 3.0 Hz,OC$\underline{H}_2$); 4.10 (1H, t, *J* = 6.2 Hz, C$\underline{H}$); 2.26-2.04 (2H, m, C$\underline{H}_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 153.93 ($\underline{C}$, Ar); 131.74 ($\underline{C}$, Ar); 129.86 ($\underline{C}$, Ar); 128.45 ($\underline{C}$H, Ar); 128.31 ($\underline{C}$H, Ar); 128.04 ($\underline{C}$H, Ar); 123.43 ($\underline{C}$H, Ar); 121.88 ($\underline{C}$H, Ar); 120.64 ($\underline{C}$H, Ar); 117.07 ($\underline{C}$H, Ar); 91.31 ($\underline{C}$); 82.21 ($\underline{C}$); 64.44 ($\underline{C}H_2$); 39.16 ($\underline{C}H_2$); 28.13 ($\underline{C}$H).

HRMS (EI): [M^+] observed 234.1044 for $C_{17}H_{14}O_1$ theoretical 234.1039.

The synthesis of 4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene (185c)



The same method was employed as described for the synthesis of the **185** with the following quantities, Cobalt complex **180c** (0.5 g, 0.93 mmol) followed by saturated solution of the CAN in methanol (35 mL). After 10 mintues tlc analysis showed the loss of the starting material and the presence of a new compound with an R_f = 0.87 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification have carried out *via* flash chromatography (petroleum ether (60 °C-80 °C): diethyl ether, 90:10) to afford the title compound as a colourless oil (188 mg, 81%).

IR vmax (neat)/cm^{-1}: 2907.3 (w), 2845.8 (w), 2035.0 (w), 1512.2 (s), 1265.3 (s), 760.2 (m).

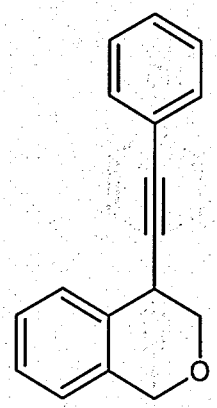
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.55-7.36 (2H, m, Ar); 7.13-7.07 (3H, m, Ar); 6.90-6.70 (3H, m, Ar); 4.75-4.67 (1H, m, OC$\underline{H_2}$); 4.67-4.60 (1H, m, OC$\underline{H_2}$); 4.50 (1H, dd, *J* = 6.5, 4.5 Hz, C$\underline{H}$); 3.95-3.90 (1H, m, C$\underline{H_2}$CH); 3.60-3.50 (1H, m, C$\underline{H_2}$CH); 2.34 (3H, s, C$\underline{H_3}$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 154.52 ($\underline{C}$, Ar); 138.15 ($\underline{C}$, Ar); 132.21 ($\underline{C}$, Ar); 132.11 ($\underline{C}$, Ar); 128.69 ($\underline{C}$H, Ar); 126.75 ($\underline{C}$H, Ar); 124.50 ($\underline{C}$H, Ar); 120.53 ($\underline{C}$H, Ar); 119.76 ($\underline{C}$H, Ar); 114.95 ($\underline{C}$H, Ar); 90.40 ($\underline{C}$); 81.34 ($\underline{C}$); 66.05 ($\underline{C}H_2$); 38.70 ($\underline{C}H_2$); 25.55 ($\underline{C}$H); 24.33 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 248), 233, 157, 144, 128, 115 (100%), 89, 77, 63, 51.

HRMS (EI): [M^+] observed 247.1117 for $C_{18}H_{16}O$ theoretical 247.1117

The synthesis of 4- (phenylethynyl)-3, 4-dihydro-1*H*-isochromene (186a)



The same method was employed as described for the synthesis of the **185** with the following quantities, cobalt complex **181a** (0.35 g, 0.67 mmol); saturated solution of the CAN in methanol (30 mL). After 10 mintues tlc analysis with an R_f = 0.6 (petroleum ether (60 °C - 80 °C): diethyl ether, 80:20) showed the loss of the starting material and the presence of a new compound. Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 90:10) to afford the title compound as a colourless oil (0.13 g, 89%).

IR ν_{max} (neat)/cm^{-1}: 2974.2 (w), 2850.1 (w), 2162.4 (w), 1463.5 (s), 864.5 (s); 755.0 (s).

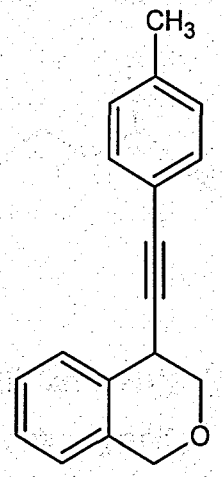
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.62 (1H, dd, *J* = 7.5, 1.7, Hz, Ar); 7.51-7.45 (2H, m, Ar); 7.35-7.26 (4H, m, Ar); 6.99 (1H, dd, *J* = 7.5, 1.0 Hz, Ar); 6.94 (1H, dd, *J* = 8.1, 1.0 Hz, Ar); 4.57 (1H, d, *J* = 11.7 Hz, Ar C$\underline{H}_2$O); 4.53 (1H, d, *J* = 11.7 Hz, Ar C$\underline{H}_2$); 4.05 (1H, dd, *J* = 6.5, 3.0 Hz, C$\underline{H}$); 3.90-3.85 (1H, m, C$\underline{H}_2$CH); 3.84-3.80 (1H, m, C$\underline{H}_2$CH).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 137.66 ($\underline{C}$, Ar); 131.81 ($\underline{C}$, Ar); 131.80 ($\underline{C}$, Ar); 128.59 ($\underline{C}$H, Ar); 128.55 ($\underline{C}$H, Ar); 128.29 ($\underline{C}$H, Ar); 127.96 ($\underline{C}$H, Ar); 127.86 ($\underline{C}$H, Ar); 122.10 ($\underline{C}$H, Ar); 118.14 ($\underline{C}$H, Ar); 86.64 ($\underline{C}$); 85.63 ($\underline{C}$); 73.62 ($\underline{C}H_2$); 73.50 ($\underline{C}H_2$); 32.25 ($\underline{C}$H).

LRMS (m/z): (M^+ 234), 202, 165, 128, 121(100%), 115, 92, 91, 65, 51.

HRMS (EI): [M+H] observed 235.1118 for $C_{17}H_{15}O$, theoretical 235.1117

The synthesis of 4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-1*H*-isochromene (186b)



The same method was employed as described for the synthesis of the **185** with the following quantities. Cobalt complex **181b** (1.00 g, 1.87 mmol); saturated solution of the CAN in methanol (35 mL). After 10 mintues tlc analysis with an R_f = 0.64 (hexane: diethyl ether, 70:30), showed the loss of the starting material and the presence of a new compound. Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) to afford the title compound as a colourless oil (0.395 g, 86 %).

IR v_{max} (neat)/cm^{-1}: 2935.0 (w), 2855.6 (w), 2198.2 (w), 1504.1 (s), 862.5 (S), 726.0 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.48 (1H, d, *J* = 8.0 Hz, Ar); 7.41-7.36 (2H, m, Ar); 7.32-7.26 (2H, m, Ar); 7.18-7.10 (1H, m, Ar); 6.98-6.82 (2H, m, Ar); 4.60 (1H, d, J=11.5 Hz, Ar C$\underline{H}_2$O); 4.55 (1H, d, *J* = 11.5 Hz, ArC$\underline{H}_2$O); 3.98 (1H, dd, *J* = 6.5, 3.0 Hz, C$\underline{H}$); 3.87-3.84 (1H, m, C$\underline{H}_2$CH); 3.66-3.57 (1H, m, C$\underline{H}_2$CH); 3.25 (3H, s, Me).

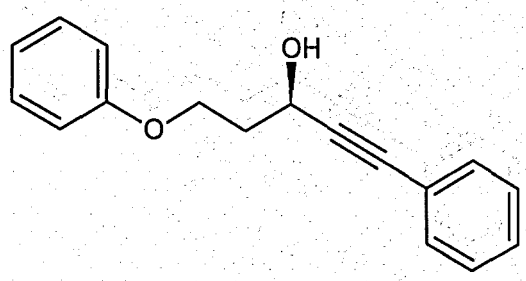
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 138.60 ($\underline{C}$, Ar); 138.20 ($\underline{C}$, Ar); 131.76 ($\underline{C}$, Ar); 131.73 ($\underline{C}$, Ar); 128.43 ($\underline{C}$H, Ar); 128.12 ($\underline{C}$H, Ar); 127.83 ($\underline{C}$H, Ar); 127.75 ($\underline{C}$H, Ar); 127.65 ($\underline{C}$H, Ar); 119.49 ($\underline{C}$H, Ar); 86.45 ($\underline{C}$); 85.21 ($\underline{C}$); 72.55 ($\underline{C}H_2$); 73.49 ($\underline{C}H_2$); 29.50 ($\underline{C}$H); 25.23 ($\underline{C}H_3$).

LRMS (m/z): (M^+ 248), 233, 157, 133, 121(100%), 115, 94, 73, 51

HRMS (EI): [M+H] observed 249.1274 for $C_{18}H_{17}O$ theoretical 249.1274

3.4.3 Novel chiral Nicholas cyclisations

The synthesis of (3R)-5-phenoxy-1-phenylpent-1-yn-3-ol (187a)

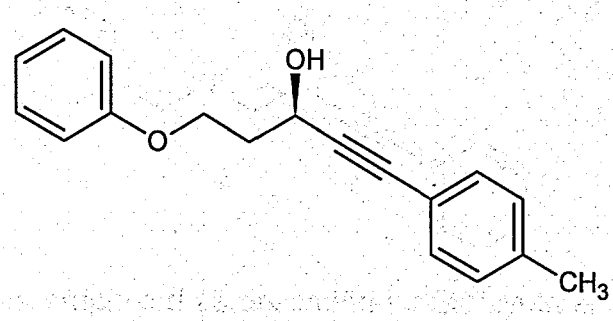


A 100 mL flask was charged with Zn $(OTf)_2$ (0.67 g, 1.84 mmol) and (+)- (1S, 2R-N-methylephedrine (0.36 g, 2 mmol) and p

urged with N_2, stirred for 15 min whereupon toluene (20 mL) and triethylamine (Et_3N) (0.4 g, 4.0 mmol) was added *via* a syringe. The resulting mixture was left to stir for 2 hours before the phenylacetylene (0.5 g, 5.0 mmol) was added by syringe in one portion. After 15 minutes of stirring aldehyde **160** (0.25 g, 1.67 mmol) was added in one portion. After completion 7 days, tlc checking showed finishing the starting material and presence of a new compound with an R_f = 0.26 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: ethyl acetate, 85:15) gave the title product as a colourless oil (0.32 g, 76.2%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **159b**. The following additional data was obtained. $[\alpha]_D$ = +17 ° (c = 1% diethyl ether); ee%= 50.45, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 7.49 major (74.61%),t_R = 14.38 minor (25.38%).

HRMS (EI): $[M+NH_4]$ observed 270.1491 for ($C_{17}H_{16}O_2NH_4$) theoretical 270.1489

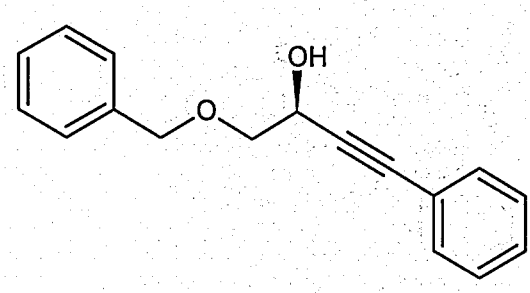
The synthesis of (3R)-1- (4-methylphenyl)-5-phenoxypent-1-yn-3-ol (187b)



The same method was employed as described for the synthesis of compound **187a**, Zn $(OTf)_2$ (1.20 g, 3.3 mmol) and (+)- (1S, 2R)-Nmethylephedrine (0.65 g, 3.6 mmol) and purged with N_2 in ambient temperature, stirred for 15 min whereupon toluene (10 mL) and triethylamine (Et_3N) (0.75 g, 7.4 mmol) was added *via* a syringe. After 2 hours, 1-ethynyl-4-methylbenzene (1.044 g, 9.0 mmol) was added by syringe in one portion. After 15 minutes of stirring aldehyde **160** (0.45 g, 3.0 mmol) was added it took 7-10 days to complete the reaction and tlc monitoring showed less amount of the remained and revealed a new spot in R_f = 0.3 (hexane: diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: ethyl acetate, 80:20) gave the title product as a colourless oil (0.19 g, 63.0%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **159b**. The following additional data was obtained. $[a]_D^{23}$ = +12 ° (c = 1%, diethyl ether), ee% = 73.8%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 19.65 major (87%), t_R = 23.98 minor (13%).

HRMS (EI): [M^+] observed 266.1300 for $C_{18}H_{17}O_2$ theoretical 266.1301

The synthesis of (2*S*)-1- (benzyloxy)-4-phenylbut-3-yn-2-ol (188a)



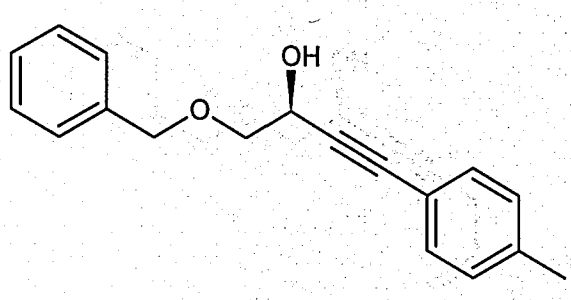
The same method was employed as described for the synthesis of the **187a** with thw following quantities; Zn $(OTf)_2$ (1.87 g, 5.14 mmol) and (+)- (1S, 2R)-*N*-methylephedrine (1.0 g, 5.60 mmol) and purged with N_2 in ambient temperature, stirred for 15 minutes whereupon toluene (10 mL) and triethylamine (Et_3N) (1.13 g, 11.21 mmol) was added *via* a syringe. After 2 h phenylacetylene (1.43 g, 14.01 mmol) was added by syringe in one portion. After 15 minutes of stirring aldehyde **173** (0.7 g, 4.67 mmol) was added. After 7-10 days to complete the reaction and tlc monitoring showed a new spot in R_f = 0.2 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: ethyl acetate, 80:20) gave the title product as a colourless oil (1.02 g, 87.0%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **174a**. The following additional data was obtained. $[\alpha]_D$ = + 15 ° (c = 1%, diethyl ether) ee% = 80.6%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 28.99 major (90.3%), t_R = 23.97 minor (9.7%).

For the enantiomer of **188a** same method has been employed how ever (-) - (1S, 2R)-N-methylephedrine have been used. The following additional data was obtained, $[\alpha]_D$ = - 15 ° (c = 1%, diethyl ether) ee% = 80.5%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 28.99 major (90.25%), t_R = 23.97 minor (9.75%).

HRMS (EI): $[M+NH_4]$ observed 270.1491for $C_{17}H_{16}O_2NH_4$ theoretical 270.1489

The synthesis of (2*S*)-1- (benzyloxy)-4- (4-methylphenyl) but-3-yn-2-ol

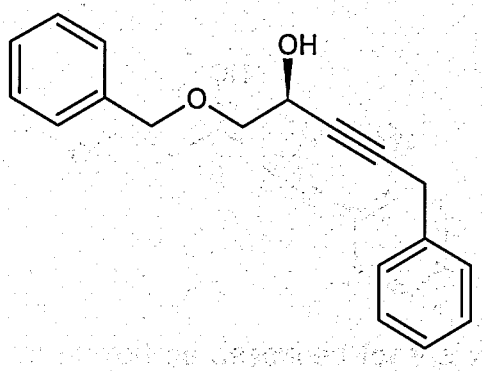
(188b)



The same method was employed as described for the synthesis of compound **187a**, with the following quantites Zn $(OTf)_2$ (1.87 g, 5.14 mmol) and (+)- (1S, 2R)-*N*-methylephedrine (1.0 g, 5.6 mmol) and purged with N_2, stirred for 15 min whereupon toluene (10 mL) and triethylamine (Et_3N) (1.13 g, 11.2 mmol) was added *via* a syringe. After 2 h 1- ethynyl – 4 - methylbenzene (1.62 g, 14.0 mmol) was added by syringe in one portion. After 15 minutes of stirring aldehyde **173** (0.7 g, 4.67 mmol) was added. After 7-10 days to complete the reaction and tlc monitoring revealed the finishing of the starting material and presence of a new spot with an R_f = 0.15 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 85:15) gave the title product as a colourless oil (1.0 g, 86.20%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **174b**. The following additional data was obtained. $[\alpha]_D$ = - 8 ° (c = 1%, diethyl ether); ee% = 82.22%. HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 10.54 major (91.11%), t_R = 16.07 minor (8.9%).

HRMS (EI): $[M^+]$ observed 266.1303 for $C_{18}H_{18}O_2$ Theoretical 266.1301

The synthesis of (2*S*)-1- (benzyloxy)-5-phenylpent-3-yn-2-ol (188c)



The same method was employed as described for the synthesis of compound **187a**, with following quantities Zn $(OTf)_2$ (1.87 g, 5.13 mmol) and (+)- (1S, 2R)-*N*-methylephedrine (1.0 g, 5.6 mmol) and purged with N_2, stirred for 15 min whereupon toluene (10 mL) and triethylamine (Et_3N) (1.13 g, 11.20 mmol) was added *via* a syringe. After 2 h 3-phenyl-1-propyne (1.62 g, 14.0 mmol) was added by syringe in one portion. After 15 min of stirring aldehyde **173** (0.7 g, 4.67 mmol) was added. After 7-10 days to complete the reaction and tlc monitoring showed less amount of the remained and revealed a new spot with an R_f = 0.23 (hexane: diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 85:15) gave the title product as a colourless oil (1.098 g, 81.47%). $[\alpha]_D$ = +10 ° (c = 1%, diethyl ether); ee% = 77.12 %. HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.32 major (88.56 %), t_R = 20.2 minor (11.4%).

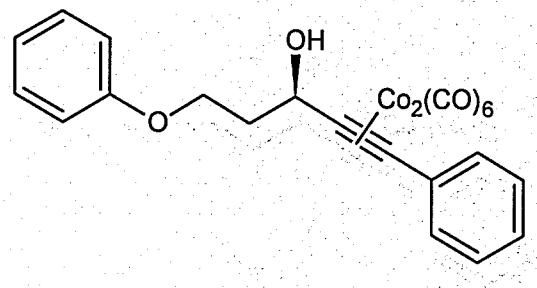
IR ν_{max} (neat)/cm^{-1}: 3025.1 (s); 2905.5 (s); 1567.4 (w); 1235.3 (m); 781.6 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.45-7.41 (2H, m, Ph); 7.39-7.34 (4H, m, Ph); 7.33-7.28 (4H, m, Ph); 6.00 (1H, td, *J* = 8.3, 5.5 Hz, C<u>H</u>); 4.65 (1H, d, *J* = 5.5 Hz, O<u>H</u>); 4.30 (1H, d, *J* = 12.0 Hz Ph$C\underline{H_2}$O); 4.27 (1H, d, *J* = 12.0 Hz, Ph$C\underline{H_2}$O); 4.05 (1H, dd, *J* = 8.3, 6.4 Hz, O$C\underline{H_2}$CH); 3.74 (1H, dd, *J* = 8.3, 6.4 Hz, O$C\underline{H_2}$CH); 3.55 (1H, d, *J* = 10.0 Hz, CH≡$C\underline{H_2}$Ph); 3.47 (1H, d, *J* = 10.0 Hz, CH≡$C\underline{H_2}$Ph).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 154.55 (<u>C</u>, Ar); 139.90 (<u>C</u>H, Ar); 138.40 (<u>C</u>, Ar); 137.79 (<u>C</u>H, Ar); 135.60 (<u>C</u>H, Ar); 129.16 (<u>C</u>H, Ar); 128.35 (<u>C</u>H, Ar); 122.37 (<u>C</u>H, Ar); 92.40 (<u>C</u>); 89.96 (<u>C</u>); 77.85 ($\underline{C}H_2$); 76.56 ($\underline{C}H_2$); 69.80 (<u>C</u>H); 54.38 ($\underline{C}H_2$).

HRMS (EI): $[M+NH_4]$ observed 284.1655 for $C_{18}H_{18}O_2NH_4$ theoretical 284.1650

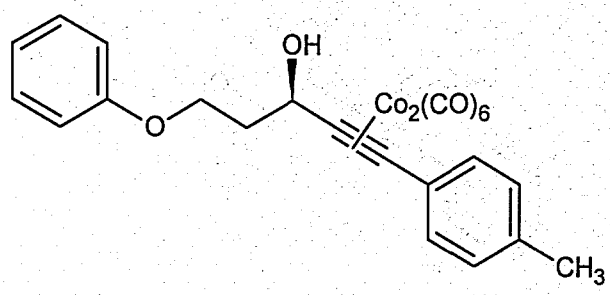
The synthesis of hexacarbonyl (3*R*)-5-phenoxy-1-phenylpent-1-yn-3-ol dicobalt (189a)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **187a** (0.24 g, 0.94 mmol) and dicobalt octacarbonyl (0.35 g, 1.035 mmol). Tlc showed a dark red spot in R_f = 0.32 (hexane: diethyl ether, 90:10). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (0.5 g, 98.62%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **177c**. The following additional data were obtained.

HRMS (EI): $[M+NH_4]$ observed. 555.9845 for $C_{23}H_{16}O_8Co_2NH_4$ theoretical. 555.9847

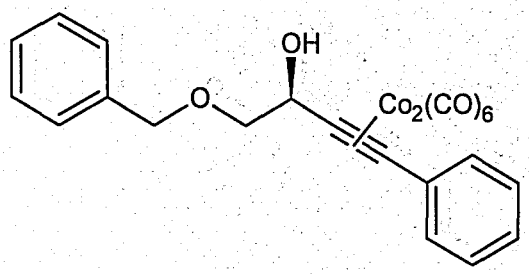
The synthesis of hexacarbonyl (3*R*)-1- (4-methylphenyl)-5-phenoxypent-1-yn-3-ol dicobalt (189b)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **187b** (0.072 g, 0.27 mmol) and dicobalt octacarbonyl (0.10 g, 0.3 mmol). Tlc showed a dark red spot in R_f = 0.53 (hexane: diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (0.13 g, 91%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **177d**. The following additional data were obtained.

HRMS (EI): $[M+NH_4]$ observed 570.002 for $C_{24}H_{18}O_8Co_2NH_4$ theoretical 570.004

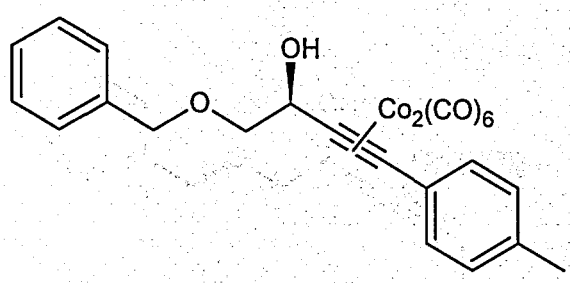
The synthesis of hexacarbonyl (2*S*)-1- (benzyloxy)-4-phenylbut-3-yn-2-ol dicobalt (190a)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **188a** (0.21 g, 0.833 mmol) and dicobalt octacarbonyl (0.32 g, 0.92 mmol). Tlc showed a dark red spot in R_f = 0.29 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethane, 95:5) gave the title product as a dark red oil (0.41 g, 91.5%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **178a**. The following additional data were obtained.

HRMS (EI): [M-CO] observed 509.9995 for $C_{22}H_{16}O_7Co_2$ theoretical 510.0000.

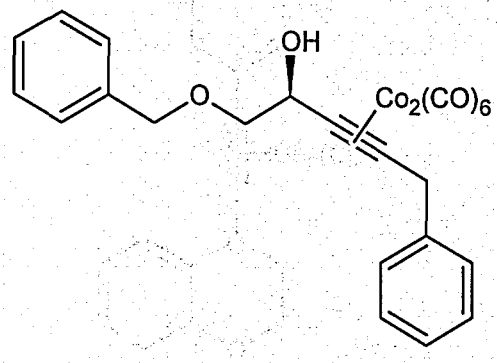
The synthesis of hexacarbonyl (2*S*)-1- (benzyloxy)-4- (4-methylphenyl) but-3-yn-2-ol dicobalt (190b)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **188b** (0.51 g, 1.88 mmol) and dicobalt octacarbonyl (0.72 g, 2.11 mmol). Tlc showed a dark red spot in R_f = 0.41 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (1.04 g, 98.11%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **178b**. The following additional data was obtained.

HRMS (EI): [M-CO] observed 524.9800 for $C_{23}H_{19}O7Co_2$ theoretical 524.9794.

The synthesis of hexacarbonyl (2*S*)-1- (benzyloxy)-5-phenylpent-3-yn-2-ol dicobalt (190c)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **188c** (0.6 g, 2.33 mmol) and dicobalt octacarbonyl (0.88 g, 2.6 mmol). Tlc showed a dark red spot in R_f = 0.35 (hexane: diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethane, 95:5) gave the title product as a dark red oil (1.0 g, 80.6%)

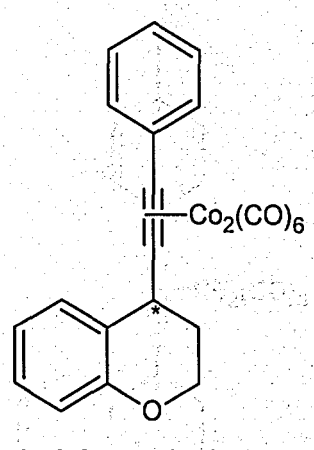
IR v_{max} (neat)/cm^{-1}: 3351.5 (s); 2930.61 (s); 2074.0 (s); 1607.10 (m); 1090.7 (w); 765.0 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.50-7.40 (2H, m, Ph); 7.40-7.30 (8H, m, Ph); 4.60 (1H, d, *J* = 6.0 Hz, O<u>H</u>); 4.49 (1H, td (brd); *J* = 8.4, 6.0 Hz, C<u>H</u>OH); 4.30 (1H, d (brd); *J* = 10.0 Hz, PhC<u>H</u>$_2$O); 4.22 (1H, d, *J* = 10.0 Hz, PhC<u>H</u>$_2$O); 4.00 (1H, dd, *J* = 8.4, 6.8 Hz, OC<u>H</u>$_2$CH); 3.90 (1H, dd, *J* = 8.4, 6.8 Hz, OC<u>H</u>$_2$CH); 3.86 (1H, d, *J* = 9.8 Hz, CH≡CC<u>H</u>$_2$Ph); 3.80 (1H, d, *J* = 9.8 Hz, CH≡CC<u>H</u>$_2$Ph).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 200.01 (<u>C</u>O); 139.21 (C, Ar); 137.40 (<u>C</u>, Ar); 134.40 (<u>C</u>H, Ar); 132.25 (<u>C</u>H, Ar); 130.00 (<u>C</u>H, Ar); 129.59 (<u>C</u>H, Ar); 128.45 (<u>C</u>H, Ar); 127.95 (<u>C</u>H, Ar); 74.90 (<u>C</u>H$_2$); 73.56 (<u>C</u>H$_2$); 71.01 (<u>C</u>H); 50.25 (<u>C</u>H$_2$).

HRMS (EI): [M+NH_4] observed 555.9837 for $C_{24}H_{18}O_8Co_2NH_4$ theoretical 555.9847

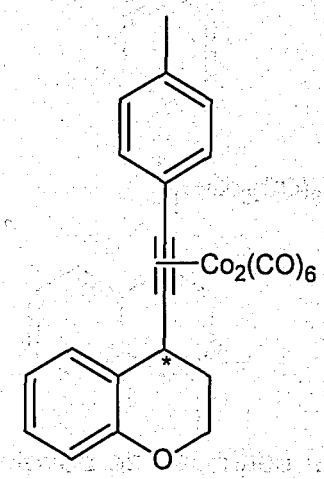
The synthesis of hexacarbonyl 4- (phenylethynyl)-3, 4-dihydro-2*H*-chromene dicobalt (191a)



Cobalt complex propargyl alcohol **189a** (0.414 g, 0.76 mmol) was placed to pre-heated round bottom flask in dry DCM (5 mL) under N_2 solution then cooled in dry ice -78 °C, $BF_3.Et_2O$ (0.21 g, 1.52 mmol) was added drop wise after 20 minutes tlc monitoring showed a faster moving compound R_f = 0.66 (Hexane: diethyl ether, 90:10). Reaction was quenched with distil water (30 mL) and extract with DCM (3 x 20 mL). Combined organic layer was separated in a separating funnel and dried over magnesium sulphate. Magnesium sulphate was filtered and DCM was removed *via vacuum*. Purification by chromatography on silica gel eluted with (hexane: dichloromethane, 90:10) gave the title product as a dark red oil (0.25 g, 63.13%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **180b**. The following additional data was obtained.

HRMS (EI): [M- 3CO] observed 435.9560 for $C_{20}H_{14}O_4Co_2$ theoretical 435.9556

The synthesis of hexacarbonyl (4*S*) - 4 - [(4 - methylphenyl) ethynyl] - 3, 4 - dihydro - 2*H* -chromene dicobalt (191b)

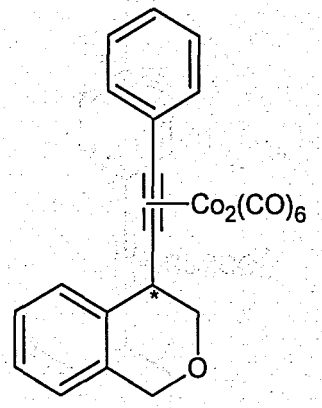


The same method was employed as described for the synthesis of compound **191a** with the following quantities; cobalt complex propargyl alcohol **189b** (0.028 g, 0.05 mmol) and $BF_3.Et_2O$ (14.4 mg, 0.1 mmol) in dry DCM (3 mL). After 20 minuts tlc monitoring showed new compound R_f = 0.61 (hexane: diethyl ether, 90:10). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (20 mg, 74%).

^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **180c**. The following additional data was obtained.

HRMS (EI): $[M^+]$ observed 534.9631 for $C_{24}H_{17}O_7Co_2$ theoretical: 534.9628

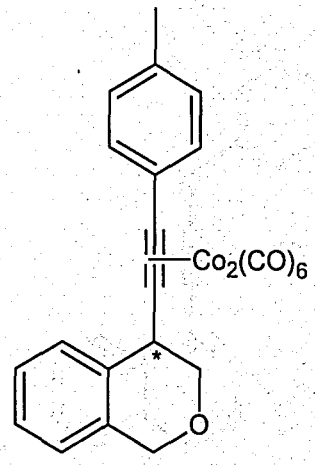
The synthesis of hexacarbonyl (4*S*)-4- (phenylethynyl)-3, 4-dihydro-1*H*-isochromene dicobalt (192a)



The same method was employed as described for the synthesis of compound **191a** with the following quantities; cobalt complex propargyl alcohol **190a** (0.448 g, 0.84 mmol) and $BF_3.Et_2O$ (0.24 g, 1.7 mmol) in dry DCM (10 mL). After 20 minutes tlc monitoring showed new compound $R_f = 0.7$ (petroleum ether (60 °C-80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (350 mg, 80.33%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **181a**. The following additional data was obtained.

HRMS (EI): [M-CO]: observed. 491.9460 for $C_{22}H_{14}O_6Co_2$ theoretical 491.9454

The synthesis of hexacarbonyl (4*S*)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-1*H*-isochromene dicobalt (192b)

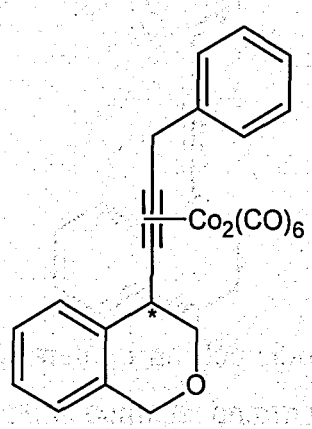


The same method was employed as described for the synthesis of compound **191a** with the following quantities; cobalt complex propargyl alcohol **190b** (1.0 g, 1.81 mmol) and $BF_3.Et_2O$ (0.51 g, 3.62 mmol) in dry DCM (10 mL). After 20 minutes tlc monitoring showed new compound $R_f = 0.8$ (Petroleum ether (60 °C-80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (706 mg, 73%).

^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **181b**. The following additional data was obtained.

HRMS (EI): [M-CO] observed 505.9615 for $C_{23}H_{17}O6Co_2$ theoretical 505.9610

The synthesis of hexacarbonyl (4*S*)-4- (3-phenylprop-1-yn-1-yl)-3,4-dihydro-1*H*-isochromene dicobalt (192c)



The same method was employed as described for the synthesis of compound **191a** with the following quantities; cobalt complex propargyl alcohol **190c** (1.0 g, 1.81 mmol) and $BF_3.Et_2O$ (0.51 g, 3.62 mmol) in dry DCM (10 mL). After 15 minutes tlc monitoring showed new compound R_f = 0.87 (hexane: diethyl ether, 80:20). Purification by chromatography on silica gel eluted with (hexane: dichloromethan, 95:5) gave the title product as a dark red oil (0.685 g, 70.80%).

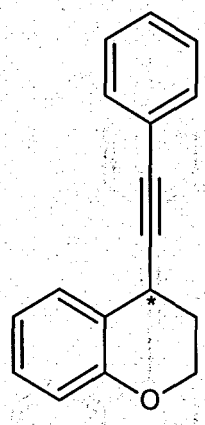
IR ν_{max} (neat)/cm^{-1}: 2967.5 (w); 1989.0 (s); 1765.0 (s); 955.0 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.70 (1H, s (brd); Ph); 7.5 (1H, s (brd); Ph); 7.40-7.20 (6H, m, Ph); 7.00 (1H, s (brd); Ph); 4.50-4.43 (2H, d (brd); *J* = 6.5 Hz, PhC$\underline{H}_2$O); 4.25-4.20 (1H, m,C$\underline{H}$); 3.90-3.80 (2H, m, C$\underline{H}_2$O); 3.40 (2H, m,PhC$\underline{H}_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 140.5 ($\underline{C}$, Ar); 139.7 ($\underline{C}$, Ar); 138.0 ($\underline{C}$, Ar); 133.3 ($\underline{C}$H, Ar); 128.50 ($\underline{C}$H, Ar); 76.0 ($\underline{C}H_2$); 75.5 ($\underline{C}H_2$); 37.2 ($\underline{C}$H); 35.0 ($\underline{C}H_2$). Due to the presence of paramagnetic impurities complete NMR data was not obtained.

HRMS (EI): [M+NH_4] observed 552.9921 for $C_{24}H_{17}O_7Co_2NH_4$ 552.9982

The synthesis of (4*S*)-4- (phenylethynyl)-3, 4-dihydro-2*H*-chromene (193a)

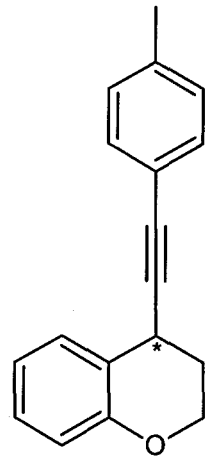


For decomplexation the same method as described for the **185** was employed with the following quantities, cobalt complex chromene **191a** (0.23 g, 0.44 mmol); saturated solution of the CAN in methanol (20 mL) in 0 °C. Tlc showed new colourless compound R_f = 0.6 (petroleum ether (60 °C- 80 °C): Et_2O, 90:10). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 75:25) gave the title product as a colourless oil (70 mg, 76.24%). $[\alpha]_D$ = – 38 ° (c = 1%, diethyl ether) ee% = 45.2, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 8.58 major (72.61%), t_R = 16.72 minor (27.4%).

^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **185b**. The following additional data was obtained.

HRMS (EI): [M^+] observed 235.1120 for $C_{17}H_{15}O$ theoretical 235.1123.

The synthesis of 4 - [(4 – methylphenyl) ethynyl] - 3, 4 – dihydro - 2*H* – chromene (193b)

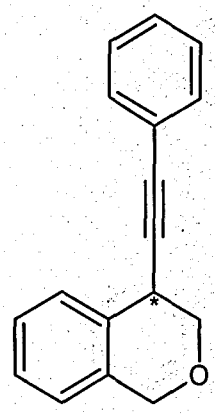


The same method as described for the **185** was employed with the following quantities, Cobalt complex chromene **191b** (0.35 g, 0.65 mmol); and saturated solution of the CAN (20 mL). Tlc showed new colourless compound R_f = 0.7 (hexane: diethyl ether, 70:30) Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a colourless oil (0.126 g, 79%). $[\alpha]_D$ = -10 ° (c = 1%, diethyl ether) ee% = 70.52%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.6 major (85.3%), t_R = 16.96 minor (14.74%).

^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **185c**. The following additional data was obtained.

HRMS (EI): [M^+] Observed 249.1281 for $C_{18}H_{17}O$ theoretical 249.1279.

The synthesis of (4*S*)-4- (phenylethynyl)-3, 4-dihydro-1*H*-isochromene (194a)

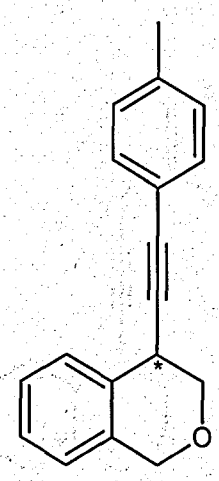


The same method as described for the **185** was employed with the following quantities, Cobalt complex isochromene **192a** (0.5 g, 0.96 mmol); and saturated solution of the CAN (25 mL). Tlc showed new colourless compound R_f = 0.85 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a colourless oil (195 mg, 86.6%). $[\alpha]_D$ = + 13 ° (c = 1%, diethyl ether) ee% = 77.34%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 16.70 major (88.7 %), t_R = 20.53 minor (11.3 %).

^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **186a**. The following additional data was obtained.

HRMS (EI): [M^+] observed 235.1125 $C_{17}H_{15}O$ theoretical 235.1123

The synthesis of (4*S*)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-1*H*-isochromene (194b)

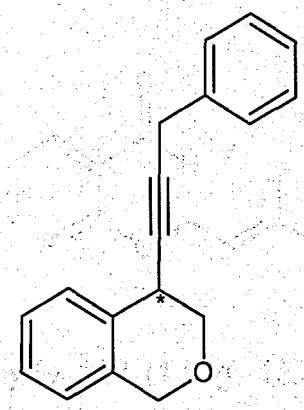


The same method as described for the **185** was employed with the following quantities, Cobalt complex isochromene **192b** (0.6 g, 1.12 mmol); and saturated solution of the CAN (30 mL). Tlc showed new colourless compound R_f = 0.56 (hexane: diethyl ether, 90:10). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a colourless oil (0.23 g, 84.3%). $[\alpha]_D$ = - 21 ° (c = 1%, diethyl ether) ee% = 81.62%. HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 10.69 major (90.81 %), t_R = 13.63 minor (9.19 %).

^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **186b**. The following additional data was obtained.

HRMS (EI): $[M^+]$ observed 249.1274 for $C_{18}H_{17}O$ theoretical 249.1274

The synthesis of 4- (3-phenylprop-1-yn-1-yl)-3, 4-dihydro-1*H*-isochromene (194c)



The same method as desicribed for the **185a** was employed for the decomplexation with the following quantities, cobalt complex isochromene **192c** (0.6 g, 1.12 mmol); saturated solution of the CAN in methanol (35 mL). Tlc showed new colourless compound R_f = 0.86 (hexane: diethyl ether, 80:20). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a colourless oil (0.247 g, 88.2 %). $[\alpha]_D$ = -9 ° (c = 1%, diethyl ether) ee%= 76.1%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 9.62 major (88.1 %), t_R = 12.03 minor (11.95 %).

IR ν_{max} (neat)/cm^{-1}: 2990.5 (w); 2125.0 (m); 1970.0 (m); 1503.5 (w); 795.0 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.62 (1H, dd, *J* = 7.5, 1.7 Hz, Ph); 7.5 (1H, d, *J* = 2.3 Hz, Ph); 7.48-7.50 (1H, m, Ph); 7.34-7.28 (4H, m, Ph); 7.00 (1H, dd, *J* = 7.5, 1.0 Hz, Ph); 6.94 (1H, dd, *J* = 8.3, 1.0 Hz, Ph); 4.48 (1H, d, *J* = 9.0 Hz, PhC$\underline{H}_2$O); 4.45 (1H, d, *J* = 9.0 Hz, PhC$\underline{H}_2$O); 4.19 (1H, dd, *J* = 6.4, 5.0 Hz, C$\underline{H}$); 3.90 (1H, dd, *J* = 8.3, 5.0 Hz, CHC$\underline{H}_2$); 3.59 (1H, dd, *J* = 8.3, 6.4 Hz, CHC$\underline{H}_2$); 3.40 (2H, d (bd); *J* = 0.3 Hz, C$\underline{H}_2$Ph)

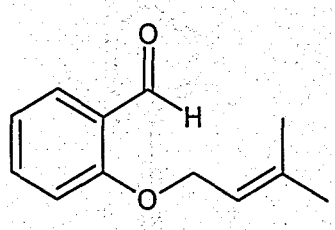
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 139.58 ($\underline{C}$, Ar); 138.86 ($\underline{C}$, Ar); 132.76 ($\underline{C}$, Ar); 131.73 ($\underline{C}$H, Ar); 128.50 ($\underline{C}$H, Ar); 128.15 ($\underline{C}$H, Ar); 128.03 ($\underline{C}$H, Ar); 127.75 ($\underline{C}$H, Ar); 127.65 ($\underline{C}$H, Ar); 119.50 ($\underline{C}$H, Ar); 86.50 ($\underline{C}$); 85.50 ($\underline{C}$); 72.60 ($\underline{C}H_2$); 73.50 ($\underline{C}H_2$); 21.69 ($\underline{C}$H); 29.10 ($\underline{C}H_2$).

LRMS (m/z): (M^+ 249), 172, 134, 158, 91, 51

HRMS (EI): [M+H] observed 249.1281 for $C_{18}H_{16}O$ theoretical 247.1279.

3.4.4 Novel racemic benzopyrans

The synthesis of 2-[(3-methylbut-2-en-1-yl) oxy] benzaldehyde (197)



To a solution of salicylaldehyde **199** (1.5 g, 12.3 mmol, 1 eq) and 4-bromo-2methyl-2-buthene (1.83 g, 12.3 mmol, 1eq) in dry DMF (20 mL) in a flame dried 150 mL round bottom flask was added finely ground anhydrous potassium carbonate (6.8 g, 49.2 mmol, 4 eq) and potassium iodide (0.2 g,1.2 mmol, 0.1 eq) were added. The reaction mixture was left to stir at room temperature under a nitrogen atmosphere for at least 3 hours. After 3 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with R_f = 0.5 (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20). The reaction mixture was poured into water (40 mL) and extracted with diethyl ether (6 x 15 mL). The organic extracts were combined and washed with LiCl saturated solution (3 x 10 mL) to remove remained DMF, dried over magnesium sulphate, filtered and concentrated in *vacuo* to afford a pure yellow oil (2.34 g, 100%) product was sufficiently pure to follow next stage.

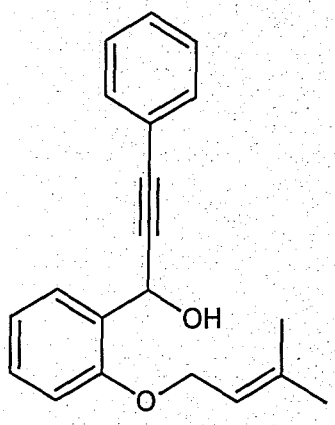
IR ν_{max} (neat)/cm^{-1}: 2976.0 (m); 1687.5 (s); 1189.5 (m); 1042.2 (w); 757.67 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 10.39 (1H, s, C<u>H</u>O); 7.78 (1H, dd, J = 7.9, 1.8 Hz, Ph); 7.51-7.44 (1H, m, Ph); 6.99-6.91 (2H, m, Ph); 5.48-5.51 (1H, t, J = 6.5 Hz, C<u>H</u>=C); 4.6 (2H, d, J = 6.5 Hz, OC<u>H</u>$_2$); 1.79 (3H, s, Me); 1.71 (3H, s, Me).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 189.88 (<u>C</u>O); 161.36 (<u>C</u>, Ar); 138.64 (=<u>C</u>); 135.84 (<u>C</u>, Ar); 128.20 (=CH); 125.10 (<u>C</u>H, Ar); 120.52 (<u>C</u>H, Ar); 119.02 (<u>C</u>H, Ar); 112.98 (<u>C</u>H, Ar); 65.46 (CH_2); 25.76 (CH_3); 18.27 (CH_3)

HRMS (EI): [M$^+$] observed 190.0996 for $C_{12}H_{14}O_2$ theoretical 190.0994

The synthesis of 1-[2-[(3-methylbut-2-en-1-yl) oxy] phenyl]-3-phenylprop-2-yn-1-ol (198a)



Method 1: Aldehyde **197** (1.6 g, 8.2 mmol, 1eq) was placed in round-bottom flask containing dry THF (15 mL) and maintained under an atmosphere of nitrogen gas. The reaction temperature was reduced to -10 °C and phenylethynyl magnesiumbromide solution (9 mL of the 1 M solution in hexane, 9 mmol) was added drop wise over a period of 20 minutes. Stirring at -10 °C was continued for about 1 hour and then allowed to reach an ambient temperature. After 3 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.47 (petroleum ether (60 °C- 80 °C): diethyl ether 60:40). The reaction mixture was quenched by the addition of HCl (30 mL of a 2M solution) and the mixture extracted with diethyl ether (3 x 30 mL). The combined organic solvent was dried over magnesium sulphate, filtered and the solvent removed*in vacuo*. Purification on silica gel eluted with hexane/diethyl ether (80:20) was carried out to afford title compound as a colourless oil (2.0g, 81.3 %).

Method 2: Propargyl alcohol **200a** (1.0 g, 4.5 mmol) was placed in a 250 mL flame dried flask under at an atmosphere of nitrogen at an ambient temperature. Anhydrous DMF (20 mL) was added followed by potassium carbonate (2.5 g, 18.0 mmol) and potassium iodide (0.075 g, 0.45 mmol) and they were left to stir for lh before 4-bromo-2methyl-2-butene (0.67 g, 4.5 mmol) was added. The reaction mixture was left to stir for 3 hours after that tlc monitoring showed the loss of the starting material and the presence of a new compound with R_f = 0.49 (petroleum ether (60 °C- 40 °C): diethyl ether 60:40). The colourless oil was isolated which was sufficiently pure for use in the next stage (0.98 g, 75%).

IR ν_{max} (neat)/cm^{-1}: 3246.1 (s); 2955.2 (s); 1951.1 (m); 1453.9 (w); 1200.5 (m); 935 (w).

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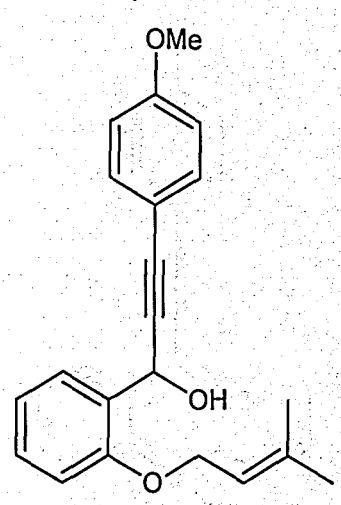
The synthesis of 3- (4-methoxyphenyl)-1-[2-[(3-methylbut-2-en-1-yl) oxy] phenyl] prop-2-yn-1-ol (198c)



The same method was employed as described for the synthesis of the **198a** with the following quantities; however [(4-methoxyphenyl) ethynyl] lithium solution was synthesised *in situ* the same method as **198b** with following quantities; 4 - ethynylanisole (1.8 g, 14.2mmol) followed by n-BuLi (9.5 mL of the 2.5 M in hexane, 23.6 mmol) after 1 hour aldehyde **197** (2.25 g, 11.8 mmol). After 3 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with an $R_f = 0.5$ (petroleum ether (60 °C- 80 °C): diethyl ether 50:50) (3.1 g, 81.5%).

IR ν_{max} (neat)/cm^{-1}: 3213.5 (s); 2985.9 (s); 1952.2 (m); 1650.9 (w); 1120.2 (m); 798.2 (w).

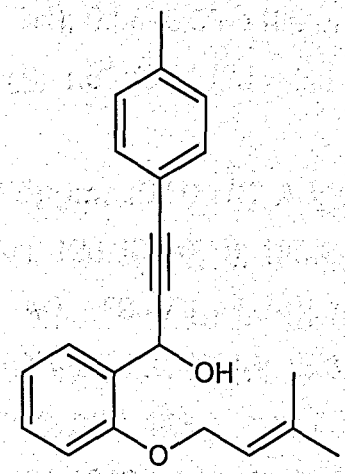
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.62 (1H, dd, J = 7.5, 1.7 Hz, Ph); 7.44-7.39 (2H, m, Ph); 7.35-7.30 (1H, m, Ph); 7.00-6.93 (2H, m, Ph); 6.86-6.80 (2H, m, Ph); 5.92 (1H, d, J = 6.1 Hz, C<u>H</u>OH); 5.56-5.50 (1H, m, =C<u>H</u>); 4.63 (2H, d, J = 6.0 Hz, C<u>H$_2$</u>); 3.80 (3H, s, OC<u>H$_3$</u>); 3.30 (1H, d, J = 6.1, O<u>H</u>); 1.83 (3H, d (br); J = 0.8 Hz, CH_3); 1.78 (3H, d (br) J = 0.8 Hz, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 159.65 (<u>C</u>, Ar); 156.26 (<u>C</u>, Ar); 138.41 (=<u>C</u>); 133.25 (<u>C</u>, Ar); 129.55 (<u>C</u>, Ar); 129.40 (<u>C</u>H, Ar); 128.10 (=<u>C</u>H); 120.86 (<u>C</u>H, Ar); 119.53 (<u>C</u>H, Ar); 115.02 (<u>C</u>H, Ar); 113.88 (<u>C</u>H, Ar); 112.20 (<u>C</u>H, Ar); 87.06 (C); 86.02 (C); 65.35 (CH); 62.09 (CH_2); 55.30 (CH_3); 25.82 (CH_3); 18.32 (CH_3).

LRMS (m/z): (M^+322) 305, 231, 205, 173.

HRMS (EI): [M^+] observed. 322.1804 for $C_{21}H_{22}O_3$, theoretical. 322.1805.

The synthesis of 1-[2-[(3-methylbut-2-en-1-yl) oxy] phenyl]-3- (4-methylphenyl) prop-2-yn-1-ol (198b)



The same method was employed as described for the synthesis of the **198a** with the following quantities; however 4-methylphenylethynyl lithium was synthesised *in situ* by addition of the 4-methylphenylethynyl (0.5 g,4.3 mmol) in round-bottom flask containing dry THF (15 mL) and maintained under an atmosphere of nitrogen gas. The reaction temperature was reduced to -78 °C then n-BuLi (3 mL of the 2.5 M in hexane, 7.2mmol) was added to the mixture drop wise after 1 hour aldehyde **197** (1.0 g, 3.3 mmol) was added to the solution in one portion. After 3 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with an $R_f = 0.5$ (petroleum ether (60 °C- 80 °C): diethyl ether 70:30). Purification on silica gel eluted with hexane/diethyl ether (80:20) was carried out to afford title compound as a colourless oil (1.5 g, 93%).

IR ν_{max} (neat)/cm^{-1}: 3105.4 (s); 2967.2 (s); 1950.1 (m); 1376.3 (w); 734.0 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.64 (1H, dd, *J* = 7.5, 1.6 Hz, Ph); 7.40-7.36 (2H, m, Ph); 7.34-7.28 (1H, m, Ph); 7.15-7.10 (2H, m Ph); 7.03-7.98 (1H, m, Ph); 6.97-6.93 (1H, m, Ph); 5.92 (1H, d, *J* = 6.2 Hz, C<u>H</u>OH); 5.56-5.50 (1H, m, =C<u>H</u>); 4.65-4.60 (2H, d, *J* = 6.5 Hz, C<u>H</u>$_2$); 3.33 (1H, d, *J* = 6.2 Hz, O<u>H</u>); 2.35 (3H, s, PhCH_3); 1.80 (3H, s, C<u>H</u>$_3$); 1.76 (3H, s, C<u>H</u>$_3$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 156.29 (<u>C</u>, Ar); 138.46 (=<u>C</u>); 138.43 (<u>C</u>, Ar); 131.70 (<u>C</u>, Ar); 130.16 (<u>C</u>, Ar); 129.33 (<u>C</u>H, Ar); 129.01 (<u>C</u>H, Ar); 128.13 (=<u>C</u>H); 120.87 (<u>C</u>H, Ar); 119.83 (<u>C</u>H, Ar); 119.53 (<u>C</u>H, Ar); 112.21 (<u>C</u>H, Ar); 87.76 (<u>C</u>); 86.22 (<u>C</u>); 65.37 (<u>C</u>H); 62.13 (<u>C</u>H$_2$); 25.82 (<u>C</u>H$_3$); 21.52 (<u>C</u>H$_3$); 18.33 (<u>C</u>H$_3$).

LRMS (m/z): (M^+306), 289, 231, 185, 157

HRMS (EI): [M-H] observed. 305.1536 for $C_{21}H_{21}O_2$ theoretical. 305.1536.

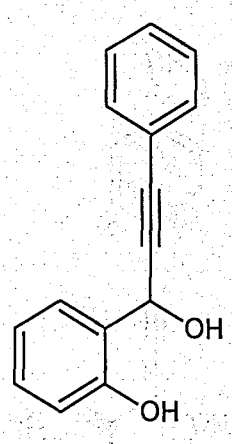
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.65 (1H, dd, *J* = 7.5, 1.5 Hz, Ph); 7.51-7.47 (2H, m, Ph); 7.34-7.28 (4H, m, Ph); 7.03-9.98 (1H, m, Ph); 6.96-6.90 (1H, m, Ph); 5.90 (1H, d, *J* = 6.2, C<u>H</u>OH); 5.56–5.50 (1H, m,=C<u>H</u>); 4.64 (2H, d, *J* = 6.7, C<u>H</u>$_2$); 3.30 (1H, d, *J* = 6.2, O<u>H</u>); 1.80 (3H, d, *J* = 0.8, C<u>H</u>$_3$); 1.75 (3H, d, *J* = 0.8, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 157.00 (<u>C</u>, Ar); 138.48 (=<u>C</u>); 131.80 (<u>C</u>, Ar); 129.62 (<u>C</u>, Ar); 129.20 (<u>C</u>H, Ar); 128.36 (=<u>C</u>H); 128.24 (<u>C</u>H, Ar); 128.11 (<u>C</u>H, Ar); 122.90 (<u>C</u>H, Ar); 120.87 (<u>C</u>H, Ar); 119.47 (<u>C</u>H, Ar); 112.210 (<u>C</u>H, Ar); 88.47 (<u>C</u>); 86.05 (<u>C</u>); 65.36 (<u>C</u>H); 62.16 (<u>C</u>H$_2$); 25.81 (<u>C</u>H$_3$); 18.31 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 292), 275, 223, 207, 143.

HRMS (EI): [M-H] observed. 291.1383 for $C_{20}H_{19}O_2$ theoretical. 291.1380.

The synthesis of 2- (1-hydroxy-3-phenylprop-2-yn-1-yl) phenol (200a)



The same method was employed as described for the synthesis of the **159** with the following quantities; 2-hydroxybenzaldehyde **199** (1 g, 8.2 mmol) and phenylethynylmagnesium bromide (9.0 mL of the 1M solution in THF, 9.0 mmol) after 2 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.2 (petroleum ether (60 °C- 80 °C): diethyl ether 70:30). Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 90:10) to afford yellowishe tissue shape powder for the title compound, (1.79 g, 97.8%). mp: 55 – 56 °C

IR ν_{max} (neat)/cm^{-1}: 3365.1 (s); 2925.0 (s); 1699.8 (m); 1569.9 (w); 1359.0 (m); 691.0 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.51-7.48 (2H, m, Ph); 7.47-7.44 (1H, m, Ph); 7.37-7.32 (3H, m, Ph); 7.30-7.24 (1H, m, Ph); 7.16 (1H, s, O<u>H</u>); 6.96-6.90 (2H, m, Ph); 5.92 (1H, d, J = 5.9 Hz, C<u>H</u>); 2.70 (1H, d, J = 5.9 Hz, PhCHO<u>H</u>).

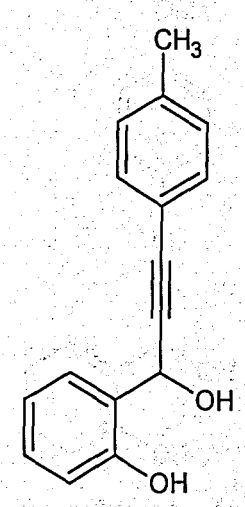
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 155.38 (<u>C</u>, Ar); 139.00 (<u>C</u>, Ar); 132.07 (<u>C</u>, Ar); 129.0 (<u>C</u>H, Ar); 128.5 (<u>C</u>H, Ar); 128.4 (<u>C</u>H, Ar); 128.2 (<u>C</u>H, Ar); 124.45 (<u>C</u>H, Ar); 121.95 (<u>C</u>H, Ar); 120.30 (<u>C</u>H, Ar); 88.38 (<u>C</u>); 86.44 (<u>C</u>); 64.56 (<u>C</u>H).

LRMS (m/z): (M^+ 224), 208, 191, 106, 92.

HRMS (EI): [M-H] observed 223.0760 $C_{15}H_{11}O_2$ theoretical 223.0765

The synthesis of 2-[1-hydroxy-3- (4-methylphenyl) prop-2-yn-1-yl] phenol

(200b)



The same method was employed as described for the synthesis of the **200a** with the following quantities; however 4-methylphenylethynyl lithium solution was synthesied *in situ* by the addition of the 4-ethynyltoluene (1.0 g, 9 mmol) in a flame dry 100 mL flask under nitrogen atmospher and -78 °C in anhydrous THF (10 mL) followed by dropwise addition of the n-BuLi (5.4 mL of the 2.5 M solution in hexane, 13.5 mmol) after 1 hour 2-hydroxybenzaldehyde **199** (1.0 g, 8.2 mmol) was added and solution left to stir for 1 hour more and then warmed up to ambient temperature, after 2 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with R_f = 0.25 (petroleum ether (60 °C- 80 °C): diethyl ether, 60:40). Purification *via* flash chromatography on silica gel (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) which resulted in the title compound as a white powder (1.5 g, 77.0 %). mp: 58 - 59 °C.

IR ν_{max} (neat)/cm^{-1}: 3334.9 (s); 2854.2 (s); 1709.8 (m); 1599.5 (w); 753.7 (m).

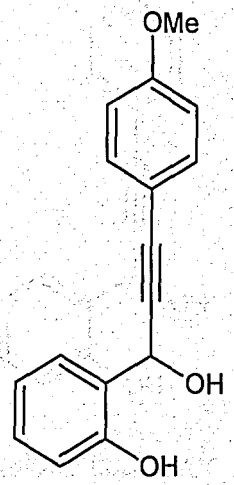
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.46-7.43 (1H, m, Ph); 7.41-7.37 (2H, m, Ph); 7.29-7.24 (1H, m, Ph); 7.16-7.12 (3H, m, Ph & O<u>H</u>); 6.94-6.90 (2H, m, Ph); 5.90 (1H, s (bd); C<u>H</u>); 3.00 (1H, s (bd); O<u>H</u>); 2.36 (3H, s, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 155.36 (<u>C</u>, Ar); 139.20 (<u>C</u>, Ar); 131.78 (<u>C</u>, Ar); 129.17 (<u>C</u>, Ar); 128.70 (<u>C</u>H, Ar); 128.54 (<u>C</u>H, Ar); 127.80 (<u>C</u>H, Ar); 120.28 (<u>C</u>H, Ar); 118.86 (<u>C</u>H, Ar); 117.20 (<u>C</u>H, Ar); 88.56 (<u>C</u>); 85.80 (<u>C</u>); 64.56 (<u>C</u>H); 21.56 (<u>C</u>H_3).

LRMS (m/z): (M^+ 238), 224, 208, 192, 106, 92.

HRMS (EI): [M-H] observed: 237.0915 for $C_{16}H_{13}O_2$ 237.0913

The synthesis of 2-[1-hydroxy-3- (4-methoxyphenyl) prop-2-yn-1-yl] phenol (200c)



The same method was employed as described for the synthesis of the **200a** with the following quantities; however 4-methoxyphenylethynyl lithium solution was synthesised *in situ* by addition of 4-ethynylanisole (1.0 g, 8.2 mmol) in a flame dry 100 mL flask under nitrogen atmosphere and – 78 °C in anhydrouse THF (10 mL) followed by dropwise addition of the n-BuLi (5 mL of the 2.5 M solution in hexane, 12.3 mmol) after 1 hour 2-hydroxybenzaldehyde **199** (1.0 g, 8.2 mmol) was added and solution left to stir for 1 hour more and then warmed up to ambient temperature, after 2 hours tlc monitoring showed the loss of the starting material and the presence of a new compound with R_f = 0.33 (hexane: diethyl ether, 60:40). Purification *via* flash chromatography on silica gel (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) resulted white tissue shap powder as a title compound (1.7 g, 85%). mp: 49-50 °C

IR ν_{max} (neat)/cm^{-1}: 3370.1 (s); 2935.0 (s); 2210.0 (m); 1700.0 (w); 1155.5 (w); 756.0 (m).

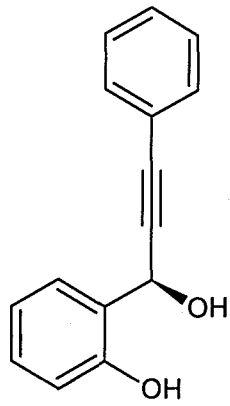
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.92-7.90 (2H, m, Ph); 7.88-7.80 (1H, m, Ph); 7.65-7.59 (1H, m, Ph); 7.35-7.20 (2H, m, Ph); 7.02-6.97 (2H, m, Ph); 6.90 (1H, s (bd); C<u>H</u>OH); 3.88 (3H, s, C<u>H$_3$</u>O); 3.87 (1H, s (bd); CHO<u>H</u>); 2.56 (1H, s, PhO<u>H</u>).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 160.00 (<u>C</u>, Ar); 136.65 (<u>C</u>, Ar); 135.51 (<u>C</u>, Ar); 131.24 (<u>C</u>, Ar); 119.50 (<u>C</u>H, Ar); 125.16 (<u>C</u>H, Ar); 123.30 (<u>C</u>H, Ar); 122.5 (<u>C</u>H, Ar); 114.50 (<u>C</u>H, Ar); 113.55 (<u>C</u>H, Ar); 89.4 (<u>C</u>); 80.3 (<u>C</u>); 61.0 (<u>C</u>H); 60.3 (<u>C</u>H$_3$).

LRMS (m/z): (M^+ 254), 237, 222, 206, 130, 106, 92

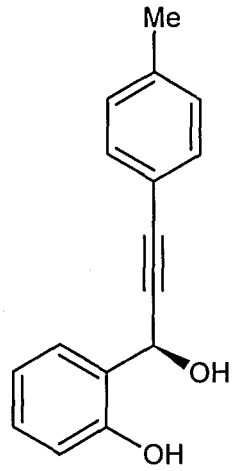
HRMS (EI): [M-OH] observed. 237.0921 for $C_{16}H_{13}O_2$ theoretical.237.0921

The synthesis of 2-[(1R)-1-hydroxy-3-phenylprop-2-yn-1-yl] phenol (200a')



In a 250 mL pre-dried round-bottom flask was added zinc triflate (4.9 g, 13.53 mmol, 1.1 eq) and (+)-(1S, 2R-N-methylephedrine (2.63 g, 14.76 mmol, 1.2 eq) and stirred under nitrogen for 15 minutes. Dry THF (20 mL) and triethylamine (3 mL, 29.52 mmol, and 2.4 eq) was added. The solution left to stir for 2 hours whereupon phenylacetylene (3.77 g, 37.00 mmol, 3.0 eq) was added and stirred for 15 minutes after which 2-hydroxybenzaldehyde **199** (1.5 g, 12.3 mmol, 1 eq) was added. The reaction was carried out for 7 days then tlc analysis showed the new compound with an R_f = 0.2 (petroleum ether (60 °C- 80 °C): diethyl ether 70:30). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a white tissue shape compound (2.23 g, 81.8%). ^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **200a**. The following additional data was obtained. $[\alpha]_D$ = + 12 ° (c = 1%, diethyl ether) ee%= 79.5%, mp = 55 – 56 °C; HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 9.89 major (89.73 %), t_R 9.42 minor (10.27 %).
HRMS (EI): [M$^+$] observed 224.0840 for $C_{15}H_{12}O_2$ theoretical 224.0837.

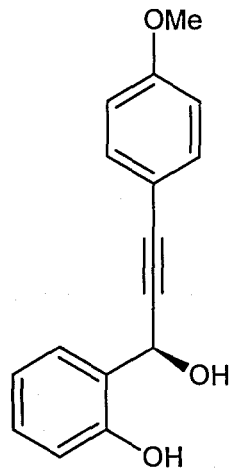
The synthesis of 2-[(1*R*)-1-hydroxy-3- (4-methylphenyl) prop-2-yn-1-yl] phenol (200b')



The same method was employed as described for the synthesis of the **200a'** with the following quantities, zinc triflate (3.3 g, 9.02 mmol, 1.1 eq) and (+)- (1S, 2R-N-methylephedrine (1.76 g, 9.84 mmol, 1.2 eq) after 15 minutes anhydrous THF (20 mL) and triethylamine (2.0 g, 19.86 mmol, 2.4 eq) was added. Then after 2 hours 4-ethyneltoluene (2.85 g, 24.6, 3.0 eq) was added and stirred for 15 minutes after that 2-hydroxybenzaldehyde **199** (1.0 g, 8.2 mmol, 1 eq) was added to the solution. Reaction was carried out for 10 days then tlc showed new compound with an R_f = 0.18 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification by chromatography on silica gel, eluted with (hexane: diethyl ether, 70:30) gave the title product as a white tissue shape compound (1.5 g, 76.9%); ^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **200b**. The following additional data was obtained. mp: 58 - 59 °C; $[\alpha]_D$ = + 19 ° (c = 1%, diethyl ether) ee% = 84.46%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 7.5 minor (7.77 %), t_R 7.83 major (92.27 %).

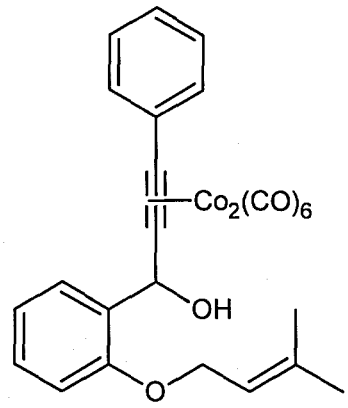
HRMS (EI): [M-H] observed: 237.0913 for $C_{16}H_{13}O_2$ theoretical 237.0913

The synthesis of 2-[(1R)-1-hydroxy-3- (4-methoxyphenyl) prop-2-yn-1-yl] phenol (200c')



The same method was employed as described for the synthesis of the **200a'** with the following quantities, zinc triflate (4.9 g, 13.53 mmol) and (+) - (1S, 2R-N-methylephedrine (2.63 g, 14.76 mmol) after 15 minutes anhydrous THF (20 mL) and triethylamin (3.0 g, 29.52 mmol, 2.4 eq was added. Then after 2 hours 4-ethynylanisole (4.87 g, 37.00 mmol, 3.0 eq) was added and stirred for 15 minutes after that 2-hydroxybenzaldehyde **199** (1.5 g, 12.3 mmol, 1 eq) was added to solution. Reaction was carried out for 10 days then tlc monitoring showed new spot with an R_f = 0.33 (petroleum ether (60 °C- 80 °C): diethyl ether 60:40). Purification by chromatography on silica gel eluted with (hexane: diethyl ether, 70:30) gave the title product as a white tissue shape compound (2.50 g, 80.05%); ^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **200c**. The following additional data was obtained. mp: 48 – 50 °C $[\alpha]_D$ = + 17 ° (c = 1%, diethyl ether); ee% = 59.44% HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.48 major (79.72 %), t_R = 13.11 minor (20.28 %).
HRMS (EI): [M^+] observed 255.1025 for $C_{16}H_{15}O_3$ theoretical 255.1021

The synthesis of hexacarbonyl 1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-phenylprop-2-yn-1-ol dicobalt (201a)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **198a** (0.3 g, 1.02 mmol) and dicobalt octahexacarbonyl (0.35 g, 1.02 mmol). After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.15 (70:30, hexane: ethylacetate). Dark red oil crude product was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ethyl ether (9:1) to afford a dark red oil product (0.55 g, 91.67%).

IR ν_{max} (neat)/cm^{-1}: 3415.6 (m); 2982 (m); 2021.3 (s); 1726.5 (s); 1599.4 (s); 1249.5 (m); 752.5 (w).

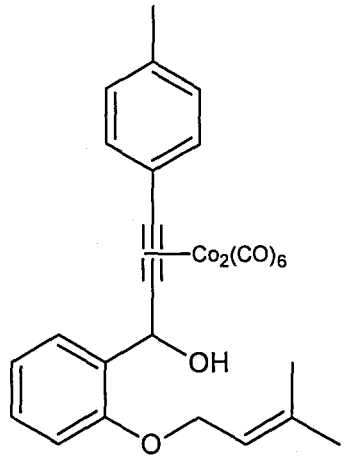
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.52-7.48 (2H, m, Ph); 7.37 (1H, dd, *J* = 7.47, 1.63 Hz, Ph); 7.33-7.24 (4H,m, Ph); 7.32 (1H, td, *J* = 7.4, 1.0 Hz, Ph); 6.89 (1H, d, *J* = 8.0 Hz, Ph); 6.26 (1H, d, *J* = 7.6 Hz C<u>H</u>OH); 5.3 (1H, m, =C<u>H</u>); 4.55-4.40 (2H, m, C<u>H</u>$_2$); 3.85 (1H, d, *J* = 7.6 Hz, O<u>H</u>); 1.73 (3H, d, *J* = 0.7 Hz, C<u>H</u>$_3$); 1.70 (3H, d, *J* = 0.7 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 155.60 (<u>C</u>, Ar); 138.41 (=<u>C</u>); 138.4 (<u>C</u>, Ar); 134.70 (<u>C</u>, Ar); 130.0 (<u>C</u>H, Ar); 129.6 (<u>C</u>H, Ar); 129.0 (<u>C</u>H, Ar); 128.1 (=CH); 127.5 (<u>C</u>H, Ar); 120.7 (<u>C</u>H, Ar); 119.1 (<u>C</u>H, Ar); 111.7 (<u>C</u>H, Ar); 72.8 (<u>C</u>H$_2$); 64.7 (<u>C</u>H); 25.6 (<u>C</u>H$_3$); 18.1 (<u>C</u>H$_3$).

LRMS (m/z): (M- 2xCO 522); 494, 341, 340, 265, 218, 122, 69

HRMS (EI): [M-3CO] observed. 494.0021 for $C_{23}H_{20}O_5Co_2$ theoretical. 494. 0028,

The synthesis of hexacarbonyl 1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-3-(4-methylphenyl) prop-2-yn-1-ol dicobalt (201b)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **198b** (1.0 g, 3.27 mmol) and dicobalt octahexacarbonyl (1.8 g, 3.30 mmol). After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.20 (70:30, hexane: ethyl acetate). Dark red oil crude product was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ethyl ether (9:1) to afford a dark red oil product (1.83 g, 95%).

IR v_{max} (neat)/cm^{-1}: 3436.2 (s); 2920.9 (m); 2021.5 (s); 1669.0 (s); 1229.8 (m); 1016.8 (m); 751.4 (w).

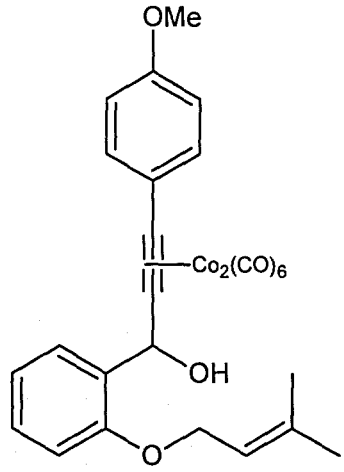
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.43-7.39 (2H, m, Ph); 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, Ph); 7.30-7.24 (1H, m, Ph); 7.14-7.10 (2H, m, Ph); 6.97 (1H, td, *J* = 7.5, 1.00 Hz, Ph); 6.89 (1H, dd (bd); *J* = 8.3, 1.0 Hz, Ph); 6.25 (1H, d, *J*= 7.6 Hz, C<u>H</u>OH); 5.37 (1H, t, *J* = 6.8 Hz, =C<u>H</u>); 4.55-4.43 (2H, m, CH_2); 3.87 (1H, d, *J* = 7.7 Hz, O<u>H</u>); 2.34 (3H, s, C<u>H</u>$_3$); 1.73 (3H, d, *J* = 1.0 Hz, C<u>H</u>$_3$); 1.70 (3H, d, J = 1.0 Hz, C<u>H</u>$_3$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 155.67 (<u>C</u>, Ar); 138.38 (=<u>C</u>); 137.64 (<u>C</u>, Ar); 135.01 (<u>C</u>, Ar); 130.87 (<u>C</u>, Ar); 129.59 (<u>C</u>H, Ar); 129.35 (<u>C</u>H, Ar); 129.03 (<u>C</u>H, Ar); 128.25 (=<u>C</u>H); 120.75 (<u>C</u>H, Ar); 119.14 (<u>C</u>H, Ar); 111.76 (<u>C</u>H, Ar); 72.94 (<u>C</u>H$_2$); 64.72 (<u>C</u>H); 25.70 (<u>C</u>H$_3$); 21.40 (<u>C</u>H$_3$); 18.13 (<u>C</u>H$_3$).

LRMS (m/z): (M – OH 575); 547, 519, 491, 442, 302, 249, 195, 157, 147, 133.

HRMS (EI): [M-Co-OH] observed. 547.0002 for $C_{26}H_{21}O_6Co_2$ theoretical: 547.0024.

The synthesis of hexacarbonyl 3- (4-methoxyphenyl)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl} prop-2-yn-1-ol dicobalt (201c)



The same method was employed as described for the synthesis of the **45** with the following quantities; propargyl alcohol **198c** (1.5 g, 4.66 mmol) and dicobalt octahexacarbonyl (2.6 g, 4.7 mmol). After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.18 (8:2) (hexane: ethyl acetate). Dark red oil crude product was purified *via* a column filled with the silica gel and mobile phase petroleum ether (60 °C- 80 °C) and diethyl ethyl ether (9:1) to afford a dark red oil product (2.73 g, 96.5%).

IR v_{max} (neat)/cm^{-1}: 3500.8 (m); 2960.7 (m); 2192.9 (s); 1727.0 (s); 1599.6 (s); 1288.7 (m); 751.9 (w).

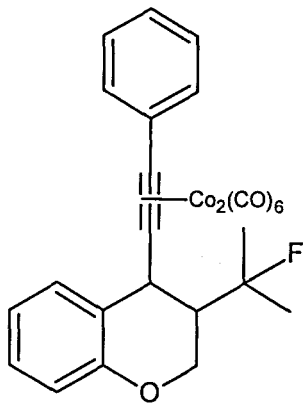
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.46 (2H, d, *J* = 8.8 Hz, Ph); 7.38 (1H, dd, *J* = 7.5, 1.4 Hz, Ph); 6.97 (1H, t, *J* = 7.5 Hz, Ph); 6.85 (1H, d, *J* = 8.8 Hz, Ph); 6.81 (2H, d, *J* = 8.8 Hz, Ph); 6.22 (1H, d, *J* = 7.6 Hz, O<u>H</u>); 5.40 (1H, t, *J* = 6.7 Hz, =C<u>H</u>); 4.51 (2H, d, *J* = 6.7 Hz , OC<u>H</u>$_2$); 3.82 (1H, d, *J* = 7.6 Hz, C<u>H</u>OH); 3.8 (3H, s, OC<u>H</u>$_3$); 1.88 (3H, s, C<u>H</u>$_3$); 1.77 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.48 (<u>C</u>O); 159.24 (<u>C</u>, Ar); 155.69 (<u>C</u>, Ar); 138.44 (=<u>C</u>); 131.08 (<u>C</u>, Ar); 130.86 (<u>C</u>, Ar); 129.95 (<u>C</u>H, Ar); 129.03 (<u>C</u>H, Ar); 128.27 (=<u>C</u>H); 120.76 (<u>C</u>H, Ar); 119.11 (<u>C</u>H, Ar); 114.11 (<u>C</u>H, Ar); 111.77 (<u>C</u>H, Ar); 101.10 (<u>C</u>); 92.75 (<u>C</u>); 72.96 (<u>C</u>H$_2$); 64.73 (<u>C</u>H); 55.35 (<u>C</u>H$_3$); 25.70 (<u>C</u>H$_3$); 18.14 (<u>C</u>H$_3$).

LRMS (m/z): (M – OH) 591; 563, 370, 318, 302, 249, 191, 173, 133.

HRMS (EI): [M-OH] observed. 590.9888 for $C_{27}H_{21}O_8Co_2$ theoretical. 590.9895

The synthesis of hexacarbonyl 3- (2-fluoropropan-2-yl)-4- (phenylethynyl)-3, 4-dihydro-2*H*-chromene dicobalt (203a)



The cobalt complex propargylic alcohol **201a** (0.5 g, 0.87 mmol) has been placed in a flame dried 250 flaskand dissolved in anhydrous DCM (10 mL); mixture then cooled to 0 °C then $BF_3.Et_2O$ (0.5 g, 0.9 mmol) was added drop waise, reaction mixture stired for just 3-5 minutes. After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.9 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Reaction was quenched with distil water and extract with DCM (3 x 20 mL). Combined organic layer was separated from aqueous by a separating funnel and dried over magnesium sulphate. Magnesium sulphate was filtered and DCM was removed *via vacuum*. Dark red oil compound was purified by solvent system petroleum ether (60 °C-80 °C) and ether (90:10); dark red oil compound was isolated (0.82 g, 82%).

IR ν_{max} (neat)/cm^{-1}: 2984.5 (m); 2091.5 (s); 1632.5 (s); 1589.0 (s); 755.0 (w).

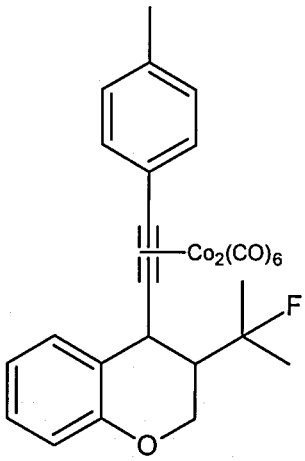
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.43-7.33 (5H, m, Ph); 7.17-7.07 (2H, m, Ph); 6.83 (1H, dd, *J* = 8.2, 1.2 Hz, Ph); 6.80-6.75 (1H, m, Ph); 4.54 (1H, s (bd); C<u>H</u>C≡); 4.38-4.34 (2H, m, C<u>H$_2$</u>); 2.46 (1H, dt, *J* = 10.8, 3.0 Hz, C<u>H</u>CF); 1.49 (3H, d, J_F = 22.6 Hz, CH_3); 1.35 (3H, d, J_F = 22.6 Hz, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.42 (<u>C</u>O); 153.85 (<u>C</u>, Ar); 138.44 (<u>C</u>, Ar); 130.78 (<u>C</u>, Ar); 129.06 (<u>C</u>H, Ar); 128.85 (<u>C</u>H, Ar); 128.63 (<u>C</u>H, Ar); 127.65 (<u>C</u>H, Ar); 124.45 (<u>C</u>H, Ar); 121.07 (<u>C</u>H, Ar); 116.89 (<u>C</u>H, Ar); 106.89 (CF, d, J_F = 169.3 Hz); 97.73 (<u>C</u>); 96.06 (<u>C</u>); 62.62 (<u>C</u>H$_2$, d, J_F = 9.6); 49.78 (<u>C</u>HCF, d, J_F = 23.1 Hz); 37.22 (<u>C</u>H, d, J_F = 4.8 Hz); 26.19 (<u>C</u>H$_3$, d, J_F = 24.6 Hz); 24.62 (<u>C</u>H$_3$, d, J_F = 24.6 Hz).

^{19}F: (376MHz) ($CDCl_3$) δppm: -132.57ppm

HRMS (EI): [M-CO] observed 551.9824 for $C_{25}H_{19}O_6FCo_2$ theoretical 551.9824

The synthesis of hexacarbonyl 3- (2-fluoropropan-2-yl)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene dicobalt (203b)



The same method was employed as described for the synthesis of the **203a** with the following quantities; cobalt complex propargylic alcohol **201b** (1.0 g, 1.68 mmol); $BF_3.Et_2O$ (0.3 g, 2 mmol). After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.9 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Reaction was quenched with distil water and extract with DCM (3 x 20 mL). Organic layer was separated from aqueous by a separating funnel and dried over magnesium sulphate. Magnesium sulphate was filtered and DCM was removed *via vacuum*. Dark red oil compound was purified by solvent system petroleum ether (60 °C- 80 °C) and ether (90:10); dark red oil compound was isolated (0.45 g, 93.55 %).

IR v_{max} (neat)/cm^{-1}: 2983.55(m); 2088.77(s);1605.43 (s);1229.06 (m);755.99 (w).

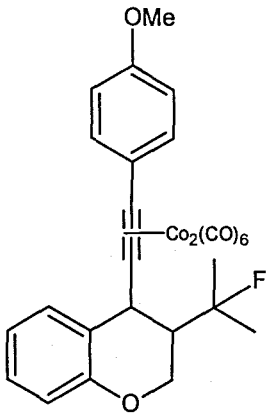
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.28 (1H, s, Ph); 7.16 (2H, d, J = 8.4 Hz, Ph); 7.14-7.08 (2H, m, Ph); 6.81 (1H, dd, J = 8.4, 1.2 Hz, Ph); 6.76 (1H, dt, J = 7.5, 1.2 Hz, Ph); 4.51 (1H, s (bd); C<u>H</u>C≡); 4.35-4.30 (2H, m, C<u>H</u>$_2$); 2.42 (1H, dt, J = 11.0, 2.7 Hz, C<u>H</u>CF); 1.45 (3H, d, J_F = 22.2 Hz, <u>C</u>H$_3$); 1.32 (3H, d, J_F = 22.2 Hz, <u>C</u>H$_3$)

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 204.61 (<u>C</u>O); 158.82 (<u>C</u>, Ar); 142.85 (<u>C</u>, Ar); 139.90 (<u>C</u>, Ar); 135.83 (<u>C</u>, Ar); 134.88 (<u>C</u>H, Ar); 133.84 (<u>C</u>H, Ar); 133.76 (<u>C</u>H, Ar); 129.95 (<u>C</u>H, Ar); 126.03 (<u>C</u>H, Ar); 121.70 (<u>C</u>H, Ar); 106.90 (<u>C</u>, d, J_F= 169.0 Hz); 102.92 (<u>C</u>); 99.93 (<u>C</u>); 67.27 (<u>C</u>H$_2$, d, J_F = 9.5); 54.51 (<u>C</u>HCF, d, J_F = 22.0); 41.74 (<u>C</u>H, d, J_F = 5.0); 30.77 (<u>C</u>H$_3$, d, J_F = 24.8 Hz); 29.85 (<u>C</u>H$_3$, d, J_F = 23.6 Hz); 26.07 (<u>C</u>H$_3$).

^{19}F: (376MHz) (CDCl3) δppm: -131.78

HRMS (EI): [M-3CO] observed. 511.0161 for $C_{27}H_{21}O_7Co_2F$ theoretical. 511.0163

The synthesis of hexacarbonyl 3- (2-fluoropropan-2-yl)-4-[(4-methoxyphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene dicobalt (203c)



The same method was employed as described for the synthesis of the **203a** with the following quantities cobalt complex propargylic alcohol **201c** (1.0 g, 1.64 mmol); $BF_3.Et_2O$ (0.5 g, 3.4 mmol). After 1 hour tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.82 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Reaction was quenched with distil water and extract with DCM (3 x 20 mL). Organic layer was separated from aqueous by a separating funnel and dried over magnesium sulphate. Magnesium sulphate was filtered and DCM was removed *via vacuum*. Dark red oil compound was purified by solvent system petroleum ether (60 °C- 80 °C) and ether (90:10); dark red oil compound was isolated (0.72 g, 72 %).

IR v_{max} (neat)/cm^{-1}: 2985.5 (m); 2051.2 (s); 2022.9 (s); 1605.5 (s); 1490.4 (m); 1230.0 (m); 756.0 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.35-7.31 (2H, m, Ph); 7.16-7.11 (2H, m, Ph); 6.91-6.89 (2H, m, Ph); 6.82-6.75 (2H, m, Ph); 4.51 (1H, s (bd); C<u>H</u>C≡C); 4.32 (2H, d, *J* = 2.8 Hz, C<u>H</u>$_2$); 3.85 (3H, s, OC<u>H</u>$_3$) 2.42 (1H, dt, *J* = 11.1, 2.8 Hz, C<u>H</u>CF); 1.46 (3H, d, *J* = 21.9 Hz, C<u>H</u>$_3$); 1.31 (3H, d, *J* = 21.9 Hz, C<u>H</u>$_3$).

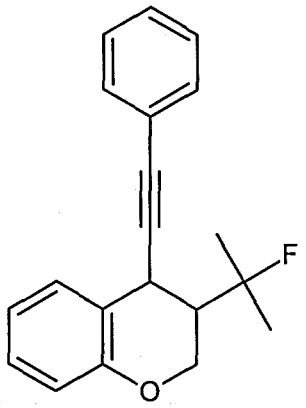
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 199.32 (<u>C</u>O); 159.25 (<u>C</u>, Ar); 153.87 (<u>C</u>, Ar); 130.79 (<u>C</u>, Ar); 130.43 (<u>C</u>, Ar); 129.93 (<u>C</u>H, Ar); 128.62 (<u>C</u>H, Ar); 124.43 (<u>C</u>H, Ar), 121.05 (<u>C</u>H, Ar), 116.86 (<u>C</u>H, Ar), 114.36 (<u>C</u>H, Ar), 106.27 (<u>C</u>F, d, J_F= 168.9 Hz); 97.80 (<u>C</u>); 94.60 (<u>C</u>); 62.57 (<u>C</u>H$_2$, d, J_F = 9.6); 55.38 (O<u>C</u>H$_3$); 49.80 (<u>C</u>HCF, d, J_F = 23.1 Hz,); 37.28 (<u>C</u>H, d, J_F = 5.1 Hz); 26.23 (<u>C</u>H$_3$, d, J_F = 24.6 Hz); 24.62 (<u>C</u>H$_3$, d, J_F = 24.6 Hz).

^{19}F: (376MHz) (CDCl3) δppm: -132.3

LRMS (m/z): (M^+610), 590, 563, 555, 534, 527

HRMS (EI): [M+H] observed. 610.9949 for $C_{27}H_{22}O_8Co_2F$ theoretical. 610.9957

The synthesis of 3- (2-fluoropropan-2-yl)-4- (phenylethynyl)-3, 4-dihydro-*2H*-chromene (204a)



The same method was employed as described for the synthesis of the **185a** with the following quantities, Cobalt complex **203**a (0.5 g, 0.29 mmol); saturated solution of the CAN in methanol (35 mL). After 10 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.78 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) to afford title compound as a colourless oil (0.65 g, 66.4%).

IR ν_{max} (neat)/cm^{-1}: 3029.0 (s); 2922.6 (m); 1768.8 (w); 1586.1 (w); 1489.7 (m); 754.5 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.52-7.46 (1H, m, Ph); 7.43-7.38 (2H, m, Ph); 7.32-7.26 (3H, m, Ph); 7.15 (1H, ddd, *J* = 8.0, 7.5, 1.2 Hz, Ph); 6.98 (1H, dt, *J* = 7.5, 1.2 Hz, Ph); 6.85 (1H, dd, *J* = 8.0, 1.2 Hz, Ph); 4.51 (1H, dt, *J* = 11.7, 3.3 Hz, C$\underline{H}_2$); 4.18 (1H, dd, *J* = 11.7, 6.0 Hz, C$\underline{H}_2$); 4.12 (1H, d, *J* = 5.6 Hz, C$\underline{H}$C≡C); 2.58-2.63 (1H, m, C$\underline{H}$CF); 1.55 (3H, d, J_F = 20.1 Hz,C$\underline{H}_3$); 1.48 (3H, d, J_F = 20.1 Hz, C$\underline{H}_3$).

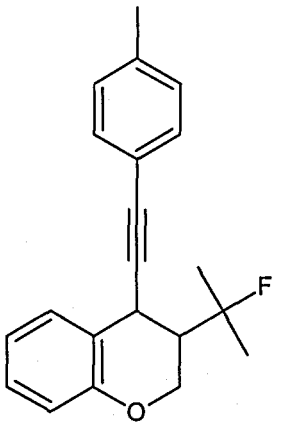
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 153.97 ($\underline{C}$, Ar); 131.59 ($\underline{C}$, Ar); 130.18 ($\underline{C}$, Ar); 128.28 ($\underline{C}$H, Ar); 128.26 ($\underline{C}$H, Ar); 128.08 ($\underline{C}$H, Ar); 123.27 ($\underline{C}$H, Ar); 121.89 ($\underline{C}$H, Ar); 121.27 ($\underline{C}$H, Ar); 116.94 ($\underline{C}$H, Ar); 96.64 ($\underline{C}$F, d, J_F = 168.5 Hz); 91.92 ($\underline{C}$); 82.58 ($\underline{C}$); 64.53 ($\underline{C}H_2$, d, J_F= 9.9 Hz); 47.57 ($\underline{C}$HCF, d, J_F = 22.5 Hz); 28.96 ($\underline{C}$H, d, J_F = 5.6 Hz); 26.16 ($\underline{C}H_3$, d, J_F = 24.5 Hz); 25.19 ($\underline{C}H_3$, d, J_F = 24.5 Hz).

^{19}F: (376MHz) ($CDCl_3$) δppm: -135.25

LRMS (m/z): (M^+259), 231, 215, 205, 189, 178, 152, 132, 115, 77, 61, 51**HRMS**

HRMS (EI): [M^+] observed. 294.1415 for $C_{20}H_{19}OF$ theoretical. 294.1414

The synthesis of 3- (2-fluoropropan-2-yl)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene (204b)



The same method was employed as described for the synthesis of the **185a** with the following quantities; cobalt complex **203b** (0.5 g, 0.84 mmol); saturated solution of the CAN in methanol (35 mL). After 10 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.72 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) to afford title compound as a colourless oil (0.18 g, 70%).

IR v_{max} (neat)/cm^{-1}: 3029.0 (s); 2922.5 (m); 1768.7 (m); 1586.1 (w); 1489.7 (m); 1141.3 (m); 754.8 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.54 (1H, d, J = 7.7 Hz, Ph); 7.35 (2H, d, J = 8.0, Ph); 7.20-7.16 (1H, m, Ph); 7.14 (2H, d, J = 7.7 Hz, Ph); 7.00 (1H, dd, J = 7.7, 1.0 Hz, Ph); 6.89 (1H, dd, J = 8.0, 1.0 Hz, Ph); 4.58 (1H, ddd, J = 11.6, 3.1, 2.4 Hz, C$\underline{H}_2$); 4.20 (1H, dd, J = 11.6, 6.0, C$\underline{H}_2$); 4.15 (1H, d, J = 4.0 Hz, C$\underline{H}$C≡C); 2.53 (1H, ddd, J = 11.6, 5.6, 3.1 Hz, C$\underline{H}$CF); 1.57 (3H, d, J_F = 19.0 Hz, $\underline{C}H_3$); 1.52 (3H, d, J_F = 19.0 Hz, $\underline{C}H_3$)

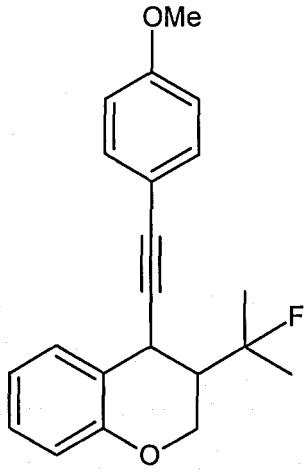
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 154.02 ($\underline{C}$, Ar); 138.16 ($\underline{C}$, Ar); 131.51 ($\underline{C}$, Ar); 130.24 ($\underline{C}$, Ar); 129.10 ($\underline{C}$H, Ar); 128.26 ($\underline{C}$H, Ar); 122.08 ($\underline{C}$H, Ar); 121.27 ($\underline{C}$H, Ar); 120.28 ($\underline{C}$H, Ar); 116.96 ($\underline{C}$H, Ar); 96.5 ($\underline{C}$F, d, J_F = 168.5 Hz); 91.22 ($\underline{C}$); 82.74 ($\underline{C}$); 64.60 ($\underline{C}H_2$, d, J_F = 10.0 Hz); 47.65 ($\underline{C}$HCF, d, J_F = 22.5 Hz); 29.09 ($\underline{C}$H, d, J_F = 5.6 Hz); 26.28 ($\underline{C}H_3$, d, J = 24.5 Hz); 25.17 ($\underline{C}H_3$, d, J_F = 24.5 Hz); 21.51 ($\underline{C}H_3$).

^{19}F: (376MHz) (CDCl3) δppm: -135.5

LRMS (m/z): (M^+308), 288, 273, 265, 247, 232, 220, 205, 189, 176, 165, 156, 132, 115, 105, 105, 91, 77, 51.

HRMS (EI): [M^+] observed. 308.1570 for $C_{21}H_{21}OF$ Theoretical. 308.1571

The synthesis of 3- (2-fluoropropan-2-yl)-4-[(4-methoxyphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene (204c)



The same method was employed as described for the synthesis of the **185a** with the following quantities, cobalt complex **203**c (0.5 g, 0.82 mmol); saturated solution of the CAN in methanol (35 mL). After 10 minutes tlc monitoring showed the loss of the starting material and the presence of a new compound with an R_f = 0.80 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30). Purification have carried out *via* flash chromatography (petroleum ether (60 °C- 80 °C): diethyl ether, 80:20) to afford title compound as a colourless oil (0.19 g, 73%).

IR ν_{max} (neat)/cm^{-1}: 3029.0 (s); 2982.7 (m); 1768.8 (w); 1586.1 (m); 1375.3 (m); 754.5 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.50-7.49 (1H, m, Ph); 7.37-7.31 (2H, m, Ph); 7.15 (1H, ddd, *J* = 8.0, 7.3, 1.6 Hz,Ph); 6.95 (1H, dd, *J* = 7.5, 1.1 Hz, Ph); 6.86-6.79 (3H, m, Ph); 4.50 (1H, dd, *J* = 11.5, 2.6 Hz, C$\underline{H}_2$); 4.17 (1H, dd, *J* = 11.5, 6.0 Hz, C$\underline{H}_2$); 4.1 (1H, d, *J* = 4.0 Hz, C$\underline{H}$C≡C); 3.79 (1H, s, O$\underline{C}H_3$); 2.50-2.45 (1H, m, C$\underline{H}$CF); 1.53 (3H, d, *J* =20.5 Hz, $\underline{C}H_3$); 1.47 (3H, d, *J* = 20.5 Hz, $\underline{C}H_3$).

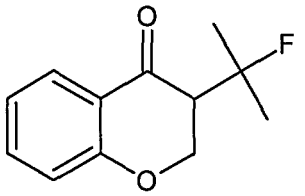
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 159.41 ($\underline{C}$, Ar); 153.91 ($\underline{C}$, Ar); 132.93 ($\underline{C}$, Ar); 130.17 ($\underline{C}$, Ar); 124.30 ($\underline{C}$H, Ar); 122.10 ($\underline{C}$H, Ar); 121.19 ($\underline{C}$H, Ar); 116.87 ($\underline{C}$H, Ar); 115.39 ($\underline{C}$H, Ar); 113.88 ($\underline{C}$H, Ar); 97.00 ($\underline{C}$F, d, J_F = 169.0 Hz); 90.36 ($\underline{C}$); 82.39 ($\underline{C}$); 64.55 ($\underline{C}H_2$, d, J_F = 10.0 Hz); 55.31 ($\underline{C}H_3$); 47.62 ($\underline{C}$HCF, d, J_F = 22.4 Hz); 29.00 ($\underline{C}$H, d, J_F = 5.9 Hz); 26.21 ($\underline{C}H_3$, d, J_F = 24.6 Hz); 25.13 ($\underline{C}H_3$, d, J_F = 24.6 Hz).

^{19}F: (376MHz) ($CDCl_3$) δppm: -133.3

LRMS (m/z): (M^+325), 282, 209, 189, 153, 135.

HRMS (EI): [M^+] observed 324.1520 for $C_{21}H_{21}O_2F$ theoretical 324.1520

The synthesis of 3- (2-fluoropropan-2-yl)-2, 3-dihydro-*4H*-chromen-4-one (205)



The fluoro chromene **204b** (0.1 g, 0.33 mmol) was left under air for 24 - 48 hours, the colourless oil compound changed to yellow nidel crystalles. Tlc showed the loss of **204b** and presence of a new compound with an R_f = 0.75 (hexane: diethyl ether 70:30) and characterise analysis confirmed the title compound (0.05 g, 71.4%).

IR v_{max} (neat)/cm^{-1}: 2920.5 (m); 1651.0 (s); 1606.9 (m); 1501.6 (w); 850.1 (m); 775.3 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.90 (1H, dd, *J* = 7.5, 1.8 Hz, Ph); 7.47 (1H, ddd, *J* = 8.0, 7.0, 1.8 Hz, Ph); 7.50-7.55 (1H, m, Ph); 6.97 (1H, dd, *J* = 8.0, 0.9 Hz, Ph); 4.55 (1H, ddd, *J* = 11.6, 3.3, 2.3 Hz, CH_2); 4.22 (1H, dd, *J* = 11.6, 6.0 Hz, CH_2); 3.06 (1H, td, *J* = 7.6, 5.1 Hz, CHCF); 1.71 (3H, d, J_F = 23.6 Hz, CH_3); 1.20 (3H, d, J_F = 23.6 Hz, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 189.99 (CO); 155.00 (C, Ar); 132.98 (C, Ar); 128.26 (CH, Ar); 122.08 (CH, Ar); 120.28 (CH, Ar); 116.96 (CH, Ar); 96.5 (CF, d, J_F = 168.5 Hz); 65.50 (CH_2, d, J_F = 9.5 Hz); 46.10 (CHCF, d, J_F = 22.0 Hz); 26.37 (CH_3, d, *J* = 24.5 Hz); 25.25 (CH_3, d, J_F = 24.5 Hz)

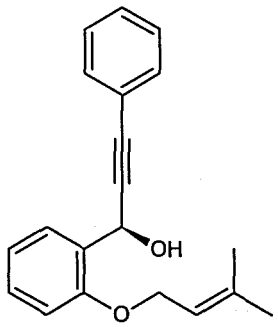
^{19}F: (376MHz) ($CDCl_3$) δppm: -135.5

LRMS (m/z): (M^+208), 188, 173, 147, 120, 92, 77, 64.

HRMS (EI): [M^+] observed. 208.0893 for $C_{12}H_{13}O_2F$ theoretical. 208.0894

3.4.5 The asymmetric synthesis of benzopyrans

The synthesis of (1*R*)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-3-phenylprop-2-yn-1-ol (206a)

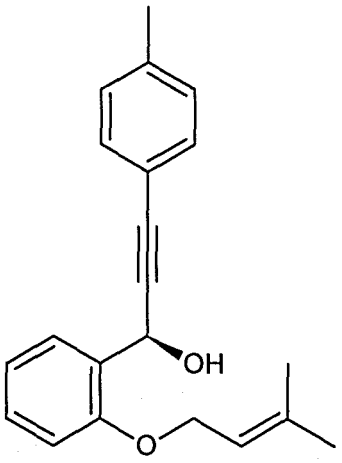


Method 1: The same method was employed as described for the synthesis of the **187a** with the following quantities; $Zn(OTf)_2$ (1.14g, 2.9mmol, 1.1eq) and (+) – (1S,2R)-N-methylephedrine (0.57 g, 3.16 mmol, 1.2 eq) and purged with nitrogen for 15 minutes. Then, toluene (15 mL) and triethylamine (0.64 g, 6.31 mmol, and 2.4 eq) were added by syringe. The resulting mixture was left to stir for 2 hours before the phenylacetylene (0.806 g, 7.9 mmol, 3 eq) was added by syringe in one portion. After 15 minutes of stirring, 2- (3-methyl-but-2-enyloxy) benzaldehyde **197** (0.5 g, 2.63 mmol, 1 eq) was added in one portion. After stirring for 7 days tlc monitoring showed new compound R_f = 0.5 (hexane: diethyl ether, 70:30); purification by chromatography on silica gel, using 80:20 light petroleum spirit (60 °C- 80 °C): diethyl ether, gave the titled chiral secondary alcohol as a colourless oil (0.56 g, 72.73%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **198a**. The following additional data was obtained. $[\alpha]_D$ = +10 °(c = 1% ethanol), 95.0% ee HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 16.59 major (97.55 %), t_R = 12.06 minor (2.45 %).

HRMS (EI): [M-H] observed 291.1383 for $C_{20}H_{19}O_2$ theoretical 291.1380,

Method 2: Propargyl alcohol **200a** (1.0 g, 4.5 mmol) was placed in a 250 flame-dry flask maintained under an atmosphere of nitrogen and at an ambient temperature and anhydrous DMF (20 mL) was added. Potassium carbonate (2.5 g, 18.0 mmol) and potassium iodide (0.075 g, 0.45 mmol) were added followed by 4-bromo-2-methyl-2-butene (0.67 g, 4.5 mmol). The reaction mixture was left to stir for 3 hours after which tlc monitoring showed the presence of a new compound with an R_f = 0.49 (petroleum ether (60 °C- 80 °C): diethyl ether 60:40). The colourless oil that was isolated was sufficiently pure. The yield was (0.85 g, 65.4%). ee % = 72%

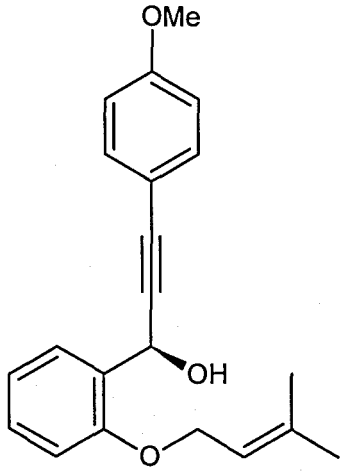
The synthesis of (1*R*)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-3- (4-methylphenyl) prop-2-yn-1-ol (206b)



The same method was employed as described for the synthesis of the **187a** with the following quantities; Zn $(OTf)_2$ (2.3 g, 5.8 mmol, 1.1 eq) and (+)- (1S,2R)-N-methylephedrine (1.15 g, 6.4 mmol, 1.2 eq) and purged with nitrogen for 15 minutes. Then, toluene (15 mL) and triethylamine (1.3 g, 12.7 mmol, and 2.4 eq) were added by syringe. The resulting mixture was left to stir for 2 hours before the 1-ethynyl-4-methylbenzene (1.86 g, 16 mmol) was added by syringe in one portion. After 15 minutes of stirring, 2- (3-methyl-but-2-enyloxy) benzaldehyde **197** (1.0 g, 5.3 mmol, and 1eq) was added in one portion. After stirring for 7 days tlc monitoring showed new compound R_f = 0.6 (hexane: diethyl ether, 70:30); purification by chromatography on silica gel, using 80:20 light petroleum spirit (60 °C- 80 °C): diethyl ether, gave the chiral secondary alcohol as a colourless oil (1.35 g, 83.85%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **198b**. The following additional data was obtained. $[\alpha]_D$ = - 13 ° (c= 1%, diethyl ether), ee% = 96% HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 7.9 (98%) major and t_R = 5.0 (2%) minor

HRMS (EI): [M-H] observed 305.1536 for $C_{21}H_{21}O_2$ theoretical 305.1536.

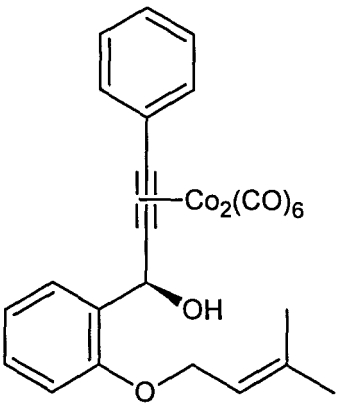
The synthesis of (1*R*)-3- (4-methoxyphenyl)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl} prop-2-yn-1-ol (206c)



The same method was employed as described for the synthesis of the **187a** with the following quantities; Zn $(OTf)_2$ (3.42 g, 8.7 mmol, 1.1 eq) and (+)- (1S,2R) - N - methylephedrine (1.70 g, 9.5 mmol, 1.2 eq) and purged with nitrogen for 15 minutes. Then, toluene (15 mL) and triethylamine (1.92 g, 19.0 mmol, 2.4 eq) were added by syringe. The resulting mixture was left to stir for 2 hours before the1-ethynyl-4-methoxybenzene (3.13 g, 23.7 mmol, 3 eq) was added by syringe in one portion. After 15 minutes of stirring, 2- (3-methyl-but-2-enyloxy) benzaldehyde **197** (1.5 g, 7.9 mmol, 1 eq) was added in one portion. After stirring for 7 days tlc monitoring showed new compound R_f = 0.48 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30); purification by chromatography on silica gel, using 80:20 petroleum ether (60 °C- 80 °C): diethyl ether, gave the chiral secondary alcohol as a colourless oil (2.35g, 92.5%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **198c**. The following additional data was obtained. $[\alpha]_D$ = + 11 ° (c = 1%, diethyl ether). ee% = 97% HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.17 major (98.53 %), t_R = 9.88 minor (1.47 %).

HRMS (EI): $[M^+]$ observed 322.1804 for $C_{21}H_{22}O_3$, theoretical 322.1805

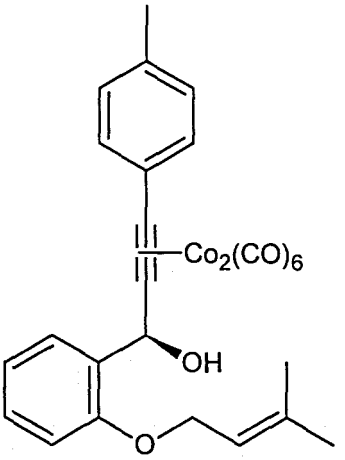
The synthesis of hexacarbonyl (1*R*)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-3-phenylprop-2-yn-1-ol dicobalt (207a)



The same method was employed as described for the synthesis of the **177a** with the following quantities; propargyl alcohol **206a** (0.4 g, 1.37 mmol) and dicobalt octacarbonyl (0.513 g, 1.5 mmol). Tlc showed a dark red spot in R_f = 0.48 (hexane: diethyl ether, 75:25). Purification by chromatography on silica gel, using 80:20 petroleum ether (60 °C- 80 °C): diethyl ether, gave the chiral secondary alcohol as a dark red oil (0.772 g, 97.5%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **201a**. The following additional data was obtained.

HRMS (EI): [M-3CO] observed 494.0021 for $C_{23}H_{20}O_5Co_2$ theoretical 494.0028

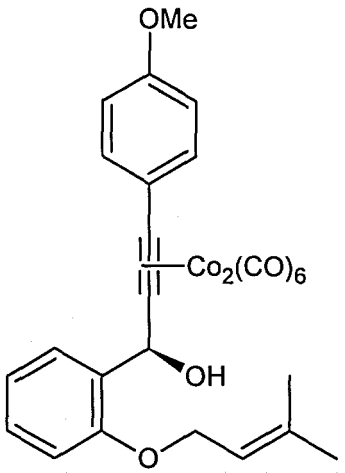
The synthesis of hexacarbonyl (1*R*)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl}-3- (4-methylphenyl) prop-2-yn-1-ol (207b)



The same method was employed as described for the synthesis of the **207a** with the following quantities; propargyl alcohol **206b** (1.2 g, 3.92 mmol) and dicobalt octacarbonyl (1.5 g, 4.31 mmol). Tlc showed a dark red spot in R_f = 0.53 (hexane: diethyl ether, 70:30). Purification by chromatography on silica gel, using 80:20 petroleum ether (60 °C- 80 °C): diethyl ether, gave the chiral secondary alcohol as a dark red oil (2.27 g, 97.84%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **201b**. The following additional data was obtained.

HRMS (EI): [M-CO-OH] observed 547.0002 for $C_{26}H_{21}O_6Co_2$ theoretical 547.0024

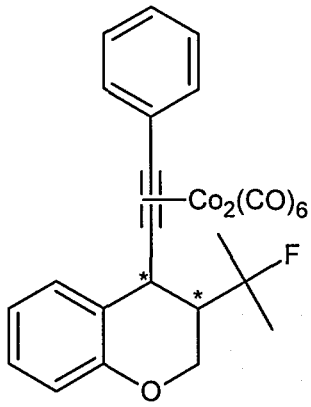
The synthesis of hexacarbonyl (1*R*)-3- (4-methoxyphenyl)-1-{2-[(3-methylbut-2-en-1-yl) oxy] phenyl} prop-2-yn-1-ol (207c)



The same method was employed as described for the synthesis of the **207a** with the following quantities; propargyl alcohol **206c** (2.2 g, 6.83 mmol) and dicobalt octacarbonyl (2.6 g, 7.5 mmol). Tlc showed a dark red spot in R_f = 0.57 (hexane: diethyl ether, 60:40). Purification by chromatography on silica gel, using 80:20 petroleum ether (60 °C- 80 °C): diethyl ether, gave the chiral secondary alcohol as a dark red oil (3.96 g, 95.4%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **201c**. The following additional data was obtained.

HRMS (EI): [M-OH]: observed 590.9888, for $C_{27}H_{21}O_8Co_2$ theoretical 590.9895

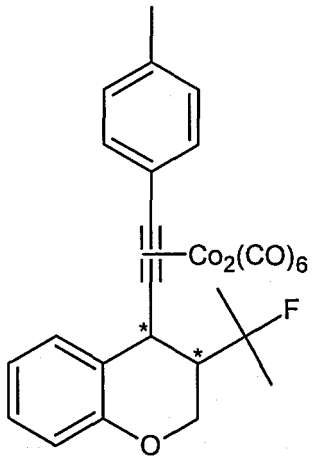
The synthesis of *syn*-hexacarbonyl-3-(2-fluoropropan-2-yl)-4-(phenylethynyl)-3, 4-dihydro-2*H*-chromene dicobalt (208a)



Cobalt complex propargyl alcohol **207a** (0.38 g, 0.66 mmol, 1 eq) was placed to preheated round bottom flask in dry DCM under nitrogen atmosphere. Solution then cooled in dry ice to -78 °C, $BF_3.Et_2O$ (0.2 g, 1.32 mmol, 2 eq) was added drop wise. Solution mixture stirred for 20 minutes. Tlc monitoring showed a faster moving compound R_f = 0.8 (hexane: diethyl ether, 70:30). Reaction was quenched with distil water (20 mL) and extract with DCM (3 x 20 mL). Combined organic layer was separated and dried over magnesium sulphate. Magnesium sulphate was filtered and DCM was removed *via vacuum*. Dark red oil crude as a title product isolated (0.29 g, 76.3%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **203a**. The following additional data was obtained.

HRMS (EI) [M-CO] observed 551.9832 for $C_{25}H_{19}O_6Co_2F$ theoretical 551.9829

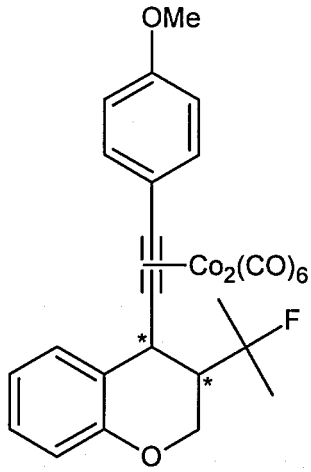
The synthesis of *syn* hexacarbonyl 3-(2-fluoropropan-2-yl)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene dicobalt (208b)



The same methos as **a** was employed with the following quantities; cobalt complex propargyl alcohol **207b** (1.5 g, 2.53 mmol) was placed to pre-heated round-bottom flask in dry DCM (15 mL) under nitrogen atmospher. Solution then cooled in dry ice till -78 °C, $BF_3.Et_2O$ (0.72 g, 5.0 mmol) was added drop wise after 20 minutes tlc monitoring showed a faster moving compound R_f = 0.9 (hexane: diethyl ether 60:40). Dark red oil crude as a title product isolated (1.17 g, 78.0%). ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **203b**. The following additional data was obtained.

HRMS (EI): [M-3CO] observed 511.0161 for $C_{27}H_{21}O_7Co_2F$ theoretical 511.0163

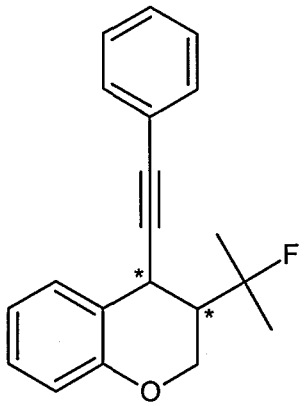
The synthesis of syn hexacarbonyl 3-(2-fluoropropan-2-yl)-4-[(4-methoxyphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene dicobalt (208c)



The same methos as **a** was employed with the following quantities; cobalt complex propargyl alcohol **207c** (3.5 g, 5.76 mmol) was placed to preheated round-bottom flask in dry DCM (25 mL) and then $BF_3.Et_2O$ (1.6 g, 11.5 mmol) was added drop wise. Solution leftt to stir for 20-30 minutes in -78 °C then tlc monitoring showed a faster moving compound R_f = 0.77 (hexane: diethylether, 70:30). Dark red oil crude as a title product isolated (2.67 g, 76.07%). NMR analysis showed cyclised compound. ^1H and ^{13}C and IR and LRMS spectra are identical with the data for compound **203c**. The following additional data was obtained.

HRMS (EI): [M+H] observed 610.9949 for $C_{27}H_{22}O_8Co_2F$ theoretical 610.9957

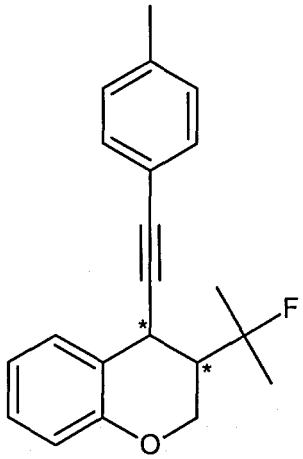
The synthesis of syn (3-(2-fluoropropan-2-yl)-4-(phenylethynyl)-3, 4-dihydro-2*H*-chromene (209a)



The same method was employed as described for the synthesis of the **185a** with the following quantities, Cobalt complex chromene **208a** (0.2 g, 0.116 mmol); and saturated solution of the CAN (25 mL). Tlc showed new colourless compound R_f = 0.87 (hexane: diethyl ether, 70:30) (65 mg, 64.4%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **204**a. The following additional data was obtained. $[\alpha]_D$ = - 9 ° (c = 1%, diethyl ether); ee% = 94.0%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.35 major (96.9 %), t_R = 9.83 minor (2.86 %).

HRMS (EI): [M^+] observed 294.1415 for $C_{20}H_{19}OF$ theoretical 294.1414

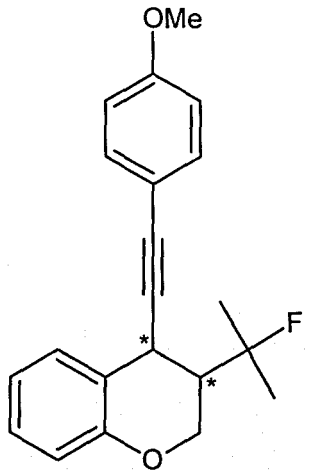
The synthesis of syn 3-(2-fluoropropan-2-yl)-4-[(4-methylphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene (209b)



The same method was employed as described for the synthesis of the **185a** with the following quantities, Cobalt complex chromene **208b** (0.8 g, 1.35 mmol); and saturated solution of the CAN (25 mL). Tlc showed new colourless compound R_f = 0.85 (hexane: diethyl ether, 70:30) (308 mg, 74.2%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **204b**. The following additional data was obtained. $[\alpha]_D$ = - 11 ° (c = 1%, diethyl ether) ee% = 88.7, major enantiomer t_R = 9.79 (94.35); minor enantiomer t_R = 7.93 (5.65)

HRMS (EI): [M^+] observed 308.1570, for $C_{21}H_{21}OF$ theoretical 308.1571

The synthesis of syn-3- (2-fluoropropan-2-yl)-4-[(4-methoxyphenyl) ethynyl]-3, 4-dihydro-2*H*-chromene (209c)

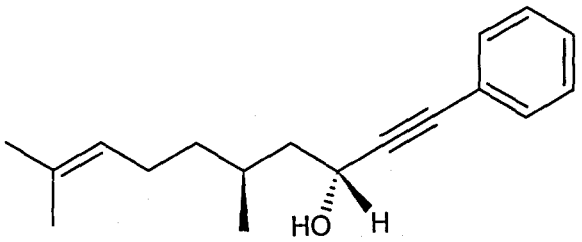


The same method was employed as described for the synthesis of the **185a** with the following quantities, Cobalt complex chromene **208c** (2.5 g, 4.09 mmol); and saturated solution of the CAN in methanol (25 mL). Tlc showed new colourless compound R_f = 0.85 (hexane: diethyl ether, 70:30) (0.98 g, 73.7%).^{1}H and ^{13}C and IR and LRMS spectra are identical with the data for compound **204**c. The following additional data was obtained. $[\alpha]_D$ = + 15 ° (c = 1%, diethyl ether) ee% = 87.3%, HPLC (Chiralcel OD-H, 10% *i*-PrOH-hexane, 254 nm): t_R = 13.22 major (93.55 %), t_R = 11.05 minor (6.25 %).

HRMS (EI): [M+] observed 324.1520 for $C_{21}H_{21}O_2F$ theoretical 324.1520.

3.4.6 Use of chiral pool and chiral auxiliary

The synthesis of (3*R*, 5*S*)-5, 9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (211a)



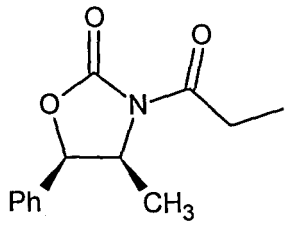
The same method was employed as described for the synthesis of the **187a**, using the following quantities Zn $(OTf)_2$ (2.64 g, 7.3 mmol) and (+)- (1S, 2R-N-methylephedrine (1.45 g, 8.0 mmol) and purged with N_2, stirred for 15 minutes whereupon toluene (40 mL) and triethylamine (Et_3N) (1.60g, 15.9mmol) was added *via* a syringe. after 2 hours phenylacetylene (2.0 g, 19.3 mmol) was added by syringe in one portion. After 15 minutes of stirring (R) - (+) - citronellal (1.02 g, 6.60 mmol, and 1 eq) was added in one portion. It took 10 days to complete the reaction and tlc monitoring showed less amount of the citronellal remained and revealed a new spot in R_f = 0.90 (petroleum ether (60 °C- 80 °C): diethyl ether, 70:30) to keep intact the diastereomers purification was not carried out. The yield of the title compound (1.5 g, 88.2%) $[\alpha]_D$ = +110 ° (c = 1%, ethanol)

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.5-7.2 (5H, m, Ph); 5.00 (1H, t brd, *J* = 6.3 Hz, C<u>H</u>); 4.55 (1H, t, *J* = 5.5, C<u>H</u>); 2.3 (1H, s, O<u>H</u>); 2.0-1.75 (2H, m, C<u>H</u>$_2$); 1.75-1.25 (2H, m, C<u>H</u>$_2$); 1.6 (3H, s, C<u>H</u>$_3$); 1.5 (3H, s, C<u>H</u>$_3$); 1.45-1.08 (3H, m, C<u>H</u> and C<u>H</u>$_2$); 0.92 (3H, d, *J* = 6.5 Hz, C<u>H</u>$_3$) major = 78%, 0.76 (3H, d, *J* = 6.5 Hz, C<u>H</u>$_3$) minor = 22%.

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 131.73 (<u>C</u>, Ar); 131.3 (=<u>C</u>); 128.5 (<u>C</u>H, Ar); 128.4 (<u>C</u>H, Ar); 126.8 (=<u>C</u>H); 124.7 (<u>C</u>H, Ar); 90.0 (<u>C</u>); 85.0 (<u>C</u>); 61.25 (<u>C</u>H); 45.36 (<u>C</u>H$_2$); 37.2 (<u>C</u>H$_2$); 29.15 (<u>C</u>H$_2$); 25.80 (<u>C</u>H); 25.45 (<u>C</u>H$_3$); 19.40 (<u>C</u>H$_3$); 17.85 (<u>C</u>H$_3$).

LRMS (m/z): (M^- 255), 223, 213, 195, 181, 171, 131, 115, 103, 91, 77, 69, 55.

The synthesis of (4*S*, 5R)-4-methyl-5-phenyl-3-propanoyl-1, 3-oxazolidin-2-one (218a)



To a stirred solution of (4S,5R)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (0.88 g, 5 mmol, 1eq) in dry THF (10 mL) at -78 °C maintained under nitrogen atmosphere, was added n-BuLi, (2 mL of a 2.5 M solution in hexane, 5 mmol, 2eq). When the addition was complete the solution went from colourless to orange. The solution was left to stir for 30 minutes after which was added propionyl chloride (0.5 g, 5.5 mmol, 1.1 eq). The mixture was left to stir at -78 °C for 30 minutes and then for 3 hours at 0 °C. Tlc monitoring showed new compound with an R_f = 0.5 (hexane: ethyl acetate 70:30). The reaction was quenched by addition of a saturated solution of NH_4Cl (10 mL) and the solvent was removed by rotary evaporation and replaced by ethyl acetate (20 mL). The organic layer was extracted and consecutively washed with saturated a solution of sodium bicarbonate (3 x 20 mL) and then brine (3 x 20 mL). Finally the organic layer was isolated, dried over anhydrous magnesium sulphate, filtered and evaporated in *vacuo*. Purification by flash chromatography on silica gel (hexane: ethyl acetat, 70:30) gave the title compound as a colourless oil (1.15g, 99%). $[\alpha]_D$ = -40 ° (c = 2% methylen chloride); (lit. value is for the enantiomer to **218a**: +42, c = 2.1% CH_2Cl_2)[98-99]

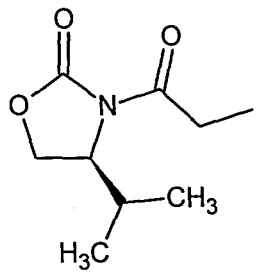
IR v_{max} (neat)/cm^{-1}: 2990.0 (m); 1785.7 (s); 1370.3 (m); 1200.0 (w); 1125.2 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.35-7.33 (5H, m, Ph); 5.63 (1H, d, *J* = 7.2 Hz, PhC<u>H</u>); 4.75-4.70 (1H, m, CH_3C<u>H</u>); 2.93 (2H, q, *J* = 7.5 Hz, C<u>H</u>$_2$); 1.17 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$); 0.88 (3H, d, *J* = 6.8 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 173.90 (<u>C</u>O); 153.20 (<u>C</u>O); 133.54 (<u>C</u>, Ar); 128.78 (<u>C</u>H, Ar); 125.73 (<u>C</u>H, Ar); 122.5 (<u>C</u>H, Ar); 79.0 (<u>C</u>H); 54.8 (<u>C</u>H); 29.37 (<u>C</u>H$_2$); 14.66 (<u>C</u>H$_3$); 8.38 (<u>C</u>H$_3$).

LRMS (m/z): (M^+233), 107, 70, 57.

The synthesis of (4*S*)-3-propanoyl-4- (propan-2-yl)-1,3-oxazolidin-2-one (218b)



The same method was employed as described for the synthesis of compound **218a**, using the following quantities (4*S*)-4- (propan-2-yl)-1,3-oxazolidin-2-one (0.645 g, 5.0 mmol); n-BuLi (2 mL of the 2.5 M in hexane, 5.0 mmol); and propionyl chloride (0.5 g, 5.5 mmol); to yield title compound (0.916 g, 99%) of as a colorless liquid, bp 60-62 °C, $[\alpha]_D$ = +83 ° (c =0.5% methylen chloride); (lit. values: +92, c = 0.38, CH_2Cl_2)[116]

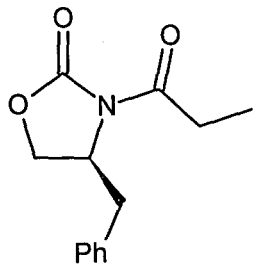
IR v_{max} (neat)/cm^{-1}: 2970.0 (m); 2880.5 (m); 1785.3 (s); 1705.6 (m); 1385.7 (w); 1370.5 (w); 1245.4 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 4.39-4.34 (m, 1 H, C<u>H</u>N); 4.19 (2H, dd, *J* = 8.0, 4.0 Hz, O<u>C</u>H_2); 2.90 (2H, q, *J* = 7.6, 2.9 Hz, C<u>H</u>$_2$CH_3); 2.33-2.29 (1H, m, CH (C<u>H</u>$_3$)$_2$); 1.09 (3H, t, *J* = 7.6 Hz, CH_2C<u>H</u>$_3$); 0.87-0.79 (3H, m, CH (C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 174.03 (<u>C</u>O); 154.2 (<u>C</u>O); 63.42 (<u>C</u>H_2O); 58.4 (<u>C</u>HN); 29.13 (<u>C</u>H_2); 28.39 (<u>C</u>H(CH_3)$_2$); 17.94 (<u>C</u>H_3); 14.63 (<u>C</u>H_3); 8.43 (<u>C</u>H_3).

LRMS (m/z): (M^+185), 142, 129 (100%), 57.

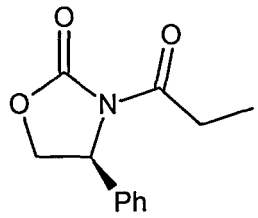
The synthesis of (4R)- (+)-4-benzyl-3-propionyl-oxazolidin-2-one (218c)



The same method was employed as described for the synthesis of compound **218a**, using the following quantities (4R)-4-Benzyl-2-oxazolidinone (0.886 g, 5.0 mmol); n-BuLi (2 mL of the 2.5 M in hexane, 5 mmol); and propionyl chloride (0.5 g, 5.5 mmol). tlc analysis revealed new compound R_f = 0.53 (hexane: ethyl acetate, 70:30). Purification by flash chromatography on silica gel (hexane: ethyl acetat, 80:20) gave the title compound as a colourless oil to yield (1.12 g, 96%); $[\alpha]_D$ +57 ° (c = 1%, methylen chloride). (Lit. values: +77.5, c = 1% CH_2Cl_2)[117]

IR v_{max} (neat)/cm-1: 3018.5 (m); 2987.0 (s); 1783.6 (s); 1273.8 (s); 780.6 (m).
^{1}H NMR (400 MHz, $CDCl_3$)δppm: 7.26-7.14 (5H, m, Ph); 4.71-4.50 (1H, m, C<u>H</u>); 4.16-4.08 (2H, m, C<u>H</u>$_2$); 3.22 (1H, dd, *J* = 13.5, 3.2 Hz, C<u>H</u>$_2$CH); 2.96-2.8 (2H, m, C<u>H</u>$_2$CH$_3$); 2.70 (1H, dd, *J* = 13.5, 9.6 Hz, C<u>H</u>$_2$CH); 1.13 (3H, t, *J* = 8.0 Hz, C<u>H</u>$_3$).
^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 174.18 (<u>C</u>O); 153.65 (<u>C</u>O); 135.42 (<u>C</u>, Ar); 129.55 (<u>C</u>H, Ar); 129.05 (<u>C</u>H, Ar); 127.40 (<u>C</u>H, Ar); 66.30 (<u>C</u>H$_2$O); 55.26 (<u>C</u>HN); 38.00 (<u>C</u>H$_2$Ph); 29.29 (<u>C</u>H$_2$); 8.35 (<u>C</u>H$_3$).
LRMS (m/z): (M^+ 233), 142, 91, 57.

The synthesis of (4S)-4-phenyl-3-propionyl-oxazolidin-2-one (218d)



The same method was employed as described for the synthesis of compound **218a**, using the following quantities (*S*)- (+)-4-phenyl-2-oxazolidinone (0.82 g, 5.0 mmol); n-BuLi (2 mL of the 2.5 M in hexane, 5.0 mmol); and propionyl chloride (0.5 mL, 5.5 mmol, 1.1 eq)Tlc analysis showed new compound R_f = 0.61 (hexane: diethyl ether 70:30). Purification by flash chromatography on silica gel (hexane: ethyl acetat, 80:20) gave the title compound (1.02 g, 98%); m.p. = 40-42 °C; $[\alpha]_D$ +47 ° (c = 1% methylen chloride). (lit. values: +48, c = 1% CH_2Cl_2)[94c]

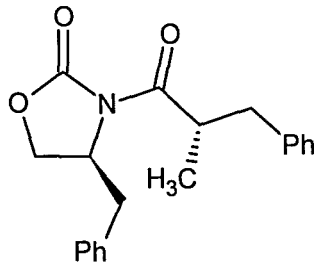
IR ν_{max} (neat)/cm^{-1}: 2991.4 (w); 1780.0 (m); 1717.1 (s); 1372.2 (s); 1350.5 (w); 1245.3 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm; 7.31-7.23 (5H,m, Ph); 5.34 (1H, dd, *J* = 8.8, 3.6 Hz, C$\underline{H}_2$);4.6 (1H, t, *J* = 8.8 Hz, C$\underline{H}$); 4.15 (1H, dd, *J* = 8.8, 3.6 Hz, C$\underline{H}_2$); 2.88 (2H, q, J = 6.5, C$\underline{H}_2$CH$_3$); 1.03 (3H, t, *J* = 6.5 Hz, CH$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 173.65 ($\underline{C}$O); 152.00 ($\underline{C}$O); 139.29 ($\underline{C}$, Ar); 129.27 ($\underline{C}$H, Ar); 128.79 ($\underline{C}$H, Ar); 126.02 ($\underline{C}$H, Ar); 70.12 ($\underline{C}$H$_2$O); 57.65 ($\underline{C}$HN); 29.31 ($\underline{C}$H$_2$); 8.22 ($\underline{C}$H$_3$).

LRMS (m/z): (M$^+$ 219), 163 (100%), 145, 104, 77, 57.

The synthesis of (4*S*)-4-benzyl-3-[(2S)-2-methyl-3-phenylpropanoy)] oxazolidin- 2-one (219a)



To a stirred solution of (S)- (+)-4-benzyl-3-propionyl-oxazolidin-2-one **218c** (1.0 g, 4.3 mmol, 1 eq) in anhydrous THF (15 mL); under an atmosphere of nitrogen, at -78 °C, was added, dropwise, LDA (4.8 mL of the 1.8 M in hexane, 8.6 mmol, 2 eq). A yellow solution ensued after 1 hour benzyl bromide (2.2 g, 13 mmol, 3 eq) was added in 30 minutes time the temperature was raised to -10 °C, then solution was left to stir for 4 hours. The solution was allowed to reach an ambient temperature. Tlc analysis showed the presence of a new compound R_f = 0.71 (hexane: ethyl acetate 50:50). The reaction mixture was then quenched by adding of a saturated ammonium chloride solution (25 mL) and the excess THF was removed in *vacuo*. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed in *vacuo*. Purification by column chromatography on silica gel (hexane: ethylacetate, 60:40) as a colourless crystalline solid which upon recrystallisation from hexane gave the title compound. (1.08 g, 77.9%) melting point = 82-84 °C $[\alpha]_D$= +123 ° (c = 1% methylene chloride), (lit. values: +130)[94c,98]

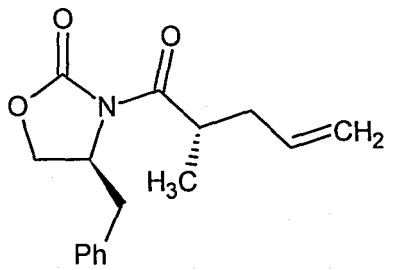
IR ν_{max} (neat)/cm^{-1}: 2982.5 (s); 1706.0 (s); 1456.8 (m); 1387.6 (s); 1246.4 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.21-7.16 (8H, m, Ph); 6.97-6.95 (2H, m, Ph); 4.60-4.55 (1H, m, C<u>H</u>); 4.07-4.00 (3H, m, C<u>H</u> & C<u>H</u>$_2$O); 3.09-2.96 (2H, m, C<u>H</u>$_2$Ph); 2.62-2.47 (2H, m, C<u>H</u>$_2$Ph); 1.11 (3H, d, *J*= 6.8 Hz, CH_3).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 174.16 (<u>C</u>O); 152.05 (<u>C</u>O); 138.00 (<u>C</u>, Ar); 135.20 (<u>C</u>, Ar); 129.54 (2 x <u>C</u>H, Ar); 127.43 (2 x <u>C</u>H, Ar); 122.5 (2 x <u>C</u>H, Ar); 66.07 (<u>C</u>H$_2$); 55.40 (<u>C</u>H); 41.50 (<u>C</u>H$_2$); 38.51 (<u>C</u>H); 37.99 (<u>C</u>H$_2$); 8.39 (<u>C</u>H$_3$).

LRMS (m/z): (M^+323), 178 (100%), 147, 119, 91.

The synthesis of (4*S*)-4-benzyl-3-[(2S)-2-methylpent-4-enoyl]-1, 3-oxazolidin-2- one (219b)



The same method was employed as for the synthesis of compound **219a**, using the following quantities (S)- (+)-4-benzyl-3-propionyl-oxazolidin-2-one **218c** (1.0 g, 4.3 mmol, 1 eq); LDA (4.77 mL of the 1.8 M in hexane, 8.6 mmol, 2 eq); allyl bromide (1.56g, 13 mmol, 3eq). Purification by column chromatography on silica gel (hexane: ethyl acetate, 50:50) was carried out to afford a colourless oil as a desired compound (1.02 g, 87.2%). $[\alpha]_D$= +75 ° (c = 1.5% CH_2Cl_2).

IR v_{max} (neat)/cm^{-1}: 2976.6 (m); 1710.0 (s); 1467.4 (m); 1383.2 (w); 1250.0 (s); 754.5 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.57-6.66 (5H, m, Ph); 5.95-5.85 (1H, m, C<u>H</u>N); 5.50-5.35 (1H, m, =C<u>H</u>); 4.60-4.58 (2H, m, =C<u>H</u>$_2$); 4.15-4.10 (2H, m, C<u>H</u>$_2$O); 3.25 (1H, dd, *J* = 10.0, 3.8Hz, C<u>H</u>$_2$Ph); 2.85-2.78 (2H, m, C<u>H</u>$_2$); 2.45 (1H, dt, *J* = 13.7, 6.7 Hz, C<u>H</u>CH$_3$); 2.10 (1H, dd, *J* = 10.0, 3.8 Hz, C<u>H</u>$_2$Ph); 1.20-1.10 (3H, m, CH$_3$).

^{13}C NMR (100 MHz) ($CDCl_3$) δppm: 176.60 (<u>C</u>O); 174.15 (<u>C</u>O); 136.75 (<u>C</u>, Ar); 135.45 (=C<u>H</u>); 129.5 (<u>C</u>H, Ar); 129.1 (<u>C</u>H, Ar); 129.0 (<u>C</u>H, Ar); 117.3 (=C<u>H</u>$_2$); 66.3 (C<u>H</u>$_2$O); 55.5 (C<u>H</u>N); 38.19 (<u>C</u>H$_2$); 38.15 (<u>C</u>HCH$_3$); 29.39 (<u>C</u>H$_2$); 8.40 (<u>C</u>H$_3$)

LRMS (m/z): (M$^+$273), 177 (100%), 117, 97, 69.

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