DICOBALTOCTACARBONYL SPECIES IN ORGANIC SYNTHESIS: A NOVEL ROUTE INTO TRICYCLIC FUSED RING SYSTEMS

By
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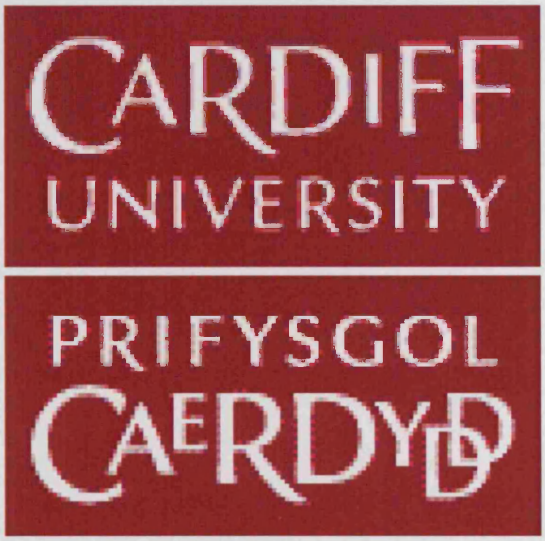

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Abstract

This thesis describes the modern uses of cobalt carbonyl complexes in organic synthesis, by focusing primarily on the Pauson-Khand Reaction (PKR). This is where an alkyne, alkene and a dicobalt complex react in a (2+2+1) cycloaddition producing an cyclopentenone adduct. The cyclopentadienone products of the PKR were used in the synthesis of hetero fused tricyclic ring systems using a diastereoselective and regioselective chemical synthesis via the addition of soft organometallic nucleophiles: The nucleophilic addition of such species allowed a spontaneous cyclocondensation that gave fused ring systems with known biological activity prevalent in a wide range of natural products. This unique synthesis was then applied to non-hetero fused tricyclic ring systems affording a triquinane skeleton analogue which possess significant levels of biological activity. These syntheses were achieved by way of a three-step sequence after an initial PKR. A 1,4-Michael addition was followed by a 1,5-cyclisation and catalytic oxidation of an olefin resulting in the target tricyclic compound.

Secondly, an investigation was performed into the regioselectivity of the PKR, using di-substituted alkynes with a high degree of conjugation, which were prepared by transition-metal catalysed cross couplings reactions. The isolation of the corresponding dicobalt alkyne complexes, and their *exo*-tricyclodecadienone products were used to assist in elucidating the mechanism by which the PKR proceeds.

The final Chapter describes the uses and mechanism, by which dinorbornadienedicobalttetracarbonyl (DDTC) was formed as a side product of the PKR. This side product was then used to promote the PKR. Surprisingly, only alkynes with electronegative oxygen atoms worked and diastereoselective control for the synthesis of cyclopentadienones was maintained at similar levels observed within the PKR with dicobaltoctacarbonyl.

Abbreviations

Atm	Atmosphere
Bu	Butyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
dba	Dibenzylidene-acetone
DCE	Dichloroethane
DCM	Dichloromethane
DDTC	Dinorbornadienedicobalttetracarbonyl
DEAD	Di-ethylazodicarboxylate
DFT	Density Functional Theory
DNPH	2,4 Dinitrophenylhydrazine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
Et	Ethyl
HRMS	High Resolution Mass Spectrometry
HOMO	Highest Occupied Molecular Orbital
IAA	Indole-3-acetic acid
IR	Infrared
LUMO	Lowest Unoccupied Molecular Orbital
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
Nuc	Nucleophile
mmol	Millimole
Ms	Mesylate
OAc	Acetate
PKR	Pauson-Khand Reaction
PGs	Prostaglandins
Ph	Phenyl
Phth	Phthalimide
PMHS	Polymethylhydrosiloxane

ppm	Parts per million
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TolBINAP	2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
Ts	Tosylate
***p*-TosCl**	*p*-toluenesulfonylchloride
VE	Valance Electrons

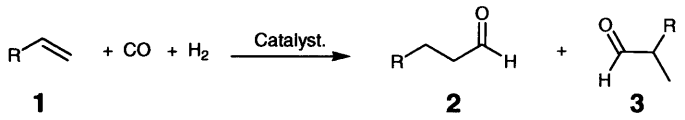
Chapter 1

palladium(0) complexes in the cross coupling of aryl halides with various nucleophiles. Dicobalt species, amongst many others, have been central to the progression and understanding of organometallic chemistry. The three main areas where organocobalt complexes are prevalent in organic chemistry are the Pauson-Khand reaction (PKR), the Nicholas reaction and hydroformylation. This thesis develops the use of the inter-molecular PKR in the synthesis of biologically relevant tricyclic ring structures as well as providing insight into the mechanism and alternative cobalt complexes to promote the PKR. As an introduction, reactions involving cobalt complexes will be summarised along with alternative methods by which cyclopentenones can be prepared.

1.1 Hydroformylation

Hydroformylation, or the 'oxo reaction' as it is otherwise known, is the simultaneous addition of carbon monoxide (CO) and hydrogen across a carbon-carbon double bond of an alkene **1** in order to form either linear **2** or branched **3** aldehydes containing one more carbon atom than the starting material (Scheme 1).[1, 2, 3, 4, 5, 6]

Hydroformylation has become a highly developed industrial process for the synthesis of a vast amount of secondary products along with the highly versatile primary aldehydes it produces. The secondary products produced from these aldehydes is also extensive from the large scale production of alcohols, carboxylic acids, plasticizers, detergents and surfactants as well as lubricants, solvents and chiral starting materials for use in the agrochemical and pharmaceutical industries.[5, 7, 8, 9]

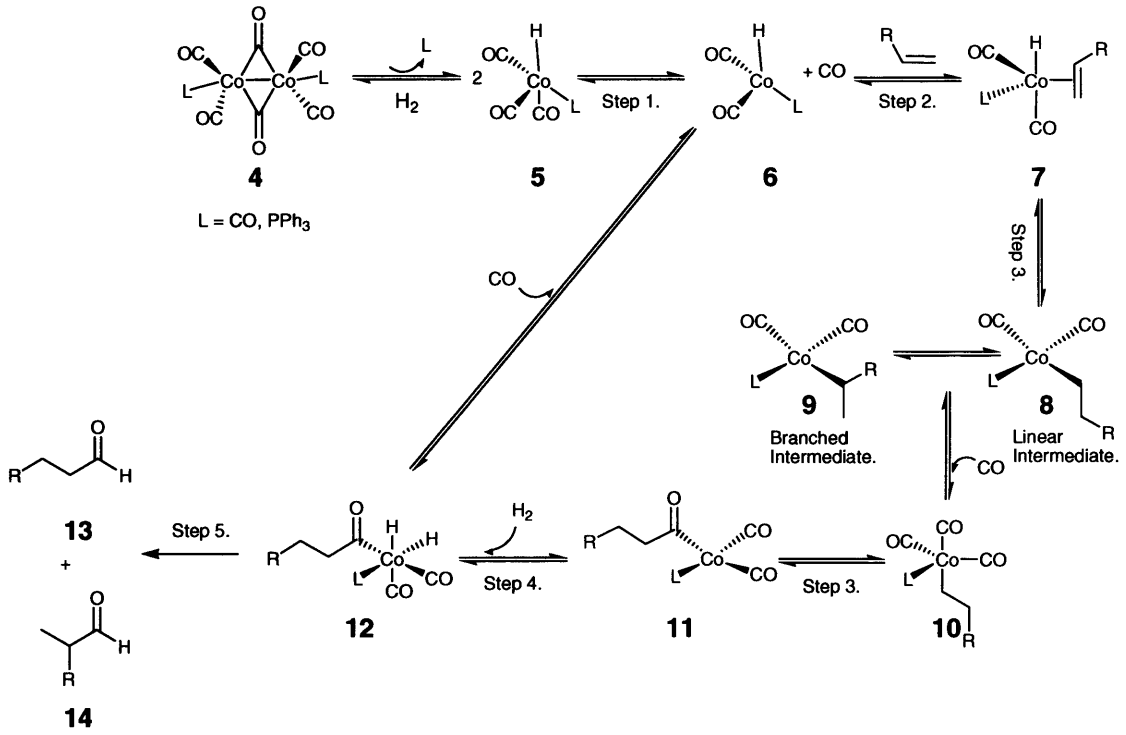


1 **2** **3**

Scheme 1

The numerous catalysts used for hydroformylation each have advantages and disadvantages depending on the formyl products desired. For industrial purposes the

most common catalysts are transition-metal complexes of rhodium or cobalt due to their relatively low cost, whilst more expensive platinum, palladium, and ruthenium catalysts are used extensively in small-scale research. The overall mechanism of hydroformylation using cobalt catalysts resembles that of homogeneous hydrogenation (Scheme 2). The reaction begins with the generation of a coordinatively unsaturated metal hydrido carbonyl complex such as $HCo(CO)_3$ **6** (Step 1). Such species readily bind alkenes, and the resulting complex **7** (Step 2) undergoes a migratory insertion reaction to form a 16 valance electron (VE) alkyl complex (Step 3). This species can either be linear **8** or branched **9** and can undergo a CO addition to form complex **10** followed by a CO insertion to form complex **11**. Hydrogen addition (Step 4) can then occur affording a metal hydride such as species **12** followed by reductive elimination to yield the aldehydes products (Step 5), (either **13** or **14**) with regeneration of the unsaturated metal hydrido carbonyl complex $HCo(CO)_3$ **6**.



Step 1 - Ligand dissociation -generation of unsturated intermediate.
Step 2 - Olefin binding to vacant co-ordinate site.
Step 3 - Ligand dissociation.
Step 4 - Hydrogen addition.
Step 5 - Reductive elimination.

Scheme 2

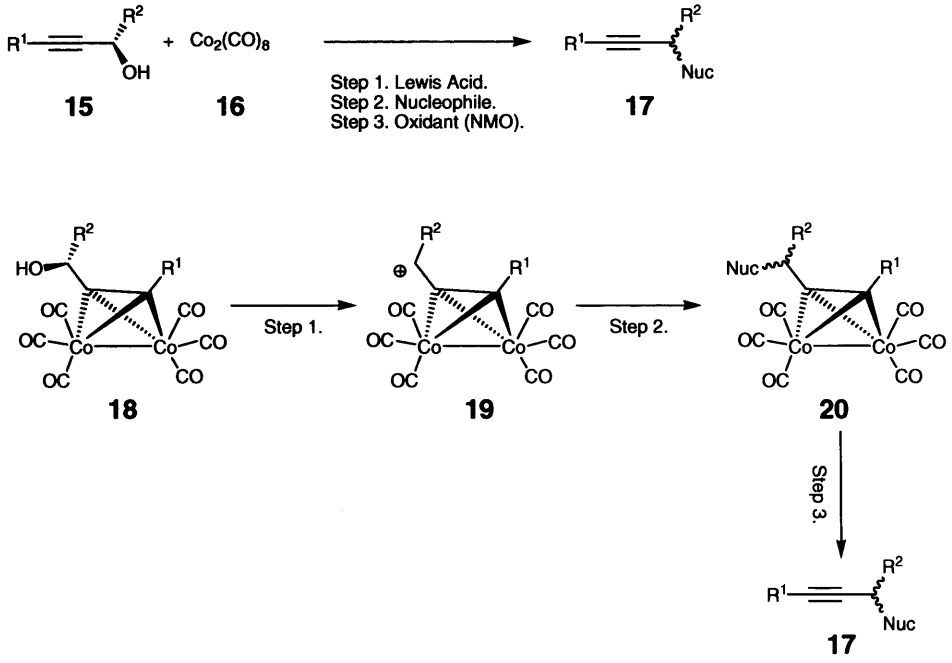
Hydroformylation has been extensively studied over the years, with numerous transition-metal complex catalysts able to enhance and/or alter the distribution of the

aldehydes produced. It is therefore a good example of the chemical diversity belonging to transition-metals, which comes from their ability to form both sigma (σ) and pi (π) bonds using the availability of their s-, p- and d-orbitals, which allow acceptance and donation of electrons. These lead to a wide range of coordination numbers, geometries and oxidation states in transition-metal chemistry.

The development and study that has stemmed from hydroformylation and many other reactions involving transition-metals, has given chemists the ability to develop more reactive and robust organometallic catalysts; from the initial cobalt catalyst, to modern day industrially relevant rhodium triphenylphosphine complexes such as the $HRh(CO)(PPh_3)_2$ catalyst, primarily developed by Union Carbide.[10]

1.2 Nicholas reaction

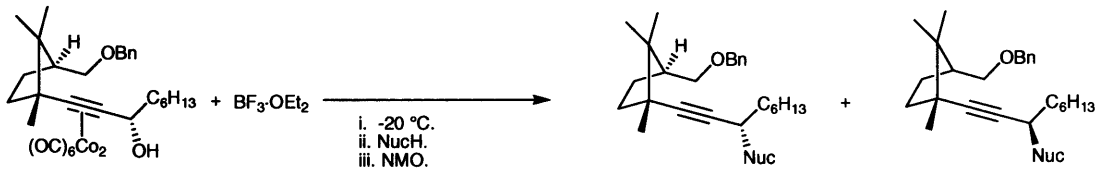
The Nicholas reaction is a very useful tool in organic synthesis,[11, 12, 13] which allows the substitution of "poor" leaving groups that normally could not be displaced by standard nucleophiles (Nuc). The reaction (Scheme 3) involves the formation of a cobalt alkyne complex **18**, which is then reacted with a Lewis acid to produce a propargylic cation **19** (Step 1). This propargylic cation **19** then undergoes nucleophilic addition (Step 2), where the cation is stabilised by the dicobalt carbonyl alkyne complex. The positive charge of the intermediate propargylic cation **19** is more stable than normal cations due to the positive charge of the intermediate being delocalised over three carbon and two cobalt atoms. This stability has been shown experimentally[11] through the use of Infrared (IR) spectroscopy, where the absorption frequencies of the ligands on the cation **19** and the parent complex **18** were compared. This showed an increase in the frequency of the carbonyl groups of the cations absorption which is consistent with greater C–O bonding as a result of decreased $d(Co)\text{-}\pi^*(CO)$ donation in the electron deficient cation. The Nuclear Magnetic Resonance (NMR) of both ^1H and ^{13}C atoms showed relatively small shifts for the α-alkyl groups, alkyne moiety and ligands of the cationic species, compared to the parent complex **18** which also suggested that significant charge dispersal occurs in the cation **19**.[14] Once the nucleophile has completely reacted to form the dicobalt alkyne complex **20**, it can be converted to the alkyne product **17** by oxidation of the dicobalt alkyne complex **20** (Step 3) using an oxidant such as *N*-methylmorpholine-*N*-oxide (NMO).



Scheme 3

An important aspect not just of the Nicholas reaction, but any organic reaction is the stereochemical control that it can provide. Over the past 2 decades, a lot of work has focused on controlling the stereochemistry of the Nicholas reaction.[15, 16, 17, 18] This is due to the racemisation of chiral propargylic starting materials on formation of a naked carbocation, that allows nucleophilic attack to occur at either face of the complex. The three main ways of controlling the selectivity of the reaction are: by introducing chiral ligands onto the dicobalt species;[16] introducing chirality by using defined chiral centres on R^1 and R^2 e.g. **21** that will control the stereochemistry at the newly formed sp^3 carbon (Scheme 4)[17]; and the use of chiral nucleophiles.[18]

These methods of achieving stereoselectivity all give varying selectivity; however, a relationship between reaction temperature and stereoselectivity has become apparent, whereby, low temperatures give greater stereochemical control. The control observed at lower temperatures is due to the kinetic product being favoured under these conditions. This observation is only true for nucleophiles that are poor leaving groups such as methanol which favours the formation of product **24**. Whereas a nucleophile that can also function as a good leaving group, for example acetic acid, the thermodynamic product is frequently observed after longer reaction times favouring the formation of product **23**.



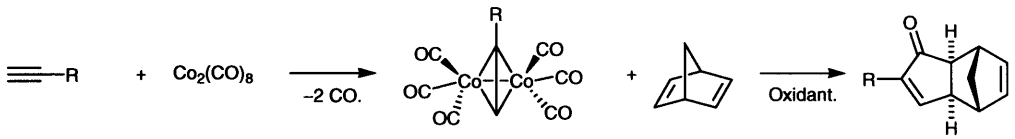
21 **22** **23** **24**

23 : 43
NucH = MeOH : 51%, 12 : 88
AcOH : 80%, 88 : 12

Scheme 4

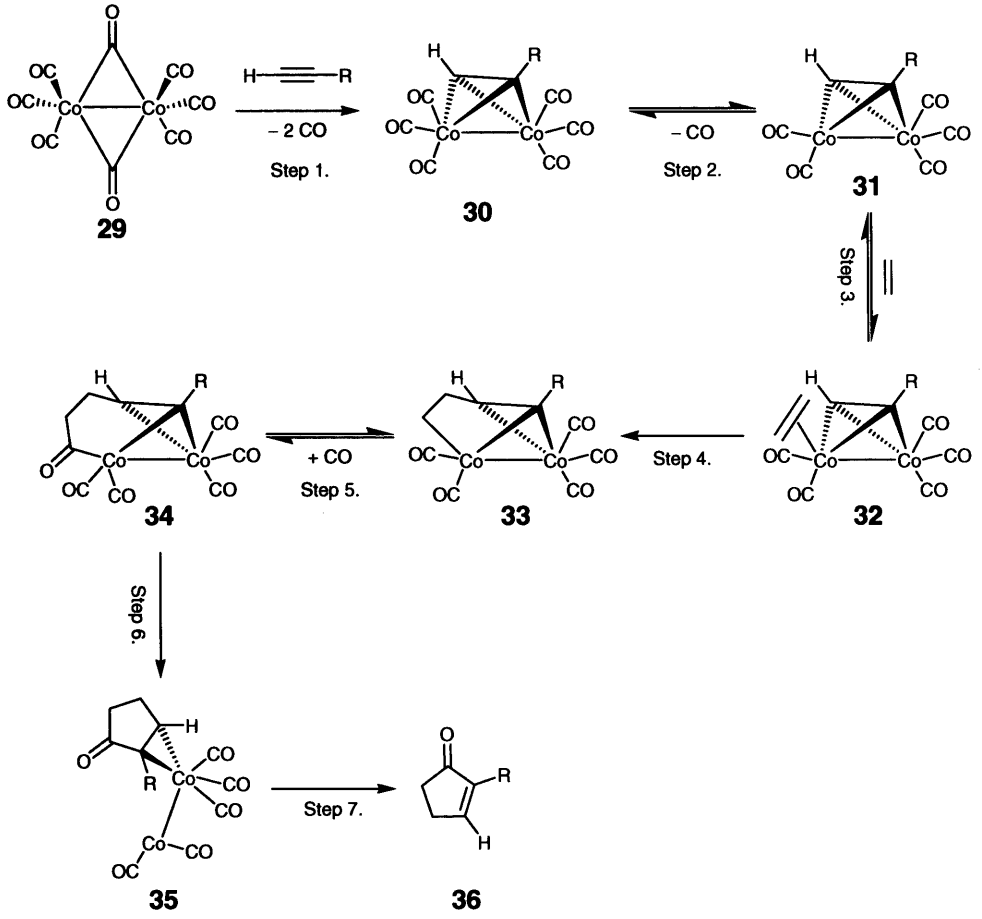
1.3 Pauson-Khand Reaction (PKR)

Pauson and Khand first observed the carbonylative cyclisation of an alkyne **25** and an alkene **27** in an overall (2+2+1) cycloaddition, which is now universally known as the Pauson-Khand Reaction PKR (Scheme 5). It was first discovered in 1971, during research on arenecobalt carbonyl complexes[19, 20, 21] and has now become a powerful tool in the synthesis of complex organic compounds. The reaction is similar to the Nicholas reaction in that the formation of a transition-metal alkyne complex **26** is required. Addition of an alkene promotes a carbonylative cyclisation (Scheme 6), resulting in the formation of cyclopentenone product **28**.[19, 20, 21]



25 **16** **26** **27** **28**

Scheme 5



Scheme 6

A substantial amount of work has been carried out on the mechanism of the PKR, which is believed to proceed through 7 key steps:

Step 1 – Formation of cobalt alkyne complex **30** (oxidative addition). – May be formed *in situ* or isolated prior to addition of the alkene. Formation is quantitative and rapid.

Step 2 – Dissociation of a CO ligand giving a vacant coordination site **31**. – Critical step that can be rate determining. Assisted sometimes by an oxidant such as *N*-methylmorpholine-*N*-oxide (NMO) in the stoichiometric version of the reaction.

Step 3 – Coordination of alkene ligand to give **32**. – If the alkene is a weak ligand, this becomes the rate-determining step.

Step 4 – Insertion of alkene into C–Co bond **33**. – Forming a new C–C bond, thought to occur at the least hindered end of the alkyne, however, an alternative mechanistic argument has questioned this proposal.[21, 22]

Step 5 – Insertion of CO into newly formed C–Co bond **34**. – Forming the second C–C bond.

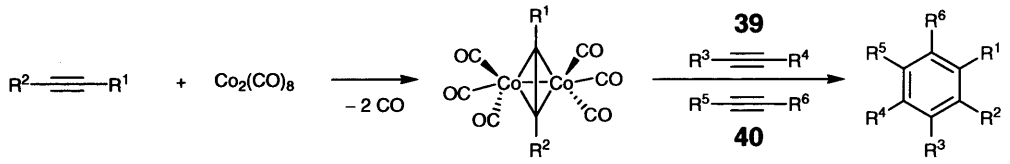
Step 6 – Reductive elimination. – Forming a final C–C bond and the cyclopentenone ring **35**.

Step 7 – Dissociation of the dicobalt fragment providing the observed product **36**. – At high pressures of CO it is possible to reform $Co_2(CO)_8$ allowing the process to be catalytic.

The PKR is performed by either a one or two-step process. The two-step process involves the isolation of the transition-metal alkyne complex **31** that is generally air stable.

Alternative transition-metal complex intermediates have proven to be useful products themselves, especially in helping to elucidate the reaction mechanism of the PKR. Their other uses include: the promotion of a stereoselective PKR by adding alternate ligands to CO such as phosphines to one of the cobalt centres. This in turn makes the bimetallic centres asymmetric, allowing for the possible preparation of enantiomerically enriched products.[23]

The transition-metal complexes formed in the PKR also have the ability to form arenes e.g. **41** through a series of insertion reactions cyclotrimerizing alkynes (e.g. **37**, **39** and **40)** through formation of the initial cobalt alkyne complex **38** (Scheme 7).[20, 24]



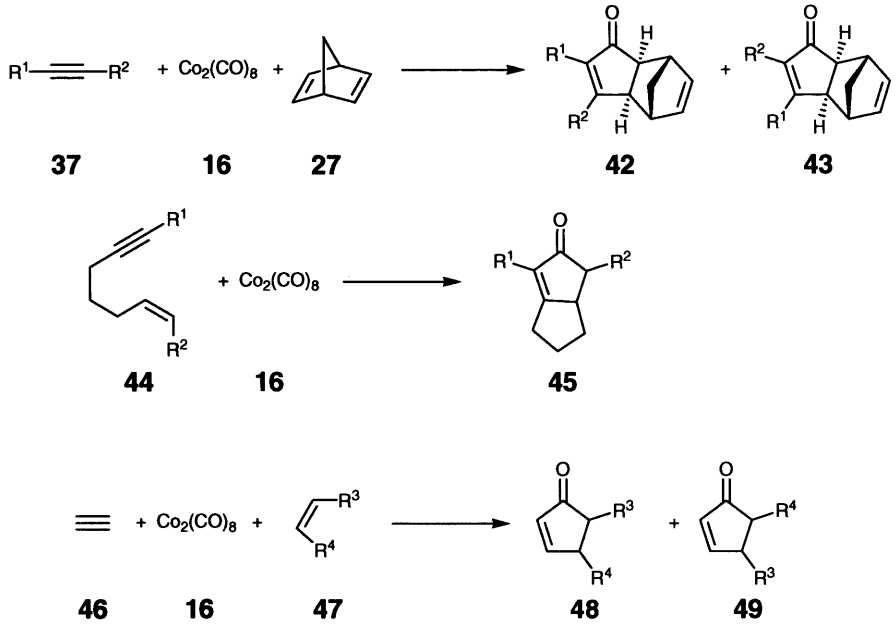
37 **16** **38** **41**

Scheme 7

Regioselectivity

The regiochemistry of a reaction is an important feature to control. In the PKR, regiochemistry is determined by which end of the alkyne undergoes olefin insertion. In the inter-molecular version of the reaction[25] disubstituted alkynes give rise to two

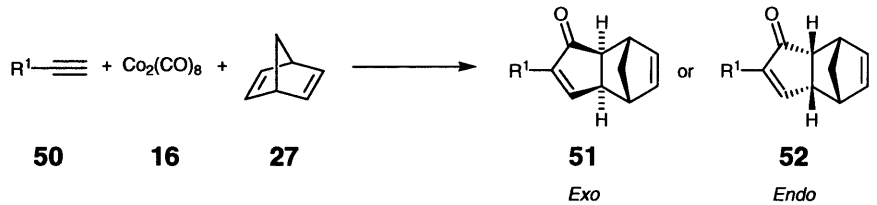
regioisomeric products (e.g. **42** and **43** or **48** and **49**) (Scheme 8). In the intra-molecular version,[25] the regioselectivity can be fixed by the carbon backbone between the alkyne and alkene of the molecule, controlling the regiochemistry of the product (e.g. **45**).



Scheme 8

Diastereoselectivity

It has been shown that inter- and intra-molecular PKR gives rise almost exclusively to *exo*-products e.g. **51** (Scheme 9), however, some *endo*-products e.g. **52** have been observed in intra-molecular versions of the reaction.[26, 27, 28] To date, only three reports of *endo*-selective PKR's have been found for the inter-molecular version.[29, 30, 31] This is thought to be due to electronic differences within the bimetallic clusters and the electronic properties of the alkynes bonded to them.[32]



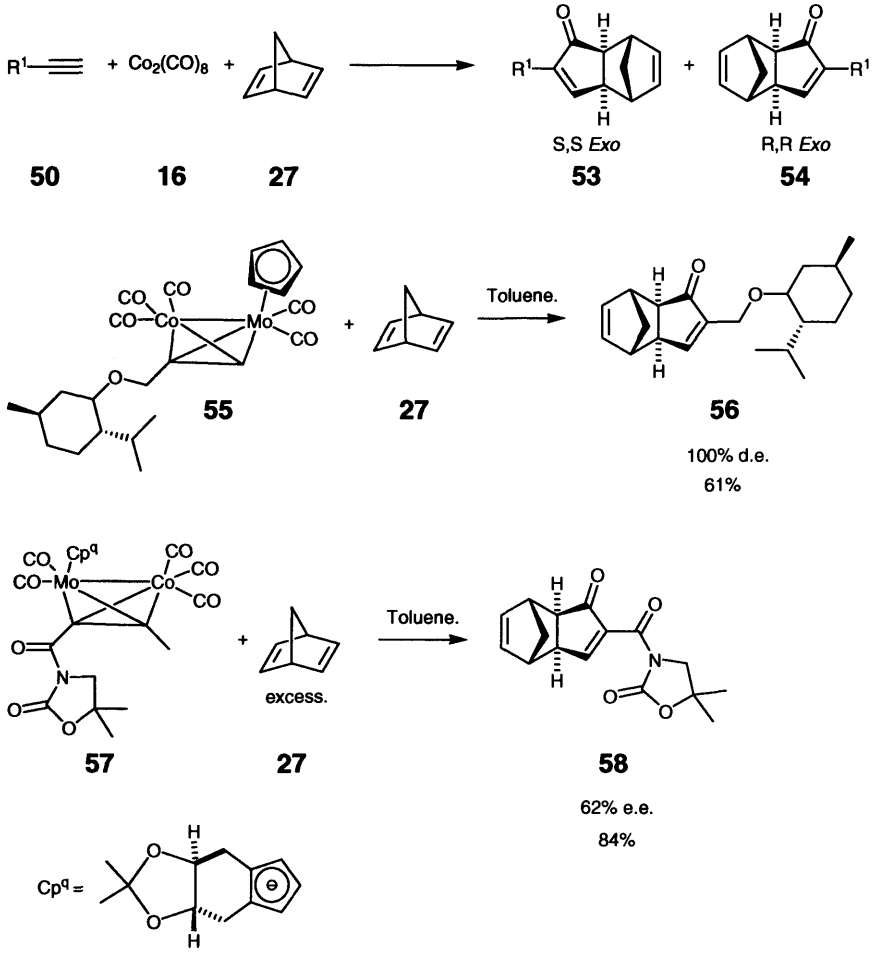
Scheme 9

Enantioselectivity

Four strategies (Scheme 10) have been adopted in order to achieve enantioselective PKR's;[33] chiral complexes, chiral auxiliaries, chiral promoters and chiral precursors.

The chiral complex methodology can be achieved using two routes; firstly, by using chiral ligands to replace one CO ligand on the cobalt atoms e.g. **55**,[34, 35] or secondly, by substituting a cobalt atom for another transition-metal such as Mo, to produce a hetero-bimetallic complex e.g. **57** that has been shown to promote the reaction at one specific chiral metal site.[36, 37]

Chiral complex

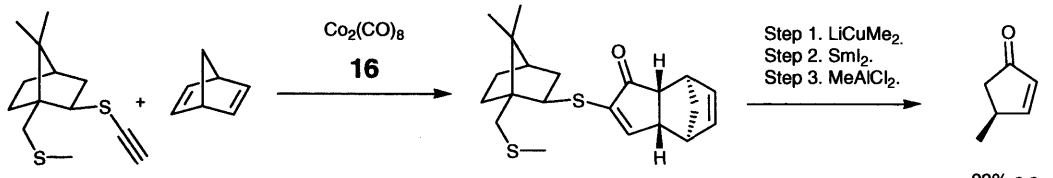


Scheme 10

Chiral auxiliaries such as **59** may also be used in the PKR (Scheme 11) and can introduce chirality into the metal complex, by either binding or co-ordinating to one or both of the metal centres of the organometallic reactant [$Co_2(CO)_8$].
Cyclopentenone **60** was isolated as a mixture of diastereomers from which the chiral

auxiliary could be removed to produce an enantiomerically enriched compound such as **61**.[33, 38, 39, 40]

Chiral auxiliaries

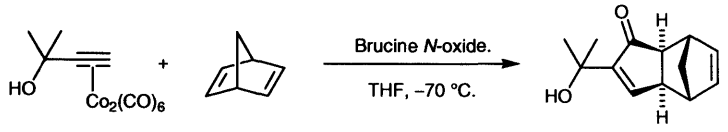


59 **27** **60** **61**

Scheme 11

The use of amine *N*-oxides has been shown to increase the rate of the PKR.[33, 41] This increase in rate is thought to occur by the oxidative removal of a carbon monoxide ligand, allowing the generation of a vacant coordination site on either of the cobalt metals. When chiral amine *N*-oxides are incorporated into the PKR (Scheme 12), it can discriminate between the two enantiotopic cobalt units of the starting complex **62**, leading to enantiomerically enriched product **63**.

Chiral promoters



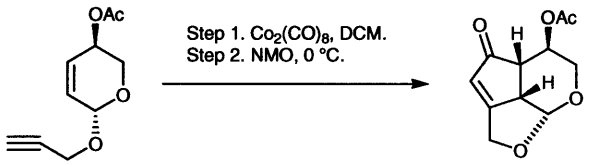
62 **27** **63**

Scheme 12

Chiral precursors take advantage of the stereoselective nature of the formal [2+2+1] cycloaddition (Scheme 13) and by incorporating chirality into the starting material e.g. **64** have subsequently affected a transfer of chirality into the PKR cycloadduct e.g. **65**.[33] Chiral precursors have, to date, had a limited number of examples reported whereby enantioselectivity has been achieved.

The four reported methods that have enabled an enantiomeric excess to be obtained using the PKR can be placed in order of success as follows: chiral auxiliaries (70–100% e.e.), chiral promoters (60–80% e.e.), chiral complexes (50–90% e.e.) and chiral precursors (40–60% e.e.).

Chiral precursors



45% e.e.

40%.

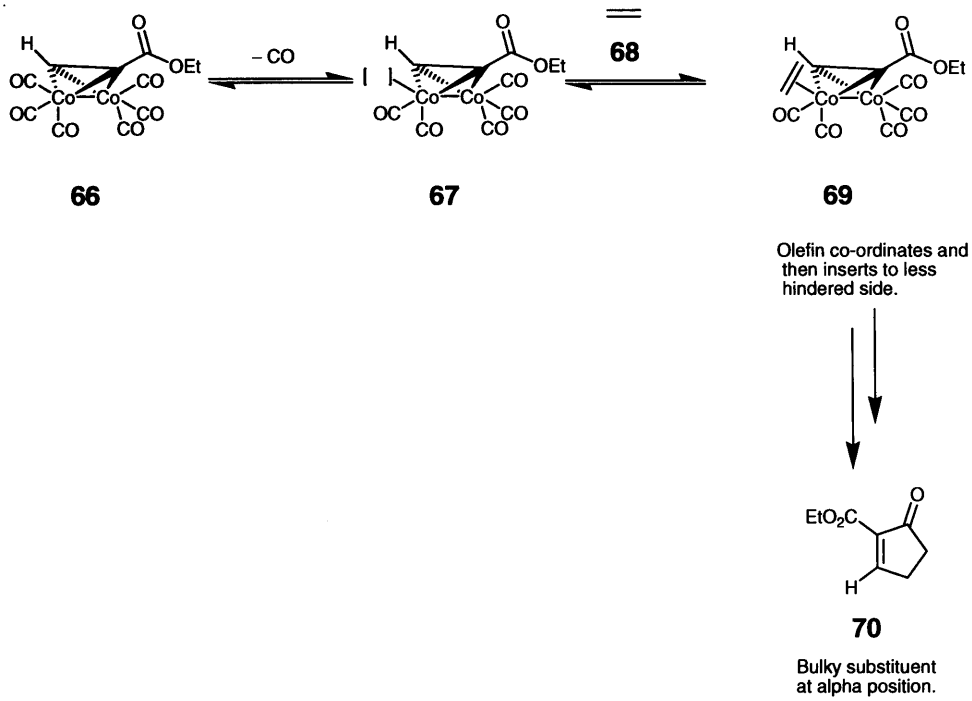
64 **65**

Scheme 13

Mechanism of the PKR

To date there are two mechanistic proposals to explain the stereochemical outcome of the PKR. These suggest either a 'steric interaction' or an 'electronic interaction' is responsible for how the alkene interacts with the cobalt alkyne complex.[21]

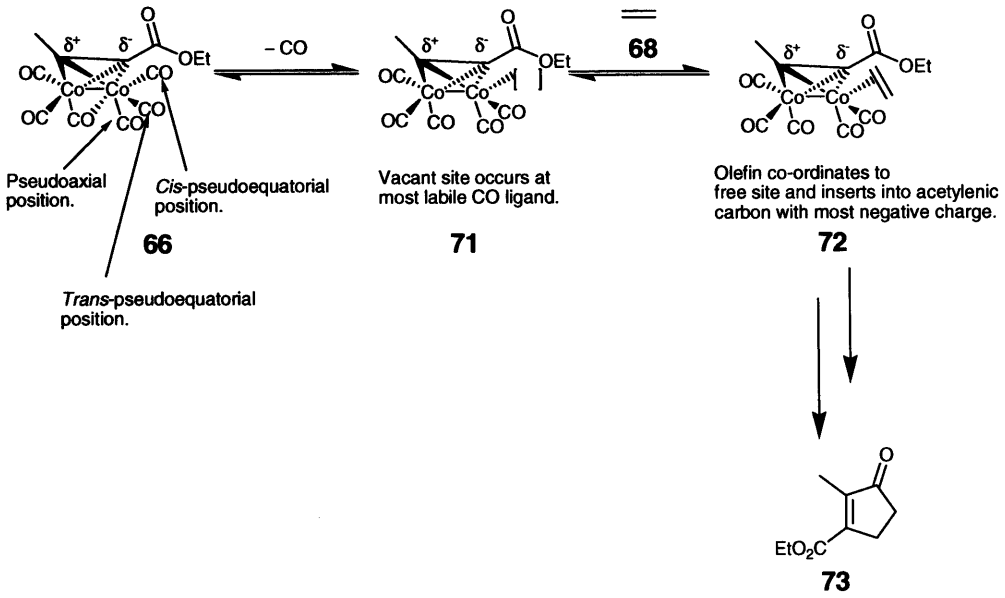
The 'steric interaction', speculates that the less bulky substituent of the alkyne in the cobalt alkyne complex **66**, creates less steric hindrance for the approaching olefin **68**. This allows the coordination of the olefin to the metal centre remote to the large group and the formation of a new C–C bond **69** with the acetylene carbon and is thought to occur at a faster rate than would be possible at the opposite end. Insertion next to the bulkier substituent would be much slower due to steric hindrance (Scheme 14). The explanation of steric forces controlling the PKR has long been accepted (with only empirical foundations) and results in the more bulky substituent being positioned at the α-position in the final cyclopentenone product **70**.[42]

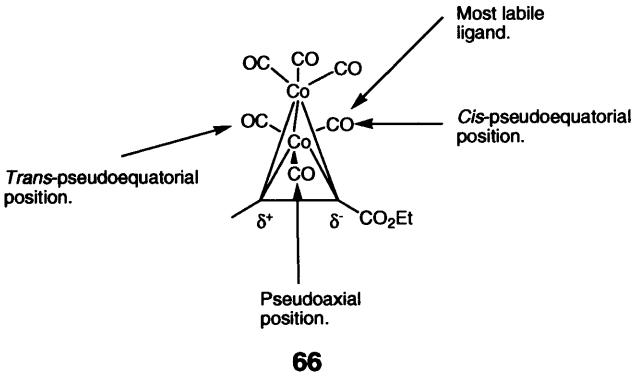


Scheme 14

There are exceptions that exist to this general rule of predicting the regiochemical outcome of the PKR, for example ethyl butynoate[43] exclusively forms the β-cyclopentenone **73** (Scheme 15), whereas under the same conditions ethyl propiolate[44] forms the α-adduct **70** exclusively.

This could be explained by an 'electronic interaction' whereby it is thought that polarisation of the acetylene bond, can affect the bond strength of the cobalt carbonyl ligands through the back donation of electrons to the metal centres. This back donation of electrons in turn makes a more labile carbonyl ligand and therefore a more favourable site for the insertion of the olefin. It has been proposed that a *trans*-effect has been previously overlooked between the transition-metal alkyne complex **70** and its *trans*-pseudoequatorial CO ligand. It can be argued that substituents on the alkyne markedly affect the electronic properties of the resulting cobalt complex which has been shown in numerous publications[45, 46, 47, 48, 49, 50, 51, 52, 53] using NMR and IR data, resulting in a correlation between electronegative substituents on the alkyne and the strengthening acceptor properties of the bridging ligand.





Scheme 15 [Lability of the carbon monoxide ligands (*cis* and *trans* positions are defined with respect to the position of CO_2Et group)]

This 'electronic interaction' would ultimately result in reduced electron back-donation from the metal to the π^*-orbitals of the carbonyl ligands. These findings led to the assumption that the transmitted electronic effects from the alkyne substituents would effect the regioselective departure of a CO ligand to form complex **71**, which in turn affects the regiochemistry of the reaction to yield **73** by allowing the olefin **68** to insert in the opposite manner to the 'steric argument'. The carbon-carbon triple bond in a dissymmetric alkyne is polarized due to dissimilar electronic effects exerted upon it by the substituents, and hence becomes more polarized upon coordination to a metal.

The increase in polarization is believed to be responsible for the discriminate loss of a CO ligand from **66**. From experimental data and Density Functional Theory (DFT)[22] calculations, it has been shown that the most electronegative (δ^-) carbon on the acetylenic ligand will increase the bond energies of the *trans*-pseudoequatorial CO ligand, thus making it less labile. In turn, this effect will also reduce the bond energies of the CO ligand which is *cis*-pseudoequatorial, making it more labile. The difference in these labilities results in different rates for the loss of CO from the Co centre, allowing the coordination of the olefin to a specific site, enabling the more (δ^+) acetylenic carbon to take up the α-position on the cyclopentenone product **73**.[22]

Catalytic PKR

Pauson[54] first observed that the PKR could be rendered catalytic,[55] however, it was not until the early 1990's that impressive developments were made in this area of the reaction. The early work done in this area used 0.1 equivalents of dicobaltoctacarbonyl **16** in the reaction of an excess of alkene, a continuous supply of gaseous alkyne and an equivalent amount of CO gas in an inert solvent. Success was dependant on the ability of the alkyne supply to trap and recycle any reactive cobalt containing fragments. These first attempts at producing a catalytic reaction yielded moderate to low yields of the cyclopentenone with very low turnovers. Nowadays, the reactions can be carried out in autoclaves, which provide high pressures of CO, preventing the conversion of $Co_2(CO)_8$ to $Co_4(CO)_{12}$ which is believed to inhibit the catalytic reaction. This conversion of $Co_2(CO)_8$ to $Co_4(CO)_{12}$ is believed to occur at around 50 °C.

Studies carried out[56, 57] determined the equilibrium constant, revealing that increasing the CO pressure enables $Co_2(CO)_8$ to become the prevalent species, even at high temperatures, thus promoting the catalytic cycle and enabling higher turnovers than previously reported (Scheme 16). Experiments showed that converting $Co_4(CO)_{12}$ to $Co_2(CO)_8$ *in situ* at high temperature and CO pressure allowed the PKR to proceed catalytically, showing that most cobalt carbonyl species exist as $Co_2(CO)_8$ under these conditions.[58]

$K_p = [Co_4(CO)_{12}]\ PCO^4 / [Co_2(CO)_8]^2$.

$\text{Log } K_p = 21.84 - 6455 / T$ (K_p in $\text{bar}^4\ \text{dm}^3\ \text{mol}^{-1}$).

Scheme 16

Other methods to alleviate the problems in forming $Co_4(CO)_{12}$ have been developed. These include: the introduction of alternate cobalt ligands, such as phosphites and phosphines that prevent formation of $Co_4(CO)_{12}$; photochemical activation; use of supercritical CO_2, however, this does lead to low turnover numbers and yields.[33]

Stoichiometric PKR

The stoichiometric PKR has been the subject of extensive investigation. Most of the techniques used to try and enhance the catalytic version of the reaction have also been applied to the stoichiometric transformation, apart from the use of CO pressure. The most significant advances made in this area are the use of *N*-oxides and other additives, ultimately leading to lower reaction temperatures and higher selectivity within the reaction.

Solid surface promotion[55] has been achieved on both silica and alumina surfaces increasing reaction rates in an aerobic atmosphere for the intra-molecular PKR. This promotion is thought to occur by the adsorption of alkyne complexes causing a conformational change, which aids the cyclic transition state, promoting the reaction by hydrophilic adsorbent centres (that interact with the alkyne complex centres) together with the repulsive interaction from the surface with the hydrophobic ends of the complex.

Polymer supported reactions [59] have also been achieved allowing the promotion of cyclopentenone products over unwanted side products, such as trimerization of the alkyne. Reduction of reaction times has also been accomplished using microwave irradiation as an alternative to conventional thermal promotion.[60]

Side products of the PKR

Since its discovery the PKR has been extensively used in the synthesis of synthetically useful cyclopentenone products using simple, readily available starting materials, and has given chemists the opportunity to develop new and previously unattainable compounds. Unfortunately, due to the many steps within the reaction, alternate pathways are possible allowing the formation of many side products.[25] These alternate products are intriguing in their own right for the possible enhancement of the PKR as well as providing methods for the synthesis of other novel and interesting compounds. The possible alternative products produced can be placed into two categories as either a pre-PK reaction or a post-PK reaction:[25]

Pre-PK reactions:

- Alkene migrations;
- Hydrogenolysis of propargylic heteroatoms.

Post-PK reactions:

- Alkene reduction;
- Isomerization of alkene;
- Elimination of leaving groups;
- Epimerization of α-position;
- Hydrogenolysis of allylic heteroatoms.

These reaction pathways can give rise to many alternative products in both inter- and intra-molecular PKR, the most common products observed being dienes and cyclic ketones with unconventional PKR motifs.

1.4 Cyclopentenones

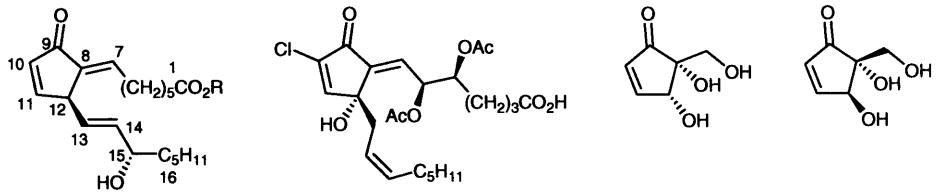
Cyclopentenones encompass a wide variety of molecules that can originate from many natural sources such as plants, marine and microbial sources. These compounds have shown great potential as drug targets for many conditions.

One of the most interesting group of naturally occurring cyclopentenones are the prostaglandins (PGs), which have been shown to play pivotal roles within the human body, controlling a number of physiological processes.[61, 62, 63, 64, 65]

The biological actions of the PGs are mainly due to the α,β-unsaturated carbonyl group within the ring structure. This biological activity[66] is often lost when the PGs do not posses the α,β-unsaturated ketone group.

Cyclopentenone PGs, such as Δ^7-PG-A_1 **74** and the related methyl ester **75** (Scheme 17), display tremendous anti tumour activity,[67, 68, 69] which is attributed to the $\Delta^{7,8}$ unsaturation. Other PGs with C-10 halogen substitution e.g. **76** and C-12 hydroxy substitution also increase the PGs potency towards antineoplastic activity. Pentenomycins **77** and **78**, which also posses the cyclopentenone scaffold, also show antibiotic activity.[62, 70, 71, 72, 73] For these reasons, the PGs and many other

cyclopentenone derivatives have attracted much interest from chemists which has led to several methods for their synthesis.



R = H **74**
R = Me **75** **76** **77** **78**

Scheme 17

1.5 Alternative transition-metal routes to cyclopentenones

Strategies

The [2+2+1] strategy that the PKR follows in cyclopentenone synthesis uses one synthetic operation which is a rare reaction due to the high entropy barriers usually involved. However, they represent the highest chemical efficiency and atom economy for forming at least two new bonds in any designed synthesis of a target molecule. A way to overcome this parameter of disorder, and promote the formation of the desired bonds, is by using transition-metals. Transition-metals may lower the barrier associated with other classical routes of synthesis by facilitating otherwise inaccessible transformations through their d-orbital hybridisation, using interactions with π and π^* orbitals of unsaturated organic molecules, producing a wide range of geometries which can change normal reactivity patterns.

The strategy uses three or more independent components to construct a cyclopentenone ring from readily available materials, providing a method that is highly selective and efficient.

Other strategies include reactions such as [3+2] and [4+1] cycloadditions as well as the use of other metal mediated routes. The following section of this Chapter presents the transition-metal species that undergo these reactions to form cyclopentenones.[74, 75, 76, 77, 78]

[2+2+1] Cycloaddition

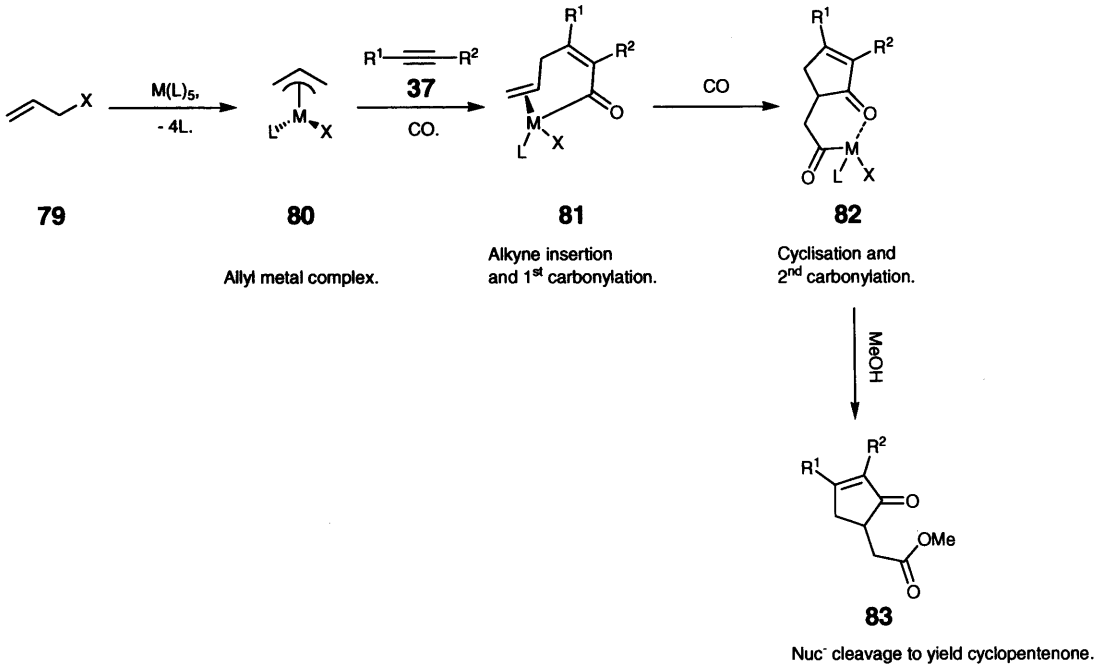
As well as the cobalt mediated PKR other transition-metals have been used, including rhodium, iridium, iron, ruthenium, chromium, tungsten and molybdenum complexes.[79] These alternative metals all follow the same [2+2+1] strategy producing cyclopentenones by the same mechanism as the PKR. Metals that accomplish the same [2+2+1] cycloaddition via alternate mechanistic pathways are titanium, zirconium, palladium and nickel.[74,75,76,77,78]

Group 10 metals

Nickel and palladium complexes have both promoted the preparation of cyclopentenones, *via* a [2+2+1] process. Nickel tetracarbonyl achieves this under mild reaction conditions, using allyl halides and alkynes as starting materials. This has attracted less attention than the PKR as it can only be carried out stoichiometrically.[79]

Complexes other than nickel tetracarbonyl such as $[Ni(CO)_3PPh_3]$ and $[Pd(dba)_2/PPh_3]$ have been used catalytically in the presence of a CO atmosphere (40-100 atm). These cyclisation/carbonylations have been used in the preparation of various natural products such as (+) and (–)–hirsutene.[79]

The mechanism by which these reactions proceed (Scheme 18) is slightly different to the PKR, in that the sequence of steps have been well defined by mechanistic studies. The mechanism follows an initial formation of an allyl metal complex **80** (*via* oxidative addition), alkyne insertion and carbonylation, followed by cyclisation and cleavage of the desired product with methanol to yield the desired cyclopentenone **83**.[80]



79 80 81 82

Allyl metal complex.

Alkyne insertion and 1st carbonylation.

Cyclisation and 2nd carbonylation.

83

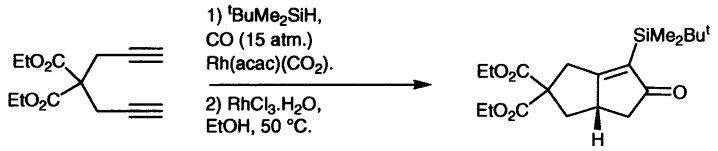
Nuc⁻ cleavage to yield cyclopentenone.

Scheme 18

These group 10 mediated cycloadditions show high regioselectivity resulting from triple bond polarisation. Steric factors do not seem to affect the mode of addition, as most functional groups on the alkyne are tolerated.[79]

Group 9 metals

The rhodium mediated PKR (Scheme 19), using rhodium carbonyl complexes and complexes with various other ligands under high pressures of CO provide good to excellent yields of the cyclopentenone adduct **85**.[76]



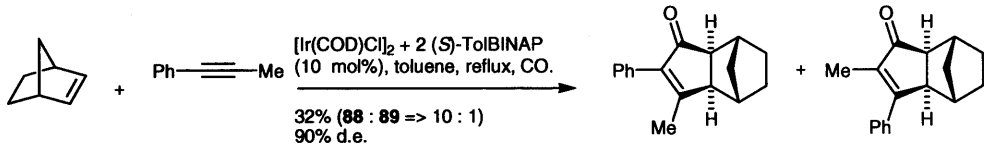
84

85

93%

Scheme 19

Iridium(I) diphosphine complexes (Scheme 20), based on chiral ligands such as (*S*)-TolBINAP as well as other chiral phosphines, have been used in the PKR, producing cyclopentenones with high enantioselectivity in both inter- and intra-molecular variants of the reaction. For example, reaction with norbornene **86** and alkyne **87** (R^1 = Ph, R^2 = Me) gives the products **88** and **89** with excellent levels of regioselectivity (up to 10:1) and enantioselectivity (up to 93% e.e.).[79]

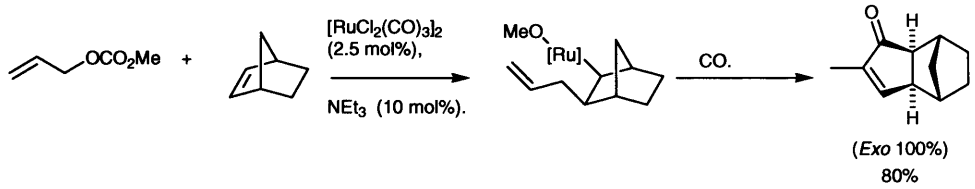


86 **87** **88** **89**

Scheme 20

Group 8 metals

Promotion of the PKR using ruthenium and iron carbonyl complexes has been observed using high CO pressures. These complexes have been used with allyl carbonates e.g. **90** (Scheme 21). It is believed that the reaction proceeds *via* a ruthenium intermediate **91**, followed by insertion of CO and intra-molecular C=C insertion into the acyl metal bond. This is followed by a β-hydride elimination/isomerization producing the observed cyclopentenone **92**.[79]

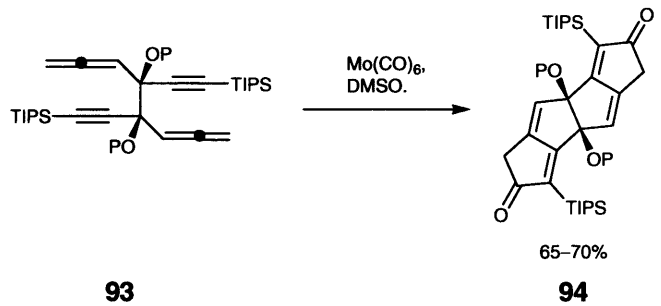


90 **86** **91** **92**

Scheme 21

Group 6 metals

Metal carbonyls such as molybdenum, chromium and tungsten as well as their anionic analogues such as $[(CO)_5MF]^-$, have been used in carbonylative cycloadditions of enynes without the use of high CO pressures. An interesting development of molybdenum carbonyl chemistry is the use on alkynyl allenes, whereby reaction of a diynediallene **93** (Scheme 22) produces the tetracycle **94**, involving the formation of six new C-C bonds in one-pot.[79]



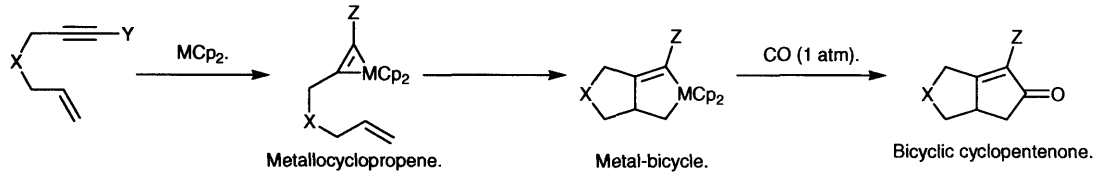
93 **94**

Scheme 22

Group 4 metals

Titanium and zirconium metals in the form of titanocene and zirconocene ($TiCp_2$ or $ZrCp_2$) are both able to promote the carbonylative cyclisation of enynes, where the alkyne moieties possess various substituents other than terminal hydrogen. They have provided valuable routes into cyclopentenone products that are unattainable by normal PKR. Group 4 metal carbonylative cyclisation generally provides good yields of the product with excellent regio, diastereo and enantioselectivities (with chiral titanocene species).[79]

The MCp_2 moiety in these reactions acts as a 14 electron species that readily reacts with enynes **95** under mild conditions (RT and CO pressure around 1 atm), to form metallocyclopropene **96** (Scheme 23). Once formed, they undergo intra-molecular metal-carbon bond addition on the alkene producing metal-bicycles **97**. These highly reactive products, upon treatment with CO, yield the cyclopentenone product **98**.[81, 82, 83, 84]



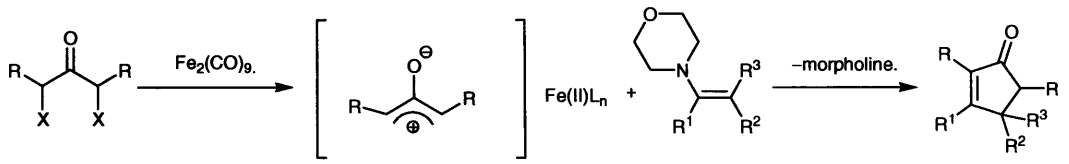
95 **96** **97** **98**

X, Y = hetero atom.

Scheme 23

[3+2] Cycloaddition

[3+2] Cycloaddition reactions mostly occur with the use of iron carbonyl species and dihaloketones **99** (Scheme 24), or 2-alkynyl iron complexes, *via* iron enolate formation **100**, followed by addition of an enamine **101**. Their use synthetically is limited due to moderate yields and poor selectivity, making this a less favoured route into cyclopentenone products **102**.[79]



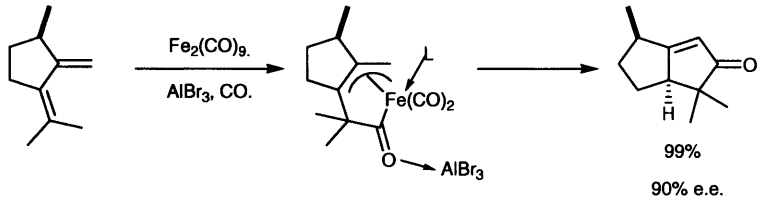
99 **100** **101** **102**

X = halogen atom.

Scheme 24

[4+1] Cycloaddition

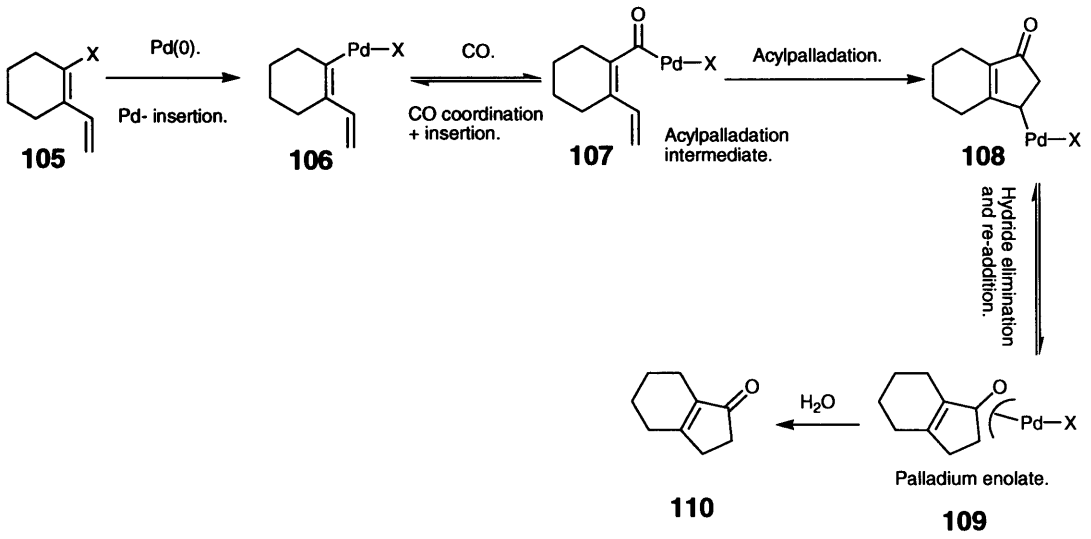
[4+1] Cycloadditions have been observed, with products formed with both iron carbonyl complexes and palladium complexes. Iron mediated [4+1] cycloadditions proceed at room temperature and atmospheric pressure with 1,3-dienes **103** (Scheme 25). These reactions are typically fast and are complete within a few minutes.[79] The mode of action by which the reaction is thought to proceed is by formation of a π-allyl complex, induced by coordination of a Lewis acid, such as aluminium tribromide ($AlBr_3$) and insertion of a CO ligand. Using this method the cyclopentenone product **104** was produced with a 90% enantiomeric excess.[85]



103 **104**

Scheme 25

The use of palladium in [4+1] carbonylative cycloadditions has been achieved on dienylhalides **105** (Scheme 26), under atmospheric pressures of CO by use of a palladium(0) species. These transformations proceed by insertion of Pd into the C-X bond to give **106**, followed by CO coordination and insertion creating the acylpalladium intermediate **107**, which undergoes acylpalladation of the neighbouring C=C bond giving **108**. This is then followed by reversible β-hydride elimination and re-addition of Pd, leading to formation of a palladium enolate **109**, which after protonation, produces the cyclopentenone product **110**.[79]

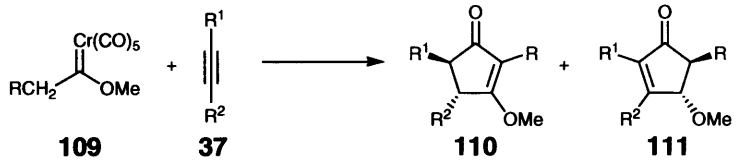


Scheme 26

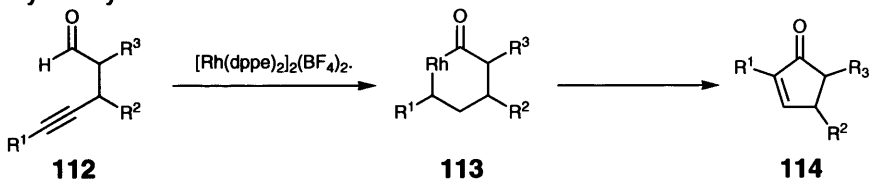
Other metal mediated routes

Metal carbene strategies (a)[81, 82] have included various metals such as chromium, ruthenium and rhodium in the formation of cyclopentenones in good yields, as well as strategies such as (b)[86, 87] hydroacylation and (c)[88] ring expansion reactions (Scheme 27). These strategies are very interesting chemically, however, they require specific substrates with specific groups that form intermediates that are air sensitive, making their use as general methods in the synthesis of cyclopentenones difficult.

a) Carbene.

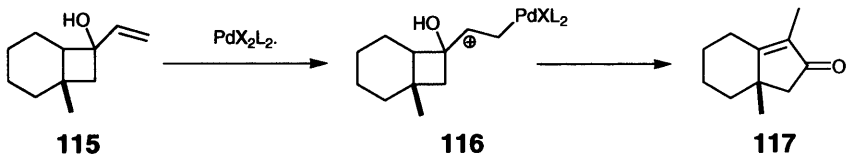


b) Hydroacylation.



dppe = 1,2-bis(diphenylphosphino)ethane.

c) Ring expansion.



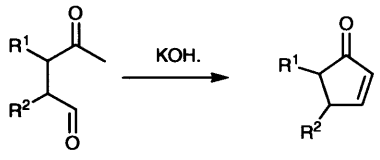
Scheme 27

1.6 Non-transition-metal mediated routes to cyclopentenones

The versatility of cyclopentenones as synthetic precursors to biologically active compounds has made them of significant interest to synthetic chemists. These interests encouraged the development of a number of general methods for their preparation with both regiochemical and stereochemical control. Before using transition-metal methodologies, which have lead to greater selectivity and reaction efficiency, non-transition-metal mediated routes were the predominant method of cyclopentenone synthesis. The following section describes the classical routes available for the synthesis of cyclopentenone ring structures that have general applicability and moderate efficiency. Synthetic routes to specific natural products are not included.

Intra-molecular aldol

The use of the aldol reaction[89] in the synthesis of cyclopentenone rings **119**, generally requires base catalysis and is an intra-molecular condensation reaction (Scheme 28) of 1,4-dicarbonyl compounds **117**, which may be prepared by a number of routes including the Friedel-Crafts reaction or enolate chemistry.

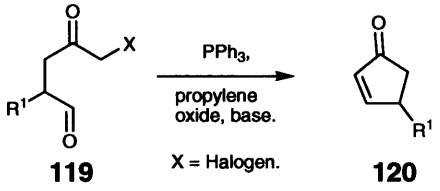


117 **118**

Scheme 28

Intra-molecular Wittig reactions

A Wittig reaction[90] may be used as an alternative to the aldol reaction by using activated 1,4-dicarbonyls **119** as starting materials, whereby the ylid intermediate is stabilised by the α-carbonyl group which undergoes an intra-molecular addition to reactive aldehydes (Scheme 29), to form the desired cyclopentenone product **120**.

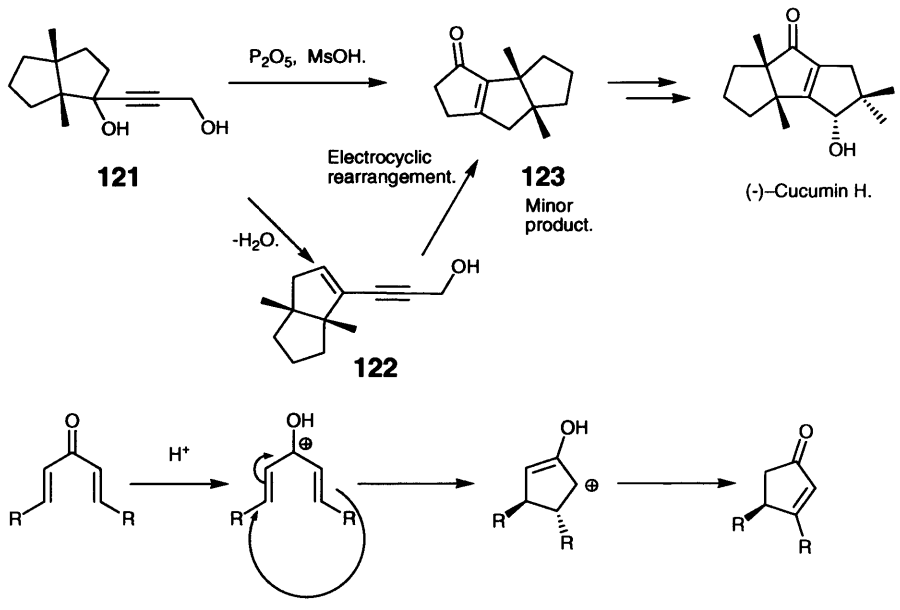


119 120

Scheme 29

Nazarov procedure

The Nazarov reaction, [91, 92, 93, 94] is an acid mediated cyclisation of allyl vinyl and divinyl ketones. The allyl vinyl ketones are isomerised to divinyl ketones before ring closure, to produce substituted cyclopentenones. The reaction has many variants that have led to elegant methods for the preparation of enantiomerically pure products such as (–)–cucumin (Scheme 30). Attachment of a third cyclopentane ring to **121** forms a complex tricyclic system **123**.[79] The Nazarov reaction requires strong Lewis or Brønsted acids, with one or more equivalents of Lewis acid frequently being necessary for the cyclisation. This reaction is a rare example of a Lewis acid-catalyzed 4-π conrotatory electrocyclic reaction. Common drawbacks are low selectivity and the use of stoichiometric amounts of the Lewis acids.



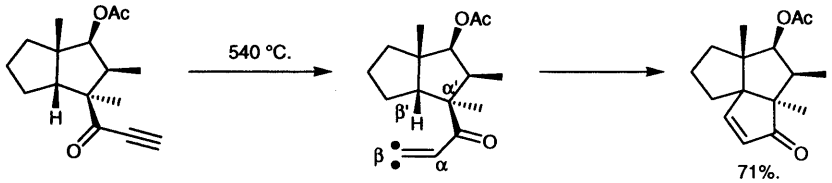
121 123 122

Scheme 30

Intra-molecular 1,5 C-H insertions

Intra-molecular 1,5 C-H insertions[95, 96] (Scheme 31) provide another method for the synthesis of cyclopentenone rings. These may be achieved regioselectively and stereoselectively using alkylidene carbenes **125**, generated in *situ* from alkynes **124**

using flash vacuum pyrolysis *via* a reversible 1,2-shift. Once the alkylidene carbene has been generated, insertion into the C-H bond occurs five carbons away, to yield the cyclopentenone product **126**. The formation of the new C-C bond between the acetylenic β-position and the non-activated carbon at the β'-position is assisted by a 1,2-migration of the hydrogen from the β-position to the α-position. These types of reactions provide versatile routes in the preparation of mono and bicyclic cyclopentenone units.



124 **125** **126**

Scheme 31

1.7 Aims

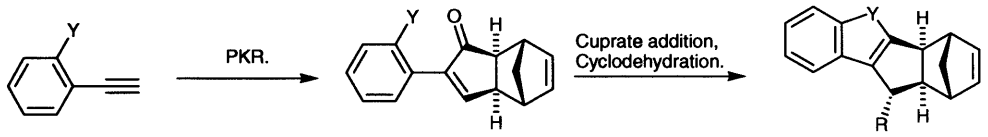
The aim of this study was to investigate the possibility of using the PKR as a synthetic tool in the synthesis of both hetero and carbon tricyclic fused ring systems. This would provide a relatively simple method to prepare complex structures with application in drug discovery. These complex ring systems may then be used as precursors in the development of new drugs from relatively simple starting materials. This study also set out to provide insight into the controversial debate as to the mechanism by which the PKR proceeds and to discover other potentially useful metal complexes capable of promoting the PKR.

Previous work within the group on the PKR involved the synthesis of alkyl cobaltoximes and their introduction into the PKR, providing highly functionalised compounds that could undergo various well documented reactions that are known for both alkylcobaltoximes and cyclopentenones.[97] One reaction of particular interest was using alkylcobaltoximes as a source of radicals by cleavage of the Co-C bond using light.

Alkylcobaltoximes have been used as model systems for the carbon-cobalt bond of coenzyme vitamin B12, a catalyst in living organisms. Due to the properties of alkylcobaltoximes as radical precursors and their ability to stabilise carbocations as a cobaltoximate π-cation, new interest in cobaltoxime chemistry has been generated.

The ability of both B12 and cobaltoximes to dehalogenate priority pollutants such as tetrachloroethene has also been of interest.[97]

The following Chapters concentrate on the synthesis of fused tricyclic ring systems. Initially, we were interested in investigating use of the PKR to synthesise heterocyclic fused tricyclic ring systems such as indoles and benzofurans, by using a short three step method, (Scheme 32). We wanted to incorporate both amine and alcohol functionalities into the alkyne starting material (e.g. **127**), in order to produce a cyclopentenone product with the hetro atom group at the α-position of the PKR product (e.g. **128**). These cyclopentenones could potentially afford fused tricyclic ring systems by spontaneous cyclodehydration, after addition of a soft nucleophile. In addition, this strategy would limit the amount of ring strain in the precursor in order for the desired heterocyclic product to be formed (e.g. **129**).

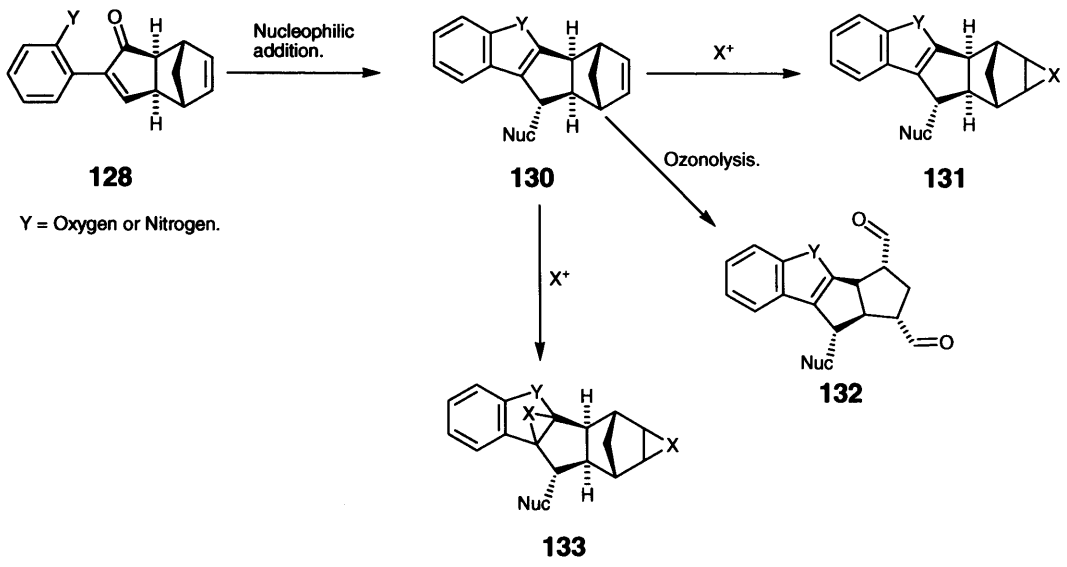


127 **128** **129**

Y = Oxygen or Nitrogen.

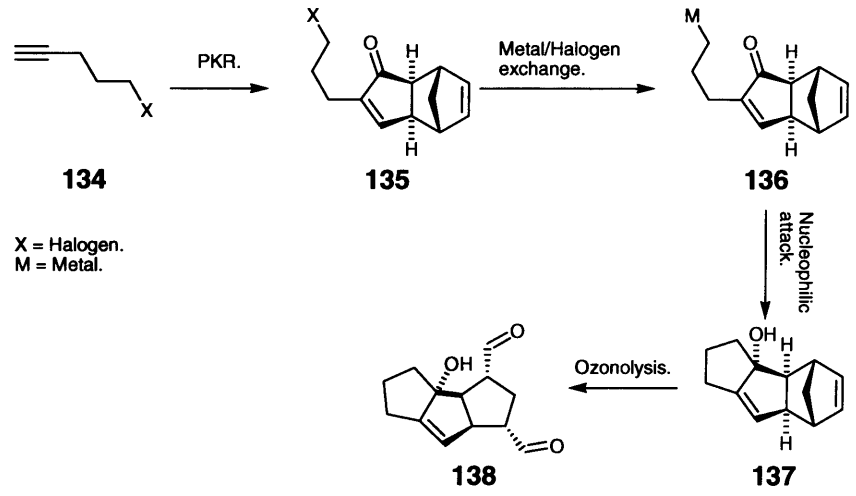
Scheme 32

To date, no examples have been reported of heteroatom or carbon tricyclic ring systems being synthesised using this protocol. The first step in investigating the plausibility of synthesising heteroatom fused ring systems would be to prepare alkynes (e.g. **127**) that would generate the desired PKR product **128**. This PKR was expected to be diastereoselective affording the *exo* isomer as well as regioselective, with the larger alkyne substituent occupying the α-position of the cyclopentenone. Once these products had been prepared, we hoped that addition of a "soft" nucleophile in a conjugate addition manner would enable the formation of the tricyclic skeleton **129**, which could then be modified by way of electrophilic addition to either of the two double bonds present. This would enhance the potential of this methodology for further functional group interconversions as a way of making functionalised fused tricyclic compounds (Scheme 33).



Scheme 33

Using the same methodology, we hoped to extend the scope of the synthesis to prepare carbon tricyclic carbon systems (Scheme 34), in an attempt to uncover a quick and relatively simple synthetic route to triquinanes. This approach would involve the PKR followed by a cyclisation using metal-halogen exchange and subsequent ozonolysis to produce the desired triquinane system (**138**). Triquinanes are frequently isolated from plants or marine sources and have been of great interest due to the diverse biological properties exhibited. These include antibiotic, antitumor and growth inhibitor properties.[98]



Scheme 34

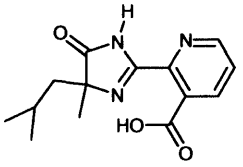
Chapter 2

2.1 Heterocycles

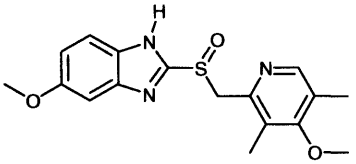
The term heterocycle comes from the Greek word "heteros" meaning different. Heterocyclic compounds are organic compounds that contain a ring structure with atoms in addition to carbon, such as nitrogen, oxygen or sulphur.

Heterocyclic compounds have been synthesised for many decades and have had an enormous impact on both the chemical and medicinal communities. Their uses have had widespread applications throughout the world, that include development and control of agriculture, with compounds such as imazapyr [99],

to drugs that are used in the treatment of many disorders and diseases, for example, omeprazole.[99]



imazapyr.



omeprazole.

Imazapyr is a heterocyclic compound used as a broad spectrum herbicide from the imidazolinone family. It acts as a systemic plant growth inhibitor.

Omeprazole is a synthetic compound belonging to a class of drugs known as proton pump inhibitors that control the production of stomach acid by blocking off the hydrogen potassium adenosine triphosphate enzyme system.

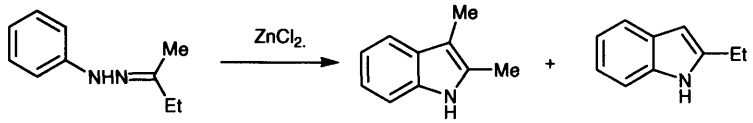
Heterocycles encompass a great number of compounds, allowing them to exhibit many unusual chemical features. These features can be explained by the position of the heteroatom or atoms in the ring structure. The positioning of lone pairs of electrons relative to the atoms around it, allows each compound to have different reactivities and properties.

Over the past three decades the PKR has been used to prepare natural products and potentially useful drug targets, using relatively simple starting materials. Both organic and inorganic chemists have extensively studied the PKR, however, most of the synthetic efforts have been used as a synthetic tool to incorporate a cyclopentenone product into a specific target molecule, rather than as a key step involved as an integral part of a methodology for accessing groups of compounds.

Many methods for synthesising indoles and benzofurans have long been established and numerous classical reactions can be found in textbooks. Three of the most noteworthy to access these types of heterocycles include:

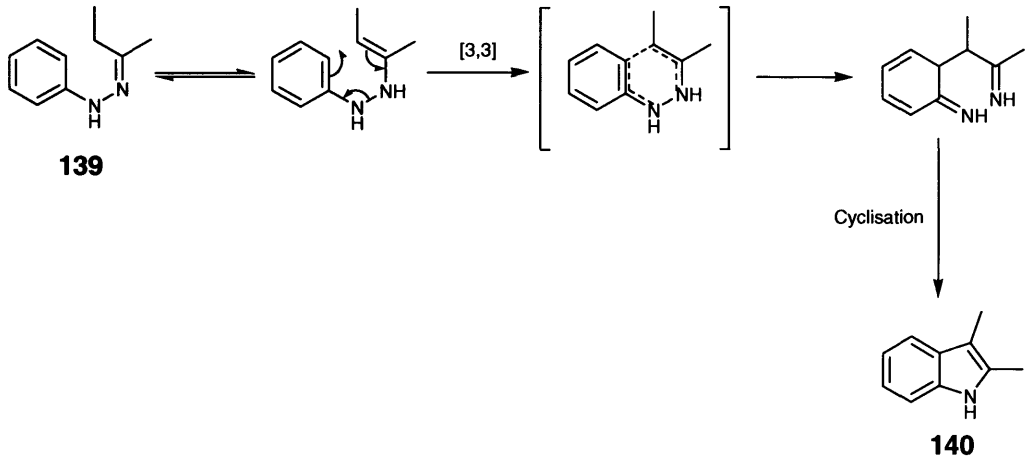
- The Fisher indole synthesis;
- The Bischler synthesis;
- The Nenitzescu synthesis;

The most famous and versatile of these reactions is the Fisher indole synthesis (Scheme 35). This transformation forms an indole from the phenylhydrazone derived from a ketone and alkyl hydrazine, for example, the hydrazone **139** can be transformed into the indoles **140** and **141** by treatment with zinc chloride.



139 **140** Major. **141** Minor.

Mechanism of reaction:

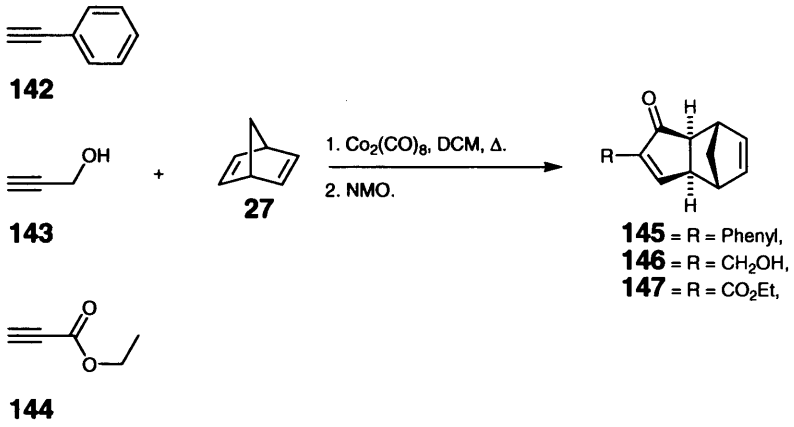


Scheme 35

The synthesis of indoles and many other heterocyclic compounds have found wide spread uses in organic chemistry, however, these classical routes are limited when the desired products consist of complex structures with several sensitive functional groups incorporated into the compound.

In pursuit of synthesising novel indoles, pyrroles, benzofurans and pyrans we initially examined the ideal reaction conditions for the PKR, using simple commercially

available alkynes such as phenyl acetylene **142,** propargyl alcohol **143**, and ethyl propiolate **144** to determine a general procedure using dicobaltoctacarbonyl **16** to yield cyclopentenones **145** (99%), **146** (70%) and **147** (35%) (Scheme 36). The ^1H NMR of all PKR products **145**, **146** and **147** showed the characteristic α,β-unsaturated proton as a doublet at δ 7.64 (**145**), as broad singlet at δ 7.12 (**146**) and as a broad singlet at δ 7.45 (**147**) ppm. This characteristic signal could be used as a convenient method to asses if reactions had been successful throughout this project.



Scheme 36

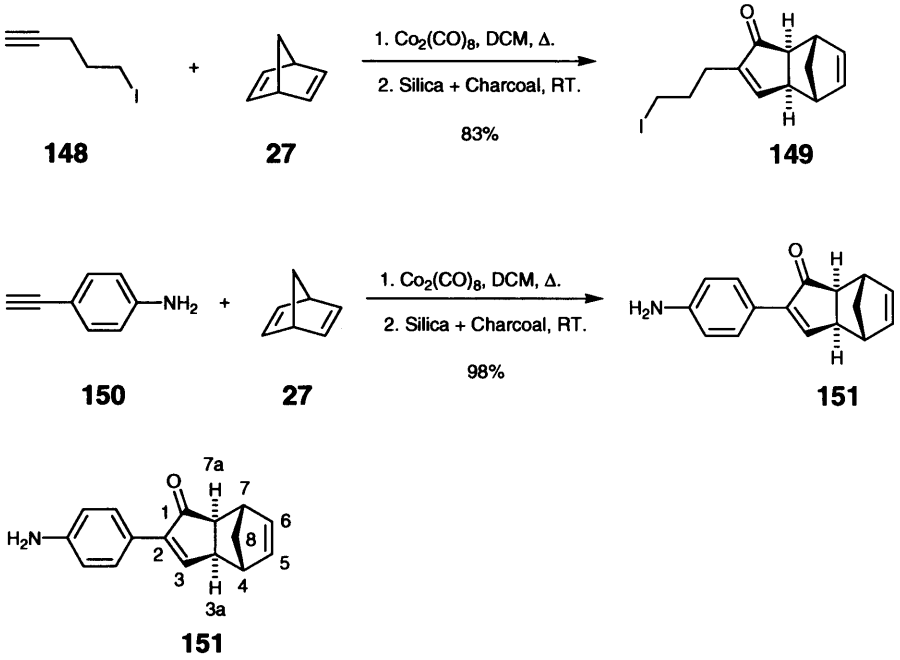
Entry	Alkyne	DCM[a]	Toluene[a]	THF[a]
1	**142**	99%	87%	86%
2	**143**	70%	67%	66%
3	**144**	35%	33%	30%

Table 1 a) Isolated yield of product. Compound **144** performed poorly in the PKR, where it is known as a poor PK substrate.[100]

From experimental work previously reported within the literature[30, 100, 101, 102] it was found that results obtained from different solvents were similar (Table 1). Therefore, DCM was chosen as a standard solvent, whilst NMO was used as an oxidising agent promoting the reaction. This method was thought to be a convenient standard PKR procedure to follow.

After applying this general protocol to alkyne substrates of interest such as 5-iodo-1-pentyne **148** and 4-ethynylaniline **150** (Scheme 37), the use of NMO was terminated, due to poor reaction yields observed (Table 2). An alternative procedure of refluxing

the alkynes **148** or **150** without adding NMO gave much better yields of the desired cyclopentenone products **149** and **151**. This method then became the standard reaction conditions used within subsequent PKR experiments.



Scheme 37

Entry	Product	NMO[a]	Silica/Charcoal[a]
1	**149**	10%	83%
2	**151**	20%	98%

Table 2 a) Isolated yield of product.

Not using NMO, however, led to substantial purification problems, resulting in unwanted organometallic by-products that were difficult to remove by chromatography. This led to a brief investigation into alternative purification methods. Stirring the crude reaction mixture with silica and activated charcoal in air overnight after the PKR had gone to completion, allowed for easier purification of products by chromatography. An alternative method to this was adding small amounts of iodine to the crude reaction mixture. This method again led to easier purification by chromatography, but unfortunately, the iodine caused unwanted reactions with the products such as the iodination of the double bonds in the cyclopentenone products and was deemed unsuitable in this application.

These initial experiments provided a general protocol for purification of the PKR products used throughout this thesis: On reaction completion (determined by no presence of cobalt alkyne complex by TLC), silica and charcoal were added and the reaction mixture stirred under air (overnight) until the majority of organometallic by-products had diminished by TLC. The desired cyclopentenone product was then purified by column chromatography. This method by which the silica/charcoal stir removes unwanted organometallic by-products uses a one-electron transfer which oxidises the unwanted organometallic species into inorganic species that could easily be separated from the products.

The PKR has been shown to be a powerful synthetic tool, both in inter and intramolecular reactions and has received much interest from many groups worldwide. Gibson and co-workers have focused on asymmetric variations based on chiral ligands and chiral bimetallic metal complexes.[103] Kraft and co-workers have developed alternative cobalt sources[104] and provided a comprehensive review on the PKR and its alternate reaction pathways.[25] To date, no real focus has been devoted to the use of alkynyl anilines in the PKR to produce highly functionalised indoles, apart from two isolated reports. The first examined the unusual products formed by the use of free amines in the PKR and their metal complexes.[105] The second provided access to 6-5 spirocyclic compounds using protected amines.[106] Neither of these investigations examined the use of alkynyl anilines to produce highly functionalised indoles and pyrroles.

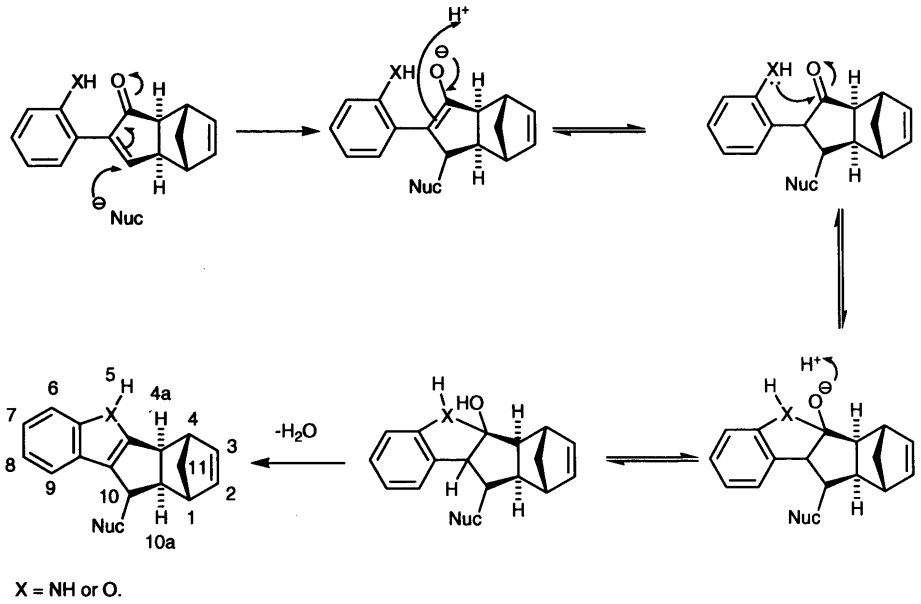
Initial experiments showed the PKR products **149** and **151** could be prepared regiochemically pure after purification. Both compounds showed the desired ^{1}H NMR spectrum appropriate with the cyclopentenone product, including the characteristic signal above δ 7.00 ppm for the α,β-unsaturated proton. ^{13}C NMR also confirmed the α,β-unsaturated carbonyl group above δ 205 ppm. The stereochemistry of *exo* or *endo* cyclopentenone compounds synthesised within this thesis was determined by ^{1}H NMR. The chemical shifts and splitting patterns of the aliphatic protons H-3a, H-4, H-7 and H-7a (Scheme 37), were in accordance with Pauson and Khand's initial publication.[19] These *exo* isomers from the PKR showed lower chemical shifts for the aliphatic protons as well as different splitting patterns, when compared to the alternative *endo* isomer.[20] Selective formation of the *exo* isomer is a result of the mechanism by which the reaction proceeds (see Scheme 9).

Different chemical shifts between the *exo* and *endo* isomers of the tricyclic products is due to more effective shielding experienced by the aliphatic protons in the *endo* isomer. The H-3, H-4, H-7 and H-7a protons in the *endo* isomer experience more shielding from the H-5 and H-6 double bond than in the *exo* isomer. This shielding effect results in a higher chemical shift being observed for H-3, H-4, H-7 and H-7a protons in the *endo* isomer.

A possible explanation for the differences exhibited between both *endo* and *exo* isomers is due to the amount of p and s character in the bonds of the two isomers. The bond angles of both isomers are not a perfect 109° due to the constrained ring within the structure and do not consist of perfect sp^3 hybridised orbitals. Therefore, the amount of s and p bond character will vary between isomers, due to the degree of ring strain experienced by each. The more s character a bond experiences, a larger coupling constant is observed due to better Fermi contacts. This could account for why the *endo* isomer experiences larger splitting patterns between protons compared to the *exo* isomer.

Within this thesis we concentrate on using alkynyl amines and alkynyl alcohols as staring materials for a PKR to develop new routes into fused tricyclic indoles, pyrroles, benzofurans and pyrans, which are potentially useful building blocks in drug discovery chemistry.

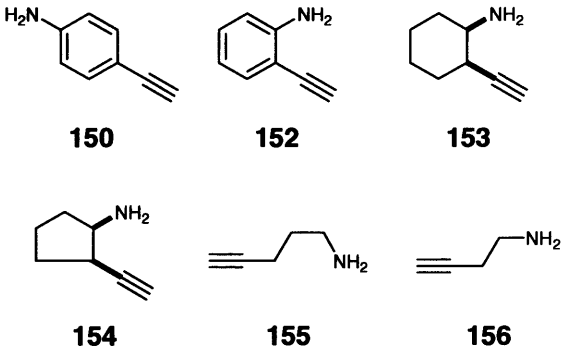
Spontaneous condensation of the synthesised PK product, using conjugate addition of soft organometallic nucleophiles to the α,β-unsaturated carbonyl of the cyclopentenone was hoped to result in a fused hetero tricyclic ring system. A 1,4 conjugate addition should also aid the process by reducing ring strain in the cyclopentenone adduct, allowing the heteroatom to perform a intramolecular addition to the carbonyl, producing a heterocyclic product after loss of water (Scheme 38).



Scheme 38

2.2 Synthesis of alkynyl amines for use in indole and pyrrole synthesis

A series of structurally interesting alkynyl amines (Scheme 39) were synthesised to explore the scope of the PKR to prepare, amine-functionalised cyclopentenones. It was envisaged that their PKR products would be viable precursors to the desired indole and pyrrole fused ring systems.



150 **152** **153**

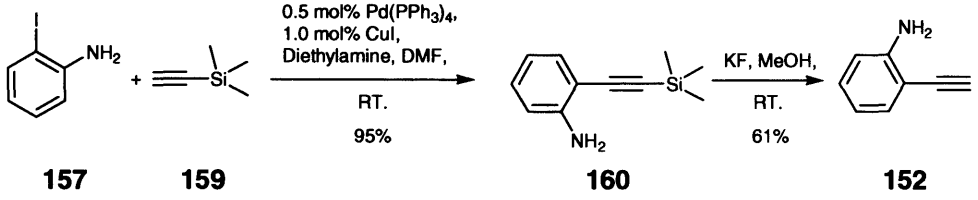
154 **155** **156**

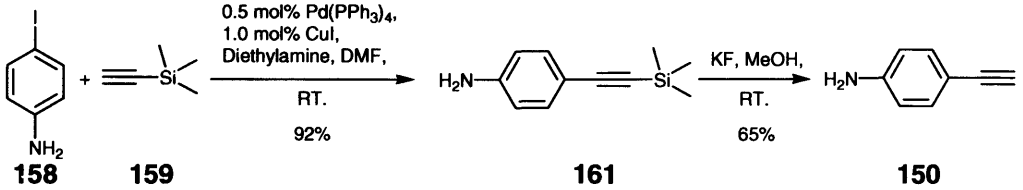
Scheme 39

Both alkynes 2-ethynylaniline **152** and 4-ethynylaniline **150** were synthesised using palladium coupling chemistry,[107] via a Sonogashira reaction of 2-iodoaniline **157** or 4-iodoaniline **158** and ethynyltrimethylsilane **159**. The trimethylsilyl (TMS) group was then removed from both 2-trimethylsilanylethynyl-phenylamine **160** (95%) and 4-trimethylsilanylethynyl phenylamine **161** (92%) by treatment with potassium

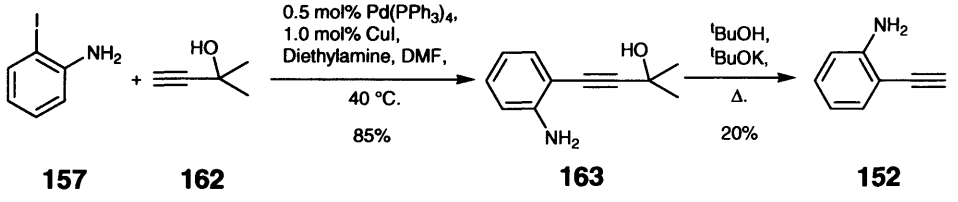
fluoride, to yield 2-ethynylaniline **152** (61%) and 4-ethynylaniline **150** (65%) (Scheme 40). A cheaper procedure was attempted, by substituting ethynyltrimethylsilane **159** with 2-methyl-3-butyn-2-ol **162** as an alternative alkyne protecting group. This was de-protected by removal of acetone, to give the desired alkynes **150** and **152** under basic conditions. By reacting 2-iodoaniline **157** or 4-iodoaniline **158**, with 2-methyl-3-butyn-2-ol **162** (Scheme 40), using the same coupling protocol as before, good yields were achieved in the coupling step.[108] Unfortunately, deprotection of **163** (85%) and **164** (87%) gave poor yields on scale up **152** (20%) and **150** (28%) and was not as efficient when compared to the initial synthesis using ethynyltrimethylsilane **159**.

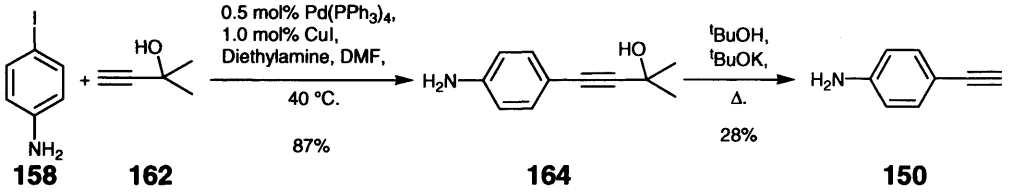
Ethynyltrimethylsilane route.





2-Methyl-3-butyn-2-ol route.





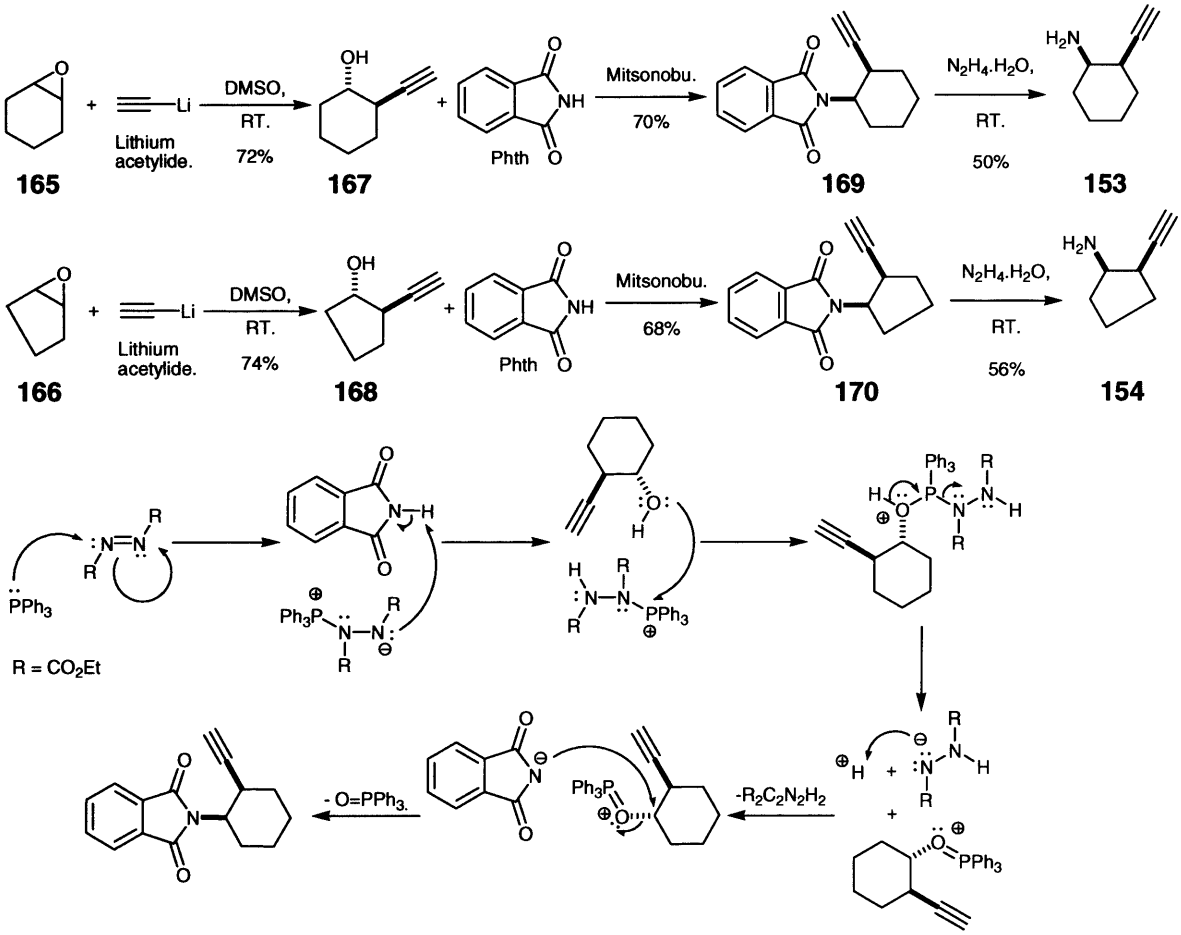
Scheme 40

All compounds were isolated and characterised by ^{1}H NMR spectroscopy Intermediate products **160**, **161**, **163** and **164** all showed the disappearance of a proton singlet consistent with the loss of a terminal alkyne proton. After deprotection,

compounds **150** and **152** were isolated and easily identified by a characteristic singlet for the terminal alkyne proton in their ^{1}H NMR spectrum.

The following two alkynyl amines of the series, 2-ethynylcyclohexanamine **153**[109] and 2-ethynylcyclopentanamine **154** were synthesised (Scheme 41) from cyclohexene oxide **165** and cyclopentene oxide **166**, using a three step protocol. The first step involved the ring opening of the epoxide with lithium acetylide, to yield alcohols **167** (72%) and **168** (74%) as racemic *trans* isomers in good yield.[110] The next step used a Mitsonobu reaction of the alcohols with phthalimide (Phth) in the presence of triphenylphosphine and di-ethylazodicarboxylate (DEAD) to give the protected *cis* amino alkynes **169** (70%) and **170** (68%).

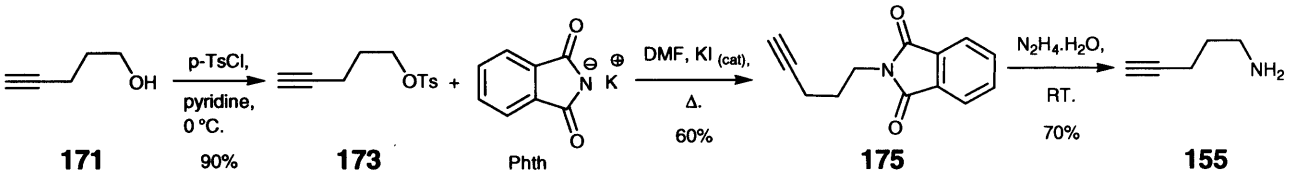
Both protected amino alkynes **169** and **170** were de-protected to yield the desired alkynyl amines **153** (50%) and **154** (56%)[111] using hydrazine to remove the phthalimide protecting group.



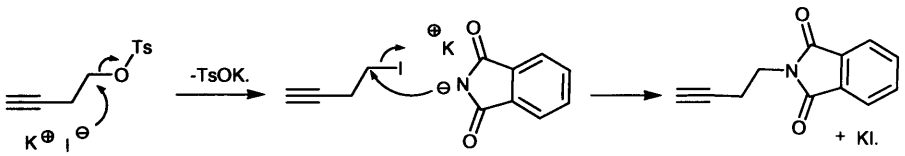
Scheme 41

The final two alkynyl amines of the series synthesised, pent-4-ynylamine **155** and but-3-ynylamine **156** was achieved by converting the alcohol starting materials **171** and **172** to there tosyl esters **173** (90%)[112] and **174** (85%),[113] using *p*-toluenesulfonylchloride (*p*-TsCl) in pyridine (Scheme 42).

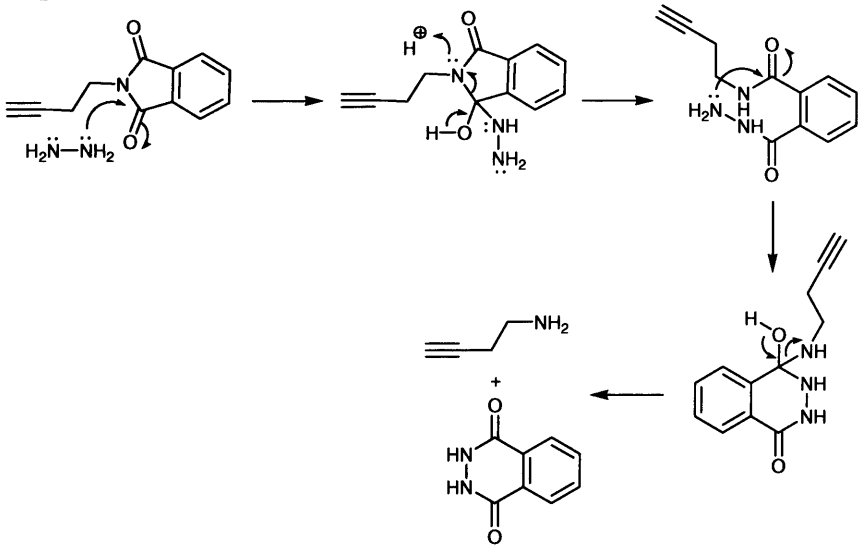
A Gabriel synthesis was next used to produce the amino alkynes **175** (60%) and **176** (70%) from the tosyl esters using potassium phthalimide.[112] deprotection of **175** and **176** by treatment with hydrazine hydrate gave the two desired alkynyl amines **155** (70%) and **156** (60%) in good yield.[114, 115]



Gabriel Mechanism.



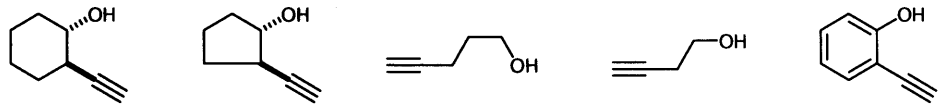
Deprotection Mechanism.



Scheme 42

2.3 Synthesis of alkynyl alcohols for use in benzofuran and pyran synthesis

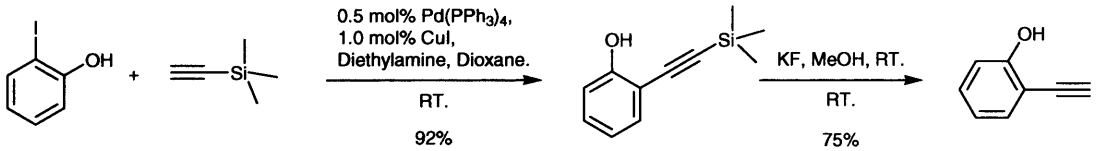
As an alternative to the series of alkynyl amines already prepared, a similar series of alkynyl alcohols **177**, **178**, **181**, **182** and **187** were synthesised to be used in the PKR for investigating the viability of synthesising benzofurans and pyrans, some of which were intermediates or starting materials in the preparation of the alkynyl amine series previously described (Scheme 43).



167 **168** **171** **172** **177**

Scheme 43

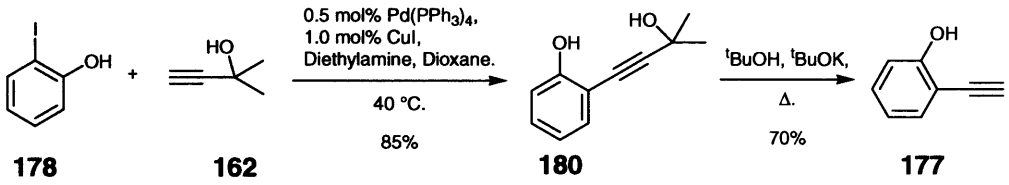
2-Ethynylphenol **177** was synthesised using the same methodology as 2-ethynylaniline **152**, using an aryl halide Sonogashira cross-coupling reaction (Scheme 44) of 2-iodophenol **178** and ethynyltrimethylsilane **159** to yield 2-trimethylsilanylethynyl-phenol **179** (92%), which upon deprotection with potassium fluoride yielded 2-ethynylphenol **177** (75%).[116, 117]



178 **159** **179** **177**

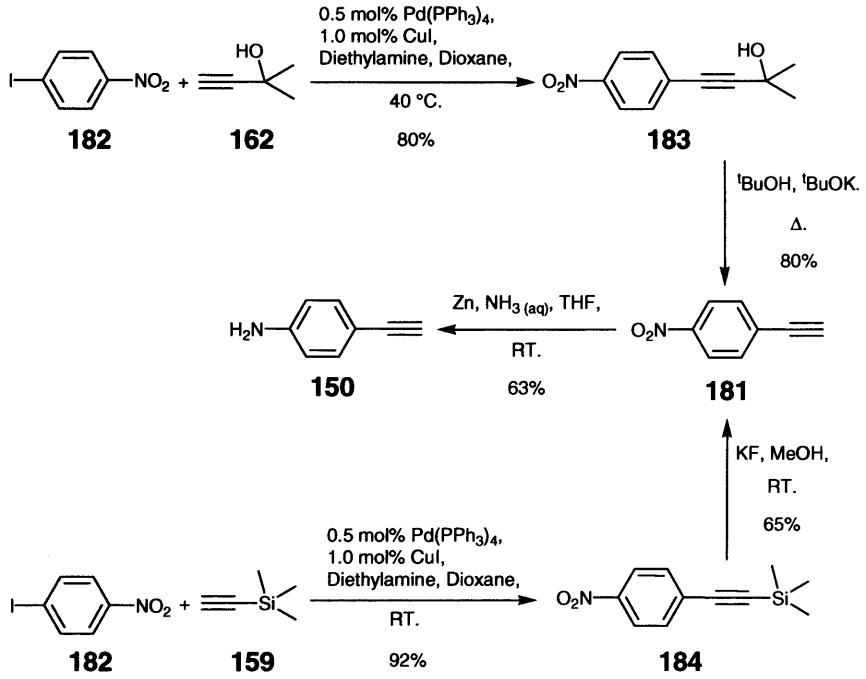
Scheme 44

Again, 2-methyl-3-butyn-2-ol **162** (Scheme 45) was also employed as an alternative reagent in the cross-coupling with 2-iodophenol **178**, yielding **180** (85%). De-protection under basic condition yielded 2-ethynylphenol **177** (70%) which was effective upon scale up of the reaction. This was again done to potentially reduce the cost of the synthesis,[118, 119] as well as determining the effects of different functional groups on the alternative deprotection steps (Table 3).



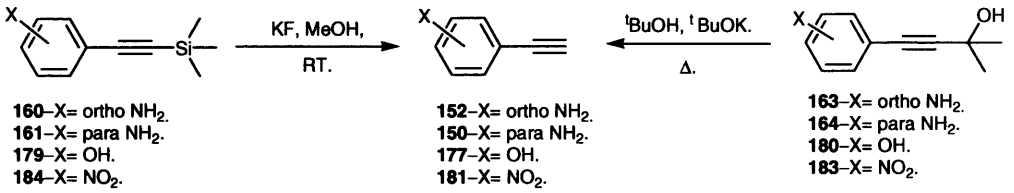
Scheme 45

An alternative method was developed for the preparation for 4-ethynylaniline **150** and is outlined in Scheme 46. A Sonogashira coupling of 1-iodo-4-nitrobenzene **182** and 2-methyl-3-butyn-2-ol **162** followed by deprotection of **183** under basic reaction conditions gave 1-ethynyl-4-nitro-benzene **181** in 64% overall yield.[120] This compound could also be accessed by deprotecting trimethyl-(4-nitro-phenylethynyl)-silane **184**.[121] Reduction of 1-ethynyl-4-nitro-benzene **181** under standard reaction conditions [122] provided alternative access to 4-ethynylaniline **150** that was amenable to scale up.



Scheme 46

A brief study into which deprotection step was more versatile to differing functional groups, showed that deprotection of the TMS group with KF was more tolerant of differing functional groups, than of acetone with K^{t}BuO, which showed poor tolerance of amines (Table 3).



160–X= ortho NH_2.
161–X= para NH_2.
179–X= OH.
184–X= NO_2.

152–X= ortho NH_2.
150–X= para NH_2.
177–X= OH.
181–X= NO_2.

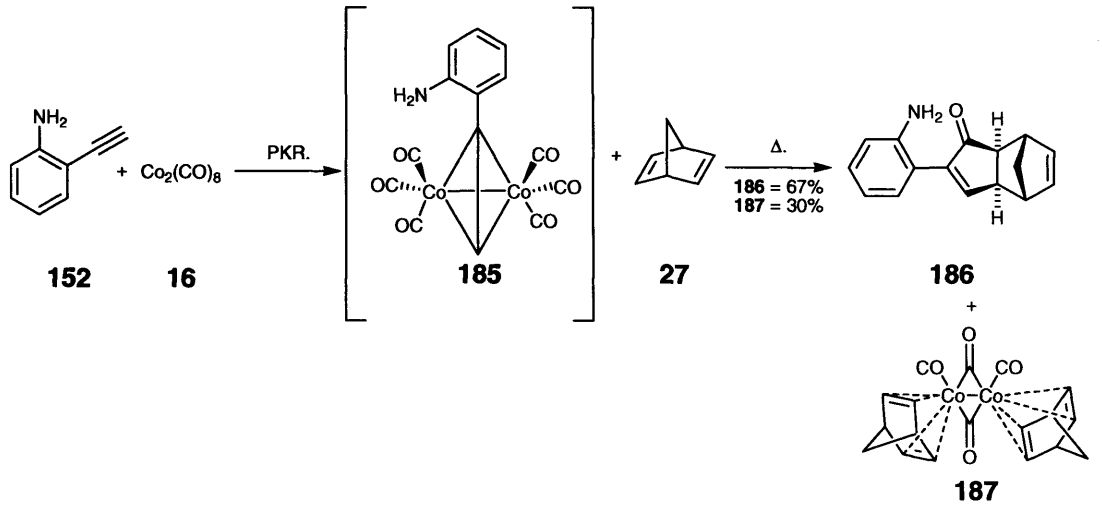
163–X= ortho NH_2.
164–X= para NH_2.
180–X= OH.
183–X= NO_2.

Entry	Product	KF	K^{t}BuO
1	**150**	65%	28%
2	**152**	61%	20%
3	**177**	75%	70%
4	**181**	65%	80%

Table 3

2.4 Synthesis of cyclopentenones from alkynyl amines

The alkynyl amines series synthesised **152–156** were transformed into their corresponding cyclopentenones using the PKR. The first compound from the series to be introduced into the PKR (Scheme 47) was 2-ethynylaniline **152** using dicobaltoctacarbonyl **16** in DCM under inert conditions, the alkynyl dicobalt complex **185** was formed (in situ) in one hour and observed as a dark high running spot by thin layer chromatography (TLC). To this the bicyclic alkene, 2,5-norbornadiene **27** was added, and the reaction monitored to completion by TLC. This showed the disappearance of the dark high running blue/black spot, and the appearance of a lower U.V. active spot, that was isolated as **186** (67%).[123]



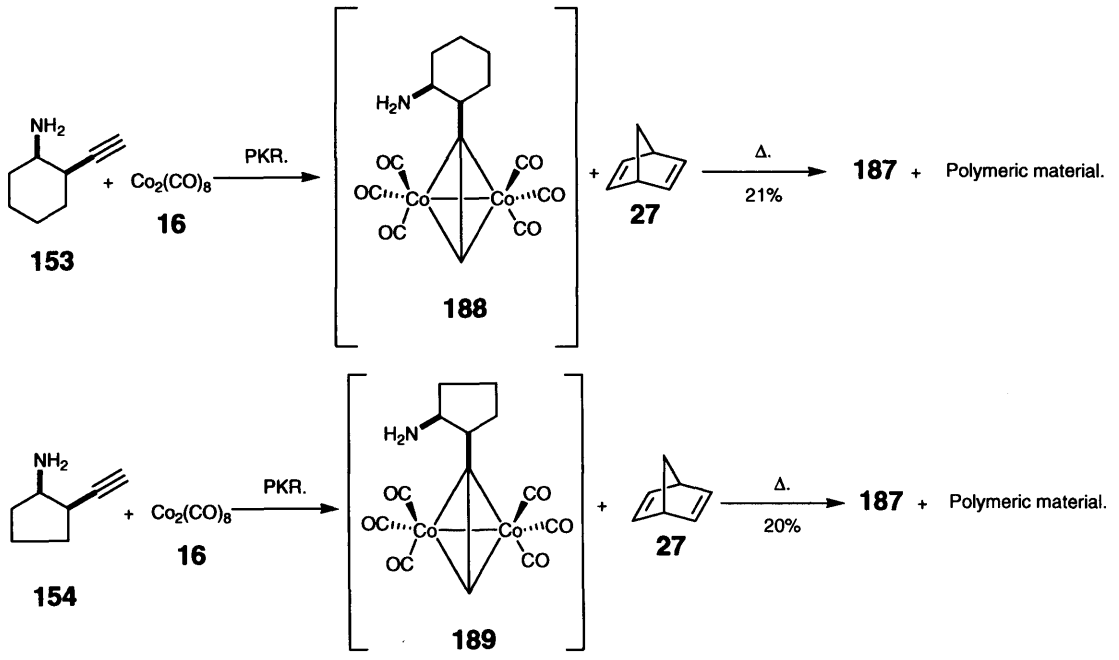
Scheme 47

During this reaction red crystals **187** (30%) were observed upon cooling of the reaction mixture. These crystals were re-crystallised from 40–60 petroleum ether under an inert atmosphere of nitrogen, and identified as dinorbornadienedicobalttetracarbonyl **187** by X-ray crystallography (Chapter 5).

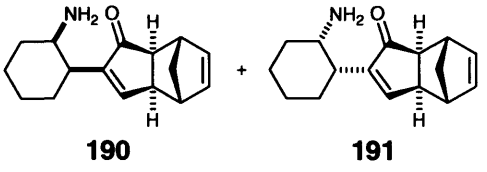
The subsequent reactions using the alkynyl amines series prepared for use in PKR showed a characteristic blue TLC spot corresponding to the alkynyl cobalt complex prior to addition of 2,5-norbornadiene **27**. Additionally a red spot was observed by TLC when the amine functionality was protected, indicative of differing electronic configurations and distribution within the metal complexes.

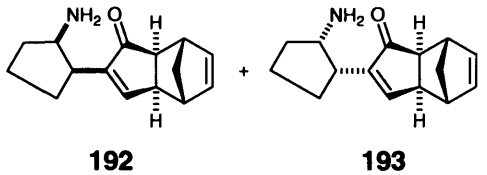
All compounds were purified by chromatography and fully characterised using ^{1}HNMR, ^{13}C-NMR, IR and High Resolution Mass Spectrometry (HMRS).

Compounds **153** and **154** were next reacted using a PKR (Scheme 48) but did not afford the expected cyclopentenone diastereoisomers **190–193**. Only dinorbornadienedicobalttetracarbonyl **187** (≈20%) was isolated from the reaction and an unwanted material, determined as polymeric by poor mobility with polar solvents on TLC plates and a multitude of multiple broad signals by ^{1}H NMR analysis. The cobalt alkyne complexes **188** and **189** in Scheme 48 were not isolated due to their highly reactive nature which led to decomposition upon isolation and were only observed as high running blue TLC spots.



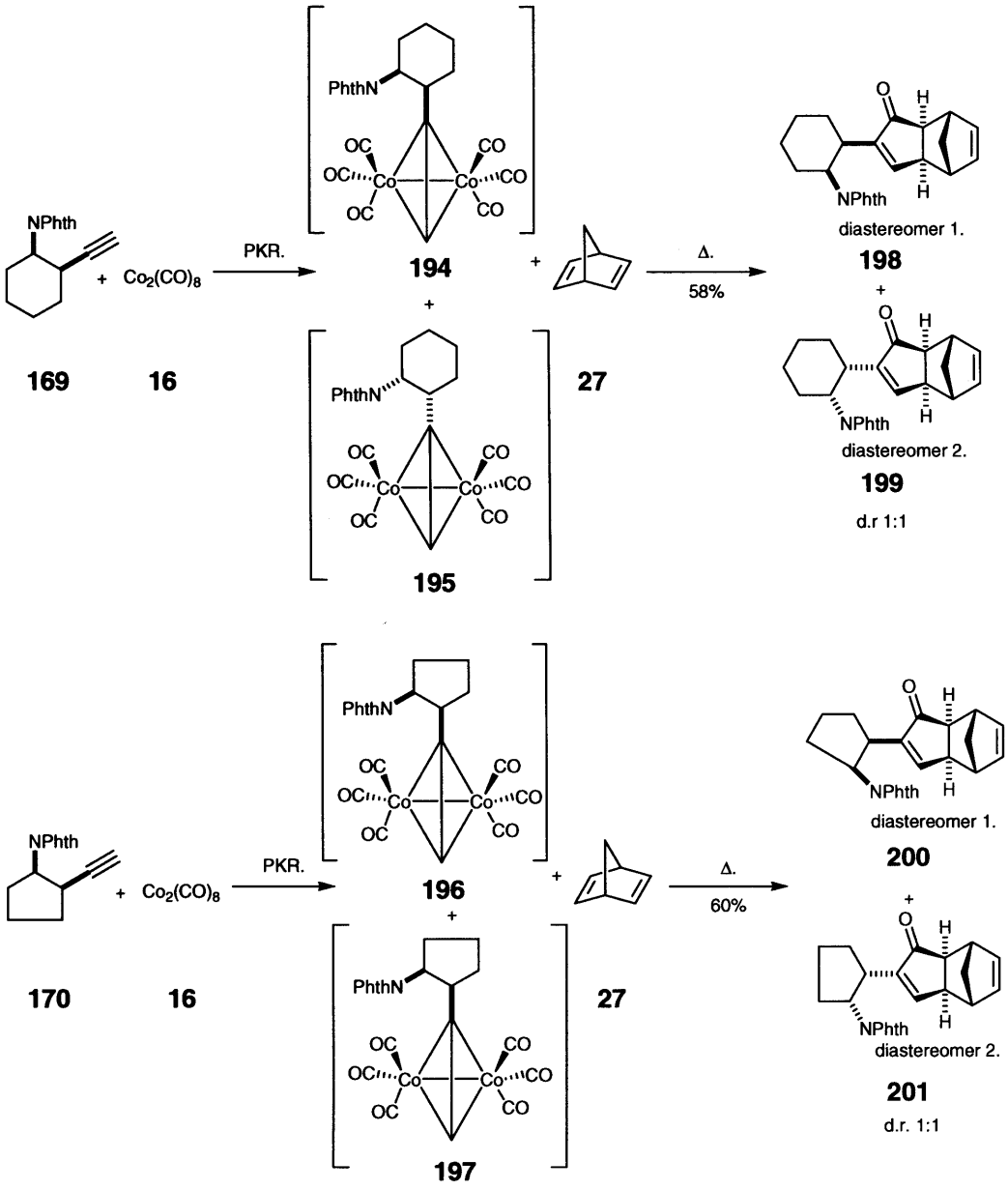
Expected compounds **190, 191, 192 and 193.**





Scheme 48

These unfortunate results led to using compounds **169** and **170**, as the phthalimide protected derivatives of the free alkynyl amine precursors in the PKR (Scheme 49), to produce the protected PKR products **198** and **199**, which could later be de-protected to the free amine. Compounds **169** and **170** reacted under the PKR conditions, yielding two diastereoisomers of the cyclopentenone products, each diastereoisomer is shown for clarity **198/199** (58%) and **200/201** (60%) with compound **187** omitted. Intermediates **194, 195, 196** and **197** have been shown for clarity, both possible configurations of the cobalt complexes will not been shown in future.



Scheme 49

Purification of compounds **198/199** by column chromatography led to a mixture of inseparable diastereoisomers. Upon recrystallisation from Et_2O/40–60 petroleum ether a single diastereoisomer was separated. The relative configuration of this single diastereoisomer was not determined and in subsequent discussions this compound, we have assigned this isomer to be **198**.

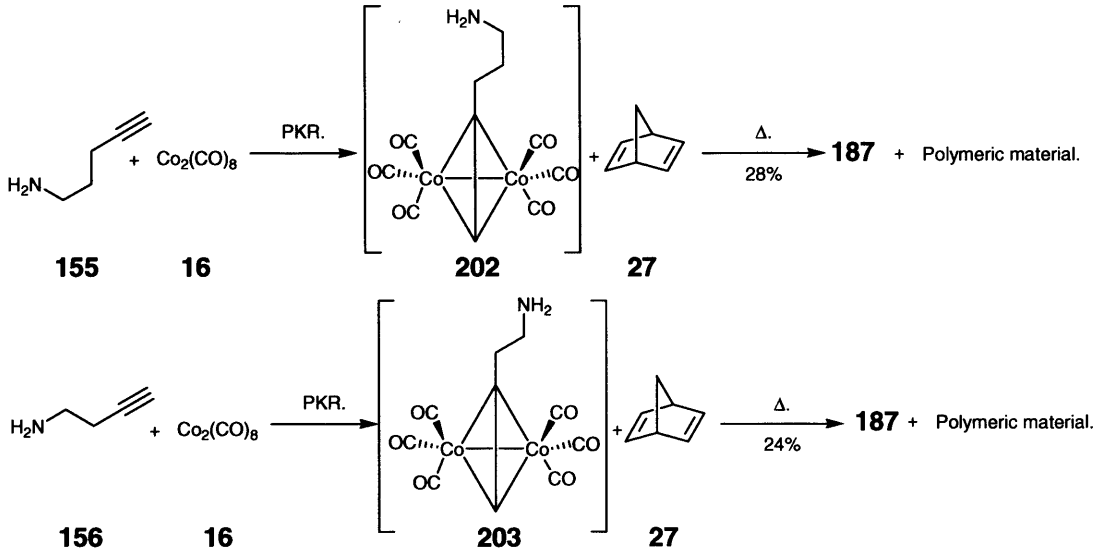
The same purification problems were encountered in the isolation of compounds **200/201**. Again recrystallisation from Et_2O/40–60 petroleum ether, resulted in a single diastereoisomer being separated. The relative configuration of this single stereoisomer

was not determined and in subsequent discussion of this compound we have assigned this isomer to be **200**.

Compound **199** and **201** known to be present were never isolated and with hindsight the mother liquors of each crystallisation should have been further investigated. Replication of this work should include examination of the mother liquors.

Crude ^{1}H NMR analysis showed a diastereomeric ratio of 1:1 as a consequence of the CHNPhth signal distinguishable at differing chemical shifts.

Compounds **155** and **156** both exhibited similar problems (Scheme 50) as encountered with alkynyl amines **153** and **154**, whereby the PKR afforded unwanted polymeric material, instead of the desired cyclopentenones **204** and **205**.



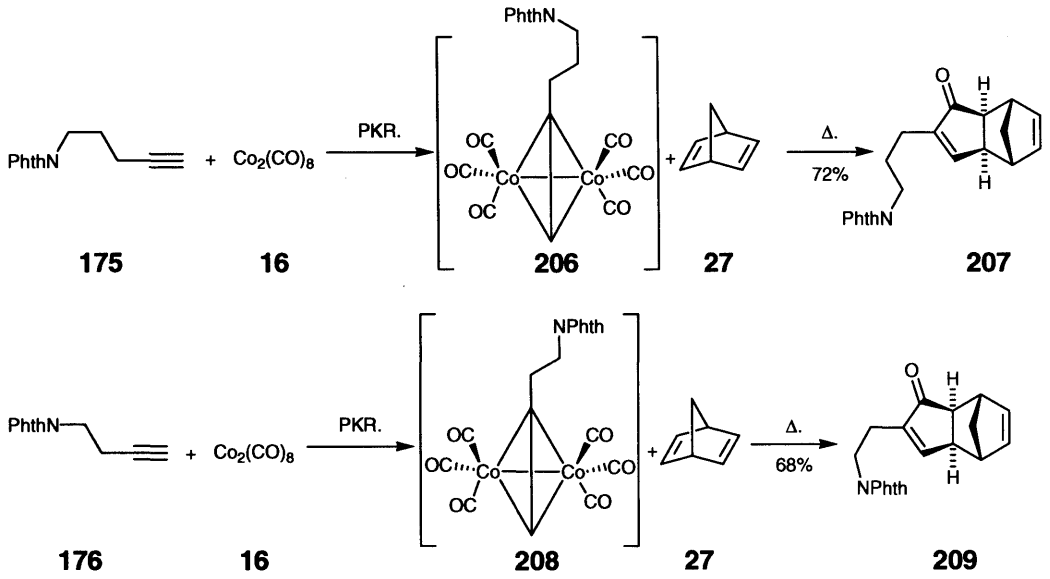
Expected Compounds

Scheme 50

Polymerisation problems occurring within the alkynyl amine series in the PKR are thought to be due to the basicity of compounds **153–156**, compared to the alkynyl aniline adducts **150** and **152**, where basicity is significantly reduced due to delocalization of the nitrogen non-bonding electron pair into the aromatic ring. The

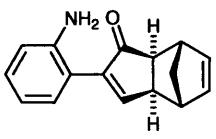
more basic amines may react intermolecularly once the PKR was complete, forming possible dimers, trimers or polymers.

Phthalimide derivatives of the cyclopentenones **207** (72%) and **209** (68%) were synthesised from compounds **175** and **176**, using the same protocol as before (Scheme 51). Both cyclopentenone products **207** (72%) and **209** (68%) were obtained in good yields after purification.

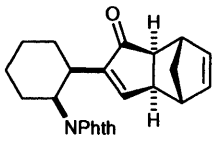


Scheme 51

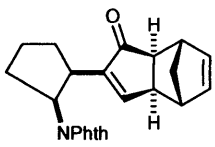
A summary of the results obtained from the PKR with both the alkynyl amine and alkynyl phthalimide series can be seen in Table 4, whereby, all protected amine alkyne cobalt complexes were red and the free amines gave a blue cobalt complex. The PKR products with a phthalimide group were achieved in moderate to good yields (58–72%).



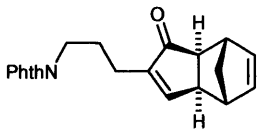
186



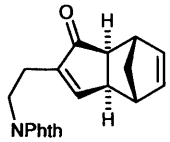
198



200



207



209

Entry	Alkyne	PKR product	Co-complex colour (TLC)	PKR product yield %
1	**152**	**186**	Blue	67%
2	**153**	None	Blue	No product
3	**154**	None	Blue	No product
4	**155**	None	Blue	No product
5	**156**	None	Blue	No product
6	**175**	**207**	Red	72%
7	**176**	**209**	Red	68%
8	**194**	**198/199**	Red	58%
9	**195**	**200/201**	Red	60%

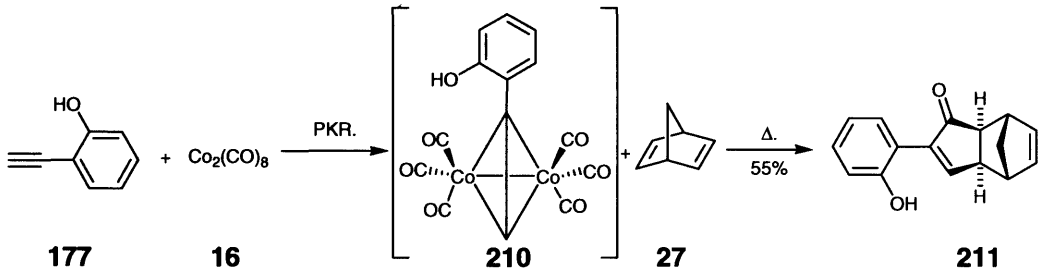
Table 4

2.5 Synthesis of cyclopentenones from alkynyl alcohols

The series of alkynyl alcohols **167**, **168**, **171**, **172** and **177** were subjected to the PKR protocol and afforded the desired cyclopentenone products with DDTC **187** as a side product again being observed.

All cobalt alkyne complexes of the alkynyl alcohols showed a characteristic red TLC spot prior to the addition of 2,5-norbornadiene **27**, and all products were purified by chromatography and characterised using ^{1}H NMR, ^{13}C NMR and IR.

The first alkynyl alcohol to be reacted (Scheme 52) was 2-ethynylphenol **177** (no cobalt alkyne complex was isolated). This reaction produced the desired cyclopentenone **211** (55%) in moderate yield.

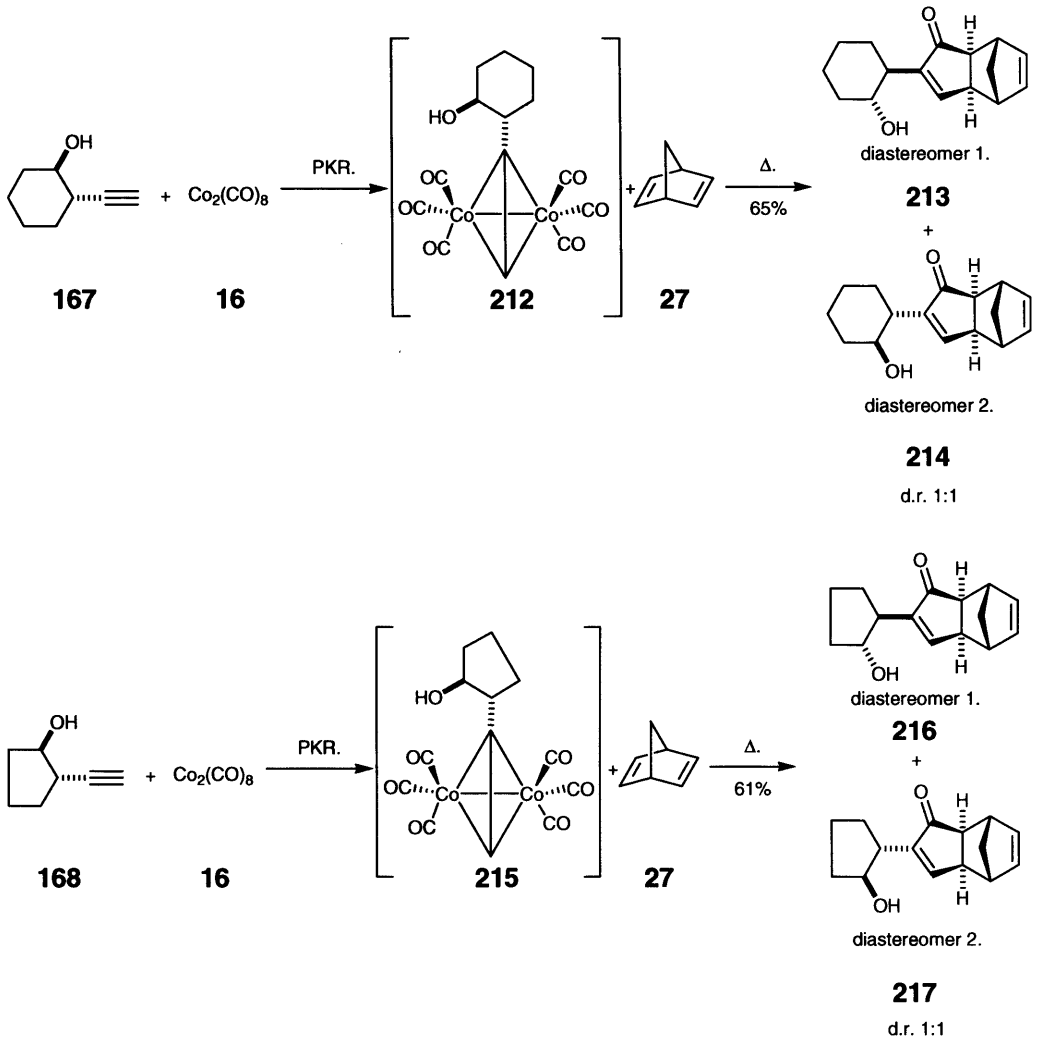


Scheme 52

The unsaturated cyclic alcohols **167** and **168** were next reacted in the PKR (Scheme 53), which produced a mixture of diastereoisomers as products **213** and **214** (65%), **216** and **217** (61%). Separation of the diastereoisomers [i] was unable to be achieved by column chromatography due to their retention times on silica being similar $R_f = 0.35$ (**213/214**) and $R_f = 0.34$ (**216/217**) however, upon recrystallisation from EtOAc/Hexane separation was achieved.

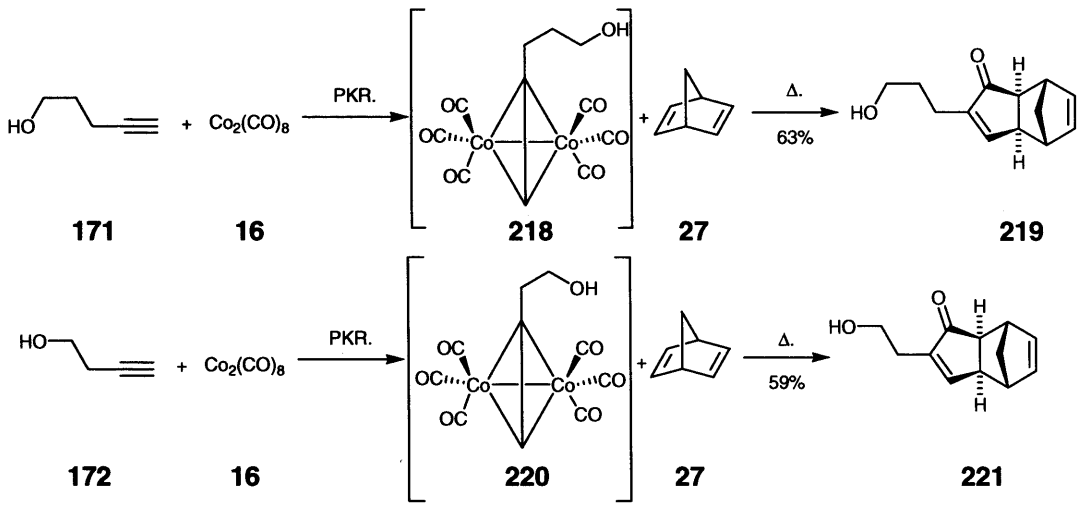
[i] The relative configurations of isomer **213** and **216** have not been determined unequivocally. See page 46 for a discussion.

The relative configuration of both isolated diastereoisomers was not determined and in subsequent discussion of these products we have assigned the isolated isomers as **213** and **216**. The diastereomeric ratio was determined as 1:1 due to racemic starting material being used and ^{1}H NMR showing a 1:1 relationship of the CHOH group in both compounds.



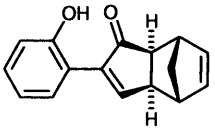
Scheme 53

Reactions of pent-4-yn-1-ol **171** and but-3-yn-1-ol **172** proceeded smoothly as expected from previous PKR's, to yield both cyclopentenone **219** (63%) and **221** (59%) in good yields (Scheme 54).

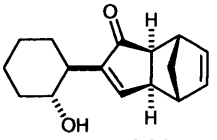


Scheme 54

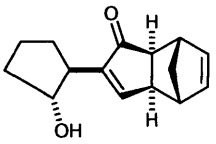
Results obtained from synthesising the cyclopentenone products of the alkynyl alcohol series using the PKR, are summarised in Table 5. Attempts were made to isolate all intermediate cobalt alkyne complexes described in this Chapter with no success due to decomposition upon purification.



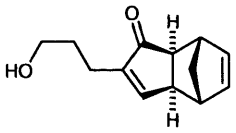
211



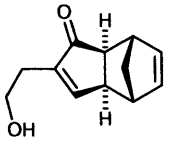
213



216



219



221

Entry	Alkyne	PKR product	Co-complex colour (TLC)	PKR product yield %
1	**177**	**211**	Red	55%
2	**167**	**213**	Red	33%
3	**168**	**216**	Red	31%
4	**171**	**219**	Red	63%
5	**172**	**221**	Red	59%

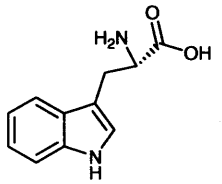
Table 5

2.6 Synthesis of indoles, pyrroles, benzofurans and pyrans

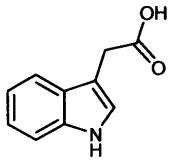
Indoles and benzofurans have found a wide spread use throughout the world as potential drug molecules, with their motifs found in many natural and synthetic compounds. Indole chemistry first found scientific interest in the form of producing dyes before the nineteenth century. Dyes such as indigo that were previously extracted from plants are now routinely synthesised.

Many indole functionalities can also be found in nature such as tryptophan (an essential amino acid) and auxins such as indole-3-acetic acid (IAA), which are plant hormones that help regulate plant growth.[123, 124]

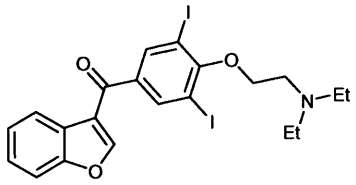
Benzofurans are the oxygen analogues of indoles, and like indoles are important motifs in many drugs, an example of which is amiodarone[125] a widely used antiarrhythmic agent, used in treating cardiac tachyarrhythmias (Scheme 55).



L-Tryptophan.



Indole-3-acetic acid (IAA).



Amiodarone.

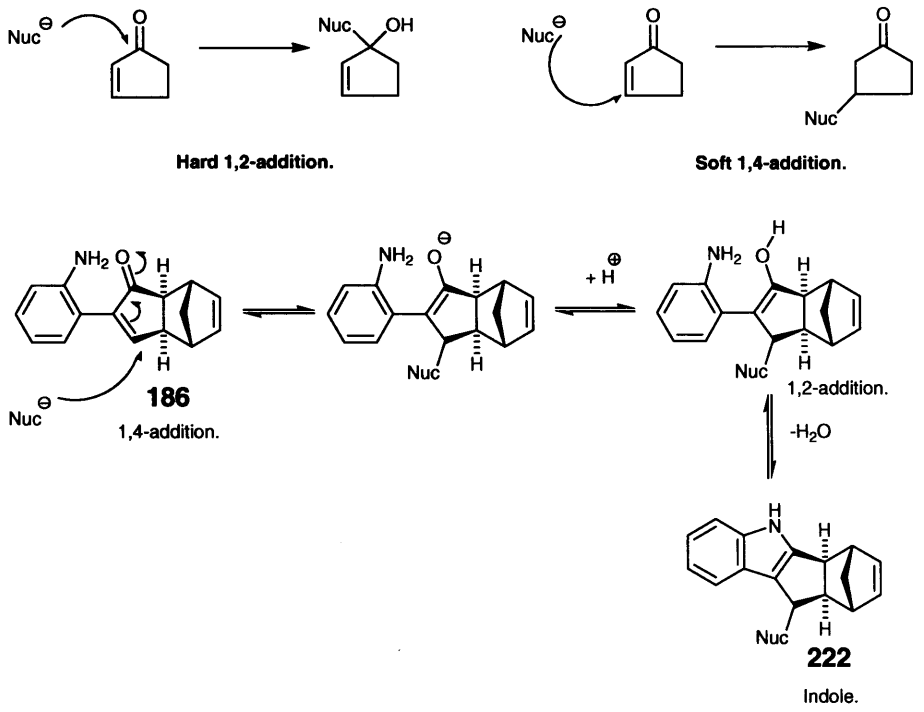
Scheme 55

The cyclopentenone products prepared from the protected alkynyl amines and alkynyl alcohols were used in an attempt to synthesise indoles, benzofurans and their analogues.

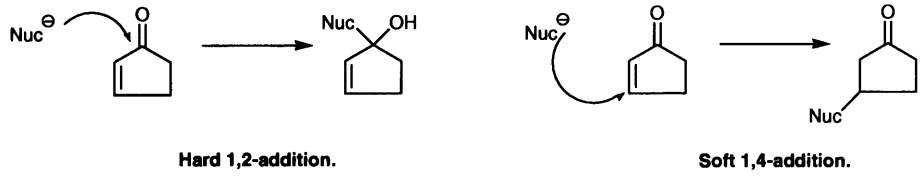
To produce such compounds, the cyclopentenone precursor would have to bear an aromatic group (indole or benzofuran) in the α-position of the cyclopentenone, consisting of either a phenol or aniline group. The method devised to achieve this synthesis was to add soft nucleophiles to promote a Michael reaction (conjugate addition), to the α,β-unsaturated ketone of the cyclopentenone, thereby releasing the strain (rigidity) upon the α-substituent, allowing the heteroatom to become more flexible and attack the carbonyl group. Attempts to cyclise the cyclopentenones prior to the removal of the α,β-unsaturated ketone all failed and are discussed briefly.

Soft nucleophiles are required for conjugate additions due to their capacity to achieve orbital overlap, with the lowest unoccupied molecular orbital (LUMO) of the β-carbon on the unsaturated ketone, by overlapping with the soft nucleophiles highest occupied molecular orbital (HOMO). Soft nucleophiles are predominantly nucleophiles with large, uncharged atoms with more diffuse orbitals. Compared to hard nucleophiles (e.g. F^-), that predominantly consist of elements from the first row of the periodic table and are small electronegative atoms that consist of high charge density and their mode of bonding is dictated by electrostatic interactions, compared to soft nucleophiles that are dictated by orbital overlaps.

Electrophiles are also categorised as being either hard (e.g. H^+) or soft (e.g. Br^+) for the same reason as described for nucleophiles. An α,β-unsaturated ketone contains sites that allow nucleophilic attack by both soft nucleophiles and hard nucleophiles. When reacted with hard nucleophiles a 1,2-addition is observed at the carbonyl group giving an alcohol. Alternatively, if a soft nucleophile attacks, then the result is a 1,4-addition at the β-carbon of the unsaturated ketone (Scheme 56) giving a saturated ketone. Table 6 shows examples of hard/soft nucleophiles.



Scheme 56

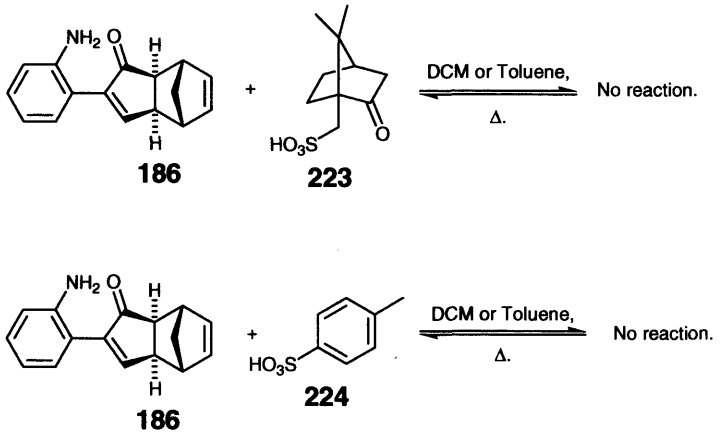


Nucleophiles		
Hard	**Intermediate**	**Soft**
F^-, OH^-, RLi, NH_3	RNH_2, Br^-, CN^-	I^-, RSH, R_3P, RS^-

Table 6

By incorporating either hard or intermediate nucleophiles in the α-position in the α,β-unsaturated cyclopentenone product we hoped to promote a spontaneous 1,2-addition directly after a 1,4-addition. The intramolecular 1,2-addition would only occurr after the rigidity of the α,β-unsaturated ketone was removed, to give an alcohol in place of the ketone that could condense to produce an indole or benzofuran cyclic ring (Scheme 56).

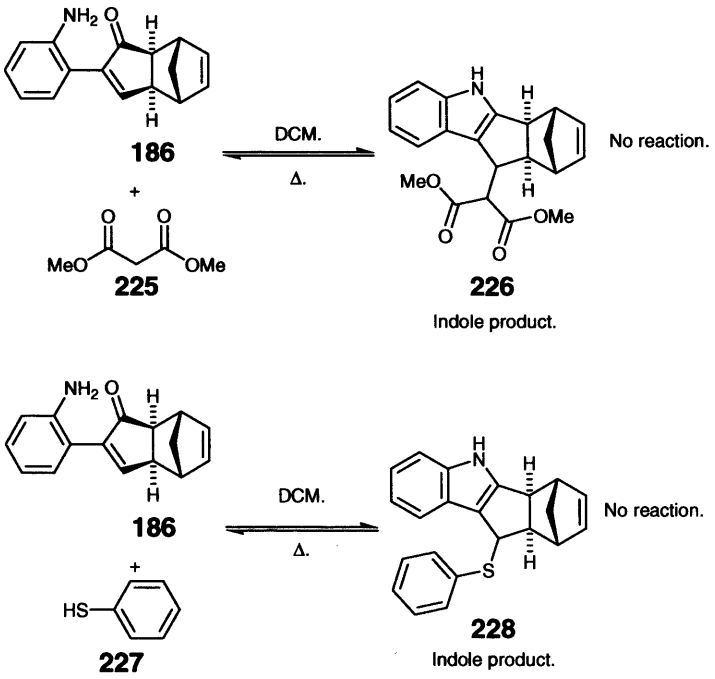
Prior to the removal of the α,β-unsaturated ketone, we examined the possibility of producing indoles by reacting compound **186** with catalytic amounts of different acids (Scheme 57), to promote condensation of the cyclopentenone. Both D-(+)-camphor-10-sulphonic acid **223** and tosic acid **224** were used as reagents, using the Dean Stark method with toluene, as well as activated molecular sieves in DCM.



Scheme 57

These reactions did not work and only starting material was recovered from the reactions, suggesting that the α,β-unsaturated ketone was indeed too rigid to allow the aniline substituent to attack at the carbonyl group.

The expected results in Scheme 57 led to two other test reactions (Scheme 58), using both dimethyl malonate **225** and thiophenol **227** as soft nucleophiles, with compound **186** to induce an intramolecular 1,2-addition. Neither reaction produced the desired indole products and only starting material was recovered, with no trace of either indole **226** or **228**.

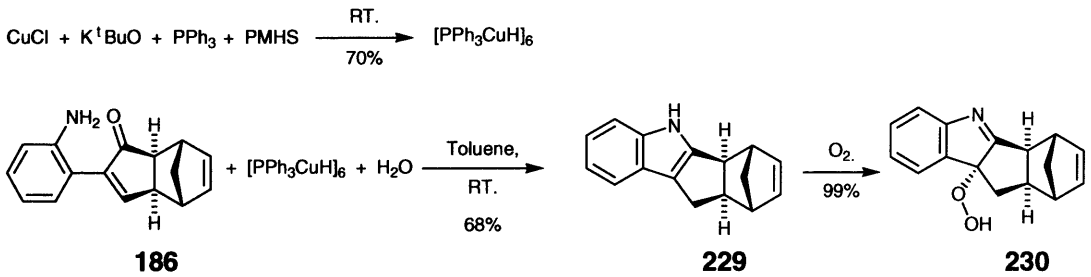


Scheme 58

These poor results led us to examine the use of soft organometallic nucleophiles such as organocopper reagents, which are well known to undergo conjugate additions.

Organocopper reagents act as soft nucleophiles due to the reduced electropositive charge around the copper atom, when compared to Grignard and organolithium reagents that have a higher electropositive charge around them and are well known to react as predominantly hard nucleophiles.

Stryker's reagent[126, 127] ($[PPh_3CuH]_6$) a soft source of H^-, was used to reduce the α,β-unsaturated ketone of compound **186**[128] and was freshly prepared from copper chloride, triphenylphosphine, potassium ^{t}butoxide and polymethylhydrosiloxane (PMHS). This afforded the desired indole product **229** (68%) (Scheme 59) in good yield.

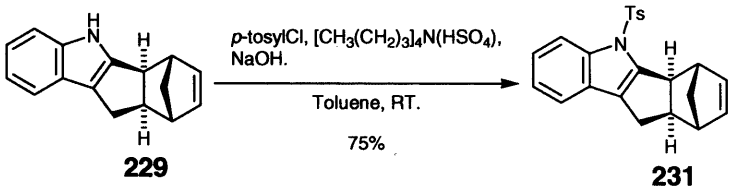


Scheme 59

Purification of **229** followed by analysis by ^{1}H NMR showed a characteristic NH indole peak at δ 7.65 ppm. During analysis of compound **229** it was noticed the indole had degraded by oxidation to the hydroperoxide species **230**. HRMS confirmed this showing an M+32 peak, consistent with compound **230**.

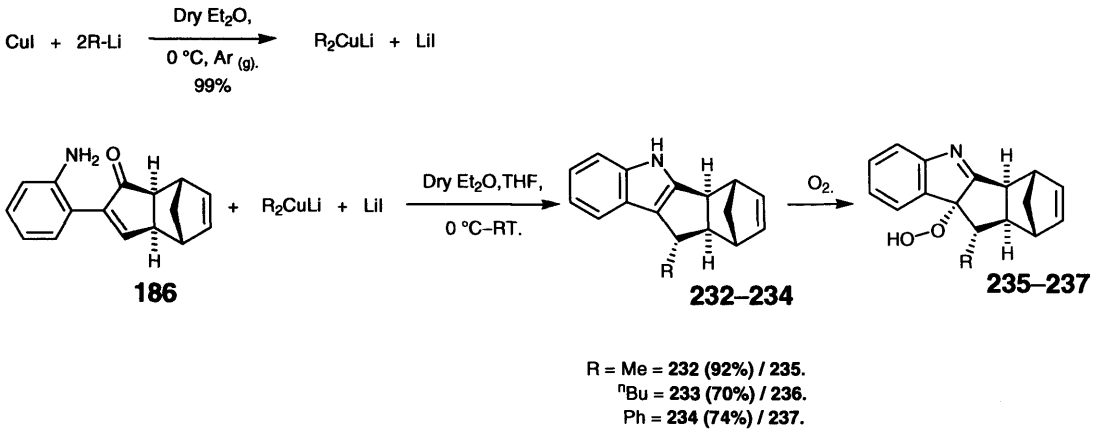
The conjugate addition procedure was then repeated and indole **229** was immediately protected to avoid oxidative degradation (Scheme 60).

The protected indole **231** (75%) was confirmed by HRMS and ^{1}H NMR; disappearance of the indole proton NH peak and presence of a tosyl group.



Scheme 60

Alternative cuprates (R_2CuLi) were then synthesised, using copper iodide and organolithium compounds (Scheme 61). These were reacted with compound **186** to produce a series of indole compounds **232–234** in good yield (Table 7). The cuprate nucleophiles attacked from the exo face as indicated by X-ray analysis (Scheme 62) of the hydroperoxide species **235**.

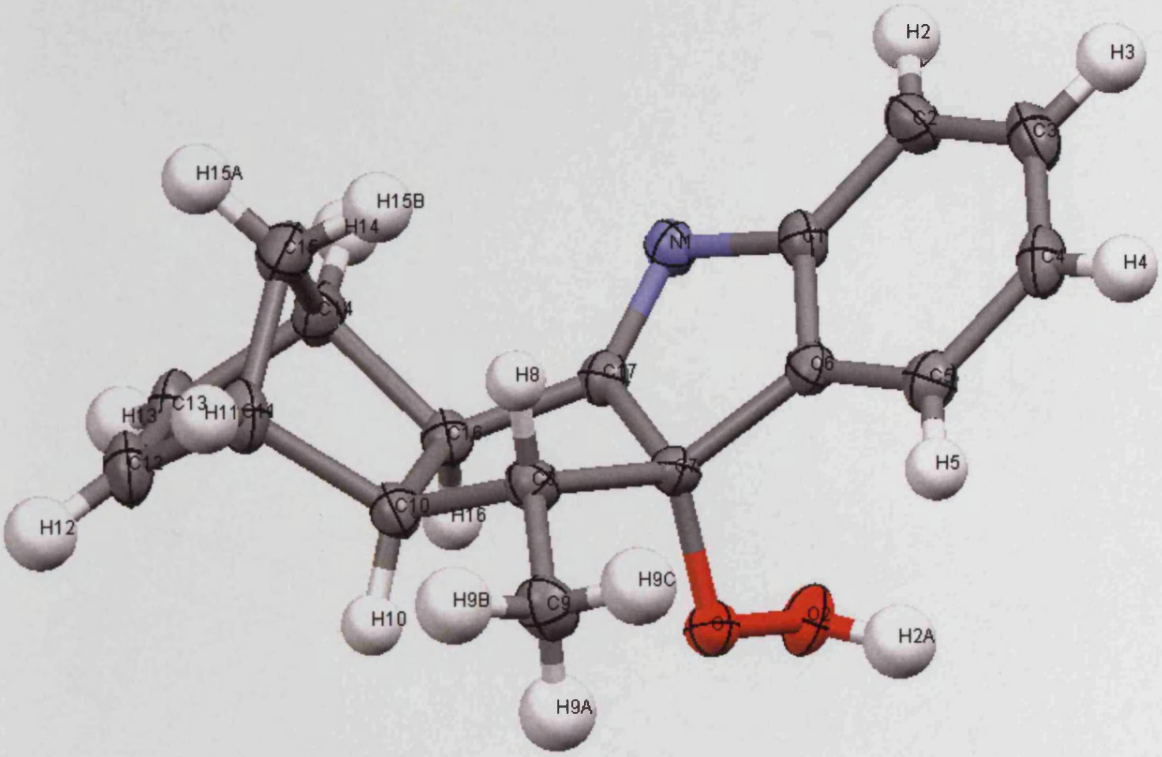


Scheme 61

Entry	R_2CuLi	Product	Yield %	Face of attack
1	Me_2CuLi	**232**	92%	Exo face
2	$^nBu_2CuLi$	**233**	70%	Exo face
3	Ph_2CuLi	**234**	74%	Exo face

Table 7

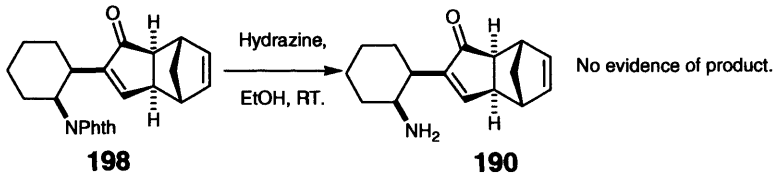
X-ray crystallography data (Scheme 62) of the hydroperoxide adduct **235** showed that both the hydroperoxide and methyl group of compound **232** were on the *endo* face. This is thought to be controlled by the cup shape of the bicyclic ring and steric forces within the resulting indole molecule. This selective control was thought to occur for compounds **233** and **234** due to the R groups (^{n}Bu and Ph) being larger than the already shown example with the methyl group, leading to larger steric interactions between the R groups of the nucleophile and the bicyclic ring structure as seen in compound **232**. Compounds **233** and **234** were not characterised by X-ray analysis and the relative configuration is assumed not proven.



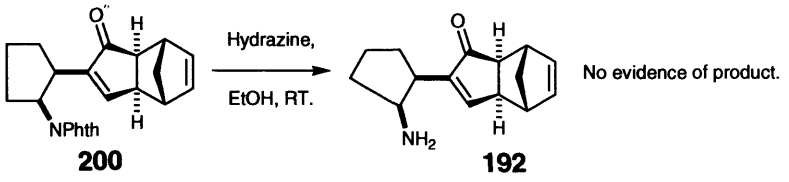
Scheme 62

Pyrrole derivatives were next attempted to be prepared from the aliphatic phthalimide PKR products **198** and **200** by first converting them to the free amine, using either hydrazine (1.1 equivalents) in ethanol (Scheme 63) or methylamine 33% in ethanol (Scheme 64) to yield compounds **190** or **192** [ii]. Unfortunately, neither method resulted in the desired products. Only partial deprotection of the phthalimide was obtained using methylamine in low to moderate yields **238** (55%) and **239** (25%). The use of hydrazine resulted in no identifiable products which is thought to of possibly reacted with either the ketone to form a hydrazone or a 1,4 addition, both of which were not investigated further with no direct evidence of either occurring.

[ii] The relative configurations of isomer **190**, **192**, **238** and **239** have not been determined unequivocally. See page 46 for a discussion.

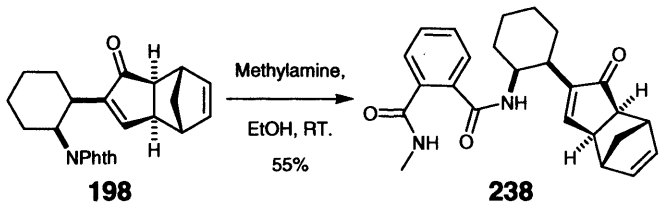


198 190

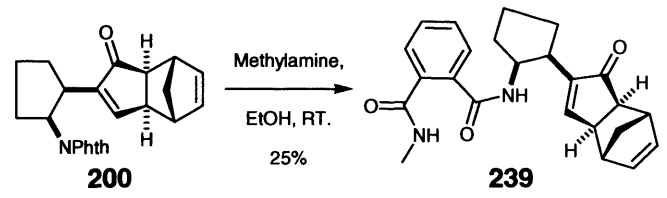


200 192

Scheme 63



198 238

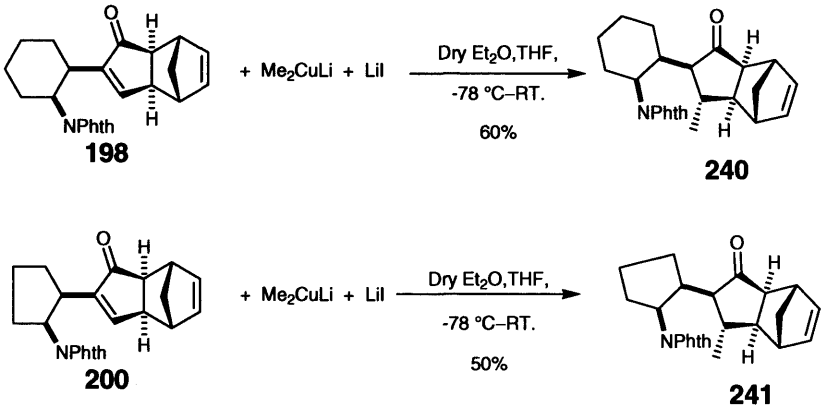


200 239

Scheme 64

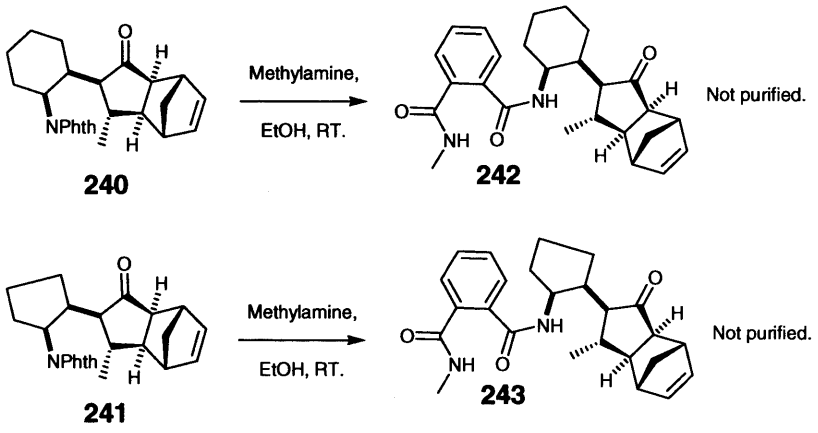
A 1,4 methylation of compound **198** and **200** was next attempted, using Me_2CuLi to give **240** (60%) and **241** (50%) (Scheme 65) [iii]. Both products **240** and **241** were determined by ^1H NMR to be single diastereomers with no α,β-unsaturated proton apparent in the products.

[iii] The relative configurations of isomer **240** and **241** have not been determined unequivocally. See page 46 for a discussion.



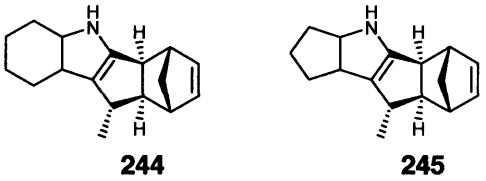
Scheme 65

Compounds **240** and **241** were reacted with methylamine (Scheme 66) to determine if the phthalimide protecting group could be cleaved to yield the free amines that could potentially undergo a 1,2 addition via spontaneous (or acid catalysed) condensation to give the desired pyrrole adducts (Scheme 67). No pyrrole products were obtained and only semi de-protected phthalimide compounds were isolated. Compound **242** and **243** were not purified or fully characterised and are omitted from the experimental section.



Scheme 66

Desired products.



Scheme 67

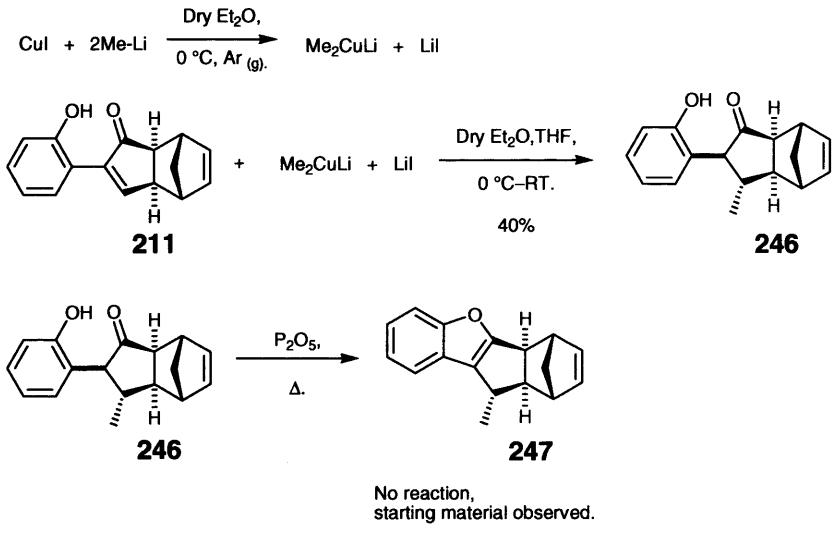
The poor deprotection of phthalimide compounds encouraged addition of a greater excess of methylamine with longer reaction times. This did not change the results obtained where partial deprotection products were evident.

In conclusion, the aniline PKR product **186** proved to be the only cyclopentenone that could to be cyclised to produce indole products in good yields. All other cyclopentenones investigated containing cyclic and straight chain aliphatic amines at the α-position of the cyclopentenone all failed to yield any pyrrole products.

Benzofurans and Pyrans

Benzofurans and pyrans were next attempted to be synthesised using the same methodology as in the synthesis of indole **232**, by reacting the hydroxy cyclopentenones **211**, **213**, **216**, **219** and **221** with Me_2CuLi. If successful, the methylated cyclopentenone product could then be reacted with a dehydrating agent such as phosphorous pentoxide to yield a benzofuran or pyran adduct.

Reacting compound **211** with Me_2CuLi (Scheme 68) yielded the methylated hydroxy cyclopentenone **246** (40%) in moderate yield. This was distinguished from the starting material by ^1H NMR spectroscopy, which showed loss of the β-proton signal at δ 7.73 ppm and appearance of a methyl doublet at δ 1.13 ppm. The relative configuration of compound **246** was not determined unequivocally, only assumed from the crystal structure obtained from compound **232** on page 60 where the newly added methyl group was observed *trans* to the α-substituent of the cyclopentenone.

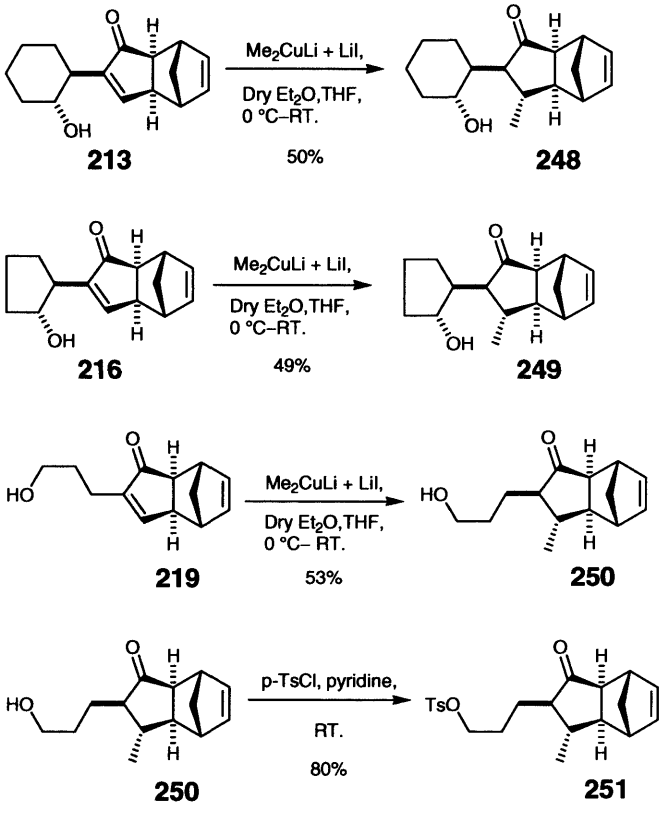


Scheme 68

A 1,2 addition by dehydration was attempted on compound **246** with phosphorous pentoxide. No reaction was observed and only starting material was evident.

Addition of Me_2CuLi was repeated for compounds **213**, **216** and **219** [iv] (Scheme 69).

All three reactions proceeded with moderate yields **248** (50%), **249** (49%) and **250** (53%). Unfortunately these compounds showed no reactivity to phosphorous pentoxide and no 1,2 cycloaddition products were evident. Compound **250** proved difficult to purify and was therefore, transformed to the tosylated (Ts) analogue **251** overall yield (67%) to characterise the compound. All products produced using the1,4 addition of Me_2CuLi all consisted of one diastereoisomer as pure starting material of undetermined relative configuration were used, structures are shown in the *trans* configuration due to the results obtained from Me_2CuLi addition to compound **186** resulting in the X-ray analysis of compound **235** showing the methyl group and α substituent of the cyclopentenone ring in a *trans* conformation.



Scheme 69

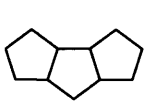
[iv] The relative configurations of isomer **248** and **249** have not been determined unequivocally. See page 46 for a discussion.

We conclude that the synthesis of indoles is viable using a two step process, the first being a PKR to produce a cyclopentenone adducts, followed by a 1,4 addition to this product which can then spontaneously condense to give the indole product. This route is only applicable to indoles with no evidence of success in synthesising pyrroles, benzofurans or pyrans using the same methodology. The relative configurations of both the unsaturated cyclic alcohol and phthalimide cyclopentenone derivatives was not determined unequivocally, however, each of these compounds was obtained and reacted diastereomerically pure.

Chapter 3

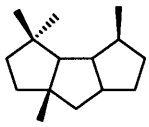
3.1 Synthesis of triquinanes via the PKR

The second part of this research focused on the synthesis of carbon fused tricyclic ring systems such as the tricyclo[6.3.0.2.6]-undecane skeleton **252** (Scheme 70). This is a common motif found in many biologically active compounds that are naturally occurring and are potential drug targets. Examples of this class of compounds are the capnellanes **253** and capnellenes **254** from the terpenoid family. These two compounds exhibit good biological activity towards cancers and can be used as antibacterial agents.[129, 130, 131] Many capnellane and capnellene compounds are found in marine invertebrates such as soft corals but have proved to be difficult to isolate in large quantities, therefore, synthetic routes to produce them are required.



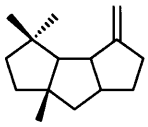
tricyclo[6.3.0.2.6]-undecane skeleton

252



Capnellane skeleton

253

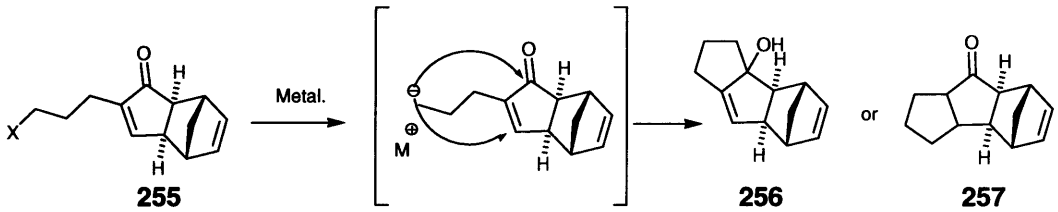


Capnellene skeleton

254

Scheme 70

By using the previous methodology developed in Chapter 2, we set out to synthesise the tricyclo[6.3.0.2.6]-undecane skeleton **252** by way of a PKR/cyclisation strategy using nucleophilic attack at either the 1,2 or 1,4 position of the cyclopentenone product. In this case, the nucleophile would be introduced intramolecularly using a halide metal exchange, forming a nucleophile on the α-substituent of cyclopentenone ring (Scheme 71), cyclisation would them follow to form the tricyclo[6.3.0.2.6]-undecane skeleton **252.**



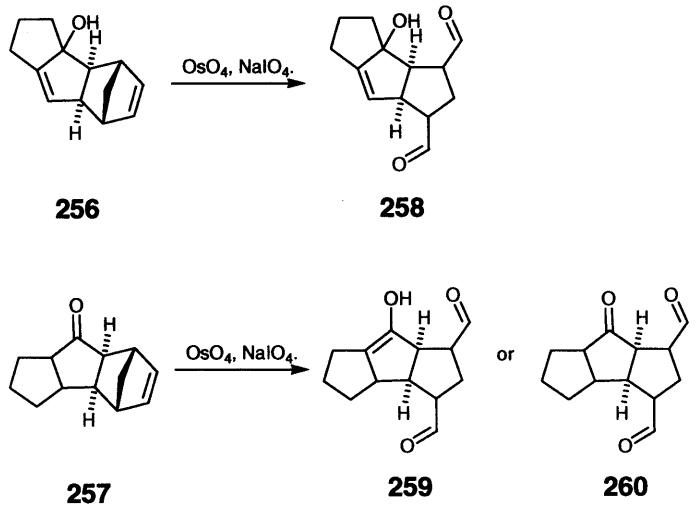
255 **256** **257**

X = halogen.
M = Metal, Li, Mg or Cu.

1,2 addition. 1,4 addition.

Scheme 71

Upon successful cyclisation of the cyclopentenone **255** via 1,4 addition, we proposed to produce the third five membered ring by way of oxidative cleavage of the norbornene double bond, selectively oxidising the double bond as shown by Chung[132] (Scheme 72). Once oxidative cleavage had been attained, compounds **258–260** would be ideal precursors to a variety of functional groups, depending on the target molecule.

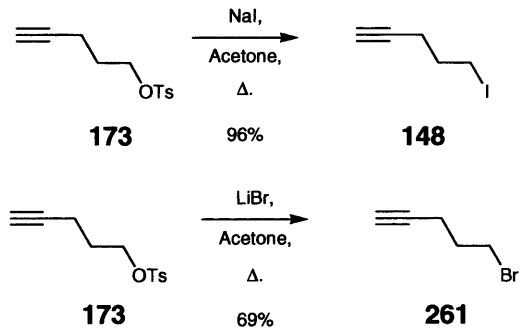


256 **258**

257 **259** **260**

Scheme 72

On embarking into this synthesis, the most likely starting materials were determined to be 5-halopent-1-ynes **148** and **261** consisting of a three-carbon unit chain which when cyclised would produce a five membered ring. A series of alkyne starting materials were produced from compound **173** (Scheme 73), by substitution of a tosyl group by a halide ion using a Finkelstien type protocol. Synthesis of 5-iodopent-1-yne **148** (96%)[133] and 5-bromopent-1-yne **261** (69%)[134] was achieved in this manner, whilst 5-chloropent-1-yne **262** was commercially available from Aldrich.



173 96% **148**

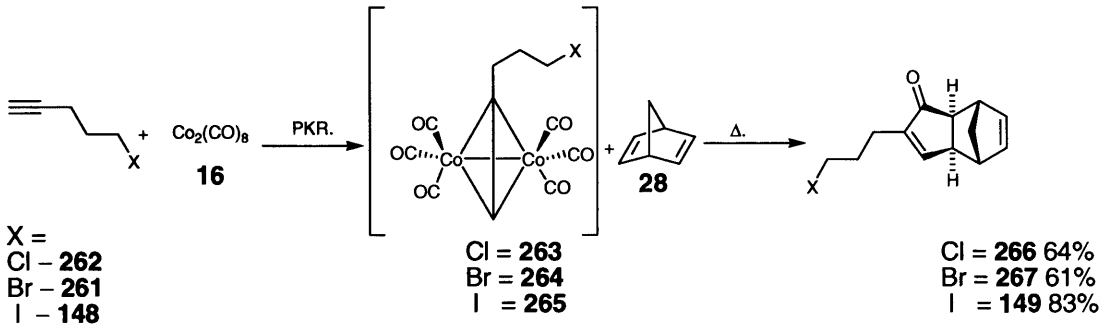
173 69% **261**

Scheme 73

Compounds **148** and **261** were confirmed by ^{1}H NMR agreeing with the literature, by the loss of the tosyl group signals and an up field shift by the alkyne proton.

All three compounds **148, 261,** and **262** were then reacted using the PKR protocol already developed, producing their corresponding cyclopentenones (no cobalt alkyne complexes were isolated) **149** (83%), **266** (64%) and **267** (61%) and compound **187** (15–30%) as a by-product previously seen (Scheme 74).

Table 8 shows a summary of the overall yields obtained from compound **173** or **262** to the final cyclopentenone products. All compounds were purified and analysed by ^{1}H NMR, ^{13}C NMR, IR and MS. ^{1}H NMR confirmed the cyclopentenone product by the characteristic doublet signal for the β-proton above δ 7.00 ppm.



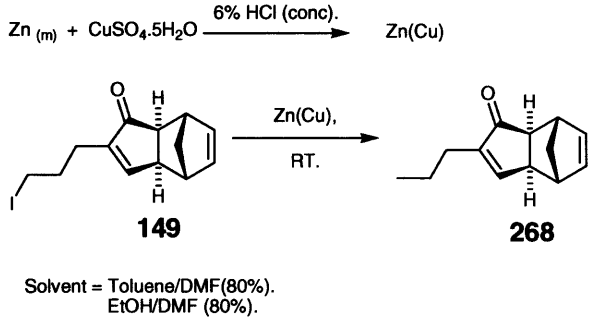
Scheme 74

Entry	Alkyne	PKR Product	Overall
1	5-iodopent-1-yne **148**	**149** 83%	79%
2	5-bromopent-1-yne **261**	**267** 61%	42%
3	5-chloropent-1-yne **262**	**266** 64%	64%

Table 8

5-Iodopent-1-yne **148** gave the best overall yield of cyclopentenone product. Hence cyclopentenone **149** was used as the starting material for the investigation into the synthesis of the tricyclo[6.3.0.2.6]-undecane skeletons **256** and/or **257**. The carbon-iodine bond also promised to be the most likely of the three cyclopentenone compounds to undergo the metal insertion step, due to it being the weakest carbon-halide bond of the series.

Compound **149** was reacted with the Simmons-Smith reagent,[135] a zinc copper couple reagent, prepared from zinc and copper iodide, or zinc and copper sulphate to achieve an oxidative insertion of zinc into the carbon halide bond (Scheme 75) to promote a 1,4 cyclisation. The reaction proceeded with disappearance of starting material that after purification by column chromatography resulted in unwanted product **268** (80%), the structure of which was elucidated by ^{1}H NMR where the carbon-iodine bond had been cleaved and replaced by a hydrogen atom showing a up-field shift from the CH_2I triplet at δ 3.10 to a methyl triplet at δ 0.85 ppm. Alternative solvent systems including ethanol and dimethylformamide (DMF) was later tried resulting in no change of product or yield.

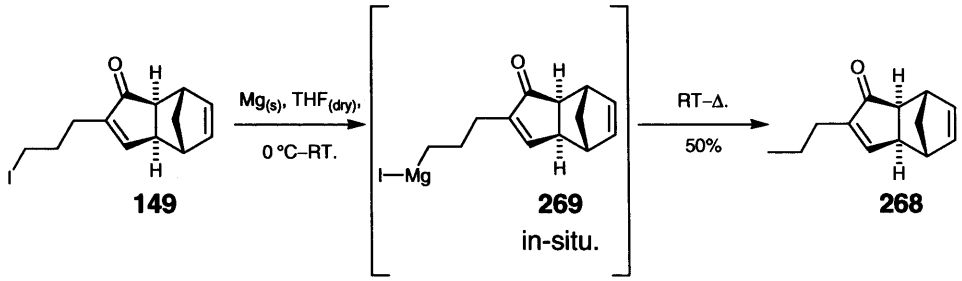


Scheme 75

This unfortunate failure led to us using magnesium as an alternative metal to insert into the carbon-iodine bond. By using a Grignard reagent[136] to promote the cyclisation step, it was most likely that a 1,2 addition would occur rather than the desired 1,4 addition.

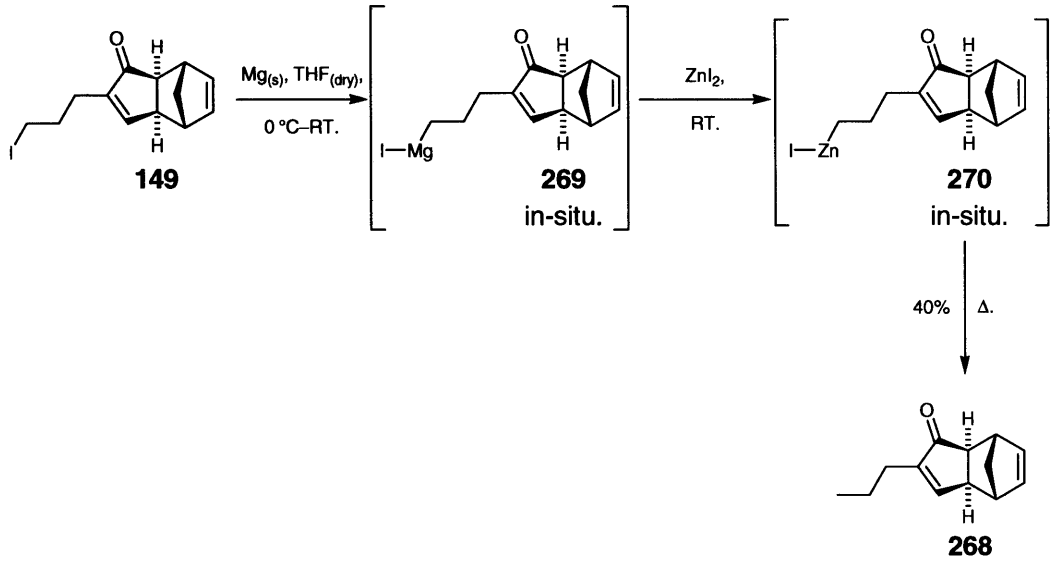
The 1,4 addition was the most desired cyclisation to achieve compound **257**, however, this type cyclisation would have to undergo a 5-endo-trig transformation, which is a disfavoured transformation according to 'Baldwin's rules',[137, 138, 139, 140, 141, 142, 143] due to the alignment of bonding and anti bonding orbitals of the reactive sites within the molecule.

The iodo-cyclopentenone **149** was reacted with activated magnesium turnings in THF under an inert atmosphere at various low temperatures -100–0 °C (Scheme 76). This produced a dispersed metallic grey solution (characteristic of Grignard formation), which after reflux, resulted once again in compound **268** (50%) being recovered.



Scheme 76

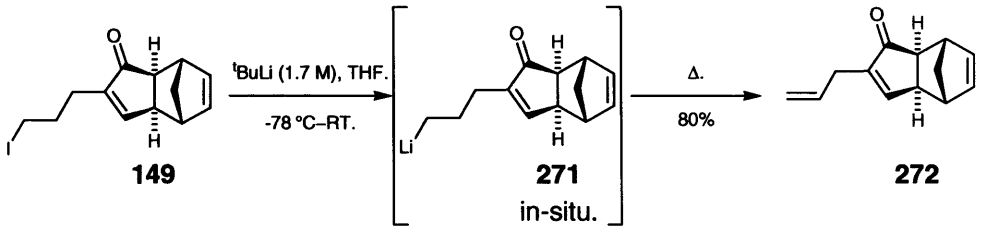
Transmetalation of magnesium by zinc iodide upon formation of the Grignard reagent was then attempted (Scheme 77) which resulted in isolation of reduced compound **268** (40%).



Scheme 77

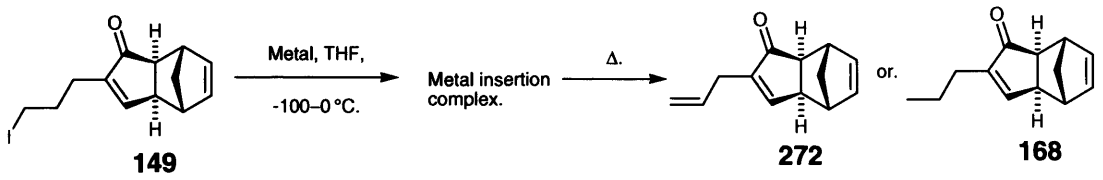
After no success was achieved using both soft (Zn) and intermediate (Mg) type nucleophiles, hard nucleophiles containing lithium were examined. Reacting organolithium species with iodocyclopentenone **149** at low temperatures -100–0 °C should encourage the 1,2 addition product.

A reaction with ^{t}BuLi was carried out (Scheme 78) and resulted in starting material **149** (20%) and the elimination product compound **272** (80%) instead of the desired 1,2 addition product **256**. Compound **272** was identified by ^{1}H NMR, showing three new alkene peaks as complex multiplets.



Scheme 78

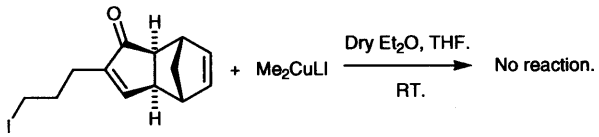
All experiments discussed involving the metalation with magnesium, zinc and lithium, were carried out at four different temperatures (-100, -78, -40 and 0 °C) to determine conditions best suited to induce metal-halogen exchange which is summarised in Table 9.



Entry	Temp	Zn/Cu **168**	Mg **168**	Zn **168**	Li **272**
1	0 °C	80%	50%	40%	100%
2	-40 °C	80%	56%	40%	82%
3	-78 °C	40%	60%	42%	60%
4	-100 °C	20%	60%	42%	60%

Table 9

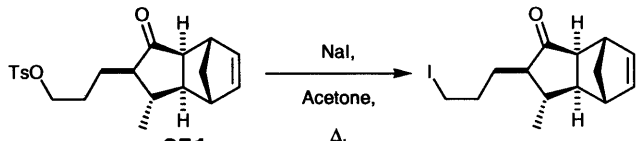
Repetitive failure from this strategy using Zn, Mg and Li with compound **149**, led us to examine reduction of the α,β-unsaturated ketone in **149** in a similar manner to that described in Chapter 2, using Me_2CuLi (Scheme 79).[136, 143] This transformation should reduce the steric strain in the molecule allowing the carbon side chain to become more flexible and facilitate the intramolecular cyclisation. Reacting compound **149** with Me_2CuLi, resulted in recovery of starting materials.



159

Scheme 79

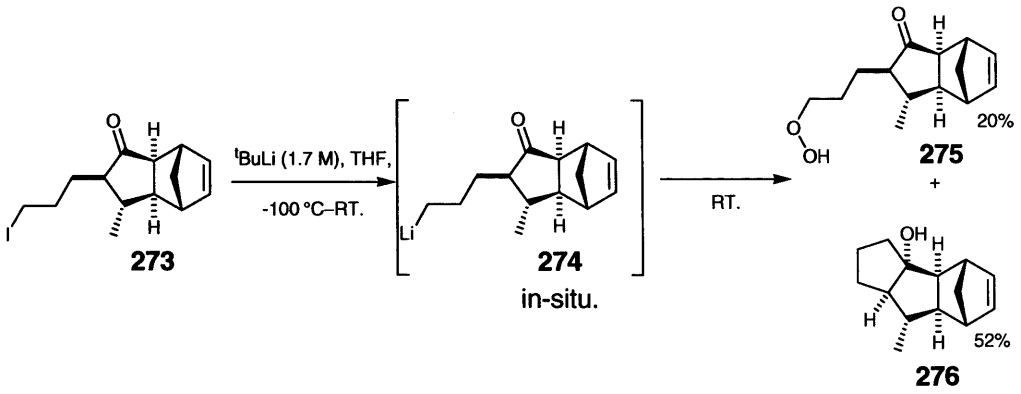
This unforeseen lack of reactivity with compound **149**, led to the synthesis of the methylated iodocyclopentenone **273** being achieved by conversion of the tosyl analogue **251** (Scheme 80) to compound **273** (80%) by way of a Finkelstein protocol, using sodium iodide. Relative configuration of compound **273** was not elucidated and assumed from Chapter 2 (page 60), whereby, the methyl group was observed to have added *trans* to the substituent in the α-position of the cyclopentenone. ^{1}H NMR and ^{13}C NMR were consistent with the elucidated structure.



251 **273**

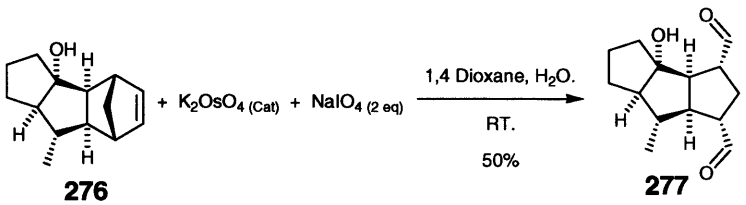
Scheme 80

Compound **273** was reacted with t-butyllithium at -100 °C (Scheme 81). The desired 1,2 cycloaddition product **276** was obtained (52%) as well as an unwanted peroxide side product, compound **275** (20%). The relative configurations of compounds **275** and **276** was not determined and was assumed from previous work in Chapter 2 (page 60), whereby, the methyl group was observed to have added *trans* to the substituent in the α-position of the cyclopentenone. The OH group of compound **276** was assigned *trans* to the α-position of the cyclopentenone due to the cup like shape of the molecule but no direct evidence for this was recorded. Both compounds were observed as single isomers with the correct number of signals in both ^{1}H NMR and ^{13}C NMR.



Scheme 81

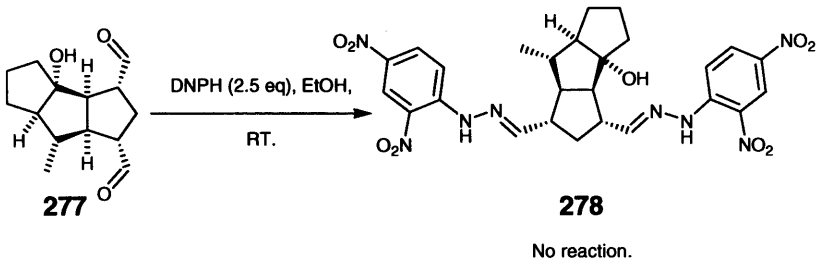
The elusive compound **276** was subjected to oxidative cleavage using OsO_4 and $NaIO_4$ (Scheme 82) to yield the desired tricyclo[6.3.0.2.6]-undecane systems **277** (50%).



Scheme 82

Compound **277** was very reactive; difficulty was experienced in separating and isolating the compound. Due to this difficulty the compound was not fully characterised and ^1H NMR spectroscopy determined the appearance of two doublets at δ 9.59 and 9.54 ppm, representative of a di-aldehyde. The relative configurations of compounds **273**, **275**, **276** and **277** has not been determined unequivocally and has been assumed from results obtained in the synthesis of compound **235** (see page 65 for discussion).

The high reactivity of compound **277** led us to adding 2,4 dinitrophenylhydrazine (DNPH) to the crude product **277** (Scheme 83), in an attempt to produce a more stable hydrazone adduct **278**. It was envisaged this compound would be less reactive and more crystalline, allowing better purification and full characterisation.



Scheme 83

Unfortunately, this procedure did not work and resulted in an orange solid the structure of which could not be elucidated upon analysis.

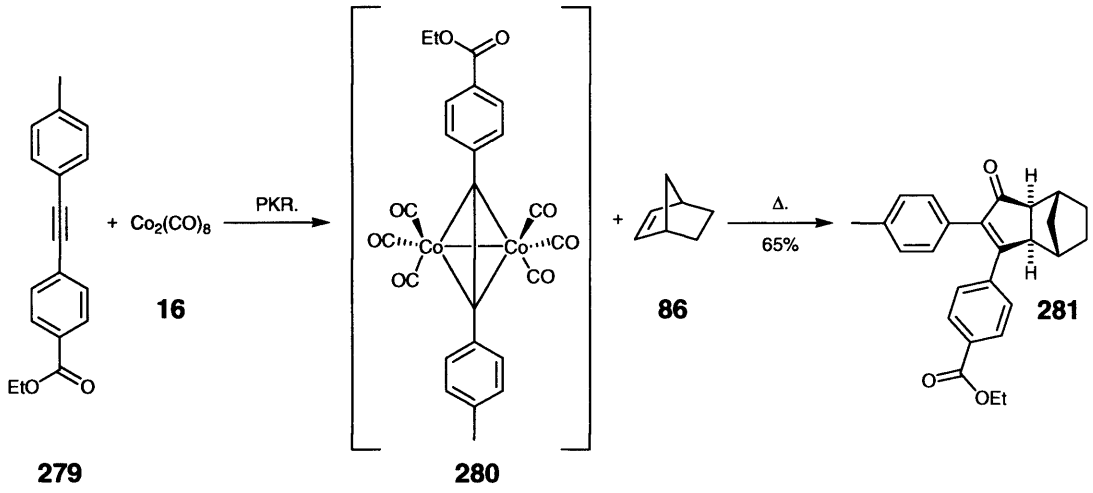
Results within this Chapter suggest a four step method into the tricyclo[6.3.0.2.6]-undecane skeleton **277** from a cyclopentenone PKR product is possible and relatively efficient. Whilst investigation into the optimisation of these findings should be pursued and trapping of the highly reactive di-aldehyde species developed.

Chapter 4

4.1 Di-substituted Alkynes

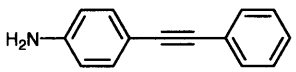
This Chapter concentrates on the regioselectivity of the PKR. There are two arguments for determining the regiochemical outcome of this reaction, one Magnus suggests [21, 144, 145], the regiochemistry of the PKR is determined by steric factors,

(the larger substituent always goes in the α-position of the product due to olefin insertion always occurring by the less hindered position). Gimbert has highlighted that the regiochemical outcome of the PKR may be due to electronic interactions within the cobalt alkyne complex,[22] (olefin insertion occurs in the vacant CO site that is most labile as a result of polarisation of the acetylenic bond upon coordination to the dicobalt species). Results obtained by Gimbert,[22] showed a PKR of 4-*p*-tolylethynyl-benzoic acid ethyl ester **279** with dicobaltoctacarbonyl **16** and norbornene **86** in toluene (Scheme 84) produced the PKR product **281** (65%) with complete selectivity with the electron deficient aromatic ring in the β-position of the cyclopentenone product.

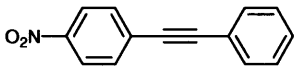


Scheme 84

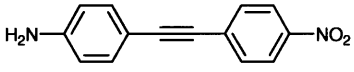
This observation inspired us to examine what effects would be observed when using more pronounced, electron donating and withdrawing groups on various alkyne substrates. The alkynes chosen as substrates were 4-phenylethynyl-aniline **282**, (4-nitro-phenyl)-phenyl-acetylene **283** and 4-(4-nitro-phenylethynyl)-aniline **284**, due to their highly conjugated nature (Scheme 85), which should allow exclusive formation of the nitrobenzene group in the β-position of the cyclopentenone product, as a single regioisomer.



282



283



284

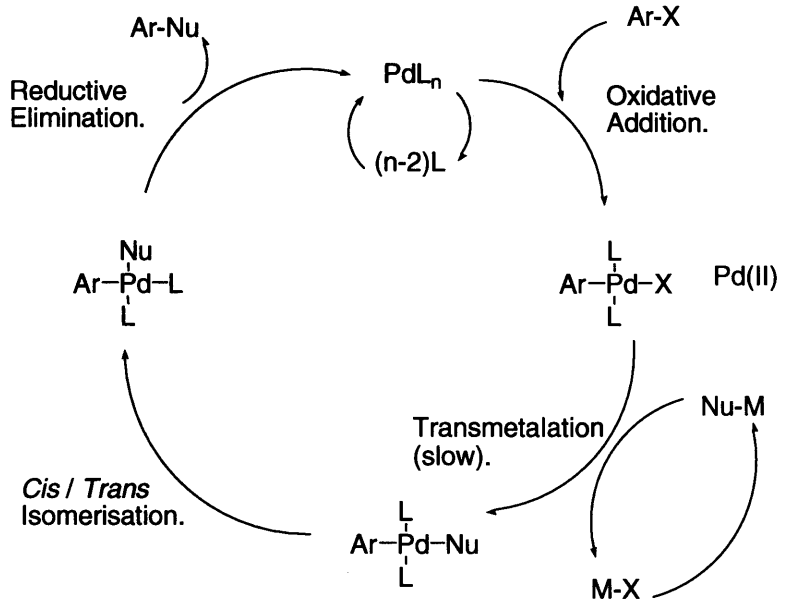
Scheme 85

Compounds **282–284** (Scheme 85) were chosen not only for their degree of polarisation on the triple bond, but because they were sterically similar allowing for any steric interactions to be relatively constant. It was postulated that these electronic differences should favour any possible *trans*-effect experienced in the PKR.[22]

Palladium Catalysis

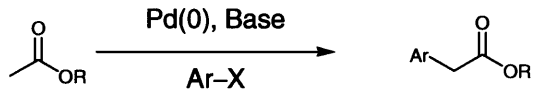
Homogeneous catalysis of aryl halides and triflates with "hard" and "soft" organometallic nucleophiles such as palladium have been widely used over the past three decades. Variations of this reaction have found widespread applications in modern organic chemistry. Variants include the Sonogashira (copper mediated),[146] Negishi (zinc mediated),[147] Stille (tin mediated),[148] Corriu-Kumada-Tamao (magnesium mediated),[149] and Suzuki (boron mediated)[150, 151] coupling reactions.

The mechanism of palladium catalysis involves the oxidative addition to the halide or triflate from the initial palladium(0) complex to produce a palladium(II) species. The key rate determining step of this reaction is the transmetalation,[146] so called because the nucleophile is transferred from the metal in the organometallic reagent, to the palladium and the counter ion moves in the opposite direction. The palladium(II) complex now with two organic ligands undergoes reductive elimination to give the coupled product and the regenerated palladium(0) species is ready for another catalytic cycle (Scheme 86).



Scheme 86

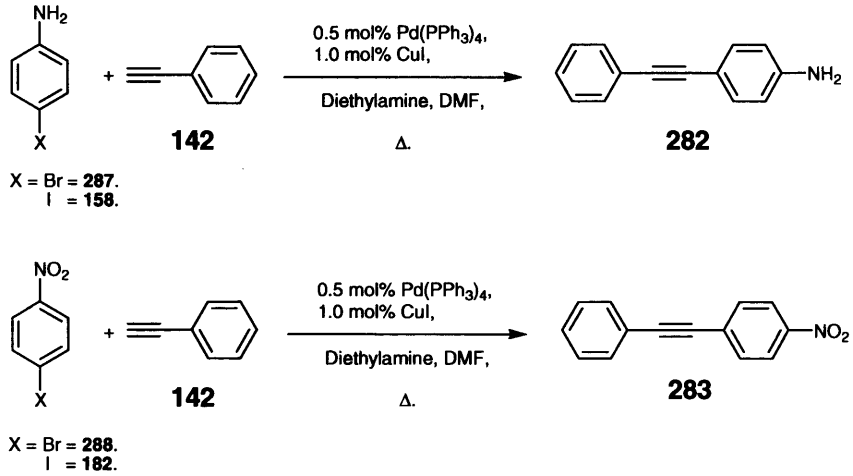
Palladium catalysed couplings of hard nucleophiles such as oxygen,[152, 153] have been extensively studied, the use of soft nucleophiles have only been explored in the last ten years. Studies by Buchwald and Hartwig coupling has proved successful with a wide range of "soft" nucleophiles such as; sulphur,[154, 155, 156, 157, 158] phosphorous,[159, 160] boron,[161, 162] and silicon based nucleophiles.[163, 164, 165, 166, 167, 168, 169] In recent years the cross-coupling of carbonyl compounds such as ketones,[170, 171, 172, 173, 174, 175, 176, 177, 178] esters[179, 180] and amides[181, 182] with aryl halides has been reported and developed by the groups of Buchwald, Hartwig and Miura (Scheme 87).



285 **286**

Scheme 87

Compounds **282–283** were all synthesised using Sonogashira reactions with various palladium catalysts (Table 10). All were produced from phenylacetylene **142** and the corresponding aryl halides, 4-bromoaniline **287**, 4-iodoaniline **158**, 4-bromo-nitrobenzene **288** and 4-iodo-nitrobenzene **182** (Scheme 88).[183, 184, 185, 186]



Scheme 88

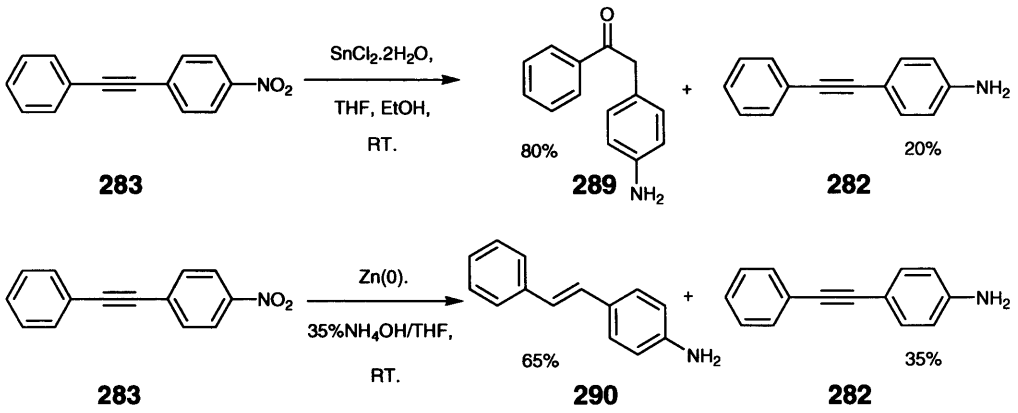
From these results, it was evident that both iodine and bromine starting materials were suitable for synthesising compounds **282** and **283**. Additionally, the use of the Pd(II) salts and Pd(0) compounds, were assessed to promote the Sonogashira reaction were also successful (Table 10). The structure of compounds **282** and **283** was supported by ^{1}H NMR showing loss of the singlet acetylene proton at δ 3.14 ppm.

Entry	Starting material	$Pd^{(II)}(OAc)_2$	$Pd^{(II)}Cl_2(PPh_3)_2$	$Pd^{(0)}$ $(PPh_3)_4$	Product
1	4-iodo-nitrobenzene **182**	97%	97%	95%	**283**
2	4-bromo-nitrobenzene **288**	90%	98%	92%	**283**
3	4-bromoaniline **287**	88%	86%	85%	**282**
4	4-iodoaniline **158**	96%	94%	90%	**282**

Table 10 Results of Sonogashira reaction with various Pd species on aryl halides.

Prior to using a Sonogashira reaction to produce compound **282**, reduction of the nitro group of compound **283** was attempted (Scheme 89); using tin chloride and hydrochloric acid which resulted in the desired compound **282** (20%) in low yield. The major product was compound **289** (80%)[187] where hydration of the alkyne had occurred along with reduction of the nitro group. ^{13}C NMR showed compound **289** by

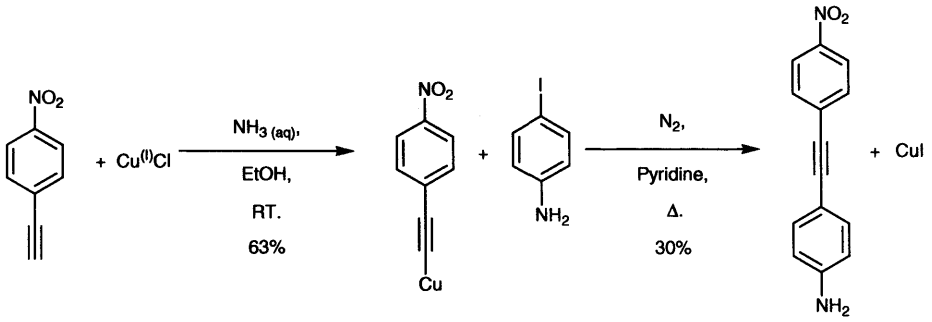
the presence of a carbonyl carbon at δ 196.0 ppm. ^{1}H NMR also showed a CH_2 group as a singlet at δ 4.10 ppm further supporting the proposed structure of **289**.



Scheme 89

An attempt to reduce the nitro group of compound **283** was also done using zinc powder with ammonium hydroxide solution (Scheme 89). This resulted in a low yield of compound **282** (35%) and reduction of the triple bond to produce compound **290** (65%). ^{1}H NMR showed doublets at δ 6.57 and δ 6.49 ppm and ^{13}C NMR showed the presence of CH groups at δ 114.8 and δ 112.6 ppm consistent with compound **290**. Therefore, cross coupling of 4-iodoaniline **158** and phenylacetylene **142**, was our chosen method for the synthesis of 4-phenylethynylaniline **282**.

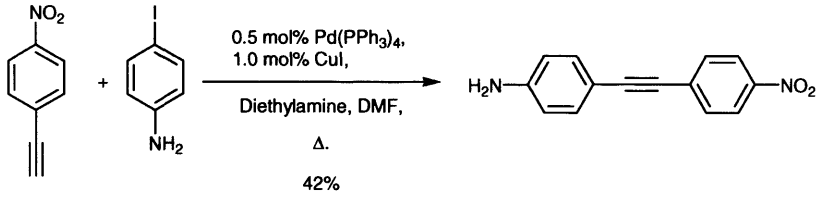
Upon satisfactory synthesis of compound **282** and **283**, the preparation of 4-(4-nitro-phenylethynyl)-aniline **284** was attempted, using previously reported methods[188, 189, 190] (Scheme 90). Copper(I) 4-nitrophenylacetylene **291** was synthesised from 4-nitrophenylacetylene **181** and copper(I) chloride. This was then reacted with 4-iodo-aniline **158** to yield **284** in poor yield (30%). Compound **284** was identified by ^{1}H NMR and IR, which showed the appropriate signals for the aromatic protons at δ 8.13, 7.53, 7.30 and 6.59 ppm and a broad single amine signal at δ 3.89 ppm. IR confirmed the presence of a triple bond adsorption at 2210 cm^{-1} and a NH_2 signal at 3480 cm^{-1} and 3376 cm^{-1}.



181 **291** **158** **284**

Scheme 90

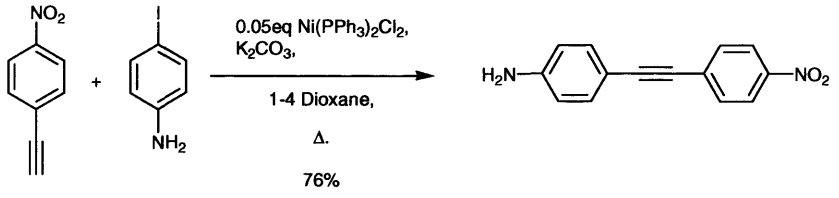
Due to the low yield of compound **284**, we also examined a Sonogashira coupling, using 4-nitrophenylacetylene **181** and 4-iodo-aniline **158** with $Pd(PPh_3)_4$ and copper iodide (Scheme 91).



181 **158** **284**

Scheme 91

Unfortunately, compound **284** was produced again in poor yield of 42%. An experiment using a nickel catalysed Sonogashira reaction[119] (Scheme 92), between 4-nitrophenylacetylene **181** and 4-iodo-aniline **158** with $Ni(PPh_3)_2Cl_2$ yielded compound **284** in a significantly improved 76% yield.

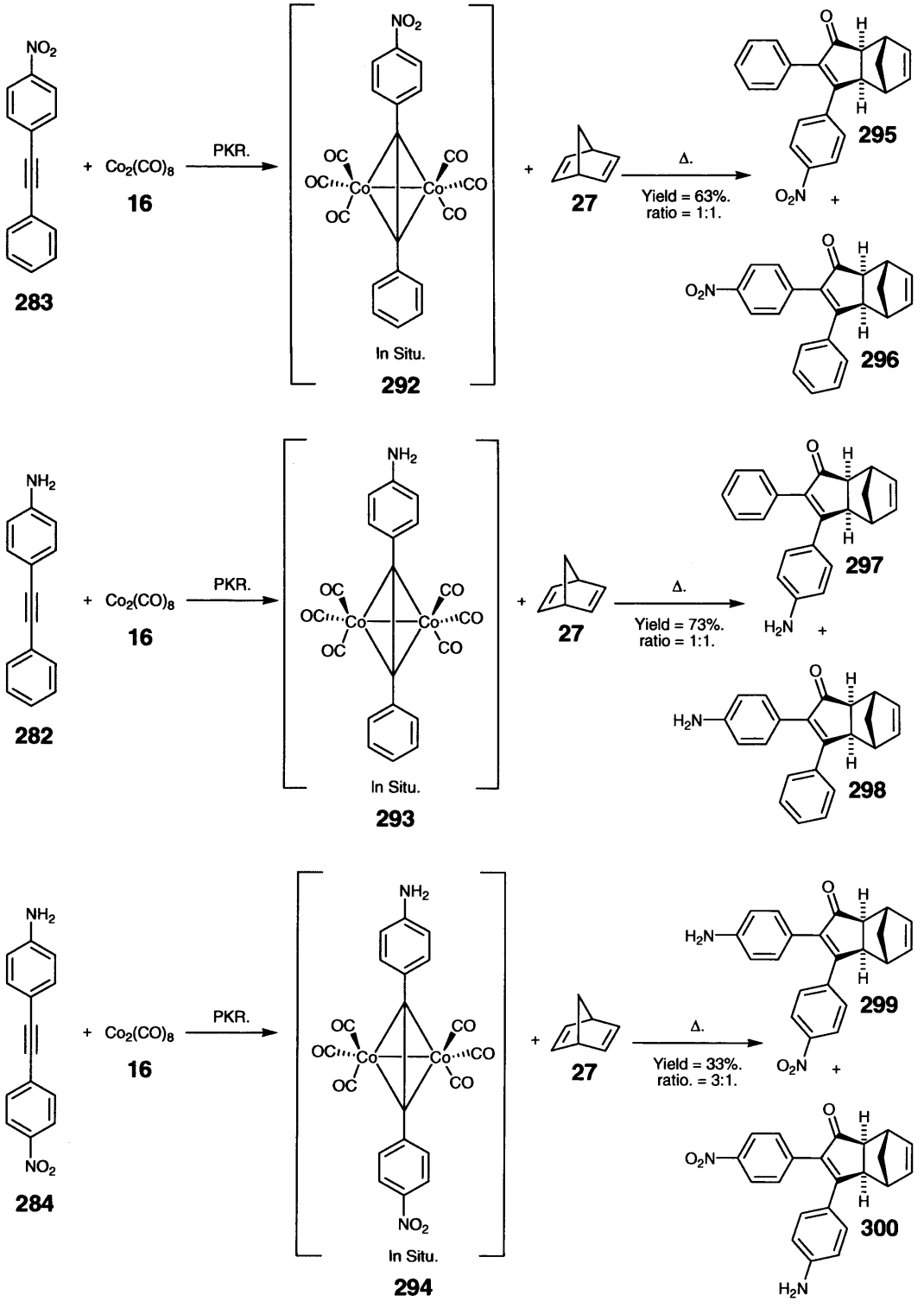


191 **158** **284**

Scheme 92

Compounds **282**, **283** and **284** were prepared in sufficient quantities and introduced into the PKR (Scheme 93), to determine the regioselectivity of the reaction. Previous results from Gimbert,[22] showed that polarising the alkyne bond with electron donating and electron withdrawing groups gave noticeable regioselective control within the PKR.

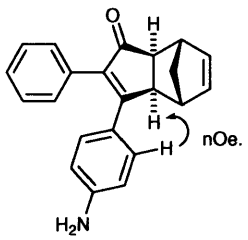
All six products **295–300** were obtained from reacting compounds **282, 283** and **284** using a PKR with 2,5-norbornadiene **27**. After being purified and characterised separately, the crude reaction mixtures were analysed, to give accurate interpretations of the regiochemical course of the reaction. Identification of compounds **295–300** was ascertained from 2D COSY experiments (proton-proton COrrelation SpectroscopY) (Scheme 94). ^{1}H NMR of these compounds showed the expected peaks relevant to each compound. ^{13}C NMR was used to confirm the presence of carbonyl groups in each of these compounds which were observed above δ 205.0 ppm.


NO2
283
+ Co2(CO)8
16
PKR.
In Situ.
292
27
Δ.
Yield = 63%.
ratio = 1:1.
295
296
NH2
282
293
Yield = 73%.
ratio = 1:1.
297
298
284
294
Yield = 33%.
ratio. = 3:1.
299
300

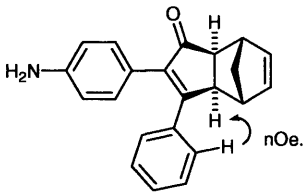
Scheme 93

Entry	Starting material	Product	Overall yield	Regioisomer ratio
1	**282**	**297/298**	73%	1:1
2	**283**	**295/296**	63%	1:1
3	**284**	**299/300**	33%	3:1

Table 11



297



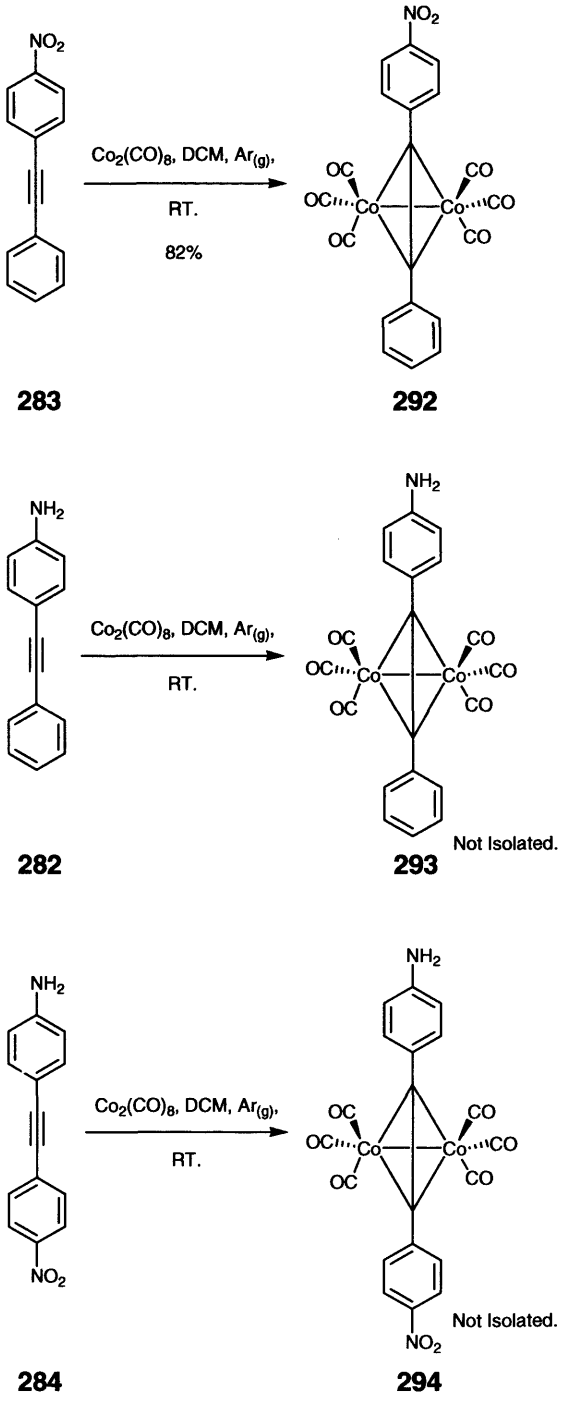
298

Observed through space coupling.

Scheme 94

No single regioisomer from compounds **295–300** was exclusively formed from the PKR's carried out. Compound **299** was observed in a 3:1 ratio with it's regioisomer **300**. Table 11 summarises the results obtained.

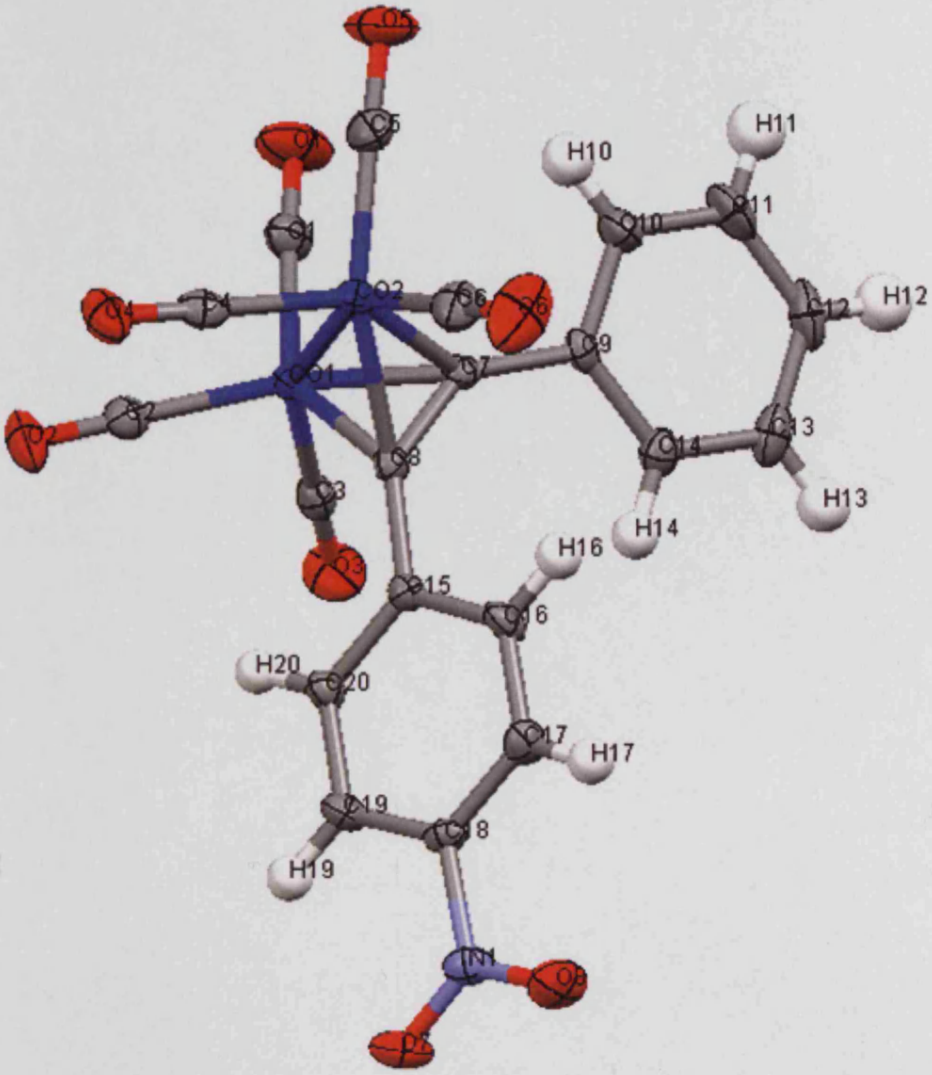
After successful synthesis and isolation of compounds **295–300**, the dicobaltoctacarbonyl alkyne complex involved in each reaction was observed by TLC as a high running red/blue spots. Isolation of these complexes **292-294** (Scheme 95) was attempted for analysis by X-ray crystallography, to determine the bond lengths of CO ligands. This would enable us to asses if any 'trans effect' could be observed with different complexes alkynes through the cobalt metal centres.



Scheme 95

All three cobalt alkyne complexes **292–294** were observed by TLC, as red/blue coloured high running spots. Compound **292** (82%) (red spot) was isolated in good yield and its crystal structure determined (Scheme 96). Compounds **293** (dark blue spot) and **294** (blue spot) could not be isolated due to their instability causing decomposition when exposed to heat and air. Complex **292** was re-crystallised from DCM/MeOH affording dark red crystals. The structure was determined by X-ray

crystallography giving some insight into the carbonyl bond lengths within the structure.



Scheme 96
(X-ray structure of (4-aminophenyl)phenylethynephenylacetylene $Co_2(CO)_6$ complex)
292

Bond	Distance Å	Bond	Distance Å	Bond	Distance Å
Co(1)–Co(2)	2.4698(1)	Co(2)–C(5)	1.8238(6)	Co(1)–C(1)	1.7962(6)
Co(1)–C(12)	1.9858(5)	Co(2)–C(6)	1.8225(6)	Co(1)–C(2)	1.8282(6)
Co(2)–C(4)	1.8084(7)	Co(2)–C(12)	1.9502(5)	Co(1)–C(3)	1.8268(6)

Table 12

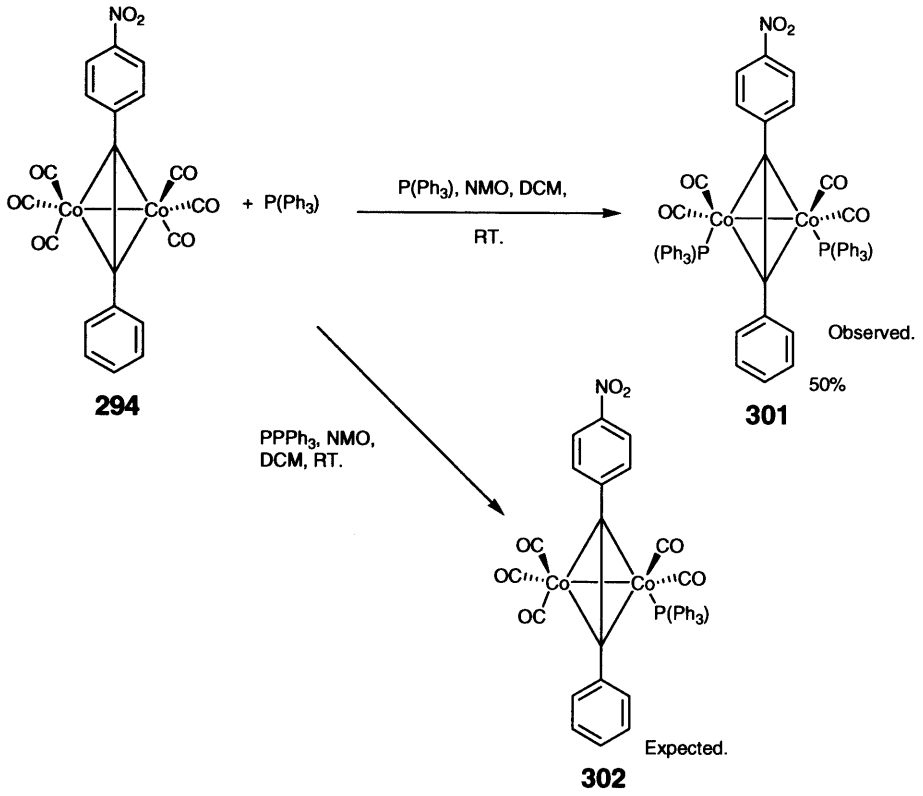
The crystal structure of compound **292** was able to give information relating to the bond lengths within the structure that are found in Table 12. It shows the longest metal to carbonyl bond to be the Co(1) atom bound to the C(2) atom, which should also be the most labile.

This bond is the *trans* equatorial CO ligand, where C(2) is *trans* to the electron donating phenyl group, as predicted by the polarisation theory of Gimbert.[22]

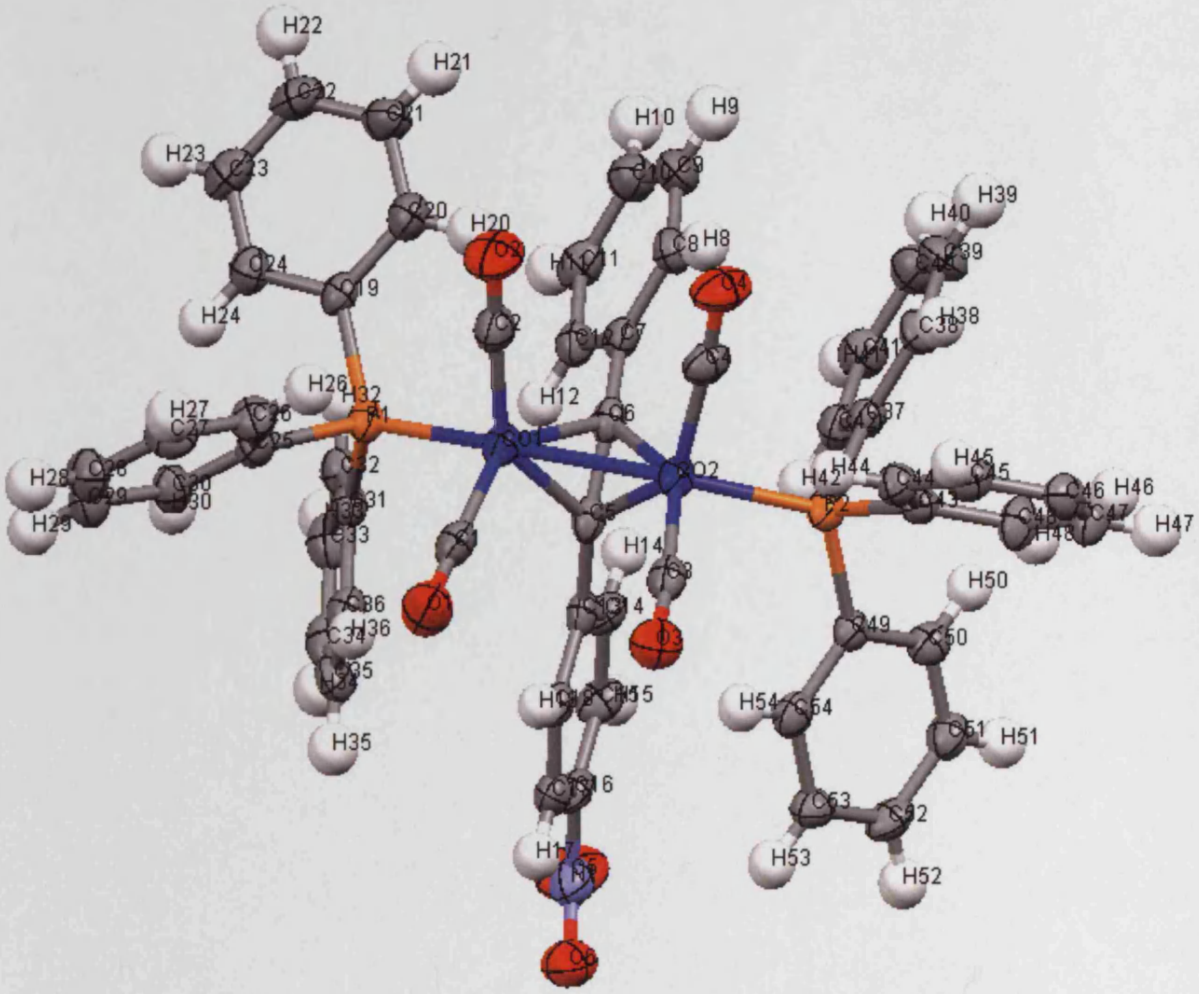
As this *trans* equatorial CO ligand (Co(1) atom bound to the C(2) atom) appears to be the weakest bond, it should be the ligand to create a vacant coordination site, allowing olefin insertion and carbonylation to occur in the PKR. This would lead to the nitrobenzene substituent in the β-position of the final cyclopentenone product **295**. However, from experiments carried out (Scheme 93) the ratio of nitrobenzene substituent in the α and β-positions are equal (1:1). This suggests that steric effects have a greater influence in the regiochemical outcome of the PKR over electronic influences.

Introducing compound **284** as a highly polarised push-pull system into the PKR, we hoped to produce a larger degree of polarisation into the triple bond than with compound **282**. This would ideally result in exclusive formation of one regioisomer of the product. Results showed that a slight increase (3:1) was observed for one regioisomers (Table 11).

However, we expected exclusive formation of compound **299** rather than the 3:1 ratio observed. Investigation of the reactive cobalt complex **292** was pursued as it was the only complex isolated from the series. Substitution of the most labile carbonyl ligand of compound **292** was attempted using triphenylphosphine (Scheme 97). Reacting compound **292** with one equivalent of triphenylphosphine (PPh_3) in DCM and one equivalent of NMO to promote removal of the weakest carbonyl ligand gave compound **301** (50%) as an unexpected product, which upon re-crystallisation from DCM/MeOH afforded black crystals. X-ray diffraction (Scheme 98), allowed bond length comparisons between both compounds **301** (Table 13) and **292**.


NO2
OC
CO
OC
Co
Co
CO
OC
CO
+ P(Ph3)
P(Ph3), NMO, DCM,
RT.
294
NO2
OC
CO
OC
Co
Co
CO
(Ph3)P
P(Ph3)
Observed.
50%
301
PPPh3, NMO,
DCM, RT.
NO2
OC
CO
OC
Co
Co
CO
OC
P(Ph3)
Expected.
302

Scheme 97



Scheme 98

(X-ray structure of (4-nitrophenyl)phenylacetylene $Co_2(CO)_4(PPh_3)_2$ complex) compound **301**.

Bond	Distance Å
CO(1)-CO(2)	2.468
CO(1)-C(1)	1.803
CO(1)-C(2)	1.799
CO(1) P(1)	2.230
CO(2)-C(3)	1.794
CO(2)-C(4)	1.785
CO(2) P(2)	2.232

Table 13

The crystal structure of **301** showed the exchange of two carbonyl ligands for two PPh_3 ligands, instead of the predicted single ligand exchange.

As a consequence, none of the exchanged ligands occurred with the (Co(1) atom bound to the C(2) atom) proposed labile ligand of complex **292** to yield complex **302**. Instead, the two ligands that exchanged proved to be the two axial carbonyls Co(1)–C(6) and Co(2)–C(3), the fourth and second weakest bound ligands (based on bond length) (Table12).

From the examples shown, it may be concluded that predicting the regiochemical outcome of the PKR is difficult and is substrate dependant. Removal of both carbonyl ligands by PPh_3 together with results obtained from the PKR for compounds **282–284** suggest that the '*trans* effect' which was thought to dictate the regiochemistry of the PKR, seems to be less effective an interaction at directing regiochemistry compared to 'steric interactions' which appear to be dominant with the substrates examined within this study

Chapter 5

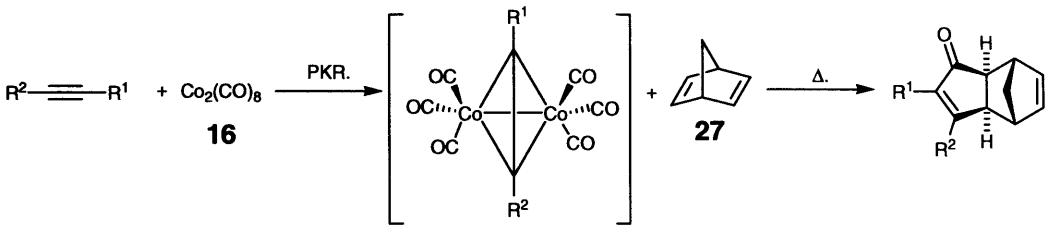
5.1 Dinorbornadienedicobalttetracarbonyl in the PKR

During our investigations into the PKR we identified Dinorbornadienedicobalttetracarbonyl (DDTC) compound **187** as a by-product[191, 192] which is another dicobalt carbonyl organometallic species (Scheme 47).

An investigation into applying this species into PK type reactions and determining its viability at promoting the PKR was examined. It was hoped this would provide insight into the PKR mechanism, by demonstrating how the alkene ligands may migrate between the metal centres to produce a cyclopentenone product.

Dinorbornadienedicobalttetracarbonyl (DDTC) **187** was first observed by Wilkinson.[191] These findings showed that this by-product was formed by displacement of the acetylenic and carbonyl ligand from the metal complex. It was also concluded through experimental observations by Pauson and Khand[192] that compound **187** did not produce significant yields of desired cyclopentenone product when reacted with various alkynes (Scheme 99). These results were repeated and various other alkynes used to investigate using DDTC as an alternative PKR substrate.

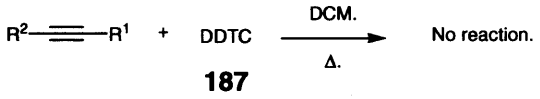
Alkynes that were reacted to repeat Pauson and Khand's experiments were phenylacetylene **142**, diphenylacetylene **303** and hex-1-yne **304** with dicobaltoctacarbonyl **16** and 2,5-norbornadiene **27**. Dicobaltoctacarbonyl **16** was then substituted with DDTC **187** in DCM with no 2,5-norbornadiene **27** shown in (Scheme 99). All substrates (**142**, **303** and **304**) reacted as expected with dicobaltoctacarbonyl **16** and 2,5-norbornadiene **27** to produce the cyclopentenone products **145**, **305** and **306** respectively. Reactions carried out with DDTC **187** showed no reactivity in line with previous observations with only starting material being recovered. Alternative solvents with higher boiling points, (THF and dichloroethane [DCE]) were examined and again led to no cyclopentenone products being isolated (using DDTC **187**). Compounds **145** and **306** had been characterised previously by Pauson and Khand and our analysis confirmed their findings, compound **305** showed the expected ^{1}H NMR signals as previously reported by Laschat[193] and Moyano.[30]



142 = R^1= Ph, R^2 = H.
303 = R^1= Ph, R^2 = Ph.
304 = R^1= $(CH_2)_3CH_3$, R^2 = H.

307 = R^1= Ph, R^2 = H.
308 = R^1= Ph, R^2 = Ph.
309 = R^1= $(CH_2)_3CH_3$, R^2 = H.

145 = R^1= Ph, R^2 = H, 90%.
305 = R^1= Ph, R^2 = Ph, 30%.
306 = R^1= $(CH_2)_3CH_3$, R^2 = H, 33%.

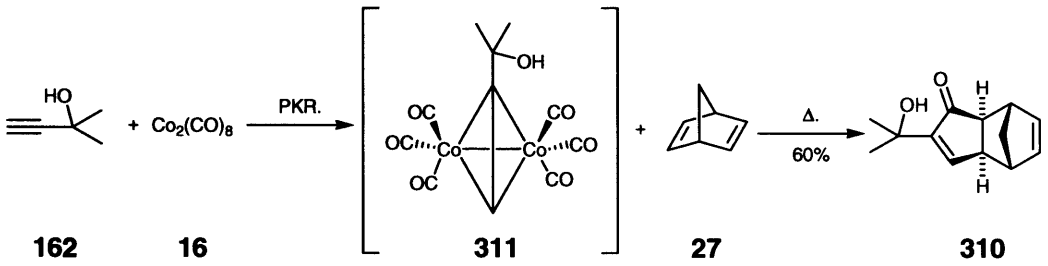


142 = R^1= Ph, R^2 = H.
303 = R^1= Ph, R^2 = Ph.
304 = R^1= $(CH_2)_3CH_3$, R^2 = H.

Scheme 99

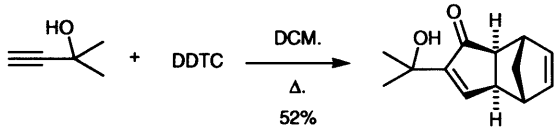
After negative results using DDTC **187** other alkynes containing heteroatoms were examined. These experiments were carried out in a similar manner to the standard PKR protocol used in previous Chapters, to ascertain if any cyclopentenone products could be isolated using DDTC.

We initially investigated 2-methyl-3-butyn-2-ol **162** with DDTC **187**, or dicobaltoctacarbonyl **16** and 2,5-norbornadiene **27** (Scheme 100). Reaction with DDTC **187**, yielded compound **310** (53%)[193] in moderate yield which was identical to the product obtained using dicobaltoctacarbonyl **16** (60%). ^{1}H NMR spectra of each product was identical containing a characteristic doublet at δ 7.17 ppm representative of the β-proton and the stereochemistry was assigned as the *exo* isomer due to the splitting patterns observed in the ^{1}H NMR being the same as observed for when the reaction was carried out using dicobaltoctacarbonyl **16**.



162 **16** **311** **27** **310**

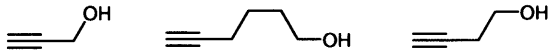
In situ.



162 **187** **310**

Scheme 100

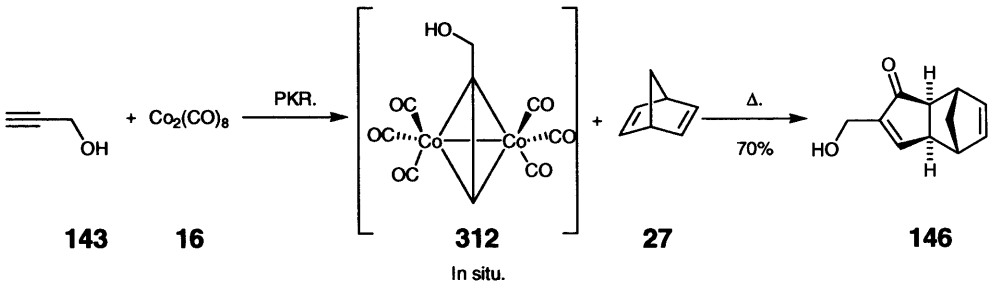
The successful results using 2-methyl-3-butyn-2-ol **162** were encouraging, this represents the first cyclopentenone product reported using DDTC **187**. Following this, the previously prepared alkynyl alcohols **143**, **171** and **172** (Chapter 2) were selected to be reacted with DDTC **187** (Scheme 101), to determine if they could also produce cyclopentenone products.

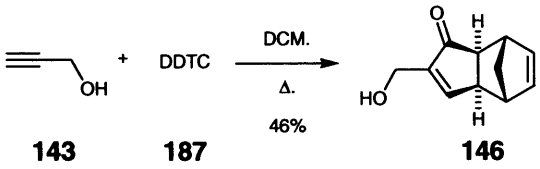


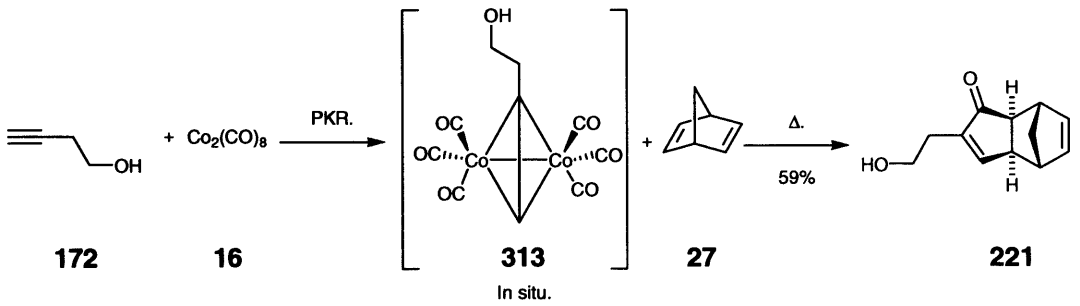
143 **171** **172**

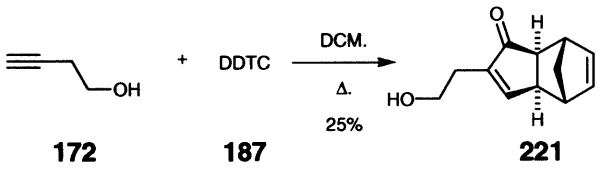
Scheme 101

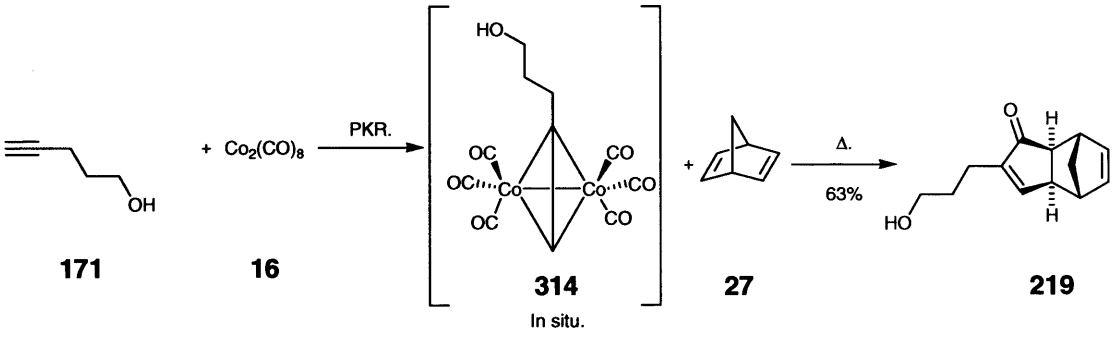
All three compounds in Scheme 101 were reacted with **16** [194, 195] or **187** to yield cyclopentenones in low to moderate yields (Table 14) (Scheme 102). All compounds synthesised using DDTC **187** were compared to cyclopentenones produced using **16** as the cobalt source. ^{1}H NMR confirmed all three compounds were identical to the products reported in Chapter 2 with the *exo* isomer being prepared selectively.

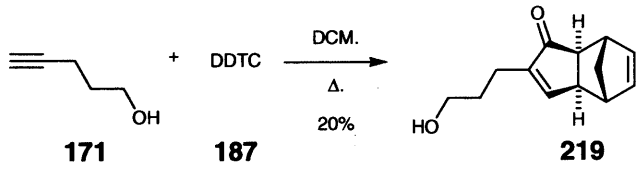

+ Co2(CO)8
PKR.
Δ.
70%
143
16
312
In situ.
27
146


DDTC
DCM.
Δ.
46%
143
187
146


+ Co2(CO)8
PKR.
Δ.
59%
172
16
313
In situ.
27
221


DDTC
DCM.
Δ.
25%
172
187
221


+ Co2(CO)8
PKR.
Δ.
63%
171
16
314
In situ.
27
219

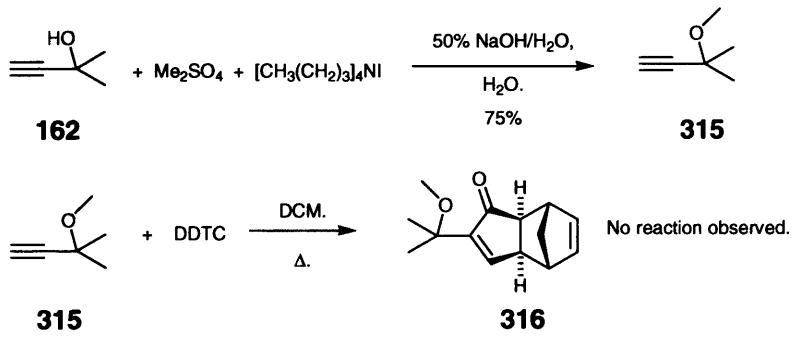

DDTC
DCM.
Δ.
20%
171
187
219

Scheme 102

Entry	Alkyne	Product	Dicobaltoctacarbonyl **16** yield %	DDTC **187** yield %
1	**143**	**146**	70%	46%
2	**171**	**219**	63%	20%
3	**172**	**221**	59%	25%

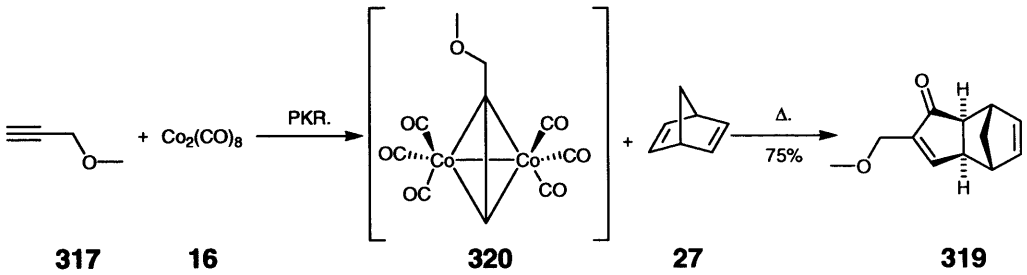
Table 14

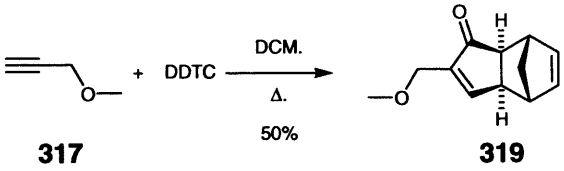
Upon confirmation that DDTC **187** produced the same cyclopentenone products obtained with dicobaltoctacarbonyl **16**, 2-methyl-3butyn-2-ol **162** was converted to the methyl ether **315** (75%), using a Williamson reaction with dimethyl sulphate, sodium hydroxide and a phase transfer catalyst. The ether derivative **315** was reacted with DDTC **187** (Scheme 103) and no reaction was observed. This suggests that the hydroxyl functionality on the alkyne substrate is essential to the new reactivity found with DDTC.

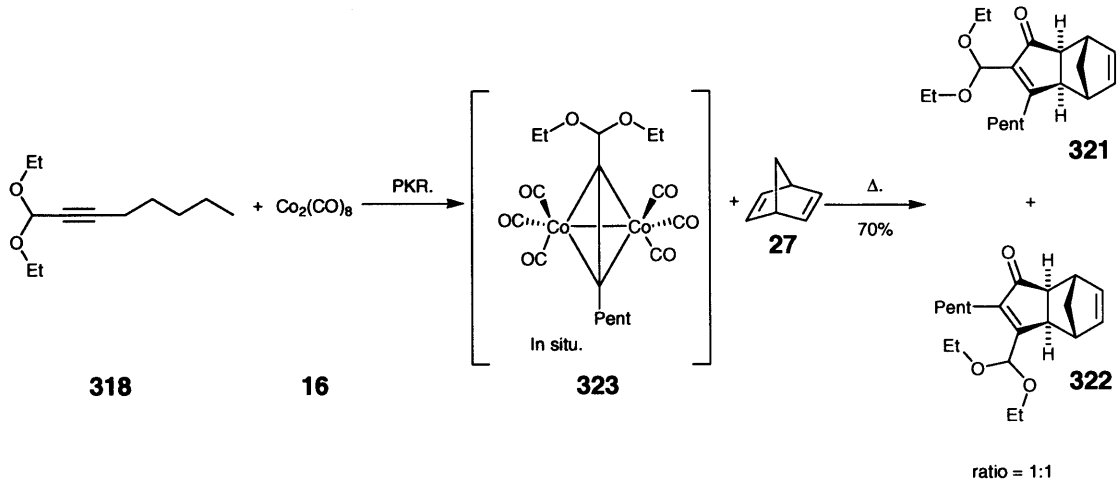


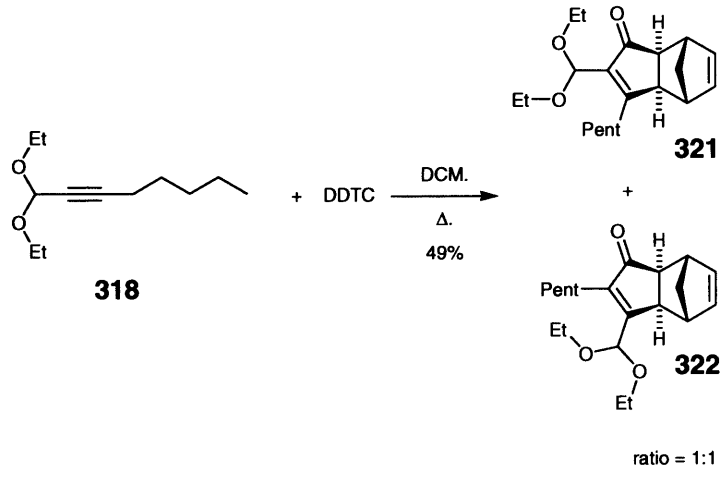
Scheme 103

The next substrates examined were 3-methoxyprop-1-yne **317** and 2-octynal diethyl acetal **318** with DDTC **187** (Scheme 104). Both compounds **317** and **318** gave the respective cyclopentenones **319** (50%), **321** and **322** (49%) in moderate yields with dicobaltoctacarbonyl **16** giving the identical cyclopentenones **319** (75%), **321** and **322** (70%) in higher yields. All cyclopentenone products **319**, **321** and **322** were identified as the *exo* conformation, compounds **321** and **322** were obtained as an inseparable 1:1 mixture of regioisomers.


+ Co2(CO)8
PKR.
OC
CO
Co
Co
CO
Δ.
75%
317
16
320
In situ.
27
319

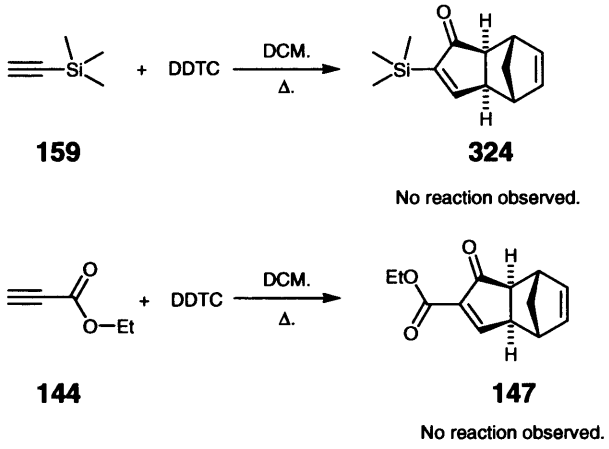

DCM.
+ DDTC
Δ.
50%
317
319


Et
+ Co2(CO)8
PKR.
OC
CO
Co
Co
CO
Pent
In situ.
27
Δ.
70%
Et
Et
Pent
321
Pent
322
318
16
323
ratio = 1:1


Et
+ DDTC
DCM.
Δ.
49%
318
Et
Pent
321
Pent
322
ratio = 1:1

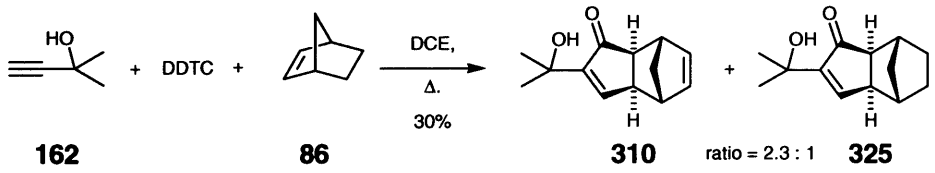
Scheme 104

Trimethylsilyl acetylene **159**[60] and ethyl propiolate **144**[102] were reacted with DDTC **187** (Scheme 105). No reaction was observed using these alternative alkynes with only starting material being recovered from the reaction mixture. These alkynes were selected due to their electronic properties with the TMS group in **159** offering electron donation into the alkyne, whilst the ester in **144** would withdraw electrons from the alkyne bond.



Scheme 105

After confirming that DDTC **187** is able to promote the formation of cyclopentenones from alkynes bearing an alcohol or ether functional group, a reaction of DDTC **187** with alkyne **162** and an excess of norbornene **86** in DCE was carried out to investigate the ability of the Co-species to exchange olefin ligands (Scheme 106). Compounds **310** (21%) and **325** (9%) were isolated in a ratio of 2.3:1 (crude mixture) showing preference for the 2,5-norbornadiene **27** over the norbornene **86**.



Scheme 106

This showed that compound **310** was produced as the major product which was unexpected, due to the excess of norbornene **86** used. For compound **310** to result from the reaction, the bound 2,5-norbornadiene ligand would have to dissociate from the metal complex, then insert into a vacant coordination site, created by removal of a carbonyl ligand.

Dissociation of the olefin from the metal centre appears to confirm the *exo* configuration of compound **310**, due to this ligand already being bound in and *endo* conformation to the DDTC starting material. It may be speculated that the rate at which 2,5-norbornadiene ligands can be replaced, by norbornene **86**, must be faster than the rate at which norbornene **86** can insert into the alkyne bond. This allows compound **310** to be the major product of the reaction and shows, not surprisingly, that norbornene **86** is a less reactive olefin compared to 2,5-norbornadiene 27 in the PKR.

Results obtained from this work suggests that promotion of a PKR using DDTC **187** probably follows the same mechanistic route as the PKR promoted by dicobaltoctacarbonyl **16** with slightly lower yields, which is not surprising considering no excess of olefin is used within DDTC promoted reactions.

An interesting result from this work is DDTC **187** only appeared to react with alkynes possessing a propargylic oxygen heteroatom. Alcohols and ethers showed moderate reactivity in most cases, compared to other substrates used, probably due to an interaction between the lone pair of electrons of the heteroatom and the cobalt centres. This suggests that the Lewis acid/base interaction (coordination) facilitates the PKR whilst an olefin dissociates from the cobalt complex and inserts into the existing C-Co bond. This could explain why other functionalities such as a trimethylsilane and aliphatic carbon were un-reactive due to their inability to stabilise the cobalt complex through donation of electrons once a carbonyl ligand had been removed. With the hindered alkyne substrate **315** it is possible that such an interaction is not possible for steric reasons.

Summary and Conclusion

In conclusion, the studies carried out into the PKR within this thesis show that the PKR is a viable synthetic tool to produce cyclopentenones with inbuilt functionality for the synthesis of tricyclic fused indoles and triquinanes; which could be adopted to simplify and enhance the synthesis of prospective drug candidates.

Attempts at synthesising benzofurans, pyrans and pyrroles using the same strategy proved elusive, due to the high reactivity of the PKR products. Pyrrole precursors proved to be too reactive prior to the cyclisation step. Benzofuran and pyrans were not

accessible by cyclisation of the cyclopentenone product of the PKR, most likely due to the lower nucleophilicity of oxygen when compared to nitrogen.

Regiochemical control of the PKR with di-substituted alkynes showed that contrary to literature speculation, regiochemical control of the PKR is achieved predominantly due to steric interactions and that any electronic control associated with the PKR is significantly less than that of the steric factors with the substrates examined.

The first examples of a DDTC mediated PKR were developed which shows identical stereochemical and regiochemical outcomes as observed for the traditional dicobaltoctacarbonyl process. Reactions using DDTC (**187**) were lower yielding, presumably due to the lower concentrations of alkyne present within the reaction mixture. It was also found that central to the progress of the PKR with DDTC was the presence of an electron donating ether or hydroxyl functionality on the alkyne substrate.

Chapter 6

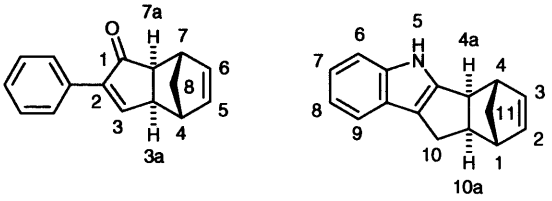
6.1 Experimental

General Considerations: Anhydrous solvents were dried over sodium wire and degassed by reflux under inert atmospheres, unless otherwise stated all other solvents used were HPLC grade from commercial suppliers.

Thin layer chromatography was carried out using Merck silica gel 60 F_{254} plates. Column chromatography was performed using silica gel 60 (220-440) mesh. Melting points were observed using an electro thermal digital melting point apparatus, model 9100. Infrared spectra were acquired for all unreported compounds using a Perkin Elmer 1600 series FTIR instrument. ^{1}H NMR and ^{13}C NMR were performed on a Bruker 500, 400 and 250 MHz spectrometer, mass spectrometry was carried out using a Fisons VG Platform II quadrupole instrument. Whilst high-resolution mass spectrometry was determined by, the EPSRC national mass spectrometry service centre at Swansea University. Elemental analyses were performed by the analytical department in the School of Chemistry, Warwick University. All starting materials were supplied by Acros, Aldrich, Fisher and Strem unless otherwise stated, the dicobaltoctacarbonyl used within this thesis was acquired from Strem 90–95 % purity stabilized with 1-5% hexane.

General procedure for PKR

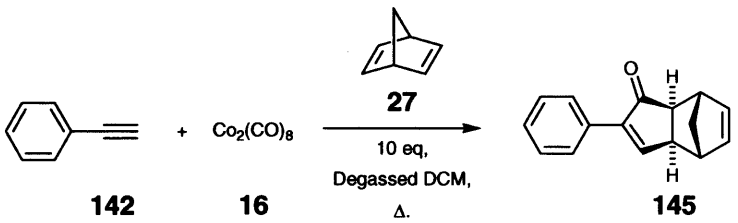
Reaction procedure for the PKR followed the same protocol where to a flame dried Schlenk flask equipped with a reflux condenser was added dicobaltoctacarbonyl (1.1 eq), alkyne (1.0 eq) and dry, degassed dichloromethane (70 eq or 4.5 ml/mmol alkyne) under an atmosphere of nitrogen. The mixture was stirred at room temperature until the dicobalthexacarbonyl alkyne complex was formed as indicated by a coloured, high running TLC spot (approx 60 min). To this reaction mixture, 2,5-norbornadiene (10 eq) was added and the reaction mixture heated at reflux until completion by TLC. Purification of all PKR reactions involved the concentration of crude reaction mixture to dryness, addition of activated charcoal (0.5 g), silica gel 60μm-200μm (3.0 g) and DCM (100 ml) stirred at RT until TLC showed virtually no organometallic impurities and filtered through celite. The resulting mixture was adsorbed onto silica gel 60μm-200μm until free flowing and columned using various solvents.



Numbering scheme for ring systems.

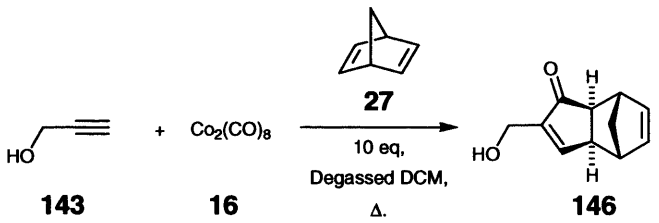
Experimental

2-Phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[192] (145)



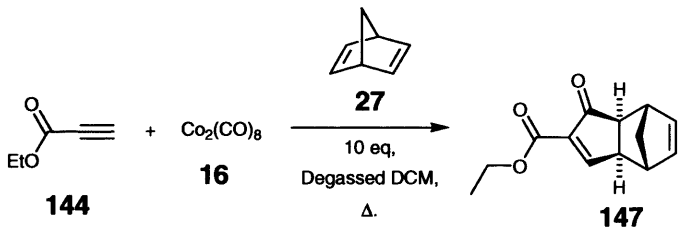
To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added phenylacetylene **142** (2.20 ml, 20.00 mmol) and dicobaltoctacarbonyl **16** (7.52 g, 22.00 mmol) in DCM (90.0 ml). After 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex. 2,5-Norbornadiene **27** (23.70 ml, 220.00 mmol) was added and the reaction heated to reflux for 5 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether), yielded 2-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **145** as a brown solid, (R_f = 0.50) (4.00 g, 18.00 mmol, 90%); m.p. 70–71 °C. FTIR (Nujol, υ_{max} cm^{-1}) 3062, 3020, 1689; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (3H, m, ArH), 7.33–7.24 (3H, m, ArH + 3-H), 6.27 (1H, dd, J = 5.0, 3.0 Hz, H-6), 6.19 (1H, dd, J = 5.0, 3.0 Hz, H-5), 2.96 (1H, bs, H-7), 2.78–2.75 (1H, bm, H-7a), 2.73 (1H, bs, H-4), 2.42 (1H, d, J = 4.7 Hz, H-3a), 1.37 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.29 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2).

2-Hydroxymethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[196] (146)



To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added propargyl alcohol **143** (1.18 ml, 20.00 mmol) and dicobaltoctacarbonyl **16** (7.52 g, 22.00 mmol) in DCM (90.0 ml). After 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex. 2,5-Norbornadiene **27** (23.70 ml, 220.00 mmol) was added and the reaction heated to reflux for 5 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 ethyl acetate/40–60 petroleum ether), yielded 2-hydroxymethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **146** as a yellow oil, (R_f = 0.30) (2.47 g, 14.00 mmol, 70%). FTIR (Nujol, υ_{max} cm $^{-1}$) 3596, 2970, 2935, 2882, 1705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, bs, H-3), 6.24 (1H, dd, J = 5.3, 3.0 Hz, H-6), 6.15 (1H, dd, J = 5.4, 2.9 Hz, H-5), 4.30 (2H, bs, CH_2OH), 2.87 (1H, bs, H-7), 2.76–2.72 (1H, bm, H-7a), 2.66 (1H, bs, H-4), 2.29 (1H, d, J = 4.2 Hz, H-3a), 2.22 (1H, bs, OH), 1.36 (1H, d, J = 9.4 Hz, ½ x H-8-CH_2), 1.22 (1H, d, J = 10.8 Hz, ½ x H-8-CH_2).

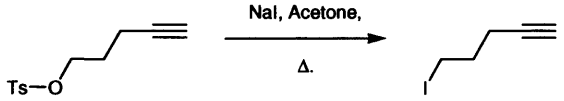
2-Ethanoate-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[197] (147)



To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added ethyl propiolate **144** (1.01 ml, 10.00 mmol) and dicobaltoctacarbonyl **16** (3.76 g, 11.00 mmol) in DCM (45.0 ml). After 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex. 2,5-Norbornadiene **27** (10.80 ml, 100.00 mmol) was added and the reaction heated to reflux for 5 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum

ether), yielded 2-ethanoate-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **147** as a brown oil, (R_f = 0.42) (0.76 g, 3.50 mmol, 35%). FTIR (Nujol, υ_{max} cm $^{-1}$) 3062, 1738, 1667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, bs, H-3), 6.30 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.20 (1H, dd, J = 5.5, 3.0 Hz, H-5), 4.17 (2H, q, J = 7.0 Hz, CO_2CH_2), 2.87 (1H, bs, H-7), 2.74–2.72 (1H, bm, H-7a), 2.73 (1H, bs, H-4), 2.30 (1H, d, J = 4.0 Hz, H-3a), 1.40 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.30 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.20 (3H, t, J = 7.0 Hz, CH_3).

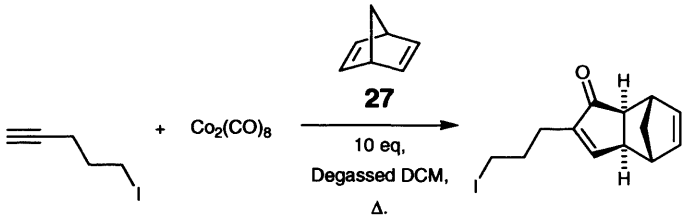
5-Iodo-1-pentyne[198] (148)



173 **148**

To a mixture of pent-4-yn-1-yl 4-methylbenzenesulfonate **173** (20.00 g, 84.00 mmol, in dry acetone (600.0 ml) potassium iodide (27.90 g, 168.00 mmol) was added and refluxed. TLC showed reaction complete after 5 hr and reaction was quenched with water (2000.0 ml) and organics extracted with 40–60 petroleum ether (500.0 ml x 3), the organic portions were combined and washed with brine (500.0 ml) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to yield 5-iodo-1-pentyne **148** as a yellow oil, (15.50 g, 80.00 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (2H, t, J = 6.6 Hz, CH_2I), 2.30 (2H, td, J = 6.5, 3.0 Hz, $CCCH_2$), 1.95 (3H, m, $C\underline{H}_2CH_2I$).

2-(3-Iodopropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (149)



148 **16** **149**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 5-iodo-1-pentyne **148** (6.20 g, 32.00 mmol) and dicobaltoctacarbonyl **16** (12.00 g, 35.00 mmol) in DCM (140.0 ml). 2,5-Norbornadiene **27** (34.50 ml, 320.00 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 5 hr. The reaction was worked up

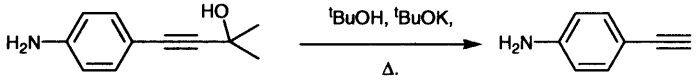
following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether), yielded 2-(3-iodopropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **149** as a clear oil, (R_f = 0.4) (8.34 g, 27.00 mmol, 83%). FTIR (Nujol, υ_{max} cm $^{-1}$) 2955, 2342, 1684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, bs, H-3), 6.23 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.15 (1H, dd, , J = 5.5, 3.0 Hz, H-5), 3.12 (2H, t, J = 6.8 Hz, CH_2I), 2.86–2.83 (1H, bs, H-7), 2.66 (1H, bs, H-7a), 2.62 (1H, bs, H-4), 2.23 (3H, m, H-3a + $C\underline{H}_2CH_2CH_2I$), 1.97 (2H, q, J = 7.0 Hz, $C\underline{H}_2CH_2I$), 1.33 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2), 1.12 (1H, d, J = 9.3 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 159.9, 148.6, 138.4, 137.1, 52.5, 47.8, 43.6, 42.9, 41.2, 31.3, 26.1, 6.1; m/z (APCI) 314.7 (100) (M + H^+); HRMS (ES) $C_{13}H_{19}NIO$ requires 332.0506 [M + NH_4]$^+$, found 332.0504.

4-Ethynylaniline[199] (150)

161 **150**

To a stirred solution of 4-(2-(trimethylsilyl)ethynyl)benzenamine **161** (5.00 g, 26.00 mmol) in MeOH (100.0 ml), potassium fluoride (4.53 g, 78.00 mmol) was added and allowed to stir at RT for 3 hr. TLC confirmed completion of the reaction, the reaction was then diluted with diethyl ether (100.0 ml) and washed with water (500.0 ml). The aqueous fraction was again extracted with diethyl ether (2 x 100.0 ml), the organic fractions were combined and washed with brine (100.0 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 4-ethylaniline **150** as a yellow solid, (1.98 g, 17.00 mmol, 65%); m.p. 100–102 °C (EtOH/H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, dd, J = 8.5, 2.2 Hz, ArH), 6.53 (2H, dd, J = 6.7, 1.8 Hz, ArH), 3.75 (2H, bs, NH_2), 2.90 (1H, s, CCH).

Alternate synthesis of 4-Ethynylaniline[200] (150)

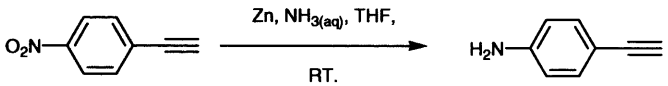


164 **150**

To a solution of 4-(4-aminophenyl)-2-methylbut-3-yn-2-ol **164** (5.00 g, 28.53 mmol) in t-butanol (50.0 ml), potassium t-butoxide (0.80 g, 7.13 mmol) was added and the reaction heated to reflux for 3 hr. Upon cooling the reaction mixture was concentrated under reduced pressure, dissolved into DCM (50.0 ml) and washed with

water (50.0 ml). The organic layer was then washed with brine (50.0 ml) dried over $MgSO_4$ and concentrated to yield 4-ethylaniline **150** as a yellow solid, (0.94 g, 8.00 mmol, 28%); m.p. 100–102 °C ($EtOH/H_2O$). Characterisation as before.

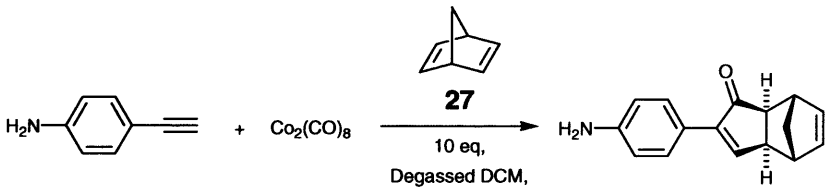
Alternate synthesis to 4-Ethynylaniline[201] (150)



181 **150**

To a stirred solution of 1-ethynyl-4-nitrobenzene **181** (5.00 g, 34.00 mmol) in THF (100.0 ml) a 35% ammonia hydroxide solution (100.0 ml) was added followed by zinc dust (11.10 g, 17.00 mmol). The reaction was kept at RT for 24 hr. TLC confirmed no starting material and the reaction was diluted with 2M HCl (300.0 ml) and extracted with diethyl ether (300.0 ml), the aqueous layer was further extracted with another two portions of diethyl ether (100.0 ml). The aqueous layer was then basified with K_2CO_3 until the pH was about 8-9, this was then extracted with diethyl ether (100.0 ml x 3) and the organic portions dried with brine (100.0 ml) and $MgSO_4$, the filtrate was then concentrated under reduced pressure to yield 4-ethylaniline **150** as a yellow solid, (2.50 g, 21.40 mmol, 63%); m.p. 100–102 °C ($EtOH/H_2O$). Characterisation as before.

2-(3-Iodopropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (151)

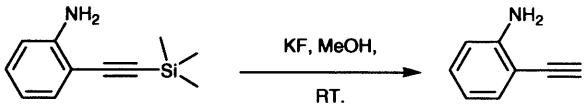


150 **16** **151**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 4-ethynyl aniline **150** (0.99 g, 8.43 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.27 mmol) in DCM (38.0 ml). 2,5-Norbornadiene **27** (9.00 ml, 84.30 mmol) was then added and after 30 min TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 diethyl ether/40–60 petroleum ether), yielded 2-(3-iodopropyl)-3a,4,7,7a-tetrahydro-

4,7-methanoinden-1-one **151** as a yellow solid, (R_f = 0.35) (1.96 g, 8.26 mmol, 98%); m.p. 112–115 °C (EtOH /H_2O). FTIR (Nujol, υ_{max} cm $^{-1}$) 3372–3335, 3050, 2358, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, J = 8.5 Hz, ArH), 7.50 (1H, d, J = 3.0 Hz, H-3), 6.63 (2H, d, J = 8.5 Hz, ArH), 6.25 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.20 (1H, dd, J = 5.6, 2.8 Hz, H-5), 3.70 (2H, bs, NH_2), 2.90 (1H, bs, H-7), 2.74–2.72 (1H, bm, H-7a), 2.70 (1H, bs, H-4), 2.37 (1H, d, J = 5.0 Hz, H-3a), 1.34 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.26 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 160.2, 147.2, 143.5, 138.5, 137.1, 128.1, 125.8, 116.0, 53.5, 46.9, 44.1, 43.4, 41.4; m/z (APCI) 238.7 (100) (M + H^+).

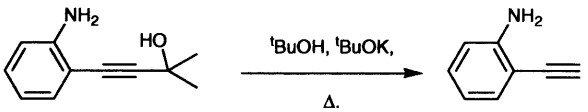
2-Ethynylaniline[199](152)



160 **152**

To a stirred solution of 2-(2-(trimethylsilyl)ethynyl)benzenamine **160** (5.00 g, 26.00 mmol) in MeOH (100.0 ml), potassium fluoride (4.53 g, 78.00 mmol) was added and allowed to stir at RT for 3 hr. TLC confirmed completion of the reaction and was diluted with diethyl ether (100.0 ml) then washed with water (500.0 ml). The aqueous fraction was again extracted with diethyl ether (2 x 100.0 ml) and the organic fractions were combined and washed with brine (100.0 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2-ethylaniline **152** as a yellow oil, (1.86 g, 16.00 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, ddd, J = 8.2, 8.2, 1.2 Hz, ArH), 6.65–6.60 (2H, m, ArH), 4.17 (2H, bs, NH_2), 3.31 (1H, s, CCH).

Alternate synthesis of 2-Ethylaniline[200](152)

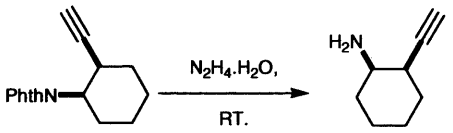


163 **152**

To a solution of 4-(2-aminophenyl)-2-methylbut-3-yn-2-ol **163** (5.00 g, 28.53 mmol) in t-butanol (50.0 ml), potassium t-butoxide (0.80 g, 7.13 mmol) was added and the reaction heated to reflux for 3 hr. TLC confirmed completion of the reaction and upon cooling the reaction mixture was concentrated under reduced pressure, dissolved into DCM (50.0 ml) and washed with water (50.0 ml). The organic layer

was then washed with brine (50.0 ml) dried over $MgSO_4$ and concentrated to yield 2-ethylaniline **152** as a yellow oil, (0.67 g, 5.70 mmol, 20%). Characterisation as before.

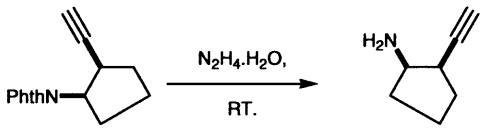
Cis-2-Ethynylcyclohexamine[202, 203] (153)



169 **153**

To a solution of *cis*-(ethynylcyclohexyl)isoindoline-1,3-dione **169** (10.00 g, 0.04 mol) in ethanol (150.0 ml) at RT, hydrazine monohydrate (4.85 ml, 0.10 mol) was added slowly and the reaction left overnight. TLC showed the reaction was complete and water (50.0 ml) added. The mixture was then acidified to pH 4 by slow addition of HCl 3M, which precipitated a white solid that was filtered off. The remaining filtrate was concentrated to approximately 20.0 ml and basified using NaOH 5M (20.0 ml) and extracted with DCM (50.0 ml x 2). A brine wash (50.0 ml) followed and the organics dried over $MgSO_4$, filtered and concentrated at atmospheric pressure to yield *cis*-2-ethynylcyclohexamine **153** as a yellow oil that was further purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield a yellow oil, (R_f = 0.26) (2.46 g, 0.02 mol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04–3.00 (1H, m, $NH_2C\underline{H}$), 2.25–2.15 (3H, m, NH_2, ring proton), 2.10 (1H, d, J = 2.4 Hz, HCC), 1.96–1.93 (2H, m, ring proton), 1.62–1.60 (1H, m, ring proton), 1.59–1.56 (1H, m, ring proton), 1.40–1.00 (4H, m, ring proton).

Cis-2-Ethynylcyclopentamine[202, 203] (154)

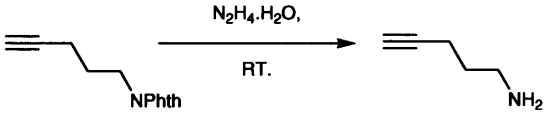


170 **154**

To a solution of *cis*-2-(ethynylcyclopentyl)isoindoline-1,3-dione **170** (10.00 g, 42.00 mmol) in ethanol (150.0 ml) at RT, hydrazine monohydrate (4.85 ml, 0.10 mol) was added slowly and the reaction left overnight. TLC showed the reaction was complete and water (50.0 ml) added. The mixture was then acidified to pH 4 by slow addition of HCl 3M, which precipitated a white solid that was filtered off. The remaining filtrate was concentrated to approximately 20.0 ml and basified using NaOH 5M (20.0 ml), this was extracted with DCM (50.0 ml x 2). Washed with brine

(50.0 ml) and dried over $MgSO_4$, the filtrate was the concentrated at atmospheric pressure to yield *cis*-2-ethynylcyclopentamine **154** as a yellow oil that was further purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield a yellow oil, (R_f = 0.30) (2.57 g, 24.00 mmol, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86–3.82 (1H, m, $NH_2C\underline{H}$), 2.64–2.60 (1H, m, HCC), 2.06–1.87 (5H, m, NH_2, ring proton), 1.72–1.48 (4H, m, ring proton).

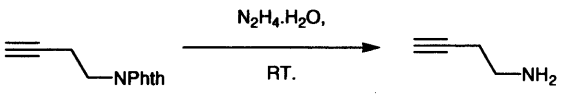
Pent-4-yn-1-amine[202, 203](155)



175 **155**

To a solution of 2-(pent-4-ynyl)isoindoline-1,3-dione **175** (2.50 g, 12.00 mmol) in ethanol (45.00 ml) at RT, hydrazine monohydrate (1.50 ml, 0.03 mol) was added slowly to the reaction and left overnight. TLC showed the reaction was complete and water (10.0 ml) was added. This mixture was acidified to pH 4 by slow addition of HCl 3M, which precipitated a white solid that was filtered off. The remaining filtrate was concentrated to approximately 5.0 ml and basified using NaOH 5M (10.0 ml) and extracted with DCM (50.0 ml x 2). A brine wash followed (50.0 ml) and the organics were dried over $MgSO_4$, the filtrate was concentrated at atmospheric pressure to yield pent-4-yn-1-amine **155** as a yellow oil that was further purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield a yellow oil, (R_f = 0.18) (0.70 g, 8.00 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (2H, t, J = 6.9 Hz, $C\underline{H}_2NH_2$), 2.20 (2H, td, J = 7.0, 2.6 Hz, $CHCC\underline{H}_2$), 1.89 (1H, t, 2.7 Hz, HCC), 1.60 (2H, qintet, J = 7.0 Hz, $C\underline{H}_2CH_2NH_2$), 1.05 (2H, bs, NH_2).

But-3-yn-1-amine[202, 203] (156)

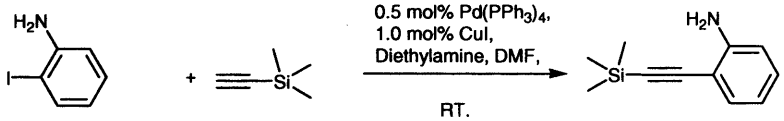


176 **156**

To a solution of 2-(but-3-ynyl)isoindoline-1,3-dione **176** (5.00 g, 25.00 mmol) in ethanol (90.00 ml) at RT, hydrazine monohydrate (3.30 ml, 63.00 mmol) was added slowly and the reaction left overnight. TLC showed the reaction was complete and water (20.0 ml) added. This mixture was acidified to pH 4 by slow addition of

HCl 3M, which precipitated a white solid that was filtered off. The remaining filtrate was concentrated to approximately 5.0 ml and basified using NaOH 5M (20.0 ml) and extracted with DCM (50.0 ml x 2). A brine wash followed (50.0 ml) and the organics dried over $MgSO_4$, the filtrate was concentrated at atmospheric pressure to yield but-3-yn-1-amine **156** as a yellow oil that was further purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield a yellow oil, (R_f = 0.15) (1.00 g, 15.00 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (2H, t, J = 6.3 Hz, $C\underline{H}_2NH_2$), 2.27 (2H, td, J = 6.4, 2.7 Hz, $C\underline{H}_2CH_2NH_2$), 1.77 (1H, t, 2.6 Hz, HCC), 1.24 (2H, bs, NH_2).

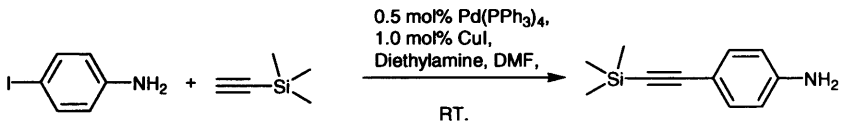
2-(2-(Trimethylsilyl)ethynyl)benzenamine[199](160)



157 **159** **160**

To a mixture of 2-iodoaniline **157** (30.00 g, 137.00 mmol), tetrakis(triphenylphosphine)palladium(0) (0.79 g, 0.70 mmol) and copper iodide (0.26 g, 1.37 mmol) in DMF (20.0 ml) and diethylamine (100.0 ml) under an atmosphere of nitrogen. Ethynyltrimethylsilane **159** (10.90 ml, 0.15 mol) was added after stirring for 10 min and left at RT for 6 hr, TLC showed complete reaction and was partitioned between water (1000.0 ml) and DCM (500.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with (2 x 250.0 ml). The organic fractions were combined and washed with brine (250.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield 2-(2-(trimethylsilyl)ethynyl)benzenamine **160** as a yellow solid, (24.64 g, 0.13 mol, 95%); m.p. 110–112 °C ($EtOH/H_2O$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, J = 7.7 Hz, ArH), 6.92 (1H, ddd, J = 7.0, 7.0, 1.2 Hz, ArH), 6.47 (2H, m, ArH), 4.04 (2H, bs, NH_2), 0.07 (9H, s, $SiMe_3$).

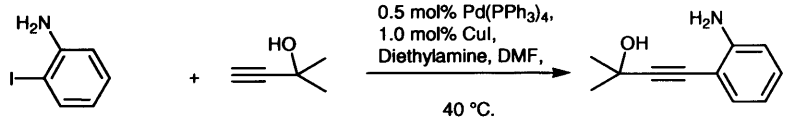
4-(2-(Trimethylsilyl)ethynyl)benzenamine[199](161)



158 **159** **161**

To a mixture of 4-iodoaniline **158** (30.00 g, 137.00 mmol), tetrakis(triphenylphosphine)palladium(0) (0.79g, 0.70 mmol) and copper iodide (0.26 g, 1.37 mmol) in DMF (20.00 ml) and diethylamine (100.0 ml) under an atmosphere of nitrogen. Ethynyltrimethylsilane **159** (10.90 ml, 0.15mol) was added after stirring for 10 min and left at RT for 6 hr, TLC showed complete reaction and was partitioned between water (1000.0 ml) and DCM (500.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with (2 x 250.0 ml). The organic fractions were combined and washed with brine (250.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield 4-(2-(trimethylsilyl)ethynyl)benzenamine **161** as a yellow solid, (23.86 g, 126.00 mmol, 92%); m.p. 98–100 °C ($EtOH/H_2O$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, d, J = 8.9 Hz, ArH), 6.39 (2H, d, J = 8.7 Hz, ArH), 3.57 (2H, bs, NH_2), 0.00 (9H, s, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 133.4, 114.5, 112.5, 106.0, 91.4, 0.4.

2-Methyl-2-(aniline)but-3-yn-2-ol[204, 205] (163)

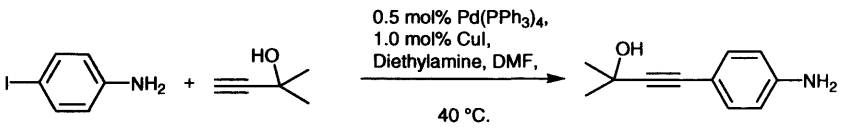


157 **162** **163**

To a mixture of 2-iodoaniline **157** (5.00 g, 23.00 mmol), tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.14 mmol) and copper iodide (44.00 mg, 0.23 mmol) in diethylamine (17.00 ml) and DMF (4.00 ml) under an atmosphere of nitrogen. 2-Methyl-3-butyn-2-ol **162** (2.47 ml, 25.30 mmol) was added after stirring for 10 min and heated to 40 °C for 6 hr, TLC showed complete reaction and was partitioned between water (100.0 ml) and DCM (50.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with (2 x 25.0 ml). The organic fractions were combined and washed with brine (25.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure and purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield 2-methyl-2-(aniline)but-3-yn-2-ol **163** as a yellow solid, (R_f = 0.26) (3.40 g, 19.55 mmol, 85%); m.p. 55–58 °C (EtOH). ^1H

NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 6.3 Hz, ArH), 7.19 (1H, ddd, J = 7.7, 7.7 1.5 Hz, ArH), 6.68–6.60 (2H, m, ArH), 4.12 (2H, bs, NH_2), 2.57 (1H, bs, OH), 1.56 (6H, s, Me_2).

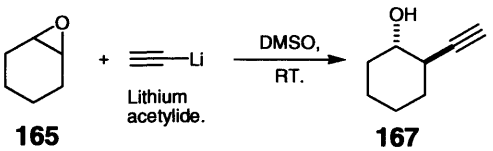
2-Methyl-4-(aniline)but-3-yn-2-ol[204, 205] (164)



158 **162** **164**

To a mixture of 4-iodoaniline **158** (5.00 g, 23.00 mmol), tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.14 mmol) and copper iodide (44.00 mg, 0.23 mmol) in diethylamine (17.00 ml) and DMF (4.00 ml) under an atmosphere of nitrogen. 2-Methyl-3-butyn-2-ol **162** (2.47 ml, 25.30 mmol) was added after stirring for 10 min and heated to 40 °C for 6 hr, TLC showed complete reaction and was partitioned between water (100.0 ml) and DCM (50.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with (2 x 25.0 ml). The organic fractions were combined and washed with brine (25.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure and purified by chromatography (1:1 ethyl acetate/40–60 petroleum ether) to yield 2-methyl-4-(aniline)but-3-yn-2-ol **164** as a yellow solid, (R_f = 0.30) (3.50 g, 20.01 mmol, 87%); m.p. 85–87 °C (EtOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.3 Hz, ArH), 6.52 (2H, d, J = 8.3 Hz, ArH), 3.74 (2H, bs, NH_2), 2.86 (1H, bs, OH), 1.52 (6H, s, Me_2).

***Trans*-2-Ethynyl-cyclohexanol[206, 207] (167)**

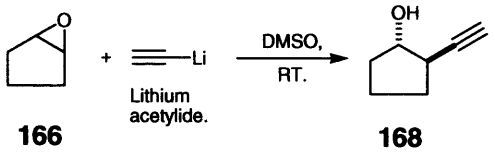


165 **167**

To a suspension of lithiumacetylide-ethylendiamine complex (27.3 g, 296.50 mmol) in DMSO (60 ml) under a nitrogen atmosphere, cyclohexene oxide **165** (10.00 ml, 99.00 mmol) was added and the reaction stirred at RT for 48 hr. TLC confirmed complete reaction and the reaction quenched with saturated aqueous ammonium chloride solution (70.0 ml), the reaction mixture was then extracted with diethyl ether (3 x 50.0 ml) and the organic portions combined and washed with brine (50.0 ml), dried over $MgSO_4$ and the filtrate concentrated at atmospheric pressure to yield *trans*-

2-ethynyl-cyclohexanol **167** as a brown oil, (8.85 g, 71.28 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41–3.38 (1H, m, OHC<u>H</u>), 2.28–2.10 (3H, m, <u>H</u>CCC<u>H</u>CH, O<u>H</u>), 1.97–1.92 (2H, m, ring proton), 1.73–1.57 (2H, m, ring proton), 1.40–1.03 (4H, m, ring proton).

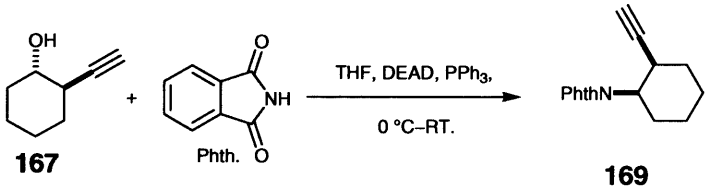
Trans-2-ethynyl-cyclopentanol[206, 207] (168)



166 **168**

To a suspension of lithiumacetylide-ethylendiamine complex (31.08 g, 346.32 mmol) in DMSO (60.0 ml, 0.85 mol) under a nitrogen atmosphere, cyclopentene oxide **166** (10.00 ml, 115.44 mmol) was added and the reaction stirred for 48 hr. TLC confirmed complete reaction and was quenched with saturated aqueous ammonium chloride solution (70.0 ml), the reaction mixture was then extracted with diethyl ether (3 x 50.0 ml) and the organic portions combined and washed with brine (50.0 ml), dried over $MgSO_4$ and the filtrate concentrated at atmospheric pressure to yield *trans*-2-ethynyl-cyclopentanol **168** as a brown oil, (9.41 g, 85.43 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17–4.14 (1H, m, OHCH), 2.51–2.48 (1H, m, OHC<u>H</u>), 2.10–1.92 (3H, m, <u>H</u>CCC<u>H</u>CHO<u>H</u>, ring proton), 1.87 (1H, bs, OH), 1.78–1.43 (4H, m, ring proton).

Cis-2-(Ethynylcyclohexyl)isoindoline-1,3-dione[202] (169)

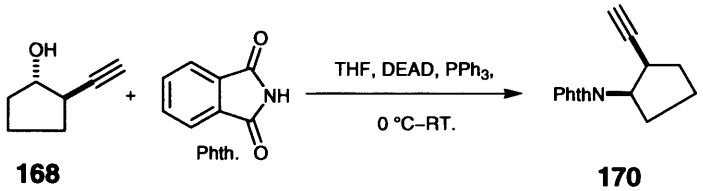


167 **169**

To a three necked RB flask under a nitrogen atmosphere *trans*-2-ethynylcyclohexanol **167** (3.50 g, 28.18 mmol) was added to phthalimide (4.56g, 31.00 mmol) and triphenylphosphine (7.40 g, 28.21 mmol) in dry THF (50.00 ml). The reaction mixture was cooled to 0 °C (ice bath) whilst stirring and DEAD (5.60 ml, 28.19 mmol) in THF (6.00 ml) added slowly over 1 hr, upon complete addition the reaction was allowed to warm to RT and stirred for 36 hr. The reaction was then partitioned between DCM (50.0 ml) and water (50.0 ml) the organic phase was then concentrated to dryness and purified by chromatography (1:1 DCM/40–60 petroleum

ether) to yield *cis*-2-(ethynylcyclohexyl)isoindoline-1,3-dione **169** as a yellow solid, (R_f = 0.11) (5.00 g, 19.72 mmol, 70%); m.p. 140–142 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 3263, 2924, 2857, 1766, 1711, 1611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, dd, J = 5.5, 3.0 Hz, ArH), 7.65 (2H, dd, J = 5.5, 3.0 Hz, ArH), 4.06 (1H, dt, J = 13.2, 3.8, Hz, PhthNCH), 3.10–3.00 (2H, m, ring proton) 1.98 (1H, d, J = 2.5 Hz, C<u>H</u>CCHCH$_2$), 1.88–1.51 (6H, m, ring proton), 1.26–1.20 (1H, m, ring proton); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 133.9, 131.9, 123.1, 83.8, 71.6, 54.8, 33.0, 30.9, 26.3, 25.1, 20.9; m/z (APCI) 254.5 (100) (M + H$^+$); $C_{16}H_{15}NO_2$ requires C, 75.87; H, 5.97; N, 5.53, found: C, 75.64; H, 6.03; N, 5.41%.

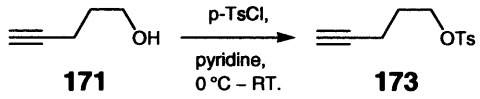
Cis-2-(ethynylcyclopentyl)isoindoline-1,3-dione[202] (170)



168 **170**

To a three necked RB flask under a nitrogen atmosphere *trans*-2-ethynylcyclopentanol **168** (3.50 g, 31.77 mmol) was added to phthalimide (5.15 g, 35.00 mmol) and triphenylphosphine (8.30 g, 31.64 mmol) in dry THF (50.00 ml). The reaction mixture was cooled to 0 °C (ice bath) whilst stirring and DEAD (5.54 ml, 31.81 mmol) in THF (6.00 ml) added slowly over 1 hr, upon complete addition the reaction was allowed to warm to RT and stirred for 36 hr. The reaction was then partitioned between DCM (50.0 ml) and water (50.0 ml) the organic phase was then concentrated to dryness and purified by chromatography (1:1 DCM/40–60 petroleum ether) to yield *cis*-2-(ethynylcyclopentyl)isoindoline-1,3-dione **170** as a white solid, (R_f = 0.15) (5.17 g, 21.60 mmol, 68%); m.p. 73–75 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 3286, 2926, 2855, 1764, 1707, 1612; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, dd, J = 5.5, 3.3 Hz, ArH), 7.65 (2H, dd, J = 5.2, 3.5 Hz, ArH), 4.78 (1H, q, J = 8.8 Hz, PhthNC<u>H</u>), 3.00–2.90 (1H, m, HCCC<u>H</u>CH$_2$), 2.54–2.41 (1H, m, ring proton), 2.21–1.97 (4H, m, ring proton), 1.82 (1H, d, J = 2.3 Hz, <u>H</u>CCCHCH$_2$), 1.52–1.41 (1H, m, ring proton); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 133.9, 131.9, 123.1, 83.2, 71.5, 52.8, 35.8, 33.6, 28.2, 25.3; m/z (APCI) 240.4 (100) (M + H$^+$); $C_{15}H_{13}NO_2$ requires C, 75.30; H, 5.48; N, 5.85, found: C, 75.14; H, 5.47; N, 5.64%.

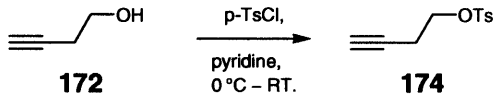
Pent-4-ynyl 4-methylbenzenesulfonate[198] (173)



171 **173**

To a stirred solution of p-toluenesulfonylchloride (34.00 g, 178.00 mmol) in pyridine (60.0 ml) at 0 °C, pent-4-yn-1-ol **171** (10 g, 119.00 mmol) was added drop wise (30 min) and the reaction allowed to reach RT, after 4 hr. TLC showed no starting material and the reaction was quenched with water (100.0 ml) and extracted with diethyl ether (2 x 50.0 ml), the organic portions were then washed with HCl 2M (2 x 50.0 ml) followed by $NaHCO_3$ (2 x 50.0 ml) and finally with brine (50.0 ml). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure to yield pent-4-ynyl 4-methylbenzenesulfonate **173** as a yellow oil, (25.52 g, 107.00 mmol, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8.1Hz, ArH), 7.34 (2H, d, J = 8.1 Hz, ArH) 4.06 (2H, t, J = 7.9 Hz, $OTsC\underline{H}_2$), 2.38 (3H, s, Ts), 2.19 (2H, td, J = 6.9, 2.6 Hz, $HCCC\underline{H}_2$), 1.82–175 (3H, m, $\underline{H}CCCH_2C\underline{H}_2CH_2OTs$).

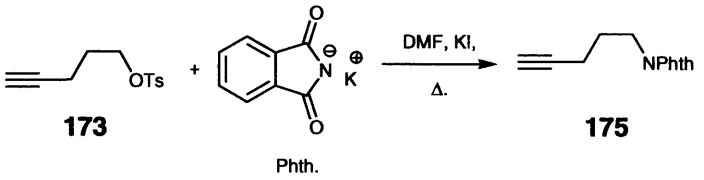
But-3-ynyl 4-methylbenzenesulfonate[198] (174)



172 **174**

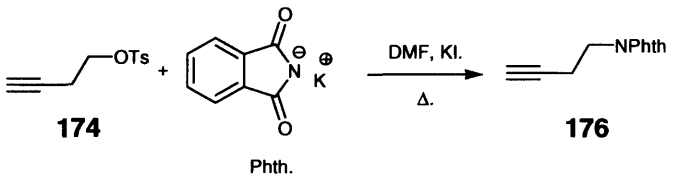
To a stirred solution of p-toluenesulfonylchloride (30.00 g, 157.00 mmol) in pyridine (60.0 ml) at 0 °C, 3-butyn-1-ol **172** (10 g, 143.00 mmol) was added drop wise (30 min) and the reaction allowed to reach RT, after 4 hr. TLC showed no starting material and the reaction was quenched with water (100.0 ml) and extracted with diethyl ether (2 x 50.0 ml), the organic portions were then washed with HCl 2M (2 x 50.0 ml) followed by $NaHCO_3$ (2 x 50.0 ml) and finally with brine (50.0 ml). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure to yield but-3-ynyl 4-methylbenzenesulfonate **174** as a yellow oil, (27.26 g, 122.00 mmol, 85 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, J = 8.3, Hz, ArH), 7.30 (2H, d, J = 8.0 Hz, ArH) 4.03 (2H, t, J = 7.1 Hz, $OTsC\underline{H}_2$), 2.50 (2H, td, J = 7.1, 2.6 Hz, $HCCC\underline{H}_2$), 2.39 (3H, s, OTs), 1.90 (1H, d, J = 2.7 Hz, $\underline{H}CCCH_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$), 145.0, 132.8, 129.9, 128.0, 78.4, 70.8, 67.4, 21.7, 19.5.

2-(Pent-4-ynyl)isoindoline-1,3-dione[208] (175)



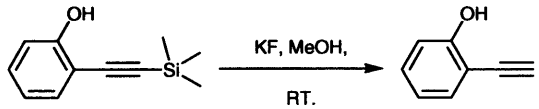
To a stirred solution of pent-4-ynyl 4-methylbenzenesulfonate **173** (7.15 g, 30.00 mmol) in DMF (50.00 ml), potassium phthalimide (6.11 g, 33.00 mmol) and potassium iodide (0.30 g, 1.8 mmol) was added and the reaction mixture heated to reflux for 12 hr. TLC showed all starting material had been consumed and the reaction was diluted with water (250.0 ml). upon dilution the reaction percipitated a white solid that was recrystallised from ethanol to yield 2-(pent-4-ynyl)isoindoline-1,3-dione **175** as a white solid, (3.82 g, 18.00 mmol, 60%); m.p. 87–90 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, dd, J = 5.5, 3.1 Hz, ArH), 7.65 (2H, dd, J = 5.5, 3.1 Hz, ArH), 3.73 (2H, t, J = 7.1 Hz, CH_2NPhal), 2.21 (2H, td, J = 7.1, 2.7 Hz, HCCC$\underline{H}_2$), 1.87–1.83 (3H, m, $\underline{H}$CCCH_2C$\underline{H}_2$CH_2NPhal).

2-(But-3-ynyl)isoindoline-1,3-dione[208] (176)



To a stirred solution of but-3-ynyl 4-methylbenzenesulfonate **174** (14.20 g, 63.31 mmol) in DMF (60.00 ml), potassium phthalimide (12.90 g, 69.65 mmol) and potassium iodide (0.30 g, 1.80 mmol) was added and the reaction mixture heated to reflux for 12 hr. TLC showed all starting material had been consumed and the reaction was diluted with water (500.0 ml). Upon dilution the reaction percipitated a white solid that was recrystallised from ethanol to yield 2-(but-3-ynyl)isoindoline-1,3-dione **176** as a white solid, (8.82 g, 44.31 mmol, 70%); m.p. 135–138 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, dd, J = 5.6, 2.7 Hz, ArH), 7.68 (2H, dd, J = 5.4, 2.5 Hz, ArH), 3.82 (2H, t, J = 7.1 Hz, CH_2NPhal), 2.55 (2H, td, J = 7.1, 2.7 Hz, HCCC$\underline{H}_2$), 1.96 (1H, t, J = 2.6 Hz, $\underline{H}$CCCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 134.3, 134.1, 132.0, 123.6, 132.4, 80.3, 70.3, 36.6, 18.4.

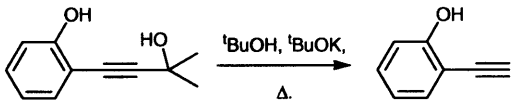
2-Ethynylphenol[199] (177)



179 **177**

To a stirred solution of 2-(2-(trimethylsilyl)ethynyl)phenol **179** (5.00 g, 26.27 mmol) in MeOH (100.00 ml), potassium fluoride (4.56 g, 78.82 mmol) was added and allowed to stir at RT for 3 hr. TLC confirmed completion and the reaction was diluted with diethyl ether (100.0 ml) and washed with water (500.0 ml). The aqueous fraction was again extracted with diethyl ether (2 x 100.0 ml), the organic fractions were combined and washed with brine (100.0 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2-ethynylphenol **177** as a yellow oil, (2.33 g, 19.70 mmol, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, J = 7.6 Hz, ArH), 7.12 (1H, ddd, J = 7.1, 7.1, 1.6 Hz, ArH), 6.80 (1H, ddd, J = 7.2, 7.2, 1.4 Hz, ArH), 6.72 (1H, dd, J = 7.6, 1.5 Hz, ArH), 5.80 (1H, bs, OH), 3.31 (1H, s, HCC).[209]

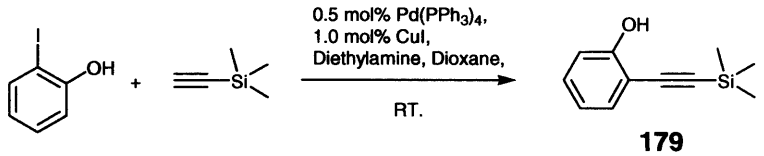
Alternate synthesis of 2-Ethynylphenol[200] (177)



180 **177**

To a solution of 2-(3-hydroxy-3-methylbut-1-ynyl)phenol **180** (5.00 g, 28.38 mmol) in t-butanol (50.00 ml), potassium t-butoxide (0.87 g, 7.09 mmol) was added and the reaction heated to reflux for 3 hr. Upon cooling the reaction mixture was concentrated under reduced pressure, dissolved into DCM (50.0 ml) and washed with water (50.0 ml). The organic layer was then washed with brine (50.0 ml) dried over $MgSO_4$ and concentrated to yield 2-ethynylphenol **177** as a yellow oil, (2.35 g, 19.87 mmol, 70%). Characterisation as before.

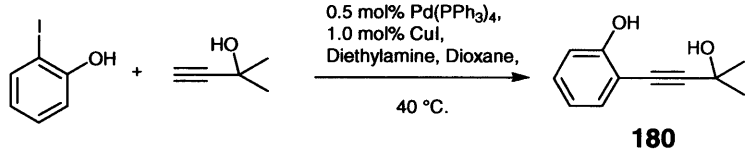
2-(2-(Trimethylsilyl)ethynyl)phenol[199] (179)



178 **159** **179**

To a mixture of 2-iodophenol **178** (10.00 g, 45.45 mmol), tetrakis(triphenylphosphine)palladium(0) (0.263g, 0.227 mmol) and copper iodide (86.56 mg, 0.45 mmol) in DMF (7.00 ml) and diethylamine (35.00 ml) under an atmosphere of nitrogen. Ethynyltrimethylsilane **159** (8.35 ml, 59.09 mmol) was added after stirring for 10 min and left at RT for 6 hr. TLC showed complete reaction and was partitioned between water (500.0 ml) and DCM (250.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with DCM (2 x 250.0 ml). The organic fractions were combined and washed with brine (250.0 ml), dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The oily residue was purified by column chromatography (1:1 ethyl acetate/40-60 petroleum ether) to afford of 2-(2-(trimethylsilyl)ethynyl)phenol **179** as a yellow oil, (8.00 g, 41.81 mmol, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, J = 7.6 Hz, ArH), 7.19 (1H, ddd, J = 8.4, 8.4, 1.6 Hz, ArH), 6.88 (1H, ddd, J = 8.4, 8.4, 1.0 Hz, ArH), 6.80 (1H, dd, J = 7.5, 1.0 Hz, ArH), 5.70 (1H, s, OH), 0.21 (9H, s, $SiMe_3$).[210]

2-(3-Hydroxy-3-methylbut-1-ynyl)phenol[204, 205] (180)

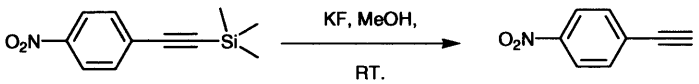


178 **162** **180**

To a mixture of 2-iodophenol **178** (10.00 g, 45.45 mmol), tetrakis(triphenylphosphine)palladium(0) (0.263g, 0.227 mmol) and copper iodide (86.56 mg, 0.45 mmol) in DMF (7.00 ml) diethylamine (35.00 ml) under an atmosphere of nitrogen. 2-Methyl-3-butyn-2-ol **162** (4.89 ml, 50.00 mmol) was added after stirring for 10 min and the reaction heated to 40 °C for 3 hr. TLC showed complete reaction and was partitioned between water (500.0 ml) and DCM (250.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with DCM (2 x 250.0 ml). The organic fractions were combined and washed with brine (250.0 ml), dried over $MgSO_4$ and the filtrate concentrated under reduced

pressure to yield 2-(3-hydroxy-3-methylbut-1-ynyl)phenol **180** as a white solid, (6.81 g, 38.63 mmol, 85%); m.p. 131–133 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 7.5 Hz, ArH), 7.38 (1H, ddd, J = 8.1, 8.1, 1.6 Hz, ArH), 7.06 (1H, ddd, J = 8.2, 8.2, 1.5 Hz, ArH), 6.97 (1H, dd, J = 7.6, 1.2 Hz, ArH), 5.53 (1H, s, ArOH), 2.40 (1H, bs, OH), 1.53 (6H, s, Me_2).

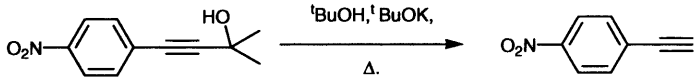
1-Ethynyl-4-nitrobenzene[211] (181)



184 **181**

To a stirred solution of 4-(2-(trimethylsilyl)ethynyl)nitrobenzene **184** (5.0 g, 25.8 mmol) in MeOH (100.0 ml), potassium fluoride (4.53 g 78.00 mmol) was added and allowed to stir at RT for 3 hr. TLC confirmed completion of the reaction and was diluted with diethyl ether (100.0 ml) then washed with water (500.0 ml). The aqueous fraction was again extracted with diethyl ether (2 x 100.0 ml) and the organic fractions were combined and washed with brine (100.0 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 1-ethynyl-4-nitrobenzene **181** as an orange solid, (2.47 g, 16.77 mmol, 65%) m.p. 148–150 °C (EtOH/H_2O), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (2H, d, J = 8.7 Hz, ArH) 7.63 (2H, d, J = 8.6 Hz, ArH), 1.48 (1H, s, CCH).[212]

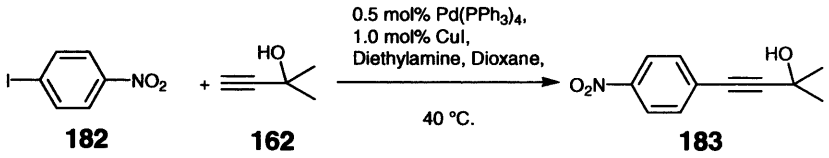
1-Ethynyl-4-nitrobenzene[211] (181)



183 **181**

To a solution of 2-methyl-4-(4-nitrophenyl)but-3-yn-2-ol **183** (5.0 g, 24.36 mmol) in t-butanol (50.0 ml), potassium t-butoxide (0.80 g, 7.13 mmol) was added and the reaction heated to reflux for 3 hr. TLC confirmed completion of the reaction and upon cooling the reaction mixture was concentrated under reduced pressure, dissolved into DCM (50.0 ml) and washed with water (50.0 ml). The organic layer was then washed with brine (50.0 ml) dried over $MgSO_4$ and concentrated to yield 1-ethynyl-4-nitrobenzene as an orange solid **181**, (2.87 g, 19.5 mmol, 80%) m.p. 148–150 °C (EtOH/H_2O). Characterisation as before.

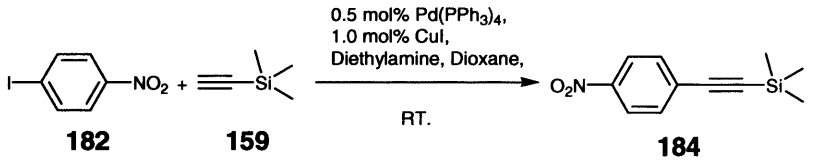
2-Methyl-4-(4-nitrophenyl)but-3-yn-2-ol[204, 205, 213] (183)



182 **162** **183**

To a mixture of 4-iodonitrobenzene **182** (10.00 g, 40.16 mmol), tetrakis(triphenylphosphine)palladium(0) (0.34 g, 0.2 mmol) and copper iodide (0.08 g, 0.40 mmol) in DMF (7.00 ml) and diethylamine (35.00 ml) under an atmosphere of nitrogen. 2-Methyl-3-butyn-2-ol **162** (4.32 ml, 44.2 mmol) was added after stirring for 10 min and the reaction heated to 40 °C for 12 hr. TLC showed complete reaction and was partitioned between water (300.00 ml) and DCM (250.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with DCM (2 x 250.0 ml). The organic fractions were combined and washed with brine (250.0 ml), dried over $MgSO_4$ and the filtrate concentrated under reduced pressure yield a brown solid that was purified by column chromatography (1:1 ethyl acetate/40-60 petroleum ether) to yield 2-methyl-4-(4-nitrophenyl)but-3-yn-2-ol **183** as a brown solid, (6.60 g, 32.13 mmol, 80%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, dd, J = 9.0, 2.0 Hz, ArH), 7.49 (2H, dd, J = 9.0, 2.0 Hz, ArH), 2.06 (1H, bs, OH), 1.57 (6H, s, Me_2).

Trimethyl(2-(4-nitrophenyl)ethynyl)silane[199] (184)

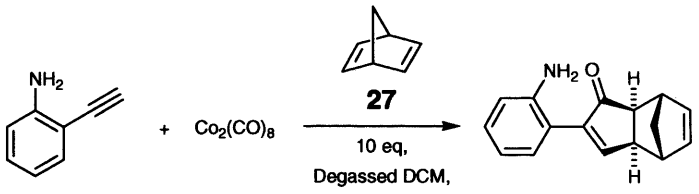


182 **159** **184**

To a mixture of 4-iodonitrobenzene **182** (20.00 g, 80.32 mmol), tetrakis(triphenylphosphine)palladium(0) (0.67 g, 0.4 mmol) and copper iodide (0.15 g, 0.80 mmol) in DMF (15.00 ml) and diethylamine (70.00 ml) under an atmosphere of nitrogen. Ethynyltrimethylsilane **159** (12.49 ml, 88.35 mmol) was added after stirring for 10 min and left at RT for 6 hr. TLC showed complete reaction and was partitioned between water (500.0 ml) and DCM (500.0 ml), the organic layer was removed and the aqueous layer extracted a further twice with DCM (2 x 250 ml). The organic fractions were combined and washed with brine (250 ml), dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (1:1 ethyl acetate/40-60 petroleum ether) to afford trimethyl(2-(4-nitrophenyl)ethynyl)silane **184** as a white solid, (16.20 g, 73.90 mmol,

92%) m.p. 96–98 °C (EtOAc/40-60 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.6 Hz, ArH), 7.53 (2H, d, J = 8.6 Hz, ArH), 0.21 (9H, s, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 130.0, 123.6, 102.7, 100.8, 100.6, -0.11.[214]

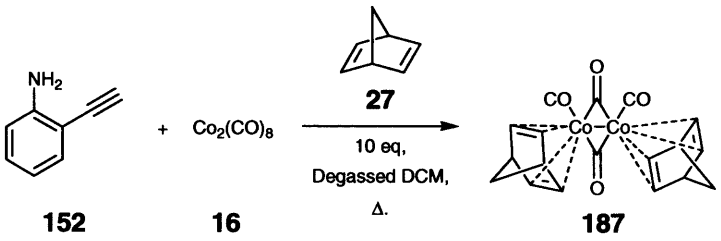
2-(2-Aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[128] (186)



152 **16** **186**

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser was added dicobaltoctacarbonyl **16** (8.72 g, 25.48 mmol), 2-ethynyl aniline **152** (2.71 g, 23.17 mmol) and dry, degassed dichloromethane (100.00 ml) under an inert atmosphere of nitrogen. The mixture was stirred at RT until the dicobalthexacarbonyl alkyne complex was formed as indicated by a high running dark spot TLC spot (ca. 30 min). To the reaction mixture, 2,5-norbornadiene **27** (25.00 ml, 231.70 mmol) was added and the reaction mixture heated to reflux for 3 hr. TLC showed no starting material and the reaction mixture was then filtered to remove the DDCT **187** by-product and the filtrate concentrated to dryness (black/brown solid), this reaction was then worked up following the general PKR procedure and upon purification by chromatography (1:1 diethyl ether/40–60 petroleum ether) yielded 2-(2-aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **186** as a yellow solid, (R_f = 0.3) (3.68 g, 15.52 mmol, 67%); m.p. 103–105 °C (EtOH/ H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 3398–3327, 3056, 1692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, J = 3.0 Hz, H-3), 7.08 (1H, d, J = 7.7 Hz, ArH), 7.04 (1H, ddd, J= 7.5, 7.5, 1.5 Hz, ArH), 6.70 (1H, ddd, J = 7.6, 7.6, 1.0 Hz, ArH), 6.66 (1H, dd, J = 8.0, 1.6 Hz, ArH), 6.30 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.20 (1H, dd, J = 5.5, 3.0 Hz, H-5), 3.98 (2H, bs, NH_2), 2.95 (1H, bs, H-7), 2.86–2.83 (1H, bm, H-7a), 2.78 (1H, bs, H-4), 2.40 (1H, d, J = 5.0 Hz, H-3a), 1.40 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.33 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 163.9, 149.4, 144.8, 138.5, 137.1, 130.1, 129.8, 118.9, 118.8, 117.0, 53.0, 48.2, 44.1, 43.1, 41.4; m/z (APCI) 238.7 (100) (M + H^+); HRMS (ES) $C_{16}H_{16}NO$ requires $[M + H]^+$ 238.1226 found 238.1226; Anal. $C_{16}H_{15}NO$ requires C, 80.98; H, 6.37; N, 5.90. found: C, 80.72; H, 6.37; N, 5.82%.

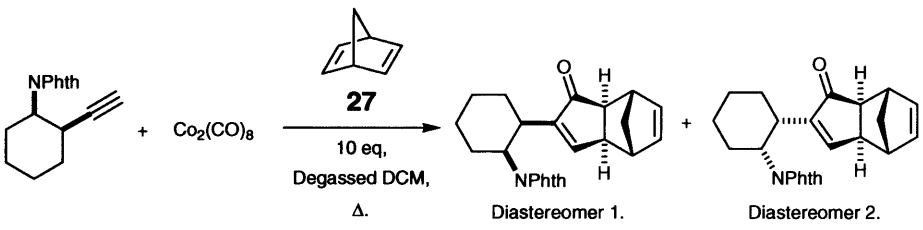
Dinorbornadienedicobalttetracarbonyl[215] (187)



152 **16** **187**

DDCT **187** was a by product from all PK reactions from dicobaltoctacarbonyl **16** (8.71 g, 25.48 mmol) in dry, degassed DCM (100.0 ml) reacting with 2,5-norbornadiene (12.50 ml, 116.00 mmol) at reflux. Upon cooling to RT red crystals formed and were filtered off under an inert atmosphere of nitrogen, the compound was observed as a streaky yellow spot upon TLC in (1:1 diethyl ether/40-60 petrol ether) (R_f = 0.7). The crystals were re-crystallised from diethyl ether and 40-60 petrol to yield dinorbornadienedicobalttetracarbonyl **187** as red crystals (3.16 g, 7.64 mmol, 30%); decomp. 147 °C (Found: C, 52.0; H, 3.8; O, 15.7; Co, 28.6%; M, 414. $C_{18}H_{16}O_4,Co_2$, requires C, 52.2; H, 3.9; 0, 15.5; Co, 28.5%; m/z (EI) 414.0 (100) (M + H^+); Anal. $C_{18}H_{16}Co_2O_4$ requires C, 52.2; H, 3.89. found: C, 52.12; H, 3.84%.

2-(Cyclohexyl)2-isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (198/199)



169 **16** **198** **199**

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (7.43 g, 21.71 mmol), *cis*-2(ethynylcyclohexyl)isoindoline-1,3-dione **169** (5.00 g, 19.74 mmol) in DCM (100.00 ml). 2,5-Norbornadiene **27** (21.30 ml, 197.4 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 6 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded **198** and **199** as a white solid containing a mixture of diastereoisomers in a ratio of 1:1 that were inseparable

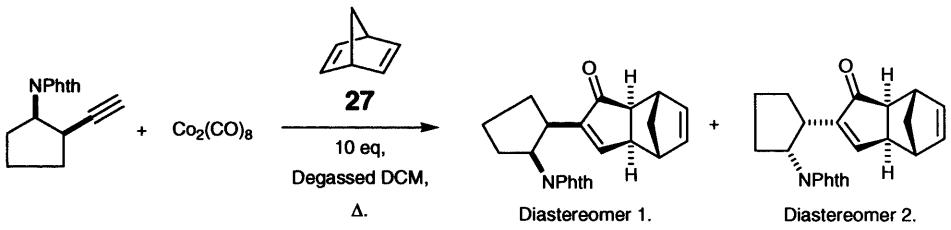
by chromatography[v], (R_f = 0.45) (4.28 g, 11.45 mmol, 58%). FTIR (Film, υ_{max} cm $^{-1}$) 2855, 2242, 1770, 1710, 1614; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (4H, dd, J = 8.2, 2.5 Hz, ArH), 7.64–7.58 (6H, m, ArH + H-3), 6.19 (1H, dd, J = 5.5, 3.0 Hz, H-6) 6.15 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.05 (1H, dd, J = 5.5, 3.0 Hz, H-5) 6.03 (1H, dd, J = 5.5, 3.0 Hz, H-5), 4.48–4.40 (1H, m, CHNPhth), 4.36–4.30 (1H, m, CHNPhth), 3.18 (2H, bs, H-7), 2.69 (2H, bs, H-7a), 2.61–2.59 (4H, bm, C<u>H</u>$_2$CHNPhth), 2.54 (2H, bs, H-4), 2.04 (2H, d, J = 5.0 Hz, H-3a), 2.0–1.0 (14H, m, ring proton), 0.98 (2H, d, J = 9.0 Hz, ½ x H-8-CH_2), 0.82 (2H, d, J = 9.2 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 209.4, 169.0, 161.5, 160.8, 150.5, 149.6, 138.4, 138.3, 137.1, 137.0, 133.8, 133.7, 131.9, 122.9, 122.8, 53.5, 53.3, 51.7, 51.5, 48.1, 43.6, 43.1, 42.9, 41.3, 41.0, 34.4, 33.9, 29.3, 29.0, 26.9, 26.0, 25.5, 25.4, 22.2, 22.0; m/z (APCI) 374 (100) (M + H$^+$); HRMS (ES) $C_{24}H_{24}NO_3$ requires $[M + H]^+$ 374.1751, found 374.1750;

A sample of the product was recrystallised from Et_2O/40–60 petroleum ether and yielded a pure diastereoisomer which was referred to as **198** in this thesis, (2.16 g, 5.73 mmol, 29%); m.p. 140–143 °C. FTIR (Film, υ_{max} cm $^{-1}$) 2855, 2242, 1770, 1710, 1614; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (2H, m, ArH + H-3), 7.60–7.55 (3H, m, ArH), 6.15 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.03 (1H, dd, J = 5.5, 3.0 Hz, H-5), 4.40–4.34 (1H, m, CHNPhth), 3.17–3.14 (1H, m, C<u>H</u>CHNPhth), 2.69 (1H, bs, H-7), 2.60–2.52 (3H, m, H-7a, H-4 + H-3a), 2.0–1.0 (8H, m, ring proton), 0.98 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 0.8 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 169.0, 161.5, 150.5, 138.4, 137.0, 133.8, 131.9, 122.9, 53.3, 51.8, 48.1, 43.6, 42.9, 41.0, 34.4, 29.0, 26.8, 25.6, 22.2.

The relative configuration of isomers **198** and **199** was not determined and the mother liquors were not examined for the second isomer known to be present. "In hind sight, repetition of this work should include examination of the filtrate.

[v] The relative configuration of compounds **198** and **199** was not determined unequivocally see page 46 for discussion.

2-(Cyclopentyl)isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (200/201)



170 **16** **200** **201**

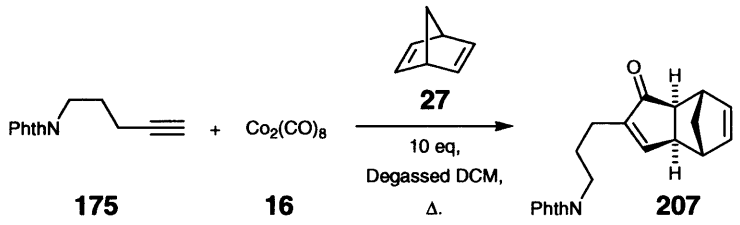
To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (7.86 g, 22.98 mmol), *cis*-2-ethynylcyclopentyl)isoindoline-1,3-dione **195** (5.00 g, 20.89 mmol) in DCM (100.00 ml). 2,5-Norbornadiene **27** (22.54 ml, 208.90 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 6 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded **200** and **201** as a white solid containing a mixture of diastereoisomers in a ratio of 1:1 that were inseparable by chromatography[vi], (R_f = 0.45) (4.50 g, 12.53 mmol, 60%). FTIR (Film, υ_{max} cm $^{-1}$) 2870, 2252, 1770, 1713, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (4H, dd, J = 8.0, 2.0 Hz, ArH), 7.59 (4H, dd, J = 8.2, 2.1 Hz, ArH), 7.13 (1H, d, J = 2.1 Hz, H-3), 7.10 (1H, d, J = 2.1 Hz, H-3), 6.10–5.95 (4H, m, H-6, H-5), 4.98–4.95 (1H, m, CHNPhth), 4.90–4.84 (1H, m, CHNPhth), 3.02–3.00 (2H, m, C<u>H</u>CHNPhth), 2.51 (2H, bs, H-7a) 2.34–2.06 (12H, m, H-7, H-4 + 2 x CH_2 ring proton), 1.92 (2H, d, J = 5.0 Hz, H-3a), 1.86–1.78 (2H, m, CH_2 ring proton), 1.60–1.43, (2H, m, CH_2 ring proton), 1.20 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.03 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 0.59 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 0.42 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 208.8, 168.4, 168.3, 160.9, 159.8, 149.7, 149.4, 138.3, 138.1, 137.0, 136.8, 133.9, 133.8, 131.8, 131.6, 123.0, 122.9, 53.1, 52.3, 52.2, 52.0, 47.9, 47.8, 43.4, 43.2, 43.0, 42.6, 41.2, 40.7, 40.5, 40.4, 31.4, 30.1, 29.8, 28.5, 24.9, 24.4; m/z (APCI) 360 (100) (M + H^+); HRMS (ES) $C_{23}H_{22}NO_3$ requires $[M + H]^+$ 360.1594, found 360.1593.

[vi] The relative configuration of compounds **200** and **201** was not determined unequivocally see page 46 for discussion.

A sample of the product was recrystallised from Et_2O/40–60 petroleum ether and yielded a pure diastereoisomer which was referred to as **200** in this thesis, (2.25 g, 6.26 mmol, 30%) m.p. 111-113 °C. FTIR (Film, υ_{max} cm $^{-1}$) 2870, 2252, 1770, 1713, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, dd, J = 8.0, 2.0 Hz, ArH), 7.59 (2H, dd, J = 8.2, 2.1 Hz, ArH), 7.10 (1H, d, J = 2.1 Hz, H-3), 6.10–5.96 (2H, m, H-6, H-5), 4.96–4.92 (1H, m, CHNPhth), 3.00–2.95 (1H, m, CHCHNPhth), 2.51 (1H, bs, H-7a), 2.34–2.06 (6H, m, H-7, H-4 + 2 x CH_2 ring proton), 1.92 (1H, d, J = 5.0 Hz, H-3a), 1.86–1.78 (1H, m, CH_2 ring proton), 1.60–1.43, (1H, m, CH_2 ring proton), 1.20 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2), 1.03 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 168.4, 160.9, 149.7, 138.1, 136.8, 133.9, 131.8, 123.0, 53.1, 52.3, 47.9, 43.2, 42.6, 41.2, 40.4, 31.4, 29.8, 24.9.

The relative configuration of isomers **200** and **201** was not determined and the mother liquors were not examined for the second isomer known to be present. "in hind sight, repetition of this work should include examination of the filtrate.

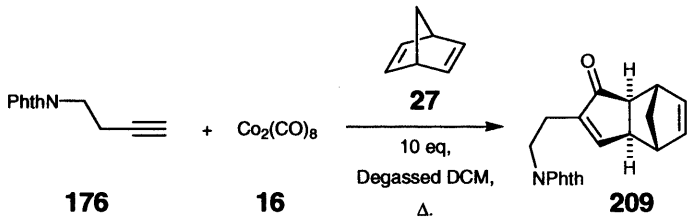
2-(Propyl)isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (207)



To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (4.23 g, 12.38 mmol), 2-(pent-4-ynyl)isoindoline-1,3-dione **175** (2.40 g, 11.23 mmol) in DCM (50.00 ml). 2,5-Norbornadiene **27** (12.12 ml, 112.30 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 6 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(propyl)isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **207** as a white solid, (R_f= 0.16) (2.62 g, 7.86 mmol, 72%); m.p. 106–108 °C (EtOH/H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, ddd, J = 8.3, 8.3, 3.2 Hz, ArH), 7.65 (2H, dd, J = 8.3, 3.2, Hz, ArH), 7.20 (1H, s, H-3), 6.20 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.12 (1H, dd, J= 5.5, 3.0

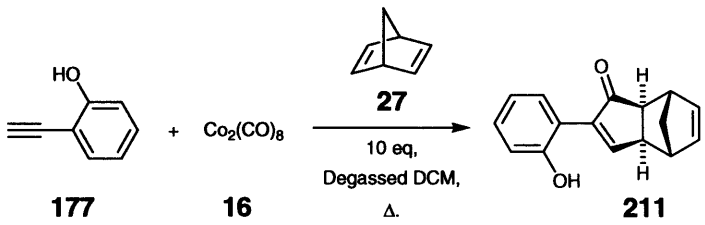
Hz, H-5), 3.63 (2H, t, J = 7.1 Hz, CH_2NPhth), 2.83 (1H, bs, H-7), 2.67–2.63 (1H, bm, H-7a), 2.60 (1H, bs, H-4), 2.21 (1H, dd, J = 5.0, 1.0 Hz, H-3a), 2.16 (2H, t, J = 7.8 Hz, $C\underline{H}_2CH_2CH_2NPhth$), 1.82 (2H, qintet, J = 14.5, 7.2 Hz, $CH_2C\underline{H}_2CH_2NPhth$), 1.30 (1H, d, J = 9.3 Hz, ½ x H-8-CH_2), 1.13 (1H, d, J = 9.4 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 168.4, 159.5, 149.2, 138.4, 137.0, 134.0, 132.0, 123.3, 52.5, 47.8, 43.7, 43.0, 41.2, 37.5, 26.5, 22.3; m/z (EICI) 334.3 (100) ($M + H^+$); HRMS $C_{21}H_{20}NO_3$ requires 334.1438 $[M + H]^+$, found 334.1437.

2-(Ethyl)isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (209)



To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (4.72 g, 13.80 mmol), 2-(pent-4-ynyl)isoindoline-1,3-dione **176** (2.50 g, 12.55 mmol) in DCM (50.00 ml). 2,5-Norbornadiene **27** (13.68 ml, 125.50 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 6 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(ethyl)isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **209** as a white solid, (R_f = 0.14) (2.73 g, 8.53 mmol, 68%); m.p. 126–128 °C (EtOH/H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, ddd, J = 7.7, 7.7, 3.1 Hz ArH), 7.64 (2H, dd, J = 7.7, 3.0 Hz, ArH), 7.18 (1H, s, H-3), 6.18 (1H, bs, H-6), 6.10 (1H, bs, H-5), 3.80 (2H, t, J = 6.4 Hz, CH_2NPhth), 2.81 (1H, bs, H-7), 2.62 (1H, bs, H-7a), 2.56–2.48 (3H, m, H-4 + $C\underline{H}_2CH_2NPhth$), 2.21 (1H, d, J = 4.4 Hz, H-3a), 1.27 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2) 1.10 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 168.2, 160.3, 147.0, 138.4, 137.1, 134.0, 132.0, 123.3, 52.3, 48.0, 45.3, 43.6, 42.9, 36.3, 24.3; m/z (APCI) 320.3 (100) ($M + H^+$); HRMS $C_{20}H_{18}NO_3$ requires 320.1281 $[M + H]^+$, found 320.1280.

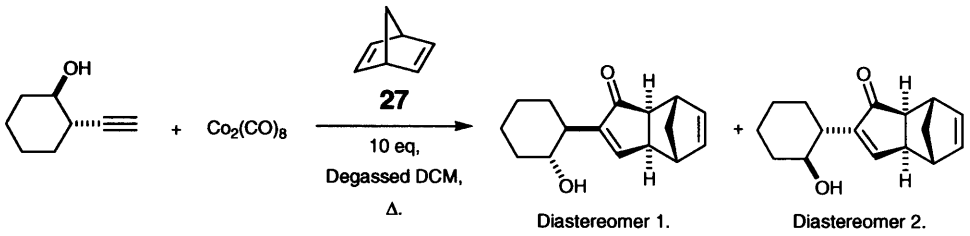
2-(2-Phenol) -3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (211)



177 **16** **211**

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (22.29 g, 65.18 mmol), 2-ethynylphenol **177** (7.00 g, 59.26 mmol) in DCM (280.00 ml). 2,5-Norbornadiene **27** (63.94 ml, 592.6 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 6 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(2-Phenol)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **211** as a white solid, (R_f = 0.4) (7.77 g, 32.60 mmol, 55%); m.p. 108–110 °C (EtO_2/40–60 petroleum ether). FTIR (Film, υ_{max} cm^{-1}) 3325, 3061, 2909, 2887, 2855, 1915, 1909, 1670, 1625; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (1H, s, OH), 7.73, (1H, d, J = 3.0 Hz, H-3), 7.25 (1H, d, J = 7.6 Hz, ArH), 7.19 (1H, ddd, J = 8.0, 8.0, 1.6 Hz, ArH), 6.91 (1H, ddd, J = 8.2, 8.2, 1.0 Hz, ArH), 6.81 (1H, dd, J = 7.7, 1.1 Hz, ArH), 6.30 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.20 (1H, dd, J = 5.5, 3.0 Hz, H-5), 2.97 (1H, bs, H-7), 2.91–2.87 (1H, bm, H-7a), 2.75 (1H, bs, H-4), 2.51 (1H, d, J = 4.7 Hz, H-3a), 1.41 (1H, d, J = 9.6 Hz, ½ x H-8-CH_2), 1.30 (1H, d, J = 9.6 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 164.8, 155.1, 148.8, 138.6, 137.0, 131.0, 128.9, 120.3, 119.4, 118.6, 53.5, 48.8, 44.2, 43.0, 41.3; m/z (EICI) 239.0 (100) (M + H^+); HRMS (ES) $C_{16}H_{15}O_2$ requires 239.1067 $[M + H]^+$,found 239.1068. $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92. found: C, 80.75; H, 6.0; N, 0.15%.

***Trans*-2-(2-cyclohexanol)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (213/214)**



167 **16** **213** **214**

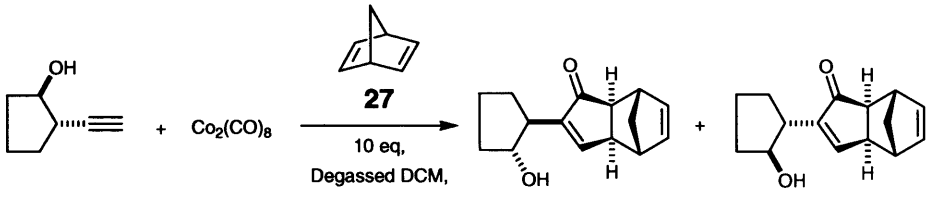
To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (3.03 g, 8.86 mmol), *trans*-2-ethynyl-cyclohexanol **167** (1.00 g, 8.05 mmol) in DCM (36.00 ml). 2,5-Norbornadiene **27** (8.69 ml, 80.5 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded **213** and **214** as a white solid containing a mixture of diastereoisomers in a ratio of 1:1 that were inseparable by chromatography [vii],(R_f = 0.35) (1.28 g, 5.23 mmol, 65%); m.p. 142-144 °C. FTIR (Film, υ_{max} cm $^{-1}$) 3432, 3060, 2930, 2855, 2238, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (2H, d, J = 2.6 Hz, H-3), 6.22 (2H, dd, J = 5.6, 3.1 Hz, H-6), 6.14 (2H, dd, J = 5.6, 3.0 Hz, H-5), 3.44–3.38 (2H, m, C<u>H</u>OH), 2.83 (2H, bs, H-7), 2.70–2.65 (2H, bm, H-7a), 2.61 (2H, bs, H-4), 2.26–2.20 (4H, m, H-3a + CH_2 ring proton), 2.14 (2H, bs, OH), 2.00–1.97 (2H m, C<u>H</u>CHOH), 1.72–1.58 (6H, m, CH_2 ring proton), 1.30–1.10 (12H, m, H-8-CH_2 + CH_2 ring proton); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 210.7, 159.5, 159.4, 152.9, 152.7, 138.4, 138.3, 137.1, 137.0, 74.5, 73.7, 52.9, 52.8, 47.9, 47.8, 43.8, 43.7, 43.1, 43.0, 42.9, 42.8, 41.2, 41.1, 36.1, 36.0, 31.0, 30.6, 25.5, 25.4, 24.9, 24.8; m/z (EICI) 245.0 (100) (M + H$^+$); HRMS (ES) $C_{16}H_{21}O_2$ requires 245.1536 [M + H]$^+$,found 245.1533.

A sample of the product was recrystallised from EtOAc/Hexane and yielded a pure diastereoisomer which was referred to as **213** in this thesis, (0.64 g, 2.61 mmol, 32%); m.p. 142-144 °C. FTIR (Film, υ_{max} cm $^{-1}$) 3432, 3060, 2930, 2855, 2238, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 2.6 Hz, H-3), 6.22 (1H, dd, J = 5.6, 3.1 Hz, H-6), 6.14 (1H, dd, J = 5.6, 3.0 Hz, H-5), 3.44–3.40 (1H, m, C<u>H</u>OH), 2.83 (1H,

[vii] The relative configuration of compounds **213** and **214** was not determined unequivocally see page 46 for discussion.

bs, H-7), 2.70–2.66 (1H, bm, H-7a), 2.61 (1H, bs, H-4), 2.30–2.20 (2H, m, H-3a + CH_2 ring proton), 2.13 (1H, bs, OH), 2.00–1.95 (1H m, C<u>H</u>CHOH), 1.73–1.52 (3H, m, CH_2 ring proton), 1.30–1.10 (6H, m, H-8-CH_2 + CH_2 ring proton); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 159.4, 152.6, 138.4, 137.1, 73.6, 52.8, 47.9, 43.7, 43.0, 42.8, 41.1, 36.0, 31.0, 25.5, 24.8.

Trans-2-(2-cyclopentanol)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (216/217)



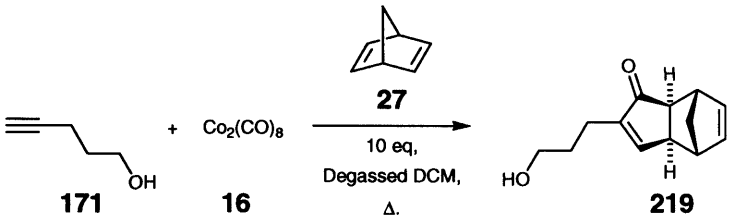
168 **16** **216** **217**

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (3.12 g, 9.99 mmol), *trans*-2-ethynyl-cyclopentanol **168** (1.00 g, 9.08 mmol) in DCM (40.00 ml). 2,5-Norbornadiene (9.80 ml, 90.8 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded **216** and **217** as a white solid containing a mixture of diastereoisomers in a ratio of 1:1 that were inseparable by chromatography [viii], (R_f = 0.34) (1.28 g, 5.53 mmol, 61%); m.p. 119–121 °C. FTIR (Film, υ_{max} cm^{-1}) 3427, 3060, 2966, 2873, 2338, 1694, 1619; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (2H, d, J = 2.0 Hz, H-3), 6.23 (2H, dd, J = 5.5, 3.1 Hz, H-6), 6.15 (2H, dd, J = 5.6, 2.9 Hz, H-5), 4.08–3.86 (2H, m, C<u>H</u>OH), 2.85 (2H, bs, H-7), 2.69 (2H, bs, H-7a), 2.62 (2H, bs, H-4), 2.56–2.47 (2H, bm, C<u>H</u>CHOH), 2.29 (2H, d, J = 5.0 Hz, H-3a), 1.96–1.93 (4H, m, OH + CH_2 ring proton), 1.82–1.41 (10H, m, CH_2 ring proton), 1.21 (4H, 2 x d, J = 9.3 Hz, H-8-CH_2) ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 212.3, 159.3, 159.1, 152.4, 152.3, 138.5, 138.4, 137.1, 137.0, 78.0, 77.6, 53.0, 52.9, 48.1, 47.9, 46.7, 46.6, 43.7, 42.9, 42.8, 41.2, 41.1, 34.0, 33.9, 29.0, 28.9, 22.8, 22.7; m/z (EICI) 248.1 (100) (M + NH_4^+); HRMS (ES) $C_{15}H_{22}NO_2$ requires 248.1645 $[M + NH_4]^+$, found 248.1643.

[viii] The relative configuration of compounds **216** and **217** was not determined unequivocally see page 46 for discussion.

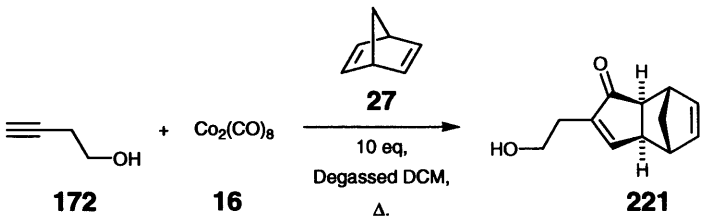
A sample of the product was recrystallised from EtOAc/Hexane and yielded a pure diastereoisomer which was referred to as **213** in this thesis, (0.64 g, 2.76 mmol, 31%); m.p. 119–121 °C. FTIR (Film, υ_{max} cm $^{-1}$) 3427, 3060, 2966, 2873, 2338, 1694, 1619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, J = 2.0 Hz, H-3), 6.23 (1H, dd, J = 5.4, 2.0 Hz, H-6), 6.15 (1H, dd, J = 5.6, 2.9 Hz, H-5), 4.08–3.86 (1H, m, C<u>H</u>OH), 2.85 (1H, bs, H-7), 2.69 (1H, bs, H-7a), 2.62 (1H, bs, H-4), 2.54–2.48 (1H, bm, C<u>H</u>CHOH), 2.29 (1H, d, J = 5.0 Hz, H-3a), 1.96–1.93 (2H, m, OH + CH_2 ring proton), 1.82–1.41 (5H, m, CH_2 ring proton), 1.21 (2H, 2 x d, J = 9.3 Hz, H-8-CH_2) ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 159.1, 152.3, 138.4, 137.0, 77.6, 52.9, 47.9, 46.6, 43.7, 42.9, 41.2, 33.9, 28.9, 22.7.

2-(2-Hydroxypropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[216] (219)



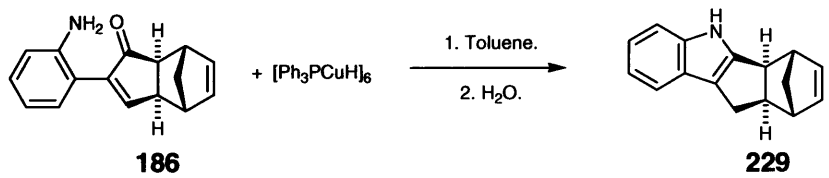
To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (13.41 g, 39.23 mmol), 4-pentyn-1-ol **171** (3.34 ml, 35.66 mmol) in DCM (160.00 ml). 2,5-Norbornadiene **27** (38.50 ml, 356.60 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-(2-hydroxypropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **219** as a yellow oil, (R_f = 0.48) (4.59 g, 22.47 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, J = 2.5 Hz, H-3), 6.22 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.14 (1H, dd, J= 5.6, 3.0 Hz, H-5), 3.54 (2H, t, J = 6.2 Hz, CH_2OH), 2.84 (1H, bs, H-7) 2.69–2.65 (1H, bm, H-7a) 2.61 (1H, bs, H-4), 2.26–2.20 (3H, m, C<u>H</u>$_2$$CH_2CH_2OH$ + H3a), 2.02 (1H, s, OH), 1.66 (2H, qintet, J = 7.0 Hz, CH_2C<u>H</u>$_2$$CH_2OH$), 1.33 (1H, dd, J = 9.2, 1.4 Hz, ½ x H-8-CH_2), 1.14 (1H, dd, J = 8.7, 1.2 Hz, ½ x H-8-CH_2); m/z (APCI) 205 (100) (M + H^+).

2-(2-Hydroxyethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[217] (221)



To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser and inert atmosphere of nitrogen was added dicobaltoctacarbonyl **16** (5.37 g, 15.70 mmol), 3-butyn-1-ol **172** (1.08 ml, 14.27 mmol) in DCM (65.00 ml). 2,5-Norbornadiene **27** (15.40 ml, 142.70 mmol) was then added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-(2-hydroxyethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **221** as a yellow oil, (R_f = 0.5) (1.60 g, 8.42 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 1.0 Hz, H-3), 6.22 (1H, dd, J = 5.4, 3.1 Hz, H-6), 6.14 (1H, dd, J = 5.4, 2.9 Hz, H-5), 3.66 (2H, t, J = 7.5 Hz, CH_2OH), 2.84 (1H, bs, H-7) 2.68–2.65 (1H, bm, H-7a) 2.62 (1H, bs, H-4), 2.57 (1H, bs, OH), 2.40 (2H, t, J = 6.0 Hz, $C\underline{H}_2CH_2OH$), 2.24 (1H, d, J = 5.0 Hz, H-3a), 1.32 (1H, d, J = 9.3 Hz, ½ x H-8-CH_2), 1.16 (1H, d, J = 9.4 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 160.8, 146.9, 137.4, 136.0, 60.1, 51.5, 47.0, 42.6, 41.8, 40.1, 28.3; m/z (APCI) 191 (100) ($M + H^+$).

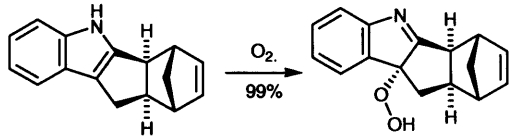
1,4,4a,5,10,10a-Hexahydro-1,4-methanoindeno[1,2b] indole[128] (229)



To a flame dried (50.0) ml Schlenk flask containing Stryker's reagent (0.33 g, 0.17 mmol) under an inert atmosphere of nitrogen, toluene (5.00 ml) was added and the mixture stirred during the addition of 2-(2-aminophenyl)- 3a,4,7,7a-tetrahydro-4,7-methano inden-1-one **186** (0.10 g, 0.42 mmol). H_2O (0.15 ml) was then added and the reaction sealed and stirred for 16 hr at RT. The reaction mixture was then evaporated to dryness under reduced pressure and purified by column

chromatography (1:1 Et_2O/40–60 petroleum ether) to yield 1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] indole **229** as a white solid, (R_f = 0.37) (63.00 mg, 0.29 mmol, 68%); m.p. 76–78 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm^{-1}) 3397, 3053, 2923, 2853; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, bs, NH), 7.33 (1H, dd, J = 6.7, 1.6 Hz, H-6), 7.21 (1H, dd, J = 6.4, 1.6 Hz, H-9), 7.05–7.00 (2H, m, H-7 + H-8), 6.10–6.04 (2H, m, H-2 + H-3), 3.00 (1H, d, J = 6.9 Hz, H-4a), 2.97–2.85 (2H, m, H-10), 2.78 (1H, bs, H-1), 2.65 (1H, bs, H-4), 2.35 (1H, td, J = 14.3, 2.4 H-10a), 1.34–1.30 (2H, m, H-11-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.8, 137.6, 137.2, 124.9, 121.5, 120.7, 119.5, 118.6, 111.4, 50.2, 48.3, 46.1, 45.6, 42.5, 29.2; m/z (APCI) 222 (100) (M + H^+); HRMS (ES) $C_{16}H_{16}N$ $[M + H]^+$ requires 222.1277, found 222.1276.

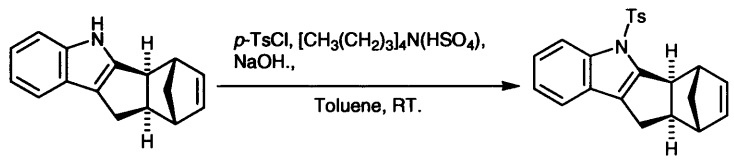
Imino-hydroperoxide of 1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] indole[128] (230)



229 **230**

1,4,4a,5,10,10a-Hexahydro-1,4-methanoindeno[1,2b] indole **229** (0.071g, 2.80 mmol) as a white solid reacted with oxygen in air to yield Imino-hydroperoxide of 1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] indole **230** as a white solid, (71.00 mg, 0.28 mmol, 99%); m/z (APCI) 254 (100) (M + H^+).

1-Tosyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] indole[218] (231)

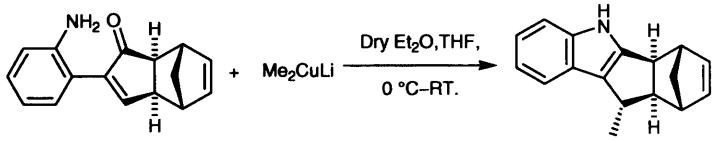


229 **231**

To a (50 ml) RB flask, under a nitrogen atmosphere 1,4,4a,5,10,10a-Hexahydro-1,4-methanoindeno[1,2b] indole **229** (1.00 g, 4.52 mmol) was dissolved in toluene (30.00 ml), t-butylammonium hydrogen sulphate (0.15 g, 0.44 mmol) and 50% aqueous sodium hydroxide (6.00 ml) was then added. After 10 min a solution of p-toluene sulphonyl chloride (0.95 g, 4.97 mmol) in toluene (20.00 ml) was added slowly to the reaction mixture and allowed to stir overnight at RT, TLC confirmed

complete reaction and a colour change from yellow to green solution observed. The reaction mixture was quenched with water (30.0 ml), partition between water / toluene (100.0ml/100.0ml). Followed by brine (50.0 ml) wash and the organic phase dried over $MgSO_4$. The filtrate was then concentrated under reduced pressure to yield 1-tosyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] indole **231** as a white solid, (1.27 g, 3.39 mmol, 75%); m.p. 128–130 °C ($EtOH/H_2O$). FTIR (Film, υ_{max} cm $^{-1}$) 3691, 3155, 3064, 2980, 2855, 2250, 1793; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, J = 8.4 Hz, ArH), 7.18–7.12 (6H, m, ArH), 6.24 (1H, dd, J = 5.5, 3.0 Hz, H-3), 6.09 (1H, dd, J = 5.5, 3.0 Hz, H-2), 3.28–3.23 (2H, m, H-10), 2.85–2.80 (2H, m, H-4 + H-4a), 2.64 (1H, bs, H-1), 2.26–2.21 (4H, m, H-10a + Ts), 1.34 (2H, 2 x d, J = 9.0 Hz, H-11-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 143.7, 140.3, 138.3, 137.0, 135.6, 129.8, 129.0, 127.4, 126.6, 123.8, 119.1, 114.7, 48.9, 48.8, 48.7, 46.4, 42.0, 29.7, 28.7, 21.6; m/z (APCI) 376 (100) ($M + H^+$); HRMS (ES) $C_{23}H_{22}NO_2S$ $[M + H]^+$ requires 376.1366, found 376.1366.

10-Methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole[219, 128] (232)

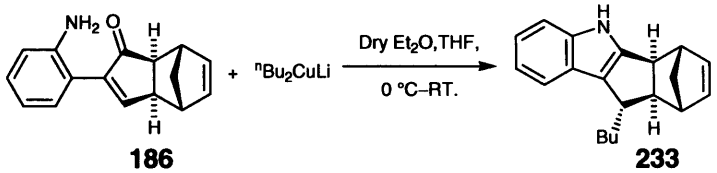


186 **232**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (0.22 g, 1.15 mmol) in dry Et_2O (2.00 ml) at 0 °C was added a solution of methyl lithium in Et_2O (1.60 M, 1.44 ml, 2.30 mmol) and stirred with cooling for 1 hr. After this time 2-(2-aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methano inden-1-one **186** (0.18 g, 0.76 mmol) was added as a solution in Et_2O/THF (2.00 ml/2.00 ml), the reaction mixture was allowed to warm to RT and stirred for 12 hr. This mixture was then diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50.0 ml). The organic layers were then dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure to yield 10-methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] **232** as a brown solid, (0.16 g, 0.70 mmol, 92%); m.p. 170–173 °C ($EtOH/H_2O$). FTIR (Film, υ_{max} cm $^{-1}$) 3375, 3053, 2958, 2864, 1796, 1673; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, bs, NH), 7.36 (1H, dd, J = 7.0, 1.7 Hz, H-6), 7.22 (1H, dd, J = 7.0, 1.8 Hz, H-9), 7.02–6.95 (2H, m, H-7 + H-8), 6.10–6.02 (2H, m, H2 + H3), 3.05 (1H, d, J = 7.0 Hz, H-4a), 2.83–2.76 (1H, m, H-10), 2.75 (1H,

bs, H-1), 2.69 (1H, bs, H-4), 2.33 (1H, dd, J = 7.1, 2.8 Hz, H-10a), 1.30 (5H, overlapped dd + s, H-11-CH_2 + Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.8, 137.6, 137.2, 126.5, 124.5, 120.7, 119.4, 118.4, 111.4, 60.1, 47.5, 45.7, 45.4, 43.0, 38.0, 22.5; m/z (EICI) 235.2 (100) (M^+); HRMS (EI) $C_{17}H_{17}N$ $[M]^+$ requires 235.1356, found 235.1353.

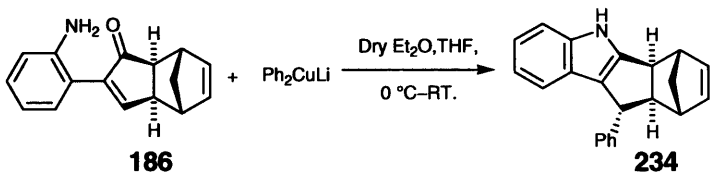
10-Butyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole[128, 219](233)



186 **233**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (0.15 g, 0.80 mmol) in dry Et_2O (2.00 ml) at 0 °C was added a solution of n-butyllithium in Et_2O (1.6 M, 1.00 ml, 1.60 mmol) and stirred with cooling for 1 hr. After this time 2-(2-aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methano inden-1-one **186** (0.10 g, 0.42 mmol) was added as a solution in Et_2O/THF (2.00 ml/2.00 ml), the reaction mixture was allowed to warm to RT and stirred for 12 hr. The reaction was then diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50.0 ml) and dried over $MgSO_4$, filtered then evaporated to dryness to yield 10-butyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole **233** as a brown solid, (82.00 mg, 0.29 mmol, 70%); m.p. 236–238 °C ($EtOH/H_2O$). FTIR (Film, υ_{max} cm^{-1}) 3404, 3045, 2951, 2871, 1790, 1685; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, bs, NH), 7.40 (1H, dd, J = 7.0, 1.5 Hz, H-6), 7.22 (1H, dd, J = 7.0, 1.5 Hz, H-9), 7.04–6.98 (2H, m, H-7 + H-8), 6.12–6.05 (2H, m, H2 + H3), 3.42–6.36 (2H, bm, ^{n}Bu), 3.03 (1H, d, J = 6.6 Hz, H-4a), 2.75–2.70 (2H, bm, H-1 + H10), 2.65 (1H, bs, H-4), 2.41 (1H, dd, J = 7.0, 2.4 Hz, H-10a), 1.80–1.71 (1H, m, ^{n}Bu), 1.51–1.29 (5H, m, ^{n}Bu + H-11-CH_2), 0.86 (3H, t, J = 7.1 Hz, ^{n}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.8, 137.7, 137.1, 125.0, 124.8, 120.6, 119.4, 118.9, 111.4, 57.6, 48.0, 45.5, 45.4, 43.7, 42.9, 37.1, 30.1, 23.1, 14.2; m/z (EICI) 277.4 (100) (M^+).

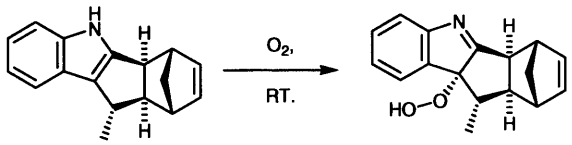
10-Phenyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole[128, 219](234)



186 **234**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (0.22 g, 1.15 mmol) in dry Et_2O (2.00 ml) at 0 °C was added a solution of phenyl lithium in Bu_2O (1.60 M, 1.44 ml, 2.31 mmol) and stirred with cooling for 1 hr. After this time 2-(2-aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methano inden-1-one **186** (0.18 g, 0.76 mmol) was added as a solution in Et_2O/THF (2.00 ml/2.00 ml), the reaction mixture was allowed to warm to RT and stirred for 12 hr. The reaction was then diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50 ml) and the organic layer dried over $MgSO_4$, filtered then evaporated to dryness under reduced pressure to yield 10-phenyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole **234** as a brown solid, (0.17 g, 0.56 mmol, 74%); m.p. 224–226 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 3335, 3062, 3968, 2251, 1791, 1678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, bs, NH), 7.86 (1H, d, J = 8.0 Hz, H-6), 7.23–7.08 (6H, m, Ph + H-7), 6.74 (1H, t, J = 7.5, H-8), 6.42 (1H, dd J = 7.5, 1.3 Hz, H-9), 6.18 (1H, dd J = 5.6, 3.0 Hz, H-2), 6.08 (1H, dd, J = 5.6, 3.0 Hz, H-3), 2.95–2.90 (2H, bm, H-4a + H-10), 2.76 (1H, bs, H-1), 2.53 (2H, d, J = 6.9 Hz, H-4 + H-10a), 1.90 (1H, d, J = 8.6 Hz, ½ x H-11-CH_2), 1.45 (1H, d, J = 8.6 Hz, ½ x H-11-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 147.5, 146.5, 137.0, 136.5, 135.2, 134.6, 129.8, 127.3, 127.1, 126.6, 126.0, 123.4, 122.6, 121.1, 85.9, 55.0, 52.0, 43.1, 41.8, 41.7, 23.5; m/z (EICI) 297.3 (100) $(M)^+$.

Imino-hydroperoxide of 10-methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b][128, 219](235)



232 **235**

10-Methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole **232** (0.16 g, 0.70 mmol) reacted with oxygen in the air to yield Imino-hydroperoxide of 10-methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] **235** as a white solid (0.15 g, 0.56 mmol). The sample reacted whilst waiting for X-ray determination of 10-Methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b]indole **232**.

Crystallography.

Crystal data for 150: $C_{17}H_{17}NO_2$, M = 267.32, Monoclinic,

a = 20.4996(7), b = 9.0822(4), c = 16.6153(7)A ° , V = 2728.70(19) A ° 3,

space group C2/c, Z = 8, Dc = 1.301 Mg/m^3, l(Mo Ka) = 0.085 mm_1,

T = 150(2) K, 8496 measured reflections, 2807 independent,

[Rint = 0.0702] R1 = 0.1141, wR_2 = 0.1321 (all data) R_1 = 0.0650,

wR_2 = 0.1138 [I > 2sigma(I)] GOF = 1.034; the data were collected

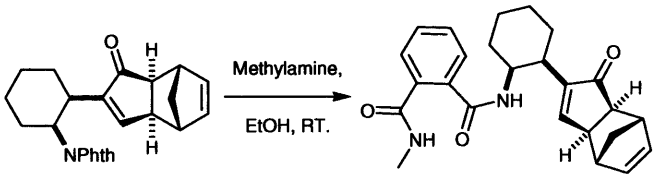
on a Nonius Kappa CCD with Mo Ka radiation (k = 0.71073 A °),

adsorption effects were calculated empirically. Full structural parameters

have been deposited at the Cambridge Crystallography Data

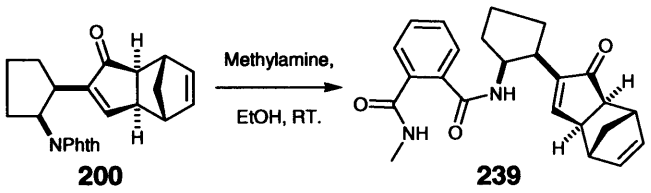
Collection CCDC No. 237829; m/z (APCI) 254.3 $[(M + H)^+$, 50%].

N^1-Methyl-N^2-(2-(3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one)cyclohexyl)phthalimide (238)



To a single diastereomer of 2-(cyclohexyl)2-isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **198** (1.00 g, 2.68 mmol), 33% methylamine in ethanol (40.00 ml, 321.00 mmol) was added an the reaction stirred at RT for 36 hr. TLC showed no starting material in the reaction, only a white precipitate that was filtered off. The filtrate was then partitioned between DCM (100.0 ml) and sodium hydrogen carbonate (sat) (100.0 ml). The aqueous was extracted twice more with DCM (2 x 50.0 ml) and the organic extracts washed with brine (50.0 ml), dried over $MgSO_4$ and filtered. The resulting filtrate was concentrated under reduced pressure to yield a yellow solid that was purified by chromatography (2:1 ethyl acetate 40-60petroleum ether) to yield N^1-methyl-N^2-(2-(3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one)cyclohexyl)phthalimide **238** as a white solid, (R_f = 0.5) (0.36 g, 0.89 mmol, 55%); m.p. 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.43 (2H, m, ArH), 7.38–7.32 (2H, m, ArH), 7.24 (1H, d, J = 7.9 Hz, ArCONH), 7.12 (1H, d, J = 2.4 Hz, H-3), 6.76 (1H, bs, ArCONHMe), 6.15 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.09 (1H, dd, J = 5.5, 2.9 Hz, H-5), 4.31 (1H, q, J = 7.7, 3.4 Hz, NHCHCH$_2$), 2.89 (3H, d, J = 4.8 Hz, NHMe), 2.81 (1H, bs, H-7), 2.65 (1H, d, 12.1 Hz, CHCHNH), 2.59 (1H, bs, H-7a), 2.44 (1H, bs, H-4), 2.18 (1H, d, 5.0 Hz, H-3a), 1.87 (1H, dd, J = 11.5, 3.1 Hz, CH_2 ring proton), 1.74 (1H, d, J = 12.5 Hz, CH_2 ring proton) 1.60–1.56 (4H, m, CH_2 ring proton), 1.36–1.29 (2H, m, CH_2 ring proton), 1.17 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2), 1.05 (1H, d, J = 9.3 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 170.3, 168.1, 160.2, 151.3, 138.4, 137.1, 134.6, 134.3, 130.2, 130.0, 128.6, 128.2, 52.6, 48.1, 47.8, 43.8, 43.0, 41.0, 37.3, 30.5, 26.8, 25.4, 25.2, 20.4; ; m/z (EICI) 405.8 (100) (M + H^+).

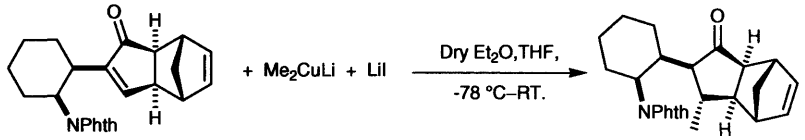
N^1-Methyl-N^2-(2-(3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one)cyclopentyl)phthalamide (239)



200 **239**

To a single diastereomer of 2-(cyclohexyl)2-isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **200** (1.00 g, 2.78 mmol), 33% methylamine in ethanol (40.00 ml, 321.00 mmol) was added an the reaction stirred at RT for 36 hr. TLC showed no starting material in the reaction mixture and the white precipitate that formed in the reaction was filtered off, the filtrate was then partitioned between DCM (100.0 ml) and sodium hydrogen carbonate (sat) (100.0 ml). The aqueous was extracted twice more with DCM (2 x 50.0 ml) and the organic extracts washed with brine (50.0 ml), dried over $MgSO_4$ and filtered, the resulting filtrate was concentrated under reduced pressure to yield yellow solid that was purified by chromatography (2:1 ethyl acetate /40-60 petroleum ether) to yield N^1-methyl-N^2-(2-(3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one)cyclopentyl)phthalimide **239** as a white solid, (R_f = 0.48) (0.27 g, 0.69 mmol, 25%); 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (2H, m, ArH), 7.42–7.35 (2H, m, ArH), 7.25 (1H, d, J = 7.9 Hz, ArCONHCHCH$_2$), 7.15 (1H, d, J = 2.4 Hz, H-3), 6.76 (1H, bs, NHMe), 6.20 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.12 (1H, dd, J = 5.5, 2.9 Hz, H-5), 4.43 (1H, q, J = 7.7, 3.4 Hz, NHCHCH$_2$), 3.02 (3H, d, J = 4.8 Hz, ArCONHMe), 2.90 (1H, bs, H-7), 2.71 (1H, d, 12.1 Hz, CHCHNH), 2.63 (1H, bs, H-7a), 2.48 (1H, bs, H-4), 2.26 (1H, d, 5.0 Hz, H-3a), 1.90 (1H, dd, J = 11.5, 3.1 Hz, CH_2 ring proton), 1.76 (1H, d, J = 12.3 Hz, CH_2 ring proton) 1.41–1.35 (4H, m, CH_2 ring proton), 1.16 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2), 1.10 (1H, d, J = 9.0 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 169.3, 168.5, 160.7, 150.5, 138.2, 137.5, 134.2, 133.6, 130.1, 129.8, 128.4, 128.0, 52.8, 48.2, 47.7, 43.5, 43.4, 41.2, 37.5, 30.8, 26.2, 25.6, 20.1; m/z (APCI) 391.8 (100) (M + H^+).

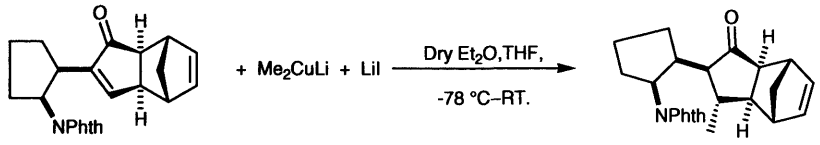
2-(Cyclohexyl)isoindoline-3methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (240)



198 **240**

To a dried Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (0.14 g, 0.74 mmol) in dry Et_2O (2.00 ml) at -78 °C was added a solution of methyl lithium in Et_2O (1.60 M, 0.93 ml, 1.48 mmol) and stirred for 1 hr. A single diastereoisomer of 2-(cyclohexyl)2-isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **198** (0.18 g, 0.49 mmol) was added as a solution in Et_2O/THF (2.00 ml/2.00 ml), the reaction mixture was allowed to warm to RT and stirred for12 hr. The reaction mixture was then diluted with Et_2O (50.0 ml) and washed with $NH_4Cl_{(sat)}$ (3 x 50.0 ml). The ethereal layer was separated and dried over $MgSO_4$ and evaporated to dryness and to yield 2-(cyclohexyl)isoindoline-3methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **240** as a white solid, (0.12 g, 0.29 mmol, 60%); m.p. 122–124 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 2845, 1769, 1731, 1709, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (2H, m, ArH), 7.63–7.59 (2H, m, ArH), 6.03 (1H, dd, J = 5.0, 3.1 Hz, H-6), 5.90 (1H, dd, J = 5.2, 3.0 Hz, H-5), 4.57–4.54 (1H, m, C<u>H</u>NPhth) 2.88 (1H, bs, H-7), 2.63 (1H, bs, H-7a), 2.54–2.40 (1H, m, C<u>H</u>CHNPhth), 2.28 (1H, d, J = 11.1 Hz, H-4), 2.07 (1H, d, J = 11.0 Hz, H-3a), 2.00–1.85 (4H, m, CH_2 ring proton), 1.76–1.70 (1H, m, H-2), 1.68 (1H, t, J = 11.1 Hz, H-3), 1.56–1.40 (2H, m, CH_2 ring proton), 1.30–1.20 (3H, m, ½ x H-8-CH_2 + CH_2 ring proton), 1.16 (3H, d, J = 7.0 Hz, Me), 0.95 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 170.2, 138.3, 137.6, 133.6, 132.2, 122.9, 63.2, 54.2, 50.7, 47.9, 47.0, 44.8, 44.7, 41.9, 38.9, 30.2, 26.5, 22.5, 22.0, 20.9; m/z (APCI) 390 (100) (M + H$^+$); HRMS (ES) $C_{25}H_{28}NO_3$ requires [M + H]$^+$ 390.2064, found 390.2068.

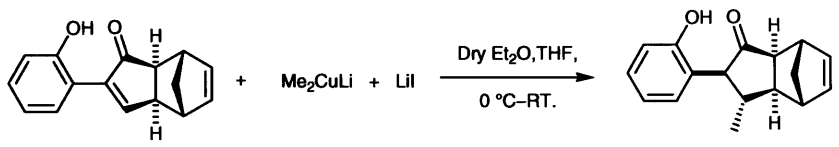
2-(Cyclopentyl)isoindoline-3methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (241)



200 **241**

To a dried (200 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (0.111 g, 0.581 mmol) in dry Et_2O (2.00 ml) at -78 °C was added a solution of methyl lithium in Et_2O (1.60 M, 0.73 ml, 1.16 mmol) and stirred for 1 hr. After this time a single diastereoisomer of 2-(cyclopentyl)2-isoindoline-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **200** (0.14 g, 0.39 mmol) isomer was added as a solution in Et_2O/THF (2.00 ml/2.00 ml), the reaction mixture was allowed to warm to RT and stirred for 12 hr. The mixture was then diluted with Et_2O (50.0 ml) and washed with $NH_4Cl_{(sat)}$ (3 x 50.0 ml). The ethereal layer was separated and dried over $MgSO_4$ and the filtrate evaporated to dryness and to yield 2-(cyclopentyl)isoindoline-3methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **241** as a white solid, (0.07 g, 0.20 mmol, 50%); m.p. 127–129 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm^{-1}) 2958, 2868, 2255, 1770, 1713, 1709, 1614; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.71 (2H, m, ArH), 7.62–7.59 (2H, m, ArH), 6.03 (1H, dd, J = 5.0, 3.1 Hz, H-6), 5.94 (1H, dd, J = 5.0, 3.0 Hz, H-5), 4.62–4.59 (1H, m, C<u>H</u>NPhth), 2.87 (1H, bs, H-7), 2.62 (1H, bs, H-7a), 2.51 (1H, d, J = 12.1 Hz, H-4), 2.35–2.26 (1H, m, C<u>H</u>CHNPhth), 2.24–2.13 (1H, m, H-3a), 2.10–1.90 (4H, m, CH_2 ring proton), 1.69 (1H, t, J = 7.7 Hz, H-2), 1.65–1.50 (2H, m, CH_2 ring proton), 1.48–1.38 (1H, m, H-3), 1.21 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2), 1.15 (3H, d, J = 6.6 Hz, Me), 0.95 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 169.8, 138.2, 137.5, 133.6, 132.3, 122.8, 59.0, 55.2, 54.3, 48.1, 46.9, 46.6, 44.8, 44.7, 40.6, 28.1, 25.3, 23.9, 20.9; m/z (EICI) 376.2 (100) (M + H^+); HRMS (ES) $C_{24}H_{26}NO_3$ requires $[M + H]^+$ 376.1907, found 376.1906.

2-(2-Phenol)-3 methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (246)

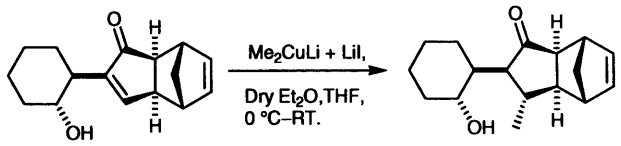


211 **246**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (1.20 g, 6.30 mmol) in dry Et_2O (25.00 ml) at 0 °C was added a solution of methyl lithium in Et_2O (1.6 M, 7.90 ml, 12.60 mmol) and stirred with cooling for 1 hr. After this time 2-(2-phenol)-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **211** (1.00 g, 4.20 mmol) was added as a solution in Et_2O/THF (5.00 ml/5.00 ml), the reaction mixture was allowed to warm to RT and stirred for 20 hr. The mixture was then diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50 ml), the organic layers was then dried over $MgSO_4$ and the filtrate evaporated to dryness to yield a white solid that was purified by chromatography (1:1 ethyl acetate/40-60 petroleum ether) yielding 2-(2-phenol)-3methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **246** as a white solid[ix], (R_f = 0.4) (0.43 g, 1.68 mmol, 40%); m.p. 133–135 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 3356, 2993, 2891, 2856, 1925, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, ddd, J = 7.5, 7.5, 1.3 Hz, ArH), 6.91 (1H, d, J = 7.5 Hz, ArH), 6.85 (1H, ddd, J = 7.5, 7.5, 0.9 Hz, ArH), 6.72 (1H, dd, J = 7.5, 1.2 Hz, ArH), 6.15 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.13 (1H, dd, J = 5.6, 3.0 Hz, H-5), 5.50 (1H, bs, OH), 3.60 (1H, dd, J = 12.4, 1.8 Hz, H-2) 3.15 (1H, bs, H-7), 2.78 (1H, bs, H-7a), 2.43 (1H, d, J = 8.7 Hz, H-4), 2.04 (1H, qintet, J = 6.4 Hz, H-3), 1.94 (1H, t, J = 8.1 Hz, H-3a), 1.39 (1H, dd, J = 9.1, 1.3 Hz, ½ x H-8-CH_2), 1.37 (1H, dd, J = 9.1, 1.3 Hz, ½ x H-8-CH_2), 1.13 (3H, d, J = 6.5 Hz, Me); m/z (APCI) 255.5 (100) $(M + H)^+$.

[ix] The relative configuration of isomer **246** has not been determined unequivocally see page 46 and 60 for discussion.

2-(2-Cyclohexanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (248)

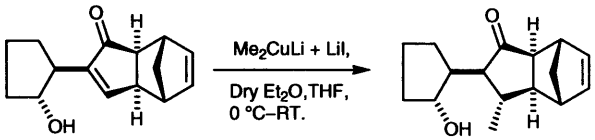


213 **248**

To a dried Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (1.20 g, 6.30 mmol) in dry Et_2O (25.00 ml) at 0 °C was added a solution of methyl lithium in Et_2O (1.6 M, 7.90 ml, 12.60 mmol) and stirred with cooling for 1 hr. After this time a single diastereoisomer of 2-(2-cyclohexanol)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **213** (1.0 g, 4.09 mmol) was added as a solution in Et_2O/THF (5.00 ml/5.00 ml), the reaction mixture was allowed to warm to RT and stirred for 20 hr. The mixture was then diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50.0 ml) dried over $MgSO_4$ and the filtrate evaporated to dryness to yield a brown oil that was purified by chromatography (1:1 ethyl acetate/40-60 petroleum ether) to yield 2-(2-cyclohexanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **248** as a pale yellow oil[x], (R_f = 0.46) (0.53 g, 2.04 mmol, 50%); FTIR (Film, υ_{max} cm $^{-1}$) 3397, 3062, 2960, 2867, 2247, 1726, 1634; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.07 (1H, dd, J = 5.5, 3.0 Hz, H-5), 3.40–3.36 (1H, bm, CHOH) 3.06 (1H, bs, H-7), 2.73 (1H, dt, J = 9.5, 2.3 Hz, H-2), 2.70 (1H, bs, H-7a), 2.24 (1H, d, J = 8.7 Hz, H-4), 1.96–1.90 (1H, bm, H-3), 1.83–1.50 (5H, m, OH + CH_2 ring proton + H-3a), 1.41–1.34 (2H, bm, CH_2 ring proton), 1.30 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2), 1.24 (3H, d, J = 6.3 Hz, Me), 1.19–1.16 (4H, m, CH_2 ring proton), 1.03 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 138.5, 137.8, 72.3, 60.8, 54.4, 49.0, 47.1, 45.1, 44.8, 43.8, 37.2, 36.6, 27.5, 25.8, 25.2, 22.6;m/z (APCI) 261.5 (100) (M + H^+); HRMS (ES) $C_{17}H_{25}O_2$ requires 261.1849 $[M + H]^+$, found 261.1848.

[x] The relative configuration of isomer **248** has not been determined unequivocally see page 46 and 60 for discussion.

2-(2-Cyclopentanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (249)

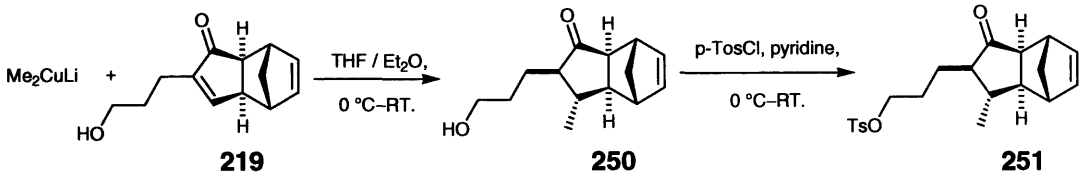


216 **249**

To a dried Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (1.20 g, 6.30 mmol) in dry Et_2O (25.00 ml) at 0 °C was added a solution of methyl lithium in Et_2O (1.6 M, 7.9 ml, 12.60 mmol) and stirred with cooling for 1 hr. After this time a single diastereoisomer of 2-(2-cyclopentanol)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **216** (0.94 g, 4.09 mmol) was added as a solution in Et_2O/THF (5.00 ml/5.00 ml), the reaction mixture was allowed to warm to RT and stirred for 20 hr. The mixture was then diluted Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50.0 ml) dried over $MgSO_4$ and the filtrate evaporated to dryness to yield a brown oil that was purified by chromatography, (1:1 ethyl acetate/40-60 petroleum ether) to yield 2-(2-cyclopentanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **249** as a pale yellow oil[xi], (R_f = 0.38) (0.49 g, 2.00 mmol, 49%); FTIR (Film, υ_{max} cm $^{-1}$) 3418, 3059, 2956, 2871, 1726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.08 (1H, dd, J = 5.5, 3.1 Hz, H-5), 3.91–3.84 (1H, bm, C<u>H</u>OH), 3.05 (1H, bs, H-7), 2.70 (1H, bs, H-7a), 2.50 (1H, ddd, J = 5.5, 1.3 Hz, H-2), 2.30 (1H, d, J = 9.0 Hz, H-4), 2.20–2.16 (1H, bm, H-3), 2.00–1.00 (14H, m, H-3a + OH+ CH_2 ring proton, H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.8, 138.3, 137.4, 69.1, 61.8, 58.3, 49.5, 47.2, 46.8, 44.8, 44.7, 35.6, 27.2, 25.3, 23.6, 22.6; (m/z (APCI) 247.3 (100) (M + H^+).

[xi] The relative configuration of isomer **249** has not been determined unequivocally see page 46 and 60 for discussion.

2-(Pentyl-4-methylbenzenesulfonate)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (251)



219 **250** **251**

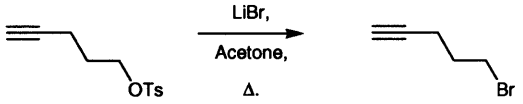
To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen containing a slurry of copper iodide (1.20 g, 6.30 mmol) in dry Et_2O (25.00 ml) at 0 °C was added a solution of methyl lithium in Et_2O (1.6 M, 7.90 ml, 12.6 mmol) and stirred with cooling for 1 hr. After this time 2-(2-Hydroxypropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **219** (0.84 g, 4.09 mmol) was added as a solution in Et_2O/THF (5.00 ml/5.00 ml), the reaction mixture was allowed to warm to RT and stirred for 20 hour. The mixture was the diluted with Et_2O (50.0 ml) and washed with NH_4Cl (sat) (3 x 50.0 ml), dried over $MgSO_4$ and the filtrate evaporated to dryness to yield a yellow oil that was further purified by chromatography (1:1 ethyl acetate/ 40-60 petroleum ether) to yield a pale yellow oil 2-(2-butanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **250** (R_f = 0.35) (0.48 g, 2.17 mmol, 53%); ^1H NMR resulted in the desired product with unknown impurities in that were un able to be removed by chromatography, so this was further purified by making the tosylate of the alcohol.

2-(2-butanol)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **250**, (0.48 g, 2.18 mmol) was then added to a stirred solution of p-toluenesulfonylchloride (0.62 g, 3.27 mmol) in pyridine (10.00 ml) at 0 °C, the reaction was then allowed to warm to RT, after 4 hr the reaction was quenched with water (50.0 ml) and extracted with diethyl ether (2 x 50.0 ml), the organic portions were then washed with HCl 2M (2 x 50.0 ml) followed by $NaHCO_3$ (2 x 50.0 ml), the resulting organic layer was washed with brine (50.0 ml) and dried over $MgSO_4$, the filtrate was then concentrated under reduced pressure to yield a yellow oil, that was further purified using chromatography (ethyl acetate/ 40-60 petroleum ether) to yield 2-(2-propyl 4-methylbenzenesulfonate)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **251** as a yellow oil[xii], (R_f= 0.48) (0.65 g, 1.74 mmol, 80%); FTIR (Film, υ_{max}

[xii] The relative configuration of isomer **251** has not been determined unequivocally see page 46 and 60 for discussion.

cm $^{-1}$) 3059, 2956, 2870, 1729; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (2H, dd, J = 6.6, 1.7 Hz, ArH), 7.27 (2H, d, J = 7.9 Hz, ArH), 6.10 (1H, dd, J = 5.7, 3.0 Hz, H-6), 6.05 (1H, dd, J = 5.7, 3.0 Hz, H-5), 3.95 (2H, sextet, J = 3.4 Hz, C$\underline{H_2}$OTs), 3.02 (1H, bs, H-7), 2.64 (1H, bs, H-7a), 2.38 (3H, s, OTs), 2.20 (1H, d, J = 9.2 Hz, H-4), 2.04–1.98 (1H, m, H-2), 1.77–1.72 (2H, m, C$\underline{H_2}$$CH_2CH_2$OTs), 1.58–1.54 (1H, m, H-3), 1.48–1.42 (1H, m, H-3a), 1.38–1.33 (1H, m, ½ x C$\underline{H_2}$$CH_2$OTs), 1.30 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2), 1.24–1.18 (1H, m, ½ x C$\underline{H_2}$$CH_2$OTs), 1.13 (3H, d, J = 6.6 Hz, Me), 0.92 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 144.7, 138.3, 137.4, 133.1, 129.9, 127.9, 70.8, 59.8, 54.2, 48.6, 46.5, 44.9, 44.3, 39.9, 31.6, 26.3, 23.2, 22.7, 21.7, 20.8; m/z (APCI) 375.5 (100) (M + H$^+$);

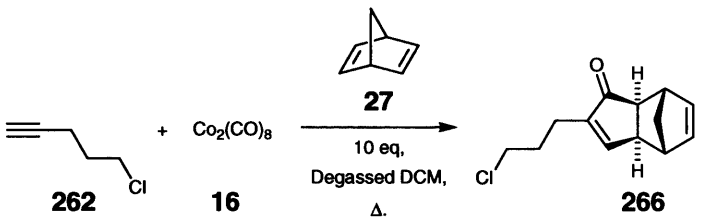
5-Bromopent-1-yne [198] (261)



173 **261**

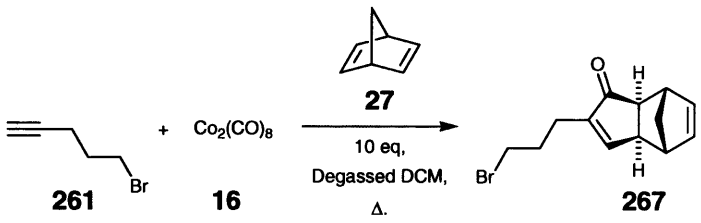
To a dried (200 ml) round bottom flask, lithium bromide (8.39 g, 42.00 mmol) was added to dry acetone (150.00 ml, dried over potassium carbonate), pent-4-yn-1-yltoluene-*p*-sulphonate **173** (5.00 g, 21.0 mmol) was then added slowly to the reaction mixture and refluxed for 5 hr, whilst being followed by T.L.C (20% diethyl ether/petroleum ether). The reaction was quenched with water (20.0 ml) and the desired compound extracted with 40-60 petroleum ether (50.0 ml x 3), the organic extracts were dried over $MgSO_4$, filtered and concentrated to yield 5-bromopent-1-yne **261** as a yellow oil (2.13 g, 14.49 mmol, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (2H, t, J = 6.7 Hz, $BrCH_2$) 2.36–2.29 (2H, m, C$\underline{H_2}$CCH) 2.06–2.01 (3H, m, $BrCH_2C\underline{H_2}CH_2CC\underline{H}$); m/z (APCI) 148.3 (100) (M + H$^+$).

2-(3-Chloro-propyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one[220] (266)



To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 5-chloropent-1-yne **262** (2.07 ml, 19.50 mmol) and dicobaltoctacarbonyl **16** (7.33 g, 21.45 mmol) in DCM (50.00 ml). 2-5-Norbornadiene (21.04 ml, 195.00 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-(3-chloro-propyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one **266** as a clear oil, (2.78 g, 12.48 mmol, 64%); FTIR (Film, υ_{max} cm $^{-1}$) 2920, 2362, 1684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, bs, H-3), 6.23 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.18 (1H, dd, , J = 5.5, 3.0 Hz, H-5), 3.26 (2H, t, J = 6.2 Hz, CH_2Cl) 2.90 (1H, s, H-7), 2.70–2.65 (1H, bm, H-7a), 2.66 (1H, bs, H-4), 2.31–2.24 (3H, m, H3a + $C\underline{H}_2CH_2CH_2Cl$), 1.98 (2H, q, J = 7.1 Hz, $CH_2C\underline{H}_2CH_2Cl$), 1.33 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2), 1.12 (1H, d, J = 9.2 Hz, ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 159.6, 148.8, 138.8, 137.2, 52.6, 47.2, 43.5, 42.7, 41.0, 31.4, 26.3, 6.5; m/z (APCI) 224.0 (100) (M + H$^+$).

2-(3-Bromo-propyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one[220] (267)



To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 5-bromopent-1-yne **261** (2.00 g, 13.60 mmol) and dicobaltoctacarbonyl **16** (5.12 g, 14.96 mmol) in DCM (60.00 ml). 2-5-Norbornadiene (14.6 ml, 136.00 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The

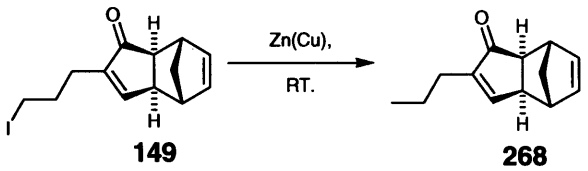
reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-(3-bromo-propyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one **267** as a clear oil, (R_f = 0.5) (2.22 g, 8.30 mmol, 61%); FTIR (Film, υ_{max} cm $^{-1}$) 2932, 2365, 1694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, bs, H-3), 6.23 (1H, dd, J = 5.5, 3.0 Hz, H-6,) 6.17 (1H, dd, , J = 5.5, 3.0 Hz, H-5), 3.21 (2H, t, J = 6.1 Hz, CH_2Br), 2.86 (1H, s, H-7), 2.68–2.65 (1H, bm, H-7a), 2.64 (1H, bs, H-4), 2.30–2.22 (3H, m, H-3a + $C\underline{H}_2CH_2CH_2Br$) 1.99 (2H, q, J = 7.2 Hz, $CH_2C\underline{H}_2CH_2Br$), 1.32 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2), 1.10 (1H, d, J = 9.1 Hz ½ x H-8-CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$), 210.2, 160.3, 149.2, 138.8, 137.4, 53.0, 47.9, 43.8, 43.1, 41.5, 31.0, 26.5, 6.2; m/z (APCI) 268.3 (100) (M + H^+).

Zinc/copper couple[135]

$$Zn_{(m)} + CuSO_4.5H_2O \longrightarrow ZnCu$$

To an Erlenmeyer flask under a nitrogen atmosphere containing zinc powder (49.2 g, 0.75 mol) and 3% hydrochloric acid (40.0 ml). The mixture was stirred rapidly for 1 min, then the supernatant liquid decanted. Similarly, the zinc powder was washed successively with three additional portions of 3% hydrochloric acid (40.0 ml), five portions of distilled water (100.0 ml), two portions of 2% aqueous copper sulphate (75.0 ml) solution. This was then washed with five portions of distilled water (100.0 ml), four portions of absolute ethanol (100.0 ml), and finally five portions of anhydrous diethyl ether (100.0 ml). The couple was finally transferred to a Büchner funnel and washed with an additional portion of anhydrous diethyl ether (50.0 ml). The solid was then placed in a Schlenk tube and suction-dried until it reached RT. The zinc-copper couple was stored under vacuum.

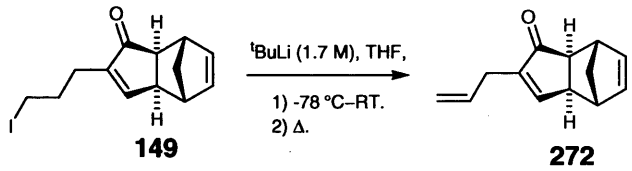
2-(Butyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (268)



149 **268**

To a Round bottom flask under a nitrogen atmosphere, containing a stirred mixture of zinc/copper couple (0.42g, 6.40 mmol), dry toluene (14.00 ml) and dry DMF (2.00 ml), 2-(3-iodopropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **149** (1.00 g, 3.20 mmol) was added and stirred at RT for 1 hr, followed by reflux for 4 hr. The reaction mixture was then quenched with 1M HCl (50.0 ml) and the reaction mixture extracted with diethyl ether (50.0 ml), the aqueous layer was extracted a further twice with diethyl ether (50.0 ml) combined, then washed with brine (50.0 ml) and dried over $MgSO_4$, the filtrate was then concentrated to yield 2-(butyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one **268** as a pale yellow oil, (0.48 g, 2.56 mmol, 80%); FTIR (Film, υ_{max} cm $^{-1}$) 2942, 2341, 1705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.02 (1H, bm, H-3), 6.21 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.13 (1H, dd, J = 5.5, 3.0 Hz H-5), 2.84 (1H, bs, H-7), 2.64–2.60 (1H, bm, H-7a), 2.60 (1H, bs, H-4), 2.20 (1H, d, J = 5.0 Hz, H-3a) 2.10–2.03 (2H, m, $C\underline{H}_2CH_2Me$), 1.43 (2H, q, J = 7.5 Hz, $CH_2C\underline{H}_2Me$), 1.30 (1H, dd, J = 9.1, 1.4 Hz, ½ x H-8-CH_2), 1.14 (1H, dd, J = 9.1, 1.4 Hz, ½ x H-8-CH_2), 0.85 (3H, t, 7.5 Hz, Me); m/z (APCI) 189.3 (100) (M + H$^+$); HRMS (ES) $C_{13}H_{16}O$ requires 189.1234 [M + H]$^+$, found 189.1236.

2-(3-Vinylbutyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (272)

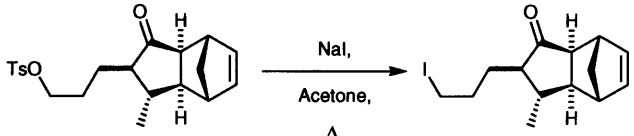


149 **272**

To a solution of 2-(3-iodopropyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **149** (1.00 g, 3.18 mmol) in THF (4.00 ml) under a nitrogen atmosphere and cooled to -100 °C, t-butyllithium in pentane (3.00 ml, 1.70 M, 5.10 mmol) was added drop wise and allowed to warm to RT for 1hr. The reaction was then refluxed for 20 hr and cooled to RT, then quenched with NH_4Cl (sat) (50.0 ml) and extracted with ethyl acetate (2 x 50.0 ml), the organic fractions were then washed with brine (50.0

ml) and dried over $MgSO_4$, the filtrate was then concentrated to yield a yellow oil that was further purified by chromatography (1:1 ethyl acetate/40-60 petroleum ether) to yield the product 2-(3-vinylbutyl)-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one **272** as a yellow oil, (R_f = 0.36) (0.47 g, 2.54 mmol, 80%); FTIR (Film, υ_{max} cm $^{-1}$) 3063, 2985, 2877, 1692, 1700,1641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.11 (1H, bm, H-3), 6.22 (1H, dd, J = 5.5, 3.0 Hz, H-6), 6.13 (1H, dd, , J = 5.5, 3.0 Hz H-5), 5.78 (1H, ddt, J = 17.0, 10.1, 6.8 Hz, $COCCH_2C\underline{H}CH_2$), 5.04 (2H, m, $COCCH_2CHC\underline{H_2}$), 2.87–2.83 (3H, m, H-7 + $COCC\underline{H_2}CHCH_2$), 2.66–2.60 (1H, bm, H-7a), 2.61 (1H, bs, H-4), 2.24–2.20 (1H, m, H-3a), 1.31 (1H, d, J = 9.2 Hz, , ½ x H-8-CH_2), 1.14 (1H, d, J = 9.2 Hz, , ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 159.6, 148.8, 138.4, 137.0, 134.5, 116.8, 52.5, 47.8, 43.7, 43.0, 41.2, 29.5; m/z (APCI) 187.0 (100) (M + H^+); HRMS (ES) $C_{13}H_{15}O$ requires 187.117 $[M + H]^+$, found 187.117.

2-(Iodopenty)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (273)



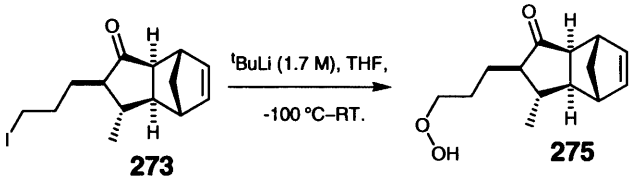
251 **273**

To a mixture of 2-(pentyl-4-methylbenzenesulfonate)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **251** (1.50 g, 4.00 mmol) in dry acetone (20.0 ml) sodium iodide (0.66 g , 4.40 mmol) was added and refluxed for 5 hr. The reaction was then quenched with water (50.0 ml) and organics extracted with diethyl ether (50.0 ml x 3), the organic portions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and the filtrate concentrated under reduced pressure to yield 2-(iodopenty)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **273** as a yellow oil[xiii], (1.06 g, 3.2 mmol, 80%); FTIR (Film, υ_{max} cm $^{-1}$) 2957, 2868, 1731, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.06 (1H, dd, J = 5.6, 3.0 Hz, H-5), 3.12 (2H, td, J = 7.0, 1.6 Hz, CH_2I), 3.05 (1H, bs, H-7), 2.67 (1H, bs, H-7a), 2.24 (1H, d, J = 9.1 Hz, H-4), 2.10–2.04 (1H, m, H-2), 1.96–1.92 (2H, m, $C\underline{H_2}CH_2I$), 1.79–1.75 (2H, m, $C\underline{H_2}CH_2CH_2I$), 1.61–1.30 (3H, m, H-3 + H3a + , ½ x H-8-CH_2), 1.17 (3H, d, J = 6.7 Hz, Me), 0.98 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); ^{13}C

[xiii] The relative configuration of compounds **273**, **275**, **276** and **277** has not been determined unequivocally see page 46 and 60 for discussion.

NMR (100 MHz, $CDCl_3$) δ 216.8, 137.3, 136.4, 58.7, 53.1, 46.3, 45.5, 43.3, 42.5, 39.0, 29.8, 27.3, 19.8, 6.0; m/z (APCI) 331.0 (100) ($M + H^+$).

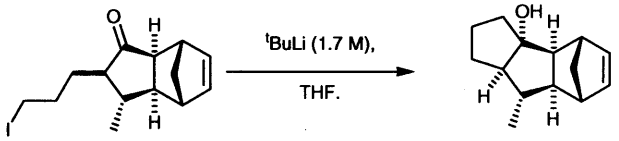
2-(Hydroperoxypenty)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (275)



273 **275**

Another compound identified from the purification of *cis*-2-hydroxy-3-methyl-1,2,3,3a,3b,4,7,7a,8,8a-decahydro-4,7-methanocyclopentaindene **276**, was a compound with higher polarity by TLC (R_f = 0.7), 2-(hydroperoxypenty)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **275** was isolated as a yellow oil (0.07 g, 0.30 mmol, 20%); FTIR (Film, υ_{max} cm^{-1}) 3454.6, 3057.3, 2958.5, 2841.7, 1690; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00–5.92 (2H, m, H-6 + H-5), 3.88 (2H, td, J = 4.0, 1.5 Hz, $C\underline{H}_2OOH$), 2.74– 2.68(1H, bm, H-7), 2.47 (1H, bs, H-7a), 2.40 (1H, d, J = 7.3 Hz, H-4), 1.95–1.90 (2H, m, $CH_2C\underline{H}_2CH_2OOH$), 1.74–1.68 (3H, m, $C\underline{H}_2CH_2CH_2OOH$ + H-2), 1.59–1.52 (2H, m, H-3 + H-2), 1.40 (1H, d, J = 8.5 Hz, H-3a), 1.24 (1H, d, J = 8.5 Hz, ½ x H-8-CH_2), 1.01–0.95 (4H, bm, Me + ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 137.2, 137.1, 66.8, 50.6, 49.1, 47.4, 43.6, 43.5, 43.0, 42.2, 22.2, 21.3, 20.2; m/z (APCI) 237.0 (100) ($M + H^+$).

2-Hydroxy-3-methyl-1,2,3,3a,3b,4,7,7a,8,8a-decahydro-4,7-methanocyclopentaindene (276)

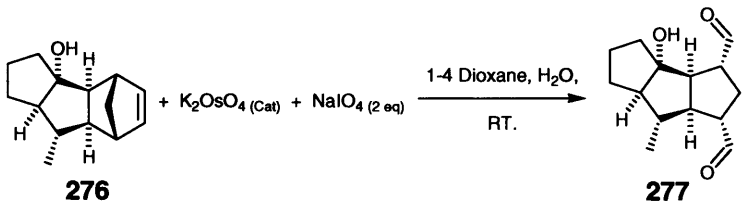


273 **276**

To a round bottom flask under an atmosphere of nitrogen containing 2-(iodopenty)-3-methyl-1,3-dione-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **273** (0.50 g, 1.51 mmol) in THF (6.00 ml) was cooled to -100 °C and t-butyllithium (1.00 ml, 1.7 M, 1.70 mmol) added drop wise and held at -100 °C for 3 hr. The reaction was then warmed to RT and stirred for a further 12 hr, the reaction was quenched with NH_4Cl (sat) (20.0 ml) and extracted with diethyl ether (3 x 20.0 ml). The organic portions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and the

filtrate concentrated under reduced pressure to give yellow oil that was purified by chromatography (1:1 diethyl ether/40-60 petroleum ether) to yield *cis*-2-hydroxy-3-methyl-1,2,3,3a,3b,4,7,7a,8,8a-decahydro-4,7-methanocyclopentaindene **276** as yellow oil[xiii], (R_f = 0.42) (0.16 g, 0.79 mmol, 52%); FTIR (Film, υ_{max} cm $^{-1}$) 3358, 3061, 2978, 1722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.00 (1H, dd, J = 5.6, 3.0 Hz, H-5), 2.64–2.56 (1H, bm, H-7a), 2.43 (1H, bs, H-7), 2.00–1.68 (6H, m, H-4 + H-2 + CH_2 ring protons), 1.48–1.28 (6H, m, CH_2 ring protons + H-3a + H-3 + OH + ½ x H-8-CH_2), 0.92–0.90 (4H, bm, Me + ½ x H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.0, 90.5, 66.2, 56.8, 54.3, 44.1, 43.3, 43.0, 42.8, 34.2, 28.0, 25.4, 19.0; m/z (APCI) 205.0 (100) [(M + H^+); HRMS (ES) $C_{14}H_{24}ON$ requires 205.1514 $[M + H]^+$, found 205.1516.

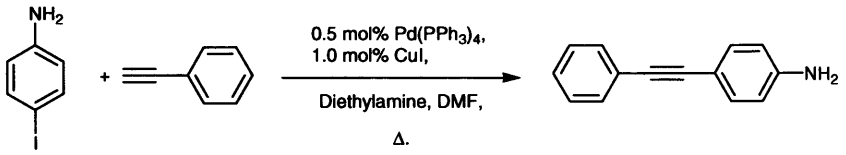
3-Hydroxy-9-methyloctahydrocyclopentapentalene-6,8-dicarboxaldehyde (277)



276 **277**

To a stirred solution of *cis*-2-hydroxy-3-methyl-1,2,3,3a,3b,4,7,7a,8,8a-decahydro-4,7-methanocyclopentaindene **276** (0.10 g, 0.49 mmol) in 1-4 dioxane (2.00 ml) and water (0.40 ml) at RT under a nitrogen atmosphere was added potassium osmate (VI) dehydrate (0.01 g, 2.7 x10^{-3} mmol), and sodium periodate (0.21 g, 0.98 mmol) the reaction stirred for 12 hr at RT and quenched using sodium bisulphate (0.30 g, 2.50 mmol) and water (10.0 ml). The reaction mixture was then concentrated to dryness and dissolved in diethyl ether (20.0 ml) and the organics were dried over $MgSO_4$ and the filtrate concentrated to yield 3-hydroxy-9-methyloctahydrocyclopentapentalene-6,8-dicarboxaldehyde **277** as a yellow oil, (0.06 g, 0.25 mmol, 50%). This compound proved very unstable affording difficult analysis, ^{1}H NMR spectra obtained confirmed the existence of the di-aldehyde proton[xiii]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (1H, d, J = 1.6 Hz, COH), 9.54 (1H, dd, J = 1.5 Hz, COH). The rest of the spectra showed what appeared to be polymeric product by extensive broad peaks in the aliphatic region as well as some starting material observed by peaks at δ 6.08 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.0 (1H, dd, J = 5.6, 3.0 Hz, H-5).

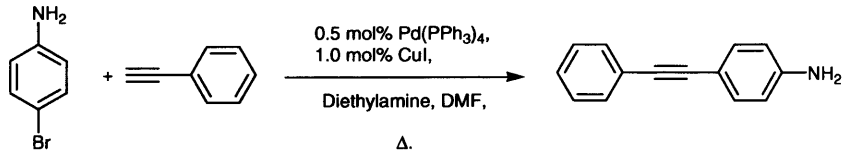
4-(2-Phenylethynyl)aniline[221] (282)



158 **142** **282**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 4-iodoaniline **158** (5.00 g, 22.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) and copper iodide (0.04 g, 0.23 mmol) in DMF (4.00 ml) and diethylamine (17.00 ml). Phenylacetylene **142** (2.75 ml, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 3 hr. TLC showed complete reaction, the reaction was then partitioned between water (100.0ml) and DCM (100.0 ml), the aqueous layer was extracted a further twice with (100.0 ml) DCM. The organic fractions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield a brown solid, this was further purified by chromatography (1:6 EtOAc/40-60 petroleum ether to yield 4-(2-phenylethynyl)aniline **282** as a brown solid, (R_f = 0.3) (3.97 g, 20.52 mmol, 90 %); m.p. 126–128 °C (DCM/Hexane). FTIR (Film, υ_{max} cm $^{-1}$) 3368, 2853, 2209; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (2H, m, $ArHNH_2$), 7.28–7.20 (5H, m, ArH), 6.56 (2H, dd, J = 8.5 Hz, $ArHNH_2$), 3.74 (2H, bs, NH_2).[221]

4-(2-Phenylethynyl)aniline[199, 221] (282)

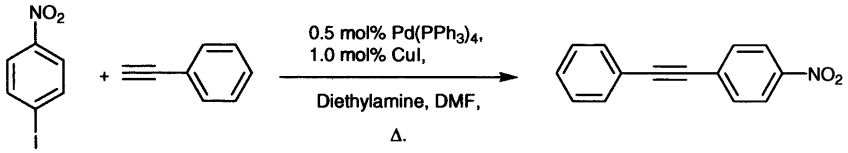


287 **142** **282**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 4-bromoaniline **287** (3.92 g, 22.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) and copper iodide (0.04 g, 0.23 mmol) in DMF (4.00 ml) and diethylamine (17.00 ml). Phenylacetylene **142** (2.75 ml, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 3 hr. TLC showed complete reaction, the reaction was then partitioned between water (100.0ml) and DCM (100.0 ml), the aqueous layer was extracted a

further twice with (100.0 ml) DCM. The organic fractions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield a brown solid, this was further purified by chromatography (1:6 EtOAc/40-60 petroleum ether to yield 4-(2-phenylethynyl)aniline **282** as a brown solid, (R_f = 0.3) (3.75 g, 19.38mmol, 85%); m.p. 126–128 °C (DCM/Hexane). Characterisation as before.

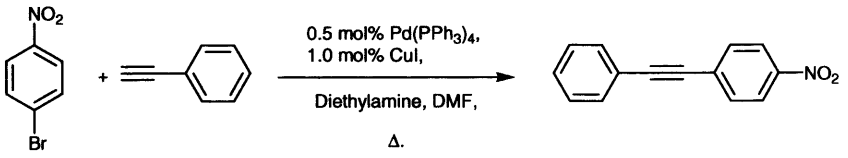
4-(2-Phenylethynyl)nitrobenzene[186] (283)



182 **142** **283**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 1-iodo-4-nitrobenzene **182** (5.68 g, 22.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) and copper iodide (0.04 g, 0.23 mmol) in DMF (4.00 ml) and diethylamine (17.00 ml). Phenylacetylene **142** (2.75 ml, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 3 hr. TLC showed complete reaction, the reaction was then partitioned between water (100.0ml) and DCM (100.0 ml), the aqueous layer was extracted a further twice with (100.0 ml) DCM. The organic fractions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield a orange solid, this was further purified by chromatography (1:6 EtOAc/40-60 petroleum ether to yield 4-(2-phenylethynyl)nitrobenzene **283** as an orange solid (4.84 g, 21.66 mmol, 95%): m.p. 120–122 °C (EtOH/H_2O). FTIR (Film, υ_{max} cm $^{-1}$) 2864, 2206; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, J = 9.0 Hz, $ArHNO_2$), 7.60 (2H, d, J = 9.0 Hz, $ArHNO_2$), 7.51–7.47 (2H, m, ArH), 7.34–7.30 (3H, m, ArH).[186]

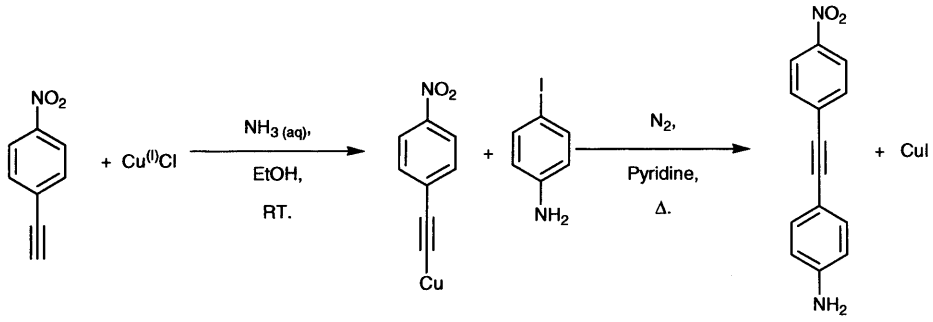
4-(2-Phenylethynyl)nitrobenzene[186] (283)



288 **142** **283**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 1-bromo-4-nitrobenzene **288** (4.61g, 22.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) and copper iodide (0.04 g, 0.23 mmol) in DMF (4.00 ml) and diethylamine (17.00 ml). Phenylacetylene **142** (2.75 ml, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 3 hr. TLC showed complete reaction, the reaction was then partitioned between water (100.0ml) and DCM (100.0 ml), the aqueous layer was extracted a further twice with (100.0 ml) DCM. The organic fractions were combined and washed with brine (50.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield a orange solid, this was further purified by chromatography (1:6 EtOAc/40-60 petroleum ether to yield 4-(2-phenylethynyl)nitrobenzene **283** as an orange solid, (4.68 g, 20.98 mmol, 92%); m.p. 120–122 °C ($EtOH/H_2O$). Characterisation as before.

4-(2-(4-Nitrophenyl)ethynyl)benzenamine[222, 223] (284)

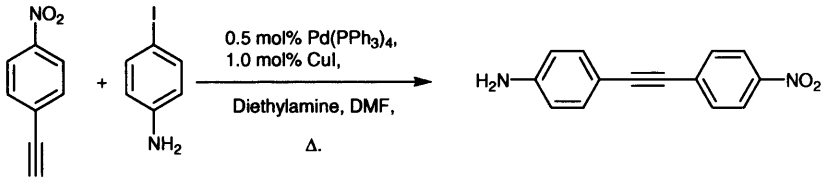


181 **291** **158** **284**

To a dried round bottom flask under a nitrogen atmosphere, a minimal amount of 35% aqueous ammonia solution (5.00 ml) was added to cupric chloride (0.98 g, 9.90 mmol) giving a blue solution, which was added slowly to a solution of 1-ethylyl-4-nitrobenzene **181** (0.63 g, 4.30 mmol) in ethanol (100 ml) at RT. This resulted in the formation of a red precipitate that was stirred for 30 min. The red precipitate was filtered and washed with water (10.0 ml), ethanol (10.0 ml) and diethyl ether (10.0

ml), followed by drying in a vacuum oven at 40 °C, resulting in the cuprate adduct of 1-ethylyl-4-nitrobenzene **291** (0.57 g, 2.71 mmol, 63%). To a stirred solution of dry, degassed pyridine (40.0 ml), cupric-1-ethylyl-4-nitrobenzene **291** (0.57 g, 2.71 mmol) was added followed by 4-iodoaniline **158** (0.65 g, 2.98 mmol) and the mixture refluxed for 12 hr. The resulting black solution was concentrated to dryness and the black solid suspended in methanol (50.0 ml) and filtered. The filtrate was concentrated to yield a dark brown oil that was further purified by chromatography (1:1 DCM/toluene), resulting in 4-(2-(4-nitrophenyl)ethynyl)benzenamine **284** as a orange solid (0.19 g, 0.81 mmol, 30%), (R_f = 0.42); m.p. 190–192 ^{0}C (DCM/Hexane). FTIR (Film, υ_{max} cm $^{-1}$) 3480, 3376, 2210, 1515, 1337; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (2H, dd, J = 7.0, 2.0 Hz, $ArHNO_2$), 7.53 (2H, dd, J = 7.0, 2.0 Hz, $ArHNO_2$), 7.30 (2H, dd, J = 6.5, 2.0 Hz, $ArHNH_2$), 6.59 (2H, dd, J = 6.5, 2.0 Hz, $ArHNH_2$), 3.86 (2H, bs, NH_2).[222]

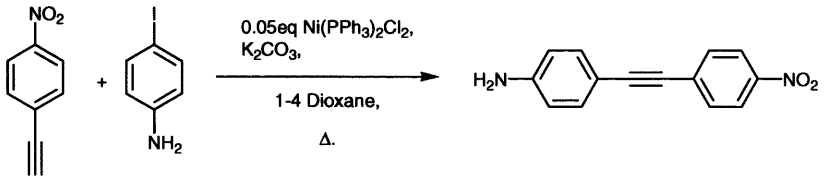
4-(2-(4-Nitrophenyl)ethynyl)benzenamine[186, 223](284)



181 **158** **284**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 4-iodoaniline **158** (5.00 g, 22.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) and copper iodide (0.04 g, 0.23 mmol) in DMF (4.00 ml) and diethylamine (17.00 ml). 1-Ethynyl-4-nitrobenzene **181** (3.69 g, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 3 hr. TLC showed complete reaction, the reaction was then partitioned between water (100.0ml) and DCM (100.0 ml), the aqueous layer was extracted a further twice with (100.0 ml) DCM. The organic fractions combined and washed with brine (50.0 ml), dried over $MgSO_4$ and filtrate concentrated under reduced pressure to yield a orange solid, this was further purified by chromatography (1:1 DCM/40-60 petroleum ether) to yield 4-(2-(4-nitrophenyl)ethynyl)benzenamine **284** as an orange solid, (2.28 g, 9.58 mmol, 42%), (R_f = 0.42); m.p. 190–192 ^{0}C (DCM/Hexane). Characterisation as before.

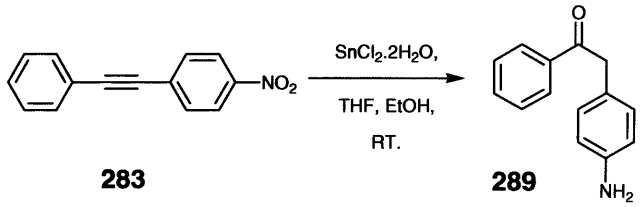
4-(2-(4-Nitrophenyl)ethynyl)benzenamine[119, 223](284)



191 **158** **284**

To a dried (50 ml) Schlenk tube under an inert atmosphere of nitrogen stirred a mixture of 4-iodoaniline **158** (5.00 g, 22.80 mmol), bis(triphenylphosphine)nickel(II) dichloride (0.75 g, 1.14 mmol) and copper iodide (0.43 g, 2.28 mmol) and potassium carbonate (6.30 g, 45.6 mmol) in 1,4-dioxane (25.0ml) and water (10.0 ml). 1-ethynyl-4-nitrobenzene **191** (3.69 g, 25.08 mmol) was added after stirring for 10 min and the reaction heated to reflux for 6 hr. TLC showed complete reaction and the reaction quenched with HCl (2M, 200.0 ml) the reaction mixture was then extracted with ethyl acetate (2 x 200 ml) and the organic fractions washed with brine (100.0 ml), dried over $MgSO_4$ and the filtrate concentrated to yield a orange solid, that was further purified by chromatography (1:1 DCM/40-60 petroleum ether) to yield 4-(2-(4-nitrophenyl)ethynyl)benzenamine **284** as an orange solid, (4.13 g, 17.32 mmol, 76%), (R_f = 0.42); m.p. 190–192 °C (DCM/Hexane). Characterisation as before.

2-(4-Aminophenyl)-1-phenylethanone[224, 225] (289)

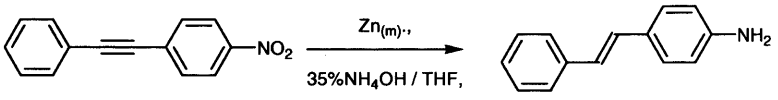


283 **289**

To a solution of 4-(2-phenylethynyl)nitrobenzene **283** (1.89 g, 8.50 mmol) in THF (50.0 ml) and ethanol (3.0 ml), tin (II) chloride dehydrate (9.59 g, 42.50 mmol) was added and the reaction stirred at RT for 16 hr under an atmosphere of nitrogen. TLC confirmed no starting material present and the reaction quenched by slow addition of aqueous potassium hydroxide 50 % w/v (50.0 ml). The reaction mixture was then extracted with ethyl acetate (2 x 50.0 ml), washed with brine (20.0 ml) and dried over $MgSO_4$. The filtrate was then concentrated to yield a brown solid that consisted of 2 spots by TLC, the solid was further purified by chromatography (1:4 ethyl acetate/40-60 petroleum ether). Isolation of both spots (R_f = 0.5 and 0.25) was

achieved, upon concentration of both spots yielded solids, 4-(2-phenylethynyl)aniline yielded a brown solid (0.33g, 1.70 mmol, 20%) **282** (R_f = 0.5) and 2-(4-aminophenyl)-1-phenylethanone **289** as an orange solid, (R_f = 0.25) (1.44 g, 6.80 mmol, 80%); m.p. 143–145 °C (EtOAc/40-60 petroleum ether). FTIR (Film, υ_{max} cm $^{-1}$) 3330, 3025, 2893, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8.9 Hz, $ArHNH_2$), 7.20–7.11 (5H, m, ArH), 6.53 (2H, dd, J = 8.6 Hz, $ArHNH_2$), 4.10 (2H, s, CH_2Ar), 4.06 (2H, bs, NH_2).[224]

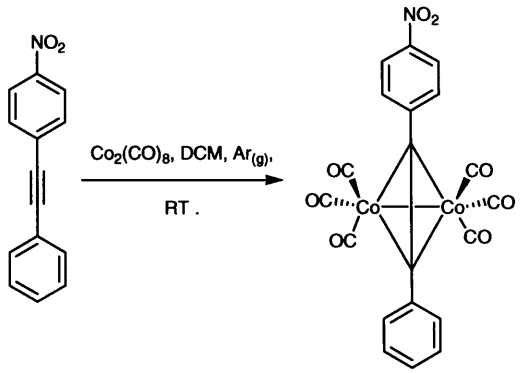
4-Styryl-aniline[226] (290)



283 **290**

To a mixture of zinc dust (1.1 g, 16.75 mmol) in THF (50 ml) and 35% ammonia solution (50.0 ml, 0.50 mol), 4-(2-phenylethynyl)nitrobenzene **283** (0.75 g, 3.40 mmol) was added in THF (10 ml) slowly. The reaction was stirred at RT for 5 hr under an inert atmosphere of nitrogen, TLC confirmed the appearance of 2 new spots and no starting material present (R_f = 0.5 and 0.6). The reaction mixture was then diluted with ethyl acetate (100.0ml) and washed with 2M HCl (2 x 100.0 ml), brine (50.0 ml) and dried over $MgSO_4$. The filtrate was concentrated to an orange solid that was further purified by chromatography (1:4ethyl acetate/40-60 petroleum ether), isolation of both spots was achieved and upon concentration of both products yielded a brown solid, 4-(2-phenylethynyl)aniline (0.23g, 1.19 mmol, 35%) (R_f = 0.5) **282**, and 4-styryl-aniline **290** as a brown solid, (0.43 g, 2.21 mmol, 65%) (R_f = 0.5), m.p. 148–149 °C (EtOAc/ 40-60 petroleum ether). FTIR (Film, υ_{max} cm $^{-1}$) 3421, 3048, 3025, 2893, 1626; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, dd, J = 7.6, 2.0 Hz, $ArHNH_2$), 7.25–7.14 (6H, m, ArH + C<u>H</u>Ar), 6.57 (2H, d, J = 8.5 Hz, $ArHNH_2$), 6.49 (1H, d, J = 8.6 Hz, C<u>H</u>ArNH_2) 3.98 (2H, bs, NH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$), 146.7, 133.0, 132.0, 131.4, 128.3, 127.7, 123.9, 116.7, 114.8, 112.6.

4-(2-Phenylethynyl)nitrobenzene)dicobalthexacarbonyl (292)



283 **292**

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser was added dicobaltoctacarbonyl **16** (3.02 g, 8.86 mmol) and 4-(2-phenylethynyl)nitrobenzene **283** (1.80 g, 8.05 mmol) to dry, degassed, dichloromethane (20.00 ml) under an inert atmosphere of nitrogen. The mixture was stirred at room temperature until the dicobalthexacarbonyl alkyne complex was formed as indicated by a high running red T.L.C spot. The reaction mixture was then concentrated to yield a black solid that was recrystallised to yield 4-(2 phenylethynyl)nitrobenzene)dicobalthexacarbonyl **292** as black crystals (3.27 g, 6.44 mmol, 82%), dec. 240 °C (Toluene). FTIR (Film, υ_{max} cm $^{-1}$) 2010.6; m/z (APCI) 509.9; $C_{20}H_9Co_2NO_8$ requires C, 47.18; H, 1.78; N, 2.75, found: C, 47.10; H, 1.81; N, 2.70%.Crystal data for 4-(2-phenylethynyl)nitrobenzene)dicobalthexacarbonyl : $C_{20}H_9Co_2NO_8$, M = 509.14, Monoclinic, a = 10.5504(3), b = 12.4376(3), c = 30.3640(8)A°, V = 3984.13(18)A ° 3, space group C2/c, Z = 8, Dc = 1.698 Mg/m^3, l(Mo Ka) = 1.714 mm_1,

T = 150(2) K, 12835 measured reflections, 4340 independent,

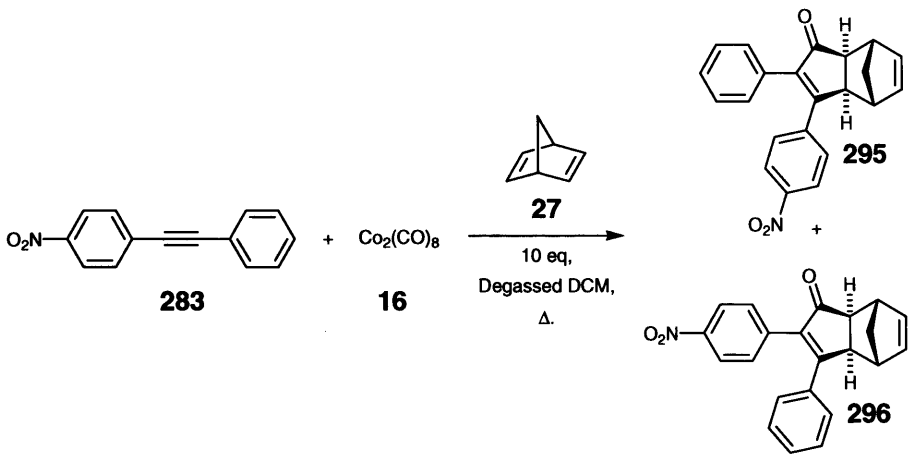
[Rint = 0.0572] R1 = 0.0542, wR_2 = 0.0793 (all data) R_1 = 0.0376,

wR_2 = 0.0737 [I > 2sigma(I)] GOF = 1.037; the data were collected

on a Nonius Kappa CCD with Mo Ka radiation (k = 0.71073 A°),

adsorption effects were calculated empirically.

2-(phenyl)-3-(4-nitrobenzene)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (295) and 2-(4-Nitrobenzene)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (296)

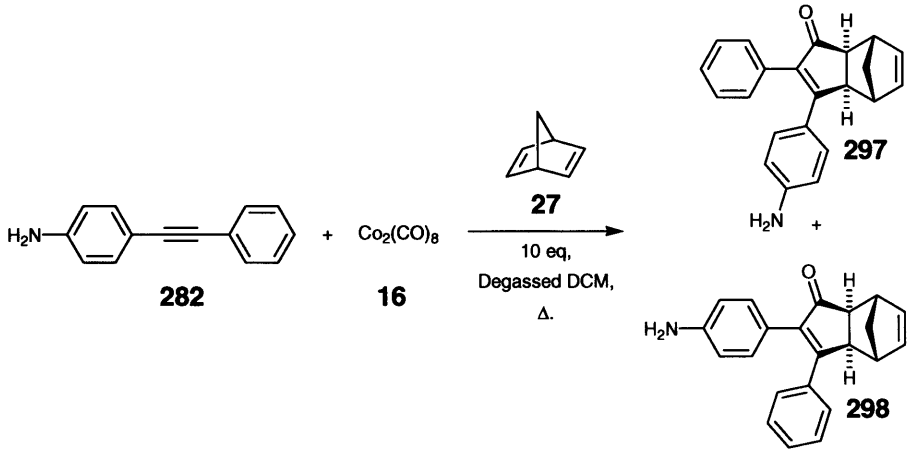


To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 4-(2-phenylethynyl)nitrobenzene **283** (1.79 g, 8.02 mmol) and dicobaltoctacarbonyl **16** (3.02 g, 8.82 mmol) in DCM (36.00 ml). 2,5-Norbornadiene **27** (8.65 ml, 80.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:4 Et_2O/40–60 petroleum ether), yielded two orange solids that were found to be a mixture of regioisomers yielding 2-(phenyl)-3-(4-nitrobenzene)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **295** as a orange solid, (R_f = 0.40) (0.87 g, 2.53 mmol, 32%); m.p. 186–188 °C (Toluene). FTIR (Film, υ_{max} cm $^{-1}$) 3056, 1692, 1607; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (2H, d, J = 8.6 Hz, NO_2ArH), 7.30–7.20 (5H, m, ArH), 7.19 (2H, d, J = 7.1 Hz, NO_2ArH), 6.26 (2H, bs, H-6 + H-5), 3.33 (1H, d, J = 5.2 Hz, H-7a), 3.05 (1H, s, H-7), 2.60 (1H, d, J = 5.3 Hz, H-3a), 2.55 (1H, s, H-4), 1.45–1.35 (2H, 2 x d, J = 9.8 Hz, H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 172.8, 147.1, 141.5, 139.0, 138.4, 138.0, 134.2, 130.4, 130.3, 129.0, 128.3, 123.6, 53.0, 50.9, 44.3, 43.3, 41.9; m/z (APCI) 344.0 (100) (M + H$^+$); HRMS (ES) $C_{22}H_{18}NO_3$ requires 344.1281 [M + H]$^+$, found 344.1285;

And 2-(4-nitrobenzene)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **296** as an orange solid, (R_f = 0.38)) (0.87 g, 2.53 mmol, 32%); m.p. 141–143 °C (Toluene). FTIR (Film, υ_{max} cm $^{-1}$) 3053, 1693, 1593; ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.01 (2H, d, J = 8.6 Hz, NO_2ArH), 7.39 (2H, d, J = 8.5 Hz, NO_2ArH), 7.28–7.04 (5H, m, ArH), 6.26 (2H, bs, H-6 + H-5), 3.28 (1H, d, J = 5.1 Hz, H-7a), 3.09 (1H, bs, H-7), 2.61 (1H, d, J = 5.1 Hz, H-3a), 2.49 (1H, s, H-4), 1.46–1.34 (2H, 2 x d, J = 9.1 Hz, H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 166.6, 148.0, 146.0, 141.8, 138.1, 130.8, 130.8, 129.3, 129.2, 129.0, 128.7, 123.8, 53.0, 50.4, 44.3, 43.0, 41.8; m/z (APCI) 344.4 (100) (M + H^+); HRMS $C_{22}H_{21}N_2O_3$ requires 361.1547 $[M + NH_4]^+$, found 361.1550.

2-(phenyl)-3-(4-aniline)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (297) and 2-(4-Aniline)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (298)

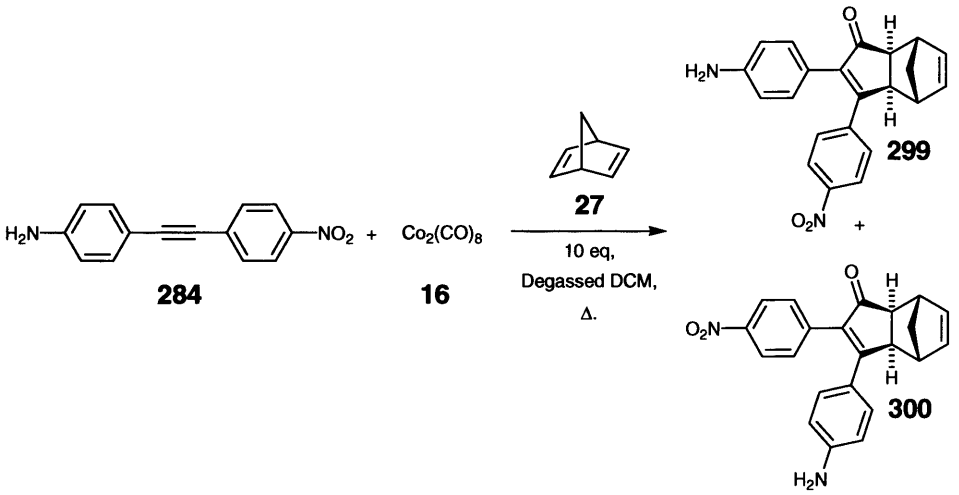


To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 4-(2-phenylethynyl)aniline **282** (1.55 g, 8.02 mmol) and dicobaltoctacarbonyl **16** (3.02 g, 8.82 mmol) in DCM (36.00 ml). 2,5-Norbornadiene **27** (8.65 ml, 80.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:2 Et_2O/40–60 petroleum ether), yielded two yellow solids that were found to be a mixture of regioisomers yielding 2-(phenyl)-3-(4-aniline)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **297** as a yellow solid, (R_f = 0.25) (0.92 g, 2.93 mmol, 37%); m.p. 230–232 °C (Toluene). FTIR (Film, υ_{max} cm^{-1}) 3408, 3064, 1678, 1622; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (7H, m, NH_2ArH + ArH), 6.46 (2H, d, J = 8.8 Hz, NH_2ArH), 6.29–6.22 (2H, 2 x dd, J = 5.5, 3.0 Hz, H-6 + H-5), 3.90 (2H, bs, NH_2) 3.26 (1H, d, J = 5.5 Hz, H-7a), 3.02 (1H, bs, H-7), 2.62 (1H, bs, H-4), 2.51 (1H, d, J = 5.5 Hz, H-3a), 1.15 (2H, bs, H-8-CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$), 207.2, 169.4,

148.3, 141.1, 138.2, 138.0, 133.3, 130.6, 129.3, 128.7, 127.6, 124.2, 114.3, 52.6, 49.6, 44.0, 42.1, 42.0; m/z (APCI) 314.0 (100) ($M + H^+$); HRMS (ES) $C_{22}H_{20}NO$ requires 314.1539 $[M + H]^+$, found 314.1539;

And 2-(4-aniline)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **298** as a yellow solid, ($R_f = 0.23$) (0.92 g, 2.93 mmol, 37%); m.p. 218–220 °C (Toluene). FTIR (Film, υ_{max} cm^{-1}) 3691, 3401, 3034, 2964, 2874,1686; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.21 (5H, m, ArH), 6.95 (2H, d, J = 8.5 Hz, NH_2ArH), 6.54 (2H, d, J = 8.5 Hz, NH_2ArH), 6.23 (2H, bs, H-6 + H-5), 3.65 (2H, bs, NH_2), 3.25 (1H, d, J = 5.4 Hz, H-7a), 3.03 (1H, bs, H-7), 2.51–2.45 (2H, bm, H-4 + H-3a), 1.40–1.32 (2H, bm, H-8-CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$), 208.0, 168.3, 143.5, 141.8, 138.3, 137.9, 135.5, 130.4, 129.3, 128.5, 128.4, 122.0, 115.0, 52.7, 50.1, 44.1, 43.2, 41.9; m/z (APCI) 314.0 (100) ($M + H^+$); HRMS (ES) $C_{22}H_{20}NO$ requires 314.1539 $[M + H]^+$, found 314.1537.

2-(4-Aniline)-3-(4-nitrobenzene)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (299) and 2-(4-nitrobenzene)-3-(4-aniline)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (300)

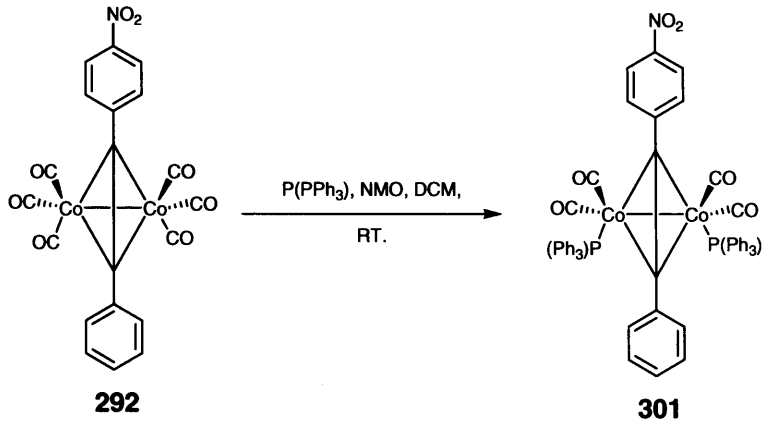


To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 4-(2-nitrophenylethynyl)aniline **284** (1.91 g, 8.02 mmol) and dicobaltoctacarbonyl **16** (3.02 g, 8.82 mmol) in DCM (36.00 ml). 2,5-Norbornadiene **27** (8.65 ml, 80.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 8 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1

Et_2O/40–60 petroleum ether), yielded two orange solids that were found to be a mixture of regioisomers yielding 2-(4-aniline)-3-(4-nitrobenzene)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **299** as a orange solid, (R_f = 0.54) (0.71 g, 1.99 mmol, 25%); m.p. 185–187 °C (Toluene). FTIR (Film, υ_{max} cm $^{-1}$) 3691, 3404, 3066, 1693, 1622; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.9 Hz, NO_2ArH), 7.45 (2H, d, J = 8.7 Hz, NO_2ArH), 6.91 (2H, d, J = 8.5, Hz, NH_2ArH), 6.53, (2H, dd, J = 8.5 Hz, NH_2ArH), 6.30–6.25 (2H, bm, H-6 + H-5), 3.71 (2H, bs, NH_2), 3.22 (1H, d, J = 5.4 Hz, H-7a), 3.06 (1H, bs, H-7), 2.56 (1H, d, J = 5.3 Hz, H-3a), 2.46 (1H, bs, H-4), 1.43–1.33 (2H, 2 x d, J = 9.2 Hz, H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 164.6, 147.7, 146.8, 145.7, 142.5, 138.2, 138.0, 130.5, 129.2, 123.8, 120.4, 115.0, 52.9, 50.1, 44.2, 43.0, 41.8; m/z (APCI) 359.0 (100) (M + H^+); HRMS (ES) $C_{22}H_{19}N_2O_3$ requires 359.1390 $[M + H]^+$, found 359.1386;

And 2-(4-nitrobenzene)-3-(4-aniline)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **300** as a yellow solid (R_f = 0.50) (0.24 g, 0.66 mmol, 8%); m.p. 229–231 °C (Toluene). FTIR (Film, υ_{max} cm $^{-1}$) 3692, 3411, 2985, 1681, 1622; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, dd, J = 9.0, 2.0 Hz, NO_2ArH), 7.37 (2H, dd, J = 9.0, 1.9 Hz, NO_2ArH), 7.08 (2H, dd, J = 8.6, 2.0 Hz, NH_2ArH), 6.49, (2H, dd, J = 8.5, 2.0 Hz, NH_2ArH), 6.30–6.25 (2H, m, H-6 + H-5), 3.95 (2H, bs, NH_2), 3.30 (1H, d, J = 5.5 Hz, H-7a), 3.05 (1H, bs, H-7), 2.63 (1H, bs, H-4), 2.56 (1H, d, J = 5.6 Hz, H3a), 1.43–1.32 (2H, 2 x d, J = 9.4 Hz, H-8-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 165.3, 148.6, 143.5, 138.3, 137.9, 135.5, 130.4, 129.3, 128.4, 128.3, 121.9, 115.0, 52.7, 50.1, 44.1, 43.2, 41.9; m/z (APCI) 359.0 (100) (M + H^+); HRMS (ES) $C_{22}H_{19}N_2O_3$ requires 359.1390 $[M + H]^+$, found 359.1388.

4-(2-Phenylethynyl)nitrobenzene dicobaltdecacarbonylbis(triphenylphosphine) (301)



292 **301**

To a solution of 4-(2-phenylethynyl)nitrobenzenedicobalthexacarbonyl complex **292** (1.0g, 1.97 mmol) in DCM (20 ml, 0.312 mol) under an inert atmosphere of nitrogen was added triphenylphosphine (0.57 g, 2.17 mmol) and NMO (0.266 g, 1.97 mmol), the reaction was stirred at RT for 12 hr then concentrated to yield a black solid, this was recrystallised from DCM/MeOH to yield 4-(2-phenylethynyl)nitrobenzene dicobaltdecacarbonylbis(triphenylphosphine) **301** as fine black crystals, (0.96 g, 0.99 mmol, 50%), dec. 268 °C (DCM/MeOH). FTIR (Film, υ_{max} cm $^{-1}$) 2018.6, 1973.4, 1932.5;

Crystal data for 4-(2-phenylethynyl)nitrobenzene dicobaltdecacarbonylbis(triphenylphosphine): C_{27} $H_{19.50}$ Co $N_{0.50}$ O_3 P, M = 488.83, Orthorhombic,

a = 12.8352(2), b = 12.9343(2), c = 27.3791(6) A° , V = 4545.32(14) A° 3,

space group P 212121, Z = 8, Dc = 1.429 Mg/m^3, l(Mo Ka) = 0.854 mm_1,

T = 150(2) K, 37034 measured reflections, 10018 independent,

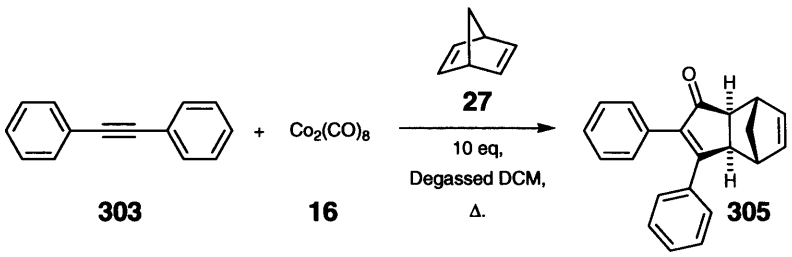
[Rint = 0.0916] R1 = 0.1099, wR_2 = 0.1130 (all data) R_1 = 0.0505,

wR_2 = 0.0967 [I > 2sigma(I)] GOF =1.021; the data were collected

on a Nonius Kappa CCD with Mo Ka radiation (k = 0.71073 A°),

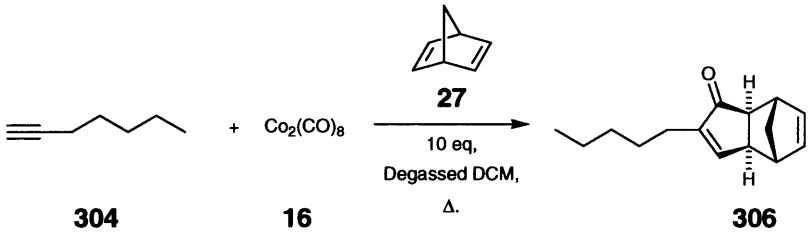
adsorption effects were calculated empirically.

2-(Phenyl)-3-(phenyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[192] (305)



To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added diphenylacetylene **303** (1.52 ml, 8.42 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.26 mmol) in DCM (38.00 ml). 2,5-Norbornadiene **27** (9.18 ml, 84.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(phenyl)-3-(phenyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **305** as a brown solid (0.75 g, 2.53 mmol, 30%) (R_f = 0.46); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.20 (10H, m, ArH), 6.25 (1H, dd, J = 5.5, 2.2 Hz, H-6), 6.15 (1H, dd, J = 5.5, 2.1 Hz, H-5), 3.01 (1H, bs, H-7a), 2.85 (1H, bs, H-7), 2.73 (1H, bs, H-4), 2.46 (1H, d, J = 5.0 Hz, H-3a), 1.39–1.26 (2H, 2 x d, J = 9.2 Hz, H8); m/z (APCI) 299.0(100) ($M + H^+$).

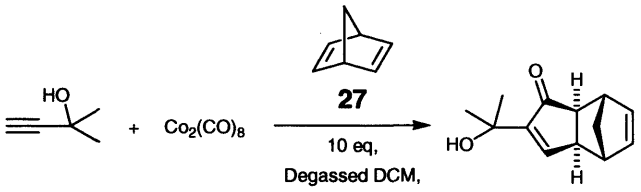
2-Hexyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[194] (306)



To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 1-octyne **304** (1.24 ml, 8.42 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.26 mmol) in DCM (38.00 ml). 2,5-Norbornadiene **27** (9.18 ml, 84.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum

ether) yielded 2-Hexyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **306** as a yellow oil, (R_f = 0.40) (0.64 g, 2.78 mmol, 33%); FTIR (Film, υ_{max} cm $^{-1}$) 1694, 1620; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, J = 1.2 Hz, H-3), 6.25 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.18 (1H, dd, J = 5.6, 3.0 Hz, H-5). 2.87 (1H, bs, H-7a), 2.71–2.61 (2H, bm, H-7 + H-4), 2.30 (1H, d, J = 5.2 Hz, H-3a), 2.13 (2H, t, J = 7.1 Hz, $C\underline{H}_2(CH_2)_4Me$), 1.48–1.16 (8H, m, $CH_2(C\underline{H}_2)_4Me$ + H-8-CH_2), 0.90 (3H, t, J = 6.5 Hz, Me); m/z (APCI) 231.0 (100) (M + H$^+$).

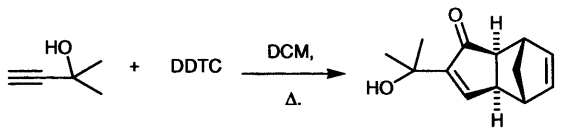
2-Propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[194] (310)



162 **16** **310**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 2-methyl-3-butyn-2-ol **162** (0.82 ml, 8.42 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.26 mmol) in DCM (38.00 ml). 2,5-Norbornadiene **27** (9.18 ml, 84.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **310** as a yellow oil, (R_f = 0.32) (1.03 g, 5.05 mmol, 60%); FTIR (Film, υ_{max} cm $^{-1}$) 3395, 1671, 1614; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (1H, d, J = 2.5 Hz, H-3), 6.24 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.14 (1H, dd, J = 5.6, 3.0 Hz, H-5), 3.64 (1H, bs, OH), 2.86 (1H, bs, H-7a), 2.64–2.58 (2H, bm, H-7 + H-4), 2.26 (1H, d, J = 5.2 Hz, H-3a), 1.36 (6H, s, Me_2), 1.27 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2) 1.17 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); m/z (APCI) 205.0 (100) (M + H$^+$).

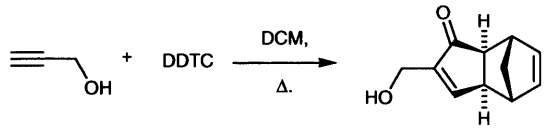
2-Propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one, using DDTC (310)



162 **187** **310**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 2-methyl-3-butyn-2-ol **162** (0.82 ml, 8.42 mmol) and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **310** as a yellow oil, (R_f = 0.34) (0.89 g, 4.38 mmol, 52%). Characterisation as before.

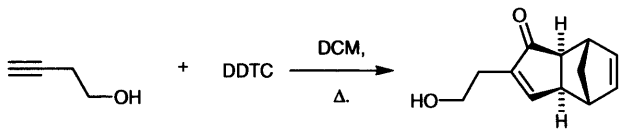
2-Hydroxymethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one, using DDTC (146)



143 **187** **146**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added propargylalcohol **143** (0.49 ml, 8.42 mmol) and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-hydroxymethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **146** as a yellow oil, (R_f = 0.41) (0.68 g, 3.87 mmol, 46%); %). Characterisation as before.

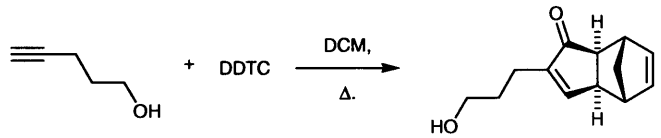
2-Hydroxyethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one, using DDTC (221)



172 **187** **221**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 3-butyn-1-ol **172** (0.64 ml, 8.42 mmol) and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-hydroxyethyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **221** as a yellow oil, (R_f = 0.5) (0.40 g, 2.11 mmol, 25%). Characterisation as before.

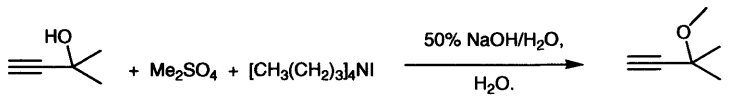
2-Hydroxyproyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one, using DDTC (219)



171 **187** **219**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 4-pentyn-1-ol **171** (0.78 ml, 8.42 mmol) and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 DCM/40–60 petroleum ether) yielded 2-(2-hydroxypropyl) -3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **219** as a yellow oil, (R_f = 0.48) (0.34 g, 1.68 mmol, 20%). Characterisation as before.

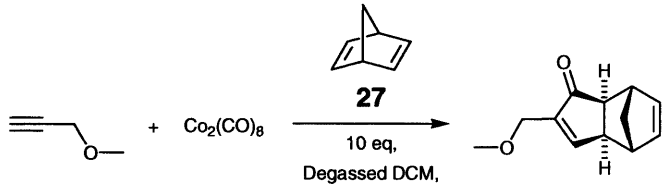
3-Methoxy-3-methylbut-1-yne (315)



162 **315**

To a solution of NaOH (15.00 g, 0.38 mol) in water (15.00 ml, 0.84 mol), t-butylammonium iodide (0.5 g, 1.4. mmol) and dimethyl sulphate (14.00 ml, 0.15 mol) was added and the mixture stirred for 10 min, 2-Methyl-3-butyn-2-ol **162** (12.00 ml, 0.12 mol) was then added and the reaction stirred for 5 hr. The reaction showed no starting material by TLC and was diluted with water (100.0 ml), the organics were extracted with ethyl acetate (2 x 100.0 ml). The organic fractions were then dried over $MgSO_4$ and the filtrate concentrated to yield a clear oil that was further purified by distillation at 82 °C at 760 mmHg, to yield 3-methoxy-3-methylbut-1-yne **315** as a clear oil (8.80 g, 0.09 mol, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (3H, s, OMe), 2.36 (1H, s, CCH), 1.40 (6H, s, Me_2); m/z (APCI) 99.3 (100) ($M + H^+$).

2-(Methoxymethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one[227] (319)

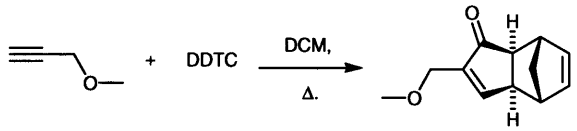


317 **16** **319**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added methyl propargyl ether **317** (0.71 ml, 8.42 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.26 mmol) in DCM (38.00 ml). 2,5-Norbornadiene **27** (9.18 ml, 84.20 mmol) was added and after 1 hr TLC confirmed the complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(methoxymethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **319** as a yellow oil, (R_f = 0.25) (1.20 g, 6.32 mmol, 75%); FTIR (Film, υ_{max} cm $^{-1}$) 3058, 2940, 1693, 1636; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, bs, H-3), 6.22 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.13 (1H, dd, J= 5.6, 3.0 Hz, H-5), 4.02 (2H, t, J = 1.7 Hz, CH_2OMe), 3.33 (3H, s, OMe), 2.86 (1H, bs, H-7a), 2.73 (1H, bs, H-7), 2.65 (1H, bs, H-4), 2.27 (1H, dt, J = 5.0, 1.4 Hz, H-3a), 1.36 (1H, d, J = 9.4 Hz, ½ x H-8-CH_2)

1.19 (1H, d, J = 9.4 Hz, ½ x 8-CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$), 208.6, 160.6, 147.3, 138.5, 137.1, 66.4, 59.0, 53.0, 48.2, 43.7, 43.0, 41.3; m/z (EICI) 191.1 (100) ($M + H^+$).

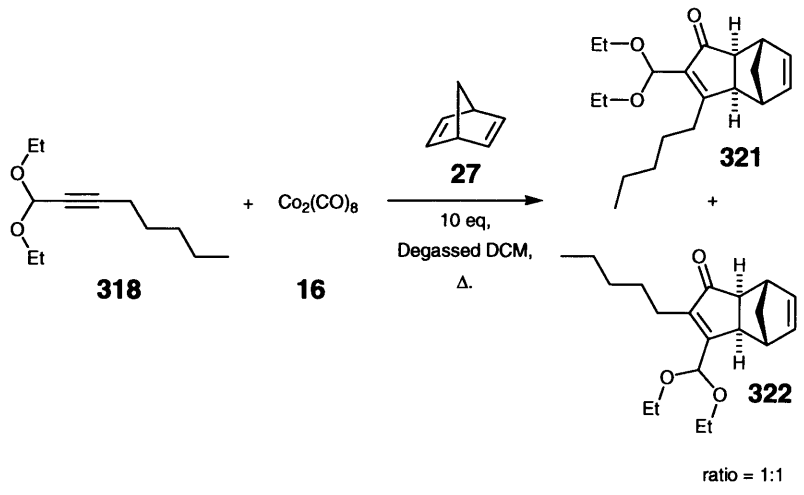
2-(Methoxymethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one using, DDTC (319)



317 **187** **319**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added methyl propargyl ether **317** (0.71 ml, 8.42 mmol) and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(methoxymethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **319** as a yellow oil, (R_f = 0.25) (0.80 g, 4.21 mmol, 50%); %). Characterisation as before.

2-(Diethoxymethyl)-3-(pentyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (321) and 2-(pentyl)-3-(diethoxymethyl))-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (322)

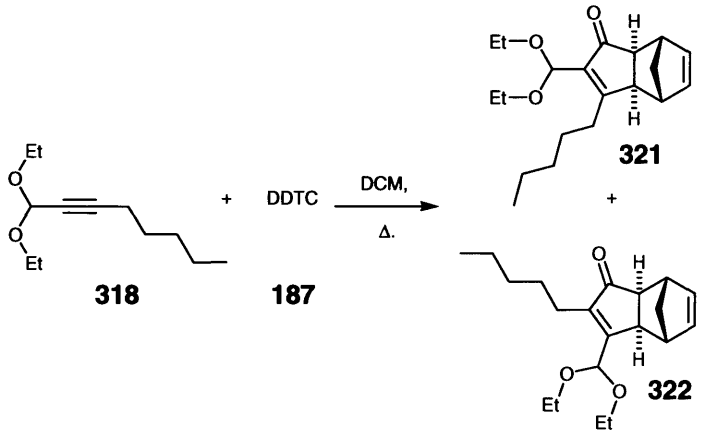


318 **16**

To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 2-octynal diethyl acetal **318** (1.90 ml, 8.42 mmol) and dicobaltoctacarbonyl **16** (3.17 g, 9.26 mmol) in DCM (38.00 ml). 2,5-Norbornadiene **27** (9.18 ml, 84.20 mmol) was added and after 1 hr TLC confirmed the

complete conversion of $Co_2(CO)_8$ to the dicobalthexacarbonyl alkyne complex and the reaction heated to reflux for 12 hr. The reaction was worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielding 2-(diethoxymethyl)-3-(pentyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **321** and 2-(pentyl)-3-(diethoxymethyl))-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **322** (inseparable by chromatography) as a yellow oil, (R_f = 0.34) (1.88 g, 5.90 mmol, 70%); FTIR (Film, υ_{max} cm $^{-1}$) 3048, 1692; m/z (APCI) 319.5 (100) (M + H^+). HRMS (ES) $C_{20}H_{31}O_3$ requires 319.2268 $[M + H]^+$, found 319.2265. The regioisomers were inseparable by chromatography and therefore the ^1H NMR was very complex showing the characteristic peaks for these products, HRMS confirmed the desired product and the crude ^1H NMR elucidated to a 1:1 ratio of regioisomers by the 1: 1 relationship of the Norbornene double bond and the OCH_2 proton.

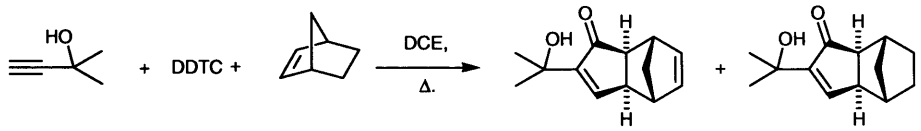
2-(Diethoxymethyl)-3-(pentyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (321) and 2-(pentyl)-3-(diethoxymethyl))-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one using DDCT (322)



To a flame dried (200 ml) Schlenk flask under an inert atmosphere of nitrogen equipped with a reflux condenser was added 2-octynal diethyl acetal **318** (1.90 ml, 8.42 mmol)and DDTC **187** (3.93 g, 9.26 mmol) in DCM (38.00 ml). The reaction was heated to reflux for 12 hr and worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded 2-(diethoxymethyl)-3-(pentyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **321** and 2-(pentyl)-3-(diethoxymethyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **322**

(inseparable by chromatography) as a yellow oil, (R_f = 0.34) (1.31 g, 4.13 mmol, 49%). Characterisation as before.

2-Propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (310) and 2-(2-hydroxypropan-2-yl)cyclopent-2-enone-3a,7a,bicyclo[2.2.1]heptane[194, 196] (325)



162 **187** **86** **310** ratio = 2.3 : 1 **325**

To a flame, dried (200 ml) Schlenk flask under an inert nitrogen atmosphere equipped with a reflux condenser was added DDTC **187** (1.00 g, 2.36 mmol), 2-methyl-3-butyn-2-ol **162** (0.25 ml, 2.60 mmol) and Bicyclo[2.2.1]hept-2-ene **86** (5.00 g, 53.10 mol) in dry, degassed DCM (20.00 ml). The reaction mixture was heated to reflux for 24 hr and the reaction worked up following the general PKR procedure and upon purification by chromatography (1:1 Et_2O/40–60 petroleum ether) yielded two separate products as yellow oils consisting of 2-propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **310** and 2-(2-hydroxypropan-2-yl)cyclopent-2-enone-3a,7a,bicyclo[2.2.1] **325**.

2-Propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **310**.(R_f = 0.34) (0.12 g, 0.60 mmol, 23%); FTIR (Film, υ_{max} cm^{-1}) 3042, 1733; ^1H NMR δ 7.17 (1H, d, J = 2.5 Hz, H-3), 6.24 (1H, dd, J = 5.6, 3.0 Hz, H-6), 6.14 (1H, dd, J = 5.6, 3.0 Hz, H-5), 3.64 (1H, bs, OH), 2.86 (1H, bs, H-7a), 2.64–2.60 (2H, bm, H-7 + H-4), 2.26 (1H, d, J = 5.2 Hz, H-3a), 1.36 (6H, s, Me_2), 1.27 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2) 1.17 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); m/z (APCI) 205.3 (100) ($M + H^+$).

2-(2-hydroxypropan-2-yl)cyclopent-2-enone-3a,7a,bicyclo[2.2.1]heptane (**325**); (R_f = 0.30) (0.04 g, 0.18 mmol, 7%); ^1H NMR δ 7.13 (1H, d, J = 2.5 Hz, H-3), 2.77 (1H, bs, OH), 2.33 (1H, bs, H-7a), 2.25 (1H, bs, H-7), 2.15–2.12 (2H, m, H-4 + H-3a), 1.66–1.45 (4H, m, H6 + H-5), 1.36 (6H, s, Me_2), 1.27 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2) 1.17 (1H, d, J = 9.1 Hz, ½ x H-8-CH_2); m/z (APCI) 207.3 (100) ($M + H^+$).

The ratio and percentage yield of the two products was determined by the crude ^1H NMR using the integration ratio of the H-3 proton, indicating a 67% excess of 2-propan-2-ol-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (**310**) over 2-(2-hydroxypropan-2-yl)cyclopent-2-enone-3a,7a,bicyclo[2.2.1] (**325**)

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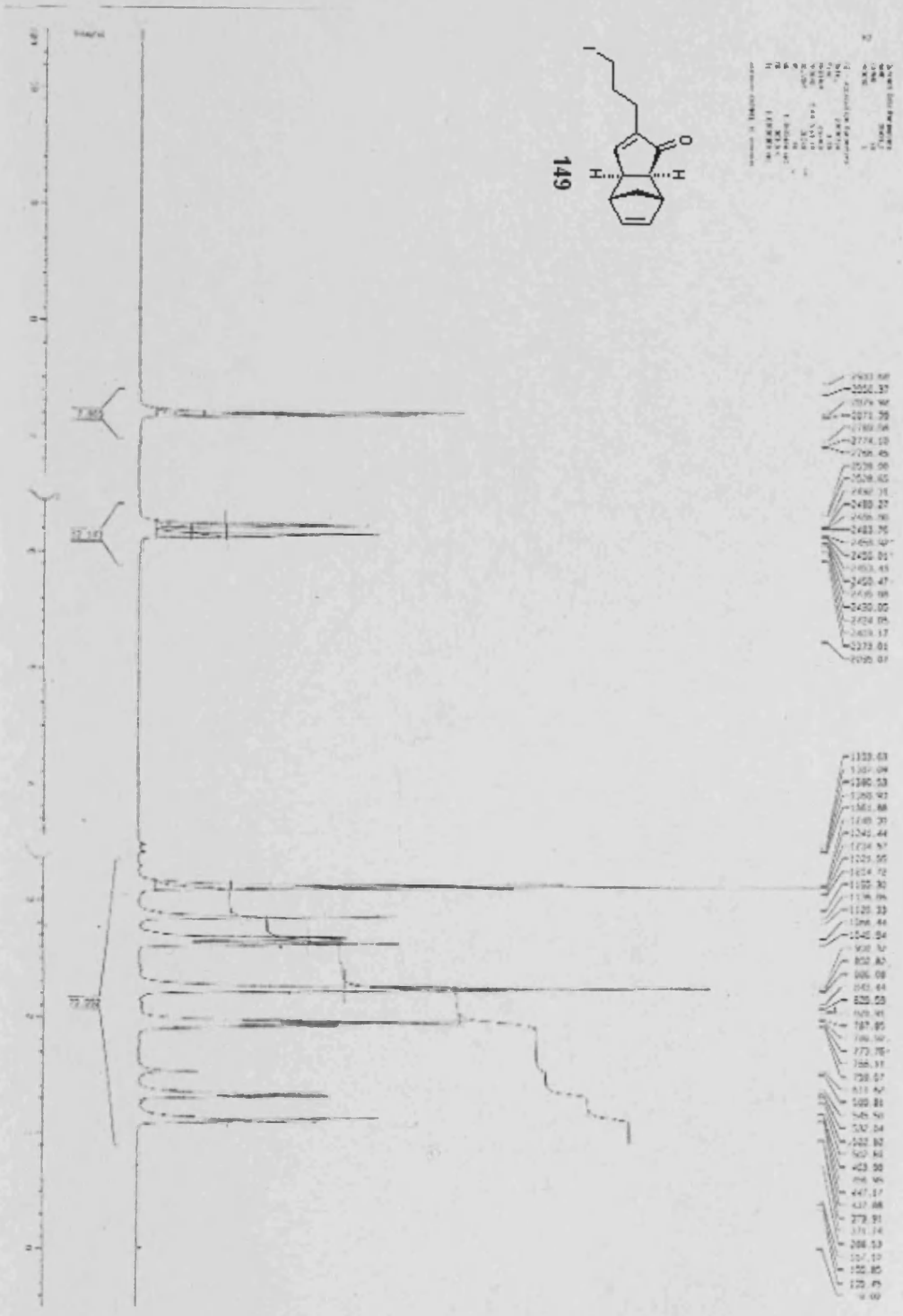
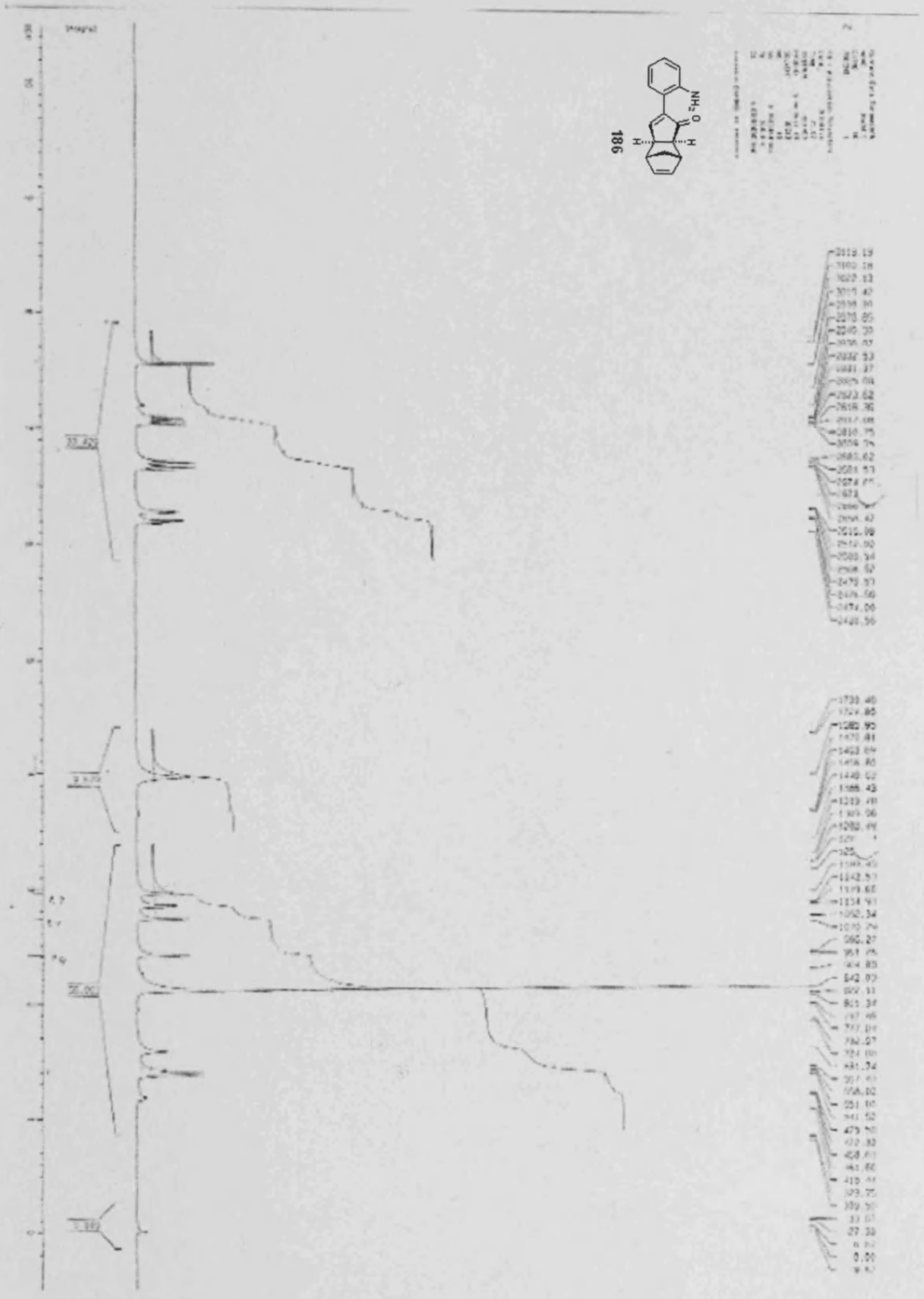
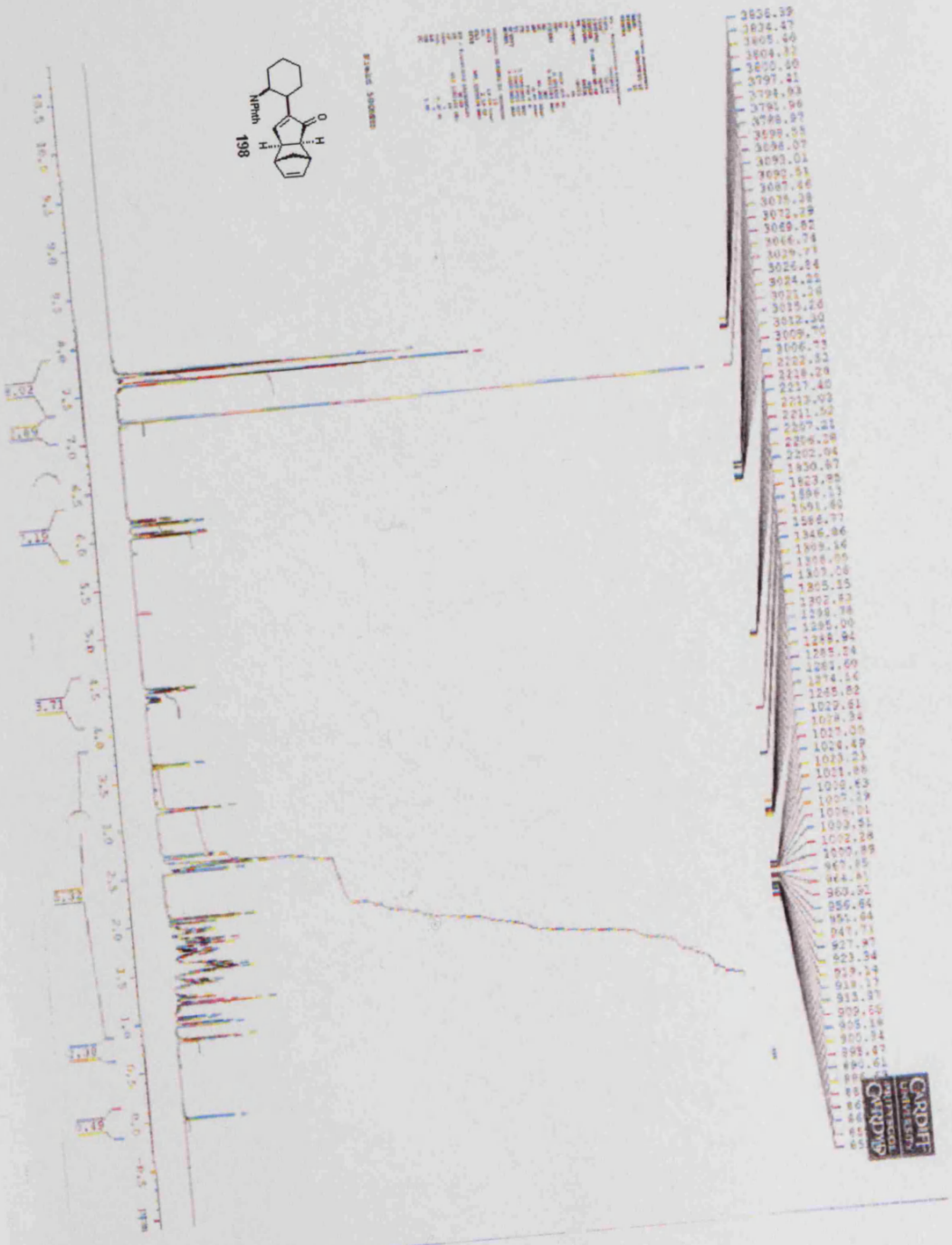
Appendix

Appendix

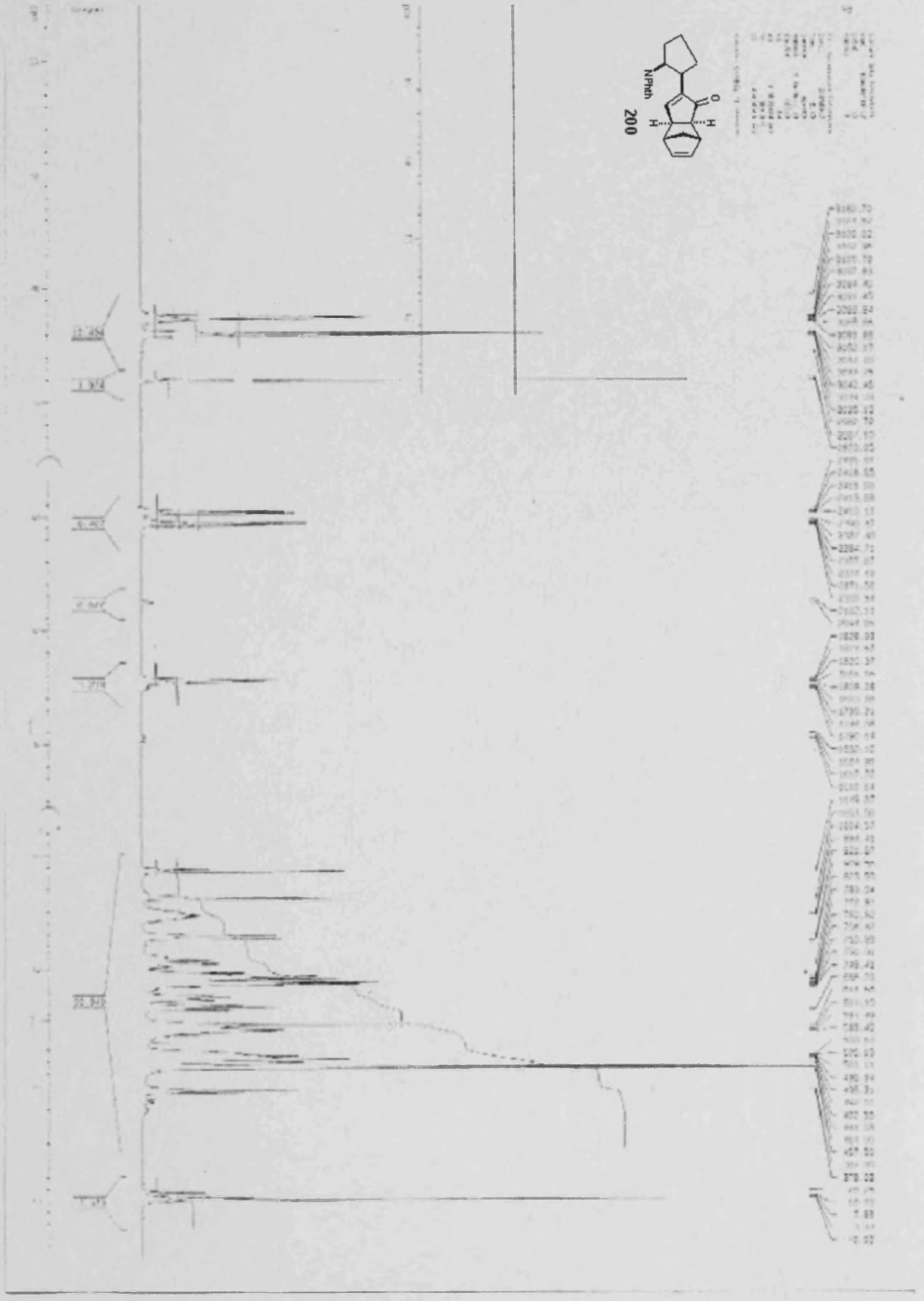



186

Appendix



Appendix



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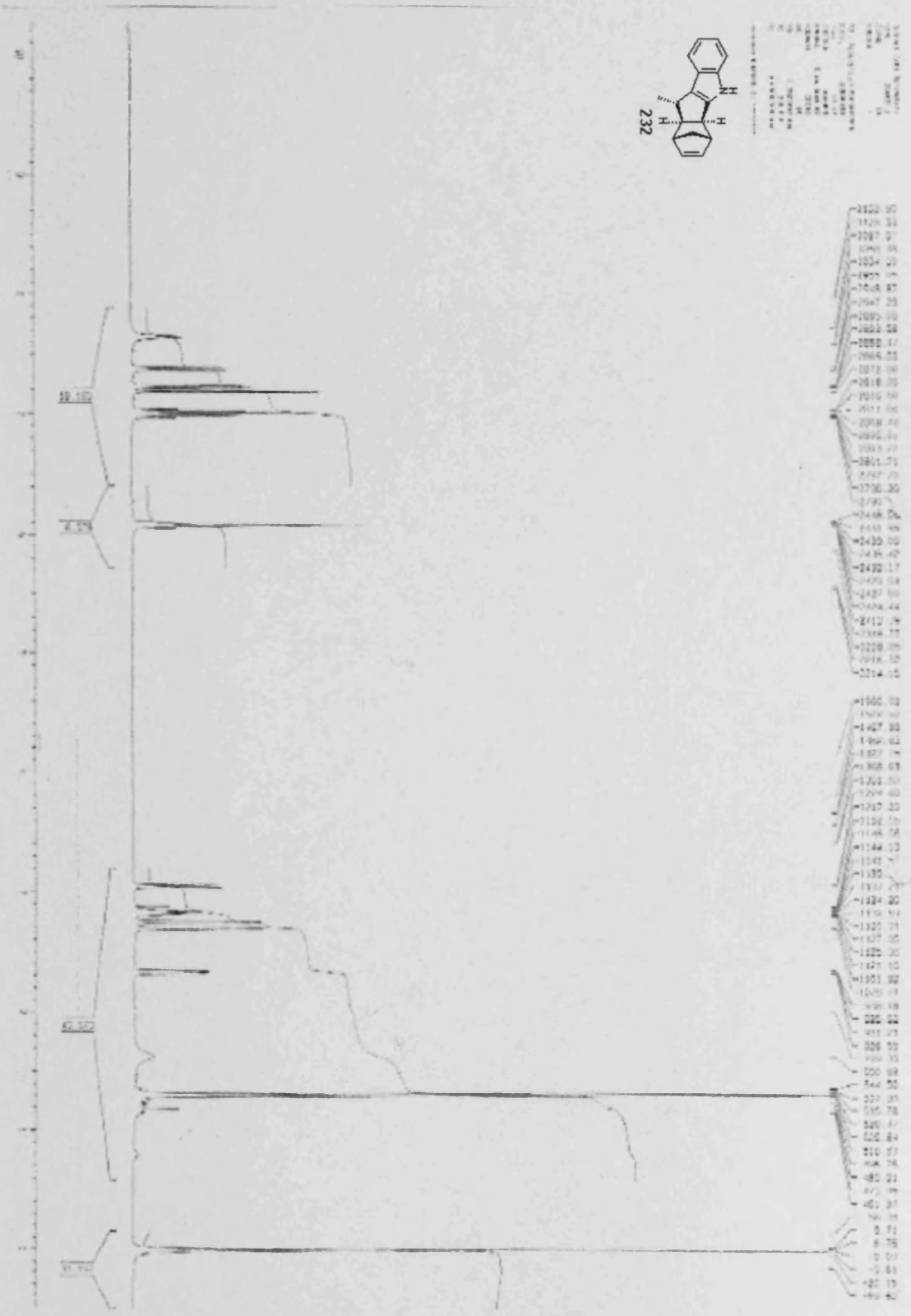

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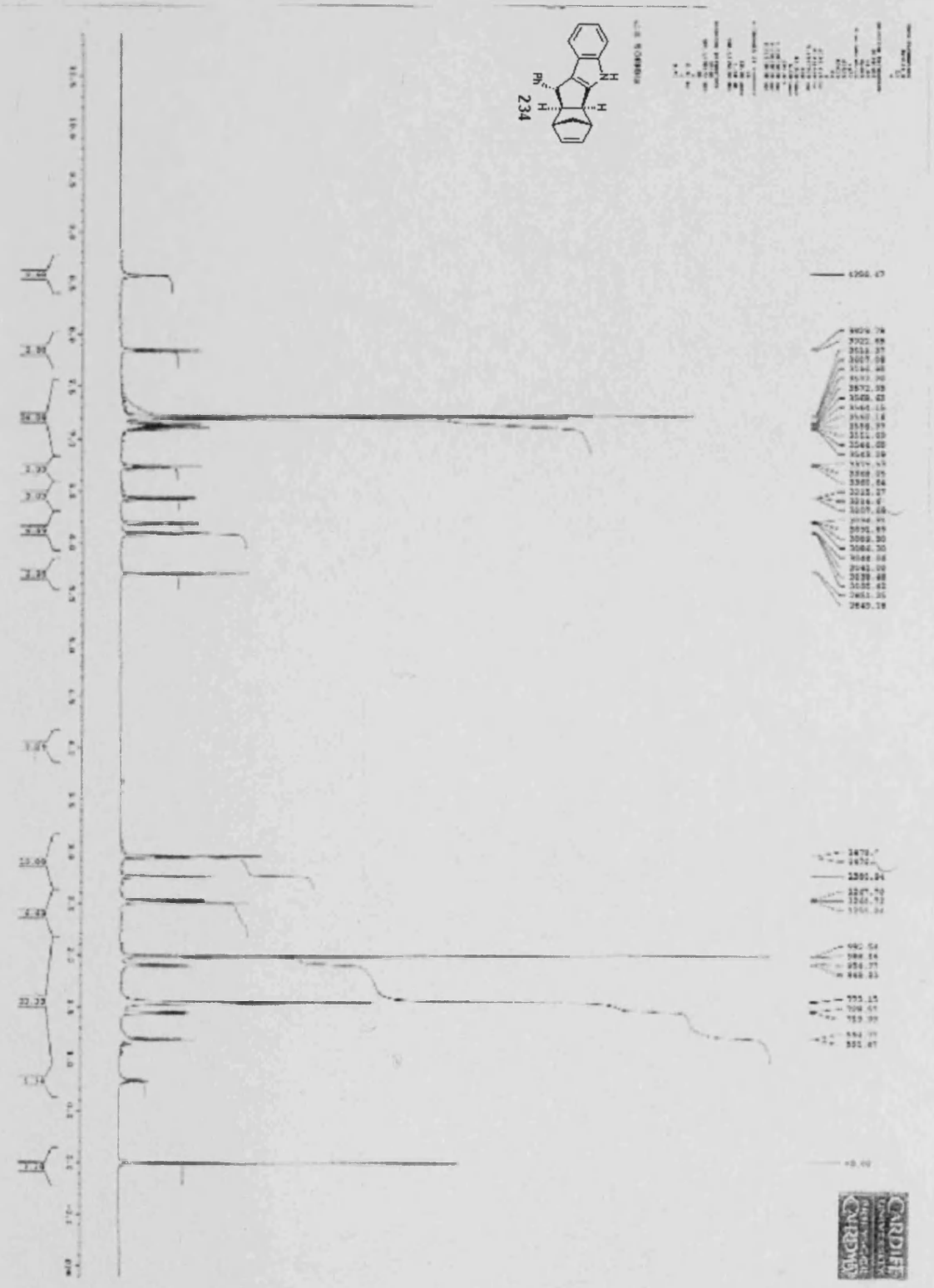

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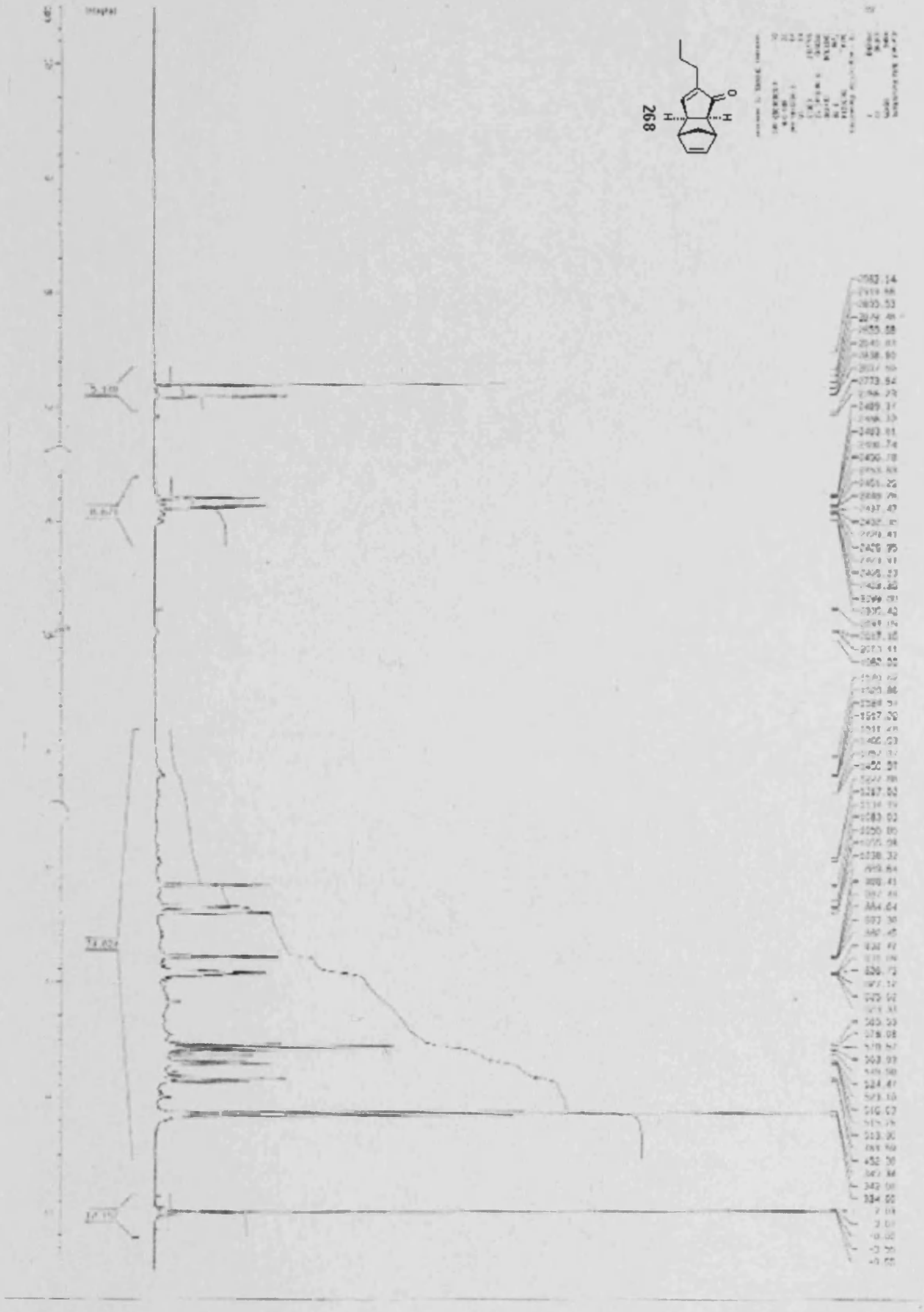
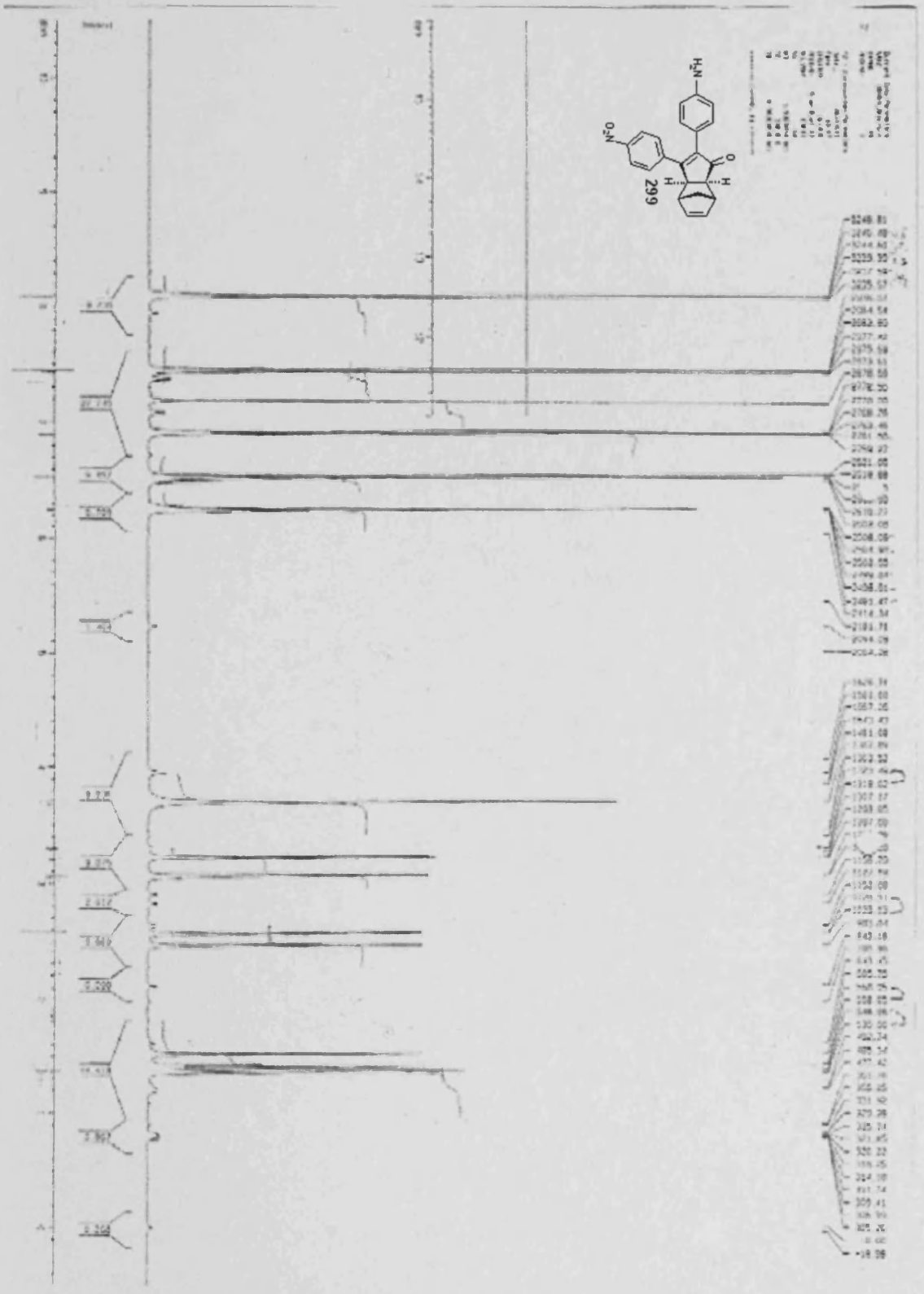
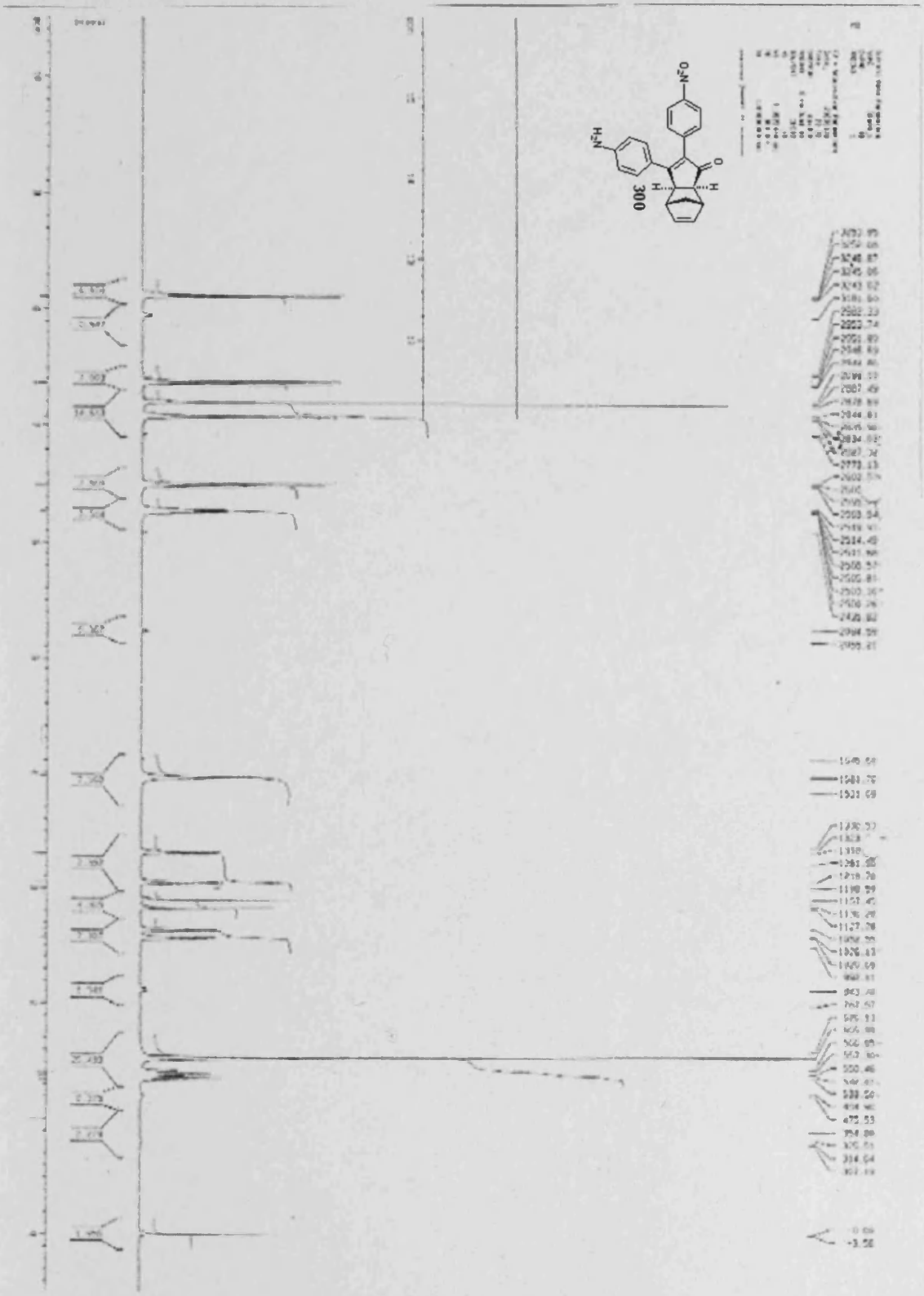
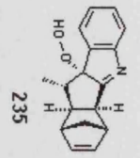


Appendix



Appendix





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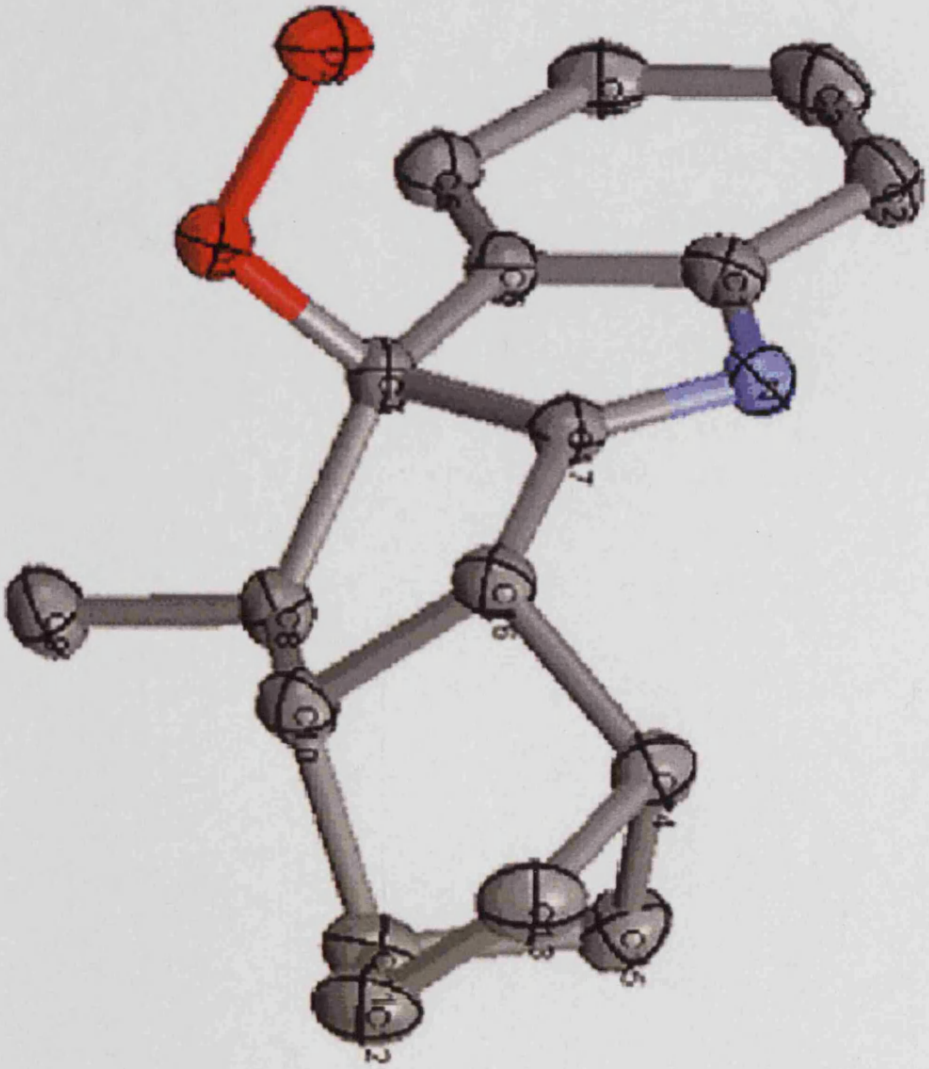

Appendix

Table 1. Crystal data and structure refinement for imino-hydroperoxide of 10-methyl-1,4,4a,5,10,10a-hexahydro-1,4-methanoindeno[1,2b] (**235**).

Identification code	mpc0409	
Empirical formula	C17 H17 N O2	
Formula weight	267.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 20.4996(7) Å	alpha= 90°.
	b = 9.0822(4) Å	beta= 118.105(2)°.
	c = 16.6153(7) Å	gamma = 90°.
Volume	2728.70(19) $Å^3$	
Z	8	
Density (calculated)	1.301 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1136	
Crystal size	0.25 x 0.23 x 0.20 mm^3	
Theta range for data collection	3.12 to 27.54°.	
Index ranges	-26<=h<=22, -11<=k<=11, -18<=l<=19	
Reflections collected	8496	
Independent reflections	2807 [R(int) = 0.0702]	
Completeness to theta = 25.00°	95.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9832 and 0.9790	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2807 / 0 / 183	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0650, wR2 = 0.1138	
R indices (all data)	R1 = 0.1141, wR2 = 0.1321	
Largest diff. peak and hole	0.216 and -0.275 $e.Å^{-3}$	

Appendix

Table 3. Bond lengths [Å] and angles [°] for (**235**).

C(1)-C(2)	1.380(3)
C(1)-C(6)	1.397(3)
C(1)-N(1)	1.446(3)
C(2)-C(3)	1.390(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.383(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.401(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.378(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.507(3)
C(7)-O(1)	1.429(3)
C(7)-C(17)	1.513(3)
C(7)-C(8)	1.546(3)
C(8)-C(9)	1.527(3)
C(8)-C(10)	1.560(3)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.554(3)
C(10)-C(16)	1.578(3)
C(10)-H(10)	1.0000
C(11)-C(12)	1.523(3)
C(11)-C(15)	1.537(3)
C(11)-H(11)	1.0000
C(12)-C(13)	1.317(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.522(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.537(3)
C(14)-C(16)	1.550(3)
C(14)-H(14)	1.0000
C(15)-H(15A)	0.9900

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C(15)-H(15B)	0.9900
C(16)-C(17)	1.486(3)
C(16)-H(16)	1.0000
C(17)-N(1)	1.282(3)
O(1)-O(2)	1.470(2)
O(2)-H(2A)	0.8400
C(2)-C(1)-C(6)	122.1(2)
C(2)-C(1)-N(1)	125.6(2)
C(6)-C(1)-N(1)	112.34(19)
C(1)-C(2)-C(3)	117.4(2)
C(1)-C(2)-H(2)	121.3
C(3)-C(2)-H(2)	121.3
C(4)-C(3)-C(2)	121.0(2)
C(4)-C(3)-H(3)	119.5
C(2)-C(3)-H(3)	119.5
C(3)-C(4)-C(5)	121.2(2)
C(3)-C(4)-H(4)	119.4
C(5)-C(4)-H(4)	119.4
C(6)-C(5)-C(4)	117.9(2)
C(6)-C(5)-H(5)	121.0
C(4)-C(5)-H(5)	121.0
C(5)-C(6)-C(1)	120.3(2)
C(5)-C(6)-C(7)	133.8(2)
C(1)-C(6)-C(7)	105.86(19)
O(1)-C(7)-C(6)	115.81(17)
O(1)-C(7)-C(17)	112.85(18)
C(6)-C(7)-C(17)	100.81(17)
O(1)-C(7)-C(8)	104.91(17)
C(6)-C(7)-C(8)	121.90(18)
C(17)-C(7)-C(8)	99.34(17)
C(9)-C(8)-C(7)	114.75(19)
C(9)-C(8)-C(10)	115.23(19)
C(7)-C(8)-C(10)	103.46(17)
C(9)-C(8)-H(8)	107.7
C(7)-C(8)-H(8)	107.7
C(10)-C(8)-H(8)	107.7

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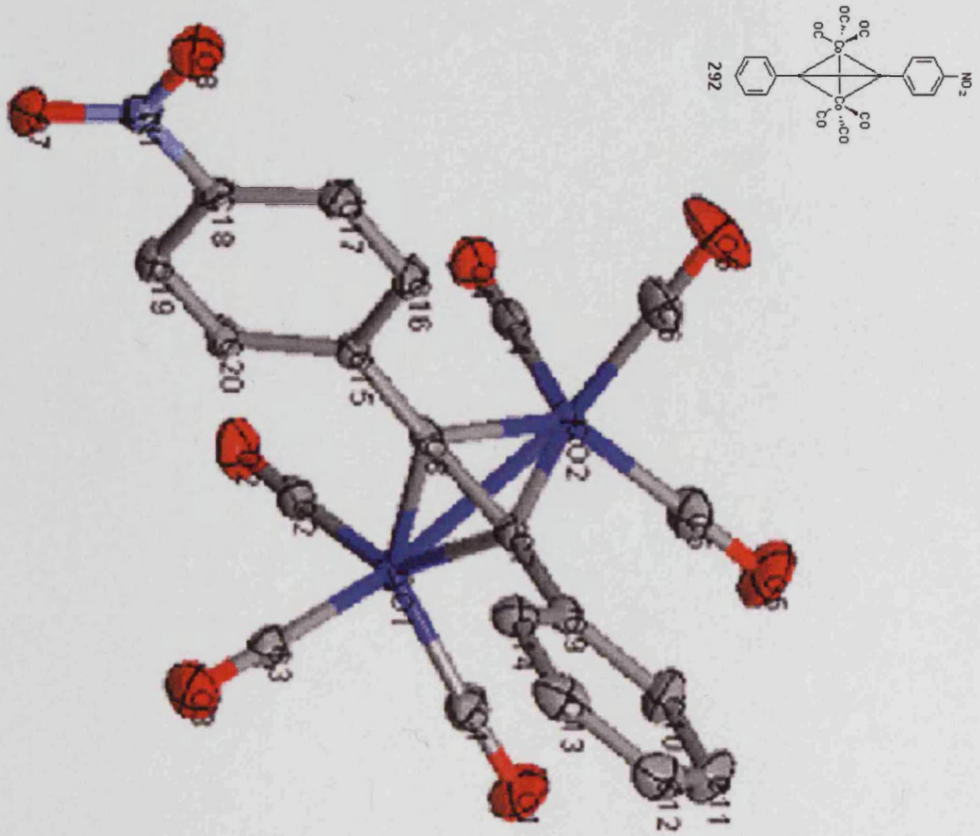
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(11)-C(10)-C(8)	116.09(18)
C(11)-C(10)-C(16)	101.35(19)
C(8)-C(10)-C(16)	107.03(17)
C(11)-C(10)-H(10)	110.6
C(8)-C(10)-H(10)	110.6
C(16)-C(10)-H(10)	110.6
C(12)-C(11)-C(15)	99.7(2)
C(12)-C(11)-C(10)	105.23(18)
C(15)-C(11)-C(10)	101.69(18)
C(12)-C(11)-H(11)	116.0
C(15)-C(11)-H(11)	116.0
C(10)-C(11)-H(11)	116.0
C(13)-C(12)-C(11)	107.8(2)
C(13)-C(12)-H(12)	126.1
C(11)-C(12)-H(12)	126.1
C(12)-C(13)-C(14)	108.1(2)
C(12)-C(13)-H(13)	125.9
C(14)-C(13)-H(13)	125.9
C(13)-C(14)-C(15)	99.52(19)
C(13)-C(14)-C(16)	104.63(19)
C(15)-C(14)-C(16)	100.52(19)
C(13)-C(14)-H(14)	116.5
C(15)-C(14)-H(14)	116.5
C(16)-C(14)-H(14)	116.5
C(14)-C(15)-C(11)	94.35(18)
C(14)-C(15)-H(15A)	112.9



Appendix

Table 1. Crystal data and structure refinement for 4-(2-phenylethynyl)nitrobenzene)dicobalthexacarbonyl (**292**).

Identification code	s92
Empirical formula	C20 H9 Co2 N O8
Formula weight	509.14
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 10.5504(3) A alpha = 90 deg.
	b = 12.4376(3) A beta = 90.6869(8) deg.
	c = 30.3640(8) A gamma = 90 deg.
Volume	3984.13(18) A^3
Z	8
Density (calculated)	1.698 Mg/m^3
Absorption coefficient	1.714 mm^-1
F(000)	2032
Crystal size	0.25 x 0.20 x 0.18 mm
Theta range for data collection	3.22 to 27.48 deg.
Index ranges	-13<=h<=13, -14<=k<=16, -32<=l<=39
Reflections collected	12835
Independent reflections	4340 [R(int) = 0.0572]
Max. and min. transmission	0.7478 and 0.6739
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4340 / 0 / 280
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0737
R indices (all data)	R1 = 0.0542, wR2 = 0.0793
Largest diff. peak and hole	0.452 and -0.398 e.A^-3

Appendix

Table 3. Bond lengths [A] and angles [deg] for (**292**).

Co(1)-Co(2)	2.4708(5)
Co(1)-C(3)	1.796(3)
Co(1)-C(1)	1.819(3)
Co(1)-C(2)	1.827(3)
Co(1)-C(8)	1.951(2)
Co(1)-C(7)	1.977(2)
Co(2)-C(6)	1.807(3)
Co(2)-C(5)	1.811(3)
Co(2)-C(4)	1.828(3)
Co(2)-C(7)	1.949(3)
Co(2)-C(8)	1.981(3)
O(1)-C(1)	1.136(3)
O(2)-C(2)	1.133(3)
O(3)-C(3)	1.131(3)
O(4)-C(4)	1.130(3)
O(5)-C(5)	1.141(3)
O(6)-C(6)	1.132(3)
O(7)-N(1)	1.227(3)
O(8)-N(1)	1.233(3)
N(1)-C(18)	1.470(3)
C(7)-C(8)	1.355(3)
C(7)-C(9)	1.467(3)
C(8)-C(15)	1.470(3)
C(9)-C(14)	1.388(4)
C(9)-C(10)	1.395(4)
C(10)-C(11)	1.385(4)
C(11)-C(12)	1.379(5)
C(12)-C(13)	1.378(4)
C(13)-C(14)	1.391(4)
C(15)-C(20)	1.398(3)
C(15)-C(16)	1.404(3)
C(16)-C(17)	1.378(4)
C(17)-C(18)	1.380(3)
C(18)-C(19)	1.391(3)
C(19)-C(20)	1.382(4)
C(3)-Co(1)-C(1)	100.24(13)
C(3)-Co(1)-C(2)	98.73(12)
C(1)-Co(1)-C(2)	107.00(12)
C(3)-Co(1)-C(8)	96.82(12)
C(1)-Co(1)-C(8)	139.64(11)
C(2)-Co(1)-C(8)	106.14(11)
C(3)-Co(1)-C(7)	100.60(11)
C(1)-Co(1)-C(7)	100.27(11)
C(2)-Co(1)-C(7)	142.94(11)

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C(8)-Co(1)-C(7)	40.35(9)
C(3)-Co(1)-Co(2)	147.08(9)
C(1)-Co(1)-Co(2)	100.48(9)
C(2)-Co(1)-Co(2)	99.32(9)
C(8)-Co(1)-Co(2)	51.62(8)
C(7)-Co(1)-Co(2)	50.50(8)
C(6)-Co(2)-C(5)	99.84(13)
C(6)-Co(2)-C(4)	99.68(12)
C(5)-Co(2)-C(4)	103.86(12)
C(6)-Co(2)-C(7)	102.81(12)
C(5)-Co(2)-C(7)	101.49(12)
C(4)-Co(2)-C(7)	142.42(11)
C(6)-Co(2)-C(8)	100.01(12)
C(5)-Co(2)-C(8)	140.22(12)
C(4)-Co(2)-C(8)	106.29(11)
C(7)-Co(2)-C(8)	40.32(10)
C(6)-Co(2)-Co(1)	149.69(10)
C(5)-Co(2)-Co(1)	101.10(9)
C(4)-Co(2)-Co(1)	96.29(8)
C(7)-Co(2)-Co(1)	51.52(7)
C(8)-Co(2)-Co(1)	50.52(7)
O(7)-N(1)-O(8)	123.4(2)
O(7)-N(1)-C(18)	118.8(2)
O(8)-N(1)-C(18)	117.8(2)
O(1)-C(1)-Co(1)	176.5(2)
O(2)-C(2)-Co(1)	177.8(2)
O(3)-C(3)-Co(1)	177.3(3)
O(4)-C(4)-Co(2)	177.7(2)
O(5)-C(5)-Co(2)	178.0(3)
O(6)-C(6)-Co(2)	179.0(3)
C(8)-C(7)-C(9)	141.5(2)
C(8)-C(7)-Co(2)	71.12(16)
C(9)-C(7)-Co(2)	138.84(19)
C(8)-C(7)-Co(1)	68.76(14)
C(9)-C(7)-Co(1)	129.77(18)
Co(2)-C(7)-Co(1)	77.99(9)
C(7)-C(8)-C(15)	139.9(2)
C(7)-C(8)-Co(1)	70.89(14)
C(15)-C(8)-Co(1)	136.08(18)
C(7)-C(8)-Co(2)	68.57(16)
C(15)-C(8)-Co(2)	134.96(18)
Co(1)-C(8)-Co(2)	77.86(9)
C(14)-C(9)-C(10)	118.6(2)
C(14)-C(9)-C(7)	119.8(2)
C(10)-C(9)-C(7)	121.6(2)
C(11)-C(10)-C(9)	120.6(3)

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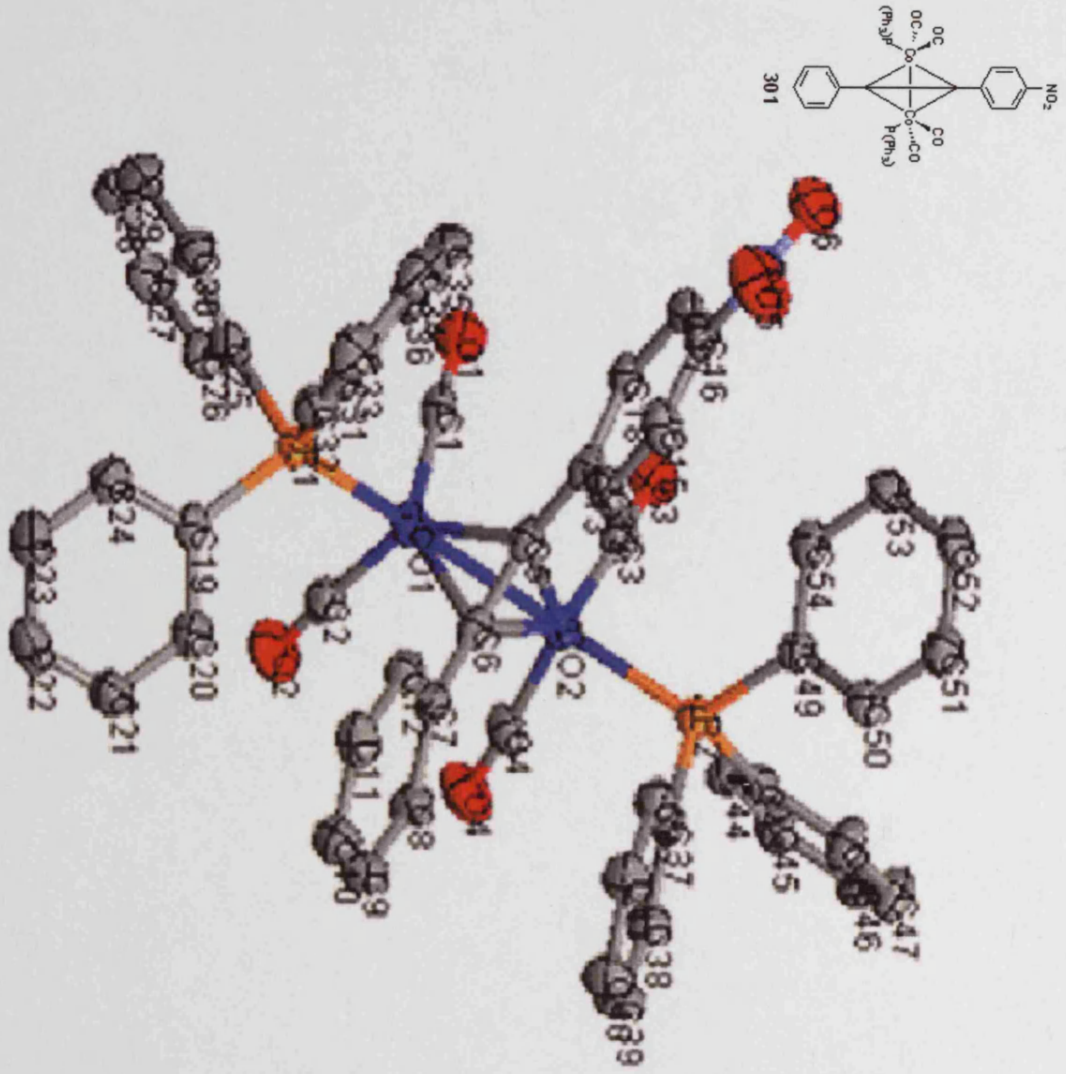
C(12)-C(11)-C(10)	120.0(3)
C(13)-C(12)-C(11)	120.4(3)
C(12)-C(13)-C(14)	119.8(3)
C(9)-C(14)-C(13)	120.7(3)
C(20)-C(15)-C(16)	118.5(2)
C(20)-C(15)-C(8)	121.6(2)
C(16)-C(15)-C(8)	119.9(2)
C(17)-C(16)-C(15)	121.0(2)
C(16)-C(17)-C(18)	118.9(2)
C(17)-C(18)-C(19)	121.9(2)
C(17)-C(18)-N(1)	119.0(2)
C(19)-C(18)-N(1)	119.2(2)
C(20)-C(19)-C(18)	118.6(2)
C(19)-C(20)-C(15)	121.1(2)

Appendix



Appendix

Table 1. Crystal data and structure refinement for 4-(2-phenylethynyl)nitrobenzene dicobaltdecacarbonylbis(triphenylphosphine) (**301**).

Identification code	mpc0406	
Empirical formula	C27 H19.50 Co N0.50 O3 P	
Formula weight	488.83	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 212121	
Unit cell dimensions	a = 12.8352(2) Å	alpha = 90°.
	b = 12.9343(2) Å	beta= 90°.
	c = 27.3791(6) Å	gamma= 90°.
Volume	4545.32(14) $Å^3$	
Z	8	
Density (calculated)	1.429 Mg/m^3	
Absorption coefficient	0.854 mm^{-1}	
F(000)	2008	
Crystal size	0.28 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.98 to 27.50°.	
Index ranges	-15<=h<=16, -16<=k<=16, -35<=l<=35	
Reflections collected	37034	
Independent reflections	10018 [R(int) = 0.0916]	
Completeness to theta = 27.50°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8478 and 0.7960	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10018 / 0 / 586	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.0967	
R indices (all data)	R1 = 0.1099, wR2 = 0.1130	
Absolute structure parameter	0.008(12)	
Largest diff. peak and hole	0.580 and -0.423 $e.Å^{-3}$	

Appendix

Table 3. Bond lengths [Å] and angles [°] (**301**).

C(1)-O(1)	1.141(5)	C(17)-H(17)	0.9500
C(1)-Co(1)	1.803(5)	C(18)-H(18)	0.9500
C(2)-O(2)	1.132(5)	C(19)-C(24)	1.390(6)
C(2)-Co(1)	1.799(5)	C(19)-C(20)	1.397(6)
C(3)-O(3)	1.147(5)	C(19)-P(1)	1.832(4)
C(3)-Co(2)	1.794(5)	C(20)-C(21)	1.381(6)
C(4)-O(4)	1.145(5)	C(20)-H(20)	0.9500
C(4)-Co(2)	1.785(5)	C(21)-C(22)	1.382(7)
C(5)-C(6)	1.335(5)	C(21)-H(21)	0.9500
C(5)-C(13)	1.463(6)	C(22)-C(23)	1.377(7)
C(5)-Co(1)	1.969(4)	C(22)-H(22)	0.9500
C(5)-Co(2)	1.975(4)	C(23)-C(24)	1.374(6)
C(6)-C(7)	1.465(6)	C(23)-H(23)	0.9500
C(6)-Co(2)	1.971(4)	C(24)-H(24)	0.9500
C(6)-Co(1)	2.011(4)	C(25)-C(30)	1.396(6)
C(7)-C(8)	1.389(6)	C(25)-C(26)	1.398(6)
C(7)-C(12)	1.408(6)	C(25)-P(1)	1.849(4)
C(8)-C(9)	1.370(6)	C(26)-C(27)	1.381(6)
C(8)-H(8)	0.9500	C(26)-H(26)	0.9500
C(9)-C(10)	1.385(7)	C(27)-C(28)	1.388(6)
C(9)-H(9)	0.9500	C(27)-H(27)	0.9500
C(10)-C(11)	1.380(6)	C(28)-C(29)	1.384(6)
C(10)-H(10)	0.9500	C(28)-H(28)	0.9500
C(11)-C(12)	1.381(6)	C(29)-C(30)	1.386(6)
C(11)-H(11)	0.9500	C(29)-H(29)	0.9500
C(12)-H(12)	0.9500	C(30)-H(30)	0.9500
C(13)-C(18)	1.390(6)	C(31)-C(32)	1.371(6)
C(13)-C(14)	1.399(5)	C(31)-C(36)	1.404(6)
C(14)-C(15)	1.379(6)	C(31)-P(1)	1.837(4)
C(14)-H(14)	0.9500	C(32)-C(33)	1.386(6)
C(15)-C(16)	1.397(6)	C(32)-H(32)	0.9500
C(15)-H(15)	0.9500	C(33)-C(34)	1.361(6)
C(16)-C(17)	1.375(6)	C(33)-H(33)	0.9500
C(16)-N(1)	1.436(5)	C(34)-C(35)	1.381(6)
C(17)-C(18)	1.376(6)	C(34)-H(34)	0.9500

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C(35)-C(36)	1.381(6)	C(53)-C(54)	1.397(6)
C(35)-H(35)	0.9500	C(53)-H(53)	0.9500
C(36)-H(36)	0.9500	C(54)-H(54)	0.9500
C(37)-C(38)	1.404(6)	Co(1)-P(1)	2.2302(11)
C(37)-C(42)	1.405(6)	Co(1)-Co(2)	2.4679(7)
C(37)-P(2)	1.816(4)	Co(2)-P(2)	2.2322(12)
C(38)-C(39)	1.385(6)	N(1)-O(6)	1.230(5)
C(38)-H(38)	0.9500	N(1)-O(5)	1.249(5)
C(39)-C(40)	1.372(6)		
C(39)-H(39)	0.9500	O(1)-C(1)-Co(1)	177.8(4)
C(40)-C(41)	1.376(6)	O(2)-C(2)-Co(1)	177.2(4)
C(40)-H(40)	0.9500	O(3)-C(3)-Co(2)	176.4(4)
C(41)-C(42)	1.385(6)	O(4)-C(4)-Co(2)	176.5(4)
C(41)-H(41)	0.9500	C(6)-C(5)-C(13)	142.5(4)
C(42)-H(42)	0.9500	C(6)-C(5)-Co(1)	72.1(2)
C(43)-C(44)	1.396(5)	C(13)-C(5)-Co(1)	135.1(3)
C(43)-C(48)	1.402(6)	C(6)-C(5)-Co(2)	70.1(2)
C(43)-P(2)	1.842(4)	C(13)-C(5)-Co(2)	131.9(3)
C(44)-C(45)	1.398(6)	Co(1)-C(5)-Co(2)	77.45(14)
C(44)-H(44)	0.9500	C(5)-C(6)-C(7)	143.1(4)
C(45)-C(46)	1.361(6)	C(5)-C(6)-Co(2)	70.4(2)
C(45)-H(45)	0.9500	C(7)-C(6)-Co(2)	138.4(3)
C(46)-C(47)	1.390(6)	C(5)-C(6)-Co(1)	68.7(2)
C(46)-H(46)	0.9500	C(7)-C(6)-Co(1)	130.1(3)
C(47)-C(48)	1.375(6)	Co(2)-C(6)-Co(1)	76.58(14)
C(47)-H(47)	0.9500	C(8)-C(7)-C(12)	117.9(4)
C(48)-H(48)	0.9500	C(8)-C(7)-C(6)	122.1(4)
C(49)-C(54)	1.390(6)	C(12)-C(7)-C(6)	119.9(4)
C(49)-C(50)	1.402(5)	C(9)-C(8)-C(7)	121.0(4)
C(49)-P(2)	1.829(4)	C(9)-C(8)-H(8)	119.5
C(50)-C(51)	1.364(6)	C(7)-C(8)-H(8)	119.5
C(50)-H(50)	0.9500	C(8)-C(9)-C(10)	121.0(4)
C(51)-C(52)	1.393(6)	C(8)-C(9)-H(9)	119.5
C(51)-H(51)	0.9500	C(10)-C(9)-H(9)	119.5
C(52)-C(53)	1.380(6)	C(11)-C(10)-C(9)	119.1(4)
C(52)-H(52)	0.9500	C(11)-C(10)-H(10)	120.4

C(9)-C(10)-H(10)	120.4	C(21)-C(22)-H(22)	120.3
C(10)-C(11)-C(12)	120.3(4)	C(24)-C(23)-C(22)	120.5(4)
C(10)-C(11)-H(11)	119.8	C(24)-C(23)-H(23)	119.8
C(12)-C(11)-H(11)	119.8	C(22)-C(23)-H(23)	119.8
C(11)-C(12)-C(7)	120.7(4)	C(23)-C(24)-C(19)	121.1(4)
C(11)-C(12)-H(12)	119.6	C(23)-C(24)-H(24)	119.4
C(7)-C(12)-H(12)	119.6	C(19)-C(24)-H(24)	119.4
C(18)-C(13)-C(14)	117.9(4)	C(30)-C(25)-C(26)	118.4(4)
C(18)-C(13)-C(5)	121.8(4)	C(30)-C(25)-P(1)	122.9(3)
C(14)-C(13)-C(5)	120.3(4)	C(26)-C(25)-P(1)	118.7(3)
C(15)-C(14)-C(13)	121.8(4)	C(27)-C(26)-C(25)	120.3(4)
C(15)-C(14)-H(14)	119.1	C(27)-C(26)-H(26)	119.9
C(13)-C(14)-H(14)	119.1	C(25)-C(26)-H(26)	119.9
C(14)-C(15)-C(16)	117.7(4)	C(26)-C(27)-C(28)	121.3(4)
C(14)-C(15)-H(15)	121.2	C(26)-C(27)-H(27)	119.3
C(16)-C(15)-H(15)	121.2	C(28)-C(27)-H(27)	119.3
C(17)-C(16)-C(15)	122.3(4)	C(29)-C(28)-C(27)	118.4(4)
C(17)-C(16)-N(1)	120.5(4)	C(29)-C(28)-H(28)	120.8
C(15)-C(16)-N(1)	117.1(4)	C(27)-C(28)-H(28)	120.8
C(16)-C(17)-C(18)	118.3(4)	C(28)-C(29)-C(30)	121.0(4)
C(16)-C(17)-H(17)	120.9	C(28)-C(29)-H(29)	119.5
C(18)-C(17)-H(17)	120.9	C(30)-C(29)-H(29)	119.5
C(17)-C(18)-C(13)	122.0(4)	C(29)-C(30)-C(25)	120.5(4)
C(17)-C(18)-H(18)	119.0	C(29)-C(30)-H(30)	119.7
C(13)-C(18)-H(18)	119.0	C(25)-C(30)-H(30)	119.7
C(24)-C(19)-C(20)	118.1(4)	C(32)-C(31)-C(36)	119.2(4)
C(24)-C(19)-P(1)	121.1(3)	C(32)-C(31)-P(1)	124.0(3)
C(20)-C(19)-P(1)	120.8(3)	C(36)-C(31)-P(1)	116.8(3)
C(21)-C(20)-C(19)	120.4(4)	C(31)-C(32)-C(33)	120.1(4)
C(21)-C(20)-H(20)	119.8	C(31)-C(32)-H(32)	120.0
C(19)-C(20)-H(20)	119.8	C(33)-C(32)-H(32)	120.0
C(20)-C(21)-C(22)	120.6(4)	C(34)-C(33)-C(32)	120.7(4)
C(20)-C(21)-H(21)	119.7	C(34)-C(33)-H(33)	119.6
C(22)-C(21)-H(21)	119.7	C(32)-C(33)-H(33)	119.6
C(23)-C(22)-C(21)	119.3(4)	C(33)-C(34)-C(35)	120.2(4)
C(23)-C(22)-H(22)	120.3	C(33)-C(34)-H(34)	119.9

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C(35)-C(34)-H(34)	119.9	C(47)-C(46)-H(46)	119.9
C(36)-C(35)-C(34)	119.7(4)	C(48)-C(47)-C(46)	119.8(4)
C(36)-C(35)-H(35)	120.1	C(48)-C(47)-H(47)	120.1
C(34)-C(35)-H(35)	120.1	C(46)-C(47)-H(47)	120.1
C(35)-C(36)-C(31)	120.0(4)	C(47)-C(48)-C(43)	121.3(4)
C(35)-C(36)-H(36)	120.0	C(47)-C(48)-H(48)	119.4
C(31)-C(36)-H(36)	120.0	C(43)-C(48)-H(48)	119.4
C(38)-C(37)-C(42)	118.2(4)	C(54)-C(49)-C(50)	117.7(4)
C(38)-C(37)-P(2)	122.0(3)	C(54)-C(49)-P(2)	119.5(3)
C(42)-C(37)-P(2)	119.5(3)	C(50)-C(49)-P(2)	122.8(3)
C(39)-C(38)-C(37)	119.7(4)	C(51)-C(50)-C(49)	121.4(4)
C(39)-C(38)-H(38)	120.1	C(51)-C(50)-H(50)	119.3
C(37)-C(38)-H(38)	120.1	C(49)-C(50)-H(50)	119.3
C(40)-C(39)-C(38)	121.3(4)	C(50)-C(51)-C(52)	120.8(4)
C(40)-C(39)-H(39)	119.4	C(50)-C(51)-H(51)	119.6
C(38)-C(39)-H(39)	119.4	C(52)-C(51)-H(51)	119.6
C(39)-C(40)-C(41)	119.9(4)	C(53)-C(52)-C(51)	118.9(4)
C(39)-C(40)-H(40)	120.1	C(53)-C(52)-H(52)	120.5
C(41)-C(40)-H(40)	120.1	C(51)-C(52)-H(52)	120.5
C(40)-C(41)-C(42)	120.2(4)	C(52)-C(53)-C(54)	120.4(4)
C(40)-C(41)-H(41)	119.9	C(52)-C(53)-H(53)	119.8
C(42)-C(41)-H(41)	119.9	C(54)-C(53)-H(53)	119.8
C(41)-C(42)-C(37)	120.7(4)	C(49)-C(54)-C(53)	120.8(4)
C(41)-C(42)-H(42)	119.7	C(49)-C(54)-H(54)	119.6
C(37)-C(42)-H(42)	119.7	C(53)-C(54)-H(54)	119.6
C(44)-C(43)-C(48)	117.8(4)	C(2)-Co(1)-C(1)	106.6(2)
C(44)-C(43)-P(2)	121.2(3)	C(2)-Co(1)-C(5)	141.14(19)
C(48)-C(43)-P(2)	121.0(3)	C(1)-Co(1)-C(5)	102.97(18)
C(43)-C(44)-C(45)	120.5(4)	C(2)-Co(1)-C(6)	104.42(19)
C(43)-C(44)-H(44)	119.7	C(1)-Co(1)-C(6)	140.33(17)
C(45)-C(44)-H(44)	119.7	C(5)-Co(1)-C(6)	39.17(16)
C(46)-C(45)-C(44)	120.4(4)	C(2)-Co(1)-P(1)	96.47(13)
C(46)-C(45)-H(45)	119.8	C(1)-Co(1)-P(1)	96.09(14)
C(44)-C(45)-H(45)	119.8	C(5)-Co(1)-P(1)	104.91(11)
C(45)-C(46)-C(47)	120.2(4)	C(6)-Co(1)-P(1)	104.36(11)
C(45)-C(46)-H(46)	119.9	C(2)-Co(1)-Co(2)	98.47(13)

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C(1)-Co(1)-Co(2)	100.06(13)
C(5)-Co(1)-Co(2)	51.38(11)
C(6)-Co(1)-Co(2)	50.98(10)
P(1)-Co(1)-Co(2)	153.81(4)
C(4)-Co(2)-C(3)	108.46(19)
C(4)-Co(2)-C(6)	100.70(17)
C(3)-Co(2)-C(6)	140.42(18)
C(4)-Co(2)-C(5)	137.98(17)
C(3)-Co(2)-C(5)	103.32(18)
C(6)-Co(2)-C(5)	39.54(16)
C(4)-Co(2)-P(2)	95.85(15)
C(3)-Co(2)-P(2)	98.17(13)
C(6)-Co(2)-P(2)	104.97(11)
C(5)-Co(2)-P(2)	106.20(11)
C(4)-Co(2)-Co(1)	97.74(14)
C(3)-Co(2)-Co(1)	96.71(13)
C(6)-Co(2)-Co(1)	52.44(11)
C(5)-Co(2)-Co(1)	51.17(11)
P(2)-Co(2)-Co(1)	155.52(4)
O(6)-N(1)-O(5)	123.8(4)
O(6)-N(1)-C(16)	117.9(4)
O(5)-N(1)-C(16)	118.3(4)
C(19)-P(1)-C(31)	104.41(18)
C(19)-P(1)-C(25)	100.90(18)
C(31)-P(1)-C(25)	101.72(18)
C(19)-P(1)-Co(1)	118.54(13)
C(31)-P(1)-Co(1)	115.85(13)
C(25)-P(1)-Co(1)	113.11(14)
C(37)-P(2)-C(49)	102.35(19)
C(37)-P(2)-C(43)	103.20(18)
C(49)-P(2)-C(43)	102.47(17)
C(37)-P(2)-Co(2)	112.56(13)
C(49)-P(2)-Co(2)	119.33(13)
C(43)-P(2)-Co(2)	114.92(14)